Severity of Liver Injury and Its Relation to Clinical Outcome and Duration of Hospitalization in COVID 19 Patients

Cokorde Istri Yuliandari Krisnawardani Kumbara, I Ketut Mariadi**, Gde Somayana**, I Dewa Nyoman Wibawa***, Dwijo Anargha Sindhughosa***

*Department of Internal Medicine, Faculty of Medicine of Udayana University, Udayana University Hospital, Badung, Bali, Indonesia
**Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine of Udayana University / Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia
***Department of Internal Medicine and Endoscopy Unit, BaliMed Hospital, Denpasar, Bali, Indonesia

Correspondence author:
Cokorde Istri Yuliandari Krisnawardani Kumbara / Department of Internal Medicine, Faculty of Medicine of Udayana University, Udayana University Hospital, Badung, Bali, Indonesia / Email: krisnawardani@unud.ac.id

ABSTRACT

Background: *Coronavirus Disease 2019 (COVID-19) can affect not only the respiratory system but also other organs such as the liver. Liver injury tends to occur in severe disease of COVID-19 patients and might contribute to clinical outcomes for patients. This study aimed to find the relationship between the severity of liver injury with clinical outcome and duration of hospitalizations.*

Methods: *This study was a retrospective study of hospitalized COVID-19 patients period April 2020 to April 2021. The inclusion criteria were severe COVID-19 patients who developed a liver injury. The severity of the liver injury was classified into mild, moderate, and severe. The relationship between the severity of liver injury with clinical outcome and duration of hospitalization was analyzed. Univariate and bivariate analyses with one-way ANOVA tests were used.*

Results: *90 samples fill the inclusion criteria. The liver injury severity was statistically significantly related to clinical outcome patients (p= 0.047), which is the increase in liver injury severity resulting in poor clinical outcomes. No significant relationship was found between the severity of liver injury with the duration of hospitalization.*

Conclusion: *liver injury increases mortality in severe COVID-19 patients.*

Keywords: *COVID-19, clinical outcome, duration of hospitalization, liver injury*

ABSTRAK

Latar Belakang: *Coronavirus Disease 2019 (COVID-19) dapat memengaruhi tidak hanya sistem pernapasan tetapi juga organ lain seperti hati. Cedera hati cenderung terjadi pada penyakit COVID-19 yang parah dan mungkin berkontribusi pada hasil klinis bagi pasien. Penelitian ini bertujuan untuk menemukan hubungan antara tingkat keparahan cedera hati dengan hasil klinis dan durasi rawat inap.*

Metode: *Penelitian ini merupakan studi retrospektif pada pasien COVID-19 yang dirawat inap periode April 2020 hingga April 2021. Kriteria inklusi adalah pasien COVID-19 yang parah dan mengalami cedera hati. Tingkat keparahan cedera hati diklasifikasikan menjadi ringan, sedang, dan berat. Hubungan antara*

tingkat keparahan cedera hati dengan hasil klinis dan durasi rawat inap dianalisis. Analisis univariat bivariat menggunakan uji ANOVA digunakan pada penelitian ini.

Hasil: *Sebanyak 90 sampel memenuhi kriteria inklusi. Tingkat keparahan cedera hati secara statistik signifikan terkait dengan hasil klinis pasien (p=0,047), di mana peningkatan tingkat keparahan cedera hati berdampak buruk pada hasil klinis. Tidak ditemukan hubungan yang signifikan antara tingkat keparahan cedera hati dengan durasi rawat inap.*

Simpulan: *Cedera hati meningkatkan angka kematian pada pasien COVID-19 yang parah.*

Kata Kunci: *COVID-19, hasil klinis, durasi rawat inap, cedera hati*

INTRODUCTION

COVID-19 (*Coronavirus Disease 2019*) which was stated by WHO (*World Health Organization*) is a pandemic caused by the SARS-CoV-2 virus (*Severe Acute Respiratory Syndrome Coronavirus-2*). Clinical findings of COVID-19 were varied but mainly related to respiratory tract symptoms such as cough and shortness of breath. Other system organs may be affected and cause various signs and symptoms related to affected organs. The liver also can be affected. Several studies reported prevalence of liver injury in COVID-19 patients varied between 14,8% to 78%.[1]

Liver injury in covid 19 patients may be caused by several mechanisms, either direct injury following SARS-CoV-2 infection or indirect mechanism of systemic inflammation, hypoxia, iatrogenic (drugs), ventilation, or exacerbation of the underlying disease.[2] Despite the cause, Liver injury in COVID-19 patients requires special attention. Deterioration of liver function in patients with severe COVID-19 can be found in liver failure and death.[3] Several studies reported a worse prognosis in severe COVID-19 patients with liver injury,[4] The median duration of hospitalization for COVID-19 patients in the Intensive Care Unit was reported to be 10 (0-37) days with a mortality of 56%. [5]

Meanwhile, there has been no research on the clinical outcome and duration of hospitalization for COVID-19 patients with severe symptoms and liver injury in Indonesia to date. This topic is essential since it can be used as basic data for further research and can be the basis for consideration in the management of further severe COVID-19 patient care, which is expected to reduce patient morbidity and mortality.

METHODS

Study subject

We conduct a retrospective study of Udayana University Hospital for one year. The study subject was taken from the medical report of hospitalized severe COVID-19-confirmed patients with liver injury from the period of April 2020 to April 2021. The inclusion criteria were adult (age > 18 years old), hospitalized confirmed COVID-19 case, had a severe manifestation of COVID-19 and had liver injury The exclusion criteria were known history of chronic liver disease, positive result of hepatitis B surface antigen (HBsAg), positive result of hepatitis C antibody test (Anti-HCV), and a history of chronic alcohol drinking.

The diagnosis of confirmed COVID-19 patients was based on criteria by the World Health Organization (WHO); patients with detection of SARS-CoV-2 nucleic acid by real-time (RT) polymerase chain reaction (PCR) in their nasopharyngeal aspirates. The ribonucleic acid (RNA) was extracted and tested by 2019-nCoV specific primer and probe in the biosafety level 2 cabinet in our hospital. A cycle threshold value (Ct-value) less than 40 was defined as a positive result, and a Ct-value of 40 or more was defined as a negative result. The severe COVID-19 case was defined based on WHO criteria; clinical signs of pneumonia with one of the following: oxygen saturation < 90% on room air; or respiratory rate > 30 breaths/minute; or severe respiratory distress.[6] This study was approved by The Research Ethics Committee Faculty of Medicine Universitas Udayana (2072/UN14.2.2.VII.14/LT/2021)

The severity of Liver Injury, Clinical Outcome, and Duration of Hospitalization Evaluations

The liver injury in COVID-19 patients was defined as an increase in aspartate transaminase (AST) or alanine transaminase (ALT) more than the upper normal limit value (AST > 35 u/l for men and > 31 u/l for women or ALT value > 45 u/l for men and > 34 u/l for women). The degree of liver injury is classified as mild (an increase of liver enzymes 1-3 times), moderate (an increase of liver enzymes > 3-5 times), and severe (an increase of liver enzymes > 5 times) (Table 1).

In the case of both AST and ALT were increase, the highest value was used to categorize the liver injury

Table 1. Classification of Liver Injury Severity

Categories		ALT (u/l)	AST (u/l)
Mild	Men	46-138	36-108
	Women	35-105	32-96
Moderate	Men	139-230	109-180
	Women	106-175	106-175
Severe	Men	> 230	> 180
	Women	> 175	> 160

AST: aspartate aminotransferase, ALT: alanine aminotransferase

The laboratory data of AST and ALT were taken from data on the day of admission. For the patients who undergo severe disease during the period of hospitalization, the laboratory data of AST and ALT were taken from the repeated measure of AST and ALT within that time, if it was not repeated the patient was excluded.

The clinical outcomes in this study were divided into two categories; discharge from the hospital (live) and death. The duration of hospitalization defines as the number of days that a patient spends in the hospital during a single hospitalization.

Statistical Analysis

The data were described descriptively and presented as mean with standard deviation, median, or percentage as appropriate. The normality of the continuous variable was tested using the Kolmogorov-Smirnov test. The one-way ANOVA test was used to determine the difference between the liver injury group. The statistical analysis was performed by IBM SPSS statistical software version 25.0.

RESULTS

A total of 1776 medical reports of COVID-19 patients were analyzed. We obtained 220 patients with severe or critical COVID-19 cases. However, only 90 patients with severe or critical COVID-19 cases with an increase in transaminase enzyme and fulfill the criteria to be included in this study. The flowchart depicted in figure 1.

The majority of the sample in this study was male (75.56%) with a mean age of 55.23 ± 13,26. The median hospitalization was 12 days. A total of 53 patients were alive (58.9%). Most of the patients had comorbidity (67.8%). The detail of the comorbidity listed in Table 2.

Analysis was performed to determine the differences of variables to the degree of liver injury. The analysis

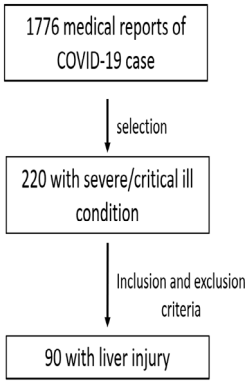

Figure 1. Flowchart of the study

obtained that there were significant differences in clinical outcomes, CT value, D-Dimer, procalcitonin, WBC, and neutrophils for the degree of liver injury. Although there was no significant difference based on comorbid disease, there was a tendency to increase the number of COVID-19 patients who had the comorbid disease in the moderate-degree liver injury group (58.8% vs 41.2% for patients with comorbidities and without comorbidities, respectively) and the severe liver injury group (100% vs 0% for patients with comorbidities and without comorbidities, respectively) (Table 3).

This study found that there was an increase in mortality and a decrease in survival along with an increase in the severity of the liver injury. In patients with mild liver injury, the number of mortality was 30% (15 patients dead, 35 patients alive), in the moderate liver injury group, the mortality was 52.9% (18 patients dead, 16 patients alive), while in the severe liver injury group, the mortality was 66.7% (4 patients death, 2 patients death) (Figure 2).

Although there was no significant difference based on the duration of hospitalization, there was a tendency to increase in hospital days along with the increase in the degree of liver injury, as depicted in Figure 3.

Additional analysis based on the duration of hospitalization were performed in patients who survived (n = 53). Patients were grouped according to the degree of liver injury (mild liver injury, n= 35; moderate liver injury, n= 16; severe liver injury, n= 2). The average duration of hospitalization in each group was 13.25 ± 5.63 vs 17.12 ± 7.63 vs 25.50 ± 12.02 days for mild, moderate, and severe liver injury groups, respectively. There was a significant difference with p-value = 0.013. This shows that there is an increase in the length of stay along with an increase in the severity of the liver injury.

Table 2. Demographic characteristics of the study

Characteristics	Value
Age (years), mean ± SD	55.23 ± 13.26
Gender, n (%)	
Male	68 (75.56)
Female	22 (24.44)
Duration of hospitalization (days), median	12
CT value	28.55 ± 5
History of contact, n (%)	
Close Contact	10 (11.1)
Traveling	17 (18.9)
Stayed at endemic area	63 (70)
Clinical outcome, n (%)	
Death	37 (41.1)
Alive	53 (58.9)
Comorbidity, n (%)	
No	29 (32.2)
Yes	61 (67.8)
Diabetes	11 (12.2)
Hypertension	10 (11.1)
Obesity	4 (4.4)
COPD/asthma	1 (1.1)
Pregnancy	2 (2.2)
Cardiovascular	6 (6.7)
Autoimmunity	1 (1.1)
HIV	1 (1.1)
Two or more comorbidity	25 (27.8)
Symptoms, n (%)	
Fever	89 (98.9)
Cough	90 (100)
Shortness of breath	90 (100)
Dysphagia	31 (34.4)
Nausea or vomiting	26 (28.9)
Diarrhea	8 (8.9)
Headache	13 (14.4)
Liver injury category, n (%)	
Mild	50 (55.6)
Moderate	34 (37.8)
Severe	6 (6.7)
ALT (U/l), median	102
AST (U/l), median	84.50
WBC (10^3/uL), median	10.33
NLR, median	11.44
Neutrophil (10^3/uL), median	8.61
Lymphocyte (10^3/uL), median	0.75
Hemoglobin (g/dl), median	13.65
Thrombocyte (10^3/uL), median	214.5
hsCRP (mg/L), median	83.45
D-Dimer (ng/ml), median	2433
BUN (mg/dl), median	17
Creatinin (mg/dl), median	0.8

ALT, alanine aminotransferase; AST, Aspartate aminotransferase; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CT, cycle threshold; HIV, human immunodeficiency virus; hsCRP, high sensitivity c-reactive protein; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell

Table 3. Characteristics of Samples Based on Degree of Liver Injury

Variables	Degree of Liver Injury			*p*
	Mild (1-3 times) n = 50	Moderate (> 3-5 times) n = 34	Severe (> 5 times) n = 6	
Age (years), mean ± SD	54.74 ± 12.15	56.47 ± 14.41	52.33 ± 17	0.726
Gender, n (%)				
Male	42 (61.8)	23 (33.8)	3 (4.4)	0.074
Female	8 (36.4)	11 (50)	3 (13.6)	
Comorbidity, n (%)				
Yes	35 (57.4)	20 (32.8)	6 (9.8)	0.122
No	15 (51.7)	14 (48.3)	0 (0)	
Clinical outcome, n (%)				
Death	15 (40.5)	18 (48.6)	4 (10.8)	**0.047**
Alive	35 (66)	16 (30.2)	2 (3.8)	
Duration of hospitalization (days), mean ± SD	12.38 ± 6.95	13.74 ± 7.37	14.17 ± 11.23	0.662
CT value, mean ± SD	29.60 ± 4.34	27.92 ± 5.19	23.32 ± 5.94	**0.008**
NLR, mean ± SD	14.30 ±13.91	18.58 ± 28.84	25.13 ± 29.98	0.421
WBC (10^3/uL), mean ± SD	10.11 ± 4.16	11.89 ± 6.86	20.82 ± 14.53	**0.001**
Neutrophil (10^3/uL), mean ± SD	8.86 ± 4.15	10.31 ± 7.09	19.61 ± 13.99	**0.001**
Lymphocyte (10^3/uL), mean ± SD	0.82 ± 0.41	0.94 ± 0.59	0.88 ± 0.58	0.556
HsCRP (mg/L), mean ± SD	109.56 ± 96.33	105.80 ± 75.74	131.42 ±129.07	0.819
D-Dimer (ng/ml), mean ± SD	5951.26 ± 8712	4058.32 ± 4470	21768 ± 23125	**0.001**
Procalcitonin, mean ± SD	0.87 ± 1.86	1.60 ± 3.52	16.32 ± 19.29	**0.001**
Hemoglobin (g/dl), mean ± SD	13.65 ± 1.40	13.37 ± 1.48	12.37 ± 1.57	0.322
Thrombocyte (10^3/uL), mean ± SD	246.58 ± 86.89	237.50 ± 92.53	258.33 ± 198.64	0.858
Creatinine (mg/dl), mean ± SD	0.86 ± 0.40	4.01 ± 18.20	1.73 ± 1.51	0.453

CT, cycle threshold; hsCRP, high sensitivity c-reactive protein; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell

There was also a significant difference based on the CT value in the three groups which showed that a lower CT value was associated with an increase in the severity of liver injury (Figure 4).

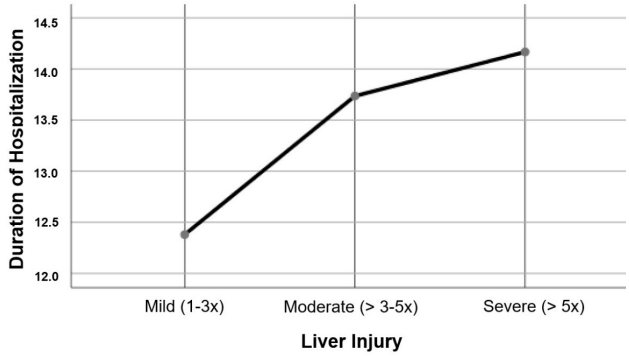

Figure 2. Curve analysis of degree of liver injury with clinical outcome (survival)

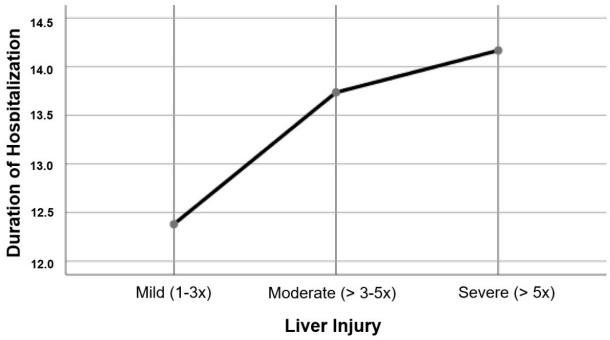

Figure 3. Curve analysis of hospitalization and degree of liver injury

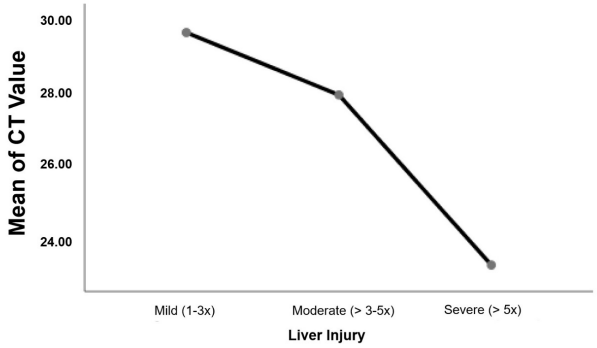

Figure 4. Curve analysis of degree of liver injury and CT value

DISCUSSION

This study evaluates the severity of the liver injury and its relationship to clinical outcomes and duration of hospitalization. The mechanism of liver injury in patients with COVID-19 can be caused by many factors including direct injury to hepatocytes by the SARS-CoV 2 virus, systemic inflammatory factors, decreased microcirculation associated with hypoxia and ischemia, and liver injury caused by drug use. These factors can overlap and occur in one patient.[7]

Liver injury is more common in patients with severe and critical COVID-19 infection. Several factors are involved in this result. First, the increase in systemic inflammation or a cytokine storm in this group of patients causes inflammation in hepatocytes. Second, patients with severe/critical symptoms tend to have ischemia/tissue hypoxia, and this also occurs in liver cells. Third, patients with severe/critical symptoms tend to receive higher amounts of medication compared to COVID-19 patients with mild or moderate symptoms, therefore the risk of liver injury due to drug effects is higher in this group of patients.[8]

Research conducted by Wang et al. in 2020[7] showed that the liver injury that occurred in patients with COVID-19 infection was mostly mild, which was characterized by an increase in liver enzymes in the range of 1-3 times the upper normal limit. The results of this study also showed that the most common degree of liver injury was mild (55.6%). In contrast to this study, the increase in ALT was more commonly found compared to AST in this study. This may be caused by the sample selection. The sample in this study was patients who have severe COVID-19 and the mechanisms that may involve the most are microcirculation disorders in organs and systemic inflammation.

The results of this study indicate that an increase in the severity of the liver injury is related to patient survival. This is in accordance with a study conducted by Wu et al. in 2020.[8] Research conducted by Taramasso et al. in 2020 also got a similar result, which increased the risk of death along with an increase in the severity of the liver injury.[9]

There is a relationship between the cycle threshold (CT value) and the severity of liver injury in this study; lower CT values in the severe liver injury group. Lower CT values were associated with a higher viral load.[10] Liver injury in conditions of high viral load is probably related to direct damage by the SARS-CoV-2 virus to the liver. The same thing was also found in the research conducted by Wong et al. in 2021.[11]

The study by Yang found a direct cytopathic effect of SARS-CoV2 on the liver. The damage to liver by the virus also similar to sepsis.[12] The research conducted reported that SARS-CoV-2 can enter liver cells via the ACE2 receptor. These receptors are also expressed on liver cells and bile ducts.[13] Expression of ACE2 receptors in hepatocytes was 2.6% of hepatocytes and

59.7% of cholangiocytes. SARS-CoV-2 can directly attach to ACE2 found on cholangiocytes and cause liver dysfunction.[14] In addition, liver damage that occurs is also associated with cytokine storms. Severe infection with COVID-19 stimulates inflammatory biomarkers such as interleukin (IL) 2, IL-6, IL7, IL-18, TNFα, interferon-γ, and ferritin.[15]

Linear relationships between the severity of the liver injury and the value of D dimer, procalcitonin, WBC, and neutrophils were found in this study. This may be related to the severity of COVID-19 infection, in which there is an increase in inflammatory cytokines in patients with severe or critical COVID-19 infection. All subjects in this study were severe/critical COVID-19, but there was an association with lower survival in patients with severe liver injury. This indicates an association of increased inflammatory cytokines in more severe degrees of COVID-19 disease. Research conducted by Ma et al. in 2021[16] also showed an association between the occurrence of liver injury and an increase in inflammatory markers including WBC, neutrophils, and HsCRP in COVID-19 patients with more severe disease degrees. In this study, there was no relationship between liver injury and age and comorbid diseases.

This research has several weaknesses. First, this study was a retrospective study conducted at one center. Participation in more centers with a bigger sample would offer substantial findings. Second, not all patients underwent serial liver enzyme examinations, therefore liver injury that occurred during treatment was not detected. Third, there is no data on complete liver function tests. This study also excludes the presence of chronic liver disease based solely on the data on history and examination of HBsAg and Anti-HCV, so that the possibility of chronic liver disease in the patient may be missed.

CONCLUSION

The severity of the liver injury is related to the clinical outcome of COVID-19 patients. The increase in the severity of the liver injury tends to have lower survival and an increase in mortality. In addition, the severity of the liver injury was not related to the length of stay of the patients. However, sub-group analysis of survived patients found that the increase in the severity of the liver injury was associated with the duration of hospitalization.

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