Research Article

Coronavirus Disease 2019 Associated Liver Injury and Disease Severity: A Cross-Sectional Study

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Abstract

Recent data on the coronavirus disease 2019 (Covid-19) outbreak has begun to shine light on the impact of the disease on the liver. However, data regarding Covid-19-associated liver injury remains limited. We analyzed whether there was a significant difference in liver injury in patients with different disease severity. A cross-sectional study was conducted for confirmed Covid-19 cases in dr. Cipto Mangunkusumo National Hospital from April 2020 until March 2021. Patients were divided based on disease severity: mild-to-moderate and severe Covid-19. Patients with existing chronic hepatitis, liver cirrhosis, fatty liver, or liver malignancies were excluded. Data on liver transaminase, prothrombin time, albumin, and bilirubin levels upon admission were analyzed for both groups. A total of 100 patients were included, consisting of 50 patients with mild-to-moderate cases and 50 patients with severe cases. Both alanine and aspartate aminotransferase levels elevation were predominantly found in the severe group (p<0.001 and p=0.002, respectively). We also found lower albumin levels in the severe group (p<0.001), but no significant difference in bilirubin level (p=0.568) and prothrombin time (p=0.253) was noted among the two groups. Liver injury is more common in severe than mild-to-moderate Covid-19 cases. This should be a consideration by physicians to handle the patients comprehensively.

Keywords: *Covid-19, disease severity, liver injury.*

Penyakit Coronavirus 2019 dan Kaitannya dengan Kerusakan Hati dan Beratnya Penyakit: Studi Potong Lintang

Abstrak

Data terbaru mengenai wabah coronavirus disease 2019 (Covid-19) mulai memberikan pencerahan dampak penyakit ini terhadap hati. Namun, data mengenai kerusakan hati terkait Covid-19 masih terbatas. Kami menganalisis apakah ada perbedaan signifikan pada kerusakan hati pasien dengan tingkat keparahan penyakit yang berbeda. Studi potong lintang dilakukan pada kasus Covid-19 yang terkonfirmasi di rumah sakit dr. Cipto Mangunkusumo pada bulan April 2020 hingga Maret 2021. Pasien dibagi berdasarkan tingkat keparahan penyakit: Covid-19 ringan hingga sedang dan Covid-19 berat. Pasien hepatitis kronik, sirosis hati, hati berlemak, atau malignan hati tidak diikutsertakan. Data transaminase hati, waktu protrombin, albumin, dan tingkat bilirubin dianalisis pada kedua kelompok. Sebanyak 100 pasien masuk dalam studi, terdiri atas 50 pasien kasus ringan hingga sedang dan 50 pasien kasus berat. Kenaikan kadar alanin dan aspartat aminotransferase terutama terjadi pada kelompok berat (p<0,001 dan p=0,002). Kadar albumin yang lebih rendah terdapat pada kelompok berat (p<0,001), tetapi tidak ada perbedaan signifikan pada kadar bilirubin (p=0,568) dan waktu protrombin (p=0,253) pada kedua kelompok. Kerusakan hati lebih banyak pada kasus Covid-19 berat daripada kasus ringan hingga sedang. Hal tersebut harus menjadi pertimbangan dokter agar dapat menangani pasien secara komprehensif.

Kata kunci: *Covid-19, keparahan penyakit, kerusakan hati.*

Introduction

Covid-19 infection is still a global pandemic that has not been resolved yet. Although the infection generally affects respiratory symptoms as the main manifestation, recent publications have shown evidence of organotropism and inflammation that can involve other organs, including the liver. Liver damage in Covid-19 infection can occur due to direct liver injury, drug toxicity, or immune-mediated response. This mechanism is rationalized by the discovery of upregulation of the angiotensin converting enzyme (ACE)2 receptor in the biliary epithelium and hepatocytes, which are the viral binding sites. However, the data regarding liver injury due to Covid-19 infection is still minimal.[1-4] We analyzed whether there was a significant difference in liver injury in Covid-19 patients with different disease severity.

Method

This cross-sectional study was conducted in dr. Cipto Mangunkusumo National Hospital in Jakarta. The sampling method used consecutive sampling techniques from hospital medical records. The inclusion criteria for this research were patients with positive Covid-19 infection as confirmed using polymerase chain reaction severe acute respiratory syndrome coronavirus-2 (PCR SARS COV-2) who were examined for liver function tests, at least transaminase levels. Exclusion criteria were patients known to have chronic hepatitis infection, positive hepatitis seromarkers, liver cirrhosis, fatty liver, or liver malignancy.

The data collected includes the baseline characteristics of the subjects, Covid-19 infection degree, and liver function test, including transaminase level, prothrombin time, albumin, and bilirubin upon hospital admission. Covid-19 patients were categorized as having mild to moderate and severe infections. A comparison of the characteristics and liver function was carried out between the two groups. The data process was done using the SPSS tools vs 20.

Results

There were 100 subjects included in this study, of which 50 patients were categorized as having mild-moderate Covid-19 infection and 50 patients having severe Covid-19 infection. The baseline characteristics of the subjects are presented in Table 1. The median age of the subjects was 55 years old, with 57% of them being female. A trend of elevated aspartate transferase (AST) was found in 48% of subjects. International normalized ratio (INR)/prothrombin time (PT), albumin, and bilirubin levels were still in the normal range, even though 22% of the subjects had albumin levels lower than the normal limit.

Table 1. Baseline Characteristics of The Subjects

Characteristics	Results
Age, median (min-max)	55.0 (22-95)
Gender, n (%)	
Male	43 (43.0)
Female	57 (57.0)
COVID-19 Severity Degree, n (%)	
Mild-moderate	50 (50.0)
Severe	50 (50.0)
AST Level, median (min-max)	46 (16-149)
AST > ULN, n (%)	48 (48.0)
ALT, median (min-max)	37 (15-156)
ALT > ULN, n (%)	11 (11.0)
INR, mean ± SD	0.948 ± 0.06
PT > control (n = 84; n (%))	13 (15.5)
Albumin, mean ± SD	3.67 ± 0.52
Albumin < LLN (n = 55, n (%))	12 (21.8)
Bilirubin, median (min-max)	0.56 (0.02-1.40)
Bilirubin > ULN (n = 30, n (%))	1 (3.3)

AST (aspartate transferase), ULN (upper limit normal), ALT (alanine aminotransferase), INR (international normalized ratio), PT (prothrombin time), LLN (lower limit normal)

The liver function of the subjects based on the degree of infection was compared between the two groups, as shown in Table 2. There was a significant proportion difference in median age (p=0.003) and sex between the two groups (p=0.001). In severe Covid-19 infection patients, there was a significantly higher median AST level (p<0.001, Figure 1) and more patients with elevated AST levels above the upper limit value (p=0.001). On the other hand, although the median ALT level was significantly higher (p=0.002, Figure 2) compared to patients with mild-moderate infection, the trend of elevated ALT above the upper limit normal was not statistically significant (p=0.110).There were neither significant INR mean differences nor the proportion of patients with PT levels above the control level between the two groups (p>0.05). Although patients with severe infection had significantly

lower albumin levels (p<0.01) compared to patients with mild-moderate infection, the proportion was not statistically significant (p>0.05). There was no significant difference in bilirubin levels, and the proportion of bilirubin was higher than the upper limit normal between the two groups (p>0.05).

Table 2. Subject Characteristics Differences Based on Covid-19 Disease Severity

Characteristics	Mild-Moderate	Severe	p-value
Age, median (min-max)	46 (21-86)	58 (21-95)	0.003
Gender, n			
Male	13	30	0.001
Female	37	20	
AST level, median (min-max)	26 (17-35)	47 (16-149)	<0.001
AST > ULN, n (%)	16/50 (32)	32/50 (64)	0.001
ALT, median (min-max)	26 (16-34)	40 (15-156)	0.002
ALT > ULN, n (%)	3/50 (6)	8/50 (16)	0.110
INR, mean ± SD	0.93±0.10	0.99±0.06	0.253
PT > control, n (%)	4/37 (11)	9/47 (19)	0.294
Albumin, mean ± SD	401±0.44	3.42±0.55	<0.001
Albumin < LLN, n (%)	2/15 (13)	10/40 (25)	0.351
Bilirubin, median (min-max)	0.42 (0.27-0.56)	0.60(0.20-1.40)	0.568
Bilirubin > ULN, n(%)	0/6 (0)	1/24 (4)	0.611

AST (aspartate transferase), ULN (upper limit normal), ALT (alanine aminotransferase), INR (international normalized ratio), PT (prothrombin time), LLN (lower limit normal)
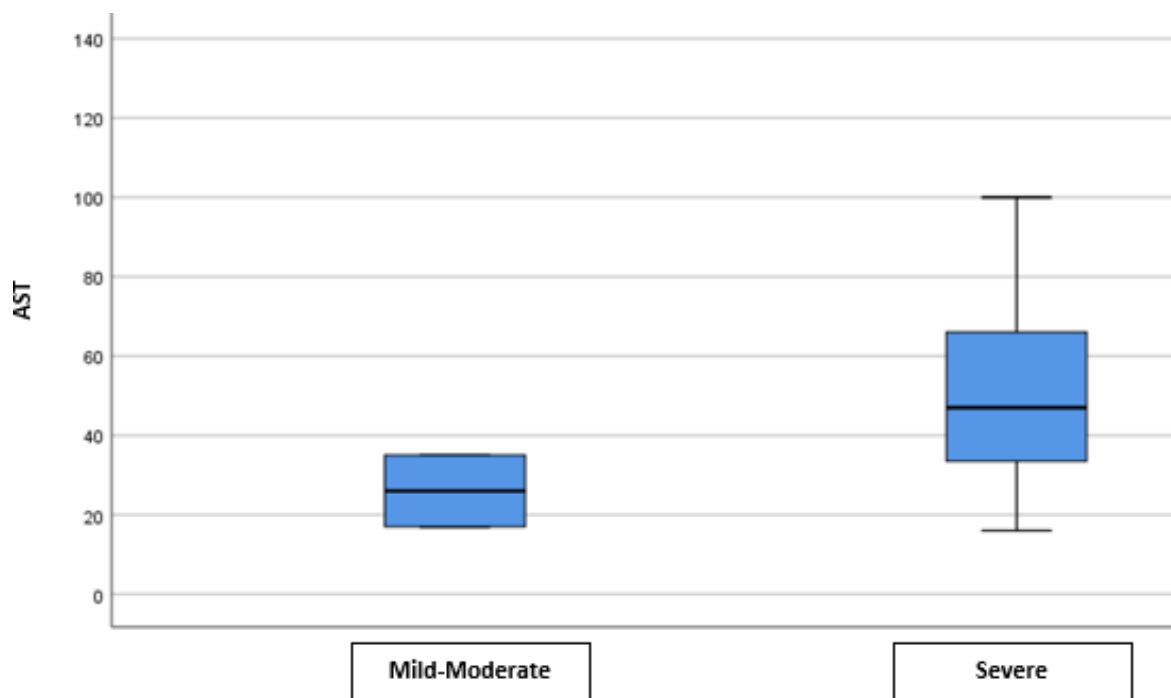
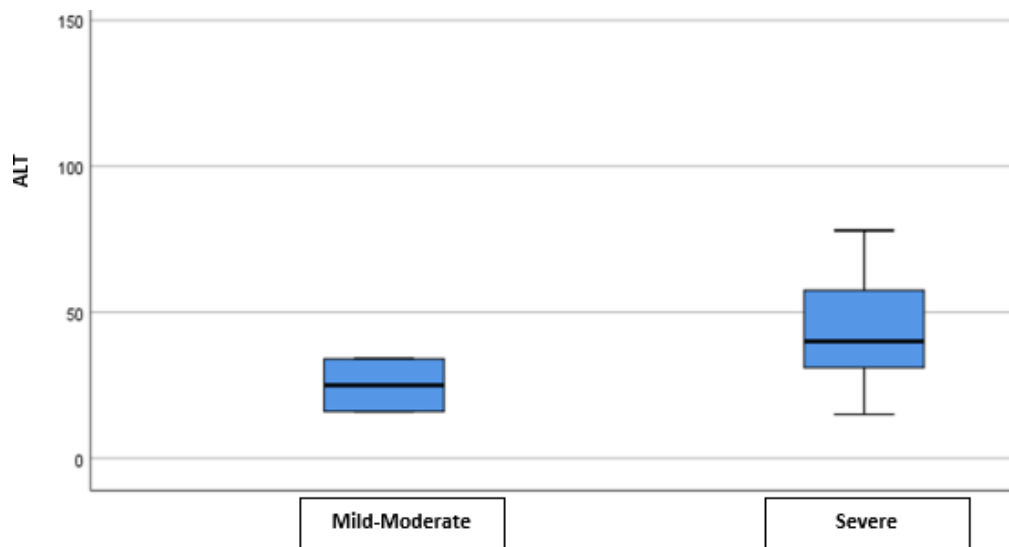**Figure 1. Difference of AST Level Based on Covid-19 Disease Severity**

Figure 2. Difference of ALT Level Based on Covid-19 Disease Severity

Discussion

This study examines liver function disorders in patients with confirmed Covid-19 infection. Liver function impairment is usually found in older adults and males. This aligns with the literature review by Salsabila et al,[5] that an increase in liver disorders indicators is commonly found at 44 years old and older in males.

The current literature states that liver function disorders in patients with Covid-19 infection are usually mild. To date, only one mortality case report is due to liver failure in Covid-19 patients without previous underlying liver disease.[6] The most common parameter found to be elevated was gamma glutamyl transferase (GGT), followed by AST, ALT, total bilirubin, and alkaline phosphatase (ALP).[5] In this study, no analysis was performed on GGT and ALP because both tests were not routinely performed on Covid-19 patients.

Impairment of liver function in Covid-19 patients is a common finding. Sharma et al[1] conducted a systematic review and meta-analysis of 12,282 confirmed Covid-19 cases and found that the prevalence of liver function injury related to COVID-19 was 26.5%. Elevated AST level was the most common finding in 41.1%, while heightened ALT level was found in 29.1% of the cases. Qin, et al[7] interpreted that the increase in AST level was higher than ALT because an increase in ALT level is generally caused by more specific infectious conditions in the liver. In contrast, a higher rise in AST can occur due to the secretion of the enzyme from the other organs, in addition to the damage of three hepatic acinus zones involving the mitochondria, thus reflecting a more severe liver damage process. Impairment of the liver function also allegedly has prognostic significance. Haryanti, et al[8] studied 108 Covid-19 mortality cases, where the majority of the subjects had a severe to critical degree of infection, and as many as 82.4% of them had elevated levels of AST. Sharma, et al[1] also discovered that liver function injury related to Covid-19 infection (odds ratio [OR] = 1.68, 95% confidence interval [CI] = 1.04-2.70, p=0.03), elevated AST (OR = 2.98, 95% CI = 2.35-3.77, p<0.01), and elevated ALT (OR = 1.85, 95% CI = 1.49-2.29, p<0.01) were associated with a significant risk of adverse outcomes. Furthermore, Wong, et al[2] did a systematic review and meta-analysis of 24 studies involving 5,961 Covid-19 subjects and found out that Covid-19 severe infection was associated with elevated AST (OR = 3.4, 95% CI = 2.3-5.0, I^2 = 56%), elevated ALT (OR = 2.5, 95% IK = 1.6-3.7, I^2 = 57%), hyperbilirubinemia (OR = 1.7, 95% CI = 1.2-2.5, I^2 = 0%), and hypoalbuminemia (OR = 7.1, 95% CI = 2.1-24.1, I^2 = 71%).

Although the findings from the meta-analysis show a decreasing trend of albumin levels, several confounding factors can contribute to low albumin levels, such as systemic inflammation reaction, malnutrition, or hospital admission time.[9] Wu et al[10] in the study showed a relationship between hypoalbuminemia in Covid-19 infection and the severity of the infection, where generally patients with a lower ratio of partial pressure of oxygen (PaO2) versus the fraction of inspired oxygen (FiO2), severe chest x-ray, and poorer 30-day survival rate. In this case, hypoalbuminemia was known as

representative of epithelial-endothelial disturbances. The liver function impairment process was found to be related to the degree of Covid-19 infection. Singh et al[11] presented thatpatients with underlying chronic liver disease, such as cirrhosis, had a higher risk of hospitalization and mortality rate. Still, this study needed to analyze this population group. Liver function impairment is thought to occur due to viral invasion of the cholangiocyte and hepatocyte through the mediation of the ACE2 receptor, where the cholangiocyte plays an integral part in liver regeneration and immune response.[3,12] Chai et al[13] showed that ACE2 receptor expression was 57.9% in the cholangiocyte and 2.6% in the hepatocyte. This is exacerbated by the viral cytopathic effect and inflammation, namely cytokine storm, common in critical Covid-19 cases.[14-16] Thus, vigilance and stricter surveillance, as well as an individualized therapeutic approach, are needed in patients with severe Covid-19 infection, especially those subjects with characteristics supporting liver injury.[4,17,18] The strength of this study is that it has attempted to rule out baseline liver disease in the subjects; thus, it can provide an overview of changes in liver function due to Covid-19 infection. The author also presented the pattern of liver function impairment by associating it with the degree of infection. However, as this is a cross-sectional study, the data collection is only done once. Moreover, the research subjects were also collected from one tertiary referral centre; thus, the number of samples obtained still needed to be increased. Further research involving several hospitals with more subjects, prospective study design, and serial liver function test monitoring is required to prove the hypothesis and clinical implications.

Conclusion

Liver injury is more common in severe than mild-to-moderate Covid-19 cases. This should be a consideration by physicians to handle patients comprehensively.

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