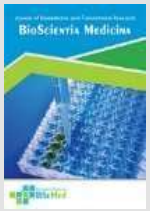
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Study Analysis of Total Bilirubin Levels on Mortality in COVID-19 Patients: A Single Center Observational Study at Dr. M. Djamil General Hospital, Padang, Indonesia

Suryo Nugroho Suhardi[1*], Rikarni[2], Dwi Yulia[2]

[1]Specialized Residency Training of Clinical Pathology, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:
COVID-19
Mortality
Total bilirubin

***Corresponding author:**
Suryo Nugroho Suhardi

E-mail address:
siswoedihardjo@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i8.1053

A B S T R A C T

Background: Coronavirus Disease 2019 (COVID-19) is caused by a positive single-stranded RNA virus. The clinical manifestations of COVID-19 are not only dominated by respiratory tract symptoms but can also show symptoms of liver damage in severe COVID-19 patients. Liver damage that occurs can cause acute liver failure and result in death. Examination of liver damage marker parameters such as total bilirubin needs to be carried out as mortality increases in COVID-19 patients. This study aims to determine the relationship between total bilirubin levels and mortality in COVID-19 patients. **Methods:** Cross-sectional analytical research was conducted on 40 COVID-19 patients treated at Dr. M. Djamil General Hospital Padang from July to December 2021. Examination of total bilirubin levels using the colorimetric diazo method. Bivariate analysis used the Mann-Whitney test to see the relationship between total bilirubin levels and mortality. **Results:** The average age of the research subjects was 61.85 (1.40) years, with 65% men and 35% women. The mortality percentage in COVID-19 patients is 65%. The median total bilirubin level was 1.95 (0.5-2.8) mg/dL. The relationship between total bilirubin levels and mortality in COVID-19 patients was found to have a p-value of <0.001. The study results showed that the median total bilirubin level in COVID-19 patients who died was relatively higher, namely 2.20 (1.4-2.8) mg/dL, compared to those who did not die, namely 0.70 (0.5-1. 6) mg/dL. **Conclusion:** The results of this study show that there is a relationship between total bilirubin levels and mortality in COVID-19 patients.

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, has become an unprecedented global health crisis. Since its emergence in Wuhan, China at the end of 2019, this virus has spread throughout the world, infecting more than 500 million people and claiming more than 6 million lives. COVID-19 is not only a respiratory disease, but can also attack various organs in the body, including the liver. Symptoms of COVID-19 vary from mild to severe, with some people showing no symptoms at all. Common symptoms include fever, dry cough, fatigue, shortness of breath, muscle aches, headaches, and loss of smell and taste. In more severe cases, COVID-19 can cause pneumonia, acute respiratory distress syndrome (ARDS), kidney failure, and even death. Apart from attacking the respiratory system, COVID-19 can also cause complications in other organs, including the liver. Liver damage in COVID-19 patients can range from mild to severe, and in some cases can progress to acute liver failure, which is fatal. The exact mechanism behind liver damage in COVID-19 patients is not fully

understood. Viruses can enter liver cells and replicate themselves, causing cell damage and inflammation. SARS-CoV-2 infection can trigger an excessive immune response, known as a cytokine storm. This cytokine storm can cause severe systemic inflammation, including liver damage. COVID-19 can cause hypoxia, or a lack of oxygen in the blood, which can damage liver cells. Some drugs used to treat COVID-19, such as hydroxychloroquine, can have hepatotoxic effects, or be toxic to the liver. Older people are more at risk of liver damage because their liver function decreases with age. People with comorbidities such as diabetes, hypertension, and chronic liver disease are more at risk of experiencing severe liver damage. Obese people are more at risk of developing hepatic steatosis, or the accumulation of fat in the liver, which can increase susceptibility to liver damage. People with weakened immune systems, such as those undergoing chemotherapy or organ transplants, are at greater risk of severe SARS-CoV-2 infection and related complications, including liver damage.[1-3]

Bilirubin is a yellow-orange pigment produced by the liver when it breaks down red blood cells. Bilirubin is then transported to the intestines and excreted in the feces. Total bilirubin levels in the blood increase when there is damage to liver cells or obstruction of bile flow. Increased total bilirubin levels can be an indicator of liver damage in COVID-19 patients. Studies have shown that COVID-19 patients with higher total bilirubin levels have a higher risk of death. Total bilirubin levels can be used as a predictor of the risk of death in COVID-19 patients so that doctors can provide more timely and aggressive treatment. Total bilirubin levels can be monitored to assess the patient's response to COVID-19 treatment. Understanding risk factors for liver damage in COVID-19 patients can help in developing prevention strategies, such as screening and early intervention.[4-6] This study aims to investigate the relationship between total bilirubin levels and mortality in COVID-19 patients.

2. Methods

This research uses a cross-sectional analytical design. This design was chosen to investigate the relationship between total bilirubin levels and mortality in COVID-19 patients at one time point. The population of this study were all COVID-19 patients treated at Dr. M. Djamil General Hospital Padang from July to December 2021. The research sample consisted of 40 patients who met the inclusion and exclusion criteria. The inclusion criteria are patients with a diagnosis of COVID-19 confirmed by PCR or serology tests, patients being treated at Dr. M. Djamil General Hospital Padang, and patients who had complete data on total bilirubin levels and death status. Meanwhile, the exclusion criteria are patients with pre-existing chronic liver disease, patients with a history of bile duct surgery, patients who are pregnant or breastfeeding, and patients who are unwilling to participate in the research.

Patient data was collected from medical records, including: Age, Gender, COVID-19 diagnosis, Date of COVID-19 diagnosis, Date of hospital admission, Date of hospital discharge, Date of death (if any), Total bilirubin levels, Death status (alive or died). Examination of total bilirubin levels was carried out using the colorimetric diazo method. This method measures total bilirubin levels in blood serum using a chemical reaction. Test results are measured in milligrams per deciliter (mg/dL). Data analysis was carried out using the SPSS statistical program version 25.0. Continuous numerical data were analyzed using the Mann-Whitney test to see differences between the groups of patients who lived and died. Categorical data was analyzed using the Chi-Square test to see the relationship between categorical variables. Mann-Whitney test: This test is used to compare median total bilirubin levels between groups of patients who lived and died. Chi-Square Test: This test is used to see the relationship between categorical variables, such as gender and age, with death status. The significance level used in this research is 0.05. This research was approved by the Health Research Ethics Committee of Dr. M. Djamil General Hospital Padang. Informed

consent was obtained from all patients participating in the study.

3. Results

This research involved 40 COVID-19 patients treated at Dr. M. Djamil General Hospital Padang between July and December 2021. The majority of respondents (65%) were men with an average age of 61.85 years. Surprisingly, the death rate for COVID-19 patients in this study was high, reaching 65%. This shows how dangerous this virus is, especially for the elderly and men. Analysis of total bilirubin levels, which is a marker of liver damage, showed that median levels in patients who died (2.20 mg/dL) were significantly higher compared to patients who lived (0.70 mg/dL). These findings support a potential link between severe liver damage and a higher risk of death in COVID-19 patients. Overall, table 1 provides an initial overview of the characteristics of respondents in this study and shows the potential relationship between high total bilirubin levels and mortality in COVID-19 patients.

Table 1. Characteristics of respondents.

Characteristics	Frequency	Percentage
Total respondents	40	100%
Gender		
Male	26	65%
Female	14	35%
Age (years)		
Average	61.85	
Mortality		
Death	26	65%
Alive	14	35%
Total bilirubin levels (mg/dL)		
Median	1.95	

Table 2 presents the results of bivariate analysis using the Mann-Whitney test to investigate the relationship between total bilirubin levels and mortality in COVID-19 patients. The median total bilirubin level in COVID-19 patients who died (2.20 mg/dL) was significantly higher compared to living patients (0.70 mg/dL). This suggests that more severe liver damage, indicated by high total bilirubin levels, is associated with a higher risk of death in COVID-19 patients. The Mann-Whitney test produces a p-value <0.001, which indicates that there is a statistically significant relationship between total bilirubin levels and mortality in COVID-19 patients. The findings in Table 2 support a potential association between severe liver damage and risk of death in COVID-19 patients. Patients with higher total bilirubin levels appear to have a worse prognosis.

Table 2. Analysis of the relationship between total bilirubin levels and mortality in COVID-19 patients.

Variable	Mortality		p-value
	Death Median (min-max)	Alive Median (min-max)	
Total bilirubin	2,20 (1,40-2,80)	0,70 (0,50-1,60)	< 0,001

4. Discussion

This study shows a significant relationship between high total bilirubin levels and mortality in COVID-19 patients. However, the mechanism of this relationship is not fully understood. One major explanation is that increased total bilirubin levels reflect more severe liver cell damage in COVID-19 patients. The SARS-CoV-2 virus, the causative agent

of COVID-19, can infect liver cells (hepatocytes) and cause direct damage. In addition, systemic inflammatory responses triggered by viruses can trigger oxidative stress and apoptosis (programmed cell death) in hepatocytes. This liver cell damage can disrupt various liver functions, including bilirubin metabolism. Bilirubin is the end product of the breakdown of heme, the protein component of hemoglobin that carries oxygen in red blood cells. The liver is responsible for converting water-insoluble bilirubin into a water-soluble form and secreting it into bile for excretion into the intestines. When hepatocytes are damaged, their ability to process bilirubin is impaired, leading to accumulation of bilirubin in the blood. This can be seen as an increase in total bilirubin levels. Several studies have shown that COVID-19 patients with high total bilirubin levels have evidence of more severe liver damage, such as increased liver enzyme levels (AST and ALT) and prolonged prothrombin time. Liver imaging studies in COVID-19 patients have shown signs of liver damage, such as hepatic steatosis (fat buildup in the liver) and liver necrosis (death of liver tissue). The mechanisms of SARS-CoV-2-induced liver damage have been investigated in animal models and in vitro studies, indicating a direct effect of the virus on hepatocytes and a role for the inflammatory response.[7-9]

The SARS-CoV-2 virus, the causative agent of COVID-19, can enter liver cells (hepatocytes) through various mechanisms, including the ACE2 receptor. Once infected, the virus can replicate within hepatocytes and cause direct cell damage. The virus ruptures the cell membrane of hepatocytes, causing leakage of cell contents and cell death. Viruses trigger the mechanism of programmed cell suicide (apoptosis) in hepatocytes. The virus disrupts the function of the ER, an important organelle in hepatocytes responsible for protein synthesis and bilirubin processing. This virus-induced hepatocyte damage can disrupt various liver functions, including bilirubin metabolism. SARS-CoV-2 infection triggers a strong systemic inflammatory response in the body, which can worsen liver damage in COVID-19 patients. This inflammatory response involves the activation of various immune cells and the release of inflammatory cytokines. Immune cells that attack viruses in the liver can inadvertently damage hepatocytes in the process. Inflammatory cytokines can trigger excessive production of oxygen free radicals (ROS), which can damage hepatocyte DNA and proteins. Inflammatory cytokines can activate apoptotic signaling pathways in hepatocytes, causing cell death. This inflammation-induced oxidative stress and apoptosis can exacerbate liver damage and disrupt bilirubin metabolism. Bilirubin is the end product of the breakdown of heme, a component of the hemoglobin protein that carries oxygen in red blood cells. The liver is responsible for converting water-insoluble bilirubin into a water-soluble form and secreting it into bile for excretion into the intestines. When hepatocytes are damaged, their ability to process bilirubin is impaired. Unconjugated bilirubin is toxic and can accumulate in the blood and tissues, causing hyperbilirubinemia. The conjugated bilirubin produced by hepatocytes cannot be excreted effectively into the bile, leading to cholestasis. Hyperbilirubinemia and cholestasis can worsen liver damage and have serious side effects on other organs, such as the brain and kidneys. Severe liver damage and liver dysfunction in COVID-19 patients can increase the risk of complications and death. Elevated total bilirubin levels in COVID-19 patients reflect more severe liver cell damage and liver dysfunction. Underlying mechanisms include direct viral infection of hepatocytes, systemic inflammatory response, and impaired bilirubin metabolism. This liver damage can increase the risk of complications and death in COVID-19 patients.[10-12]

Severe liver cell damage in COVID-19 patients can cause liver dysfunction, which is a decrease in the liver's ability to carry out its vital functions. This liver dysfunction can have serious consequences for the prognosis of COVID-19 patients, increasing the risk of complications and death. Liver dysfunction in COVID-19 patients can worsen the course of the disease through several mechanisms. The liver is responsible for producing blood proteins that are important for

blood clotting. Liver dysfunction can cause a deficiency of this protein, increasing the risk of spontaneous bleeding and serious complications such as brain hemorrhage. When the liver cannot remove toxins from the blood effectively, they can build up in the brain and cause hepatoencephalopathy. Symptoms include confusion, disorientation, drowsiness, and even coma. Liver failure is the final stage of liver dysfunction where the liver can no longer carry out its vital functions. Liver failure is often fatal, and patients require a liver transplant to survive. The liver plays an important role in regulating the body's inflammatory response. Liver dysfunction can worsen already severe systemic inflammation in COVID-19 patients, which can increase the risk of respiratory complications and death. The liver is responsible for metabolizing medications, including antiviral and anti-inflammatory drugs used to treat COVID-19. Liver dysfunction may interfere with the metabolism of this drug, reducing the effectiveness of treatment and increasing the risk of side effects. COVID-19 patients with liver dysfunction have a much worse prognosis compared with patients without liver dysfunction. Research shows that the risk of death in COVID-19 patients with liver dysfunction is 10-20 times higher than in patients without liver dysfunction. Several patient factors increase the risk of liver dysfunction in COVID-19 patients. Elderly patients are more susceptible to liver damage and liver dysfunction. Patients with comorbidities such as diabetes, chronic liver disease, and obesity have a higher risk of experiencing liver dysfunction when exposed to COVID-19. Patients with severe COVID-19 are at greater risk of liver dysfunction. Liver dysfunction is a serious complication in COVID-19 patients which can increase the risk of complications and death. Understanding the mechanisms and consequences of liver dysfunction in COVID-19 patients is critical for the development of effective prevention and treatment strategies. Liver dysfunction can worsen the prognosis of COVID-19 patients by increasing the risk of complications and death. COVID-19 patients with high total bilirubin levels are more at risk of experiencing liver dysfunction, such as coagulopathy and hepatoencephalopathy. Liver dysfunction is one of the main predictors of death in critical COVID-19 patients. Research suggests that liver dysfunction may worsen systemic inflammation and immune responses in COVID-19 patients, which may increase the risk of death.[13-15]

The liver is a vital organ that plays an important role in various body functions, including drug metabolism. Drug metabolism is the process by which the body converts drugs into more active or inactive forms and then excretes them from the body. In COVID-19 patients, liver damage caused by the SARS-CoV-2 virus and systemic inflammatory response can compromise the liver's ability to metabolize drugs. Antiviral drugs such as remdesivir and favipiravir are used to inhibit the replication of the SARS-CoV-2 virus. Metabolism of this drug in the liver produces active metabolites that have antiviral effects. Liver damage can reduce the liver's ability to metabolize antiviral drugs, so that the levels of active metabolites in the blood are reduced and the effectiveness of treatment decreases. Anti-inflammatory drugs such as corticosteroids are used to reduce severe systemic inflammation in COVID-19 patients. Metabolism of this drug in the liver helps regulate blood levels of the drug and prevent excessive side effects. Liver damage can interfere with the metabolism of anti-inflammatory drugs, increasing the risk of serious side effects such as immune system suppression and hyperglycemia. Incomplete metabolism of antiviral drugs in the liver can cause the accumulation of toxic drug metabolites in the blood. This may increase the risk of serious drug side effects, such as kidney damage, neurotoxicity, and allergic reactions. High levels of anti-inflammatory drugs in the blood due to impaired metabolism can increase the risk of serious side effects, such as immune system suppression, hyperglycemia, and increased blood pressure. Liver damage can affect the metabolism of other drugs the patient takes, including drugs used to treat comorbid conditions. This can increase the risk of dangerous drug interactions. In COVID-19 patients with liver damage, it is important

to monitor blood drug levels closely and adjust drug doses if necessary. This can help ensure the effectiveness of treatment and minimize the risk of side effects. The more severe the liver damage, the more likely it is that drug metabolism will be impaired. Some drugs are more sensitive to changes in liver function than others. The kidneys also play a role in excreting drugs from the body. Kidney damage can exacerbate the effects of impaired drug metabolism. Liver damage in COVID-19 patients can have serious consequences on drug metabolism, which can reduce the effectiveness of treatment and increase the risk of side effects. Monitoring blood drug levels and adjusting drug doses is important to ensure the safety and effectiveness of treatment in patients with liver damage. Several studies have shown that COVID-19 patients with high total bilirubin levels had lower levels of antiviral drugs in their blood, indicating impaired drug metabolism. COVID-19 patients with high total bilirubin levels are more at risk of experiencing serious drug side effects. Impaired drug metabolism may contribute to treatment failure and increased risk of death in COVID-19 patients.[16-18]

The liver is a vital organ that plays an important role in detoxifying the body. Detoxification is the process in which the body neutralizes and eliminates toxins and waste products from the blood. These toxins can come from various sources, including food, drugs, and body metabolic products. In COVID-19 patients, liver damage caused by the SARS-CoV-2 virus and systemic inflammatory responses can interfere with the liver's ability to detoxify. The SARS-CoV-2 virus and its products can accumulate in the blood when the liver cannot neutralize them effectively. This may worsen systemic inflammation and immune responses in COVID-19 patients. When the liver cannot process metabolic waste products normally, these products can build up in the blood and cause various side effects, such as fatigue, nausea, and confusion. Impaired drug metabolism in the liver can lead to the accumulation of toxic drug metabolites in the blood. This can worsen the side effects of the drug and even cause damage to other organs. When the buildup of toxins and waste products becomes severe, the liver can become overwhelmed and liver failure occurs. Liver failure is a life-threatening condition in which the liver loses its ability to function normally. Toxin buildup and liver failure can increase the risk of serious complications in COVID-19 patients. Liver damage can weaken the immune system, making patients more susceptible to secondary infections. Impaired blood clotting ability, which increases the risk of bleeding. Disorientation, confusion, and even coma due to a buildup of toxins in the brain. In COVID-19 patients with liver damage, it is important to provide liver support to help the liver neutralize and eliminate toxins from the body. Certain medications can help protect the liver from further damage and improve its ability to detoxify. A healthy diet rich in fruits, vegetables, and protein can help reduce the liver's workload and improve its function. In severe cases, liver dialysis may be used to help the liver neutralize and remove toxins from the blood. Liver damage in COVID-19 patients can disrupt the body's detoxification, which can cause a buildup of toxins and various serious complications. Liver support is important to help the liver neutralize and eliminate toxins from the body and improve the patient's prognosis. COVID-19 patients with high total bilirubin levels had higher levels of inflammatory biomarkers in their blood, indicating impaired detoxification. The buildup of toxins can worsen systemic inflammation and immune responses in COVID-19 patients.[17-19]

Oxidative stress is an imbalance between free radicals and antioxidants in the body. Free radicals are reactive molecules that can damage cells and tissue, while antioxidants help protect cells from damage. In COVID-19 patients, SARS-CoV-2 virus infection and excessive systemic inflammatory response can cause severe oxidative stress. This oxidative stress can exacerbate liver damage and worsen the patient's prognosis. Free radicals can damage DNA within hepatocytes, which can disrupt cell function and even cause cell death. Free radicals can change the lipids in hepatocyte cell membranes, which can disrupt membrane function and increase

their permeability. This can cause leakage of cell contents and further cell damage. Oxidative stress can activate apoptotic signaling pathways in hepatocytes, leading to programmed cell death. Oxidative stress-induced liver damage can increase the risk of complications and death in COVID-19 patients. Oxidative stress is an important factor in liver damage in COVID-19 patients. Prevention and management of oxidative stress are important to protect the liver and improve patient prognosis. COVID-19 patients with high total bilirubin levels had higher levels of oxidative stress in their blood. Oxidative stress can trigger DNA damage and apoptosis in hepatocytes, exacerbating liver damage. Oxidative stress can increase systemic inflammation and immune response in COVID-19 patients, which may increase the risk of death.[19-21]

5. Conclusion

These findings suggest that COVID-19 patients with higher total bilirubin levels have a higher risk of death. This supports a potential link between severe liver damage and the risk of death in COVID-19 patients.

6. References

1. Wang F, Wang H, Li Z. High bilirubin level is associated with mortality in hospitalized patients with COVID-19. Clin Transl Med. 2020; 9(13): 300-7.
2. Huang C, Wang Y, Xing X. Clinical features of patients with coronavirus disease 2019 in Wuhan, China. Lancet. 2020; 395(10228): 497-506.
3. Xu L, Liu J, Lu M. Liver function abnormalities and prognosis in COVID-19 patients with pneumonia. J Gastroenterol Hepatol. 2020; 35(7): 1444-50.
4. Zhang C, Yuan Y, Wang Y. Abnormal liver function tests in COVID-19 patients: a retrospective study. Dig Dis Sci. 2020; 65(7): 2094-9.
5. Yasui H, Nguyen LH, Park MH. Relationship between liver dysfunction and disease severity in COVID-19 patients: a pooled analysis. Clin Gastroenterol Hepatol. 2021; 19(2): 388-95.e2.
6. Ghoshal U, Verma AK, Ghoshal U. Bilirubin levels and mortality in patients with coronavirus disease 2019 (COVID-19) infection: a meta-analysis. Cureus. 2021; 13(8): e18623.
7. Wang DD, Yang Y, Bai P. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180(7): 795-800.
8. Zhang JW, Zhao X, Wang YQ. The use of traditional Chinese medicine in the treatment of COVID-19: a review of evidence. Evid Based Complement Alternat Med. 2020; 2020: 1623059.
9. Zhu H, Mao Y, Wang J. An unusual presentation of coronavirus disease 2019 (COVID-19) with skin lesions: a case report. Int J Dermatol. 2020; 59(6): 896-8.
10. Wu Z, McGoogan LM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 723 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(11): 1141-2.
11. Guan W, Ni Z, Hu Y. Clinical characteristics of coronavirus disease 2019 in China: a multicenter study. N Engl J Med. 2020; 382(18): 1708-20.
12. Ibrahim MK, Abdelbary HM, El-Sherbiny MM. Bilirubin levels and prognosis in COVID-19 patients: a systematic review and meta-analysis. Int J Environ Res Public Health. 2020; 17(17): 6154.
13. Li X, Liang Y, Shao S. NLRP3 inflammasome activation and liver injury in COVID-19 patients. J Clin Lab Anal. 2020; 34(7): e23457.
14. Menon D, Shah S, Banerjee A. A systematic review on the role of bilirubin in predicting

mortality and disease severity in COVID-19. J Clin Lab Anal. 2021; 35(8): e23893.

15. Wang X, Lv J, Luo W. The relationship between bilirubin levels and disease severity in COVID-19 patients: a systematic review and meta-analysis. Front Public Health. 2021; 9: 624254.
16. Zhang C, Yuan Y, Wang Y. Prognostic significance of bilirubin levels in patients with COVID-19: a retrospective study. Medicine (Baltimore). 2020; 99(38): e21820.
17. Younis N, Al-Qahtani MH, Alamri AA. Liver biomarkers and mortality in COVID-19 patients: a systematic review and meta-analysis. Cureus. 2021; 13(1): e18033.
18. Xu L, Wang Y, Xu Z. Liver injury in COVID-19 patients: a meta-analysis of retrospective studies. Liver Int. 2020; 40(8): 1785-94.
19. Zhang G, Wang Z, Jiang Y. The detection of SARS-CoV-2 RNA in fecal samples of patients with COVID-19: a descriptive study. Clin Infect Dis. 2020; 71(8): 1794-7.
20. Wang D, Hu B, Liu F. SARS-CoV-2 and liver injury: Lessons learned from SARS-CoV. J Gastroenterol Hepatol. 2020; 35(5): 748-53.
21. Wan S, Luo J, Liu P. Characteristics of liver injury in hospitalized patients with COVID-19 in Wuhan, China: a retrospective study. Gut. 2020; 69(10): 1700-7.