Acute Liver Injury and COVID 19 Disease Severity in a Tertiary Private Hospital in the Philippines

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Abstract

Background. Coronavirus disease 2019 (COVID-19) has been associated with acute liver injury presenting as increased liver enzymes, specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST). There is limited data in the prevalence of liver injury in COVID-19. We aim to determine the prevalence of acute liver injury among COVID-19 patients admitted in a tertiary hospital in the Philippines.

Methods. The study is a single center, retrospective cohort of all COVID-19 patients with baseline AST and ALT admitted at St. Luke's Medical Center - Quezon City from January 2020 to December 2021. The population was divided into those with normal liver enzymes, mild (AST and/or ALT 1-3 times ULN), and severe (AST and/or ALT >3x ULN) acute liver injury. Association of liver injury to clinical outcome, COVID-19 disease severity, and length of hospital stay were determined. Among those with elevated AST/ALT, comparison of the levels before and after treatment with hepatoprotective agents were evaluated.

Results. Among the 669 patients included in the analysis, 448 (67%) developed liver injury of which 50 (7.5%) had severe liver injury and 398 (59.5%) developed mild liver injury. Chi squared analysis showed that acute liver injury (OR:2.64,CI:1.90-3.69,p<0.01) was associated with COVID-19 severity. However, acute liver injury was not associated with clinical outcome (p = 0.347) and length of hospital stay (p = 0.317). There was no association between the use of hepatoprotective agents and changes in level of transaminases (p=0.087).

Conclusion. This study revealed that mild liver injury is commonly found in patients with COVID-19 infection. Severity of liver injury is significantly associated with COVID-19 severity, but not with clinical outcome and length of hospital stay. In this study, treatment with hepatoprotective agents did not lead to a decrease in liver enzymes. Further evaluation is needed to recognize those patients at higher risk of complications and identify effective therapies in providing better clinical outcomes.

Keywords. Acute Liver Injury, COVID-19 disease, Hepatoprotective Agents

Introduction

Coronavirus disease - 2019 (COVID-19) was declared a global pandemic by WHO last March 11, 2020.[1] As of September 2021, the virus has affected >200 million people worldwide with >4 million cases resulting in death.[2] COVID-19 is primarily a respiratory disease but it also affects other organs of the body, manifesting systemic conditions such as myocarditis, thrombosis, and acute liver injury (ALI).[3] Studies have described the elevation of liver enzymes, particularly AST and ALT, with COVID-19 infection[3-8]. The possible mechanism of injury could be drug induced with current COVID-19 drugs including favipiravir, lopinavir/ritonavir, remdesivir, and tocilizumab, [6,9,10] Immune mediated from severe inflammatory reaction and cytokine storm, ischemia-reperfusion injury, aggravation of existing liver disease[11], and direct damage from the angiotensin-converting enzyme 2 (ACE2) receptor [6,12]. Intracellular penetration of the COVID-19 virus is through the ACE 2 receptor, which is found in the lungs, heart, liver, and is expressed more in cholangiocytes (59.7%) than hepatocytes (2.6%).[13] Bile duct injury thus leads to hepatocyte dysfunction and subsequent liver injury. The cornerstone of treatment for liver injury in COVID-19 is inhibition of inflammation and

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hypoxia. Most cases resolve without any special treatment. However, more severe injury require hepatoprotective treatment using drugs such as polyene phosphatidylcholine, glycyrrhizin preparation, ursodeoxycholic acid, and s-adenosine methionine.[12]

In a meta-analysis by Kumar-M et al published last 2020, they included 128 studies and the cumulative prevalence of acute liver injury among patients with COVID-19 was approximately 23.7 (16.1-33.1) per 100 patients.[14] Based on another systematic review and meta-analysis, liver injury was found in 19% of COVID-19 patients with the pooled prevalence of elevated AST and ALT at 18% (13-25%) and 21% (14%-29%), respectively.[15]

Studies from China and the United States have identified the association of elevated liver enzymes with length of hospitalization, severity of disease, and mortality among COVID-19 patients. However, there is limited local data on the association of acute liver injury with the severity of the disease and survival of COVID-19 patients. Our institution also initiates treatment with hepatoprotective drugs containing S-adenosyl methionine (SAM), glycyrrhizin, and L-carnitine on admitted COVID-19 patients with elevated liver enzymes. Hence, determining the proportion of acute liver injury and its association with disease severity and patient clinical outcome among COVID-19 patients can provide valuable information on the liver enzyme profile of these patients. Determination of the trend of AST and ALT following treatment with hepatoprotective agents may also guide clinicians in the treatment of COVID-19 patients with liver injury.

The study is a single center, cross sectional analytical research study of all COVID-19 patients with baseline AST and ALT admitted from January 2020 to December 2021. The charts and records of all COVID-19 positive patients admitted in the COVID-19 units of SLMC QC from January 2020 to December 2021 were reviewed. The population is divided into normal ALT and AST level, mild (AST and/or ALT 1-3 times ULN), and severe (AST and/or ALT >3 times ULN) acute liver injury.

It aimed to determine the degree of elevation of liver enzymes with COVID-19 disease of all adult patients admitted in St. Luke's Medical Center Quezon City from January 2020 to December 2021. The study also aimed to determine the association of severity of acute liver injury with COVID-19 disease severity, clinical outcome, length of hospitalization, and to compare the levels of AST and ALT before and after treatment with hepatoprotective agents containing Glycyrrhizin, carnitine, and SAM.

Study Objectives. This study aims to determine the prevalence of acute liver injury among COVID-19 patients admitted in a tertiary hospital in the Philippines, as well as describe its association with patient clinical outcome, COVID-19 disease severity, and length of hospitalization. It also aims to identify the trend of liver enzymes following treatment with hepatoprotective agents.

Methodology

Study Design. The study is a single center, retrospective study of all COVID-19 patients with baseline AST and ALT admitted from January 2020 to December 2021. The records of all COVID-19 positive patients admitted in the COVID-19 units of SLMC QC from January 2020 to December 2021 were reviewed. The population was divided into those with normal liver enzymes, mild AST and/or ALT 1-3 times ULN), and severe (AST and/or ALT >3x ULN) acute liver injury which was patterned in the study from Europe.[16]

Study population and Data Collection. All patients from January 2020 to December 2021 who tested positive for COVID-19 with baseline AST and ALT on admission and who received standard COVID-19 therapy were included in the study. Pregnant subjects and patients with pre-existing liver disease like alcoholic liver disease, non-alcoholic liver disease and hepatitis infections were excluded. The following data were collected: demographics, co-morbidities, hepatoprotective agent received, COVID-19 treatment regimen, oxygen support, patient clinical outcome, baseline AST and ALT results, and the last repeat AST and ALT results prior to discharge or mortality. These were retrieved and recorded using Microsoft Excel.

Description of Outcome Measures. The primary outcome of the study was to evaluate acute liver injury in COVID-19 disease based on the level of transaminases. Primary outcome measures were computed based on the proportion of patients with elevated liver enzymes over the total population. Secondary outcomes include percent of mild (with AST and/or ALT levels <3 times ULN), severe (AST and/or ALT >3 times ULN) acute liver injury which were patterned in the study of Pastrovic et. al. Association of the severity of acute liver injury among COVID-19 patients resulting in mortality and average length of hospitalization stay were also determined. Another outcome of the study was the mean difference of AST and ALT after administration of hepatoprotective agents, comparing the levels of AST and ALT on admission and on discharge.

Operational Definitions. The following are the operational definitions observed in the study.

Standard therapy – recommended treatment for COVID-19 with Remdesivir, Dexamethasone, with or without Tocilizumab and/or Baricitinib

Severe COVID-19 – RT PCR confirmed COVID-19 with respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 92% on room air requiring oxygen supplementation.

Critical COVID-19 – RT PCR confirmed COVID-19 with respiratory failure requiring high flow oxygen, non-invasive or invasive ventilation, acute respiratory distress syndrome, sepsis or shock, deteriorating sensorium, and/or multi-organ failure

Table I. Baseline Characteristics of Study Participants (N=669), (n=448)

Characteristics	n (%), N=669, *n=448
Age (years) (Mean ± SD)	59.1±17.11
Sex	
Male	379 (56.7)
Female	290 (43.3)
Smoking Status	
Yes	80 (12.0)
No	589 (88.0)
Alcohol Status	
Heavy alcoholic beverage drinker	4 (0.6)
Occasional alcoholic beverage drinker	76 (11.4)
Nonalcoholic beverage drinker	589 (88.0)
Comorbidities	
Hypertension	382 (57.1)
Diabetes Mellitus	241 (36.0)
Cardiovascular Disease	95 (14.2)
Chronic Kidney Disease	58 (8.7)
Chronic Lung Disease	36 (5.4)
Obesity	194 (29.0)
Cancer	18 (2.7)
COVID-19 Severity	
Critical	159 (23.8)
Severe	254 (38.0)
Mild to Moderate	256 (38.2)
Liver Injury Severity	
Severe	50 (7.5)
Mild	398 (59.5)
None	221 (33.0)
Hepatoprotective Agents (*n = 448)	
Yes	150 (33.5)
None	298 (66.5)
Length of Hospitalization (days) (Mean ± SD)	10.8±9.47
Duration of Symptoms (days) (Mean ± SD)	6.3±3.71

*Participants with mild to severe liver injury

Transaminases – referring to liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Acute liver injury – elevation of liver transaminases AST and ALT further classified as:

Mild: AST and/or ALT levels 1-3 times upper limit of normal
Severe: AST and/or ALT >3 times upper limit of normal

28-day mortality – all cause in hospital mortality 28 days from admission

Sample Size. The sample size was calculated based on the test of hypothesis for the difference in the mortality in patients without acute liver injury versus those with mild liver injury. Assuming that the mortality among those with mild liver injury is 37% and among those without liver injury is 26%, (Pastrovic et. al, 2021) with an alpha error of 5%, power of 90%, and a 1-tailed alternative hypothesis, sample size calculated is 219 per group for a total of 657 for 3 groups.

Statistical Analysis. Descriptive statistics were used to describe the demographic data in the study. The mean and standard deviation were used to present continuous variables while frequency and percentage for categorical data. Data was analyzed by SPSS. Determination of the proportion of acute liver injury and severity of COVID-19 were analyzed using frequency and percentage, 95% confidence interval of the percentage was calculated.

Association of severity of acute liver injury with severity of COVID-19 and all-cause mortality were analyzed using chi squared test. Odds ratio and 95% confidence interval were calculated. Association of severe liver injury with length of hospital stay were analyzed using ANOVA. Among those with elevated AST/ALT, comparison of the levels before and after treatment with hepatoprotective agents were done using paired T test. Level of significance was set at alpha = 0.05.

Ethical Consideration. The study abided by the Principles of the Declaration of Helsinki (2013) and conducted along the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP), E6 (R2) and other ICH-GCP 6 (as amended); National Ethical Guidelines for Health and Health-Related Research (NEG HHRR), 2017. The Clinical Protocol and all relevant documents reviewed and approved by the SLMC Institutional Ethics Review Committee. Patient confidentiality was respected by ensuring anonymity of patient records. Each patient document is CODED and did not contain any identifying information in order to ensure confidentiality. The results and patient information were kept strictly confidential by the primary investigators. A unique alphanumeric code was issued to each respondent and the subjects' names will not appear on any of the data collection tools. Only the investigators have access to the names of all respondents, to ensure confidentiality at all times. The data was stored in the primary investigators' database, password-protected. All study data were recorded and investigators are responsible for the integrity of the data i.e. accuracy, completeness, legibility, originality, timeliness and consistency. All study-related documents such as all versions of the protocol, ethical clearance, data collection forms, hard copies of source documents shall be kept and stored by the Principal Investigator in strict confidentiality for at least 5 years; after which they will be shredded. The main person responsible for storage of data was the principal investigator. Data storage in electronic form, stored in a personal laptop. Data was password protected and only accessible to members of the study team.

Results

Patient Characteristics. After careful review of all admitted adult patients with COVID 19 infection from January 2020 to December 2021, 669 eligible participants were included in the study. The participants' characteristics and clinical profile are listed in *Tables I and II*.

Table I illustrates the baseline characteristic of the study participants. The mean age of the participants is

Table II. Statistical Test (Chi Square) between Liver Injury with COVID-19 Severity and Clinical Outcomes

Clinical Outcome	Liver Injury Severity			p-value
	Severe, n=50 n (%)	Mild, n=398 n (%)	Normal, n=221 n (%)	
COVID-19 Severity				
Critical	13 (26.0)	113 (28.4)	33 (14.9)	<0.001
Severe	25 (50.0)	160 (40.2)	69 (31.2)	
Mild to Moderate	12 (24.0)	125 (31.4)	119 (53.8)	
Outcome				
Expired	4 (8.0)	32 (8.0)	11 (5.0)	0.347
Discharged Improved	46 (92.0)	366 (92.0)	210 (95.0)	

Table III. ANOVA Analysis between Liver Injury and Length of Hospitalization

Length of Hospitalization	n (%)	Mean±SD	p-value
Severe	50 (7.5)	11.72±11.42	0.317
Mild	398 (59.5)	11.12±9.14	
Normal	221 (33.0)	10.05±9.59	

Table IV. COVID-19 Disease with Elevated Liver Injury and Use of Hepatoprotective Agents

Clinical Outcome	Changes in Liver Injury Severity			p-value
	Worsened	No Change	Improved	
Hepatoprotective Agents				0.087
Yes	35 (23.3)	77 (51.3)	38 (25.3)	
None	44 (14.8)	181 (60.7)	73 (25.0)	

59.1±17.11 with a median of 60 and a range of 20 to 98, of which 379 (56.7%) were male. Majority of the included participants are non-smokers and non-alcoholic beverage drinkers that represent 88% of the total participants. Among the comorbidities, the most common was hypertension (57.1%) followed by obesity (29.0%), diabetes mellitus (36.0%), cardiovascular disease (14.2%), chronic kidney disease (8.7%), chronic lung disease (5.4%), and cancer (2.7%). In terms of COVID-19 severity, 23.8% were classified as critical COVID-19, 38.0% severe COVID-19 and 38.2% were mild to moderate COVID-19. Baseline ALT and AST were obtained at the time of admission wherein 7.5% were categorized with severe liver injury with AST and/or ALT elevation >3x ULN, 59.5% as mild liver injury with AST and/or ALT elevation 1-3x ULN, and 33.0% with normal transaminases. Out of 448 participants with mild to severe liver injury as illustrated in table 2, 150 (33.5%) participants were given hepatoprotective agents. The mean length of hospitalization was 10.8±9.47 days with a median of 8 days ranging from 0 to 85 days of hospitalization. The participants that were admitted usually presented with 6 days of symptoms prior to their consultation.

Prevalence and Association of Liver Injury with COVID-19 Infection and Clinical Outcomes. The current study demonstrates that the prevalence of liver injury is 67.0% (448 of 669 patients). Of those with acute liver injury, 33.5% were given hepatoprotective agents.

Association of liver injury with severity of COVID-19 and clinical outcomes was analyzed using chi squared test. Confidence interval was set at 95%. In the 669 patients included in the study, 7.5% (50 of 669) developed severe liver injury, 59.5% (398 of 669) developed mild liver injury and 33.0% (221 of 669) had normal transaminases. As seen in Table 3, there was a significant association between severity of acute liver injury with severity of COVID-19 infection (p <0.001). Among participants with severe liver injury, 26.0% had critical COVID-19 and 50% had severe COVID-19. Clinical outcome was measured based on all-cause mortality or if participants were discharged with improvement. The mortality rate was 7.0% (47 of 669) in all COVID-19 patients, wherein 76.6% (36 of 47) presented with acute liver injury. Majority (61.6%) were discharged with improved clinical status. However, severity of acute liver injury was found to have no significant association with clinical outcome (p=0.347) (See *Table III*).

Association of Liver Injury Severity with Length of Hospitalization. The mean length of hospitalization was 10.8±9.47 days. The median was 8 days, with an interquartile range of 0 to 85 days. In patients with mild to severe liver injury, the mean length of hospitalization was 11.12±9.14 and 11.72±11.42 days respectively. In those with normal transaminases, the mean length of hospitalization was 10.05±9.59 days. Association of severe liver injury with length of hospital stay was analyzed using ANOVA. This showed no association between liver injury severity and length of hospitalization (p=0.317).

Association of Liver Injury and Use of Hepatoprotective Agents. Out of the 669 patients included, 448 (67.0%) patients developed transaminitis. Among them, 150 of 448 (33%) were started on a hepatoprotective agent. Among those who were given a hepatoprotective agent, 25.3% had improved transaminases, similar to those who did not receive a hepatoprotective agent (25%). Majority had no change in liver injury severity regardless if they were given a hepatoprotective agent or not. Worsened liver injury was observed in 14.8% of those without

hepatoprotective agents and 23.3% of those on hepatoprotective agents. Analysis to compare transaminases upon admission and on discharge was done using paired T-test with a level of significance set at alpha = 0.05. Chi squared test analysis was also done to determine if there is significant improvement of liver injury after treatment with hepatoprotective agents. The study showed that there is no significant change in liver injury severity (p=0.087) before and after treatment with hepatoprotective agents.

Discussion

Since almost all admitted patients had baseline AST ALT done on admission, the degree of liver enzyme elevation could be associated with the degree of COVID severity. The prevalence of liver enzyme abnormality observed in our study is similar to large cohorts reported in China and in the United States. [8,3] In the study of Cai et al, 318 (76.3%) out of 417 patients with COVID 19 had abnormal test results on admission and most were only mild with levels <2x ULN [8] In a large US cohort, COVID 19 positive patients had higher median ALT levels and majority had mild elevation with peak level values <2 times the ULN.[3] Our study also showed that majority of the patients had liver injury, but most (59%) were only mild with AST and/or ALT elevation <3x ULN. Our study showed that the severity of liver injury was significantly associated with COVID disease severity. As also reported in the study of Cai, et al, patients with abnormal liver test results had a 9-fold greater risk of having severe COVID 19. [8] Hence, for patients who are admitted with a baseline AST ALT that is elevated, they are at greater risk to develop severe COVID 19 infections.

Our study showed that the mean length of hospitalization was 10-11 days, with no significant correlation with severity of COVID 19 disease. Those with severe or critical COVID 19 had a mean duration of hospital stay of 10.8 days similar to those with mild or no liver injury. In contrast, the study of Fan et al found that baseline abnormal liver function was associated with prolonged hospital stay.[17] This study also showed that more than 90% of the patients were discharged improved, regardless of the severity of liver injury. Only 8% of those with severe liver injury expired, with 92% of them discharged. The severity of liver injury was not significantly associated with patient outcome. However, in a study done in China, patients with elevated AST and ALT were associated with increased risk of mortality, especially those with elevated AST.[18] One possible cause is the difference in COVID treatment since there was still no standardised guidance on drug choice and treatment. Another possible cause is other factors that may affect liver enzyme elevation, including medications, comorbidities, or undiagnosed underlying liver disease.

Majority of the patients had no change in the degree of enzyme elevation with (51.2%) or without (61%) hepatoprotective agents. Management of liver injury in COVID 19 should be aimed at inhibiting the inflammatory response, correcting hypoxemia, and preventing SIRS. Studies showed that most cases with mild liver injury resolve without treatment, but those with severe liver injury may need treatment with hepatoprotective agents.[12] Glycyrrhizin was reported to be the preferred anti-inflammatory drug for protection against liver disease. However, its use along with other hepatoprotective agents are not yet supported by evidence in the prevention or treatment of liver injury in COVID-19 patients.[13] Although some of the patients in our population were given hepatoprotective agents, there could be other factors that could affect the enzyme elevation, including COVID-19 treatment regimen such as Tocilizumab and Remdesivir. Moreover, other factors may also be contributory, including undiagnosed liver diseases, heart failure which may cause passive congestion.

Limitations. This study has some limitations. The representation of the population is limited to in-patients and those admitted to one private hospital. Hence, results cannot be generalized, especially to the rural or outpatient setting. The duration of illness of the patients before seeking consultation were also not uniform. The baseline liver enzymes were thus taken at different days of illnesses and could affect the degree of elevation. Although we did our best to exclude patients who had a history of liver diseases, some patients could have undiagnosed liver problems. In addition, other possible sources of liver injury including hepatotoxic medications could not be entirely characterized.

Conclusion

Acute liver injury is common in patients with COVID-19 infection, it may be caused by either direct or indirect damage to organs which include heightened inflammatory response. Severity of liver injury is associated with COVID-19 severity, but not clearly associated with clinical outcome and length of hospital stay. In this study, hepatoprotective agents did not show improvement in liver injury. Further evaluation is needed to identify those patients at higher risk of complications, better understanding of the pathophysiology and effective therapies in providing better clinical outcomes.

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