



St. Paul's Hospital Millennium Medical college

Magnitude of Liver Biochemical Test Abnormalities and its Effect on Patient Outcomes Among Patients Admitted to St. Paul's COVID-19 Treatment Center.

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Addis Ababa. Ethiopia

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Acronyms and abbreviations

ACE2: angiotensin converting enzyme 2

ALP: alkaline phosphatase

ALT: alanine aminotransferase

ARDS: acute respiratory distress syndrome

AST: aspartate aminotransferase

DB: direct bilirubin

ICU: intensive care unit

IRB: Institutional Review Board

MERS-COV: Middle east respiratory syndrome-coronavirus

MOD: multiorgan dysfunction

MOF: multiorgan failure

MV: mechanical ventilation

PCR: polymerase chain reaction

SARS-COV: severe acute respiratory syndrome-coronavirus

SARS-COV-2- severe acute respiratory syndrome-coronavirus 2

SPHMMC: saint Paul hospital millennium medical collage

SPSS: Statistical Package for the Social Sciences

TB: total bilirubin

UNL: upper normal limit

USA: United States of America

Summary

Background: Coronavirus disease (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 virus. In addition to its pulmonary manifestations, COVID-19 also causes extrapulmonary manifestations which includes liver involvement. Understanding the prevalence of liver biochemical test abnormalities and identifying the relationship between elevation in liver biochemical tests and adverse clinical outcomes can help improve care of patients.

Objective: The aim of the study is to measure the prevalence of liver biochemical test abnormalities and its association with adverse patient outcomes in patients admitted to SPHMMC COVID-19 treatment center.

Methods: A descriptive and analytical cross-sectional study was conducted in SPHMMC COVID-19 treatment center between May 2022 to August 2022. From a total of 2200 of patients, 331 patients were included in the study using systemic random sampling. A structured checklist was used to screen records for completeness. The data was entered, cleaned, analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. Bivariate and multivariate analysis between dependent and independent variables was performed.

Results: Prevalence of abnormal liver biochemical test abnormalities was determined among patients admitted to SPHMMC COVID-19 treatment center. Elevations in alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase were present at baseline in 40.2%, 43.8% and 48.3% of patients, respectively. Assessment of relationships between elevated liver biochemical tests and adverse patient outcomes was also conducted. Parameters that were associated with increased risk of death were baseline elevation in ALT (OR = 3.271; 95% CI = 1.349-7.931; P = 0.009), in-hospital elevation in AST (OR = 2.192; 95% CI = 1.273-3.773; P = 0.005) and in hospital elevation in ALP (OR = 6.047; 95% CI = 2.863-12.773; P < 0.001). In-hospital elevation in AST was also found to be predictor of increased risk of transfer to the ICU and Mechanical ventilator (OR = 2.030; 95% CI = 1.099-3.749; P <0.024).

Conclusion: Abnormalities in liver biochemical tests are common among patients admitted with COVID-19 patients. Elevation in parameters such as AST and ALP, particularly during the course of hospitalization should be looked after as it may signal an increased risk of transfer to the ICU, requirement of MV and death.

Keywords: Coronavirus-19, liver dysfunction, hepatitis, severe acute respiratory syndrome coronavirus 2.

1. Introduction

1.1. Background

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). The first known cases of COVID-19 were identified in Wuhan, China. Since then, the virus has spread globally to infect millions of people. As of October 14, 2022 the virus has infected 629,034,009 people and is responsible for the death of 6,568,527 worldwide. In Ethiopia 493,738 are infected and 7,572 are dead from the virus (1).

Clinical manifestations of COVID-19 infection ranges from minor disease with mild pneumonia in up to 81% of patients, to severe disease characterized by dyspnea and hypoxia in 14% of patients. In up to 5% of patients, critical disease with respiratory failure, shock and multiorgan involvement has been described (2).

Although COVID-19 is most well-known for its respiratory manifestations, it can also cause multitude of manifestations which are extrapulmonary. Among described extrapulmonary manifestations include, thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologic illnesses, ocular symptoms, and dermatologic complications (3).

Hepatobiliary system injury is one of the extrapulmonary manifestations of COVID-19 infection. Some of the suggested mechanisms for liver injury in patients affected with COVID-19 include direct cytopathic effect of the virus, drug induced liver injury and uncontrolled immune response related liver injury (4,5). Clinical studies have indicated that presence of liver injury is associated with disease severity, requirement of mechanical ventilation and increased mortality (7,8).

Commonly measured laboratory parameters which detect injury to hepatobiliary system include, the serum aminotransferases, namely alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP) and serum bilirubin. Elevated serum

aminotransferases and alkaline phosphatase, despite being non-specific, are sensitive indicators of hepatocellular and biliary tract damage, respectively (6).

Investigators have found the spike proteins of SARS-COV-2 engage with angiotensin converting enzyme-2 (ACE2) for entry into target cells, stating ACE2 as a functional receptor for SARS-COV2 infection. The causative agent of the previous coronavirus epidemic, SARS-COV is also known for utilizing similar receptor (6). Hepatocytes and cholangiocytes are demonstrated to express ACE2 receptors, with cholangiocytes expressing 20 times in abundance of hepatocytes making these cells a potential target organ for SARS-COV-2 infection (10).

Prevalence of liver function abnormalities have been described in different studies globally, albeit largely inconsistent across different study populations. The relationship between these abnormalities and their significance also has not been clearly stated. To the author's knowledge there is no any local clinical study done with primary focus on this clinical problem. Studying the prevalence of liver injury among patients with COVID-19 and its correlation with adverse outcomes in our population would give an important insight on how to approach and manage these patients.

1.2. Statement of the problem

Clinical characteristics of pulmonary features of COVID-19 as the most common manifestations and leading cause of death have been the primary areas of concern and studies. Efforts in understanding the extra pulmonary manifestations of COVID-19 like the hepatobiliary system are made but haven't been as expansive.

Liver function test abnormalities are reported with variable frequencies. Elevated transaminases were described in 25% to 56% of hospitalized patients (8,25). In most of the patients the elevation is said to be less than 5 times the upper limit of normal, although higher elevations and patients with severe fulminant hepatitis have been described (23). Reported Elevation in transaminases is higher than bilirubin and ALP (11-13).

In addition to the described ACE2 expression in hepatobiliary system, early post-mortem autopsies

in patients with critical COVID-19 infection from China have shown micro-vesicular steatosis, hepatocellular degeneration, lobular focal necrosis, portal immune infiltration and micro-thrombosis with congestion of the hepatic sinuses-findings that are consistent with ischemic or hypoxic or ischemic liver damage (9).

In Ethiopia, a study done at millennium COVID-19 care center demonstrated baseline elevation in AST is found to be predictor of developing severe COVID-19 infection (10). Studies looking at prevalence and patterns of different liver function tests at admission and during the course of hospitalization and their relationship with disease outcome are lacking.

Studying the degree to which the liver is involved and its association and significance for patients hospitalized with COVID-19 infection is very important. The knowledge might guide our approach to patients with COVID-19 who develop liver injury with or without known prior liver injury.

1.3. Significance of the study

Understanding the prevalence of liver biochemical test abnormalities and its associated factors in our population will enhance our knowledge of interaction between the liver and SARS-COV2 infection.

For clinicians, having the knowledge of the prevalence and the degree of liver injury among patients affected with COVID-19 will guide their decision in the follow up, avoidance of potential hepatotoxic medications and overall individualization of care to their patients.

For higher administrator bodies, the data can be helpful in planning and designing the system in which those patients can be treated with the specialized care they need according to their risk. Patients also can benefit from getting special attention to their problem.

Future researchers can use this information as a basis for future research on studying the mechanism of liver injury in SARS-COV2 infection, as well as the impact of COVID-19 in patients with chronic liver disease from any cause with underlying liver damage and limited functional hepatocyte reserve.

2. Literature review

2.1 Liver and prior coronavirus epidemics

When severe acute respiratory syndrome coronavirus emerged as a global pandemic in 2003 GC, in addition to its pulmonary manifestations, severe cases were associated with multiorgan involvement. While liver injury was described in up to 60% of affected patients, data regarding the mechanism of liver injury and potential implication of liver injury was far from definite. Presumed mechanisms of liver injury were direct viral infection of hepatocytes, inflammatory response and drug induced hepatotoxicity (11).

Middle east respiratory syndrome (MERS) is caused by MERS-COV virus. The first cases were described from Saudi Arabia in 2012. In severe cases of MERS, in addition to pulmonary and renal manifestations, about half of the critically ill patients develop liver injury which are characterized by elevation in serum aminotransferases. One study from Saudi Arabia showed, among liver biochemical test abnormalities, low albumin level was found to be predictor of disease severity (17).

2.2 Prevalence and Outcome of Liver Injury Among COVID-19 Patients

Abnormalities in biochemical liver test are also described in SARS COV2 infection. Liver involvement in patients with COVID-19 ranges from mild elevations in transaminases to acute fulminant hepatitis (13).

One of the earliest studies done to address the pattern of liver biochemical tests was a single center retrospective study involving 105 patients from China by Qi Wang et al. and they demonstrated 56.2% of the patients had abnormal AST, ALT or total bilirubin. In majority of the patients the elevation was less than 3 times of the upper normal limit. The association between the severe disease and elevation in the liver enzymes was found to be statistically significant ($P=0.001$)(14) .

A retrospective study involving 2,912 patients from a makeshift hospital in China by Yong Lv et al. also assessed the association between abnormalities in liver function tests and adverse clinical outcomes. They found 48.6% patients have abnormal liver function test results. Baseline abnormal

liver function test were associated with increased risk for mortality ($p=0.002$), ICU admission ($p < 0.001$) and mechanical ventilation ($p < 0.001$). From the parameters, abnormalities in AST and albumin had association with poor outcomes (16).

Elsewhere, a study from Portugal also assessed the impact of liver test abnormalities on the clinical outcomes of COVID-19 infection. They found out 50.1% of patients had elevation in the liver enzymes and from the subgroup analysis, elevation in AST was found to be associated with severe covid, increased mortality and ICU admission. ALP was found to be elevated in 11.4% of patients and it was associated with development of critical covid and gamma glutamyl transferase was elevated in 24.6% of patients and it was associated with ICU admission (19).

In the United States of America, a single center retrospective study involving 200 patients by Yadlapati et al. also assessed the predominant pattern of liver enzymes elevation and association with poor outcomes. AST, ALT and ALP were elevated in 55%, 20% and 28% of cases respectively. Like the above studies, elevation in AST was found to be associated with inpatient death ($P=0.035$), vasopressor use ($P=0.001$) and intubation ($P=0.002$) (20).

A single center retrospective study was carried out in Pakistan to examine the prevalence of liver biochemical tests and their correlation with adverse patient outcomes. Elevation in AST, ALT and ALP was reported in 41.55%, 28.57 and 14.28% of patients, respectively. Elevated AST levels were associated with higher mortality and ICU admissions among liver biochemical tests (26).

Because AST is known to be less specific for liver than ALT, a meta-analysis involving 1,555 patients from the USA was done looking for degree of elevation of ALT and association with adverse clinical outcomes. From 1555 patients 74% had elevation in ALT, from which 3% was more than 20 times the upper normal limit. Abnormality in ALT level was associated with increased mortality and increased length of stay (26).

Contrary to the points made from the above literatures, a study from Netherlands which included 282 patients didn't find any association between the presence of liver injury and patient outcomes in COVID-19 patients in terms of duration of hospital stay, transfer to the ICU and mortality (22).

A case report described a patient who presented with acute icteric hepatitis. A study group from university of Missouri described a 29-year-old male patient with mild COVID-19 symptoms but

significantly elevated liver enzymes with ALT and AST being 65 and 40 times the upper limit of normal respectively, while ALP was twice the upper limit normal. Total bilirubin and direct bilirubin were 16 mg/dl and 10 mg/dl respectively. Despite developing severe injury, this patient was asymptomatic from his respiratory condition and did not need treatment with steroids or supplemental oxygen (23,24). In addition, a study from Turkey that included 156 patients did not show any adverse outcomes in patients co-infected with Hepatitis B virus and SARS-COV2.

A recently conducted meta-analysis which included 64 studies across the globe and 11,245 patients found prevalence of liver injury among patients affected with COVID-19 is approximately 25% and is associated with disease severity and adverse patient outcomes (25).

Finally, a retrospective cohort study was conducted in Ethiopia involving 425 patients in a makeshift hospital. The study assessed laboratory biomarkers associated with disease severity. The prevalence of abnormalities in ALT, AST and ALP were reported in 43.6%, 24.5% and 18.2% of the patients, respectively. Among liver biochemical tests, elevation in AST was found out as a predictor of disease severity (15).

2.3 Pathophysiology and Pathology of Liver Injury Among COVID-19 Patients

Even though the presence of liver injury is described in different studies, the mechanism by which this injury occurs is yet to be defined. Presumed mechanism include direct cytopathic effect mediated via ACE2 receptors, inflammatory response mediated, hypoxia related and hepatotoxic effect of drugs (23).

Histologic examination done in patients affected with COVID-19 is non-specific and it shows mild steatohepatitis and mild lobular and portal activity. In addition, coronavirus spike proteins inside the hepatocytes have also been identified (10).

3. Objectives

3.1. General objective

To assess the magnitude of abnormal liver biochemical tests and its effect on outcome among COVID-19 patients admitted to St. Paul's hospital millennium medical college COVID-19 treatment center.

3.2. Specific objectives

- To assess the magnitude of liver biochemical test abnormalities among COVID-19 patients admitted to St. Paul's hospital millennium medical college COVID-19 treatment center
- To assess the effect of abnormal liver biochemical tests on mortality
- To assess the effect of abnormal liver biochemical tests on risk of transfer to the ICU.
- To assess the effect of abnormal liver biochemical tests on increasing requirement of mechanical ventilation.

4. Methods

4.1. Study design

A hospital based retrospective and cross-sectional study was conducted on the magnitude of abnormal liver biochemical tests and its impact on disease outcome. Chart review was used to collect data.

4.2 Study area and period

4.2.1 Study area

This study was conducted in St Paul's hospital millennium medical college, the second largest tertiary hospital in Addis Ababa, Ethiopia.

The college has more than 2,800 clinical, academic and administrative and support staff that provide medical specialty services to patients who are referred from all over the country, teaching medicine and nursing students and doing basic and applied researches. While the inpatient capacity is more than 700 beds, the College sees an average of 1,200 emergency and outpatient clients daily (29).

SPHMMC opened its COVID-19 treatment center on April 2020 and since then it has been providing service to its COVID-19 patients in regular ward and intensive care unit without interrupting its regular clinical activities. As of October 2021, around 2,000 patients are seen at the COVID-19 treatment center, as per SPHMMC information desk.

4.2.2 Study period

The study was conducted at SPHMMC COVID-19 treatment center from December 2021 to February 2022.

4.3. Population

4.3.1 Source population

Patients who were admitted to SPHMMC COVID-19 treatment center and fulfill the inclusion criteria were included in the study.

4.3.2 Study population

All randomly selected patient cards who were admitted to SPHMMC COVID-19 treatment center and fulfill the inclusion criteria.

4.4 Eligibility criteria

4.4.1 Inclusion criteria

- Age >18 years old.
- Patients admitted to SPHMMC COVID-19 treatment center with Positive PCR result or positive rapid antigen test result.
- Patients admitted to SPHMMC COVID-19 treatment center and have a liver biochemical test determined on at least once during hospitalization.

4.4.2 Exclusion criteria

- Patients who were admitted during study period.

4.5. Sample size determination and sampling technique

4.5.1 Sample size determination

Sample size was calculated by using the single population proportion formula.

$$n_o = (Z_{\alpha/2})^2 P \times (1-P)/d^2$$

n_o = required sample size

Z= confidence level at 95% (standard value of 1.96)

d= margin of error = 5%

P= estimated prevalence liver biochemical test abnormalities in patient with COVID-19 which is from a study done at Millennium COVID-19 Care Center, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, is 43% (10).

Therefore:

$$n_o = (1.96)^2 \times (0.43 \times 0.57) / (0.05)^2 = 376$$

The total number of patients admitted to St Paul COVID-19 treatment center before the beginning of the study is <2000, hence sample size determination using the finite population correction factor will be:

$n = n_o / (1 + n_o / N)$, where: n is corrected sample size, n_o is sample size determined for infinite population and N is the study population. Therefore:

$$n = 376 / (1 + 376/2000) = 316$$

The corrected sample size is 316.

Sample size for secondary outcomes was calculated by the double population formula using the aid of the epi-info software.

$$n_o = (Z_{\alpha/2} + Z_B)^2 (P_1Q_1 + P_2Q_2) / (P_1 - P_2)^2$$

- For the assessment of the effect of abnormal liver biochemical tests on mortality; considering a power of 80% and confidence interval of 95%, assuming P1 of 10%, P2 of 22%, the values for $Z_{a/2} = 1.96$ & $Z_B = 0.842$ (5),
The sample size is 293.
- For the assessment of the effect of abnormal liver biochemical tests on risk of transfer to the ICU; considering a power of 80% and confidence interval of 95%, assuming P1 of 8%, P2 of 20%, the values for $Z_{a/2} = 1.96$ & $Z_B = 0.842$ (5),
The sample size is 262.
- For the assessment of the effect of abnormal liver biochemical tests on risk of increasing requirement of mechanical ventilation; considering a power of 80% and confidence interval of 95%, assuming P1 of 6%, P2 of 16%, the values for $Z_{a/2} = 1.96$ & $Z_B = 0.84$ (5),
The sample size is 307.

The largest calculated sample size is 316, considering a 10% rate of incomplete medical records, the final sample size for the study became 347.

4.5.2 Sampling technique and procedures

Sampling was done by systematic random sampling method. As of October 2021, a total of 2,000 of patients were admitted to SPHMMC COVID-19 treatment center, according to SPHMMC information desk. From which, 347 patients were included in the study, the first patient was elected randomly and then every 5th patient was part of the study based on patient's chart number

4.6. Operational definition

COVID-19 infection- a case identified by a positive SARS-COV2 PCR test or positive rapid antigen test (24).

Mild COVID-19 infection: uncomplicated upper respiratory tract viral infection, patients may have fever, fatigue, cough with or without sputum production, anorexia, muscle pain, sore throat, nasal congestion, headache, loss of smell or taste (27).

Moderate COVID-19 infection: is described as patient having mild pneumonia, but has no hypoxemia or no need supplemental oxygen (27).

Severe COVID-19 infection: is described as patient having severe pneumonia, acute respiratory distress syndrome (ARDS) or sepsis. These are group of patients responding to non-invasive management (27).

Critical COVID-19 infection: Respiratory failure, septic shock, and/or multiple organ dysfunctions (MOD) or failure (MOF) and it need invasive or special management (27).

Risky alcohol use: refers to consumption of an amount of alcohol that puts an individual at risk for health consequences (30).

- ✓ Males under age 65- 14 drinks/week or >4 drinks on any day.

- ✓ Females and males older than 65 years- 7 drinks/week or >3 drinks on any day.

Normal values for basic liver blood chemistries are based on normal values from SPHMMC laboratory.

ALT: 0-33 IU/L

AST: 10-35 IU/L

ALP: 45-87 IU/L

TB: 0-1.20 mg/dl

DB: 0-0.20 mg/dl

4.7. Study variables

Independent variables:

- Sociodemographic factors: age, sex.
- Disease severity: mild, moderate, severe and critical COVID-19.
- Duration of hospital stay
- Previously known diagnosis of liver cirrhosis.
- Serostatus for hepatitis B and hepatitis C.
- History of alcohol use
- Blood pressure
- Vasopressor use
- Drug use including but not limited to acetaminophen, amoxicillin-clavulanate, sulfamethoxazole/Trimethoprim, isoniazid and statins.
- Liver imaging findings including but not limited to fatty liver and cirrhosis.
- Co-morbidities including but not limited to DM, heart failure, hypertension, COPD and CKD
- Coagulation profile including PT, aPTT and INR.
- Serum albumin.

Dependent variable

- Liver biochemical test results including AST, ALT, ALP, serum albumin, PT, TB and DB, determined initially at baseline and peak value during hospitalization
- Transfer to the ICU
- Requirement of mechanical ventilation.
- Mortality

4.8. Data collection tools and techniques

Data was collected from patient cards. Data collection checklist containing age, sex, oxygen saturation on admission, duration of hospital stay, alcohol use history, serologic status for viral hepatitis B and C, patient outcomes, standard liver blood chemistry results which were determined at admission and during hospital stay was collected based on review of similar literature (13,7,28).

Data collection was conducted on March 2022 by retrieving from patient chart by trained data collectors (7 internal medicine residents) after a day-long training before data collection. Records of the study population will be assessed for completeness before data entry and the entered data was checked by the data supervisor on a daily basis for any incompleteness and/or inconsistency.

4.9. Data processing and analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 26.0. Categorical variables were recorded as percentages and frequency. Continuous variables were recorded as mean, and standard deviation and were compared by Student's t test. Bivariate analysis between dependent and independent variables was performed using binary logistic regression. Variables with p value <0.2 were included in multivariate logistic regression to detect whether abnormal liver biochemical tests are independently associated with clinical outcomes which are mortality, transfer to the ICU and requirement of mechanical ventilation. If the p value was <0.05 , then the difference between various parameters was considered statistically significant.

4.10. Ethical considerations

Ethical clearance was obtained from SPHMMC research office and SPHMMC Institutional Review Board (IRB) prior to conducting the research. Permission was sought from the school administration to carry out the research. Each patient's name and other identification revealing information will be kept confidential.

4.11. Result dissemination

The results of this study will be submitted to the department of internal medicine and public health, SPHMMC in partial fulfillment of the requirement for a specialty certificate in internal medicine. It will also be presented to the Gastroenterology and hepatology unit. In addition, the findings will be distributed to the major COVID-19 treatment centers in the country. The results will be published in the peer reviewed journals

5. Result

5.1 Baseline characteristics of patients

Demographic and clinical characteristics of patients is summarized in Table 1. From a total of 2200 patients admitted with COVID-19 to Saint Paul Hospital Millennium Medical College (SPHMMC), 331 patients met the inclusion criteria and are included in the analysis of this study. The mean age was 50 years (range 18-79), and 201 (60.7%) of the patients were men. Of all patients, 77 (23.3%), 85 (25.7%) and 92 (27.8%) were admitted for mild, moderate and severe COVID-19 respectively, while 77 (23.3%) had critical disease. The mean duration of hospital stay

was 12.6 days (range: 1-47 days). Low blood pressure that required vasopressor and/or inotrope use was present in 35 (10.6), while 296 (89.4%) had normal blood pressure.

Only 3 patients had previously diagnosed liver disease. During the course of admission, 80 patients had their Hepatitis B surface antigen (HBsAg) status determined. From which 10 of them were reactive while 70 were non-reactive. Among patients who were reactive to HBsAg, elevation in ALP, AST and ALP were present in 30%, 30% and 40%, respectively. Similar number of patients were tested for anti-hepatitis C antibody (anti-HCV Ab). None of the admitted patients were reactive for anti-HCV Ab. Of all admitted patients, 251 of them weren't tested for both HBsAg and anti-HCV Ab.

A risky alcohol use was reported in 3 of patients, while 59 patients were stated as not having such history. While the status of alcohol use wasn't reported in 272 patients. A history of potentially hepatotoxic drug use of reported in 42 (12.7%) of patients, from which the use of statins has the highest frequency. Use of statins was reported in 30 (9.1%) of patients, it was followed by use of non-steroidal anti-inflammatory drugs (NSAIDs) in 3 (0.01%) patients, anti-tuberculosis drugs in 3 (0.01%) patients, augmentin in 2 (0.006) patients, amitriptyline in 2 (0.006) patients and unspecified herbal medications in 2 (0.006) patients.

Comorbidities were reported in 273 (82.4%) of patients. The most common comorbidity was hypertension 58.4%, followed by type 2 diabetes mellitus which was present in 47.1% of patients. from other chronic medical conditions, CKD which was reported in 37 (11.17%) of patients while CHF, IHD and cirrhosis were documented in 9, 5 and 3 patients, respectively. Of all patients, 58 (17.5%) didn't have any known comorbidity.

Table 1 Demographic and clinical characteristics of patients admitted to the wards and ICU of SPHMMC COVID-19 treatment center, Addis Ababa, 2022.

Characteristics	No. (%)
Age	
<30	67 (20.2)
31-40	34 (10.3)
41-50	48 (14.5)
51-60	81 (24.5)
61-70	58 (17.5)
>71	43 (13.0)
Gender	
Male	201 (60.7)
Female	130 (39.3)
Disease severity	
Mild	77 (23.3)
Moderate	85 (25.7)
Severe	92 (27.8)
Critical	77 (23.3)
Priorly diagnosed Liver disease	
Yes	3 (0.9)
No	328 (99.1)
HBsAg	
Positive	10 (3.0)
Negative	70 (21.1)
Unknown	251 (75.8)
HCV AB	
Positive	0 (0)
Negative	80 (24.2)
Unknown	251 (75.8)
Hepatotoxic drug use	
Statins	30 (9.1)
Others	12 (3.6)
No	289 (87.3)
Co-morbidities	
HTN	194 (58.4)
DM	156 (47.1)
Others	61 (18.4)
None	58 (17.5)
Vasopressor use	
Yes	35 (10.6)
No	296 (89.4)

HBsAg = hepatitis B surface antigen, HCV AB= anti-hepatitis C antibody, HTN = hypertension, DM =diabetes Mellitus

5.2 Liver biochemical test abnormalities at baseline

Baseline and in-hospital liver biochemical test frequencies are summarized in Table 2. Liver biochemical test abnormalities were common in patients admitted with COVID-19. On admission, abnormalities in ALT were present in 40.2% of patients. From these, 25.7%, 9.1% and 5.4% of patients had 1-2 times, 2-3 times and more than 3 times the UNL, respectively.

Baseline elevations in AST were present in 43.8% of patients. Elevation that was 1-2 times the UNL was seen in 28.1% of patients, while 2-3 times and more than 3 times the UNL was seen in 10% and 5.7% of patients, respectively.

Elevations in ALP at baseline were seen in 48.3% of patients, 36.9% of patients had elevation of ALP that was 1-2 times the UNL, while 9.7% and 1.8% of patients had elevations that were 2-3 times and more than 3 times the UNL, respectively.

Abnormalities in TB and DB were not as common as abnormalities in liver enzymes. TB elevation that was 1-2 times the UNL and more than 2 times the UNL was seen in 3.1% and 1.3% of patients, respectively. Serum albumin level wasn't determined in majority of patients (84%). From the available values in 53 patients, 75.5% of patients were found to have lower values than the lower normal limit (LNL).

The other important liver biochemical test is prothrombin time (PT), which was determined in 49.5% of patients. From those, 49.4% of patients had prolonged PT, while 50.6% of patients had normal values.

Table 2. Liver biochemical test profiles of patients at baseline and during hospitalization

Liver biochemical tests	No. (%) - Baseline	No. (%) during hospitalization
ALT		
$\leq 1 \times \text{UNL}$	198 (59.8)	99 (48.3)
$1-2 \times \text{UNL}$	85 (25.7)	41 (20.0)
$2-3 \times \text{UNL}$	30 (9.1)	28 (13.7)
$> 3 \times \text{UNL}$	18 (5.4)	37 (18.0)
N/A	0	126
AST		
$\leq 1 \times \text{UNL}$	186 (56.2)	67 (32.7)
$1-2 \times \text{UNL}$	93 (28.1)	78 (38.0)
$2-3 \times \text{UNL}$	33 (10.0)	31 (15.1)
$> 3 \times \text{UNL}$	19 (5.7)	29 (14.1)
N/A	0	126
ALP		
$\leq 1 \times \text{UNL}$	171 (51.7)	60 (28.8)
$1-2 \times \text{UNL}$	122 (36.9)	86 (41.3)
$2-3 \times \text{UNL}$	32 (9.7)	39 (19.0)
$> 3 \times \text{UNL}$	6 (1.8)	20 (9.6)
N/A	0	126
Total Bilirubin		
$\leq 1 \times \text{UNL}$	215 (95.6)	108 (92.3)
$1-2 \times \text{UNL}$	7 (3.1)	9 (7.7)
$> 2 \times \text{UNL}$	3 (1.3)	0 (0)
N/A	106	214
Direct Bilirubin		
$\leq 1 \times \text{UNL}$	213 (95.9)	106 (86.9)
$1-2 \times \text{UNL}$	6 (2.7)	13 (10.7)
$> 2 \times \text{UNL}$	3 (1.4)	3 (2.5)
N/A	109	209
Albumin		
$> 3.5 \text{ mg/dl}$	14 (24.6)	3 (16.7)
$3-3.5 \text{ mg/dl}$	7 (12.3)	6 (33.3)
$< 3 \text{ mg/dl}$	36 (63.2)	9 (50.0)
PT		
$\leq 14 \text{ seconds}$	83 (50.6)	37 (42.0)
$> 14 \text{ seconds}$	81 (49.4)	51 (58.0)

ALT= alanine aminotransferase, AST= aspartate aminotransferase, ALP= alkaline phosphatase, PT= prothrombin time

5.3 Liver biochemical test abnormalities after admission

During the course of hospitalization, elevations in ALT were seen in 51.7% of patients, 1-2 times, 2-3 times and more than 3 times the UNL was seen in 20.0%, 13.7% and 18.0% of patients, respectively. Abnormalities in values of AST after admission were seen more frequently than at baseline. Elevated values were seen in 67.2% of patients, 38.0% had elevation that was 1-2 times the UNL, while 15.1% and 14.1% of patients had 2-3 times and more than 3 times the UNL, respectively. ALP was elevated in 71.1% of patients, from which 41.3%, 20.2% and 9.6% had elevation that were 1-2 times, 2-3 times and more than 3 times the UNL, respectively.

During hospitalization, TB values were determined only in 117 (34.7%) of patients. From the available results, values that were 1-2 times the UNL were present in 7.7% of patients, while none of the patients had results that were more than 2 times the UNL. DB values after admission were also available for only 36.8% of patients. From those, 10.7% and 2.5% of patients had elevations that were 1-2 times and more than 2 times the UNL, respectively. After admission, only 88 (26.5%) of patients had PT values determined. From those, 58.0% of patients have prolonged values. Abdominal ultrasound was done only in 4 patients, evidence for cirrhosis was present in all 4 patients.

5.4 Association between liver biochemical test abnormalities and clinical outcomes

Association between liver biochemical test abnormalities and clinical outcomes is summarized in Table 3. On bivariate logistic regression age, disease severity on admission, presence of comorbid condition, vasopressor use and elevation of AST and ALP at baseline and during hospitalization were found be correlated with increased risk of mortality.

Multivariate binary logistic regression was done to determine whether the aforementioned variables were associated increased of death or not. The variables that were associated with increased risk of death disease severity on admission (OR = 5.864; 95% CI = 3.103-11.082; P < 0

.001), use of vasopressor (OR = 21.387; 95% CI = 4.125-110.882; $P < 0.001$) and presence of comorbid condition (OR = 223.655; 95% CI = 22.530-2220.166; $P < 0.001$). From the liver biochemical tests, the parameter that is found to be a predictor of increased risk of death are baseline elevation in ALT (OR = 3.271; 95% CI = 1.349-7.931; $P = 0.009$), in-hospital elevations in AST (OR = 2.192; 95% CI = 1.273-3.773; $P = 0.005$) and in hospital ALP (OR = 6.047; 95% CI = 2.863-12.773; $P < 0.001$).

On multivariate binary logistic regression, variables that were found to be predictors of increased risk of transfer to the ICU and requirement of MV were increased patient age (OR = 1.772; 95% CI = 1.179-2.661; $P = 0.006$) and severe disease on admission (OR = 6.100; 95% CI = 3.328-11.181; $P < 0.001$). Among liver biochemical tests only in hospital elevation in AST (OR = 2.030; 95% CI = 1.099-3.749; $P < 0.024$) was found to be predictor of increased risk of transfer to the ICU and requirement of MV.

Table 3. Association (Odds ratio) between baseline and in-hospital liver biochemical tests with patient death.

	Crude OR	95% CI	<i>P</i> value	Adjusted OR	95% CI	<i>P</i> value
Age in range (10 year increase)	1.710	1.448-2.019	.000	1.217	.798-1.857	.361
Female sex	.843	.527-1.349	.477			
Disease severity on admission	4.960	3.491-7.048	.000	5.864	3.103-11.082	<0.001
Co-morbidity	3.946	1.801-8.647	.001	223.655	22.530-2220.166	<0.001
Vasopressor use	9.363	4.195-20.897	.000	21.387	4.125-110.882	<0.001
Baseline values						
ALT (X times the UNL)	1.458	1.126-1.887	.004	3.271	1.349-7.931	.009
AST (X times the UNL)	1.606	1.241-2.078	<0.001	.207	0.086-0.498	.000
ALP (X times the UNL)	1.90	1.38-2.60	<0.001	.805	0.398-1.628	.546
In-hospital values						
ALT (X times the UNL)	1.136	.895-1.443	.295			

AST (X times the UNL)	1.739	1.303-2.320	<0.001	2.192	1.273-3.773	.005
ALP (X times the UNL)	3.049	2.094-4.440	<0.001	6.047	2.863-12.773	<0.001

ALT= alanine aminotransferase, AST= aspartate aminotransferase, ALP= alkaline phosphatase, UNL= upper normal limit

Table 4. Association (Odds ratio) between baseline and in-hospital liver biochemical tests with transfer to the ICU and requirement of MV.

	Crude OR	95% CI	P value	Adjusted OR	95% CI	P value
Age in range (10 year increase)	1.609	1.382-1.873	<0.001	1.772	1.179-2.661	0.006
Female sex	0.990	0.633-1.548	0.964			
Disease severity on admission	8.051	5.259-12.326	<0.001	6.100	3.328-11.181	<0.001
Co-morbidity	0.897	0.841-0.956	0.001	1.022	0.178-5.859	0.980
Vasopressor use	4.140	2.067-8.289	<0.001	1.673	0.622-4.502	0.308
Baseline						
ALT (X times the UNL)	1.491	1.153-1.930	0.002	1.021	0.440-2.367	0.962
AST (X times the UNL)	1.547	1.198-1.998	0.001	1.370	0.604-3.111	0.451
ALP (X times the UNL)	1.070	0.795-1.440	0.654			
In-hospital						
ALT (X times the UNL)	1.184	0.926-1.513	0.179	0.653	0.381-1.120	0.121
AST (X times the UNL)	1.765	1.306-2.384	<0.001	2.030	1.099-3.749	0.024
ALP (X times the UNL)	1.884	1.359-2.613	<0.001	1.586	0.920-2.732	0.097

ALT= alanine aminotransferase, AST= aspartate aminotransferase, ALP= alkaline phosphatase,

6. Discussion

Globally, COVID-19 is still an ongoing clinically problem. The respiratory manifestations aspect of the condition has been extensively studied. This study assessed one of the extra-pulmonary manifestations of COVID-19, which is liver injury. This study assessed the prevalence of abnormalities in baseline and in hospital ALT, AST and ALP, which are sensitive laboratory tests of liver injury. According to this study, abnormalities in ALT, AST and ALP at baseline were present in 40.2%, 43.8% and 48.3% of patients, respectively. Majority of the patients had minor elevations in these signs of liver injury. However, significant liver injury which is more than 3 times the UNL for ALT, AST and ALP was present in 5.4%, 5.7% and 1.8% of patients, respectively.

The prevalence of liver biochemical test abnormalities in this study was comparable with the other studies done during the course of the pandemic. A study from USA by Yadlapati et al. included 200 patients and reported elevations of AST, ALT and ALP 55%, 20% and 28% of cases, respectively (17). A study from Portugal also reported abnormalities in AST, ALT and ALP in 40.3%, 15.6% and 11.4% of patients, respectively (16).

Studies looking at the prevalence of abnormal liver biochemical tests among COVID-19 patients in Africa also reported less frequent results. A single retrospective study from Egypt reported elevation in 32.2% of patient for both AST and ALT (26). The lower prevalence of elevations in liver biochemical test abnormalities in this study may be explained by exclusion of patients that have underlying liver problems such as Hepatitis B, Hepatitis C, alcoholic liver disease and cirrhosis.

The prevalence of liver biochemical abnormalities in this study is higher than what's reported in a meta-analysis by Wijarnpreecha et al, which is a global study including 64 studies with 11,243 patients. The meta-analysis has found abnormalities of ALT, AST and ALP in 23.2%, 21.2% and 4.0%, respectively. The lower prevalence of abnormal liver chemistries in this meta-analysis could be attributed to the heterogeneity in the studies included in the meta-analysis (22).

Regardless of the variation in exact prevalence of liver biochemical test abnormalities, it can be concluded that liver is significantly involved in COVID-19 infection. The information in this study

is not complete with regard to other potential causes of liver damage, such as alcohol and hepatitis B. This makes it challenging to link every abnormality in the liver biochemical tests to the COVID-19 infection. The exact mechanism of how liver injury occurs remains to be exactly determined. The presumed mechanisms are direct cytopathic effect mediated via ACE2 receptors, inflammatory response mediated, hypoxia related and hepatotoxic effect of drugs (26).

Several studies were conducted to determine whether abnormalities in liver biochemical tests predispose to increased risk of adverse patient outcomes, which are transfer to the ICU, requirement of MV and death. These studies have found conflicting results. From the liver biochemical tests, elevation in in-hospital value of AST was consistently found to be a predictor of increased risk transfer to the ICU, mechanical ventilator requirement and death by several studies, including a study done in a makeshift COVID-19 treatment center in Ethiopia (8,15,20). Contrary to the above studies, a study from Netherlands which included 282 patients didn't find any association between elevation in liver biochemical test abnormalities and increased risk of adverse patient outcomes (22). This study has also found out elevations in baseline values of ALT as well as in-hospital elevations in AST and ALP during the course of admission to be associated with increased risk of death. In addition, elevations in values of AST during the course of admission is found to be associated with increased risk of transfer to the ICU and requirement of MV. These findings are largely consistent with the studies mentioned above. Reasons for discrepancies between this and other studies mentioned above with the results of the aforementioned study from Netherlands is not obvious.

Other important clinical parameters that significantly impacted adverse patient outcomes were older patient age, presence of comorbid condition, severe disease on admission and use of vasopressors.

Strength of the study

The major strength is filling the void of local data on how prevalent liver biochemical test abnormalities are among COVID-19 patients in our population. To our knowledge this is the first study that has aimed at this question in our country.

The other strength of this study is trying to assess over liver function rather than liver enzymes only. While liver enzymes could serve as a sensitive markers of liver injury, the parameters among liver biochemical tests such as albumin, bilirubin and prothrombin time provide important information in overall assessment of liver function.

These findings emphasize on the point COVID-19 should be consider as more of a systemic disease and importance of having a more comprehensive laboratory data in managing these patient population.

Limitation of the study

Due to the retrospective nature of the study, there were missing data that could have made the study more complete. Had they been determined in larger proportion of patients, serum albumin, prothrombin time, serum gamma glutamyl transferase and serum bilirubin could have made the interpretation of the results of the study more complete. The lack of complete data on serostatus of viral hepatitis and alcohol use history is a limitation of this study. Data on abdominal ultrasound to look for underlying liver disease which could impact liver biochemical tests is also lacking.

The underrepresentation of patients with prior underlying liver problems makes the assessment of impact of COVID-19 on already injured liver difficult.

The other limitation of the study is its single-center nature, which may limit its representativeness.

7. Conclusion

This study demonstrated how abnormalities in liver biochemical tests such as ALT, AST and ALP are common among patient admitted with COVID-19. Older age and severe disease on admission were found to be predictors of abnormalities of laboratory parameters of liver injury.

This study also showed baseline ALT and in-hospital elevation in serum ALP to be predictor of increased risk of death. In hospital elevation in AST was also found to be significant predictor of increased risk of transfer to the ICU, requirement of MV and death.

Recommendations

For treating physicians:

- Look actively for abnormal liver biochemical test results, as elevation in parameters such as in-hospital AST and ALP (both baseline and in-hospital elevations) could be an important predictor of mortality and increased risk of transfer to the ICU and requirement of MV.
- Develop a habit of a more comprehensive determination of liver biochemical tests including serum bilirubin, albumin and prothrombin time.
- Consider COVID-19 as a systemic disease which could involve multiple organ systems in different patterns.

For fellow researchers:

- Prospective study is needed with incorporation of all important parameters which otherwise could be missed in a retrospective study.

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Annexes

1. Information sheet

Research title: Magnitude of Liver Biochemical Test Abnormalities and its Effect on Patient Outcomes Among Patients Admitted to St. Paul's COVID-19 Treatment Center.

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: Aman Yesuf (MPH/Epidemiology)

Sponsor: St. Paul's Hospital Millennium Medical Collage

2 data collection check-list:

Chart number		
Age		
Sex	Male	Female

Disease severity on admission		Mild		Moderate		Severe		Critical	
Duration of hospital stay									
Date of Diagnosis									
Physician diagnosed liver cirrhosis		Yes				No			
Serostatus for viral hepatitis		HBsAg				Anti HCV ab			
History of alcohol use disorder		Yes,				No			
		If yes, Amount in grams							
History of potentially hepatotoxic drug use		Yes				No			
		If yes, mention the drug							
Co-morbidity		DM	HTN	IHD	CHF	COPD	Other, specify		
Blood pressure									
Vasopressor use		Yes				No			
		If yes, specify							
Liver biochemical test results		Base line		Peak (nadir)		Discharge			
		Value	X×UNL	Value	X×UNL	Value	X×UNL		
	ALT								
	AST								
	ALP								
	TB								
	DB								
	Albumin								
	PT								
Patient outcomes		Improved and discharged		Transferred to the ICU	Required mechanical ventilation	Death			

3. Declaration

I the undersigned resident declare that this thesis is my original work, in partial fulfillment of the requirement for certificate of specialty in internal medicine. I also declare that it has never been

presented in this or any higher institution and all the resources and materials used in the research work have duly acknowledged.

Name of the Resident: _____

Signature: _____

Date: _____

Approval of Advisors

Name of Public Health Advisor: _____

Signature: _____

Date: _____

Name of Clinical Advisor: _____

Signature: _____

Date: _____