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Original Article

Elevated Liver Enzymes as a Predictor of acute kidney injury in hospitalized patients with COVID-19

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Abstract

Background :A higher rate of abnormal LFTs and AKI is linked to the new coronavirus infection (COVID-19). The prognosis of COVID-19-positive hospitalized patients is still unknown, nevertheless.

Purpose: This study's objective is to examine the prevalence of liver injury at admission and how it affects AKI development, COVID-19 severity, and outcomes.

Materials and methods: 80 hospitalized COVID-19-positive patients were split into three subgroups based on the degree of their infection: mild, moderate, and severe. All patients were investigated by a full lab at admission and during admission and followed up for occurrence of liver injury or kidney injury.

Results : At admission, 42.5% (34) of the patients had high levels of aminotransferases. in the register, AKI was seen in 22.5% of cases. ICU patients had AKI more frequently than non-ICU patients did (61.1% vs. 38.9%, p.001). In-hospital mortality was substantially greater in the AKI group (patients with AKI had a mortality rate of 50% vs. 9.67%, respectively, p.001) than in patients who did not develop AKI. ICU patients had a greater incidence of increased AST and/or ALT than non-ICU patients (61.8% Vs 38.2%, p.001). When compared to patients without elevated aminotransferases upon admission, patients with elevated aminotransferases developed AKI at a greater rate (32.4% vs. 15.2%, p=0.005) and died in the hospital at a higher rate (26.5% vs. 13%, p=0.005).

Conclusion: Elevated AST and/or ALT levels at admission were independent predictors for the development of AKI and in-hospital death.

Keywords: COVID-19, AKI, Liver injury.

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Introduction

The WHO was notified by the China Health Authority towards the end of 2019 that many cases of pneumonia of unknown origin had appeared in Wuhan City in central China. Cases have been documented since the first week of December, and it has been discovered that many of the patients have ties to the Huanan Seafood Wholesale Market or have lived nearby or worked there in the past.[1]

The number of cases started to increase rapidly, some of which didn't have any relation to the seafood market, referring to the fact that human-to-human transmission is possible.[2]

On January 30, the World Health Organization (WHO) classified the SARS-CoV-2 outbreak as a PHEIC (Public Health Emergency of International Concern).[3]

Except for Antarctica, there have been about 6 million confirmed cases of COVID-19 infection to date. [4]

The (SARS-CoV-2) infection, which likewise has substantial morbidity and fatality rates, affects numerous organ systems[1]. Between 5% and 14% of SARS-CoV-2 patients develop critical illness.[5] Since respiratory tract infection is the typical first sign of coronavirus disease 2019 (COVID-19), it can be harmful to any organ system. Therefore, to guide proper early management and optimize outcomes, doctors should rapidly look for multi-organ involvement. [4]

The kidney is the most vulnerable organ to COVID-19 among the damaged organs. The angiotensin-converting enzyme 2 (ACE2) receptor is shared by SARS-CoV-2 and other organs (including the lung, heart, and kidney). [4]

To start the infection process, SARS-CoV-2 binds to the membrane's active receptors on a host cell. When COVID-19 patients were examined postmortem, different amounts of acute tubular necrosis, lymphocyte infiltration, and viral RNA were discovered., suggesting a direct invasion of renal tubules. Acute kidney injury (AKI) can also happen due to a number of many processes than the virus itself, including sepsis-induced acute tubular necrosis, hypoxia, hypo-perfusion, rhabdomyolysis, nephrotoxic medications, and others.[4]

AKI is a common COVID-19 infection complication in critically ill patients, occurring in roughly 23% to 43% of cases overall, and was closely associated with negative clinical outcomes.[4] Liver function tests (LFTs) in COVID-19 patients are elevated by 14% to 75%. According to numerous studies, individuals have severe COVID-19 pneumonia and those who passed away from the infection had greater levels of liver transaminases. [6]

The clinical importance of LFT abnormalities has been disputed, with some research finding a link to the severity of COVID-19 pneumonia and others nt. [7] Early research indicates that the novel coronavirus infection (COVID-19) is linked to an increased incidence of abnormal LFTs and AKI. The results of hospitalized patients with COVID-19 and elevated AST and ALT levels upon admission, as well as their associations with AKI, are yet unknown, however.[7]

Patients and methods

Patients' selection

Our study enrolled 80 patients who were admitted to the isolation department at Sohag University hospitals

Inclusion criteria

All patients in the Sohag University Hospital who have tested positive for COVID-19 and are Older than 18 years old. (PCR from nasopharyngeal or oropharyngeal samples used for confirmation).

Exclusion criteria

Patients whose ages are <18 years old.

Methods

A prospective, observational cohort study of 80 COVID-19 hospital patients at Sohag University Hospital was conducted between December 2021 and April 2022. All participants had given their informed consent written form before the study began.

The standard laboratory parameters were measured after a thorough physical examination. At the time of admission, demographic, clinical, radiological, and laboratory data were gathered. Medical history details, such as comorbidities, infection symptoms, and medications taken within the 14 days before admission will be gathered. Vital indicators, including heart rate, blood pressure, body temperature, and pulse oxygen saturation (SatO2), were gathered. The laboratory tests performed at admission and one week later to look at the relationship between illness severity and AKI included alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, total protein, serum creatinine, blood urea nitrogen, serum electrolytes, and bilirubin.

Mild, moderate, and severe COVID-19 disease were classified into three categories of individuals. The following criteria will be used to determine whether a patient has a severe case of pneumonia: respiratory rate >30 breaths/min; severe respiratory distress; or SpO2 less than 90% on room air. These patients must also have clinical signs of pneumonia (fever, cough, dyspnea, rapid breathing) in addition to one of the other criteria. Patients with pneumonia who don't match the severity criteria mentioned above will be classified as having moderate instances of pneumonia.

Clinical outcomes

This study's goal is to examine the prevalence of liver injury upon admission, how it contributes to

the development of acute kidney injury (AKI), and how these factors relate to the severity of COVID-19 infection.

Statistical analysis of data

Data was gathered, coded, and entered into a spreadsheet using Microsoft Excel 2016 for Windows, part of the Microsoft Office suite, 2016 of Microsoft Corporation, United States. SPSS, IBM's 21st edition statistical package for social sciences software, Significant was defined as a statistical value below 0.05.

Analytic statistics

Chi-square test, which is employed to investigate the relationship between two qualitative variables.
Unpaired student t-test; applied to compare two groups with quantitative variables that are normally distributed Mann-Whitney test is used to compare two groups with quantitative variables that have an irregular distribution.

Results

Demographic characteristics of the study population

The study included 80 patients hospitalized in the isolation sector at Sohag University hospital, Patients' ages ranged from 20 to 91 years, with a mean of 64 years and a standard deviation of 14.8 years. The gender of patients included was 62% males and 38% females, most of the patients were from Rural areas (88.8%) Vs 11.2% from Urban areas. 51.2% of patients with hypertension, 25% of patients with Diabetes Mellitus, 7.5 % of patients with COPD, 6.3% of patients with CKD and 5% of patients with CLD. The most common symptoms of COVID-19 were Fever ≥38°C (86.25%), 47.5% presented with dyspnea, 58.75% presented with cough, 27.5% presented with fatigue, 12.5% presented with diarrhea, 10% presented with DCL. These signs and symptoms are similar to Fever, cough, and myalgia or weariness were the three symptoms that first 41 patients most frequently experienced, respectively (98%, 76%, and 44%). Less frequently occurring symptoms were sputum production, headache, hemoptysis, and diarrhea (28%, 8%,5% , and 3%) respectively. Additionally, dyspnea occurred in over 50% of the patients. [7]

Seven days with an IQR (3-10) separated the onset of symptoms from hospital admission.

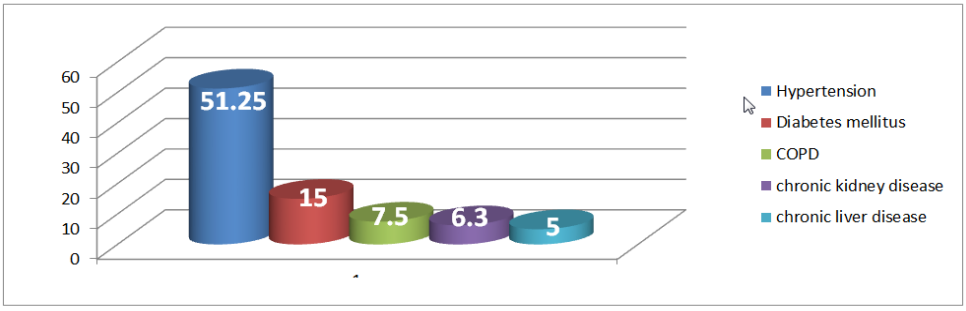

Fig. 1: Percentage of comorbid conditions among included patients

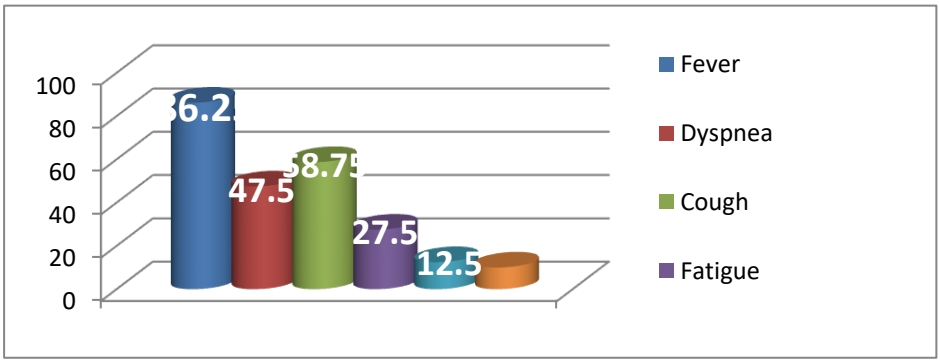

Fig. 2 : Percentage of different presentations among included patients

Table1: Demographic data of included patients

Variable	N 80
Age (years) Min- Max Mean (years)± Sd	 20 – 91 64 ± 14.8
Gender (male) – n (%) (female) –n (%)	 50 – (62%) 30 – (38%)
Residency (Rural) – n (%) (Urban) – n (%)	 71 – (88.8%) 9 – (11.2 %)
Hypertension- (%)	51.2%
Diabetes – (%)	25%
COPD – (%)	7.5%
CKD – (%)	6.3%
CLD –(%)	5%

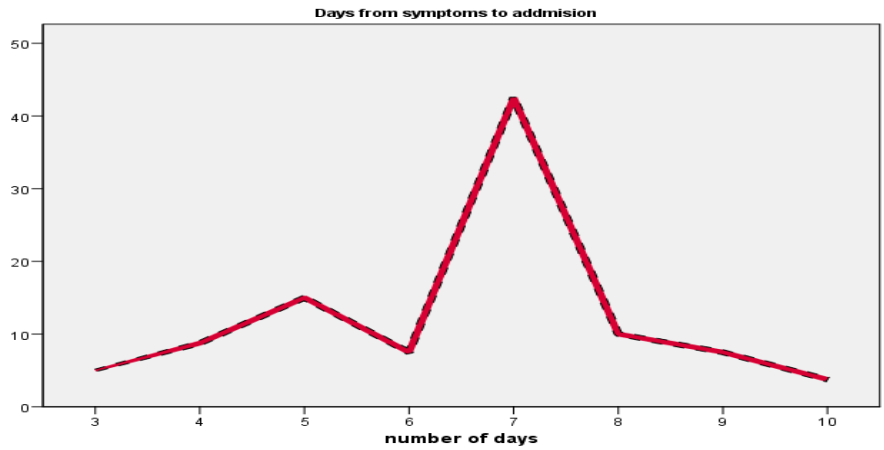

Fig. 3: Days from the appearance of symptoms to admission

Outcomes 34 patients which present (42.5%) out of the total patients included developed abnormal elevation in Aminotransferases, Elevated AST was more common than Elevated ALT, (91.2% Vs 55.9% respectively) out of the 34 patients with increased LFTs, elevation in T.Bil. represents only 17.6% out of patients of with increased LFTs. There were about 18 patients who developed AKI which represents about 22.5% of the total patients included, AKI was more common in the group of Abnormal LFTs (11 patients (32.4%) Vs 7 patients (15.2%)) with a P.value ≤ .005. Patients with Elevated Serum creatinine have higher rates of ICU admission. AKI occurred more frequently in ICU patients compared to non-ICU patients (61.1% Vs 12.5%, p.001). In-hospital mortality was noticeably greater in the AKI group (patients with and without AKI development, respectively, had mortality rates of 50% Vs 9.67%, p.001). When comparing patients with and without the development of abnormal LFTs, the in-hospital mortality was considerably greater in the group with abnormal LFTs (26.5% vs. 13%, respectively; p.001).

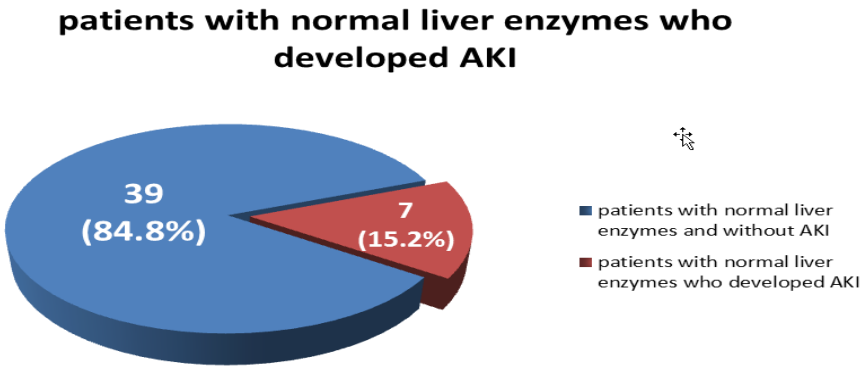

Fig. 4: AKI prevalence in patients with normal liver enzymes

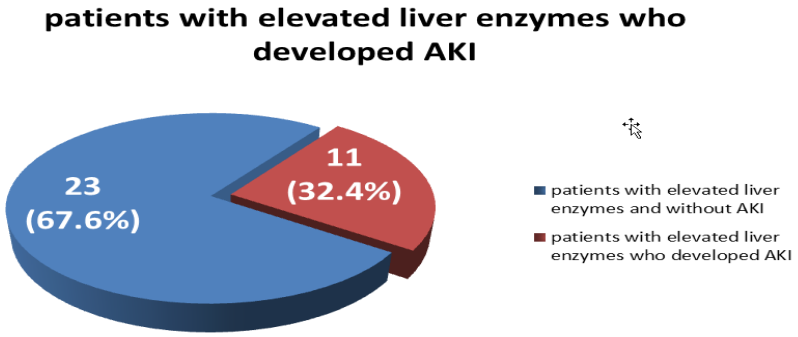

Fig. 5: patients with elevated liver enzymes who developed AKI

Table 3: Different outcomes of included patients

Variable	ICU admission (N 24)	Non-ICU admission (N 56)	In-hospital mortality (N 15)	P.Value
Patients with↑↑Serum creatinine (N 18)	11 (61.1%)	7 (38.9%)	9(50%)	≤.005
Patients with Abnormal LFTs(N 34)	21 (61.8%)	13(38.2%)	9(26.5%)	≤.005
Patients with Normal Serum creatinine (N 62)	13(21%)	49(87.5%)	6(9.67%)	≤.001
Patients with Normal liver function tests (N46)	3(6.5%)	43(76.7%)	6(13%)	≤.001

Discussion

Patients with COVID-19 have frequently shown abnormal LFTs, although the clinical importance and the exact cause of liver damage are yet unknown. The term "COVID-19- associated liver injury" refers to any liver damage that develops in COVID-19 patients throughout their illness and treatment, whether or not they already have liver disease. [8,9]

This covers a wide range of potential pathomechanisms, including right heart failure, endo-thelitis or cardiac congestion from right heart failure, drug-induced liver injury, immune-mediated liver damage caused by COVID-19's severe inflammatory response/systemic inflammatory response syndrome (SIRS), hypoxic changes brought on by respiratory failure, vascular changes brought on by coagulopathy, immune-mediated liver damage caused by COVID-19's severe inflammatory response, and exacerbation.[10]

This covers a wide range of potential pathome-chanisms, including right heart failure, endo-thelitis or cardiac congestion from right heart failure, drug-induced liver injury, immune-mediated liver damage caused by COVID-19's severe inflamm-atory response/systemic inflammatory response syndrome (SIRS), hypoxic changes brought on by respiratory failure, vascular changes brought on by coagulopathy, immune- mediated liver damage caused by COVID-19's severe inflammatory response, and exacerbation Between 2.5% and 76.3% of COVID-19 patients have increased liver transaminases (ALT and AST).[11]

The pooled rates for AST and ALT over the reference range were, respectively, 20%-22.5% and 14.6%-20.1% in a recent meta-analysis.[11] Up to 35% of the time, these anomalies are connected to mildly elevated total bilirubin levels.

While increases in the cholestatic liver enzymes gamma glutamyl-transferase (γGT) and alkaline phosphatase (ALP) were once thought to be rather uncommon.[12]

There were increased levels of ALP and γGT in 6.1% and 21.1%, respectively, of COVID-19 patients. [12] Most of these studies lacked the focus necessary to evaluate LFT abnormalities in COVID-19 patients and neglected to account for potential confounders such as prior liver illness and/or concurrent therapies. Does the clinical course of patients with abnormal LFTs at admission differ from those with normal LFTs? is a concern that other researchers thought of aberrant LFTs during the stay as a whole. Here, we demonstrated that 42.5% of COVID-19 patients with hospital admissions had abnormal LFTs and that these abnormalities are independently related to a composite outcome of death or transfer to the intensive care unit.

Therefore, on a clinical level, aberrant LFTs at admission should be seen as a sign of severe disease, prompting doctors to closely monitor these patients and prepare for a quick worsening of their clinical symptoms. This may foresee the prospective need for ICU beds, which is pertinent given the scarcity that was seen in some areas during the COVID-19 pandemic.[13] In our study, A total of 80 patients were enrolled, of whom 51.2% had hypertension, 25% had diabetes mellitus, 7.5% had COPD, 6.3% had CKD, and 5% had CLD. ICU admissions accounted for 30% (24) of all patients' admissions, and deaths accounted for 18.75% (15) of all patients. Elevated AST was more prevalent than ALT at the time of admission, accounting for 91.2% of all patients with abnormal LFTs compared to 55.9% (N 31) of all patients with abnormal LFTs. At admission, 42.5% (34) of all patients had abnormal levels of aminotransferases.

In 65% of patients with abnormal LFTs, the alteration of LFTs was below two times ULN, between two and three times ULN in 22%, and above three times ULN in 13% of patients.

Table 3: Elevated liver enzymes among included patients

Variable	Number	The Percentage of abnormal LFTs group	The Percentage of Total patients included	P value
AST	31	91.2%	38.8%	≤ .001
ALT	19	55.9%	23.8%	≤ .001
T.Bil	6	17.6%	7.5%	≤ .001
Total number of elevated LFTs	34	100%	42.5%	

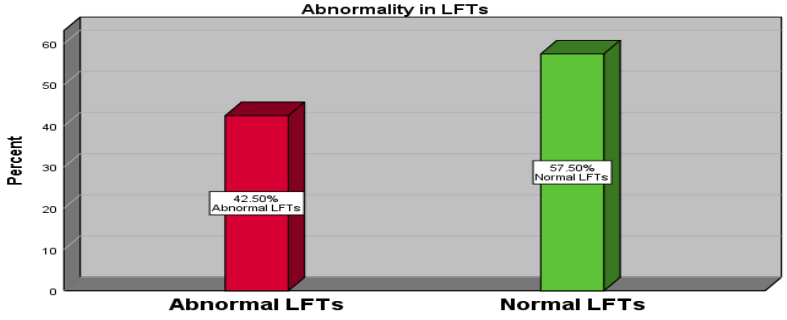

Fig 6 : Percentage of Elevated liver enzymes among included patients

The AKI incidence in the register was 22.5%. The prevalence of AKI in COVID-19 has been the subject of numerous investigations, with variable rates of Occurrence, which may be related to the variations in patient severity and baseline circumstances between studies[14]

More proof that SARS-CoV-2 can infect the kidney directly has been presented by recent clinical trials and autopsy. The published findings indicate that Viral replication in

In another study, kidney abnormalities were examined in 26 COVID-19 patient corpses, nine of which revealed clinical signs of kidney impairment.[15]

Collapsing glomerulopathy was seen in individuals with COVID-19 who underwent AKI biopsy, and over 90% of the GBM had considerable foot process effacement, according to an ultrastructural study of the GBM. The discovery of viral particles in podocytes indicates that SARS-CoV-2 can directly target these cells and result in collapsed glomerulopathy.[16]

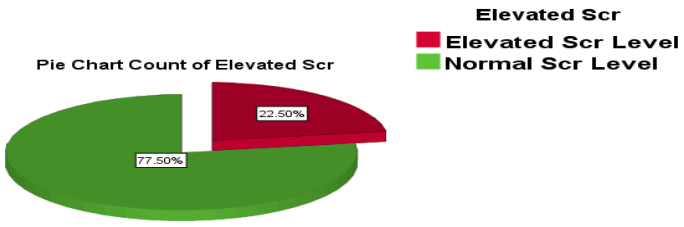

Fig. 7 : Pie chart showing the percentage of AKI among patients included

AKI was present more in ICU patients than in non-ICU patients (61.1% vs. 38.9%, p=.001). In-hospital mortality was noticeably greater in the AKI group (patients with and without AKI development, respectively, had mortality rates of 50% Vs 9.67%, p=.001). ICU patients had a greater rate of increased

AST and/or ALT than non-ICU patients (61.8% Vs 38.2%, p.001). When compared to patients without elevated aminotransferases upon admission, patients with elevated aminotransferases developed AKI at a greater rate (32.4% vs. 15.2%, p=.005) and died in the hospital at a higher rate (26.5% vs. 13%, p=.005).

Hepatic involvement in COVID-19-infected patients has been frequently reported reaching up to half of the infected cases. Hepatic injury is usually mild and transit with few exceptions.[17]

Elevated ALT and/or AST upon admission were independent predictors for the development of AKI and in-hospital death.

Conclusion

The development of AKI and the severity of the illness were connected to elevated levels of aminotransferases at admission, and they are predictors of AKI development and in-hospital death in this cohort. We showed that 42.5% of patients with COVID-19, of whom 32.3% had increased serum creatinine levels, had abnormal LFTs upon admission.

A composite end point of death or transfer to the intensive care unit (ICU) is connected by these abnormalities on an individual basis.

Accordingly, abnormal LFTs at admission and any increase in serum creatinine should be viewed on a clinical basis as indicators of the severity of the disease. This should prompt doctors to closely monitor these patients and be ready for any potential rapid deterioration of their clinical

conditions. This may foresee the prospective need for ICU beds, which is pertinent given the scarcity that was seen in some areas during the COVID-19 epidemic.

Limitations of the study

There were some limitations of the study such as the small number of patients and the need for longer follow-up as AKI may take a longer time for returning to baseline and some patients had started some medications before admission that may have nephrotoxicity or hepatotoxicity adverse effects. Also, patients included in the study were at different stages of the disease, different ages with wide range variability.

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