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Study on liver disease in COVID-19 and its association with COVID disease severity and mortality

Basavaraj V. Savadi[1], B.M. Rashmi[2], Raveendra D. Totad[3] and Shrish Patil[4*]

[1]Department of Biochemistry, Basaveshwara Medical College & Hospital, S.J.M Campus, N.H.4 (48) Bypass Road, Chitradurga-577502, Karnataka, India, [2]Department of Community Medicine, Basaveshwara Medical College & Hospital, S.J.M Campus, N.H.4 (48) Bypass Road, Chitradurga, Karnataka, India, [3]Department of Microbiology, Al Ameen Medical College and Hospital, Athani Road, Vijayapur-586108, Karnataka, India and [4]Department of Anatomy, Basaveshwara Medical College & Hospital, S.J.M Campus, N.H.4 (48) Bypass Road, Chitradurga-577502, Karnataka, India

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Abstract: *Background:* COVID-19, a respiratory illness caused by SARS-CoV-2virus, has been implicated in hepatic injury. Abnormal liver function tests are found in 14-53% of COVID-19 cases. *Objectives:* Present study was conducted to study the spectrum of hepatic injury and its association with COVID-19 disease severity among patients aged ≥18 years treated at a tertiary care hospital in Central Karnataka. *Methods:* It was a retrospective study based on review of medical records of diagnosed COVID-19 patients aged ≥18 years treated on in-patient basis at a tertiary care hospital. Patients' COVID disease severity and in-hospital outcomes were noted. Presence of COVID associated hepatic injury such as hepatocellular, cholestatic and mixed type liver injuries were documented. *Results:* Severe COVID-19 disease and death rates were significantly higher among patients with COVID-19 associated Hepatic injury' (73.1%, 46.3% respectively). Inflammatory markers such as D-dimer, CRP, LDH and Ferritin were significantly elevated in 'COVID-19 associated Hepatic injury (Q2: 442ng/ml, 07mg/dl, 588U/L, 838ng/ml respectively). *Conclusion:* Hepatic injuries in COVID patients are due to SARS-CoV-2 associated inflammation and were significantly associated with severe COVID disease and mortality. For physicians at Emergency Department, it gives crucial information to decide whether patient requires hospital admission or scheduled outpatient re-evaluation.

Keywords: Liver Disease, Severe COVID-19 Disease, Mortality, COVID-19 Associated Hepatic Injury.

Introduction

The corona virus disease 2019 (COVID-19) is a respiratory illness caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). The World Health Organization declared COVID-19 as a pandemic in March 2020. The disease has affected millions of people worldwide with mortality rates of 3.5%-61% [1-4].

First COVID wave reached its peak in September 2020, which was followed by a second wave. Nearly six months after the peak of first wave. Compared to the first wave, the second wave had severe consequences in terms of number of severe cases and mortality. From 11th March 2020 until 1stMarch 2023, India has witnessed more than 40 million COVID-19 cases, 3.5million (8.5%) hospitalizations and 2.9 lakh (0.7%) deaths [1-4].

SARS-CoV-2 virus is primarily responsible for respiratory illness that can end up with multiorgan failure and death. SARS-CoV-2 utilizes the angiotensin - converting enzyme-2 (ACE-2) receptor for cellular entry, which is primarily expressed in type II alveolar epithelial cells and bile duct cells [4-9].

As per the scientific literature, SARS-CoV-2 has been implicated in hepatic injury. Abnormal liver function tests have been documented in 14-53% of COVID-19 cases. Hepatic dysfunction was found to be associated with severe COVID disease [4-9]. In a study done by Huang C, *et al*., presence of moderate microvascular steatosis and mild lobular inflammation were documented in liver biopsy specimen of COVID-19 patients [6]. With this background, we conducted the

present study with following *aim and objectives:* To study the spectrum of hepatic injury and its association with COVID-19 disease severity among patients aged 18 years and above treated at a tertiary care hospital in Central Karnataka.

Material and Methods

After obtaining institutional ethics committee clearance, present study was conducted at Basaveshwara Medical College & Hospital, Chitradurga, located in Central Karnataka. It was a retrospective study based on review of in-patient medical records of all COVID-19 infected patients aged 18 years and above, treated at Basaveshwara Medical College & Hospital between 1st March 2021 and December 2022. COVID-19 disease was diagnosed as per the Government of India guidelines. Those patients who got discharged against medical advice and those referred to higher centres were excluded from the study.

Those patients who fulfilled study eligibility criteria were considered for the study. In-Patient (IP) medical records were reviewed information were collected in a pre-designed semi-structured proforma. Information included patient's socio-demographic profile, medical history, pre-existing comorbid conditions, baseline clinical, laboratory and radiological parameters at the time of admission. Patients' clinical severity grade classification (mild, moderate or severe grade disease) were done according to guidelines by the Ministry of Health & Family Welfare, Government of India, given in the 'Clinical guidance for management of adult COVID-19 patients' [10].

a. *Mild disease:* Upper respiratory tract symptoms and/or fever without shortness of breath or hypoxia with SpO2: ≥93%;
b. *Moderate disease* included any one of the following:
    1. Respiratory rate > 24/min, breathlessness
    2. SpO2: 90% to ≤ 93% on room air;
c. *Severe disease* included any one of the following:
    1. Respiratory rate >30/min, breathlessness
    2. SpO2 < 90% on room air.

As per the baseline Liver Function Test (LFT) results, patients were categorised as having 'COVID-19 associated Hepatic injury' if they had any 'one' of the following conditions [11-12]: ALT or AST exceeding 3 times the upper limit of the normal value and/or ALP, GGT or TBIL exceeding 2 times the upper limit of the normal value.

These 'COVID-19 associated Hepatic injury' were further classified as hepatocellular, cholestatic and mixed type. Patients were diagnosed to be having 'Hepatocellular Liver injury' if they had elevated ALT and/or AST more than 3 times the upper limit of normal (ULN). Patients were diagnosed to be having 'Cholestatic Liver injury' if they had elevated ALP or AST more than 2 times the upper limit of normal (ULN). Patients were diagnosed to be having 'Mixed Type of Liver injury' when they had both elevated ALT and/or AST more than 3 times the upper limit of normal (ULN) and elevated ALP or GGT more than 2 times the upper limit of normal (ULN) [11-12].

Followed by this, other information that were collected included patient's clinical course during hospital stay like treatment history, whether they were treated at intensive care units, their disease outcomes (cured or worsened) including data about in-hospital deaths.

Statistical Analysis: Data was compiled in Microsoft excel worksheet and analysed using SPSS software v:16 (Statistical Package for the Social Sciences version 16, SPSS Inc., SPSS for Windows, Chicago, USA). All characteristics were summarized descriptively. For continuous variables, summary statistics of N, mean, standard deviation about the arithmetic mean were used and Categorical data were represented as frequency and percentages.

To test significance of associations, chi-square tests (for categorical data), independent student t' test (for continuous independent variables with parametric distribution), Mann Whitney U test (for continuous variables with non-parametric distribution) were applied. Those associations with p-value of <0.05 were considered to be statistically significant at 95% confidence interval.

Results

The present study included 358 COVID-19 patients who fulfilled the study eligibility criteria. Among them, the prevalence of diabetes mellitus and hypertension were 26.8% (96 diabetics out of 358 COVID-19 patients) and 18.2% (65/358) respectively. Other comorbidities found were cardiovascular diseases 6.1% (09/358), asthma 1.6% (06/358) and hypothyroidism 2.2% (8/358) (Table 1).

COVID-19 patients were categorised according to their liver function tests into those with normal hepatic function tests and patients with 'COVID-19 associated Hepatic injury'. There were 18.7% patients with 'COVID-19 associated Hepatic injury'. A significant majority of males (24.3%) had 'COVID-19 associated Hepatic injury' compared to females (8.6%). The average duration of hospital stay (9.6±6.8days) and average baseline scores of chest tomography (CT) (16.6±5.9) were significantly higher among patients with 'COVID-19 associated Hepatic injury compared to that among COVID patients with normal LFT. (7.8±4.04 days and 14.5±5.7 respectively) (Table 1).

Severe COVID-19 disease and death rates were significantly higher among patients with 'COVID-19 associated Hepatic injury' (73.1%% and 46.3% respectively) compared to the severe COVID disease and death rates among patients with normal LFT (46.7% and 21.0% respectively) (Table 2).

Table-1: Distribution of clinical presentation and comorbidities according to 'COVID-19 associated Hepatic injury'

Characteristics	Normal LFT n (%)	'COVID-19 associated Hepatic injury' n (%)	Total n (%)	p-value
Sex				
Males n (%)	174(75.7%)	56(24.3%)	230 (100%)	0.001
Females n (%)	117(91.4%)	11(8.6%)	128 (100%)	
Duration of hospital stay (in days) (Mean ± SD)	7.8±4.04	9.6±6.8	8.2±4.7	0.005
CT severity score(Mean ± SD)	14.5±5.7	16.6±5.9	14.9±5.7	0.030
CORAD score(Mean ± SD)	4.8±0.7	4.9±0.5	4.8±0.7	0.327
SPO2 (%)	86.5±10.4	79.0±15.2	85.06±10.8	0.001
Pre-existing Co-morbid Conditions				
Diabetes Mellitus (%)	79(82.3%)	17(17.7%)	96(100%)	0.768
Hypertension n (%)	56(86.2%)	09(13.8%)	65 (100%)	0.266
Cardiovascular disease n (%)	09(0%)	0(0%)	09 (100%)	0.003
Asthma / COPD	06(100.0%)	0(0%)	06(100%)	0.236
Hypothyroidism n (%)	07(87.5%)	01(12.5%)	8 (100%)	0.649
Total	291 (81.3%)	67 (18.7%)	358 (100.0%)	

Table-2: Association of COVID-19 disease severity and mortality rates with abnormal liver function tests

Characteristics	Normal LFT n (%)	'COVID-19 associated Hepatic injury' n (%)	Total n (%)	p-value
Disease Severity				
Mild	47(16.2%)	05(7.5%)	52 (14.5%)	0.001
Moderate	108(37.1%)	13(19.4%)	121(33.8%)	
Severe	136(46.7%)	49(73.1%)	185(33.8%)	
Clinical Outcome				
Survivor	230(79.0%)	36(53.7%)	266 (74.3%)	0.001
Deceased	61(21.0%)	67(46.3%)	92(25.7%)	
Total	291 (81.3%)	67 (18.7%)	358 (100.0%)	

Table 3 enumerates various treatments provided to COVID-19 patients at Basaveshwara hospital. Higher proportion of COVID patients with 'COVID-19 associated Hepatic injury' required intensive medical care (44.8%) compared that of COVID patients with normal LFT (26.5%) and this association was found to be statistically significant. Corticosteroids (87.2%), low molecular heparin (82.4%) were mainstay of treatment for the patients. Remdesevir was given to 67.3% patients. Oxygen supplementation by non-rebreather mask (NRBM)/ BiPAP was provided to 32.1% patients. It was found that a significant majority of patients with COVID-19 associated Hepatic injury' received low molecular heparin (92.5%) and Remdesevir antiviral drug (79.1%) when compared to COVID patients with normal LFT (85.6%, 80.1%, 64.6% respectively).

Table-3: The distribution of treatment modalities according to 'COVID-19 associated Hepatic injury'

Treatment History	Normal LFT n (%)	'COVID-19 associated Hepatic injury' n (%)	Total n (%)	p-value
ICU Admission	77(26.5%)	30(44.8%)	107(29.9%)	0.003
Steroids	249(85.6%)	63(94.0%)	312 (87.2%)	0.062
LMW Hep	233(80.1%)	62(92.5%)	295 (82.4%)	0.016
Remdesevir	188(64.6%)	53(79.1%)	241 (67.3%)	0.023
NRBM/BiPAP	88(30.2%)	27(40.3%)	115 (32.1%)	0.112
Total	283 (100.0%)	75 (100.0%)	358 (100.0%)	

*LMW: Low Molecular Weight Heparin; BiPAP: Bilevel Positive Airway Pressure; NRBM: Non-rebreather mask (NRBM)

Table 4 enumerates distribution of median levels of various inflammatory markers among COVID-19 patients according to 'COVID-19 associated Hepatic injury'. It was found that there was a significant increase in the levels of D-dimer, C-reactive protein, Lactate dehydrogenase and Ferritin in 'COVID-19 associated Hepatic injury (Q2: 442ng/ml, 07mg/dl, 588U/L, 838ng respectively) compared to that among COVID patients with normal LFT (Q2: 310ng/ml, 05mg/dl, 579.9U/L, 780.9 ng/ml respectively).

Table-4: The distribution of inflammatory markers according to 'COVID-19 associated Hepatic injury'

Biochemical parameters	Normal LFT Median (Q1, Q3)	'COVID-19 associated Hepatic injury' Median (Q1, Q3)	Total Median (Q1, Q3)	p-value
D-dimer (ng/ml)	310(193,651)	442(226,892)	324.5(197.5,674.0)	0.020
CRP (mg/dl)	05(02,07)	07(03,09)	5.0(2.0,8.0)	0.001
LDH (U/L)	579.9(361.2,591.9)	588.3(515.0,600.8)	580.6(366.4,593.0)	0.004
Ferritin (ng/ml)	780.9(726.6,850.1)	838.4(735.0,864.4)	783.3(712.3,852.4)	0.007

Patients with 'COVID-19 associated Hepatic injury' were further classified as 'Hepatocellular Liver injury' if they had elevated ALT and/or AST more than 3 times the upper limit of normal (ULN); 'Cholestatic Liver injury' if they had elevated ALP or AST more than 2 times the upper limit of normal (ULN); 'Mixed Type of Liver injury' when they had both elevated ALT and/or AST more than 3 times the upper limit of normal (ULN) and elevated ALP or GGT more than 2 times the upper limit of normal (ULN). The rates of severe COVID-19 disease and mortality were estimated for the various types of liver injuries. In the present study, a significant majority of COVID-19 patients with Hepatocellular, Cholestatic and Mixed Liver injuries (88%, 69% and 81.2% respectively) had severe COVID disease

compared to those without Hepatocellular, Cholestatic and Mixed Liver injuries (48.9%, 48.3% and 50.3% respectively) (Table-5). Similarly, COVID-19 mortality rates were significantly higher among patients with Hepatocellular injury (56.0%) and Cholestatic Injury (39.7%) compared to patients without these liver injuries (23.4%, 23.0% respectively). Death rates were also higher among patients with Mixed Liver injury (37.5%) compared to those without the mixed liver injury (25.1%), this association was not statistically significant (Table 5).

Table-5: The distribution of rates severe COVID disease and mortality according to the status of hepatic dysfunction

Types of 'COVID-19 associated Hepatic injury'	Status of Hepatic Injury	Total number of patients	Clinical Severity			Mortality		
			Non-severe	Severe	p-value	Survivor	Deceased	p-value
Hepatocellular injury	Present	25	03(12.0%)	22(88.0%)	p: 0.001	11(44.0%)	14(56.0%)	p: 0.001
	Absent	333	170(51.1%)	163(48.9%)		255(76.6%)	78(23.4%)	
Cholestatic injury	Present	58	18(31.0%)	40(69.0%)	p: 0.004	35(60.3%)	23(39.7%)	p: 0.008
	Absent	300	155(51.7%)	145(48.3%)		231(77.0%)	69(23.0%)	
Mixed Liver injury	Present	16	03(18.8%)	13(81.2%)	p:0.015	10(62.5%)	06(37.5%)	p: 0.382
	Absent	342	170(49.7%)	172(50.3%)		256(74.9%)	86(25.1%)	
Total		358	89(100.0%)	105(100.0%)		136(100.0%)	58(100.0%)	

Discussion

This retrospective study conducted on COVID-19 patients treated on in-patient basis at a tertiary care hospital in Central Karnataka has shown an overall prevalence of 18.7% for COVID-19 associated liver injuries. These liver injuries were predominantly found among males compared to females (Table 1). Similar results have been found in the studies conducted by Singhai A et al., and Cai Q et al., [4, 11].

In the present study, a significantly higher CT severity scores (16.6±5.9) and significantly lower SPO2 levels (79.0±15.2) were also found among patients with COVID-19 associated liver injuries (Table 1). Higher rates of Severe COVID-19 disease (73.1%) and higher rates of mortality (46.3%) were found to be significantly associated with COVID-19 associated liver injuries. These finding are consistent with studies conducted elsewhere [8,11-12, 14].

As per existing scientific literature, Angiotensin-converting enzyme 2 (ACE2) receptors are abundantly distributed on the epithelial cells of bile duct and liver. These ACE-2 receptors are expressed by 2.6% of hepatocytes and 59.7% of cholangiocytes, these receptors provide easy access for SARS CoV-2 to bind directly and disrupt liver function. Medications used to treat COVID-19 directly or its associated symptoms such as antipyretics, antibiotics, antivirals and steroids are known to cause liver injury [5, 13-16].

Another potential cause for liver injury is systemic inflammatory response caused by COVID-19. In this situation, there is a uncontrolled production of inflammatory cytokines that lead to cytokine storm. The more inflammatory cytokines are released, the greater is the magnitude of tissue and organ injury like acute lung injury and acute respiratory distress syndrome (ARDS). Hence, cytokine storm indicates progression of the disease and injury to the major organs like lungs and liver (elevated liver enzymes). Cytokine storm is predominant determinant of

death [4-5]. The present study findings are in concordance with these mechanism, wherein significantly elevated levels of inflammatory markers: D-dimer, CRP, LDH and Ferritin are found among patients 'COVID-19 associated Hepatic injury' (Q2: 442ng/ml, 07mg/ dl, 588U/L, 838ng/ml respectively) (Table 4) Hypoxia is one of the characteristic features of ARDS. During systemic stress there is a compromise in the blood flow to the liver in spite of dual supply. In the situation, liver is unable to extract sufficient oxygen leading to hepatocellular hypoxia, which is reflected as COVID-19 associated liver injuries [4-5].

Conclusion

In the present study, COVID-19 patients presented with a wide spectrum of hepatic injuries. These injuries were due to SARS-CoV-2 associated inflammation and were significantly associated with severe COVID disease and mortality. Thus, assessment of hepatic function is useful in aid decision-making in the Emergency Department, assisting in decision making for hospital admission or scheduled outpatient re-evaluation. In the absence of any definitive treatment and prophylactic measures, hepatic injury in COVID-19 patients is expected to persist. Hence, Liver function should be evaluated in all symptomatic COVID-19 patients. In patients with pre-existing liver diseases, special attention should be paid to monitoring and treatment.

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*All correspondences to: Dr. Shrish Patil, Professor & Head, Department of Anatomy, Basaveshwara Medical College & Hospital, S.J.M Campus, N.H.4 (48) Bypass Road, Chitradurga-577502, Karnataka, India. E-mail: patilssp_2003@yahoo.co.in