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Original Article

Impact of COVID-19 Infection on Patients with Chronic Liver Disease in Sohag University Hospital

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Abstract

The pandemic of the coronavirus disease 2019 (COVID-19) has significantly impacted global public health and presented diverse clinical symptoms. Liver involvement in COVID-19 is notable, affecting a significant proportion of patients.

Methods: A retrospective cross-sectional study was conducted at Sohag University Hospital. A comparative analysis between chronic liver disease (CLD) patients with and without COVID-19. The study employed logistic regression and receiver operating characteristic (ROC) curve analysis to explore predictors of COVID-19 severity in CLD patients.

Results: 272 participants were included: 66 in the control group and 206 with varying COVID-19 severity. White blood cell count (WBC) was notably higher in severe cases compared to mild ,moderate and the control group . Absolute lymphocytic count also displayed significant differences, with the control group having higher values (2.25 ± 0.73) compared to mild (1.9 ± 0.86), moderate (1.27 ± 0.52), and severe cases (1.3 ± 0.78). Furthermore, C-reactive protein (CRP) varied significantly, with the highest levels in severe cases (92.9 ± 46), followed by moderate cases (46.7 ± 40.2), mild cases (13.49 ± 19.5), and the control group (5.6 ± 1.9). Elevated CRP (P = 0.001) with a sensitivity of 98%, D-dimer (P = 0.008) with a sensitivity of 95.7%, ESR (P = 0.008) with a sensitivity of 78.7%, and LDH (P = 0.013) with a sensitivity of 72.3% were significantly associated and predicted increased COVID-19 severity.

Conclusion: This research enhances understanding of COVID-19's impact on individuals with CLD, highlighting the significance of CRP, D-dimer, ESR, and LDH as a predictors of severity.

Keywords: COVID-19, Chronic liver disease, Cross-sectional, Laboratory parameters, Inflammatory markers

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Introduction

Coronavirus disease 2019 (COVID-19) is an extremely infectious respiratory disorder caused by the novel coronavirus SARS-CoV-2. [1,2]It has resulted in a global pandemic characterized by a wide spectrum of symptoms, from moderate respiratory issues to severe pneumonia. It has significantly affected public health.[3–5] Some individuals experience gastrointestinal symptoms such as nausea, diarrhea, or

abdominal discomfort.[6–8] Liver problems, as indicated by abnormal liver enzyme levels, were observed in around 33% to 50% of COVID-19 patients. [9,10]

Chronic liver disease (CLD) encompasses a range of pathological conditions, including viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and autoimmune liver disorders .[11]These problems often progress slowly, leading to fibrosis, cirrhosis, and an elevated susceptibility to hepatocellular carcinoma. [12] Patients with CLD may have various complications such as ascites, hepatic encephalopathy, and variceal hemorrhage. [13,14] These complications need ongoing medical treatment and close monitoring.

Recent literature has shed light on the relationship between COVID-19 and chronic liver disease (CLD). Individuals with liver issues might face a higher risk of experiencing severe COVID-19 effects. [15,16] This relationship is not straightforward and has various contributing factors. Liver problems in CLD can weaken the immune system, making it less effective in fighting the virus. [17] Additionally, some medications used to treat CLD might interact with COVID-19 treatments or harm the liver. [18] Moreover, the inflammation and blood clotting issues in severe COVID-19 can worsen liver damage in those with existing liver conditions. [19,20] This cross-sectional study at Sohag University Hospital investigates the impact of COVID-19 on individuals with Chronic Liver Disease, encompassing the assessment of complete blood picture (CBC), liver enzymes, and inflammatory markers.

Methods

Study Design:

This retrospective cross-sectional study was conducted on patients with CLD admitted to Sohag University Hospital between April 2020 and April 2021.

Study Population:

Patients diagnosed with CLD were included. They were further subdivided into two groups: 1) the COVID-19 group, which included patients with CLD and laboratory-confirmed COVID-19, and 2) the control group, which included patients with CLD and negative COVID-19. COVID-19 diagnosis relied on detecting SARS-COV-2 RNA or viral proteins via antigen tests, with a positive nucleic acid amplification test (NAAT) or antigen test confirming infection. [21] Patients not meeting inclusion criteria and those with negative COVID-19 tests were excluded.

Data Collection:

Data were extracted from medical records, including demographic, clinical, laboratory, treatment, and outcome parameters. Comorbidities such as hypertension, diabetes, coronary heart disease, and chronic lung disease were recorded within the 12 months preceding admission. NAFLD was determined using the hepatic steatosis index (HSI) or abdominal ultrasounds. Chronic hepatitis B (CHB) was confirmed by positive Hepatitis B Surface Antigen (HBsAg) status for at least 6 months. CLD was defined through various criteria, including Fibrosis-4 Index (FIB-4) > 3.25, Aspartate Aminotransferase to Platelet Ratio Index (APRI) > 1.5, CHB, or HSI > 36 + BARD score 2–4. [36,37] Acute-on-Chronic Liver Failure (ACLF) was identified based on the Asian Pacific Association for the Study of the Liver (APASL) criteria.[38]

Statistical Analysis:

Data analysis was conducted using SPSS version 25. Qualitative variables were summarized using numbers and percentages. Normally distributed quantitative variables were assessed with independent samples T-test and one-way ANOVA for independent comparisons, and paired samples T-test and repeated measurements ANOVA for dependent comparisons. Non-normally distributed quantitative variables underwent non-parametric Mann-Whitney and Kruskal-Wallis tests for independent comparisons, and dependent comparisons were assessed through Wilcoxon-signed rank and Friedman tests. Linear relationships between variables were evaluated using correlation analysis. P values below or equal to 0.05 were considered statistically significant.

This study has been ethically authorized by our university's ethics committee**.**

(IRB Registration number: Soh-Med-23-03-01PD).

Results:

The study initially enrolled 305 participants, but 33 were subsequently excluded due to not meeting eligibility criteria. The remaining 272 participants were divided into two groups: a control group (N=66) and symptomatic cases further categorized as mild (N=97), moderate (N=62), and severe (N=47) based on COVID-19 severity.

Socio-demographic characteristics of the studied group:

The age distribution significantly varied (P < 0.001) among the severity groups. Patients with severe COVID-19 were markedly older than patients with mild or moderate COVID-19 and the control group. The control group had the lowest mean age (50.15±12.36), while the severe cases group had the highest (57.02±12.8). Patients with severe COVID-19 are strongly associated with comorbidities such as diabetes (DM) (P < 0.001) and hypertension (HTN) (P = 0.033). **Table 1.**

Table (1): Socio-demographic characteristics of the studied group. (n=272)

Variable	Total (N=272)	Control (N=66)	Symptomatic			p-value
			Mild cases (N=97)	Moderate cases (N=62)	Severe cases (N=47)	
Sex						
Male	137 (50.4%)	34 (51.5%)	43 (44.3%)	35 (56.5%)	25 (53.2%)	0.472 *
Female	135 (49.6%)	32 (48.5%)	54 (55.7%)	27 (43.5%)	22 (46.8%)	
Age (mean±SD)	50.15±12.36	51.1±9.32	48.77±13.14	46.08±11.53	57.02±12.8	**<0.001** **
<25 years	5 (1.8%)	0 (0%)	3 (3.1%)	2 (3.2%)	0 (0%)	
25-35years	25 (9.2%)	1 (1.5%)	11 (11.3%)	9 (14.5%)	4 (8.5%)	
≥35years	242 (89%)	65 (98.5%)	83 (85.6%)	51 (82.3%)	43 (91.5%)	0.078
BMI (mean±SD)	26.8±1.9	26.74±1.92	26.68±1.74	27.1±1.87	26.95±2.26	0.538 **
DM						
Yes	65 (23.9%)	8 (12.1%)	18 (18.6%)	18 (29%)	21 (44.7%)	**<0.001** *
No	207 (76.1%)	58 (87.9%)	79 (81.4%)	44 (71%)	26 (55.3%)	
HTN						
Yes	60 (22.1%)	15 (22.7%)	14 (14.4%)	14 (22.6%)	17 (36.2%)	**0.033** *
No	212 (77.9%)	51 (77.3%)	83 (85.6%)	48 (77.4%)	30 (63.8%)	

BMI: body mass index. DM: diabetes mellitus. HTN: hypertension.
*: Chi-square test.
**: One-way ANOVA test. Cells that carry the same letter are statistically significantly different (p<0.05).

Differences between the control group and other groups in CBC parameters:

WBCs demonstrated a significant difference among groups (P < 0.001). The control group exhibits lower WBC count values (5.3±1.8) compared to mild cases (6.39±3.3), moderate cases (9.5±6.2), and severe cases (10.45±3.9).

Absolute lymphocyte count also showed significant variations across groups (P < 0.001), as the control group exhibited higher absolute lymph values (2.25±0.73) compared to mild cases (1.9±0.86), moderate cases (1.27±0.52) and severe cases (1.3±0.78).

However, hemoglobin (HB), red blood cells (RBCs), and platelet levels did not show significant differences among the groups (P = 0.424, P = 0.276, and P = 0.104, respectively).**Table 2.**

Table (2): Differences between the control group and other groups in CBC parameters.

Variable	Total (N=272)	Control (N=66)	Symptomatic			p-value *
			Mild cases (N=97)	Moderate cases (N=62)	Severe cases (N=47)	
WBCs (mean±SD)	7.54±4.5	5.3±1.8	6.39±3.3	9.5±6.2	10.45±3.9	**<0.001**
Absolute lymph (mean±SD)	1.74±0.84	2.25±0.73	1.9±0.86	1.27±0.52	1.3±0.78	**<0.001**
HB (mean±SD)	12±1.7	11.9±1.36	12.18±1.68	12.02±2.02	11.68±1.8	0.424
RBCs (mean±SD)	4.84±3.16	5.49±6.29	4.69±0.64	4.63±0.66	4.5±0.79	0.276
Platelets (mean±SD)	241.08±87.2	222.7±84.9	246.9±80.3	235.9±86.3	261.5±101.3	0.104

CBC: Complete blood count. WBCs: white blood cells. HB: hemoglobin. RBCs: red blood cells.
*: One-way ANOVA test. Cells that carry the same letter are statistically significantly different (p<0.05).

Differences between the control and other groups in acute phase reactants and inflammatory markers:

CRP levels significantly varied across groups (P < 0.001), with the control group showing lower values (5.6±1.9) compared to the symptomatic categories: mild cases (13.49±19.5), moderate cases (46.7±40.2) and severe cases (92.9±46). Serum ferritin also showed significant variations across groups (P < 0.001), with the control group having lower levels (143.6±75.8) than mild cases (227.2±213.5), moderate cases (96.8±49.7), and severe cases (192±93.6). Also, D-dimer levels showed a significant difference (P < 0.001), with the control group showing lower values (146.5±57.9) compared to mild cases (487.07±710.04), moderate cases (1573.8±1701.8), and severe cases (1476±1233.7). ESR Followed a similar significant pattern (P < 0.001), with the control group showing lower levels (19.16±9.18) compared to mild cases (52±30.6), moderate cases (70.6±20.2), and severe cases (82.8±21.4). LDH levels also varied significantly (P < 0.001) among groups, with the control group exhibiting lower values (208.5±41.3) compared to Mild cases (357.9±154.9), Moderate cases (540.8±356.6) and Severe cases (779±377.7). **Table 3.**

Table (3): Differences between the control group and other groups in acute phase reactants and inflammatory markers.

Variable	Total (N=272)	Control (N=66)	Symptomatic			p-value *
			Mild cases (N=97)	Moderate cases (N=62)	Severe cases (N=47)	
CRP (mean±SD)	32.9±42.9	5.6±1.9	13.49±19.5	46.7±40.2	92.9±46	**<0.001**
Serum ferritin (mean±SD)	171.16±149.1	143.6±75.8	227.2±213.5	96.8±49.7	192±93.6	**<0.001**
D dimer (mean±SD)	823.07±1201.8	146.5±57.9	487.07±710.04	1573.8±1701.8	1476±1233.7	**<0.001**
ESR (mean±SD)	53.6±32.07	19.16±9.18	52±30.6	70.6±20.2	82.8±21.4	**<0.001**
LDH (mean±SD)	436.16±315.4	208.5±41.3	357.9±154.9	540.8±356.6	779±377.7	**<0.001**

CRP: C-reactive protein. ESR: erythrocyte sedimentation rate. LDH: lactate dehydrogenase.
*: One-way ANOVA test. Cells that carry the same letter are statistically significantly different (p<0.05).

Differences between the control group and other groups in chemistry:

Blood glucose levels exhibited significant differences among groups (P < 0.001), with the control group showing significantly lower values (116.8±27.07) than the symptomatic categories: mild cases (128.6±50.1), moderate cases (171.5±84.5), and severe cases (198.9±130.2). Similarly, ALT and AST levels showed significant differences in disease severity (*P* < 0.001 and *P* = 0.006). ALT values were notably lower in the mild cases group (35.36±20.3) and higher in the moderate cases (57.16±55) and severe cases (57.2±33.3) compared to the control group (40.27±15.7). AST levels followed a similar pattern, with the control group (50.39±15.7) showing lower values compared to mild cases (35.3±19.9) and higher values in moderate cases (57.7±78.3) and severe cases (51.04±25.4).

Furthermore, bilirubin levels were significantly (*P* < 0.001) higher in the control group (1.29±0.84) compared to mild cases (0.85±0.23), moderate cases (1.02±0.75), and severe cases (1.16±0.58). Also, urea levels showed a significant difference across groups (P = 0.001), with the control group (37.19 ± 15.6) having higher values than mild cases (30.9 ± 9.7) and moderate cases (34.8 ± 21.8) but lower than severe cases (43.5 ± 27.4). Similarly, Creatinine levels showed significant differences (*P* = 0.021) among groups, with the control group (1.1 ± 0.55) showing relatively similar values compared to mild cases (1.09 ± 0.23), and higher values observed in moderate cases (1.18 ± 0.9) and severe cases (1.49 ± 1.27).

Conversely, Albumin levels remained relatively stable across all groups, with no statistically significant difference observed (*P* = 0.499). **Table 4.**

Table (4): Differences between control group and other groups in chemistry.

Variable	Total (N=272)	Control (N=66)	Symptomatic			p-value *
			Mild cases (N=97)	Moderate cases (N=62)	Severe cases (N=47)	
Blood glucose (mean±SD)	147.7±80.6	116.8±27.07	128.6±50.1	171.5±84.5	198.9±130.2	**<0.001**
ALT (mean±SD)	45.29±34.26	40.27±15.7	35.36±20.3	57.16±55	57.2±33.3	**<0.001**
AST (mean±SD)	46.82±42.08	50.39±15.7	35.3±19.9	57.7±78.3	51.04±25.4	**0.006**
Bilirubin (mean±SD)	1.05±0.63	1.29±0.84	0.85±0.23	1.02±0.75	1.16±0.58	**<0.001**
Albumin (mean±SD)	3.92±3.91	3.9±5.7	4.15±0.39	4.17±5.7	3.15±0.57	0.499
Urea (mean±SD)	**35.49±18.7**	**37.19±15.6**	**30.9±9.7a**	**34.8±21.8**	**43.5±27.4a**	**0.001**
Creatinine (mean±SD)	**1.18±0.76**	**1.1±0.55a**	**1.09±0.23b**	**1.18±0.9**	**1.49±1.27a,b**	**0.021**

ALT: Alanine Transaminase. AST: aspartate transaminase.

*: One way ANOVA test. Cells that carry the same letter are statistically significantly different (p<0.05).

Predictors of severity of COVID-19 cases:

Among the significant predictors, elevated CRP level was a highly significant predictor of COVID-19 severity [OR =1.04 (95% CI: 1.02-1.05), *P* = 0.001]. Similarly, greater D-dimer exhibited a significant predictor [OR = 0.999 (95% CI: 0.999-0.9998), *P* = 0.008]. Elevated ESR also significantly predicted COVID-19 severity [OR = 1.036 (95% CI: 1.01-1.06), *P* = 0.008]. Increased LDH levels also significantly predicted COVID-19 severity [OR = 1.002 (95% CI: 1.00-1.004), P = 0.013].

On the other hand, several variables, including Age, WBC count, absolute lymphocyte count, Serum

ferritin, Blood glucose, ALT, AST, Bilirubin, Urea, and Creatinine, did not show statistically significant associations with COVID-19 severity (p-values > 0.05). **Table 5.**

Table (5): Predictors of severity of COVID-19 cases.

Variable	P-value	Odds ratio	95% CI for odds ratio
Age	0.071	1.039	0.99-1.08
WBCs count	0.291	1.05	0.95-1.17
Absolute lymphocyte count	0.40	0.69	0.3-1.6
CRP	**<0.001**	1.043	1.024-1.062
Serum ferritin	0.421	0.996	0.99-1.002
D dimer	**0.008**	0.999	0.999-0.9998
ESR	**0.006**	1.036	1.01-1.06
LDH	**0.013**	1.002	1.00-1.004
Blood glucose	0.22	1.004	0.99-1.01
ALT	0.12	1.02	0.99-1.04
AST	0.098	0.980	0.95-1.004
Bilirubin	0.576	1.35	0.4-3.9
Urea	0.125	1.03	0.99-1.07
Creatinine	**0.026**	0.332	0.126-0.875

ROC curve analysis of predictors of COVID-19 case severity:

First, CRP emerged as a significant predictor (*P* = 0.001), with a cutoff value of ≥27.5, achieving an impressive AUC of 0.923. and had a high sensitivity of 98% and specificity of 80.4%, along with a significant p-value of 0.001. Similarly, D-dimer, ESR, and LDH demonstrated significant predictive potential, with AUC values ranging from 0.812 to 0.830 and associated p-values of 0.001. In comparison, they exhibited varying levels of sensitivity (95.7%, 78.7%, and 72.3%, respectively) and specificity (63.1%, 74.2%, and 85.3%, respectively). Conversely, Creatinine was not a significant predictor (*P* = 0.873), with an AUC of only 0.493. **Table 6.**

Table (6): ROC curve analysis of predictors of covid-19 cases severity.

Predictors	Cut-off	Sensitivity	Specificity	AUC 95%CI	P-value
CRP	≥27.5	98%	80.4%	0.923 (0.892-0.954)	**0.001**
D dimer	≥440 ng/ml	95.7%	63.1%	0.812 (0.761-0.864)	**0.001**
ESR	≥69.5	78.7%	74.2%	0.819 (0.765-0.873)	**0.001**
LDH	≥540 u/l	72.3%	85.3%	0.830 (0.760-0.901)	**0.001**

Discussion:

The study investigated the impact of COVID-19 on 272 patients with CLD at Sohag University Hospital between April 2020 and April 2021. Several significant findings emerged from the analysis. The study revealed a notable age-dependent increase in COVID-19 severity, with higher proportions of comorbidities like diabetes and hypertension in severe cases. Laboratory parameters significantly varied across severity groups, including WBC, absolute lymphocyte count, CRP, D-dimer, ESR, and LDH. Blood glucose, ALT, and AST levels correlate with disease severity. CRP exhibited high predictive potential for COVID-19 severity, with remarkable sensitivity and specificity.

Several reports have brought attention to different levels of CLD among individuals diagnosed with

COVID-19.[22-24] The observed capacity of the virus to penetrate liver cells via the angiotensin-converting enzyme 2 (ACE2) receptor, primarily in cholangi-ocytes, can potentially induce damage to these specific cell types. [25] Moreover, it has been obse-rved that COVID-19 can trigger a cytokine storm, leading to the release of proinflammatory cytokines that could potentially cause damage to the liver.[26] Finally, complications such as coagulation disorders and respiratory failure contribute to the exacer-bation of liver disease through the induction of ischemia and oxidative stress. [27]

Similar to previous studies, elevated levels of liver enzymes such as ALT, AST, and total bilirubin were commonly reported in COVID-19 patients. [28] Also, in line with earlier research, our study found that factors associated with liver injury in COVID-19 patients included having HTN or DM and older.[29] The incidence of liver injury manif-ested as abnormal liver enzyme levels were obse-rved in a range of 14.8% to 53.0%.[30] Also, our study found significant differences in CBC param-eters, particularly elevated WBC counts and altered lymphocyte counts among severity groups, which aligns with previous literature. [31,32] Finally, Elevated CRP levels were consistently identified as a strong predictor of disease severity, corroborating previous studies. [33,34]

Our findings have important clinical implications for managing COVID-19 in patients with CLD. This study highlights the significance of factoring in age and comorbid conditions, particularly diabetes and hypertension, when assessing the likelihood of severe COVID-19 in CLD patients. [35] Consistent monitoring of key laboratory indicators such as CRP, D-dimer, ESR, and LDH can aid in the early identification of patients at heightened risk for severe outcomes. [36] The findings imply that healthcare professionals should maintain close vigilance, effectively manage blood glucose levels, and monitor ALT and AST in CLD patients with COVID-19, as these markers can offer valuable insights into disease progression. [37]Given CRP's exceptional sensitivity and specificity, it is a valuable tool for risk assessment and timely intervention. [38]

A significant strength of this study is its comprehensive analysis of a relatively large cohort of CLD patients with confirmed COVID-19 cases. The study's detailed examination of clinical and laboratory parameters adds depth to our understanding of COVID-19's impact on this specific patient population. However, limitations include its retrospective nature, which may introduce selection bias, and the study's single-center design, potentially limiting the generalizability of findings.

In conclusion, this research offers valuable knowledge regarding the clinical and laboratory profiles of individuals with CLD who also have COVID-19. Laboratory parameters, including CRP, D-dimer, ESR, and LDH, are strongly associated with COVID-19 severity in this population. These findings emphasize the importance of tailored monitoring and early intervention in CLD patients with COVID-19, especially those with identified risk factors. Further research, including prospective studies and investigations into the impact of specific treatments, is warranted to enhance our understanding and improve the care of CLD patients affected by COVID-19.

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