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Review of Liver Enzymes Abnormalities in Patients with SARS-CoV-2 Infection

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Abstract: *Background*: Liver function derangements have been reported in COVID-19, but reported rates are variable. Treatment in intensive care units (ICU) has become a major challenge; therefore, early recognition of severe and critical cases is absolutely essential for timely triaging of patients. Objectives: to review incidence of acute liver injury in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *Patients and methods*: obtaining clinical records and laboratory results prospectively from one hundred patients with PCR-confirmed or radiography-confirmed COVID-19, who are admitted to the isolation wards and emergency departments of three different hospitals in Baghdad from 1st of December 2020 to 31st of March 2021. *Results*: The mean age group of study sample was (61.2±12.36) years, males formed 59%. GI manifestations were recorded in 47% of total cases, and were statistically correlated with disease severity (P value 0.001). Wide range of LFT abnormalities are found in patients with COVID-19, but none of which showed statistical significance in relation to disease severity. When LFT results were reviewed in relation to previous comorbidities, GGT was found to be statistically correlated with the underlying CLD (P value 0.001), and ALP with both underlying CLD and DM (P values <0.001 and 0.029, respectively) and even in the absence of underlying comorbidity (P value 0.006). *Conclusion*: Liver enzyme derangements are increasingly reported in patients with COVID-19, but are not necessarily correlate with disease severity. Cholestatic picture of liver enzyme derangement is a more commonly recorded manifestation.

Keywords: COVID-19, SARS-CoV-2, Hepatitis, Liver Enzymes, Cholestasis

1. Background

COVID-19 related liver injury is defined as any liver damage occurring during the course of the disease and treatment of COVID-19 patients, with or without underlying liver disease [1-3].

Potential pathological mechanisms including: (1) direct cytotoxicity from active viral replication of SARS-CoV-2 in the hepatocytes, (2) immune-mediated liver damage due to the severe inflammatory response/systemic inflammatory response syndrome (SIRS) in COVID-19, (3) hypoxic changes induced by respiratory failure, (4) vascular changes due to coagulopathy, (5) endotheliitis or cardiac congestion from right heart failure, (6) drug-induced liver injury and (7) exacerbation of underlying liver disease [4, 5].

Although COVID-19-associated liver injury has been reported to be mild, it may affect a significant proportion of patients, especially those with a more severe disease course. Hepatic injury is more frequent in seriously ill patients that can be explained by a high level of inflammatory mediators during this stage of the disease (cytokine storm). However, this not explained the elevation of transaminases during the mild stage of the disease [3, 6, 7].

Abnormalities of LFTs are observed in many patients with COVID-19 at admission to hospitals worldwide and they are independently associated to a composite endpoint of transfer to the ICU or death, particularly when the pattern of alteration is mixed. Thus, on clinical ground abnormal LFTs at admission should be considered as a marker of disease

severity and should lead physicians to closely follow-up these patients and to be prepared for potential rapid worsening of clinical conditions. This could anticipate the potentially need for ICU beds, which is relevant considering the shortage observed in some regions during COVID-19 pandemic [2, 8].

The presence of hepatic inflammation in histopathological examination raises the attention for the probability of drug-induced hepatic injury (DILI). Most of these medications contain acetaminophen that is well known to cause hepatic injury. Also, multiple antiviral drugs can induce hepatic injury that also used in treatment schedule [2, 3].

This study aimed to review incidence of acute liver injury in patients with Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2) infection.

2. Patients and Methods

2.1. Study Design and Setting

A cross sectional hospital-based study was performed during the period from 1st of December 2020 to 31st of March 2021, enrolling patients admitted to the isolation wards and emergency departments at Al-Immamain Al-Kadhumein Medical City, Al-Salam 1 Hospital and Abu Ghraib General Hospital. All patients were informed about the study and a verbal consent was taken.

2.1.1. Inclusion Criteria

All patients with confirmed diagnosis of SARS-Co-V-2 infection based on the symptoms and the clinical signs, Reverse Transcription polymerase chain reaction (RT-PCR) test and chest CT scan findings according to the world health organization (WHO) interim guidance, who are admitted to the isolation wards were randomly included in this study.

2.1.2. Exclusion Criteria

Asymptomatic or mild cases who were confirmed to get infected with SARS-Co-V-2 but were not admitted to hospital.

2.2. Method and Data Collection

For each patient proper intervention was performed at the time of admission to define demographic information, clinical information, RT-PCR, chest CT scan and liver function test in addition to inflammatory markers like C-reactive protein (CRP), D-dimer, ferritin and lactate dehydrogenase (LDH).

Laboratory reference values were considered as: alanine aminotransferase (0-45 units/L), aspartate aminotransferase (0-45 units/L), alkaline phosphatase (36-90 units/L), γ-glutamyl transferase (0-30 units/L), total bilirubin (0.3-1.2 mg/dL), total protein (6.0-7.8 g/dL), albumin (3.5-5.5 g/dL), prothrombin time (11-13 seconds), international normalization ratio (≤1.1), C-reactive protein (0.0-0.8 mg/L), D-dimer (<0.5 mg/dL), ferritin (15-200 ng/mL), lactate dehydrogenase (60-100 units/L) [9].

Serum liver tests were considered abnormal if levels were above the following thresholds: ALT>45 units/liter (U/L), AST>45 U/L, GGT>85 U/L, ALP>95 U/L, and Total bilirubin (TBILI)>1.2 mg/dl. High aminotransferase level is defined as ALT or AST is>2 upper limit of normal (ULN) according to EASL (European Association for the Study of Liver) guidelines [10].

2.3. Disease Severity Classification

To date, the clinical spectrum of COVID-19 infection ranges from asymptomatic to life-threatening conditions. Meanwhile, many groups classify patients according severity through scores and classification systems to help clinicians in care and triage. [11]

2.4. Statistical Analysis

All statistical analysis were performed using SPSS statistical software, version 25 (IBM corporation, USA). Quantitative variables were subjected for normality test (Shapiro Wilk test) and were found to be non-normally distributed. Accordingly, they were expressed as median and range. Comparison between groups was made by Mann Whitney U test (for two groups) or Kruskal Wallis (for three groups). Categorical variables were expressed as counts and percentages and analyzed with chi-square test was performed. For all tests, a significant level of statistics was considered when $P<0.05$.

3. Results

3.1. Laboratory Parameters

At least one of liver enzymes abnormalities was recorded in 60% of patients. Hypoalbuminemia was found in 35%, with a mean albumin level was 3.52±0.6 g/dL (range 2.0 to 5.8 g/dL). Gamma glutamyl transferase (GGT) elevation was found in 27% with a mean level of 100.92±142.0 U/L (range 16.0 to 958.0 U/L). Alanine aminotransferase (ALT) was found to be high in 16% of cases with a mean level of 64.12±84.05 U/L (range 9.0-698 U/L), while aspartate aminotransferase (AST) was elevated in 12% ranging from 8.0 to 818.0 U/L with a mean level of 33.98±89.21 U/L. Mean alkaline phosphatase (ALP) level was normal (116.12±122.17 U/L) although some had reached to 1000 U/L, unlike total bilirubin which was normal in most of patients, and when elevated it didn't reach to clinical detection (0.2-3.1 mg/dL), as shown in table 1.

Table 1. *Liver enzymes parameters in patients (n=100).*

Variables	Mean±SD	Range
AST, U/L	33.98±89.21	8.0-818.0
ALT, U/L	64.12±84.05	9.0-698
ALP, U/L	116.12±122.17	18.0-1000
GGT, U/L	100.92±142.0	16.0-958.0
TSB, mg/dl	0.92±0.52	0.2-3.1
Albumin, g/dl	3.52±0.6	2.0-5.8
INR	1.35±0.45	0.7-2.6

3.2. Classification of Disease Severity in Relation of Liver Enzymes Derangement

Patients were distributed evenly among three groups of severity: moderate (27%), severe (34%) and critical (39%). However, mild cases were not included in this study. Assessment of any of the clinical characteristics and groups of severity revealed non-significant relation apart from digestive symptoms (P value was 0.001). Respiratory symptoms were reported but did not reach significance. The use of antiviral therapy also showed significant relation with disease severity (P-value was 0.008), table 2.

Table 2. *Association of clinical and laboratory characteristics with disease severity.*

Variables	Moderate (n=27, 27%)	Severe (n=34, 34%)	Critically-ill (n=39, 39%)	p-value
Duration of symptoms, days				
Median	5.0	7.5	7.0	0.106
Range	1-30	3-30	1-30	
Comorbidities				
None	15 (55.56%)	23 (67.65%)	26 (66.67%)	0.118
Diabetes	12 (44.44%)	10 (29.41%)	13 (33.33%)	0.084
Liver disease	2 (7.4%)	1 (2.94%)	1 (2.56%)	0.570
Constitutional symptoms				
Yes	22 (81.48%)	32 (94.12%)	35 (89.74%)	0.228
No	5 (18.52%)	2 (5.88%)	4 (10.26%)	
Respiratory symptoms				
Yes	25 (92.59%)	34 (100%)	39 (100%)	0.063
No	2 (7.41%)	0 (0%)	0 (0%)	
GIT symptoms				
Yes	16 (59.26%)	19 (55.88%)	8 (20.51%)	0.001
No	11 (40.74%)	15 (44.12%)	31 (79.49%)	
PCR				
Positive	25 (92.59%)	28 (82.35%)	34 (87.18%)	0.497
Negative	2 (7.41%)	6 (17.64%)	5 (12.82%)	
SpO_2, %				
Mean±SD	93.7±3.05	91.03±3.98	79.87±12.8	<0.001
Range	87-98[a*]	83-98[a]	40-95[b]	
Lung involvement, %				
Mean±SD	29.79±15.28	51.82±22.5	55.39±22.82	<0.001
Range	5-50[a]	15-90[b]	15-90[b]	
Antiviral drugs				
None	6 (22.22%)	7 (20.59%)	7 (17.95%)	
Remdisivir	4 (14.81%)	8 (25.53%)	21 (53.85%)	0.008
Favipiravir	17 (62.96%)	19 (55.88%)	11 (28.21%)	
Convalescent plasma				
Yes	27 (100%)	30 (88.24%)	36 (92.31%)	0.197
No	6 (22.22%)	4 (11.76%)	3 (7.69%)	

Table 3. *Association of liver function test results and disease severity.*

Variables	Moderate (n=27, 27%)	Severe (n=34, 34%)	Critically-ill (n=39, 39%)	p-value
ALT, UL				
Normal	18 (66.67%)	24 (70.59%)	23 (58.97%)	0.495
Elevated	9 (33.33%)	10 (29.41%)	16 (41.03%)	
AST, UL				
Normal	16 (59.26%)	19 (55.88%)	18 (46.15%)	0.529
Elevated	11 (40.74%)	15 (44.12%)	21 (53.84%)	
ALP, UL				
Normal	24 (88.89%)	29 (85.29%)	30 (76.92%)	0.404
Elevated	3 (11.11%)	5 (14.71%)	9 (23.08%)	
GGT, UL				
Normal	16 (59.26%)	12 (35.29%)	16 (41.03%)	0.154
Elevated	11 (40.74%)	22 (64.71%)	23 (58.97%)	
TSB, mg/dl				
Normal	22 (%81.48)	21 (61.74%)	3179.48 (%)	0.133
Elevated	5 (18.52%)	13 (38.24%)	8 (20.51%)	
Albumin, g/dl				
Normal	20 (74.07%)	20 (58.82%)	24 (61.54%)	0.430
Reduced	7 (25.93%)	14 (41.18%)	15 (38.46%)	

Wide range of variations was found concerning liver function test results in COVID-19 patients that made no specific observation to be reported with an ALT range (9.0-698 U/L), AST (8.0-818 U/L), ALP (18.0-1000 U/L), GGT

(16.0-958 U/L), albumin (2.0-5.8 g/dL) and TSB (0.2-3.1 mg/dL). However, none of which showed statistical significance with disease severity (P values=0.495, 0.529, 0.404, 0.154, 0.430 and 0.133, respectively), table 3.

3.3. Relationship of Comorbidities and Presenting Symptoms with Severity of Liver Enzymes Derangement

For purpose of study, liver enzymes were reviewed in relation to various postulated risk factors like previous comorbidity of diabetes mellitus and chronic liver disease. It was found that only ALP had a significant relationship with those mentioned comorbidities (DM and CLD), as well as a significant relationship even in the absence of such risk factors, where P values were 0.029, <0.001 and 0.006, respectively, as shown in table 4. Similarly, ALP was the only liver enzyme that reached significance threshold with GI manifestations, while neither duration of symptoms, nor other presenting features had shown any significant relation with any type of LFT abnormalities, table 5.

Table 4. *Impact of PMH on LFT abnormalities in SARS-CoV-2 infection.*

LFT parameters		Previous comorbidities		
		None	DM	CLD
ALT	Normal (n=84)	33 (38.37%)	33 (38.37%)	3 (3.49%)
	Elevated (n=16)	6 (37.5%)	5 (31.25%)	1 (6.25%)
	P value	0.893	0.544	0.616
AST	Normal (n=88)	52 (59.90%)	35 (39.77%)	4 (4.55%)
	Elevated (n=12)	9 (75%)	3 (25%)	0 (%)
	P value	0.289	0.323	0.451
ALT&AST (together)	Normal (n=93)	56 (60.22%)	36 (38.71%)	4 (4.30%)
	Elevated (n=7)	5 (71.43%)	2 (28.57%)	0 (%)
	P value	0.557	0.594	0.575
ALP	Normal (n=88)	30 (34.09%)	30 (34.09%)	1 (1.14%)
	Elevated (n=12)	9 (75%)	8 (66.67%)	3 (25%)
	P value	0.006	0.029	<0.001
GGT	Normal (n=74)	44 (59.46%)	30 (40.54%)	0 (%)
	Elevated (n=26)	17 (65.38%)	8 (30.77%)	4 (15.38%)
	P value	0.594	0.377	0.001
Albumin	Normal (n=65)	36 (55.38%)	29 (44.61%)	1 (1.54%)
	Low (n=35)	25 (71.43%)	9 (25.71%)	3 (8.57%)
	P value	0.117	0.063	0.087
INR	Normal (n=86)	54 (62.79%)	31 (36.05%)	2 (2.33%)
	Elevated (n=14)	7 (50%)	7 (50%)	2 (14.29%)
	P value	0.363	0.319	0.034

Table 5. *Impact of presenting manifestations on LFT abnormalities.*

LFT parameters		Duration of symptoms, days	Presenting manifestations		
			Constitutional manifestations	Respiratory manifestations	GIT manifestations
ALT	Normal (n=84)	7 (1.0-30)	75 (87.21%)	82 (95.45%)	38 (44.19%)
	Elevated (n=16)	7 (1.0-30)	14 (87.5%)	16 (100%)	5 (31.25%)
	P value	0.678	0.831	0.533	0.300
AST	Normal (n=88)	7 (1.0-30)	78 (88.64%)	86 (97.73%)	37 (42.05%)
	Elevated (n=12)	6 (2.0-25)	11 (91.67%)	12 (100%)	6 (50%)
	P value	0.545	0.753	0.598	0.602
ALT & AST (together)	Normal (n=93)	7.0 (1.0-30)	82 (88.17%)	91 (97.85%)	40 (43.01%)
	Elevated (n=7)	7 (2.0-25)	1 (14.29%)	2 (28.57%)	4 (57.14%)
	P value	0.855	0.335	0.695	0.994
ALP	Normal (n=88)	7.0 (1.0-30)	79 (89.77%)	86 (97.73%)	41 (46.59%)
	Elevated (n=12)	5 (2-30)	10 (83.33%)	12 (100%)	2 (16.67%)
	P value	0.835	0.504	0.598	0.05
GGT	Normal (n=74)	7 (1.0-30)	65 (87.84%)	72 (97.30%)	34 (45.95%)
	Elevated (n=26)	7 (2-30)	24 (92.31%)	26 (100%)	9 (34.62%)
	P value	0.343	0.531	0.379	0.315
Albumin	Normal (n=65)	7 (1-17)	60 (92.31%)	63 (96.92%)	31 (47.69%)
	Low (n=35)	7 (1-30)	29 (82.86%)	35 (100%)	12 (34.29%)
	P value	0.069	0.150	0.295	0.196
INR	Normal (n=86)	7 (1-30)	77 (89.53%)	84 (97.67%)	38 (44.19%)
	Elevated (n=14)	8 (1-25)	12 (85.71%)	14 (100%)	5 (35.71%)
	P value	0.838	0.672	0.564	0.553

3.4. Relation of Therapeutic Interventions with Severity of Liver Enzyme Derangement

All patients enrolled in the study had received supportive treatment on admission, such as antipyretics, intravenous fluids, oxygen and vitamins, corticosteroids and anticoagulation in various doses according to patients' condition. Thirty-three (33%) had received Remdesivir, forty-seven (47%) *had received Favipiravir and only seven (7%) had got convalescent plasma* during their admission period. GGT had shown a significant relationship with the use of antivirals where P-value was 0.031, while it just reached significance threshold with the use of convalescent plasma, table 6.

Table 6. *Impact of treatment lines on LFT abnormalities in SARS-CoV-2 infection.*

LFT parameters		Treatment lines		
		Antivirals		Convalescent plasma
		Favipiravir	Remdesivir	
ALT	Normal (n=84)	40 (46.51%)	27 (31.40%)	5 (5.81%)
	Elevated (n=16)	7 (43.75%)	6 (37.5%)	2 (12.5%)
	P value	0.916		0.347
AST	Normal (n=88)	40 (45.45%)	30 (34.09%)	5 (5.68%)
	Elevated (n=12)	7 (58.33%)	3 (25%)	2 (16.67%)
	P value	0.700		0.162
ALT&AST (together)	Normal (n=93)	43 (46.24%)	31 (33.33%)	6 (6.45%)
	Elevated (n=7)	4 (57.14%)	2 (28.57%)	1 (14.29%)
	P value	0.847	0.433	
ALP	Normal (n=88)	43 (48.86%)	28 (31.82%)	5 (5.68%)
	Elevated (n=12)	4 (33.33%)	5 (41.67%)	2 (16.67%)
	P value	0.600		0.162
GGT	Normal (n=74)	39 (52.70%)	19 (25.68%)	3 (4.05%)
	Elevated (n=26)	8 (30.77%)	14 (53.85%)	4 (15.38%)
	P value	0.031		0.05
Albumin	Normal (n=65)	36 (55.38%)	19 (29.23%)	3 (4.62%)
	Low (n=35)	11 (31.43%)	14 (40%)	4 (11.43%)
	P value	0.062		0.203
INR	Normal (n=86)	39 (45.35%)	29 (33.72%)	6 (6.98%)
	Elevated (n=14)	8 (57.14%)	4 (28.57%)	1 (7.14%)
	P value	0.698		0.982

3.5. Relation of Inflammatory Markers with Severity of Liver Enzyme Derangement

No definite relationship was found between any of the inflammatory markers and severity of liver enzyme derangement apart from GGT which showed significant relationship with ferritin-, where P values were found to be 0.024, respectively. The analysis of serum level of inflammatory markers reveals mean ferritin level (in ng/ml) of 875.9±561.1, mean CRP level (in mg/dL) of 8.11±5.58 and mean lactate dehydrogenase level (in U/L) of 566.0±313.6 although the median for each marker is different for each severity classification, table 7.

Table 7. *Impact of inflammatory markers on LFT abnormalities in SARS-CoV-2 infection.*

LFT parameters		Inflammatory markers			
		LDH, U/L	CRP, mg/dL	D-dimer, mg/dL	Ferritin, ng/mL
ALT	Normal (n=84)	508 (114-2330)	9.6 (0.4-24.2)	2.75 (0.1-16.7)	740 (105-3770)
	Elevated (n=16)	482 (216-819)	6.45 (1.1-10)	2.7 (0.5-7.2)	576.5 (110-1832)
	P value	0.510	0.120	0.686	0.286
AST	Normal (n=88)	508 (114-1687)	9.35 (0.4-24.2)	2.7 (0.1-16.7)	802 (105-3770)
	Elevated (n=12)	501.5 (242-2830)	7.85 (1.8-20)	3.3 (0.5-6.07)	659.5 (110-1832)
	P value	0.524	0.605	0.799	0.766
ALT&AST (together)	Normal (n=93)	506 (114-2330)	9.1 (0.4-24.2)	2.7 (0.1-16.7)	790 (105-3770)
	Elevated (n=7)	745 (242-819)	8.9 (2.1-10)	3.6 (0.5-4.34)	599 (110-1832)
	P value	0.259	0.729	0.787	0.813
ALP	Normal (n=88)	502.5 (114-1687)	9.35 (0.4-24.2)	2.8 (0.1-16.7)	733.5 (105-3777)
	Elevated (n=12)	675 (291-2330)	7.21 (1.1-22.1)	1.7 (0.8-7.1)	928.5 (110-1750)
	P value	0.123	0.605	0.181	0.340
GGT	Normal (n=74)	502.5 (114-1687)	8.95 (0.-24.2)	2.75 (0.1-16.7)	718.5 (105-2000)
	Elevated (n=26)	568 (172-2330)	9.15 (1.1-20)	2.7 (0.4-14.4)	970 (110-3770)
	P value	0.571	0.678	0.966	0.024
Albumin	Normal (n=65)	507 (114-2330)	8.9 (0.4-24.2)	2.7 (0.1-16.7)	735 (128-3780)
	Low (n=35)	473 (145-825)	9.6 (0.5-20)	3.5 (0.1-13.7)	790 (105-2000)
	P value	0.113	0.810	0.488	0.497

LFT parameters		Inflammatory markers			
		LDH, U/L	CRP, mg/dL	D-dimer, mg/dL	Ferritin, ng/mL
INR	Normal (n=86)	506.5 (114-1687)	9.35 (0.4-24.2)	2.7 (0.1-16.7)	802 (105-3770)
	Elevated (n=14)	519.5 (172-2330)	6.65 (0.5-22.1)	3.05 (0.2-13.7)	563 (110-1750)
	P value	0.933	0.590	0.980	0.170

4. Discussion

Increment in GGT levels was found to be statistically associated with the presence of underlying chronic liver disease (P-value=0.001). Similarly, ALP levels were highly associated with the underlying chronic liver disease (P value=<0.001), diabetes mellitus (P-value=0.029) and even in the absence of neither of them (P-value=0.006), unlike the rest of liver function test results. The reason behind this was again related to ACE2 expression [12, 13]. Chai et al analyzed the expression of ACE2 receptors in liver tissue and showed that cholangiocytes express ACE2 receptors much more strongly (59.7%) than hepatocytes (2.6%), giving the characteristic cholestatic feature of liver derangement [12]. It is still unclear if GGT and ALP elevations are related to acute inflammatory stress or are marker of biliary injury and further evaluation is necessary to clarify this finding. GGT elevation was also significantly correlated with the use of antiviral therapy (p value 0.031), which may be explained by macrovascular steatosis with mild hepatic inflammation indicating the possibility of mitochondrial damage dueto drug induced liver injury [14]. Previously, it has been reported that patients suffering from viral infections, such as hepatitis C and human immunodeficiency virus (HIV), are more susceptible to develop drug-induced liver injury (DILI). It is unclear whether SARS-CoV-2 also predisposes to DILI. Increased serum levels of monocyte chemoattractant protein-1 (MCP-1) were found in patients suffering from COVID-19, which is a chemokine known to perpetuate steatohepatitis, especially when agonized by the hepatotoxic effect of antiviral therapy [15].

Ferritin is an acute-phase reactant that can be secreted from damaged hepatocytes. Elevated ferritin level has been previously recognized in conditions of liver enzyme derangement or metabolic syndrome. Statistical correlation between high circulating GGT levels and ferritin was found in this study, although no significant correlation was found between high ferritin level and transaminases. Cao P et al has demonstrated that COVID-19 patients with hyperferritinemia possessed more risk of liver injury and severity of illness [16].

5. Conclusion

Liver enzyme abnormalities are quite common in patients with COVID-19, but are not necessarily correlate with disease severity, with cholestatic picture derangement as a more common manifestation. Ferritin is still an easy-to-use tool to identify liver injury and severity illness.

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