Research Article

Liver and COVID-19 – Experience of a Regional Hospital

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Abstract

The pandemic caused by the novel coronavirus SARS-Co V-2 (COVID-19) has resulted in more than 5 million deaths worldwide and this number continues to rise. Liver enzyme abnormalities often occur in patients diagnosed with COVID-19 and it has been noted that the mortality rate is higher in patients with COVID-19 and severe acute liver injury (ALI) than without ALI. In our department, we treated 173 patients hospitalized with COVID-19 between March to August 2020, for whom follow-up data was available. In this paper we report on our observations of the association between COVID-19 and ALI. Data was collected from the 'Ofek' computer software. We found a statistically significant relationship between higher admission AST levels and severity of COVID-19 infection condition on admission (H= 7.139, P=0.028) which is consistent with previously reported studies.

A higher proportion of patients had pre-existing liver disease (9%) than previously reported and we found a statistically significant relationship between underlying liver disease and COVID-19 severity on discharge (P=0.039). Mortality for hospitalized patients with COVID-19 was 9.2%, which is less than the mortality previously reported. The significant association between AST levels and severity of COVID-19 infection highlights the need to test liver enzyme levels in all patients admitted with COVID-19.

Keywords: Acute Liver Injury; Remdesivir; COVID-19

1. Introduction

Coronavirus Disease 2019 (COVID-19) has caused a pandemic and is responsible for millions of fatalities. COVID-19 is a ribonucleic acid (RNA) virus which binds to the angiotensin-converting enzyme 2 (ACE-2) and is endocytosed into the host cells [1]. The ACE-2 receptor is found in many organs, including the lungs, liver, heart and kidneys [2]. It has been reported in a meta-analysis that the fatality rate for COVID-19 amongst 13398 hospitalized patients was 17.1%. The rate reduced to 11.5% when patients who were admitted to intensive care units were excluded from the analysis [3]. Liver enzyme abnormalities have been noted in more than 40% of cases [4, 5]. One study, comprising 2273 patients who tested positive for COVID-19 and 1108 patients who were negative, showed that COVID-19 positive patients had higher initial and peak alanine transaminase (ALT) levels (28 vs 21 U/L and 45 vs 25 U/L, P<0.001) [6]. Another study showed an increase during the first 2 weeks of hospitalisation in ALT, aspartate aminotransferase (AST), total bilirubin and gamma glutamyl transferase (GGT) levels [7].

Most patients have mild liver function abnormalities. In one large study, 45% of COVID-19 patients with elevated ALT levels had a mild acute liver injury (ALI) (<2 times the upper limit of normal (ULN)), 21% had moderate injury (2-5 times ULN) and 6.4% had a severe injury (>5 times ULN) [8]. The significance of the liver function test abnormalities seen in COVID-19 is unclear. A study of 147 hospitalized COVID-19 patients, compared 93 patients with liver injury in 54 patients without liver injury and they found a similar mortality rate [9]. A larger study of 5771 patients with COVID-19 in China found a strong association between elevated AST and mortality with an odds ratio (OR) 4.81 P<0.001 with AST 40-120 U/L and OR 14.87 P 0.001 with AST > 120 U/L [10] and another study of 2273 COVID-19 positive patients found that patients with severe acute liver injury were more likely to be admitted to intensive care, require intubation or renal replacement therapy and they had higher mortality. The peak ALT level was associated with the likelihood of death or discharge to a hospice (OR 1.14 P<0.044) [6]. Due to the mixed reports of the significant of liver function test abnormalities in COVID-19, this study seeks to use data from a regional hospital to provide further clarification. Liver enzyme abnormalities have also been shown to correlate with COVID-19 severity. A study of 1827 patients included a multivariate analysis, which showed an association between abnormal liver function tests and severe COVID-19 [11].

2. Materials and Methods

In our internal medicine department in a regional hospital, we treated 173 patients between March to August 2020 who were hospitalized due to COVID-19. This excluded patients who were admitted to the intensive care unit. Patient demographics and clinical information were recorded on the computer software 'Ofek'. It was therefore possible to obtain information, including COVID-19 severity on admission and discharge, comorbidities, treatment received and mortality during admission. The 'Ofek' system also provided results from blood tests performed at another hospital and in community healthcare settings which facilitate the compilation of pre-admission blood test results. Treatments administered included remdesivir which was guided by local protocol and provided to consenting patients with severe COVID-19. The treatment protocol involved an initial intravenous loading dose treatment

of 200mg which was then followed by 100mg daily for a further 4 days. Convalescent plasma therapy was administered to consenting patients with moderate or severe COVID-19. The protocol consisted of 2 units of plasma administered at least 12 hours apart. Routine laboratory results tests were reviewed to identify liver enzyme abnormalities. For each patient, COVID-19 severity was determined by:

- Mild- symptoms of COVID-19 (presence of fever, cough, weakness, loss of taste and smell)
- Moderate- clinical or X-ray diagnosis of COVID-19 pneumonia
- Severe- COVID-19 diagnosis and one of the following criteria:
    - Respiratory rate of over 30 per minute
    - Blood oxygen saturation of 93% or lower without oxygen support
    - PaO2/FiO2 ratio lower than 300

A non-parametric Kruskal-Wallis test was used to assess for data variance and unpaired T-tests were used to compare mean CRP, D-dimer and fibrinogen levels in patients with severe and non-severe disease on admission.

3. Results

175 patients were included in the analysis, 93 (53%) were male (average age 65.2) and 82 (47%) were female (average age 64.3). Demographics are displayed in Table 1. On admission, clinical severity was recorded as mild in 83 patients (48%), moderate in 37 (21%) and severe in 53 (31%). On discharge, 106 (61%) patients were mild, 45 (26%) were moderate and 6 (4%) were in a severe condition. 16 patients died in hospital (9.2%) and 1 patient was transferred to the intensive care unit. 17 patients (9%) had an ultra-sound evidence of liver disease, prior to admission, 2 patients (1%) had chronic hepatitis B, 2 patients (1%) had chronic hepatitis C and 1 patient had autoimmune hepatitis (1%). 56 patients (32%) had a recorded diagnosis of diabetes mellitus. 14 patients were treated with the drug remdesivir and 40 patients received convalescent plasma therapy. Liver enzyme results pre-admission and during admission are shown in Tables 2-5. Pre-admission, ALT, AST, alkaline phosphatase (AP) and GGT results were elevated above the reference ranges in 4.2%, 11%, 4.4% and 32.2% respectively. The results were further elevated for all enzymes on admission aside from AP (11.3%, 42.6%, 53.3%). The percentage of abnormal AST, ALT and GGT results peaked 1 week after admission (38.3%, 46.2%, 67.2%). The percentage of abnormal AP results began to rise 1 week after admission and peaked 3 weeks after admission (21%) (Table 2). The pre-admission mean AST, ALT and AP levels were within the reference range for each COVID-19 severity level (Table 3). Mean GGT levels were elevated in mild and severe COVID-19 disease (48 and 60 U/L) (Table 3).

On admission, mean CRP levels were statistically higher in patients with severe disease (13.7 vs 8.1, P=0.0001). Mean D-dimer and fibrinogen levels were also higher in patients with severe disease although they were not statistically significant (3.09 vs 1.9, P=0.13 and 539 vs 498, P=0.28 respectively). There was a statistically significant relationship between higher AST levels and the severity of the COVID-19 infection condition of admission (P=0.028) (Table 4). Mean GGT levels were raised above the reference range in patients with mild, moderate and severe COVID-19 (58, 51 and 88 U/L) (Table 4). There was a weak relationship between GGT levels and COVID severity, although this was not statistically significant (P=0.059). Mean AST was raised only in patients

with moderate disease (71 U/L) and not in patients with mild or severe disease (40 and 47 U/L). Mean ALT and AP levels were not raised in any severity of disease subgroup (ALT 35, 37, 35, AP 77, 75, 83 U/L) (Table 4). There was no statistically significant relationship between the patient condition on admission and ALT or AP levels on admission (P=0.059, 0.960). After 1 week, mean ALT was elevated above the reference range in patients with severe COVID-19 (60 U/L) (Table 5). Mean AST and GGT levels were raised in patients with any severity of COVID-19 (AST 55, 39, 42, GGT 88, 66, 120 U/L) and mean AP levels were within the normal range. There was no statistical significance between the change of liver enzyme levels during admission and COVID-19 severity on discharge (P=0.716, 0.207, 0.307, 0.619). There was no statistical relationship between treatment with remdesivir and change in liver enzymes during admission. (P=0.797, 0.799, 0.495, 0.942). We found a statistically significant relationship between underlying liver disease and COVID-19 severity on discharge (P=0.039).

Gender	**Male (93)**	**Female (82)**
Mean age	65	64
Chronic liver disease	2	3
Diabetes mellitus	37	19
Received remdesivir alone	2	3
Received convalescent plasma therapy alone	21	11
Received both remdesivir and convalescent plasma therapy	6	3

Table 1: Patient demographics.

	ALT	**AST**	**AP**	**GGT**
Reference range (U/L)	**0-55**	**May-34**	**40-150**	**Sep-36**
Pre-admission				
Total results	143	136	137	118
Number of results above reference range	6	15	6	38
Percentage of results above reference range (%)	4.2	11	4.4	32.2
Admission				
Total results	168	148	169	165
Number of results above reference range	19	63	7	88
Percentage of results above reference range (%)	11.3	42.6	4.1	53.3
1 week after admission				
Total results	60	52	59	58
Number of results above reference range	23	24	9	39
Percentage of results above reference range (%)	38.3	46.2	15	67.2

2 weeks after admission				
Total results	25	24	25	25
Number of results above reference range	5	7	4	15
Percentage of results above reference range (%)	20	29.2	16	60
3 weeks after admission				
Total results	19	18	19	15
Number of results above reference range	4	7	4	5
Percentage of results above reference range (%)	21.1	38.9	21	33.3

Table 2: Liver enzyme results pre-admission and during admission.

COVID-19 severity on admission		**ALT**	**AST**	**AP**	**GGT**
Reference range (U/L)		**0-55**	**5-34**	**40-150**	**9-36**
Mild	Mean	21.31	24.55	85.16	48.01
	Std. Deviation	15.02	20.15	51.40	87.64
	N	67	65	63	59
Moderate	Mean	21.59	24.19	72.63	33.55
	Std. Deviation	12.97	12.96	29.69	22.99
	N	29	27	27	20
Severe	Mean	25.52	29.02	86.48	60.29
	Std. Deviation	16.00	17.54	34.87	64.55
	N	46	43	46	38

Table 3: Mean liver enzyme levels and COVID-19 severity pre-admission.

COVID-19 severity on admission		**ALT**	**AST**	**AP**	**GGT**
Reference range (U/L)		**0-55**	**5-34**	**40-150**	**9-36**
Mild	Mean	34.96	40.14	77.04	57.87
	Std. Deviation	53.65	37.58	48.98	88.71
	N	79	65	79	76
Moderate	Mean	37.06	71.28	75.08	50.50
	Std. Deviation	53.60	188.49	32.13	34.50
	N	35	32	36	36
Severe	Mean	34.81	46.91	82.56	88.29
	Std. Deviation	16.75	42.31	50.75	95.27
	N	52	47	52	51

Table 4: Mean liver enzyme levels and COVID-19 severity on admission.

COVID-19 severity on admission		**ALT**	**AST**	**AP**	**GGT**
Reference range (U/L)		**0-55**	**5-34**	**40-150**	**9-36**
Mild	Mean	40.73	54.78	89.90	88.57
	Std. Deviation	41.34	48.46	63.24	128.75
	N	22	18	21	21
Moderate	Mean	45.50	39.25	95.38	66.00
	Std. Deviation	39.87	33.98	47.78	48.98
	N	8	8	8	7
Severe	Mean	59.76	42.08	99.93	120.17
	Std. Deviation	37.65	30.15	56.94	105.97
	Mean	29	24	29	29

Table 5: Mean liver enzyme levels 1 week post admission.

4. Discussion

The mortality rate in our cohort (9.2%) was similar to the rate previously noted in the literature amongst COVID-19 patients (excluding patients admitted to intensive care units) [3]. Additionally, CRP levels were significantly elevated in patients with severe disease on admission as compared with non-severe disease. This indicates worsened systemic inflammation in patients with severe disease and is an indirect marker of hepatic injury. More liver enzyme test results were elevated above the reference range on admission when compared with pre-admission blood test results. ALT, AST and GGT peaked after 1 week (means 48, 95 and 91 U/L) and AP began to increase after 1 week and peaked after 3 weeks (53 U/L). This is consistent with the biphasic pattern of liver damage noted to occur in COVID-19 [12] and the increases in the means are similar to those previously reported [6, 7]. There is a range of possible reasons that might explain the liver enzyme abnormalities seen in COVID-19. The presence of chronic liver disease (approximately 3% of patients with COVID-19) [13] bears some responsibility.

Studies have shown that patients with pre-existing liver disease demonstrate a higher proportion (44-81%) of increased liver enzymes at admission [14, 15]. In our cohort, a higher proportion of patients had pre-existing liver disease (9%) and we found a statistically significant relationship between underlying liver disease and COVID-19 severity on discharge (P=0.039) which is in agreement with previous studies [16, 17]. In future studies it would be interesting to independently study liver disease subtypes to identify if particular liver disease etiologies confer a higher risk of severe COVID-19 disease. This is particularly relevant since it has been previously noted that patients with cirrhosis have higher rates of hepatic decompensation and death following COVID-19 infection [18]. We found a statistical association between AST levels on admission and the severity of COVID-19 infection on admission (H= 7.139, P= 0.028). This is consistent with previous studies [11] and highlights the usefulness of liver enzyme test results on all patients admitted due to COVID-19. There was no statistical significance between the change of liver enzyme

levels during admission and COVID severity on discharge. This is not in agreement with other larger studies [11] and could be due to the small sample size of our cohort and the need to group patients with different comorbidities together for the purposes of the analysis.

The virus may enter the portal circulation of the liver via the brush border on interests which highly express ACE-2 receptors [19]. Hepatic Kupffer cells produce an inflammatory response which can cause liver enzyme abnormalities [20]. In chronic liver disease, the reninangiotensin system has a key role in the development of fibrosis and portal hypertension [21]. It is possible that patients with chronic liver disease may experience further liver injury when the renin-angiotensin system is further induced by COVID-19. Liver injury may also occur in patients with COVID-19 due to hypoxia hepatitis. Acute cardiac failure resulting from sepsis impairs hepatic arterial perfusion, causing hypoxic damage to hepatocytes. In addition the cytokine storm phenomenon associated with the COVID-19 infection can also lead to acute liver injury. Cytokines stimulate chemokines, which increase vascular permeability and generate reactive oxygen species that cause vascular leakage and a systemic inflammatory response which can damage hepatocyte, resulting in liver enzyme abnormalities. Hypoxic hepatitis and the cytokine storm phenomenon are less likely to have caused liver enzyme abnormalities in our cohort owing to the small number of patients with severe disease and the exclusion of patients who were admitted directly to the intensive care unit. 87% of the patients in our cohort had mild or moderate disease and therefore liver enzyme abnormalities are more likely to have been due to pre-existing liver disease or direct liver injury owing to COVID-19 infection. Some of the drugs used in COVID-19 may also exert a hepatotoxic effect. In our center, the drug remdesivir was frequently used which has previously been shown to cause an elevated ALT level in 7% of patients [22]. However, in our cohort, there was no statistical relationship between treatment with remdesivir and change in liver enzymes during admission.

5. Conclusions

Our data are consistent with previous reports that both initial AST level and underlying liver disease are factors associated with COVID-19 severity. This reinforces the importance of testing liver enzyme levels in patients admitted with COVID-19 and being cautious with patients with underlying liver disease. No statistical relationship was found between the use of the drug remdesivir and liver enzyme levels and this should provide reassurance for its continued use.

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