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ORIGINAL ARTICLE

Deranged Liver Enzymes in COVID-19 Patients; and its Impacts on Prognosis

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ABSTRACT

Objectives: The objective of this study was to investigate derangement of liver enzymes in COVID-19 patients. The prevalence of deranged hepatic enzymes with COVID-19 infection, its association with other co-morbidities and any changes in its prognosis were investigated.

Methodology: This study was conducted in Mayo hospital from 1st June 2021 till 31st September 2021. A number of 224 patients were included in this study. Both male and female patients of varying age groups were included in the study. Laboratory tests were conducted to collect data related to liver enzyme values of each patient. Liver function test (LFT) was performed twice, first on day 1 and then on day 7 to observe any further changes in liver enzymes values in COVID-19 patients. The LFTs of the patients told us Bilirubin, Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), C-reactive protein (CRP), Ferritin and D-dimer levels in the body. The data were analyzed by SPSS analysis. The t-test used was for the comparison of standard features in both groups. The P value less than 0.05 was regarded significant. Data about co-morbidities, autoimmune disease and its treatment, and outcome was also collected. Gender, autoimmune disease and COVID-19 PCR data was analyzed using descriptive analysis. Prevalence of deranged liver enzymes in COVID-19 patients was analyzed using paired sample test. Association with co-morbidities and prognosis was also analyzed by frequency analysis.

Results: Sample consists of 224 individuals among them the ratio of male and female was 50:50 with age ranging 17-90 years. There were 220 COVID-19 PCR positive patients, 1 negative and 3 suspected patients with about 89.7 per cent patients having no autoimmune disease. The results showed that bilirubin, ALT and D-dimer show significant derangement in COVID-19 patients while ALP, CRP and Ferritin did not. The patients with both diabetes mellitus and hypertension showed the highest percentage of association with the value being 25 percent. Other co-morbidities like asthma, chronic liver disease and hepatitis C among many other also showed association with corona virus disease. And the results of prognosis showed that 33 percent, of the patients were shifted to the ICU. 18.8 percent of the patients were admitted in the hospital. 20.5 percent of the patients died. 18.8 percent were discharged and 6.3 percent shifted to the HDU.

Conclusion: As the results show liver enzyme ALT, D-dimer and bilirubin show significant derangement in COVID-19 patients. This concludes that some, but not all, of the liver enzyme derangement is prevalent in COVID-19 patients. The patients with both diabetes mellitus and hypertension showed highest association with COVID-19. The patients being shifted to the ICU was the highest prognosis of disease. Other than that a large number of patients died, some were admitted to the hospital due to worsening condition, some discharged and others shifted to the HDU.

Keywords: Deranged liver enzymes, Liver enzymes, COVID-19, Patients, Prevalence, Association, Prognosis, Outcome.

INTRODUCTION

In December 2019, SARS-CoV-2 emerged in China. It caused a severe disease, corona virus disease, which was declared a pandemic by WHO. This disease effected people worldwide and many countries faced health crisis. It is a highly contagious disease, which makes its spread easy and thus large number of people getting the virus and becoming ill [1]. Till date this virus has caused almost 4.3 million deaths worldwide.

SARS-CoV-2 is a single stranded RNA virus. It belongs to Coronaviridae family and is a positive-sence virus [1]. Previously in 2002, SARS-CoV caused Severe Acute Respiratory Syndrome. It was a mass spreading virus that infected more than 8 thousand people in different countries and caused a large number of deaths [2]. Then again in 2012, another virus of Coronaviridae family, MERS-CoV, caused Middle East respiratory syndrome [3]. In comparison to these two viruses, SARS-CoV-2 is highly more contagious and has the ability to persist on different surfaces for as long as days [4]. Other than direct contact with the infected individual, this is another major cause of rapid spread of virus.

The corona virus disease not only effects the lungs and respiratory track but also the other parts and systems of the body. Along with respiratory changes, this virus causes leukopenia, which is low leukocytes in the body [5]. The laboratory tests also showed increased C- reactive protein levels in the body that indicated presence of some kind of inflammation in the body and elevated Erythrocyte Sedimentation Rate (ESR) value [6]. This elevated value also indicates inflammation in the body. COVID-19 also interrupts liver function that in turn deranges its enzymes level. About 60 percent of the COVID- patients show liver dysfunction [7].

Co-morbidities are also associated with the COVID-19. They either increase the risk of getting the virus or decrease the chance of recovery after getting the virus. [18]

All of this also changes the prognosis of disease. Patients of COVID-19 with deranged liver enzymes and co-morbidities have higher chance of ending up in the ICU or death. [13]

This study focuses on the investigation of derangement of liver enzymes in COVID-19 patients. The prevalence of deranged hepatic enzymes with COVID-19 infection, its association with other co-morbidities and any changes in its prognosis.

METHOD

This study was conducted in Mayo Hospital from 1st june 2021 till 31st September 2021. A number of 224 patients were included in this study. Both male and female patients of varying age groups were included in the study. The number of male and female patients was evaluated using descriptive analysis.

Laboratory tests were conducted to collect data related to liver enzyme values of each patient. Liver function test (LFT) was performed twice, first on day 1 and then on day 7 to observe any further changes in liver enzymes levels in COVID-19 patients. The LFTs of the patients told us Bilirubin, Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), C-reactive protein (CRP), Ferritin and D-dimer values. Prevalence of deranged liver enzymes in COVID-19 patients was analyzed using paired sample test. The

result of this analysis told us about the prevalence of deranged liver enzymes in COVID-19 patients.

The data were analyzed by SPSS analysis. The t-test used was for the comparison of standard features in both groups. The P value less than 0.05 was regarded significant.

The normal value of bilirubin was 1.2mg/dL, Alanine aminotransferase (ALT) 7 to 55 U/L, Alkaline Phosphatase (ALP) 44 to 147 IU/L, C-reactive protein (CRP) below 3.0 mg/L, Ferritin 24 to 336 mg/liter for men and 11 to 307 mg/ liter for women and D-dimer less than 0.50.

Data about co-morbidities, autoimmune disease and its treatment was also collected. The co-morbidities included diabetes mellitus (DM), hypertension (HTN), asthma, ischemic heart disease (IHD), chronic liver disease (CLD), chronic obstructive pulmonary disease (COPD), hepatitis C (HCV), stroke, myasthenia, schizophrenia, tuberculosis and tetralogy of fallot (TOF). The frequency analysis of this data gave us information about associations of COVID-19 and deranged liver enzymes patients with different co-morbidities.

The prognosis was evaluated on the basis of descriptive analysis of the outcome data. It included the frequency of patients admitted, shifted to ICU and HDU, discharged and died.

Autoimmune disease and COVID-19 PCR data was analyzed using descriptive analysis.

RESULTS

Sample consists of 224 individuals among them the ratio of male and female was 50:50 with age ranging 17-90 years. This result is shown in Table 1.

Table 1: Gender Frequency

Gender

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	male	112	50.0	50.0	50.0
	female	112	50.0	50.0	100.0
	Total	224	100.0	100.0	

There were 220 COVID-19 PCR positive patients, 1 negative and 3 suspected patients with about 89.7 per cent patients having no autoimmune disease. These results are shown in Table 2 and Table 3.

Table 2: COVID PCR Results

Frequency		Percent	Valid Percent	Cumulative Percent
Positive	220	98.2	98.2	98.2
Negative	1	0.4	0.4	98.7
Suspected	3	1.3	1.3	100.0
Total	224	100.0	100.0	

Mostly the patients of autoimmune disease were treated with NSAIDS and steroids.

Table 3: Autoimmune Disease

Frequency		Percent	Valid Percent	Cumulative Percent
1	23	10.3	10.3	10.3
2	201	89.7	89.7	100.0
Total	224	100.0	100.0	

The prevalence of deranged liver enzymes in COVID-19 patients was estimated by analyzing the level of different liver enzymes in patients from LFTS. The descriptive analysis of different liver enzymes is given in Table 4.

Table 4: Paired Sample Statistics

Mean		N	
Pair 1	bilirubin-1	1.1577	222
	bilirubin-7	1.8423	222
Pair 2	ALT-1	57.7072	222
	ALT-7	71.0180	222
Pair 3	ALP-1	184.4279	222
	ALP-7	188.1937	222
Pair 4	CRP-1	59.1982	219
	CRP-7	79.3228	219
Pair 5	Ferritin-1	920.5275	218
	Ferritin-7	986.4083	218
Pair 6	D-dimers-1	1863.8413	214
	D-dimers-7	1491.1124	214

Table 5 shows the significance of correlation of different liver enzymes. Bilirubin (pair 1), ALT (pair 2), ALP (pair 3), Ferritin (pair 5), D-dimers (pair 6) show significant correlation but CRP (pair 4) do not show significant correlation.

Table 5 Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	bilirubin-1 & bilirubin-7	222	0.363	0.000
Pair 2	ALT-1 & ALT-7	222	0.380	0.000
Pair 3	ALP-1 & ALP-7	222	0.740	0.000
Pair 4	CRP-1 & CRP-7	219	0.093	0.168
Pair 5	Ferritin-1 & Ferritin-7	218	0.529	0.000
Pair 6	D-dimers-1 & D-dimers-7	214	0.755	0.000

The Table 6 shows the prevalence of deranged liver enzymes in COVID-19 patients. The data was collected via LFTs of the patients and analyzed by paired samples test. The results show that bilirubin, ALT and D-dimer show significant derangement in COVID-19 patients. P value is the decision criteria of this t test. The result of ALT and D-dimer shows significance i.e. p value less than 0.05. Bilirubin is statistically significant at 10 percent level of confidence. ALP, CRP and Ferritin are not significant i.e. p value more than 0.05.

The data were analyzed by SPSS analysis. The t-test used was for the comparison of standard features in both groups. The P value less than 0.05 was regarded significant.

Table 6: Paired Samples Test showing prevalence of deranged liver enzymes in COVID-19 patients

		Paired Differences					t	Df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	bilirubin-1 - bilirubin-7	-.68468	5.43490	.36477	-1.40355	.03418	-1.877	221	.062
Pair 2	ALT-1 - ALT-7	-13.31081	82.64605	5.54684	-24.24228	-2.37934	-2.400	221	.017
Pair 3	ALP-1 - ALP-7	-3.76577	101.13572	6.78778	-17.14284	9.61130	-.555	221	.580
Pair 4	CRP-1 - CRP-7	-20.12466	246.48924	16.65620	-52.95245	12.70314	-1.208	218	.228
Pair 5	Ferritin-1 - Ferritin-7	-65.88073	832.28512	56.36946	-176.98248	45.22101	-1.169	217	.244
Pair 6	D-dimers-1 - D-dimers-7	372.72888	1596.82835	109.15694	157.56266	587.89509	3.415	213	.001

The data collected about co-morbidities included the disease: diabetes mellitus (DM), hypertension (HTN), asthma, ischemic heart disease (IHD), chronic liver disease (CLD), chronic obstructive pulmonary disease (COPD), hepatitis C (HCV), stroke, myasthenia, schizophrenia, tuberculosis and tetralogy of fallot (TOF). The frequency analysis of this data gave us information about associations of COVID-19 and deranged liver enzymes patients with different co-morbidities.

Table 7 shows the results of associations. Patients with both diabetes mellitus and hypertension show the highest percentage of

association with the value being 25 percent. While diabetes mellitus alone show 11.2 percent association in COVID-19 patients, this is the second highest value. The third highest value is 9.4 percent, it belong to hypertension patients. 23.2 percent of the total patients did not have any other disease or co-morbidity.

Table 7: Associations with different Co-morbidities

Frequency		Percent	Valid Percent
ASTHMA	3	1.3	1.3
ASTHMA+PNEUMONOCONIOSIS	1	0.4	0.4
CLD	1	0.4	0.4
CLD+COPD	1	0.4	0.4
COPD	2	0.9	0.9
DM	25	11.2	11.2
DM+HEP C	1	0.4	0.4
DM+HTN	56	25.0	25.0
DM+HTN +CLD	3	1.3	1.3
DM+HTN+ASTHMA	5	2.2	2.2
DM+HTN+ASTHMA+STROKE	1	0.4	0.4
DM+HTN+CL+STROKE	1	0.4	0.4
DM+HTN+COPD+ASTHMA	1	0.4	0.4
DM+HTN+HCV	1	0.4	0.4
DM+HTN+IHD	12	5.4	5.4
DM+HTN+IHD+CLD	10	4.5	4.5
DM+HTN+IHD+CLD+COPD+STROKE	3	1.3	1.3
DM+HTN+IHD+COPD	3	1.3	1.3
DM+HTN+IHD+COPD+STROKE	1	0.4	0.4
DM+HTN+IHD+STROKE	7	3.1	3.1
HTM+CLD	1	0.4	0.4
HTN	21	9.4	9.4
HTN+ASTHMA	1	0.4	0.4
HTN+STROKE	1	0.4	0.4
IHD	5	2.2	2.2
MYASTHENIA	1	0.4	0.4
NO	52	23.2	23.2
SCHIZOPHERNIA	1	0.4	0.4
STROKE	1	0.4	0.4
TOF	1	0.4	0.4
TUBERCULOSIS	1	0.4	0.4
Total	224	100.0	100.0

Table 8 shows the prognosis of the disease. Highest percentage, 33 percent, of the patients were shifted to the ICU. 18.8 percent of the patients were admitted in the hospital. 20.5 percent of the patients died. 18.8 percent were discharged and 6.3 percent shifted to the HDU.

Table 8: Prognosis

Frequency		Percent	Valid Percent	Cumulative Percent
	6	2.7	2.7	2.7
Admitted	42	18.8	18.8	21.4
Death	46	20.5	20.5	42.0
Discharged	42	18.8	18.8	60.7
HDU	14	6.3	6.3	67.0
ICU	74	33.0	33.0	100.0
Total	224	100.0	100.0	

DISCUSSION

In this study we found significant derangement of ALT, D-dimer and bilirubin in COVID-19 patients, highest association with diabetes mellitus and hypertension, and the most prominent prognosis being shifted to the ICU. However, ALP, CRP and Ferritin did not show significant prevalence of derangement in COVID-19 patients.

The elevated level of ALT can be due to hepatic injury or some gall bladder conditions or other conditions that are not directly related to liver i.e. muscle disease, thyroid disorder, inflammatory bowel disease, heart disease and bone disorders [1]. ALT is a special marker of liver disease.

Many studies have proved that COVID do impact the functioning of liver. It can do so in one of the following two ways: first by directly attacking the liver and secondly by systemic inflammation that will eventually catch up with liver and impair its functioning. [8]

According to a study, COVID-19 virus was found in trachea and lungs, which are part of respiratory system, and also in other non-respiratory organs i.e. stomach, renal tubules of the kidney, adrenal glands, parathyroid glands, pituitary gland, liver, cerebrum, sweat glands, small intestine and pancreas. [9]

This presence of the virus in digestive system i.e. stomach, intestine, pancreas and liver, suggest that the patients ingested the virus via contaminated food or water. It also suggests that along with the respiratory system, the virus can also target other systems and organs i.e. digestive system and liver. The pathological effect of the virus can be due to direct attack of virus on organ or by systemic inflammation. [9]

So, if along with respiratory system, digestive system is also involved in corona virus disease, as some studies show. Then the virus can be transmitted via feces and urine along with respiratory droplets. [9, 10, 11]

According to another study's results albumin levels decreased in almost 98 percent of the patients, in 28 percent ALT increased, in 18 percent bilirubin increased and in 35 percent AST increased [12]. Studies also show that more percentage of COVID patients with elevated liver enzymes required intensive care then those patients without any elevated enzymes [13].

In a study, MERS-CoV showed some liver changes including immunity cells infiltration, liver cells necrosis and fatty changes [14].

Systemic inflammation during COVID causes increased cytokines i.e. interleukins and tumor necrosis factor. This can derange the levels of liver enzymes [15]. Elevated CRP in turn also increases liver enzyme levels [16, 17].

More studies should be conducted for understanding the prevalence, association with co-morbidities and prognosis of deranged liver enzymes in COVID-19 patients.

CONCLUSION

As the results show liver enzyme ALT, D-dimer and bilirubin show significant derangement in COVID-19 patients. This concludes that some, but not all, of the liver enzyme derangement is prevalent in COVID-19 patients. The patients with both diabetes mellitus and hypertension showed highest association with COVID-19. The patients being shifted to the ICU was the highest prognosis of disease. Other than that a large number of patients died, some were admitted to the hospital due to worsening condition, some discharged and others shifted to the HDU.

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