Research Article

Derangements of Liver Enzymes in Covid-19 Positive Patients of Pakistan: A Retrospective Comparative Analysis with other Populations

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Abstract

Background & Objectives: COVID-19 is a global pandemic, also affecting Pakistan with its first case reported on 26th February 2020. Since then, it has been a total of 217,809 positive cases and 4473 deaths in Pakistan so far. Deranged liver function enzymes levels are prominently detected extra-pulmonary clinical manifestation of COVID-19 reported by at least one-half of the patients. Our study aimed to evaluate these derangements in our population.

Methods: A retrospective, observational study was conducted to include all the admitted patients having COVID-19 positive, and evaluated those for derangements of liver function enzymes (n=77). The statistical analysis was conducted to compare those derangements amongst the disease severity, prognostic markers, and death.

Results: Out of the 77 patients, 55 were admitted in the ward, 22 were in ICU, 61 of them recovered, while 16 deaths reported. The most deranged liver enzyme was found out to be Gamma-glutamyl transferase (51.94%), followed by Aspartate transferase (41.55%), Alanine transferase (28.57%), and Alkaline phosphatase (14.28%). Total bilirubin was deranged in only 10 patients, however, direct bilirubin was above the normal range in 33 patients, while indirect component in only 4 patients. Increased direct bilirubin, Aspartate aminotransferase, and Gamma-glutamyl transferase were associated with increased mortality, increased ICU admissions, increased neutrophils, lymphocytopenia, leukocytosis, and neutrophil to lymphocyte ratio>3, while Alanine aminotransferase and Alkaline phosphatase were not associated with the above factors.

Conclusion: The deranged values of liver function enzymes in COVID-19 are correlated with an increased number of ICU admissions, mortalities as well as prognostic markers.

Keywords: COVID-19; Coronavirus; Liver function enzymes; Intensive care unit; Derangement

Introduction

Deranged liver function enzymes levels are prominently detected extra-pulmonary clinical manifestation detected in inhabitants suffering from severe acute respiratory syndrome coronavirus disease 19 (SARS Covid-19), approximately reported by at least one-half of the patients [1]. Studies conducted in recent intervals are suggestive of ~15% to ~45% sufferers reported to encounter manifestations of liver damage during infection [2,3]. Patients in intensive care units (ICU) and critical states are more likely to have their liver biochemical markers deranged denoting the severity of infection [4]. Pathogenesis of SARS-COVID 19 ensures the utilization of angiotensin-converting enzyme 2 (ACE-2) receptor as a target for cell entrance, this receptor plays a vital role in the propagation of virus as it is scattered on endothelial cells of bile duct predominantly and liver making liver a prominent organ to be infected [5]. Post-mortem outcomes encountered within deceased patients revealed moderate microvascular steatosis and mild lobular and portal activity denoting that dysfunction might be the result of COVID-19 drug potentiated hepatic injury [6,7]. Other histological post-mortem outcomes are suggestive of enlargement of the liver, liver cells degeneration, lobular focal necrosis along with neutrophil and lymphocyte aggregations in the portal site, and congestion of hepatic sinuses with micro-thrombosis [7].

Hepatic derangements detected within severe patients of Covid-19 are slight high levels of alanine transaminase (ALT 30.3%), aspartate aminotransferases (AST 29.2%), alkaline phosphatase (ALP 17%) and total bilirubin (10.2%) [2,8]. Liver biochemical markers dysfunction are designated as ALT >40 unit/liter (U/L), AST >40 unit/liter (U/L), gamma-glutamyl transferase (GGT) >55 unit/liter (IU/L), Alkaline phosphatase (ALP) >135 unit/liter (IU/L) and total bilirubin >17 unit/liter (IU/L) [6,7]. Based on standardized readings, abnormalities of liver function enzymes are categorized into three classes: hepatic, cholestatic, and mixed. Sufferers reporting deranged levels of AST and ALT exceeding 3 times the upper ranges are categorized as hepatic, sufferers reporting elevated levels of GGT and ALP twice the upper ranges are categorized as cholestatic, while elevated levels of a combination of both ALT/AST thrice the upper ranges and GGT/ALP twice the upper ranges were categorized as mixed type [7].

Clinical manifestation observed within individuals suffering from COVID-19 with deranged liver function enzymes is severe pneumonia [6]. Utilization of medications that trigger damage of liver such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antiviral agents like ribavirin, lopinavir, ritonavir, herbal drugs, and interferon add to the severity of infection [6]. Uncontrollable immune manifestation and cytokines storm mediated systemic inflammation results in injury to the liver resulting in derangement of biochemical markers of liver, individuals suffering from COVID-19 were detected with high levels of TH17, CD8 T cells, interleukin-2, interleukin-6, interleukin-7, interleukin-10, tumor necrosis factor-alpha (TNF-alpha), granulocyte-colony stimulating factor, interferon-inducible protein 10, high levels of C-reactive protein in samples of their peripheral blood triggering dysfunction of liver enzymes [7,8].

In our study, we documented the derangements of liver function enzymes caused by Covid-19 in patients suffering from the infection in a tertiary care hospital of Pakistan, analyzed them amongst the patients who are recovering against those requiring critical care, and then comparing those statistics with other populations as well.

Methods

The study was conducted as a single centered, retrospective, observational study, from 27th February till 30th April 2020 after taking the ethical approval, and included all patients who were diagnosed as COVID-19 positive via either nasopharyngeal or oropharyngeal swab for PCR. The outcomes of the disease were followed throughout the hospital course. Out of the total patients evaluated for the derangements of liver function enzymes, those with a known history of pre-existing liver disease were excluded from the study to remove a confounding factor. The study was focused on documenting the liver enzymes derangements on admission caused by COVID-19, and their significance on disease course and prognosis.

Out of the 77 admitted patients, 61 were recovered and discharged with negative PCR for Covid-19. A total of 16 deaths occurred so far due to COVID-19. Out of the 77 included patients, 41 were males and 26 were females, 55 were having mild to moderate disease severity hence admitted in the isolation wards, while 22 were having severe disease according to the National guidelines of COVID management [9], hence were admitted in Intensive care unit. The normal values of liver function enzymes were considered as <40 IU/L for ALT and AST, <55 IU/L for GGT, between 53 to 135 IU/L for ALP, total bilirubin as 0.3 to 1.0 mg/dl, direct bilirubin as 0.0-0.3 mg/dl, and indirect bilirubin as 0.25-0.9 mg/dl.

The statistical analysis was conducted by the Statistical Package for the Social Sciences (SPSS version 25.0). All continuous variables were described as both mean & standard deviation as well as median & interquartile range. The reason behind this strategy was the data being normally distributed in certain laboratory investigations while not normally distributed in the other. The means were then compared using both independent sample t-test and Mann Whitney U-test, and amongst them the p-value was considered more significant according to Levene statistics. The comparison of categorical data was done either using the Chi-square test or Fisher's exact test according to the limitation of data. A p-value of <0.05 was considered statistically significant. All the highly significant values of <0.001 were rounded off as 0.001.

Results

The demographic data of all the admitted patients (n=77) is described in Table 1. The mean age of the study population was 52.91 ± 16.65, with elderly patients are more likely to be admitted in the intensive care unit (p=0.007). The median age for males is 57.50 while that for females is 49 years. The most age group affected was 50-75 years. More than two-thirds were admitted to the isolation ward while remaining in the intensive care unit. The disease outcomes were more severe and deaths were more reported from ICU patients (p=0.001).

Now, coming to evaluation for liver enzymes derangements, the liver enzymes mostly deranged was found out to be gamma-glutamyl transferase, in 51.9% of the patients, having mean values of 77.94 ± 84.18 but a median of 56.00 as shown in Table 2. Gamma-glutamyl transferase was more likely to be elevated in ICU patients (p=0.150), deceased patients (p=0.056), were elevated in 12 out of 16 deceased patients as compare to half of the recovered patients (p=0.038). It was also more likely to be elevated with lymphopenia (p=0.145) and increased neutrophil to lymphocyte ratio-NLR >3 (p=0.106).

The second most affected enzyme was found to be AST, deranged in 32 out of 77 patients (41.6%), having mean values of 73.71 ± 172.20 and a median of 41.00. The median was more likely to be elevated in ICU patients (p=0.019) as shown in Table 3, markedly increased in deceased patients (p=0.001), 12 out of 16 deceased patients showed increased levels as compared to one-third of the recovered (p=0.002), also outnumbering ICU patients as compared to the number of ward patients (p=0.013), associated with lymphopenia (p=0.056), neutrophilia (p=0.058), and NLR >3 (0.001). ALT was deranged in 28.6% of the patients in our study, mean values of 66.49 ± 157.00, median of 34.00, elevated values not significantly associated with ICU stay or death, neutrophil or lymphocyte counts. Alkaline phosphatase was the least affected enzyme in COVID-19 patients, being elevated in only 11 patients (14.3%), with a mean value of 113.10 ± 136.09 and a median of 94.00. Strikingly, ALP was also found below the normal range in 13% of the patients (n=10).

Total bilirubin was elevated in only 13% of the study population, however, it was significantly associated with increased neutrophil count (p=0.009), lymphocytopenia (p=0.003), Leukocytosis (0.003), and NLR>3 (p=0.011). Direct bilirubin was strikingly much higher than indirect bilirubin in Covid-19 patients with 33 patients (42.9%) showing elevated direct bilirubin although total bilirubin remains within the normal range in majority of them, while only 4 patients showed elevated indirect bilirubin (5.2%). The elevation of direct bilirubin was significantly associated with increased neutrophil counts (p=0.001), lymphocytopenia (p=0.001), leukocytosis (0.001), NLR>3 (0.001), and median values also higher in ICU patients (p=0.005) as well as deceased patients (p=0.001), while 13 of the 16 deceased patients showed elevated levels as compared to one-third of the recovered patients (p=0.001).

Lastly, only 3 patients out of 77 (3.9%) presented with fulminant hepatitis having peak values of total bilirubin (11.03 mg/dl), direct bilirubin (3.22 mg/dl), indirect bilirubin (7.81 mg/dl), ALT (1163 IU/L), AST (1246 IU/L), ALP (1211 IU/L), and GGT (567 IU/L). These results altered the means and standard deviations; hence medians were used for non-normal distribution of the data.

Table 1: Demographic data of the study population (n=77)

S.no #	Characteristics	Total (n=77)	Ward (n=55)	ICU (n=22)	p-value
1	Median age (IQR)	55.00 (38.50-65.70)	50.00 (33.50-63.50)	64.00 (56.00-68.00)	0.009”
	Mean age (in years)	52.91 ± 16.65	49.57 ± 17.84	61.52 ± 8.66	0.007*
2	**Males (n=51)** Median (IQR)	57.50 (44.50-70.00)	55.00 (37.25-70.50)	62.50 (53.00-68.50)	0.344”
	Mean ± SD	56.27 ± 15.29	54.40 ± 17.13	60.28 ± 9.67	0.239*
3	**Females (n=26)** Median (IQR)	49.00 (31.00-63.00)	40.00 (31.00-55.00)	65.00 (62.00-68.00)	0.005”
	Mean ± SD	46.75 ± 17.58	41.94 ± 16.59	65.00 ± 3.60	0.006*
4	**Age groups**	**0-50**	**51-75**	**>75**	-
		34 (44.15%)	40 (51.94%)	03 (3.89%)	
	Males (n=51)	22 (43.13%)	26 (50.98%)	3 (5.88%)	0.307**
	Females (n=26)	12 (46.15%)	14 (53.84%)	0 (0.0%)	
	Ward (n=55)	32 (58.18%)	20 (36.36%)	3 (5.45%)	0.001**
	ICU (n=22)	2 (9.09%)	20 (90.90%)	0 (0.0%)	
5	Confirmation of diagnosis	Nasopharyngeal swab (PCR): 35 (45.45%)	Oropharyngeal swab (PCR): 42 (54.54%)		-
6	Occupation	Medical: 8 (10.38%)	Non-medical: 69 (89.61%)		
7	Hospital stay	Isolation ward: 55 (71.42%)	Males: 35 (63.63%)		0.335^
			Females: 20 (36.36%)		
		Intensive care unit: 22 (28.57%)	Males: 16 (72.72%)		
			Females: 6 (27.27%)		
8	Recovered patients (n=61)		Deceased patients (n=16)		-
	Males: 39	Females: 22	Males: 12	Females: 4	0.289**
	Ward: 53	ICU: 8	Ward: 2	ICU: 14	0.001**

^ indicates Chi-square test used to compute the p-value. “ indicates Mann Whitney U-test to compute the p-value. * indicates Independent sample t-test used to compute the p-value. ** indicates Fisher’s exact test to compute the p-value.

Table 2: Descriptive statistics of Liver function enzymes in Covid-19 patients and correlation of deranged LFT's with other biochemical and prognostic parameters (n=77)

Liver Function tests	**Characteristic values of Covid-19 patients**			
Total bilirubin (Normal range: 0.3-1.0 mg/dl)	**<1.0 mg/dl**	**1.0-2.0 mg/dl**	**>2.0 mg/dl**	
	n=67 (87.0%)	n=7 (9.1%)	n=3 (3.9%)	
	Mean ± SD	**95% confidence interval**	**Median**	**Interquartile range**
	0.77 ± 1.32	0.47-1.07	0.50	0.30-0.76
Direct bilirubin (Normal range: 0.0-0.3 mg/dl)	**<0.3 mg/dl**	**0.3-0.6 mg/dl**	**>0.6 mg/dl**	
	n=44 (57.1%)	n=25 (32.5%)	n=8 (10.4%)	
	Mean ± SD	**95% confidence interval**	**Median**	**Interquartile range**
	0.45 ± 0.95	0.24-0.67	0.26	0.15-0.43
Indirect bilirubin (Normal range: 0.25-0.8 mg/dl)	**<0.25 mg/dl**	**0.25-0.8 mg/dl**	**>0.8 mg dl**	
	n=45 (58.4%)	n=28 (36.4%)	n=4 (5.2%)	
	Mean ± SD	**95% confidence interval**	**Median**	**Interquartile range**
	0.30 ± 0.39	0.21-0.39	0.22	0.14-0.32
Aspartate aminotransferase (Normal range: <45 IU/L)	**<45 IU/L**	**45-60 IU/L**	**61-100 IU/L**	**>100 IU/L**
	n=45 (58.4%)	n=16 (20.8%)	n=12 (15.6%)	n=4 (5.2%)
	Mean ± SD	**95% confidence interval**	**Median**	**Interquartile range**
	73.71 ± 172.20	34.62-112.80	41.00	28.50-56.00
Alanine aminotransferase (Normal range: <45 IU/L)	**<45 IU/L**	**45-60 IU/L**	**61-100 IU/L**	**>100 IU/L**
	n=55 (71.4%)	n=7 (9.1%)	n=10 (13.0%)	n=5 (6.5%)
	Mean ± SD	**95% confidence interval**	**Median**	**Interquartile range**
	66.49 ± 157.00	30.85-102.12	34.00	23.00-49.00
Gamma glutamyl transferase (Normal range: <55 IU/L)	**<55 IU/L**	**55-70 IU/L**	**71-100 IU/L**	**>100 IU/L**
	n=37 (48.1%)	n=9 (11.7%)	n=12 (15.6%)	n=19 (24.7%)
	Mean ± SD	**95% confidence interval**	**Median**	**Interquartile range**
	77.94 ± 84.18	58.83-97.05	56.00	32.00-102.00
Alkaline phosphatase (Normal range: 53-135 IU/L)	**<53 IU/L**	**53-135 IU/L**	**136-200 IU/L**	**>200 IU/L**
	n=10 (13.0%)	n=56 (72.7%)	n=6 (7.8%)	n=5 (6.5%)
	Mean ± SD	**95% confidence interval**	**Median**	**Interquartile range**

			113.10 ± 136.09	82.21-143.99	94.00	66.00-115.50			
#	**Characteristics values of other biomarkers**		**Deranged Liver function tests (n= no. of subjects)**						
			T.B (n=10)	**D.B (n=33)**	**I.B (n=04)**	**ALT (n=22)**	**AST (n=32)**	**GGT (n=40)**	**ALP (n=11)**
1	**Neutrophils** (40-75%)	>75 (n=35)	n=9	n=23	n=4	n=11	n=19	n=20	n=6
		<75 (n=42)	n=1	n=10	n=0	n=11	n=13	n=20	n=5
	p-value		**0.009***	**0.001**^	**0.038***	0.589^	0.058^	0.365^	0.530*
2	**Lymphocytes** (20-45%)	<20 (n=41)	n=10	n=27	n=4	n=13	n=21	n=25	n=8
		>20 (n=36)	n=0	n=6	n=0	n=9	n=11	n=15	n=4
	p-value		**0.003***	**0.001**^	0.122*	0.628^	0.056^	0.145^	0.325*
3	**TLC** (4.0-11.0 x10^9/L)	>11 (n=25)	n=8	n=17	n=1	n=8	n=12	n=13	n=5
		<11 (n=52)	n=2	n=16	n=0	n=14	n=20	n=27	n=6
	p-value		**0.003***	**0.001**^	**0.008***	0.557^	0.530^	0.841^	0.306*
4	**Neutrophil to Lymphocyte ratio** (1-3)	>3 (n=47)	n=9	n=28	n=4	n=16	n=26	n=28	n=8
		<3 (n=30)	n=1	n=5	n=0	n=6	n=6	n=12	n=3
	p-value		**0.011***	**0.001**^	0.291*	0.201^	**0.001**^	0.106^	0.514*
5	**Ward (n=55)**		n=5	n=18	n=1	n=14	n=18	n=27	n=8
	ICU (n=22)		n=5	n=15	n=3	n=8	n=14	n=13	n=3
	p-value		0.138*	**0.005**^	0.068*	0.338^	**0.013**^	0.428^	1.000*
6	**Recovered (n=61)**		n=5	n=20	n=1	n=15	n=20	n=28	n=8
	Deceased (n=16)		n=5	n=13	n=3	n=7	n=12	n=12	n=3
	p-value		**0.028***	**0.001**^	**0.027***	0.212*	**0.002**^	**0.038**^	0.689*

^ indicates Chi-square test used to compute p-value. * indicates Fisher's exact test to compute p-value. T.B: total bilirubin, D.B: direct bilirubin, I.B: indirect bilirubin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: gamma glutamyl-transferase.

Table 3: Correlation of initial laboratory investigations amongst the patients of Covid-19.

#	**Laboratory investigation**	**Ward (n=55)**	**ICU (n=22)**	p-value	**(Ward n=55)**	**(ICU n=22)**	p-value
		Mean ± Standard deviation			Median (Inter-quartile range)		
1	**Hemoglobin** (g/dl)	13.12 ± 2.19	11.43 ± 2.00	**0.005***	13.20 (11.85-14.67)	11.90 (10.20-13.30)	**0.005**^
2	**TLC** ($10^{\wedge 9}$/L)	8.61 ± 4.11	13.76 ± 8.93	**0.016***	7.00 (5.30-9.95)	11.60 (7.20-17.90)	**0.009**^
3	**Platelets** ($10^{\wedge 9}$/L)	236.69 ± 78.77	289.57 ± 133.91	0.052*	225.00 (185.75-284.00)	295.00 (185.00-365.00)	0.108^
4	**Neutrophils** (%)	64.41 ± 14.99	80.68 ± 10.39	**0.001***	66.00 (52.50-73.25)	82.00 (75.00-88.00)	**0.001**^
	Lymphocytes (%)	26.21 ± 12.48	11.78 ± 7.69	**0.001***	26.00 (18.75-35.00)	9.00 (6.00-17.00)	**0.001**^
	Neutrophil to lymphocyte ratio	3.90 ± 4.15	11.45 ± 10.34	**0.006***	2.42 (1.32-4.10)	9.11 (4.52-14.66)	**0.001**^
5	**Total bilirubin** (mg/dl)	0.54 ± 0.32	1.35 ± 2.36	0.122*	0.46 (0.28-0.75)	0.61 (0.43-0.96)	**0.027**^
	Direct (mg/dl)	0.28 ± 0.16	0.89 ± 1.71	0.105*	0.24 (0.15-0.36)	0.36 (0.24-0.58)	**0.005**^
	Indirect (mg/dl)	0.23 ± 0.17	0.45 ± 0.66	0.143*	0.20 (0.12-0.31)	0.26 (0.17-0.39)	0.112^
6	**ALT** (IU/L)	61.20 ± 154.74	79.72 ± 165.47	0.643*	32.00 (22.00-46.00)	38.00 (26.50-54.75)	0.248^
7	**AST** (IU/L)	64.29 ± 163.75	97.27 ± 193.78	0.451*	38.00 (27.00-52.00)	49.50 (41.75-64.25)	**0.019**^
8	**γGT** (IU/L)	72.54 ± 81.90	91.45 ± 90.18	0.377*	50.00 (25.00-95.00)	73.50 (36.50-116.50)	0.150^
9	**ALP** (IU/L)	98.07 ± 51.47	150.68 ± 241.12	0.126*	88.00 (62.00-118.00)	95.00 (73.00-228.80)	0.346^
10	**LDH** (IU/L)	436.88 ± 352.09	821.80 ± 434.06	**0.025***	304.00 (249.00-567.00)	847.00 (505.30-920.50)	**0.002**^
11	**Ferritin** (ng/ml)	498.59 ± 646.45	823.77 ± 795.28	0.190*	187.38 (118.71-599.35)	434.36 (165.20-2000.00)	0.149^
12	**CRP** (mg/L)	79.06 ± 90.68	173.92 ± 100.78	**0.002***	39.80 (6.15-124.30)	173.65 (116.05-271.42)	**0.001**^
#	Laboratory investigation	**Recovered (n=61)**	**Deceased (n=16)**	p-value	**Recovered (n=61)**	**Deceased (n=16)**	p-value
		Mean ± Standard deviation			Median (Inter-quartile range)		
1	Hemoglobin	13.27 ± 1.92	12.71 ± 2.18	0.431*	13.40 (11.85-14.67)	12.80 (10.67-13.42)	0.218^
2	TLC	8.34 ± 3.89	16.28 ± 10.99	**0.050***	7.95 (5.30-9.95)	13.70 (7.05-23.95)	**0.038**^
3	Platelets	245.17 ± 82.90	285.50 ± 150.72	0.275*	225.00 (197.50-313.75)	264.50 (166.00-403.00)	0.327^
4	Neutrophils	64.20 ± 14.80	84.10 ± 7.78	**0.001***	65.50 (56.25-72.25)	83.50 (76.50-92.50)	**0.001**^
	Lymphocytes	26.02 ± 12.38	10.20 ± 6.81	**0.001***	26.50 (18.00-33.25)	9.00 (4.00-16.50)	**0.001**^
	Neutrophil - lymphocyte ratio (NLR)	3.72 ± 3.27	14.98 ± 13.55	**0.028***	2.35 (1.45-4.01)	10.74 (4.57-21.81)	**0.001**^
5	Total bilirubin	0.53 ± 0.31	1.70 ± 2.71	0.105*	0.45 (0.28-0.71)	0.73 (0.50-1.49)	**0.002**^
	Direct	0.28 ± 0.16	1.13 ± 1.97	0.108*	0.24 (0.15-0.36)	0.45 (0.31-0.81)	**0.001**^
	Indirect	0.23 ± 0.16	0.56 ± 0.75	0.097*	0.20 (0.11-0.31)	0.27 (0.19-0.67)	**0.008**^

6	ALT	58.16 ± 147.17	98.25 ± 192.09	0.367*	32.00 (22.00-45.50)	41.50 (31.25-66.75)	0.053^
7	AST	61.63 ± 155.64	119.75 ± 224.72	0.232*	38.00 (27.00-50.50)	49.50 (44.50-66.50)	**0.001**^
8	γGT	71.65 ± 79.19	101.93 ± 100.23	0.202*	49.00 (25.50-94.50)	75.00 (52.50-123.50)	0.056^
9	ALP	98.47 ± 48.38	168.87 ± 283.34	0.065*	89.00 (64.50-113.50)	95.50 (70.00-127.50)	0.669^
10	LDH	385.00 ± 180.60	967.01 ± 531.30	0.070*	303.00 (248.00-567.00)	911.00 (559.03-1403.00)	**0.006**^
11	Ferritin	336.37 ± 439.71	777.41 ± 728.83	0.089*	181.64 (103.17-422.63)	672.00 (244.39-1363.15)	0.091^
12	CRP	71.71 ± 89.84	181.42 ± 85.46	**0.003***	25.70 (3.70-116.30)	171.25 (126.00-274.80)	**0.001**^

* indicates P-Value calculated by independent sample t-test (highly significant values are written as 0.001).

^ indicates P-Value calculated by Mann Whitney U-test (highly significant values are written as 0.001).

Discussion

In our study, approximately the majority of patients are above 50 years old, markedly more than half of sufferers reported deranged liver function biochemical markers at the time of admission. The ratio of elevated levels of Alanine transaminase (ALT) and Aspartate aminotransferase (AST) is lower in patients admitted at the initial phase of infection with a majority of patients reporting levels below the normal range (<45 IU/L) coinciding with outcomes of many studies conducted before [1,5-7]. The ratio of elevated levels of Gamma-glutamyl transferase (GGT), another significant liver functional biochemical marker was reported to be highest at the time of admission synchronizing with outcomes of a countable number of studies [1,3,5,7]. Contrasting to numerous studies, we encountered a considerable ratio of sufferers reporting elevated levels of alkaline phosphatase (ALP) at the initial phase of infection [1,3,5,7]. Slightly elevated levels of total bilirubin in a limited ratio of sufferers were encountered in our study correlates with many studies [1,3,5-7]. The medians of deranged liver functional enzymes calculated in our study population with ALT (33.50), AST (40.00), GGT (58), ALP (93) and total bilirubin (0.50) are mostly higher than study similarly conducting medians of deranged liver function enzymes at time of admission with results of ALT (27), AST (34), GGT (36.45), ALP (93), and total bilirubin (0.56) [7]. Our study, quoted significantly elevated levels of GGT and ALP, while in contrast we encountered low median values of total bilirubin in comparison with the study quoted above. All these outcomes reported regarding deranged liver functions are supportive of the fact that COVID-19 associated with liver dysfunction is significant in the early days of infection.

According to outcomes detected in our study population at intervals of admission into isolation wards, the ratio of elevation of gamma-glutamyl transferase (GGT) was highest followed by Aspartate aminotransferase (AST) being second. while Alanine transaminase (ALT) elevation being third and Alkaline phosphatase (ALP) and total bilirubin being lowest elevated coinciding with outcomes of limited studies in regards with ALT and AST while contrasting elevations of GGT [7,8]. The medians of dysfunctional liver biochemical markers in our study population admitted to isolation wards with ALT (33.00), AST (38.00) and total bilirubin (0.49) are higher than study synchronous with calculating medians of patients at the time of admission in isolation wards with ALT (23), AST (29), while the median value

of total bilirubin (0.54) was near to our findings [10].

High spiking levels of Aspartate transaminase (AST) followed by elevated levels of gamma-glutamyl transferase (GGT) at second while alanine transaminase (ALT) being third while the lowest elevation of total bilirubin (TB) was detected in our sample population at the time of admission in intensive care unit (ICU), with elevations of ALT, AST, and TB coinciding with outcomes of numerous studies while the elevation of GGT is coinciding with few studies [5,7,8,11,12]. Medians calculated of ICU patients within our study are AST (49.00), GGT (76.00), ALT (38.00) and TB (0.60) with our values of AST and TB being lower than the study conducted in a similar pattern with AST (52) and TB (11.5) and higher in values of ALT (35), thus contrasting our outcomes [11]. In our study we also encountered elevated count of neutrophils, decreased count of lymphocytes, increased total leukocyte counts and elevated neutrophil to lymphocyte ratio in the patients of COVID-19 with deranged liver function parameters at the time of admission coinciding with outcomes of few studies [1,3,5]. The length of hospital stay was not affected by deranged liver enzymes on admission in our study contrasting to other studies, although the derangements during hospitalization were not documented in our study [1].

The limitations of the study included a relatively small sample size which may not be reflecting the whole disease burden of our population, however still able to reflect the trends of liver enzymes derangements in Covid-19 patients. Other than that, the follow up of liver enzymes were not included in this study during hospital course, which may demand a separate follow up study on the course of liver enzymes during hospital stay and its prognostic significance.

Conclusions

The deranged values of liver function enzymes in Covid-19 are considered of lesser concern in the literature while our study showing the correlation of liver enzymes with the increased number of ICU admissions as well as prognostic markers, hence demanding further follow up studies in this domain to document the derangements of liver enzymes during hospitalization and their relation to clinical outcomes of the patients. Strikingly, alkaline phosphatase was not significantly affected by Covid-19 as opposed to gamma-glutamyl transferase was most significantly affected, it gives a new dimension to molecular pathologists to investigate the molecular pathogenesis of liver injury in Covid-19, as the previous theory of ACE receptor-associated bile duct endothelial disruption is not justifying the opposing derangements of cholestatic liver enzymes.

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Ethical Approval Statement

Ethical approval was taken in this study from institutional review board, and consent to participate has been taken from all the patient’s guardian with informed written consent.

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