EFFECT OF COVID-19 ON LIVER FUNCTION TESTS; RESULT FROM A TERTIARY CARE HOSPITAL IN PAKISTAN

Rashk e Hinna, Samina Fida, Muhammad Asif Farooq, Asma Asghar, Muhammad Uzair, Talha Rehman Zahid*

Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan, *Combined Military Hospital Badin/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine the changes in liver function tests if any in patients of COVID-19.
Study Design: Cross sectional study.
Place and Duration of Study: Combined Military Hospital Lahore, from Apr 2020 to Jun 2020.
Methodology: A total of 209 confirmed cases of COVID-19 positive by RT-PCR patients presenting to Combined Military Hospital, Lahore were included in the study. Their demographic details were recorded. Patients were grouped into mild- moderate and severe disease groups according to the symptoms, complications and oxygen or ventilation requirements. Liver function tests of all these patients were advised.
Results: Amongst confirmed COVID-19 patients, 187 (89.5%) had mild to moderate disease whereas 22 patients (10.5%) had severe disease. Liver test abnormalities were defined as the elevation of the following liver enzymes in serum: ALT >42 U/L, AST >45 U/L, GGT >49 U/L, ALP >300 U/L, albumin<35g/L and total bilirubin (TBIL) >17.1. In LFTs, Bilirubin was increased in 20 (9.6%) patients), ALT in 32 (15.3%) patients, of which 8 had severe disease, 38 patients having high AST levels (>45) 28 had mild-moderate disease and 10 had severe disease. ALP was raised in 24 (11.5%) patients with 8 being in severe disease and rest in mild moderate disease. Albumin was low in 35 (16.7%) patients of which 12 had severe disease and 23 had mild-moderate disease.
Conclusion: About 15-20% of the confirmed cases of COVID-19 have deranged liver function tests and it correlates with severity of the disease.

Keywords: Acute respiratory distress syndrome (ARDS), COVID-19, LFTs, Liver function tests, Non severe, Mild to moderate disease.

INTRODUCTION

Since December 2019, corona virus disease (COVID-19) has been a significant threat to global human health. The outbreak of COVID-19 caused by corona virus emerged in Wuhan china in December1and within three months it has spread to >120 countries[2]. COVID-19 was declared as public health emergency by WHO in February 2020[3]. By June 2020, Corona virus has spread in 216 countries, >8,000,000 people were infected and greater than 400,000 have been died due to it 2 and a total of 154,760 cases of COVID-19 with 2975 deaths in Pakistan have been confirmed[4]. Unfortunately, there is no specific antiviral therapy nor vaccine therefore the number of both infected patients and fatalities will continue to grow[5].

Corona virus is enveloped, single stranded RNA virus[6]. It attaches to angiotensin converting enzyme 2 (ACE2) receptors and enters in the cell. As ACE2 receptors are present on endothelial cells of liver So this virus not only effect lungs but Liver is also potential target for (SARS-CoV-2) Liver is the most frequently affected organ outside the respiratory system and various studies have been performed to understand the mechanism of liver injury by virus. Virus also affects other systems like heart, kidneys and can lead to circulatory and multi organ failure[7].

Liver injury had been reported with SARS-COV-2 infection but mechanism has been remained unclear so is the case with COVID-19. It seems that liver injury occurs due to direct cytopathic effects to liver by virus and by exaggerated inflammatory responses to virus. Medications

Correspondence: Dr Rashk e Hinna, Dept of Gastroenterology, Combined Military Hospital Lahore, Pakistan
Received: 23 Jun 2020; revised received: 22 Jul 2020; accepted: 08 Aug 2020

being used In treatment might be aggravating situation and need to be used carefully when patient has abnormal LFTs levels[8].

Pakistan has been hit by COVID-19 in Feb 2020 and cases have been gradually increasing. Although in almost all government and major private hospitals, covid wards have been made along with quarantine centers along with government measures to control and treat disease by ensuring lockdown and social distancing still situation is not satisfactory for disease control[9].

Less research work has been published locally and might be in process of reporting and publishing at the moment[10].

We studied LFTs changes in COVID patients to know about the liver changes with COVID-19 so that we can understand virus effects on liver along with other organs and can be cautious while treating these patients and avoiding hepatotoxic drugs.

METHODOLOGY

This study was conducted in CMH Lahore in division of Medicine, from April 2020 to June 2020, after approval from Institutional Review Board (IRB number192/2020), CMH Lahore. A total of 209 patients were selected after calculating the sample size by using EPI sampling technique (95% Confidence level, power of study 80%, 10% margin of error and taking frequency of deranged LFTs as 25% (10-40%)[11,19,22]. All these patients presenting with muscle pains and lethargy, fever, sore throat, flue like illness and having COVID-19 PCR positive were included. While those patients with other infections like malaria, typhoid, dengue or any other co-morbid like uncontrolled diabetes mellitus, complicated liver, kidney or heart disease were excluded from the study.

Written informed consent was taken from each patient for participation in study and confidentiality was maintained. Their demographic profiles (i.e. age, sex, occupation) were also noted using a structured questionnaire.

Symptoms severity, chest x-ray finding and oxygen requirement were recorded and patients were grouped into mild/moderate illness and severe disease categories and were treated in ward and ICU accordingly. LFTs of all of the patients were sent to lab and values of each test was recorded.

All the collected information was entered analyzed using SPSS version 22.0 and analyzed. Age, Bilirubin, ALT, AST, alkaline phosphatase levels, albumin, gamma GT were presented as mean ± fequency tables were made for gender, age, severity of disease, and levels of LFTs. Liver test abnormalities were defined as the elevation of the following liver enzymes in serum: ALT >42 U/L, AST >45 U/L, gamma-glutamyltransferase (GGT) >49 U/L, alkaline phosphatase (ALP) >300 U/L, albumin <35g/L and total bilirubin (TBIL) >17.1. Cross tabs were made to know the association between age, LFTS with disease severity using chi-square and Odds ratio. A *p*-value <0.05 was considered significant.

RESULTS

Amongst confirmed COVID-19 positive patients 54 (25.8%) were young, 123 (58.9%) of middle age and 32 (15.3%) were of old age (mean age 44, SD ± 15.6). Male patients were more (89%) as compared to females (11%). Out of all the patients 187 (89.5%) had mild to moderate disease with mild cough, fever, body aches and maintain saturation on room air whereas 22 patients (10.5%) had severe disease and needed oxygen to maintain oxygen saturation >90%.

Mean Bilirubin level was 9.74 micromole/L with standard deviation ± 6, increased bilirubin levels in 20 (9.6%) patients. (Normal 0-17 micromole/L). Mean SGPT/ALT level was 35.3, SD ± 24.6 with increased ALT in 32 (15.3%) patients. (Normal value 0-42 U/L). Mean AST was 41U/L ± 14.2 with increased levels in 38 (18.2%) patients. (Normal value 5-45U/L). Mean alkaline phosphatase was 227 with SD ± 126, was with increased levels in 24 (11.5%) patients (normal value 65-300U/L) whereas GGT Mean level was 44.7, SD ± 36.7 with increased levels in 46(22%) patients.

Mean albumin level was 39g/L, SD ± 5.9 (normal value 35-50g/L) Albumin was low in 35 (16.7%) patients (table-I).

Patient age and LFTs showed correlation with increased severity of the disease. Out of 54 young patients (<30 years of age) 51 had mild/ moderate whereas 3 had severe disease, Out of 123 middle aged patients (31-60 years), 110 had mild-moderate and 13 had severe disease. Thirty two patients were from old age group (>60 years of age) and out of these 6 had severe disease and rest had mild to moderate disease. Severity of disease was associated with advancing age (chi square 3.715, *p*-value <0.05), 189 patients had normal bilirubin levels with 173 having mild/ moderate disease and 16 were having severe disease. Rest of 20 patients had high Bilirubin levels (>17 micromole/L) with 14 had mil/ moderate disease and 6 had severe disease, chi square calculated as 8.9, *p*-value <003 and odds ratio 4.6, ALT was found to be normal in 177 patients with 163 of mild-moderate disease and 14 of severe disease whereas from 32 patients

Table-I: Demographic profile.

	Minimum	Maximum	Mean ± SD
Age in years	6	78	44.76 ± 1.086
Bilirubin µmol/L	3	39	9.74 ± 0.424
Aspartate Aminotransferase U/L	11	102	41.1483 ± 0.98
Albumin g/L	18	53	39.52 ± 0.42
Alkaline Phosphatase U/L	14	886	227.89 ± 8.8
Alanine Aminotransferase U/L	10	177	35.30 ± 1.7
Gamma-Glutamyle Transferase U/L	12	533	44.7 ± 2.5

Table-II: Liver function tests in COVID-19 patients (n=209).

Liver Function Tests	Normal	Abnormal	*p*-value
Bilirubin µmol/L	189 (90.4%)	20 (9.6%)	<0.001
Alanine Aminotransferase U/L	177 (84.7%)	32 (15.3%)	<0.001
Aspartate Aminotransferase U/L	171 (81.8%)	38 (18.2%)	<0.001
Alkaline Phosphatase U/L	185 (88.5%)	24 (11.5%)	0.001
Gamma-Glutamyle Transferase U/L	163 (78%)	46 (22%)	0.09
Albumin g/L	174 (83.3%)	35 (16.7%)	0.001

Table-III: Relationship of liver function tests with disease severity in COVID-19 patients.

Variables		Not severe (mild –moderate disease)	Severe	*p*-value	Odds Ratio For Severity
Age in Years	Young age	51	3	0.05	
	Middle age	110	13		
	Old age	26	6		
Bilirubin µmol/L	Normal	173	16	0.003	4.6
	Hyperbilirubinemia	14	6		
Alanine Aminotransferase U/L	Normal	163	14	0.004	3.88
	Increased	24	8		
Aspartate Aminotransferase U/L	Normal	159	12	<0.001	4.7
	Increased	28	10		
Alkaline Phosphatase U/L	Normal	171	14	<0.001	6.1
	Increased	16	8		
Gamma-Glutamyle Transferase U/	Normal	152	11	0.001	4.3
	Increased	35	11		
Albumin g/L	Normal	164	10	<0.001	4.7
	Hypoalbuminemia	23	12		

having high ALT levels 8 were from severe disease showing an association of increased ALT levels with severity of COVID 19 chi square was 8.4, *p*-value 0.004 and odd ratio calculated was 3.88 (table-II).

One hundred fifty nine patients from normal AST levels had mild-moderate disease and 12 had severe disease whereas out of 38 patients having high AST levels (>45), 28 suffered from mild-moderate disease and 10 from severe disease. Ch square 12.2, *p*-value 0.000 and Odds ratio 4.7 showing more elevations of AST in severe disease.

Higher levels of alkaline phosphatase (>300) were observed in 24 patients with 8 being in severe disease and rest in mild moderate disease whereas out of 185 patients having normal levels of alkaline phosphates 14 suffered from severe disease. Chi-square 14.9. *p*-value 0.000 and OR 6.1, confidence interval 95%. GGT levels were increases in 46 patients with 11 of severe disease and 35 of mild moderate disease. Normal GGT was found in 163 patients with 11 of severe disease and 152 of mild/moderate disease. Chi square 11.2, *p*-value 0.001 and OR 3.3 with CI 95%.

Out of 174 patients having normal albumin levels 164 had mil-moderate and 10 had severe disease whereas out of 35 hypoalbuminemic patients 12 had severe disease and 23 had mild moderate disease. Chi square 25.1, OR 4.7, *p*-value .000 and CI of 95%.

LFTs were found to be raised in significant number of patients with more elevations seen in severe disease (table-III).

DISCUSSION

End of 2019 had come with novel corona virus introduced later as COVID-19 in wuhan China where it played havoc resulting overall case-fatality rate (CFR) 2.3% (1023 deaths among 44,672 confirmed cases)[12] found to spread from person to person like droplet infections[13] and was found to be highly contagious resulting in city lockdown to prevent spread of disease[14]. It started spreading to all of the countries of the world and reached Pakistan in February 2020[4,10]. Clinical manifestations include malaise, fever, nonproductive cough, dyspnea, fatigue, loss of sense smell and taste, GI complains like vomiting, abdominal pain and diarrhea, clinical and radiographic evidence of pneumonia. Organ dysfunction (eg, shock, acute respiratory distress syndrome acute cardiac injury, and acute kidney injury), liver injury and death can occur in severe cases[15,16].

Liver injury ranges from mild elevation of transaminases to acute hepatitis and liver necrosis, findings being worse in the one who already have some form of liver disease and more caution is needed[17,18]. Derangement in liver enzymes was first documented by Chen *et al*[5]. Among 99 cases with COVID-19 from Wuhan, 43 cases (43.4%) had increased serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactic acid dehydrogenase. Another similar study from Portugal showed changes in liver test values in about 46% of patients with alanine aminotransferase in 28% of patients, aspartate aminotransferase in 35%, and total bilirubin in 18%[19]. Aroniadis *et al* reported abnormal liver function tests (LFTs) in approximately 15%-50% of affected patients[20]. Xie *et al* reported 31.6%, 35.4% and 5.1% of patients with elevated ALT, AST and TBIL, respectively[21]. In these studies it has been found that impairment of LFTs worsens with severity of disease. In a study from China by Zhang *et al*, mean level of ALT or AST in severe COVID-19 patients is higher than that in mild[22].

In our study we had abnormal bilirubin, ALT, AST, alkaline phosphatase and GGT levels in 9.6%, 15.3%, 18.2%, 15.3%, 11.5% and 22% patients respectively. These levels correlate with severity of disease being worse in severe disease as compared to mild-moderate one with significant relationship found with odds ration >3 in all. LFTs abnormality in our study is little lower than reported in previous studies more likely because of the fact that we have lesser number of patients in serious category.

COVID-19 is still new to literature and new advances in clinical, biochemical manifestations, complications and management strategies are developing day by day. There are no local studies on complications or biochemical manifestations of the disease in Pakistan so our study will add to literature especially local one to improve knowledge about liver changes associated with COVID-19 so that it can be managed accordingly. This pandemic is lesson for all of us to improve healthcare[23]. Prevention is the key and social distancing, personal protective equipment is mandatory for healthcare workers being frontliners[24].

In our study we were not able to get imaging in our patients to look for liver status to look for extent of ongoing liver injury and to rule out any silent liver pathology as we had to avoid contact with healthcare workers because of limited PPEs. Moreover patients being admitted is tip of iceberg of real cases as patients are still not reporting or getting their test done adequately.

CONCLUSION

There is significant impairment of liver function tests in COVID-19 patients and abnormality correlates with severity of the disease.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH,Ou CQ,He JX et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382(18): 1708-20.
2. World Health Organization (WHO). Coronavirus disease (COVID-19) pandemic. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
3. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020; 76(80): 51-52.
4. Confirmed cases of Coronavirus in Pakistan. Available at: http://covid.gov.pk/june
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395 (10223): 507-13.
6. Gao Y, Yan L, Huang Y, Liu F, Zhao Y, Cao L, et al. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Science 2020; 368(6492): 779-82.
7. Chau TN, Lee KC, Yao H, Tsang TY, Chow TC, Yeung YC, et al. SARS-associated viral hepatitis caused by a novel coronavirus: Report of three cases. Hepatology 2004; 39(2): 302-10.
8. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020; 40(5): 998-1004.
9. Saqlain M, Munir MM, Ahmed A, Tahir AH, Kamran S. Is Pakistan prepared to tackle the coronavirus epidemic? Drugs Ther Persp 2020; 36(3): 213-14.
10. Waris A, Atta UK, Ali M, Asmat A, Baset A. COVID-19 outbreak: current scenario of Pakistan. New Microbes New Infect 2020; 35(5): 100681.
11. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical features of COVID-19 related liver functional abnormality. Clin Gastroenterol Hepatol 2020; 18(7): 1561-66.
12. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. J Am Med Assoc 2020; 323(13): 1239-42.
13. Chan JFW, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; S0140-6736(20): 30154-59.
14. Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ, et al. Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. N Engl J Med 2020; 382(9): 872-74.
15. Huang C, Wang Y, Li X, Rn L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497-506.
16. Tahir F, Arif TB, Ahmed J, Malik F, Khalid M. Cardiac manifestations of coronavirus disease 2019 (COVID-19): A Comprehensive Review. Cureus 2020; 12(5): e8021.
17. Mao R, Liang J, Shen J, Ghosh S, Zhu LR, Yang H, et al. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol 2020; 5(5): 425-27.
18. Li J, Fan JG. Characteristics and mechanism of liver injury in 2019 coronavirus disease. J Clin Transl Hepatol 2020; 8(1): 13-17.
19. Peixea P, Calinas F, Marinho RT. Hepatology in the COVID Era: Another C Virus, again Challenging the Liver. GE Port J Gastroenterol 2020; 27(4): 230-36.
20. Aroniadis OC, DiMaio CJ, Dixon RE, Elmunzer BJ, Kolb JM, Mendelsohn R et al. Current knowledge and research priorities in the digestive manifestations of COVID-19. Clin Gastroenterol Hepatol 2020; 18(8): 1682-84.
21. Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. Liver Int 2020; 40(6): 1321-26.
22. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single center in Wuhan city, China. Liver Int 2020; 1(1): 1-9.
23. Bukhari MH. The current COVID-19 (SARS-2 COV-19) pandemic: A lesson for all. J Pak Med Assoc 2020; 70(7): 1115-16.
24. Bukhari MH, Mahmood K, Zahra SA. Over view for the truth of COVID-19 pandemic: A guide for the Pathologists, Health care workers and community'. Pak J Med Sci 2020; 36(COVID19-S4): S111-14.