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Drug Induced Liver Injury in COVID-19 Patients; what do we know a year into the Pandemic

Dr. Eyad Gadour[1], Dr Zeinab Hassan[2], Dr Tamer Mohamed[3], Dr Abdalla Hassan[4]

[1]Consultant Gastroenterologist, University Hospitals of Morecambe Bay NHS Foundation Trust, eyadgadour@doctors.org.uk
[2]The National Ribat University-Faculty of Medicine, department of internal medicine, Khartoum-Sudan
[3]Blackpool Teaching Hospitals NHS Foundation Trust, department of Acute Medicine, Blackpool-UK
[4]University Hospitals of Morecambe Bay NHS Foundation Trust, department of Gastroenterology, Lancaster-UK

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ABSTRACT

Introduction: Liver impairment was seen in 60% of cases of COVID-19. Drug induced Liver Injury in COVID-19 patients has not been thoroughly reviewed yet. We aim to study this phenomenon and test the available data.
Methodology: Comprehensive retrospective review was conducted to see the drug-induced liver damage due to COVID-19. One author was assigned to do systematic search from the Advanced Cochrane library, and PubMed from all reported studies and data from December 2019 to December 2020. Search keywords were COVID-19 and liver, COVID-19 and liver injury, SARS-CoV-2 and liver, SARS-CoV-2, and liver injury. Results were checked and reviewed using SPSS version 27.
Results: A Single-Centre Cross-Sectional Study, Cai Q, *et al*. 2020, 417 patients reported the association of raised liver tests with liver injury and severity of pneumonia. Abnormal liver tests including AST, ALT, and GGT were reported in 76.3% of patients and 21.5% acquired liver injury during admission. Liver enzymes were more prominently high during hospital stay over 3ULN (upper limit units), specifically ALT and GGT 37 % and 41% (p = .006) respectively whereas AST and TBIL was raised up to 20% and 10% (p = .002). Retrospective case series of 113 deceased patients, Chen T, *et al*. 2020, analysed to understand the risk factors. All 113 deceased received treatment of Antiviral therapy Eighty-nine (79%), Glucocorticoid therapy Ninety-nine (88%), Antibiotics 105 (93%), Intravenous immunoglobulin therapy 39% (n=44), Interferon inhalation 22% (n=22), Oxygen treatment 113 (100%) including high flow nasal cannula 68% (n=77). Lopinavir and ritonavir were reportedly linked with COVID-19 associated liver injury whereas, in this retrospective analysis few deceased cases 89; 79% (p = .009) received monotherapy or combined treatment of oseltamivir, arbidol, or lopinavir and ritonavir.
Conclusion: Lopinavir and ritonavir have been associated with liver injury development in COVID-19 patient. Elevated AST levels with the use of antifungals. Drug-induced liver injury in COVID-19 patients is a complex process and more critical research needs to be conducted.

1. Introduction

The current pandemic of Corona virus first began in China – Wuhan and spread worldwide, affecting thousands of people's lives, the global economy, and indeterminable medical costs and become a most crucial healthcare challenge [1, 2]. Undoubtedly, a significant number of exposed individuals remain asymptomatic or appear very mild or inconsiderable symptoms. The general symptoms appearance of COVID-19 is more or less similar to pneumonia-like SARS or MERS, include dyspnea, fever, coughing, and desaturation. Only 5-10% of COVID-19 exposed individuals exhibit critical oxygen deprivation and essentially require intensive care support and mechanical intubation [1]. The high-risk group of covid-19 infection is reportedly highly seen in older age adults, individuals having hypertension, heart disease, and diabetics [2]. The target site of COVID-19 is the human lungs, but this virus can damage other organs also. The liver is one of the most vital body organs, and its involvement in COVID 19 infection would be an additional worrisome for healthcare providers. Although, the exact mechanism is still unclear and questionable that at what extent of liver damage can participate in infection severity and mortality risk [2]. Liver impairment was seen in 60% of cases. Biopsy testing reveals the extent of liver damage and viral nucleic acid presence. It is also a

* Corresponding author.
Dr. Eyad Gadour, Consultant Gastroenterologist, University Hospitals of Morecambe Bay NHS Foundation Trust.
Ph: 0152465944
E-mail address: eyadgadour@doctors.org.uk

strong presumptive that it possibly be due to the specific therapeutics, such as hepatotoxic antiviral medications, antibiotics, and steroids. The possibly included drugs were hydroxychloroquine, azithromycin, lopinavir/ritonavir, interferon beta, baricitinib, imatinib, remdesivir, umifenovir, and darunavir [2-4].

The hyperimmune response is also associated with progression of liver damage elevated CRP, tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6) reported in the majority of patients [2].

The associated laboratory tests on admitted patients showed raised C-reactive protein (CRP), and Ferritin levels. Liver enzymes including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) mostly reported raised. Literature reported an increase of ALT levels along with other liver enzymes was seen in 14–53% of infected cases [1, 3]. Other enzymes lactate dehydrogenase (LDH) may also be raised in most cases. The raised enzyme levels including AST, ALT, and LDH is an indication of liver injury. Studies reported that Liver injury is mostly associated with severe cases of COVID-19 cases rather than mild cases and elevated ALT levels are an indicator [1]. Though, high ALT levels with low Albumin and Platelet count are associated with high mortality [2].

Drug-Induced Liver damage, pathogenesis, mechanism, and laboratory findings

Abnormal liver enzymes are not always associated with serious liver damage and treatment. Observational clinical studies reported that most COVID-19 patients with abnormal liver function tests (LFTs) recover without specific hepatic treatment. This would categorize as Type 1. The second type of patients present with true liver damage and must necessarily require medical help [5].

The pathological studies data on liver injury and COVID-19 is still limited. Autopsy testing of COVID patients reveals a very mild type of sinusoidal dilation along with lymphocytes infiltration in sinusoidal spaces resulting in sinusoidal dilatation. This sinusoidal dilatation slows down the cardiogenic venous outflow especially in severely ill admitted patients. Canalicular cholestasis was rarely seen [5].

The COVID-19 patient with decreased blood oxygen levels with compromised cardiac functionality leads to rising liver vulnerability to damage. Although, it's a multifactorial process and vary among individuals [5].

The hepatic injuries due to COVID-19 can be categorized into three, based on their histological microscopic findings. The first one is due to a direct viral attack. The second one is because of underlying liver disorder such as Hepatitis, and nonalcoholic fatty liver disease – NAFLD and COVID-19 exposure lead to secondary liver damage [4]. The third is due to the hyperinflammatory response due to COVID-19 exposure which leads to liver damage.

Fourth and the last is the liver injury caused in response to certain drugs, used for the treatment of COVID-19. There is still no definitive treatment of COVID-19, supportive treatments, and drugs are used according to the patient. There are many drugs used for supportive therapy of COVID- 19 include non-steroidal anti-inflammatory drugs (NSAIDS), hydroxychloroquine, azithromycin, and herb remedies. All these therapeutics can cause diverse hepatotoxicity, not in all COVID-19 positive patients but the patients with symptoms of pneumonitis are more prone to hepatoxicity [5]. This is maybe due to when a Hepatitis B or C, NAFLD, or Cirrhosis patient expose to COVID-19, the specific liver damage treatment was stopped and COVID-19 treatment including steroids or other drugs exponentially leads to liver inflammation and its severe damage. However, Clinical affirmation is still awaited for this hypothesis [5].

Liver enzymes including elevated ALT, AST levels play a presumptive approach towards liver damage. Some studies also reported GGT, Total Bilirubin, and Lactate dehydrogenase levels but reportedly they are less significant [4]. The studies mainly reported AST and ALT levels. Although GGT and TBIL may also moderately rise with a slight rise of prothrombin time (PT). A recent study reported the rise of ALT, AST, and GGT levels up to 82, 75, and 72%, respectively [2]. Intensive Care (ICU) is an additional feature of COVID-19 severe case, 63% of ICU cases reported high AST levels in comparison with non ICU admitting cases [4].

There is no definite treatment available for COVID-19. Supportive therapeutics were adapt according to the severity of COVID-19 infection. There are few therapeutics, used for COVID-19 that are presumptively associated with a liver infection. Lopinavir/ritonavir, Remdesivir, Hydroxychloroquine, Azithromycin, and Tocilizumab, all associated with hepatotoxicity [6].

2. Methods

We conducted this comprehensive review to see the drug-induced liver damage due to COVID-19, its identification parameters, and outcome in adult patients had severe or non-severe COVID-19 infection.

Participants Type and Study Outcome

All COVID-19 positive adult patients and a baseline liver disease. Studies reported diagnostic markers specifically serum alanine aminotransferase (ALT) and disease outcomes are included in this study. Other parameters including) serum aspartate aminotransferase (AST), Gamma-Glutamyl transferase (GGT), and Albumin testing would also consider.

Search Scheme

One author was assigned to do a comprehensive search from the Advanced Cochrane library, and Pubmed till December 10, 2020. Search keywords were Covid-19 and liver, Covid-19 and liver injury, SARS-CoV-2 and liver, SARS-CoV-2, and liver injury. The search was confined to Adult patients only.

Selection Criteria

Studies were selected from data based on defined selection criteria.

1. Covid – 19 positive
2. Underlying liver disease
3. Adult
4. Reporting of any liver enzyme

Abnormal Results

- Aspartate aminotransferase AST > 40 U/L,
- Alanine aminotransferase ALT > 40 U/L,
- Gamma-glutamyl transferase (GGT) > 49 U/L
- Albumin ALB 3.4 to 5.4 g/dL

Table 1: Characteristics of selected studies

S. No	Author, year & Reference Number	Country	Study Type	Sample size	Age years (Median/ IQR)	Male (n, %)	Baseline CLD (%)
1	Cai Q, *et al*. 2020 [7]	Shenzhen, China	Cross sectional study	417	47 (34-60)	48	5
2	Chen T, *et al*. 2020 [8]	Wuhan, China	Retrospective case series	274	62 (44-70)	62	4
3	Jin X, *et al*. 2020 [9]	Zhejiang, China	Retrospective study	651 (GI symptoms: 74)	*45.2 (14.4)	51	4

4	Lian J, *et al*. 2020 [10]	Zhejiang, China	Retrospective study	788 (Age <60: 652 Age≥ 60: 136)	44.8 (13.4)	52	4
5	Wu C, *et al*. 2020 [11]	Wuhan, China	Retrospective cohort study	201	51 (43-60)	64	4
6	Wan S, *et al*. 2020 [12]	Chongqing, China	Retrospective study	135	47 (36-55)	72 (53.3)	1.48
7	Wang D, *et al*. 2020 [13]	Hubei, China	Retrospective study	138	56 (42-68)	75 (54.3)	2.9
8	Huang C, *et al*. 2020 [14]	Beijing, China	Prospective Study	41	49·0 (41-58)	30 (73)	2.44
9	Wang Z, *et al*. 2020 [15]	Wuhan, China	Retrospective study	69	42 (35-62)	32 (46)	1.45
10	Cao J, *et al*. 2020 [16]	Wuhan, China	Cohort study	102	54 (37-67)	52	2
11	Li T, *et al*. 2020 [17]	Sichuan, China	Single-center retrospective study	30	61 (33-87)	18	None
12	Lin Y, *et al*. 2020 [18]	Chongqing, China	Multicenter study	133	48 (45 - 51)	11 (64.71)	17 HBV inactive carriers
13	Xu X, *et al*. 2020 [19]	Zhejiang, China	Retrospective case series	62	41 (32-52)	56	11
14	Abe K, *et al*. 2020 [20]	Japan	Multicenter retrospective cohort study	22	47	9	7
15	Anastasiou OE, *et al*. 2020 [21]	Germany	Cohort Study	147	51 (44.5–66.5)	10	11 (6.8%)
16	Richardson S, *et al*. 2020 [22]	USA	Retrospective Study	5700	63 (52-75)	3437 (60.3)	0.52
17	Huang H, *et al*. 2020 [23]	Wuhan, China	Retrospective analysis	675	51.50 (35.75-60.25)	42 (80.77%)	Chronic liver disease: 10(2.70%) Abnormal: 14(5.53%) liver injury: 3(5.77%)
18	Guo H, *et al*. 2020 [24]	Shanghai, China	Single center study	332	50 (36–64)	174 (52.4%)	98 (29.5%)
19	Chu H, *et al*. 2020 [25]	United States	Retrospective study	838	61 (49–69)	280 (65.3)	429
20	Fang L, *et al*. 2020 [26]	China	Multicenter retrospective cohort study	5,771	59 (48-66)	656 (55.3%)	1,186

Table 2: Laboratory findings and adapted Treatments of Selected Studies

S. No	Author, year & Reference Number	AST, U/L, Median (IQR)	ALT-(Median IQR)	GGT, U/L, Median (IQR)	Albumin (Median IQR)	Drugs used
1	Cai Q, *et al*. 2020 [7]	63 (36-101)	90.5 (53-145)	130.5 (77-187)	NP	Antibiotics, NSAID, Ribavirin, Oseltamivir, Herbal medications, Interferon , Lopinavir/ ritonavir
2	Chen T, *et al*. 2020 [8]	45.0 (31.0-67.0) >40 U/L: 59 (52)	28.0 (18.0-47.0) >41 U/L: 30 (27)	NP	30.1 (27.9-33.0) <32 g/l: 74 (65)	Antiviral therapy, Glucocorticoid therapy, Antibiotics, Intravenous immunoglobulin therapy, Interferon inhalation, Oxygen treatment, Continuous renal replacement therapy, Extracorporeal membrane oxygenation
3	Jin X, *et al*. 2020 [9]	29.35 (20.87–38.62)	25.0 (15.75–38.47	NP	40.13 (35.95–42.60)	Anticoronavirus treatment, Mechanical ventilation, CRRT, ECMO, Glucocorticoids, Antibiotic treatment, ICU admission
4	Lian J, *et al*. 2020 [10]	Age <60:24.0(19.0-32.0), Age≥ 60:28.0(22.0-36.0)	Age <60: 22.0(15.0-35.0), Age≥ 60:21.0(16.0-29.0)		Age <60: 41.7(39.0-44.1), Age≥60:39.2(36.0-42.0)	Anti-coronavirus treatment, antiviral therapy, Interferon-α+Lopinavir/Ritonavir, Lopinavir/ Ritonavir+ Arbidol, Interferon-α+ Arbidol, Mechanical Ventilation, Glucocorticoids , IVIGt, Admission to intensive care unit
5	Wu C, *et al*. 2020 [11]	59 of 198 (29.8%)	43 of 198 (21.7%)	NP	32.75 (29.10-35.40)	Oxygen therapy, Methylprednisolone, Antibiotic, Antiviral, Immunomodulator, Antioxidant

6	Wan S, *et al*. 2020 [12]	33.4 (27.8-43.7)	26 (12.9-33.15)	NP	40.5 (37-43.4)	Antiviral therapy, Antibiotic therapy, Use of corticosteroid, Traditional Chinese medicine, Continuous renal replacement therapy, Oxygen support, Noninvasive ventilation or high-flow nasal cannula, Invasive mechanical ventilation
7	Wang D, *et al*. 2020 [13]	31 (24-51) ≤40 50/69 (72%)	24 (16-40) ≤35 46/69 (67%)	NP	NP	Antiviral therapy, Glucocorticoid therapy, CKRT, Oxygen inhalation, NIV, IMV, ECMO
8	Huang C, *et al*. 2020 [14]	34 (26-48)	32 (21-50)	NP	31·4 (28·9-36)	Antiviral therapy, Antibiotic therapy, Use of corticosteroid, Continuous renal replacement therapy, Nasal cannula, Non-invasive ventilation or high-flow nasal cannula, Invasive mechanical ventilation, Invasive mechanical ventilation and ECMO
9	Wang Z, *et al*. 2020 [15]	28 (22-42)	23 (17-40)	–	–	Antiviral therapy, Antibiotic therapy, Antifungal therapy, Corticosteroids, Arbidol
10	Cao J, *et al*. 2020 [16]	NP	48/101, 47.5%	NP	NP	Antiviral therapy, Antibiotic treatment, Intravenous immunity therapy, Glucocorticoid therapy, Chinese medicine treatment
11	Li T, *et al*. 2020 [17]	gradually Increase with disease progression	gradually Increase with disease progression	NP	decreased	Lopinavir/Ritonavi
12	Lin Y, *et al*. 2020 [18]	31.20 (22.00-49.10)	33.00 (22.00-56.10)	36.00 (19.00-83.00)	NP	Antiviral, Arbidol, Lopinavir/ritonavir, Interferon, Antibiotic, Methylprednisolone
13	Xu X, *et al*. 2020 [19]	26 (20-32) <40: 52 (84) ≥40: 10 (16.1)	22 (14-34)	NP	NP	Antiviral treatment, Interferon alpha inhalation, Lopinavir/ritonavir, Arbidol+interferon alpha inhalation, Lopinavir/ritonavir+interferon alpha inhalation, Arbidol+lopinavir/ritonavir, Arbidol+lopinavir/ritonavir+interferon alpha inhalation, Antibiotics, Corticosteroid and gamma globulin
14	Abe K, *et al*. 2020 [20]	levels varies greatly, ranging from 2.5% to 50.0%	ALT level was observed in 12 (54.5%) of the 22 patients	Elevated GGT levels in 12 patients (54.5%)	3.9 (3.4–4.1)	Ciclesonide, Favipiravir, Ventilator
15	Anastasiou OE, *et al*. 2020 [21]	140 (60–159)	88 (55–101)	560 (38–92)	2.8 (2.4–4)	–
16	Richardson S, *et al*. 2020 [22]	46 (31-71) >40 U/L: 3263 (58.4)	33 (21-55) >60 U/L 2176 (39.0)	NP	NP	Intensive care Invasive mechanical ventilation Kidney replacement
17	Huang H, *et al*. 2020 [23]	58.50 (45.00-90.50)	105.00 (49.25-159.50)	53.50 (32.75-85.25)	NP	–
18	Guo H, *et al*. 2020 [24]	59 (49–82)	72 (55.5–99.5)	105 (78.5–128)	NP	Lopinavir/ritonavir, Arbidol, Hydroxychloroquine , Darunavir cobicostat, Azithromycin, Quinolones, Cephalosporin, Glucocorticoids, Thymopeptides, Interferon spray, Sedatives and Hypnotics, Analgesic-antipyretic, Antilipemic agents, Hypotensor, Hypoglycemic agents, Drug for coronary heart disease, Lianhua Qingwen granules, Shufeng Jiedu capsules, Xuanfei Zhike mixture.
19	Chu H, *et al*. 2020 [25]	44 (31–59)	49 (32–71)	49 (26–93)	30.8 (27.1–35.2)	Umifenovir, Lopinavir /litonavir, Ribavirin, Interferon
20	Fang L, *et al*. 2020 [26]	31.0 (21.0-46.0)	26.0 (17.0-45.0)		35.7 (32.2-38.9)	Antiviral drugs, Antibiotic drugs, Systemic corticosteroids, Antifungal drugs

NP: Not performed, NSAID: Non-steroidal anti-inflammatory drugs, ECMO:Extracorporeal membrane oxygenation

A Single-Center Cross-Sectional Study, Cai Q, *et al*. 2020 [7]

This cross-sectional study of 417 patients reported the association of raised liver tests with liver injury and severity of pneumonia. Abnormal liver tests including AST, ALT, and GGT were reported in 76.3% of patients and 21.5% acquired liver injury during admission. Alkaline Phosphatase (ALP) was also tested in this study, but not working as a prominent differentiating factor. Liver injury was associated with underlying liver infections including Non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and Hepatitis B. However, abnormal liver tests at the time of hospital admission also a predictor for the severity of pneumonia.

Liver enzymes were more prominently high during hospital stay over 3ULN (upper limit units), specifically ALT and GGT 37 % and 41% respectively whereas AST and TBIL was raised up to 20% and 10%. Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, Chinese herbal therapeutics, and interferon therapy were linked to development of severity but not evidently the risk of liver injury except for lopinavir/ritonavir. Lopinavir and ritonavir showed an odd ratio of 4.44 for liver damage severity and reportedly high levels of GGT and TBIL. Ten cases from the severe ones were presented with multi-organ dysfunction. In addition to COVID complications, these cases had additional complexities including septic shock (9/10), renal failure (8/10), liver failure and intravascular coagulation (2/10), and gastrointestinal hemorrhage (1/10). All these secondary complications were related to intensive care requirements and ICU admission. Three patients died during the course of the disease, and one was due to liver failure.

Retrospective case series of 113 deceased patients, Chen T, *et al*. 2020 [8]

Covid-19 is not only associated with the pulmonary syndrome but also cause systemic malfunctioning leading towards multi-organ failure. This study analyzed the 113 deceased cases to understand the risk factors. The most common complication was sepsis, cardiac malfunction, and heart attack. Acute liver injury was less common and seen in 10 patients.

The 113 deceased patients receive treatment of Antiviral therapy 89 (79%), Glucocorticoid therapy 99 (88%), Antibiotics 105 (93%), Intravenous immunoglobulin therapy 44 (39%), Interferon inhalation 25 (22%), Oxygen treatment 113 (100%) including high flow nasal cannula 77 (68%), Mechanical ventilation 93 (82%) of Non-invasive 76 (67%) and Invasive 17 (15%), Continuous renal replacement therapy 3 (3%) , and Extracorporeal membrane oxygenation 1 (1%).

Lopinavir/ritonavir was reportedly linked with COVID-19 associated liver injury [7] whereas, in this retrospective analysis few deceased cases 89; 79% received monotherapy or combined treatment of oseltamivir, arbidol, or lopinavir/ritonavir.

The concentration of liver enzymes including AST and ALT was reportedly higher in deceased cases than in recovered ones. 52% deceased cases and 16% of recovered ones had raised AST levels with significantly low levels of Serum Albumin. Hypoalbuminaemia was seen in 65%, and 14% of deceased and recovered patients respectively.

A retrospective analysis of 651 patients, Jin X, *et al*. 2020 [9]

This analysis reported the cases of COVID-19 with gastrointestinal symptoms (GI) and associated complications like acute respiratory distress syndrome (ARDS), livery injury, and sepsis. Liver injury was seen in 17.57% of patients having GI symptoms, while it was less in patients with no GI symptoms i.e. 8.84%.

The given treatment was Anticoronavirus treatment in 89.19% including), lopinavir/ritonavir, interferon-α sprays and arbidol hydrochloride capsules. Mechanical ventilation was given to 6.76%, Glucocorticoids 14.86%, Antibiotic treatment 41.89% and Admission to intensive care unit was 6.76%.

Epidemiological and Clinical analysis of COVID-19 older patients - Lian J, *et al*. 2020 [10]

This study categorized 788 patients into two groups of <60 years and Age ≥60 years. Less than 60 years group comprises of 652 patients and reported Chronic liver disease in 25 (3.83%)patients, whereas, more than or equal to 60 years of patients 6 (4.41%) from 136 patients group. Liver functional abnormalities were also seen in 11.04%, and 7.35% in <60 and ≥60 years of patients respectively. Interferon-α+Lopinavir/Ritonavir was reportedly used in 140 (21.47%), and 136 (18.38%) of <60 and ≥ 60 years of the group respectively. A combination of Lopinavir/Ritonavir+ Arbidol was given to 9.36% and 8.82% patients <60 and ≥60 years respectively. This study reported the liver injury as the most reported complication in COVID-19 patients followed by acute respiratory distress syndrome (ARDS) and acute renal disease.

Analysis of Associated Risk Factors Wu C, *et al*. 2020 [11]

A retrospective cohort study of 201 COVID-19 patients, seven enrolled patients had associated liver comorbidity. Eighty-four patients developed ARDS, and 44 were died due to ARDS. This study reported the association of older age with comorbidities including liver injury and development of ARDS as a leading cause of mortality.

Most patients received empirical treatment of antibiotics 97.5%, and antivirals therapeutics 84.6%. Antivirals including oseltamivir 66.7%, ganciclovir 40.3%, lopinavir/ritonavir 14.9%, and interferon alfa 10.9%. Antioxidant therapy was given to 52.7% of patients. Methylprednisolone was used for 30.8%, and immunomodulators for 34.8% of patients.

Clinical Characteristics and COVID-19 therapeutics Wan S, *et al*. 2020 [12]

The study was based on 135 patients with underlying chronic liver disease of 2 (1.5%) patients. One case was categorized in a mild category and one had severe COVID-19 infection. Severe category patients had more pronounced liver function damage.

The administered treatment was Antiviral therapy to 100% patients, Antibiotic therapy 43.7%, corticosteroid 26.7%, Traditional Chinese medicine (TCM) 91.8%, Continuous renal replacement therapy 3.7%, Oxygen support 66.7%, Noninvasive ventilation or high-flow nasal cannula 25.2%, and Invasive mechanical ventilation to 0.7% patients. Kaletra or Lopinavir / Ritonavir, and TCM were reportedly the prime therapeutics for COVID-19.

Clinical features of Admitted COVID-19 patients, Wang D, *et al*. 2020 [13]

This study was based on 138 hospitalized COVID-19 patients with baseline Chronic liver disease of 4 patients. This study did not report a drug-induced liver injury, although 4 infected patients already had associated comorbidity of liver disease. The reported complications were Shock, Acute cardiac injury, Arrhythmia, ARDS, and acute kidney injury. All patients received antibiotic treatment, antiviral therapy was given to 90% of cases, and methylprednisolone was given to 45% of patients.

COVID- 19 patients and its characteristics, Huang C, *et al*. 2020 [14]

This study enrolled 41 patients, 13 were in ICU care and 28 without ICU care. Chronic liver disease was reported in 2% of patients. AST levels were reportedly increased in 37% of patients, 62% of ICU, and 25% of non-ICU patients.

The lopinavir/ritonavir reportedly had clinical benefit with some adverse effects. All patients received antibiotic therapy. Antiviral therapy was given to 93% of patients and a corticosteroid to 22% of patients. This study reported a 15% mortality rate.

69 Cases of Corona Virus, Wang Z, *et al*. 2020 [15]

The study reported 69 adult Covid-19 positive patients with associated comorbidities such as hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, malignancy, asthma, and chronic hepatitis. Antiviral and Antibiotic therapy was given to 98.5% of patients. Antifungal, corticosteroids, and Arbidol were used for 11.9%, 14.9%, 53.7% respectively, 16% deaths reported in Arbidol – untreated group.

102 Patients COVID-19 patients and their Short-term Outcomes Cao J, *et al*. 2020 [16]

This study enrolled Covid-19 positive patients with associated comorbidities of hypertension, diabetes mellitus, cardiovascular and

cerebrovascular disorder, respiratory diseases, chronic kidney disease, malignancy, and chronic liver disease. Two enrolled patients had baseline chronic liver disease.

Reported treatment complication was Shock, ARDS, Acute infection, Acute cardiac injury, Arrhythmia, Acute kidney injury, Lymphopenia, and Acute liver injury Acute liver injury complication was reported in 34 patients, 13 in the non-survivor group and 21 in the survivor group. The level of alanine aminotransferase levels was increased by 62.7%.

The used therapeutics was antibiotics including quinolones 85.3%, cephalosporins 33.3%, carbapenems 24.5%, and linezolid 4.9%. Administered antivirals were Arbidol 34.3%, oseltamivir 64.7%, and lopinavir 27.5%. Other therapeutics for immunity was immunoglobulin 10.8% and methylprednisolone sodium succinate 50.0%. This study reported a high mortality rate of 16.7%, this is maybe due to the enrolment of more severe cases with associated comorbidities.

A single-center retrospective study, Li T, *et al*. 2020 [17]

This study was based on 30 severe COVID–19 patients and their liver damage characteristics. This 30 ICU admitted patients based study reported that the elevated levels of liver enzymes including AST, ALT, and TBIL are an important indicator of liver damage including a raised Prothrombin time (PT). Another indicator was Serum Albumin levels, which were reportedly high in most patients. All patients had AST and AST levels reaching the upper limit when they admit to ICU and levels were gradually raised. This study clearly demonstrates the use of Lopinavir/Ritonavir in covid -19 severe patients increase the incidence of liver dysfunction and liver dysfunctional Covid-19 patients reportedly had a slow recovery. Liver protection therapeutics should also administer in those patients who had at risk of liver dysfunction.

SARS-CoV-2 and HBV coinfection, Lin Y, *et al*. 2020 [18]

This study enrolled 119 hospitalized Covid-19 patients, and divided into two groups 116 with negative hepatitis B antigen (HBsAg) and 17 inactive hepatitis B carriers.

All patients of Covid-19 and HBV group received Lopinavir/ritonavir, 10 patients received Arbidol, and Interferon were given to 16 patients. Fifteen patients received Antibiotics and Methylprednisolone was given to two patients. The AST and ALT levels were much higher in the co-infection group, 64.71% (11/17) had abnormal AST and ALT levels. The inflammatory response was also investigated through lactate dehydrogenase, Ddimer, and interleukin-6, and seen abnormal in the co-infection group. 14.29% of patients of the co-infection group developed a liver injury.

Retrospective case series of 62 Covid-19 patients, Xu X, *et al*. 2020 [19]

Seven enrolled patients (11%) had underlying liver disease. Increased AST levels were reported in 10 patients. This study enrolled mild cases and no mortality was reported. Antiviral treatment was given to 55 patients in different combinations. Interferon-alpha inhalation to 8 patients, Lopinavir/ritonavir used for 4 patients, Arbidol+interferon alpha inhalation for 1 patient only, Lopinavir/ritonavir+interferon alpha inhalation to 21, Arbidol+lopinavir/ritonavir to 17, and Arbidol+lopinavir/ritonavir+interferon alpha inhalation to 4 patients. Antibiotics were used for 28, Corticosteroid, and gamma globulin for 16 patients. In this study only one patient admitted to ICU due to acute respiratory distress syndrome.

COVID-19 and Liver Injury in Japanese Population, Abe K, *et al*. 2020 [20]

This 22 Covid-19 positive patient study reported the raised liver enzymes associated with increasing body temperature but not with disease severity and mortality. Underlying liver disease was present in 2 enrolled patients. From all 22 patients, the Liver injury was reported in 15 patients. The given treatment for liver injury patients was Ciclesonide in 6 patients, Favipiravir for 7, and ventilator for 3 patients. Two mortality cases were reported, one from the liver injury group.

Mild versus Severe Liver Injury and Covid-19, Anastasiou OE, *et al*. 2020 [21]

This cohort study reported 147 covid-19 patients and categorize into three groups, 54 patients with normal ALT and bilirubin levels, 82 patients with elevated ALT or bilirubin, and 11 acute liver failure patients. Liver injury was predominately reported in males. This study reported a high percentage of liver injury case at the time of admission and during hospital treatment, 50.7% and 63% respectively. This study reported the liver injury during treatment was associated with mortality.

5700 Hospitalized Patients study, Richardson S, *et al*. 2020 [22]

Baseline liver cirrhosis was reported in 19 patients, Hepatitis B in 8, and Hepatitis C in 3 patients. Acute hepatic injury was reported in 56 cases, 03 were discharged alive, 25 died of 18-65 years of age, and 28 from >65 years. Hospitalized acute liver injury patients were 33. The 15 times or more than the upper limit of AST and ALT were the criteria for acute liver injury.

During hospital stay, 14.2% of patients were admitted to an intensive care unit, and 12.2% received invasive mechanical ventilation. Other given treatments were kidney replacement therapy to 81 patients and 21% of patients died.

Liver Injury markers and its outcome, Huang H, *et al*. 2020 [23]

This retrospective analysis of 675 patients was based on the analysis of normal and raised liver enzymes and liver injury. The patients were categorized into three groups, 28 liver injury patients in the mild group, 8 in the severe category, and 16 were in critical one.

The AST and ALT levels were reportedly the more significant indicator in liver injury patients and also connected to mortality rate. The >3-fold the upper limit of AST levels presented with high risk or mortality and required mechanical ventilation. This study concluded the significant connection of AST, ALT levels with Covid-19 severity, and prognosis and recommended to closely monitor to prevent mortality and better patient outcome.

Evaluation of liver injury factors in 332 Covid-19 patients, Guo H, *et al*. 2020 [24]

Patients were categorized into two groups, 306 in the non-critical group, and 26 were the critical ones. Ninety-eight enrolled patients had baseline liver injury, 80 were in the noncritical category and 18 were in the critical one. Twenty-five patients from baseline 98 enrollments had improved prognosis and liver enzyme results, and 73 patients had deteriorating liver enzymes. This study also reported that liver injury is strongly associated with gender, and males were the predominant ones. Liver injury developments required 4-13 days.

The medications given to abnormal liver function enzymes were, Lopinavir/ritonavir 48%, Arbidol 42%, Hydroxychloroquine 32%, Darunavir cobicostat 5%, Azithromycin 2% Quinolones 36% Cephalosporin 10%, Glucocorticoids 24%, Thymopeptides 21% Interferon spray 77% Sedatives and Hypnotics 25%, Analgesic-antipyretic 23%, Antilipemic agents 8% Hypotensor 20%, Hypoglycemic agents 11%, Drug for coronary heart disease 12%, Lianhua Qingwen granules 5%, Shufeng Jiedu capsules 34%, Xuanfei Zhike mixture 13%.

Liver Injury Patterns, Chu H, *et al*. 2020 [25]

This multicenter retrospective analysis enrolled 838 hospitalized patients, 409 patients had a normal hepatic function and 429 with liver injury. Liver impairment was further subcategorized into hepatocellular pattern included with 48 patients, a mixed pattern of 211 patients, and a Cholestatic pattern of 170 patients.

This study evaluates the link between lopinavir/ritonavir and liver injury and did not report a significant correlation between treated patients and non-treated patients with lopinavir/ritonavir.

The rate of mortality and severe cases were high in a mixed pattern and Cholestatic group. The mortality cases were 12, 48, and 47 in the Hepatocellular, Cholestatic, and mixed pattern groups respectively.

Association between Liver injury markers and mortality, Fang L, *et al*. 2020 [26]

This multicenter retrospective cohort study was based on 5,771 patients. Patients were evaluated into two groups, non-severe Patients (n = 4,585) and Severe Patients (n = 1,186), based on baseline liver

function parameters. Patient distribution of severity and non-severity cases was comprehensively based on AST levels. This study reported the associated factors with liver injury were elevated neutrophil and low lymphocyte count, and also reported the high association with the male gender. Elevated AST levels more specifically associated with male gender, systemic use of corticosteroids, decrease lymphocyte count, increase neutrophil count, and increase body temperature. AST levels elevation associated with antifungal drugs, decrease lymphocyte, systemic use of corticosteroids, male gender, and chronic liver disease.

3. Conclusion

Our findings based on the available literature concluded that baseline comorbidities including hypertension, Shock, acute heart and kidney injury, Arrhythmia, ARDS and liver diseases increase the severity of Covid-19 infection, lengthen the hospital stay, the possibility of ICU admission, and narrow down the therapeutic options [11,13,15,16,22,24,26]. Some therapeutics like Lopinavir/ritonavir also increases the chances of liver injury development [7,817]. Distinctive treatment strategies should be followed according to the patient's age, sex, and baseline comorbidities history. Liver enzyme testing and its elevated levels, more specifically AST and ALT is an important indicator for liver injury, although they are not specific and not raised in all cases. However, its increased levels associated with disease severity [23,27]. A large-scale study also linked elevated AST levels with the use of antifungals [26]. Hypoalbuminemia also linked with liver injury [8,17]. Some studies reported old age and male gender, an important associated risk factor for liver injury [21,24,26].

Covid-19 itself is a lethal respiratory infection and responsible for multiple other associated infections including ARDS and multi-organ failure. The more worrisome situation is limited available supportive therapeutics, as there is no defined therapeutic available for COVID-19 infection. In case, of baseline comorbidities, the treatment becomes more crucial and also increases the chances of mortality [11,16,21,23,25,28].

4. Future perspective

The phenomenon of Drug-induced liver injury in COVID-19 patients is a complex process and more critical research needs to be conducted to understand its mechanism and therapeutic connection. The liver is the vital body organ; selective therapeutics needs to be administered with minimal adverse effects on other body organs [28].

5. Conflict of interest

The authors have no conflict of interests

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