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Case Series

Antiviral use in liver function abnormalities and Covid-19 patients: Serial cases

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ABSTRACT

Introduction: Some SARS-CoV-2 patients have liver function abnormalities due to anti-viral drug effects.
Methods: The design of this study was a case series reported using retrospectives. Data collection was carried out from December 2020 to February 2021. All participants were diagnosed with SAR-CoV-2 and received an anti-viral drug which identified liver function abnormalities.
Results: The patients' average age was 54.56 ± 14.46 years old. Most patients experienced shortness of breath and cough, with hypertension as the accompanying comorbid. Increased AST and ALT were found in one patient who used Lopinavir-Ritonavir. The increase was 1.0 times to 2.0 times the expected value. Increased CRP, D-dimer and procalcitonin were also found, with a mean of 12.27 ± 15,34, 1861.29 ± 1828.85 and 1.54 ± 2.84, respectively. One of the patients in the Lopinavir-Ritonavir group died while receiving treatment.
Conclusion: SAR-CoV-2 is one of the risk factors that cause liver function abnormalities supported by anti-viral drugs that cause liver work to increase.

1. Introduction

Coronavirus disease 2019 (COVID-19) cases have increased steadily since first discovered in Indonesia on March 2, 2020. As of February 21, 2021, more than 1 million people were confirmed positive for COVID-19, with 34,316 death confirmed [1,2]. This indicates that curative and preventive therapies must be developed to prevent the spread of COVID-19. Symptoms of patients with COVID-19 range from minimal symptoms, such as cough, to severe respiratory failure with multiple organ failure. Radiological examination (CT scan) typically finds ground glass opacification in the lung of COVID-19 patients, even in asymptomatic patients [3]. Patients with COVID-19 may also experience liver function abnormalities. Liver function abnormalities can be directly caused by SARS-CoV2 cytotoxicity, a history of prior liver disease, or the side effects of drugs used in the treatment [4]. There is still no guideline in COVID-19 therapy, with different centres using different anti-viral drugs such as Remdesivir, Lopinavir-Ritonavir combination, and Favipiravir. This report aimed to evaluate the effect of Remdesivir, Lopinavir-Ritonavir, and Favipiravir on liver function in a case series of 9 patients with COVID-19.

2. Methods

The design of this study was a prospective study reported, and data collection was carried out from December 2020 to February 2021 at the hospital. The diagnosis of COVID-19 was obtained using real-time polymerase chain reaction (PCR) taken from nasopharyngeal swabs [1,2,5]. Participants were identified for liver function abnormalities using anti-viral treatment (Favipiravir or Avigan, Lopinavir-Ritonavir combination or Lopivia, and Remdesivir). Indicators of liver function abnormalities include ALT, AST, albumin, total bilirubin, and direct bilirubin, which were monitored every 3 days [6,7]. We report based on Preferred Reporting of Case Series in Surgery (PROCESS) 2020 guidelines [8].

3. Results

A total of 9 patients were included in the study. Based on the treatments given, 3 patients received Favipiravir (Avigan), 3 received Lopinavir-Ritonavir combination (Lopivia), and 3 received Remdesivir. There were 1 critically ill patient, 2 severe disease patients, and 6 moderates. Most patients experienced cough and shortness of breath. All patients were adults, with a mean age of 54.56 ± 14.46 years old and

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most patients had comorbidity (Type 2 Diabetes Mellitus). None of the nine patients had any underlying liver disease, and all tested negative for HbsAg and anti-HCV. ALT, AST, albumin, total bilirubin, and direct bilirubin levels were monitored every 3 days during hospitalization. Increased CRP, D-dimer and procalcitonin were also found, with the mean being 12.27 ± 15.34, 1861.29 ± 1828.85 and 1.54 ± 2.84, respectively. Different drugs were used with an anti-viral drug, the most common being N-acetylcysteine, while Levofloxacin was the most common antibiotic. The mean length of stay was 28.11 ± 20.81, with one death recorded within the Lopinavir-Ritonavir group. Further data relating to patient characteristics, clinical symptoms, comorbidities, laboratory parameters, treatment and outcome can be seen in Table 1. The dynamics of changes in levels of AST, ALT, albumin, total bilirubin, and direct bilirubin can be seen in Figs. 1–3.

4. Discussion

Drug-Induced Liver Injury (DILI) is an increase in serum ALT more than 3.0 times the standard value with symptoms of hepatitis or more than 5.0 times the standard value with or without symptoms of liver damage immediately after taking a drug. Symptoms generally appear within the first 2 months of treatment, such as jaundice, abdominal pain, nausea, vomiting, and fatigue. DILI can be caused by various hepatotoxic drugs [9]. Drugs that can cause DILI include non-Steroidal Anti--Inflammatory Drugs (NSAIDs), anesthetics, anti-tuberculosis (Isoniazid, Rifampicin, and Pyrazinamide), antibiotics (beta-lactams, cephalosporins, and macrolides), anti-fungals, oral hypoglycaemics, statins, and anti-retroviral drugs [10].

Avigan, a drug that contains Favipiravir, is an anti-viral that works by inhibiting the viral RNA-dependent RNA polymerase (RdRp) [11]. It is metabolized in the liver by aldehyde oxidase and partially converted to a hydroxylated form by xanthine oxidase. The dose used in COVID-19 treatment is higher than what is commonly used but still considered safe, and the study shows no significant side effects [12]. The first study was conducted in the UK. It found no significantly increased risk of liver damage in COVID-19 patients treated with Favipiravir than those not treated with Favipiravir [13]. The second study was conducted in China, finding that side effects were more common in the control group, with minor liver damage occurring in COVID-19 patients treated with Favipiravir (2.86%) than those not receiving Favipiravir (6.67%) [14]. Albumin levels decreased initially but returned to normal on the ninth day. Similar results were found in a study conducted in China. It found that albumin decreased in 88% of COVID-19 patients treated with Favipiravir. However, the study also showed decreased albumin in 90% of the control group who were not given Favipiravir. Most likely, albumin decrease is a direct cause of COVID-19 infection and not a side effect of Favipiravir administration [15].

Lopivia is a combination of Lopinavir and Ritonavir. Lopinavir is an aspartate protease inhibitor antiretroviral drug, while Ritonavir is a retroviral protease inhibitor. The combination of the two drugs is commonly used to treat HIV and AIDS patients [16]. Further studies later found that Lopinavir is a significant protease inhibitor of SARS-CoV. The Lopinavir-Ritonavir combination is also effective against the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in guinea pig specimens [17]. The first study in France found that 14–53% of patients experienced increased transaminases and liver enzymes after Lopinavir-Ritonavir administration. There were 4 cases of discontinuation of the Lopinavir-Ritonavir combination due to suspected DILI [18]. The second study was conducted in China and found that the Lopinavir-Ritonavir combination increased the risk of liver damage by 4 times [19]. Albumin levels decreased and mostly stayed under standard value. These results differ from a study conducted in China, which found that the Lopinavir-Ritonavir combination could increase albumin levels in patients with COVID-19. The difference between our studies is that their cases are higher in number, and most are mild COVID-19 cases [20].

Table 1
Clinical, treatments, and outcome characteristics of confirmed COVID-19 patients.

Characteristics	Overall (n = 9)	Favipiravir (Avigan) (n = 3)	Lopivia (n = 3)	Remdesivir (n = 3)
Gender				
Male	4 (44.44)	0 (0.00)	2 (66.67)	2 (66.67)
Female	5 (55.56)	3 (100.00)	1 (33.33)	1 (33.33)
Age	54.56 ± 14.46	59.67 ± 11.59	57.33 ± 14.74	46.67 ± 14.19
Clinical symptoms				
Shortness of breath	7 (77.78)	2 (66.67)	2 (66.67)	3 (100.00)
Cough	7 (77.78)	3 (100.00)	2 (66.67)	2 (66.67)
Fever	5 (55.56)	2 (66.67)	1 (33.33)	2 (66.67)
Anosmia	2 (22.22)	0 (0.00)	1 (33.33)	1 (33.33)
Diarrhea	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Nausea & vomiting	2 (22.22)	0 (0.00)	2 (66.67)	0 (0.00)
Comorbidities				
Obesity	2 (22.22)	0 (0.00)	1 (33.33)	1 (33.33)
Type 2 diabetes mellitus	5 (55.56)	2 (66.67)	1 (33.33)	2 (66.67)
Hypertension	4 (44.44)	2 (66.67)	2 (66.67)	0 (0.00)
Laboratory examination				
ALT (IU/L)	50.88 ± 33.10	47.50 ± 10.61	70.67 ± 56.59	33.33 ± 1.15
AST (IU/L)	54.00 ± 26.32	42.00 ± 16.97	77.00 ± 35.00	39.00 ± 11.27
Albumin (g/dL)	3.39 ± 0.21	3.45 ± 0.07	3.39 ± 0.18	3.35 ± 0.37
Total bilirubin (mg/dL)	0.56 ± 0.27	0.22 ± 0.00	0.72 ± 0.30	0.59 ± 0.16
Direct bilirubin (mg/dL)	0.31 ± 0.19	0.14 ± 0.00	0.45 ± 0.28	0.22 ± 0.06
Neutrophil (%)	75.37 ± 13.47	80.35 ± 5.73	74.03 ± 19.74	76.70 ± 12.20
Lymphocytes (%)	15.76 ± 8.52	14.35 ± 6.58	15.50 ± 13.08	16.97 ± 9.65
NLR (%)	21.02 ± 45.05	6.36 ± 2.35	45.95 ± 74.78	5.86 ± 3.76
APTT (sec)	28.06 ± 5.21	28.45 ± 0.21	31.50 ± 5.09	20.4 ± 0.00
PTT (sec)	11.20 ± 1.62	12.10 ± 2.55	10.60 ± 1.13	10.6 ± 0.00
CRP (mg/dL)	12.27 ± 15.34	7.20 ± 3.61	16.67 ± 14.52	3.65 ± 5.02
D-dimer (ng/dL)	1861.29 ± 1828.85	900.00 ± 480.83	1655.00 ± 332.34	2639.67 ± 2826.26
Procalcitonin (ng/dL)	1.54 ± 2.84	0.17 ± 0.00	5.18 ± 0.00	0.1 ± 0.1
Treatment				
Levofloxacin	4 (44.44)	1 (33.33)	0 (0.00)	3 (100.00)
Moxifloxacin	1 (11.11)	0 (0.00)	1 (33.33)	0 (0.00)
Ceftriaxone	1 (11.11)	0 (0.00)	1 (33.33)	0 (0.00)
Paracetamol	4 (44.44)	2 (66.67)	1 (33.33)	1 (33.33)
N-acetylcysteine	7 (77.78)	3 (100.00)	2 (66.67)	2 (66.67)
Curcuma	4 (44.44)	1 (33.33)	3 (100.00)	0 (0.00)
Albumin	6 (66.67)	2 (66.67)	1 (33.33)	3 (100.00)
Dexamethasone	5 (55.56)	1 (33.33)	1 (33.33)	3 (100.00)
Outcome				
Length of stay (days)	28.11 ± 20.81	38.33 ± 30.98	26.33 ± 21.38	19.66 ± 6.80
Death	1 (11.11)	0 (0.00)	1 (33.33)	0 (0.00)

Remdesivir is a phosphoramide pro-drug of a nucleoside analogue. It can inhibit viral replication by competing with endogenous nucleotides to bind viral RNA replicating via RNA-dependent RNA polymerase (RdRp) [10]. Remdesivir is the substrate of some cytochrome P450 enzymes in vitro, and the clinical implications remain unclear because pro-drugs are rapidly metabolized by plasma hydrolase [21]. The baseline AST and ALT levels for this particular patient are already higher than usual, hypothesized to be due to having grade 2 obesity and dyslipidaemia. Several studies show that obesity and dyslipidaemia could

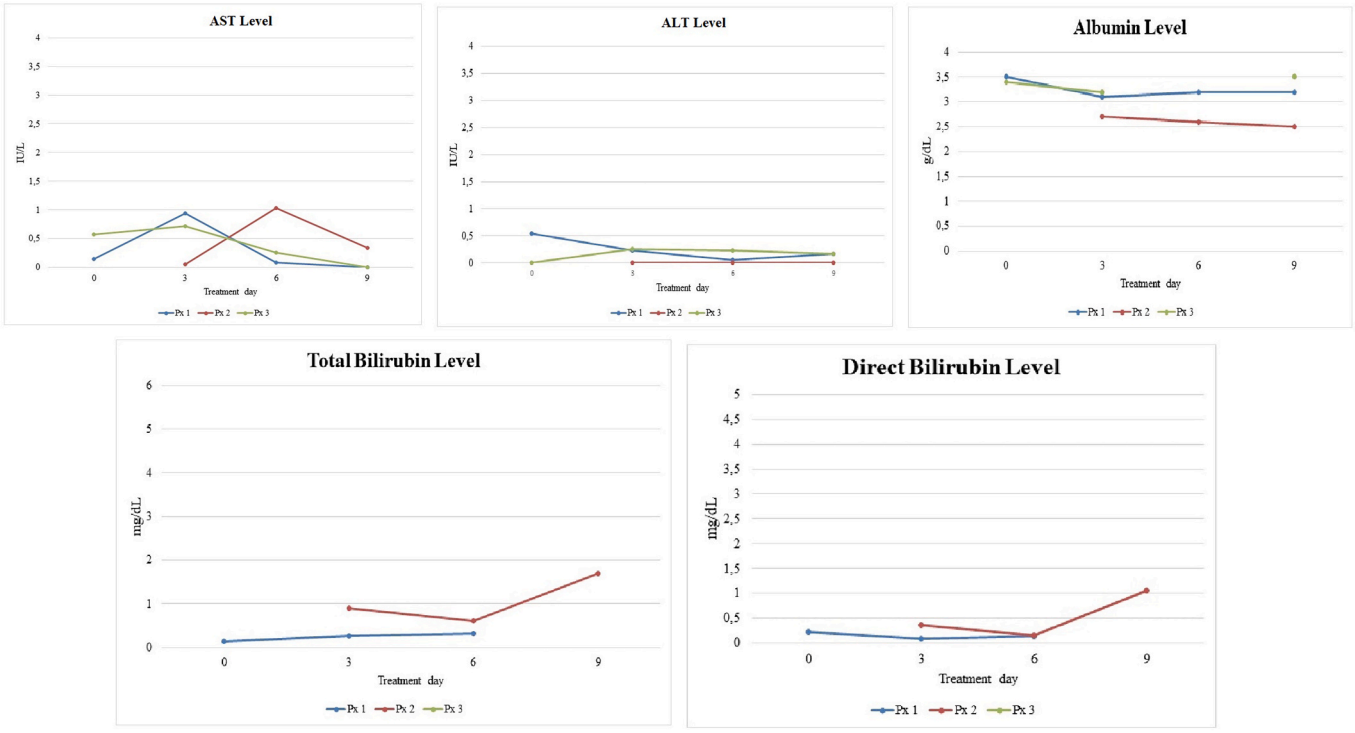

Fig. 1. Changes in ALT, AST, albumin, total bilirubin, and direct bilirubin when receiving Avigan (Favipiravir).

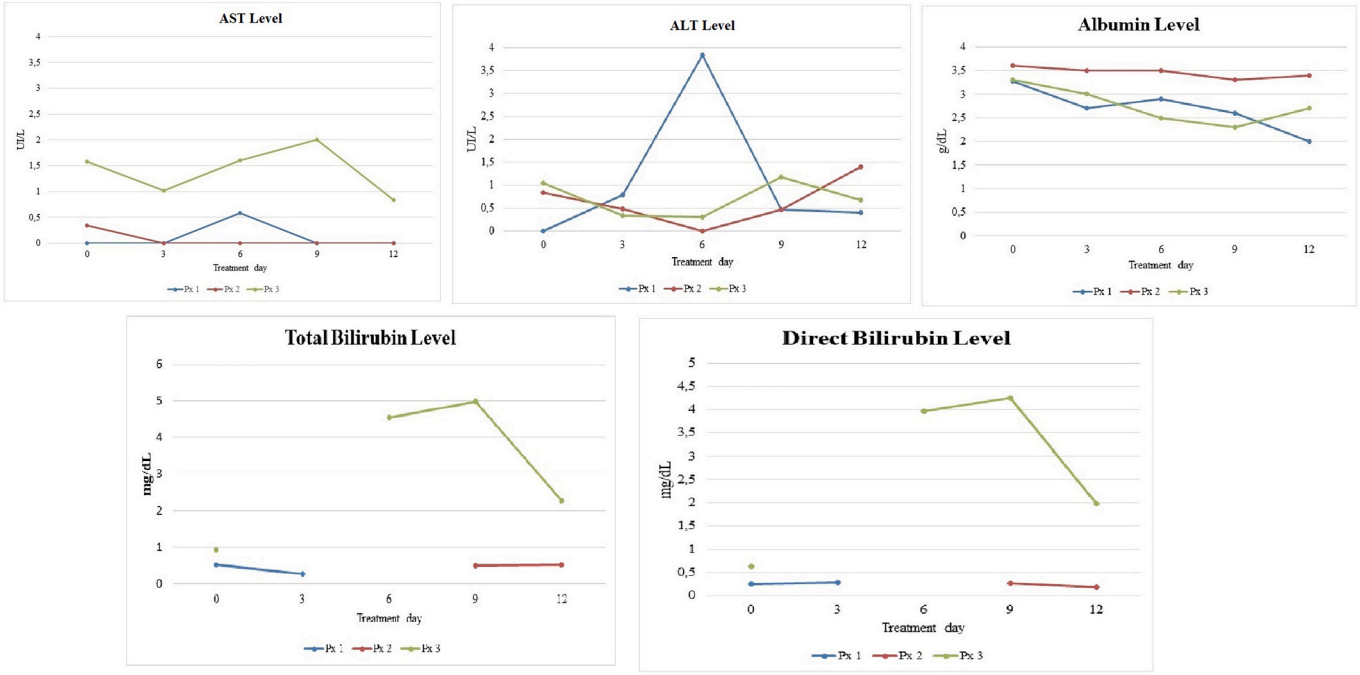

Fig. 2. Changes in ALT, AST, albumin, total bilirubin, and direct bilirubin when receiving Lopivia (Lopinavir + Ritonavir).

lead to Non-Alcoholic Fatty Liver Disease (NAFLD) [22,23]. Similar cases with similar results were found in a study conducted in North America, Europe, and Japan. It reported that 12 patients (23%) had severe liver enzyme elevations after taking Remdesivir [24]. Another study comparing Remdesivir and placebo found that the incidence of elevated serum aminotransferases in those treated with Remdesivir (22 cases; 4.1%) was lower than in the placebo group (31 cases; 5.9%) [10,21]. Albumin levels decreased initially but returned to normal on the ninth day. Similar results were found in a study conducted in China. No abnormalities occurred in albumin in COVID-19 patients receiving Remdesivir [25].

5. Conclusion

There has been no therapy that has been scientifically proven to cure COVID-19 yet. COVID-19 therapy now focuses primarily on supportive therapy and complication prevention. Effective and safe anti-viral agents are indispensable to ease the burden on health services. In this

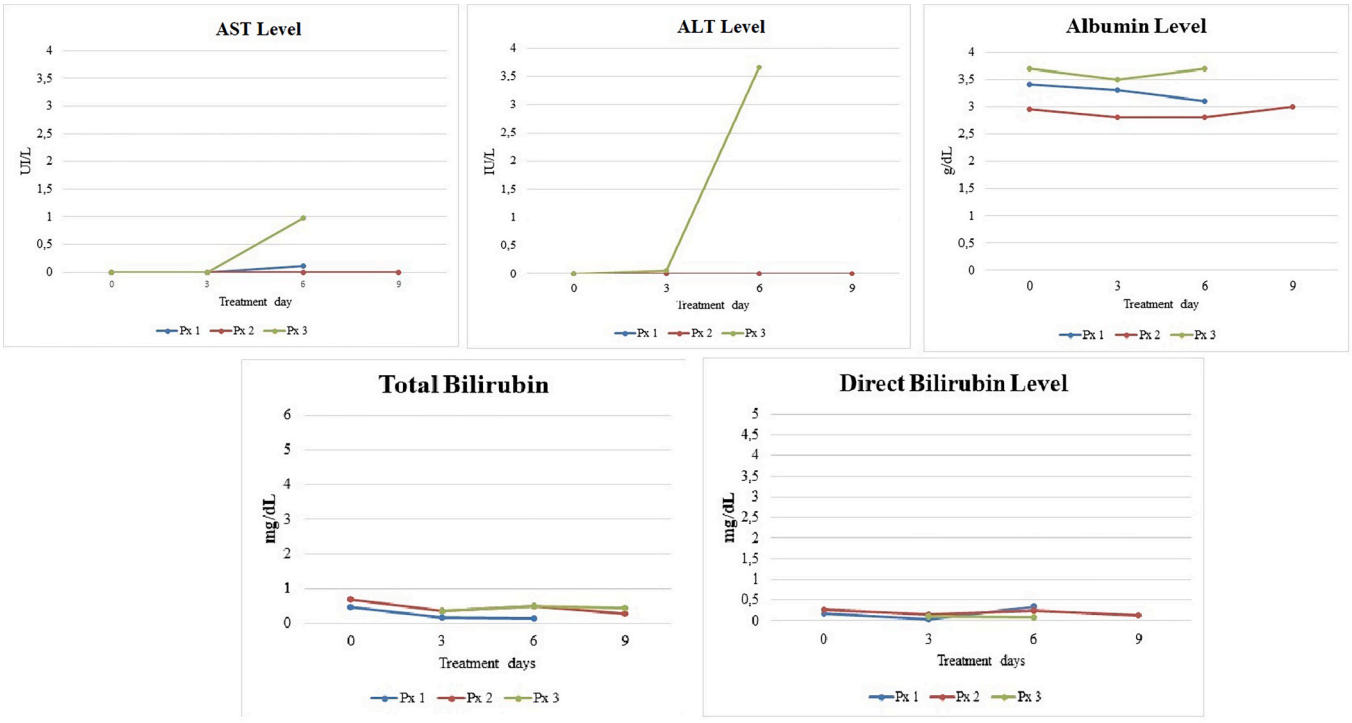

Fig. 3. Changes in ALT, AST, albumin, total bilirubin, and direct bilirubin when receiving Remdesivir.

report, the administration of Remdesivir, Lopinavir-Ritonavir, and Favipiravir causes liver abnormalities characterized by an increase in AST or ALT in some but not all patients. Further research with a more significant number of samples and exclusion of patients with liver abnormality before therapy is needed to address further the effects of Remdesivir, Lopinavir-Ritonavir, and Favipiravir on liver function.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104876.

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