

## Evaluation of Remdesivir in Liver Functions Covid-19 Patients at Bhayangkara H.S Samsoeri Mertojoso Hospital Surabaya

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### Abstract

Remdesivir is one of the effective anti-viral drugs used as a Covid-19 therapy at moderate, severe and critical degrees. Side effects that need to be considered in the use of remdesivir is hepatotoxicity. The active metabolite of remdesivir (GS-44152) is thought to play a role in mitochondrial damage in liver cells, inhibiting bile acid transport, and inducing oxidative stress. This study was conducted to evaluate the use of remdesivir associated with changes in liver function SGOT and SGPT. This study was retrospective observation of moderate, severe and critical COVID-19 patients receiving remdesivir with inclusion criteria of all inpatient medical records at Bhayangkara Hospital Surabaya for the period of August 2020-July 2021. The results showed that significant increase of liver enzymes occurred in SGPT (Pre 29.50; Post 33.50) while in SGOT (Pre 33.00; Post 26.00), enzymes were significantly decreased. The decrease was greater in the SGPT (Pre 69.00; Post 47.00) and SGOT (Pre 56.00; Post 32.00) hepatoprotector groups. The use of remdesivir had no effect on liver function as indicated by an increase in SGPT value and a decrease in SGOT value, both of which were still in the normal range.

**Keywords:** remdesivir, covid-19, hepatotoxicity

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### 1 Introduction

Severe infection with SARS-CoV-2 will trigger an immune response as a protective

measure. Cytokine storm is a response to this new SARS-CoV-2 infection causing multiple organ injury, one of which is in the liver which

causes an increase in SGOT and SGPT. [1]. In patients with Covid-19, the parameter for the increase in SGOT/SGPT was greater than that of gamma-glutamyltransferase (GGT) and alkaline phosphatase (AF). A study in China with 156 patients with Covid-19 showed that 41% of patients had an increase in SGOT/SGPT [2], [3]. Cytokine storms due to Covid-19 infection are associated with disease severity [4], [5]. Direct hepatocyte infection or the occurrence of a cytokine storm can stimulate hyperactivation of liver cells signaling mTOR and the occurrence of hepatic steatosis in patients caused by Covid-19 [6]. The mechanism of remdesivir related to an increase in the value of liver enzymes SGOT/SGPT plays a direct role in mitochondrial and proximal tubule damage, inhibits bile acid transport, mitochondrial dysfunction as an electron transport chain, induces oxidative stress [7].

According to FDA 2020, in patients using Ventilator/ECMO remdesivir is used for a loading dose (1×200 mg) iv drip 30-120 minutes on day 1, followed by a maintenance dose (1×100 mg) iv drip 30-120 minutes until day 1. -10, while patients who did not use Ventilator/ECMO used remdesivir for a loading dose (1×200 mg) iv drip 30-120 minutes on day 1, followed by a maintenance dose (1 × 100 mg) iv drip 30-120 minutes until day 1. -5, if there is no clinical improvement can be continued until the 10th day.

Remdesivir is contraindicated in patients with hepatic impairment (SGPT 5x the upper limit of normal or there is SGPT elevation associated with elevated direct bilirubin, alkaline phosphatase, or INR) [8].

Research data in Indonesia related to the evaluation of liver function from the use of remdesivir is still not available. Therefore, it is necessary to evaluate the administration of remdesivir related to side effects on liver function without/or with a hepatoprotector carried out in moderate, severe and critical Covid-19 patients at Bhayangkara H.S Samsoeri Mertojoso Hospital Surabaya.

## 2 Method

Retrospective observation on moderate, severe and critical COVID-19 patients receiving remdesivir with the inclusion criteria of all inpatient medical records at Bhayangkara

Hospital Surabaya for the period of August 2020-July 2021. Data collection was carried out from November 24 to December 29, 2021, after obtaining multiplication ethics approval from the Health Research Ethics Committee, Bhayangkara HS Samsoeri Mertojoso Hospital, Surabaya based on the certificate of ethical qualification (Ethical Exemption) No. 24/XI/2021/KEPK/RUMKIT dated November 15, 2021.

The instruments used are data collection sheets, master tables and Health Medical Records (RMK) of patients with a Covid-19 diagnosis at Bhayangkara H.S Samsoeri Mertojoso Hospital Surabaya and based on the results of daily observation sheets for the period of August 2020-July 2021.

Data analysis utilized SPSS ver 26 program. Descriptive analysis of gender, age, comorbidities, symptom groups (moderate, severe and critical) and whether patients use a hepatoprotector or not, was described as a frequency distribution presented in tabular form. Comparative Analysis of Pre vs Post SGOT and SGPT applied Wilcoxon where it is stated that there is a difference between pre vs post if the significance value is < 0.05.

## 3 Results and Discussion

Data collection was carried out for 1 month in November-December 2021, and 189 patients who met the inclusion criteria were obtained from 217 patients whose medical records were accessible.

The inclusion criteria in this study were patients with a confirmed diagnosis of Covid-19 who received remdesivir with complete clinical laboratory data marked by pre and post SGOT and SGPT examinations. 28 patients belonged to the exclusion criteria because the patient's pre and post laboratory examination data were incomplete, there were no post-SGOT and SGPT examinations.

Result of patient characteristics in table 1 shows that male patients were 123 patients (65.1%) more than female patients were 66 patients (34.9%). While the highest age was in the age range of 46-60 years as many as 73 patients (38.6%), then followed by patients in the age range 31-45 years as many as 65 patients (34.4%), age >60 years as many as 28

patients (14.8%) and patients aged 18-30 years as many as 23 patients (12.2%).

Table 1 Patient Demography

Patient Characteristics	Total patient (n=189)	
	Number	Percentage (%)
Sex		
Male	123	65.1
Female	66	34.9
Age		
18-30 years old	23	12.2
31-45 years old	65	34.4
46-60 years old	73	38.6
>60 years old	28	14.8
Comorbid		
None	94	49.7
DM	30	15.9
cardiac	29	15.3
DM and cardiac	36	19.1
Severity		
Moderate	101	53.4
Severe	68	36.0
Critical	20	10.6
Hepatoprotector		
None	150	79.4
Yes	39	20.6

This is because in men, the hormone testosterone has an immunosuppressant effect, while in women, estrogen can increase the immunity of the immune system [9], [10]. From this study, data was obtained that from 94 patients (49.7%) did not have comorbidities when hospitalized, while patients with diabetes comorbidities were 30 patients (15.9%), patients with cardiac comorbidities were 29 patients (15.3%), and patients with comorbid diabetes and heart as many as 36 patients (19.1%).

According to the PDPI 2021, the degrees of COVID-19 disease are divided into mild degrees, moderate degrees, severe degrees and critical degrees [11]. The degree criteria analyzed in this study were limited to moderate, severe and critical degrees. The most patients were Covid-19 patients with moderate degrees of 101 patients (53.4%), followed by severe degrees with 68 patients (36.0%) and critical degrees with 20 patients (10.6%).

A study on COVID-19 found that of 22 patients with liver injury, the proportion of injuries was significantly higher ( $P = 0.011$ ) in 16 patients (72.7%) with underlying disease than in patients without underlying disease. Liver injury is observed in all types of COVID-19, especially in severe and critical types [12]. In

this study, it is discovered that 39 patients (20.6%) used hepatoprotectors compared to 150 patients (79.4%) who did not use hepatoprotectors.

Among patients without hepatoprotectors, 50 patients had mild cases of liver injury. This is in line with a systematic review and meta-analysis where the results showed that most of the liver injuries were mild cases [13]. Meanwhile, of the 39 patients who used remdesivir with hepatoprotector, 1 patient had severe liver injury, 5 patients had moderate liver injury, and 28 patients had mild liver injury. A SGPT increase in patients without hepatoprotector was found in 24 patients with mild liver injury. In patients with hepatoprotectors there were 1 patient with severe liver injury and 3 moderate liver injury. In patient code 84, there was an increase in liver function parameters after remdesivir administration, even though it was supplemented with a hepatoprotector. Elevated liver biochemistry is mostly associated with severe and critical Covid-19 conditions for multifactorial reasons, such as drug-induced liver function abnormalities, liver involvement in critical illness and hypoxic disorders [14]. Severe cases are more likely to have severe liver injury when compared to mild cases [13], [15], [16].

A study conducted by Gilead and the FDA does not recommend the use of remdesivir for Covid-19 patients with an SGOT/SGPT increase of five times the normal value [17]. In our study at Bhayangkara Hospital there were 4 patients out of 39 patients (11%) with an increase in pre SGOT or SGPT  $> 5x$  the normal value, namely code 35 SGPT 191, code 49 SGOT 161 SGPT 178, code 93 SGOT 170 SGPT 279, code 137 SGOT 429 SGPT 153. Remdesivir is still given to Covid-19 patients whose pre-SGOT and SGPT values increase with additional hepatoprotector supplementation providing an improvement in post-SGOT and SGPT values. In our study, it can be seen in Table 2 that a significant increase in liver enzymes occurred in SGPT while in SGOT it was significantly decreased and the decrease was greater in the hepatoprotector group.

Table 2 Result of Comparative Analysis of pre vs post SGOT and SGPT

Hepatoprotector	Parameter	SGOT		SGPT	
		Pre	Post	Pre	Post
No	N	150	150	150	150
	Median	33,0	26,0	29,5	33,5
	Minimum	9	9	6	11
	Maximum	112	128	110	354
Yes	N	39	39	39	39
	Median	56,0	32,0	69,0	47,0
	Minimum	21	15	22	16
	Maximum	429	205	279	760

In the study, 24 patients using remdesivir were treated for the period May to July 2021 when the delta variant Covid-19 outbreak occurred with 50% of patients experiencing an increase in laboratory parameters of liver function SGOT and SGPT, the highest increase occurred in two patients with three to four times the normal value. There were five patients who received hepatoprotector supplementation and all of them had laboratory improvement of liver function. Patients who did not receive a hepatoprotector as many as 14 people also experienced improvements in laboratory results, only five people experienced an increase in SGOT and SGPT in the range between one to two times the normal value. Remdesivir itself clinically improves the condition of Covid-19 patients and also reduces the occurrence of serious side effects in several meta-analyses studies showing significantly lower serious side effects in the remdesivir group compared to controls [18]. Although statistically there was a decrease in SGOT and SGPT values in patients using hepatoprotectors, in our study 4 patients (patient codes 82, 84, 102, 181) experienced an increase in post scores of up to two to 13 times. In a study related to remdesivir, a randomized trial in Covid-19 patients showed an equivalent increase in liver enzymes between the treatment and control groups [19]. In a study conducted by Grein et al. In 2020, in Covid-19 patients, 22% of hospitalized patients with SARS-CoV2 infection using remdesivir experienced an increase in liver enzymes [20].

#### 4 Conclusion

In this study the use of remdesivir had no effect on liver function as indicated by the increase in the SGPT value and the decrease in the SGOT value which was still within the normal range. Further, it is suggested that the

effectiveness of hepatoprotectors among Curcuma, HP Pro, Lecichol, Hepamerz, SNMC which have cost effectiveness in Covid-19 patients.

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#### 6 Author Contributions

Maria Angelia Yoshida as data collector, analyzes and writes articles. Didik Hasmono as the main supervisor and research director. Ruddy Hartono as justification for pharmaceutical aspects at Bhayangkara Hospital Surabaya. Mohammad Subkhan as justification for clinical aspects at Bhayangkara Hospital Surabaya. All authors work together to produce clinically and scientifically acceptable writing.

#### 7 Ethics

Ethics approval from the Health Research Ethics Committee, Bhayangkara HS Samsoeri Mertojoso Hospital, Surabaya based on the certificate of ethical qualification (Ethical Exemption) No. 24/XI/2021/KEPK/RUMKIT dated November 15, 2021.

#### 8 Conflict of Interest

There is no conflict of interest in this research.

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