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Original Article

Sorbitol Dehydrogenase and Other Liver Enzymes Before and After Five Days Remdesivir Therapy in Covid-19 Patients

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ABSTRACT

The antiviral remdesivir has the potential to cause drug-induced liver injury in Covid-19 patients as seen in increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Sorbitol dehydrogenase (SDH) is a cytoplasmic liver enzyme and can increase in acute liver injury, so it has been proposed as an alternative biomarker in liver injury. This study aimed to analyze the differences in serum SDH levels and other liver enzymes before and after 5 days of remdesivir therapy in Covid-19 patients. This was a prospective observational cohort conducted at RSUD Dr. Soetomo Surabaya, East Java between September and November 2022. The samples included in this study were selected consecutively. The venous blood sample were collected twice from each patient of 34 Covid-19 patients with positive real-time polymerase, namely on the first day of admission before receiving remdesivir therapy and after the fifth day of remdesivir therapy. Venous blood samples are then processed to obtain serum which will be used to measure SDH levels using the sandwich Enzyme-linked immunosorbent assay (ELISA) method and liver enzyme with Alinity-c analyzer. There were 34 subjects, 18 males and 16 females with median ages 56 years old. The median of serum SDH before and after 5 days therapy, respectively, was 0.75 U/L (SD=1.88) and 0.85 U/L (SD=1.32). The median difference of AST, ALT, direct bilirubin, total bilirubin, alkaline phosphatase (ALP), and gamma-glutamil transferase (GGT), respectively, were -3.75 mg/dL, -2 mg/dL, 0.045 mg/dL, 0.05 mg/dL, -3.5 mg/dL, and -1 mg/dL.

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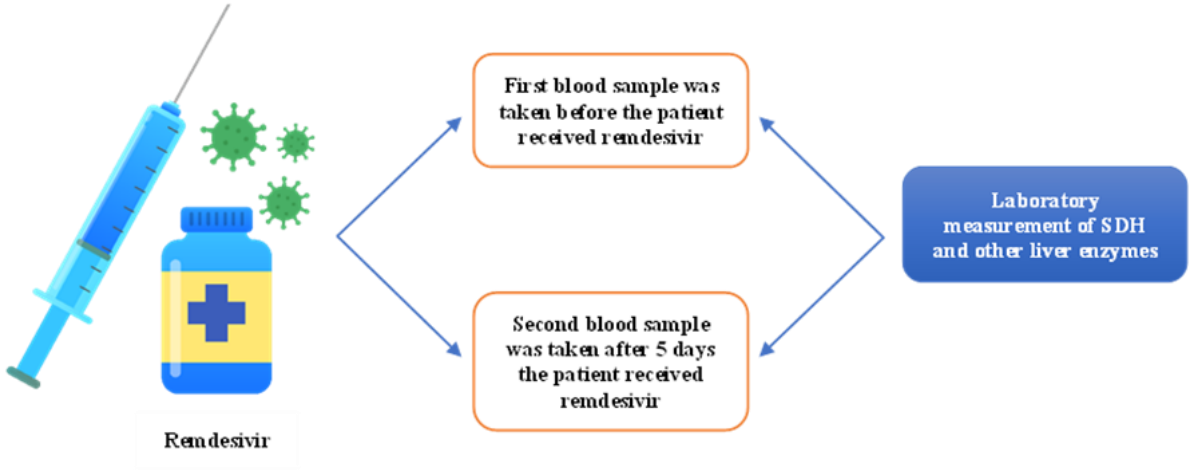
GRAPHICAL ABSTRACT



Introduction

Remdesivir is a monophosphoramidate prodrug, a broad-spectrum antiviral used as therapy for Covid-19 caused by severe acute coronavirus-2 (SARS Cov-2) that will be converted into its active form, remdesivir triphosphate. Remdesivir triphosphate is a nucleotide analogue that competes with ATP and interferes with viral RdRp activity, stopping viral RNA replication. Remdesivir as a nucleotide analogue is suspected to cause hepatocyte damage, that can trigger mitochondrial injury by inhibiting the host's DNA and RNA polymerase. This can cause hepatocyte mitochondrial damage resulting in increased levels of transaminase [1-3]. Another mechanism that is thought to cause hepatocyte damage by remdesivir is that Remdesivir's metabolism mainly occurs in the liver (80%). Remdesivir can inhibit the action of CYP3A4 (cytochrome P450 family) which functions as a drug biotransformation enzyme, causing the elimination process of remdesivir's active metabolite to decrease. Remdesivir's active metabolite buildup is hepatotoxic, causing hepatocyte damage [4]. Another susceptible mechanism is the interaction of remdesivir with P-glycoprotein (P-gp) inhibitory agents. P-glycoprotein is an efflux transporter located in the membranes of several human cells including hepatocytes. The P-gp transporter functions to transport xenobiotics out of the cells into the bile ducts. Drug interactions that occur can inhibit the action of P-gp resulting in remdesivir efflux. This will lead to accumulation of active metabolite remdesivir and toxic to hepatocyte [5].

Several studies describe the side effects that often found in the use of remdesivir; increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with an incidence of around 6-23% which indicates the potential for drug induced liver injury (DILI) [6-8]. The clinical features of DILI can mimic those of other liver diseases, making it difficult to establish DILI diagnosis [9]. Temporary increases in transaminases and/or other liver enzymes can occur in patients with Covid-19 in the range of 10.5–53.1% [10-12]. Elevated ALT and AST levels are indicative of hepatocellular damage, while serum bilirubin levels indicate the secretory capacity of the liver. In Covid-19, cholangiocyte cell injury can also be found, especially characterized by bile duct proliferation, bile duct obstruction with increased levels GGT and ALP [13, 14]. Biomarker liver injury that commonly are AST and ALT, but these parameters are not specific.

Alternative biomarker which is more specific is needed to detect and assist in the DILI diagnosis. Sorbitol dehydrogenase (SDH) is an enzyme that is mainly present in the hepatocyte's cytoplasm, and only about 20% present in the kidney and seminal vesicles. SDH levels in normal serum are usually very low but increase during acute episodes of hepatocyte damage so that SDH can be a specific indicator of hepatocyte damage [15-17].

SDH activity remains stable (does not decrease) at -70 ºC storage for up to 6 months. The normal

value of SDH levels in humans is <3 U/L [18]. In addition, until now there has been no study assessing SDH levels as a biomarker of liver injury in the administration of antivirals, especially remdesivir. This study aimed to evaluate SDH serum levels and other liver enzymes before and after 5 days administration of remdesivir antiviral therapy.

Materials and Methods

This prospective observational cohort analytic study was conducted in Isolation ward and Intensive Care Unit for Covid-19 of RSUD Dr. Soetomo Surabaya, East Java between September and November 2022. All participants had given their written informed consent before participating in the study and their anonymity was preserved. The study was approved by the Institutional Ethics Committee of RSUD Dr. Soetomo Surabaya, East Java, No. 0369/KEPK/II/2022.

The samples included in this study were selected consecutively. Inclusion criteria were male or female adult patient, aged more than 18, diagnosed with Covid-19 confirmed by PCR, patients receive antiviral therapy for at least 5 days, willing to participate in the study by signing an informed consent (represented by the family/legal guardian for incompetent sufferers). Exclusion criteria including patients with a history of concomitant liver disease, autoimmune, malignancy, and immunodeficiency, also patients with HBsAg and/or reactive Anti-HCV and hemolysis blood specimen. Fifty two Covid-19 patients with positive PCR were recruited for this study; 18 patients were excluded from this study because they died before receiving therapy or died before day 5 of therapy, resulting in a total of 34 subjects for this study.

Blood sampling was performed twice for each patient; namely, on the first day of admission before receiving remdesivir therapy and after the fifth day of remdesivir therapy. A total of 5 ml venous blood sample was drawn from each patient and put into serum separator tubes, SST™, BD Vacutainer®. Sample tubes were centrifuged at 3000 rpm to obtain serum. The hemolyzed sample was discarded. Serum divided into 2-3 aliquot which each aliquot contains 200-300 uL serum and stored at -80 °C until the required number of samples is met. The sandwich ELISA method (MyBioSource®) was used to examined SDH levels. Other liver enzymes (AST, ALT, Direct Bilirubin, Total Bilirubin, ALP, and GGT) were examined using the Alinity c analyzer, Abbott®. The research flow is briefly explained in Figure 1.

The collected data were entered into Microsoft Excel. Statistical analysis using SPSS version 25.0 and p-value is considered significant when $p < 0.05$. The data normality test uses the Kolmogorov-Smirnov test for data > 50 and the Shapiro Wilk test for data ≤50. Paired T-test was used to analyze differences in serum SDH levels before and after administration of remdesivir therapy in Covid-19 patients if the data was normally distributed. Data with abnormal distribution were analyzed using the Wilcoxon test. Analysis of the relationship between serum SDH levels and liver biochemical parameters in Covid-19 patients after receiving remdesivir therapy using the Pearson test if the data is normally distributed, if the data is not normally distributed using the Spearman test. Results are significant when $p<0.05$.

Result and Discussion

Thirty-four patients were recruited for this study which characteristics of the patients are shown in Table 1. The number of male subjects was greater than female subjects, with 18 male subjects (52.9%) and 16 female subjects (47%). The mean age was 52.47 ± 15.21, with a median of 56 years and the lowest age was 22 years old and the highest was 89 years old. The results of this study are inconsistent with data on the spread of Covid-19 in Indonesia, which is dominated by the age group 31-45 years old (Covid-19 Task Force, 2022), but did not correlate with SDH levels because it is not affected by age and sex [18]. This study found 29 subjects had comorbidities and each patient had combination two or more comorbid which are diabetes mellitus (58.6%), hypertension (72.4%), and CKD (17.2%).

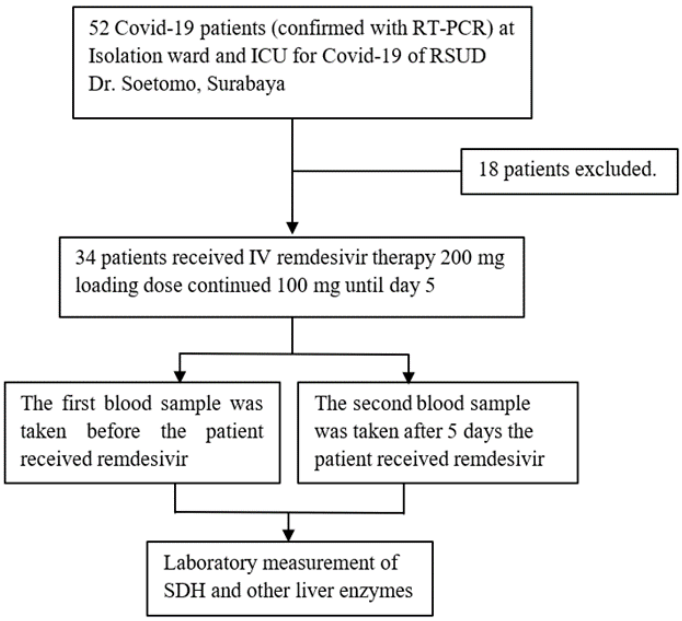


Figure 1: Schematic description of the research flow

Table 1: Characteristics of the study subjects (n=34)

Characteristics	n	%
Age (year)		
Range	22-89	
Median	56	
Sex		
Male	18	52.9
Female	16	47.1
Comorbid		
Yes	29	85.3
No	5	14.7
Comorbid type		
Hypertension	21	72.4
DM	17	58.6
CKD	5	17.2
Others*	11	37.9
Severity		
Critically ill	12	35.3
Severe	7	20.6
Moderate	12	35.3
Mild	3	8.8
Outcome		
Survived	26	76.5
Non-survived	8	23.5

**other comorbid, obesity, and asthma*

This information is important because several conditions can affect the results of the examination, especially SDH that can be affected by conditions of hyperglycemia. An alternative pathways of glucose metabolism in hyperglicemia will increase through the polyol pathway catalyzed by sorbitol dehydrogenase [18, 19]. In a study by Nagasaka *et al.* found 2.4 times increment of SDH activity and the rate of sorbitol synthesis at 50 mmol/1 (900 mg/dL) glucose compared to 5 mmol/1 (90 mg/dL) glucose [20]. This study found no significant correlation (p

>0.05) between blood glucose levels and SDH levels before and after remdesivir therapy. The possible cause for this difference are the average blood glucose level of the subjects in this study was 250 mg/dL, the range of the lowest levels to the highest of SDH is very wide so it showed no significantly difference and SDH activity did not measured in this study.

Clinical details, symptoms, results of an objective examination, and the statistical comparison of values related to patients from the first and the second group are depicted in Figure 1.

The Wilcoxon test was used to see the difference before and after administration of Remdesivir because the results of data normality test using the Shapiro Wilk test showed that all data were not normally distributed (p <0.05). The results of this study indicated that the SDH levels of all study subjects were within normal limits, this was based on a study conducted by Rose *et al.* which stated that normal SDH levels were <3 U/L. The median of serum SDH before and after therapy, respectively, was 0.75 U/L and 0.85 U/L. The median difference of AST, ALT, direct bilirubin, total bilirubin, alkaline phosphatase (ALP), and gamma-glutamil transferase (GGT), respectively, were -3.75 mg/dL, -2 mg/dL, 0.045 mg/dL, 0.05 mg/dL, -3.5 mg/dL, and -1 mg/dL, as presented in Table 2. The results of the Wilcoxon test showed no significant difference in SDH level and other liver enzymes before and after Remdesivir therapy (p > 0.05) in Covid-19 patients.

To date, there have been no other studies assessed SDH levels in Covid-19 patients receiving remdesivir or other antiviral therapy. Therefore, we tried to compare these results with other studies evaluating the SDH level after administration of hepatotoxic drugs. Our study results showed different result with other study. The study of Singhal *et al.* on 67 healthy adults were treated with cholestyramine and observed for 23 days, showed that 11 subjects had significant increase in SDH levels [21]. These results are in accordance with the study of Harril *et al.* on 48 healthy people who received heparin showed an increase in SDH levels on the third day of observation of heparin administration, so that it has the potential to be a marker of acute liver injury [22]. Study on 61 patients who received remdesivir therapy with an initial dose of 200 mg intravenously and continued with 100 mg for 10 days found increased liver enzymes in 12 patient [23].

This study also showed that there was no significant difference in liver function biomarker levels before and after remdesivir therapy (p>0.05), as indicated in Table 2. These results are different from those reported in several studies where there was an increase in biochemical parameters of liver function, especially AST and ALT. Grein *et al.* investigated the effect of 5 to 10 days of remdesivir on changes in the oxygen-requiring category of patients in 53 patients. The most common side effect in this study was an increase in transaminase enzymes with an incidence of 23% [7] . Similar results are consistent with a study in 402 patients to evaluate optimal timing for intravenous remdesivir, conducted by Goldman *et al.*, which found a 1-2-fold increase in ALT and AST (7 and 6%, respectively) and was reported as the most frequent side effects [8]. In Covid-19, cholangiocyte cell injury can also be found, especially characterized by bile duct proliferation, bile duct obstruction and increased levels of GGT and ALP. This study did not show an increase in GGT levels at the beginning of the examination, so it can be concluded that there was no injury to cholangiocyte cells.

We found that there was no significant difference in SDH levels and liver function biomarker levels before and after remdesivir therapy (p>0.05) based on comorbidities and outcome, as provided in Table 3. Likewise, this study aims to assess differences in SDH and other liver enzyme levels before and after remdesivir therapy based on severity, as presented in Table 4. We found that there was no significant difference (p>0.05). We suspect that the short exposure time to remdesivir is one the reason for no visible differences in SDH or liver enzyme levels in this study, although in this study there was a trend of increasing SDH levels before and after administration of remdesivir therapy in 17 study subjects, but not statistically significan.

Table 2: Differences of SDH and other liver enzymes levels before and after remdesivir therapy

Parameter (n = 34)	Median(min – max)		Median difference (Min-max)	P-value
	Before	After		
SDH (U/L)	0.75 (0.2-6.4)	0.85 (0.2-5.8)	0 (-4.9-1.8)	0.984
AST(U/L)	36.44 (14-731)	34 (14-443)	-3.75 (-296.3-48)	0.140
ALT (U/L)	30.43 (11-321)	30.2 (9-290)	-2 (-110.23-52.5)	0.301
Total bilirubin (mg/dL)	0.49 (0.12-7.78)	0.50 (0.1-3.62)	0.05 (-7.16-2.53)	0.567
Direct Bilirubin (mg/dL)	0.15 (0.08-1.63)	0.24 (0.08-2.68)	0.045 (-1.34-1.74)	0.091
ALP (U/L)	85 (30-1.103)	87.5 (37-1.226)	-3.5 (-596-1.116)	0.313
GGT (U/L)	64.5 (4-924)	71 (6-1.532)	-1 (-486-1.378)	0.871

SDH: sorbitol dehydrogenase, AST: aspartate aminotransferase, ALT: alanine transferase, ALP: alkaline phosphatase, and GGT: gamma-glutamyl transferase.

Table 3: Differences of SDH levels and liver enzyme based on comorbidities and outcome

Parameter	Comorbid		Outcome	
	DM (n=17)	CKD (n=5)	Survived (n=26)	Non-survived (n=8)
SDH (U/L)				
Before[a]	0.7(0.4-5.5)	1.2(0.2-2.8)	0.75(0.2-6.4)	0.65(0.40-1.60)
After[b]	1.2(0.5-5.8)	1(0.4-3.1)	1.2(0.3-5.8)	0.50(0.20-1.60)
Difference[c]	0.1(-3-1.7)	-0.1(-0.2-1.7)	0.05(-4.9-1.8)	0(-1.1-0.30)
P-value	0.566		0.943	0.307
AST (U/L)				
Before[a]			34.50(14-325)	47.3(16.5-731)
After[b]	NA		31.15(14-99)	43.65(25-443)
Difference[c]			-2(-296-48)	-7.5(-288-23.4)
P-value			0.264	0.327
ALT (U/L)				
Before[a]			28.5(11-118)	55.50(14.5-321)
After[b]	NA		29.50(9-58)	32.20(13.8-290)
Difference[c]			-0.025(-71-27)	-26.15(-110-52.5)
P-value			0.638	0.106
Total bilirubin (mg/dL)				
Before[a]			0.48(0.19-7.78)	0.44(0.12-2.24)
After[b]	NA		0.49(0.10-1.50)	0.54(0.20-3.62)
Difference[c]			0.06(-7.16-1.29)	0.40(-1.84-2.53)
P-value			0.675	0.716
Direct Bilirubin (mg/dL)				
Before[a]			0.15(0.08-1.63)	0.13(0.10-1.40)
After[b]	NA		0.23(0.08-0.80)	0.37(0.10-2.68)
Difference[c]			0.04(-1.34-0.7)	0.04(-1.10-1.74)
P-value			0.125	0.534
ALP (U/L)				
Before[a]			73.5(30-1,103)	122.5 (52-248)
After[b]			83(37-1.226)	106 (52-186)
Difference[c]	NA		-2.0(-596-1116)	-3.5 (-126-28)
P-value			0.501	0.352
GGT (U/L)				
Before[a]			58(4-924)	77(26-321)
After[b]	NA		67(4.0-924)	91.5(21-221)
Difference[c]			5.5(-486-1,378)	-16.6(-14-177)
P-value			0.402	0.623

[a,b] Median (min-max);[c]median difference (min-max); NA: not applicable, DM: diabetes mellitus, CKD: chronic kidney disease, SDH: sorbitol dehydrogenase, AST: aspartate aminotransferase, ALT: alanine transferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase.

Table 4: Differences of SDH levels and liver enzyme based on severity

Parameter	Severity [Mean(SD)]			
	Mild (n=3)	Moderate (n=12)	Severe (n=7)	Critical(n=2)
SDH (U/L)				
Before	3.20(1.56)	1.46 (1.81)	1.17 (2.12)	1.55(1.82)
After	1.56(1.05)	1.10 (0.93)	2.12(2.04)	1.28(1.19)
Difference	-1.63(1.83)	-0.366 (1.03)	- 6.40 (19.27)	-0.26(1.17)
P-value	0.829	0.655	0.272	0.449
AST (U/L)				
Before	3.2(2.92)	1.14(1.81)	43.35(17.61)	102.3(199.7)
After	78.60(116.8)	78.60(116.8)	1.56(1.05)	1.10(0.93)
Difference	2.66(4.72)	37.76(90.68)	-6.40(19.27)	-23.76(87.44)
P-value	0.431	0.099	0.413	1.000
ALT (U/L)				
Before	19.66(5.50)	53.16(42.95)	44.44(43.11)	54.35(84.67)
After	59.94(73.86)	59.94(73.86)	23.66(5.50)	28.87(17.75)
Difference	4.00(9.53)	-24.29(30.68)	-10.68(46.13)	5.59(21.13)
P-value	0.543	0.19	1.000	0.379
Total bilirubin (mg/dL)				
Before	0.48(0.12)	0.66(0.71)	0.60(0.25)	1.12(2.12)
After	0.61(0.27)	0.61(0.27)	0.72(0.41)	0.48(0.34)
Difference	0.24(0.34)	-0.18(0.80)	0.36(0.98)	-0.51(2.13)
P-value	0.345	0.445	0.368	0.422
Direct Bilirubin (mg/dL)				
Before	0.18(0.04)	0.35(0.54)	0.27(0.29)	0.30(0.27)
After	0.36(0.16)	0.36(0.16)	0.20(0.05)	0.24(0.19)
Difference	0.02(0.04)	-0.10(0.55)	0.28(0.64)	0.06(0.27)
P-value	0.510	0.518	0.287	0.457
ALP (U/L)				
Before	61.33(32.02)	181.5(292.9)	107.28(63.86)	101.2(60.36)
After	66.66(30.27)	216.5(342.5)	91.14(42.58)	92.58(25.67)
Difference	-8.66(51.22)	-8.66(51.22)	5.33(3.51)	34.9(380.1)
P-value	0.119	0.756	0.315	0.570
GGT (U/L)				
Before	20.66±11.37	158.7±251.7	109.57±106.08	72.25±56.61
After	99.22±70.04	99.22±70.04	26.33±9.23	214±430.8
Difference	5.66±12.70	55.25±440.46	5.28±88.19	26.97±62.87
P-value	0.521	0.672	0.879	0.165

SDH: sorbitol dehydrogenase, AST: aspartate aminotransferase, ALT: alanine transferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase.

Other possible causes are the effect of remdesivir administration on the subjects of this study also appeared to show very varied results, as seen in the range of the lowest concentration to highest concentration is very wide resulting not statistically significant.

The results of Spearman correlation test showed that there was no significant relationship between SDH levels and other liver enzymes, both before and after therapy ($p > 0.05$), but it showed the difference in SDH levels was significantly related to total bilirubin and GGT ($p < 0.05$), as presented in Table 5. The possible cause of this result is the range of the lowest levels to the highest of SDH is very wide. Different results were obtained from a study by Singhal *et al.* with study subjects 67 healthy adults who received cholestyramine treatment (therapy) and

were observed for 23 days, obtained results 11 subjects with increased AST and ALT 3x ULN also showed a significant increase in SDH levels (8 x ULN) [21]. In this study, only 2 research subjects (34 subjects in total) showed an increase in AST and ALT levels after administration of remdesivir, but not followed by an increase in SDH levels.

This research had several limitations, including researchers only analyzed differences in SDH levels and did not analyze SDH activity on remdesivir antiviral therapy, remdesivir exposure time is short (5 days). Therefore, it did not give the expected test results; researchers did not perform serial blood glucose levels as a confounding factor in the study.

Table 5: Correlation of SDH levels and biochemical parameters of liver function before and after remdesivir therapy

Correlation between SDH levels and	Spearman's correlation coefficient (P-value)		
	Before therapy (n = 34)	After therapy (n = 34)	Delta (n = 34)
AST (U/L)	0.037 (0.835)	0.109 (0.540)	-0.166 (0.349)
ALT (U/L)	0.110 (0.537)	0.248 (0.158)	0.136 (0.444)
Direct Bilirubin (mg/dL)	0.108 (0.542)	-0.059 (0.742)	-0.305 (0.080)
Total bilirubin (mg/dL)	0.157 (0.374)	0.048 (0.787)	-0.339 (0.049)
ALP (U/L)	-0.170 (0.337)	-0.247 (0.159)	-0.228 (0.194)
GGT (U/L)	-0.116 (0.513)	-0.174 (0.324)	-0.343 (0.047)

SDH: sorbitol dehydrogenase, AST: aspartate aminotransferase, ALT: alanine transferase, ALP: alkaline phosphatase, and GGT: gamma-glutamyl transferase.

Conclusion

There was no difference in SDH levels or the levels of biochemical parameters of liver function before and after administration of remdesivir therapy in patients with Covid-19. There is no correlation between SDH levels and biochemical parameters of liver function before and after receiving remdesivir therapy in Covid-19 patients. Further research is needed regarding SDH activity in patients receiving remdesivir antiviral therapy with a sample size taking into account confounding factors to provide more accurate results**.**

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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