RJPT
Research Journal of Pharmacy and Technology

RESEARCH ARTICLE

Differences in Glutamate Dehydrogenase (GLDH) and Other Liver Biochemistry Levels before and after Remdesivir Treatment in COVID-19

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ABSTRACT:
Background: Remdesivir (RDV) is a broad-spectrum antiviral approved by the Food and Drug Administration (FDA) for the treatment of Covid-19 patients, known to have the potential to cause toxic effects on the liver. Routine monitoring of liver biochemical parameters such as AST, ALT, bilirubin, ALP and GGT, can help detect liver injury. Drug-induced liver injury, according to Hy's law, is characterized by an increase in ALT > 5x ULN, or ALP > 2x ULN, or an increase in ALT > 3x and total bilirubin > 2x ULN, simultaneously. Glutamate dehydrogenase (GLDH) is a sensitive and specific hepatic marker, which can detect liver injury and loss of mitochondrial integrity earlier than other liver biochemical parameters. This study aimed to analyze GLDH levels and liver biochemical parameters before and after RDV therapy in patients with Covid-19. We also analyze several factors that affect liver function and suggest renal function. **Methods:** This study used an observational analytical with a prospective cohort design, in a population of Covid-19 patients receiving RDV therapy at the infectious emergency department and isolation ward Dr. Soetomo Surabaya for September-November. Consecutive sampling was taken. The subject had drawn blood twice; once before therapy and 5 days after receiving intravenous RDV. GLDH examination is using sandwich ELISA method, while ALT, AST, ALP, GGT, direct and total bilirubin were determined spectrophotometrically. Mann-whitney, the Wilcoxon rank test and Spearman correlation test were used to analyze the data. **Results:** The number of samples was 34 participants with an average age of 52.47 ± 15.21 years. Concomitant medications were dominated by n-acetylcysteine (94.1%), antioxidants (91.2%) and immunomodulators (82.4%). None of the subjects suffered liver injury induced by RDV according to Hy's Law. Median GLDH serum levels before RDV treatment 1,14 U/L and after 5 days RDV administration 0,85 U/L (p=0,945), AST (36,4 U/L; 34, 00U/L; p=0,140), ALT (30,43 U/L; 30,20 U/L; p=0,301), DBI (0,15mg/dL; 0,24mg/dL; p=0,090), TBI (0,49mg/dL; 0,50mg/dL; p=0,567), ALP (85,0U/L; 87, 5 U/L; p=0,313) dan GGT (64,5U/L; 71,0U/L; p=0,871). The use of concomitant medication was thought to have protective properties against hepatocytes. **Conclusion:** After 5 days of RDV treatment, there is no evidence of liver injury. There are no significant differences in GLDH levels and other liver biomarker parameters compared to baseline. There is no difference in delta GLDH levels between groups with and without renal impairment.

KEYWORDS: GLDH, Liver Biochemistry, Remdesivir, Liver Injury, Covid-19.

INTRODUCTION:
SARS-CoV-2 infection, known as Coronavirus Disease-19 (Covid-19), has become a global health crisis since the first case was reported in Wuhan, China in December 2019[1,2]. A variety of therapies including

therapeutic modalities have been employed to reduce morbidity and mortality due to SARS-CoV-2 infection[3,4]. The use of this therapy has been reported to cause hepatotoxicity in the treatment of other viral infections[4]. Meta-analysis studies have found that drug use (drug-induced liver injury) is a potential cause of liver injury in Covid-19 patients[5,6].

Antivirals are known to cause liver damage in Covid-19 patients, including remdesivir (23%), lopinavir/ ritonavir (57.8%), and favipiravir (1 case)[4]. Remdesivir (RDV) is the only broad-spectrum antiviral drug approved by the Food and Drug Administration (FDA) for the treatment of hospitalized patients with Covid-19 and has been shown to reduce recovery time and mortality[5–7]. According to Hy's Law, the presence of drug-induced liver injury, is characterized by an increase in ALT >5x ULN, or an increase in ALP >2x ULN (in the absence of bone lesion), or an increase in ALT >3x and total bilirubin >2x ULN simultaneously[4,6,8,9].

The results of this study indicated that RDV is less likely to cause tubular mitochondrial damage and hepatocyte necrosis. The hepatotoxic effect of RDV in patients with renal impairment has only been reported after long-term treatment[10]. The FDA withdrew its recommendation for the use of RDV in Covid-19 patients with a glomerular filtration rate <30 mL/min/1.73m^2 due to increased reports of hepatotoxicity (42.8%)[8,9]. The relationship between decreased renal filtration and its impact on the incidence of liver injury is not clearly understood.

Monitoring liver biochemical parameters can help detect liver injury in patients with Covid-19. Routinely used liver chemical biomarkers are ALT, AST, Bilirubin, ALP and GGT[4,5,11,12]. Weaknesses of these parameters may be increased in other diseases and are not specific to drug-induced liver injury[13]. Serum GLDH level has sensitive and specific early warning markers of liver damage and loss of mitochondrial integrity, as GLDH is a liver-specific enzyme and is expressed in the mitochondrial matrix of hepatocytes[11,13]. Advantages of GLDH parameter when compared to others are not affected by muscle mass, age or gender[14,15]. There has been limited investigation into GLDH as a specific marker of drug-induced liver impairment. Two animal experiments using furosemide and antituberculosis medications support the use of GLDH values as sensitive and specific indicators of hepatocellular injury[16,17]. Research on healthy persons or patients receiving acetaminophen medication had similar findings[18]. However, to date, no studies have analyzed GLDH for liver damage caused by the use of RDV.

Based on the explanation above, we expected diferences in GLDH levels and other liver biochemistry parameters following 5 days of RDV administration. This study aimed to analyze GLDH levels and liver biochemical parameters before and after RDV treatment in Covid-19 patients, so it is hoped that GLDH levels in Covid-19 patients can be used as a marker for evaluating liver function to detect RDV-induced liver injury so that the use of potentially hepatotoxic drugs can be avoided.

MATERIALS AND METHODS:
A. Study Design and Patients Population:
It is prospective observational study conducted at Dr. Soetomo General Hospital, Surabaya, Indonesia from September-November 2022. Study protocol had been reviewed and ethical clearance was granted by Ethical Committee of Dr. Soetomo General Hospital, Surabaya, East Java (Ethical number 0369/KEPK/II/2022).

Study population were covid-19 patients receiving RDV therapy who were hospitalized in infectious emergency department and isolation ward of Dr. Soetomo General Hospital, Surabaya, Indonesia from September-November 2022. The patient was selected according to the inclusion and exclusion criteria. The inclusion criteria were (1) adult patients that are 18 years or above, (2) Covid-19 confirmed by RT PCR SARS CoV-2 (3) received RDV therapy for at least 5 consecutive days. Meanwhile, the exclusion criteria were (1) patients with co-existing history of liver disease, autoimmune and malignancy, (2) patients with reactive HBsAg and/or anti-HCV, (3) hemolyzed specimen.

All patients were assessed since the first day of admission until at least 5 days after RDV administration. RDV was administered intravenously by clinician as a 200mg loading dose on day 1, followed by a 100mg maintenance dose administered daily.

Basic characteristic patients were extracted from hospital information system. The data on age, gender, severity, comorbiditiy, clinical diagnoses, clinical outcome, treatment and glomerular filtration rate were collected for this study. The co-existing of disease history was collected by interview. The characteristic data were categorized as severity stratified into mild, moderate, severe and critical; clinical outcome into survive and non-survive; glomerular filtration rate less than 60mL/min/1.73m^2 as renal impairment and greater than 60mL/min/1.73m^2 as without renal impairment.

B. Specimens Collection and Preparation:
The subject had drawn blood twice; once before therapy and in fifth days after receiving RDV. Whole blood was collected in serum separate tubes. The serum immediately separated by a 3000rpm centrifugation process for 15minutes. The serum obtained was then storage in separated aliquots and frozen at -80ºC until all

samples were collected for biomarker analysis. All collected serum were examined for GLDH and liver biochemistry (ALT, AST, DBI, TBI, ALP, and GGT).

C. GLDH Measurement:
GLDH in human serum demonstrates acceptable stability at room temperature up to 48 hours, refrigerated up to 14 days, and frozen at -80ºC up to 18 months. GLDH in human serum demonstrates acceptable stability for 4 freeze thaw cycles. All samples were analyzed with in the stability windows.

GLDH serum levels were determined using a polyclonal antibody-based sandwich ELISA by Elabscience® Biotechnology Inc., the USA. The ELISA microplates included in this kit were coated with antibodies specific for human GLDH. Standards or samples were added to the wells of the ELISA microplate and combined with specific antibodies. A biotinylated detection antibody specific for human GLDH and an avidin-horseradish peroxidase (HRP) conjugate were then sequentially added to each microplate well and incubated. The free components were then rinsed. The substrate solution was put to each well. Only wells containing human GLDH, biotinylated detection antibody, and avidin-HRP conjugate were shown in blue. The enzyme-substrate reaction was stopped by adding a stop solution and the color changes to yellow. Optical density was measured with a spectrophotometer at a wavelength of 450nm ± 2 nm. OD values were proportional to the concentration of human GLDH. By comparing the sample OD to the standard curve, the concentration of human GLDH in the sample can be calculated.

D. Liver Biochemistry Measurement:
All liver biochemistry parameters (ALT, AST, DBI, TBI, ALP, and GGT) were determined spectrophotometrically and measured on the Alinity C Analyzer using proprietary reagents and calibrators provided by Abbott Diagnostics. All enzymatic methods were previously validated by showing their optimal alignment to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference measurement procedures.

E. Statistical Analyses:
Descriptive statistics were used to describe the demographics, severity, comorbidity, and clinical outcome. The paired T-test (or Wilcoxon rank test if the data were not normally distributed) were used to analyze differences in GLDH levels before and after RDV administration. Comparison of GLDH levels in Covid-19 patients with and without renal impairment was analyzed using the T-test 2 free samples (or Mann Whitney test if the data were not normally distributed). The Saphiro wilk showed data not normally distribute (p< 0.05). Relationships between groups were analyzed using the Spearman correlation Test. A value of P<0.05 was determined significant. Statistical analysis was carried out using IBM SPSS ver. 22.0.

RESULT:
General Characteristics:
The number of study participants who met the inclusion and exclusion criteria was 34 patients admitted to the infectious emergency department and the isolation ward of Dr. Soetomo Surabaya. The average age of study participants was 52, with the highest proportion of men. Based on disease severity, patients in this study predominated in the severe to moderate category. Hypertension (61.8%) and diabetes mellitus (50%) were the most common complications experienced by study participants. Other comorbidities identified in study participants were renal, cardiovascular, and cerebrovascular disease (Table 5.2). Subjects in this study also received concomitant therapy in addition to RDV, most receiving N-acetylcysteine (94.1%) and antioxidants (92.1%). In this study, his 76.5% of patients showed favorable results.

Examination of GLDH levels and liver biochemical parameters was performed twice in this study, ie, days 0 and 5 after intravenous RDV administration. Two participants already had liver injury before receiving RDV. One patient had ALT >5x ULN and one patient had her ALP >2x ULN without any bone abnormalities or pregnancy. None of the study participants met Hy's law criteria for liver injury on the fifth day of the study.

Table 1: General Characteristics and Patients Demography

Variable	Frequency (n)	Percent (%)
Age (year). mean± standard deviation	52.47 ± 15.21	
Gender		
Male	18	52.9
Female	16	47.1
Severity		
Mild	3	8.8
Moderate	12	35.3
Severe	7	20.6
Critical	12	35.3
Outcome		
Survived	26	76.5
Non-survived	8	23.5
Comorbidity	29	85.3
Hypertension	21	61.8
Diabetes mellitus	17	50.0
Renal Impairment	5	14.7
Cerebrovascular disease	2	5.9
Cardiovascular disease	1	2.9
Concomitant medication		
N-acetylcysteine (NAC)	32	94.1
Antioxidant	31	91.2
Immunomodulator	28	82.4
Antibiotic	28	82.4
Anticoagulant	19	55.9
Steroid	15	44.1

Table 2: Differences in GLDH Levels and Liver Biochemistry of Covid-19 Patients Receiving RDV Treatment

Parameter	Before treatment (n=34)	After treatment (n=34)	p	Survived (n=26)	Non-Survived (n=8)	p
	Median (min-max)			Median (min-max)		
GLDH (U/L)	1.14 (0.31-13.09)	0.85 (0.31-17.02)	0.945	0.77 (0.31-17.02)	1.92 (0.31-16.92)	0.180
AST (U/L)	36.44 (14-731)	34.00 (14-443)	0.140	31.15 (14-99)	43.65 (25-443)	0.138
ALT (U/L)	30.43 (11-321)	30.20 (9-290)	0.301	29.50 (9.0-58.0)	32.20 (13.8-290.0)	0.310
DBI (mg/dL)	0.15 (0.08-1.63)	0.24 (0.08-2.68)	0.090	0.23 (0.08-0.80)	0.37 (0.10-2.68)	0.200
TBI (mg/dL)	0.49 (0.12-7.78)	0.50 (0.10-3.62)	0.567	0.50 (0.10-1.50)	0.54 (0.20-3.62)	0.655
ALP (U/L)	85.00 (30-1.103)	87.50 (37-1226)	0.313	83 (37-1226)	106 (52-186)	0.187
GGT (U/L)	64.50 (4-924)	71.00 (6-1532)	0.871	67 (6-1532)	91.5 (21-221)	0.503

Note: GLDH, Glutamate Dehydrogenase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; DBI, Direct Bilirubin; TBI, Total Bilirubin; ALP, Alkali Phosphatase; GGT, Gamma Glutamyl Transferase; p<0,05.

GLDH levels and liver biochemical parameters pre and after RDV treatment in Covid-19 patients:

Serum GLDH levels and liver biochemical parameters of the fifth day of RDV treatment were lower than pretreatment, and showed no significant difference in serum GLDH levels before and after RDV therapy. A follow-up analysis (Table 2) performed in non-survived group showed that values of all laboratory parameters (GLDH and liver biochemical parameters) were higher after administration of RDV therapy than in survived group. Results from the Wilcoxon rank test showed that GLDH levels and liver biochemical parameters did not differ significantly between subjects with survived and non-survived outcomes.

Associations between GLDH levels and liver biochemical parameters in Covid-19 patients receiving RDV therapy:

Results of Spearman's correlation test between GLDH levels and AST, ALT, DBI, TBI, ALP or GGT were tested according to those listed in Table 3. GLDH and liver biochemical parameters showed no significant relationship between.

Delta GLDH Based on Glomerular Filtration Rate in Covid-19 Patients:

A total of 14 subjects had renal dysfunction characterized by a drop in glomerular filtration rate below 60mL/min/1.73 m2 before RDV administration (Table 4). It was reported that 4 of her subjects in the renal impairment group (3 severe and 1 moderate) did not survive.

Table 3: Relationship between GLDH and liver biochemical parameters in Covid-19 patients receiving RDV therapy

Correlation	n	r	p
GLDH - AST	34	0.118	0.506
GLDH - ALT	34	-0.089	0.615
GLDH - DBI	34	0.082	0.643
GLDH - TBI	34	0.006	0.974
GLDH - ALP	34	-0.002	0.990
GLDH - GGT	34	0.033	0.852

Note: GLDH, Glutamate Dehydrogenase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; DBI, Direct Bilirubin; TBI, Total Bilirubin; ALP, Alkali Phosphatase; GGT, Gamma Glutamyl Transferase; r, Spearman coefficient correlation; p<0,05.

Table 4: Relationship between GLDH and liver biochemical parameters in Covid-19 patients receiving RDV therapy

Glomerular Filtration rate	n	Severity				Outcome	
		Mild	Moderate	Severe	Critical	Survived	Non-survived
< 60	14	1	5	2	6	10	4
> 60	20	2	7	5	6	16	4

Note: glomerular filtration rate in mL/min/1.73m^2

Mann-Whitney test results showed that there was no significant difference between the GLDH deltas of the group of patients with and without renal impairment.

Table 5: Delta GLDH differences based on glomerular filtration rate

Parameter	Glomerular filtration rate (n)		p
	< 60 (n=14)	>60 (n=20)	
Median Delta GLDH Min-Max	-0.120 (-1.49) – 14.14	-0.075 (-5.00) – 3.83	0.564

Note: Delta GLDH, GLDH after RDV treatment-GLDH before treatment; glomerular filtration rate in mL/min/1.73m^2; p < 0.05.

DISCUSSION:
General characteristics:

Study participants consisted of 34 patients diagnosed with Covid-19 who were treated in the Infectious Emergency Installation Room or Isolation Ward, both ICU and non-ICU. The average age of subjects in this study was 52.47±15.21 years, with a male predominance. Age and gender characteristics in this study did not differ from previous studies. A multicenter study to Covid-19 patients who received RDV therapy had an average age of 58.6±14.6 years and the majority of genders were male (65.1%)[7]. The incidence of drug-related liver injury is increasing in women and has also been reported to be associated with increasing age[11,19]. However, a study conducted by Meunier and Larrey stated that gender as a risk factor for developing liver damage remains controverisal[11].

The most common comorbidities in this study were hypertension and Diabetes Mellitus. Christanto *et al.* mentioned that the comorbidity profile in Covid-19

patients in Indonesia is dominated by hypertension (40%), heart failure (35%) and diabetes (25%)[20]. It also reported by Collins and Gupte *et al.*, Covid-19 patients who received RDV therapy, that 98.2% of the subjects had comorbidities mostly Diabetes (29.69%) and Hypertension (20.33%)[21,22]. Increasing age is also associated with an increase comorbidities profile. It may affect the subject susceptibility to hepatotoxicity. However, there was very limited evidence of an association between comorbidity factors and the incidence of acute liver injury[11].

Subjects in this study received concomitant treatment in addition to RDV therapy because most had moderate to critical disease severity. Concomitant therapy seen in nearly all subjects in this study was NAC (94.1%) and antioxidants (91.2%). Maharianingsih *et al.* are reported patients diagnosed with moderate to severe Covid-19 in Bali, also received NAC therapy (67%) and vitamin C (71%)[23]. The results of this study are not significantly different from previous studies. NAC not only acts as a mucolytic agent, but as antioxidant at higher doses[23,24]. It is expected to ameliorate the hyperinflammatory state and cause increased ROS production due to oxidative stress and phagocyte activation. This increased metabolic and inflammatory response may reduce intracellular and intravascular concentrations of antioxidants[25]. The provision of exogenous antioxidants is in line with WHO recommendations. Thus, vitamin C is administered as adjunctive therapy for Covid-19 cases[26].

Differences in Serum GLDH Levels and Liver Biochemical Parameters Before and After RDV Treatment:
GLDH is a liver-specific protein and elevated serum levels reflect mitochondrial membrane dysfunction or entry of all mitochondrial components into circulation due to hepatocyte necrosis or apoptosis[27]. Liver damage is characterized by an increase in the biochemical parameters of the liver, at least 1 criterion on the Hy's Law. The FDA states an increase in GLDH levels of more than 2.5 times ULN, can substitute ALT criteria[28]. As a result of this study, he found that none of the subjects had liver damage according to Hy's law. This study showed that serum GLDH levels and liver biochemistry showed no significant difference before and after 5 days of RDV administration. This indicates that administration of RDV for 5 days does not lead to acute liver damage in Covid-19 patients.

The results of this study contradict those of the study by Lin *et al.* and Carothers *et al.,* that acute liver injury presents 5 days after RDV administration with marked increases in ALT and AST[29,30]. Research in healthy subjects treated with RDV for 7-14 days only a modest increase in ALT/AST (< 5x ULN) with no other evidence of clinical liver injuries[31]. This may be due to the short exposure time of RDV. However, the results of this study are consistent with those of a controlled study, in which ALT levels in the RDV-treated group were significantly different from placebo. Levien and Baker reported increases in ALT and AST greater than 5-fold ULN, mainly in patients with multiple organ failure, or on highly potent hepatotoxic concomitant medication such as amiodarone[31]. None of the subjects of this study received hepatotoxic high-risk therapy.

This study showed that the levels of bilirubin, ALP, and GGT between before and after RDV treatment were not significantly different. This is in consistent with a report that patients who received RDV therapy appeared to have no changes in serum bilirubin levels or ALP and GGT within 1-5 days after initiation treatment, although there has been a mild increase in transaminase enzymes [31]. *The European Association for the Study of the Liver* (EASL) recommends the use of TBI and ALP parameters for the detection of chronic drug-related liver injury, whereas GGT is used as a surrogate marker for ALP[11].

The absence of subjects with liver injury conditions in this study may also be due to the administration of concomitant medication. The most common concomitant medications other than RDV found in this study were NAC, antioxidants and immunomodulators. Covid-19 patients receiving RDV therapy experienced decreased in ALT and AST levels 2 days after administration of NAC therapy in previous case studies. NAC is thought to play a role in improving liver function in cases of acute liver failure due to RDV[29,30]. Although NAC is used as an antidote for acetaminophen-induced hepatotoxicity, FDA also recommends that it be used in cases of acute liver failure due to other than acetaminophen/ *Non-Acetaminophen Induced Acute Liver Failure* (NAI-ALF)[30]. NAC acts as a glutathione precursor in cases of liver failure due to acetaminophen. NAC prevents toxicity by inhibiting the formation and accumulation of *N-acetyl-p-benzoquinoneimine,* acting as a substitute for glutathione, and increasing its conjugation with non-toxic sulfate compounds. This mechanism produces antioxidant, anti-inflammatory, inotropic, and vasodilatory effects, thereby improving blood flow microcirculation and oxygenation of vital organs[32]. The mechanism of action of NAC in the case of NAI-ALF is debatable, but NAC administration was associated with decreased risk of mortality, length of hospital stay, and organ damage in NAI-ALF patients compared to the placebo NAI-ALF group[32,33].

Administration of exogenous antioxidants and immunomodulators is also thought to play a protective role in preventing hepatocellular toxicity. Exogenous

antioxidants such as vitamin C may reduce inflammatory processes, improve cell-mediated immunity, improve microvascular regulation, and prevent the development of thrombosis. Parenterally administered vitamin C also correlates well with reduced rates of sepsis-induced organ damage[21,25]. Vitamin D, the most commonly administered immunomodulator to subjects in this study, is known to play a role in maintaining hepatocyte membrane integrity through disruption of inflammatory pathways. Experimental study in animals given high-dose of vitamin C and D regimens have also reported reduction in liver enzyme activity in cases of paraquat-induced hepatotoxicity [34]. Nearly all subjects in this study received RDV plus concomitant therapy with NAC (94.2%), antioxidants (91.2%), and immunomodulators (82.4%). Providing combination therapy may be a factor in helping prevent cell and liver damage.

Further analysis of deceased study participants showed that level of liver biochemical parameters after administration of RDV therapy were higher than those of non-survived subjects, although not statistically significant. No significant difference was shown, which is consistent with the study by Shakir et al. In Covid-19 patients receiving RDV therapy, AST and ALT levels were significantly increased in the lethal group compared with the living external group. This may be influenced by the severity of the degree of disease exacerbation, leading to organ dysfunction[35]. The study conducted by Salik *et al*, also supports the study's findings that elevated levels of ALT, AST, total bilirubin, GGT, and ALP are associated with increased mortality in Covid-19 patients. This study also showed an increase in GLDH levels in the external death group compared with the living external group, although the difference was not statistically significant. This may be caused by drug interactions increase with longer duration and worsening disease, thereby increasing the risk of liver cell damage.[36]

Association of GLDH Levels with Liver Biochemical Parameters in Covid-19 Patients receiving RDV:
Associations between GLDH levels and liver biochemical parameters in Covid-19 patients undergoing RDV The relationship between GLDH levels and liver biochemical parameters resulted in p>0.05. *A Spearman* correlation test concluded that there was no association between GLDH levels and AST, ALT, DBI, TBI, ALP, or GGT in Covid-19 patients who received RDV therapy.

Studies examining the correlation of GLDH levels with biochemical parameters in RDV-treated Covid-19 patients were very limited. Most GLDH studies were observed in conditions of acetaminophen-induced liver injury in humans or experimental animals. Both RDV and acetaminophen are mitotically toxic to hepatocytes. Studies in experimental animals that had acetaminophen-induced liver injury, showed GLDH correlated strongly with the degree of liver injury suffered. Follow-up research in patients treated with a diagnosis of acetaminophen-induced liver injury, showed GLDH levels were strongly correlated with ALT in detecting acute liver injury[16,37]. Both studies used enzymatic methods for GLDH examination. Examination using enzymatic methods can better describe GLDH activity. This study measured GLDH levels using the ELISA sandwich method that measures the quantity of enzymes. Differences in the population of the study subject, examination methods, toxicity mechanisms in drugs that may be different, may result in differences in the results of current studies with existing studies.

Difference in GLDH Delta based on glomerular filtration rate in Covid-19 patients who received RDV:
In this study test concluded that the GLDH delta between groups of patients with and in the absence of renal impairment, there was no meaningful difference. This is in consistent with a study which stated that GLDH levels were not affected by impaired renal excretion. The effect of RDV hepatotoxicity in patients with decreased renal function was reported to occur only after long-term treatment[10]. The study also showed the presence of renal impairment in 14 subjects prior to administration of RDV. Four subjects from the renal impairment group reported death (3 critical and 1 moderate). This indicates that poor end outcomes in the renal impairment group, can result from the severity of the disease and not due to liver damage due to the induction of remdesivir therapy.

CONCLUSION:
After 5 days of RDV treatment, there is no evidence of liver injury. There are no significant differences in GLDH levels and other liver biomarker parameters compared to baseline. There is no difference in delta GLDH levels between groups with and without renal impairment. Further research is needed on GLDH activity using enzymatic methods, as well as comparing other specific parameters of necrosis and apoptosis of hepatocytes, such as cytokeratin-18 and microRNA-122.

CONFLICT OF INTEREST:
The authors have no conflicts of interest regarding this investigation.

ACKNOWLEDGMENT:

HK/2022). The author (s) expresses their gratitude to all staff in infectious emergency department, isolation wards, and central clinical pathology laboratory of Dr. Soetomo General Hospital, as well as all participating patients and family members for their cooperation in conducting this study.

REFERENCES:

1. WHO. Weekly epidemiological update on COVID-19 - 1 March 2022, https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-march-2022 (2022).
2. Ansori ANM, Nidom R V., Kusala MKJ, et al. Viroinformatics investigation of B-cell epitope conserved region in SARSCoV-2 lineage B.1.1.7 isolates originated from Indonesia to develop vaccine candidate against COVID-19. J Pharm Pharmacogn Res 2021; 9: 766–779.
3. Ansori ANM, Kharisma VD, Fadholly A, et al. Severe Acute Respiratory Syndrome Coronavirus-2 Emergence and Its Treatment with Alternative Medicines: A Review. Res J Pharm Technol. 2021; 14: 5551–5557.
4. Sodeifian F, Seyedalhosseini ZS, Kian N, et al. Drug-Induced Liver Injury in COVID-19 Patients: A Systematic Review. Front Med; 8. Epub Ahead of Print. 2021. DOI: 10.3389/fmed.2021.731436.
5. Aleem A, Mahadevaiah G, Shariff N, et al. Hepatic manifestations of COVID-19 and effect of remdesivir on liver function in patients with COVID-19 illness. Baylor Univ Med Cent Proc. 2021; 34: 473–477.
6. Diaz GA, Christensen AB, Pusch T, et al. Remdesivir and Mortality in Patients With Coronavirus Disease 2019. Clin Infect Dis. 2021; 74: 1812–1820.
7. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020; 383: 1813–1826.
8. Shah S, Ackley TW, Topal JE. Renal and hepatic toxicity analysis of remdesivir formulations: Does what is on the inside really count? Antimicrob Agents Chemother. 2021; 65: 6–10.
9. Sunny S, Samaroo-Campbell J, Abdallah M, et al. Is remdesivir safe in patients with renal impairment? Experience at a large tertiary urban medical center. Infection. Epub Ahead of Print. 2022. DOI: 10.1007/s15010-022-01850-7.
10. van Laar SA, de Boer MGJ, Gombert-Handoko KB, et al. Liver and kidney function in patients with Covid-19 treated with remdesivir. Br J Clin Pharmacol. 2021; 87: 4450–4454.
11. Meunier L, Larrey D. Drug-Induced Liver Injury : Biomarkers , Requirements , Candidates , and Validation. 2019; 10: 1–8.
12. Parohan M, Yaghoubi S, Seraji A. Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of retrospective studies. Hepatol Res. 2020; 50: 924–935.
13. Church RJ, Watkins PB, Law HYS. The transformation in biomarker detection and management of induced liver injury. 2017; 1582–1590.
14. Schmidt ES, Schmidt FW. Glutamate dehydrogenase: biochemical and clinical aspects of an interesting enzyme. Clin Chim Acta. 1988; 173: 43–55.
15. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020; 382: 2327–2336.
16. Church RJ, Schomaker SJ, Eaddy JS, et al. Glutamate dehydrogenase as a biomarker for mitotoxicity; insights from furosemide hepatotoxicity in the mouse.PLoS One. 2020;15:1–12.
17. He B, Cheng X, Xiang H-R, et al. Glutamate Dehydrogenase combined with ferrochelatase as a biomarker of liver injury induced by antituberculosis drugs. Br J Clin Pharmacol. 2023; 89: 3092–3104.
18. Schomaker S, Warner R, Bock J, et al. Assessment of Emerging Biomarkers of LiverInjury in Human Subjects.2013;132:276–283.
19. Forsblom E, Silén S, Kortela E, et al. Male predominance in disease severity and mortality in a low Covid-19 epidemic and low case-fatality area–a population-based registry study. Infect Dis (Auckl). 2021; 53: 789–799.
20. Christanto A, Listyoko AS, Putra NPP. Analisis Komorbiditas dan Hubungannya dengan Tingkat Severitas Penyakit dan Mortalitas pada Pasien Covid-19 yang Dirawat di Rumah Sakit. J Respirol Indones. 2022; 42: 18–25.
21. Gupte V, Hegde R, Sawant S, et al. Safety and clinical outcomes of remdesivir in hospitalised COVID-19 patients: a retrospective analysis of active surveillance database. BMC Infect Dis. 2022; 22: 1–8.
22. Collins S. Predictors of response to remdesivir in GS-5773 COVID-19 study. HIV i-Base, https://i-base.info/htb/38476 (2020, accessed 17 November 2021).
23. Maharianingsih NM, Sudirta IK, Suryaningsih NPA. Karakteristik Pasien dan Penggunaan Obat Pada Pasien Covid-19 Derajat Sedang Hingga Berat. Indones J Pharm Educ. 2022; 2: 101–109.
24. De Alencar JCG, Moreira C de L, Müller AD, et al. Double-blind, Randomized, Placebo-controlled Trial with N-acetylcysteine for Treatment of Severe Acute Respiratory Syndrome Caused by Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 2021; 72: E736–E741.
25. Wei X biao, Wang Z hua, Liao X long, et al. Efficacy of vitamin C in patients with sepsis: An updated meta-analysis. Eur J Pharmacol; 868. Epub Ahead of Print. 2020. DOI: 10.1016/j.ejphar.2019.172889.
26. World Health Organization. A coordinated global research roadmap: 2019 novel coronavirus. Geneva World Heal Organ.
27. Harrill AH, Roach J, Fier I, et al. The effects of heparins on the liver: Application of mechanistic serum biomarkers in a randomized study in healthy volunteers. Clin Pharmacol Ther. 2012; 92: 214–220.
28. FDA. Guidance for Industry Drug-Induced Liver Injury : Premarketing Clinical Evaluation Guidance for Industry Drug-Induced Liver Injury : Premarketing Clinical Evaluation. Food Drug Adm.
29. Lin K, Gausman V, Poles M, et al. Acute Liver Failure Secondary to Remdesivir in the Treatment of COVID-19. Am Coll Gastroenterol. 2022; 9: 2–4.
30. Carothers C, Birrer K, Vo M. Acetylcysteine for the Treatment of Suspected Remdesivir-Associated Acute Liver Failure in COVID-19: A Case Series. Pharmacotherapy. 2020; 40: 1166–1171.
31. Levien TL, Baker DE. Remdesivir. Hosp Pharm. 2021; 58: 420–430.
32. Mumtaz K, Azam Z, Hamid S, et al. Role of N -acetylcysteine in adults with non-acetaminophen- induced acute liver failure in a center without the facility of liver transplantation. Hepatol Int. 2009; 3: 563–570.
33. Darweesh SK, Ibrahim MF. Effect of N -Acetylcysteine on Mortality and Liver Transplantation Rate in Non-Acetaminophen-Induced Acute Liver Failure : A Multicenter Study. Clin Drug Investig. Epub Ahead of Print. 2017. DOI: 10.1007/s40261-017-0505-4.
34. Okolonkwo BN. The antioxidant effects of vitamin C on liver enzymes : aspartate aminotransferase , Paraquat insult m co m on er ci al us e on l co m er al. J Xenobiotic; 3. Epub Ahead of Print. 2013. DOI: 10.4081/xeno.2013.e5.
35. Shakir A, Bhasin N, Swami R, et al. Renal and Hepatic Outcomes after Remdesivir Therapy in Coronavirus Disease-2019-Positive Patients with Renal Dysfunction at Baseline or after Starting Therapy. Saudi J Kidney Dis Transplant. 2021; 32: 1034–1042.
36. Salık F, Uzundere O, Bıçak M, et al. Liver function as a predictor of mortality in COVID-19: A retrospective study. Ann Hepatol; 26. Epub Ahead of Print 2021. DOI: 10.1016/j.aohep.2021.100553.
37. Schomaker S, Potter D, Warner R, et al. Serum glutamate dehydrogenase activity enables early detection of liver injury in subjects with underlying muscle impairments. PLoS One. 2020; 15: 1–13.