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RESEARCH ARTICLE

Safety outcomes of Remdesivir for treatment of COVID-19 hospitalised patients in Indonesia

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Abstract

Background: Remdesivir has been granted emergency use authorisation for hospitalised COVID-19 patients. However, the available evidence in Indonesia is limited to related liver and kidney injuries. **Objective:** This study aims to assess the safety of remdesivir based on liver and kidney function and its association with comorbidity and disease severity. **Method**: This retrospective study evaluated remdesivir's efficacy in hospitalised COVID-19 patients of varying severity by collecting baseline and follow-up data on aspartate aminotransferase (AST), alanine aminotransferase (ALT), Glomerular filtration rate (GFR) and Blood urea nitrogen (BUN). **Result:** In this study, 189 patients with elevated transaminase enzyme levels were given hepatoprotection therapy. Patients who did not receive the treatment experienced a significant rise in ALT levels ($p < 0.001$), while BUN levels increased significantly ($p = 0.001$) but within the normal range. There was no worsening of GFR value ($p < 0.001$), and no significant association was found between AST and ALT levels with comorbidity and disease severity ($p < 0.001$; OR 50.202). **Conclusion:** Remdesivir demonstrated good tolerability despite increased ALT and BUN without correlating to comorbidity or disease severity in COVID-19.

Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. The World Health Organisation (WHO) declared SARS-CoV-2 as a pandemic on March 11, 2020 (Dos Santos, 2020; Yulistiani, 2022). Several therapeutic agents have been evaluated for COVID-19 treatment with repurposing antiviral drugs. Antiviral agent remdesivir (initially named GS-5734) is a phosphonamidite prodrug analogue of its nucleoside parent GS-441524 (Ansems *et al*., 2021). Remdesivir and its metabolite active (GS-441524) have shown inhibitory effects on SARS-CoV-2 in vitro and animal models (Dos Santos, 2020). It inhibits viral replication by competing with endogenous nucleotides for incorporation into replicating viral RNA via RNA-dependent RNA polymerase (RdRp) (Sisay, 2020). Therefore, the Food and Drug Agency (FDA) and the European Medicine Agency (EMA) recommended remdesivir to treat patients hospitalised for COVID-19.

The use of Remdesivir has been linked to potential harm to the kidneys and liver, which may manifest as nephrotoxicity and hepatotoxicity. Previous clinical trials have observed that remdesivir leads to an increase in liver enzymes, specifically alanine transaminase (ALT) and aspartate transaminase (AST) (Carothers *et al.,* 2020; Gurala *et al.,* 2020). There are some reports of renal injury, elevated blood creatinine levels, renal impairment, and a reduction in glomerular filtration rate (Charan *et al.,* 2021). Limited data exists on liver and renal function changes during remdesivir treatment in Indonesia. This study aims to investigate the use and safety outcomes of remdesivir therapy, focusing on the difference between liver and kidney function at baseline and follow-up.

Methods

Design

This retrospective, observational study of patients with COVID-19 was conducted at Bhayangkara H.S Samsoeri Mertojoso Hospital Surabaya from August 2020 to July 2021. This study included all adult patients consecutively hospitalised with PCR-confirmed SARS-CoV-2. The severity of the disease was determined based on the guidelines of the Indonesian Pulmonary Specialist Association in 2021. Moderate severity was defined by clinical symptoms of pneumonia (fever and respiratory symptoms) with SpO_2 of ≤ 93% at room air and radiological imaging of less than 50% lung involvement. Severe severity was defined by respiratory distress >30 breaths per minute with clinical symptoms of pneumonia and SpO_2 of ≤ 93% at room air. Patients requiring mechanical ventilation, shock, or other organ failure were classified as critical. Patients who received remdesivir for at least five, seven, or ten days were included. Patients with incomplete clinical data or allergies to remdesivir were excluded.

Assessment

The demographic data, underlying comorbidities, clinical data, and laboratory parameters were collected and reviewed from the patient's medical records. Laboratory parameters AST, ALT, serum creatinine (SCr), Glomerular filtration rate (GFR), and Blood Urea Nitrogen (BUN) were collected before and after treatment.

The hospital's local ethics committee approved the study protocol on November 15th, 2021, protocol number 24/XI/2021/KEPK/RUMKIT.

Data analysis

Descriptive analysis was presented as means ± standard deviations. Comparison of baseline and follow-up laboratory results was evaluated with paired Wilcoxon. The results were then evaluated regarding disease severity and comorbidity using the non-parametric Kruskal-Wallis Test. Statistical analyses were conducted using the SPSS software package ver. 26.0. A *p*-value equal to or less than 0.05 was considered significant.

Results

A total of 189 adults who had both clinical symptoms and laboratory confirmation of COVID-19 were eligible for inclusion. Table I shows the baseline demographic and clinical characteristics of eligible patients. COVID-19 was observed to be more common among males aged between 46 and 60 years (38.6%). Out of the total patients, 101 (53.4%) had a moderate severity of the disease, 68 (36.0%) had a severe severity, and 20 (10.6%) were in critical condition. Half of the patients had comorbidities such as diabetes (16%) and cardiovascular disease (15%). Most patients with both comorbidities were categorised as critical severity. Hepatoprotective drugs were administered to patients with elevated liver function. Out of 39 patients, four (10.6%) had AST or ALT levels greater than five times the upper limit of normal.

Table I: Demographic and baseline characteristics of COVID-19 patients

Characteristic		Disease severity		
	N (%)	Moderate	Severe	Critical
Gender				
Male	123 (65)	59 (58)	52 (76)	12 (60)
Female	66 (35)	42 (71)	16 (31)	8 (67)
Age group (years)				
18-30	24 (13)	21 (21)	2 (3)	1 (5)
31-45	64 (34)	39 (39)	21 (31)	4 (20)
46-60	79 (42)	31 (31)	39 (57)	9 (45)
>60 years	28 (15)	10 (10)	12 (18)	6 (30)
Comorbid				
None	94 (50)	70 (69)	21 (31)	3 (15)
Diabetes	30 (16)	8 (8)	19 (28)	3 (15)
Cardiovascular	29 (15)	15 (15)	12 (18)	2 (10)
Diabetes and Cardiovascular	36 (19)	8 (8)	16 (24)	12 (60)
Using hepatoprotective agent				
No	150 (79)	86 (85)	52 (76)	12 (60)
Yes	39 (21)	15 (15)	16 (24)	8 (40)
All	189	101	68	20

At the beginning of the treatment, the median baseline levels of AST and ALT in patients not receiving the hepatoprotective agent were 35.5 ± 17.4 and 34.1 ± 19.2, respectively. After receiving remdesivir therapy, AST levels showed a significant reduction (31.5 ± 19.3; $p = 0.019$), while ALT levels increased (44.3 ± 39.9; $p < 0.001$). This study included 24 patients with a mild increase in ALT, but this increase was still within the normal range. A total of four out of 39 patients who received hepatoprotective agents experienced a five-fold increase in both AST and ALT levels above the upper limit of normal. At baseline, AST was 70.8 ± 65.2, and ALT was 72.1 ± 49.8. Early follow-up showed AST improvement.

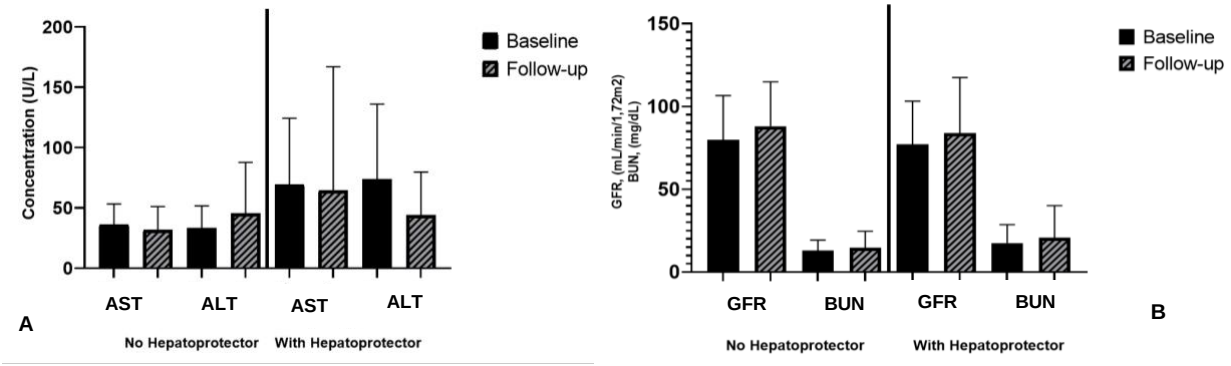

Figure 1: The dynamic laboratory parameters for liver function (A) and kidney function (B) in COVID-19 patients regarding remdesivir use in the presence of hepatoprotection use

The study revealed that patients who did not take hepatoprotection had a significant correlation between changes in AST and ALT ($p < 0.001$) and changes in GFR and AST levels ($p = 0.030$). On the other hand, patients who took hepatoprotection showed a marked improvement in both AST and ALT levels ($p < 0.001$). However, kidney function had no significant impact ($p > 0.05$). During the follow-up, BUN levels increased significantly ($p = 0.001$) but remained within the normal range, and there was no worsening in GFR values ($p < 0.001$). There was a significant statistical difference observed between the severity of disease and comorbidity ($p < 0.001$; or 50.202) (Figure 2d). This study found that patients with more co-morbidities had greater disease severity, independent of liver and kidney function.

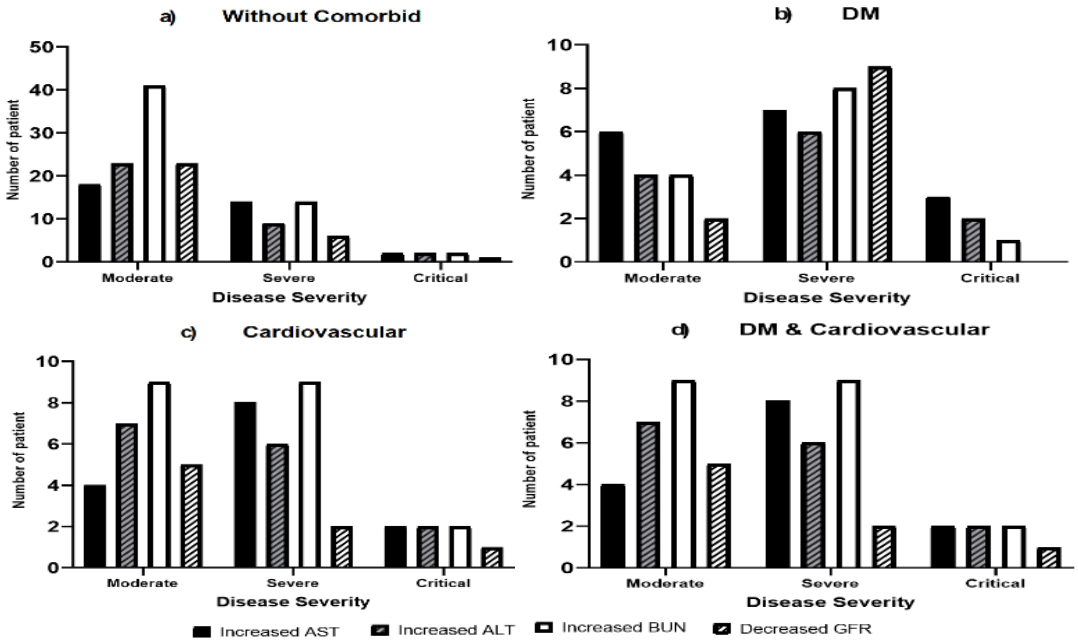

Figure 2: Changes of liver and kidney function associated with comorbid and severity of disease a) Without comorbid b) Diabetes mellitus c) Cardiovascular d) Diabetes mellitus & Cardiovascular

Discussion

Remdesivir leads to elevated liver enzymes and kidney injury by damaging liver cells and renal tubular cells' mitochondria by inhibiting DNA and RNA polymerases (Adamsick *et al.,* 2020). This study aimed to assess the safety of remdesivir by analysing retrospective data on hospitalised COVID-19 patients who received this agent. The study measured the changes in liver and kidney function levels before and after treatment with remdesivir. Despite the patients having underlying liver disease, they were still given remdesivir. The study found significant changes in AST, ALT, and GFR (Figure 1).

Previous investigations had shown a correlation between disease severity and worsening liver transaminase levels, especially AST (Lei *et al.,* 2020). Despite the progression of COVID-19, remdesivir therapy may elevate serum transaminases. Our study showed that patients who received no hepatoprotective agent had significant elevations in ALT and AST levels after treatment. A double-blind, multicentred study found that 5% of remdesivir-treated patients experienced elevated aminotransferases (Wang *et al.,* 2020). The study found that patients given hepatoprotective agents had higher ALT levels but lower AST levels. A double-blinded, placebo-controlled clinical trial found that the use of acetylcysteine as hepatoprotection in 42 severe COVID-19 patients led to significantly reduced levels of AST and ALT (Mousapour *et al.,* 2022).

Remdesivir is rapidly converted to its active metabolite, nucleoside triphosphate (GS-443902). The plasma half-life of this metabolite is prolonged, lasting 24.5 hours (Jorgensen *et al.,* 2020). The prolonged plasma half-life of remdesivir's metabolites and the accumulation of SBECD carriers have raised safety concerns regarding induced kidney injury (Buxeda *et al.,* 2021). Our study revealed a significant decrease in GFR associated with remdesivir treatment. Remdesivir and placebo showed a similar incidence of acute kidney injury. The glomerular filtration rate (GFR) is a superior kidney function biomarker to BUN, especially in unstable urea production and impaired liver function. (Kiapidou *et al.,* 2020). Recent cross-sectional research has shown that severe COVID-19 patients experience a decrease in their GFR (Okwor *et al.,* 2023).

A correlation has been found between disease severity and comorbidity. Patients with multiple comorbidities experience more severe symptoms (Figure 2). One-third of patients who had both diabetes and cardiovascular disease (33.3%; $p < 0.001$) were in the critical stage with elevated GFR and BUN. One study demonstrated that cytokine storms are responsible for severe pneumonia, organ damage, and abnormal lab values, particularly in patients with severe or critical disease (Li & Fan, 2020). A recent study found no significant differences in COVID-19 prevalence among races and comorbidities. However, older males are more prone to cytokine storms, indicating that age and gender play a more significant role in COVID-19 severity than race and specific comorbidities (Caricchio *et al.,* 2021).

This study aims to compare laboratory values of Indonesian patients before and after treatment. The number of patients with critical severity COVID-19 was limited, making it the smallest sample size compared to those with moderate and severe severity. However, the value is still compared to other disease severity and correlated with laboratory findings. The findings of this study may contribute to a better understanding of the safety of remdesivir treatment in the Indonesian population.

Conclusion

Remdesivir demonstrated good tolerability in patients with moderate to critical COVID-19 patients. Furthermore, the findings indicate that the drug does not adversely impact renal function, as evidenced by normal BUN and GFR levels.

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References

Adamsick, M. L., Gandhi, R. G., Bidell, M. R., Elshaboury, R. H., Bhattacharyya, R. P., Kim, A. Y., Nigwekar, S., Rhee, E. P., & Sise, M. E. (2020). Remdesivir in patients with acute or chronic kidney disease and COVID-19. *Journal of the American Society of Nephrology*, **31**(7), 1384–1386. https://doi.org/10.1681/ASN.2020050589

Ansems, K., Grundeis, F., Dahms, K., Mikolajewska, A., Thieme, V., Piechotta, V., Metzendorf, M. I., Stegemann, M., Benstoem, C., & Fichtner, F. (2021). Remdesivir for the treatment of COVID-19. *The Cochrane Database of Systematic Reviews*, **2021**(8). https://doi.org/10.1002/14651858.CD014962

Buxeda, A., Arias-Cabrales, C., Pérez-Sáez, M. J., Cacho, J., Cabello Pelegrin, S., Melilli, E., Aladrén, M. J., Galeano, C.,

Lorenzo, I., Mazuecos, A., Saura, I. M., Franco, A., Ruiz-Fuentes, M. del C., Sánchez-Cámara, L. A., Siverio, O., Martin, M. L., González-García, E., López, V., Martin-Moreno, P. L., Crespo, M. (2021). Use and safety of remdesivir in kidney transplant recipients with COVID-19. *Kidney International Reports*, **6**(9), 2305–2315. https://doi.org/10.1016/j.ekir.2021.06.023

Caricchio, R., Gallucci, M., Dass, C., Zhang, X., Gallucci, S., Fleece, D., Bromberg, M., & Criner, G. J. (2021). Preliminary predictive criteria for COVID-19 cytokine storm. *Annals of the Rheumatic Diseases*, **80**(1), 88–95. https://doi.org/10.1136/ANNRHEUMDIS-2020-218323

Carothers, C., Birrer, K., & Vo, M. (2020). Acetylcysteine for the treatment of suspected remdesivir-associated acute liver failure in COVID-19: A case series. *Pharmacotherapy*, **40**(11), 1166. https://doi.org/10.1002/PHAR.2464

Charan, J., Kaur, R. J., Bhardwaj, P., Haque, M., Sharma, P., Misra, S., & Godman, B. (2021). Rapid review of suspected adverse drug events due to remdesivir in the WHO database: Findings and implications. *Expert Review of Clinical Pharmacology,* **14**(1), 95–103. https://doi.org/10.1080/17512433.2021.1856655

Dos Santos, W. G. (2020). Natural history of COVID-19 and current knowledge of treatment therapeutic options. *Biomedicine & Pharmacotherapy*, **129**, 110493. https://doi.org/10.1016/J.BIOPHA.2020.110493

Jorgensen, S. C. J., Kebriaei, R., & Dresser, L. D. (2020). Remdesivir: Review of pharmacology, pre-clinical data, and emerging clinical experience for COVID-19. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, **40**(7), 659–671. https://doi.org/10.1002/phar.2429

Kiapidou, S., Liava, C., Kalogirou, M., Akriviadis, E., & Sinakos, E. (2020). Chronic kidney disease in patients with non-alcoholic fatty liver disease: What the Hepatologist should know? *Annals of Hepatology*, **19**(2), 134–144. https://doi.org/10.1016/j.aohep.2019.07.013

Gurala, D., Moussawi, H. Al, Philipose, J., & Abergel, J. R. (2020). Acute liver failure in a COVID-19 patient without any preexisting liver disease. *Cureus*, **12**(8). https://doi.org/10.7759/CUREUS.10045

Lei, P., Zhang, L., Han, P., Zheng, C., Tong, Q., Shang, H., Yang, F., Hu, Y., Li, X., & Song, Y. (2020). Liver injury in patients with COVID-19: Clinical profiles, CT findings, the correlation of the severity with liver injury. *Hepatology International*, **14**(5), 733–742. https://doi.org/10.1007/s12072-020-10087-1

Li, J., & Fan, J.-G. (2020). Characteristics and mechanism of liver injury in 2019 Coronavirus disease. *Journal of Clinical and Translational Hepatology*, **8**(1), 1–5. https://doi.org/10.14218/JCTH.2020.00019

Mousapour, P., Farahani, R. H., Mosaed, R., Asgari, A., & Hazrati, E. (2022). Efficacy and safety of acetylcysteine for the prevention of liver injury in COVID-19 intensive care unit patients under treatment with remdesivir. *Gastroenterology and Hepatology from Bed to Bench*, **15**(3), 241–248. https://doi.org/10.22037/GHFBB.V15I3.2565

Okwor, C., Meka, I., Nto-Ezimah, U., Nto, N., Nduka, N., Akinwande, K., & Edem, V. (2023). Association of SARS-CoV-2 viral load with biochemical profile of COVID-19 patients: A Nigerian experience. *Nigerian Journal of Clinical Practice*, **26**(1), 109. https://doi.org/10.4103/njcp.njcp_1828_21

Sisay, M. (2020). Available evidence and ongoing clinical trials of remdesivir: Could it be a promising therapeutic option for COVID-19? *Frontiers in Pharmacology*, **11**, 791. https://doi.org/10.3389/FPHAR.2020.00791/BIBTEX

Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., Wang, Y., Ding, D., Wu, F., Tang, X., Ye, Z., Ye, Y., Liu, B., Yang, J., Yin, W., Wang, A., Fan, G., Zhou, F., Liu, Z., Gu, X., Xu, J., Shang, L., Zhang, Y., Cao, L., Guo, T., Wan, Y., Qin, H., Jiang, Y., Jaki, T., Hayden, F.G., Horby, P.W., Cao, B., & Wang, C. (2020). Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*, **395**(10236), 1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9

Yulistiani, Izka A, H., Rindang A, M., & A W, P. (2022). Tocilizumab therapy in COVID-19 patients. *Pharmacy Education*, **22**(2), 259–262. https://doi.org/10.46542/pe.2022.222.259262