Original Article

Acute Kidney Injury Incidence in COVID-19 Patients Receiving Remdesivir Therapy at Awal Bros Panam Hospital

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ARTICLE INFO

Article history:
Received: May 31, 2024
Accepted: August 5, 2024
Published Online: August 24, 2024

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ABSTRACT

Background: Remdesivir is one of the pharmacological therapies for moderate COVID-19 patients. Remdesivir is an antiviral that can increase the risk of nephrotoxicity.
Objective: The study aims to evaluate the incidence of acute kidney injury (AKI) in COVID-19 patients receiving remdesivir.
Methods: This is a cross-sectional analytic study of 238 COVID-19 patients receiving remdesivir therapy at Awal Bros Panam Hospital for the period 2020–2022. AKI was diagnosed using the KDIGO criteria. The chi-square test was used to determine the correlation of AKI incidence with age, gender, and comorbidities, with a significance level of $p < 0.05$.
Results: AKI was found in 32 patients (13.4%). The majority of AKI patients (75%) were aged 60 years or older, with 65.6% being male. Additionally, 84.4% of these patients had comorbidities, and 53.1% of them died. Around half of the patients were diagnosed with stage 1 AKI, and the majority, specifically 84.4%, did not undergo renal replacement therapy (RRT). The association between the incidence of AKI and age and comorbidities was shown to be statistically significant (p=0.000; RR 5.11; 95% CI 2.44-10.8 and p=0.009; RR 3.05; 95% CI 1.22-7.64, respectively).
Conclusion: The main risk factors for AKI are primarily observed in the older population and individuals with several medical conditions. Greater emphasis should be placed on administering remdesivir to COVID-19 patients who are elderly and have comorbidities, as they are at a higher risk of developing AKI.
Keywords: acute kidney injury, COVID-19, remdesivir, KDIGO.

Introduction

Acute kidney injury (AKI) refers to a deviation from normal kidney structure and function that is identified within 48 hours using blood, urine, tissue, or radiological tests.[1] AKI is a rapid deterioration in kidney function in previously healthy kidneys, sometimes necessitating dialysis treatment.[2] It is associated with a rise in death rates and the risk of developing chronic kidney disease (CKD).[3]

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus.[4] The lungs are the primary organ affected by COVID-19. However, other organs such as the kidneys and liver are also implicated. The majority of the medications administered to individuals with COVID-19 are eliminated from the body through the renal system. Hence, alterations in kidney function can significantly affect the levels of medication in the body as a result of poor elimination and breakdown, which may result in either harmful effects or diminished effectiveness.[5]

According to the World Health Organization, from December 31, 2019 to July 30, 2023, there were 768,633,601 confirmed cases

Cite this as:
Reslina AN, Monita F, Sembiring LP. Acute Kidney Injury Incidence in COVID-19 Patients Receiving Remdesivir Therapy at Awal Bros Panam Hospital. InaKidney. 2024;1(2):12-19. doi: 10.32867/inakidney.v1i2.127

of COVID-19, resulting in 6,953,107 deaths. The case fatality rate (CFR) was 0.90%.[4] As of July 2023, Indonesia has recorded a total of 6,812,949 confirmed cases of COVID-19, with 161,909 deaths (CFR = 2.38%) and 6,646,181 recoveries. These cases are distributed throughout 34 provinces.[6] Riau Province has recorded a total of 154,874 confirmed cases of COVID-19, with 150,280 individuals having recovered from the virus. Pekanbaru City has the highest number of confirmed COVID-19 cases in the province of Riau, with a total of 65,371 cases. Additionally, there have been 63,936 recoveries in the city.[7] Awal Bros Panam Hospital recorded a cumulative total of 4,938 confirmed cases of COVID-19 between 2020 and 2022, including both outpatients and inpatients.[8]

Within the COVID-19 management protocol, patients with moderate and severe symptoms are treated with pharmacological therapy, which includes the administration of antiviral drugs. One of the options for antiviral treatment is remdesivir.[9] Other options include nirmatrelvir with ritonavir (paxlovid), azvudine, molnupiravir, oseltamivir, famsiclovir, and favipiravir.[10] Apart from COVID-19, remdesivir is a broad-spectrum antiviral medication that has demonstrated its effectiveness against various viruses.[11] To monitor potential kidney damage, it is crucial to monitor the glomerular filtration rate (GFR) in COVID-19 patients who are being treated with remdesivir. Remdesivir treatment is discontinued when the GFR decreases to 50% of the initial level. The frequency of AKI in COVID-19 patients receiving remdesivir medication is exacerbated by several risk variables, including age, gender, and concomitant disorders.[12] The antivirals that are safe to use in kidney impairment include azvudine, molnupiravir, nirmatrelvir with ritonavir (Paxlovid), and oseltamivir and famsiclovir, which are now undergoing clinical trials.[10]

A study in Tiongkok in 2020 of 20 patients with mild-moderate COVID-19 with azvudine therapy showed no kidney-related side effects, and in other studies, kidney function parameters were found to be normal.[13, 14] A study conducted in Hong Kong involving 860 COVID-19 patients who received remdesivir treatment while hospitalized indicated that the occurrence of AKI was 15.9%.[15] A study conducted in Brazil indicated that out of the 2,922 cases of remdesivir use in COVID-19 patients, 493 cases (16.9%) were associated with renal and urinary tract diseases. The most common disorder observed was AKI, which occurred in 338 cases (11.6%).[16]

Currently, there is a scarcity of data on the occurrence of AKI in COVID-19 patients undergoing remdesivir therapy in Indonesia. Hence, the objective of this study is to determine the occurrence rate of AKI in COVID-19 patients who are undergoing remdesivir treatment at Awal Bros Panam Hospital.

Methods

Design and participants

This is a cross-sectional study. Data was taken from the medical records of Remdesivir-treated COVID-19 patients at Awal Bros Panam Hospital from November 2020 to December 2022 and analyzed. Inclusion criteria are PCR-diagnosed COVID-19 individuals over 18 years old who received remdesivir were the study subjects. Exclusion criteria are patients with a GFR < 30ml/min/1.73m2, regular hemodialysis patients, and incomplete medical records were removed. Total sampling was used as the sample method for subjects who satisfied the inclusion and exclusion criteria. This study measures age, gender, comorbidities, AKI stage, renal replacement therapy (RRT), and patient outcomes. The study ran from June to September 2023.

According to KDIGO 2012, AKI is defined as a rise in serum creatinine of 0.3 mg/dl within 48 hours, ≥1.5 times from baseline within 7 days, or urine volume below 0.5 ml/kgBB/hour for 6 hours. The creatinine baseline was the mean level measured 7–365 days preceding hospitalization, or the lowest level measured in the hospital. Stage 1 was defined as an increase in serum creatinine of 0.3 mg/dl within 48 hours or 1.5–1.9 times from baseline within 7 days; stage 2 was an increase of 2–2.9 times from baseline; and stage 3 was an increase of 3 times or more from

baseline or an increase > 4 mg/dl or the start of RRT.[17]

COVID-19 patients receiving remdesivir therapy were categorized as adults aged 18–59 and geriatrics aged ≥ 60. Patient genders are male and female. Remdesivir-treated COVID-19 patients have pre-COVID-19 comorbidities such as hypertension, diabetes, and heart disease. AKI treatment includes hemodialysis and conservative therapy. COVID-19 patients with remdesivir therapy have a life-or-death outcome after hospitalization.

Statistical analysis

Demographic data were also reported. Numeric variables were reported as mean and standard deviation, and categorical variables were reported as percentages. Bivariate analysis was performed using an unpaired t-test and a chi-square test. Statistical significance was set at $p < 0.05$. Researchers calculated the relative risk (RR) and 95% confidence interval to determine how age, sex, and comorbidities affected AKI incidence. All analyses were performed using SPSS version 25.0 for Windows (SPSS, Inc.).

Results

During the period November 2020 to December 2022, there were 1,620 COVID-19 patients hospitalized at Awal Bros Panam Hospital. A total of 389 patients received remdesivir therapy. However, 151 patients were excluded because 4 patients were < 18 years old, 7 patients underwent routine hemodialysis, and 140 data were incomplete. This study had 238 patients in total.

According to this study, 13.4% of COVID-19 patients receiving remdesivir medication experienced an incidence of AKI (Figure 1). Table 1 indicates that 75 percent of the 32 patients who experienced AKI belonged to the age group of 60 years or older. The gender of most AKI patients is male, at 65.6%. In patients with comorbidities, the incidence of AKI is higher at 84.4%. The population of AKI patients who died was 53.1%, while the living population was 46.9%. AKI patients based on KDIGO criteria are dominated by stage 1 AKI, which is 50%. Furthermore, only 5 patients (15.6%) out of the 32 AKI patients underwent RRT.

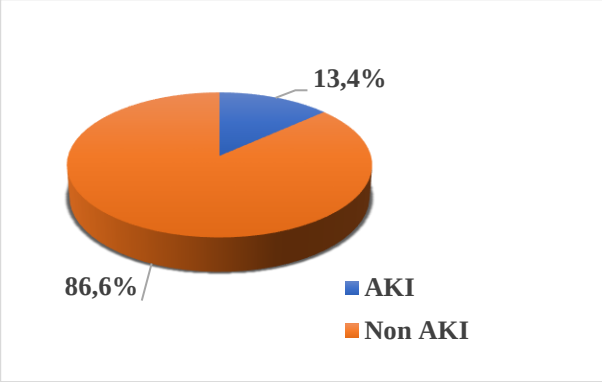

Figure 1. Distribution of COVID-19 patients with remdesivir therapy

Table 1. Characteristics of COVID-19 patients receiving remdesivir therapy

Variable	AKI n (%)	Non-AKI n (%)
Age (years)		
≥ 60	24 (75)	64 (31,1)
18-59	8 (25)	142 (68,9)
Gender		
Male	21 (65,6)	110 (53,4)
Female	11 (34,4)	96 (46,6)
Comorbid condition	27 (84,4)	125 (60,7)
Yes	5 (15,6)	81 (39,3)
No		
Patient Outcome		
Discharge	15 (46,9)	189 (91,7)
Deceased	17 (53,1)	17 (8,3)
AKI Stage (KDIGO)	16 (50)	
Stage 1	7 (21,9)	
Stage 2	9 (28,1)	
Stage 3		
RRT Requirement	5 (15,6)	
HD	27 (84,4)	
No need for RRT		

RRT*: renal replacement therapy*

In COVID-19 patients who were 60 years of age or older and received remdesivir, the incidence of AKI was found to be 27.3%, while at the age of 18–59 years, the incidence of AKI was only 5.3%. Remdesivir-treated male COVID-19 patients had an AKI incidence of

16%, not much different from female patients with an AKI incidence of 10.3%. For COVID-19 patients with comorbidities who get remdesivir, the incidence of AKI is found to be 17.8%, while patients without comorbid AKI incidence is only 5.8%.

Based on the results of the analysis using the chi-square test, there was a significant relationship ($p < 0.05$) between patient age and comorbidities and the incidence of AKI Patient age ≥ 60 years has a relative risk of AKI 5.11 times compared to age 18–59 years. Patients with comorbidities had a relative risk of AKI 3.05 times compared to those without comorbidities, With a p value > 0.05, there was no statistically significant correlation found between the gender variable and the frequency of AKI (Table 2).

Table 2. Correlation of AKI incidence with age, gender, and comorbidities

Variable	AKI n (%)	Non-AKI n (%)	Total n (%)	P	RR	CI (95%)
Age (years)						
≥ 60	24 (27,3)	64 (72,7)	88 (100)			
18-59	8 (5,3)	142 (94,7)	150 (100)	0,000	5,11	2,40−10,8
Gender						
Male	21 (16)	110 (84)	131 (100)			
Female	11 (10,3)	96 (89,7)	107 (100)	0,196	1,55	0,78−3,08
Comorbid condition						
Yes	27 (17,8)	125 (82,2)	152 (100)			
No	5 (5,8)	81 (94,2)	86 (100)	0,009	3,05	1,22−7,64

Discussion

This study found that the administration of remdesivir to patients with COVID-19 resulted in a 13.4% incidence of AKI. Remdesivir binds to the RNA chain of SARS-CoV-2 and functions as an adenosine triphosphate (ATP) analog. As a result, during viral RNA replication, the RNA chain synthesis process is terminated and the RNA-dependent RNA polymerase (RdRp) enzyme is inhibited.[18] Remdesivir has limited aqueous solubility; therefore, sulfobutylether-beta-cyclodextrin sodium (SBECD) is added to the formulation as a solubility-enhancing agent. SBECD is filtered and excreted by the kidneys, so patients with renal impairment are at risk of SBECD accumulation and an increased risk of nephrotoxicity.[19] Remdesivir is effective against a variety of viruses in addition to COVID-19, including filoviruses (like Ebola and Marburg), coronaviruses (like SARS-CoV and MERS-CoV), paramyxoviruses (like parainfluenza type III, Nipah, Hendra, measles, and mumps), and Pnemoviridae.[11]

Wu's (2021) study showed a substantial correlation between the administration of remdesivir and the occurrence of AKI in individuals with COVID-19. Remdesivir had a 2.81-fold higher likelihood of causing AKI compared to alternative drugs considered the main treatment. The mean time until the development of AKI in the remdesivir group was 4.91 ± 7.25 days.[20]

In Sham's study conducted in 2023, it was found that there was no correlation between the use of remdesivir therapy and the risk of AKI. The AKI occurrences mentioned are likely to be complications arising from COVID-19. Although the condition is typically recognized as a respiratory infection, it can also sporadically lead to multi-system disease, impacting other body systems, including the kidneys. Multiple investigations have shown a clear connection between COVID-19 and AKI, with the occurrence ranging from 0.5% to 46%, depending on the severity of COVID-19.[21]

Alongside respiratory failure and low oxygen levels, COVID-19 often presents as kidney disease. The histopathologic findings emphasize the resemblances between those experiencing AKI in sepsis cases not connected to COVID-19 and those with AKI in COVID-19 patients. Acute tubular injury results in a reduction in renal function. Systemic hemodynamic instability contributes to the development of tubular injury. Despite COVID-19 being labeled as a cytokine storm disease, individuals with non-COVID-19 associated acute respiratory distress syndrome often exhibit lower amounts of circulating cytokines. Endothelial damage and microvascular thrombus formation are two important factors contributing to kidney injury, which are caused by tissue inflammation and infiltration of immune cells. The identification of a significant amount of virus in patients with AKI who are close to death suggests that the invasion of the kidneys by the virus may have had a role.[22]

The study found that the majority of COVID-19 patients who received remdesivir medication and experienced AKI were aged 60 years or older (75%) and had underlying health conditions (84.4%). The analysis employing the chi-square test indicated a statistically significant connection ($p < 0.05$) between the patient's age and comorbidities and the occurrence of AKI. This finding aligns with the research conducted by Wu (2022), which indicates that the incidence of AKI is most prevalent among those aged 65 years or older.[20] In Schaubroeck's study (2022), the findings of a multivariable regression analysis were presented, demonstrating the correlation between age and AKI. The reason for this can be attributed to the fact that patients with AKI tend to be of advanced age, have a higher body mass index, and are more frequently afflicted with diabetes and hypertension compared to individuals without AKI.[23]

Physiological renal function starts to decrease between the ages of 30 and 40 due to the reaction of the renal vasculature to mediators such as acetylcholine and angiotensin. Glomerulosclerosis often appears as fibrosis within the glomerular capsule, thickening of the glomerulus, and collapse of the blood vessels. The process of aging also leads to the formation of tubular atrophy and interstitial fibrosis, characterized by the accumulation of collagen. Additionally, as individuals grow older, they are more susceptible to the development of arteriosclerosis, medial hypertrophy, and hyalinosis of the arterioles. These conditions can result in ischemia, nephron degeneration, and glomerular disease.[24]

Several variables increase the likelihood of developing AKI in individuals who are 65 years of age or older. Comorbidities such as diabetes mellitus, heart failure, and hypertension can cause damage to the renal vasculature. The use of medications such as angiotensin receptor blockers or angiotensin-converting enzyme inhibitors is often associated with comorbidities that can increase the risk of AKI. Nephrotoxic substances, such as nonsteroidal anti-inflammatory drugs and contrast agents containing iodine, are more commonly utilized in older individuals and are recognized to elevate the likelihood of acute kidney injury in patients. Due to their compromised immune systems, the elderly are particularly prone to sepsis, which also increases their susceptibility to developing AKI.[24]

Among COVID-19 patients treated with remdesivir, it was shown that male patients had a much greater occurrence of AKI, with a prevalence of 65.6%. The chi-square test analysis indicated that there was no statistically significant association between the gender variable and the occurrence of AKI. These findings align with Hidayat's (2020) research, which indicates that the chi-square test results show no statistically significant disparity in gender between patients with AKI and those without AKI.[25]

The findings of this study indicate that the mortality rate among COVID-19 patients with AKI who were treated with remdesivir was 53.1%, which is higher than the survival rate. According to Wu's (2022) study, individuals with AKI had a mortality rate of 36.5%. The administration of remdesivir therapy is limited to

patients who are hospitalized with COVID-19 of intermediate severity, which contributes to a poorer prognosis for these individuals. Furthermore, individuals with COVID-19 who experience AKI generally have a more critical medical state compared to people who do not have any kidney impairment.[20]

According to the KDIGO criteria, this study found that 50% of AKI patients had stage 1 AKI. These findings align with Silver's (2021) research, which indicates that stage 1 AKI is the most common, representing 44% of all cases. Stage 3 ranks second with a percentage of 34%, while stage 2 follows with a percentage of 19%.[26]

Out of the 32 patients with AKI included in this study, only 5 patients (15.6%) had RRT in the form of hemodialysis. There is a lack of patients receiving continuous renal replacement therapy (CRRT) methods. Patients receiving RRT have stage 3 AKI. According to a comprehensive study of 154 trials, about 10% of COVID-19 patients who showed AKI had undergone RRT.[26] In Hirsch's (2020) research, 285 COVID-19 patients with AKI requiring RRT were treated using therapeutic methods including intermittent hemodialysis (54%), CRRT (24.6%), and a combination of both therapies (21.4%).[27] KDIGO provides two suggestions about the timing of RRT administration. Immediately, in the case of critical changes in fluid, electrolyte, or acid-base equilibrium, RRT can be promptly commenced. The second guideline is to adopt a comprehensive clinical approach when determining the need for RRT, taking into account various illnesses that can potentially benefit from its administration.[17] These findings align with the results of the study, which showed that 5 patients with AKI who underwent RRT followed the recommendations set by KDIGO guidelines.

Conclusion

The incidence of AKI in COVID-19 patients on remdesivir therapy at Awal Bros Panam Hospital was 13.4%. The older group, namely 65.6% of them, were the primary risk factors for AKI. Additionally, this group had comorbidities in 84.4% of cases. Greater emphasis should be placed on administering remdesivir to COVID-19 patients who are elderly and have comorbidities, as they are at a higher risk of developing AKI.

Limitations of the Study

The limitation of this study is that the majority of patients did not have initial creatinine values; hence, the diagnosis of AKI was only based on the rise in creatinine levels upon hospital admission and the subsequent period of waiting until remdesivir was given. Furthermore, the absence of a control group in this research precluded the examination of the relationship between the incidence of AKI and the administration of remdesivir treatment in patients with COVID-19.

Declarations

Ethics approval and consent to participate

This study was authorized by Awal Bros Panam Hospital's Research Ethics Committee No. 011/RSAB-PNM/KOMED/06.

Competing interests

The authors have no conflicts of interest to declare.

Funding source

This research receives no external funding.

Acknowledgments

We thank Awal Bros Panam Hospital for the support and opportunity to conduct this study. We are also grateful to Fajri Marindra, MD, for the advice provided in this study.

Author's Contribution

Idea/concept: LPS. Design: ANR, FM. Control/supervision: LPS. Data collection/processing: ANR, FM. Extraction/Analysis/interpretation: ANR, FM, LPS. Literature review: ANR, FM, LPS. Writing the article: ANR, FM, LPS. Critical review: ANR,

FM, LPS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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