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Analysis Of Risk Factors For Acute Kidney Injury (AKI) With The Use Of Favipiravir And Remdesivir In Covid-19 Patients At Fatmawati Central General Hospital

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ABSTRACT
COVID-19 patients are very vulnerable to complications of Acute Kidney Injury (AKI), there are many factors causing complications one of which is kidney toxic therapy, antiviral therapy is considered potentially toxic to the kidneys because most of it is excreted through the kidneys. This study was conducted to examine the risk factor profile of AKI in COVID-19 patients taking antivirals Remdesivir and Favipiravir. This study is an observational study with a cross-sectional design at Fatmawati Hospital. The sampling method uses total sampling during the period August 2020-July 2021. The data used is medical record. Bivariate analysis uses Chi-square, and multivariate analysis uses logistic regression. a sample of 208 patients who met the inclusion criteria in the period August 2020-July 2021 in the COVID-19 isolation room of Fatmawati Hospital. 135 patients using Favipiravir, 37 identified as having an AKI event and 73 patients using Remdesivir, 19 were identified as having an AKI event. Multivariate analysis with logistic regression showed that male sex and severity of severe to critical severity significantly influenced the incidence of AKI. The use of Favipiravir and Remdesivir in COVID-19 patients is not a risk factor for AKI.

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by a new type of Coronavirus which causes respiratory infections. This virus is transmitted through droplets that come out when someone who is infected coughs, sneezes or talks (Aditia, 2021). Common symptoms of COVID-19 include fever, fatigue, dry cough, muscle aches, and in critical patients it can progress to Acute Respiratory Distress Syndrome (ARDS), sepsis, coagulation dysfunction, acute kidney injury (AKI), and death (Zhou et al., 2020). AKI is a sudden decrease in kidney function, complications of AKI in COVID-19 patients can occur due to cytopathic effects and from the use of toxic kidney therapy, hypoxia, or multiple organ dysfunction. The reported incidence of AKI in COVID-19 patients is 0.5% to 46%. (Wang et al., 2020) (Guan et al., 2020). Antivirals have been proven to reduce the length of stay in hospital and reduce mortality rates, however, some antiviral regimens are secreted

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through the kidneys so they have the potential to increase the incidence or incidence of AKI. The incidence of AKI in COVID-19 patients has been reported as a high-risk complication (Zheng et al., 2020).

The antivirals most commonly used in hospitalized patients are Remdesivir and Favipiravir. Pharmacokinetic data for the use of Remdesivir in patients with normal renal function shows that most of Remdesivir and its active metabolites (74%) are eliminated via the kidneys. Because Remdesivir is secreted through the kidneys and is a DNA and RNA-Polymerase inhibitor, this drug is considered to have potential kidney toxicity (Pettit et al., 2021). Pharmacovigilance studies show a significant relationship between Remdesivir and AKI, the average time to onset of AKI is more than four days with a mortality rate of 36% in elderly male patients (Wu et al., 2022). Favipiravir is also one of the recommended antivirals, Favipiravir is a nucleotide analogue that inhibits RNA-Polymerase, this drug is used orally with 100% bioavailability, the elimination pathway for Favipiravir is the kidneys and the non-active metabolites it secretes in the urine making it possible to have an effect on functional decline kidney (Nguyen et al., 2017). Research regarding the effects of Favipiravir on the kidneys is still very minimal, in India there were two reports of AKI (men aged 38 and 51 years) when using Favipiravir in COVID-19 patients, who recovered when Favipiravir was stopped (Aldebary et al., 2021). Apart from antiviral regimens, risk factors for AKI in COVID-19 are age, hypertension, cardiovascular disease, diabetes, and the severity of COVID-19 (Hirsch et al., 2021). Hemodynamic changes, the effects of intensive therapy such as ventilators, and nephrotoxic drugs are also factors in the occurrence of AKI (Hirsch et al., 2020). The high number of COVID-19 cases causes high mortality rates and complications, especially kidney function disorders that can lead to kidney failure. Research on antivirals as a risk factor for AKI in the world, especially in Indonesia, including at Fatmawati General Hospital, South Jakarta, is still very limited. including research on predictors of AKI in COVID-19 patients is also still very limited.

METHOD

Description of materials and sample collection techniques

This research was conducted observationally with a cross-sectional design at Fatmawati General Hospital. The population of this study was all COVID-19 inpatients who used Favipravir and Remdesivir at Fatmawati General Hospital in August 2020-July 2021. Data was searched retrospectively using total sampling. The inclusion criteria for this study were adult COVID-19 patients (>18 years) who were taking Favipiravir or Remdesivir and had keratinin checked initially and 72 hours after antiviral administration. The exclusion criteria for this study were incomplete medical record data, patients diagnosed with impaired kidney function, using more than one antiviral, and patients who died.

Explanation regarding the description of the course of the research

The independent variables in this research are age, gender, education, employment, history of chronic drug use, type of comorbidity, number of comorbidities, degree of severity, and type of antiviral. The dependent variable is the presence or absence of AKI events. Data

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will be analyzed using statistical analysis. Univariate analysis is presented descriptively. Next, bivariate analysis using the Chi-Square test. Independent variables that have p<0.25 will be analyzed using the logistic regression method. For all statistical tests used, a p value <0.05 was considered to have a significant effect. Data were collected and processed using SPSS version 25.

RESULTS

During the period August 2020-July 2021, as many as 623 COVID-19 patients used Favipiravir and Remdesivir at Fatmawati Hospital, consisting of 415 patients excluded, namely 47 patients with impaired kidney function, 272 medical record data were incomplete, and 96 patients used more than one antiviral. . Meanwhile, there were 208 patients who met the sample selection criteria and could carry out statistical analysis, of which 135 patients were using Favipiravir and 73 patients were using Remdesivir. For sociodemographic and clinical characteristics (table 1), the majority are aged 50 years and over, female (52%), highly educated (85%) and have a job (54%), with severe severity (62%), have one comorbid (21%) with comorbid types supporting AKI (58%), history of chronic drug use (5%), using the antiviral Favipiravir (65%), Remdesivir (35%).

Table 1. Sociodemographic and clinical characteristics

No.	Variable	Favipiravir group (n=135, %)	Group Remdesivir (n=73, %)	Total (n=208, %)	P-*value*
1	Average age	50	54		
2	Gender				
	Male	62 (46%)	38 (53%)	100 (48%)	0.375
	Female	73 (54%)	35 (47%)	108 (52%)	
3	Education				
	lowly	19 (14%)	11 (15%)	30 (15%)	0.776
	High	116 (86%)	62 (85%)	178 (85%)	
4	Work				
	Work	71 (53%)	41 (56%)	41 (56%)	0.795
	Doesn't work	64 (47%)	32 (44%)	32 (44%)	
5	Degree of Severity				
	Currently	55 (41%)	17 (23%)	72 (35%)	0.002
	Heavy	79 (59%)	50 (68%)	96	

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No.	Variable	Favipiravir group (n=135, %)	Group Remdesivir (n=73, %)	Total (n=208, %)	P-*value*
				(46%)	
	Critical	1 (1%)	6 (8%)	7 (3%)	
6	Type of comorbidity				
	AKI support	31 (23%)	27 (37%)	58 (28%)	0.094
	Non-support for AKI	3 (2%)	2 (3%)	5 (2%)	
7	Number of comorbidities				
	1 comorbid	24 (18%)	20 (27%)	44 (21%)	
	>1 comorbid	10 (7%)	9 (13%)	19 (9%)	0.075
	There are no comorbidities	101 (75%)	44 (60%)	145 (70%)	
8	History of Drug Use (RPO)				
	There are RPOs	4 (3%)	7 (10%)	11 (5%)	0.078
	There are no RPOs	131 (97%)	66 (90%)	197 (95%)	
9	Clinical outcome of COVID-19 is recovery	135	73	208 (100%)	

Based on the results of the bivariate analysis in table 2, it shows that age, gender, type of comorbidity, number of comorbidities, and degree of severity are significant risk factors for the incidence of AKI. Next, a multivariate analysis was carried out using multiple logistic regression analysis on these variables. The results of the multivariate analysis in Table 3 show that male gender (p= 0.004 and OR= 3.506) and severity of COVID-19 (p= 0.003 and OR= 3.135) are risk factors for AKI in COVID-19 patients.

Table 2. Bivariate analysis test results

No.	Variable	AKI incidence		Total (n=208)	Pearson Chi-Square (Sig.)
		AKI occurs (n=56, %)	AKI does not occur (n=152, %)		
1	Average Age	55	50		0.014
2	Gender				
	Male	38 (38%)	63 (62%)	101	0.002
	Female	19 (18%)	88 (82%)	107	
3	Education				
	Low	11 (38%)	18 (62%)	29	0.252
	High	46 (26%)	133 (74%)	179	
4	Work				

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No.	Variable	AKI incidence		Total (n=208)	Pearson Chi-Square (Sig.)
		AKI occurs (n=56, %)	AKI does not occur (n=152, %)		
	Working	34 (31%)	77 (69%)	111	0.296
	Doesn't work	23 (24%)	74 (76%)	97	
5	Comorbid Type				
	AKI support	29 (50%)	29 (50%)	58	0.001
	Non-support for AKI	1 (20%)	4 (80%)	5	
6	Number of comorbidities				
	1 comorbid	19 (42%)	26 (58%)	45	0.001
	>1 comorbid	10 (59%)	7 (41%)	17	
	There are no comorbidities	28 (20%)	118 (80%)	146	
7	History of Drug Use (RPO) chronic				
	There are RPOs	8 (62%)	5 (38%)	13	0.011
	There are no RPOs	49 (25%)	146 (75%)	195	
8	Degree of severity				
	Currently	13 (18%)	59 (82%)	72	0.001
	Heavy	38 (29%)	91 (71%)	129	
	Critical	6 (85%)	1 (15%)	7	
9	Type of antiviral				
	Favipiravir	37 (27%)	98 (73%)	135	1.000
	Remdesivir	20 (27%)	53 (73%)	73	
10	Clinical outcome improved	56	152	208	

Sig.= significant value; n= number of samples

Table 3. Multivariate analysis test results

No.	Variable	Sig.	OR	R Nagelkerke
1	Gender	0,004	3,506	
2	Degree of severity	0,003	3,135	

OR= odd ratio; Sig.= significance value

Discussion

From the research results (table 2), it was found that 56 patients experienced AKI and 152 did not experience AKI. The results of the research after carrying out the Chi-Square test showed that age had a p value of 0.014 where the p value was <0.05 so that the age variable was significant in the incidence of AKI. These results are in line with research by Xiao et al. which stated that as many as 287 patients, 55 with AKI and 232 without AKI,

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older patients had a significant impact on the incidence of AKI, namely p = 0.001 (42). Similar results also showed that 27.06% (23/85) of patients experienced AKI, and patients aged >60 years experienced a higher incidence of AKI development (69.57%) (46). The results are the same for the gender variable, namely it has a significant value of 0.002 where the p value <0.05 which means that gender has a significant result on the incidence of AKI, this is in line with research by Xiao et al. which states that the incidence of AKI is more likely to be male with p = 0.03 (42.47).

The results of the bivariate analysis for the type of comorbidity show that the variable of the type of comorbidity supporting AKI has a significant value of 0.001 where the p value <0.05 which means that the presence of comorbidities supporting AKI has a significant result on the incidence of AKI, where the comorbidities supporting AKI are Diabetes Mellitus, Hypertension , and Cardiovascular. This is in line with previous research which states that one of the risk factors for AKI in COVID-19 patients is patients with comorbidities (41). And according to the research results of Xiao et al. COVID-19 patients confirmed to have AKI are generally patients who have comorbidities such as hypertension with a p value = 0.04 and cerebrovascular disease with a p value = 0.02 (42).

It can be seen (table 2) that the severity variable for the incidence of AKI shows a significant value of 0.001, where the p value is <0.05, which means there is a relationship between the incidence of AKI and the degree of severity. This is in line with previous research which states that AKI is reported in hospitalized patients on average 11% in severe to critical patients, patients who use ventilators also have a large potential for AKI (48,49). And based on research by Cui et al. Of the 116 patients, AKI developed in 21 patients with more severe or critical organ dysfunction, where the SOFA (Sequential Organ Failure Assessment) score was obtained (4.5 ± 2.1 vs 2.8 ± 1.4, OR 1.498, 95 % CI (1.047–2.143) (50).

The final bivariate analysis on the antiviral variables Favipiravir and Remdesivir showed insignificant results on the incidence of AKI with a significance value of 1,000. These results are not in line with research by Qian et al. which states that Remdesivir has the potential to cause AKI when used in COVID-19 patients with a mitochondrial toxicity mechanism (51). Meanwhile, the results of Favipiravir are also not in line with research by Yildirim et al. which stated that there was a significant relationship between the use of Favipiravir and the incidence of AKI with a value of p = 0.001 (52).

After obtaining the results of the bivariate analysis, a multivariate analysis was then carried out to determine the independent variables that were predictors of AKI. From the results of the multivariate test, it was found that men have the potential to experience AKI 3,617 times, this is in line with research on COVID-19 by Wu et al. at the West China Hospital of Sichuan University stated that there was a significant relationship between the incidence of AKI in COVID-19 patients and elderly men (9). The results of this research are also supported by Non-COVID-19 research by Schiffl. at the University Hospital LMU Munich Germany which stated that the presence of the hormone testosterone is a risk factor for Hospital-Acquired Acute Kidney Injury (HA-AKI) compared to the hormone estrogen

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(53). Another non-COVID-19 study was also conducted by Hecking et al. at the Department of Internal Medicine, Medical University of Vienna Austria where it was found that the risk of kidney damage in women was 23% lower (95% CI, 0.63-0.95) compared to men (95% CI, 1.64-2.60) (54). These results are also supported by Non-COVID-19 research by Beckwith et al. at the Department of Renal Medicine, Imperial College London UK who stated that most glomerular problems occur in men compared to women (55).

In the results (table 3) the degree of severity is also a significant risk factor for the incidence of AKI with a Sig value. 0.002 and OR = 3.173 indicate that patients with a critical degree of disease severity have a 3.173 times greater chance of experiencing AKI compared to patients who have a mild degree of severity. This is in accordance with research by Jonathan et al. at UKRIDA Hospital Jakarta which stated that COVID-19 patients undergoing intensive care had a greater potential for experiencing kidney problems, where 33% of ICU patients experienced AKI (56). This is also in line with other COVID-19 research at the Medical Intensive Care Unit, Hospital Saint-Louis Paris which states that AKI in COVID-19 patients is reported to be an average of 11% in severe to critical patients, patients who use ventilators also have great potential on the incidence of AKI (48,49). And based on COID-19 research by Cui et al. at the Department of Pulmonary and Critical Care Medicine, Beijing, China, which stated that out of 116 COVID-19 patients with AKI, 21 patients developed more severe or critical organ dysfunction, where the SOFA (Sequential Organ Failure Assessment) score was obtained (4, 5 ± 2.1 vs 2.8 ± 1.4, OR 1.498, 95% CI (1.047–2.143) (50). From the results of this study, it was not found that this type of antiviral was a predictor of AKI, but in COVID-19 patients with male gender and severe to critical severity has a large potential for increasing risk factors for AKI. Different results were found in research by Wahab et al in the Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University, North Sulawesi, which stated that the risk factors for AKI in patients COVID-19 is a dominant comorbid disease, namely hypertension, diabetes mellitus, COPD, cardiovascular disease, respiratory diseases and nephrotoxic drugs (41).

There are several limitations to this research. First, this study used a retrospective design taken from patient medical record data so it was unable to describe the causal relationship of the variables used. Second, the research sample used only came from one research location. Third, there are many other factors that cannot be analyzed in this study due to limited data in the patient's medical records. Fourth, deceased patients were not included in the research sample.

CONCLUSION

In this study it can be concluded that the use of the antivirals Favipiravir and Remdisivir is not a risk factor for AKI, but male gender and severe to critical severity are risk factors for AKI.

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