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Clinical Outcomes of Antiviral Therapy on Comorbid and non-Comorbid T2-DM COVID-19 Patients at Rasidin Hospital

Luaran Klinik Terapi Antivirus pada Pasien Komorbid dan non-Komorbid T2-DM COVID-19 di RSUD Rasidin

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ABSTRACT

Patients with comorbidity is vulnerable to being attacked by COVID-19. Diabetes mellitus comorbid patients have experience of higher severity viral infections than those without diabetes mellitus. The objective of the research was to evaluate the impact of Type 2 Diabetes Mellitus (T2-DM) comorbidity and antiviral therapy on the clinical outcome of COVID-19 patients. The study was performed following a cross sectional design from April 2020 to March 2021 at Hospital dr Rasidin Padang. Data were collected retrospectively from the patient's medical record. Treatment and clinical outcomes of patients were analyzed using the Kruskal Wallis, Mann-Withney U Test, Repeated Measured ANOVA, and Friedman Test. Results showed that the respiratory rate on T2-DM comorbid and non-comorbid patients were 20.58±0.25 and 20.15±0.08 times/minutes, respectively ($p<0.05$). While, oxygen saturation was 97.95±0.16 and 98.38±0.06%, respectively ($p<0.05$). Patient's length of stay after the treatment of oseltamivir and favipiravir on non-comorbid COVID-19 patients were 14.76±0.861 and 9.96±0.488 days, respectively ($p<0.01$). While on comorbid patients were 16.00 ±3.17 and 10.47±0.77, respectively ($p<0.01$). Comorbidity had a significantly impacted on the patient's respiratory rate and oxygen saturation. The use of oseltamivir and favipiravir had a highly significant different on the LOS of comorbid and non-comorbid patients.

Keywords: COVID-19, diabetes, antivirus, comorbidity, outcome

ABSTRAK

Pasien komorbiditas rentan terserang COVID-19. Penderita diabetes melitus mengalami infeksi virus dengan tingkat keparahan yang lebih tinggi dibandingkan dengan yang tidak menderita diabetes melitus. Tujuan penelitian ini adalah untuk mengetahui pengaruh komorbiditas Diabetes Mellitus Tipe 2 (DMT2) dan terapi antivirus terhadap luaran klinis pasien COVID-19. Penelitian dilakukan dengan metode analitik dengan desain cross sectional dari April 2020 hingga Maret 2021 di Rumah Sakit dr Rasidin Padang. Data dikumpulkan secara retrospektif dari rekam medis pasien. Pengobatan dan luaran klinis pasien dianalisis menggunakan Kruskal Wallis, Mann-Withney U Test, Repeated Measured ANOVA, dan Friedman Test. Hasil penelitian menunjukkan bahwa laju nafas pada pasien komorbid dan non-komorbid masing-masing adalah 20.58±0.25 and 20.15±0.08 per menit, sementara saturasi oksigen masing-masing adalah 97.95±0.16 dan 98.38±0.06%. Lama rawat inap pasien setelah pengobatan oseltamivir dan favipiravir pada pasien non komorbid COVID-19 masing-masing adalah 14,76±0,861 dan 9,96±0,488 hari ($p<0,01$). Sedangkan pada pasien komorbid berturut-turut adalah 16,00±3,17 dan 10,47±0,77 hari ($p<0,01$). Komorbiditas berpengaruh signifikan terhadap rata-rata laju pernapasan dan saturasi oksigen pasien ($p<0,05$). Penggunaan

oseltamivir dan favipiravir memberikan perbedaan yang sangat bermakna terhadap LOS pasien komorbid maupun non komorbid.

Kata kunci: COVID-19, diabetes, antivirus, komorbiditas, luaran klinik.

INTRODUCTION

COVID-19 (Coronavirus Disease-2019) is a disease caused by the SARS-CoV-2 corona virus which primarily spreads through respiratory droplets with the most common symptoms being cough, fever, and shortness of breath with an incubation period of 5, 9, 12, and 19 days. Therefore, experts recommend isolating COVID-19 sufferers for 14 days (Guan et al., 2020; Gupta & Misra, 2020). Until now, no specific antiviral drug for COVID-19 has been found, so the COVID-19 pandemic requires research to quickly find effective therapeutics. One is to test currently known antiviral agents and verify their efficacy. All medication options are based on the experience of treatments such as SARS-CoV, MERS-CoV and influenza viruses (Ramatillah & Isnaini, 2021).

The severity of COVID-19 also varies, from a mild flu-like illness that can heal on its own to fulminant pneumonia, respiratory failure, to death. There is regional variation in COVID-19 mortality rates, and these estimates are changing rapidly as more data becomes available. Based on the situation reported by WHO (World Health Organization) on May 16, 2021, confirmed cases were recorded as 162,184,263 cases, with 3,364,446 deaths worldwide. In Indonesia, 1,736,670 confirmed cases were recorded as of May 16, 2021, with a total death of 47,697 people (Gupta & Misra, 2020). Zhou et al. (2020) found that 54 patients of 191 COVID-19 patients in two hospitals in Wuhan died.

There were 91 patients (48%) who had comorbidity, including hypertension in 58 patients (30%), diabetes in 36 patients (19%), and coronary heart disease in 15 patients (8%). Wu's study (2020) also found that of 84 patients, 4 of them have died, 23 of 84 (27.4%) patients had comorbid hypertension, and 16 of 84 patients (19%) had comorbid diabetes (Wu et al., 2020; Zhou et al., 2020).

Satria and co-workers reported that 66 (18%) of 358 patients confirmed positive for COVID-19 at the Bhakti Dharma Husada Hospital Surabaya were dying. 83.3% of the patients have risk factors for diabetes mellitus and 30.3% of them have risk factors for death (Satria et al., 2020). Docherty (2020) has also conducted studies related to the characterization of patient's clinical outcome and exploring risk factors associated with death caused by COVID-19 infection in a hospital. 77.5% of 20,133 patients had comorbidity. The most common comorbidity of COVID-19 patients was chronic heart disease (31%) and diabetes mellitus (21%).

Factors associated with hospital mortality in COVID-19 patients include increasing age, male gender, obesity, and comorbidities such as diabetes, requiring hospital admissions, and higher levels of care. Early isolation, diagnosis, and early management may collectively contribute to reducing mortality (Guan et al., 2020).

Parapasan (2020) stated in his research that the population with comorbidity was vulnerable to being attacked by COVID-19. The high risk of experiencing Acute Respiratory Distress Syndrome (ARDS) and multiorgan failure in comorbid diabetes can be the main cause of the high mortality rate in patients with comorbid diabetes. The patients stated as COVID-19 infected with comorbid diabetes must carry out a diabetes drug regimen and blood sugar control and continue to live a healthy lifestyle (Parapasan, 2020).

In their meta-analysis study, Lestari and Ichsan (2021) reported that 10,807 COVID-19 patients, 2,129 of them with comorbid diabetes mellitus. Patients with diabetes mellitus could increase the severity of COVID-19 patients by 1.55 times compared to patients without diabetes mellitus in terms of worsening clinical symptoms, length of stay in the hospital, and requiring intensive care. In addition, there was an increase in the number of patients requiring ICU (Intensive Care Unit) treatment 1.49 times more than patients without diabetes mellitus.

COVID-19 patients with diabetes mellitus require 14.4 days of treatment, 1.5 times longer than patients without comorbidity, which require 9.8 days of treatment. In addition to diabetes

mellitus, the severity of COVID-19 is also influenced by several other comorbid factors, i.e. hypertension, male gender, and active smokers (Lestari & Ichsan, 2021).

Ramatillah & Isnaini (2021) have conducted a study of 72 confirmed COVID-19 patients, stating that comorbidity is associated with length of stay and patients clinical outcomes while using different antivirals associated with clinical outcomes of patients.

From the various studies above, it can be concluded that comorbid T2-DM in COVID-19 patients is one of the risk factors that affect the success of therapy and clinical outcomes in COVID-19 patients. Therefore, therapy on COVID-19 patients with or without comorbid diabetes mellitus is a concern by researchers to examine the Analysis of the Impact of Therapy on Clinical Outcomes of Patients with COVID-19 with or without comorbid T-2 DM, so that the level of care needed by patients can be observed.

MATERIALS AND METHOD

Materials

Materials used were medical records of patients obtained from RSUD dr Rasidin Padang. Computer and computer program for analyzing of data.

The inclusion criteria were all confirmed positive COVID-19 in-patients and moderate symptoms with or without comorbid T2-DM with criteria > 18 years of age at RSUD dr Rasidin Hospital. Comorbid T2DM was only included in this research, no other comorbid. Exclusion criteria were patients with medical records that not found or incomplete, 18 years old and below, patients with other comorbidity, patients referred from and to other hospitals, and patients discharged at their own request.

Methods

The research was an analytic observational study with retrospective data collection and performed using cross-sectional design. The population in this study were hospitalized COVID-19 patients at RSUD dr Rasidin Padang from April 2020 to March 2021, confirmed positive for COVID-19 by PCR test with or without comorbid T2DM. Samples were determinated using a stratified sampling technique. Sampling was performed by dividing the population into strata, selecting a simple random sample from each stratum, and combining it into a sample (Maturoh et al., 2018). The population of without comorbid T2DM was 439 patients, while with comorbid was only 33 patients. Samples was calculated using Daniel-Cross equation (Daniel & Cross, 2019). The samples of without comorbid and with comorbid COVID-19 were 197 and 33 patients, respectively.

The data were analyzed by descriptive quantitative analysis. Percentage and frequency were used for categorical variables (gender and type of drug used). The average value and standard deviation were used for patient clinical outcome variables i.e respiratory rate, oxygen saturation, pulse rate, body temperature, and length of stay. The ANOVA (Analysis of Variance) statistical test was used to evaluate the impact of comorbidity and therapy on the patient's clinical outcome. If the ANOVA assumption was not met, then the analysis was continued with the Kruskal Wallis and Friedman. The level of significant and highly significant used was 0.05 and 0.01, respectively.

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RESULT AND DISCUSSION

Figure 1 showed the characteristics of COVID-19 patients at Rasidin Hospital.

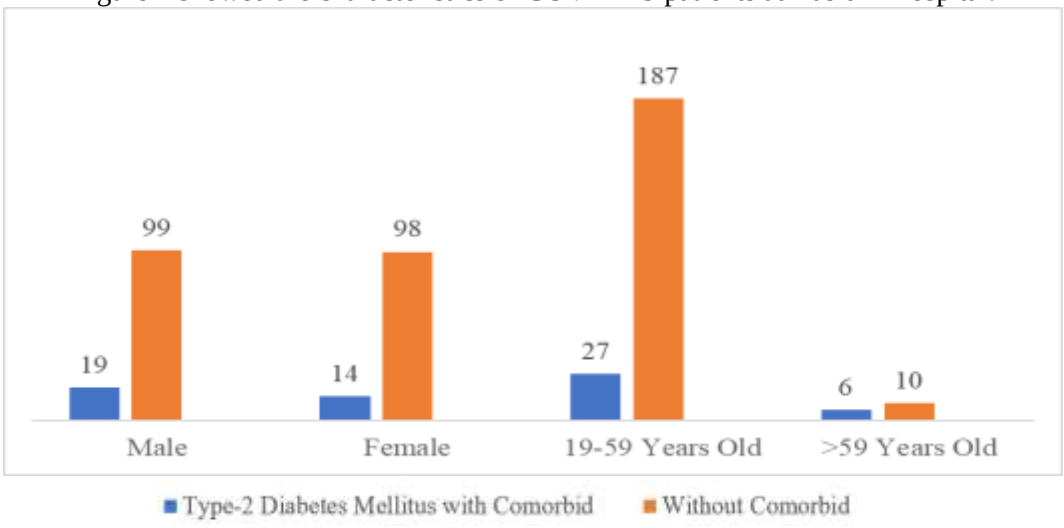

Figure 1. Characteristics of COVID-19 patients

These results were consistent with the reports of Ducerty's (2021) study, which evaluated the characteristics of COVID-19 patients in hospitals in the United Kingdom, where the number of male patients was more (59.9%) than female patients (40.1%) (Docherty et al., 2020). Abdallah (2021) also compared the characteristics and outcomes of COVID-19 patients without comorbid and comorbid T2-DM, and it was found that there were more male patients (52%) in patients without comorbid T2-DM and (62.6%) in patients with T2-DM (Al-Salameh et al., 2021). In addition, the prevalence of symptomatic COVID-19 was found to be higher in men than women. The high prevalence of smoking and alcohol consumption contributes to the high prevalence of COVID-19 among men.

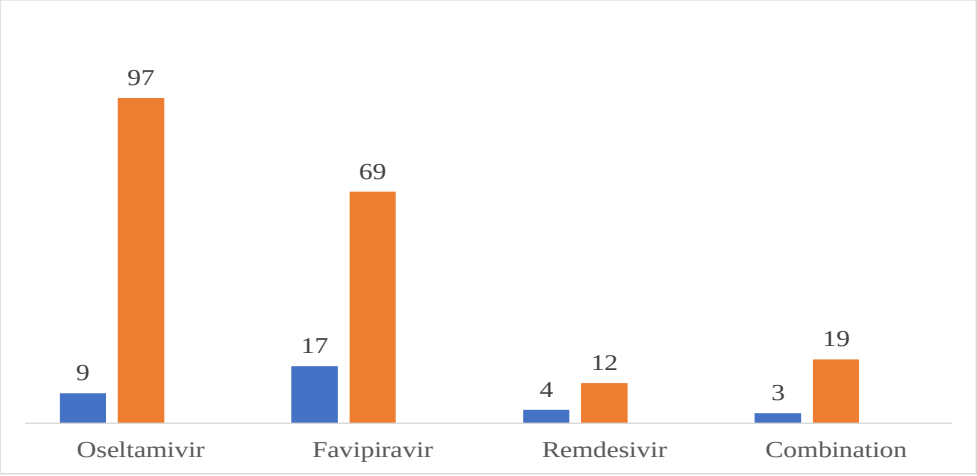

Figure 2. Profile of therapy received by patients.

Overall, th r, favipiravir, combination therapy, and remdesivir (Figure 2). The therapy profile of comorbid and non-comorbid Covid-19 was following the guideline available in Indonesia i.e *Pedoman Tatalaksana* COVID-19. Wang et al. (2020) found that 82.3% of the total COVID-19 patients used antiviral therapy (Wang et

al., 2020). Arief (2021) and Kusumawardani (2021) in their research reported that the antivirals oseltamivir and favipiravir were the most widely used antivirals in COVID-19 patients in 2020 (Arief et al., 2021; Kusumawardani et al., 2021).

Based on the COVID-19 Management Guidelines First Edition issued in May 2020, oseltamivir and favipiravir are recommended antivirals for use in patients with moderate symptoms of COVID-19, followed by using of chloroquine or hydroxychloroquine. However, in the Third Edition of the COVID-19 Management Guidelines issued in December 2020 and subsequently revised in July 2021, the Fourth Edition of the COVID-19 Management Guidelines, and the COVID-19 Drug Informatorium in Indonesia published in September 2021, chloroquine, hydroxychloroquine, and oseltamivir are no longer included in the treatment of moderately symptomatic COVID-19. Then the recommended antiviral for moderate symptoms of COVID-19 patients is remdesivir. If no remdesivir is available, the antiviral administration is substituted with favipiravir, molnupiravir, or nirmatrelvir/ritonavir (PDPI et al., 2020a, 2020b; Wang et al., 2020; Arief et al., 2021; Food and Drug Supervisory Agency, 2021; Kusumawardani et al., 2021; Burhan et al., 2022;). However, because the research data taken were from March 2020 to April 2021, the most widely used therapies are oseltamivir, favipiravir, and remdesivir.

In Indonesia, oseltamivir and favipiravir are the options for COVID-19 patients with mild to critical symptoms. The combination of lopinavir + ritonavir or remdesivir can be used as an alternative option. Oseltamivir is recommended because these drugs are easily found in Indonesia and are already produced domestically (Lukito, 2020). Therefore, research on the impact of antivirals on clinical outcomes of COVID-19 patients as consideration for COVID-19 management is eeded to be carried out.

Table 1. Impact of Age and Sex on Patient's Length of Stay (LOS)

Characteristics	Length of Stay (days) Average ± SE	*p-value*
Age (years)		
- **Non-Comorbid**		
19-59	13.29 ± 0.536	0.832
≥60	14.00 ± 3.152	
- **Comorbid T2-DM**		
19-59	12.30 ± 1.238	0.655
≥60	14.33 ± 5.181	
- **Total**		
19-59	13.16 ± 0.493	0.747
≥60	14.13 ± 2.661	
Sex		
- **Non Comorbid**		
Male	13.39 ± 0.762	0.805
Female	13.26 ± 0.743	
- **Comorbid T2-DM**		
Male	12.89±1.896	0.927
Female	12.36±1.918	
- **Total**		
Male	13.31±0.705	0.830
Female	13.14±0.690	

Mann-Withney U test

There was no significant impact of age and gender on the length of stay of COVID-19 patients without comorbid or with comorbid T2-DM (p>0.1). Male and female patient's average length of stay in RSX Padang were 13.31 ± 0.705 and 13.14 ± 0.690 days, respectively (Table 1). This was in line with Diana's (2021) research that there is no relationship between age and gender with the patient's length of stay (Ramatillah & Isnaini, 2021). However, Marliana & Marliani (2021) reported that patients aged >60 years received the longest length of treatment compared to younger age categories (Marliana & Marliani, 2021). This number may be due to the unequal proportion of age categories. Voinsky et al. (2020) wrote that women are less likely to develop severe acute respiratory distress (ARDS) or a fatal outcome due to SARS-CoV-2 infection than men. The reason for this sex difference is still unclear, but it is stated that higher androgen hormones in men than in women drive the transcription of TMPRSS2, a protease encoding gene important for SARS-CoV-2 entry (Voinsky et al., 2020).

Table 2. Impact of Comorbidity on Patient's Length of Stay

Characteristics	Length of Stay (days) Average ± SE	*p-value*
Comorbidity		
No Comorbid	13.32±0.531	0.506
Comorbid T-2DM	12.67±1.342	

There was no significant effect of comorbidity on patient length of stay (p>0.1). Guan et al (2020) reported that the median of the length of stay for COVID-19 patients with non-severe symptoms was 11 (10-13) days. While, Arief (2021) also reported that patients with moderate symptoms had an average length of stay of 12.5 ± 4.27 days.

Baihaqi and Rumaropen (2021) reported that there was no significant relationship between the presence of comorbid diabetes mellitus and the length of stay of COVID-19 patients (p> 0.1) (Baihaqi & Rumaropen, 2021; Raghavan et al., 2021). This result is different from the study of Al-Salameh (2020), which compared the length of stay of COVID-19 patients with and without comorbid T2-DM. The researchers reported that there were differences that tended to be significant (p < 0.1), where the length of stay of patients with comorbid T2-DM was longer than that without comorbidity (Al-Salameh et al., 2021). While, Nafakhi and co-workers (2021) with the same subject found that there was a significant difference (p<0.05) in the length of stay of COVID-19 patients with comorbid Type Diabetes Mellitus with patients without comorbid T2-DM, where patients with T2-DM have a longer average length of stay (Nafakhi et al., 2021).

This result occurs due to differences in patient conditions, such as differences in the period of exposure to symptoms and time of hospital admission, age, gender, and the presence of comorbidity. For example, Thiruvengadam et al. (2021) found that patients with comorbidity of more than two chronic diseases had a significant relationship with the patient's length of stay (Ramatillah & Isnaini, 2021; Thiruvengadam et al., 2021).

Table 3. Impact of Comorbidity on The Patient's Heart Rate, Respiratory Rate, Body Temperature, and Oxygen Saturation

Comorbidity	Heart Rate Average±SE	N	*p-value**
Without Comorbid	86.53±0.65	197	0.396
Comorbid T2-DM	88.07±1.89	33	
Comorbidity	**Respiratory Rate Average±SE**	**N**	
Without Comorbid	20.15±0.08	197	0.014*
Comorbid T2-DM	20.58±0.25	33	

Comorbidity	**Body Temperature Average±SE**	N	
Without Comorbid	36.388±0.02	197	0.617
Comorbid T2-DM	36.386±0.06	33	
Comorbidity	**Oxygen Saturation Average±SE**	**N**	
Without Comorbid	98.381±0.06	197	0.007*
Comorbid T2-DM	97.950±0.16	33	

There was no significant effect of comorbidity on the patient's average heart rate ($p>0.1$) (Table 3). Wang et al. (2020) found that the average heart rate of recovered COVID-19 patients was 90 beats/minute. 16.1% of the sample had a major comorbid T2-DM (Wang et al., 2020). Zhou et al. (2020) found that none of the recovered patients had a heart rate of 125 beats/minute (Zhou et al., 2020). Maloberti and co-workers (2021) found a decrease in the patient's average heart rate at admission and after returning from the hospital. The average heart rate at admission and after returning from the hospital was 90±18 and 80±2 beats per minute, respectively (Maloberti et al., 2021). Because in this study, the sample was a patient with moderate symptoms with not severe pneumonia, the clinical condition of the patient could be categorized as not bad.

There was a significant effect of comorbidity on the patient's average respiratory rate ($p<0.05$). However, Nafakhi and co-workers (2021) looked at the outcome and improvement of COVID-19 patients with or without Type Diabetes Mellitus in their study. They found no significant differences in symptoms of shortness of breath in patients with or without comorbid diabetes mellitus (Nafakhi et al., 2021).

Individuals with diabetes have elevated ACE-2. Acute hyperglycemia increases ACE-2 expression, which will increase viral binding. In contrast, chronic hyperglycemia is known to down regulate ACE-2 and make the cells susceptible to the inflammatory effects and damage of the virus (Kun'ain et al., 2020). This process can be attributed to the possibility of an increased respiratory rate.

There was no significant effect of comorbidity on the patient's average body temperature ($p>0.1$) (Table 3). These results were in accordance with Nafakhi's (2021) study. The researcher evaluated the outcome and improvement of COVID-19 patients with or without T2-DM. There were no significant differences in fever symptoms in patients with or without comorbid T2-DM (Nafakhi et al., 2021). Guo et al. (2020) also found no significant difference in temperature in patients with and without comorbid T2-DM. However, there was a significant difference in body temperature without comorbid compared with comorbid T2-DM COVID-19 patients and with other comorbidities. This result indicates that other comorbidity affects the patient's body temperature (Guo et al., 2020).

The impact of comorbidity was significant ($p<0.05$) on the patient's oxygen saturation (Table 5). Bagi and co-workers (2021) reported that the average percentage of oxygen saturation in COVID-19 patients with moderate symptoms was 94.91 ± 2.09% (Bagi et al., 2021). Maloberti et al. (2021) also reported that the patient's average oxygen saturation at admission and discharge was 95±4% and 97±2%, respectively (Maloberti et al., 2021). Mejia and co-workers (2021) also found that out of 186 cured patients, 60.22% of patients had an oxygen saturation of 90% and 35 had comorbid diabetes (Mejía et al., 2020). While Fata and Febriana (2021) evaluated the oxygen saturation in COVID-19 patients. Out of 185 patients, 41.4% did not have hypoxemia or an oxygen saturation of 95%, while more had hypoxemia or oxygen saturation <95% (Fata & Febriana, 2021).

Minuljo and co-workers (2020) observed the characteristics and outcomes of COVID-19 patients with T2-DM and found that the average oxygen saturation of recovered patients was 91.1%. The researchers also reported that patients with mild to moderate symptoms were treated in isolation.

As a results, there were almost entirely able to discharge from the hospital in good condition (Minuljo et al., 2020). In this study, the samples were COVID-19 patients with moderate symptoms, according to the COVID-19 Management Guidelines, had an oxygen saturation of 93% (Burhan et al., 2022).

Table 4. Impact of Antiviral Therapy on the Patient's Length of Stay

Characteristics	Length of Stay (days) Average ± SE	*p-value**
Antiviral Therapy		
- **Without Comorbid**		
Oseltamivir	14.76 ± 0.861	0.000[2*]
Favipiravir	9.96 ± 0.488	
Combination	17.16 ± 1.839	
Remdesivir	15.00 ± 1.741	
- **Comorbid Type 2 Diabetes Mellitus**		
Oseltamivir	16.00±3.167	
Favipiravir	10.47± 0.768	0.353[2]
Combination	19.67 ±10.269	
Remdesivir	9.25 ± 0.946	
- **Total**		0.000[2*]
Oseltamivir	14.87±0.828	
Favipiravir	10.06 ±0.419	
Combination	17.50 ±1.977	
Remdesivir	13.56 ±1.458	

There was a significant impact of the type of antiviral on the length of stay of COVID-19 patients without comorbidity and cumulative total patients ($p<0.05$). This result was in line with the results of the study by Marliana & Marliani (2021), a study conducted in Japan (2021), and Ivashchenko et al. (2021) stated that the average length of stay using favipiravir was shorter than patients receiving placebo, oseltamivir, or standard therapy (Ivashchenko et al., 2021; Marliana & Marliani, 2021). However, Bosaeed and co-workers (2021) reported that favipiravir therapy in moderately symptomatic COVID-19 patients did not shorten the viral clearance time within 15 days of treatment (Bosaeed et al., 2020). Furthermore, Arief (2021) also found that the drug use group had a non-significant relationship with the patient's length of stay, where two of the four groups were in the category of antiviral therapy (Arief et al., 2021).

Table 5. Impact of Antivirals on The Patient's Pulse, Respiratory Rate, Body Temperature, and Oxygen Saturation

Comorbidity	Antiviral Therapy	Heart Rate Average±SE	N	*p-value**
Without Comorbid	Oseltamivir	86.3470±1.039	97	0.352
	Favipiravir	87.4106 ±0.885	69	
	Combination	84.3333 ±1.950	19	
	Remdesivir	86.4167± 2.934	12	
Comorbid T2-DM	Oseltamivir	92.4815 ±3.360	9	0.125
	Favipiravir	83.8824 ±2.627	17	
	Combination	95.7778 ±1.736	3	
	Remdesivir	90.1667 ±5.816	4	
Comorbidity	**Antiviral Therapy**	**Respiratory Rate Average±SE**	**N**	***p-value****
Without Comorbid	Oseltamivir	20.093±0.080	97	0.720
	Favipiravir	20.109±0.145	69	

	Combination	20.311±0.296	19	
	Remdesivir	20.600±0.579	12	
	Oseltamivir	20.767±0.246	9	
Comorbid T2-DM	Favipiravir	20.741±0.412	17	0.592
	Combination	19.633±1.202	3	
	Remdesivir	20.175±0.335	4	
Comorbidity	**Antiviral Therapy**	**Body Temperature Average±SE**	**N**	***p-value****
	Oseltamivir	36.400±0.023	97	
Without Comorbid	Favipiravir	36.324±0.031	69	0.005*
	Combination	36.539±0.064	19	
	Remdesivir	36.414±0.067	12	
	Oseltamivir	36.592±0.173	9	
Comorbid T2-DM	Favipiravir	36.300±0.062	17	0.169
	Combination	36.122±0.128	3	
	Remdesivir	36.483±0.106	4	
Comorbidity	**Antiviral Therapy**	**Oxygen Saturation Average±SE**	N	***p-value****
	Oseltamivir	98.546±0.059	97	
Without Comorbid	Favipiravir	98.261±0.098	69	0.001*
	Combination	98.246±0.307	19	
	Remdesivir	97.944±0.183	12	
	Oseltamivir	97.889±0.329	9	
Comorbid T2-DM	Favipiravir	98.078±0.211	17	0.809
	Combination	97.889±0.294	3	
	Remdesivir	97.583±0.762	4	

There was no significant effect of antiviral on the average heart rate of COVID-19 patients ($p>0.1$) without comorbidity and COVID-19 patients with comorbid T2-DM (Table 5). The patient's overall heart rate was within the normal heart rate range. Garibaldi et al. (2021) reported that there was a significant difference in the median heart rate of COVID-19 patients before remdesivir therapy (97.6±18.0 beats/minute) compared to controls (96.9±19.5 beats/minute) and after treatment of remdesivir (96.4±19.6 beats/min) compared to controls (97.7±18.7 beats/min) (Garibaldi et al., 2021). Brunetti and co-workers (2021) also found a significant decrease in heart rate of COVID-19 patients treated with remdesivir compared to basic therapy (Brunetti et al., 2021). Maloberti et al. (2021) reported no significant relationship between the use of chloroquine/hydroxychloroquine on the patient's heart rate (Maloberti et al., 2021).

There was no significant effect of antivirals on COVID-19 patients respiratory rate ($p>0.1$) without comorbidity and COVID-19 patients with comorbid T2-DM (Table 5). There was a significant effect of antiviral on the average body temperature of COVID-19 patients without comorbidity ($p<0.05$), but no antiviral effect on the average of the patient's body temperature ($p>0.1$) on COVID-19 patients with comorbid Type-2 Diabetes Mellitus (Table 6). In addition, Garibaldi et al. (2021) found that there was an insignificant difference in the median body temperature of patients before remdesivir therapy compared to controls. However, there was a significant difference in average body temperature after receiving remdesivir therapy (37.8 ± 0.8) compared to control (37.9±0.9) (Garibaldi et al., 2021).

Antiviral use's significant impact on the average oxygen saturation ($p<0.05$) on COVID-19 patients without comorbidity treated with oseltamivir showed the highest mean oxygen saturation

compared to the use of other antivirals. But, there was no effect of antiviral use on the average of oxygen saturation (p>0.1) on COVID-19 patients with comorbid T2-DM (Table 5). No references were found related with the effect of antiviral use on the oxygen saturation.

Patients with Type Diabetes Mellitus hospitalized with COVID-19 infection tend to have more severe forms of infection and hyperglycemia resulting in poor outcomes. Diabetic patients with multiple comorbid conditions are more likely to have a severe infection that results in higher adverse outcomes (Raghavan et al., 2021). Izzi-Engbeaya (2020) stated that diabetes alone was not the main factor contributing to the risk of death/ICU admission. Still, there was a relationship with metabolic syndrome, especially Iskemic Heart Disease (IHD) which gave a higher risk of poor outcomes (Izzi-Engbeaya et al., 2021).

Research conducted on comorbidity and antiviral therapy for COVID-19 patients with or without comorbid T2-DM on the clinical outcomes of patients in terms of length of stay and vital signs (pulse, respiratory rate, body temperature, and oxygen saturation) of patients during patient care is expected to be able to represent reality. The results of this study strengthen the evidence that comorbidity and antiviral therapy were factors that affect the clinical outcome of COVID-19 patients with or without comorbid T2-DM.

CONCLUSION

It can be concluded that there was a significant impact of comorbidity on the patient's average respiratory rate and oxygen saturation. The use of oseltamivir and favipiravir had a highly significant different on the LOS of comorbid and non-comorbid patients.

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