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ORIGINAL RESEARCH

Remdesivir versus Favipiravir in Hospitalized Patients with Moderate to Severe COVID-19 Pneumonia: A Propensity Score-Matched Retrospective Cohort Study

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Background: Remdesivir treatment was associated with a reduced 28-day mortality and recovery time among patients hospitalized with severe COVID-19. Favipiravir is broadly used to treat COVID-19. However, various studies have had conflicting results on the efficacy of favipiravir for COVID-19. We hypothesized that remdesivir is more effective in clinical outcomes regarding the 29-day mortality rates, length of stay, and recovery rate than favipiravir in patients with moderate to severe COVID-19 pneumonia.

Methods: We performed a retrospective cohort study that included adult hospitalized COVID-19 pneumonia patients with hypoxemia. Patients were classified into two groups according to the antiviral drugs. Age, oxygen saturation, fraction of inspired oxygen, and Charlson comorbidity index were used for propensity score matching. The primary objective was to determine whether the type of antiviral agent is associated with 29-day mortality. Other outcomes were the 15-day recovery rate and the length of intensive care unit or hospital stay.

Results: A total of 249 patients with moderate to severe COVID-19 pneumonia were included. With an adjustment for propensity score-matched, there were 204 patients for further analysis (102 patients in each antiviral drug group). Remdesivir patients had higher Radiographic Assessment of Lung Edema (RALE) scores on Chest X-ray (14.32±9.08 vs 11.34±8.46; standardized mean difference =33.9%). The Charlson Comorbidity Index Scores were comparable. The prevalences of diabetes, obesity, hypertension, and non-HIV immunocompromised state were higher in the remdesivir group. Regarding the primary outcomes, after adjusting by diabetes, obesity, and RALE score, there was no difference in the 29-day mortality rate between both groups [26 patients (25.5%) in the remdesivir group vs 28 patients (27.5%) in the favipiravir group]. The Kaplan-Meier curve analysis at 29 days indicated no significant difference in cumulative survival rate. The two groups' adjusted hazard ratio was 0.72; 95% CI, 0.41 to 1.25, p=0.24. A Kaplan-Meier analysis on the 15-day cumulative survival rate observed a trend towards a higher survival rate in the remdesivir group (adjusted hazard ratio 0.41; 95% CI, 0.20 to 0.84; p= 0.02) The proportion of patients who recovered on day 15, the length of intensive care unit(ICU) stays, and the hospital stay were not different between remdesivir and favipiravir groups (62 patients (60.8%) vs 56 patients (54.9%), p=0.39; 11.48 ± 11.88 days vs 10.87 ± 9.31 days, p=0.69; and 16.64±14.28 days vs 16.59 ±11.31 days, p=0.98, respectively).

Conclusion: In patients with moderate to severe COVID-19 pneumonia, Remdesivir did not demonstrate superior benefits over Favipiravir regarding 29-day mortality, 15-day recovery rates, or hospital and ICU stay lengths. However, further investigation into the 15-day cumulative survival rate revealed a trend towards improved survival in the Remdesivir group.

Keywords: remdesivir, favipiravir, moderate to severe COVID-19 pneumonia

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Introduction

The global pandemic Coronavirus disease 2019(COVID-19) was officially declared by the World Health Organization (WHO). The outbreak has profoundly impacted the healthcare and socioeconomic systems of many countries.[1] Studies on COVID-19 fatality rates among hospitalized patients have shown variations over time. The reports from 2020 to 2021 indicated mortality rates of around 17 to 50%. A study in 2023 stated that the global hospital mortality rate of COVID-19 among general patients was 16%, with variations observed across different geographic areas.[2] Several therapeutic strategies have been attempted, including antiviral drugs, corticosteroids, and immunomodulator therapy.[3]

The rationale behind using antiviral agents in treating COVID-19 is inhibiting viral replication, reducing disease severity, and mitigating cytokine storms by dampening the exaggerated immune response. Early administration of antiviral drugs during the initial stages of infection may help to curb viral replication and decrease the spread of the virus in the body. This approach can prevent the development of severe complications and reduce the overall burden of the disease.[4]

Remdesivir, the antiviral medication, contains an active metabolite that disrupts the activity of viral ribonucleic acid (RNA)-dependent RNA polymerase, halting RNA synthesis and reducing the replication of the virus.[5,6] Recently, two randomized controlled trials (RCT)s have demonstrated that remdesivir, either alone or in combination with baricitinib, is more effective than a placebo or routine supportive treatment in reducing the time to recovery of COVID-19 patients.[7,8] Remdesivir has substantial evidence supporting its efficacy in treating outpatients at high risk for disease progression and moderate and severe COVID-19 cases. It improves recovery time in hospitalized patients, potentially provides a mortality benefit for patients with minimal oxygen requirements, and reduces the risk of hospitalization or death in outpatients at high risk for disease progression.[9]

In the retrospective cohort study of 24,856 patients with COVID-19 and propensity score–matched control patients in the United States, remdesivir treatment was associated with a significantly reduced 28-day mortality among patients hospitalized with severe COVID-19.[10]

Many countries, including Thailand, have recommended using remdesivir and corticosteroids to treat hospitalized COVID-19 pneumonia patients with hypoxemia.[11] However, the WHO had conditionally recommended using remdesivir to treat COVID-19 pneumonia, citing data from the WHO Solidarity trial[12] that demonstrated no reduction in mortality rates among COVID-19 pneumonia patients treated with remdesivir.[13]

Favipiravir is another antiviral agent that targets RNA polymerase. It has been utilized to treat influenza and is associated with reduced time to alleviate illness.[14,15] It has also been used as a treatment option for symptomatic COVID-19. Before November 30, 2022, Thailand's Department of Medical Services had launched a COVID-19 treatment guideline that recommended favipiravir for mild symptomatic COVID-19.[11] There have been conflicting results on the efficacy of favipiravir as a treatment for COVID-19 across various studies. In a retrospective observational study, patients treated with favipiravir exhibited a Day-7 clinical improvement rate of 66% and a 4.8% 28-day mortality rate.[16] Real-world data analysis in Thailand demonstrated that favipiravir monotherapy outperformed supportive treatment, shortening recovery time in early symptomatic COVID-19 patients and reducing the 28-day mortality risk in severe COVID-19.[17] Whereas, in mild to moderate COVID-19, there was no difference in the time to sustained clinical recovery between patients who received favipiravir compared with placebo.[18] In a prospective observational cohort study, favipiravir treatment is associated with a more extended hospital stay and a higher mortality rate compared to treatments not involving favipiravir.[19] A multicenter RCT reported that compared with a placebo, favipiravir does not reduce the time of recovery in patients admitted to hospital with COVID-19.[20]

We aimed to compare the efficacy of remdesivir and favipiravir in terms of mortality outcomes, length of hospital stay, and recovery rate. We hypothesized that remdesivir is more effective in clinical outcomes regarding the 29-day mortality rates, length of stay, and recovery rate than favipiravir in hospitalized patients with moderate to severe COVID-19 pneumonia. Therefore, we conducted a propensity score-matched retrospective study to compare these parameters.

Materials and Methods

Design

Study Population

A retrospective cohort study was performed on 300 adult patients. The inclusion criteria were those older than 18 and admitted to the intensive-care unit (ICU) of Ramathibodi Hospital with moderate to severe COVID-19 pneumonia; this study had no upper age limit. COVID-19 infection confirmed by a positive COVID-19 real-time reverse-transcriptase polymerase chain reaction test of nasopharyngeal swab. Disease severity is determined by World Health Organization (WHO) criteria.[21] Moderate COVID-19 pneumonia is characterized by clinical signs of pneumonia, chest imaging (radiograph, computer tomography scan, ultrasound) for assisting in diagnosis, and no signs of severe pneumonia, including oxygen saturation (SpO_2) ≥ 90% on room air. For a diagnosis of severe COVID-19 pneumonia, one of the following conditions must be present: a respiratory rate exceeding 30 breaths per minute, severe respiratory distress, or a SpO_2 level below 90% while breathing room air.

The exclusion criteria were pregnant patients, those who denied treatment, those who received both antiviral drugs, those who received all other anti-SARS-CoV-2 agents, and patient data not accessible through the hospital electronic database from the study.

The study was conducted in 2021. The institutional COVID-19 treatment guidelines recommend prescribing favipiravir as an antiviral agent until June 30, 2021; after that date, remdesivir was recommended for moderate to severe COVID-19 pneumonia.

Given the ongoing uncertainty regarding the ideal dosage of favipiravir for COVID-19 treatment, the 2020 Thailand National Clinical Practice Guidelines suggested an initial fixed oral loading dose of 1600 mg twice daily on Day 1, followed by 600 mg twice daily from Days 2 to 10. Patients with a BMI of ≥35 may require a higher loading dose (60 mg/kg/day, MKD) and maintenance dose (20 MKD).[16] The initial administration of Remdesivir consists of a 200 mg intravenous loading dose on the first day, followed by a continuous daily IV dose of 100 mg for up to 9 additional days.[22]

The Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, approved this study (COA. MURA2021/859). Due to the study's retrospective nature, the ethics committee has waived the requirement of the informed consent process. The research involves no more than minimal risk to the subjects. We confirmed that the data was anonymized and maintained with confidentiality and compliance with the Declaration of Helsinki.

Sample Size Calculation

To determine the appropriate sample size, we retrospectively collected the preliminary data in our hospital to estimate the crude mortality rate, as no previous studies were available to compare the mortality rates of COVID-19 between the use of remdesivir and favipiravir as antiviral agents in moderate to severe COVID-19 pneumonia patients. We performed the pilot survey and collected data from 24 patients who received remdesivir and 26 who received favipiravir in our hospital. The 29-day mortality rate was 8.3% and 34.6% for the remdesivir and favipiravir groups, respectively. The obtained mortality rates were used to estimate the required sample size using a statistical power of 90% and a two-sided *P*-value of 0.05. It was determined that a minimum of 75 patients per group would need to be enrolled to detect a statistically significant difference in mortality rates between the use of remdesivir and favipiravir.

Study Variables

The data collected for this study included demographic characteristics such as age, sex, Body mass index, underlying disease, Charlson comorbidity index score,[23] smoking status, and COVID-19 vaccination status. Additionally, we recorded COVID-19 treatment-related information, namely the date of infection, the date of antiviral medication administration, S_PO_2 and a fraction of inspired oxygen (F_IO_2) levels upon admission, as well as the type of antiviral agent, and the dosage and type of systemic corticosteroids and immunomodulating agents administered. The clinical data for the first 15 days of admission was also gathered, including the WHO ordinal clinical severity scale, laboratory results, complete blood count, C-reactive protein, liver function test, creatinine and estimated glomerular filtration rate, D-dimer and lactate dehydrogenase. The Radiographic Assessment of Lung Edema (RALE) scores on Chest X-ray (CXR)s were collected upon

admission.[24] An experienced pulmonologist (Y.S.) scored the first available CXRs. The CXR divided lung fields into quadrants following the RALE score protocol. Each quadrant was assigned a number, and the extent (consolidation score, from 0 to 4) and density of alveolar opacities were determined (from 0 to 3). The final RALE score, ranging from 0 to 48, was calculated by summing the product of consolidation and density scores for each quadrant.[25]

The WHO ordinal clinical severity scale for COVID-19 ranges from level 0, which denotes an absence of clinical or virological evidence of infection, to level 8, which means death. There are intermediate categories between these, including level 1 for ambulatory patients without activity restrictions, level 2 for non-hospitalized patients with activity limitations or home oxygen requirement, level 3 for hospitalized patients who no longer require ongoing medical care or supplemental oxygen, level 4 for hospitalized patients who need continuing medical care but not supplemental oxygen, level 5 for hospitalized patients who require low flow supplemental oxygen, level 6 for hospitalized patients who need non-invasive ventilation or high-flow oxygen devices, and level 7 for hospitalized patients who require intubation and invasive mechanical ventilation, and other forms of support like vasopressors or extracorporeal membranous oxygenation.[26]

Finally, treatment outcomes were recorded, including mechanical ventilator use and complications such as hospital-acquired pneumonia, sepsis, pneumothorax, acute respiratory distress syndrome, acute kidney injury, in-hospital death, time to death, and time to improvement.

Outcomes

The study's primary objective was to compare the 29-day mortality rates of patients based on the type of antiviral drugs, favipiravir or remdesivir, they received. The secondary outcomes were the length of hospital stay, ICU stay, and the recovery rate at day 15 between patients who received favipiravir or remdesivir. The study's definition of recovery or improvement relied on two criteria: 1) a minimum reduction of one level in the WHO ordinal clinical severity scale at admission and 2) gaining a score level between 0 and 4.

Statistical Analysis

Propensity-score estimation was performed to mitigate bias in a retrospective study. A propensity score was estimated for each participant in the study using logistic regression to predict the likelihood of receiving the treatment based on potential covariates, including the severity of COVID-19 pneumonia, encompassing age, S_PO_2, F_IO_2 at admission, and the Charlson comorbidity index score. After calculating the propensity scores, participants in the favipiravir and remdesivir groups were matched based on their propensity scores using a caliper of 0.1. The standardized mean difference (SMD) was used to assess the balance of covariates after matching—the SMD of <10% was considered acceptable.

The categorical variables were converted into numerical values represented as percentages and analyzed using the Chi-square test with a significance level of $p < 0.05$. The continuous variables were presented as mean ± standard deviation (S.D.) or median [interquartile range] and compared using an independent *t*-test with a significance level of *P*-value less than 0.05. The mortality and recovery rates were analyzed using hazard ratio, risk ratio, and 95% confidence interval (CI). The cumulative 29-day survival rate was estimated using the Kaplan-Meier method with the Cox regression statistic. All analyses were conducted using SPSS software version 18 and Stata version 18 (StataCorp).

Results

Patients and Baseline Characteristics

The study included electronic documents from 300 patients from April to August 2021. The delta-variant SARS-CoV-2 was the prevalent strain spreading in Thailand. After excluding fifty-one patients according to the exclusion criteria, data was collected from 249 patients (49.8% female, mean age 62.05±14.65 years): 125 received favipiravir, and 124 received remdesivir. Notable baseline characteristics include diabetes (109, 43.8%), hypertension (168, 67.5%), and a mean body mass index of 27.52±6.62 kg/m2. At baseline, before the propensity score matched, 94.8% were diagnosed with severe COVID-19 pneumonia. The percentage of obese patients and the RALE score were higher in the remdesivir group than in the favipiravir group (66.9% vs 52.0%, SMD=30.7%, 15.05±9.69 vs.11.41±8.36; SMD=40.1%, respectively). The

days of infection at admission in the remdesivir group were longer than the favipiravir group (6.95 ± 2.97 days vs 5.33 ± 3.07 days; SMD=53.7%). Only three patients in this study (two in the favipiravir group and one in the remdesivir group) received COVID-19 vaccines. All patients received corticosteroids to treat COVID-19 pneumonia (Table 1).

Propensity Scores Matched Patients

After applying propensity score matching by age, S_PO_2, F_IO_2, and Charlson comorbidity index score, the mean age was 62.02±14.57, and 50% were female (Table 1). Each group included one hundred and two patients for further analysis (Figure 1). Days of infection at admission were still more prolonged in the remdesivir group than in the favipiravir group for both groups (6.83±3.01 days for remdesivir vs 5.38±3.23 days for favipiravir; SMD=46.6%). The timings of the antiviral treatment initiation were similar for both groups. Proportions of moderate and severe COVID-19 pneumonia were comparable across the treatment groups. Remdesivir patients had higher RALE scores (14.32±9.08 vs 11.34±8.46; SMD=33.9%). The Charlson Comorbidity Index Scores were comparable. The prevalences of comorbidities like diabetes, obesity, hypertension, and non-HIV immunocompromised state were higher in the remdesivir group.

In comparison, the prevalence of chronic lung disease and bedridden status were higher in the favipiravir group. Vaccination rates were comparable between the groups. Finally, the usage of corticosteroids, Tocilizumab, and JAK 2 inhibitors was similar across both treatment groups (Table 1).

Outcomes

Despite the authors' efforts to apply propensity score matching with age, S_PO2, F_IO_2, and Charlson comorbidity index, an imbalance between the groups was nonetheless observed. Consequently, the primary outcome was analyzed by adjusting for these variables (including diabetes, obesity, and RALE score) in the final model using a multivariable Cox proportional hazards regression model.

Regarding the primary outcomes, after adjusting by diabetes, obesity, and RALE score, there was no difference in the 29-day mortality rate between both groups [26 patients (25.5%) in the remdesivir group vs 28 patients (27.5%) in the favipiravir group]. The Kaplan-Meier curve analysis indicated no significant difference in cumulative survival rate. The two groups' adjusted hazard ratio was 0.72; 95% CI, 0.41 to 1.25. (Figure 2). A Kaplan-Meier analysis on the 15-day cumulative survival rate observed a trend towards a higher survival rate in the remdesivir group (adjusted hazard ratio 0.41; 95% CI, 0.20 to 0.84; p= 0.02) (Figure 3)

After propensity score matching, the proportion of patients who recovered on day 15, the length of ICU stays, and the hospital stay were not different between remdesivir and favipiravir groups [62 patients (60.8%) vs 56 patients (54.9%), p=0.39; 11.48 ± 11.88 days vs 10.87 ± 9.31 days, p=0.69; and 16.64±14.28 days vs 16.59 ±11.31 days, p=0.98, respectively] (Table 2). The need for invasive mechanical ventilation was lower in the remdesivir group but did not meet statistical differences. Additionally, in intubated patients, the duration of invasive mechanical ventilation was shorter for the favipiravir group. The univariate and multivariate analyses found no statistically significant correlation or association between the variables and mortality rate.

Regarding complication events throughout the study period, there was no difference in the presence of hospital-acquired pneumonia, septic shock, pneumothorax, acute respiratory distress syndrome, or acute kidney injury between the two groups (Table 3).

Discussion

Our analysis revealed no significant differences between remdesivir and favipiravir regarding the reduction of the 29-day mortality rate, 15-day recovery rate, the need for invasive mechanical ventilation, and length of ICU or hospital stay in patients with moderate to severe COVID-19 pneumonia. There was a trend toward decreasing the need for invasive mechanical ventilation in the remdesivir group, but it was not statistically significant. However, in intubated patients, patients in the remdesivir group had a longer duration of mechanical ventilation.

However, our analysis of the Kaplan-Meier curve, after adjusting for the presence of diabetes, obesity, and RALE score, represented the 29-day cumulative survival rate as shown in Figure 2, suggesting the possibility of a difference in survival rates at day 15. To further investigate this, we conducted a Kaplan-Meier analysis on the 15-day cumulative

Table 1 Demographic and Clinical Characteristics of the Patients at Admission

Characteristics	Before Propensity Score-Matched			After Propensity Score-Matched		
	Remdesivir (N = 124)	Favipiravir (N = 125)	Standardized Mean Difference	Remdesivir (N = 102)	Favipiravir (N = 102)	Standardized Mean Difference
Age – year	60.91 ± 13.60	63.18 ± 15.60	15.5%	61.94 ± 13.50	62.10 ± 15.64	1.1%
Female sex – no. (%)	66 (53.23)	58 (46.40)	13.6%	54 (52.94)	48 (47.06)	11.7%
BMI – Kg/m^2	28.24 ± 6.40	26.82 ± 6.80	21.4%	28.17 ± 6.60	26.92 ± 6.87	18.6%
Day of infection at admission– day	6.95 ± 2.97	5.33 ± 3.07	53.7%	6.83 ± 3.01	5.38 ± 3.23	46.6%
Timing of Antiviral Treatment Initiation after symptoms onset-day	7.27±2.85	5.28±3.09	67%	6.47±3.31	6.20±2.87	9%
Severities of COVID pneumonia – no. (%)						
Moderate COVID pneumonia	7 (5.6)	6 (4.8)	3.7%	5(4.9)	4(3.9)	4.8%
Severe COVID pneumonia	117 (94.4)	119 (95.2)	3.7%	97(95.1)	98(96.1)	4.8%
RALE score	15.05±9.69	11.41±8.36	40.1%	14.32±9.08	11.34±8.46	33.9%
WHO ordinal clinical severity scale – no. (%)						
4 (no supplemental oxygen)	10 (4.0)	0 (0)	41.5%	3 (2.9)	3 (2.9)	0%
5 (supplemental oxygen)	17 (13.7)	56 (44.8)	72.4%	27 (26.5)	33 (32.4)	12.9%
6 (HFNO or NIV)	85 (68.6)	51 (40.8)	57.8%	59 (57.8)	54 (52.9)	9.8%
7 (IMV or ECMO)	22 (17.7)	8 (6.4)	35.2%	13 (12.8)	12 (11.8)	3.0%
Absolute lymphocyte count – cell/mm^3	708.03 ± 464.23	653.87 ± 445.67	6.5%	715.30 ± 474.70	653.60 ± 437.70	13.5%
D-dimer – mcg/mL	720 (486,1135)	844 (486,1537.5)	14.7%	758.5 (475,1141)	825 (502,1376)	13.2%
CRP – mg/L	110.00 ± 74.04	100.25 ± 69.32	11.9%	104.98 ± 72.51	100.93 ± 71.84	5.6%
LDH – IU/L	418.95 ± 180.23	463.91 ± 188.57	24.4%	431.44 ± 165.62	454.01 ± 191.35	12.6%
AST[a] – IU/L	82.50 ± 89.73	72.43 ± 46.65	17.4%	71.74 ± 61.35	70.49 ± 43.38	2.3%
ALT[b] – IU/L	73.08 ± 87.48	46.12 ± 46.92	38.4%	57.79 ± 76.79	49.78 ± 37.80	13.2%
e-GFR – mL/min/1.73m²	80.28 ± 29.78	72.73 ± 32.08	24.2%	78.78 ± 30.26	74.53 ± 31.30	13.8%

S_PO_2 – %	94.31 ± 1.07	94.76 ± 1.19	15.0%	94.45 ± 1.06	94.44 ± 0.96	0.9%
F_IO_2 – %	0.54 ± 0.19	0.40 ± 0.18	82.4%	0.48 ± 0.19	0.47 ± 0.18	5.6%
Charlson comorbidity index score	3.44 ± 2.30	3.90 ± 2.97	17.9%	3.65 ± 2.36	3.69 ± 2.96	1.4%
Underlying diseases – no. (%)						
Diabetes mellitus	58 (46.8)	51 (40.8)	12.0%	49 (48.04)	38 (37.25)	21.8%
Hypertension	83 (66.9)	85 (68.0)	2.3%	70 (68.63)	64 (62.75)	12.4%
Chronic lung disease	6 (4.8)	11 (8.8)	15.7%	5 (4.90)	9 (8.82)	15.5%
Chronic liver disease	3 (2.4)	6 (4.8)	12.7%	3 (2.94)	4 (3.92)	5.3%
Bedridden	3 (2.4)	10 (8.0)	25.1%	3 (2.97)	6 (5.88)	14.1%
Obesity[c]	83(66.9)	65(52.0)	30.7%	67(65.7)	55(53.9)	24.1%
HIV infection	2(1.6)	1(0.8)	7.4%	2(1.9)	1(1)	8.1%
Non-HIV immunocompromised	9(7.3)	5(4.0)	14.1%	8(7.8)	4(3.9)	16.6%
Smoking status – no. (%)						
Never	71 (57.2)	66 (52.8)	8.9%	58 (56.9)	55 (53.9)	5.9%
Current smoking	14 (11.3)	21 (16.8)	15.8%	11 (10.8)	20 (19.6)	24.6%
Quit smoking	39 (31.5)	38 (30.4)	2.3%	33 (32.4)	27 (26.5)	12.9%
Patients who received the vaccine- no. (%)	1(0.8)	2(1.6)	7.3%	1(0.98)	2(1.96)	8.1%
Concomitant medications						
Corticosteroids	124 (100)	125 (100)	0%	102(100)	102(100)	0%
Tocilizumab	18 (14.5)	23 (18.4)	10.4%	18(17.6)	17(16.7)	2.6%
JAK 2 inhibitors	51 (41.1)	56 (44.8)	7.4%	42(41.2)	45(44.1)	5.9%

Notes: [a,b]After propensity score-matched data of AST and ALT were missing for 16 and 15 patients in the favipiravir and remdesivir groups, respectively. [c]Defined as BMI 25 or higher in Asian population. Data are presented as mean ± SD, median (25th,75th percentiles), or frequency(percentage). The standardized mean difference was used to assess the balance of covariates after matching. The standardized mean difference of <10% was considered acceptable.
Abbreviations: BMI, body mass index; WHO, World Health Organization; CRP, C reactive protein; LDH, Lactate dehydrogenase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase;eGFR, estimated glomerular filtration rate; S_PO_2,oxygen saturation; F_IO_2, Fraction of inspired oxygen; RALE score, Radiographic Assessment of Lung Edema score; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HFNO, high-flow nasal oxygen; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation.

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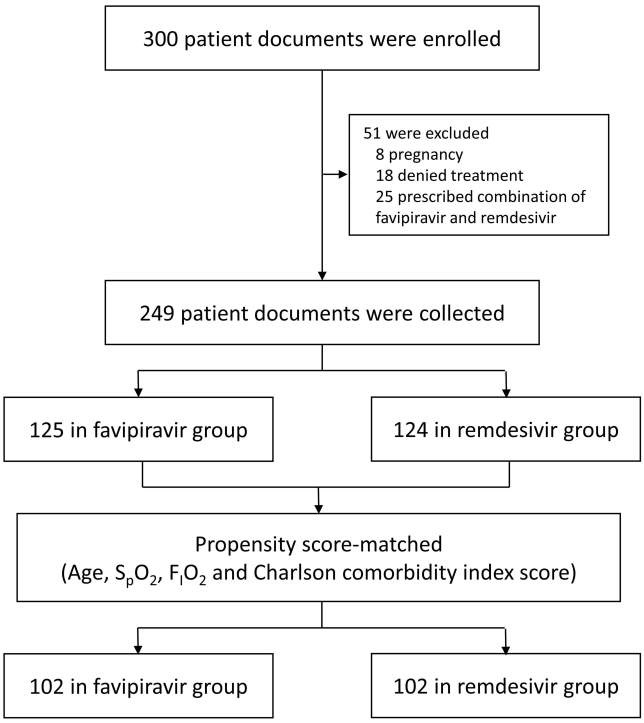

Figure 1 Enrollment and propensity score-matched.

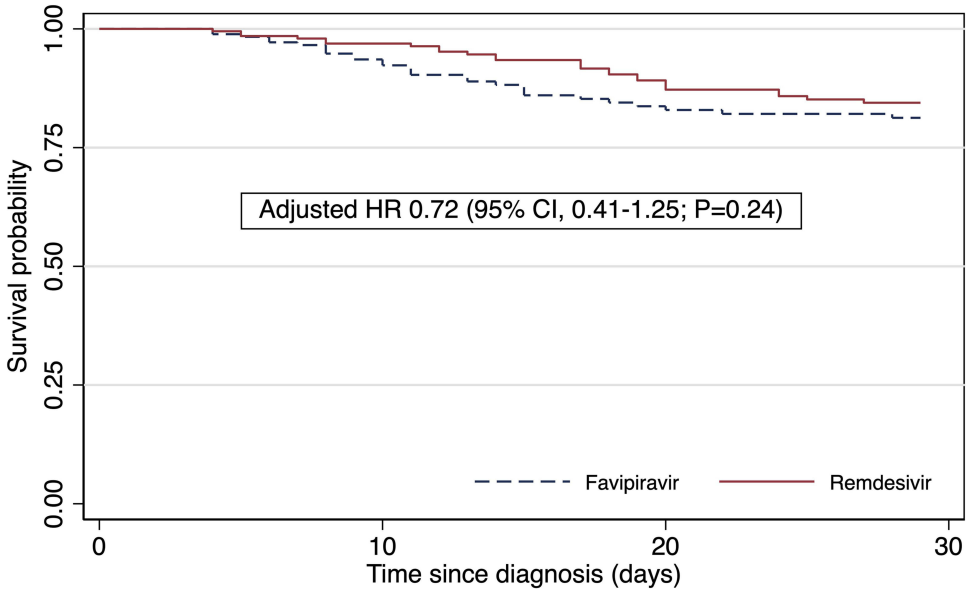

Figure 2 Kaplan-Meier estimates a 29-day cumulative survival rate adjusted by the presence of diabetes, obesity, and RALE score between remdesevir and favipiravir group.

survival rate and observed a trend towards a higher survival rate in the remdesivir group (adjusted hazard ratio 0.41; 95% CI, 0.20 to 0.84; p= 0.02) (Figure 3). We speculated that this advantage of remdesivir might be due to its ability to reduce viral replication in the early phase (viral phase). However, during the later immune stage and when combined with complications from critical illness, this advantage might not persist, as evidenced by the lack of a significant difference in the 29-day cumulative survival rate. Moreover, there was no difference in the complications, such as the presence of

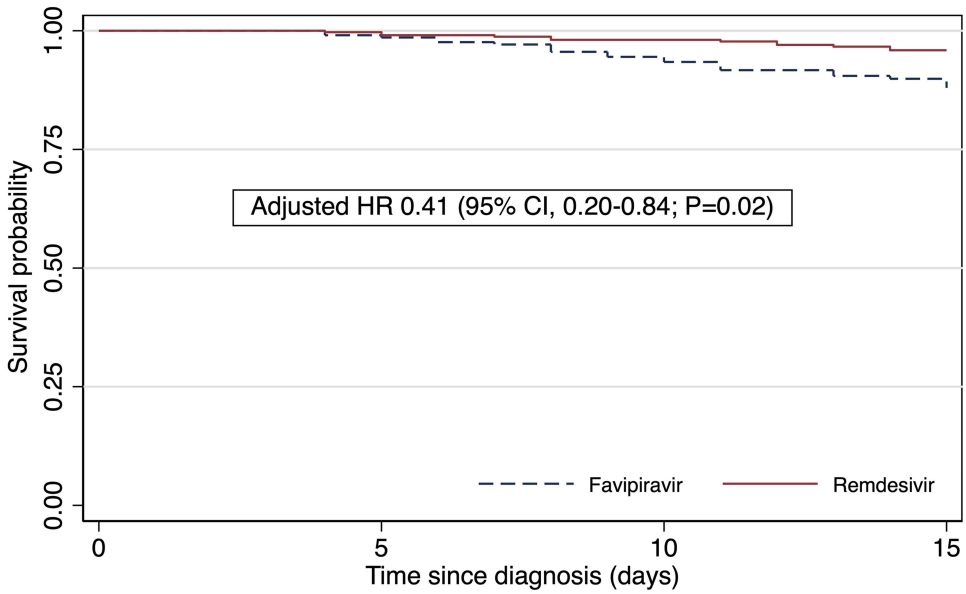

Figure 3 Kaplan-Meier estimates of the 15-day cumulative survival rate adjusted by the presence of diabetes, obesity, and RALE score between remdesivir and favipiravir group.

hospital-acquired pneumonia, septic shock, pneumothorax, acute respiratory distress syndrome, or acute kidney injury, between the two groups.

The ACTT-1 study compared remdesivir to a placebo and discovered that the overall 29-day mortality rate in the remdesivir group was 11.4%, showcasing a potential trend towards statistical significance in reducing mortality compared to the placebo group's rate of 15.2%. This finding contrasted with our study's results. However, this variance could be attributed to the fact that most patients in the ACTT-1 trial had a lower clinical severity (WHO Ordinal Clinical Severity Scale 4) compared to the higher severity level (mostly level 6) observed in our study. Upon examining the identical severity subgroup, we observed that the 29-day mortality rate of the remdesivir group in the ACTT-1 trial was 20%, which did not significantly differ from the placebo group's rate, aligning with our study's findings.[7]

Wang et al conducted a study comparing remdesivir with placebo and reported no difference in mortality and recovery rates. Among patients with symptom duration ≤ 10 days, patients receiving remdesivir had a faster time to clinical improvement than those receiving a placebo but did not reach a statistically significant difference. Half of the patients in this study were initiated with antiviral agents after more than ten days of symptoms.[27] In patients at elevated risk of severe COVID-19 outcomes but not hospitalized, a short, three-day regimen of remdesivir was found to be safe and significantly reduced the risk of hospitalization or death by 87% compared to those who received a placebo.[28]

Table 2 Secondary Outcomes Between Remdesivir and Favipiravir Group

Outcomes	Before Propensity Score-Matched				After Propensity Score-Matched			
	Remdesivir (N = 124)	Favipiravir (N = 125)	Risk Ratio (95% CI)	P value	Remdesivir (N = 102)	Favipiravir (N = 102)	Risk Ratio (95% CI)	P value
15-day recovery rate – no. (%)	76 (61.3)	68 (54.4)	1.15 (0.89 to 1.47)	0.27	62 (60.8)	56 (54.9)	1.12 (0.85 to1.48)	0.39
Length-of-ICU stay	11.28±9.55	11.17±12.35	-	0.93	11.48 ± 11.88	10.87 ± 9.31	-	0.69
Length-of-hospital stay	16.81±11.78	16.16±14.97	-	0.70	16.64 ± 14.28	16.59 ± 11.31	-	0.98
Need for invasive mechanical ventilation – no. (%)	35 (28.2)	33 (26.4)	1.04 (0.78 to1.39)	0.74	24 (23.5)	31 (30.4)	0.84 (0.63 to1.12)	0.26
Duration of invasive mechanical ventilation	10 (4.75,15.75)	10 (5.5,15)	-	0.69	12(8,18)	7(4.75,13)	-	0.024

Notes: Data are presented as mean ± SD, median (25th,75th percentiles), or frequency(percentage). The significance of the comparison was determined by a *t*-test, a Mann–Whitney *U*-test, or a Pearson chi-square test. P values <0.05 were considered statistically significant.
Abbreviations: ICU, intensive care unit; CI, confidence interval.

Table 3 Complications Between Remdesivir and Favipiravir Group

Complications – no. (%)	Before Propensity Score-Matched				After Propensity Score-Matched			
	Remdesivir (N = 124)	Favipiravir (N = 125)	Risk Ratio (95% CI)	P value	Remdesivir (N = 102)	Favipiravir (N = 102)	Risk Ratio (95% CI)	P value
Hospital-acquired pneumonia	33(26.6)	35(28.0)	0.96 (0.73 to 1.27)	0.80	28(27.5)	26(25.55)	1.05 (0.76 to 1.44)	0.75
Pneumothorax and/or pneumomediastinum	7(5.6)	6(4.8)	1.09 (0.59 to 1.99)	0.76	5(4.9)	5(4.9)	1.00 (0.53 to 1.88)	1
Septic shock	34(27.4)	34(27.2)	1.00 (0.76 to 1.32)	0.96	28(27.5)	25(24.5)	1.08 (0.78 to 1.49)	0.63
ARDS	22(17.7)	31(24.8)	0.82 (0.62 to 1.07)	0.17	20(19.6)	22(21.6)	0.94 (0.67 to 1.30)	0.73
Acute kidney injury	22(17.7)	24(19.2)	0.95 (0.70 to 1.29)	0.76	19(18.6)	19(18.6)	1.00 (0.70 to 1.42)	1

Notes: Data are presented as frequency (percentage). A Pearson chi-square test determined the significance of the comparison. P values <0.05 were considered statistically significant.

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval.

Another study in immunocompromised patients reported that prompt initiation of remdesivir within two days is associated with significant survival benefits across all variant waves.[29] In contrast, Our study administered the medication approximately on day six after symptom onset. Earlier administration could potentially reduce mortality rates.

The WHO Solidarity trial found that remdesivir may reduce mortality rate compared to standard of care in low-risk patients. However, the overall data did not show a statistically significant lower mortality rate.[13] Based on this data, the WHO recommended using remdesivir in high-risk patients with hospitalization or severe COVID-19 pneumonia and conditionally recommended against use in critical COVID-19 cases.[30]

A study had shown that patients who did not require oxygen supplements and were younger showed early improvement within seven days of receiving favipiravir.[16] Srisubat et al compared the efficacy of favipiravir to supportive treatment without antiviral agents during the delta-variant outbreak. They observed a reduction in the 28-day mortality rate to 27% among patients with severe COVID-19.[17] Similarly, our study focused on the Delta variant, in which 96.6% of the patients had severe COVID-19 pneumonia; the 29-day mortality rate in the Favipiravir group was 27.5%, aligning with the findings reported by Srisubat et al. However, several studies found that favipiravir was not significantly different from the standard of care in reducing mortality, shortening hospital stays, preventing disease progression, or improving viral shedding.[31–33] As a result, the WHO and the latest guideline by the Department of Medical Services of Thailand do not recommend the use of favipiravir in the treatment of COVID-19.[30,34]

Krongsut et al[35] examined the effects of remdesivir versus favipiravir on clinical improvement and mortality in hospitalized COVID-19 patients at a local hospital in Thailand, analyzing 362 patients through propensity score matching. They discovered that remdesivir was associated with enhanced clinical improvement, decreased in-hospital mortality, and reduced oxygen support needs. These results differed from ours. Our study also administered the drug around day 6 of symptom onset, similar to this study. The differences in outcomes could be attributed to 1) higher initial day of infection at admission and RALE scores in the remdesivir group in our study, even after propensity score matching, indicating that these patients might have had more severe symptoms and slower treatment initiation; 2) baseline differences, with our study population having more obese patients and fewer vaccinated individuals. Furthermore, while the 28-day mortality rates in the remdesivir groups were comparable across both studies at 27%, the favipiravir group experienced a higher mortality rate of 43% in the study by Krongsut et al, suggesting potential variations in treatment protocols within this group.[35]

A recent study by our study was conducted when multiple antiviral agents were effectively used to treat COVID-19. While we did not find any statistically significant differences between the two treatments in primary and secondary outcomes, after further investigation on the 15-day cumulative survival rate and observing a trend towards a higher survival rate in the remdesivir group, our results may support the current COVID-19 treatment guidelines, which

recommend early administration of remdesivir to patients with COVID-19 pneumonia to increase the likelihood of survival.

Limitations

Although our study was retrospective and subject to confounding variables, we attempted to mitigate bias through propensity score-matching techniques. Nevertheless, some sources of bias could not be fully controlled, including differences in the timing of antiviral agent administration, which may have impacted viral strain and disease severity. Even after applying propensity score matching, the days of infection at admission and RALE scores remained higher in the remdesivir group than in the favipiravir group. These suggested that patients in the remdesivir group may have experienced more severe symptoms and received treatment at a slower pace. Consequently, no clear difference was observed between the remdesivir and favipiravir groups. Variations in other medications, such as antibiotics and supportive treatments, may have influenced outcomes. Conducting a RCT should address this issue. Additionally, there is an absence of data on long-term consequences due to the unavailability of information on re-ICU or re-hospital admissions within 4–6 weeks post-discharge.

Conclusion

In patients with moderate to severe COVID-19 pneumonia, Remdesivir did not demonstrate superior benefits over Favipiravir regarding 29-day mortality, 15-day recovery rates, or hospital and ICU stay lengths. However, further investigation into the 15-day cumulative survival rate revealed a trend towards improved survival in the Remdesivir group. These findings may support current treatment guidelines that advocate for the early use of Remdesivir in COVID-19 pneumonia to improve survival.

Abbreviations

COVID-19, Coronavirus disease 2019; WHO, World Health Organization; F_IO_2, Fraction of inspired oxygen; RNA, Ribonucleic acid; RCT, Randomized controlled trial; ICU, Intensive-care unit; S_PO_2, Oxygen saturation; RALE, Radiographic Assessment of Lung Edema; CXR, Chest X-ray; S.D, Standard deviation; CI, Confidence interval; SMD, Standardized mean difference.

Data Sharing Statement

The dataset used and analyzed during the current study is available from the corresponding author upon reasonable request.

Ethics Approval

The Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, approved this study (COA. MURA2021/859). Due to the study's retrospective nature, the ethics committee has waived the requirement of the informed consent process. The research involves no more than minimal risk to the subjects. We confirmed that the data was anonymized and maintained with confidentiality and compliance with the Declaration of Helsinki.

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The abstract of an earlier study, 'Remdesivir versus favipiravir in hospitalized patients with moderate COVID-19 pneumonia: A propensity score-matched retrospective cohort study was presented at the 2023 ERS International Congress, in the session, 'Inflammatory endotyping: the macrophage across disease areas' as a poster presentation/ conference talk with interim findings. The poster's abstract was published in the European Respiratory Journal:

https://erj.ersjournals.com/content/62/suppl_67/PA1686.[36]

Author Contributions

All authors contributed significantly to the work reported, including the conception, study design, execution, data acquisition, analysis, and interpretation.

All authors have drafted, written, substantially revised, or critically reviewed the article.

All authors have agreed on the Journal to which the article will be submitted.

All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage.

All authors agree to take responsibility and be accountable for the article's contents.

Disclosure

The authors report no conflicts of interest in this work.

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