COMPARISON OF THE EFFECTIVENESS OF REMDESIVIR VERSUS FAVIPIRAVIR ON CLINICAL IMPROVEMENT AND MORTALITY AMONG PATIENTS WITH COVID-19 PNEUMONIA: A RETROSPECTIVE SINGLE-CENTER STUDY

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Abstract

Background: Antiviral drug administration in the early phase of COVID-19 during peak viremia can reduce the progression to severe disease. The optimal antiviral treatment against severe coronavirus disease 2019 (COVID-19) has not been proven.

Objective: The study aimed to examine the effectiveness of remdesivir versus favipiravir to treat patients with COVID-19 pneumonia on clinical improvement and mortality.

Methods: This retrospective observational cohort study was conducted in the modular intensive care unit and cohort ward from 1 June 2021 to 31 December 2021. Patients were screened for COVID-19 pneumonia. A propensity score was used to handle selection bias and potential confounding factors. The propensity score estimation was obtained from the multivariable logistic regression model, including prognostic covariates. Then 1:1 matching was performed. Finally, the balance after matching was checked concerning the *p*-value.

Results: Overall, 362 patients were matched using propensity score analysis; they were enrolled and divided in 2 groups: remdesivir and favipiravir (181:181). Remdesivir was associated with an increased proportion of clinical improvement (70.72 vs. 56.91%, adjusted HR=1.52 [1.16-2.01]; p=0.002), reduced inhospital mortality (adjusted HR=0.68 [0.47-0.99]; p=0.047), an increased proportion of being free from the use of a high flow nasal cannula (HFNC) and a low flow oxygen cannula (LFNC) (74.34 vs. 56.10%, adjusted HR 1.79 [1.32-2.45]; p<0.001; 86.4% vs. 74.8, adjusted HR=1.34 [1.01-1.78]; p=0.037, respectively), increased median survival time (26 vs. 24 days, median survival time difference of 2 days [IQR, 2-6]; p=0.048). In addition, patients treated with remdesivir showed a significantly higher proportion of discharge from the hospital measured using the WHO ordinary scale (66.85 vs. 53.04%, adjusted HR =1.19 [1.01-1.41]; p=0.035).

Conclusion: Among hospitalized patients with COVID-19 pneumonia, receiving oxygen supplementation, remdesivir was associated with increased clinical improvement, reduced in-hospital mortality and reduced need for HFNC and LFNC.

Keywords: COVID-19, Remdesivir, Favipiravir, Effectiveness, Mortality, Clinical improvement
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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), was first reported in China and has spread worldwide. In Thailand, COVID-19 began to spread in Bangkok in May 2020 and affected many provinces nationwide. As a result, Thailand recorded 2,361,702 patients and 22,000 deaths (data as of January 21, 2022), with the highest number of daily deaths reported August 18, 2021, at 312.[1] Reducing the infection rates, deaths or severe illness is important.

SARS-CoV-2 causes severe acute respiratory syndrome, and may require hospitalization. Morbidity and mortality are linked to several factors, such as age and coexisting medical conditions. Efforts have been made to develop novel treatment strategies for SARS-CoV-2 and determine the effectiveness of antiviral, anti-inflammatory and immunomodulatory drugs, which are to be used with public health policy measures.[2]

Remdesivir, a nucleotide drug, has shown antiviral activity against beta coronaviruses, severe acute respiratory syndrome-associated coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus and SARS-CoV-2 by inhibiting viral RNA polymerase in vitro. The first experimental study was conducted in China. A randomized controlled trial (RCT) found that remdesivir contributed to good treatment outcomes for COVID-19 pneumonia.[3] A phase 3 RCT (the Adaptive COVID-19 Treatment Trial-1 [ACTT-1]) found that remdesivir reduced the median recovery time among patients with COVID-19 pneumonia requiring oxygen supplementation.[4]

Based on recent empirical studies, the effects of remdesivir on clinical improvement and mortality remained unclear. Evidence to show the effects of remdesivir on mortality in a subgroup of ventilation-treated patients was insufficient. Future studies should be conducted to provide more information on the efficacy and safety outcomes of remdesivir treatment, especially for different populations. This would allow us to draw more convincing conclusions about the potential benefits and harms of remdesivir.[5]
Favipiravir is used to treat COVID-19 globally. An open-label control study in China on the therapeutic effectiveness of favipiravir with lopinavir/ritonavir to treat COVID-19 showed a better therapeutic response for COVID-19 in terms of disease progression and viral clearance. However, some studies indicated that favipiravir did not correlate with clinical improvement or reduced mortality. In addition, data from large, prospective, blinded and placebo-controlled studies of favipiravir to treat severe COVID-19 still need to be included.[6] The authors investigated the potential benefits and harms of remdesivir compared with favipiravir treatment.
Currently, more data are needed concerning specific antiviral drugs to treat COVID-19. Several treatments are used.[7] Related studies have focused on clinical outcomes of remdesivir treatment with different results depending on the study design, i.e., time to start antiviral treatment and the severity of patients.[2, 8, 9] The present study was conducted to analyze the effects of remdesivir on clinical improvement, 14- and 28-day mortality and inhospital mortality of hospitalized patients with COVID-19 pneumonia at a local hospital in Thailand.

Methods

Study design

This study was approved by the Human Research Ethics Committee of Saraburi Hospital following international standards of human research ethics guidelines including the Declaration of Helsinki, the Belmont Report, the CIOMS Guideline, and the International Conference on Harmonization in Good Clinical Practice (Certificate No. EC036/2564).

This study comprised a nonrandomized therapeutic investigation using a retrospective observational cohort design including patients with COVID-19 pneumonia admitted to the modular ICU and the cohort ward at Saraburi Hospital, a provincial tertiary hospital, Thailand, between 1 June 2021 and 31 December 2021. Data were collected from Saraburi Hospital medical records such as demographic data, clinical data, severity scores, laboratory data and complications evaluating the therapeutic effects of remdesivir

(intervention group) and favipiravir (control group) along with standard care treatment. COVID-19 pneumonia was identified based on the International Classification of Diseases, Tenth Revision, and Clinical Modification codes (ICD-10) with diagnosis code J12.82.

The sample size was calculated based on samples of 30 patients with COVID-19 pneumonia in our pilot study, indicating that the proportion of clinical improvement was 0.63 in the remdesivir group and 0.48 in the favipiravir group. The authors determined the minimum sample size required to detect an absolute difference of 0.63 − 0.48 = 0.15 with 80% power using a two-sided test at $\alpha = 0.05$. A total sample of 344 individuals (172 individuals per group) was required to detect an absolute difference of 0.15 between the remdesivir and favipiravir groups. The sample size estimation was adequate based on the baseline adjustment using the propensity score method.

Inclusion criteria were as follows: (i) age ≥18 years; (ii) confirmed diagnosis of COVID-19 pneumonia (chest radiography [CXR] confirmed pneumonia and nasopharyngeal swab RT-PCR for COVID was positive); (iii) oxygen saturation (SpO2) ≤96%or a decrease in SpO2 of ≥3% from the initial measurement upon exercise (exercise-induced hypoxemia); (iv) a need for a low flow oxygen cannula (LFNC) of ≥5 L/min, for the use of a high flow nasal cannula (HFNC), or invasive mechanical ventilation (IMV) (WHO ordinary scale of clinical status = 4–6); (v) early phase of the disease (≤10 days from onset of symptoms) and (vi) alanine aminotransferase <5 times the upper limit of normal. Exclusion criteria were as follows: (i) patients with no need for oxygen supplementation (WHO ordinary scale of clinical status =1–3); (ii) patients using extracorporeal membrane oxygenation; (iii) patients lost to follow-up due to transfer to another hospital and (iv) patients with missing data such as COVID-19 vaccination history and laboratory results.

Clinical management

Remdesivir and favipiravir have been included in several local protocols worldwide. National clinical practice guidelines in Thailand recommend using favipiravir as the primary antiviral agent to treat COVID-19. Favipiravir is used alone among adults and children with a high risk of disease progression or with corticosteroids in cases of hypoxia or progressed pulmonary infiltrates. The favipiravir regimen suggested for adults is 2 × 1800 mg the first day and 2 × 800 mg daily days 2 to 5 or 2 to 10.

Patients with confirmed COVID-19 pneumonia became hypoxic (resting SpO2 ≤96%), showed a decrease in SpO2 of ≥3% upon exercise (exercise-induced hypoxemia) or had progression of pulmonary infiltration as shown by CXR. Therefore, depending on the clinical condition, Favipiravir 5 to 10 days is recommended. Patients should be closely monitored for symptoms. If not responding to treatment, a change to remdesivir may be considered in the following cases: (i) severe pneumonia less than ten days after symptom onset with an oxygen cannula of ≥5 L/min but with SpO2 <95% or when receiving HFNC/NIV or using an invasive mechanical ventilator, (ii) pregnancy with pneumonia or (iii) oral administration is contraindicated, or the patient has problems with absorption.

In addition, patients were provided anticoagulant therapy when they presented severe symptoms, no contraindications, no bleeding risk upon anticoagulant therapy and at least one of the following indications: d-dimer ≥6 times the upper normal limit, a history of venous thromboembolism or thrombophilia, active cancer, body mass index (BMI) ≥30 kg/m^2 and pregnancy.[10]

Data collection and measurements

The medical records of all enrolled patients were obtained from the digital database. Collected baseline prognostic factors included age, sex, BMI, symptoms, underlying disease, vital signs, SpO2, disease severity (pneumonia severity index [PSI/PORT score], quick sepsis-related organ failure assessment [qSOFA] and CURB-65), history of vaccination against

COVID-19, WHO ordinal scale[11] at baseline and 28 days after admission, length of hospital stay, CXR results (categorized in five groups: category 1=normal, no abnormality detected; category 5=multifocal, bilateral peripheral opacities or opacities with round morphology)[12] and laboratory results **(Table 1).**

The primary objective was to compare the effectiveness of remdesivir versus favipiravir in treating COVID-19 pneumonia. Clinical improvement was defined as patients being discharged alive and not having ≥2-point reduction in the WHO disease severity score during hospital treatment. The secondary objective was to compare 14-and 28-day mortality, in-hospital mortality, free from oxygen supplementation (without MV, HFNC and LFNC) and the WHO ordinary scale at day 28 between patients with COVID-19 pneumonia treated with remdesivir versus favipiravir. They were assessed using an ordinal eight-category WHO ordinary scale, where 1 to 2=ambulatory state, 3 to 4=hospitalized mild disease, 5 to 7=hospitalized severe disease and 8=dead.[11] Adverse events were also recorded.

Statistical analysis

Data were analyzed using Stata, Version 16.0 (StataCorp, Lakeway, TX, USA). A two-sided *p*-value of <0.05 was considered significant for all statistical analyses. For all clinical characteristics and relevant variables, descriptive statistics were calculated. Categorical data are presented as percentages, and continuous variables are presented as mean and standard deviation or median and interquartile range, as appropriate. Continuous variables were compared between the two groups with either the t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-square or Fisher's exact tests.

Statistical analyses were based on the objectives of the study using the propensity score method. The propensity score estimate was obtained from the multivariable logistic regression model: propensity matching scores were analyzed between the remdesivir and favipiravir groups at a 1:1 ratio. The covariate analyzed in the nearest neighbor propensity score matching model was selected based on risk factors affecting selection bias and a literature review, as well as some imbalanced covariates with significant differences between the two groups from the univariate analysis ($p<0.05$), i.e., age ≥60 years, sex, obesity (BMI ≥30 kg/m^2), diabetes, chronic kidney disease, cardiovascular disease, PSI/PORT score, CRP level,[13] and concomitant medication (tofacitinib), to reduce selection bias and confounding factors.[14]

Clinical improvement was compared, 14- and 28-day mortality, inhospital mortality, free from IMV, HFNC, LFNC and the WHO ordinary scale at day 28 between the two groups using multivariable Cox proportional hazard regression analysis and Kaplan–Meier estimator curves. Differences between the groups were shown using a stratified log-rank test. Complications and adverse events were also analyzed using a relative risk regression analysis reported as adjusted relative risk.

Results

Data were retrieved from 481 medical records from 1 June 2021 to 31 December 2021. Of these, 44 showed ineligible criteria: 25 had alanine aminotransferase >5 times the upper limit of normal, and 12 did not need oxygen supplementation. Four hundred thirty-seven patients with COVID-19 pneumonia met the inclusion criteria. Twenty-five were excluded because 13 had missing data, and 12 were referred to other hospitals. Four hundred twenty-five were included in this cohort; 244 were treated with remdesivir and 181 with favipiravir. **Table 1** shows demographic data, prognostic factors and confounding factors among 425 patients. After propensity score matching at a ratio of 1:1, 362 patients were enrolled and divided in the remdesivir and favipiravir groups (n=181 patients per group) **(Figure 1)**

Demographic characteristics and clinical symptoms of patients with COVID-19 pneumonia

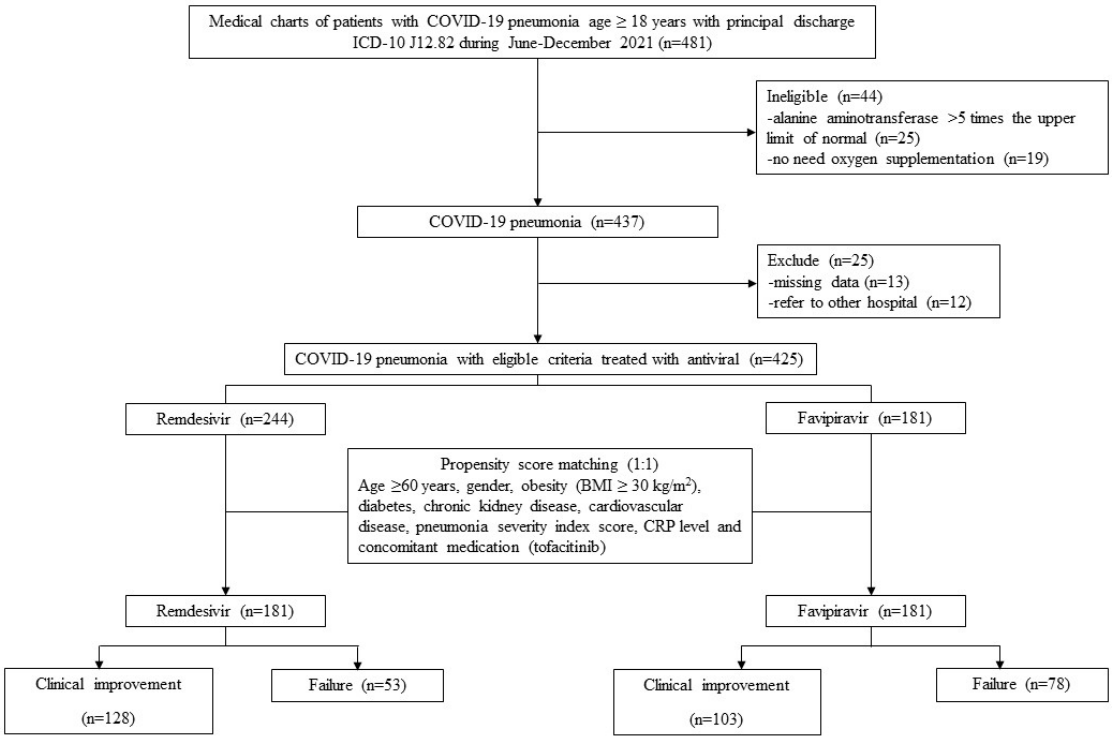

Figure 1. Study flow diagram of the patients' cohort

Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia by unmatched and propensity score-matched group

Characteristic	Unmatched cohort			Matched cohort		
	Remdesivir (n=244)	Favipiravir (n=181)	*p*-value	Remdesivir (n=181)	Favipiravir (n=181)	*p*-value
General characteristic						
Age, years	59.13±16.49	62.04±14.07	0.056	60.02± 17.29	62.04±14.07	0.223
Male, gender (%)	105(43.03)	81(44.75)	0.724	82(45.30)	81(44.75)	0.916
BMI, kg/m^2	29.46±7.57	28.57±6.54	0.205	28.86±7.39	28.57±6.54	0.688
Coexisting condition (%)						
Diabetes	121(49.59)	86(47.51)	0.672	91(50.28)	86(47.51)	0.599
Obesity	96(39.34)	65(35.91)	0.471	66(36.46)	65(35.91)	0.913
COPD	6(2.46)	3(1.66)	0.739	5(2.76)	3(1.66)	0.723
Cardiovascular disease	18(7.38)	20(11.05)	0.189	16(8.84)	20(11.05)	0.482
Cerebrovascular disease	21(8.61)	7(3.87)	0.051	13(7.18)	7(3.87)	0.167
Cirrhosis	3(1.23)	5(2.76)	0.294	2(1.10)	5(2.76)	0.449
Chronic kidney disease	21(8.61)	32(17.68)	0.005	21(11.60)	32(17.68)	0.137
Immunocompromise	0	2(1.10)	0.181	0	2(1.10)	0.499
Use steroid before	3(1.23)	0	0.265	3(1.66)	0	0.248
Hypertension	137(56.15)	111(61.33)	0.284	99(54.70)	111(61.33)	0.201

Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia by unmatched and propensity score-matched group (Cont.)

Characteristic	Unmatched cohort			Matched cohort		
	Remdesivir (n=244)	Favipiravir (n=181)	*p*-value	Remdesivir (n=181)	Favipiravir (n=181)	*p*-value
Dyslipidemia	98(40.16)	54(29.83)	0.028	71(39.23)	54(29.83)	0.060
Alzheimer's disease	1(0.41)	0	1.000	1(0.55)	0	1.000
History of malignancy	3(1.23)	4(2.21)	0.466	3(1.66)	4(2.21)	1.000
Thalassemia	1(0.41)	1(0.55)	1.000	1(0.55)	1(0.55)	1.000
Autoimmune disease	3(1.23)	2(1.10)	1.000	3(1.66)	2(1.10)	1.000
HIV infection	1(0.41)	1(0.55)	1.000	1(0.55)	1(0.55)	1.000
Gout	16(6.56)	4(2.21)	0.039	15(8.29)	4(2.21)	0.010
Psychiatric disorder	2(0.82)	1(0.55)	1.000	2(1.10)	1(0.55)	1.000
Symptoms						
Fever	199(81.56)	135(74.59)	0.083	143(79.01)	135(74.59)	0.319
Cough	226(92.62)	165(91.16)	0.583	167(92.27)	165(91.16)	0.703
Diarrhea	25(10.25)	40(22.10)	0.001	19(10.50)	40(22.10)	0.003
Sore throat	24(9.84)	13(7.18)	0.337	16(8.84)	13(7.18)	0.561
Anosmia	20(8.20)	29(16.02)	0.012	11(6.08)	29(16.02)	0.003
Nausea	25(10.25)	19(10.50)	0.933	17(9.39)	19(10.50)	0.725
Vital sign						
Body temperature (°C)	37.89±4.05	37.51±1.09	0.213	38.04±4.66	37.51±1.09	0.135
RR(/min)	30.23±5.57	30.00±6.84	0.705	30.14±5.85	30.00±6.84	0.836
SpO2 room air (%)	85.31±7.35	86.72±7.39	0.052	85.87±7.17	86.72±7.39	0.270
Disease severity						
PSI	3.29±1.22	3.49±1.22	0.095	3.34±1.23	3.49±1.22	0.267
qSOFA	1.35±0.63	1.42±0.74	0.315	1.37±0.64	1.42±0.74	0.497
CURB 65	1.5(1,3)	2(1,3)	0.252	2(1,3)	2(1,3)	0.640
Baseline WHO ordinal scale of clinical status (%)						
4 = LFNC	28(11.48)	60(33.15)	<0.001	25(13.81)	60(33.15)	<0.001
5 = HFNC	191(78.28)	96(53.04)	<0.001	137(75.69)	96(53.04)	<0.001
6 = MV	26(10.66)	26(14.36)	0.249	20(11.05)	26(14.36)	0.430
Duration of oxygen support, days (IQR)	10(7,16)	10(7,18)	0.993	10(6,15)	10(7,18)	0.437
Hospital, days	13(10,18)	13(9,19)	0.707	12(9,17)	13(9,19)	0.485
Vaccine immunization (%)						
No vaccination	179(73.36)	152(83.98)		130(71.82)	152(83.98)	
CoronaVac	31(12.70)	14(7.73)		26(14.36)	14(7.73)	
CoronaVac / CoronaVac	5(2.05)	4(2.21)	0.111	5(2.76)	4(2.21)	0.063
AZ	20(8.20)	8(4.42)		15(8.29)	8(4.42)	
AZ/AZ	1(0.41)	1(0.55)		0(0)	1(0.55)	
CoronaVac /AZ	8(3.28)	2(1.10)		5(2.76)	2(1.10)	
Laboratory						
Routine peripheral blood						
WBC (x 10^3/μL) (IQR)	9.0 (6.45,11.25)	8.3 (5.70,12.20)	0.391	8.8 (6.10,10.90)	8.3 (5.70,12.20)	0.795
CBC neutrophil %	81.69±9.68	80.23±12.18	0.169	81.14±9.83	80.23±12.18	0.431
CBC Lymph % (IQR)	12 (7,19)	12 (7,19)	0.836	12(7,20)	12(7,19)	0.859

Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia by unmatched and propensity score-matched group (Cont.)

Characteristic	Unmatched cohort			Matched cohort		
	Remdesivir (n=244)	Favipiravir (n=181)	*p*-value	Remdesivir (n=181)	Favipiravir (n=181)	*p*-value
ANC (x 10^3/μL) (IQR)	7.37 (4.78,9.73)	6.48 (4.22,10.21)	0.408	7.24 (4.49,9.43)	6.48 (4.22,10.21)	0.787
ALC (x 10^3/μL) (IQR)	0.98 (0.66,1.36)	935 (665,2380)	0.887	0.98 (0.60,1.38)	0.94 (0.67,2.38)	0.977
Hct (%)	37.43±6.51	36.73±6.49	0.274	36.91±6.92	36.73±6.49	0.800
Platelet (x 10^3/μL)	240±98	239±106	0.933	238±103	239±106	0.948
Blood biochemistry						
BUN (mg/dL) (IQR)	18.9 (12.6,28.35)	21.4 (13.7,37.6)	0.026	19.9 (13,31.3)	21.4 (13.7,37.6)	0.153
Cr (mg/dL) (IQR)	0.86 (0.65,1.18)	0.97 (0.69,1.42)	0.069	0.89 (0.68,1.27)	0.97 (0.69,1.42)	0.552
TB (mg/dL) (IQR)	0.60 (0.46,0.83)	0.63 (0.50,0.85)	0.145	0.61 (0.46,0.85)	0.63 (0.50,0.85)	0.277
DB (mg/dL) (IQR)	0.16 (0.10,0.25)	0.14 (0.10,0.27)	0.786	0.16 (0.10,0.26)	0.14 (0.10,0.27)	0.973
DB/TB ratio (IQR)	0.26 (0.21,0.32)	0.24 (0.20,0.31)	0.108	0.26 (0.21,0.32)	0.24 (0.20,0.31)	0.097
AST (U/L) (IQR)	51 (36,72)	48 (34,75)	0.721	47 (33,72)	48 (34,75)	0.822
ALT (U/L) (IQR)	38 (24.5, 59)	36 (33, 61)	0.648	35 (22,53)	36 (33,61)	0.149
Albumin (g/dL)	3.42±0.98	3.40±0.49	0.764	3.46±1.12	3.40±0.49	0.539
Blood sugar (mg/dL) (IQR)	172.5 (129,254)	171 (132,298)	0.325	171 (126,252)	171 (132,298)	0.162
Inflammatory marker						
CRP (mg/dL) (IQR)	98.2 (53.9,128.0)	76.9 (39.3,120.3)	0.010	91.2 (52.3,124.6)	76.9 (39.3, 120.3)	0.131
LDH (U/L) (IQR)	399.5 (325,588)	425 (309,559)	0.750	384 (298,561)	425 (309,559)	0.355
PT (sec) (IQR)	12.6 (11.8,13.55)	12.3 (11.7,13.2)	0.079	12.6 (11.8,13.6)	12.3 (11.7,13.2)	0.115
PTT (sec)	24.29±4.34	25.18±6.70	0.098	24.54±4.58	25.18±6.70	0.283
CT- value (N gene)	20.95±4.92	20.98±4.71	0.952	20.91±4.90	20.98±4.71	0.897
CXR category						
Category 1/2/3	9(3.69)	24(13.26)	<0.001	9(4.97)	24(13.26)	0.017
Category 4	27(11.07)	26(14.36)		23(12.71)	26(14.36)	
Category 5	208(85.25)	113(72.38)		149(82.32)	113(72.38)	
Onset of symptoms before antiviral initiation	6 (3.5, 8)	6 (2, 8)	0.256	6 (3, 8)	6 (2, 8)	0.155
Treatment						
Anti-inflammatory drugs						

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Characteristic	Unmatched cohort			Matched cohort		
	Remdesivir (n=244)	Favipiravir (n=181)	*p*-value	Remdesivir (n=181)	Favipiravir (n=181)	*p*-value
Dexamethasone	228(93.44)	172(95.03)	0.492	169(93.37)	172(95.03)	0.500
IVMP	20(8.20)	14(7.73)	0.862	17(9.39)	14(7.73)	0.573
Hydrocortisone	20(8.20)	8(4.42)	0.121	16(8.84)	8(4.42)	0.091
Tocilizumab	8(3.28)	5(2.76)	1.000	6(3.31)	5(2.76)	0.759
Tofacitinib	73(29.92)	8(4.42)	<0.001	10(5.52)	8(4.42)	0.629
Baricitinib	27(11.07)	4(2.21)	0.001	27(14.92)	4(2.21)	<0.001
Hemoperfusion	8(3.28)	1(0.55)	0.085	5(2.76)	1(0.55)	0.215
Hemodialysis	4(1.64)	1(0.55)	0.399	4(2.21)	1(0.55)	0.372
Mean propensity score	0.37±0.19	0.50±0.12	<0.001	0.49±0.06	0.51±0.07	0.010

IQR, Interquartile range; BMI, body mass index; RR, respiratory rate; PSI, pneumonia severity index; qSOFA, quick sepsis related organ failure; COPD, chronic obstructive pulmonary disease; LFNC, low flow nasal canular; HFNC, high flow nasal canular; AZ, AstraZeneca vaccine (ChAdOx1-S/nCoV-19 [recombinant] vaccine); ANC, Absolute neutrophil count; ALC, Absolute lymphocyte count; CXR, chest radiograph; IVMP, intravenous methylprednisolone

revealed 186 males (43.8%) and 239 females (56.2%), with a mean age of 61.0±15.8 years, a mean hospital duration of 14.7 ± 8.9 days, a median onset of symptoms before antiviral initiation of 6 days [IQR, 3–8] and a mean BMI of 28.7 ± 6.9 kg/m^2. Among co-existing conditions, hypertension was the most prevalent (248 patients, 58.4%), followed by diabetes (207 patients, 48.7%) and obesity (161 patients, 37.9%). The use of HFNC at baseline was higher in the remdesivir group than in the favipiravir group (78.3 vs. 53.0%; p <0.001), but the use of LFNC was lower in the remdesivir group than in the favipiravir group (11.5 vs. 33.2%; p<0.001). The use of tofacitinib (29.9 vs. 4.4%; p <0.001) and baricitinib (11.1 vs. 2.2%; p=0.001) was higher in the remdesivir group. The proportions of diarrhea (10.3 vs. 22.1%; p=0.001) and chest X-ray category 1 to 3 (3.7 vs. 13.3%; p<0.001) were lower in the remdesivir group than in the favipiravir group. No difference was noted in the duration of oxygen support, length of hospital stay, disease severity, vaccine immunization and the onset of symptoms before antiviral initiation between the two groups. The mean CRP level was significantly higher in the remdesivir group than in the favipiravir group (median, 98.2 [IQR, 53.9–128.0] vs. median, 76.9 [IQR, 39.3–120.3]; p=0.010) **(Table 1).**

The propensity scores were calculated with a multivariable logistic model using covariates comprising the abovementioned variables **(Table 2).** The mean propensity scores in each group significantly differed before matching (0.37 ± 0.19 vs. 0.50 ± 0.12; p<0.001) **(Table 1, Figure 2).** After 1:1 matching, 181 patients were allocated in each treatment group. This resulted in a decreased magnitude of the difference in mean propensity between the groups, but a significant difference remained between the groups (0.49 ± 0.06 vs. 0.51 ± 0.07; p=0.010). The propensity score model is shown in **Figure 3.** The propensity matching variables showed no statistically significant difference between the two groups: age (60.0 ± 17.3 vs. 62.0 ± 14.1; p=0.223), sex (male: 45.3 vs. 44.8%; p=0.916), obesity (BMI≥30 kg/m^2; 36.5% vs. 35.9%; p=0.913), diabetes (50.3 vs. 47.5%; p=0.599), chronic kidney disease (11.6 vs. 17.7%; p=0.137), cardiovascular disease (8.8 vs. 11.1%; p=0.482), pneumonia severity index score (PSI; 3.34±1.23 vs. 3.49±1.22; p=0.267), tofacitinib (5.5 vs. 4.4%; p=0.629) and CRP level (median,

Table 2. Derivation of propensity score equation from covariate by multivariate binary logistic regression

Covariates	Coefficient	95% confident interval	*p*-value
Age ≥60 years	-0.0954677	-0.569909,0.3789736	0.693
Male gender	0.0331352	-0.3907013,0.4569717	0.878
Obesity (BMI ≥30 kg/m^2)	-0.0204748	-0.464773,0.4238234	0.928
Diabetes	0.1698097	-0.2539996,0.593619	0.432
Chronic kidney disease	-0.587818	-1.26025,0.0846142	0.087
Cardiovascular disease	-0.079309	-0.8351409,0.6765229	0.837
PSI score	-0.1251413	-0.3355914,0.0853088	0.244
CRP level	0.0039724	0.0000179,0.0079269	0.049
Tofacitinib	2.177759	1.407167,2.94835	<0.001

PSI, pneumonia severity index; BMI, body mass index; CRP, c-reactive protein

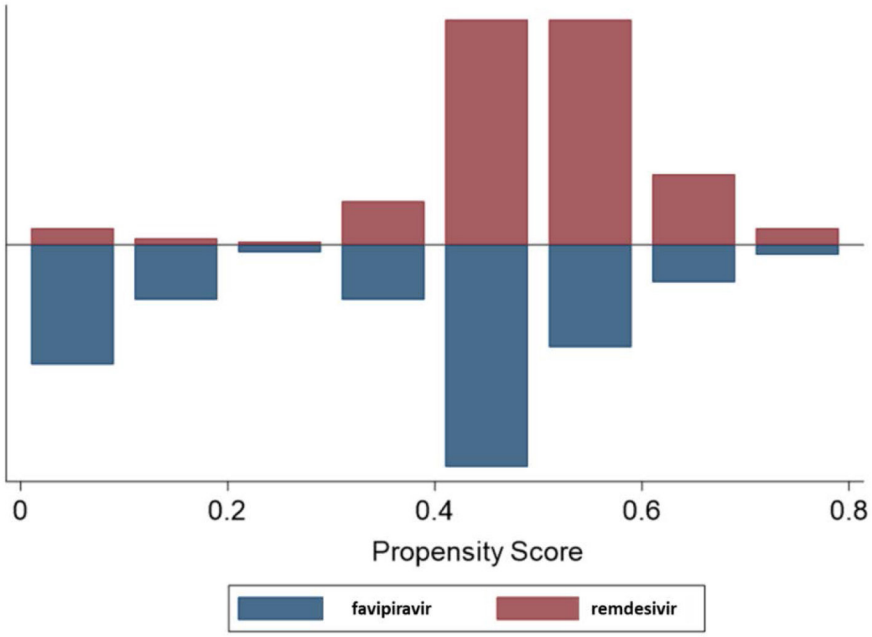


Figure 2. Mean propensity scores in each group

91.16[IQR,53.86–127.98]vs.median,76.92[IQR, 39.27–120.34]; *p*=0.131) **(Table 1).**

In addition, after matching, variables with an imbalance between groups ($p<0.05$) were CXR category 1 to 5 ($p=0.012$), HFNC (75.7 vs. 53.0%; $p<0.001$), LFNC (13.8 vs. 33.2; $p<0.001$), baricitinib (14.9 vs. 2.2%; $p<0.001$), gout (8.3 vs. 2.2%; $p=0.010$), diarrhea (10.5 vs. 22.1%; $p=0.003$), and anosmia (6.1 vs. 16.0%; $p=0.003$). Gout, diarrhea and anosmia were not associated with the outcomes[15], whereas CXR categories 1 to 5, HFNC, LFNC and baricitinib might be potential confounding factors influencing outcomes. Even though the authors tried to use propensity score matching with significant variables, an imbalance between groups was still found **(Table 1).**

Therefore, primary and secondary outcomes were analyzed by adjusting these variables in the final model with a multivariable Cox proportional hazard regression model **(Table 3)** and comparative analysis for complications and

adverse events in each group using multivariable logistic regression to adjust for residual confound bias **(Table 4).** As a result, remdesivir increased the proportion of clinical improvement by 52% (70.72 vs. 56.91%, adjusted HR=1.52 [1.16–2.01]; $p = 0.002$), reduced in-hospital mortality (adjusted HR=0.68 [0.47–0.99]; p=0.047) **(Table 3, Figures 4 A and 4D)**, increased the proportion of patients free from HFNC and LFNC use (74.34vs.56.10%, adjusted HR =1.79 [1.32–2.45]; p<0.001)(86.43 vs. 74.80%, adjusted HR=1.34 [1.01–1.78]; p=0.037) **(Figures 5B and 5C)**, and increased the median survival time (26 vs. 24 days, median survival time difference of 2 days [IQR, 2–6]; p=0.048). In addition, remdesivir significantly increased the proportion of WHO ordinary scale 1 to 2 (ambulatory with hospital discharge) (66.85vs.53.04%, adjusted HR=1.19 [1.01–1.41]; p=0.035) **(Table 3).**

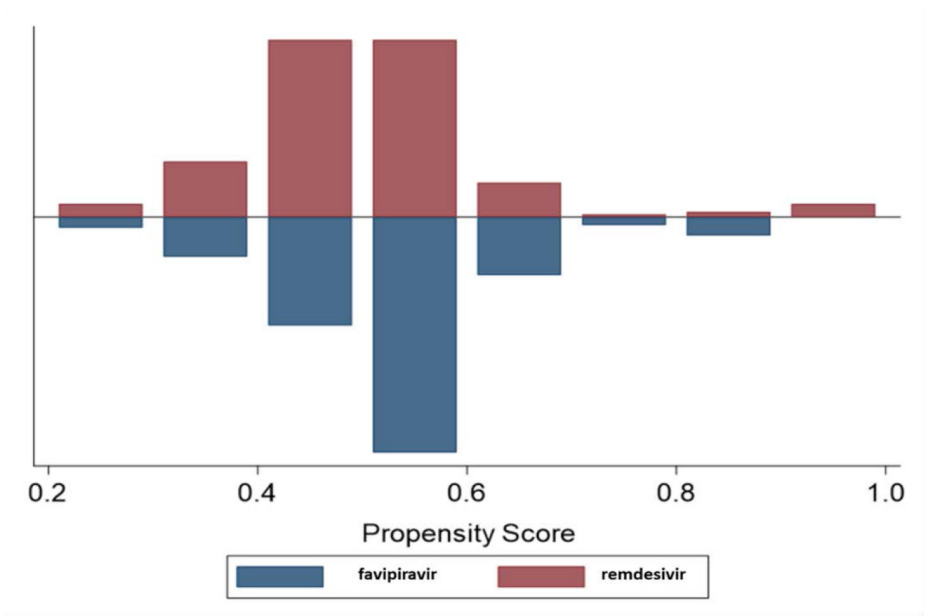


Figure 3. Distribution of the propensity scores between the two groups (remdesivir and favipiravir) among patients with COVID-19 pneumonia (after propensity score matching)

Table 3. Primary and secondary outcomes

Outcome	Treatment N (%)		Unadjusted analysis		Adjusted analysis	
	Remdesivir (n=181)	Favipiravir (n=181)	Crude HR 95%CI	*p*-value	Adjusted HR[a] 95%CI	*p*-value
Clinical improvement	128(70.72)	103(56.91)	1.39 (1.07,1.81)	0.013	1.52 (1.16,2.01)	0.002
Mortality						
14 days mortality	50(27.62)	76(41.99)	0.73 (0.51,1.04)	0.087	0.71 (0.49,1.04)	0.081
In-hospital mortality	50(27.62)	78(43.09)	0.70 (0.49,1.01)	0.053	0.68 (0.47,0.99)	0.047
28 days mortality	50(27.62)	78(43.09)	0.74 (0.52,1.05)	0.101	0.70 (0.48,1.02)	0.066
Median survival time,95%CI	26(21,33)	24(19,27)			2[b] (2-6)	0.048

Table 3. Primary and secondary outcomes (Cont.)

Outcome	Treatment N (%)		Unadjusted analysis		Adjusted analysis	
	Remdesivir (n=181)	Favipiravir (n=181)	Crude HR 95%CI	*p*-value	Adjusted HR[a] 95%CI	*p*-value
Free from oxygen supplementation						
Free from MV	8(22.22)	7(11.67)	1.22 (0.43,3.39)	0.702	1.17 (0.40,3.45)	0.765
Free from HFNC	113(74.34)	69(56.10)	1.81 (1.33,2.44)	<0.001	1.79 (1.32,2.45)	<0.001
Free from LFNC	121(86.43)	95(74.80)	1.35 (1.03,1.76)	0.029	1.34 (1.01,1.78)	0.037
WHO ordinary scale at day 28			OR(95%CI)		OR(95%CI)	
Ambulatory with hospital discharge at day 28 (WHO 1-2)	121(66.85)	96(53.04)	1.26 (1.06,1.49)	0.008	1.19 (1.01,1.41)	0.035
Hospitalized mild to severe disease (WHO 3-7)	11(6.08)	10(5.52)	1.1 (0.47,2.52)	0.822	1.44 (0.61,3.44)	0.405

HR, hazard ratio; OR, odds ratio; MV, invasive mechanical ventilator; HFNC, high flow nasal canular; LFNC, low flow nasal canular; WHO ordinary scale, World Health Organization Ordinal Scale; [a] multivariable analysis adjusted for potential confounders (CXR category, HFNC, LFNC and baricitinib); [b] median survival time difference

Regarding complication events throughout the study period, 128 (70.72%) occurred in the remdesivir group and 103 (56.91%) in the favipiravir group. Remdesivir was associated with a significantly red0uced risk of acute respiratory failure (COVID-19 pneumonia progression) (29.8 vs. 34.8%, adjusted RR=0.96 [0.96–0.97]; $p<0.001$). In addition, remdesivir reduced the risk of shock and transaminitis more than favipiravir (18.8 vs. 28.2%, adjusted RR=0.66 [0.47–0.91]; $p=0.014$) (10.5 vs. 20.4%, adjusted RR=0.51 [0.30–0.88]; $p=0.015$) **(Table 4).**

Table 4. Comparison of complications and adverse events among patients with COVID-19 pneumonia in each group

Complication event	Remdesivir (n=181)	Favipiravir (n=181)	Adjusted RR[a] (95% CI)	*p*-value
Acute respiratory failure	54(29.83)	63(34.81)	0.96(0.96, 0.97)	<0.001
Secondary bacterial infection	38(20.99)	37(20.44)	1.26(0.87, 1.79)	0.212
Coinfection organism				
Acinetobacter baumannii	20(11.05)	16(8.84)	1.59(0.88,2.89)	0.123
Pseudomonas aeruginosa	6(3.31)	12(6.63)	0.47(0.16,1.35)	0.164
Klebsiella pneumoniae	15(8.29)	8(4.42)	2.23(0.95,5.22)	0.063
Candida spp.	16(8.84)	13(7.18)	1.07(0.50,2.31)	0.848
Escherichia coli	13(7.18)	7(3.87)	1.77(0.69,4.51)	0.227
Staphylococcus aureus	1(0.55)	3(1.66)	0.34(0.03,3.35)	0.358

Table 4. Comparison of complications and adverse events among patients with COVID-19 pneumonia in each group (Cont.)

Complication event	Remdesivir (n=181)	Favipiravir (n=181)	Adjusted RR[a] (95% CI)	*p*-value
Aspergillus spp.	6(3.31)	3(1.66)	1.58(0.36, 6.89)	0.538
Enterococcus cloacae	3(1.66)	2(1.10)	1.68(0.27,10.30)	0.571
Stenotrophomonas spp.	2(1.10)	1(0.55)	1.85(0.16, 20.78)	0.615
Urinary tract infection	14(7.73)	11(6.08)	1.25(0.56, 2.78)	0.572
Acute kidney injury	42(23.20)	45(24.86)	0.97(0.67, 1.40)	0.891
Shock	34(18.78)	51(28.18)	0.66(0.47, 0.91)	0.014
DIC	2(1.10)	4(2.21)	0.64(0.11,3.50)	0.611
Metabolic acidosis	15(8.29)	22(12.15)	0.67(0.36, 1.25)	0.217
Pneumothorax	5(2.76)	3(1.66)	1.79(0.40,7.93)	0.439
UGIH	7(3.87)	6(3.31)	1.44(0.47, 4.33)	0.515
Transaminitis	19(10.50)	37(20.44)	0.51(0.30,0.88)	0.015
Alcohol withdrawal syndrome	1(0.55)	4(2.21)	0.22(0.02,1.96)	0.176
DKA	4(2.21)	7(3.87)	0.69(0.20,2.39)	0.569
CRBSI	7(3.87)	1(0.55)	7.31(0.89,59.78)	0.063
AF with RVR	4(2.21)	4(4.42)	0.54(0.16,1.79)	0.319

RR, relative risk; DIC, disseminated intravascular coagulation; UGIH, upper gastrointestinal hemorrhage; DKA, diabetic ketoacidosis; CRBSI, catheter-related blood stream infection; AF with RVR, atrial fibrillation with rapid ventricular response. [a] multivariable analysis adjusted for potential confounders (CXR category, HFNC, LFNC and baricitinib)

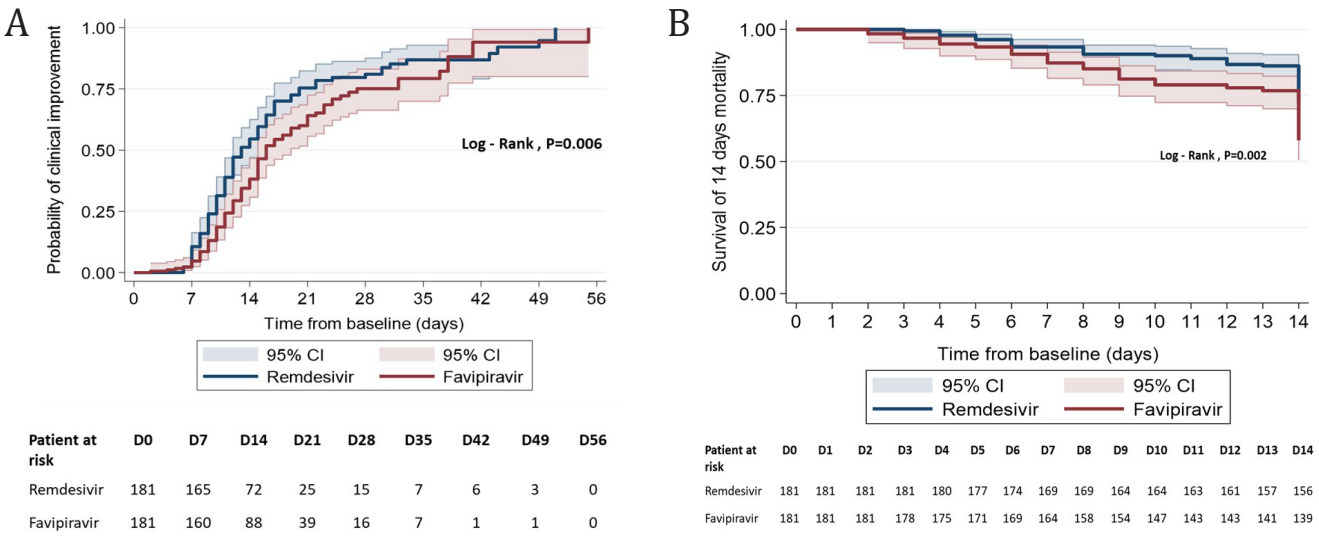
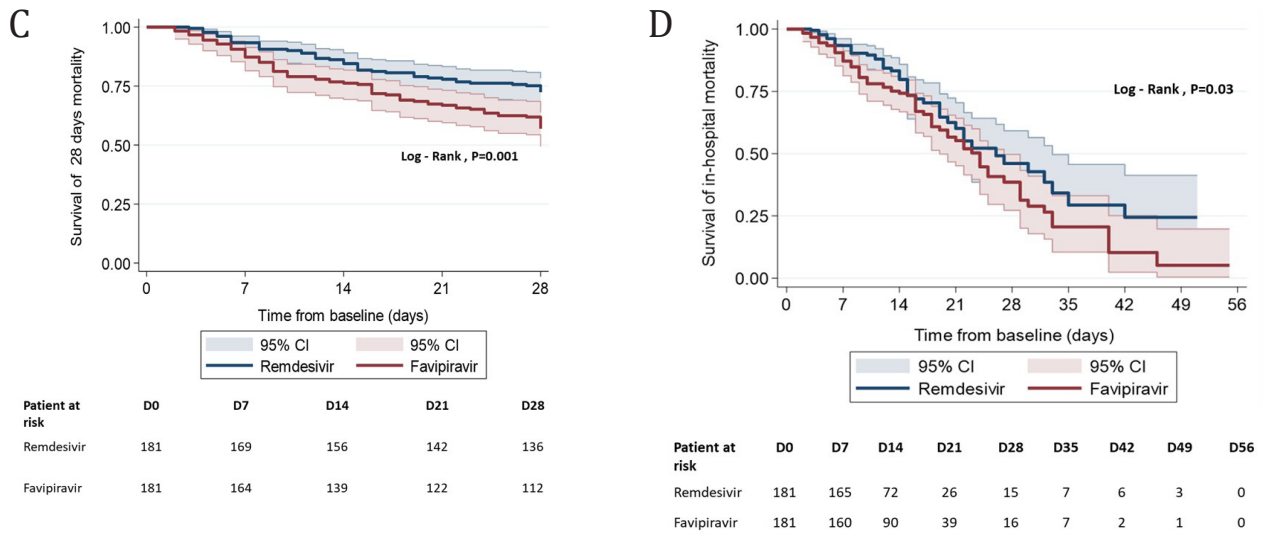


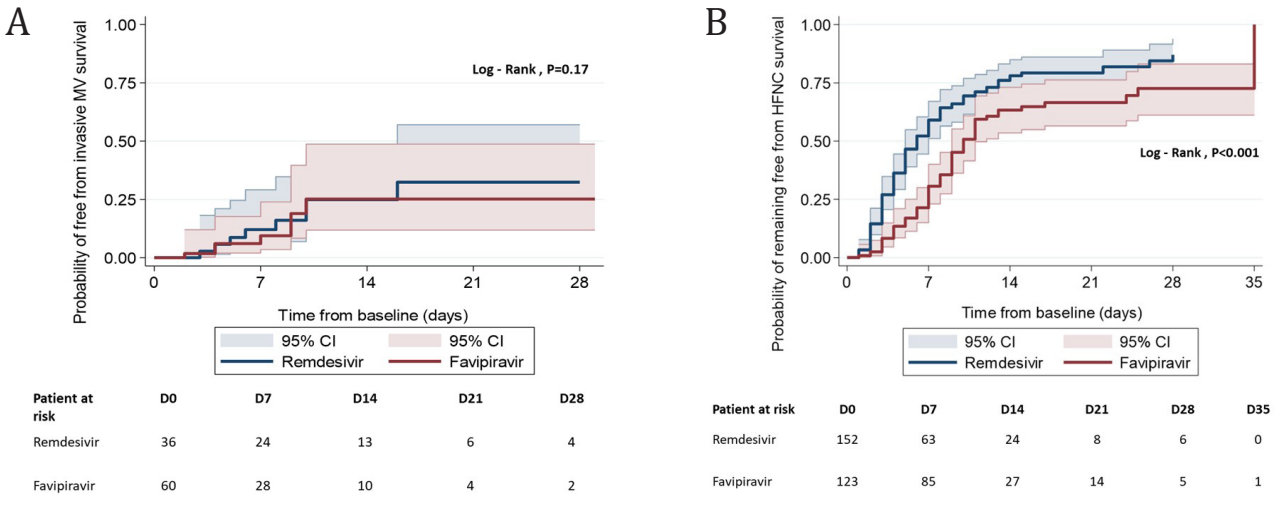
Figure 4. Survival plots of clinical improvement (A), 14-day mortality (B), 28-day mortality (C) and in-hospital mortality (D) from cause specific hazard analysis between the remdesivir and favipiravir treatment groups



Patient at risk	D0	D7	D14	D21	D28
Remdesivir	181	169	156	142	136
Favipiravir	181	164	139	122	112

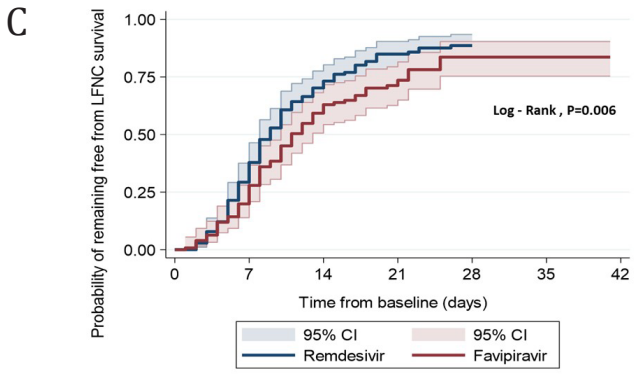
Patient at risk	D0	D7	D14	D21	D28	D35	D42	D49	D56
Remdesivir	181	165	72	26	15	7	6	3	0
Favipiravir	181	160	90	39	16	7	2	1	0

Figure 4. Survival plots of clinical improvement (A), 14-day mortality (B), 28-day mortality (C) and in-hospital mortality (D) from cause specific hazard analysis between the remdesivir and favipiravir treatment groups (Cont.)



Patient at risk	D0	D7	D14	D21	D28
Remdesivir	36	24	13	6	4
Favipiravir	60	28	10	4	2

Patient at risk	D0	D7	D14	D21	D28	D35
Remdesivir	152	63	24	8	6	0
Favipiravir	123	85	27	14	5	1



Patient at risk	D0	D7	D14	D21	D28	D35	D42
Remdesivir	140	99	40	18	10	0	0
Favipiravir	126	100	44	25	11	1	0

Figure 5. Kaplan-Meier curves for the probability of remaining free from invasive mechanical ventilation (A), HFNC (B), and LFNC (C). Remaining free from oxygen supplementation was evaluated by cause specific hazard analysis between remdesivir and favipiravir treatment groups

Discussion

The first double-blind, randomized, placebo-controlled trial to study the efficacy of remdesivir among adults was the ACTT-1. Results showed that remdesivir was superior to placebo in terms of shortening the time to recovery among hospitalized patients with COVID-19 pneumonia (rate ratio for recovery, 1.29; 95%CI, 1.12–1.49; p<0.001, log-rank test).[16]

This presented study showed that remdesivir significantly increased the proportion of clinical improvement and reduced in-hospital mortality. The results of this study were consistent in clinical improvement and mortality benefit, with several related studies examining the efficacy of remdesivir.[16, 19, 20] Remdesivir treatment in the early stages of COVID-19 is important, as remdesivir phase 3 trials showed that both 10-and 5-day remdesivir treatment improved the time to recovery for hospitalized patients with COVID-19 pneumonia.[17] In a subsequent RCT, remdesivir, administered within seven days after the onset of COVID-19, among patients with high risk COVID-19 progression (age ≥60 years, hypertension, cardiovascular disease, cerebrovascular disease, diabetes, immuno-compromised, mild to moderate chronic kidney disease, chronic liver disease, chronic lung disease, current cancer or sickle cell disease) reduced the risk of hospitalization and death.[18] Although remdesivir was the standard treatment for patients with COVID-19 pneumonia requiring oxygen supplementation, the benefits of remdesivir treatment remained unclear. In the present study, the authors compared the efficacy of remdesivir vs. favipiravir, in which both groups received standard care, corticosteroid and anticoagulant treatment, as indicated. During this study, 57% (244/425) of patients received remdesivir, and 43% (181/425) received favipiravir at the modular ICU and cohort ward. The results of this study agreed with a retrospective comparative study by Garibaldi et al.[19] reporting that remdesivir was associated with faster clinical improvement. This was consistent with a related study. The results of the ACTT-1 study suggest that remdesivir could shorten recovery time among patients with COVID-19 and lower respiratory tract infections requiring oxygen supplementation. In addition, patients receiving LFNC had the greatest benefit from remdesivir.[16] This was similar to our findings in that remdesivir significantly increased the proportion of cases free from HFNC and LFNC, while all patients in our cohort had COVID-19 pneumonia requiring oxygen supplementation at baseline. This current study showed similar clinical improvement benefits to those mentioned studies, especially among patients requiring oxygen supplementation. In conclusion, remdesivir might enhance clinical improvement and significantly increase the proportion of cases free from HFNC and LFNC use.

This might be explained by the fact that each antiviral drug has a different antiviral effect. Almoosa et al.[6] reported that favipiravir was not associated with significantly improved clinical symptoms among patients with severe COVID-19 pneumonia. They also found that patients receiving favipiravir presented a longer duration of fever and were more likely to require IMV and experience ARDS progression compared with the control group. Favipiravir may produce a weak antiviral effect in treating patients with severe COVID-19. Although no significant reduction was noted in 14- and 28-day mortality among patients receiving both remdesivir and corticosteroids, possibly due to the small sample size, this combination tended to reduce deaths. In the present study, remdesivir was significantly associated with a reduction of 32% in in-hospital mortality compared with favipiravir. Our findings were consistent with a study conducted in Denmark[20] and the ACTT-1,[16] reported that remdesivir could reduce 30-day mortality. An open-label, randomized clinical trial in Malaysia[21], conducted to study the efficacy of favipiravir compared with standard care, revealed that early treatment with oral favipiravir did not prevent their disease progression from nonhypoxia to hypoxia, nor did it significantly reduce in-hospital mortality among patients with COVID-19 at high risk of

disease progression (2.0 vs. 0%; OR=2.54; 95% CI: 0.76–207.84; p=0.08).

In the present study, favipiravir exhibited fewer effects on clinical improvement and mortality than remdesivir. A systematic review and meta-analysis by Hassanipour et al.[22] revealed that favipiravir might not reduce mortality among patients with COVID-19 with mild to moderate symptoms. In vitro studies have shown that remdesivir was highly effective in inhibiting pathogenic human coronaviruses, including SARS-CoV, Middle Eastern respiratory syndrome coronavirus, SARS-CoV-2 and Ebola virus.[23]

Additionally, in animal studies, Szemiel et al.[24] reported the effects of high dose favipiravir for treating SARS-CoV-2-positive hamsters. The drug had an antiviral effect but was not found to improve recovery rates. Simultaneously, remdesivir was studied in monkeys with SARS-CoV-2. Remdesivir reduced pulmonary infiltration on CXR and virus titer in bronchoalveolar lavages after 12 hours of treatment, although viral shedding from the upper respiratory tract did not decrease. This suggested that remdesivir possessed a potential anti-SARS-CoV-2 activity that may be more pronounced in the early treatment of infection.[25] No evidence of benefit exists comparing efficacy between remdesivir and favipiravir. Therefore, based on our results, remdesivir may be a promising drug for treating COVID-19 pneumonia requiring oxygen supplementation.

An inconsistency with the WHO Solidarity Trial was noted, which reported that remdesivir, hydroxychloroquine, lopinavir and interferon regimens had little effect on reducing overall mortality, IMV and length of hospital stay.[26] Subsequently, one trial reported that remdesivir had no clinical benefit among patients with COVID-19 pneumonia requiring oxygen supplementation. Moreover, in a double-blind, placebo-controlled, multicenter trial in China, remdesivir showed no difference in time to clinical improvement (HR =1.23 [95% CI 0.87–1.75]) compared with controls.[8] Most patients in this study (approximately 80%) were treated with corticosteroid 65 to 70 %, presenting mild symptoms and requiring LFNC. The remaining 10 to 20% were patients requiring HFNC or NIV. In two studies, a conflict was observed with our findings concerning clinical improvement. This might have stemmed from patients in the WHO solidarity cohort presenting less severe symptoms and a smaller proportion of HFNC use, so no significant difference was found in the clinical benefit of remdesivir. However, in our study, the majority of cohort patients had HFNC use 60 to 70% and LFNC use 30 to 40%, showing greater symptom severity than that of the WHO solidarity trial. This might explain the significant clinical benefit of remdesivir in a recent study.

Regarding complications, the present study indicated that remdesivir reduced the risk of acute respiratory failure (COVID-19 pneumonia progression). This was consistent with a prospective, observational study by Falcone et al.,[27] reporting that remdesivir could reduce the risk of progression to severe disease among up to 55% of hospitalized patients with COVID-19 pneumonia within five days of symptom onset. Another RCT, which included 562 nonhospitalized patients with a high risk of COVID-19 progression treated with remdesivir for three days, showed that remdesivir could reduce the risk of hospitalization and death by 87% compared with placebo.[18]

In this study, the proportion of transaminitis was smaller in the remdesivir group compared with the favipiravir group. The mechanism of drug-induced liver injury might be the idiosyncratic reaction of favipiravir or its derivatives. This remains unknown as favipiravir is metabolized via the liver by aldehyde oxidase and xanthine oxidase.[28] Kaur et al.[29] reported common side effects of favipiravir are increases in hepatic enzyme levels (23.7%), QT prolongation (5.4%) and skin and subcutaneous tissue disorders (15.4%). On the other hand, remdesivir has also been reported to be involved in drug-induced liver injury. It may have resulted from a reaction between P-glycoprotein (P-gp) inhibitors and remdesivir, where P-gp inhibitors result in decreased excretion of remdesivir from hepatocytes, leading to increased hepatocyte concentrations beyond the toxic threshold and

direct hepatotoxic effects. Elevations of AST and ALT levels were associated with the use of remdesivir for treating COVID-19, which were generally mild to moderate in severity and symptoms and often resolved on their own without jaundice; therefore, the liver enzyme should be monitored periodically during treatment.[30]

The strength of this study was that the treatments were based in routine clinical practice, consistent with the context of the local practice guidelines in Thailand. During treatment, side effects and complication events were monitored. Moreover, double adjustment was used to remove residual confounding factors. After propensity score matching, we also found an imbalance of the variables in both groups. Therefore, using multivariable regression adjustment could dramatically remove residual confounding bias.[14]

However, this study encountered several limitations. Firstly, it employed a retrospective observational cohort design; residual and unmeasured confounders could not be controlled, which might have interfered with evaluating treatment outcomes. Secondly, the sample size was small. Especially the results should be confirmed through analyses with propensity scores matching larger sample sizes. This should be tested in an RCT. Thirdly, the mean propensity score in both groups remained significantly different. The authors attempted to adjust the propensity score in the final model to reduce residual confounders. However, the results did not change the direction of treatment outcomes. Finally, the time from symptom onset to the start of antiviral treatment might have affected the outcomes. The authors could not adjust this variable for analyzing the outcomes because insufficient data records were in the digital database.

In the future, more RCTs should be conducted to determine the effectiveness of remdesivir among patients with COVID-19 pneumonia, including sufficient sample size. This will help to confirm our findings and better understand the efficacy of remdesivir treatment. In addition, further studies on the effectiveness of remdesivir at higher doses and coadministration with other antiviral drugs (SARS-CoV-2 neutralizing antibodies) and IL-1, IL-6, or TNF-α inhibitors to reduce immunopathological host responses affecting the severity of COVID-19 should be conducted in the future.

Conclusion

In summary, the present study provides evidence that patients with COVID-19 pneumonia requiring oxygen supplementation should be treated with remdesivir to increase clinical improvement, reduce in-hospital mortality and increase cases free from HFNC and LFNC use. However, this should only occur when compared to favipiravir treatment in a specific population.
Availability of data and materials

Acknowledgments

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Competing interests

The authors declare they have no conflicts of interest directly relevant to the content of this article.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

All authors have made substantial contributions to this work and have approved the final version of the manuscript. Concept and design: SK and WN. Acquisition of data: SK. Statistical analysis: PTd. Interpretation of data: SK, WN, and PTd. Writing original draft: SK, PTc, and WN. Writing review and editing: all authors.

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