Effectiveness of Favipiravir monotherapy in the treatment of COVID-19: real world data analysis from Thailand

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Summary

Background Previous studies showed that Favipiravir, a selective viral ribonucleic acid dependent-ribonucleic acid polymerase inhibitor, exhibited a trend of clinical improvement within 14 days and promoted viral clearance by day 7, without reduction of mortality rate in COVID-19.

Methods During the COVID-19 pandemic, Department of Medical Services (Thailand) formulated National Clinical Treatment Guidelines for COVID-19 and approved Favipiravir to eight medical centres. After treatment with Favipiravir monotherapy, we compared real-world data analysis to supportive treatment without antiviral agents.

Findings We analysed 12,888 COVID-19 patients between June 1, 2021, and July 31, 2021. This group study excluded 66 asymptomatic and 4634 COVID-19 patients treated with other antiviral agents. The 4896 mild, 2357 moderate, and 935 severe COVID-19 patients were analysed. All patients neither had previous SARS-CoV-2 infection nor received an mRNA vaccine during study period. Favipiravir monotherapy reduced the 28-day mortality risk in severe COVID-19 by relative risk (RR) = 0.72 (95% CI 0.58–0.91 P = 0.006) after adjustment for aging and hypertension. However, in mild and moderate COVID-19, Favipiravir monotherapy did not significantly reduce 28-day mortality risk by RR = 0.59 (95% CI 0.06–5.43 P = 0.65) after adjustment for aging, and RR = 0.60 (95% CI 0.32–1.13 P = 0.11) after adjustment for aging and obesity, respectively. In the patient with recovery, Favipiravir monotherapy exhibited a shortening time to recovery when compared to supportive treatment without antiviral agents (mean ± SD by 9.6 ± 7.1 vs. 12.9 ± 7.6 days: P < 0.0001, 10.0 ± 5.9 vs. 12.4 ± 5.3 days: P < 0.0001, and 11.2 ± 7.8 vs. 13.1 ± 8.0 days: P < 0.0001 in mild, moderate, and severe COVID-19 respectively).

Interpretation Real-world data analysis showed that favipiravir monotherapy was superior to supportive treatment without antiviral agents in shortening the recovery time in surviving patients and significantly reducing 28-day mortality risk in severe COVID-19.

Funding Department of Medical Services, Ministry of Public Health, Thailand.

Keywords: Favipiravir; Molnupiravir; Paxlovid; Nirmatrelvir; Remdesivir; COVID-19; Mortality rate; Time to recovery

Introduction

Favipiravir, a selective viral ribonucleic acid dependent-ribonucleic acid polymerase inhibitor, approved in Thai National Guideline for the treatment of COVID-19 in 2021.[1] Department of Medical Services, Ministry of Public Health of Thailand, the formal national authority for contributed National Clinical Treatment Guideline for COVID-19 and analysing treatment outcomes in Thailand and contributed Favipiravir for all registered COVID-19 patients in the national database. The Food and Drug Administration of Thailand (Ministry of Public Health) in emergency approved Favipiravir for treatment of COVID-19. From June 1, 2021, to July 31, 2021, delta-variant SARS-CoV-2 was the dominant strain spreading in Thailand, and all people had not yet received mRNA vaccine, which proved to be effective prevention of delta-variant SARS-CoV-2 infection.

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Research in context

Evidence before this study

The National health crisis in Thailand, the second country hit by COVID-19 since December 2019, forced Department of Medical Services, Ministry of Public Health, Thailand to develop guidelines for treating COVID-19 using Favipiravir monotherapy without evidence base support in early 2020. A real-world analysis was performed to analyse the effectiveness of favipiravir in July 2020 (delta variant period of COVID-19 pandemic) to prove the results of Thai national guidelines, which systematically collect the data in the DMS data bank and National Database of the health system. The previous clinical evidence of a randomised controlled trial never showed the effectiveness/efficacy of favipiravir in reducing mortality risk due to a small sample size.

Added value of this study

During the SARS-CoV-2 delta variant period in Thailand, the clinical course of COVID-19 symptoms was reduced significantly after early treatment within seven days from the onset of first symptoms. To the best of our knowledge, this is the first report of effectiveness that included both improvement of clinical outcomes in all patients and reduce mortality risk in severe COVID-19 after early treatment with favipiravir.

Implications of all the available evidence

The early treatment within five days after the first symptom was the critical success factor for treatment success. The current evidence indicates that favipiravir is effective in COVID-19, both moderate to severe and severe pulmonary involvement. The benefit of early treatment with Favipiravir monotherapy is reduced mortality risk, especially in elderly (>65 years), hypertension, and obesity patients.

In a previous systematic review and meta-analysis, Favipiravir monotherapy showed promising improvement in clinical outcomes of treatment in mild to moderate and moderate to severe COVID-19 patients within seven days after hospitalisation. In meta-analysis, the mortality rate in the Favipiravir group was approximately 23% lower than in the control group, but this finding is not statistically significant (RR = 0.77, 95% CI: 0.26–2.19; P = 0.625, I^2 = 0.0%, P = 0.585),[2] however, Favipiravir promoted viral clearance in 7 days without requiring supplemental oxygen therapy and transferred to the intensive care unit, and reduced the hospitalisation duration in mild-to-moderate COVID-19 patients, which can reduce the risk of severe disease outcomes in patients. The significantly higher viral clearance rate than those in the control group 10 and 14 days after initiation of treatment [RR: 1.13 (95% CI: 1.00, 1.28), P = 0.04; I^2 = 39% for day 10 and RR: 1.16 (95% CI: 1.04, 1.30), P = 0.008; I^2 = 38% for day 14] and a significantly shorter hospital stay [MD: –1.52 (95% CI: –2.82, –0.23), P = 0.02; I^2 = 0%]. Conclusions FVP significantly promotes viral clearance.[3] However, other studies had small sample sizes and did not show reduced time to recovery and mortality risk.[4–12]

To identify the effectiveness of Favipiravir monotherapy in National Treatment Guidelines for COVID-19, we performed real-world data analysis to diminish the inadequate power of previous clinical randomised control trials by using a real-world data model in the COVID-19 emergency treatment period.[13]

Methods

Department of Medical Services, Ministry of Public Health, Thailand is the leader team of government which contribute update national clinical treatment guideline of COVID-19 and supply Favipiravir for all patients in eight medical centres and registered clinical data of all patients into real-time electronic database system[12] which grading by severity index of COVID-19 composed of asymptomatic which not recommended for antiviral treatment, mild COVID-19 without pneumonia and no risk factors to severe disease progression (severity index <5) probably treated with Favipiravir as soon as possible within 7 days after first symptom up to clinical judgment of attending physicians, mild COVID-19 with pneumonia or with any one of risk factors to severe disease progression such as chronic obstructive pulmonary disease, cardiovascular disease, congenital heart disease, stroke, uncontrolled diabetes mellitus, obesity with body mass index ≥30, cirrhosis, immunocompromised and lymphopenia less than 1000 cell/mm^3 (severity index 5–8), may be treated with Favipiravir for at least five days or more, as soon as possible within seven days after the first symptom up to the clinical judgment of attending physicians, and finally severe COVID-19 patients with severe pneumonia (desaturation of blood oxygen less than 96% or drop >3% from baseline or exercise induce hypoxemia or pulmonary infiltration progression) (severity index ≥9), should be treated with corticosteroid intravenously and may be treated with Favipiravir for 5–10 days as soon as possible within seven days after the first symptom or may be treated with Remdesivir or other antiviral agent, up to the clinical judgment of attending physicians.[1] Favipiravir dosage was 1800 mg twice on the first day followed by 800 mg per day for at least five days in patients with body weight less than 90 kg, and 2400 mg twice on the first day followed by 1000 mg twice per day for at least five days in patients with body weight less

than 90 kg. Dexamethasone dosage was 6–20 mg per day, depending on physician judgment in severe COVID-19 patients.[1] All patients treated with Remdesivir, Lopinavir-ritonavir, and other antiviral agents were excluded from real-world data analysis.

We performed the prospective observational study, by using collected real-world data entry into the database for demographics, clinical status, and final clinical outcomes of all COVID-19 patients in eight medical centres under the operation management of the Department of Medical Services, Ministry of Public Health of Thailand at https://ecrf.dms.go.th/form-covid/dashboard.php.[12] This real-world data analysis was part of registered protocol NCT04303299. We analysed the clinical status and outcomes in a non-randomised real-world data model between June 1, 2021, and July 31, 2021. All patients were admitted to the hospital, and were analysed by sub-categories mild, moderate, and severe COVID-19 by national clinical treatment guidelines of COVID-19[1] and severity index. Mean and SD was used to analyse continuous data such as age and the time to recovery in survive patients, excluding death before analysis, using student *t*-test and Log-rank test. We used the Pearson chi-square test to analyse gender and other risk factors. The 28-day mortality rate was analysed by relative risk with a 95% confidence interval (CI), Number Need to Treat (NNT) with a 95% confidence interval, and log-rank test, excluding death before analysis. We adjusted relative risk in mild COVID-19 by aging ($P = 0.005$), we also adjusted the relative risk of the moderate COVID-19 group by aging and obesity ($P < 0.001$), the patients with severe COVID-19 was adjusted by aging ($P < 0.001$) and hypertension ($P = 0.001$), which affect outcomes of death after being treated with Favipiravir compared to supportive treatment without antiviral agents. Other risk factors did not affect death outcomes after being treated with Favipiravir compared to supportive treatment without antiviral agents.

All individuals did not consent to clinical research in the study but consent for regular in-patient treatment in the hospital and discussed with attending physician to choose treatment. We included all recovery patients in Log-rank test for time to recovery and excluded all deaths before the time to recovery analysis. All authors had permission from a government authority, the Department of Medical Services of the Ministry of Public health, to analyse real-world data for emergency use of Favipiravir in COVID-19. Furthermore, Thai Food and Drug Administration approved Favipiravir for treatment of COVID-19 in the emergency guideline of the Department of Medical Services.

Role of funding source

The funders had no role in study design, data collection or analysis, preparation of the manuscript or decision to publish.

Results

A total of 12,888 COVID-19 patients were analysed in the era of delta variant of the SARS-CoV-2 outbreak between June 1, 2021 and July 31, 2021, in Thailand (Fig. 1). The 66 asymptomatic and 4634 COVID-19 patients treated with other antiviral agents were excluded. The 4896 mild, 2357 moderate, and 935 severe COVID-19 patients were analysed. All patients had no history of previous SARS-CoV-2 infection and did not receive an mRNA vaccine in this study period (Table 1). Demographic data showed no difference in the baseline of gender, previous SARS-CoV-2 infection history, obesity, days from onset to treatment < 7 days, presence or absence of steroid administration, severity score at admission, and ventilator/ECMO use, in each severity

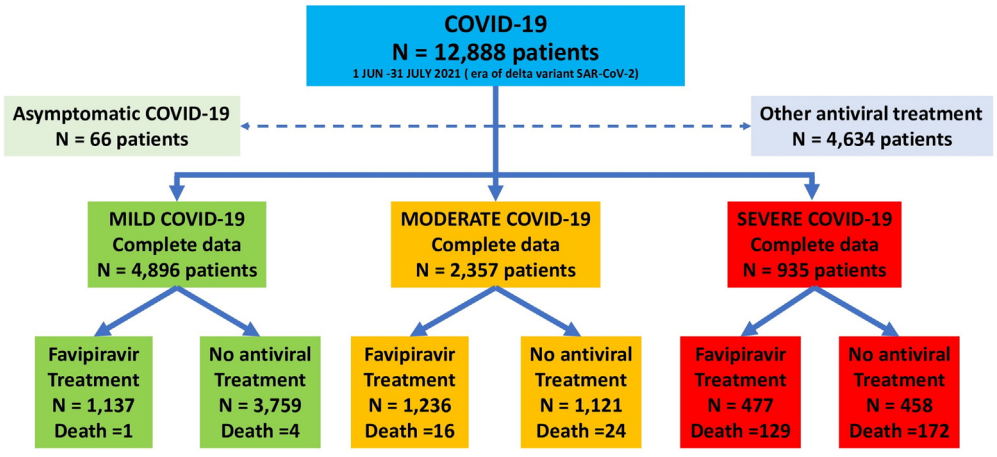

Fig. 1: Real world data from Thailand—treatment and deaths in mild, moderate, and severe COVID-19 patients.

	Favipiravir	No antiviral agents	P value
Mild COVID-19 (n)	1137	3759	
Age mean ± SD	36.6 ± 21.8	35.5 ± 17.5	0.07
Gender male n, (%)	499 (43.8)	1800 (47.4)	0.03
Risk factors Number, (%)			
Elderly >60 Years	179 (15.7)	344 (9.0)	<0.001
Diabetes mellitus	57 (5.0)	121 (3.1)	0.003
Obesity (BMI >30)	43 (3.7)	158 (4.1)	0.56
Hypertension	179 (15.7)	234 (6.1)	<0.001
Moderate COVID-19 (n)	1236	1121	
Age mean ± SD	43.2 ± 19.1	44.0 ± 17.7	0.29
Gender male n, (%)	573 (50.3)	526 (46.9)	0.09
Risk factors n, (%)			
Elderly >60 Years	253 (20.4)	221 (19.7)	0.64
Diabetes mellitus	139 (11.2)	136 (12.1)	0.77
Obesity (BMI >30)	98 (7.9)	86 (7.6)	0.81
Hypertension	265 (21.4)	205 (18.2)	0.05
Severe COVID-19 (n)	477	458	
Age mean ± SD	56.3 ± 16.3	572 ± 16.2	0.40
Gender male n, (%)	241 (50.5)	231 (50.4)	0.97
Risk factors n, (%)			
Elderly >60 Years	218 (45.7)	215 (46.9)	0.70
Diabetes mellitus	120 (25.1)	117 (25.5)	0.89
Obesity (BMI >30)	24 (5.0)	23 (5.0)	0.89
Hypertension	198 (41.5)	195 (42.5)	0.74

Table 1: **Demographic data.**

group. Only a significantly higher number of patients with diabetes mellitus, hypertension, and elderly in mild COVID-19 patients treated with Favipiravir compared to supportive treatment without antiviral agents ($P \leq 0.003$) but no difference in baseline demographic data in moderate and severe COVID-19 patients (Table 1).

The incidence of COVID-19 death within 28 days was lower in the Favipiravir group than supportive treatment without antiviral agents in mild, moderate and severe COVID-19 patients (0.08% [1 of 1137 patients] in the Favipiravir group as compared with 0.1% [4 of 3759 patients] in supportive treatment without antiviral agents in mild, 1.29% [16 of 1236 patients] in Favipiravir group as compared with 2.14% [24 of 1121 patients] in supportive treatment without antiviral agents in moderate, and 27.0% [129 of 477 patients] in Favipiravir group as compared with 37.5% [172 of 458 patients] in supportive treatment without antiviral agents in severe COVID-19 group) (Fig. 1).

In mild COVID-19, Favipiravir monotherapy did not reduce 28-day mortality risk by RR = 0.83 (95% CI 0.09–7.46 P = 0.16), RR = 0.59 (95% CI 0.06–5.43 P = 0.65) after adjustment for aging, as well as in moderate COVID-19 RR = 0.60 (95% CI 0.32–1.13 P = 0.11) for both before and after adjustment for aging and obesity. Interestingly, Favipiravir monotherapy reduced 28-day mortality risk in severe COVID-19 by RR = 0.72 (95% CI 0.59–0.86 P = 0.0007), RR = 0.72 (95% CI 0.58–0.91 P = 0.006) after adjustment for aging and hypertension. When combining data of moderate and severe COVID-19 patients, Favipiravir monotherapy reduced 28-day mortality risk by RR = 0.68, 95% CI (0.55–0.831) P = 0.0002, RR = 0.65 (95% CI 0.52–0.81 P = 0.0001) after adjustment for aging and hypertension (Tables 2 and 3)

In those recovery patients, Favipiravir monotherapy exhibited a shortening time to recovery when compared to supportive treatment without antiviral agents in mild COVID-19 (mean ± SD by 9.6 ± 7.1 vs. 12.9 ± 7.6 days: P < 0.0001), moderate COVID-19 (mean ± SD by 10.0 ± 5.9 vs. 12.4 ± 5.3 days: P < 0.0001), and severe COVID-19 (mean ± SD by 11.2 ± 7.8 vs. 13.1 ± 8.0 days: P < 0.0001) (Table 2). The log-rank test also showed a significant shortening in the time to recovery in all groups (Fig. 2). The real-world data analysis did not show significant differences in adverse events.

Discussion

The evidence base of Favipiravir monotherapy for the treatment of COVID-19 was limited due to the small sample size and power in previous randomised controlled studies.[2–12] Remdesivir monotherapy was approved to treat mild COVID-19 without evidence of improved mortality in severe COVID-19.[14] Early

	Favipiravir	No antiviral agents	P value
Mild COVID-19 (n)	1137	3759	
Time to recovery (day)	9.6 ± 7.1	12.9 ± 7.6	<0.0001
Mortality rate (%)	1 (0.08)	4 (0.10)	0.87
Relative Risk (95% CI)	0.83 (0.09–7.46)		0.16
Relative Risk (95% CI) after adjustment for aging ≥60 years	0.59 (0.06–5.43)		0.65
Number need to treat (benefit)	5739.4 (516.9 Harm to 438.0 benefit)		
Moderate COVID-19 (n)	1236	1121	
Time to recovery (day)	10.0 ± 5.9	12.4 ± 5.3	<0.0001
Mortality rate (%)	16 (1.29)	24 (2.14)	0.11
Relative Risk (95% CI)	0.60 (0.32–1.13)		0.11
Relative Risk (95% CI) after adjustment for aging ≥60 years and obesity (BMI ≥30)	0.60 (0.32–1.13)		0.11
Number need to treat	118.1 (507.2 Harm to 52.9 benefit)		
Severe COVID-19 (n)	477	458	
Time to recovery (day)	11.2 ± 7.8	13.1 ± 8.0	0.0001
Mortality rate (%)	129 (27.0)	172 (37.5)	0.0001
Relative Risk (95% CI)	0.72 (0.59–0.86)		0.0007
Relative Risk (95% CI) after adjustment for aging >60 years and hypertension	0.72 (0.58–0.91)		0.006
Number need to treat	9.5 (6.0 benefit to 21.9 benefit)		

Table 2: **Results.**

treatment of Molnupiravir, synthetic nucleoside derivative N4-hydroxycytidine and exerts its antiviral action through the introduction of copying errors during viral RNA replication, approved to treat mild to moderate COVID-19 by reducing the risk of hospitalisation or death in at-risk, unvaccinated adults with COVID-19.[15] Unfortunately, FDA Thailand approved Favipiravir without evidence supporting the risk reduction of death in a previous publication.[4–12,16] Previous systematic review showed that Favipiravir monotherapy enhances viral clearance in 14 day[3] and contributes to clinical improvement, especially fever,[17] and reduces requiring supplemental oxygen therapy[11] in mild to moderate COVID-19 patients. Although the trend is to improve clinical parameters but not reduce hospitalisation.[11] Early treatment with Favipiravir loading 45 mg/kg/day on the first day favours good clinical outcomes but early treatment within seven days was not significant in any

Mild COVID-19	**Relative risk (95% confidence interval)**	**P value**
Favipiravir oral * Death in mild COVID-19 [This study]	0.83 (0.09–7.46)	0.16
Monupiravir oral * Death or hospitalised in non-hospitalized patients[15]	0.69 (0.48–0.99)	0.04
Paxlovid oral		
* Death in non-hospitalised patients[19]	0.06 (0.003–1.15)	0.06
* Death or hospitalised in non-hospitalized patients[19]	0.11 (0.03–0.35)	0.0003
Remdesivir intravenous * Death or hospitalised in non-hospitalized patients[14]	0.13 (0.03–0.58)	0.007
Moderate/Severe COVID-19	**Relative risk (95% confidence interval)**	**P value**
Favipiravir oral [This study] * Death in moderate COVID-19	0.60 (0.32–1.13)	0.11
Favipiravir oral [This study] * Death in severe COVID-19	0.72 (0.59–0.86)	0.0007
Favipiravir oral [This study] * Death in moderate and severe COVID-19	0.68 (0.55–0.83)	0.0002
Favipiravir oral [This study] * Death in moderate and severe COVID-19 after adjustment for aging (≥60 years) and hypertension	0.65 (0.52–0.81)	0.0001
Remdesivir intravenous * Death in moderate to severe COVID-19[14]	0.73 (0.53–1.01)	0.06

Table 3: **Comparison of the relative risk reduction of mortality rate, death or hospitalisation in various antiviral studies [references [14,15,19] and this study].**

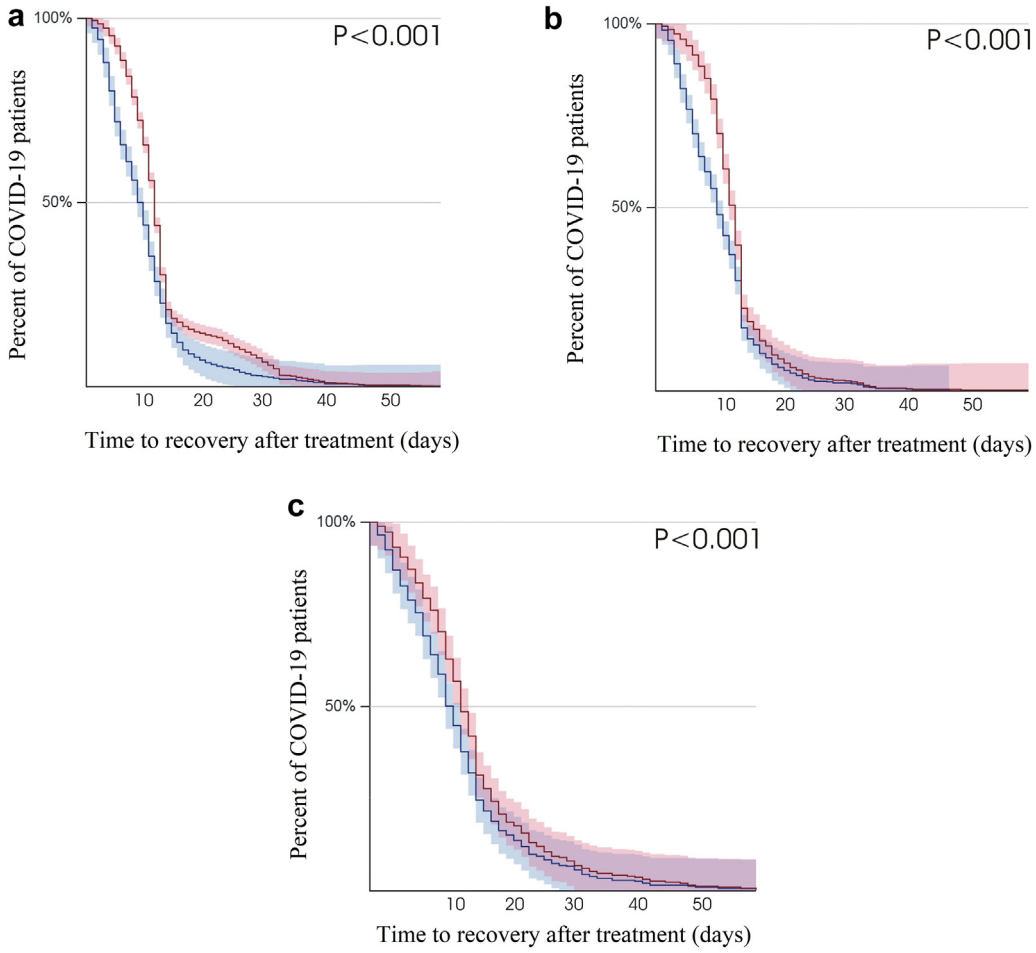

Fig. 2: Log rank test analysis of time to recovery/hospitalisation after treatment with Favipiravir (blue line) in mild [a], moderate [b], severe [c] COVID-19 compared to supportive treatment without antiviral agents (red line). Patients who died were excluded from analysis.

significant clinical outcome.[11] Our study showed the first non-randomised data to prove the effectiveness in shortening the time to recovery in COVID-19 and reducing the risk of mortality in severe COVID-19 and moderate to severe COVID-19. This study may be the effect of adequate sample size and power to determine the effectiveness of Favipiravir monotherapy in each COVID-19 subgroup.

When compared to FIGHT COVID-19 study,[18] the randomized control trial, which investigated the combination of Favipiravir and other antiviral agents in severe COVID-19, we found that the death rate in this study, favipiravir monotherapy, was 27.0% vs. 8.0% in Favipiravir plus Darunavir-ritonavir plus hydroxychloroquine (400 mg/day). Which administration of Favipiravir in FIGHT COVID-19 study was much higher in both dosage (Ebola dosage) and duration of treatment.

When comparing the relative risk reduction of mortality rate in various antiviral studies, we found a significant reduction of oral Nirmatrelvir/ritonavir (Paxlovid; 0/389 death in treatment group compare to 7/385 death in placebo), RR = 0.06, 95% CI (0.003–1.15) P = 0.06 and reduction of death or hospitalisation (Paxlovid; 3/389 in treatment group compare to 27/385 in placebo), RR = 0.11, 95% CI (0.03–0.35) P = 0.0003,[19] and intravenous Remdesivir (2/277 hospitalised or death in the treatment group compared to 15/268 hospitalized or death in placebo; RR = 0.13, 95% CI (0.03–0.58) P = 0.007) in mild non-hospitalisation COVID-19.[14] When we combined the data of moderate and severe COVID-19 in this study, there was a significant reduction in 28-day mortality rate after being treated with oral were RR = 0.68, 95% CI (0.55–0.831) P = 0.0002. There was no significant relative risk reduction of the 28-day mortality rate of Favipiravir and Monupiravir[14] in mild COVID-19 patients and Remdesivir[14] in moderate to severe COVID-19 patients (Table 3).

In this study, most patients did not receive mRNA vaccine, which proved to protect delta variant SARS-CoV-2 effectively in the study period and also no

patient with history of SARS-CoV-2 infection, so the baseline immunity from vaccination in all patients was not interfere with the main outcomes as confounding factors. However, there was no anti-SARS-CoV-2 antibody screening in this real-world data analysis, the effect of anti- SARS-CoV-2 antibody from previous SARS-CoV-2 infection in mortality risk were undetermined. The limitation of the study was only clinical judgment to treat or not treat with Favipiravir monotherapy in mild COVID-19 group with a significantly higher number of patients with diabetes mellitus, hypertension, and elderly in mild COVID-19 patients but not effect in moderate and severe COVID-19 groups, and this data analysis may be susceptible to the potentially selective bias by comparing treatments in real-world practice. Moreover, some risk factors related to mortality rate, such as D-dimer and interferon levels were not thoroughly explored in this real-world situation.

In conclusion, real world data analysis showed that Favipiravir monotherapy was superior to supportive treatment without antiviral agents in shortening the time to recovery in survival patients and significant reducing the 28-day mortality risk in severe COVID-19.

Contributors

Drafting the template and reviewing the literature search, figures, study design, data collection, data analysis, data interpretation, and writing - SK, AS, BM, and NM. Review before the final submission - SK. AS performed Thai-DMS-MoPH Database management and ST. SA is the Head of the Department of Medical Services, Ministry of Public Health, Thailand, who authorised the use of the data from the Thai-DMS-MoPH Database.

Data sharing statement

Data used for the current study is available with the corresponding author.

Declaration of interests

BM has received honoraria and travel reimbursement from Lundbeck, Pfizer, and Servier. NM has received travel reimbursement from Lundbeck and Pfizer. AS, ST, SA, and SK report no conflicts of interest in this work. Narong Maneeton and Benchalak Maneeton are husband and wife. Benchalak Maneeton is the sister of Subsai Kongsaengdao. The funders had no role in study design, data collection or analysis, preparation of the manuscript or decision to publish.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2023.100166.

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