ASSESSEMENT OF OUTCOMES FOLLOWING IMPLEMENTATION OF ANTIVIRAL TREATMENT GUIDELINES FOR COVID-19 DURING THE FIRST WAVE IN THAILAND

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Abstract. Thailand encountered its first coronavirus disease 2019 (COVID-19) outbreak in March 2020 and the Thailand Ministry of Public Health rapidly developed COVID-19 treatment guidelines. In this study we aimed to describe the outcomes among patients treated following those initial guidelines and determine factors significantly associated with poor outcomes in order to inform efforts to improve COVID-19 treatment guidelines for Thailand. Nine hospitals in Bangkok submitted data from their COVID-19 patients using standardized case record forms. A poor outcome was defined as death, ICU admission, requiring intubation or requiring high-flow oxygen. Factors associated with these outcomes were assessed. A total of 744 patients (48.8% male) were included in the study. The median (interquartile range) age of study subjects was 37 (27-48) years; 8.4% were aged >60 years, 5.6% of subjects were obese and 16.5% had underlying conditions: obesity, immunocompromised status, diabetes, chronic conditions of lungs, kidneys, liver, cardiovascular or cerebrovascular systems or had an absolute lymphocyte count <1,000 cells/mm^3. Among symptomatic patients, factors significantly independently associated with a poor outcome were: age >60 years (adjusted odds ratio (aOR): 2.50, 95% confidence interval (CI): 1.17-5.36, p = 0.018), having an underlying risk condition (aOR: 2.36, 95%CI: 1.27-4.39, p = 0.007), presenting with pneumonia (aOR: 6.60, 95%CI: 3.48-12.49,

p <0.001) and azithromycin use (aOR: 2.36, 95%CI: 1.30-4.31, p = 0.005). Among symptomatic patients, the factor significantly associated with lower odds of having a poor outcome was hospital admission within 4 days of symptom onset (aOR: 0.44, 95%CI: 0.24-0.82, p = 0.009). Subgroup analysis revealed hospital admission within 4 days of symptom onset was significantly associated with a lower risk of a poor outcome only among patients who received treatment that included favipiravir (crude odds ratio (cOR): 0.320, 95%CI: 0.152-0.662, p = 0.003), but not among those who received a ritonavir boosted protease inhibitor (lopinavir or darunavir) or hydroxychloroquine (or chloroquine) without favipiravir (cOR: 0.58, 95%CI: 0.18-1.91, p = 0.372). In summary, the factors significantly associated with greater odds of having a poorer outcome were: age >60 years, having an underlying risk condition, presenting with pneumonia and azithromycin use; and with lower odds of having a poor outcome was being treated with favipiravir within 4 days of symptom onset. Thai guidelines have been updated to include early initiation of favipiravir, particularly among those with underlying risk conditions. Further studies are needed to determine if implementation of guidelines taking into account of all these factors will result in improved outcomes.

Keywords: antivirals, favipiravir, COVID-19, COVID-19 outcomes, treatment guidelines, Thailand

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INTRODUCTION

Thailand encountered its first outbreak of coronavirus disease 2019 (COVID-19) in early March 2020 originating from attendees of a famous Thai Boxing competition in Bangkok which rapidly spread to individuals in surrounding bars and night clubs resulting in more than 2,500 cases (WHO, 2020). Due to this outbreak, the Thailand Ministry of Public Health (MoPH) held meetings with multidisciplinary experts, including infectious diseases specialists, pulmonologists, intensivists and policymakers, to develop clinical practice guidelines to guide clinicians using the scientific evidence available about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at that time (Cai *et al*, 2020; Cao *et al*, 2020; Chu *et al*, 2004; Liu *et al*, 2020; Wang *et al*, 2020).

The guidelines included the overall management of COVID-19, diagnosis, use of potential antiviral agents, isolation

and infection control measures. The first version of the COVID-19 guidelines in Thailand was posted on March 21, 2020 (Department of Medical Services, 2020), and recommended antiviral treatment as follows: 1) no antiviral treatment for asymptomatic patients, 2) combination antiviral treatment directed against different viral targets for symptomatic cases with the regimen dependent on the presence or absence of COVID-19 with pneumonia. The treatment protocol for those with COVID-19 with pneumonia consisted of: a triple drug combination of chloroquine (500 mg, twice daily) or hydroxychloroquine (600 mg twice daily on the first day then 400 mg twice daily) (CQ/HCQ), a ritonavir boosted protease inhibitor (bPI) (lopinavir/ritonavir 400/100 mg twice daily or darunavir/ritonavir 600/100 mg twice daily) and favipiravir (FPV), which is an oral RNA dependent RNA polymerase inhibitor (at a dosage of 1,600 mg or 60 mg/kg/day twice daily on the first day, then 600 mg or 20 mg/kg/day twice daily afterwards) (Department of Medical Services, 2020). For patients with COVID-19 and no pneumonia but having any of the following risk factors, age >60 years or <5 years, a body mass index (BMI) >35 kg/m^2, being immunocompromised, having diabetes, a chronic condition of the lungs, kidneys, liver, cardiovascular or cerebrovascular system or an absolute lymphocyte count <1,000 cells/mm^3, the treatment consisted of CQ or HCQ and a bPI (Department of Medical Services, 2020). The use of FPV for only COVID-19 pneumonia cases was due to the limited availability of FPV at that time. FPV is relatively safe and well tolerated (Hassanipour *et al*, 2021). The duration of treatment specified for our study subjects was 5 days but this could be extended to 10 days in cases of severe pneumonia. Azithromycin was recommended as adjunctive treatment for symptomatic cases only from May to September 2020, particularly for severely ill patients.

The COVID-19 treatment guidelines in Thailand have continuously been updated based on emerging knowledge. CQ/HCQ, bPI, and azithromycin are no longer recommended and steroid use is now recommended in severe cases. The MoPH now provides free diagnostic testing and antiviral treatment for all confirmed cases.

In this study we aimed to determine the clinical outcomes and identify factors associated with a poor clinical outcome following the implementation of initial Thai treatment guidelines. The results from this study can inform efforts to improve COVID-19 treatment guidelines for Thailand.

MATERIALS AND METHODS

Nine large hospitals in Bangkok submitted data on their virologically confirmed COVID-19 patients using standardized case record forms. Data were collected from March to June 2020, from the initial guidelines implementation until the first outbreak

(first wave) was controlled. The data collected were demographics, initial diagnoses (date and clinical symptoms), antiviral treatment (CQ, HCQ, bPI, or FPV), adverse effects of treatment, clinical outcomes, including the need for oxygen therapy (intubation and mechanical ventilation, high-flow, or low-flow rate oxygen support), intensive care unit (ICU) admission and death. This study was approved by the Siriraj Institutional Review Board (approval no. Si 319/2020).

At the time of data collection, all confirmed COVID-19 cases in Thailand were hospitalized for 14 days following the national outbreak control policy. For cases meeting treatment criteria, the antiviral medication was supplied by the MoPH and initiated on the day of admission except for favipiravir which may have been delayed at some study hospitals due to the approval and drug delivery process.

Data were analyzed using STATA software, version 11.2 (StataCorp, LP, College Station, TX). Independent two-group comparisons of continuous variables and categorical variables were performed using Mann-Whitney U and Chi-squared tests, respectively. Potential factors associated with poor outcomes, defined as death, ICU admission, requiring intubation, or requiring high-flow oxygen were analyzed with univariate logistic regression analysis. Factors identified as significant on univariate analysis were included in stepwise multivariate logistic regression analysis.

RESULTS

A total of 744 COVID-19 subjects (48.8% male) were included in this study. The median (interquartile range) age of study subjects was 37 (27-48) years (8.4% were aged >60 years). Forty-two subjects (5.6%) were obese and 123 (16.5%) had underlying conditions. On hospital admission, 211 (28.4%) were asymptomatic, 374 (50.2%) had non-pneumonia illnesses, of which 85 (22.7%) had risk factors and 159 (21.4%) had pneumonia (Fig 1). Among 533 symptomatic patients, 45 (8.4%) received CQ/HCQ alone, 10 (1.9%) received bPI alone, 197 (37.0%) received CQ/HCQ with bPI and 140 (26.3%) received FPV with CQ/HCQ and/or bPI. Of 132 patients who received azithromycin, 121 (91.7%) also received CQ/HCQ. Overall, 637 subjects (85.6%) received antiviral treatment in compliance with the guidelines at that time. There were 8 deaths (1.1%). Sixty-six subjects (8.9%) required ICU admission, 17 (2.3%) required intubation and 19 (2.6%) required high-flow oxygen. Seventy patients (9.4%) had at least one of these (poor) outcomes.

On univariate analysis of symptomatic patients, factors significantly associated with greater odds of a poor outcome were: being male (crude odds ratio (cOR): 1.89, 95% confidence interval (CI): 1.12-3.20, p = 0.018), aged >60 years (cOR: 4.42, 95%CI: 2.36-8.27, p <0.001), obesity (cOR: 2.79, 95%CI: 1.32-5.88, p = 0.007),

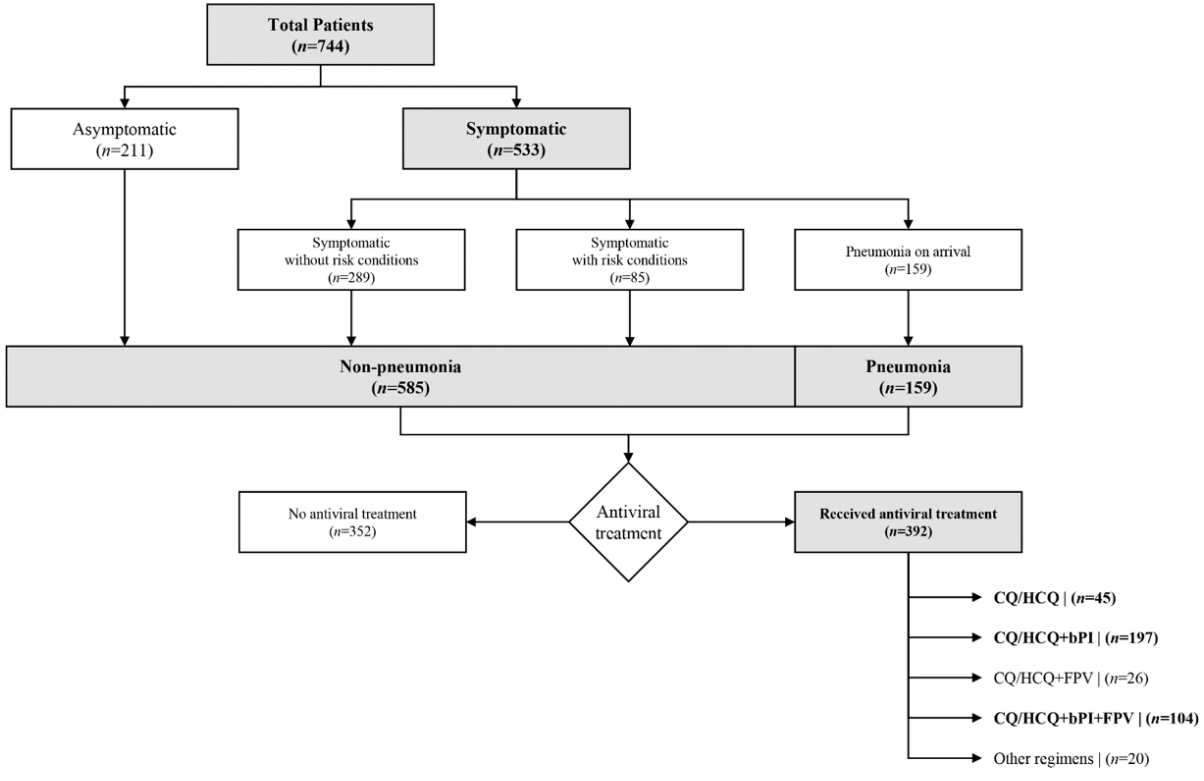

Fig 1 - Summary of distribution of study subjects by clinical presentation, risk conditions and initial antiviral treatment

bPI: boosted protease inhibitor (ritonavir boosted lopinavir or darunavir); CQ: chloroquine; FPV: favipiravir; HCQ: hydroxychloroquine

Risk conditions for this study were: age >60 years or <5 years, obesity defined as a BMI>35 kg/m^2 or other conditions potentially associated with severe COVID-19 illness, including immunocompromised conditions, diabetes, chronic conditions of the lungs, kidneys, liver, cardiovascular or cerebrovascular systems or a total lymphocyte count <1,000 cells/mm^3

having an underlying risk condition (cOR: 4.14, 95%CI: 2.45-6.99, p <0.001), having pneumonia on admission (cOR: 11.51, 95%CI: 6.32-20.94, p <0.001) and azithromycin use (cOR: 4.52, 95%CI: 2.68-7.62, p <0.001) (Table 1). Admission to the hospital within 4 days of symptom onset was associated with significantly lower odds of having a poor outcome (cOR: 0.30, 95%CI: 0.17-0.52, p <0.001); this remained significant among patients with pneumonia at presentation (cOR: 0.34, 95%CI: 0.16-0.72, p = 0.005) but not among patients with non-pneumonia illness (cOR: 0.65, 95%CI: 0.24-1.77, p = 0.397). The longer the time between symptom onset and hospital admission the greater the odds of having a poor outcome (cOR: 1.10, 95%CI: 1.04-1.16, p = 0.001). For each day between symptom onset and hospital admission the odds of having a poor outcome increased by 10%.

On multivariate analysis of symptomatic patients, factors significantly associated with greater odds of having a poor outcome were age >60 years (adjusted odds ratio (aOR): 2.50, 95% CI: 1.17-5.36, p = 0.018), having an underlying risk condition (aOR: 2.36, 95%CI: 1.27-4.39, p = 0.007), presenting with pneumonia (aOR: 6.60, 95%CI: 3.48-12.49, p <0.001) and azithromycin use (aOR: 2.36, 95%CI: 1.30-4.31, p = 0.005). On multivariate analysis, the factor significantly associated with lower odds of having a poor outcome was admission within 4 days of symptom onset (aOR: 0.44, 95% CI: 0.24-0.82, p = 0.009). On multivariate subgroup analysis, subjects admitted within 4 days of symptom onset who received FPV had significantly lower odds of having a poor outcome than those admitted after 4 days of symptom onset who received FPV, even after adjusting for confounding factors (aOR: 0.320, 95%CI: 0.152-0.662, p = 0.003) (Table 2). The benefit of admission and treatment within 4 days of symptom onset seen with those who received FPV noted above was not observed for patients receiving CQ/HCQ plus bPI without FPV (cOR: 0.58, 0.18-1.91, p = 0.372).

Adverse events due to COVID-19 treatment were reported in 78 subjects (39.6%) who received CQ/HCQ plus bPI and 31 subjects (29.8%) who received CQ/HCQ plus bPI plus FPV (Fig 2). Eighty-nine of the 109 (81.6%) reported adverse events were gastrointestinal and all were mild to moderate. Elevated transaminases were reported in 3 subjects (1.5%) who received CQ/HCQ plus bPI and 4 subjects (3.8%) who received FPV in combination with other treatments; the median (range) of alanine transaminase levels was 430 (35-826) U/l.

DISCUSSION

Our analysis of COVID-19 patients during the first outbreak (wave) in Thailand found being elderly (>60 years), having an underlying health condition and presenting with pneumonia were significantly associated with a poor

Table 1

Evaluation of factors significantly associated with requiring high-flow oxygen therapy, being intubated and requiring mechanical ventilation, admission to ICU or death on univariate and multivariate analyses (N = 533)

Patient characteristics	Total *n* (%)	Poor outcome		Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
		Yes (*n* = 70) *n* (%)	No (*n* = 463) *n* (%)				
Gender							
Male	279 (52.3)	46 (65.7)	233 (50.3)	1.89 (1.12-3.20)	0.018	-	-
Female	254 (47.7)	24 (34.3)	230 (49.7)	1		-	
Age							
Age <60 years	478 (89.7)	51 (72.9)	427 (92.2)	1		1	
Age ≥60 years	55 (10.3)	19 (27.1)	36 (7.8)	4.42 (2.36-8.27)	<0.001	2.50 (1.17-5.36)	0.018
Underlying risk conditions*							
Yes	120 (22.5)	34 (48.6)	86 (18.6)	4.14 (2.45-6.99)	<0.001	2.36 (1.27-4.39)	0.007
No	413 (77.5)	36 (51.4)	377 (81.4)	1		1	
Obesity							
Yes	40 (7.5)	11 (15.7)	29 (6.3)	2.79 (1.32-5.88)	0.007	-	-
No	493 (92.5)	59 (84.3)	434 (93.7)	1		-	
Presented with pneumonia							
Yes	159 (29.8)	54 (77.1)	105 (22.7)	11.51 (6.32-20.94)	<0.001	6.60 (3.48-12.49)	<0.001
No	374 (70.2)	16 (22.9)	358 (77.3)	1		1	

Table 1 (cont)

Patient characteristics	Total *n* (%)	Poor outcome		Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
		Yes (*n* = 70) *n* (%)	No (*n* = 463) *n* (%)				
Time from onset of symptoms to hospital admission							
<4 days	284/531 (53.5)	20/70 (28.6)	264/461 (57.3)	0.30 (0.17-0.52)	<0.001	0.44 (0.24-0.82)	0.009
>4 days	247/531 (46.5)	50/70 (71.4)	197/461 (42.7)	1		1	
Received Azithromycin							
Yes	129 (24.2)	37 (52.9)	92 (19.9)	4.52 (2.68-7.62)	<0.001	2.36 (1.30-4.31)	0.005
No	404 (75.8)	33 (47.1)	371 (80.1)	1		1	

*Underlying risk conditions among study subjects: immunocompromised (*n* = 23), diabetes (*n* = 49), chronic lung conditions (*n* = 10), kidney conditions (*n* = 5), liver conditions (*n* = 11), cardiovascular conditions (*n* = 13), hypertension (*n* = 63) and cerebrovascular conditions (*n* = 7). Some patients had more than one conditions.

CI: confidence interval; OR: odds ratio

Table 2

Multivariable logistic regression analysis of factors potentially associated with needing high flow oxygen, being intubated and receiving mechanical ventilation, being admitted to the ICU or death among study subjects who received medical treatment with favipiravir within 4 days of symptom onset (N = 140)

Variables	Adjusted OR (95%CI)	% Change in OR from base model	*p*-value
Received favipiravir alone or with other drugs within 4 days of symptom onset	0.320 (0.152-0.662)	Reference	0.003
Adjusted for:			
Age in years	0.341 (0.161-0.723)	6.6%	0.005
Age >60 years	0.328 (0.156-0.691)	2.5%	0.003
Gender	0.330 (0.156-0.696)	3.1%	0.004
Having an at-risk condition	0.316 (0.150-0.666)	1.3%	0.002
Obesity	0.331 (0.156-0.700)	3.4%	0.004
Having at least one risk factor	0.325 (0.153-0.689)	1.6%	0.003
Having received azithromycin	0.340 (0.159-0.726)	6.3%	0.005
Compliance with Thai guidelines	0.302 (0.142-0.643)	5.6%	0.002

CI: confidence interval; OR: odds ratio

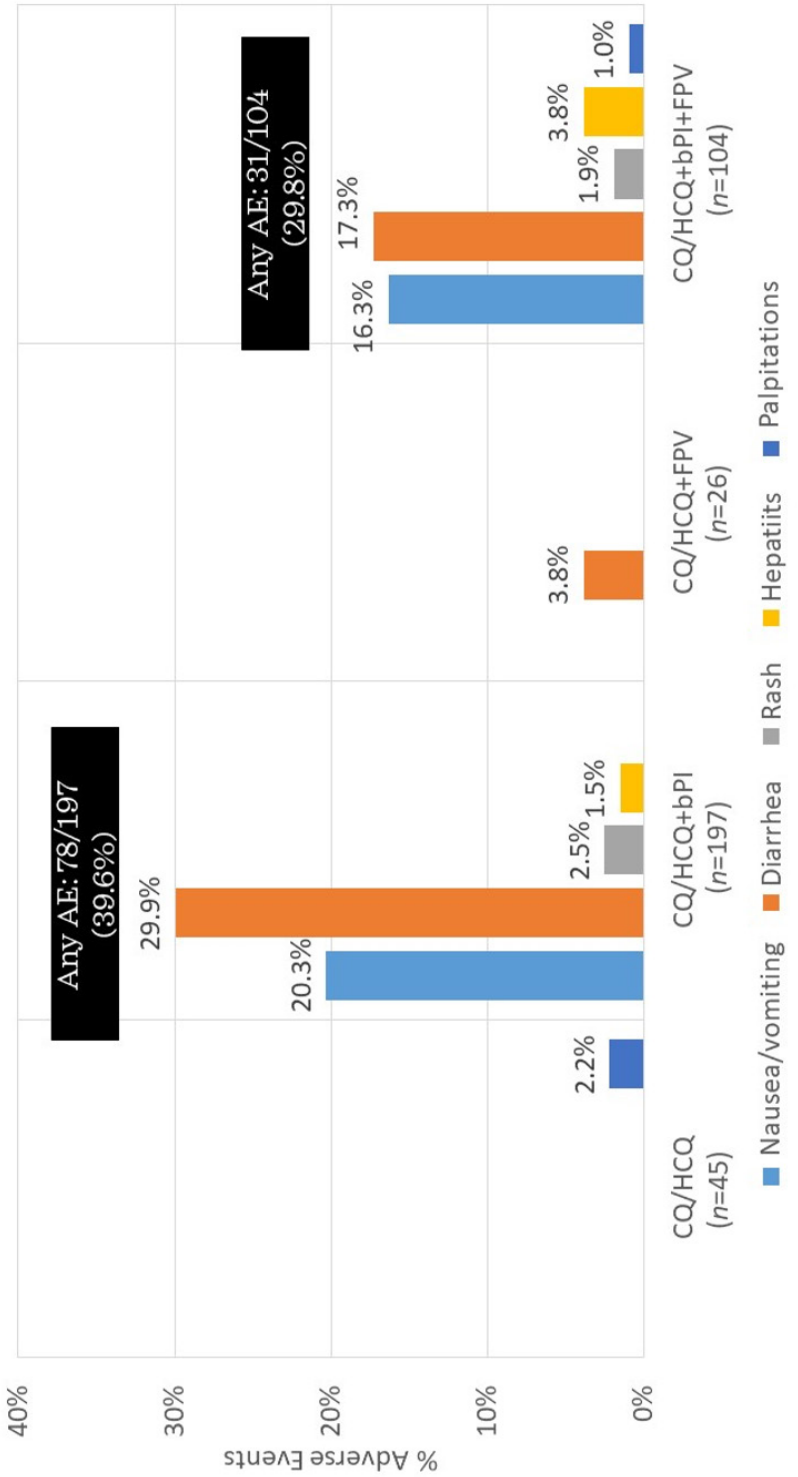

Fig 2 - Adverse events among study subjects who received antiviral treatment

AE: adverse event; bPI: boosted protease inhibitor (ritonavir boosted lopinavir or darunavir); CQ: chloroquine; FPV: favipiravir; HCQ: hydroxychloroquine

outcome, similar to previous studies (Hu and Wang, 2021; Sim *et al*, 2020; Wolff *et al*, 2021). We also found using azithromycin for COVID-19 treatment was significantly associated with a poor outcome, which is consistent with a recent study (Rosenberg *et al*, 2020). The timing of COVID-19 treatment initiation was also identified an important factor in our analysis as starting treatment within 4 days of symptom onset was significantly associated with a reduced risk of a poor outcome. However, it is important to note that comparison of individual treatment regimens was not possible in our analysis due to varying criteria for using the various regimens but it was clear that the inclusion of FPV in the early onset treatment regimen was significantly associated with a reduced risk of a poor outcome.

Several studies have assessed the efficacy of different drugs in treating COVID-19 patients. We found no significant association between using lopinavir/ritonavir in the treatment regimen and lower odds of having a poor outcome. In two separate randomized trials, lopinavir/ritonavir was shown not to be an effective treatment for COVID-19 (Cao *et al*, 2020; RECOVERY Collaborative Group, 2020b). We found no significant reduction in the odds of having a poor outcome by using hydroxychloroquine. Several studies have found and reported hydroxychloroquine treatment was not significantly associated with lower in-hospital mortality (Rosenberg *et al*, 2020; RECOVERY Collaborative Group, 2020a; Cavalcanti *et al*, 2020).

Favipiravir is an oral RNA dependent RNA polymerase inhibitor. Previous studies have reported favipiravir to be effective in SARS-CoV-2 viral clearance and improved clinical outcomes compared to lopinavir/ritonavir (Cai *et al*, 2020), arbidol (Chen *et al*, 2020) and no antiviral treatment (Ivashchenko *et al*, 2020). Initiation of FPV during the first 5 days after symptom onset as compared to initiating FPV >6 days after symptom onset was significantly associated with a shorter time to defervescence in a study from Japan among Japanese adults admitted with COVID-19 who were asymptomatic or only mildly symptomatic (Doi *et al*, 2020). A study from Thailand reported finding a significant reduction in SARS-CoV-2 viral load among patients who received combination regimens including FPV after 3 days of treatment (Manosuthi *et al*, 2021). A meta-analysis of COVID-19 subjects treated with favipiravir found its use was significantly associated with clinical improvement compared to subjects not treated with favipiravir but the reduction in mortality was not significant (Hassanipour *et al*, 2021). Adverse reactions reported with FPV use were: an increase in the serum uric acid level (4.79%), diarrhea (4.79%), a decrease in the neutrophil count (1.80%) and an increase in transaminase levels (1.80%) (FUJIFILM Toyama Pharmaceutical Co Ltd, 2017). In our study, the rate of elevated transaminase levels was low (3.8%) among subjects who received FPV in combination with other drugs. Other studies have also

reported low rates of elevated transaminases among subjects who received FPV (Cai *et al*, 2020; Chen *et al*, 2020; Hassanipour *et al*, 2021; Ivashchenko *et al*, 2020).

In our study, receiving FPV within 4 days of symptom onset was significantly associated with lower odds of a poor outcome. Another study reported early onset of antivirals also resulted in better outcomes while delay in treatment onset increases the risk of an inflammatory response (Weiss *et al*, 2020) requiring the need for glucocorticoids to reduce mortality (RECOVERY Collaborative Group, 2021).

Our retrospective study had several limitations. First, the chest x-rays were read clinicians, not radiologists, possibly resulting in greater variability of interpretations. Second, the determination of antiviral treatment was at the discretion of the attending clinician which may have resulted in bias for prescribing FPV in patients with more severe disease.

The Thai guidelines continue to be updated as new evidence is obtained. CQ/HCQ with bPI is no longer used and FPV is now used early in the course of symptomatic patients and those with increased risk factors for poor outcomes. Corticosteroids are now used for more severe cases and those at risk for complications. Further studies of outcomes with updates treatment guidelines are needed with each regimen change to determine if there is significant improvement in reducing poor outcomes in the study population.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

Cai Q, Yanga M, Liu D, *et al*. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering (Beijing)* 2020; 6: 1192-8.

Cao B, Wang Y, Wen D, *et al*. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med* 2020; 382: 1787-99.

Cavalcanti AB, Zampieri FG, Rosa RG, *et al*. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. *N Engl J Med* 2020; 383: 2041-52.

Chen C, Zhang Y, Huang J, *et al*. Favipiravir versus arbidol for COVID-19: a randomized clinical trial, 2020 [cited 2021 Jul 25]. Available from: URL: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v4.full.pdf+html

Chu CM, Cheng VC, Hung IF, *et al*. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; 59: 252-6.

Department of Medical Services. Clinical practice guideline on COVID-19 [cited 2021 Jul 25]. Available from: URL: https://covid19.dms.go.th/backend/Content/Content_File/Covid_Health/Attach/25630324214342PM_%E0%B9%81%E0%B8%99%E0%B8%A7%E0%B8%97%E0%B8%B2%E0%B8%87%E0%B8%81%E0%B8%B2%E0%B8%A3%E0%B8%94%E0%B8%B9%E0%B9%81%E0%B8%A5%E0%B8%A3%E0%B8%B1%E0%B8%81%E0%B8%A9%E0%B8%B2%2021%20%B8%A1%E0%B8%B5%E0%B8%84%2063.pdf [in Thai]

Doi Y, Hibino M, Hase R, *et al*. A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. *Antimicrob Agents Chemother* 2020; 64: e01897-20.

FUJIFILM Toyama Pharmaceutical Co Ltd. AVIGAN Tablets 200mg: Prescribing information, 2017 [cited 2021 Jul 25]. Available from: URL: https://www.cdc.gov.tw/File/Get/ht8jUiB_MIaKnlwstwzvw

Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials. *Sci Rep* 2021; 11: 11022.

Hu J, Wang Y. The clinical characteristics and risk factors of severe COVID-19. *Gerontology* 2021; 67: 255-66.

Ivashchenko AA, Dmitriev KA, Vostokova NV, *et al*. AVIFAVIR for treatment of patients with moderate COVID-19: interim results of a Phase II/III multicenter randomized clinical trial. *Clin Infect Dis* 2020; 73: 531-4.

Liu J, Cao R, Xu M, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020; 6: 16.

Manosuthi W, Jeungsmarn S, Okada P, *et al*. Nasopharyngeal SARS-CoV-2 viral load response among COVID-19 patients receiving favipiravir, 2021 [cited 2021 Jul 25]. Available from: URL: https://www.jstage.jst.go.jp/article/yoken/advpub/0/advpub_JJID.2020.827/_article

RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021; 384: 693-704.

RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med* 2020a; 383: 2030-40.

RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020b; 396: 1345-52.

Rosenberg ES, Dufort EM, Udo T, *et al*. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. *JAMA* 2020; 323: 2493-502.

Sim B, Chidambaram S, Wong X, *et al*. Clinical characteristics and risk factors for severe COVID-19 infections in Malaysia: a nationwide observational study. *Lancet Reg Health West Pac* 2020; 4: 100055.

Wang M, Cao R, Zhang L, *et al*. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res* 2020; 30: 269-271.

Weiss A, Jellingsø M, Sommera MOA. Spatial and temporal dynamics of SARS-CoV-2 in COVID-19 patients: a systematic review and meta-analysis. *EBioMedicine* 2020; 58: 102916.

World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) WHO Thailand Situation Report - 20 March 2020, 2020 [cited 2021 Jul 25]. Available from: URL: https://reliefweb.int/report/thailand/coronavirus-disease-2019-covid-19-who-thailand-situation-report-20-march-2020

Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for COVID-19 severity and fatality: a structured literature review. *Infection* 2021; 49: 15-28.