

# Early diagnosis by antigen test kit and early treatment by antiviral therapy

## An ambulatory management strategy during COVID-19 crisis in Thailand

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### Abstract

This study aimed to assess the clinical characteristics of patients who registered at the Siriraj Favipiravir Clinic and to share our experiences in this comparatively unique clinical setting.

This retrospective study included patients who registered at the Siriraj Favipiravir Clinic during August 11, 2021 to September 14, 2021. Included adult patients were those with severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) infection confirmed by antigen test kit (ATK) or real-time reverse transcription-polymerase chain reaction, no favipiravir contraindication, no prior COVID-19 treatment, and not receiving care from another medical facility. Demographic data and outcomes were collected and analyzed.

Of the 1168 patients (mean age: 44.8 ± 16.4 years, 55.7% female) who registered at the clinic, 117 (10%) did not meet the treatment criteria, and 141 (12%) patients did not pick up their medication. One-third of patients had at least 1 symptom that indicated severe disease. Higher proportion of unvaccinated status (56.7% vs 47.5%,  $P = .005$ ), higher proportion of persons with risk factors for disease progression (37.7% vs 31.3%,  $P = .028$ ), and longer duration between the date of clinic registration and the date of positive diagnostic test (3 vs 2 days,  $P = .004$ ) were significantly more commonly observed in the severe disease group compared to the nonsevere disease group. The duration between symptom onset and the date of clinic registration was significantly longer in the real-time reverse transcription-polymerase chain reaction group than in the ATK group (6 vs 4 days,  $P < .001$ ). Most patients (90.0%) had completed favipiravir treatment regimen. The improvement and mortality rates were 86.7% and 1.2%, respectively.

COVID-19 severity is associated with vaccination status, baseline risk factors, and timing between disease detection and treatment. The use of ATK influences patients to seek treatment significantly earlier in ambulatory setting. Our early diagnosis and antiviral treatment strategy yielded favorable results in an outpatient setting during a COVID-19 outbreak in Thailand.

**Abbreviations:** ATK = antigen test kit, CI = confidence interval, COVID-19 = coronavirus disease 2019, IQR = interquartile range, RNA = ribonucleic acid, RT-PCR = reverse transcription-polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

**Keywords:** early diagnosis, antigen test kit, RT-PCR, early treatment, favipiravir, ambulatory, COVID-19, Thailand

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The authors have no conflicts of interest to disclose.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Siriraj Institutional Review Board (protocol code: 731/2564 and date of approval: September 21, 2021). Informed consent was obtained from all subjects involved in the study.

The authors declare that they have no competing interests.

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## 1. Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]) infection started in late 2019 and has since evolved into a major global public health problem. As of August 1, 2021, there were 198,597,091 confirmed cases and 4,234,090 deaths for a mortality rate of 2.13%. The scope of this crisis has resulted in insufficient hospital beds, healthcare personnel, and resources to treat patients. Therefore, new patient care strategies, such as field hospitals and outpatient care centers, have been established to ameliorate these healthcare-related challenges.<sup>[1,2]</sup>

During the first week of August 2021 in Thailand, 615,314 people were infected with and 4990 died from COVID-19. Deaths from COVID-19 infection accounted for 0.81% of all deaths in Thailand during this period, and similar to what occurred in many other countries around the world, the scope of this disease placed unprecedented demands on the healthcare system and caused shortages in therapeutic resources.<sup>[3]</sup> However, during this period, most patients had mild disease symptoms, which means that they could be treated in an ambulatory care setting within home isolation and/or community isolation framework.<sup>[4]</sup> The Department of Medical Services of the Thailand Ministry of Public Health then issued a guideline regarding how healthcare professionals are to manage patients with COVID-19 in home isolation. The criteria for home isolation are flexible according to the physician's judgment concerning patient safety and disease control.<sup>[5]</sup>

However, the capability of real-time reverse transcription-polymerase chain reaction (RT-PCR) test, which is the mainstay diagnostic method, was found to be insufficient during the peak incidence period with >20,000 newly diagnosed patients per day. To remedy this bottleneck in the disease diagnosis process, an antigen test kit (ATK) was also used for COVID-19 screening and diagnosis, and access to treatment was increased. The Ministry of Public Health also introduced a policy to allow people to register in the COVID-19 treatment system if they had a positive COVID-19 result either by standardized self-tested ATK at home or by healthcare personnel-tested ATK at healthcare centers.

After the implementation of this policy, the number of confirmed cases of COVID-19 infection substantially increased. However, due to the resource insufficiencies caused approximately 9000 new cases per day in Bangkok and surrounding areas, these people were unable to access healthcare treatment and remained untreated at home. In an effort to bridge this gap, the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, developed an ambulatory management strategy to specifically treat patients with COVID-19 infection who remained untreated at home. To that end, the Siriraj Favipiravir Clinic was established to improve access to healthcare for this subset of COVID-19 patients. The backbone treatment strategy was to prescribe favipiravir. This antiviral drug was available in Thailand and was one of the most appropriate for treating COVID-19 infection, according to the evidence at that time. A previously published systematic review reported that patients treated with favipiravir showed better clinical improvement by day 14 and a higher virus elimination rate on day 7 after the onset of COVID-19 symptoms compared to those who did not receive the drug.<sup>[6]</sup> Similarly, a prospective randomized open-label study conducted in Japan compared the

efficacy of favipiravir administered on day 1 with the efficacy of favipiravir administered on day 6, counting from the first day of illness onset. They found the duration of fever symptoms to be 1 day less in the group that received favipiravir on the first day of symptom onset.<sup>[7]</sup> The aforementioned evidence-based data emphasize the importance of rapid access to both healthcare services and appropriate antiviral medication immediately after the onset of symptoms to improve treatment outcomes in terms of clinical improvement and to reduce the further spread of COVID-19.<sup>[8]</sup>

The aim of this study was to assess the clinical characteristics of patients who registered at the Siriraj Favipiravir Clinic and to share our experiences in this comparatively unique clinical setting.

## 2. Methods

### 2.1. Study design and participants

This retrospective study included patients with COVID-19 infection who registered at the Siriraj Favipiravir Clinic from August 11, 2021, to September 14, 2021. The protocol for this study was approved by the Scientific Ethics Committee of the Siriraj Institutional Review Board (approval number: 732/2021), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The eligibility criteria for this study were COVID-19 infection confirmed by either ATK or real-time RT-PCR technique, age  $\geq 18$  years, not pregnant, no underlying cirrhosis or severe hepatic impairment, had not received prior favipiravir treatment, and was not in the care of another medical facility to treat the infection.

### 2.2. Data collection

Demographic data, clinical characteristics, and baseline parameters related to clinical outcomes were collected from the electronic medical registration database of the Siriraj Favipiravir Clinic. We also contacted the patients by telephone at 6 months after COVID-19 infection to follow up about the favipiravir use, government healthcare system accessibility, oxygen supplement use, and final outcomes, including improvement status and death.

### 2.3. Definitions

The Siriraj Favipiravir Clinic is an ambulatory care management clinic that was opened to treat patients with confirmed COVID-19 infection, as diagnosed by either ATK or real-time RT-PCR, during the COVID-19 pandemic. All ATKs that patients used such as Standard Q COVID-19 Ag Home Test (SD Biosensor Inc., Korea), SARS-CoV-2 Antigen Test Kit (Shenzhen Kisshealth Biotechnology Co. Ltd, People's Republic of China), SARS-CoV-2 Antigen Rapid Test Kit (Beijing Lepu Medical Technology Co. Ltd, People's Republic of China), and Panbio COVID-19 Antigen Self-Test (Abbott Diagnostics Korea Inc., Korea) were approved by Food and Drug Administration, Thailand. Favipiravir and supportive medications were prescribed to all patients without favipiravir contraindication, as follows: patients aged  $\geq 60$  years or having any comorbidities or having a body weight of  $\geq 90$  kg who had onset of symptoms

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or positive diagnostic test, but who were asymptomatic for <7 days. If the onset of symptoms was >7 days, but did not exceed 14 days, only symptomatic patients would be prescribed the medications; and patients aged <60 years with no comorbidities and body weight <90 kg were prescribed the medications if they were symptomatic with onset of symptoms <14 days.

The doctor's prescription was classified into 2 different sets of medication according to the patient's body weight. Each set consisted of favipiravir and supportive medications, including dextromethorphan, paracetamol, cetirizine, and M. tussis mixture. Set 1, which was prescribed for patients with a body weight of <90 kg, included a favipiravir regimen of 9 tablets twice daily on day 1 followed by 4 tablets twice daily until the 5-day course was completed (total 50 tablets). Set 2, which was prescribed for patients with a body weight of ≥90 kg, included a favipiravir regimen of 12 tablets twice daily on day 1 followed by 5 tablets twice daily until the 5-day course was completed (total 64 tablets).

Patients registered at the Siriraj Favipiravir Clinic who had medications prescribed could receive their prescribed medications either by government or private delivery service, or they could pick up their medication at the Siriraj drive-thru service within 24 hours after registration. Only people living in Bangkok or surrounding areas were eligible for the first option. If option 2 was selected, patients were informed that a non-infected patient relative or representative must be able to collect the medication from the drive-thru the day after Siriraj Favipiravir Clinic registration.

On the date of registration at the Siriraj Favipiravir Clinic, patient symptoms were categorized as either severe or nonsevere. Patients with dyspnea, shortness of breath, chest pain or tightness, hemoptysis, desaturation, and/or nausea and vomiting were considered to have severe symptoms. Patients without symptoms or with symptoms other than those considered to be severe were classified as having nonsevere symptoms. COVID-19 vaccination status was classified into 3 categories, as follows: fully vaccinated status was defined as the patient having had a second dose of any COVID-19 vaccine >14 days prior to Siriraj Favipiravir Clinic registration; partially vaccinated status was defined as the patient having had a second dose of any COVID-19 vaccine <14 days prior to Siriraj Favipiravir Clinic registration or having had only 1 dose of any COVID-19 vaccine >14 days prior to Siriraj Favipiravir Clinic registration; and unvaccinated status was defined as the patient having had a single dose of COVID-19 vaccine <14 days prior to Siriraj Favipiravir Clinic registration or having had received no COVID-19 vaccination.

#### 2.4. Sample size calculation and statistical analysis

No prior study has investigated COVID-19 treatment from an antiviral drug clinic in an ambulatory setting, and there was no comparison of treatment outcomes, so sample size could not be calculated for this retrospective assessment of patients who registered at the Siriraj Favipiravir Clinic. We, therefore, collected and analyzed the data of all patients enrolled to the clinic.

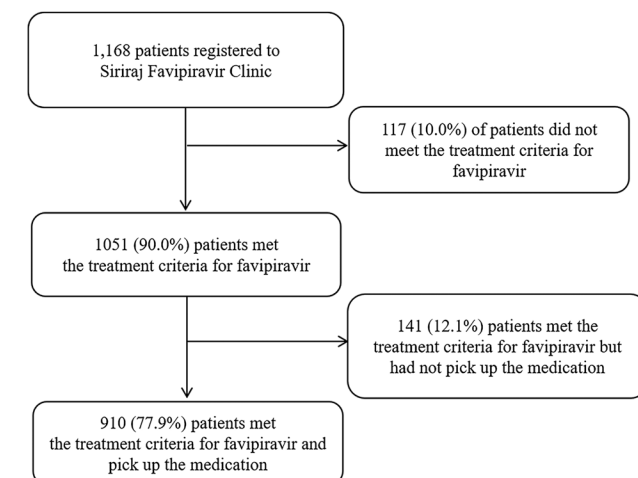
Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Categorical variables are presented as frequency and percentage. Continuous variables with normal distribution are given as mean ± standard deviation, and continuous variable with nonnormal distribution are shown as median and interquartile range (IQR). Comparisons of categorical data were performed using Fisher exact test. Comparisons of normally and nonnormally distributed continuous data were performed using Student *t* test and Mann–Whitney *U* test, respectively. A *P* value of <.05 was considered statistically significant. All statistical analyses were performed using Stata Statistical Software: Release 15 (StataCorp LP, College Station, TX).

### 3. Results

A total of 1168 adult patients with confirmed COVID-19 infection registered at the Siriraj Favipiravir Clinic between August 11, 2021, and September 14, 2021, which was the period with the highest rate of new COVID-19 infection in Thailand. Of those, 117 (10.0%) patients did not meet the criteria for favipiravir treatment, and 141 patients (12.1%) did not come to the clinic to collect their medications (Fig. 1). The reasons given for not picking up medications included receiving treating at another hospitals (*n* = 61; 43.3%), already received the drugs from another facility (*n* = 34; 24.1%), unable to contact (*n* = 32; 22.7%), and unknown (*n* = 14; 9.9%).

Baseline demographic and clinical characteristics of COVID-19 patients who registered at the Siriraj Favipiravir Clinic are shown in Table 1. The mean age of patients was 44.8 ± 16.4 years, and over half were female (55.7%). There were 396 patients (33.9%) who had at least 1 of 3 risk factors evidently associated with severe disease, including age ≥60 years, body weight ≥90 kg, and having any comorbidity. One-fifth of patients (*n* = 234) were ≥60 years of age, 185 patients (15.8%) had at least 1 significant comorbidity, and 103 patients (8.8%) had a body weight of ≥90 kg. Most patients (1143; 97.9%) had symptoms of COVID-19, and 25 patients (2.1%) were asymptomatic. The reported symptoms at clinic registration included cough (75.8%), sore throat (61.0%), fever (56.9%), productive cough (54.0%), rhinorrhea (51.4%), anosmia (44.1%), dyspnea (37.7%), loss of taste (29.0%), and others (15.2%). Overall, there were 469 patients (40.2%) who presented with severe symptoms at registration, and 699 patients (59.8%) presented with nonsevere symptoms. The symptoms of 673 patients (57.6%) remained stable at the registration date compared to the date of symptom onset, 290 patients (24.8%) experienced worsening of symptoms, and the symptoms of 205 patients (17.6%) had improved. The median time from the onset of COVID-19 symptoms to the date of clinic registration was 5 days (IQR: 3–7). Just over half of registered patients were unvaccinated (*n* = 598; 51.2%). Only 90 patients (7.7%) were fully vaccinated. The remaining 480 patients (41.1%) were partially vaccinated. More COVID-19 infections were confirmed by ATK than by real-time RT-PCR testing (692, 59.2% vs 476, 40.8%, respectively).

Gender, diagnostic method, vaccination status, risk factors for disease progression, level of disease burden, period of disease burden, date of symptom onset to clinic registration, date of COVID-19 testing to clinic registration, and symptoms progression at the registration date compared between the nonsevere and severe COVID-19 patient groups are shown in Table 2.



**Figure 1.** Flowchart of the COVID-19 patients who registered at the Siriraj Favipiravir Clinic. COVID-19 = coronavirus disease 2019.



**Table 1**  
**Baseline demographic and clinical characteristics of COVID-19 patients who registered at the Siriraj Favipiravir Clinic.**

Parameters	Total (N = 1168)
Age, yr	44.8 ± 16.4
Gender, n (%)	
Female	651 (55.7)
Risk, n (%)	
At least 1 risk factor	396 (33.9)
Age ≥60 yr	234 (20.0)
Comorbidities	185 (15.8)
Body weight ≥90 kg	103 (8.8)
Symptom characteristics, n (%)	
Asymptomatic	25 (2.1)
Symptomatic	1143 (97.9)
DOS to registry, d (IQR)	5 (3–7)
Symptoms at the registration date, n (%)	
Cough	885 (75.8)
Sore throat	713 (61.0)
Fever	664 (56.9)
Productive cough	631 (54.0)
Rhinorrhoea	600 (51.4)
Loss of smell	515 (44.1)
Dyspnea	440 (37.7)
Loss of taste	339 (29.0)
Others	177 (15.2)
Clinical severity, n (%)	
Severe	469 (40.2)
Nonsevere	699 (59.8)
Symptoms progression at the registration date, n (%)	
Stable	673 (57.6)
Worse	290 (24.8)
Improved	205 (17.6)
COVID-19 diagnostic test, n (%)	
ATK	692 (59.2)
Real-time RT-PCR	476 (40.8)
Vaccinated status, n (%)	
Unvaccinated	598 (51.2)
Partially vaccinated	480 (41.1)
AstraZeneca	414 (86.3)
Sinopharm	40 (8.3)
Sinovac	24 (5.0)
Fully vaccinated	90 (7.7)

ATK = antigen test kit, COVID-19 = coronavirus disease 2019, DOS = date of symptoms, IQR = interquartile range, RT-PCR = reverse transcription-polymerase chain reaction.

There was a significantly higher proportion of unvaccinated patients in the severe group than in the nonsevere group (266, 56.7% vs 332, 47.5%, respectively;  $P = .005$ ). Not surprisingly, we found significantly more patients with risk factors for severe disease in the severe group than in the nonsevere group (117, 37.7% vs 219, 31.3%, respectively;  $P = .027$ ). The median duration of 5 days (IQR: 3–7) from the onset of symptoms to clinic registration in the severe group was significantly longer than the median duration of 4 days (IQR: 3–7) in the nonsevere group ( $P < .001$ ). The median duration of 3 days (IQR: 1–5) from the date of diagnostic testing to the date of clinic registration in the severe group was significantly longer than the median duration of 2 days (IQR: 1–4) in the nonsevere group ( $P = .004$ ). Regarding symptom stability, as expected, patients in the severe group had significantly more worsening of symptoms compared to patients in the nonsevere group (183, 39.0% vs 107, 15.3%, respectively;  $P < .001$ ).

The date of symptom onset to clinic registration and the date of COVID-19 testing to clinic registration compared between the ATK and real-time RT-PCR diagnostic method groups are shown in Table 3. The median duration of 4 days (IQR: 2–6) from onset of symptoms to clinic registration in the ATK group was significantly shorter than the median duration of 6 days (IQR: 4–8) in the real-time RT-PCR group ( $P < .001$ ). The

median duration of 2 days (IQR: 1–4) from the date of diagnostic testing to the date of clinic registration in the ATK group was significantly shorter than the median duration of 3 days (IQR 2–5) in the real-time RT-PCR group ( $P < .001$ ).

Clinical severity, the date of symptom onset to clinic registration, the date of COVID-19 testing to clinic registration, and the COVID-19 diagnostic testing method compared between the before August 20, 2021 group and the August 20, 2021 and later group are shown in Table 4. Regarding clinical severity, the numbers and proportions of severe and nonsevere patients were not significantly different between the 2 time periods. The median duration of 5 days (IQR: 3–7) from the date of symptom onset to the date of clinic registration in the before August 20 group was significantly longer than the median duration of 4 days (IQR: 2–6) in the after August 20 group ( $P < .001$ ). The median duration of 3 days (IQR: 1–5) from the date of COVID-19 diagnostic testing to the date of clinic registration in the before August 20, 2021 group was significantly longer than the median duration of 2 days (IQR: 1–4) in the August 20, 2021 and later group ( $P = .001$ ). During high burden period, the use of real-time RT-PCR testing was significantly higher and the median times to registration were about 1 day longer than the low burden period.

Of 910 patients who complied with the favipiravir treatment criteria, we were able to contact 732 patients (80.4%) via telephone follow-up. The information on favipiravir use, healthcare system accessibility, place of isolation, oxygen supplement, and final outcomes of the patients who registered to the Siriraj Favipiravir Clinic are shown in Table 5. When the patients received the medication from the clinic, we found that 657 patients (90%) took complete regimen of favipiravir treatment. Less than half of patients (46.9%) were willing to contact the official healthcare registration system via telephone. Eventually, the most common places of isolation were home isolation or self-isolation (63.1%) due to insufficient hospital resources (Table 5). Most patients had good clinical outcomes at the end of isolation. We explored and illustrated the outcomes of patients who had completed regimen of favipiravir treatment versus those who had not, as shown in Table 6. The proportion of death tended to be lower in patients who completed the antiviral treatment, but this did not reach statistical significance.

#### 4. Discussion

A previous study reported that approximately 80% of COVID-19 patients had only mild symptoms.<sup>11</sup> The number of actively infected patients and the mortality rate were both high during the outbreak period evaluated in this study, and not all of those patients could access treatment or be hospitalized. In this overwhelming burden scenario, some patients were triaged to care for themselves at their own residence, especially asymptomatic or mildly symptomatic patients, so outpatient care assumed a major role during this outbreak crisis. In Thailand, the peak burden period was early August 2021 with >20,000 newly diagnosed COVID-19 cases per day, and 9000 of those cases per day occurred in and around Bangkok. Due to the scope of the problem, the healthcare resources available in our country were insufficient for dealing with this large number of patients. The Thailand Ministry of Public Health and many medical centers developed strategies designed to manage asymptomatic and/or mildly symptomatic cases. Those strategies included the development of “hospitals,” which are hotels that are temporarily converted into hospitals, a home isolation system, and other innovative outpatient strategic plans, including the Siriraj Favipiravir Clinic. Admission to hospital was reserved for severe or critical COVID-19 patients.

In August 2021, only 3 antiviral therapies were available in Thailand. These included oral favipiravir, oral lopinavir-ritonavir, and intravenous remdesivir. We chose favipiravir as a

**Table 2****Clinical parameters and clinic accessibility periods of the nonsevere and severe COVID-19 patient groups.**

Parameters	Nonsevere (N = 699)	Severe (N = 469)	P value
Gender, n (%)			
Female	384 (54.9)	267 (56.9)	.509
COVID-19 diagnostic test, n (%)			
ATK	423 (60.5)	269 (57.4)	.302
Real-time RT-PCR	276 (39.5)	200 (42.6)	
Vaccinated status, n (%)			
Unvaccinated	332 (47.5)	266 (56.7)	.005
Partial vaccinated	305 (43.6)	175 (37.3)	
Fully vaccinated	62 (8.9)	28 (6.0)	
Risk factors of disease progression, n (%)			
At least 1 risk factor	219 (31.3)	177 (37.7)	.027
Level of outbreak burden, n (%)			
High burden	365 (52.2)	256 (54.6)	.518
Moderate burden	278 (39.8)	171 (36.5)	
Low burden	56 (8.0)	42 (9.0)	
Disease period, n (%)			
Before August 20, 2021	365 (52.2)	256 (54.6)	.437
After August 20, 2021	334 (47.8)	213 (45.4)	
DOS to registry, d (IQR)	4 (3–7)	5 (3–7)	<.001
DOT to registry, d (IQR)	2 (1–4)	3 (1–5)	.004
Symptoms progression at the registration date, n (%)			
Stable	434 (62.1)	239 (51.0)	<.001
Worse	107 (15.3)	183 (39.0)	
Improved	158 (22.6)	47 (10.0)	

ATK = antigen test kit, COVID-19 = coronavirus disease 2019, DOS = date of symptoms, DOT = date of test, IQR = interquartile range, RT-PCR = reverse transcription-polymerase chain reaction.

**Table 3****Date of symptom onset to clinic registration, and date of COVID-19 testing to clinic registration compared between the ATK and real-time RT-PCR diagnostic method groups.**

Parameters	ATK (n = 692)	Real-time RT-PCR (n = 476)	P value
DOS to registry, d (IQR)	4 (2–6)	6 (4–8)	<.001
DOT to registry, d (IQR)	2 (1–4)	3 (2–5)	<.001

ATK = antigen test kit, COVID-19 = coronavirus disease 2019, DOS = date of symptoms, DOT = date of test, IQR = interquartile range, RT-PCR = reverse transcription-polymerase chain reaction.

treatment of choice for our management strategy because this drug profile was acceptable and other antiviral drugs were restrictively prescribed. The Siriraj Favipiravir Clinic allowed patients to gain early access to favipiravir treatment without admission to the hospital. The clinic could be accessed by online registration, and the medications could be obtained via delivery service or collection by a noninfected friend or family member of the patient. COVID-19 cases confirmed by either ATK or real-time RT-PCR within 2 weeks were allowed to register with the

Siriraj Favipiravir Clinic. We hypothesized that faster favipiravir administration would yield better outcomes and reduce the burden on the healthcare system by lowering the rate of disease progression from mild to severe. Favipiravir is a selective inhibitor of RNA-dependent RNA polymerase in RNA viruses. Some prior studies reported promising benefits of favipiravir relative to shortening both the duration of viral clearance, which is a febrile phase, and the time to cure. Favipiravir was also able to improve radiological findings.<sup>[6,7,9–13]</sup> Somewhat contrarily, a meta-analysis by Hassanipour et al<sup>[14]</sup> found that favipiravir administration only effectuated significant clinical improvement during 7 days after hospitalization when compared with controls that did not receive favipiravir, but no difference in viral clearance, oxygen requirement, or mortality was observed between groups. In part, based on a previously reported study, we postulated that favipiravir would improve clinical severity, patient quality of life, and COVID-19-related disease treatment burden in an ambulatory care setting.<sup>[15]</sup> Regarding the potential development of viral resistance, even though a previous study found scanty resistance by influenza virus to antivirals,<sup>[16]</sup> we suggest that physicians and policymakers adopt a cautious and well-considered approach when developing antiviral treatment policies.

**Table 4****Clinical parameter, clinic accessibility periods, and diagnostic methods of the before August 20, 2021 group and the August 20, 2021 and later group.**

Parameters	Before August 20, 2021 (N = 621)	After August 20, 2021 (N = 547)	P value
Clinical severity, n (%)			
Severe	256 (41.2)	213 (38.9)	.437
Nonsevere	365 (58.8)	334 (61.1)	
DOS to registry, d (IQR)	5 (3–7)	4 (2–6)	<.001
DOT to registry, d (IQR)	3 (1–5)	2 (1–4)	.001
COVID-19 diagnostic test, n (%)			
ATK	347 (55.9)	345 (63.1)	.014
Real-time RT-PCR	274 (44.1)	202 (36.9)	

ATK = antigen test kit, COVID-19 = coronavirus disease 2019, DOS = date of symptoms, DOT = date of test, IQR = interquartile range, RT-PCR = reverse transcription-polymerase chain reaction.

**Table 5**  
Six-month outcomes of Siriraj Favipiravir Clinic.

Outcomes	Total (N = 732)
Favipiravir use, n (%)	
Known	730 (99.7)
Complete dose of treatment	657 (90.0)
Incomplete dose of treatment	20 (2.7)
Not take the medication	46 (6.3)
Not received the medication	7 (1.0)
Unknown	2 (0.3)
Healthcare system accessibility, n (%)	343 (46.9)
Places of isolation, n (%)	
Hospital	99 (13.5)
Field hospital	51 (7)
Hospital	113 (15.4)
Community isolation	7 (1.0)
Home isolation or self-isolation	462 (63.1)
Oxygen supplement use, n (%)	52 (7.1)
Types of oxygen supplement, n (%)	
Oxygen cannula	31 (59.6)
Oxygen mask	2 (3.8)
High flow nasal cannula	9 (17.3)
Endotracheal tube	5 (9.6)
Unknown	5 (9.6)
Final outcomes, n (%)	
Improved	635 (86.7)
Not changed	74 (10.1)
Not improved	13 (1.8)
Death (within 30 d)	9 (1.2)
Unknown	1 (0.1)

**Table 6**  
Outcomes of patients who completed regimen of favipiravir treatment versus who did not.

Outcomes	Complete regimen of favipiravir treatment (N = 656)	Incomplete regimen of favipiravir treatment (N = 73)	P value
Improved	570 (86.9%)	64 (87.7%)	.065
Not changed	70 (10.7%)	4 (5.5%)	
Not improved	10 (1.5%)	3 (4.1%)	
Death (within 30 d)	6 (0.9%)	2 (2.7%)	

In this study, we found that more than half of patients with observable severe symptoms at the clinic registration date were unvaccinated and that there were higher proportions of partially and fully vaccinated patients in the nonsevere symptom group. This finding may support vaccination as an effective prevention strategy for reducing disease severity and disease burden during an outbreak. Although there are limited data specific to the effectiveness of the vaccine against the severe symptoms of COVID-19, some previous studies reported that vaccination lowered rates of hospitalization and intensive care unit admission. A multistate study in the United States reported the effectiveness of full mRNA vaccination to be 89% against laboratory-confirmed COVID-19 infection leading to hospitalization, 90% against infection leading to intensive care unit admission, and 91% against infection leading to an emergency department or urgent care visit. The effectiveness of viral vector vaccine was 68% against infection leading to hospitalization and 73% against infection leading to an emergency department or urgent care visit.<sup>[17]</sup> We, therefore, hypothesized that at least 1 dose of any type of COVID-19 vaccination should, in some way, be able to reduce the probability of disease progression and severe symptoms when compared to patients who are unvaccinated. Inactivated vaccine and viral vector vaccine are both currently used in

Thailand, and data specific to the effectiveness of either vaccine remain scarce.

Other clinical parameters that showed association with severe symptomatic status among our patients were the risk factors for severe disease, which include older age, certain comorbidities, and obesity. This finding is consistent with those reported in previous studies.<sup>[17,18]</sup> Those studies, most of which were conducted in China or were review articles, found older age status, pregnancy, and comorbidities such as diabetes, chronic lung disease, heart disease, liver disease, kidney disease, malignancies, and immunodeficient states to be risk factors for COVID-19 progression to severe and critical stages.<sup>[17,18]</sup>

The duration from the onset of symptoms to the date of Siriraj Favipiravir Clinic registration was longer in patients with severe symptoms than in the nonsevere group. Similarly, the duration from the date of diagnostic testing to the date of clinic registration was longer in the severe group than in the nonsevere group. From this, we can infer that a longer infection duration prior to treatment accessibility was related to more severe disease. Rapid diagnosis in at-risk population is, therefore, very important for early detection that can be followed by early treatment. In this study, we found that patients who were diagnosed using real-time RT-PCR technique had a longer median duration from the date of symptom onset or the date of positive test to the date of clinic registration than the group of patients who were diagnosed by ATK. Reasons that explain this difference include the fact that real-time RT-PCR must be performed at a hospital or a standardized government facility and that patients might also have to queue up and wait for a test since the number of tests conducted test per day is limited according to healthcare personnel and resource availability. These findings and factors suggest that ATK might be a better diagnostic technique during an outbreak, which is a scenario that requires that more patients have early access to treatment and medication. Early diagnosis and treatment should lead to better clinical outcomes in patients with COVID-19 infection. Despite the lower sensitivity and variability of the rapid ATK test,<sup>[19,20]</sup> we think that the diagnostic value of the ATK test outweighs the disadvantages in this type of outbreak crisis setting.

The significantly different parameters between the group of patients that registered during the high epidemic period (before August 20, 2021; 15,000–25,000 new infections per day) and the group of patients that registered during the low epidemic period (August 20, 2021, and later; 10,000–15,000 new infections per day) in Thailand included the durations from the onset of symptoms or the date of confirmed COVID-19 diagnosis to the date of registration at the Siriraj Favipiravir Clinic and the proportions of the methods used to diagnose COVID-19. Not surprisingly, the duration from the date that the infection was detected to treatment accessibility was shorter in the low epidemic period than in the high epidemic period. The proportion of patients diagnosed by real-time RT-PCR was higher during the high burden period, which may have resulted in later accessibility to treatment. However, this finding is confounded by the fact that ATK was more readily available during the latter period (low-burden period), which made it easier to access and use. If the national COVID-19 management policy had not been amended to allow the use of ATK in the ambulatory setting and continued to require only real-time RT-PCR to diagnose the disease, the time of access to favipiravir and other medications would likely have been longer, which would have increased the disease burden due to increased disease progression. Although an ATK is not a standard diagnostic test, its performance is acceptable, especially in extraordinary circumstances like the one described in this report. The sensitivity and specificity of ATK are 72% and 99.2%, respectively. An ATK can be used instead of real-time RT-PCR if its performance meets the World Health Organization's recommended minimal requirement of  $\geq 80\%$  sensitivity and  $\geq 97\%$  specificity compared to a reference assay.<sup>[21]</sup> There was a trial conducted in Thailand that evaluated



the test performance of rapid antigen detection of COVID-19, and the results revealed a sensitivity of the test of 98.33% (95% confidence interval 4: 91.06%–99.96%) and specificity of 98.73% (95% confidence interval: 97.06%–99.59%).<sup>[22]</sup> A systematic review and meta-analysis reported the overall sensitivity and specificity of the rapid antigen test to detect COVID-19 of 68.4% and 99.4%, respectively.<sup>[23]</sup> To our knowledge, no strong recommendation has yet been proposed or published regarding the use of ATK as a standard test for COVID-19 diagnosis. However, there is also no recommendation or evidence against the use of ATK for detecting COVID-19. As such, the amendment to national healthcare policy permitting the use of ATK to diagnose this infection has delivered far more benefit than harm by facilitating earlier diagnosis and treatment, which it can be argued resulted in decreased healthcare burden from COVID-19 during the August 11, 2021, to September 14, 2021, outbreak in Thailand.

Among the followed patients, the outcomes of Siriraj Favipiravir Clinic were that only 46.9% of registered patients were finally able to access the governmental healthcare system. Home isolation and self-isolation became the alternative choices of management during the crisis period. The overall outcomes were satisfied with regard to the improvement rate of 86.7% and the death rate within 30 days of 1.2% in all spectrums of severities. The lower death rate among patients who completed favipiravir treatment regimen as compared to those who did not in this study could not illustrate that favipiravir was able to prevent the COVID-19–related mortality. However, this treatment approach might, at least, relieve the patient's anxiety in real practice.

This study is the first to investigate and report the implementation of a novel healthcare strategy to help cope with high disease burden caused by a COVID-19 outbreak in Thailand. The results of this study suggest early disease detection and early antiviral treatment as an efficacious strategy for optimizing healthcare resources. Our finding of symptom severity is significantly associated with vaccination status, baseline risk factors for COVID-19 disease progression, and timing between disease detection and treatment will be useful for expanding current strategies and developing new strategies for coping with high-burden outbreaks in the future.

This study has some mentionable limitations. The crucial limitation of this study is a retrospective design, which increased its vulnerability to certain biases and missing or incomplete data, such as drug compliance, adverse drug reactions, and health-related outcomes. It was not designed to handle such biases to provide rigid clinical outcomes related to favipiravir effectiveness. To our knowledge, currently, a few randomized controlled trials and a large observational study demonstrated the absence of its effectiveness in the examined endpoints consisting of time of viral shedding, hospitalization rate, mechanical ventilator requirement, and mortality rate.<sup>[24–26]</sup> The fact that the Thailand Ministry of Public Health reported that new infections decreased to 1500 cases per day in Bangkok and surrounding areas after the “early testing and early treatment” policy was implemented suggests the potential efficacy of this strategy. Another possible indication of the success of this initiative is that the Siriraj Favipiravir Clinic was able to close within 5 weeks of opening due to the decrease in new cases to a level that could be successfully managed by the normal healthcare system.

## 5. Conclusions

COVID-19 severity was found to be significantly associated with vaccination status, baseline risk factors for COVID-19 disease progression, and timing between disease detection and treatment. The use of ATK influences patients to seek treatment significantly earlier in ambulatory setting. Delivery of our early diagnosis and antiviral treatment strategy via the Siriraj Favipiravir Clinic yielded favorable results during a COVID-19 outbreak in Thailand. However, the treatment strategy should be adapted follow to further knowledge and future COVID-19 infection situation.

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## Author contributions

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