ORIGINAL ARTICLE

Clinical Characteristics and Severity of Omicron Variant in Thailand: A Comparative Study from Two Secondary Hospitals

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Background: The highly transmissible nature of the Omicron variant raises concerns globally.

Objective: To investigated the clinical characteristics and severity of COVID-19 patients infected with the Omicron variant in Thailand, comparing it to the previously dominant Alpha and Delta variants.

Materials and Methods: Retrospective data from two secondary hospitals in Thailand during the Omicron variant's prevalence were analyzed. Demographic and clinical information, including age, comorbidities, symptoms, lab results, and outcomes, were compared with the Alpha and Delta variants. Severity was assessed based on the presence of pneumonia and mortality.

Results: Preliminary findings revealed distinct clinical characteristics in COVID-19 patients with the Omicron variant compared to the Alpha and Delta variants. Common symptoms like fever, cough, sore throat, and fatigue varied in frequency and severity across the variants. Breakthrough infections were more prevalent with the Omicron variant. Differences in the development of pneumonia were observed.

Conclusion: This comparative study provides initial insights into the clinical characteristics and severity of COVID-19 patients with the Omicron variant in Thailand. Further research is required to validate these findings and improve understanding of Omicron's impact on disease outcomes. This knowledge will inform effective strategies to mitigate the spread and severity of COVID-19 caused by the Omicron variant.

Keywords: Omicron variant; Clinical characteristics; Severity; COVID-19; Delta variant; Alpha variant

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in China in December 2019 and has become a global pandemic. Many variants of concern (VOCs) subsequently emerged. B.1.1.7 (Alpha), first detected in the United Kingdom in October 2020, successfully spread globally, including in Thailand. More hospitalization and pneumonia were reported compared to the ancestral strain[1,2]. The Delta (B.1.617.2) variant subsequently replaced the Alpha variant with 97% increased transmissibility compared with the ancestral variant but with more severe illnesses requiring intensive care unit (ICU) admission and probably death compared with the Alpha variant[3,4]. Recently, B.1.1.529 (Omicron) emerged as a dominant variant replacing the Delta with increased transmissibility but decreased hospitalization, ICU admission, and death compared with the Delta variant[5-7]. However, residual confounders may coexist in those reports regarding vaccination status and other risk factors for severe disease; thus, after adjusting for these factors, the Omicron's severity may be comparable to other previous VOCs[8].

In the present study, the authors demonstrated the clinical manifestations, predictors for severe coronavirus disease 2019 (COVID-19), laboratory features, and outcomes among patients with COVID-19 with the Omicron-dominant period

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compared to the previous Delta-dominant and Alpha-dominant periods.

Material and Methods

Study design and setting

The authors retrospectively reviewed the medical records of COVID-19 patients admitted to two secondary care centers in Maha Sarakham Province during the COVID-19 pandemic between April 1, 2021 and January 10, 2022. The first center, Suddhavej Hospital, Mahasarakham University, is a university hospital with a 120-bed facility and oversees field hospital caring for COVID-19 patients with a 94-bed capacity. Mahasarakham International Hospital is a private hospital with a 30-bed facility. There were 3 waves in the present study province during the study period: the first wave with the Alpha variant starting between April 1, 2021 to June 15, 2021, the second wave with the Delta-dominant variant between June 16, 2021 and December 23, 2021, and the third wave with the Omicron-dominant variant starting from 24 December 2021 in which the first Omicron variant was first detected in the province. All confirmed COVID-19 patients, regardless of severity, required hospitalization for at least 10 days according to the Thai National Guidelines on the diagnosis, treatment, and prevention of COVID-19 in hospitals during the study period.

Ethical approval

The present study was approved by the Ethics Committees of Mahasarakham University (no. 034-024/2565) and of both hospitals.

Population

Inclusion criteria were 1) age ≥15 years old and 2) diagnosed with COVID-19 confirmed with real-time reverse transcriptase polymerase chain reaction (rRT-PCR) from nasopharyngeal and/or throat swabs. The exclusion criteria were inadequate medical records for review.

Data collection and definition

Medical records from both electronics and papers were retrospectively reviewed in a structured format. COVID-19 vaccination was reviewed from the medical records and electronic database collaborated with the Ministry of Public Health immunization dashboard. Fully vaccinated status was defined as a completion of at least 2 doses of COVID-19 vaccines within 14 to 90 days after the last dose for the Omicron variant and 14 to 180 days for the Delta variant. The incubation period was estimated from a recalled history of possible exposure during an early outbreak. Risk factors for severe COVID-19 were 1) atherosclerotic vascular disease, 2) hypertension, 3) diabetes mellitus, 4) cirrhosis, 5) chronic obstructive lung disease, 6) malignancy, 7) chronic kidney disease, and 8) immunosuppressive therapy. Obesity, defined as body mass index (BMI) ≥25 kg/m², was presented separately.

Clinical severity was classified into 7 groups: 1) asymptomatic, 2) symptomatic without pneumonia, 3) pneumonia without oxygen requirement, 4) pneumonia with low-flow oxygen requirement, 5) pneumonia with high-flow oxygen requirement, 6) pneumonia requiring mechanical ventilation, and 7) symptomatic with multisystem inflammatory syndrome in children or adults (MIS-C or MIS-A). Patients with severe COVID-19 was defined as those who required any oxygen therapy for hypoxemia, mechanical ventilation, MIS-C or MIS-A. Clinical severity was defined based on the final clinical and radiographic features and outcome.

The treatment protocol for both centers followed the Thai National Guidelines on the diagnosis, treatment, and prevention of COVID-19 in hospitals. According to both hospitals' protocols, all chest radiography during hospitalization was reviewed by radiologists. COVID-19 pneumonia was defined as any feature highly suspicious of or compatible with COVID-19 pneumonia. The treatment outcomes were as follows: 1) improvement and discharge, 2) referral to a tertiary care center with an outcome of improvement or no improvement, and 3) death. All transferred patients to a tertiary center will be confirmed for final outcomes.

Statistical analysis

Differences among the 3 groups were compared using the t-test or Mann-Whitney U test for continuous data and the chi-square test for categorical data. Kruskal-Wallis and Dunn's correction for multiple comparisons was used to compare nonnormally distributed continuous data with more than 2 groups. Odds ratios were calculated by logistic regression and presented with 95% confidence intervals (CIs). IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9 were used for statistical analysis. A p-value of less than 0.05 was statistically significant.

Results

There were 426 COVID-19 cases during the

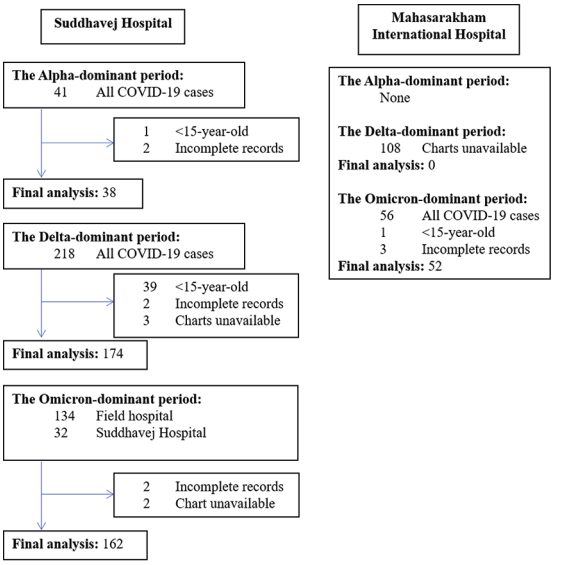

Figure 1. Diagram of inclusions and exclusions.

present study period: 38 (8.92%) cases during the Alpha-dominant period, 174 (40.85%) cases during the Delta-dominant period, and 214 (50.23%) cases during the Omicron-dominant period. Figure 1 illustrated a flowchart outlining the case selection.

Demographic data

The demographic data and clinical characteristics of the patients were shown in Table 1. The median age in the Delta-dominant period was 40 years (IQR 26 to 52.25), higher than that in the Alpha- and Omicron-dominant periods (p<0.001). There were significantly higher percentages of students and college students during the Omicron period (67.8% versus 39.5% during the Alpha and 15.5% during the Delta, p<0.001). The percentages of fully vaccinated individuals were higher in the Omicron-dominant period than in other periods (69.2% versus 18.5% during the Delta and 0% during the Alpha, p<0.001). Heterologous primary series were the most common COVID-19 vaccines used during both the Omicron-dominant and Delta-dominant periods: 60% and 59%, respectively. CoronaVac followed by ChAdOx1 nCoV-19 consisted of 47.2% and 60% among fully vaccinated individuals in the Omicron-dominant and Delta-dominant periods, respectively. Higher BMI was observed in the Delta-dominant period than in the Omicron period (p<0.001) but not in the Alpha period. Proportions of individuals with risk factors for severe COVID-19 were more frequently observed during the Delta-dominant variant (25.3%) than during the Omicron-dominant period (2.3%) (p<0.001) (Table 1).

Incubation times during the Omicron-dominant period were available from 83 individuals with a median of 1 day (IQR 0 to 3). The days of illness to admission were shorter during the Alpha than the Omicron period: median 2 days (IQR 1 to 3) versus 3 days (IQR 2 to 4) (p=0.016).

Both the Alpha- and Delta-dominant periods had higher proportions of pneumonia occurrence than the Omicron-dominant period: 39.5% and 49.4% versus 4.7%, respectively (p<0.001).

Clinical characteristics, severity, treatment, complications, and outcome

Fever tended to be higher during the Omicron than the other two variants (Table 1). The proportions of hyposmia-anosmia were higher during the Alpha and Delta periods than during the Omicron period, but the odds ratios were not significantly different (Figure 2). Blood-streaked sputum was a unique symptom only found during the Omicron-dominant period (Table 1). Both the Alpha- and Delta-dominant periods had higher proportions of cough, breathlessness, and dyspnea than the Omicron-dominant period (Table 1). The odds of having breathlessness and dyspnea among the Alpha and Delta remained significant after adjusting for vaccination status: adjusted odds ratios of 3.015 (95% CI 1.184 to 7.679, p=0.021) and 2.236 (95% CI 1.161 to 4.307, p=0.016), respectively (Figure 2). Diarrhea and rash were prominent features during the Alpha- and Delta-dominant periods, with unadjusted odds ratios for diarrhea of 8.066 (95% CI 3.008 to 21.628, p<0.001) and 3.09 (95% CI 1.375 to 6.943, p=0.006), and for rash of 9.149 (95% CI 2.962 to 28.264, p<0.001) and 2.535 (95% CI 0.931 to 6.905, p=0.069) for Alpha and Delta, respectively.

The crude and adjusted odds ratios of each symptom among each variant compared with the Omicron-dominant period as a reference were shown in Figure 2. Odds for chills, night sweats and blood-streaked sputum were not calculated due to very low proportions of cases.

Among the 3.5% of the total cohort (15/426), 9 Deltas, 5 Omicrons, and 1 Alpha were considered severe COVID-19. One case required endotracheal intubation (6.67%, 1/15). Eighty percent (12/15) required either low- or high-flow oxygen therapy, while 13.33% (2/15) met the definition of MIS-C. Forty percent (6/15) were considered fully vaccinated. The median time from the last vaccination to hospitalization was 50 days (IQR 31 to 109.3). The

Table 1. Demographic data, clinical characteristics, and severity comparison between each variant

	Total (n=426)	Variants of concern			p-value
		Alpha-dominant (n=38)	Delta-dominant (n=174)	Omicron-dominant (n=214)	
Age (years); median (IQR)	24 (20 to 40.25)	25.5 (22 to 36)	40 (26 to 52.25)	21 (19 to 23.25)	<0.001
Sex; n (%)					0.624
Female	221 (51.9)	17 (44.7)	90 (51.7)	114 (53.3)	
Male	205 (48.1)	21 (55.3)	84 (48.3)	100 (46.7)	
Nationality; n (%)					<0.001
Thai	418 (98.1)	30 (78.9)	174 (100)	214 (100)	
Cambodia	8 (1.9)	8 (21.1)	-	-	
Occupation; n (%)					<0.001
Students	24 (5.6)	-	2 (1.1)	22 (10.3)	
College students	163 (38.3)	15 (39.5)	25 (14.4)	123 (57.5)	
Others	239 (56.1)	23 (60.5)	147 (84.5)	69 (32.2)	
COVID-19 vaccination status; n (%)					<0.001
Unvaccinated	257 (60.3)	38 (100)	149 (85.6)	70 (32.7)	
Fully vaccinated	169 (39.7)	-	25 (14.4)	144 (67.3)	
• Homologous prime regimen	65 (38.5)	-	10 (40.0)	55 (38.2)	-
- CoronaVac	7 (4.1)	-	7 (28.0)	-	-
- BBIBP-CorV	15 (8.9)	-	3 (12.0)	12 (8.3)	-
- ChAdOx1	11 (6.5)	-	-	11 (7.6)	-
- BNT162b2	32 (18.9)	-	-	32 (22.2)	-
• Heterologous prime regimen	100 (59.2)	-	15 (60.0)	85 (59.0)	-
- CoronaVac - ChAdOx1	83 (49.1)	-	15 (60.0)	68 (47.2)	-
- CoronaVac - BNT162b2	6 (3.6)	-	-	6 (4.2)	-
- ChAdOx1 - BNT162b2	9 (5.3)	-	-	9 (6.3)	-
- BBIBP-CorV - ChAdOx1	1 (0.6)	-	-	1 (0.7)	-
- ChAdOx1 - BBIBP-CorV	1 (0.6)	-	-	1 (0.7)	-
• Boosted	4 (2.4)	-	-	4 (2.8)	-
- CoronaVac - CoronaVac - ChAdOx1	2 (1.2)	-	-	2 (1.4)	-
- CoronaVac - BBIBP-CorV - ChAdOx1	1 (0.6)	-	-	1 (0.7)	-
- CoronaVac - ChAdOx1 - mRNA-1273	1 (0.6)	-	-	1 (0.7)	-
Time from last vaccination; median (IQR)	54 (34 to 73)	-	59.7 (41.5 to 76)	54 (33.3 to 72.8)	0.381
Past COVID-19 infection; n (%)	1 (0.23)	-	-	1 (0.47)	0.609
BMI (kg/m^2); median (IQR)	21.96 (19.22 to 25.83)	22.43 (20.51 to 24.38)	24.38 (20.95 to 27.89)	20.56 (18.41 to 23.42)	<0.001
BMI ≥30 kg/m^2; n (%)	40 (9.4)	3 (7.9)	26 (14.9)	11 (5.1)	<0.001
Presence of any risk factors for severe disease; n (%)	49 (11.5)	-	44 (25.3)	5 (2.3)	<0.001
Comorbidity; n (%)					
Diabetes mellitus	30 (7.0)	-	26 (14.9)	4 (1.9)	<0.001
Hypertension	30 (7.0)	-	29 (16.7)	1 (0.5)	<0.001
Chronic kidney disease	9 (2.1)	-	9 (5.2)	-	0.001
HIV infection	2 (0.5)	1 (2.6)	1 (0.6)	-	0.088
Asthma or chronic obstructive lung disease	3 (0.7)	3 (7.9)	-	-	<0.001
Pregnancy	4 (9.4)	-	4 (2.3)	-	<0.001
Active malignancy	2 (0.5)	-	2 (1.1)	-	0.112
Exposure to symptom onset (days); median (IQR)	NA	NA	NA	1 (0 to 3) (n=83)	-
Days of illness to admission (days); median (IQR)	3 (2 to 4)	2 (1 to 3)	3 (1 to 5)	3 (2 to 4)	0.009
Severity; n (%)					
Asymptomatic	15 (3.5)	1 (2.6)	5 (2.9)	9 (4.2)	-
Symptomatic without pneumonia	300 (70.4)	23 (60.5)	83 (47.7)	194 (90.7)	-
Pneumonia without oxygen requirement	96 (22.5)	13 (34.2)	77 (44.3)	6 (2.8)	-
Pneumonia with low-flow oxygen requirement	11 (2.6)	1 (2.6)	8 (4.6)	2 (0.9)	-

BMI=body mass index; MIS-C=multisystem inflammatory syndrome in children; MIS-A=multisystem inflammatory syndrome in adults; CTPA=computed tomography pulmonary angiogram; NA=not available

Table 1. Demographic data, clinical characteristics, and severity comparison between each variant

	Total (n=426)	Variants of concern			p-value
		Alpha-dominant (n=38)	Delta-dominant (n=174)	Omicron-dominant (n=214)	
Pneumonia with high-flow oxygen requirement	1 (0.2)	-	-	1 (0.5)	-
Pneumonia requiring mechanical ventilation	1 (0.2)	-	-	1 (0.5)	-
Symptomatic with MIS-C or MIS-A	2 (0.5)	-	1 (0.6)	1 (0.5)	-
Presence of pneumonia; n (%)	111 (26.1)	15 (39.5)	86 (49.4)	10 (4.7)	<0.001
Symptoms; n (%)					
Fever	229 (55.7)	18 (48.6)	93 (55)	118 (57.6)	0.587
Cough	314 (76.4)	31 (83.8)	140 (82.8)	143 (69.8)	0.007
Sore throat	195 (47.4)	18 (48.6)	65 (38.5)	112 (54.6)	0.008
Chills	24 (5.8)	-	2 (1.2)	22 (10.7)	<0.001
Night sweats	17 (4.1)	-	-	17 (8.3)	<0.001
Running nose	133 (32.4)	10 (27.0)	54 (32.0)	69 (33.7)	0.722
Nasal congestion	32 (7.8)	4 (10.8)	6 (3.6)	22 (10.7)	0.028
Myalgia	93 (22.6)	13 (35.1)	24 (14.2)	56 (27.3)	0.002
Hyposmia or anosmia	48 (11.7)	6 (16.2)	22 (13.0)	20 (9.8)	0.413
Breathlessness or dyspnea	75 (18.2)	11 (29.7)	40 (23.7)	24 (11.7)	0.002
Headache	70 (17.0)	10 (27.0)	29 (17.2)	31 (15.1)	0.207
Blood-streaked sputum	6 (1.5)	-	-	6 (2.9)	0.047
Diarrhea	40 (9.7)	10 (27.0)	21 (12.4)	9 (4.4)	<0.001
Rash	26 (6.3)	8 (21.6)	12 (7.1)	6 (2.9)	<0.001
Treatment; n (%)					
Steroid use	126 (29.6)	16 (42.1)	97 (55.7)	13 (6.1)	<0.001
• High dose steroid use (>6 mg of dexamethasone)	34 (8.0)	-	30 (30.9)	4 (1.9)	<0.001
• Date of illness to steroid administration (days); median (IQR)	5 (3 to 8)	4.5 (3 to 7.75)	5 (3 to 8)	6 (4 to 8)	0.849
• Duration of steroid use (days); median (IQR)	8 (7 to 10)	7 (5 to 10)	10 (7 to 10)	5 (3 to 8)	0.002
Antiviral agents	391 (91.8)	21 (55.3)	160 (92)	210 (98.1)	<0.001
• Favipiravir	386 (98.7)	21 (100)	155 (96.9)	210 (100)	<0.001
• Remdesivir	5 (1.3)	-	5 (3.1)	-	0.026
• Lopinavir-ritonavir	4 (0.9)	2 (5.3)	2 (1.2)	-	0.008
• Duration of antiviral agent use (days); median (IQR)	5 (5 to 10)	5 (5 to 10)	10 (10 to 10)	5 (5 to 5)	<0.001
Any anticoagulant use	5 (1.17)	-	5 (2.9)	-	0.026
Inhaled corticosteroid use	19 (4.5)	4 (10.5)	2 (1.2)	13 (6.1)	0.012
Complication; n (%)	8 (1.9)	1 (2.6)	6 (3.4)	1 (0.5)	0.158
Tonsillitis	1 (0.2)	1 (2.6)	-	-	-
Urinary tract infection	2 (0.5)	-	2 (1.1)	-	-
Septicemia	2 (0.5)	-	1 (0.6)	1 (0.5)	-
Pulmonary atelectasis	1 (0.2)	-	1 (0.6)	-	-
Pulmonary embolism confirmed by CTPA	2 (0.5)	-	2 (1.1)	-	0.233
Outcome; n (%)					
Improve and discharge	424 (99.5)	38 (100)	174 (100)	212 (99.1)	0.370
Referral to the tertiary care center (outcome: improve)	1 (0.2)	-	-	1 (0.5)	
Referral to the tertiary care center (outcome: death)	1 (0.2)	-	-	1 (0.5)	

BMI=body mass index; MIS-C=multisystem inflammatory syndrome in children; MIS-A=multisystem inflammatory syndrome in adults; CTPA=computed tomography pulmonary angiogram; NA=not available

median time from the last vaccination did not differ among non-severe and severely and fully vaccinated individuals (median 54 days, IQR 34 to 73 versus 50 days, IQR 31 to 109.3, p=0.773). Among 6 fully vaccinated individuals, 5 (83.3%) received non-mRNA-based COVID-19 vaccines, including the following: 3 prime CoronaVac + boosted ChAdOx1 nCoV-19 and 2 prime and boosted with BBIBP-CorV. All vaccinated individuals had at least one risk factor for severe COVID-19, except for 2 cases with MIS-C.

Antiviral agents were given in 91.8% of cases in the cohort and were mostly given during the Omicron

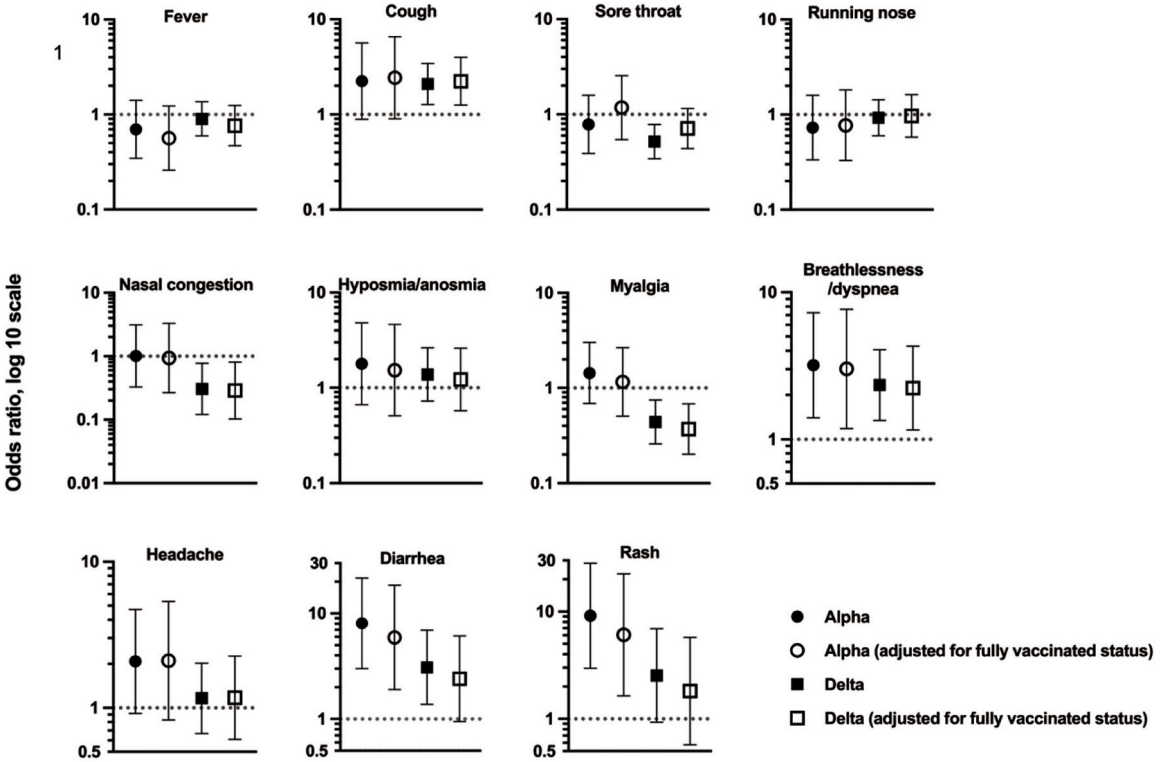

Figure 2. Forest plot of odds ratios for each clinical symptom between the Alpha (B.1.1.7) and Delta (B.1.617.2) compared with the Omicron (B.1.1.529) as a reference.

Solid circle and error bars: unadjusted odds ratios for the Alpha (B.1.1.7) versus the Omicron (B.1.1.529) as a reference.

Blank circle and error bars: adjusted odds ratios for fully vaccinated status for the Alpha (B.1.1.7) versus the Omicron (B.1.1.529) as a reference.

Solid square and error bars: unadjusted odds ratios for the Delta (B.1.617.2) versus the Omicron (B.1.1.529) as a reference.

Blank square and error bars: adjusted odds ratios for fully vaccinated status for the Delta (B.1.617.2) versus the Omicron (B.1.1.529) as a reference.

Error bars represent the 95% confidence interval.

and Delta periods rather than the Alpha periods (p<0.001). Favipiravir accounted for 98.7% of all antiviral agents used. The duration of antiviral agents was longer during the Delta period than during the Alpha and Omicron periods: median 10 days (IQR 10 to 10) versus 7 days (IQR 5 to 10) (p=0.016) and 5 days (IQR 5 to 5) (p<0.001), respectively.

A total of 126 (29.6%) individuals in the cohort received corticosteroids, of whom 73% (92/126) had radiographic evidence of pneumonia and 11.9% (15/126) had severe COVID-19. The proportions of corticosteroid use were significantly lower during the Omicron period: 6% versus 55.7% during the Delta period and 42.1% during the Alpha period (p<0.001). An initial dose of 6 milligrams (mg) of dexamethasone daily was given for most patients, except for individuals with high severity (data not shown). High-dose corticosteroids of more than 6 mg of dexamethasone were used during the Delta period than during the Omicron period: 30.9% versus 1.9%, respectively (p<0.001) (Table 1). The median time from onset of illness to corticosteroid admiration was 5 days (IQR 3 to 8). Among 25 individuals with early corticosteroid use within 5 days of illness onset, 60% (15/25) subsequently required antibiotics (crude odds ratio 13.5, 95% CI 1.34 to 135.98, p=0.027).

The overall complication rate was 1.6% (7/426) of the total cohort (Table 1).

Predictors for COVID-19 pneumonia and severe COVID-19

Compared with the Omicron, crude odds for the development of COVID-19 pneumonia were 13.304 (95% CI 5.361 to 33.016, p<0.001) for the Alpha and 19.936 (95% CI 9.891 to 40.184, p<0.001) for the Delta. After adjusting for variants, age, BMI, days of illness to admission, fully vaccinated status, and presence of any risk factors for severe disease, the Alpha and Delta variants, age, BMI, and days of illness to admission, were independent predictors for

Table 2. Predictors for COVID-19 pneumonia and severe disease, including oxygen use, from the logistic regression

	Predictors							
	Univariate analysis				Multivariate analysis			
	Pneumonia Crude OR (95% CI)	p-value	Oxygen use or severe disease Crude OR (95% CI)	p-value	Pneumonia§ Adjusted OR (95% CI)	p-value	Oxygen use or severe disease§ Adjusted OR (95% CI)	p-value
Variant								
B.1.1.529 (Omicron)	Ref.		Ref.		Ref.		Ref.	
B.1.1.7 (Alpha)	13.304 (5.361 to 33.016)	<0.001	1.130 (0.128 to 9.947)	0.912	12.690 (4.208 to 38.268)	<0.001	1.366 (0.121 to 15.448)	0.801
B.1.617.2 (Delta)	19.936 (9.891 to 40.184)	<0.001	2.280 (0.750 to 6.933)	0.146	7.357 (3.052 to 17.736)	<0.001	0.543 (0.117to 2.523)	0.436
Age (per 1 year)	1.081 (1.062 to 1.099)	<0.001	1.052 (1.024 to 1.081)	<0.001	1.058 (1.034 to 1.083)	<0.001	1.040 (0.998 to 1.083)	0.064
BMI (per 1 kg/m2)	1.161 (1.108 to 1.217)	<0.001	1.140 (1.060 to 1.225)	<0.001	1.100 (1.038 to 1.165)	0.001	1.150 (1.048 to 1.261)	0.003
Days of illness to admission (per 1 day)	1.091 (1.005 to 1.185)	0.038	0.973 (0.797 to 1.188)	0.788	1.142 (1.030 to 1.266)	0.012	0.964 (0.823 to 1.129)	0.649
Fully vaccinated status	0.263 (0.156 to 0.445)	<0.001	1.014 (0.354 to 2.904)	0.979	1.160 (0.513 to 2.623)	0.722	2.078 (0.566 to 7.630)	0.270
Last vaccination ≥90 days	0.768 (0.219 to 2.692)	0.680	2.350 (0.473 to 11.679)	0.296	-	-	-	-
Any risk factors for severe disease	7.906 (4.140 to 15.099)	<0.001	10.314 (3.557 to 29.901)	<0.001	1.176 (0.467 to 2.960)	0.119	3.444 (0.748 to 15.854)	0.112
Any antiviral agents use	13.310 (1.800 to 98.420)	0.011	1.263 (0.161 to 9.895)	0.824	-	-	-	-
Steroid use	40.019 (21.771 to 73.56)	<0.001	<0.001 (0.000 to NA)	0.993	-	-	-	-

BMI=body mass index; OR=odds ratio; CI=confidence interval

§ Adjustment for variants, age, BMI, days of illness to admission, fully vaccinated status, and any risk factors for severe disease

pneumonia (Table 2).

After adjusting for variants, age, BMI, days of illness to admission, fully vaccinated status, and presence of any risk factors for severe disease, BMI was an independent predictor for severe COVID-19 with an adjusted odds ratio of 1.15 (95% CI 1.048 to 1.261, p=0.003) (Table 2).

Discussion

In the present retrospective study, the authors aimed to investigate the clinical presentations of COVID-19 patients infected with the Omicron, Alpha, and Delta variants, focusing on young adults with mild to moderate disease. The present study is the largest in Thailand to compare the clinical characteristics of these variants. The authors observed low rates of in-hospital complications, with only one fatality occurring during the Omicron-dominant period.

Regarding symptom comparison, anosmia-hyposmia was prominent during the Alpha and Delta periods, consistent with a previous study[9]. However, the proportions of hyposmia-anosmia in the present study were lower than the previously reported[9], possibly due to previous immunity from vaccination and reduced inflammatory cytokine response during the Omicron period[10]. Another study conducted in Thailand before the Alpha or Delta periods reported a higher rate of hyposmia-anosmia[11], suggesting potential differences in olfactory bulb tropism among the variants[9,12].

Lower respiratory tract symptoms such as cough, breathlessness, and dyspnea were more prevalent during the Delta period compared to the Omicron period, contradicting a previous study[9]. Systemic symptoms like chills and night sweats were more common with the Omicron variant, consistent with the previous reports[9]. Diarrhea was also more prevalent during the Delta period, similar to the previous findings[9]. Blood-streaked sputum, a unique symptom, was observed only in cases infected with the Omicron variant, possibly indicating increased viral replication and inflammation in the respiratory bronchi[13].

The incubation period for the Omicron variant was shorter, with a median of 1 day (IQR 0 to 3), compared to 3 days (IQR 33 to 75 hours) reported in the previous studies[15,16]. This finding suggests the need for early SARS-CoV-2 testing among close contacts, even within 5 days after exposure.

Pneumonia occurred at significantly higher rates during the Alpha and Delta periods compared to the Omicron period, even after adjusting for confounding factors. BMI was identified as the only predictor for severe COVID-19. However, the proportion of severe cases in the present study cohort was too small to observe a significant difference between the variants after adjusting for multiple factors. Previous large-scale studies have demonstrated lower hospitalization, ICU admission, and risk of mortality during the Omicron period compared to the Delta period, considering multiple risk factors, previous SARS-CoV-2 infection, and vaccination status[17-23].

Two cases of MIS-C were diagnosed in the present study cohort, highlighting the increase in MIS-C cases among young adults during the Omicron

pandemic globally[24,25]. Vaccination coverage among young adults has not kept pace with the transmission rates of the Omicron variant[26]. The mRNA-based vaccines have been shown to decrease severe COVID-19, including MIS-C, in young adults and children[27], emphasizing the importance of vaccination in this population.

Asymptomatic infection accounted for 4.2% during the Omicron variant period. This proportion is much lower than over 80% asymptomatic infection reported during the Omicron variant among adolescents, an age similar to our study population[28]. However, a meta-analysis showed a much lower proportion of asymptomatic infection during the Delta variant of 8.4%, close to 2.9% in the present study cohort[28]. During the present study period, all close contacts, and individuals with exposure or traveling risks, were traced, tested, and if positive, hospitalized irrespective of severity for at least 10 days. This policy tends to favor a more precise estimation of true asymptomatic infection in the present study. Approximately 50% of asymptomatic infection was actually pre-symptomatic infection[29], citing that asymptomatic infection might have been over-estimated.

The use of antiviral agents and steroids showed an association with COVID-19 pneumonia, but caution is warranted in interpreting these findings. Antiviral agents were prescribed during the Alpha and early Delta periods only for symptomatic COVID-19 with risk factors for severe disease or individuals with pneumonia. Remdesivir was reserved for cases with progressive hypoxemia or contraindications to oral antiviral agents. A meta-analysis excluding new randomized-controlled trials[30-32] showed a shorter time to clinical improvement with favipiravir but did not show a benefit towards lower mortality[33].

Based on the provided information, it appears that Thailand's National Guidelines initially endorsed the use of favipiravir as a first-line agent for the treatment of COVID-19. However, recent large randomized controlled trials (RCTs) have shown that favipiravir does not prevent disease progression or reduce mortality in high-risk individuals, even when administered early in the course of the disease[30-32]. RCTs for the use of favipiravir in low-risk asymptomatic to mild symptomatic COVID-19 cases have also shown no benefit in terms of viral clearance or symptom resolution[32]. A meta-analysis excluding these RCTs did show a shorter time to clinical improvement in the favipiravir-treated group compared to standard care or other repurposed drugs, but this does not support the routine use of favipiravir[33].

Corticosteroid treatment was commonly prescribed during the Delta variant period, even for patients without hypoxemia. The decision to administer corticosteroids was based on an increase in C-reactive proteins along with radiographic changes compatible with pneumonia. However, the association between steroid use and pneumonia may have been influenced by bias in the protocols. The Infectious Diseases Society of America (IDSA) and Thai National Guidelines suggest corticosteroids for hypoxemic COVID-19 cases[34,35], but the present study found overall favorable outcomes despite early corticosteroid treatment, with low rates of proven secondary bacterial infection. However, there was a slight increase in the risk of subsequent antibiotic use when corticosteroids were administered within 5 days of illness onset. Ongoing randomized controlled trials are investigating early steroid therapy for non-critically ill or non-hypoxemic COVID-19 patients[36]. Multiple retrospective studies, including the present, suggested that steroid use may not reduce disease progression or mortality and could potentially prolong viral shedding[37-42].

It was important to acknowledge the limitations of the present study, such as the focus on mild to moderate cases, potential missing data, the inability to accurately predict the progression of COVID-19 pneumonia during admission, lack of sequential laboratory data, potential residual confounding bias, and incomplete variant confirmation in the cohort.

In conclusion, individuals infected with the Omicron variant tended to experience more systemic symptoms and less pneumonia compared to the Alpha or Delta variants. However, it's crucial to recognize that the Omicron variant can still cause severe disease in susceptible individuals. The routine use of favipiravir is not supported by recent evidence, and corticosteroid treatment in non-hypoxemic COVID-19 patients may not reduce disease progression or mortality. Further research and ongoing trials are necessary to gain a better understanding of optimal treatment strategies for different subsets of COVID-19 patients.

What is already known on this topic?

Clinical manifestations of each SARS-CoV-2 variant had a unique feature. However, an extensive comparison of clinical presentations, predictors, and outcomes between the Alpha, Delta, and Omicron variants in Thailand was scarce.

What this study adds?

This study found a unique symptom of COVID-19 among young adults during the Omicron variant. Systemic symptoms such as fever and myalgia but less pneumonia, were a prominent feature during the Omicron variant. However, in susceptible individuals especially obesity, the Omicron can cause a severe COVID-19 disease.

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Conflicts of interest

All authors declare no competing interests.

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