The Omicron variant of COVID-19 and its association with croup in children: a single-centre study in Hong Kong

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ABSTRACT

Introduction: The fifth wave of the coronavirus disease 2019 (COVID-19) pandemic in Hong Kong was dominated by the Omicron variant, which may cause more upper airway involvement in children. This study was performed to identify any associations between the Omicron variant of COVID-19 and croup in children.

Methods: This retrospective study reviewed the electronic medical records of patients admitted to Tuen Mun Hospital in Hong Kong from 1 January 2018 to 31 March 2022 under the diagnostic code for croup (J05.0 in the International Classification of Diseases 10th Edition). Patients were categorised into three groups according to their admission periods, namely, non–COVID-19, COVID-19–pre-Omicron, and COVID-19–Omicron groups. Disease associations and severity were compared according to incidence, Westley Croup Score, length of hospital stay, medication use, respiratory support, and intensive care unit admissions.

Results: The COVID-19 incidence among patients with croup was significantly higher in the COVID-19–Omicron group than in the COVID-19–pre-Omicron group (90.0% vs 2.0%; P<0.001). Compared with patients in the COVID-19–pre-Omicron and non–COVID-19 groups, patients in the COVID-19–Omicron group also had a higher Westley score (moderate and severe disease in the COVID-19–Omicron group: 56.7%; COVID-19–pre-Omicron group: 22.0%, P=0.004; non–COVID-19 group: 24.8%, P<0.001), longer median hospital stay (COVID-19–Omicron group: 3.00 days; COVID-19–pre-Omicron group: 2.00 days, P<0.001; non–COVID-19 group: 2.00 days, P=0.034), and higher mean dexamethasone requirement (COVID-19–Omicron group: 0.78 mg/kg; COVID-19–pre-Omicron group: 0.49 mg/kg, P<0.001; non–COVID-19 group: 0.58 mg/kg, P=0.001).

Conclusion: The Omicron variant of COVID-19 is associated with croup and can cause more severe disease in Hong Kong children.

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New knowledge added by this study

- The Omicron variant is associated with higher risk of croup than previously circulating variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- The presence of croup in a patient infected with the Omicron variant of SARS-CoV-2 could lead to a more prolonged and severe disease course.
- Omicron-associated croup may require more doses and a larger total amount of dexamethasone, as well as a longer hospital stay.

Implications for clinical practice or policy

- Paediatricians should be aware of the potential for prolonged courses of croup during the Omicron era of the coronavirus disease 2019 (COVID-19) pandemic.
- More healthcare resources may be needed for paediatric patients with croup in the Omicron era of the COVID-19 pandemic.
- Further research and policies promoting COVID-19 vaccination may be warranted to prevent COVID-19 and associated complications in children.

Introduction

Coronavirus disease 2019 (COVID-19) was first detected in Wuhan, China on 31 December 2019.[1] Since then, COVID-19 has affected adults and children worldwide. On 31 December 2021, the Centre for Health Protection of Hong Kong announced that the fifth wave of the pandemic, also known as the 'Omicron surge', had begun.[2] There was evidence that the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replicated more rapidly and effectively than other strains in bronchial and nasal epithelial cells,

resulting in higher infectivity and transmissibility, along with more severe upper respiratory tract manifestations.[3,4]

Croup, or laryngotracheitis, is an upper airway disease that primarily affects children aged 6 months to 3 years. Causative viruses infect the nasopharyngeal epithelium and spread along the respiratory tract up to the laryngotracheal region, leading to upper airway narrowing, inspiratory stridor, barking cough, and hoarseness.[5,6] Thus far, parainfluenza viruses have been the most common causative agents of croup.[7]

Compared with other SARS-CoV-2 variants and other respiratory viruses, the new Omicron variant of SARS-CoV-2 may have a stronger association with croup.[3,4] Case reports and case series have been published regarding COVID-19–associated croup[8-12]; however, few studies in Hong Kong or other countries have focused on possible causative relationships between the Omicron variant and croup.[8,12] Analyses of epidemiological data from Hong Kong are needed to guide further management of croup in children during the COVID-19 pandemic.

By exploring the incidence, clinical characteristics, treatment options, and outcomes of croup before and after the emergence of COVID-19, as well as after the emergence of the Omicron variant, this study aimed to identify differences among these three groups of patients and provide insights concerning COVID-19–associated croup in Hong Kong.

新冠病毒的Omicron變異株與兒童嘶哮症的關聯：香港單一中心研究

林頌恩、林樹仁

引言：香港新冠肺炎第五波疫情主要由Omicron變異病毒株引起。有研究顯示這種變異病毒株比起其他病毒株對於兒童的上呼吸道有更大影響。我們希望透過本研究瞭解Omicron變異病毒株與兒童嘶哮症有否關連。

方法：我們從屯門醫院的電子醫療記錄找出於2018年1月1日至2022年3月31日期間被診斷出有嘶哮症的兒童進行回顧性研究，並把他們根據感染時期分成三組：非新冠組、新冠Omicron前期組和新冠Omicron組。我們根據感染率、用來分析嘶哮症嚴重程度的Westley評分、留院日數、用藥情況、呼吸支持及深切治療部入住率，希望找出嘶哮症與Omicron變異病毒株的關聯性及嚴重程度。

結果：在確診嘶哮症的兒童中，90.0%的新冠Omicron組病人感染新冠病毒，遠多於新冠Omicron前期組的感染人數（2.0%；P<0.001）。新冠Omicron組兒童的Westley分數同時也較高，反映他們的嘶哮症更嚴重（中度及嚴重：新冠Omicron組：56.7%；新冠Omicron前期組：22.0%，P=0.004；非新冠組：24.8%，P<0.001）。相比另外兩組病人，新冠Omicron組的留院時間較長（新冠Omicron組：3.00天；新冠Omicron前期組：2.00天，P<0.001；非新冠組：2.00天，P=0.034），也需要更多地塞米松用作治療（新冠Omicron組平均值：0.78 mg/kg；新冠Omicron前期組平均值：0.49 mg/kg，P<0.001；非新冠組平均值：0.58 mg/kg，P=0.001）。

結論：新冠病毒的Omicron變異病毒株與嘶哮症相關，而且可以導致兒童有更嚴重的嘶哮症。

Methods

Study design

This retrospective observational study was conducted in the Department of Paediatrics and Adolescent Medicine at Tuen Mun Hospital, a large public hospital serving a population of >1.1 million (15% of the total Hong Kong population),[13] among which >15% are children.[14,15] Clinical data and medical records were retrieved from the Clinical Data Analysis and Reporting System of the Hospital Authority.

Inclusion and grouping criteria

All hospital admissions with a diagnostic code of 'Croup' (J05.0 in the International Classification of Diseases 10th Edition) from 1 January 2018 to 31 March 2022 were included in this study. Patients were grouped into the following three admission periods: (1) non–COVID-19 (1 January 2018 to 31 December 2019); (2) COVID-19–pre-Omicron (1 January 2020 to 31 December 2021); and (3) COVID-19–Omicron (1 January 2022 to 31 March 2022). This grouping approach coincided with the World Health Organization's announcement of the discovery of a novel coronavirus in Wuhan, China on 31 December 2019[1] and the Centre for Health Protection's announcement that the fifth wave of the pandemic (also known as the 'Omicron surge') had begun in Hong Kong on 31 December 2021.[2] The 2-year cohort from 2018 to 2019 (before the World Health Organization's announcement) was included for comparisons of characteristics before and after the emergence of SARS-CoV-2.

Exclusion criteria

The study population was limited to inpatients at Tuen Mun Hospital, excluding individuals solely managed in the Emergency Department. The study also excluded patients with a final diagnosis (eg, foreign body inhalation) that could mimic the clinical presentation of croup.

Clinical data and outcome measurements

Baseline clinical characteristics including age, sex, ethnicity, and significant medical history were retrieved from the medical records of the included patients. Diagnoses of COVID-19 were made by laboratory confirmation of viral infection through real-time polymerase chain reaction (RT-PCR) assays of nasopharyngeal specimens. Diagnoses of specific respiratory viruses were also confirmed by RT-PCR

assays of patients' nasopharyngeal specimens. The incidences of all viruses were analysed.

The total numbers of admitted patients with confirmed COVID-19 in the COVID-19–pre-Omicron and COVID-19–Omicron groups were retrieved from the Clinical Data Analysis and Reporting System. Among these patients, individuals with a diagnosis of croup were identified to determine the incidence rate of croup in each group.

The Westley Croup Score was calculated on the basis of physical findings documented in the retrieved medical records. It evaluates croup severity using five clinical parameters[16]: (1) level of consciousness (normal=0, disoriented=5); (2) cyanosis (none=0, with agitation=4, at rest=5); (3) stridor (none=0, with agitation=1, at rest=2); (4) air entry (normal=0, mildly decreased=1, substantially decreased=2); and (5) retraction (none=0, mild=1, moderate=2, severe=3). The raw score ranges from 0 to 17; croup can be categorised as mild (score 0-2), moderate (score 3-5), severe (score 6-11), or impending respiratory failure (score ≥12).

The following outcome measurements were also assessed:

(i) Length of hospital stay (days);
(ii) Dexamethasone use (number of doses and total amount used);
(iii) Use of nebulised adrenaline;
(iv) Respiratory support (oxygen therapy and high-flow nasal cannula oxygen therapy);
(v) Paediatric intensive care unit admission;
(vi) Other associated medical co-morbidities during the same admission (febrile convulsion, wheezing attacks/acute bronchiolitis, gastrointestinal symptoms, pneumonia, poor feeding/dehydration requiring intravenous fluid therapy, or readmission/abnormal blood test results).

Multivariate analysis was performed to examine a range of risk factors. Age, sex, ethnicity, history of croup, history of respiratory diseases, and timing of croup diagnosis were included as possible factors affecting croup severity. The Westley score and number of doses of dexamethasone used were selected as outcome measurements for croup severity.

History of croup and history of respiratory diseases were included in multivariate analyses because they are known risk factors for severe or recurrent croup.[17,18] Patients in the COVID-19–Omicron group were younger; thus, we regarded age as a possible confounding factor. Considering that croup had a male predominance in previous studies, sex was included as a potential risk factor. Ethnicity was included to determine whether the predominately Chinese population in Hong Kong would influence the outcomes compared with findings in previous studies primarily involving Caucasians or Asians.

Statistical analysis

The statistical significance of categorical variables was determined using the Pearson Chi squared test or Fisher's exact test. The Mann-Whitney *U* test and Kruskal–Wallis test were utilised to identify any statistically significant differences among groups regarding continuous variables (eg, age and length of stay). Multivariate analysis was performed by logistic regression. SPSS software (Windows version 28.0; IBM Corp, Armonk [NY], United States) was used for statistical analysis.

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was followed when preparing this article.

Results

In total, 423 inpatients were diagnosed with croup during the study periods: 343 were diagnosed in the non–COVID-19 period, 50 were diagnosed in the COVID-19–pre-Omicron period, and 30 were diagnosed in the COVID-19–Omicron period.

Baseline characteristics

The baseline characteristics for patients in each time period are shown in Table 1. There were no significant differences (P>0.05) across the three groups in terms of sex ratio, ethnicity, history of prematurity, or significant medical history (including histories of croup and/or respiratory, neurodevelopmental, and cardiac diseases). Male sex predominance was observed across all groups (male-to-female ratio in the non–COVID-19 group=1.77; COVID-19–pre-Omicron group=2.33; COVID-19–Omicron group=5; P=0.079). Most patients were Chinese (non–COVID-19 group: 92.4%, COVID-19–pre-Omicron group: 92.0%, COVID-19–Omicron group: 93.3%; P=0.725), born at term (non–COVID-19 group: 90.1%, COVID-19–pre-Omicron group: 94.4%, COVID-19–Omicron group: 100.0%; P=0.223), and had previous good health (non–COVID-19 group: 66.5%, COVID-19–pre-Omicron group: 72.0%, COVID-19–Omicron group: 70.0%; P=0.143).

Patients in the COVID-19–Omicron group had a median age of 11.0 months (interquartile range [IQR]=11), which was significantly younger than the median ages of patients in the COVID-19–pre-Omicron group (19.5 months, IQR=22) and the non–COVID-19 group (17.0 months, IQR=13) [P=0.008].

Incidence

Among patients diagnosed with croup, one (infection rate=2.6%) and 27 (infection rate=90.0%)

TABLE 1. Baseline characteristics of patients with croup in the three time periods in the current study*

	Non–COVID-19 group (n=343)	COVID-19–pre-Omicron group (n=50)	COVID-19–Omicron group (n=30)	P value
Sex				0.079†
Male	219 (63.8%)	35 (70.0%)	25 (83.3%)	
Female	124 (36.2%)	15 (30.0%)	5 (16.7%)	
Male-to-female ratio	1.77	2.33	5	
Ethnicity				0.725†
Chinese	317 (92.4%)	46 (92.0%)	28 (93.3%)	
Pakistani	11 (3.2%)	1 (2.0%)	1 (3.3%)	
Nepalese	7 (2.0%)	2 (4.0%)	0	
Black	3 (0.9%)	0	0	
Other Asian	4 (1.2%)	0	1 (3.3%)	
White	1 (0.3%)	1 (2.0%)	0	
History of prematurity	n=263	n=36	n=22	0.223†
Term (delivery at ≥37 weeks)	237 (90.1%)	34 (94.4%)	22 (100.0%)	
Preterm (delivery at <37 weeks)	26 (9.9%)	2 (5.6%)	0	
Significant medical history				0.143†
Previous good health	228 (66.5%)	36 (72.0%)	21 (70.0%)	
Croup	30 (8.7%)	2 (4.0%)	0	
Respiratory diseases	21 (6.1%)	2 (4.0%)	0	
Neurodevelopmental diseases	24 (7.0%)	7 (14.0%)	2 (6.7%)	
Cardiac diseases	8 (2.3%)	0	2 (6.7%)	
Others	32 (9.3%)	3 (6.0%)	5 (16.7%)	
Age at admission, mo				0.008‡
Median (25th-75th percentile)	17.0 (11.00-24.00)	19.5 (10.00-31.50)	11.0 (8.00-19.00)	
Interquartile range	13	22	11	
	Subgroup analysis for median age at admission: COVID-19–Omicron vs non–COVID-19: P=0.004§ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.008§ COVID-19–pre-Omicron vs non–COVID-19: P=0.264§			

Abbreviation: COVID-19 = coronavirus disease 2019

* Data are shown as No. (%), unless otherwise specified

† Pearson Chi squared test

‡ Kruskal–Wallis test

§ Mann-Whitney *U* test

were SARS-CoV-2–positive in the COVID-19–pre-Omicron and COVID-19–Omicron groups, respectively (Table 2). Patients diagnosed with croup in the COVID-19–Omicron group were more likely to be SARS-CoV-2–positive than patients with such a diagnosis in the COVID-19–pre-Omicron group (P<0.001) [Table 2].

Additionally, 386 and 170 paediatric patients (aged 0-18 years) admitted to Tuen Mun Hospital were SARS-CoV-2–positive in the COVID-19–Omicron and COVID-19–pre-Omicron groups, respectively. Among these patients, 27 were diagnosed with croup in the COVID-19–Omicron group and one was diagnosed with croup in the COVID-19–pre-Omicron group; these values indicated that the incidence of croup among patients with COVID-19 was much higher in the COVID-19–Omicron group (rate=7.0%, 95% confidence interval [CI]=4.61%-10.17%; P=0.0019) than in the COVID-19–pre-Omicron group (rate=0.59%, 95% CI=0.015%-3.28%; P=0.0019). Compared with other SARS-CoV-2 variants, the Omicron variant may be more strongly associated with croup.

Respiratory virus infection

Before the emergence of Omicron, among patients with croup, there were no differences in the rates of infection by respiratory viruses such as influenza

TABLE 2. Incidences of respiratory viruses in patients with croup across the three time periods in the current study*

	Non–COVID-19 group (n=251)	COVID-19–pre-Omicron group (n=39)†	COVID-19–Omicron group (n=30)	P value
SARS-CoV-2	N/A	1 (2.6%)	27 (90.0%)	<0.001‡
Parainfluenza	104 (41.4%)	19 (48.7%)	2 (6.7%)	<0.001‡
Influenza	50 (19.9%)	4 (10.3%)	0	0.011‡
Respiratory syncytial virus	27 (10.8%)	1 (2.6%)	1 (3.3%)	0.195§
Enterovirus/rhinovirus	40 (15.9%)	11 (28.2%)	0	0.007‡
Others‖	27 (10.8%)	2 (5.1%)	0	0.101§
No respiratory virus detected	32 (12.7%)	7 (17.9%)	27 (90.0%)	0.066‡
Co-infection rate (≥2 other respiratory viruses detected)	32 (12.7%)	2 (5.1%)	0	0.046§
	Subgroup analysis for co-infection rate: COVID-19–pre-Omicron vs non–COVID-19: P=0.281§ COVID-19–Omicron vs non–COVID-19: P=0.501§ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.033§			

Abbreviations: COVID-19 = coronavirus disease 2019; N/A = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

* Data are shown as No. (%), unless otherwise specified

† Nasopharyngeal specimen respiratory virus panel

‡ Pearson Chi squared test

§ Fisher's exact test

‖ Included human coronavirus and human metapneumovirus

(non–COVID-19 group: n=50, 19.9% vs COVID-19–pre-Omicron group: n=4, 10.3%; P=0.149), respiratory syncytial virus (non–COVID-19 group: n=27, 10.8% vs COVID-19–pre-Omicron group: n=1, 2.6%; P=0.146), and enterovirus/rhinovirus (non–COVID-19 group: n=40, 15.9% vs COVID-19–pre-Omicron group: n=11, 28.2%; P=0.061). Parainfluenza virus was the main respiratory virus detected in both groups (non–COVID-19 group: n=104, 41.4% vs COVID-19–pre-Omicron group: n=19, 48.7%; P=0.392). There was also no difference in the co-infection rate in the two groups (≥2 other respiratory viruses detected) [non–COVID-19 group: n=32, 12.7% vs COVID-19–pre-Omicron group: n=2, 5.1%; P=0.281] (Table 2).

However, after the emergence of Omicron, the SARS-CoV-2 Omicron variant became the main respiratory virus among patients with croup (co-infection in the COVID-19–Omicron group: n=0, vs non–COVID-19 group: n=32, rate=12.7%; P=0.033).

Because the respiratory viruses infecting patients with croup were similar between the COVID-19–pre-Omicron and non–COVID-19 groups, a pooled analysis was performed by grouping patients with croup in the two groups and compared with patients in the COVID-19–Omicron group. The results revealed that patients with croup in the COVID-19–Omicron group had significantly lower rates of infection with parainfluenza (COVID-19–Omicron group: n=2, 6.7% vs pre-Omicron group [non–COVID-19 group and COVID-19–pre-Omicron group]: n=123, 42.4%; P<0.001), influenza (COVID-19–Omicron group: n=0 vs pre-Omicron group: n=54, 18.6%; P=0.011), and enterovirus/rhinovirus (COVID-19–Omicron group: n=0 vs pre-Omicron group: n=51, 17.6%; P=0.007). There was no difference in the rate of infection with respiratory syncytial virus (COVID-19–Omicron group: n=1, 3.3% vs pre-Omicron group: n=28, 9.7%; P=0.499) between the time before and after the emergence of Omicron. The rates of infection with individual viruses are shown in Table 2.

Westley Croup Score

In the COVID-19–Omicron group, significantly more patients with croup had moderate disease (50.0%) or severe disease (6.7%) according to the Westley score, compared with the non–COVID-19 (moderate disease: 23.9%; severe disease: 0.9%; P<0.001) and COVID-19–pre-Omicron groups (moderate disease: 22.0%; severe disease: 0%; P=0.004). The distribution of severity, according to the Westley score, was similar between the non–COVID-19 and COVID-19–pre-Omicron groups (P=0.780) [Table 3].

Length of hospital stay

Because causative agents were similar between the non–COVID-19 and COVID-19–pre-Omicron groups, they were grouped together for analysis again

TABLE 3. Westley Croup Score in patients with croup across the three time periods in the current study*

	Non–COVID-19 group (n=343)	COVID-19–pre-Omicron group (n=50)	COVID-19–Omicron group (n=30)
Mild (0-2)	258 (75.2%)	39 (78.0%)	13 (43.3%)
Moderate (3-5)	82 (23.9%)	11 (22.0%)	15 (50.0%)
Severe (6-11)	3 (0.9%)	0	2 (6.7%)
Impending respiratory failure (≥12)	0	0	0
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P<0.001† COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.004† COVID-19–pre-Omicron vs non–COVID-19: P=0.780†		

* Data are shown as No. (%)
† Pearson Chi squared test

and compared with the COVID-19–Omicron group. Patients with croup had a significantly longer hospital stay in the COVID-19–Omicron group (mean=3.63 days, median=3.00, IQR=2) than the pre-Omicron group (mean=2.67 days, median=2.00, IQR=3; P=0.016). This finding indicated that patients with croup who were infected with the Omicron variant of SARS-CoV-2 required longer hospitalisation, implying that such patients had more severe disease than patients infected with other viruses in the pre-Omicron period.

Management strategies and outcomes

Table 4 illustrates treatments and management outcomes during the study periods.

Dexamethasone use

Most patients required zero to one dose of dexamethasone (COVID-19–Omicron group: 66.7%; non–COVID-19 group: 87.5%; COVID-19–pre-Omicron group: 90.0%; P=0.020). Significantly more patients required ≥2 doses in the COVID-19–Omicron group than in the non–COVID-19 (33.3% vs 12.5%; P=0.005) and COVID-19–pre-Omicron groups (33.3% vs 10.0%; P=0.010). A need for repeated doses of dexamethasone indicated more severe disease, considering that guidelines recommend ≥2 doses of dexamethasone for patients with croup who display suboptimal clinical improvement.[5,6,19,20] The difference remained statistically significant when the total amount of dexamethasone given was normalised according to the body weight of the patient; patients in the COVID-19–Omicron group required a larger total amount of dexamethasone (mean=0.78 mg/kg) compared with patients in the other two groups (mean of the non–COVID-19 group=0.58 mg/kg, P=0.001; mean of the COVID-19–pre-Omicron group: 0.49 mg/kg, P<0.001).

Nebulised adrenaline use

Nebulised adrenaline is often administered to patients with severe croup.[5,6,19,20] Most patients in the study did not require nebulised adrenaline. During the non–COVID-19 period, 1.5% of patients (n=5) were given one dose, 0.9% (n=3) were given two doses, and 0.3% (n=1) were given three doses; in the COVID-19–Omicron and COVID-19–pre-Omicron groups, only 6.7% (n=2) and 2.0% (n=1) of the patients, respectively, were given a single dose. No patients in the COVID-19–Omicron and COVID-19–pre-Omicron groups required more than one dose. Overall, there was no significant difference in the need for nebulised adrenaline (P=0.551).

Respiratory support

Overall, 6.4% (n=22) of patients admitted in the non–COVID-19 period required oxygen therapy, whereas 2.0% (n=1) required oxygen in the COVID-19–pre-Omicron period and 13.3% (n=4) required oxygen in the COVID-19–Omicron period. Although the oxygen requirement tended to be higher in the COVID-19–Omicron group than in the other two groups, this difference was not statistically significant (P=0.134).

Respiratory support also included the use of humidified high-flow oxygen. No patients required intubation or other forms of mechanical ventilation. Humidified high-flow oxygen was required by 1.2% (n=4) of patients in the non–COVID-19 period, 6.7% (n=2) in the COVID-19–Omicron period, and 0% in the COVID-19–pre-Omicron period. There were no differences among the groups concerning humidified high-flow oxygen use (Table 4).

Paediatric intensive care unit admissions

In total, 2.9% (n=10), 2.0% (n=1), and 6.7% (n=2) of patients required paediatric intensive care unit admission while hospitalised among the non–COVID-19, COVID-19–pre-Omicron, and COVID-19–Omicron groups, respectively; there was no significant difference across the three groups (P=0.467) [Table 4].

TABLE 4. Management strategies in patients with croup across the three time periods in the current study*

	Non–COVID-19 group (n=343)	COVID-19–pre-Omicron group (n=50)	COVID-19–Omicron group (n=30)	P value
Dexamethasone use, No. of doses				
0-1	300 (87.5%)	45 (90.0%)	20 (66.7%)	0.020†
≥2	43 (12.5%)	5 (10.0%)	10 (33.3%)	
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.005‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.010† COVID-19–pre-Omicron vs non–COVID-19: P=0.609†			
Amount of dexamethasone used, mg/kg				
Mean (95% confidence interval)	0.58 (0.55-0.62)	0.49 (0.40-0.58)	0.78 (0.63-0.92)	<0.001§
Median (25th-75th percentile)	0.60 (0.60-0.60)	0.60 (0.15-0.60)	0.60 (0.60-1.20)	
Interquartile range	0.00	0.45	0.60	
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.001‖ COVID-19–Omicron vs COVID-19–pre-Omicron: P<0.001‖ COVID-19–pre-Omicron vs non–COVID-19: P=0.012‖			
Use of nebulised adrenaline, No. of doses given				
0	334 (97.4%)	49 (98.0%)	28 (93.3%)	0.551†
1	5 (1.5%)	1 (2.0%)	2 (6.7%)	
2	3 (0.9%)	0	0	
3	1 (0.3%)	0	0	
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.223† COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.553‡ COVID-19–pre-Omicron vs non–COVID-19: P=0.880†			
Oxygen therapy				
Required	22 (6.4%)	1 (2.0%)	4 (13.3%)	0.134†
Not required	321 (93.6%)	49 (98.0%)	26 (86.7%)	
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.147‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.063‡ COVID-19–pre-Omicron vs non–COVID-19: P=0.336‡			
Humidified high-flow oxygen				
Used	4 (1.2%)	0	2 (6.7%)	0.034†
Not used	339 (98.8%)	50 (100.0%)	28 (93.3%)	
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.077‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.138‡ COVID-19–pre-Omicron vs non–COVID-19: P=1.000‡			
PICU status				
Admitted	10 (2.9%)	1 (2.0%)	2 (6.7%)	0.467†
Not admitted	333 (97.1%)	49 (98.0%)	28 (93.3%)	
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.250‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.553‡ COVID-19–pre-Omicron vs non–COVID-19: P=1.000‡			

Abbreviations: COVID-19 = coronavirus disease 2019; PICU = paediatric intensive care unit

* Data are shown as No. (%), unless otherwise specified

† Pearson Chi squared test

‡ Fisher's exact test

§ Kruskal–Wallis test

‖ Mann-Whitney *U* test

Other co-morbidities

Patients with croup had a higher overall incidence of co-morbidities in the COVID-19–Omicron group (46.7%, n=14) than in the non–COVID-19 (25.4%, n=87) and COVID-19–pre-Omicron groups (30.0%, n=15) [Table 5]. Patients with croup had a significantly higher incidence of new co-morbidities in the COVID-19–Omicron group than in the non–COVID-19 group, with an odds ratio (OR) of 2.575 (95% CI=1.207-5.491; P=0.012); this incidence did not differ between the COVID-19–pre-Omicron and non–COVID-19 groups (OR=1.427, 95% CI=0.749-2.718; P=0.278).

With respect to specific co-morbidities (Table 5), there were no significant differences in the rates of febrile convulsion, pneumonia, intravenous fluid therapy requirement, readmission, or abnormal blood test results. However, significantly more patients in the COVID-19–Omicron group had gastrointestinal symptoms compared with patients in the other groups. Thus, the Omicron variant was associated with more concomitant gastrointestinal manifestations among patients with croup compared with such patients in the non–COVID-19 (OR=9.250, 95% CI=3.039-28.151; P<0.001) and COVID-19–pre-Omicron groups (OR=3.086, 95% CI=2.217-4.292; P=0.002).

Importantly, no patients with croup in the COVID-19–Omicron group had concomitant wheezing attacks or bronchiolitis (n=0), compared with a rate of approximately 1 in 10 during the other two groups (non–COVID-19: n=42, 12.2%; COVID-19–pre-Omicron: n=5, 10.0%). However, the overall difference was not statistically significant (P=0.119) [Table 5].

Risk factors

The results in Table 6 indicate that differences in

TABLE 5. Specific co-morbidities in patients with croup across the three time periods in the current study*

	Non–COVID-19 group (n=343)	COVID-19–pre-Omicron group (n=50)	COVID-19–Omicron group (n=30)	P value
Febrile convulsion	7 (2.0%)	2 (4.0%)	2 (6.7%)	0.250†
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.158‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.628‡ COVID-19–pre-Omicron vs non–COVID-19: P=0.321‡			
Wheezing attacks/bronchiolitis	42 (12.2%)	5 (10.0%)	0	0.119†
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.105‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.151‡ COVID-19–pre-Omicron vs non–COVID-19: P=0.648†			
Gastrointestinal symptoms	9 (2.6%)	0	6 (20.0%)	<0.001†
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P<0.001‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.002‡ COVID-19–pre-Omicron vs non–COVID-19: P=0.611‡			
Pneumonia	6 (1.7%)	1 (2.0%)	2 (6.7%)	0.201†
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.129‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=0.553‡ COVID-19–pre-Omicron vs non–COVID-19: P=1.000‡			
Poor feeding/dehydration requiring intravenous fluid therapy	12 (3.5%)	4 (8.0%)	2 (6.7%)	0.254†
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.313‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=1.000‡ COVID-19–pre-Omicron vs non–COVID-19: P=0.126‡			
Readmission/abnormal blood test results	11 (3.2%)	3 (6.0%)	2 (6.7%)	0.433†
	Subgroup analysis: COVID-19–Omicron vs non–COVID-19: P=0.281‡ COVID-19–Omicron vs COVID-19–pre-Omicron: P=1.000‡ COVID-19–pre-Omicron vs non–COVID-19: P=0.402‡			

Abbreviation: COVID-19 = coronavirus disease 2019

* Data are shown as No. (%), unless otherwise specified

† Pearson Chi squared test

‡ Fisher's exact test

age (P=0.619), sex (P=0.588), ethnicity (P=0.090), history of croup (P=0.501), and history of respiratory diseases (P=0.253) did not affect the risk of greater croup severity. The timing of croup diagnosis was a significant risk factor for greater croup severity. After adjustment for the other factors, the OR for greater croup severity in the COVID-19–Omicron group was 3.94 (95% CI=1.79-8.62; P<0.001) compared with the non–COVID-19 group. Comparison of the COVID-19–Omicron and COVID-19–pre-Omicron groups revealed an OR of 4.46 (95% CI=1.63-12.20; P=0.004) [Table 5].

The results were consistent when the number of doses of dexamethasone was regarded as the analysis outcome. Patients diagnosed with croup in the COVID-19–Omicron group had an increased risk of greater croup severity. The OR for requiring ≥2 doses of dexamethasone in the COVID-19–Omicron group, compared with the non-COVID group, was 3.02 (95% CI=1.26-7.25; P=0.013). Comparison of the COVID-19–Omicron and COVID-19–pre-Omicron groups showed an OR of 3.66 (95% CI=1.07-12.50; P=0.039) [Table 5].

Discussion

Link between the Omicron variant and croup

Our results showed that SARS-CoV-2 became the predominant virus in patients with croup after emergence of the Omicron variant, surpassing parainfluenza virus, which was previously considered the most common viral cause of croup.[7] This contrasts with the COVID-19–pre-Omicron group, during which there were no differences in the rates of detected respiratory viruses compared with the non–COVID-19 group. Thus, the Omicron variant was associated with a higher risk of croup, compared with other SARS-CoV-2 variants.

Additionally, among patients admitted for treatment of COVID-19, the incidence of croup was significantly higher in the COVID-19–Omicron group than in the COVID-19–pre-Omicron group, indicating that the Omicron variant was associated with a higher risk of croup, compared with other SARS-CoV-2 variants. This finding is consistent with previous reports that the Omicron variant preferentially replicates in the upper respiratory tract,[3,4] which differs from observations concerning other variants.

The lower co-infection rate during the COVID-19–Omicron period (0%), compared with the non–COVID-19 period (12.7%), could be attributed to the greater replication capacity and infectivity of the Omicron variant of SARS-CoV-2. Another possible explanation for the lower co-infection rate and the shift in predominant respiratory virus from parainfluenza to the Omicron variant of SARS-CoV-2 could have been the implementation of social distancing policies outlined in the Prevention and Control of Disease Ordinance [Cap 599 (F, G, I) of the Laws of Hong Kong][21-23] and school suspension[24-29] in Hong Kong, which may have effectively reduced the transmission of upper respiratory tract infections. These effects were revealed through the reduction in the total number of patients with croup admitted during the 2-year interval since the emergence of COVID-19 in 2020. In the COVID-19–pre-Omicron period, only 50 patients were admitted for croup, compared with 343 during the non–COVID-19 period.

Increased croup severity in patients with the Omicron variant

The present study revealed the Omicron variant is causing greater croup severity compared with other variants and respiratory viruses, in terms of a significantly higher Westley score, longer hospitalisation, greater requirement for dexamethasone, and more concomitant gastrointestinal manifestations. Multivariate analysis also showed that patients in the COVID-19–Omicron group, when the Omicron variant of

TABLE 6. Multivariate analysis of factors affecting croup severity by logistic regression

	Westley Croup Score		No. of doses of dexamethasone used	
	OR (95% CI)	P value	OR (95% CI)	P value
COVID-19–Omicron vs non–COVID-19	3.94 (1.79-8.62)	<0.001	3.02 (1.26-7.25)	0.013
COVID-19–Omicron vs COVID-19–pre-Omicron	4.46 (1.63-12.20)	0.004	3.66 (1.07-12.50)	0.039
Sex	0.876 (0.541-1.416)	0.588	0.990 (0.532-1.841)	0.975
Age at admission	0.996 (0.979-1.013)	0.619	0.991 (0.969-1.015)	0.466
Ethnicity	0.387 (0.129-1.159)	0.090	0.698 (0.200-2.214)	0.572
History of croup	1.380 (0.540-3.530)	0.501	2.126 (0.728-6.214)	0.168
History of respiratory diseases	1.692 (0.687-4.168)	0.253	0.719 (0.161-3.199)	0.664

Abbreviations: 95% CI = 95% confidence interval; COVID-19 = coronavirus disease 2019; OR = odds ratio

SARS-CoV-2 was the predominant virus, were more likely to develop severe disease.

The decrease in the number of patients with concomitant wheezing attacks or bronchiolitis could be attributed to a lower viral load in the lower respiratory tract (relative to the upper respiratory tract), as observed in hamsters,[19,30] along with the greater infectivity of the Omicron variant in nasal epithelial cells.[3,4] Considering that wheezing attacks and bronchiolitis mainly affect small airways in the lower tract, these findings may explain the lower risks of such co-morbidities in patients with croup who exhibit the Omicron variant of COVID-19.

Regarding the length of stay, confounding factors such as quarantine policies, parental anxiety about hospitalisation, and various discharge criteria based on physician preferences could affect the observed correlation with disease severity.

During the 'Omicron surge', hospital discharge criteria were revised to allow early discharge for clinically stable patients without repeated RT-PCR testing; conversely, in the COVID-19–pre-Omicron group, negative RT-PCR results (or RT-PCR results with certain cycle threshold values) were required prior to discharge.[31-33] A longer length of stay in patients with croup during the COVID-19–Omicron period despite these relaxed discharge criteria indicates that croup severity was greater in the COVID-19–Omicron period, although other co-morbidities in patients with COVID-19 may also have contributed to the increased length of hospital stay.

The potentially greater severity of croup in patients with the Omicron variant of COVID-19 and the diverse range of co-morbidities in such patients had considerable impacts on patient health, caregiver stress, and the public health burden. More healthcare resources, such as in-hospital backup nebulising facilities, may be required during the Omicron-dominant era. The results of the present study will enable paediatricians to be more vigilant and predict a possibly longer disease course, along with the need for repeated dexamethasone administration or enhanced treatment, in patients with COVID-19–Omicron–associated croup.

Limitations

There were several limitations in this study. First, it was a single-centre study, limiting its ability to represent the overall population; thus, a more extensive study should be performed in the future.

Second, there was no unified treatment protocol for croup in our hospital. Exact medication dosing and timing (eg, concerning addition or repetition) were largely based on clinical decisions by multiple physicians, which may have considerably varied although all administered oral dexamethasone as first-line medication; repeated doses were given as needed, and nebulised adrenaline was reserved for patients with more severe disease.[5,6,19,20] These factors could have affected the assessments of severity across study periods by modifying the doses of medication administered.

Third, measurement of the Westley score could have been under- or overestimated because it was based on clinical records, where data may have been omitted by attending physicians. These missing data could affect measurements of croup severity across study periods.

Finally, patients with croup admitted during the Omicron period (median age=11.0 months) were younger than such patients in previous periods (COVID-19–pre-Omicron group: 19.5 months; non–COVID-19 group: 17.0 months). Possible explanations include the greater transmissibility of the Omicron variant in younger populations compared with other variants[34] and the lack of eligibility for SARS-CoV-2 vaccination among patients aged <3 years.[35] Thus, overall protection could be compromised in the younger age-group. Other possible confounding factors, such as family history of croup and parental smoking habits, could not be assessed in this study because the data were not available in clinical records.

Future directions

This study focusing on croup and its associations with COVID-19 among Hong Kong children provides important insights that can help guide management of the Omicron variant. However, additional population-based studies involving patients from various centres in Hong Kong are needed to achieve a sample size that can facilitate the development of management protocols specifically targeting Omicron-associated croup. In the future, prospective studies could be performed to analyse the long-term outcomes of such patients, thereby facilitating the planning and allocation of healthcare resources in Hong Kong.

Conclusion

This retrospective study demonstrated that the Omicron variant of COVID-19 is associated with croup in children; on admission, croup severity was greater compared with past observations of disease.

Author contributions

Concept or design: MCY Lam.
Acquisition of data: MCY Lam.
Analysis or interpretation of data: Both authors.
Drafting of the manuscript: MCY Lam.
Critical revision of the manuscript for important intellectual content: DSY Lam.

Both authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

Both authors have disclosed no conflicts of interest.

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Ethics approval

This research was approved by the New Territories West Cluster Research Ethics Committee of Hospital Authority, Hong Kong (Ref No.: NTWC/REC/22030). Informed patient consent waiver was granted by the Committee due to the retrospective nature of the study.

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Answers to CME Programme

Hong Kong Medical Journal December 2023 issue

Hong Kong Med J 2023;29:514-23

I. Ten-year territory-wide trends in the utilisation and clinical outcomes of extracorporeal membrane oxygenation in Hong Kong

A	1. False	2. True	3. False	4. False	5. True
B	1. False	2. True	3. False	4. True	5. False

Hong Kong Med J 2023;29:532-41

II. Consensus recommendations for the screening, diagnosis, and management of Helicobacter pylori infection in Hong Kong

A	1. True	2. True	3. True	4. False	5. False
B	1. False	2. True	3. True	4. True	5. True