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The combined manifestations of dramatically sore throat, congested and edematous mucosa, no-swelling tonsil are specific in acute Omicron pharyngitis

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Abstract

Objective To identify specific clinical signs of Omicron pharyngitis infection.

Methods A clinical cross-sectional retrospective study was designed to analyze the primary symptoms of pharyngitis in outpatients seeking treatment for sore throat. Pharyngeal congestion, mucosal edema, were measured using a visual analogue assessment score (0–10) while the presence of ulcers, no-tonsil-swelling, no-tonsil-exudate. They were recorded as "yes" or "no "as two-Categorical data by two senior clinicians, respectively. Significant clinical signs were selected and combined to form a diagnostic panel using SPSS software to differentiate between Omicron pharyngitis and other sore throat cases. The efficiency of the panel was calculated.

Results A total of 39 sore throat patients were included in the study, including 15 confirmed cases of Omicron pharyngitis through nuclear acid or Sars-Cov-2 virus antigen testing, and 24 cases of common pharyngitis caused by other pathogens. Mucosal congestion and edema were identified as the most significant symptoms and consolidated into a single working group. When combined with the third significant symptom of no-tonsil-swelling, the three-sign-combined diagnostic panel was found to have a high diagnostic efficiency. Mucosal congestion and edema were the most significant signs. When mucosal congestion and edema were consolidated into a single working panel, the cut-off values were determined to be 7.5 and 1, respectively. When combined with the third significant symptom no-tonsil-swelling, the three-sign diagnostic panel was found to have a high diagnostic efficiency. When compared with the gold standard measurement of Sars-Cov-2 virus antigen or nucleic acid, the diagnostic panel has a sensitivity of 66.7% and a specificity of 91.7%.

Conclusion A combination of three signs may be a useful diagnostic tool for Omicron pharyngitis. Clinical signs of dramatic mucosal congestion and edema, non-swollen tonsils are the characteristics of Omicron pharyngitis.

Keywords Omicron pharyngitis, Specific manifestations, Mucosa congestion, Mucosa edema, No-tonsil-swelling

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Table 1 The statistic results of signs of pharyngitis between Omicron group and control group

	Non-Omicron ($n=24$)	Omicron ($n=15$)
Congestion	6.04 ± 1.37	7.80 ± 2.19* ($P=0.001$)
Edema	1.00 ± 2.08	3.40 ± 3.85* ($P=0.005$)
Ulcer	2/24	5/15 ($P=0.048$)
No-tonsil-swelling	8/24	15/15* ($P=0.000$)
No-tonsil-exudation	19/24	15/15 ($P=0.058$)

Measurement data (mucosa congestion and edema); Count data (mucosa ulcer, no tonsil-swelling and no-tonsil-exudate). *$P<0.05$

Introduction

Covid-19 Omicron variant has spread rapidly around the world. Compared to previous variants, the Omicron variant decreased replication rates and pathogenicity, but enhanced transmissibility [1–3]. The virus has infected many people in China since December 2022 abruptly. Fever, fatigue, sore throat, and cough are among the most common clinical complaints of patients in the early stages of infection. Some patients may also experience pharyngeal pain, dryness, and swallowing difficulties caused by this pathogen, which are often associated with other upper airway infections. In fact, the clinical manifestations of Omicron pharyngitis are impressive and disturbing at first sight. As a novel virus with strong pathogenicity and infectivity, it also has unique pathogenic mechanisms and pathophysiological processes. We try to collect and analyze its clinical signs and pathogenic mechanisms, which can be useful for differential diagnosis.

Materials and methods

Record the main signs of Omicron pharyngitis and data fitting.

We analyzed the clinical characteristics of 15 Omicron patients who had a definite diagnosis with positive Covid-19 antigen or nucleic acid results and 24 other patients who all complained of sore throat. The 15 Omicron patients included those who came to the hospital to see a doctor and those who sought help through the Internet for medical services. The five clinical signs of mucosa congestion, mucosa edema, ulcers, no-tonsil-swelling, and no-tonsil-exudate were desperately recorded by the two senior clinicians. The former two signs were recorded using the visual analogue scale (VAS score). The 10 cm line represents the severity of clinical manifestations with the leftmost point of the line indicating no manifestation recorded as 0, and the rightmost point indicating the most severe manifestation recorded as 10. Clinicians recorded the severity of clinical signs by marking a spot on the line with the severity increasing to the right. The distance between the leftmost and marked spot is the score of clinical signs. They are measurement data. The last three signs were recorded as "yes" or "no." They are two-category data. Then, we obtained two sets of data for five clinical signs.

For fitting data, the VAS scores of the former two signs were average for each clinical sign, and the latter three signs were recorded as "no" if they were contradicted by two clinicians.

Statistical analysis

Data from five clinical signs were analyzed using the student t-test for the former two signs and chi-squared test for the latter three signs with SPSS 25 software, respectively. A p-value of <0.05 was considered statistically significant.

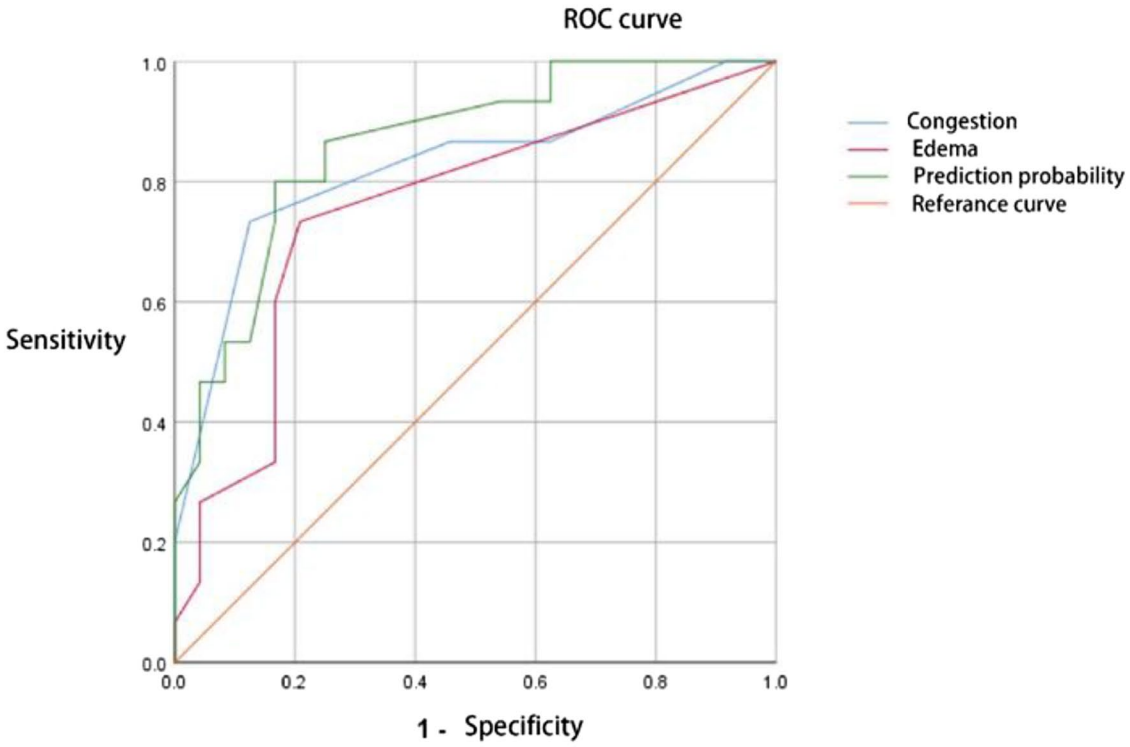
Diagnosis the sore throat patients with the clinical signs panel.

Through statistical analysis, clinical signs of significant difference were selected as the most representative manifestations of Omicron pharyngitis. They combined as a diagnostic panel for diagnosing whether the 39 cases who had acute sore throat but not gastroesophageal reflux disease were omicron pharyngitis or not. Test results for Sars-Cov-19 antigen or nucleic acid were the gold

(See figure on next page.)

Fig. 1 The new diagnosis mode was fitted with Two signs: mucosa congestion and edema. The new mode had goodness through logistic regression. The former two signs were fitted through logistic regression because they are both measurement data exclusively. **A** The three receiver operating characteristic curves (ROC curve) of the former two signs and their fitting mode were drawn and analyzed respectively. The fitted diagnosis mode with Two signs: mucosa congestion and edema, has goodness through logistic regression. The former two signs were fitted through logistic regression because they are both measurement data exclusively. **B** The Fitting degree was valuated through hosmer–lemeshow goodness of fit test and the P value = 0.733 > 0.05, It is an excellent result which revealed a good discrimination. C The area under fitting ROC curve is 0.863 > 0.75, showed the fitting two-sign-combined group had good working efficiency

A



B

Hosmer-Lemeshow test

	Chi-square	V.	Sig.
1	4.394	7	.733

C

Area under ROC

Variable	Area	Standard Error	Sig.	95% confidence interval for difference	
				Lower	Superior
congestion	.825	.075	.001	.679	.971
edema	.756	.083	.008	.592	.919
Prediction probability	.863	.060	.000	.746	.979

Fig. 1 (See legend on previous page.)

standard for diagnosis. The sensitivity and specificity of the panel were calculated.

This study was approved by Zhongshan hospital ethics committee, approval number: B2023-094.

Results

A total of 15 Omicrons pharyngitis patients (11 female,4 male) and 24 other sore throat patients(15 female,9 male) were included in this study with median age of 28 and 32 years old (age range from 22 to 81 years old and 26–73 years old,respectively). In the main five signs of pharyngitis: pharyngeal mucosa congestion, mucosa edema, ulcer, no-tonsil-swelling and no-tonsil-exudate analyzed, the signs of pharyngeal mucosa congestion, mucosa edema, no-tonsil-swelling had significance of difference ($p < 0.05$) (Table 1). It was the apical three signs of Omicron pharyngitis differential from other pharyngitis. They were chosen to compose a diagnosis panel to judge the 39 sore throat patients whether they were caught Omicron pharyngitis or not. At first, the former two signs were fitted through logistic regression with hosmer–lemeshow goodness of fit test because they were both measurement data exclusively. The two dimensions of discrimination and calibration of the fitted curve was evaluated. The area under the ROC curve showed the discrimination, the value is $0.863 > 0.75$. meaning the fitting working panel can distinguish the difference of the clinical data. Calibration quantified the accuracy of the estimated probability of the outcome. P value $= 0.733 > 0.05$. It meant that the two-sign-combined panel has accuracy estimated probability [4]. Then, the three receivers operating characteristic curves (ROC curves) of the former two signs and their fitting group were drawn and analyzed respectively (Fig. 1). Statistic results showed the cut-off value: congestion = 7.5, edema = 1. The Value of two clinical signs is higher than congestion = 7.5, edema = 1, is the most effective combined group to diagnosis Omicron pharyngitis. Added to the no-tonsil-swelling, the three-sign-combined diagnosis panel has the most optimized combination. The sensitivity and specificity of the diagnosis panel in Omicron pharyngitis diagnosis was 66.7% and 91.7%, respectively (Table 2).

Table 2 The diagnosis results using two ways: golden standard and three-sign-combined panel

		Golden standard		Total
		Positive	Negative	
Three-sign-combined panel	positive	10	2	12
	negtive	5	22	27
Total		15	24	39

Sensitivity of three-sign-combined panel is 66.7% (true positive/(true positive + false negative)); specificity is 91.7%(true negative/(true negative + false positive)).golden standard: Sars-cov-2 virus antigen or nuclear acid results; Three-sign-combined panel: congestion > 7.5, edema > 1 and no-tonsil-swelling

Figure 2 showed pharyngeal presentation in several Omicron infected cases. The figures were taken by

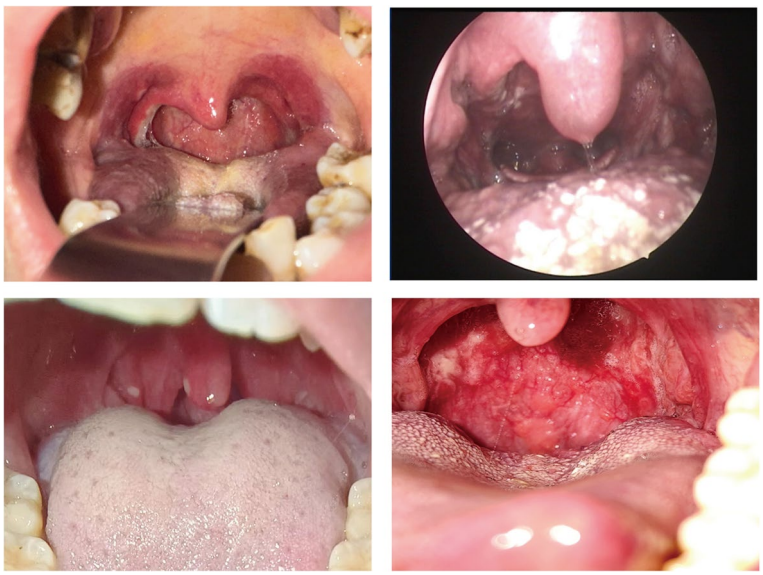


Fig. 2 The pharyngeal presentations in several Omicron infected cases. The figures were taken by doctors under face-to-face service condition or provided by patients themselves who sought help through internet medical service. Pharyngeal mucosa is congested and edematous, companied with no-swelling and no-exudate coated tonsil. Ulcer of mucosa is often seen in manifestations of omicrons pharyngitis

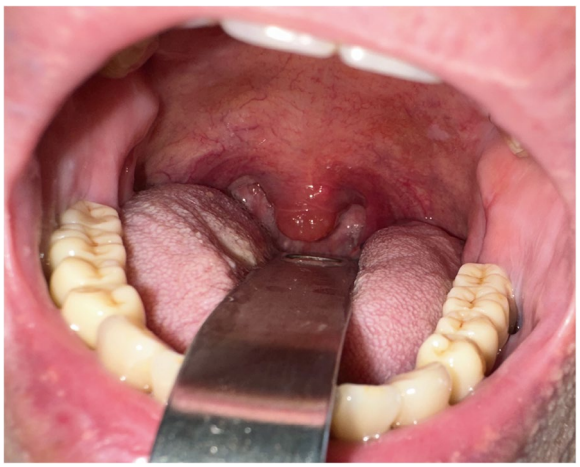


Fig. 3 An edema uvula, it was a common phenomenon in Omicron pharyngitis. An edema uvula was swollen and the soft palatine was more thickened than normal

doctors under face-to-face service conditions or provided by patients themselves who sought help through internet medical service. Pharyngeal mucosa is congested and edematous, companied with no-swelling and no-exudate coated tonsil. Ulcer of mucosa is often seen in manifestations of omicrons pharyngitis. Figure 3 showed an edema uvula, it was a common phenomenon in Omicron pharyngitis. An edema uvula was swollen and the angle of conjunction between uvula and soft palatine was more obtuse than normal. Figure 4 showed laryngeal presentation in acute Omicron pharyngitis: obviously congested(left), and pseudo-membranous exudation due to infected epithelial cell shedding(right).

Discussion

Sars-CoV-2 variant Omicron infect the airway epithelial through angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2(TMPRSS2), The former is the spike (S) protein binding protein, while the latter cleave S1/S2 domains and allow the fusion of the viral envelope with the cellular membrane [5]. The mutant of S protein of Omicron variant virus raises its viral transmissibility [3, 6]. Compare with the other Sars-cov-2 variant infected the lower airway and lung, Omicron variant virus is not liable to infect lung due to S protein mutant so that TMPRSS2(transmembrane protease serine protease) expressing in alveoli can't cleave the S protein easily as usual [7]. So, the clinical complains of omicrons infection were attenuated about lower airway and commoner related with the upper airway condition: sore throat, cough, stuffy nose, pus and bloody nasal discharge and sputum.

Omicron pharyngitis has not always happened after Omicron infection, and it might be similar with the symptoms of the upper airway infection due to other pathogens that we had usually met with theoretically. But in fact, the presentation of Omicron pharyngitis looks more dangerous. It looks dramatically congested and edematous. The painful sensation is also more obvious.

It due to the overdose bradykinin produced and released. Bradykinin is the inflammatory production of the coagulation system induced by several pathogens. It induces fluid extravasation and recruitment of leucocytes. ACE2 is crucial in Sars-Cov-2 virus adhere and enter airway epithelium. Otherwise, ACE2 /DABK/ bradykinin B1 receptor axis exit in covid-19 infection [8, 9]. It is one part of the cytokine storm mechanism. ACE2 hydrolyzed the active bradykinin metabolite des-Arg9-bradykinin (DABK) into an inactive form under healthy physical condition. As the Sars-Cov-2 virus consumes the ACE2, DABK accumulates which binds to bradykinin receptors type 1 [10]. As a result, the mucosa infected with Sars-Cov-2 is significantly prone to edema. We often judge the mucosa edema through the swelling uvula, and it always accompany with edematous epiglottis. Bradykinin storm is the reason acute epiglottitis is common during the stage of Omicrons infection. In fact, mucosa edema does not exist in every patient. Some Omicron pharyngitis showed dramatic mucosa congested, but not

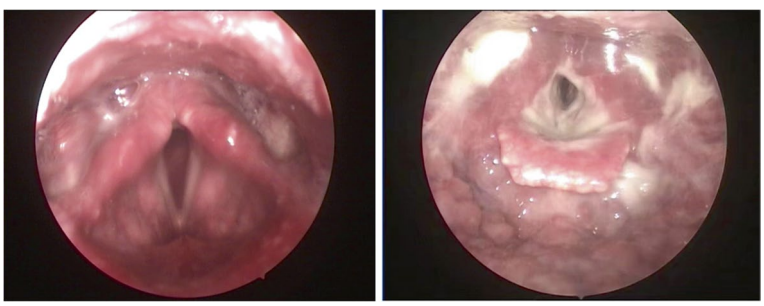


Fig. 4 The laryngeal presentations in acute Omicron pharyngitis: obviously congested(left), and pseudo-membranous exudation due to infected epithelial cell shedding(right)

edema. The ACE2 /DABK/ bradykinin B1 receptor axis seem not to play a role in all of Omicron pharyngitis.

At the same time, bradykinin induce the release of the PG [11], exacerbate the dilation of blood vessel, It is the reason mucosa congested and sense of painful dramatically.

Usually a virus infected upper airway such as respiratory syncytial virus (RSV) [12], it bounds the receptors on the epithelial cells including toll-like receptor (TLR), promoted The epithelial cells product cytokine and chemokine including IFN,IL-6,IL-8,IL-33 and TSLP [13, 14], which recruit innate immunity cell such as leukocyte and macrophage. excessive neutrophil-associated inflammation happened [15]. It happened immediately in infected initial several hours. After virus replicating and translating, the symbolized protein is presented to CD4+T help lymphocyte by dendritic cells, then leads to proliferation of the CD8+cytotoxic T lymphocytes and B lymphocytes. The effector immunity cells kill the infected cell through phagocytosis, complement opsonization and cell lysis. This is the adaptive immunity stage. It starts at the fifth day-seventh day after infection at most times. Other virus infected respiratory tract has the similar pathogenic mechanism [16]. As palatine tonsils consist of several structural cells including T lymph cells, B lymph cells, epithelial cells, dendritic cells, macrophage etc. [17], it is related with immune reaction of the upper airway, or regional immune reaction at least. Interesting, so as the main parts of waldeyer's ring, palatine tonsil should show swelling in acute phase and being chronic enlarged that would be observed in the infection of group A α-hemolytic streptococcus theoretically [17]. In fact, we did not find tonsil swelling and exudation in any case of Omicron pharyngitis. Sometimes, the palatine tonsil is smaller and unobservable even. It was related with the Sars-cov-2 virus of ever-expanding innate immune response and delayed adapt immunity probably [18]. Whether tonsil is swelling or not is always to judge whether infection and inflammation exist according to previous opinions, especially as centor criteria mentioned [19]. The tonsil hypertrophy had always been related to bacterial infection or EB virus infection. In our research, the relationship did not seem to exist, and the swelling or no-swelling tonsil both be seen in virus' pharyngitis. We cannot judge the type of infection depending on the tonsil swelling or not. We also found pharyngeal mucosa edema often seemed not to exist with a swelling tonsil at same time in clinical practice. The edema mucosa implied a potent innate immunity, and swelling tonsils may be related to a radical adaptive immunoreaction. The two clinical signs usually could not exist at the same time. Otherwise, it is not the same concept entirely that tonsil hypertrophy and swelling. The acute immunoreaction of lymphocyte induces the tonsil tissue swelling which is not related with the size of tonsil, while chronic and recurrence inflammation induces tonsil hypertrophy. Maybe it is the key point to observing whether it exits appropriate adaptive immunity or not. The duration after onset of infection can help to understand the processes.

Mucosa ulcer is also the common sign in Omicrons infection. Infected epithelial cells shedding might elucidate the mucosa ulcer [20], which is similar with herpetic pharyngitis. In our research, one acute pharyngitis case due to herpetic virus companied with Herpes Labialis is liable to confuse with Omicron pharyngitis. Generally, the level of painfulness, mucosa congestion and edema in Omicron pharyngitis is higher and tonsil should be not swelling in Omicron. Fever occurs in almost of Omicron cases. These were useful to differential diagnosis. The clinical signs panel is highly specified.

Conclusions

Using the diagnose panel with three-sign-combination, we could almost differentiate Omicrons pharyngitis from other common upper airway infection with several clinical signs.

It is believed that mucosa congestion and edema, no-swelling and no-exudate coated tonsil, is the characteristic manifestation of Omicron pharyngitis.

Abbreviations

VAS	Visual analog scale
ROC curve	Receiver operating characteristic curve
ACE2	Angiotensin-converting enzyme 2
TMPRSS2	Transmembrane protease serine 2
DABK	Des-Arg9-bradykinin
PG	Prostaglandin
TLR	Toll-like receptor
IFN	Interferon
CD4	Cluster differentiation 4
CD8	Cluster differentiation 8
IL	Interleukin
TLSP	Thymic stromal lymphopoietin

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Authors' contributions

Dr. Feng Xu designed the study, diagnosed the disease, and drafted the manuscripts as the corresponding auther. Dr. Lei Zhou provided the most photos of Omicron's pharyngitis and diagnosed the disease as first auther. Prof. Lineng Zhang designed the study, assisted with statistical analysis of the data, and revised the paper.

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Data availability

Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
This study was approved by Zhongshan hospital ethics committee, approval number: B2023-094.

Consent for publication
Informed consent to participate was obtained from all the participants in the study.

Competing interests
The authors declare no competing interests.

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