

# SARS-CoV-2 Infection Caused COVID-19 Related Otitis Media Is Commonly Existed with Good Prognosis

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## Abstract

Otitis media with effusion is a common disease in otolaryngology. Bacteria are the most common pathogen of otitis media with effusion, and other factors such as viruses have also been reported. The present study is aimed to investigate whether the increasing otitis media cases recently is correlated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and the COVID-19-related otitis media is commonly existed. Thirty-two patients with otitis media were enrolled Blood cell analysis, C-reactive protein, interleukin-6 test bacterial and fungal cultures were tested. Nine patients were identified with positive SARS-CoV-2 RNA in middle ear discharge. All the subjects had the common symptoms of stuffy ear, hearing loss, and echoacousia. No positive results were found in cultures for bacterial and fungus of middle ear discharge. The levels of C-reactive protein (CRP) were significantly up-regulated in positive cases ( $P = 0.0335$ ). The levels of proinflammatory cytokine interleukin-6 (IL-6) were higher in positive cases. There were no significant differences of age, gender and prothrombin time (PT) between positive and negative cases. Nasal sprays, ciliary stimulants, and prophylactic antibiotics or low-dose steroid treatments were sequentially used in the otitis media patients caused by SARS-CoV-2 infection. All the patients had improvements of typical symptoms within two to four weeks during the following-up. Thus, SARS-CoV-2 infection caused COVID-19 related otitis media is commonly existed, and the prognosis is good after treatments.

## Keywords

Otitis Media, COVID-19, SARS-CoV-2, IL-6

## 1. Introduction

Otitis media with effusion is a common disease in otolaryngology, with a significantly higher incidence in children than in adults [1]. The pathogenesis can be divided as an interaction with exogenous or endogenous. Bacteria are the most common pathogen of otitis media with effusion, and other factors such as viruses and allergy have also been reported [2] [3] [4]. While during the endogenous factors, eustachian tube dysfunction plays the most significant underlying mechanism of otitis media with effusion, especially in infants and children. Besides, patients who suffer from acute otitis media are more susceptible to otitis media with effusion [5]. Depending on the different stages of otitis media with effusion, it is divided into acute otitis media, chronic otitis media, and otitis media with effusion [6] [7]. In the stage of otitis media with effusion, there is a typical accumulation of secretions in the tympanic cavity and mastoid.

To our knowledge, since the outbreak of Coronavirus Disease 2019 (COVID-19) pandemic, there has been a significant correlation between the incidence of serious otitis media and social conditions as well as mask restrictions in the area [8]-[13]. There are various explanations for this phenomenon [14] [15]. It is speculated that either the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as a pathogen exists in otitis media or other pathogens have reduced their transmission due to quarantine restrictions. Theoretically, the COVID-19-related otitis media is reasonable. However, only two cases with otitis media with effusion have shown the presence of the SARS-CoV-2 isolated from the middle ear, while other cases were tested positive for SARS-CoV-2 nucleic acid in the nasopharynx without certain evidence of SARS-CoV-2 infection in the middle ear [16] [17] [18] [19] [20]. Here, we report a group of outpatient cases in which the nucleic acid of SARS-CoV-2 was tested positively in the middle ear effusion, demonstrating the previous speculation that the SARS-CoV-2 can infect the middle ear [12] [21] [22] [23].

## 2. Methods

### 2.1. Study Design and Subjects

All the patients were enrolled in the department of Otolaryngology-Head and Neck Surgery, Sir Run Run Shaw Hospital, Medical College of Zhejiang University, from Jan. 13<sup>th</sup> to Jan. 20<sup>th</sup> 2023. Thirty-two patients were enrolled, and 9 patients were identified (**Table 1**). The inclusion criteria: patients meet the diagnostic criteria of secretory otitis media [24]. Exclusion criteria: 1) patients with COVID-19 who had a severe illness with organ failure; 2) Rhinopharynx SARS-CoV-2 RNA still tests positive within active phase of COVID-19; 3) Patients diagnosed but unwilling to participate in the study with personal reasons. The current study was carried out in accordance with the *Declaration of Helsinki*. Informed consents were obtained from all subjects.

**Table 1.** SARS-CoV-2 RNA results and Laboratory tests of subjects with otitis media.

No.	Age	Gender	SARS-CoV-2 RNA		Cultures for bacterial and fungus	CRP (mg/L)	IL-6 (pg/mL)	PT (s)	Routine analysis of blood
			Ear discharge	Nasopharynx					
1	56	M	Positive	Negative	Negative	-	-	-	Normal
2	58	M	Positive	Negative	Negative	-	-	-	Normal
3	68	M	Positive	Negative	Negative	-	-	-	Normal
4	65	F	Positive	Negative	Negative	-	-	-	Normal
5	37	F	Positive	Negative	Negative	-	-	-	Normal
6	65	F	Negative	Negative	Negative	-	-	-	Normal
7	51	F	Negative	Negative	Negative	0.2	1.5	13.6	Normal
8	71	M	Positive	Negative	Negative	4.1	7.7	14.2	Normal
9	64	M	Negative	Negative	Negative	3.3	0.5	12.7	Normal
10	20	M	Negative	Negative	Negative	-	-	-	Normal
11	58	M	Negative	Negative	Negative	-	-	-	Normal
12	43	M	Negative	Negative	Negative	-	-	-	Normal
13	81	M	Negative	Negative	Negative	-	-	-	Normal
14	56	F	Negative	Negative	Negative	-	-	-	Normal
15	26	M	Negative	Negative	Negative	-	-	-	Normal
16	68	F	Negative	Negative	Negative	-	-	-	Normal
17	56	M	Positive	Positive	Negative	-	-	-	Normal
18	45	M	Negative	Negative	Negative	0.5	2.8	14.3	Normal
19	69	M	Negative	Negative	Negative	1	6.1	13	Normal
20	82	M	Negative	Negative	Negative	2	6.9	12.8	Normal
21	31	F	Negative	Negative	Negative	2.2	3.9		Normal
22	59	F	Negative	Negative	Negative	1.8	3.6	12.8	Normal
23	22	M	Negative	Negative	Negative	-	6.7	12.9	Abnormal
24	55	F	Negative	Negative	Negative	0.6	3	12.8	Normal
25	21	M	Positive	Negative	Negative	-	2	13.1	Normal
26	53	F	Positive	Positive	Negative	6.6	23.7	13	Normal
27	56	M	Negative	Negative	Negative	1	4.1	12.9	Normal
28	68	F	Negative	Negative	Negative	5.5	18.2	13.7	Abnormal
29	66	F	Negative	Negative	Negative	3.6	0.7	12.5	Normal
30	66	F	Negative	Negative	Negative	3.7	0.3	13.4	Normal
31	78	M	Negative	Negative	Negative	3.7	0.9	12.7	Normal
32	78	M	Negative	Negative	Negative	4.4	1.8	13.3	Normal

## 2.2. Sample and Laboratory Test

Venous blood from all patients was collected for blood cell analysis, C-reactive protein and interleukin-6 test. Unilateral/bilateral tympanic effusions were sent

for bacterial and fungal culture as well SARS-CoV-2 RNA test. Samples from rhinopharynx collected via transnasal endoscope were also sent for SARS-CoV-2 RNA test.

### 2.3. Data Statistics

The laboratory results were collected at the time of the first visit. Categorical variables were described as frequency or percentages, and continuous variables as mean and standard deviation (SD) if they were normally distributed or median and interquartile range (IQR) if not. Categorical variables were compared, using the  $\chi^2$  test. Means for continuous variables were compared, using an independent group test between two groups when the data were normally distributed; otherwise, the Mann-Whitney U test was used.  $P < 0.05$  was considered significant. Data and basic information for patients were analyzed by SPSS Statistics 26 (IBM, Armonk, NY, USA).

## 3. Results

### 3.1. Clinical Characteristics of Otitis Media Caused by SARS-CoV-2 Infection

There were 32 subjects (19 males, 13 females) enrolled in this study. The age range was 21 to 82 years old. All the subjects had the common symptoms of stuffy ear, hearing loss, and echoacousia. Pre-existing underlying diseases mainly include hypertension and diabetes. No positive results were found in cultures for bacterial and fungus of middle ear discharge. SARS-CoV-2 RNA tests in middle ear discharge were detected positively in 9 cases (28.125%). Only two cases were found positive SARS-CoV-2 RNA in nasopharyngeal discharges (**Table 1**).

### 3.2. Laboratory Test of Otitis Media Caused by SARS-CoV-2 Infection

Comparing laboratory tests of otitis media patients with positive or negative SARS-CoV-2 RNA in middle ear discharge, it was found that the levels of C-reactive protein (CRP) were significantly up-regulated in positive cases ( $P = 0.0335$ ) (**Table 2**). The levels of proinflammatory cytokine interleukin-6 (IL-6) were higher in positive cases ( $P = 0.0712$ ). There were no significant differences of age, gender and prothrombin time (PT) between positive and negative cases (**Table 2**).

### 3.3. Treatments and Clinical Outcomes of Otitis Media Caused by SARS-CoV-2 Infection

Nasal sprays, ciliary stimulants, and prophylactic antibiotics or low-dose steroid treatments were sequentially used in the otitis media patients caused by SARS-CoV-2 infection (**Table 3**). All the patients had improvements of typical symptoms within two to four weeks during the following-up. Five of them had no obvious symptoms, 3 cases were lost, and 1 had slight symptoms in three months follow-up (**Table 3**).

**Table 2.** Laboratory results in patients with positive or negative SARS-CoV-2 RNA in ear discharge.

	SARS-CoV-2 RNA result in ear discharge in otitis media patients		P value
	Positive	Negative	
Case (N, N%)	9, 28.125%	23, 71.875%	
Age	54 ± 16	57 ± 18	0.6755
Gender (M%, M/F)	66.7%, 6/3	56.5%, 13/10	0.7036
Positive results of cultures for bacterial and fungus	0	0	
CRP (mg/L)	5.35 ± 1.77	2.39 ± 1.65	0.0335
IL-6 (pg/mL)	11.13 ± 11.25	4.07 ± 4.49	0.0712
PT (s)	13.43 ± 0.67	13.10 ± 0.50	0.3325
Abnormal results of routine analysis of blood	0/9	2/23	

**Table 3.** Clinical characteristics and outcomes of patients with positive SARS-CoV-2 RNA in ear discharge.

No.	Gender	Age	Chief complaint	Treatments	Follow-up and outcomes
1	M	56	Bilateral hearing loss for half a month	Budesonide nasal spray, Eucalyptol mucolytic agent, and 250 mg Clarithromycin orally twice a day for bacterial infection prevention	After half a month of treatment, there was still effusion in the middle ear, so the medication was stopped and a tympanostomy tube was placed. No middle ear effusion was found in the half month postoperative checkup and no obvious symptoms were found in a telephone follow-up after three months.
2	M	58	Hearing loss in the left ear for 1 week	A tympanocentesis was performed. No medication was used.	The patient was followed up by phone and reported no obvious symptoms after three months.
3	M	68	Hearing loss in the left ear for 10 days	Barnidipine 8 mg, Spironolactone 20 mg, and Rosuvastatin 10 mg orally once a day, budesonide nasal spray and clarithromycin 250 mg orally twice daily to prevent infection.	The patient stated that he had no obvious symptoms after three months.
4	F	65	Hearing loss in the right ear with tinnitus for 1 month	Budesonide nasal spray, Eucalyptol mucolytic diluent, and clarithromycin 250 mg orally twice a day for infection prevention.	The patient stated significant improvement after 20 days. The patient was followed up after three months and reported no obvious symptoms.
5	F	37	Ear stuffy in the right ear for 2 weeks	Budesonide nasal spray and a moxifloxacin antibiotic.	Lost to follow-up.
6	M	71	Hearing loss in the right ear for several months	Nasonex nasal spray and cefuroxime tablets 250 mg orally twice a day to prevent bacterial infection.	One month later, the middle ear effusion disappeared. After that, lost to follow-up.

**Continued**

7	M	56	Ear loss in the right ear for several days	Nasonex, Cefuroxime Axetil Tablets (250 mg per dose, twice daily) and Dexamethasone Tablets (0.75 mg per dose, once daily in the morning). Three weeks later, the patient was re-examined and fluid was still accumulating in the right tympanic membrane. The treatment was changed to Dexamethasone Tablets (0.75 mg per dose, once daily in the morning) and Levofloxacin Tablets (0.5 g per dose, once daily).	The symptoms were improved after three months. The patient is still under following-up.
8	M	32	Ear stuffy in the right ear for 1 week	Loratadine tablets (8.8 mg, orally once daily), Eucalyptol diluent (0.3 g, orally three times daily), and Cromolyn sodium nasal spray (10 ml, 2 sprays in each nostril, twice daily).	Lost to follow-up.
9	F	53	Ear stuffy in the left ear for 1 week	1.5 mg oral dexamethasone tablets, 60 sprays of mometasone nasal spray (2 sprays per nostril) every morning, 20 mg omeprazole enteric-coated capsules once daily and 250 mg cefuroxime axetil tablets twice daily	The patient had no obvious symptoms after three months.

### 3.4. Detailed Medical History of the COVID-19 Related Otitis Media Patients

Case 1, 56-year-old male retired patient presented with “hearing loss for half a month” on 12 Jan 2023. He had a history of COVID-19 and past medical history includes splenectomy 40 years ago, 10 years of epilepsy, chronic hepatitis B, 10 years of decreased platelet count. The patient is currently taking one tablet of Levetiracetam daily. Otoscopic examination revealed bilateral middle ear effusion. With agreement of the patient, a myringocentesis was performed, nucleic acid of SARS-CoV-2 was detected in the middle ear effusion with a Cycle Threshold (CT) value of 26. The patient was given Budesonide nasal spray, Eucalyptol mucolytic agent, and 250 mg Clarithromycin orally twice a day for bacterial infection prevention. After half a month of treatment, there was still effusion in the middle ear, so the medication was stopped and a tympanostomy tube was placed on 31 Jan 2023. No middle ear effusion was found in the half-month postoperative checkup. The patient had no obvious symptoms on 24 Mar. 2023 in a telephone follow-up.

Case 2, male, 58 years old, retired, came to the hospital on January 12, 2023, with a complaint of “left ear stuffiness for a week.” One week before the onset, his family had a SARS-CoV-2 infection, and he had no symptoms and was not tested for SARS-CoV-2 RNA. He had a history of left small intestinal lipoma and left adrenal nodule for more than two years. He also had a history of poorly controlled gout for three years. Previous physical examinations suggested left atrial enlargement on an electrocardiogram. On examination, there was middle ear effusion in the left ear, and test for SARS-CoV-2 RNA in the middle ear effusion was positive with a CT value of 35 after a tympanocentesis was performed. No medication was used. On March 24, 2023, the patient was followed up by phone

and reported no obvious symptoms.

Case 3, male, 68 years old, retired, on January 12, 2023, with a complaint of “left ear hearing loss, cough for more than 10 days”. He has a history of SARS-CoV-2 infection. He has appendectomy 20 years ago, peritonitis surgery 20 years ago, intestinal adhesion surgery 20 years ago, second intestinal adhesion surgery 8 years ago, hypertension for more than 20 years, hyperlipidemia for more than 10 years, lumbar disc herniation surgery 8 years ago, left limb injury 6 years ago, and history of secretory otitis media 5 years ago. He has Barnidipine 8 mg, Spironolactone 20 mg, and Rosuvastatin 10 mg orally once a day. Physical examination showed that there was fluid accumulation in the left eardrum. The hearing test showed mixed hearing loss (moderate) in the left ear and sensory neural hearing loss (mild) in the right ear. The left ear was of the B type in the tympanogram, and the right ear was of the Ad type. After the tympanocentesis, test for SARS-CoV-2 RNA in the middle ear fluid was positive with a CT value of 35. He was given budesonide nasal spray and clarithromycin 250 mg orally twice daily to prevent infection. On March 24, 2023, during a telephone follow-up, the patient stated that he had no obvious symptoms.

Case 4, female, 65 years old, retired. On January 12th, 2023, she reported “decreased hearing in the right ear with tinnitus for one month” and came for medical treatment. She has a history of SARS-CoV-2 infection. Her medical history is unknown. Physical examination showed bilateral middle ear effusion. Tympanocentesis was performed and test for SARS-CoV-2 RNA was positive in the middle ear effusion. She was prescribed budesonide nasal spray, Eucalyptol mucolytic diluent, and clarithromycin 250 mg orally twice a day for infection prevention. The patient stated significant improvement after 20 days. On February 2nd, 2023, the hearing test showed mixed hearing loss in the left ear (moderate to severe) and mixed hearing loss in the right ear (severe). The tympanogram type was B in both ears. On March 24th, 2023, the patient was followed up by phone and reported no obvious symptoms.

Case 5, a 37-year-old female nurse presented on January 12, 2023, with a complaint of “Ear stuffy in the right ear for 2 weeks”. She had undergone B-type impedance testing in an external hospital before the onset of symptoms on day 4 (the image was not provided). The patient had a history of recurrent low-grade fever caused by SARS-CoV-2 infection from 3 weeks ago. Physical examination revealed bilateral middle ear effusions. Chest Computerized Tomography scan demonstrated mild inflammatory fibrotic foci in the lower left lobe, accompanied by benign nodules and a small amount of pulmonary emphysema. Local pleural thickening was also present. Hematology examination showed that the patient had a C-reactive protein (CRP) level of 0.2 (<6.0 mg/L), a white blood cell count of 5.7 ( $3.5 - 9.5 \times 10^9/L$ ), and a platelet count of 116 ( $125 - 350 \times 10^9/L$ ). The patient underwent a middle ear puncture and test for SARS-CoV-2 RNA in the middle ear effusion was positive with a CT value of 34. The patient was treated with budesonide nasal spray and a moxifloxacin antibiotic. A telephone follow-up on March 24, 2023, was attempted but unsuccessful.

Case 6, a 71-year-old retired male patient presented on January 16th, 2023, with a complaint of “Hearing loss in the right ear for several months”, no dizziness, and no ear discharge. During a physical examination 9 months ago, he was found to have coronary artery atherosclerotic heart disease, chronic non-atrophic gastritis with erosion, old duodenal ulcer, varicose veins in both lower limbs, prostate hyperplasia with calcification, right pulmonary nodule, multiple liver cysts, renal cysts, and bilateral epidural fluid. He had a history of hernia surgery in 1996, gout for 6 years, alcoholic cirrhosis ascites for 3 years, hernia surgery again 4 years ago, and type 2 diabetes for 1 year. He was taking pantoprazole enteric-coated tablets 40 mg orally twice a day, sustained-release potassium chloride tablets 1 g orally twice a day, torasemide capsules 50 mg orally three times a day, ribavirin tablets 100 mg orally three times a day, atorvastatin tablets 20 mg orally once a day, clopidogrel tablets 75 mg orally once a day. Nasopharyngoscopy showed congestion and a small amount of secretion adhesion of the bilateral nasal cavity and nasopharyngeal mucosa. Otoscope examination showed bilateral effusion in the tympanic membrane. Hematologic examination: interleukin-6 (IL-6) was 7.7 (0.0 - 6.6 pg/mL) and highly sensitive CRP was 4.1 (<6.0 mg/L). Prothrombin time (PT) and coagulation function was normal. The patient underwent myringotomy, and test for SARS-CoV-2 RNA in the middle ear fluid was positive. He was given Nasonex nasal spray and cefuroxime tablets 250 mg orally twice a day to prevent bacterial infection. On January 25th, 2023, the middle ear effusion disappeared. On March 24th, 2023, the patient was lost to follow-up during a telephone follow-up.

Case 7, a 56-year-old male presented with decreased hearing in his right ear for a few days on January 6th, 2023. He was infected with SARS-CoV-2 for 3 - 4 days prior to the onset of symptoms. He had a history of hypertrophic cardiomyopathy, which had recurred in the past 2 years after undergoing atrial fibrillation (AF) ablation, and kidney disease for over 10 years. Seven years ago, he had a history of puncture due to secretory otitis media and had experienced hyperglycemia for the past 2 years. In physical examination, fluid was found to be accumulating in the right tympanic membrane and a tympanic puncture was performed. He was given nasal spray of Nasonex, Cefuroxime Axetil Tablets (250 mg per dose, twice daily) and Dexamethasone Tablets (0.75 mg per dose, once daily in the morning) to prevent infection. On January 13th, he was re-examined and middle ear effusion was still present. Tympanic puncture was performed again, and test for SARS-CoV-2 RNA in middle ear effusion was positive with a CT value of 34, as well as a positive SARS-CoV-2 RNA test in the nasopharynx. He continued to receive treatment with Nasonex, Cefuroxime Axetil Tablets (250 mg per dose, twice daily) and Dexamethasone Tablets (0.75 mg per dose, once daily in the morning) to continue to prevent infection. On January 20th, he was re-examined and fluid was still accumulating in the tympanic membrane. The effusion culture taken one week ago did not detect any fungus, and there was no bacterial growth. The results of the hematological examination showed: CRP 1.1 (<6.0 mg/L), white blood cell count 5.0 (3.5 - 9.5 ×



$10^9/L$ ), and low platelet count of 119 ( $125 - 350 \times 10^9/L$ ). Tympanic puncture was continued, and the nucleic acid test for the SARS-CoV-2 in the ear effusion was negative, as well as in the nasopharynx. On February 10th, the patient was re-examined and fluid was still accumulating in the right tympanic membrane. The treatment was changed to Dexamethasone Tablets (0.75 mg per dose, once daily in the morning) and Levofloxacin Tablets (0.5 g per dose, once daily). The patient's symptoms improved on February 17th with the disappearance of fluid accumulation in the tympanic membrane. He continued to receive the same treatment. On March 13th, follow-up revealed no obvious ear effusion, and the tympanic graph showed type A on the left ear and type C on the right ear. The patient had mixed hearing loss in the right ear (moderate to severe) and sensory neural hearing loss in the left ear (mild to moderate). Then, the treatment was switched to Ambroxol Hydrochloride Dispersible Tablets (30 mg per dose, three times daily) and Mometasone Nasal Spray (60 doses, twice daily) on an outpatient basis. The patient is still under following-up.

Case 8, a 32-year-old male office worker presented on January 19, 2023 with a one-week history of discomfort in his right ear. No obvious liquid discharge was observed. He had a history of middle ear infection in 2018 and had experienced tremors for 5 years without medication. Physical examination revealed fluid accumulation in the right eardrum. Hematological examination showed a PT of 13.1 (11.5 - 14.5 s), IL-6 of 2.0 (0.0 - 6.6 pg/mL), a white blood cell count of 7.8 ( $3.5 - 9.5 \times 10^9/L$ ), and a platelet count of 272 ( $125 - 350 \times 10^9/L$ ). SARS-CoV-2 RNA testing of the middle ear effusion was positive with a CT value of 36; however, test of SARS-CoV-2 RNA in the nasopharynx was negative. One week later, no bacterial or fungal growth was detected by culture of the effusion. The patient was given loratadine tablets (8.8 mg, orally once daily), Eucalyptol diluent (0.3 g, orally three times daily), and Cromolyn sodium nasal spray (10 ml, 2 sprays in each nostril, twice daily). Follow-up by telephone on March 24, 2023 was unsuccessful due to loss of contact.

Case 9, female, 53 years old, visited the hospital on January 19th, 2023, complaining of "ear stuffy in the left ear for 1 week". The ear symptoms started two days after the onset of fever due to the SARS-CoV-2 infection. She had a history of urticaria. Physical examination revealed bilateral effusion in the tympanic membrane. Laboratory examination showed IL-6 at 23.7 pg/mL (normal range: 0.0 - 6.6), hypersensitive CRP at 6.6 mg/L (normal range: <6.0), PT at 13.0 seconds (normal range: 11.5 - 14.5), white blood cell count at  $8.3 \times 10^9/L$  (normal range:  $3.5 - 9.5 \times 10^9/L$ ), and platelet count at  $274 \times 10^9/L$  (normal range:  $125 - 350 \times 10^9/L$ ). The test for SARS-CoV-2 RNA of the middle ear effusion was positive with a CT value of 34, and test SARS-CoV-2 RNA via nasopharyngeal swab was positive. The patient was treated with 1.5 mg oral dexamethasone tablets, 60 sprays of mometasone nasal spray (2 sprays per nostril) every morning, 20 mg omeprazole enteric-coated capsules once daily and 250 mg cefuroxime axetil tablets twice daily. Two weeks later, the effusion persisted on re-examination. Bacterial culture from the puncture fluid was negative for growth, and no fungus

was detected. Test for SARS-CoV-2 RNA was not performed after the tympanocentesis, and the patient continued to use nasal spray and oral steroids. Follow-up by phone on March 24th, 2023 revealed that the patient had no obvious symptoms.

#### 4. Discussion

In this series of reports, we identified nine patients who tested positive for SARS-CoV-2 RNA in their middle ear effusion. Four patients had simultaneous nasal and middle ear positive tests of SARS-CoV-2, and two of them tested positive for both locations, indicating that not all patients were tested with positive results both in nasal and middle ear at the same time. Case 7 was particularly interesting, as the patient initially had positive SARS-CoV-2 tests both in middle ear and nasal, and turned negative two weeks later when the patient returned for follow-up after a planned trip. Generally, the middle ear is connected to the nasal cavity through the eustachian tube, with the latter being a high-risk factor for purulent otitis media caused by pathogenic bacterial secretion [3, 4]. Comparing the positive test results of these patients, we speculate that the virus can be detected in the middle ear in a certain period. In the early stage of the disease, the virus attacks the upper respiratory tract [25], causing a series of symptoms such as fever and cough [26]. At the same time, the virus is transmitted to the middle ear via the Eustachian tube, inducing secretory otitis media. As the disease progresses, viral activity in the upper respiratory tract or throughout the body decreases, or the virus is gradually cleared, but due to the limitations of its own structure or local immunity, the middle ear takes longer time than the entire body to clear the virus, resulting in continued inflammatory reactions. At the same time, the SARS-CoV-2 has different retention times throughout the body [27], and the middle ear becomes a hidden location.

The limitations of the present study were as follows. First, when we optimized the policy on COVID-19 prevention and control in mainland China, especially when a large number of adults with otitis media rushed into the hospital, we did not completely synchronize the collection of data on SARS-CoV-2 in the middle ear and nasopharynx, which may have missed the positive incidence of nasopharyngeal and middle ear effusion at different stages. Second, we did not perform SARS-CoV-2 RNA detection for each effusion and dynamically understood the duration of virus presence in the middle ear. Third, although we knew that some patients were at high risk of SARS-CoV-2 infection, we did not give a full-body examination to some early patients and did not correlate the condition of the patients' middle ears with their systemic conditions. Fourth, our hospital only accepted adult patients and did not accept children under 14 years old. We do not know whether there is a SARS-CoV-2 in the middle ear effusion in children under 14 years old with secretory otitis media.

Reviewing past literature, we learned that the SARS-CoV-2 primarily attacks the respiratory epithelium [27]. As a part of the respiratory epithelium, the mid-

middle ear has been experimentally proven to have ACE2, TMPRSS2, and Furin receptors that can be targeted by the virus [28]. Therefore, some authors speculate that attacking the mucous membrane of the ear by the SARS-CoV-2 is possible [29]. Previous autopsy specimens have also shown the presence of the virus in the middle ear [22] [30]. There has been reported that one case where the result of middle ear effusion tested positive for the virus [16], and another case where a patient with an open middle ear, infected with SARS-CoV-2 in the lungs, tested positive for virus RNA four weeks later [20]. Other cases show that patients have positive virus RNA in their nasal or lung passages, with concurrent middle ear infections, but the presence of the virus in the middle ear is not explicitly stated [16] [17] [18] [19]. From a logical standpoint, whether there is a virus infection in the middle ear is not directly proven by previous data, and our case report fills in the missing link. Furthermore, we have cultured bacteria and fungi from the middle ear effusion, and the results were negative. We are willing to refer to these secretion-type middle ear infections with positive SARS-CoV-2 RNA as COVID-19 related middle ear infections.

Treatment for COVID-19-related otitis media is not well-established. We refer to the treatment recommendations for viral otitis media in the past, such as nasal sprays, ciliary stimulants, and prophylactic antibiotics for some patients with prolonged effusion or low-dose steroid treatment. Some doctors may use tympanostomy tubes. In general, most patients gradually improve after two to four weeks. There are reports of antiviral treatment for complications of otitis media caused by past lung viral infections [18]. However, it is recommended to exercise caution in considering antiviral treatment for patients with coronavirus-related otitis media [11], as most of our patients have underlying diseases.

The positive detection of the SARS-CoV-2 in middle ear effusion highlights the possibility of the virus persisting throughout the body even after respiratory symptoms have disappeared during the COVID-19 pandemic. The presence of dizziness and tinnitus in COVID-19 patients [31] [32] may also be related to viral attacks on the middle and inner ear or the induction of related immune responses. This should also be considered. Additionally, we support the proposal made by other researchers that healthcare workers in otolaryngology-head and neck surgery departments should take precautions for self-protection and protection of others during surgical treatment of patients during the COVID-19 pandemic [33]. If the patient's immune status is different, attention should also be paid to the possibility of the virus still present even after the COVID-19 symptoms have disappeared [22].

What is particularly confusing is that for most patients, their medical history shows symptoms only appear 2 - 4 weeks after infection with SARS-CoV-2, which is later than the onset of other respiratory diseases. The reason behind this is not clear. Moreover, considering that healthy middle ears can also have different virus settlements, and viruses in the active and dormant phases have different activities [2], it remains to be seen if the SARS-CoV-2 also exhibits such changes.

As there is a possibility of repeated infections and immunity after re-infection with the SARS-CoV-2 in mainland China, we will also be monitoring patients with otitis media to understand the progression of their illness. We hope to find out if there are any long-term changes in patients who develop otitis media due to SARS-CoV-2 infection.

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### Author Contributions

JS and GZ designed the project. GZ and FZ wrote the manuscript. All authors have read and appreciated the final version of this manuscript.

### Informed Consent

Informed verbal consent was obtained from each study participant.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this manuscript.

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