REVIEW ARTICLE

Prevalence and prognosis of otorhinolaryngological symptoms in patients with COVID-19: a systematic review and meta-analysis

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Abstract

Objective A systematic review and meta-analysis were performed to evaluate the prevalence and prognosis of otorhinolaryngological symptoms in patients with the diagnosed coronavirus disease 2019 (COVID-19).

Methods A systematic search of PubMed, Embase, Web of Science, and Google Scholar databases was performed up to August 19, 2020. We included studies that reported infections with COVID-19 and symptoms of otolaryngology. The retrieved data from the respective studies were evaluated and summarized. The study's immediate result was to assess the combined prevalence of otorhinolaryngological symptoms in patients with COVID-19. However, the secondary result was to determine the exacerbation of COVID-19 infection in patients with otorhinolaryngological symptoms.

Results Fifty-four studies with 16,478 patients were included. Olfactory dysfunction, sneezing and sputum production were the 3 most prevalent otorhinolaryngological symptoms in patients with COVID-19. The pooled prevalence amongst the prevalent symptoms was 47% (95% CI 29–65; range 0–98; $I^2 = 99.58\%$), 27% (95% CI 11–48; range 12–40; $I^2 = 93.34\%$), and 22% (95% CI 16–30; range 2–56; $I^2 = 97.60\%$), respectively. The proportion of severely ill patients with sputum production and shortness of breath was significantly higher among patients with COVID-19 infections (OR 1.66 [95% CI 1.08–2.54]; $P = 0.02$, $I^2 = 51\%$ and 3.29 [95% CI 1.57–6.90]; $P = 0.002$, $I^2 = 49\%$, respectively). Subgroup analysis showed no statistically significant differences between the incidence of otolaryngology symptoms in severely ill patients and non-severely ill patients (OR 1.43 [95% CI 1.12–1.82]; $P = 0.07$ $I^2 = 53.1\%$). In contrast, the incidence of shortness of breath in severely ill patients was significantly increased (3.29 [1.57–6.90]; $P = 0.002$, $I^2 = 49\%$).

Conclusion Our research shows that otorhinolaryngology symptoms in patients with COVID-19 are not uncommon, which should attract otorhinolaryngologists' attention.

Keywords COVID-19 · Otorhinolaryngological symptoms · Review · Meta-analysis

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Introduction

COVID-19 is a new infectious disease caused by a new coronavirus strain (SARS-CoV-2), first reported in Wuhan, China, in 2019 [1]. The disease has a high infection rate with widespread infectivity and has become a global health threat [2]. SARS-CoV-2 is primarily transmitted via the respiratory tract, and the symptoms are similar to that of upper respiratory tract infections, such as fever, dry cough, and fatigue [3]. In severely ill patients, pneumonia manifestations such as dyspnea, imaging abnormalities, and acute respiratory distress syndrome (ARDS) may occur [4]. Moreover, there is evidence that olfactory or taste dysfunction is also one of the early symptoms of COVID-19 [5]. Giacomelli et al. has pointed out that olfactory and taste disorders occur in 34%-59% of COVID-19 patients [6]. Significantly, the British

Association of Otorhinolaryngology has proposed olfactory or taste dysfunction as one of the primary screening symptoms of COVID-19 [7]. The discovery has, however, aroused widespread concern among otorhinolaryngologists. Studies have shown that otorhinolaryngological symptoms such as nasal congestion, rhinorrhea, and sore throat were also found in COVID-19 patients [8, 9]. The above reports of otorhinolaryngological symptoms are of great significance to diagnosing and treating individual cases, but systematic reviews to summarize the otorhinolaryngological symptoms of COVID-19 patients are scarce.

When patients with upper respiratory symptoms are admitted, otorhinolaryngology and respiratory diseases departments are crucial in treating them. Hence, it is paramount to summarize the otorhinolaryngological characteristics of COVID-19. Thus, the results of a systematic review and meta-analysis study will provide a reference point and better equip otorhinolaryngologists on the diagnosis and treatment of patients with COVID-19 infections.

According to the recently reported studies, the study aims to (i) systematically review and meta-analyze the otorhinolaryngological characteristics of COVID-19 patients, (ii) evaluate the prevalence of otorhinolaryngological symptoms in COVID-19 patients, and (iii) determine if the existence of these symptoms will affect the aggravation of the disease.

Methods

Search strategy and selection criteria

In the present study, we searched PubMed, Embase, Web of Science, and Google Scholar data bases from the date of establishment to August 19, 2020, using the keywords "COVID-19" and "Signs and Symptoms." We modified the keywords according to the vocabulary of each database and combined them with the Boolean operators. To retrieve more related papers, we also screened the list of references in the included research.

The literature search was limited to articles published in English. The search strategy was designed by XY, a reviewer with experience in the database search, and later modified by other authors. Endnote (version X9.0) was used to exclude duplicates from the retrieved literature and select qualified studies. All eligible studies reported the otorhinolaryngological symptoms of COVID-19 patients. The following studies were excluded: reviews; editorials; preprint; and small case series (≤ 10 cases).

According to these selection criteria, two reviewers (XY, LL) with experience in systematic reviews independently screened titles and abstracts. When differences exist among reviewers, they are resolved by consensus or by a third reviewer (JQ). Two reviewers (XY, LL) independently rated

the included studies' quality using the National Institutes of Health (NIH) quality assessment tool. Differences between the two reviewers were resolved by the third reviewer (JQ).

Data extraction and definitions

Two researchers (XY and LL) who conducted literature retrieval independently extracted data from the included studies. Any differences between the reviewers will be resolved through discussion and consensus or by a third reviewer (JQ). Data extracted from each study included: title; first author; date; study design; country; total sample size; the number of patients with severe and non-severe diseases; otorhinolaryngological symptoms, namely sore throat, nasal congestion, rhinorrhea, and olfactory dysfunction. The present study followed the PRISMA guidelines on systematic review and meta-analysis based [10].

Data synthesis and statistical analysis

We conducted a meta-analysis on the prevalence rate of otorhinolaryngological symptoms and calculated the combined prevalence rate with a 95% confidence interval (CI). The odds ratio (OR) was used to describe the probability ratio of events in severely and non-severely ill COVID-19 patients. Due to the heterogeneity within and between studies, we use the random effect model to estimate the average effect and its accuracy as it will provide a conservative estimate of 95% CI.

We also conducted a subgroup analysis based on the severity of the disease to observe if the severity of COVID-19 impacted the survey results' estimated prevalence rate. I^2 statistic was used to evaluate heterogeneity between studies, and I^2 values > 50% indicate significant heterogeneity. Meta-analysis was carried out using the metaprop command in STATA (version 15.0) to merge single-arm ratios. We used Review-Manager (version 5.3) to carry out all other statistical analyses. Funnel charts were used to evaluate publication bias [11].

Results

Characteristics of included studies

A total of 2201 published articles were retrieved from the electronic database ($n = 2143$) and other sources ($n = 58$). After removing the duplicates, 1252 published articles were left. After a preliminary review of the title and abstract for each published article, 116 articles were considered to meet the full-text review criteria. After the full-text screening, 54 papers [4, 12–64], including 16,478 COVID-19 patients, were included in the present systematic review. Figure 1

Fig. 1 Study selection
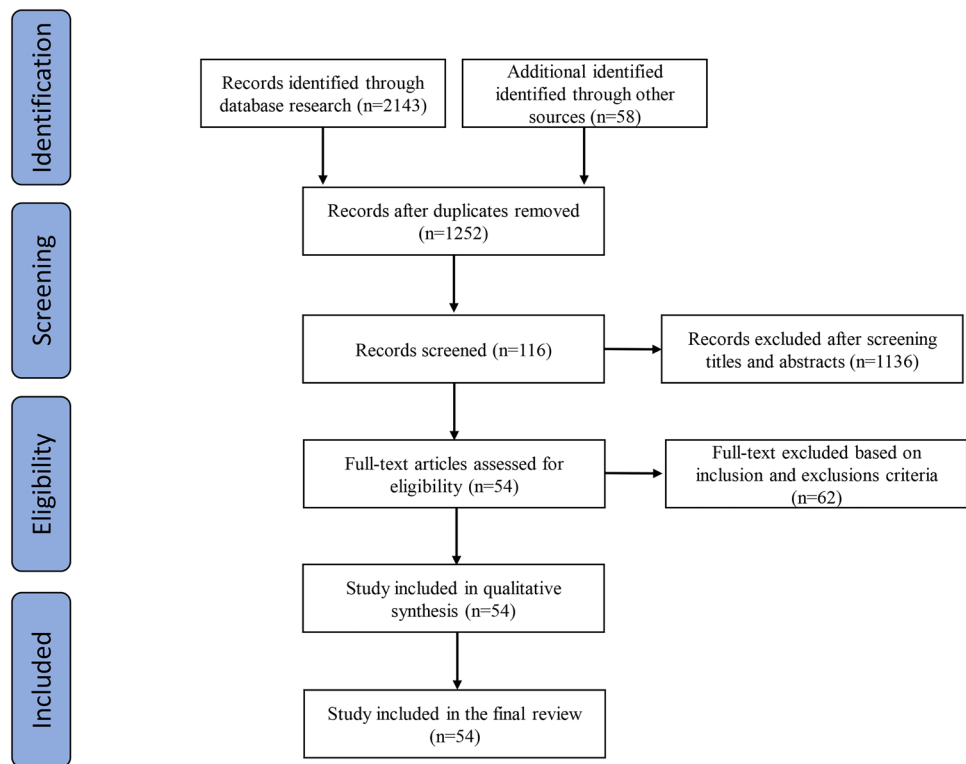
shows the Prisma flow chart of the research included in the system review.

The main characteristics of the studies and patients included in the meta-analysis are shown in Table 1. All the subjects in the included studies for the present meta-analysis were all adult patients. Based on the included studies, 1523 and 3876 were in severe and non-severe conditions, respectively. All the included studies were published in 2020. The countries included in the study were: 26 studies in China, 8 in the United States, 6 in Italy, and 3 in South Korea. Kuwait, Canada, Bolivia, Germany, France, Brazil, Belgium, Iraq, Iran, Poland, and Switzerland each conducted one study.

Among the studies carried out in China, eleven were from Hubei province, three from Zhejiang province, three from Chongqing city, two from Henan province, and one from Jilin province, Shandong province, Jiangsu province, Taiwan province, Hunan province; and Anhui province. The included reports were all graded as to quality studies according to the NIH quality assessment tool.

Prevalence of otorhinolaryngological symptoms

The present meta-analysis showed that the three most prevalent otorhinolaryngological symptoms among patients with confirmed COVID-19 were olfactory dysfunction, sneezing, and nasal congestion. The pooled prevalence of olfactory dysfunction, from 24 studies ($n = 8992$), was 47% (95%

CI 29–65; range 0–98; $I^2 = 99.58\%$). The prevalence of sneezing with COVID-19 infection was reported in three studies. Eighty-nine reported sneezing from a total of 333 patients with a pooled prevalence of 27% (95% CI 11–48; range 12–40; $I^2 = 93.34\%$). Among the 24 studies reporting sputum production, the overall prevalence ranged from 2 to 56%. One thousand two hundred and twenty-four of the 6472 patients with COVID-19 infection reported sputum production with a pooled prevalence of 22% (95% CI 16–30; $I^2 = 97.60\%$). We also analyzed the prevalence of other otorhinolaryngological symptoms, such as nasal congestion, sore throat, shortness of breath, dizziness, and rhinorrhea. Among them, the pooled prevalence of nasal congestion was 19% (95% CI 11–29; range 0–59; $I^2 = 98.60\%$), sore throat 16% (95% CI 12–20; range 1–51; $I^2 = 95.57\%$), rhinorrhea 14% (95% CI 9–20; range 0–57; $I^2 = 97.18\%$), shortness of breath 12% (95% CI 4–22; range 2–20; $I^2 = 93.97\%$), and dizziness 9% (95% CI 4–16; range 2–20; $I^2 = 93.97\%$). Figure 2 shows the forest plots for the prevalence of otorhinolaryngological symptoms.

The proportion of severely ill COVID-19 patients with or without otorhinolaryngological symptoms

We analyzed the differences in the proportion of severely ill patients amongst patients with otorhinolaryngological symptoms and those without otorhinolaryngological symptoms. The results are shown in Fig. 3. The proportion of patients

Table 1 Characteristics of the included studies

references	Design	Center	Country	No. of pts (overall)	No. of pts (severe)	No. of pts (non-severel)	Male N(%)	Median Age Yrs (IQR) or Mean ± SD*
Almazeedi2020	Retrospective	1	Kuwait	1096	42	1054	888	41 (25.0–75.0)
Aggarwal 2020	Retrospective	1	USA	16			12	67 (38–95)
Andrikopoulou 2020	Retrospective	1	New York (USA)	158	34	124	0	
Argenziano2020	Retrospective	1	New York (USA)	1000	236	764	596	63 (50.0–75.0)
Boscolo-Rizzo 2020	Cross-sectional		Italy	214				
Burke 2020	questionnaire	16	USA	164			92	50
Carignan 2020	Case–control	1	Canada	134			64	57.1 (41.2–64.5)
Cecconi 2020	Retrospective	1	Italy	239	70	169	169	65.2 (53.8–74.5)
Chen 2020	descriptive	1	Wuhan (China)	99			67	55.5 ± 13.1
Dell'Era 2020	cross-sectional	1	Italy	355			192	50
Du 2020a	Retrospective	1	Jilin (China)	12			7	45.25 (23–79)
Du 2020b	Retrospective	1	Shandong (China)	53	1	52	26	41.47 (21–65)
Duan 2020	Retrospective	1	Luoyang (China)	25			15	52 ± 19.30
Duanmu 2020	Cross-sectional	1	Northern California	100	13	87	56	45(0.5–91)
Escalera-Antezana 2020	Retrospective	1	Bolivia	12			6	39 (25.3–43.4)
Haehner 2020	Cross-sectional	1	Dresden	34				
Huang 2020a	Prospective	1	Wuhan (China)	41	13	28	30	49·0 (41·0–58·0)
Huang 2020b	Retrospective	8	Jiangsu (China)	202	23	179	116	44.0 (33.0–54.0) 。
Kim 2020a	Retrospective	9	Korean	28	6	22	15	40 (20.0–73.0)
Kim 2020b	questionnaire	1	Korea	172			66	26 (22.0–47.0)
Klopfenstein	Retrospective	1	France	54			18	47 ± 16
Kosugi	online survey		Brazil	145			68	36 (31.0–44.0)
Lechien	online questionnaire		Belgium	86			30	41.7 ± 11.8
Lee	prospective	1	Korea	3191			1161	44.0 (25.0–58.0)
Li2020a	Retrospective	279	Henan (China)	655	72	583	367	
Li2020b	Retrospective	8	Chongqing (China)	83	25	58	44	45.5 ± 12.3
Liu2020a	Retrospective	1	Taiwan (China)	321			150	
Liu2020b	Retrospective	9	Hubei (China)	137			61	57 (20–83)
Merza	prospective	1	Iraqi	15	1	14	9	28.06 ± 16.42
Moein	control	1	Iran	60	6	54	40	46.55 ± 12.17
Sierpiński	cross -sectional	1	Poland	1942			773	50median
Speth	Prospective, cross-sectional	1	Switzerland	103			50	46.8 ± 15.9
Vaira2020a	Retrospective	1	Sassari	72			27	49.2 ± 13.7
Vaira2020b	prospective	2	Sassari	106			53	49.6 (43.0–55.2)

Table 1 (continued)

| references	Design	Center	Country	No. of pts (overall)	No. of pts (severe)	No. of pts (non-severel)	Male N(%)	Median Age Yrs (IQR) or Mean ± SD*
Vaira2020c	cohort	4	Italian	345	27	318	146	48.5 ± 12.8
Wan	Retrospective	1	Chongqing (China)	135	40	95	72	47 (36.0–55.0)
Wang2020a	Retrospective	2	Wuhan (China)	107	19	88	57	51 (36.0–65.0)
Wang2020a	Retrospective	1	Wuhan (China)	1012	100	912	524	50 (39e58)
Wang2020a	Retrospective	1	Wuhan (China)	69	14	55	32	42.0 (35.0–62.0)
Wei	Retrospective	1	Zengdu (China)	276	14	262	155	51.0 (41.0–58.0)
Wu2020a	Retrospective	1	Yancheng (China)	80	3	77	39	46.10 ± 15.42
Wu2020a	Retrospective	1	Chongqing (China)	80			42	44 ± 11
Xu	Retrospective	7	Zhejiang (China)	62	1	61	36	41 (32–52)
Yan2020a	cross-sectional	1	USA	59			29	
Yan2020b	Retrospective	1	USA	128			61	
Yan2020c	Retrospective	1	Wuhan (China)	337			154	44 (34–55)
Yang2020a	Retrospective	1	Washington	124			58	75.7 ± 13.2
Yang2020b	Retrospective	3	Wenzhou (China)	149			81	45.11 ± 13.35
Yin	Retrospective	1	Hunan (China)	33			16	46(31.5−65)
Yu	Retrospective	1	Wuhan (China)	1663	864	799	838	64.0(52.0−71.0)
Zhang	Retrospective	1	Zhejaing (China)	645			328	
Zhao2020a	Retrospective	2	Anhui (China)	19			8	35 (27.0–46.0)
Zhao2020b	Retrospective	1	Huibei (China)	91	30	61	49	
Zheng	Retrospective	1	Wuhan (China)	73	0	73	40	
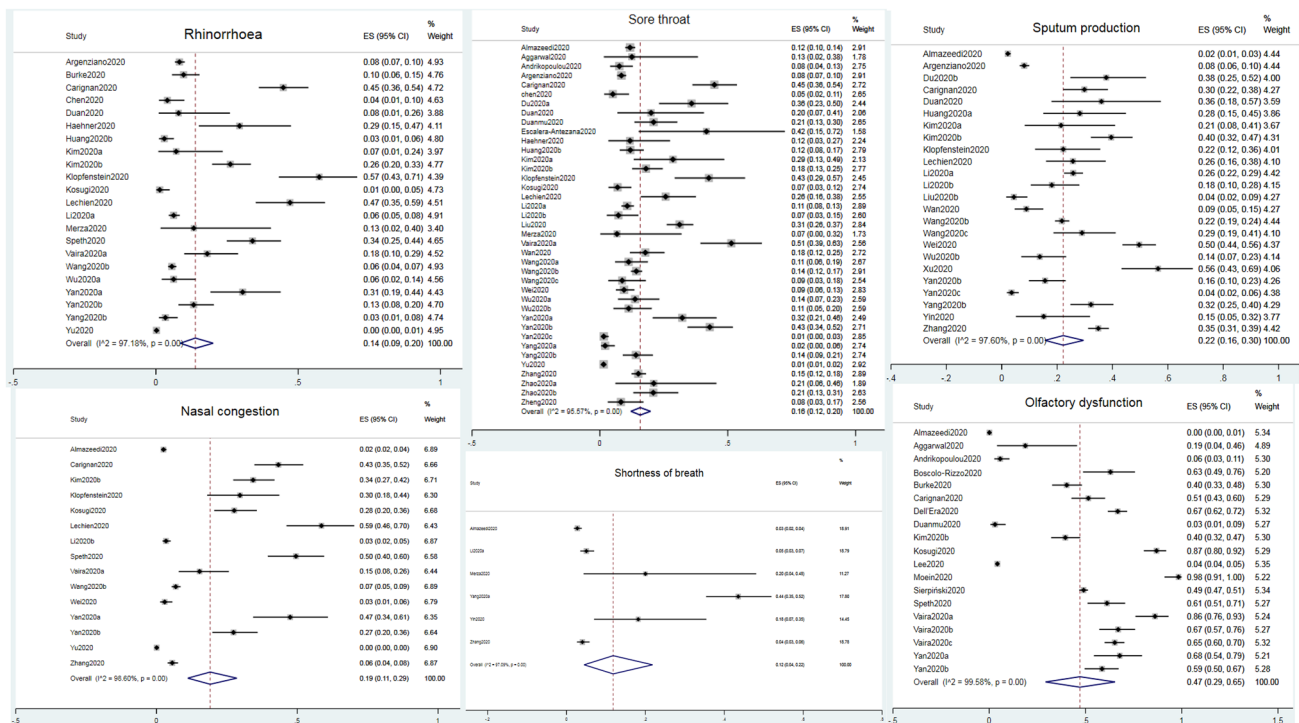
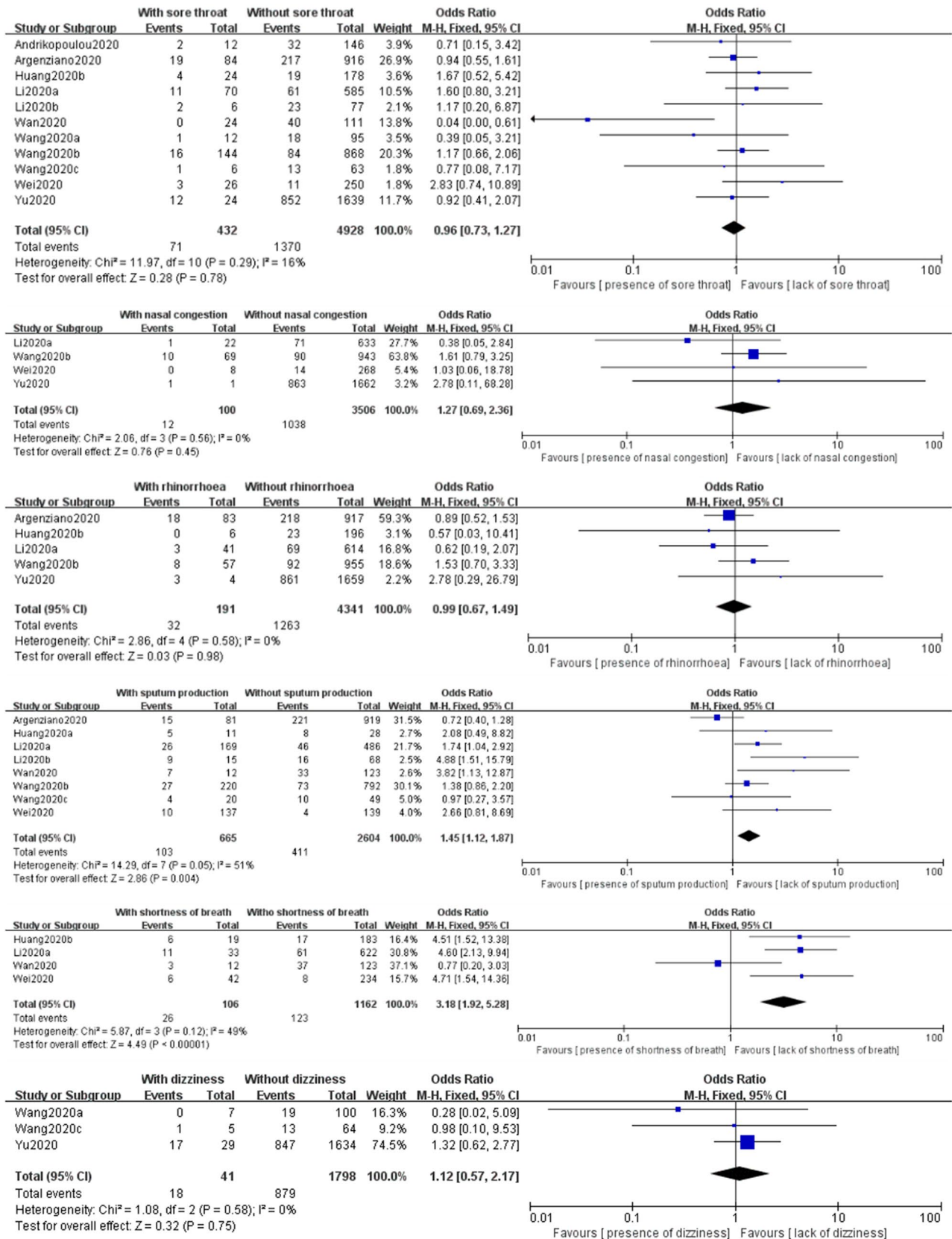**Fig. 2** Forest plots for the prevalence of the otorhinolaryngological symptoms of COVID-19

Fig. 3 Effect of otorhinolaryngological symptoms on the severity of COVID-19

with severe COVID-19 was increased in patients with sputum production compared with those without sputum production (OR 1.66 [95% CI 1.08–2.54]; $P = 0.02$, $I^2 = 51\%$).

Similarly, the proportion of severely ill COVID-19 patients with shortness of breath was higher than in patients without shortness of breath (OR 3.29 [95% CI 1.57–6.90]; $P = 0.002$, $I^2 = 49\%$). However, the pooled rate of severity was similar between patients with and without rhinorrhoea (OR 1.02[95% CI 0.68–1.53]; $P = 0.93$, $I^2 = 0\%$). Concerning the analytical results of rhinorrhea, we found out that there was no significant difference in the proportion of severely ill COVID-19 patients with or without nasal congestion (OR 1.39[95% CI 0.74–2.63]; $P = 0.31$, $I^2 = 0\%$), sore throat (OR 1.10[95% CI 0.79–1.54]; $P = 0.56$, $I^2 = 16\%$), or dizziness (OR 1.17[95% CI 0.59–2.34]; $P = 0.65$, $I^2 = 0\%$).

The differences in otorhinolaryngological symptoms between severe and non-severely ill patients

We analyzed the differences in otorhinolaryngological symptoms between severe and non-severely COVID-19 patients (Fig. 4). Patients with severe disease were similar to have otorhinolaryngological symptoms compared with those with non-severe disease (OR 1.43 [95% CI 1.12–1.82]; $P = 0.07$ $I^2 = 53.1\%$). Correspondingly, we found no significant difference between severely and non-severely ill patients with sputum production (1.52 [0.99–2.33]; $P = 0.05$; $I^2 = 49\%$), sore throat (1.15[0.84–1.58]; $P = 0.39$; $I^2 = 13\%$), rhinorrhea (1.02 [0.68–1.53]; $P = 0.93$; $I^2 = 0$), or nasal congestion (1.28 [0.62–2.67]; $P = 0.51$, $I^2 = 5\%$). However, severely ill patients were more likely to have shortness of breath than non-severely ill patients with the disease (3.29 [1.57–6.90]; $P = 0.002$, $I^2 = 49\%$).

Discussion

Several studies have reported on the otorhinolaryngological symptoms of COVID-19 patients. The present study is the first systematic review and meta-analysis of otorhinolaryngological symptoms in COVID-19 patients. Significantly, otorhinolaryngological symptoms are not uncommon in patients with COVID-19, for which the incidence of olfactory dysfunction, sneezing, sputum production, nasal congestion and sore throat exceeds 15%. With the increase in the severity of the disease, shortness of breath becomes more apparent. Patients with sputum production or shortness of breath have an increased risk of developing associated complications, severely impacting patients' prognosis.

The study results show that the incidence of otorhinolaryngological symptoms in COVID-19 is 47% for olfactory dysfunction, 27% for sneezing, 22% for sputum production, 19% for nasal congestion, 16% for sore throat, 14%

for rhinorrhea, 12% for shortness of breath, and 9% for dizziness. Although the occurrence of otorhinolaryngological symptoms is less threatening to patients' lives, its incidence has nonetheless exceeded that of digestive system symptoms such as diarrhea and nausea [65].

Olfactory dysfunction is the otorhinolaryngological symptom with the highest incidence in the study, and it is also a recognized WHO sign for COVID-19 infection [39]. Initially, a few scholars have conducted a separate systematic evaluation of the incidence of olfactory dysfunction in COVID-19 patients. In a study by Agyeman et al., the incidence of olfactory dysfunction was 41% [66], while in another study by Gramel Tong et al. was 52.73% [67]. The present study results show that olfactory dysfunction is 47%, which is similar to the results of the previous two studies.

The cause of olfactory dysfunction caused by SARS-CoV-2 is not completely clear. A previous study has proposed that SARS-CoV-2 can enter epithelial cells by directly binding to angiotensin-converting enzyme 2 (ACE2) on the cell surface. Simultaneously, ACE2 is highly expressed in the nasal mucosal epithelium, especially in ciliated epithelium and goblet cells, which may be one reason for SARS-CoV-2's olfactory dysfunction [68]. Also, the theory that the upper respiratory tract virus destroys olfactory nerve epithelium and leads to chronic olfactory dysfunction has been reported in previous literature [69].

An expert who carried out animal experiments has confirmed that coronavirus is highly neurotropic and can directly affect olfactory neurons, which might be another fundamental cause of olfactory dysfunctions induced by the novel coronavirus [70]. When the potential target of SARS-CoV-2 is located in non-neuro-olfactory epithelial cells, the patient's olfactory function often recovers within 2 to 4 weeks [71]. Significantly, once the virus infects olfactory stem cells, such as horizontal basal cells, it can cause long-term olfactory dysfunctions [72]. Notably, Kaye et al. pointed out that olfactory dysfunction as the first symptom appeared in 26.6% of COVID-19 patients [73].

Hence, it is of the utmost importance for otorhinolaryngologists to be well equipped in the vast symptoms of COVID-19 to avoid missed diagnosis. Simultaneously, timely treatment should be given after the diagnosis of COVID-19 to prevent long-term olfactory dysfunction. Nasopharyngeal swabs and oropharyngeal swabs are the primary sites for collecting upper respiratory tract samples because the nasopharynx or oropharynx is the central location of COVID-19 infection and the primary source of transmission of the infection [2]. SARS-CoV-2 damage to the nasopharynx is the leading cause of nasopharyngeal symptoms. In the present study, the incidence of sneezing and sputum production was > 15%, and the emergence of both symptoms was also the primary way of COVID-19's transmission. Thus, otolaryngologists should take necessary
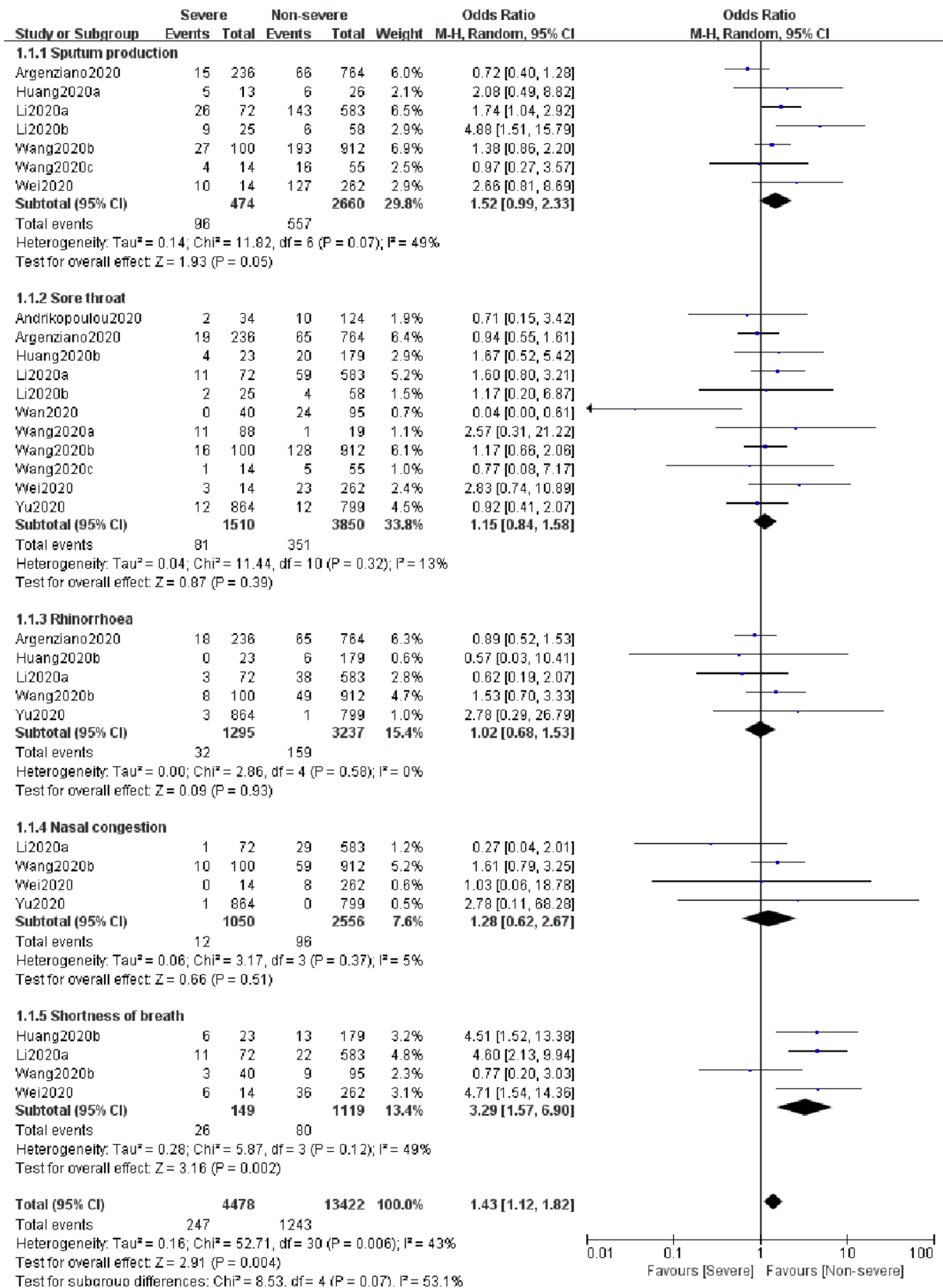
Fig.4 Otorhinolaryngological symptoms according to COVID-19 severity (severe vs non-severe)

protective measures while improving the current diagnostic criteria.

We further investigated the effects of different otorhinolaryngological symptoms on the various causes of COVID-19. We found that severe illness incidence in patients with sputum production or shortness of breath was significantly higher than patients without sputum production or shortness of breath. The occurrence of symptoms such as nasal congestion, rhinorrhea, sore throat, or vertigo had no significant effect on the incidence of COVID-19. Li et al. pointed out that sputum production is one of the signs of severe COVID-19 infection, while shortness of breath was a common symptom of critically ill COVID-19 patients [34]. Therefore, we believe that the occurrence of sputum production or shortness of breath has a particular value in predicting the severity of the disease. The emergence of these symptoms should attract otorhinolaryngologists' intense attention, and timely control should be carried out at the early onset of symptoms to prevent the disease from progressing to a severe stage with adverse effects on patient's lives.

We analyzed the incidence of various otorhinolaryngological symptoms in severely and non-severely ill patients to understand further the relationship between otorhinolaryngological symptoms and the severity of COVID-19. We found out that the prevalence rate of shortness of breath in severely ill COVID-19 patients was significantly higher than non-severely ill patients. The results were also in line with previously published studies [4, 34]. Therefore, one can consider the shortness of breath as a sign of intensive care for confirmed cases. However, when various symptoms such as sputum production, sore throat, nasal congestion, and rhinorrhea were considered, there was no significant difference in the prevalence of otorhinolaryngological symptoms between severely ill patients and non-severely ill patients.Wei et al. analyzed the data of 276 patients in Hubei Province and found no significant difference in the incidence of sputum production and sore throat between severely ill patients and non-severely ill patients [49]. The study of Wang et al. also provided support for the present study analysis. After following up on the patients' progress in the square cabin hospital, there were no significant differences in nasal congestion and rhinorrhea between the aggravated patients and the non-aggravated patients [47].The above results show that most otorhinolaryngological symptoms are common in severely ill and non-severely ill patients. Otorhinolaryngologists should maintain a high degree of clinical suspicion during the epidemic and implement active protection strategies to prevent the widespread nosocomial infection caused by negligence in diagnosis.

In conclusion, the study results show that the otorhinolaryngological symptoms of COVID-19 patients are not uncommon. Otorhinolaryngologists should improve their understanding of otorhinolaryngology symptoms in COVID-19 patients and pay keen attention to their differentiation. Simultaneously, otorhinolaryngologists should pay special attention to the symptoms of shortness of breath and sputum production in COVID-19 patients to prevent aggravating the disease and causing irreversible damage to patients.

Declarations

Conflict of interest There is no conflict of interest in this study.

Consent to participate Not applicable.

Consent for publication Not applicable.

Ethics approval Not applicable.

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