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Respiratory Symptoms in Patients with Mpox: A Systematic Review and Meta-Analysis

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Abstract

Background Monkeypox (Mpox) is a zoonotic disease caused by the mpox virus, which has posed a serious threat to global public health security, especially since the worldwide outbreak in 2022. Nevertheless, current studies on the respiratory symptoms of Mpox remain limited. This analysis aims to estimate the pooled prevalence and explore sources of heterogeneity.

Methods We searched PubMed, Embase, and other databases for Mpox studies published up to December 2024. The included studies were observational studies that reported at least one respiratory symptom. We employed the metaprop command in Stata software (Version 12.0) to obtain the pooled prevalence and its 95% confidence interval (*CI*).

Results Finally, a total of 25 studies on the respiratory symptoms of Mpox patients were included in the analysis. The primary reported respiratory symptoms included sore throat (18%, 95% *CI* 13%-23%), oral lesions (17%, 95% *CI* 13%-22%), cough (16%, 95% *CI* 9%-24%), and tonsillar signs (7%, 95% *CI* 4%-12%). Subgroup analysis was performed according to the male proportion and geographic region of the study population, in an effort to identify the source of heterogeneity.

Conclusions Sore throat is the most prevalent respiratory symptom in Mpox patients, followed by oral lesions, cough, and tonsillar signs. Further research is needed to explore potential respiratory transmission modes in mpox patients, the possibility of inducing respiratory diseases in clinical settings, and identify typical respiratory indicators that can aid in early diagnosis. This work will contribute to developing more effective and accurate prevention and control strategies.

Keywords respiratory symptoms; Mpox; meta-analysis; systematic review

Introduction

Monkeypox (Mpox) is a viral zoonotic disease caused by the mpox virus. The virus was first detected in monkeys in a Danish laboratory in 1958 and has since been endemic mainly in the Congo Basin and tropical rainforest regions of West Africa. In 2003, the first documented outbreak of mpox outside of Africa occurred in the United States[1]. Since 2022, however, numerous non-endemic countries have reported mpox cases to the World Health Organization (WHO). As the outbreak escalated, global case numbers surged, and the WHO has twice declared the mpox outbreak a "public health emergency of international concern."

Previous studies have shown that the Mpox virus is primarily transmitted through respiratory droplets and direct contact with exposed skin and mucosal surfaces[2]. The typical clinical presentations of mpox include systemic manifestations such as fever, fatigue, muscle pain, headache, lymphadenopathy, and rash. However, recent research indicates a significant shift in its epidemiology, with Mpox outbreaks now exhibiting sustained human-to-human transmission characteristics. This can occur through close intimate contact, oral and respiratory secretions, droplets, skin lesions, or contact with contaminated surfaces[3]. During the 2022 outbreak, novel complications emerged, including respiratory-related symptoms such as epiglottitis and peritonsillar abscess. Also, cough was one of the common complications[4]. This shift has drawn researchers' attention to the potential respiratory complications of mpox infection. Additionally, the rapid spread of the Mpox virus has led to efforts to develop antigen rapid diagnostic tests (Ag-RDT) for upper respiratory samples from infected patients. These tests aim to address the urgent need for fast and cost-effective detection and diagnosis of early-stage cases[5]. Experimental findings have also shown that respiratory specimens can be valuable for diagnosing Mpox, investigating asymptomatic patients, and monitoring virus shedding in non-skin

samples[6]. The present study aims to evaluate the association and impact of the mpox virus on respiratory diseases through a systematic review and meta-analysis, aiming to fill existing research gaps and provide scientific evidence for the prevention and treatment of mpox and its related respiratory complications in various populations.

Methods

The systematic review and meta-analysis were conducted in strict compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Method 1). The study protocol was developed by four reviewers (Yuchen Gao, Mingchun Ma, Minghui Sun and Yanji Qin) and has been formally registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD420251102246).

Search Strategy

This systematic review and meta-analysis incorporated studies published in both English and Chinese. A comprehensive literature search was conducted across multiple databases, including English databases (PubMed, Embase, and the Cochrane Library) and Chinese databases (SinoMed, WanFang Data, and China National Knowledge Infrastructure). The literature search encompassed mpox-related studies published up to December 2024. Given that the descriptions of respiratory symptoms are frequently dispersed throughout the studies, the research team implemented a rigorous search strategy to ensure comprehensiveness and reliability. Through consensus, the core search terms were "mpox" and "symptom". Furthermore, search methods were tailored to accommodate the characteristics of each database (Supplementary Method 2). Data on the clinical symptoms of the respiratory system in patients with mpox were collected through keyword screening and manual search methods.

Eligibility Criteria

Following the initial database search, duplicate records were identified and removed based on title and author information. Subsequently, by reading the titles and abstracts, some study types (e.g., reviews, etc., that are not original) were excluded, and studies that did not meet the inclusion criteria were further excluded. The final included studies comprised observational studies, such as cohort studies, case series, cross-sectional studies, etc., and incorporated both retrospective and prospective study designs. Eligible study should also contain raw data, be available in the original text, have at least 10 cases in the study, and report at least one respiratory symptom. The study selection process is detailed in the PRISMA Flow Diagram.

Study Selection & Data Extraction

Two independent reviewers (Mingchun Ma and Minghui Sun) performed data extraction from the included studies and recorded the following information using an Excel sheet designed by the investigators: (1) first author, publication year, and source database, (2) study design type, (3) baseline characteristics: total case number, age distribution, gender composition (number and proportion of males), the continental distribution of the race of study population, HIV infection status, sexual orientation data, respiratory pathogens co-infection status, (4) respiratory manifestations in mpox patients: sore throat, oral lesions, cough, tonsillar signs, shortness of breath, nasal congestion, dysphagia, oral ulcers, pneumonia, parotiditis, pharyngitis, rhinorrhea, respiratory signs, influenza-like symptoms, oropharyngeal symptoms. To ensure consistency, differences of opinion between two reviewers are independently reviewed and arbitrated by a third reviewer (Yuchen Gao).

Quality Assessment

Standardized assessment tools were employed to evaluate the quality of the included studies.

Specifically, 15 cohort studies were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS); 8 case series and 2 cross-sectional studies were appraised using the Joanna Briggs Institute (JBI)'s Critical Appraisal Checklist. The quality assessment process was conducted independently by two reviewers (Minghui Sun and Yanji Qin). In case of disagreement, resolution was achieved through independent evaluation by a third reviewer (Yuchen Gao).

Data Synthesis

A single-arm meta-analysis was performed to estimate the pooled prevalence of four common respiratory symptoms (sore throat, oral lesions, cough, and tonsillar signs). Analysis was conducted with the metaprop command in Stata version 12.0. Because of the anticipated substantial heterogeneity, a random-effects model was employed to calculate pooled prevalence estimates with corresponding 95% confidence interval (*CI*). Between-study heterogeneity was quantified using the I^2 statistic. To investigate potential sources of heterogeneity, we conducted subgroup analyses by the proportion of men and the continental distribution of the race of the study population, revealing statistically significant differences. Test for subgroup differences was performed, and a p-value for the interaction of <0.05 indicates a statistically significant difference between subgroups.

Assessment of the Credibility of Evidence

We classified certainty of evidence as high, moderate, low, or very low, based on GRADE (Grading of Recommendations, Assessment, Development and Evaluations), considering the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Assessment of the Publication Bias

Publication bias was evaluated qualitatively using the Funnel Plot analysis. Subsequently, publication bias was further evaluated quantitatively using the Egger's test. A statistically significant publication bias was indicated when a *p*-value <0.05.

Results

Study Selection & Study Characteristics

Through retrieval, we obtained a total of 4691 studies from six electronic databases. After duplication, screening of title and abstract, and further full-text review, a total of 25 qualified and eligible studies were finally identified. In the eligible studies, a total of 2159 Mpox patients were included in the following meta-analysis and systematic review (Fig. 1, Supplementary Tables S1). Among the 25 studies included, there were fifteen cohort studies, eight case series studies, two cross-sectional studies. In addition, the studies vary in terms of the main continental distribution of their population's race, with six from Europe, eight from Asia, three from the America, and eight including African race. Based on statistical analysis, there are a total of six studies that have identified the presence of other respiratory virus infections among the cases, and additionally, there are twelve studies where the entire subject population consists solely of males (Table 1).

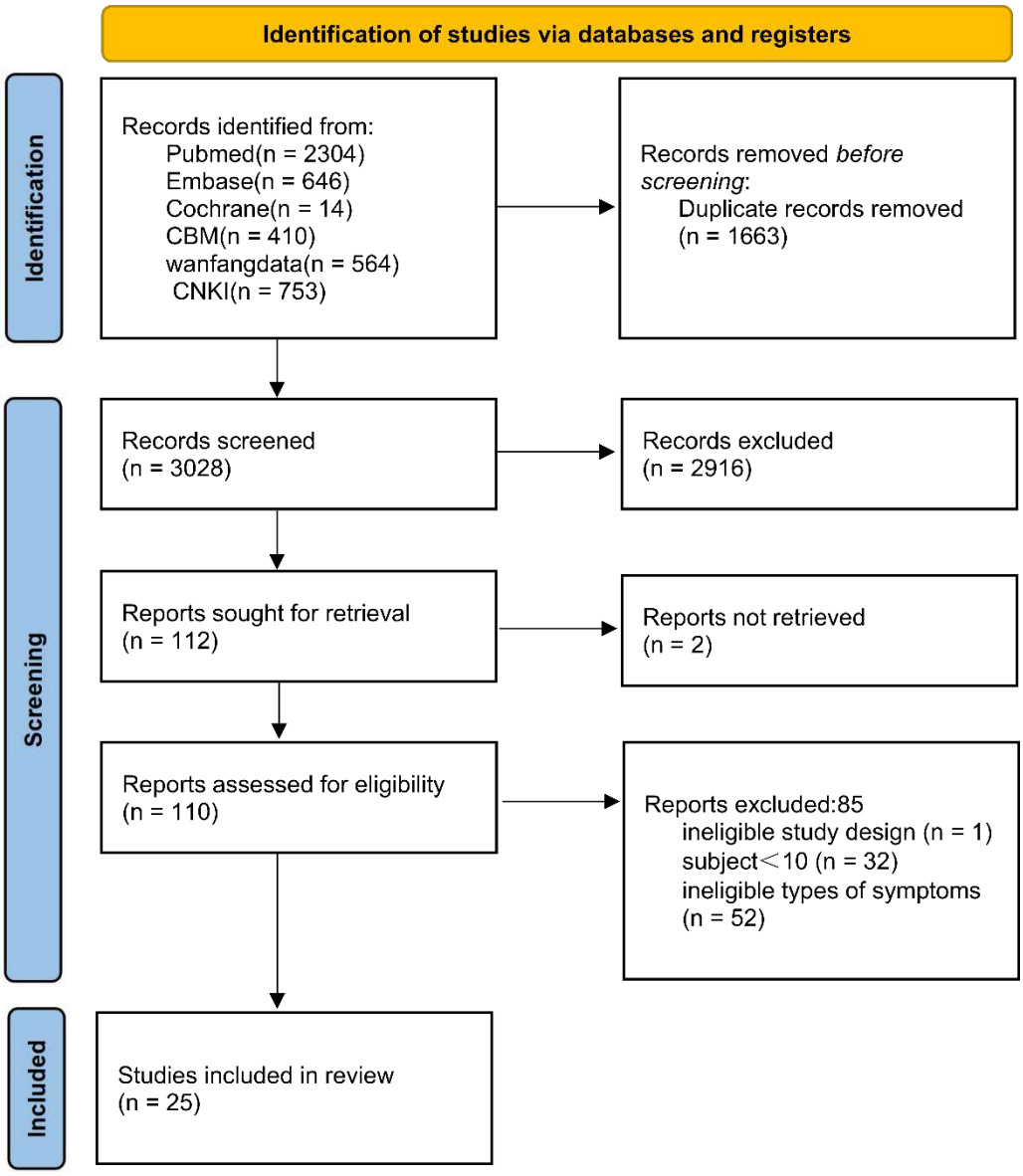


Fig. 1 Preferred Reporting Items for Systematic Review and Meta-Analysis 2020 Flow Diagram for Study Selection

Table 1 Baseline Study Characteristics of Mpox Patients Included in the Study

No	Study (Author Year)	Study design	*N*	Continent distribution	Other respiratory pathogens *n*(%)	HIV negative *n*(%)	Male sex *n*(%)	Age,years mean±*SD*/median(*IQR*)	Sexual orientation *n*(%)		
									Heterosexual	MSM	Bisexual
1	Dimie 2023[7]	Retrospective cohort study and prospective cohort study	160	Africa	NR	69 (43)	114 (71)	30.5（22-38）	142 (89)	8 (5)	
2	Michael 2023[8]	Case series report	79	Africa	Chlamydia co-infection 2 (2.5); Strep pharyngitis 5 (6)	40 (51)	79 (100)	34 (21-61)		MSM 73 (92); Non-MSM 3 (4); Unknown 3 (4)	
3	Zoha 2023[9]	Retrospective cohort study	36	Africa	Chlamydia 5/25 (20)	0	35 (97.22)	37.58 ± 10.75	2 (5.56)	32 (88.89)	2 (5.56)
4	Alejandro 2023[10]	Cohort study	30	Asia	NR	16 (53)	30 (100)	32.73 ± 6.33		30 (100)	
5	Caterina 2023[11]	Cohort study	140	Europe	NR	74 (53)	137 (98)	37 (33-43)		134 (96)	
6	Morgane 2022[12]	Cohort study	264	Asia	NR	191 (72)	262 (99)	35 (30-41)		245 (95)	
7	Nicolò 2022[13]	Retrospective cohort study	54	Africa	NR	41 (76)	54 (100)	41 (34-45)		54 (100)	2 (4)
8	Eloy 2022[14]	Prospective cohort study	181	America	Chlamydia 10 (6)	109 (60)	175 (97)	37 (31-42)	15 (8)	166 (92)	
9	So 2023[15]	Retrospective cohort study	60	Asia	Mycoplasma hominis 1/51 (2)	35 (58)	58 (97)	32 (28-38)		51 (85)	
10	Ellora 2024[16]	Cross-sectional study	115	Africa	NR	77(67.0)	Cisgender male 103 (89.6)	36 (29-42)		NR	
11	Wang 2024[17]	Retrospective cohort study	48	Asia	NR	24 (50)	48 (100)	29.6 ± 5.9		34 (70.83)	
12	Valeria 2023[18]	Case series report	30	Europe	Chlamydial pharyngitis 3(10)	18 (60)	30 (100)	37.5 (21-65)		30 (100)	
13	Eva 2022[19]	Case series report	48	Europe	NR	29 (60.4)	48 (100)	35 (29-44)		42 (87.5)	22 (45.8)
14	Aatish 2022[20]	Case series report	197	Europe	NR	125 (63.5)	197 (100)	38 (21-67)		196（99.5）	
15	Nadim 2022[21]	Retrospective cohort study	136	Europe	Chlamydia trachomatis 4/127 (3.1)	115 (84.6)	133 (97.8)	36 (30-42)	5 (3.7)	125 (91.9)	
16	Romain 2022[22]	Case series report	50	Europe	NR	28 (56)	50 (100)	34 (29–40)	1 (2)	49 (98)	
17	Hannah 2023[23]	Case series report	118	Africa	NR	47 (40)	108 (92)	18-29years 20 (17%); 30-39years 62 (53%); 40-49years 27 (23%); >50years 9 (8%)	14 (12)	Gay or lesbian 64 (54)	21 (18)
18	Fu 2023[24]	Cross-sectional study	115	Asia	NR	50 (43.5)	115 (100)	31.0 (27.0-36.5)	6/113 (5.3)	101/105 (96.2)	5/113 (4.4)
19	Yan 2023[25]	Retrospective cohort study	31	Asia	NR	10 (32.3)	31 (100)	HIV positive group 27.0 (25.0-35.0); HIV negative group 25.5 (23.0-31.0)		31 (100)	
20	Xu 2023[26]	Retrospective cohort study	38	Asia	NR	17 (44.7)	38 (100)	29.6 ± 6.1		38 (100)	
21	Luo 2024[27]	Retrospective cohort study	56	Asia	NR	33 (58.9)	56 (100)	31.6 ± 5.9 (19-51)		56 (100)	10 (17.9)
22	E. 2016[28]	Case series report	12	Africa	NR	NR	6 (50)	25.5 (1-41)		NR	
23	Gregory 2005[29]	Retrospective cohort study	34	America	NR	NR	18 (52.9)	26 (6-47)		NR	
24	Dimie 2020[30]	Retrospective cohort study	40	Africa	NR	31 (77.5)	31 (77.5)	32(range 28 days to 54 years)		NR	
25	CDC 2003[31]	Case series report	87	America	NR	NR	12(60)	28 (1-55)		NR	

Quality Assessment of Included Studies

We employed the Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies to assess the quality of 15 cohort studies, and utilized JBI's Critical Appraisal Checklist to evaluate the quality of 8 case series studies, as well as 2 cross-sectional studies (Supplementary Tables S2, S3 and S4). In fifteen cohort studies, eight were rated as high quality, scoring 7 or higher, while the remaining studies were classified as moderate quality. None of the studies were categorized as low quality. Among the eight case series, five were eligible for inclusion, while three required additional information but were ultimately not excluded. Additionally, two cross-sectional studies were also included.

Respiratory Symptoms in Mpox Patients

All studies included in this systematic review reported at least one respiratory symptom. These symptoms comprised sore throat (17 studies), oral lesions (11 studies), cough (8 studies), and tonsillar signs (9 studies). Other respiratory symptoms identified in the study include pneumonia, shortness of breath, nasal congestion, dysphagia, and others (Supplementary Tables S5). The pooled prevalence of sore throat was 18% (95% *CI* 13%-23%), that of oral lesions was 17% (95% *CI* 13%-22%), that of cough was 16% (95% *CI* 9%-24%), and that of tonsillar signs was 7% (95% *CI* 4%-12%) (Fig. 2). Moderate to high heterogeneity was observed across the included studies for all symptoms, with I^2 values ranging from 71.57% to 82.58%. The Funnel Plot analysis revealed asymmetry, which suggests a potential risk of publication bias (Fig. 3). However, Egger's test indicated that there is no significant risk of publication bias quantitatively ($p = 0.685$) (Fig. 4, Supplementary Tables S6).

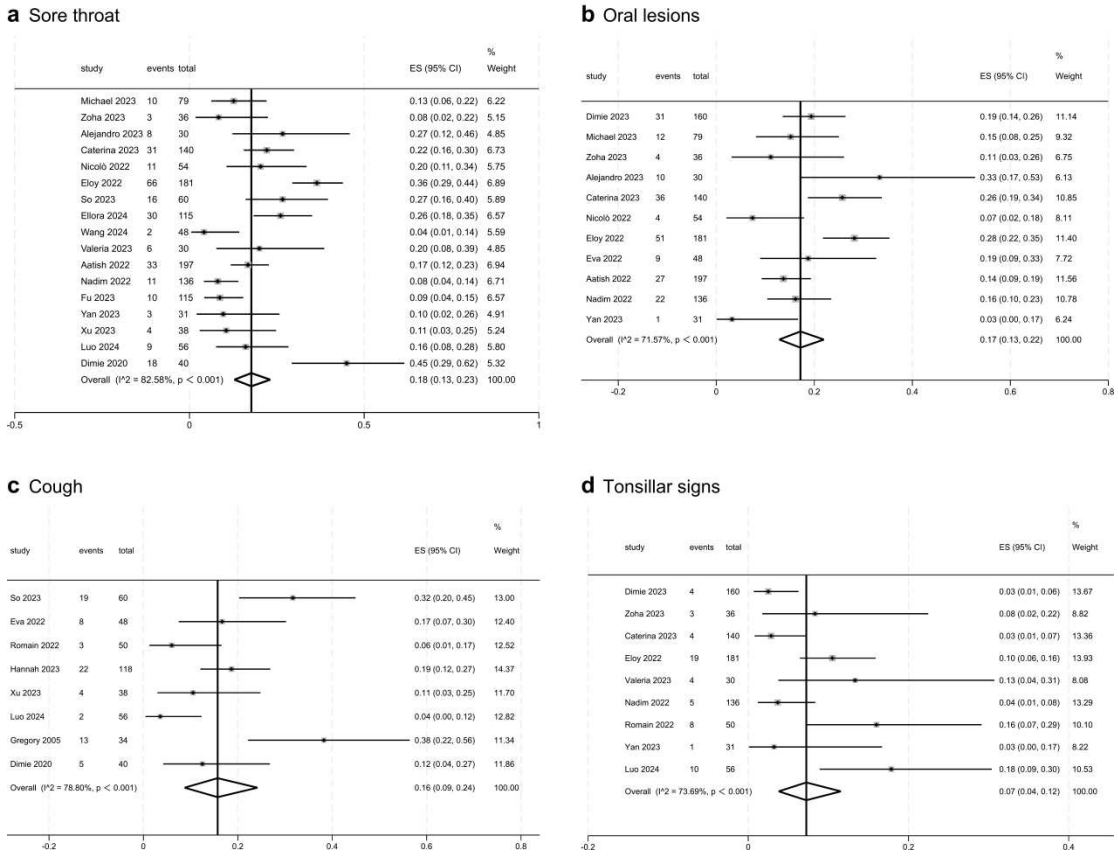


Fig. 2 Pooled Prevalence of Respiratory Symptoms in Mpox Patients **a** shows the pooled prevalence of sore throat. **b** shows the pooled prevalence of oral lesions. **c** shows the pooled prevalence of cough. **d** shows the pooled prevalence of tonsillar signs.

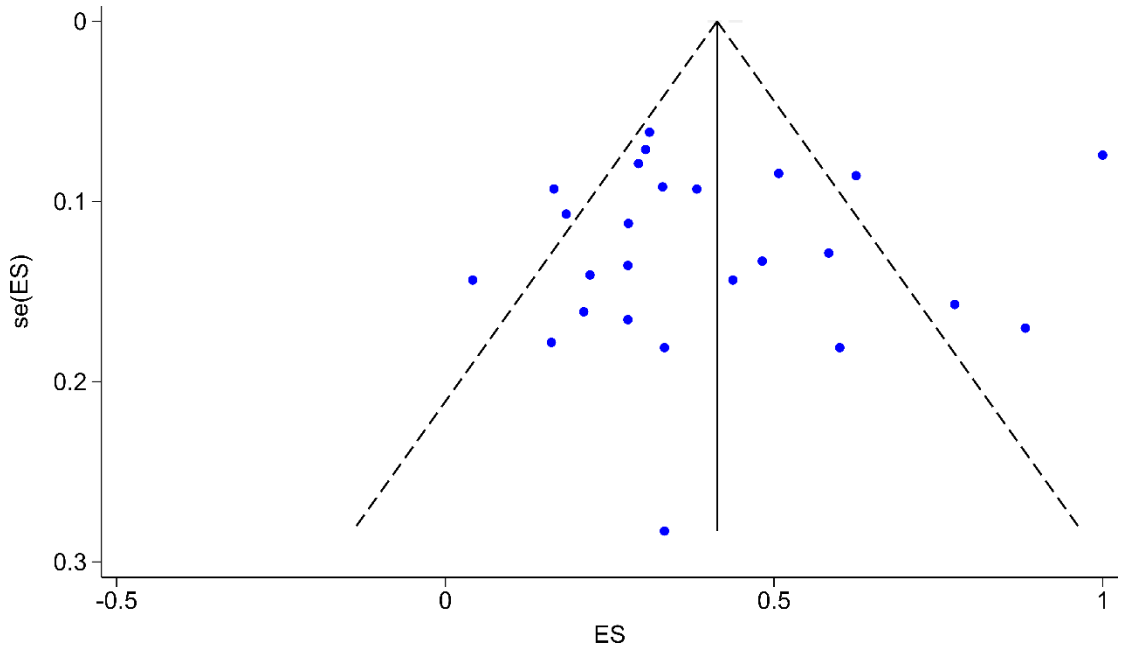


Fig. 3 Funnel Plot Assessing Risk of Publication Bias for Respiratory Symptoms

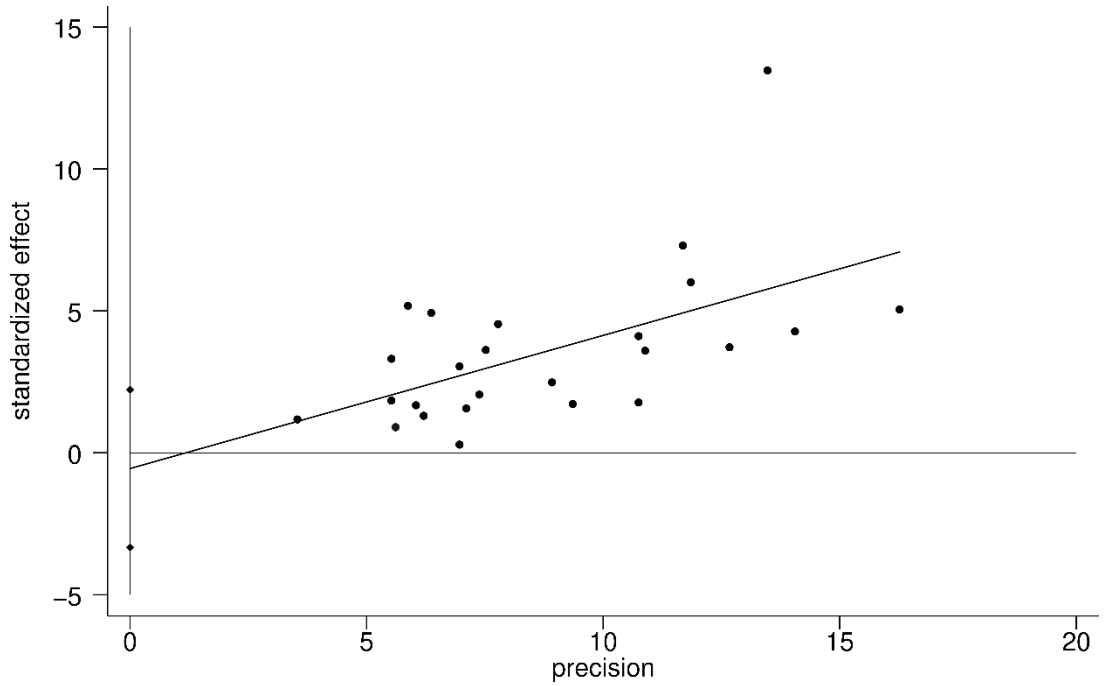


Fig. 4 Egger's Publication Bias Plot of Respiratory Symptoms

The prevalence was analyzed further based on two factors: the proportion of men and the the continent distribution of the race of study population. This analysis aimed to determine if significant differences in prevalence existed between subgroups, with the goal of exploring the source of heterogeneity (Table 2). From the perspective of the continental distribution of ethnic groups within the study population (*p*-interaction=0.00), the prevalence of sore throat (36%; 95%*CI* 29%-44% vs. 12%; 95%*CI* 6%-19%) and oral lesions (28%; 95%*CI* 22%-35% vs. 3%; 95%*CI* 0%-17%) was highest in the American study and lowest in Asia. In the study involving the African population, the prevalence of sore throat (21%; 95%*CI* 12%-33% vs. 17%; 95%*CI* 11%-24%) was higher than that observed in

Europe, although the prevalence of oral lesions (14%; 95%*CI* 9%-20% vs. 20%; 95%*CI* 14%-26%) was lower than that observed in Europe. Additionally, when considering the male proportion in the studies, the prevalence of cough (8%; 95%*CI* 4%-15% vs. 24%; 95%*CI* 14%-35%) (*p*-interaction=0.008) in the study with 100% male patients was lower than that in studies with mixed-gender populations. However, the incidence of tonsillar signs (13%; 95%*CI* 7%-20% vs. 5%; 95%*CI* 2%-9%) (*p*-interaction=0.017) in the study of all male patients was significantly higher than in the studies that included patients of both genders.

Table 2 Subgroup Analysis of Respiratory Symptoms in Mpox based on the Proportion of Men and Population Continent Distribution

				Random effect model	
	Subgroup	**Study (n)**	I^2	**Prevalence (%) (95%*CI*)**	***p*-interaction**
	Population Continent Distribution				
	Europe	5	71.63	17(11-24)	
Sore throat	Asia	6	64.77	12(6-19)	0
	America	1	-	36(29-44)	
	Africa	5	80.12	21(12-33)	
	Population Continent Distribution				
	Europe	5	66.01	20(14-26)	
Oral lesions	Asia	1	-	3(0-17)	0
	America	1	-	28(22-35)	
	Africa	4	40.79	14(9-20)	
	the Proportion of Men				
Cough	All Male	4	46.78	8(4-15)	0.008
	Not All Male	4	70.52	24(14-35)	
	the Proportion of Men				
Tonsillar signs	All Male	4	35.66	13(7-20)	0.017
	Not All Male	5	69.51	5(2-9)	

Furthermore, some other diseases that can cause respiratory symptoms were also mentioned in the included studies, such as oral ulcers (10%; 95% *CI* 1%-25%) in four studies and pneumonia (8%; 95% *CI* 5%-12%) in only three studies (Fig. 5). Due to the limited number of studies, the representativeness and persuasiveness of the pooled prevalence of these two symptoms are relatively low. Therefore, additional research data is needed in the future to evaluate the prevalence of these relatively less frequently reported symptoms more accurately. Based on the GRADE approach, 4 statistically significant meta-analytical associations (16%) met the high certainty criteria, 13 (52%) moderate certainty, 7 associations (28%) met the low certainty, and 1 associations (4%) met the very low certainty (Supplementary Tables S7).

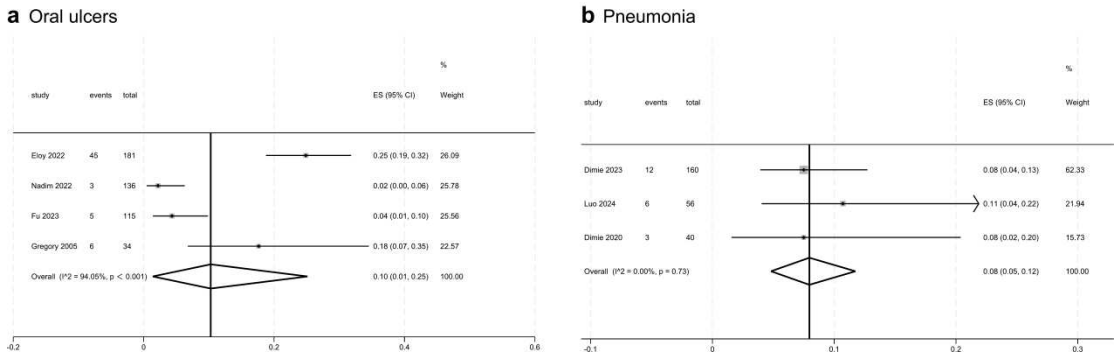


Fig. 5 Pooled Prevalence of Other Respiratory Symptoms in Mpox Patients **a** shows the pooled prevalence of oral ulcers. **b** shows the pooled prevalence of pneumonia.

Discussion

This meta-anlysis investigates the respiratory symptoms of Mpox patients, addressing some of the limitations and deficiencies of the existing research on this topic. Previous studies primarily focused on the general clinical symptoms of Mpox, such as fever, skin lesions, and lymphadenopathy[32], with limited attention given to respiratory symptoms. In the studies included in this review, the most frequently reported respiratory symptoms were sore throat, oral lesions, cough, signs of tonsillitis, and pneumonia. We observed moderate to high heterogeneity in the statistical results for these symptoms, with I^2 values ranging from 70% to 85%. The most common respiratory symptoms were sore throat (18%), followed by oral lesions (17%), cough (16%), and tonsil signs (7%). In addition, the prevalence rates of oral ulcer (10%) and pneumonia (8%) is also relatively high. While only a limited number of studies have reported these two manifestations, it is imperative to consider them in clinical practice. The potential for these symptoms to contribute to the development of additional respiratory diseases should not be disregarded. Overall, the prevalence of these respiratory symptoms not only suggests a potential association with Mpox patients but also indicates, to some extent, that the mpox virus may possess potential pathways for respiratory transmission, particularly in light of its recent epidemiological shift towards human-to-human transmission. Research indicates that the virus can be transmitted through various means, including close intimate contact, oral and respiratory secretions, droplets, skin lesions, and contact with contaminated surfaces[3]. Our findings also suggest that the virus may invade the human body via the respiratory system, specifically through the nasal passages and pharynx, and can subsequently disseminate along the respiratory tract. Furthermore, there exists a possibility that the virus may cause infections in additional respiratory organs, potentially resulting in more severe respiratory diseases. This information is crucial for the development of targeted prevention and treatment measures, as well as for enhancing differential diagnosis strategies in clinical practice.

In the decades since Mpox was first identified, different respiratory symptoms have been reported at different stages of historical outbreaks. For instance, a 2013 study reported that Mpox lesions were often present in the oral cavity[33]. Since the outbreak of Mpox clade II in 2022, relevant cases with oral lesions have also been reported[34, 35]. Prior to 2022, approximately half of the patients with Clade I and Clade II Mpox exhibited cough symptoms[36]. After the global outbreak in 2022, there were also reports of symptoms such as sore throat[14, 20, 34, 35, 37]. However, it should be noted that during the new COVID-19 pandemic in 2022, the respiratory symptoms of the novel coronavirus infection were similar to those of some Mpox patients, which had some interference with our discussion of the results. At the same time, the increased detection of respiratory symptoms may also be related to changes in medical diagnosis practices during this epidemic. Recent studies have done

research on the respiratory transmission of Mpox virus[38], which provides a certain degree of reference for the discussion of the relationship between Mpox and respiratory symptoms.

It is worth noting that our subgroup analysis results indicate that the prevalence of sore throat and oral lesions is highest in the study population from the Americas, followed by Africa and Europe, and lowest in Asia. The vast majority of research data from the Americas, especially North America, and Europe stems from the global outbreak of Mpox in 2022. A significant characteristic of this epidemic is its primary transmission among men who have sex with men (MSM), especially through sexual contact[35]. Numerous research studies indicate that the incidence of oral and genital mucosal lesions, including sore throat, in MSM patients is unusually high. This may be linked to the direct inoculation of the virus to the oral and genital mucosa during sexual contact. The research data from Africa, particularly from central and West Africa, predominantly comes from endemic regions of Mpox. In these areas, the mode of transmission is typically associated with animal-to-human contact, often occurring through familial or communal interactions. Consequently, the reporting frequency may vary compared to the epidemic predominantly associated with MSM in 2022. In the epidemic situation in 2022, most Asian countries were classified as non-endemic areas, with cases primarily stemming from imported infections or limited local transmission. The overall number of studies and sample sizes is far lower than those in the Americas and Europe. At the same time, the potential impact of virus clade on the analytical results should be taken into account. Historically, Clade I was considered to be more pathogenic and more severe than Clade II. The global epidemic in 2022 was mainly driven by clade IIb. Clade IIb (the former West African clade) is the main clade in America. Clade I and II are prevalent in Africa[39]. However, there is no clear evidence that clade IIb itself is more likely to cause oral or throat symptoms. At the same time, the high mucosal lesion rate of the epidemic in 2022 is mainly due to the mode of transmission (sexual contact), rather than the inherent pathogenicity difference of the virus clade.

In addition, in the study of all male patients, the prevalence of cough was low, while the prevalence of tonsillar signs was high. This result may be affected by the specific characteristics of these study groups, most of which consisted of men who have sex with men (MSM). Therefore, the virus tends to cause significant local inflammation and symptoms, such as tonsillitis, in the direct contact sites (including the oral cavity, tonsils, genitalia, and anus), while the systemic respiratory symptoms, such as cough, caused by inhalation through the respiratory tract, are relatively less prominent. This finding emphasizes the impact of transmission routes on the clinical manifestations of Mpox, rather than simply due to biological gender differences. Due to the lack of research that mainly consists of women or contains a sufficient number of non-MSM men, a precise gender comparison is currently not feasible. Future studies need to include more diverse populations for comprehensive analysis.

This meta-analysis has some limitations. Firstly, the analysis includes some studies with low evidence credibility, especially since the included studies are observational studies. Secondly, there is significant heterogeneity in the analysis of most respiratory symptoms, which may be affected by different baseline characteristics of patients, such as co-infection with other respiratory pathogens and age distribution, among other factors.

Conclusions

In conclusion, among the common respiratory symptoms of Mpox patients, sore throat is the most prevalent, followed by oral lesions, cough, and tonsillar signs. These symptoms offer valuable insights

into the respiratory transmission pathways of the mpox virus and contribute to the advancement of its differential diagnosis, as well as the prevention and management of related complications. So further research is still needed to ascertain whether patients exhibiting respiratory symptoms experience more severe manifestations and/or a poorer prognosis, and additional studies and comprehensive analysis are warranted to enhance our understanding and improve clinical outcomes in this area.

Ethics approval and consent to participate Not Applicable.

Consent for publication Not Applicable.

Competing interests The authors have no competing interests to declare that are relevant to the content of this article.

Author contributions Junwen Luan, Daoqun Li and Yuchen Gao contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yuchen Gao, Mingchun Ma, Minghui Sun and Yanji Qin. The first draft of the manuscript was written by Yuchen Gao and edited by Junwen Luan. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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Availability of data and materials All data generated or analysed during this study are included in this published article and its supplementary information files.

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