Review Article

Prevalence of *Mycoplasma pneumonia* Coinfection among Patients with COVID-19: A Systematic Review

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Abstract

COVID-19 pneumonia signs and symptoms are not specific and it may be similar to other cases of pneumonia caused by other microorganisms such as *Mycoplasma pneumonia*. This study aimed to investigate the prevalence of M. pneumonia co-infection among patients with COVID-19 by a systematic review and meta-analysis.

Two authors performed the search process independently in Scopus, Web of sciences, and PubMed for studies reporting COVID-19-associated *Mycoplasma pneumonia* co-infections published in the English language from December 2019 to 1st June 2020. The MeSH terms used in the present review were; "COVID-19", "co-infection", "secondary infection", "2019 novel coronavirus", "2019-nCoV", "COVID-19 virus", "coronavirus disease 2019 virus", "*Mycoplasma pneumoniae*", "*M. pneumoniae*", "prevalence", and "respiratory pathogens". Data analyzed using Comprehensive Meta-analysis (CMA) software. Heterogeneity among included studies was checked by I2 statistic and the Q2 test. M. pneumonia co-infection was varied between 1 and 40.6% in the included studies. The combined prevalence of *M. pneumoniae* co-infection among patients with COVID-19 was reported by 17% (95% CI: 7.4–34.3).

Overall, our systematic review and meta-analysis showed a quite high co-infection of M. pneumonia in patients with COVID-19 infection, therefore, routine diagnostic tests are recommended for respiratory pathogens like *M. pneumonia*, because on-time treatment has a beneficial effect on patient survival. Also, an increasing number of cases of asymptomatic COVID-19 infection, the differentiation and diagnosis of pneumonia caused by COVID-19 from non-COVID-19 pneumonia be considered. It helps avoid unnecessary quarantine and waste of medical resources.

Keywords: COVID-19; SARS-CoV-2; Coronavirus; Coinfection; Prevalence; *Mycoplasma pneumoniae*.

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Introduction

As we know since December 2019, the infection caused by 2019 novel coronavirus (COVID-19) was detected for the first time in Wuhan, Hubei Province, China (1). According to pieces of evidence, the source of the virus is probably bats, which have been transmitted to humans through unidentified intermediate animals (2). The route of transmission is infected respiratory droplets and contact, and the incubation period of which is estimated to be between 2 and 14 days (3). Overall, infection occurs by inhaling infected infectious particles or by contact with virus-infected surfaces and then touching the eyes, nose, and mouth (2). So far, several cases of people with the disease and the resulting mortalities are being reported every day around the world, which is on the rise (2). According to reports, the highest incidence of morbidity and mortality is seen in elderly people with underlying diseases (4). To our knowledge, the infection can transmit from asymptomatic people and also before the starting of early symptoms (3). It is noteworthy that while the number of new cases in China has gradually decreased, they have increased exponentially in other countries of the world (5). Some studies reported the co-infection with respiratory pathogens in clinical settings (6, 7). One of these opportunistic bacteria that can infect the respiratory tract is Mycoplasma pneumoniae. Mycoplasma pneumoniae is a type of "atypical" microorganisms that generally causes mild infections of the respiratory tracts. Actually, pneumonia caused by *M. pneumoniae* is

alternatingly denoted as "walking pneumonia" because symptoms are milder than pneumonia caused by other bacteria (8). Although it is important to identify SARS-CoV-2 infection and causes the clinicians to take proper infection control measures and treatment, they should not forget SARS-CoV-2 co-infection (9). Thus, this study aimed to investigate the prevalence of *M. pneumonia* co-infection among patients with COVID-19 within a systematic review and meta-analysis.

Methods

Search strategy

Two authors performed the search process independently in Scopus, Web of sciences, and PubMed for studies reporting COVID-19-associated mycoplasma pneumonia co-infections published in English language from December 2019 to 1th June 2020.

The MeSH terms used in the present review were; "COVID-19", "coinfection", "secondary infection", "2019 novel coronavirus", "2019-nCoV", "COVID-19 virus", "coronavirus disease 2019 virus", "*Mycoplasma pneumoniae*", "*M. pneumoniae*", "prevalence", and "respiratory pathogens".

Selection criteria

And cohort studies included in the present review that met the following eligibility criteria: Cross-sectional and cohort studies in English language that were conducted on reporting COVID-19-associated mycoplasma pneumonia co-infections were considered. Also, studies used the standard molecular and phenotypic methods for the detection of COVID-19 and *M. pneumonia* were included.

Exclusion criteria

Studies with no address this subject, abstracts, case series, case reports, letters to editor, editorials, article with missed data, articles reported in languages other than English, and all kinds of literature reviews were excluded.

Quality assessment

Here it was used Briggs Institute (JBI) critical appraisal checklist for quality assessment. Based on, 10 questions were designed with "yes" and "no" answers. Finally, studies were categorized into three groups; high (>5 scores), intermediate (4–5 scores), and low quality (<4 scores) (10).

Data extraction

As presented in Table 1, to authors extracted the following data; from each eligible study; first author, publication year, location (country), sample size, patients' age, gender (men, and women), coinfection (prevalence of *M. pneumonia*), methods used for the detection of COVID-19.

Table 1. Characteristics of included studies

First Author	Publication	Settings	Sample size	*M. pneumonia*	Age (Year)	Detection method of COVID-19	Diagnostic methods of *M. pneumonia*	Gender (%) Men	Gender (%) Women
Blasco (23)	2020	Spain	103	1	61; range: 24-84	RT-PCR	Phenotypic methods	60.2	39.8
Dawei Wang (24)	2020	China	138	56	56 y (interquartile range, 42-68; range, 22-92)	RT-PCR	Phenotypic methods	54.3	45.7
Heng Liu (22)	2020	China	4	1	63	RT-PCR	Phenotypic methods	55.2	44.8
Quan-sheng Xing (18)	2020	China	30	7	50 (37-59)	RT-PCR	Phenotypic methods	40	60
S. Richardson (25)	2020	USA	42	1	63 (52-75)	RT-PCR	Phenotypic methods	60.3	39.7
Hui Li (26)	2020	China	40	13	5.09 y (4.71)	RT-PCR	Phenotypic methods	57.5	42.5

Meta-analysis

Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ) was used for data analysis. The results were presented as percentage and 95% confidence intervals (95% CIs). Heterogeneity among included studies was checked by I2 statistic and the Q2 test. Regarding heterogeneity between studies, the random-effects model was applied. Funnel plot and Egger regression test were used to assess publication bias among studies included.

Results

Study selection

Overall, 6 out of 198 studies searched through electronic databases met the eligibility criteria for inclusion as shown in Figure 1.
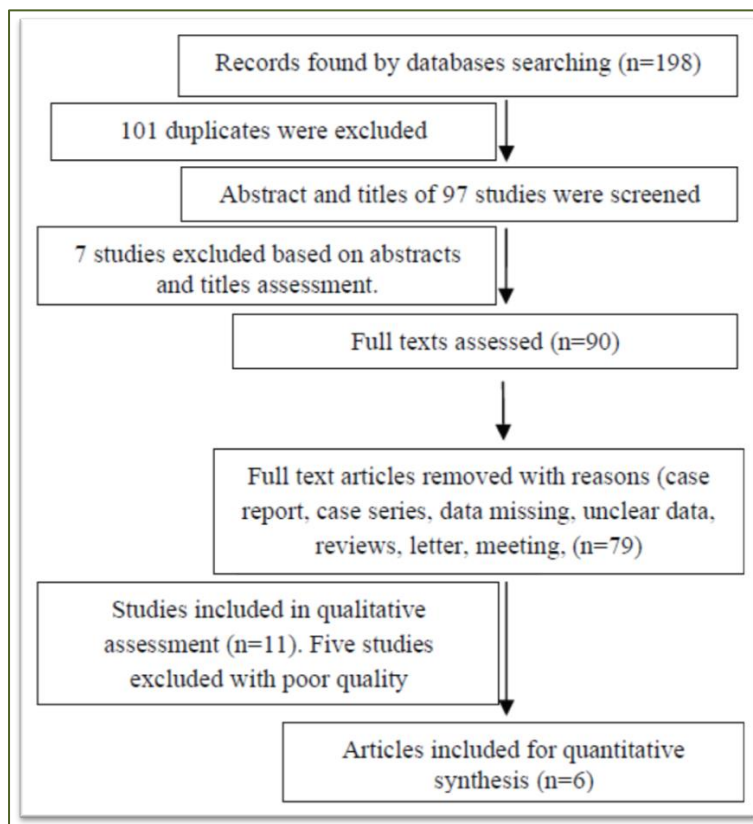

Figure 1. Flow chart of inclusion process

Characteristics of included studies

According to Table 1, most studies were from China (n = 4), Spain (n = 1), and USA (n = 1). Patients aged between 16 days and 84 years. All studies used of RT-PCR technique for the detection of COVID-19. Also, most patients were male.

Overall effects

M. pneumonia coinfection was varied between 1% and 40.6% in included studies. Figure 2 shows the combined prevalence of *M. pneumoniae* coinfection among patients with COVID-19 was reported by 17% (95% CI: 7.4–34.3), Q = 28.9 and Z = 3.3, I2 =82.7, and t= 3.3.
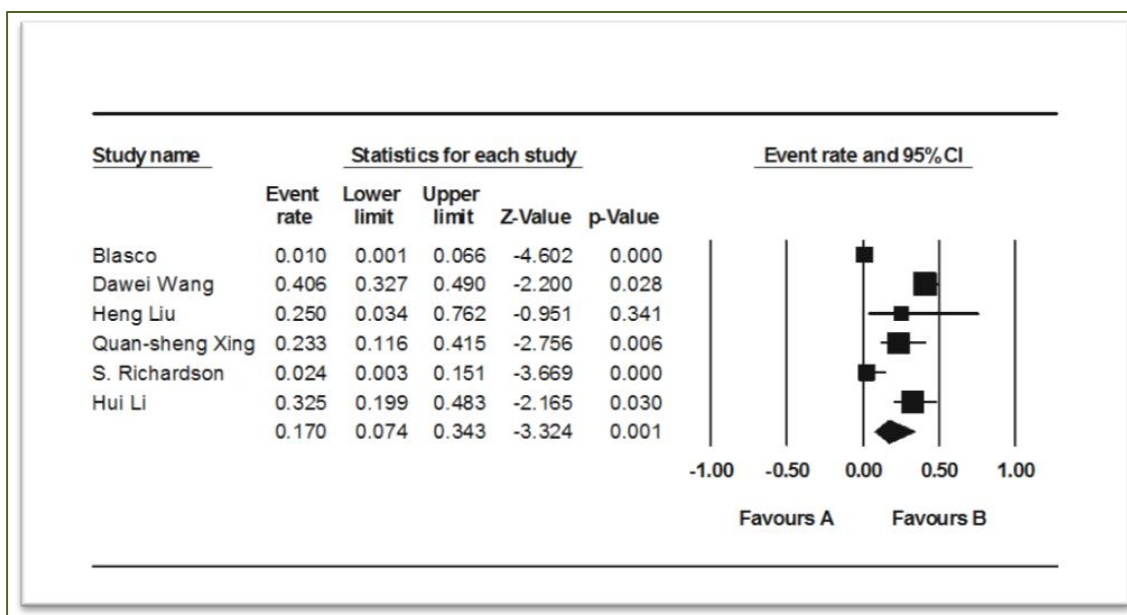
Figure 2. Forest plot of the meta-analysis of the prevalence of *M. plasma* coinfection among patients with COVID-19.

Sources of heterogeneity

Funnel plot shows the publication bias among the included studies (Figure 3). Also, Egger's linear regression test was used to further reveal publication bias. Findings of Egger's linear regression test revealed publication bias, too ($p = 0.028$).
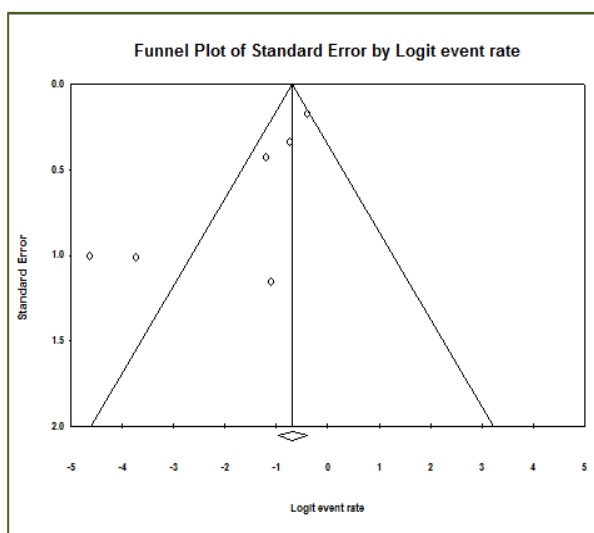

Figure 3. Funnel plot of the meta-analysis of the prevalence of M. plasma coinfection among patients with COVID-19.

Discussion

Our study showed that M. pneumonia co-infection was varied between 1% and 40.6% in included studies. Overall, the combined prevalence of *M. pneumoniae* co-infection among patients with COVID-19 was reported by 17%. *M. pneumoniae* is among the commonest causes of community-acquired pneumonia (CAP), predominantly in young adults (11). *M. pneumoniae* is responsible for 7–20% of CAP (12, 13). Typical CT imaging characteristics of COVID-19 pneumonia have been discussed by several studies (14, 15), nevertheless, their signs and symptoms are not specific and it may be similar to other cases of pneumonia caused by other microorganisms such as *M. pneumonia* (16, 17). Considerations on the impact of respiratory pathogens co-infection on COVID-19 infection are controversial. One of the studies included in this review despite the report of co-infection in their study cannot conclude that co-infection can make people more susceptible to COVID-19 infection (18). In line with this study, others didn't confirm whether this subject would impact the outcome of SARS and MERS due to restricted data (19, 20). Another study found that co-infection with respiratory pathogens such as

Mycoplasma pneumoniae would exacerbate COVID-19 infection if the infection was not diagnosed and treated. Eventually, it leads to more patients staying in the ICU unit (21). Assuming that co-infection with other respiratory microorganisms does not impact on COVID-19 infection, an increasing number of cases of asymptomatic COVID-19 infection, the differentiation and diagnosis of pneumonia caused by COVID-19 from non-COVID-19 pneumonia be considered. It helps avoid unnecessary quarantine and waste of medical resources (22). A chest CT scan alongside with RT-PCR technique can be used to quickly and early identification of COVID-19 pneumonia (22). The most important limitation of this review is that it has been done with a small number of studies and studies in a short period from three countries: The United States, Spain, and especially China.

Conclusion

Overall, our systematic review and meta-analysis showed a quite high co-infection of M. pneumonia in patients with COVID-19 infection, therefore, routine diagnostic tests are recommended for respiratory pathogens like *M. pneumonia*, because on-time treatment has a beneficial effect on patient survival. Also, an increasing number of cases of asymptomatic COVID-19 infection, the differentiation and diagnosis of pneumonia caused by COVID-19 from non-COVID-19 pneumonia be considered. It helps avoid unnecessary quarantine and waste of medical resources.

Conflict of Interest

The author declared that they have no conflict of interest.

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