

Association Between Symptoms and Severity of Disease in Hospitalised Novel Coronavirus (COVID-19) Patients: A Systematic Review and Meta-Analysis

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Background: Symptoms of the novel coronavirus disease (COVID-19) are well known, although asymptomatic cases were also reported due to this rapidly evolving viral disease. However, there has been limited research with inconsistent findings on symptoms of COVID-19 and disease severity. We aimed to evaluate the association between symptoms and severity of disease in adult patients with confirmed COVID-19 by performing a meta-analysis.

Methods: We conducted this study by searching four online databases (Medline, Web of Science, EMBASE and Cochrane library) of published studies that included symptoms of COVID-19 cases and severity of the disease between January 1, 2020, and October 31, 2021. PRISMA and MOOSE guidelines were followed, and only articles published in English were selected. We performed meta-analysis using Mantel-Haenszel random-effects model. Note that we included peer-reviewed studies conducted in Wuhan and published in the English language that reported the clinical characteristics of COVID-19, particularly the symptoms of novel coronavirus patients with their prevalence and distribution of patients based on the severity of the disease.

Results: Out of 255 articles identified, a total of twenty articles, including 5390 participants, met the inclusion criteria and were included. Among the participants, 2997 (55.60%) were males, and 974 (18.07%) reported severe conditions. Fever was the most commonly reported symptom in the reported COVID-19 confirmed cases (88.47%, 95% CI: 80.74–93.35%), which was followed by cough, fatigue, and less proportionally dyspnea and myalgia. Dyspnea was the only symptom, which was associated with severity of COVID-19 (OR 2.43, 95% CI: 1.52–3.89).

Conclusion: Dyspnoea was found to be associated with severity of COVID-19. People with existing respiratory illnesses, such as chronic obstructive pulmonary diseases need to be careful about the onset of such symptom and should seek medical attention.

Keywords: coronavirus, COVID-19, symptoms, respiratory, severity

Introduction

The novel coronavirus disease 19 (COVID-19) is a pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The condition has received enormous worldwide attention due to its high human-to-human transmissibility following the first cases reported in Wuhan, China, in December 2019.^{1,2} COVID-19 belongs to the same subgroup of coronavirus diseases. However, it is homologically far different from its predecessors like severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus

(MERS-CoV).³ Although the disease is mild in most people, it may progress to severe illness like pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction causing a fatality.

The clinical spectrum of COVID-19 varies from asymptomatic or presenting few symptoms to symptomatic forms as the first symptoms usually appear after five to six days, according to the World Health Organization (WHO) reports.⁴ Common symptoms include fever, fatigue, dry cough, sore throat and dyspnea while pneumonia, sneezing, malaise, diarrhea, headache and conjunctivitis,^{5–9} loss of taste and smell¹⁰ have also been reported. Due to its typical progressive and aggravation process, COVID-19 has been classified from mild to severe types based on the severity of the disease by the Beijing Centers for Diseases Control and Prevention (NHC China, 2020).¹¹ Globally, 80% of the reported COVID-19 cases presented with mild respiratory symptoms, 15% of cases required hospitalization and 5% cases were critical in nature.¹²

COVID-19 affects human body in a number of ways. Although the virus is known for affecting the respiratory systems drastically,¹³ other parts of the body including heart, CNS, renal, liver, and gastrointestinal functions.^{14–16} Persons with immunosuppressed and underlying conditions are often at a high risk of severe COVID-19 outcome despite vaccinations.¹⁷ However, the severity of COVID-19 outcomes varied among different age, sex, race, gender and other subgroups. Besides biological factors, social determinants such as income, education, social class, etc., are found to be associated with COVID-19 outcomes.¹³

Health researchers are ceaselessly working on understanding which symptoms are more closely associated with severe cases as the pandemic evolves. To get a more convincing idea about symptoms are associated severity of COVID-19, we attempt to provide a systematic and detailed evaluation from the recent data through our meta-analysis. The study will not only estimate the prevalence of symptoms of COVID-19 among the patients, but also assess the risk of severity in patients compared to non-severe patients. This analysis will help patient management and strategic interventions including policy measures to prevent and combat COVID-19 in coming days.

Materials and Methods

Search Strategy and Selection Criteria

This systematic review and meta-analysis were conducted according to PRISMA and MOOSE guidelines.^{18,19} An extensive search strategy was designed to retrieve all published articles from January 1, 2020 to October 31, 2021, in PubMed (Medline), Web of Science, EMBASE, and Cochrane Library databases. Search results were compiled using the bibliographic software Endnote™ X9.2. Based on the criteria of different databases, we used the following search terms: “2019-nCoV”, or “2019 novel coronavirus”, or “COVID-19”, or “clinical characteristics of COVID-19” or ‘symptoms of coronavirus’. We additionally screened the list of references for each selected article to identify studies that may have been missed during the initial search. Two independent researchers (AT and SRR) screened retrieved articles. The same investigators independently assessed full texts of records deemed eligible for inclusion. Any discrepancies were resolved by discussion and consensus with a senior investigator (SMSI).

We included peer-reviewed studies conducted in Wuhan and published in the English language that reported the clinical characteristics of COVID-19, particularly the symptoms of novel coronavirus patients with their prevalence and distribution of patients based on the severity of the disease. All the included studies’ patients were hospitalised cases of COVID-19, confirmed by the laboratory-based Real-Time Reverse Transcription Polymerase Chain Reaction Assay (RT-PCR). We excluded studies that focused on children and did not reported the clinical diagnostic criteria along with duplicate publications, single case reports, reviews, editorials, letters or (c) studies provide insufficient information on the relevant topic.

Data Extraction and Variables

Two authors (AT and SRR), who involved in the literature screening, also extracted the data independently from the selected studies. Differences were settled by conversation or a third analyst (SMSI). We obtained the following variables: first author, year of publication, number of patients, age, sex, number of severe and non-severe patients, and the prevalence of several symptoms including fever, cough, myalgia or fatigue, dyspnea and headache. “Patients with any

of the following features at the time of, or after, admission was classified as severe cases: (1) respiratory distress (≥ 30 breaths per min); (2) oxygen saturation at rest $\leq 93\%$; (3) ratio of the partial pressure of arterial oxygen to the fractional concentration of oxygen inspired air ≤ 300 mm Hg; or (4) severe disease complications (eg, respiratory failure, the requirement of mechanical ventilation, septic shock, or non-respiratory organ failure).¹¹

Data Analyses

All analyses were performed by R software (version 3.6.1). The odds ratios (OR) was considered to describe the severity of clinical symptoms in severe patients compared to non-severe patients. Due to the presence of heterogeneity in studies, Mantel-Haenszel random-effect models were utilised to estimate the average effect along with its precision, which can provide a more reliable estimate of the 95% confidence intervals (CI). To assess heterogeneity, we used the I^2 statistic and Cochran's Q test.

Study Quality and Publication Bias

We used The Newcastle-Ottawa Scale (NOS) for assessing the quality of studies in meta-analysis.²⁰ The NOS summarised 8 aspects of each study: case definition adequacy, representativeness of the cases, selection of controls, the definition of controls, comparability of cases and controls on the basis of the design or analysis, ascertainment of exposure, the same method of ascertainment for cases and controls, and comparison of nonresponse rate between cases and controls. Studies with a score 6 or more out of 9 total points were considered as high-quality studies. We used funnel plot and Egger's test to assess the publication bias. Furthermore, we utilized the Quality In Prognosis Studies (QUIPS) tool to assess the risk of bias which includes six domains such as (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting.

Ethical Approval

This study needs no ethical approval since our study used published article for data collection.

Results

The search produced 255 articles. Out of these, we excluded 160 duplicate articles and considered the remaining 95. After a screening of the title and abstract, 52 articles were excluded. Finally, we reviewed the full text and removed 23 articles since they were reviews, case reports, editorials and had lack of information. Twenty articles^{6,8,21–38} including 5390 COVID-19 patients eventually met the inclusion criteria and were included. All the included studies were hospital-based cross-sectional. The flow diagram of the literature search is shown in [Figure 1](#).

Among the participants, 2997 (55.60%) were males, and 974 (18.07%) reported severe conditions ([Table 1](#)). Fever (88.47%, 95% CI: 80.74–93.35%) was the most prevalent symptoms observed in COVID-19 patients, followed by cough (64.65%, 95% CI: 58.42–70.43%), fatigue (38.45%, 95% CI: 32.52–44.74%), dyspnea (23.59%, 95% CI: 16.48–32.58%) and myalgia (22.46%, 95% CI: 16.36–30.02%). The prevalence was estimated from random effect model and significant ($p < 0.05$) heterogeneities were observed for the estimates with I^2 ranging from 91% to 98% (see [Figure 2](#)).

We found that all studies reported the presence of pneumonia and abnormal chest imaging in most of the patients on admission. Four studies reported that ground-glass opacity was the most common feature on chest computed tomography (CT), which was followed by bilateral patchy shadowing.^{6,8,21,23} The findings from the CT were almost similar to the CXR as reported by the studies. The most prevalent comorbidities were hypertension and diabetes,²² which are followed by acute respiratory distress syndrome (ARDS)^{6,8,21} and among them, a large proportion of patients worsened in a shorter period of time and developed multi-organ disorder.

[Figure 3](#) shows the meta-analysis of the association between symptoms with severe and non-severe patients. Higher odds of dyspnea (OR 2.43 95% CI: 1.52–3.89) was observed in the severe group. The odds of fever (OR 1.04, 95% CI: 0.85–1.28), cough (OR 1.12, 95% CI: 0.91–1.38), fatigue (OR 1.14, 95% CI: 0.96–1.36), and myalgia (OR 0.78, 95% CI: 0.54–1.13) were also found higher in the severe COVID-19 patients. However, except dyspnea, our meta-analysis did not find any statistically significant association with the severity of the disease.

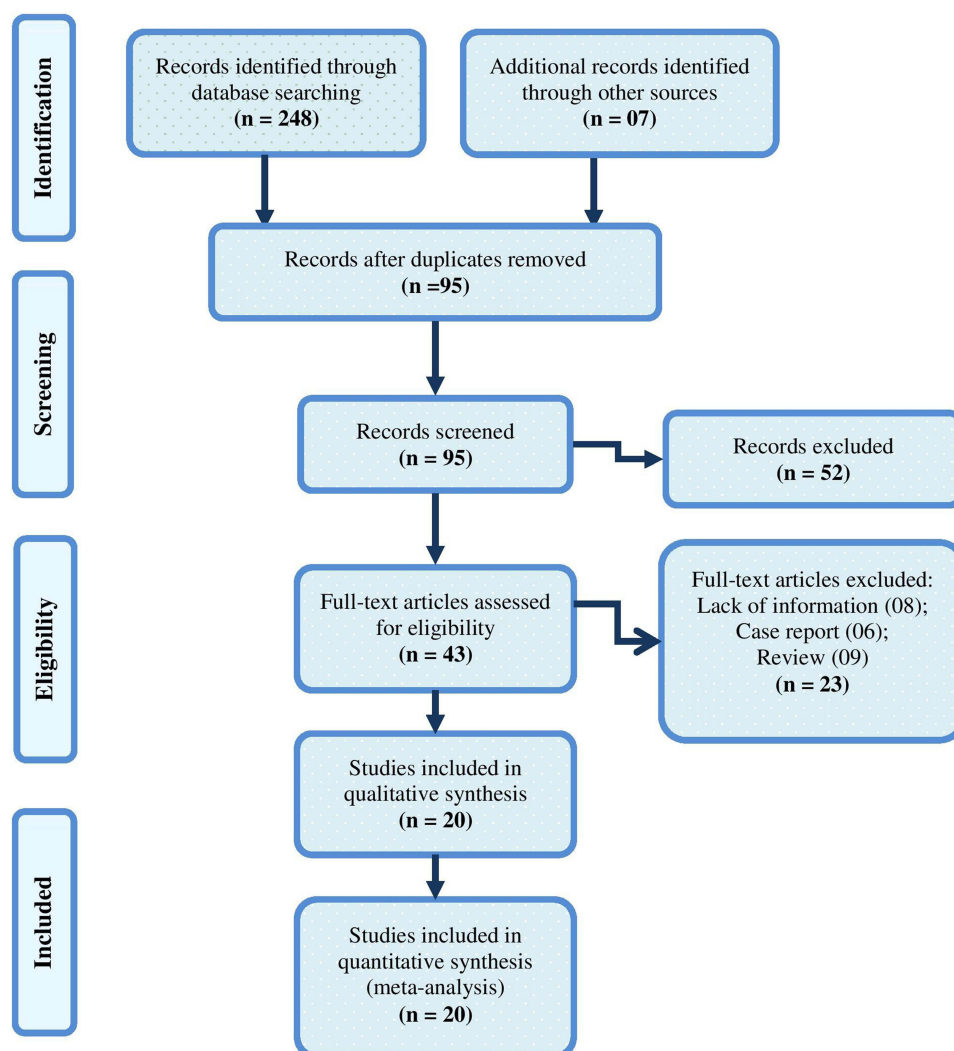


Figure 1 Flow diagram of literature search for including studies in meta-analysis.

Study Quality and Publication Bias

All studies included for the meta-analysis were ranked as high-quality studies ([Supplementary Tables 1 and 2](#)). The publication bias was examined for the following symptoms: fever, cough, fatigue, dyspnea and myalgia. [Figure 4](#) shows the results of possible publication bias, which were assessed by funnel plots and Egger's test. The results of the Egger's test (all $p < 0.05$) suggest that there exist no significant publication bias.

Discussion

This systematic review and meta-analysis provide a recent summary of findings of the association between COVID-19 symptoms and its association with disease severity. Our findings suggest patients with dyspnea had more than twice the odds of having a severe COVID-19 illness at the time of hospital admission. This indicates that COVID-19 patients with dyspnea having more than double chance of becoming a severe patient. However, we did not find a significant association between fever, cough, myalgia or fatigue and headache with the severity of symptoms, which is contradictory to the previous systematic review and meta-analysis.^{39,40} The main reason for this difference could be the stricter inclusion criteria in our study that limits the inclusion of some low-powered case-series studies. Furthermore, previous studies only analysed the prevalence of symptoms, while we meta-analysed and presented the Mantel-Haenszel (MH) odds ratio of the severity of symptoms, which is the first time since the outbreak occurred.

Table I Basic Characteristics of Included Studies in the Meta-Analysis and Estimating Prevalence of Several Symptoms Related to Novel Coronavirus (COVID-19) Patients

First Author (Year)	Sample Size (n)	Male (n)	Female (n)	Mean/Median Age (Years)	Severe Patients (n) %	Symptoms				
						Fever (%)	Cough (%)	Fatigue (%)	Dyspnoea (%)	Myalgia (%)
Xu et al ²⁶	62	35	27	41	NR	77.42	80.65	51.61	NR	51.61
Guan et al ²³	1099	640	459	47	173 (16%)	43.04	67.79	38.13	NR	NR
Guan WJ et al ²²	1590	904	686	49	254 (16%)	84.97	66.16	36.73	NR	NR
Huang et al ⁶	41	30	11	49	13 (31%)	97.56	75.61	43.90	53.66	43.90
Guo et al ²⁷	187	91	96	58.50	NR	NR	NR	NR	NR	NR
Zhou et al ²⁸	191	119	72	56	66 (34.55)	94.24	79.06	23.04	NR	15.18
Zhang et al ²⁵	140	71	69	57	58 (41%)	78.57	64.29	64.29	NR	NR
Liu et al ²⁹	137	61	76	57	NR	81.75	48.18	32.12	18.98	32.12
Wang et al ⁸	138	75	63	56	36 (26%)	98.55	59.42	69.57	31.16	34.78
Chen TL et al ³⁰	203	108	95	54	19 (9.36)	89.16	60.10	7.88	1.48	26.60
Liu J et al ²⁴	61	31	30	40	17 (28%)	98.36	63.93	57.38	4.92	NR
Chen et al ²¹	99	67	32	55.5	NR	82.83	81.82	NR	NR	NR
Yang et al ³¹	52	35	17	59.7	52 (100.00)	98.08	28.85	NR	23.08	3.85
Wu C et al ³²	201	128	73	51	53 (26.37)	93.53	81.09	32.34	39.80	32.34
Jie Li et al ³³	17	09	8	45.1	NR	70.59	76.47	47.06	NR	23.53
Mo et al ³⁴	155	86	69	54	55 (35.48)	81.29	62.58	38.71	1.29	NR
Rong-Hui et al ³⁵	179	97	82	57.6	NR	98.88	81.56	39.66	49.72	18.99
Chen et al ³⁶	274	171	103	62	113 (41.24)	90.88	67.52	50.00	NR	21.90
Deng et al ³⁷	225	73	152	69	NR	42.22	20.89	13.33	34.22	13.33
Wang et al ³⁸	339	166	173	69	65 (19.17)	91.74	52.80	39.82	40.71	4.72
Total	5390	2997	2393	-	974	-	-	-	-	-
Overall Prevalence (95% CI)						88.47	64.65	38.45	23.59	22.46
I² (%)						(80.74, 93.35)	(58.42, 70.43)	(32.52, 44.74)	(16.48, 32.58)	(16.36, 30.02)
p for heterogeneity						98	94	94	92	91
						<i>p</i> < 0.01	<i>p</i> < 0.01	<i>p</i> < 0.01	<i>p</i> < 0.01	<i>P</i> < 0.01

Note: Meta-analysis for the prevalence was calculated from binary random-effects model analysis (see, Figure I for details).

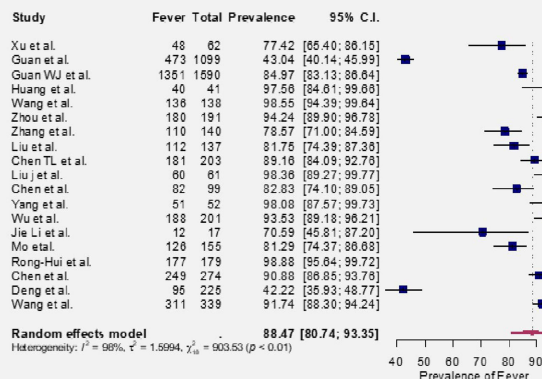
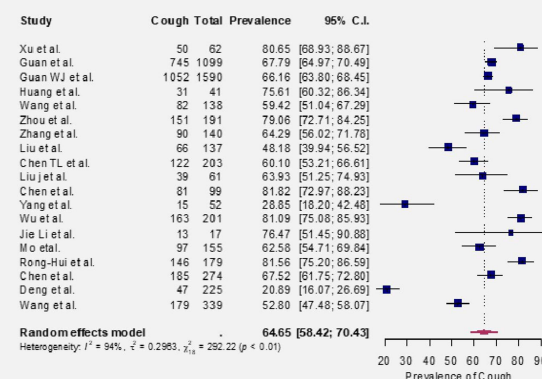
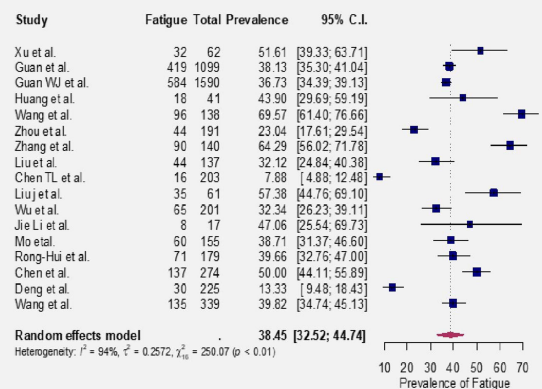
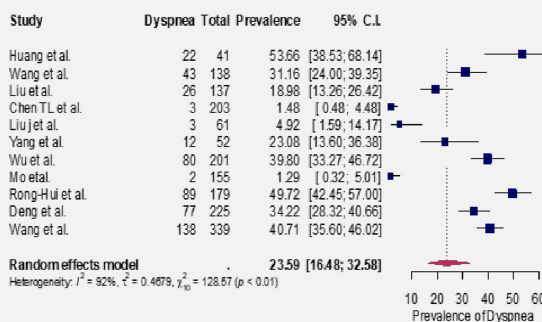
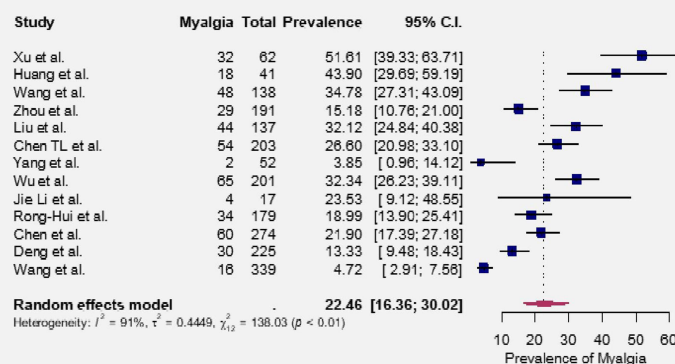
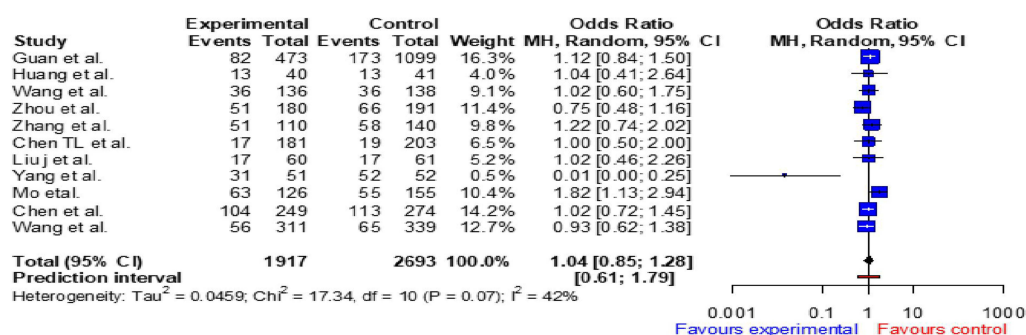
A Fever**B Cough****C Fatigue****D Dyspnoea****E Myalgia**

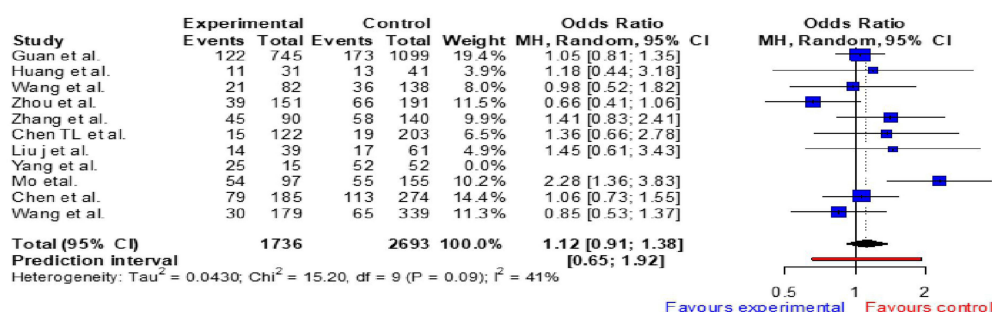
Figure 2 Meta-Analysis of symptoms of COVID-19. **A–E** represent the prevalence of fever, cough, fatigue, dyspnoea and myalgia, respectively.

Our meta-analysis found that fever is the predominantly reported clinical manifestation in COVID-19 confirmed cases. This was followed by cough, myalgia or fatigue and less proportionally dyspnea and headache. Furthermore, we identified that most of the included studies were limited to middle-aged to older adults, and commonly included male.

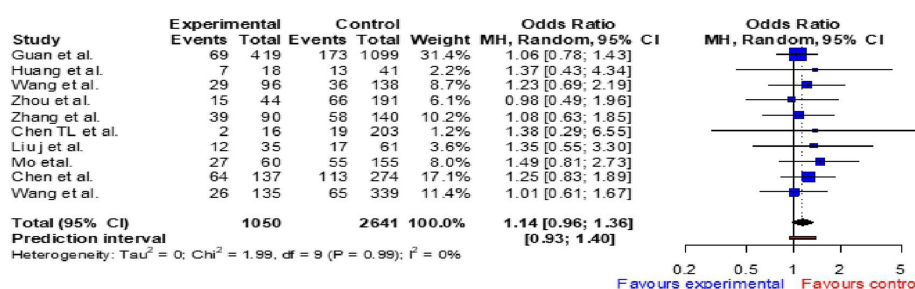
A Fever



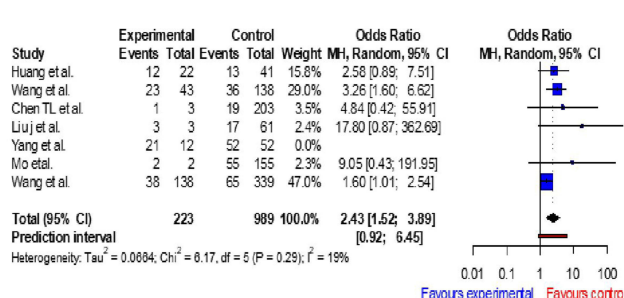
B Cough



C Fatigue



D Dyspnoea



E Myalgia

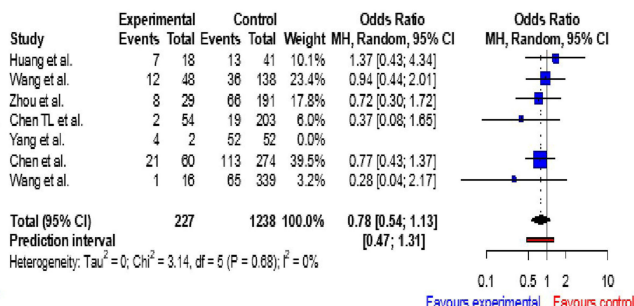


Figure 3 Meta-Analysis representing severity of symptoms in COVID-19 patients. **A–E** represent Mantel-Haenszel (MH) odds ratio of fever, cough, fatigue, dyspnoea and myalgia, respectively.

Notes: In all figures, “Experimental Events” represents the no. of severe patients having corresponding symptom; “Control Events” represents all the severe patients reporting in the particular study.

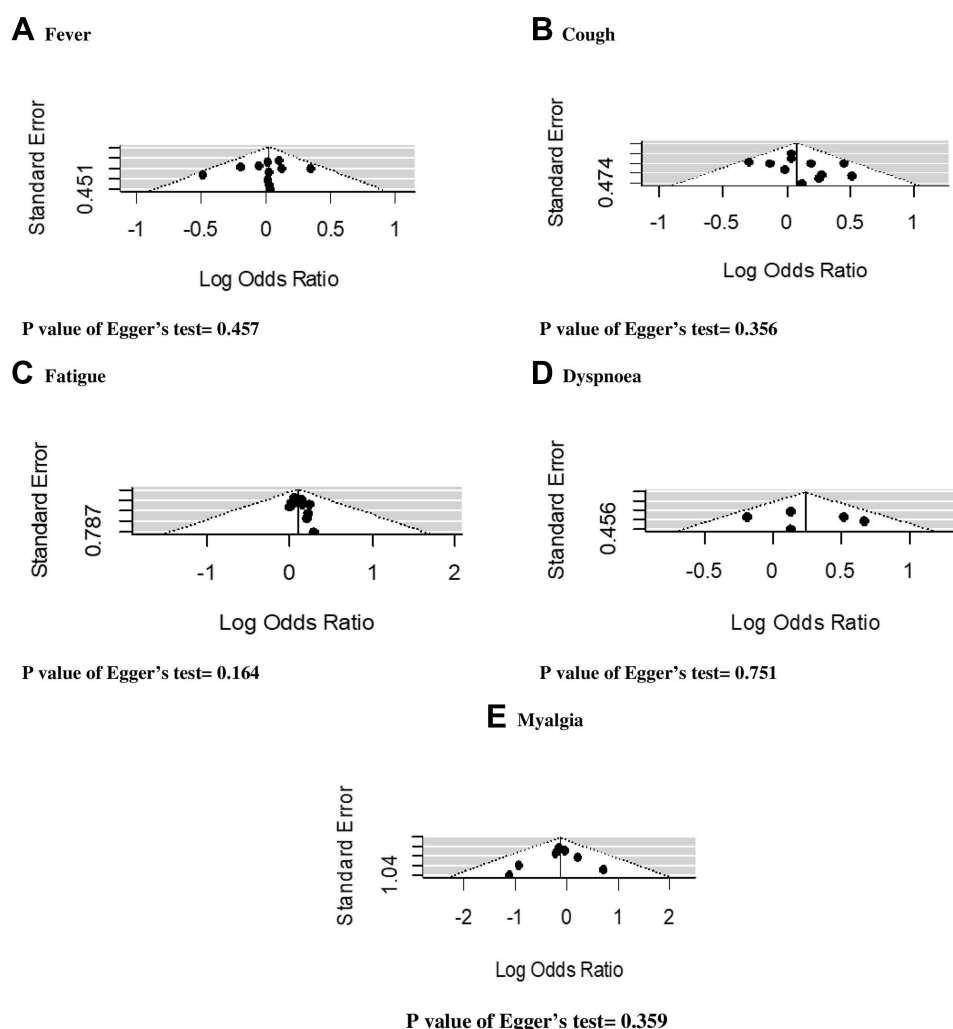


Figure 4 Funnel plot with Egger's test for assessing publication bias. (A) Fever; (B) cough; (C) fatigue; (D) dyspnoea; (E) myalgia.

Our finding is consistent with previous systematic review and meta-analysis that reported significantly higher prevalence of fever and less commonly cough, fatigue and headache (all $p < 0.05$).^{39,40} The prevalence of fever was 92% (95% CI: 89.4–96.2)²⁷ and 83.3% (95% CI: 78.4–87.7),³⁹ while we found fever in 87.89% (95% CI: 83.22–81.39%). However, we only included adults, while the previous studies also included children. The frequency of fever in COVID-19 patients on admission is similar in SARS and MERS outbreak, but the prevalence of cough is higher in SARS and COVID-19, compared to MERS.^{41,42}

Despite a comprehensive analysis, several limitations should be taken into consideration in our study. Firstly, we only included studies from the Wuhan, which limits the number of studies, as well as clinical and demographic characteristics of patients, may be different from other parts of the world, in particular, we were unable to include clinical studies from Europe and America. This also limits the geographical and ethnic differences that were not excluded. Secondly, in the pooled analysis, the varying treatment pattern from the hospitals could not be identified, which could vary greatly. Finally, substantial heterogeneities were predominantly observed in several parameters in the meta-analysis given the variation of patient recruitment, intervention technique and treatment provided.

Further Study

This is a study conducted at the early stage of COVID 19 outbreak. Therefore, we were not able to get enough information regarding the disease. However, in the future, we will be able to conduct the meta-analysis with more

information. We believe that meta-analysis with more information can help us to better identify the association between symptoms and severity of disease in hospitalized novel coronavirus (COVID-19) patients.

Conclusion

Our review suggests that dyspnoea is associated with the severity of COVID-19. Therefore, besides the new onset of such symptom, people with existing respiratory illnesses, such as chronic obstructive pulmonary diseases, need to be careful about the onset of such symptom and should seek medical attention early.

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Disclosure

The authors declare that they have no known competing interests.

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