Alarming Symptoms Leading To Severe COVID-19 Pneumonia: A Meta-Analysis

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Abstract

Background: To identify alarming symptoms that could potentially lead to severe form of COVID-19 pneumonia (i.e. novel coronavirus pneumonia: NCP), a disease that is now having pandemic spread.

Methods: Articles from PubMed, Embase, Cochrane database and Google up to 24 February 2020 were systematically reviewed. 18 publications that had documented cases of COVID-19 pneumonia were identified. The relevant data were extracted, systematically reviewed and further evaluated using meta-analysis. We define severe COVID-19 pneumonia as the disease status that requires admission to the intensive care unit (ICU) and respiratory/circulatory support, which is in align with the guideline from the World Health Organization (WHO).

Results: 14 studies including 1,424 patients were considered eligible and analyzed. Symptoms such as fever (89.2%), cough (67.2%), fatigue (43.6%) were quite common; but dizziness, hemoptysis, abdominal pain and conjunctival congestion/conjunctivitis were relatively rare. The incidence of dyspnea was significantly higher in patients with severe than non-severe COVID-19 pneumonia (42.7% vs.16.3%, $p<0.0001$). Similarly, fever and diarrhea were also drastically more common in patients with severe form ($p=0.0374$ and 0.0267). Further meta-analysis using three high-quality China-based studies confirmed such findings and showed that dyspnea, fever and diarrhea were 3.53 (OR: 3.53, 95%CI: 1.95-6.38), 1.70 (OR: 1.70, 95%CI: 1.01-2.87), and 1.80 (OR: 1.80, 95%CI: 1.06-3.03) folds higher respectively in patients with severe COVID-19 pneumonia.

Conclusion: Dyspnea, fever and diarrhea are significantly more prevalent in patients with severe COVID-19 pneumonia, suggesting they are alarming symptoms that warrant close attention and timely management.

Background

In December 2019, a series of mystical pneumonia cases appeared and soon followed by an outbreak in Wuhan China, with clinical manifestations similar to those of viral pneumonia[1]. It was soon discovered that this virus outbreak was due to a novel coronavirus which is now named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2]. At present, this novel coronavirus caused disease (COVID-19) has spread throughout China and is rapidly sweeping through countries all over the world[3–5]. Human-to-human transmission of this virus is clearly proven[6, 7]. The clinical presentation of COVID-19 pneumonia can be very diversified, and in severe cases it could present as acute respiratory distress syndrome (ARDS) that is often followed by death[8–11].

Methods

Sources and search criteria

We conducted a comprehensive systematic search in PubMed, Embase, Cochrane database and Google to identify all published studies that describe the clinical characteristics of COVID-19 pneumonia, using the search terms “novel coronavirus”, “SARS-CoV-2”, “COVID-19” and “novel coronavirus pneumonia”. Two independent researchers then reviewed all the results, selected and classified the studies.

Inclusion and exclusion criteria

Publications must have described clinical signs and symptoms of COVID-19 pneumonia. If there were duplicates of study population, the publication with the largest sample size was used. Studies that did not describe the clinical features of COVID-19 pneumonia, as well as those were duplicated, were excluded. Articles published by the same author were carefully screened to rule out duplication.

Data extraction and analysis

All studies that met the above-mentioned criteria were carefully analyzed and strictly reviewed. We collected relevant clinical information including the population data (e.g. age, gender), number of patients in the studies, and documented clinical manifestations. Full-text versions of relevant articles were reviewed, and clinical characteristics were extracted. The Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the quality of included studies[12]. A scale ranges from 0 to 9, with higher points indicating higher quality was applied. The two authors (WJ and XG) used a unified data table to extract data independently, and resolved controversial issues through further discussion. We define severe COVID-19 pneumonia as the disease status that requires ICU admission with respiratory/circulatory support[10, 11, 13, 14]. We compared the clinical characteristics of severe and non-severe COVID-19 pneumonia, followed by a meta-analysis using three high quality China-based studies.

Statistical analysis

SAS 9.4 and Review Manager 5.3 software were used for analysis and data presentation. Continuous variables were represented by median and interquartile range (IQR). Classification variables were summarized as counts and percentages in each category. The age, gender, number and clinical signs of COVID-19 pneumonia patients were statistically described. Cochran-mantel-Haenszel test (stratified chi-square test) was used to compare the differences between severe and non-severe forms of COVID-19 pneumonia. With odds ratio (OR) as the effect size we used Mantel-Haenszel test with fixed or random effect for further meta-analysis of the clinical signs, and presented using the forest map. The study precision/bias was measured using the funnel plot.

Results

Search result

A total of 333 relevant publications on PubMed and other databases were identified. 68 were removed because of duplication, and 224 were removed based on above-mentioned inclusion/exclusion criteria. 23 publications did not report clinical signs, and four were excluded due to overlapped cases[8, 9, 15, 16]. Finally, 14 articles were included for analysis[10, 11, 13, 17–27]. Figure 1 is the study selection flowchart. Data from all eligible studies were obtained from published manuscripts.

Synthesis of results

A systematic review showed that 610 patients (42.8%) with COVID-19 pneumonia were female. Fever (89.2%) and cough (67.2%) were the most common symptoms, followed by fatigue (43.6%), phlegm (28.6%), and shortness/difficulty of breathing (21.7%). The less common symptoms were dizziness (0.9%), hemoptysis (0.8%), abdominal pain (0.8%), and conjunctiva congestion/conjunctivitis (0.7%). 1,377 cases were divided into groups of severe (1,110) and non-severe COVID-19 pneumonia (267). Stratified chi-square test showed that there was no significant difference in gender between the two groups ($p > 0.05$), and the median age of severe patients was slightly older (details in Table 2). Dyspnea in patients of severe group was significantly more common than that in non-severe group (42.7% vs.16.3%, $p < 0.0001$). The incidence of fever and diarrhea were also significantly higher in severe group ($p = 0.0374$ and 0.0267 respectively). Although conjunctival congestion/conjunctivitis ($p = 0.0176$), hemoptysis ($p = 0.0344$), anorexia ($p = 0.0008$), dizziness ($p = 0.0023$) and abdominal pain ($p = 0.0015$) all appeared to be much more common in severe patients, as the dates of these symptoms were only reported in one or two literatures, the inter-group comparisons of these symptoms should be treated with caution. (See Tables 1 and 2)

Table 1

A summary of clinical presentations from COVID-19 pneumonia*

	Article 1 [10] N = 1099	Article 2 [11] N = 138	Article 3 [13] N = 140	Article 4 [17] N = 13	Article 5 [18] N = 15	Case reports summary (9 articles [19–27]) N = 19	Total N = 1424
Age,median (IQR or range)	47.0 (35.0–58.0)	56 (42–68)	57 (25–87)	34 (34–48)	43 (8–66)	31 (1–49)	-
Gender, n (%)	459 (41.8)	63 (45.7)	69/140 (49.3)	3 (23.1)	6 (40.0)	10 (52.6)	610 (42.8)
Fever, n (%)	966 (87.9)	136 (98.6)	110/120 (91.7)	12 (92.3)	14 (93.3)	15 (78.9)	1253 (89.2)
Cough,n (%)	744 (67.7)	82 (59.4)	90/120 (75.0)	6 (46.2%)	11 (73.3)	11 (57.9)	944 (67.2)
Sore throat,n (%)	153 (13.9)	24 (17.4)	-	-	7 (46.7)	3 (15.8)	187 (14.7)
Sputum,n (%)	367 (33.4)	37 (26.8)	-	2 (15.4)	-	1 (5.3)	407 (32.1)
Fatigue,n (%)	419 (38.1)	96 (69.6)	90/120 (75.0)	-	4 (26.7)	3 (15.8)	612 (44.0)
Dyspnea,n (%)	204 (18.6)	43 (31.2)	44/120 (36.7)	8 (61.5)	1 (6.7)	5 (26.3)	305 (21.7)
Nausea/vomiting,n (%)	55 (5.0)	14 (10.1)	24/139 (17.3)	-	1 (6.7)	2 (10.5)	96 (6.8)
Diarrhea,n (%)	41 (3.7)	14 (10.1)	18/139 (12.9)	1 (7.7)	5 (33.3)	3 (15.8)	82 (5.8)
Muscle/joint pain,n (%)	163 (14.8)	48 (34.8)	-	3 (23.1)	2 (13.3)	4 (21.1)	220 (17.1)
Chilly,n (%)	125 (11.4)	-	-	-	-	3 (15.8)	128 (11.4)
Headache,n (%)	150 (13.6)	9 (6.5)	-	3 (23.1)	3 (20.0)	1 (5.3)	166 (12.9)
Nasal discomfort (congestion, overflow, runny),n (%)	53 (4.8)	-	-	1 (7.7)	5 (33.3)	6 (31.6)	64 (5.6)
Conjunctival congestion/conjunctivitis,n (%)	9 (0.8)	-	-	-	-	1 (5.3)	10 (0.9)
Hemoptysis,n (%)	10 (0.9)	-	-	-	-	1 (5.3)	11 (1.0)
Apocleisis,n (%)	-	55 (39.9)	17/139 (12.2)	-	-	-	72 (26.0)
Dizzy,n (%)	-	13 (9.4)	-	-	-	-	13 (9.4)
Abdominal pain,n (%)	-	3 (2.2)	8/139 (5.8)	-	-	-	11 (4.0)

*If certain clinical sign/symptoms was not reported, case “0” was used for analysis. Article 3 clearly stated that not all the data from 140 patients were collected (e.g., the fever data was collected from only 120 patients). Therefore the actual documented cases were used for calculation.

Table 2

The comparison of clinical features from severe vs. non-severe COVID-19 pneumonia*

	Article 1 [10]		Article 2 [11]		Article 3 [13]		Total		*P* value
	Non-severe (N = 926)	Severe (N = 173)	Non-severe (N = 102)	Severe (N = 36)	Non-severe (N = 82)	Severe (N = 58)	Non-severe (N = 1110)	Severe (N = 267)	
Age,median (IQR or range)	45.0 (34.0–57.0)	52.0 (40.0–65.0)	51 (37–62)	66 (57–78)	51.5 (26–78)	64 (25–87)	-	-	-
Gender,n (%)	386 (41.7)	73 (42.2)	49 (48.0)	14 (38.9)	44/82 (53.7)	25/58 (43.1)	479/1110 (43.2)	112/267(41.9)	0.4588
Fever,n (%)	808 (87.3)	158 (91.3)	100 (98.0)	36 (100)	59/67 (88.1)	51/53 (96.2)	967/1095 (88.3)	245/262 (93.5)	0.0374
Cough,n (%)	622 (67.2)	122 (70.5)	61 (59.8)	21 (58.3)	45/67 (67.2)	45/53 (84.9)	728/1095(66.5)	188/262 (71.8)	0.1418
Sore throat,n (%)	130 (14.0)	23 (13.3)	12 (11.8)	12 (33.3)			142/1028 (13.8)	35/209 (16.7	0.3136
Sputum,n (%)	306 (33.0)	61 (35.3)	29 (28.4)	8 (22.2)			335/1028 (32.6)	69/209 (33.0)	0.7974
Fatigue,n (%)	350 (37.8)	69 (39.9)	67 (65.7)	29 (80.6)	51/67 (76.1)	39/53 (73.6)	468/1095 (42.7)	137/262(52.3)	0.3552
Dyspnea,n (%)	139 (15.0)	65 (37.6)	20 (19.6)	23 (63.9)	20/67 (29.9)	24/53 (45.3)	179 /1095(16.3)	112/262 (42.7)	< 0.0001
Nausea/vomiting,n (%)	43 (4.6)	12 (6.9)	10 (9.8)	4 (11.1)	19/82 (23.2)	5/57 (8.8)	72/1110 (6.5)	21/266 (7.9)	0.7600
Diarrhea,n (%)	31 (3.3)	10 (5.8)	8 (7.8)	6 (16.7)	9/82 (11.0)	9/57 (15.8)	48/1110 (4.3)	25/266 (9.4)	0.0267
Muscle/joint pain,n (%)	133 (14.4)	30 (17.3)	36 (35.3)	12 (33.3)	-	-	169/1028 (16.4)	42/209 (20.1)	0.4404
Chilly,n (%)	99 (10.7)	26 (15.0)	-	-	-	-	99/926 (10.7)	26/173 (15.0)	0.0992
Headache,n (%)	124 (13.4)	26 (15.0)	6 (5.9)	3 (8.3)	-	-	130/1028 (12.6)	29/209(13.9)	0.4836
Nasal discomfort (congestion, overflow, runny),n (%)	47 (5.1)	6 (3.5)	-	-	-	-	47/926 (5.1)	6/173 (3.5)	0.3652
Conjunctival congestion/conjunctivitis,n (%)	5 (0.5)	4 (2.3)	-	-	-	-	5/926 (0.5)	4/173 (2.3)	0.0176
Hemoptysis,n (%)	6 (0.6)	4 (2.3)	-	-	-	-	6/926 (0.6)	4/173 (2.3)	0.0344
Apocleisis,n (%)	-	-	31 (30.4)	24 (66.7)	9/82 (11.0)	8/57 (14.0)	40/184 (21.7)	32/93 (34.4)	0.0008
Dizzy,n (%)	-	-	5 (4.9)	8 (22.2)	-	-	5/102 (4.9)	8/36 (22.2)	0.0023
Abdominal pain,n (%)	-	-	0 (0)	3 (8.3)	2/82 (2.4)	6/57 (10.5)	2/184 (1.1)	9/93 (9.7)	0.0015

*Symptoms such as conjunctival congestion/conjunctivitis, hemoptysis, anorexia, dizziness, and abdominal pain, etc. were documented in only some of the studies. Therefore, only studies that reported were included in the final analysis of the relevant symptoms.

Meta-analysis results

Three high-quality studies, all of which were from China and clearly classified COVID-19 pneumonia as severe and non-severe were used for subsequent meta-analysis. When used to study fever, these studies included in total 262 cases in the severe group (245 cases with fever, 93.51%) and 1,095 cases in the non-severe group (967 cases with fever, 88.31%), and were considered to be homogeneous as they fit the fixed effect model nicely ($Chi^2 = 0.88$, $P = 0.64$, $I^2 = 0\%$). The pooled effect was 1.70 (95%CI, 1.01–2.87; Fig. 2A), indicating that the incidence of fever in the severe group was 1.70 times higher than that of non-severe group. On symptoms of dyspnea, there were 262 cases in the severe group (112 dyspnea, 42.75%) and 1095 cases in the non-severe group (179 dyspnea, 68.32%). Q-test and I^2 statistic test showed that certain heterogeneity exists ($Chi^2 = 5.26$, $P = 0.07$, $I^2 = 62\%$), therefore the random effect model was adopted. The individual OR effect showed inconsistently that *Article 1* and *Article 2* show the severe patients have a higher incidence of dyspnea and *Article 3* shows there is no statistically significant difference, but combined OR effect was 3.53 (95%CI, 1.95–6.38; Fig. 2B), indicating that the incidence of dyspnea in the severe group was 3.53 times higher than that of non-severe group. On symptoms of diarrhea, we included 266 cases in the severe group (25 cases with diarrhea, 9.40%) and 1,110 cases in the non-severe group (48 cases with diarrhea, 4.32%). Model test showed homogeneity among these studies ($Chi^2 = 0.32$, $P = 0.85$, $I^2 = 0\%$), and therefore the fixed effect model was used. The combined OR value was 1.80 (95%CI, 1.06–3.03; Fig. 2C), indicating the incidence of diarrhea in the severe group was 1.80 times higher than that of non-severe group. Importantly, the funnel plots of fever, dyspnea and diarrhea are all largely symmetrical, suggesting no significant publication deviation exists (Fig. 3).

Discussion

To our knowledge, this is among the first systematic review and arguably the first meta-analysis of China-based studies comparing the clinical symptoms between patients with severe vs. non-severe form of COVID-19 pneumonia. We observed no gender difference, which is consistent with the latest report[11, 13, 15, 16]. Although fever and cough are relatively common symptoms, we found the incidences of fever, dyspnea and diarrhea are all significantly higher in patients with severe COVID-19 pneumonia, suggesting they could be alarming symptoms that worth extra medical attention. Although our findings in dyspnea were similar to previous reports[10, 11], we have to point out that certain discrepancy exists: for example, some reported no difference in the incidence of fever and diarrhea[10, 11, 13], or even dyspnea[13]. One possible explanation is that in those reports, the sample size was relatively small and studies were reported at relatively early phase of this pandemic COVID-19 pneumonia.

The early symptoms/signs of COVID-19 pneumonia can be indistinguishable from those of other common respiratory infectious diseases, and could exhibit certain similarities to those of severe acute respiratory syndrome associated coronavirus (SARS-CoV) and middle East respiratory syndrome coronavirus (MERS-CoV) infections[28, 29]. However, patients with COVID-19 rarely had obvious signs and symptoms of upper respiratory tract (e.g. nasal obstruction, rhinorrhea, runny nose, sore throat). In addition, intestinal signs and symptoms such as diarrhea were less common in COVID-19 pneumonia patients (below 10% even in severe form), while about 20–25% of patients with MERS-CoV or SARS-CoV infection presented with diarrhea[29]. It should be noted however that fever in COVID-19 pneumonia patients (10.8%) was more common than SARS-CoV (1%) and MERS-CoV (2%)[30].

As COVID-19 pneumonia can have a full spectrum of clinical presentations, it is therefore crucially important to recognize alarming symptoms that signal progression to severe form[14], as such information will not only help us better triage our patients, but also wisely use our medical resources which are often in shortage during pandemic crisis. This study has clearly shown that fever, dyspnea and diarrhea could be such alarming symptoms that warrant timely medical attention. However certain limitation exists in this study: 1) since most data are from retrospective studies and case reports, which intend to report successful management, selection bias could exist. However, considering some studies reported that most patients were still hospitalized at the time of publication (for example, 93.6% (1029/1099) in *Article 1* and 61.6% (85/138) in *Article 2*, Fig. 2), the selection bias could have little impact; 2) the data collection in some cases is not complete, especially for rare symptoms such as hemoptysis and conjunctivitis, hence the statistical power should be carefully interpreted for those symptoms; 3) from data analysis perspective using published studies, although symmetry was observed, it is challenging to evaluate publication bias due to limited number of studies included. However, since COVID-19 is new disease entity, both positive and negative results will likely have the chance to be published, which should theoretically reduce the publication bias for future secondary analysis.

Conclusion

Fever, dyspnea and diarrhea were significantly more common in patients with severe COVID-19 pneumonia, suggesting they are alarming symptoms that warrant urgent medical attention.

Abbreviations

NCP: novel coronavirus pneumonia; ARDS: acute respiratory distress syndrome; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; NOS: Newcastle-Ottawa quality assessment scale; IQR: interquartile range; OR: odds ratio; SARS-CoV: severe acute respiratory syndrome associated coronavirus; MERS-CoV: middle East respiratory syndrome coronavirus

Declarations

Ethical approval

Not obtained as this is a systematic review and meta-analysis of published studies.

Consent for publication

Consent from patients not obtained due to reason above. All authors approved for the submission of the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

WJ, JZ, XG designed and wrote the initial draft; GB and XD extracted data; ZC and XC performed data verification and statistical analysis; JZ and XS criticized and revised the manuscript. All authors reviewed and approved the final article.

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CRediT authorship contribution statement

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Figures

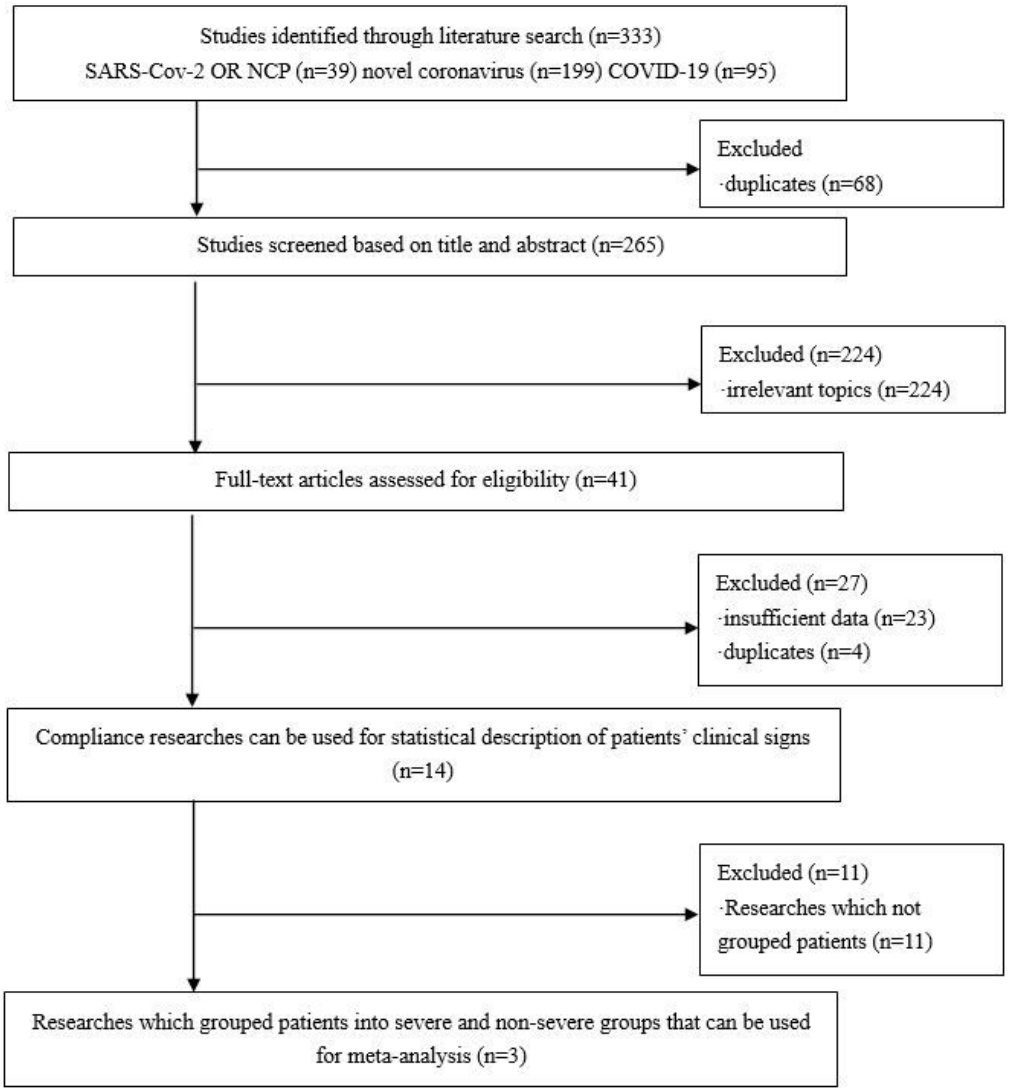

Figure 1

The flowchart of selecting studies for this analysis. Careful screening and stringent criteria were used.

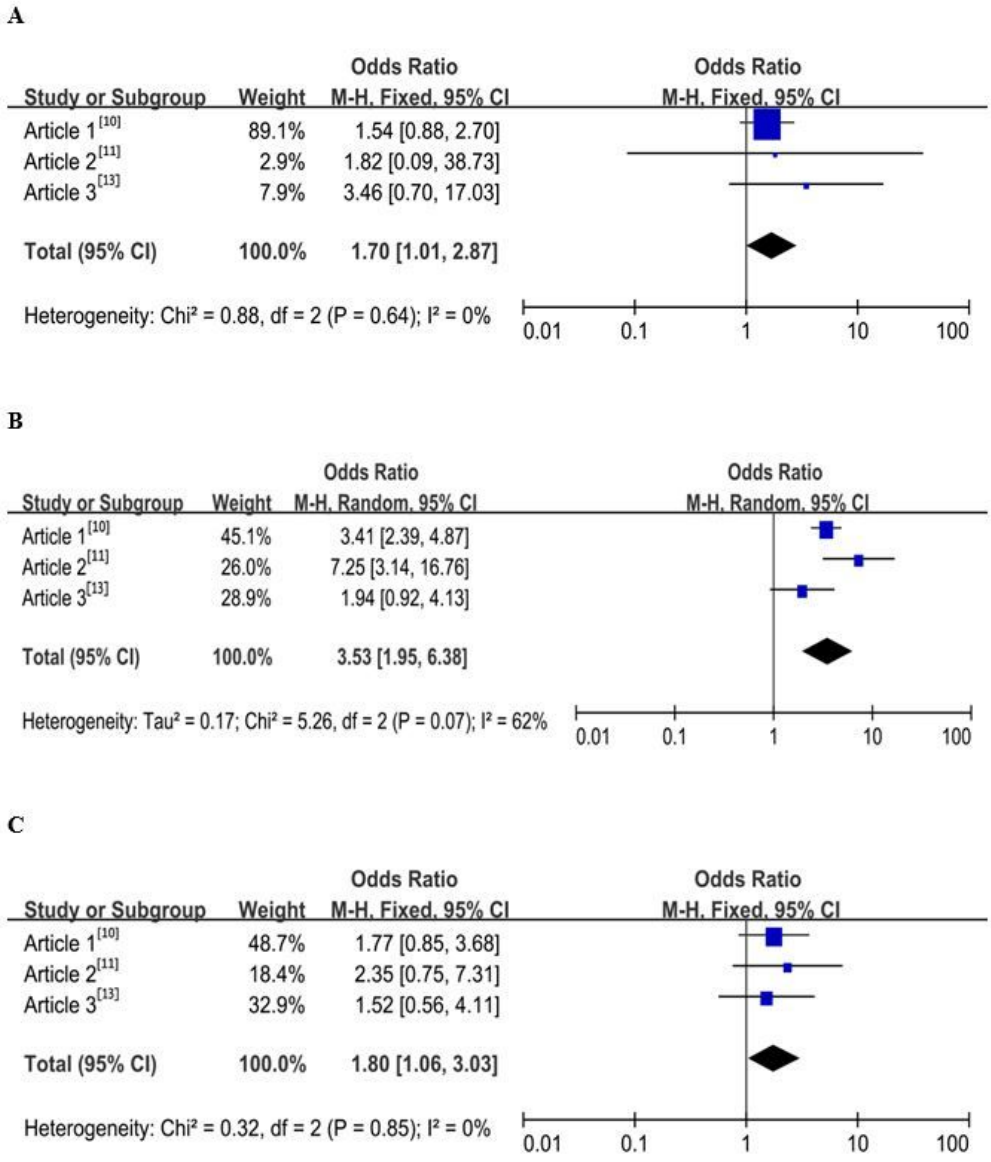

Figure 2

The forests plots of fever (A), dyspnea (B) and diarrhea (C). In all cases, these symptoms were found significantly enriched in patients with severe COVID-19 pneumonia.

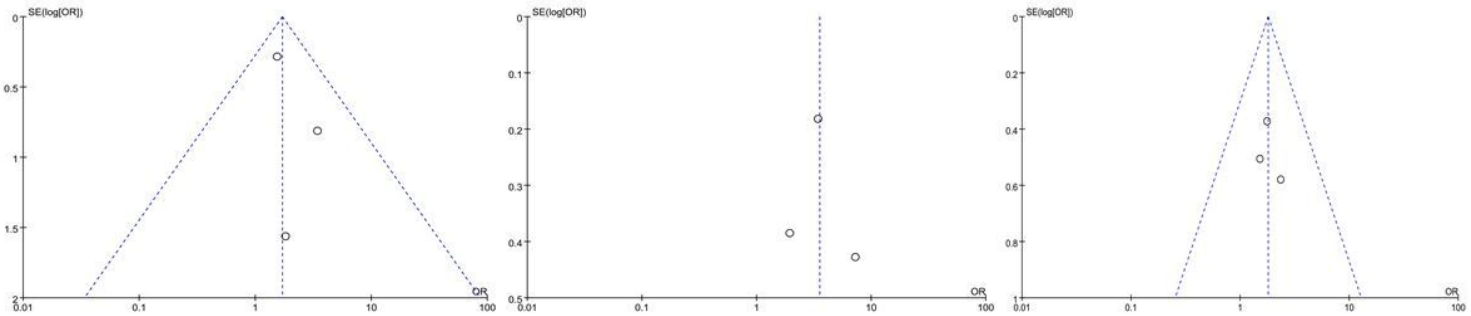

Figure 3

The funnel plot of fever, dyspnea and diarrhea. They are all largely symmetrical, suggesting no significant publication deviation exists.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009FlowDiagramMSWord.doc
- PRISMA2009ChecklistMSWord.doc