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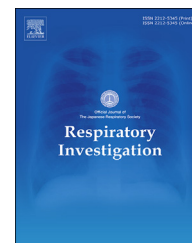
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## Original article

# Trends in clinical features of novel coronavirus disease (COVID-19): A systematic review and meta-analysis of studies published from December 2019 to February 2020

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## ABSTRACT

**Background:** Since novel coronavirus disease (COVID-19) emerged, various clinical features of COVID-19 have been reported.

**Methods:** We conducted a systematic review of published studies reporting the clinical features of COVID-19. Two investigators independently searched PubMed (December 2019–February 2020) for eligible articles. A meta-analysis was performed to measure the frequencies of clinical outcomes and symptoms of COVID-19. A stratified analysis was conducted according to the timeline of outbreak and exposure histories: Group I, most patients were exposed to the Hunan seafood wholesale market and lived in Wuhan, Hubei province; Group II, patients lived in Hubei province but were not directly exposed to the market; and Group III, patients lived outside Hubei.

**Results:** Thirteen studies, all from China, were eligible. The estimated mortality rate among all studies was 2.12%, but that in Group I was 8.66%. The incidence of acute respiratory distress syndrome in Group I was 20.00%. Both fever and cough were major symptoms, and their frequencies were higher in Group I than in Groups II and III, while the frequency of diarrhea in Group I was lower than that in Group III. The estimated frequency of dyspnea in Group I was 37.18%, while those in Groups II and III were 16.95% and 7.03%, respectively.

**Conclusions:** The trends in the clinical features of COVID-19 changed from December 2019 to February 2020. During this observation period, as the infection continued to spread, the clinical conditions for majority of patients became less severe with the changes in the route of transmission.

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**Abbreviations:** COVID-19, novel coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus; WHO, World Health Organization.

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## 1. Introduction

In December 2019, an acute respiratory illness, now known to be caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), occurred in Wuhan, the capital city of Hubei province, China [1–3]. The disease caused by the virus was termed COVID-19, and it rapidly spread from Wuhan to the rest of China and other countries. On March 11, 2020, the World Health Organization (WHO) declared that COVID-19 can be characterized as a pandemic [4]. The WHO-China Joint Mission recently summarized the prognosis, signs, and symptoms of COVID-19 and indicated that 13.8% of patients had severe disease, while approximately 80.0% of patients had mild to moderate disease [5]. However, in the early stage of the COVID-19 outbreak in China, serious pneumonia that led to acute respiratory distress syndrome (ARDS) and death was reported [2,6]. Most of these patients had an epidemiological link to the Hunan seafood wholesale market in Wuhan city [2,6]. The disease thereafter spread within and beyond China, and both mild and asymptomatic cases have since been reported [7], as have various transmission routes including sustained human-to-human transmission [8–10], transmission from an asymptomatic patient [11], and transmission from a pre-symptomatic patient [12]. In addition, a study on the pneumonia presenting with COVID-19 in Wuhan indicated that the differences in exposure risks depended on time points between December and January [13]. Currently, the number of countries and individual people affected by COVID-19 have been rapidly increasing worldwide [14]. We hypothesized that changes in the exposure risks and timeline of the outbreak influence the clinical features of COVID-19, including the disease severity. Elucidation of the patterns of change in the disease features of COVID-19 is crucial for discussing the clinical response to and control measures for COVID-19.

Thus, the purpose of the present study was to elucidate the clinical features of COVID-19 using a meta-analysis with a stratified analysis according to the timeline and the changes in the exposure risks before the disease was declared as a pandemic.

## 2. Materials and methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the statement by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group [15,16].

### 2.1. Search strategy

Two investigators (T.M. and H.A.) independently searched for eligible studies in PubMed published from December 2019 to March 1, 2020. We used the following key words: “novel coronavirus” OR “new coronavirus” OR “emerging coronavirus” OR “2019-nCoV” OR “COVID-19” OR “SARS-CoV-2.” The

search was limited to studies written in English. We also reviewed the reference lists of eligible studies using Google Scholar and performed a manual search to ensure that all appropriate studies were included.

### 2.2. Eligibility criteria and outcome measures

Studies fulfilling the following selection criteria were included in the meta-analysis: (1) study design and language: cohort studies and case series involving >20 patients written in English; (2) population: patients with SARS-CoV-2 infection who were hospitalized or treated in clinics; (3) primary outcome variables: distributions of clinical outcomes, including death, ARDS, acute cardiac injury, and acute renal injury in patients with COVID-19; and (4) secondary outcome variables: distributions of sex, comorbidities, symptoms, and signs. Studies were excluded based on the following criteria: (1) reporting of surveillance data, (2) no reporting of outcome variables, (3) no clear determination of the epidemiological exposure history of patients, and (4)  $\leq 20$  patients.

A stratified analysis was conducted according to the exposure history and the timeline of the COVID-19 outbreak: Group I, most patients were exposed to the Hunan seafood wholesale market in the initial stage of the outbreak; Group II, patients lived in Hubei province but could not be linked to the Hunan seafood wholesale market or community exposure after 1 January; and Group III, patients lived outside of Hubei province.

### 2.3. Data extraction

Two reviewers extracted the data independently. Articles retrieved in the search were stored in a citation manager (EndNote X8; Thomson Reuters, New York, NY, USA). After removing redundant articles, titles and abstracts and then full-text articles were investigated. We extracted the following data: study design, observational period, study site, and inclusion/exclusion criteria of each study. Outcome variables were extracted into predesigned data collection forms. We verified data accuracy by comparing the collection forms of each investigator; any discrepancies were resolved through discussion together with other authors.

### 2.4. Data analysis

Throughout the meta-analysis, we calculated the prevalence of each outcome variable with 95% confidence intervals (CIs) using a random-effects model (generic inverse variance method). To assess the prevalence of each variable among patients with COVID-19, the standard error was calculated using the Agresti–Coull method [17]. Heterogeneity among the original studies was evaluated using the  $I^2$  statistic [18]. Publication bias was examined using a funnel plot. For all analyses, significance levels were two-tailed, and  $p < 0.05$  was considered significant. All statistical tests were performed using Review Manager (RevMan) ver. 5.3.5 (Cochrane Collaboration, Copenhagen, Denmark) [19].

### 3. Results

#### 3.1. Study selection and characteristics

Of the 482 references screened, 13 studies [2,6,7,20–29] reported the outcome variables (Fig. 1). In these 13 studies, we identified 2397 patients with COVID-19, and all eligible studies were reports from China. Among the 13 eligible studies, 3 [2,6,20] were identified as Group I ( $n = 279$ ), 3 [21–23] were identified as Group II ( $n = 1356$ ), and 7 [7,24–29] were identified as Group III ( $n = 743$ ) (Table 1).

Table 1 shows the characteristics of the included studies. The observational period (initial to end of observation date) in the eligible studies for each group was December 19, 2019 to January 28, 2020 in Group I, December 30, 2019 to January 31, 2020 in Group II, and January 17, 2020 to February 14, 2020 in Group III. The age distribution was similar in all studies, and the median or mean age was around 50 years. The frequency

of male patients among all groups or each group was estimated using a meta-analysis. The estimated frequency of male patients in all 13 eligible studies was 51.91% (95% CI, 48.08–55.75); however, the subgroup analysis showed that the estimated frequency of male patients decreased from Group I (64.30%; 95% CI, 53.11–75.49) to Group III (52.12%; 95% CI, 48.75–55.52) (Supplementary Fig. S1).

The frequency of comorbidities in patients with COVID-19 was estimated and compared among the three groups (Table 2; Supplementary Fig. S2i - S2viii). Hypertension (17.08%) showed the highest frequency among observed comorbidities, followed by cerebrovascular disease (8.26%), diabetes (7.98%), and cardiovascular disease (7.69%). The frequencies of hypertension, cardiovascular disease, and diabetes in Group I was higher than those in Groups II and III, while the estimated frequencies of cerebrovascular disease (16.79%) and chronic liver disease (2.81%) in Group I were lower than those in Groups II and III.

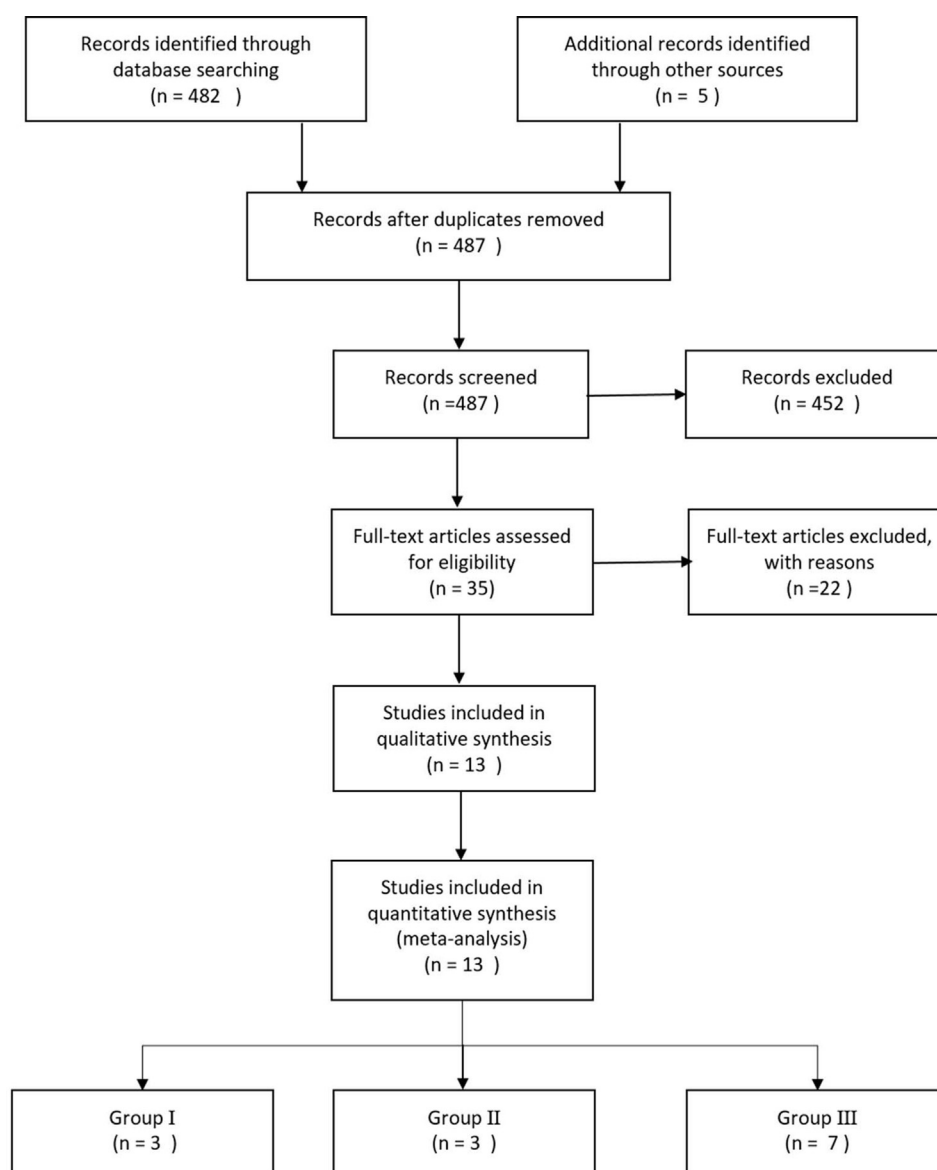


Fig. 1 – Systematic review flow diagram. n is the number of articles.

**Table 1 – Backgrounds of patients with COVID-19 in the eligible studies.**

Study (publication date)	Province in China	Observational period	No. of patients	Exposure history to Hunan Seafood Wholesale Market in Wuhan, n (%)	Sex-male, n (%)	Age, median (IQR), yr.
Group 1						
Huang C [2] (Jan 24, 2020)	Hubei	Dec 16, 2019–Jan 2, 2020	41	27 (66)	30 (73.1)	49.0 (41.0–58.0)
Chen N [6] (Jan 29, 2020)	Hubei	Jan 1, 2020–Jan 20, 2020	99	49 (49)	67 (67.7)	55.5 (13.1) <sup>a</sup>
Wang D [20] (Feb 7, 2020)	Hubei	Jan 1, 2020–Jan 28, 2020	138	12 (8.7)	75 (54.3)	56 (42–68)
Group 2						
Liu K [21] (Feb 7, 2020)	Hubei	Dec 30, 2019–Jan 24, 2020	137	None	61 (44.5)	57 (range, 20–83)
Zhang JJ [22] (Feb 19, 2020)	Hubei	Jan 16, 2020–Feb. 3, 2020	140	Living in Wuhan	71 (50.7)	57 (25–87)
Guan W [23] (Feb 28, 2020)	30 provinces	Dec 11, 2019–Jan 31, 2020	1099	Living in Wuhan, 489 (44.5) Recently visited Wuhan, 193/616 (31.3)	637 (58.1)	47 (35–58)
Group 3						
Song F et al. [24] (Feb 6, 2020)	Shanghai	Jan 20, 2020–Jan 27, 2020	50	50 (98) had some contact with individuals from Wuhan	25 (49)	49 (16) <sup>a</sup>
Xu XW [25] (Feb 19, 2020)	Zhejiang	Jan 10, 2020–Jan 26, 2020	62	Exposure history in Wuhan > 2 weeks, 23 (37)	35 (56)	≤18, 2 (3) 19–40, 25 (40) 41–65, 33 (53) ≥66, 2 (3)
Xu YH [26] (Feb 25, 2020)	Hebei	January and February 2020	50	Wuhan or nearby, 30 (60) Close contact, 18 (36)	29 (58)	<18, 5 (10) 18–50, 30 (60) >50, 15 (30)
Tian S [7] (Feb 26, 2020)	Beijing	Jan 20, 2020–Feb 10, 2020	262	Had been to Wuhan in 14 days, 106 (40.5) Contacted with a symptomatic case in 14 days, 129 (49.2)	127 (48.5)	47.5 (range, 1–04)
Yang W [27] (Feb 27, 2020)	Zhejiang	Jan 17, 2020–Feb 10, 2020	149	Stayed in Wuhan, 80 (53.7); stayed in provinces other than Wuhan 5 (3.4); contacted with people in Hubei, 49 (32.9); no relation with Hubei	81 (54.4)	45.11 (13.35) <sup>a</sup>
Xu X [28] (Feb 28, 2020)	Guangdong	Jan 23, 2019–Feb 4, 2020	90	Wuhan or infected patient	39 (43)	50 (18–86)
Wu J [29] (Feb 29, 2020)	Jiangsu	Jan 22, 2020–Feb 14, 2020	80	None	39 (48.6)	46.10 (15.42) <sup>a</sup>

<sup>a</sup> Mean (standard deviation); IQR, interquartile range.

**Table 2 – Estimated frequencies of comorbidities in patients with COVID-19.**

	Total			Group I			Group II			Group III		
	No. of studies	No. of patients	Estimated frequency (95% CI)	No. of studies	No. of patients	Estimated frequency (95% CI)	No. of studies	No. of patients	Estimated frequency (95% CI)	No. of studies	No. of patients	Estimated frequency (95% CI)
Cerebrovascular disease	6	1668	8.26% (3.19–13.32)	1	138	5.10% (1.18–9.02)	2	1239	1.45% (0.69–2.20)	3	291	16.79% (0.37–33.21)
Cardiovascular disease	6	596	7.69 (3.87–11.50)	2	178	14.52% (9.32–19.72)	2	277	7.90% (4.58–11.21)	2	140	2.84% (–0.78–6.46)
Hypertension	8	1757	17.08% (11.71–22.45)	2	179	23.42% (7.18–39.66)	3	1376	17.58% (9.07–26.08)	3	202	12.32 (5.62–19.01)
Diabetes	8	1757	7.98% (5.46–10.51)	2	179	13.44% (4.52–21.76)	3	1376	8.90% (6.06–11.75)	3	202	3.91% (0.66–7.16)
Malignancy	8	1833	1.33% (0.45–2.20)	3	278	3.46 (–0.79–7.71)	2	1236	0.93% (0.35–1.50)	3	319	1.49% (–0.41–3.39)
COPD	8	1757	1.20% (0.65–1.74)	2	179	2.81% (–0.21–5.84)	3	1376	1.13% (0.57–1.69)	3	202	1.40% (–1.19–3.99)
Chronic liver disease	5	371	2.94% (0.49–5.38)	2	179	2.81% (–0.21–5.84)	–	–	–	3	172	3.90% (–1.31–9.11)
Chronic renal disease	5	1519	0.81% (0.26–1.37)	1	138	2.90% (–0.43–1.31)	2	1239	0.73% (0.16–1.31)	2	142	1.42% (–1.64–4.48)

COPD, Chronic obstructive pulmonary disease; CI, confidence interval.

### 3.2. Frequency of clinical outcomes among patients with COVID-19

Among the studies that reported patients' clinical outcomes, more than half of the patients remained in hospitals at the end of the observational period, except one study in Group I in which 14.6% of patients died and 68.3% were discharged [2]. The estimated case fatality rate in all 13 eligible studies was 1.80% (95% CI, 0.47–3.14), while the estimated case fatality rates in Groups I and II were 8.66% and 2.96%, respectively (Fig. 2). In Group III, the mortality was reported in only one study (3 cases among 262 patients, 1.15%) [7].

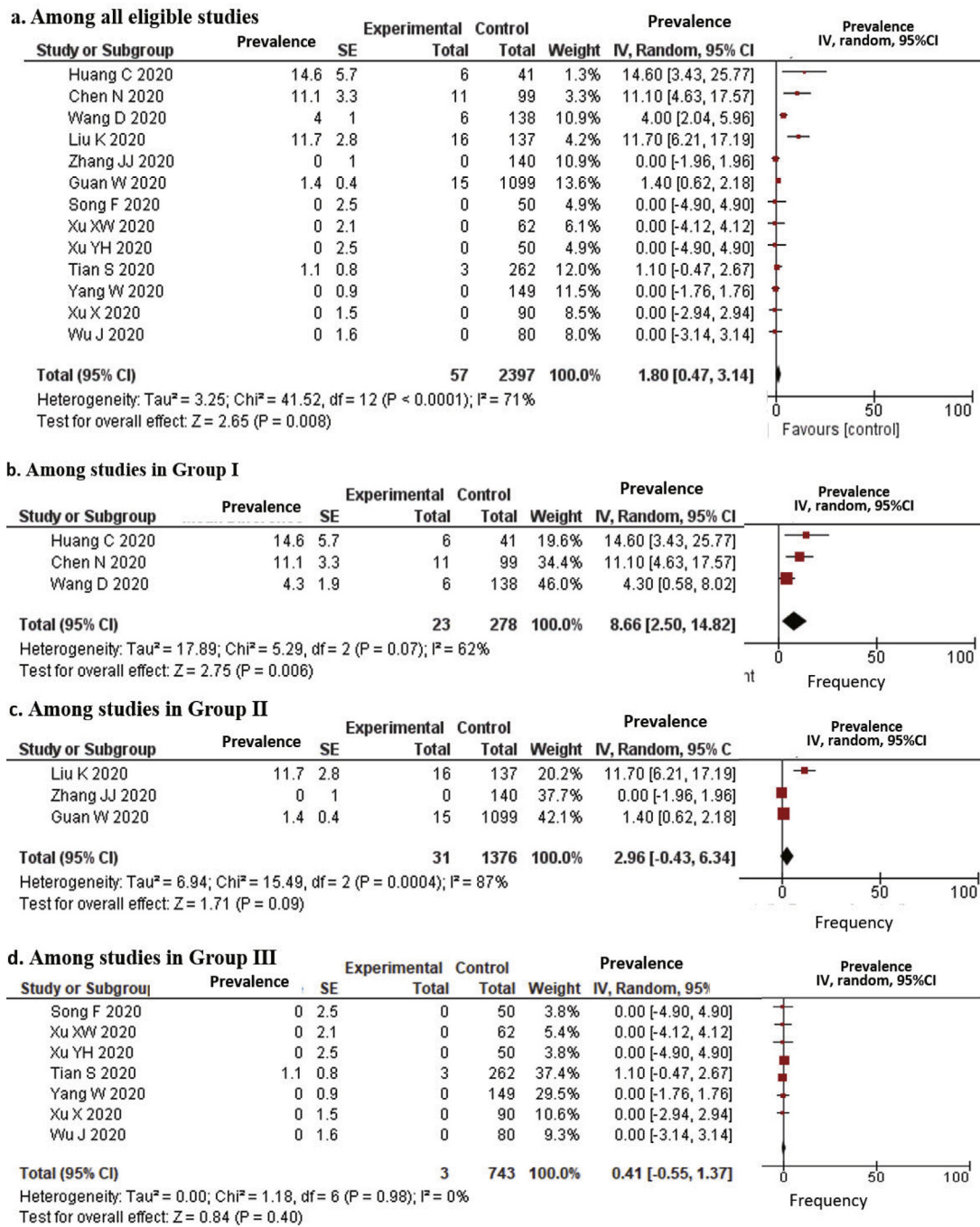
With respect to complications, the frequencies of ARDS, cardiac injury, renal injury, and shock were estimated and are shown in Fig. 3. These complications were not reported from studies in Group III. ARDS was reported in all three studies in Group I and one study in Group III. The estimated frequency of ARDS in Group I was 20.0% (95% CI, 14.79–25.20), while the prevalence of ARDS in a study in Group II was 3.37% [23] and no studies in Group I (Fig. 3). The estimated frequencies of cardiac injury, renal injury, and shock were reported only in Group I (estimated frequencies of 7.97%, 3.65%, and 6.29%, respectively), except one study in Group II for shock (1.09%) [23].

### 3.3. Frequency of symptoms among patients with COVID-19

The estimated frequencies of symptoms among all available studies and stratified groups are shown in Table 3 and Supplementary Fig. S3i–S3ix. Fever and cough were the major symptoms and were reported in all eligible studies. The estimated frequency of fever was 82.46% in 13 eligible studies, and the frequency in Group I was 93.39% and was the highest among the three groups (Table 3; Fig. S3i). The estimated frequency of cough was 62.36% in all 13 eligible studies, and those in Groups I and III were 72.14% and 57.36%, respectively (Table 3; Fig. S3ii). Dyspnea was reported in all three studies in Group I and two studies each in Groups II and III. The estimated prevalence of dyspnea was higher in Group I (37.18%) than in Group II (24.12%) and Group III (6.16%) (Table 3; Fig. S3iii). The prevalence of myalgia varied among the studies; the estimated frequency was similar in Group I (22.84%) and Group III (20.82%) (Table 3; Fig. S3iv). The estimated frequency of fatigue was quite high, especially in Groups I (69.60%) and II (56.37%); however, the frequency in Group III was 22.44% (Table 3; Fig. S3v). The estimated frequencies of headache, sore throat, and diarrhea were lower in Group I (7.17%, 11.09%, and 4.91%, respectively) than in Group III (11.13%, 13.32%, and 6.06%, respectively) (Table 3; Fig. S3vi, S3vii, S3ix). The estimated frequency of expectoration in Group III (29.21%) was the third highest among the observed symptoms in Group III and higher than the estimated frequency of expectoration in Group I (7.11%) (Table 3; Fig. S3viii).

## 4. Discussion

The present systematic review and meta-analysis revealed that the trend of clinical features of COVID-19 in China changed from December 2019 to the end of February 2020. The

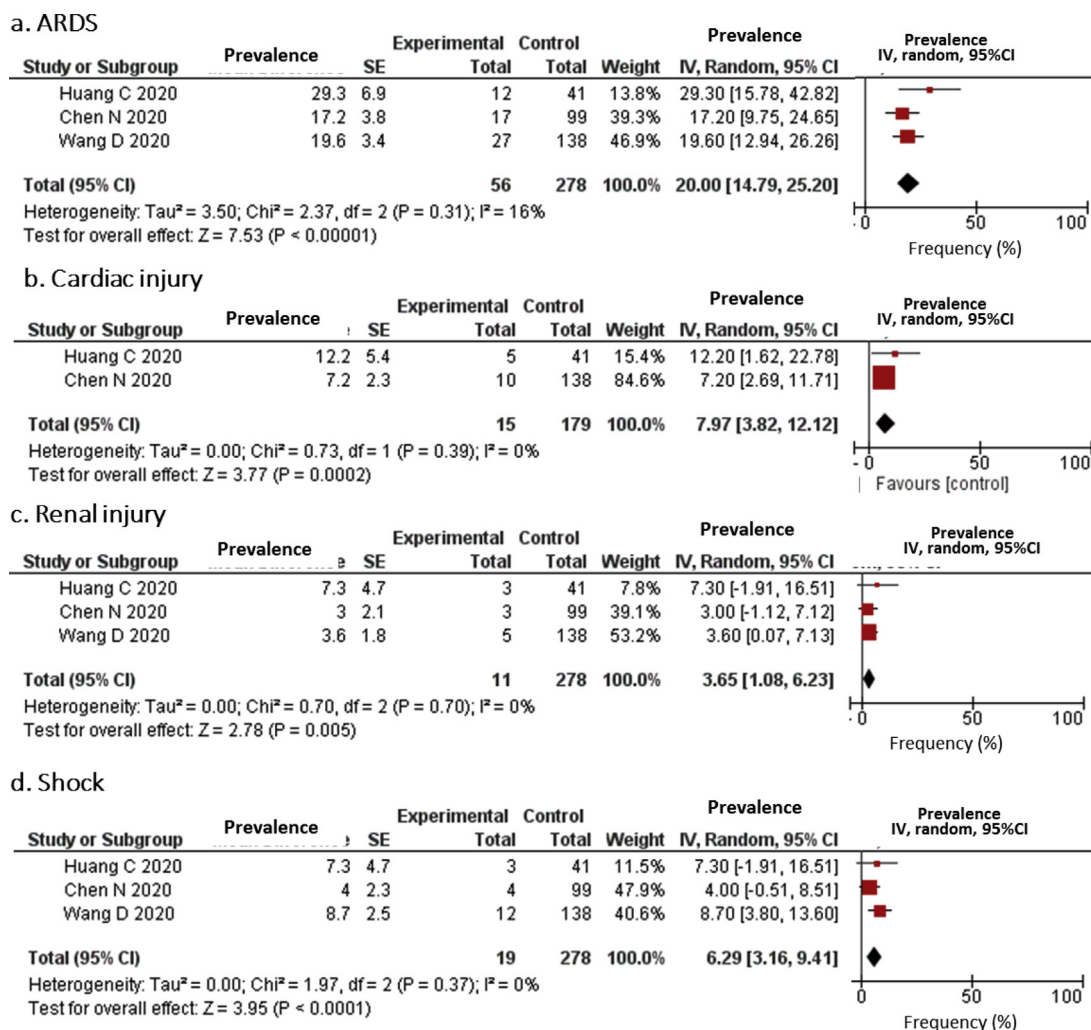


**Fig. 2 – Forrest plots for case fatality among patients with COVID-19. SE: standard error; IV: inverse variance method; 95% CI: 95% confidence interval.**

estimated frequencies of death and complications of ARDS, cardiac injury, and renal injury as well as symptoms of dyspnea in the initial stage of the outbreak were higher than those in the later times. These results indicated that at the time of the outbreak, the disease severity was greater in the initial phase than at later times.

The previous studies mentioned that most affected patients were thought to be workers in the Hunan seafood wholesale market in the initial time of the outbreak [2,6]. In the present study, although none of the studies mentioned the prevalence of workers in the Hunan seafood wholesale

market, the estimated frequency of male patients in Group I was higher than that in Groups II and III. It seemed reasonable that the patients with COVID-19 during the initial period of the outbreak included many workers in the Hunan seafood wholesale market. After that initial phase, most affected patients were no longer only linked to the Hunan seafood wholesale market, and the proportions of males and females became similar. More importantly, the patients who had an exposure history to the Hunan seafood wholesale market were not all of the patients in Group I (Table 1). In particular, Wang et al. [20] found that only 8.7% of patients were exposed



**Fig. 3 – Forrest plots for complications among patients with COVID-19. SE: standard error; IV: inverse variance method; 95% CI: 95% confidence interval.**

to the Hunan seafood wholesale market. The results indicated that human-to-human transmission was presumed to have occurred even at the initial phase of the outbreak in China. Notably, our evaluation indicated that the estimated case fatality was 8.66%, which is much higher than the crude fatality ratio in China (3.6%) reported by the WHO as of March 1, 2020 [4], and the estimated prevalence of ARDS decreased over time from Groups I to III. These results indicated that the disease prognosis was worse in the initial period than at the later phases of the COVID-19 outbreak in China. A study reported that angiotensin converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2 [30], and men had a higher ACE level in their alveolar cells than women [31,32]. In addition to the exposure risk, it may be possible that the cause of the higher prevalence in male patients in the early phase of the outbreak in China was that male sex contributed to the severity of COVID-19.

Coronavirus mainly causes respiratory tract infections, and some strains have high infectivity and mortality [33]. SARS-CoV-2 has at least 70% similarity in its genetic sequence to SARS-CoV [28]. One report stated that the severity of some cases of COVID-19 mimicked that of SARS [23], which affected 8098 people in 26 countries and caused 774 deaths from 2002

to 2003 [34]. Besides the pathogenicity of coronavirus, one cause of the high severity and mortality during the initial outbreak in China may have been the lack of knowledge and recognition of the disease among residents, clinicians, and policymakers in Wuhan city, since Wuhan was the place where the infection initially occurred. In the present study, the symptoms with the highest overall estimated frequencies were fever and cough in all three groups, while the characteristic symptoms of COVID-19, such as olfactory and taste disorders, are reported after the disease spread globally [35]. These flu-like symptoms may not have prompted people to seek health care. However, with the development of more serious symptoms, such as dyspnea, the patients went to the hospital and underwent delayed initiation of treatment. The same phenomenon occurred in the early stage of the 2009 influenza pandemic in Mexico, where the first patient with H1N1pdm09 virus infection was identified [36]. Delayed access to health care and delayed initiation of proper treatments for COVID-19 may also lead to greater disease severity. Additionally, one study indicated that the viral load of SARS-CoV in upper respiratory tract specimens was low during the first week of illness, peaking around 10 days after illness onset [37].



Table 3 – Estimated frequencies of symptoms among patients with COVID-19.

	Total											
	Group I				Group II				Group III			
	No. of studies	No. of patients	Estimated frequency (95% CI)	No. of studies	No. of patients	Estimated frequency (95% CI)	No. of studies	No. of patients	Estimated frequency (95% CI)	No. of studies	No. of patients	Estimated frequency (95% CI)
Fever	13	2377	82.46% (69.62–95.30)	3	278	93.39% (84.25–102.53)	3	1356	72.10% (38.02–106.18)	7	743	82.64% (76.45–88.71)
Cough	13	2377	62.36% (55.67–69.05)	3	278	72.14% (57.05–87.23)	3	1356	63.92% (51.58–76.26)	7	743	57.36% (47.38–67.33)
Dyspnea	10	2145	21.06% (13.41–28.71)	3	278	37.18% (25.69–48.67)	3	1356	24.12% (14.77–33.47)	4	511	6.16% (1.38–10.95)
Myalgia	7	1705	20.10% (12.08–28.11)	2	237	22.84% (–0.38–46.07)	1	1099	14.90% (12.74–17.06)	4	369	20.82% (3.82–37.83)
Fatigue	6	1759	41.11% (25.08–57.13)	1	138	69.60% (61.96–77.24)	2	1219	56.37% (20.21–92.53)	3	402	22.44% (16.63–28.25)
Headache	12	2254	10.05% (6.72–13.39)	3	275	7.17% (3.93–10.42)	2	1236	12.25% (8.48–16.03)	7	856	11.13% (5.87–16.39)
Sore throat	8	1755	12.71% (8.95–16.47)	2	237	11.09 (–0.96–23.14)	1	1099	13.90% (11.94–15.86)	5	419	13.32% (7.40–19.23)
Expectoration	8	1764	26.09% (14.68–37.51)	2	177	27.11% (20.69–33.52)	2	1236	19.08% (–9.64–47.79)	4	351	29.21% (12.76–45.67)
Diarrhea	10	2000	6.25% (4.06–8.44)	3	164	2.12% (–1.23–5.46)	3	1375	7.68% (2.32–13.04)	4	351	6.60% (3.74–9.45)

CI, confidence interval.

This reflected in the fact that the first patient with COVID-19 in Korea had no clinical features suggesting pneumonia during the first 3 days [38]. Our evaluation suggested that the estimated frequency of atypical flu-like symptoms such as diarrhea was higher in Group III than Group I. Although the pathophysiology of SARS-CoV-2 may not be the same as that of SARS-CoV, the characteristics of the virus may contribute to delayed diagnosis leading to delayed early initiation of treatments, especially for initially mild cases. In addition, after the spreading outside Hubei province, it can be presumed that the availability of sufficient medical facilities can contribute to reduce the severity of disease [26].

As the timeline progressed from Group I to Groups II and III, the proportion of mild cases increased, especially in Group III, in which most patients lived outside of Hubei province, China, and none of the patients had a history of contact with the Hunan seafood wholesale market. This manner of spread is different from that of avian influenza (H7N9) virus infection, the reported cases of which were only concentrated in the mainland of China even over 1500 human cases had been reported for the 5 years following 2013 [39]. This suggests that, in COVID-19, human-to-human transmission or ongoing transmission from a market or other primary sources likely existed. Another aspect from the etiological point-of-view for a pandemic disease is that, in general, pathogens tend to reduce their virulence in order to maximize their between-host transmission [40], and hosts are selected to reduce the harm caused by the pathogen [41,42]. The route of transmission or source of exposure might influence the disease severity of COVID-19. In addition to the virulence factors of the pathogen, the host's immune status is another important factor preventing infection and reducing severity [43].

In terms of comorbidities, the results of the present study indicated that hypertension, cardiovascular disease, and diabetes can be risk factors for the severity of COVID-19. A study among critically ill patients with COVID-19 in the US reported that the prevalence of diabetes mellitus (58%) was the highest among those showing comorbidities, followed by chronic kidney disease (21%) [44]. These heterogenous results suggested that comorbidities of patients with COVID-19, as the risks for severe conditions, may be different according to the characteristics of patients in each country and region, and any comorbidities in patients with COVID-19 yielded poor clinical outcomes than those without. Additionally, most of the reported comorbidities in these previous studies were collected from the patients' self-report, and it is not clear if their comorbidities were controlled or treated. Considering the presence of various risk factors relating to severity of COVID-19, comorbidities would not be considered the only factor related to poor outcomes of COVID-19.

Our study has some limitations, including those inherent to the nature of systematic reviews and meta-analyses. The study was limited to articles written in English. We collected data on the clinical features of patients with COVID-19 from previously published studies. Because the reported symptoms, signs, and clinical outcomes varied among the studies, the number of studies focusing on each clinical feature varied in this meta-analysis. Unreported symptoms, comorbidities, and complications in each study may exist due to the low prevalence. The prevalence of various manifestations of

disease severity, including ARDS, may be influenced by the number of people in whom the infection was confirmed using PCR. This study was not a meta-analysis using individual patients' data, so we were unable to obtain data for the number of patients with multiple symptoms or comorbidities. Some patients in each study remained in the hospitals at the end of the observational period. Therefore, the clinical outcomes, such as the number of patients who died or were discharged, may have differed at the final outcomes.

## 5. Conclusion

The disease severity and the frequencies of clinical outcomes and symptoms of COVID-19 changed from December 2019 to February 2020 in accordance with increasing variations in both the transmission route and the risk of exposure. After the disease spread globally, the disease severity for the majority of patients with COVID-19 became less severe in China, while explosive outbreaks with many fatal cases occurred in countries such as the US, Italy, Spain and the UK. More importantly, even though patients with COVID-19 initially showed mild conditions, some patients developed severe conditions later. Further studies are needed with patients whose final outcome can be determined, especially after the spread of COVID-19 as a pandemic.

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## Author contributions

T.M. and K.K. conceived the study. T.M. and H.A. conducted the literature search, compiled and screened the list of articles, selected the relevant documents, reviewed the eligible articles, and extracted the data. T.M. analyzed the data. All authors interpreted the study results. T.M. wrote the initial draft of the manuscript. All authors read and approved the final manuscript.

## Conflict of Interest

The authors have no conflicts of interest to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resinv.2020.05.005>.

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