Original Article

Did patients with COVID-19 receive timely treatment in the early epidemic?—a systematic review and meta-analysis

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Background: Corona virus disease 2019 (COVID-19) showed a significant difference in case fatality rate between different regions at the early stage of the epidemic. In addition to the well-known factors such as age structure, detection efficiency, and race, there was also a possibility that medical resource shortage caused the increase of the case fatality rate in some regions.

Methods: Medline, Cochrane Library, Embase, Web of Science, CBM, CNKI, and Wanfang of identified articles were searched through 29 June 2020. Cohort studies and case series with duration information on COVID-19 patients were included. Two independent reviewers extracted the data using a standardized data collection form and assessed the risk of bias. Data were synthesized through description and analysis methods including a meta-analysis.

Results: A total of 109 articles were retrieved. The time interval from onset to the first medical visit of COVID-19 patients in China was 3.38±1.55 days (corresponding intervals in Hubei province, non-Hubei provinces, Wuhan, Hubei provinces without Wuhan were 4.22±1.13, 3.10±1.57, 4.20±0.97, and 4.34±1.72 days, respectively). The time interval from onset to the hospitalization of COVID-19 patients in China was 8.35 ±6.83 days (same corresponding intervals were 12.94±7.43, 4.17±1.45, 14.86±7.12, and 5.36±1.19 days, respectively), and when it was outside China, this interval was 5.27±1.19 days.

Discussion: In the early stage of the COVID-19 epidemic, patients with COVID-19 did not receive timely treatment, resulting in a higher case fatality rate in Hubei province, partly due to the relatively insufficient and unequal medical resources. This research suggested that additional deaths caused by the out-of-control epidemic can be avoided if prevention and control work is carried out at the early stage of the epidemic.

Trial Registration: CRD42020195606.

Keywords: Corona virus disease 2019 (COVID-19); first diagnosis; hospitalization; time interval; meta-analysis

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Introduction

The corona virus disease 2019 (COVID-19) epidemic outbreak began in December 2019 (1-3). By the end of 2020, the total number of confirmed cases worldwide had exceeded 80.64 million, and the death toll had exceeded 1.76 million (4). Currently, no specific medicine for the treatment of COVID-19 has been found globally (5,6). The World Health Organization (WHO) recommended that the treatment of COVID-19 should be mainly based on supportive treatment, including oxygen therapy for severe patients and those at risk of serious diseases, and more advanced respiratory support for critically ill patients (7). Timely hospitalization is a significant factor in prognosis and the risk of disease and death, especially patients with underlying diseases or the elderly (8-10). The timely treatment mainly depends on whether the medical resources in the area where patients live are sufficient, meanwhile, to a certain extent, it also depends on the patient's willingness to pay a medical visit (11). Through the collection and analysis of articles, this research compared the time intervals from onset to first medical visit and onset to the hospitalization of COVID-19 patients in different regions and assessed the supply and demand status of medical resources, to provide an evidence-based reference for authorities to guide people's health-related behaviors during epidemics, to stem the spread of the disease, reduce health care burden and death rate. We present the following article in according with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-1975/rc).

Methods

Search strategy

This systematic review was registered in International prospective register of systematic reviews (PROSPERO) on June 29, 2020, with the protocol of CRD42020195606. Articles publishing before June 29, 2020, that reported medical information of COVID-19 patients were included in this research, the following databases were comprehensively searched, including the Cochrane Library, PubMed, EMBASE, Web of Science, CBM (China Biology Medicine disc), CNKI (China National Knowledge Infrastructure), and Wanfang database. The following search formulas were used in this research, including ("COVID 19" OR "COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus" OR "2019-nCoV" OR "2019-CoV" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "Novel coronavirus" OR "2019-novel coronavirus") AND ("symptom onset" OR "illness onset" OR "first symptom" OR "onset of illness") AND ("admission" OR "hospitalization") AND ("see a doctor" OR "first medical visit" OR "first medical care" OR "visit hospital"). Besides, WHO, Chinese Center for Disease Control and Prevention (CCDC), National Health Commission of the People's Republic of China, USA National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov), International Standard Randomized Controlled Trial Number (ISRCTN) registry, Google Scholar, the preprint servers medRxiv (https://www.medrxiv.org/) and bioRxiv (https://www.biorxiv.org/), and Social Science Research Network (SSRN, https://www.ssrn.com/index.cfm/en/) were also included as retrieval sources. The retrieval strategy for this research was reviewed by information experts.

Inclusion and exclusion criteria

Case series and cohort studies that reported the medical visit time of COVID-19 patients were included. Abstracts, case reports, letters, news, guidelines, comments, and articles that were unable to obtain all relevant data or full texts were excluded. There were no restrictions on language or publication status.

Article screening

After deleting duplicates in all the retrieved articles, two reviewers (P Du and Q Shi) used EndNote to independently screen these articles in two steps. The first step was to filter the title and summary using predefined criteria. The second step was to review the articles that were likely to meet the requirements by reading the full text and determine whether they will be finally included. The reasons for the exclusion of all unqualified articles were recorded, PRISMA flowcharts were used to record the process of article screening, and screening objections were resolved through discussion or consultation with a third reviewer (X Luo).

Data extraction

Data were extracted independently by two reviewers (P Du and Q Shi) using a standardized data collection form, and all objections were resolved through discussion or consultation with a third reviewer (X Luo). The third reviewer was responsible for checking the consistency and accuracy of the data. Data extraction includes the following three aspects: (I) basic information (title, author, country, date of publication, research type), (II) patient information (number, gender, age, disease type, sample size, grouping variables), (III) result information (the interval from first symptom onset to the first medical visit, the interval from the first symptoms onset to the first hospitalization, clinical outcome).

Data analysis

The 1st time interval was defined as the interval from the first symptom onset to the first medical visit of COVID-19 patients, and the 2nd time interval was defined as the interval from the first symptoms onset to the first hospitalization of COVID-19 patients. The medical institution was defined as the designated hospitals which are accredited for COVID-19 detection and treatment, since general clinics and isolation sites are unable to provide systematic measures. The clinical classification of COVID-19 patients in China is based on Guidelines on the Novel Coronavirus-Infected Pneumonia Diagnosis and Treatment issued by the National Health Commission of People's Republic of China (12). A mild case was defined as mild clinical symptoms and no radio graphic evidence of pneumonia. A moderate case was defined as a confirmed case with fever, respiratory symptoms and radio graphic evidence of pneumonia. A severe case was defined as a confirmed case meets any of the following criteria: (I) shortness of breath, RR ≥30 times/min; (II) oxygen saturation ≤93% at rest; (III) alveolar oxygen partial pressure/fraction of inspiration O2 (PaO2/FiO2) <300 mmHg. A critical case was defined as a confirmed case meets any of the following conditions: (I) respiratory failure requiring mechanical ventilation; (II) shock; (III) patients combined with other organ failure needed intensive care unit (ICU) monitoring and treatment. Exposure history was defined as COVID-19 patients with a history of travel to the source of the outbreak or a history of exposure to confirmed cases. The duration of viral shedding was defined as the number of days from the onset of the symptoms until the successive negative detection of SARS-CoV-2 RNA.

Statistical analysis

In the retrieval articles, the statistics of the 1st and 2nd time intervals were described by mean ± standard deviation or median (interquartile range), while some research only provided point estimates, maximum and minimum values. This research used an estimation method proposed by Luo (13) and Wan (14) *et al.* to unify the time intervals of all research as mean ± standard deviation, and the sample size weighting method was used to calculate the weighted mean of each time interval sample. Linear or nonlinear regression was used to fit the trend of time interval of patients in different periods. The patients were divided into two groups according to the severity of the disease: common patients (mild and moderate cases) and severe patients (severe and critical cases) in the meta-analysis. Heterogeneity was defined as $P<0.05$ and $I^2>50\%$ (15). Mean difference (MD) with 95% confidence intervals (CI) was used as the effect size. Sensitivity analysis was conducted by comparing the difference between the fixed-effect model and the random effect model. Two-sided P values <0.05 were considered statistically significant. All statistical analysis was implemented on RStudio (Version 1.2.5033).

Assessment of risk of bias

Two reviewers (P Du and Q Shi) independently assessed the risk of bias for each research, resolved objections by discussion, and consulted a third reviewer (X Luo) if necessary. Appropriate assessment tools were selected to assess the risk of bias according to research types in the article: the Newcastle-Ottawa scale which consists of eight parts, with each part using a star rating, should

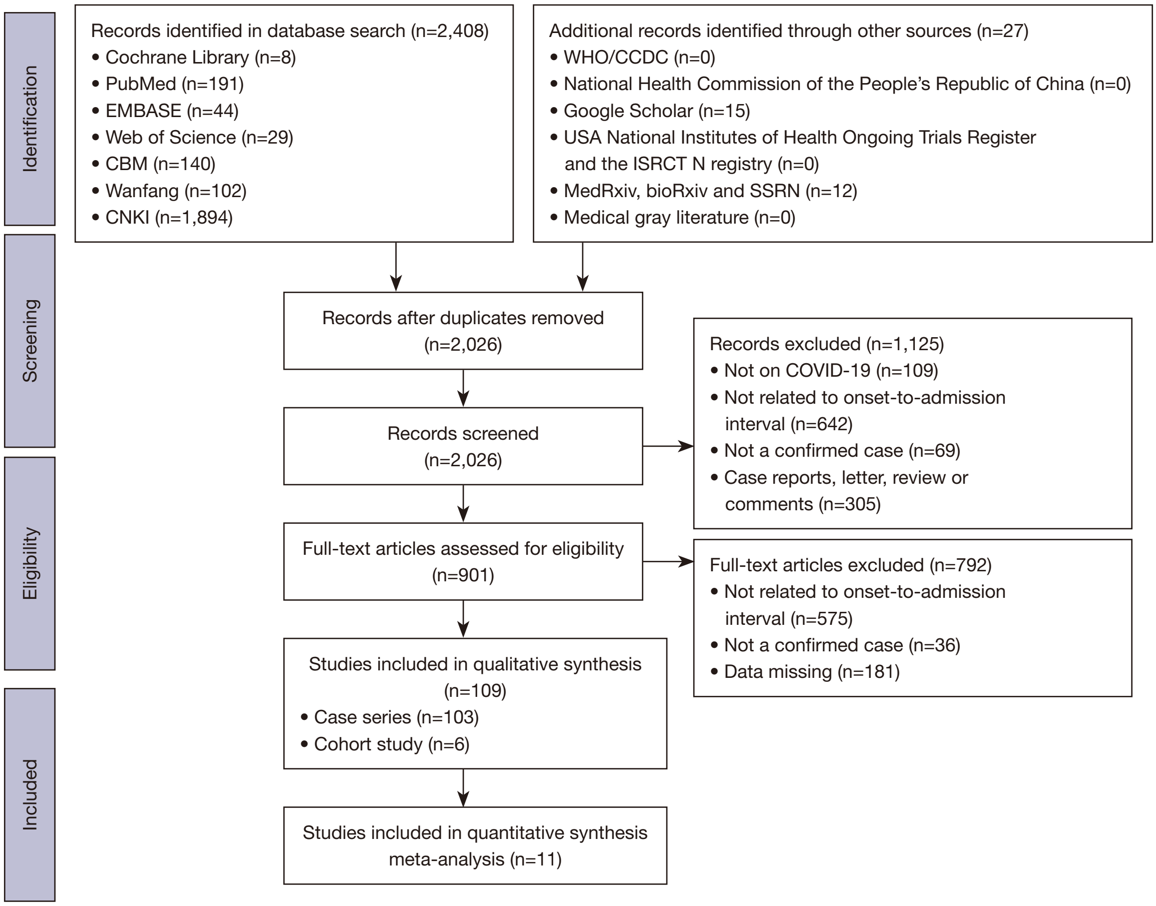

Figure 1 The processes of article retrieval and screening.

be used for the cohort study (16). The more the stars, the lower the risk of bias. Furthermore, for a case series study, methodological assessment tools recommended by the National Institute for Health and Care Excellence (NICE) should be used (17). The risk of bias was assessed against 8 criteria, and the results were summarized using a scoring method with 1 point for "Yes" and 0 point for "No". The higher the scores, the lower the risk of bias.

Quality of evidence assessment

Two reviewers (P Du and Q Shi) used Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (18,19) to independently assessed the quality of evidence and used GRADEpro to create a form, in which the results of each research included in the meta-analysis were classified for evidence quality. The overall quality was downgraded based on 5 factors (risk of bias, inconsistency, imprecision, indirectness, and publication bias) and upgraded based on 3 factors (large effect size, dose-effect relationship, and negative bias). The overall quality of evidence was classified as high, medium, low, or very low, reflecting the trust degree that the effect estimates were accurate.

Results

Article research results

After a systematic retrieval, 2,435 articles were retrieved for the first time. After deleting duplicates, 109 articles were finally included in the evaluation through screening titles, abstracts, and full texts, including 103 case series and 6 cohort studies, and the patient information of 101 articles (92.7%) was collected before April 2020. The processes of article retrieval and screening were shown in *Figure 1*.

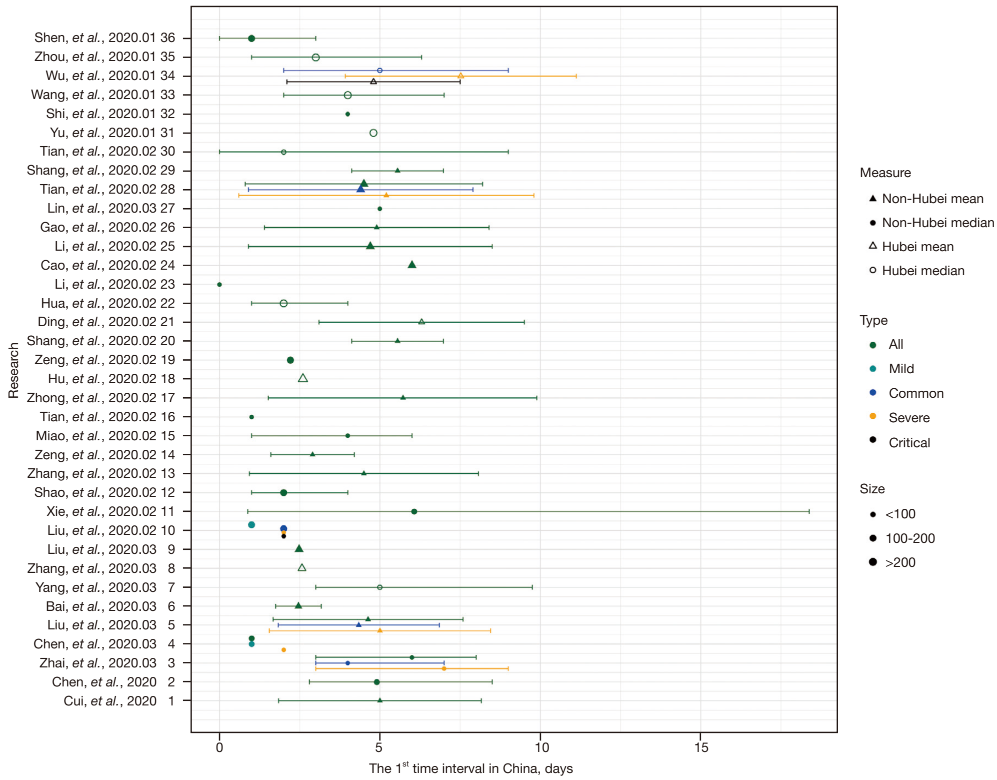

Figure 2 The distribution of the 1st time interval of COVID-19 patients in China. The articles are sorted by the follow-up time end date, with the most recent at the top. Hollow points and solid points represented articles from Hubei province and non-Hubei provinces respectively. The mean was represented by a triangle and the median was represented by a circle. The length of a line segment was determined by the standard deviation of the interval and the interquartile spacing, and the point estimate had no corresponding line segment. Patients with different severity of disease were shown in different colors. The sample size was represented by the size of the points. COVID-19, corona virus disease 2019.

A total of 18,777 patients were included in this research, including 8,405 females (44.8%), 9,671 males (51.5%), and 701 patients (3.7%) with unknown gender. China contributed 100 (91.7%) articles, 38 (34.9%) of which were from Hubei province (the most affected province in China). The remaining 9 (8.3%) articles were from abroad shown in Table S1 [two articles from Singapore (20,21), two articles from Korea (22,23), two articles from the United States (24,25), one article from Germany (26), one article from Japan (27) and 1 article from French (28)].

This research intended to assess whether the patient had received treatment in time by collecting the 1st and 2nd time intervals. Among the included 109 articles, 30 articles only reported the 1st time interval, 73 articles only reported the 2nd time interval, and 6 articles reported both time intervals. The included articles' assessment of the risk of bias was provided in Tables S2,S3.

Time interval from onset to the first medical visit

Figure 2 showed the 1st time interval in 36 articles, of which 10 articles (27.8%) were from Hubei Province and 26 articles (72.2%) were from non-Hubei provinces. The 1st time interval was not mentioned in the included articles outside China. The 1st time interval was mostly concentrated in about 5 days, the minimum time interval was 0 (median) days [an article from Shenyang, China (29), 65.38% (17 out of 26) of COVID-19 patients paid a medical visit on the day of onset), the maximum time interval was 7.52 (mean) days (an article from Hubei Province researching on severe patients (30)]. In terms of the 1st time interval, no significant difference was found between patients from Hubei province and non-Hubei provinces.

Part of the articles made statistics of COVID-19 patients' 1st time interval in groups according to the severity of the disease, exposure history, time around Wuhan's cordon sanitaire, etc. Firstly, 6 articles grouped patients according to the severity of the disease, and the results showed that the longer the 1st time interval, the worse the patient's health condition. However, a research of Wuhan showed that the 1st time interval in severe patients (7.52 days) was longer than that in common patients (5.35 days), whereas the 1st time interval of critically ill patients was shorter (4.8 days) (30). Secondly, an article from Shenyang grouped patients according to whether they had an exposure history, and the result showed that patients without an exposure history (4 days) had a longer 1st time interval compared with those who had one (0 days) (29). Thirdly, an article from Hunan province indicated that the 1st time interval of patients after January 23 (cordon sanitaire day of Wuhan) (1 day) was shorter than that before January 23 (3 days) (31).

Time interval from onset to hospitalization

Figure 3 showed the 2nd time interval in 70 articles, of which 31 (44.3%) articles were from Hubei province (27 articles from Wuhan), and 39 (55.7%) articles were from non-Hubei provinces. The 2nd time interval was 1 (median) day to 25.9 (mean) days among the 70 articles, the minimum value appeared in an article from non-Hubei provinces (32) and the maximum value appeared in an article from Wuhan that researched 55 COVID-19 patients' delayed treatment cases (33). The 2nd time interval of Hubei COVID-19 patients was 3 days to 25.9 days, and it was 1 day to 8.5 days for non-Hubei COVID-19 patients. In general, COVID-19 patients in Hubei province had a longer 2nd time interval than those in non-Hubei provinces. Equally, an included article showed the same research result (5.7 days in Hubei province and 4.5 days in non-Hubei provinces) after compared the 2nd time interval in 647 patients from Hubei province and 943 patients from non-Hubei provinces (34).

Part of the articles made statistics of COVID-19 patients' 2nd time interval in groups according to clinical outcome, the severity of the disease, and the duration of viral shedding. There were 4 articles from Hubei province dividing COVID-19 patients into two groups (cure and death) according to clinical outcome. Two of them indicated that the 2nd time interval of the cured group was shorter than that of the dead group clearly (35,36) (3 days/5 days and 7 days/10 days in the 2 articles respectively). Additionally, 8 articles grouped patients according to the severity of the disease, and the results showed that the longer the 2nd time interval, the worse the patients' health condition. Moreover, 3 articles grouped patients by the duration of viral shedding (37-39), and the results showed that the longer the 2nd time interval, the longer the duration of viral shedding.

Figure 4 summarized the 2nd time interval in 9 articles outside China, ranging from 3.5 days to 8 days. An article from South Korea divided COVID-19 patients into two groups according to whether they were admitted to the ICU, and results showed that the 2nd time interval of the patients admitted to the ICU (4.7 days) was shorter than the patients did not admit to the ICU (8.2 days) (23). A German article divided COVID-19 patients into two groups according to whether they had ARDS, and the results showed that the 2nd time interval of ARDS patients (7 days) was longer than common patients (3 days) (26).

Estimation of the 1st time interval and the 2nd time interval

Figure 5A indicated the daily number of newly confirmed COVID-19 cases in Wuhan, Hubei province without Wuhan and non-Hubei provinces from January 20, 2020 to March 10, 2020. As shown in the figure, most of the new cases confirmed in the early and middle of February. In *Figure 5B* and *5C*, this research took the median follow-up time point as the horizontal axis, and the 1st and 2nd time intervals were taken as the vertical axis to draw scatter plots. There was a decreasing trend for the 1st time interval in Wuhan, and no obvious trend in non-Hubei provinces or Hubei province without Wuhan. *Figure 5C* showed that the 2nd time interval of COVID-19 patients had a relatively obvious trend of gradual increase since February in Wuhan. Non-Hubei provinces had a trend of decrease, and no obvious trend was observed in Hubei province without Wuhan because only four articles were included.

Through research, the 1st time interval of COVID-19 patients in China was approximately 3.38±1.55 days, with a median of 2.60 (2.35, 4.70) days. In Hubei province, it was 4.22±1.13 days, with a median of 4.35 (3.46, 4.84) days. In non-Hubei provinces, it was 3.10±1.57 days, with a median of 2.48 (2.31, 4.50) days. In Hubei province without Wuhan, it was 4.34±1.72 days, with a median of 3.79 (2.57, 5.35) days. In Wuhan, it was 4.20±0.97 days, with a median of 4.35 (3.46, 4.84) days. There was no estimation of patients' the 1st time interval outside China due to a lack of relevant data.

The 2nd time interval of COVID-19 patients was

Figure 3 The distribution of the 2nd time interval of COVID-19 patients in China. The description was the same as *Figure 2* except for the 2nd time interval. COVID-19, corona virus disease 2019.

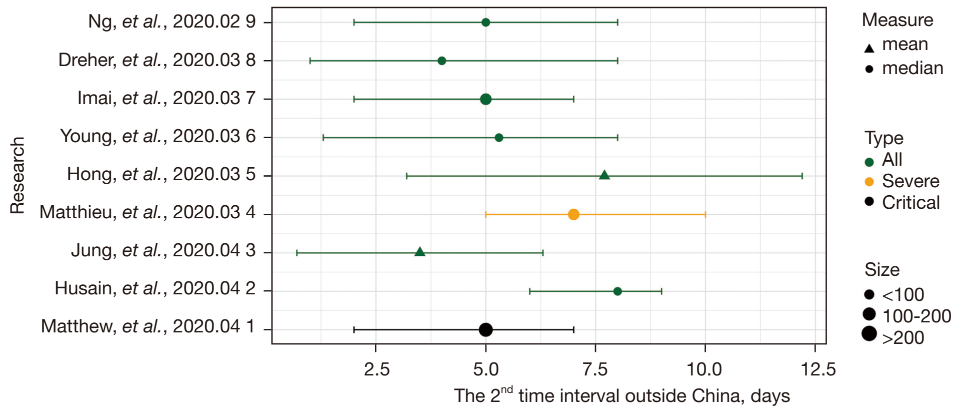

Figure 4 The distribution of the 2nd time interval of COVID-19 patients outside China. The articles are sorted by the follow-up time end date, with the most recent at the top. Hollow points and solid points represented articles from Hubei province and non-Hubei provinces. The mean was represented by a triangle and the median was represented by a circle. The length of a line segment was determined by the standard deviation of the interval and the interquartile spacing. The sample size was represented by the size of the points. COVID-19, corona virus disease 2019.

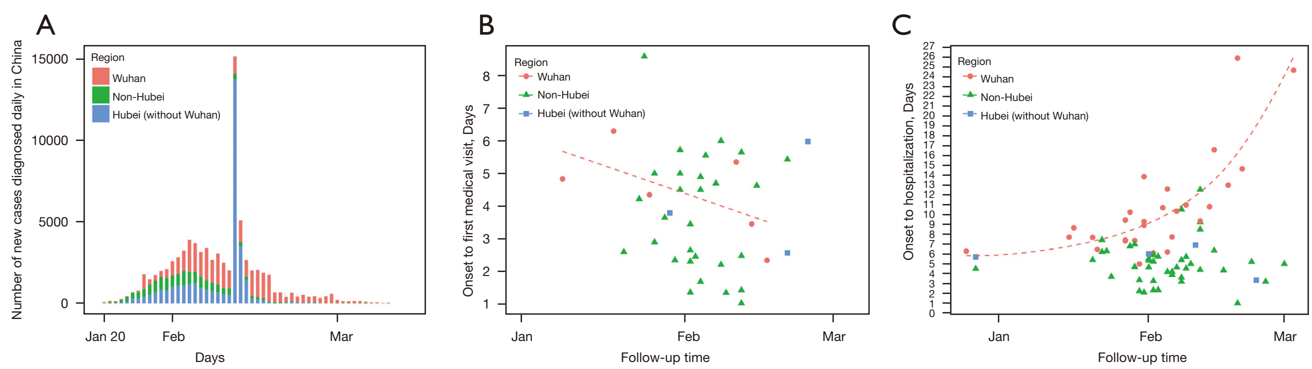

Figure 5 Estimation of the 1st time interval and the 2nd time interval in China. (A) was a stacked histogram of the number of daily new confirmed COVID-19 cases in Wuhan, Hubei province without Wuhan, and non-Hubei provinces from January 20, 2020 to March 10, 2020. (B) was a scatter plot of the median follow-up time point and the 1st time interval. (C) was a scatter plot of the median follow-up time point and the 2nd time interval. COVID-19, corona virus disease 2019.

approximately 8.35±6.83 days, with a median of 5.39 (3.35, 10.54) days. In Hubei province, it was 12.94±7.43 days, with a median of 10.81 (6.90, 24.65) days. In non-Hubei provinces, it was 4.17±1.45 days, with a median of 4.35 (3.20, 4.65) days. In Hubei province without Wuhan, it was 5.36±1.19 days, with a median of 5.7 (5.70, 6.00) days. In Wuhan, it was 14.86±7.12 days, with a median of 11.00 (9.35, 24.65) days. Outside China, it was 5.27±1.19 days, with a median of 4.65 (4.65, 5.00) days.

Meta-analysis of the time interval of common patients and severe patients

Six articles from China [one article (30) from Hubei province and five articles (31,40-43) from non-Hubei provinces] had reported the 1st time interval according to the severity of disease of COVID-19 patients. the meta-analysis results showed that compared with common patients, the 1st time interval of severe patients was longer MD =−1.25, 95%

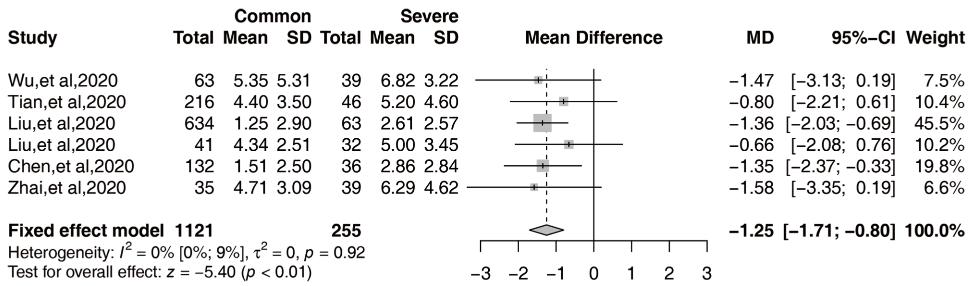

Figure 6 Meta-analysis of the 1st time interval of common and severe patients.

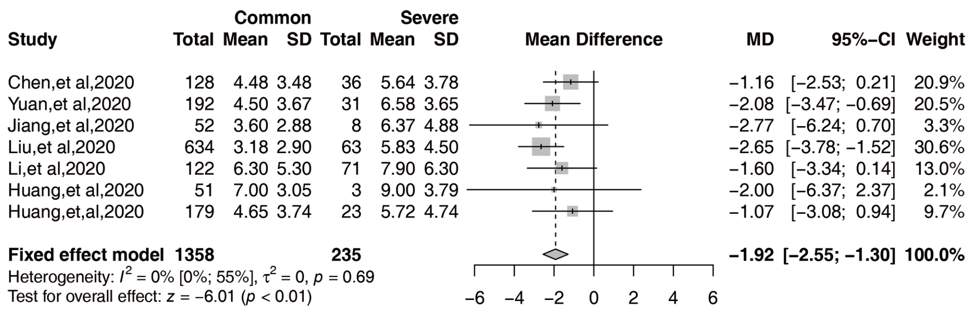

Figure 7 Meta-analysis of the 2nd time interval of common and severe patients.

Table 1 Sensitivity-analysis of the time interval of common patients and severe patients

Research factors	Fixed effect model, MD (95% CI)	Random effect model, MD (95% CI)
Duration from symptom onset to first medical visit	−1.25 (−1.71, −0.80)	−1.25 (−1.71, −0.80)
Duration from symptom onset to admission	−1.92 (−2.55, −1.30)	−1.92 (−2.55, −1.30)

MD, mean difference; CI, confidence interval.

CI (−1.71, −0.80), P<0.01, I^2=0% (*Figure 6*).

Eight articles from China [two articles (44,45) from Hubei province and six articles (31,41,46-49) from non-Hubei provinces] had reported the 2nd time interval according to the severity of disease of COVID-19 patients. One of the eight articles (44) showed that the 2nd time interval for severe patients and common patients in Wuhan were 6 and 5 days, respectively, however, it was excluded from the meta-analysis since it only provided a point estimate. The meta-analysis results showed that compared with common patients, the 2nd time interval of severe patients was longer MD =−1.92, 95% CI (−2.55, −1.30), P<0.01, I^2=0% (*Figure 7*).

Sensitivity analysis and quality of evidence

By comparing the difference between the fixed-effect model and the random effect model, the results of the sensitivity analysis showed that MD values and 95% CI results were close either in the 1st time interval or in the 2nd time interval, which indicated that the meta-analysis in this research was stable. The details of the sensitivity analysis can be found in *Table 1*.

The qualities of the evidence included in the articles were very low according to the GRADE quality assessment. Details were provided in Table S4.

Discussion

COVID-19 was a highly infectious emerging disease that had caused a global pandemic (50). The rapid development of the epidemic had exposed the deficiencies in epidemic prevention and control, public health systems, and health care systems of various countries. In some areas, the unequal allocation of medical resources directly led to the delay of patient medical visits and treatment (51).

The results of this research showed that the 1st time interval of COVID-19 patients in China was 0 days to 7.52 days, with an estimated value of 3.38±1.55 days, and it was 4.22±1.13 days in Hubei Province and 3.10±1.57 days in non-Hubei provinces. Overseas articles did not involve the time data. The 1st time interval was approximately 1 day longer for COVID-19 patients in Hubei than in non-Hubei areas, whereas the time interval between Wuhan and the rest of Hubei province was relatively similar. This indicated that people in Hubei province had poorer access to health care than other provinces during the outbreak, which had further contributed to the spread of COVID-19 there.

The lack of public awareness of COVID-19 at the beginning of the epidemic, coupled with the fact that most SARS-CoV-2 infected individuals have mild symptoms and the early clinical manifestations of the disease are difficult to distinguish from the common cold, might lead infected individuals to ignore the initial mild symptoms and not pay a timely medical visit. As shown in *Figure 5B*, the cordon sanitaire policies implemented from January 23 in Wuhan had strengthened people's attention to COVID-19, and the 1st time interval had been significantly shortened after these cordon sanitaire policies (31). Therefore, timely disclosure of the outbreak and strong preventive and control measures can help raise the awareness of the public.

At the end of January, China implemented the highest level of public health emergency response policies, including quarantine and medical observation for people with an exposure history, case tracing, and screening of close contacts. An article from Shenyang showed that the 1st time interval of patients with an exposure history was shorter than that of those without an exposure history, which was related to these policies (29). Nevertheless, the outbreak of COVID-19 caused a certain degree of social panic, and some suspected patients were afraid of paying a medical visit and handled by themselves through home isolation, which was also a reason leading to the delay of patients' medical visits and treatment (52,53). Therefore, during the critical period of epidemic prevention and control, national and local authorities should disclose information in an understandable, timely, transparent and coordinated manner to reduce public panic. At the same time, the authorities should strengthen epidemiological investigation, health education, public awareness of medical visits, to urge the patients to pay a medical visit in time.

The 2nd time interval of COVID-19 patients in China was 1 to 15 days, with an estimated value of 8.35±6.83 days, and it was 12.94±7.43 days in Hubei Province, and 4.17 ±1.45 days in non-Hubei provinces. The 2nd time interval outside China was 3 days to 8 days, with an estimated value of 4.89±0.89 days. If the regional disparities in the 2nd time interval of COVID-19 patients between China and outside China might be influenced by lifestyle, health systems, and patient treatment (26), then the more obvious differences among multiple regions in China were more likely due to the variances in the supply and demand status of medical resources. The mean of the 2nd time interval in Hubei provinces was obviously longer and the standard deviation was strongly bigger than those non-Hubei provinces of China may indicate that Hubei Province had not only the longest 2nd time interval but also a huge difference in system composition compared with other regions. *Figure 5B* showed that there was a slight difference in the 1st time interval of patients between Wuhan and non-Hubei provinces, while *Figure 5C* showed that the 2nd time interval of patients in Wuhan was significantly longer than that in non-Hubei provinces, and the trend of increasing over time in *Figure 5C* could be considered consequently caused by medical overwhelmed in Wuhan with the rapid accumulation of cases (48,54). Therefore, the length of the 2nd time interval, to some extent, reflected the inadequacy of medical resources in Wuhan during the health emergency. However, as a provincial capital city, the number of tertiary hospitals in Wuhan ranked ahead in China (55), and the proportion of medical staffs (10.19 health technical personnel per thousand, 3.69 licensed physicians per thousand, 5.07 registered nurses per thousand) were much higher than national average level, in which corresponding numbers were 7.26, 2.77 and 3.18 (56,57). If the outbreak is out of control at the initial stage, the shortage of medical resources in a specific period cannot be avoided even in an area with relatively sufficient self-resource reserves and supplements mobilized from other areas.

Of the 109 articles included, 6 articles compared the 1st time interval, and 8 articles compared the 2nd time interval in COVID-19 patients with various disease severities. The results showed that both time intervals were longer in patients with severe disease than in patients with mild disease and common patients. Meta-analysis comparing the length of the 2nd time interval between common patients and severe patients revealed that delayed hospitalization may be an influential factor in the exacerbation of the patient's condition. Although one research from Wuhan reported a shorter the 1st time interval in critically ill patients than in the common patients, this may be related to the fact that the average age of critically ill patients (69 yrs old) is higher than that of the common patients (43 yrs old) (30), and numerous researches have confirmed the strong correlation between age and severity of disease in patients with COVID-19 (6). Some research indicated that delayed treatment would also affect virus shedding time (37), resulting in a higher risk of infection among close contacts, easy spread, and the occurrence of cluster outbreaks, which was not conducive to the national epidemic prevention and control.

Advantages and limitations

This research analyzed whether COVID-19 patients receive treatment in time by summarizing the 1st and 2nd time intervals from the 109 articles. In terms of advantages, our research demonstrated the supply and demand status of medical resources in the early stage of the epidemic by comparing the differences in the 1st time interval and the 2nd time interval of patients in different regions and with various disease severities, to analyze whether there is an increase in case fatality rate caused by insufficient medical resources and provide a reference for national or regional medical resource allocation, personnel scheduling, and prevention and control policy decisions.

The research had several limitations. Firstly, only nine articles outside China were included in this research, which may have caused some bias. Secondly, the estimation of time intervals may affect the accuracy of the research results due to the sample size weighting method and the conversion method of median to estimate the mean, as well as missing data in some articles. Thirdly, the progression of the patient's condition is not only related to the time of visit, but the patient's gender, age, physical health status, and the medical resources will lead to the bias of the results.

Conclusions

It was found that the 1st time interval was similar between Hubei and non-Hubei patients, but the 2nd time interval of Hubei was much longer than that of non-Hubei patients. The 2nd time interval of COVID-19 patients outside China was close to that of non-Hubei provinces. Both the 1st and 2nd intervals were longer in severe patients than in common patients. This phenomenon supported that there was a medical overwhelmed resource and patients with COVID-19 did not receive timely treatment in Hubei province at the beginning of the epidemic, and this could explain why the case fatality rate in Hubei province was much higher than that in other parts of China at the beginning of the outbreak. Besides detection efficiency, the relative lack of medical resources was another important reason that was ignored.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-1975/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-1975/coif). The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Characteristics of included articles

Study ID	Study location	Study type	Time	Sample size	Sex (%,man)	Age (year)
Luo 2020 (11)	Wuhan	Case series	2020/01/30–2020/02/25	403	193 (47.9)	56.0 (39.0, 68.0)**
Young 2020 (20)	Singapore	Cohort study	2020/01/22–2020/03/06	100	56 (56.0)	46.0*
Ng 2020 (21)	Singapore	Case series	2020/01/02–2020/02/29	100	60 (60.0)	42.5*
Jung 2020 (22)	South Korea	Case series	2020/02/01–2020/04/01	14	6 (42.9)	63.5±14.5*
Hong 2020 (23)	South Korea	Case series	To 2020/03/29	98	38 (38.8)	55.4±17.1*
Husain 2020 (24)	The United States	Case series	2020/03/13–2020/04/06	41	30 (73.2)	49.0 (41.0, 63.0)**
Cummings 2020 (25)	The United States	Cohort study	2020/03/02–2020/04/01	257	171 (66.5)	62.0 (51.0, 72.0)**
Dreher 2020 (26)	Germany	Case series	2020/02/01–2020/03/01	50	33 (66.0)	65.0 (58.0, 76.0)**
Imai 2020 (27)	Japan	Case series	2020/02/11–2020/03/31	112	64 (57.1)	67.0 (45.0, 74.0)**
Mahévas 2020 (28)	French	Case series	2020/03/12–2020/03/31	173	125 (72.3)	60.0 (52.0, 68.0)**
Gao 2020 (58)	Shanxi	Case series	2020/01/21–2020/02/18	40	19 (47.5)	41.0±16.4*
Fu 2020 (59)	Chongqing	Case series	2020/01/21–2020/02/25	51	27 (52.9)	60.9±14.9*
Liu 2020 (31)	Hunan	Case series	2020/01/21–2020/02/13	697	–	–
Liu 2020 (60)	Wuhan	Case series	To 2020/03/11	47	32 (68.1)	–
Huang 2020 (61)	Wuhan	Case series	2019/12/29–2020/02/27	305	167 (54.8)	54.5±14.4*
Liu 2020 (40)	Guangdong	Case series	2020/01/01–2020/03/31	73	37 (0.5)	52.2±15.6*
Liu 2020 (62)	Henan	Case series	To 2020/02/08	15	10 (66.7)	46.5*
Han 2020 (44)	Wuhan	Case series	2020/01/12–2020/02/16	120	63 (52.5)	53.0±14.0*
Yu 2020 (63)	Beijing	Case series	2020/01/21–2020/02/25	50	32 (64.0)	40.0±18.4*
Xia 2020 (64)	Hunan	Case series	From 2020/01/16	33	19 (57.6)	39.0**
Chen 2020 (41)	Hainan	Case series	2020/01/22–2020/03/04	168	81 (48.2)	51.0**
Ye 2020 (33)	Wuhan	Case series	2020/02/15–2020/02/25	55	29 (52.7)	59±13.1*
Yang 2020 (65)	Jiangsu	Case series	–	57	29 (50.9)	37.0**
Li 2020 (66)	Henan	Case series	2020/01/21–2020/02/24	256	159 (62.1)	–
Cao 2020 (67)	Chongqing	Case series	2020/01/24–2020/02/23	223	105 (47.2)	46.5±16.1*
Yuan 2020 (46)	Chongqing	Case series	2020/01/24–2020/02/23	223	106 (47.5)	46.5±16.1*
Zeng 2020 (68)	Chongqing	Case series	2020/01/21–2020/02/25	353	193 (54.7)	46.3*
Chen 2020 (69)	Fujian	Case series	–	111	57 (51.4)	49.5**
Hu 2020 (70)	Hunan	Case series	2020/01/01–2020/02/08	852	460 (51.8)	44.0**
Zhang 2020 (71)	Hubei	Case series	2020/02/06–2020/03/07	120	73 (60.8)	–
Yang 2020 (72)	Hubei	Case series	2020/01/30–2020/03/21	40	22 (55.0)	51.2*
An 2020 (73)	Wuhan	Case series	2020/01/24–2020/02/19	110	44 (40.0)	–
Liu 2020 (74)	Shanxi	Case series	2020/01/23–2020/03/02	245	131 (53.5)	46.2*
Li 2020 (29)	Liaoning	Case series	2020/01/26–2020/02/29	26	14 (53.9)	43.9±11.9*
Shi 2020 (75)	Zhejiang	Case series	2020/01/17–2020/01/29	65	37 (57.0)	42.0**
Lei 2020 (76)	Wuhan	Case series	2020/01/10–2020/01/30	51	25 (49.0)	55.0**
Sun 2020 (77)	Henan	Case series	2020/01/24–2020/02/26	129	59 (45.7)	45.0**
Bai 2020 (78)	Shanxi	Case series	2020/01/01–2020/03/06	120	63 (52.5)	49.4±18.2*
Chen 2020 (79)	Jiangsu	Case series	2019/12/01–2020/03/01	30	17 (56.7)	48.9±13.1*
Zhong 2020 (80)	Hainan	Case series	2020/01/21–2020/02/10	62	40 (64.5)	51.8±13.5*
Zhu 2020 (81)	Anhui	Case series	2020/01/18–2020/03/08	79	44 (55.7)	56.1±12.7*
Li 2020 (45)	Hubei	Case series	2020/01/21–2020/03/02	193	112 (58.0)	50.7±16.2*
Zhang 2020 (82)	Anhui	Case series	2020/01/23–2020/02/15	36	20 (55.6)	(8,75)***
Zhang 2020 (83)	Wuhan	Case series	2020/01/19–2020/02/08	10	7 (70.0)	74.5**
Xia 2020 (84)	Wuhan	Case series	2020/01/15–2020/02/08	52	23 (44.2)	54.0±12.8*
Zheng 2020 (85)	Wuhan	Case series	2020/01/01–2020/02/01	71	35 (49.3)	62.0 (53.5, 70.0)**
Sun 2020 (86)	Wuhan	Case series	2020/02/09–2020/02/27	51	27 (52.9)	68.0*
Sun 2020 (87)	Henan	Case series	2020/01/24–2020/02/16	150	67 (44.7)	45.0±16.0*
Xu 2020 (54)	Zhejiang	Case series	2020/01/10–2020/01/26	62	35 (56.5)	41.0 (32.0, 52.0)**
Tian 2020 (88)	Hubei	Case series	2020/01/13–2020/02/13	25	11 (44.0)	38.0**
Chen 2020 (89)	Guangdong	Case series	2020/01/11–2020/02/02	12	8 (66.7)	63.0*
Yin 2020 (90)	Wuhan	Case series	2020/01/31–2020/02/10	95	34 (35.8)	35.0**
Yu 2020 (91)	Beijing	Case series	From 2020/01/21	40	26 (65.0)	39.9±18.2*
Cui 2020 (92)	Gansu	Case series	–	8	5 (62.5)	40.1*
Shang 2020 (93)	Anhui	Case series	2020/01/22–2020/02/19	36	21 (58.3)	38.6±10.6*
Hao 2020 (94)	Zhejiang	Case series	2020/01/17–2020/02/12	788	407 (51.6)	46.0 (35.0, 55.8)**

Table S1 (*continued*)

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Table S1 (*continued*)

Study ID	Study location	Study type	Time	Sample size	Sex (%,man)	Age (year)
Wang 2020 (95)	Shandong	Case series	2020/01/31–2020/02/12	26	11 (42.3)	42.0 (34.0, 53.0)**
Tian 2020 (96)	Shandong	Case series	–	37	17 (45.9)	44.3±16.7*
Xu 2020 (37)	Zhejiang	Case series	2020/01/13–2020/02/19	113	66 (58.4)	52.0 (43.0, 63.0)**
Zhu 2020 (97)	Anhui	Case series	2020/01/24–2020/02/20	116	56 (48.3)	40.0 (27.0, 53.0)**
Huang 2020 (47)	Hunan	Case series	2020/01/17–2020/02/10	54	28 (51.9)	41.0 (31.0, 51.0)**
Jiang 2020 (48)	Zhejiang	Case series	2020/01/16–2020/01/31	60	35 (58.3)	41.0**
Xu 2020 (54)	Zhejiang	Case series	2020/01/10–2020/02/26	62	35 (56.5)	41.0 (32.0, 52.0)**
Huang 2020 (35)	Hubei	Case series	2020/01/25–2020/03/24	299	160 (53.5)	53.4±16.7*
Huang 2020 (2)	Wuhan	Case series	2019/12/16–2020/01/02	41	30 (73.2)	49.0 (41.0, 58.0)**
Lauer 2020 (98)	Outside of Hubei	Case series	2020/01/04–2020/02/24	181	108 (59.7)	44.5 (34.0, 55.5)**
Xie 2020 (99)	Shanghai	Case series	2020/01/01–2020/02/15	105	54 (51.4)	44.1±18.1*
Shi 2020 (100)	Shanghai	Case series	2020/01/20–2020/02/07	184	99 (53.8)	49.0±15.0*
Hu 2020 (32)	Shandong	Cohort study	2020/01/29–2020/03/12	59	28 (47.5)	46.0 (33.0, 57.0)**
Liang 2020 (34)	China	Cohort study	2019/11/21–2020/01/31	1590	904 (57.3)	48.9±16.3*
Deng 2020 (36)	Wuhan	Case series	2020/01/01–2020/02/21	225	124 (55.1)	–
Hua 2020 (101)	Wuhan	Case series	2020/02/07–2020/02/26	205	112 (54.6)	51.0 (39.0, 57.0)**
Lu 2020 (102)	Jiangsu	Case series	2020/01/23–2020/02/26	28	17 (60.7)	48.3±13.5*
Shen 2020 (103)	Shanghai	Case series	2020/01/20–2020/02/29	325	168 (51.7)	50.0*
Tian 2020 (42)	Beijing	Case series	2020/01/20–2020/02/10	262	127 (48.5)	47.5 (45.1, 49.9)**
Shi 2020 (104)	Wuhan	Case series	2020/01/20–2020/02/10	416	205 (49.3)	64.0 (21.0, 95.0)**
Hung 2020 (105)	Hongkong	Case series	2020/02/10–2020/03/20	127	68 (53.5)	52.0 (32.0, 62.0)**
Zhao 2020 (106)	Hubei	Case series	2020/01/16–2020/02/17	136	68 (50.0)	49.0 (33.0, 63.0)**
Qi 2020 (38)	Guangdong	Cohort study	2020/01/24–2020/03/08	147	80 (54.4)	42.0 (35.0, 54.0)**
Yu 2020 (107)	Wuhan	Case series	2020/02/13–2020/02/28	129	56 (43.4)	64.0 (56.0, 69.0)**
Zhou 2020 (39)	Wuhan	Cohort study	2020/01/15–2020/03/15	238	102 (42.9)	55.5 (35.0, 67.3)**
Xia 2020 (108)	Wuhan	Case series	2020/02/04–2020/03/30	1568	797 (50.8)	63.0 (55.0, 71.0)**
Miao 2020 (109)	Shanghai	Case series	2020/01/12–2020/02/13	54	28 (51.9)	45.1±13.4*
Huang 2020 (49)	Jiangsu	Case series	2020/01/22–2020/02/10	202	116 (57.4)	44.0 (33.0, 54.0)**
Lam 2020 (110)	Hongkong	Case series	2020/01/23–2020/05/31	1084	588 (54.2)	37.5*
Wang 2020 (111)	Wuhan	Case series	To 2020/02/10	107	57 (53.3)	51.0 (36.0, 65.0)**
Zeng 2020 (112)	Sichuan	Case series	2020/01/16–2020/02/05	20	12 (60)	57.4±16.5*
Zou 2020 (113)	Wuhan	Case series	2020/01/01–2020/01/29	15	10 (66.7)	61.7±9.6*
Ding 2020 (114)	Wuhan	Case series	2020/01/01–2020/02/03	56	30 (53.6)	54.6±15.5*
Li 2020 (115)	Henan	Case series	2020/01/20–2020/02/17	40	20 (50.0)	50.9*
Wu 2020 (30)	Hubei	Case series	2020/01/01–2020/03/22	102	75 (73.5)	51.6±19.3*
Wang 2020 (116)	Wuhan	Case series	2020/01/20–2020/02/14	96	46 (47.9)	–
Zhai 2020 (43)	Anhui	Case series	2020/01/22–2020/03/04	74	41 (55.4)	54.9±11.8*
Tian 2020 (117)	Jiangsu	Case series	2020/01/23–2020/02/16	23	10 (43.5)	49.7±13.1*
Yu 2020 (118)	Wuhan	Case series	2020/12/18–2020/01/29	608	398 (65.5)	60.2±8.7*
Tian 2020 (119)	Jiangsu	Case series	2020/01/23–2020/02/10	26	14 (53.9)	47.9±13.1*
Shang 2020 (120)	Anhui	Case series	2020/01/22–2020/02/19	36	21 (58.3)	38.6±10.6*
Zeng 2020 (121)	Hunan	Case series	2020/01/24–2020/02/19	79	41 (51.9)	45.9±12.7*
Hong 2020 (122)	Guangdong	Case series	2020/01/17–2020/03/01	18	9 (50.0)	63.5 (51.5, 67.5)**
Wang 2020 (123)	Wuhan	Case series	2020/01/10–2020/02/08	312	145 (46.5)	52.0 (42.0, 62.0)**
Lin 2020 (124)	Zhejiang	Case series	2020/01/15–2020/02/05	71	22 (31.0)	50.3±14.6*
Tu 2020 (125)	Wuhan	Case series	2020/01/10–2020/02/29	75	53 (70.7)	68.0 (62.0, 74.0)**
Liu 2020 (126)	Wuhan	Case series	2020/01/16–2020/02/15	64	23 (35.9)	35.0 (29.0, 43.0)**
Chen 2020 (127)	Guangdong	Case series	2020/01/20–2020/03/15	284	131 (46.1)	48.0 (33.0, 62.0)**
Chen 2020 (128)	Wuhan	Case series	2020/01/01–2020/03/02	30	14 (46.7)	60.5 (32.0, 77.0)**
Yao 2020 (129)	Wuhan	Case series	2020/01/26–2020/02/18	55	37 (67.3)	70.7±13.5*
Zhang 2020 (130)	Wuhan	Case series	2020/01/20–2020/02/29	564	286 (50.7)	60.0 (48.0, 67.0)**
Duan 2020 (131)	Wuhan	Case series	2020/01/01–2020/01/31	116	58 (50.0)	62.5 (55, 68.3)**
Leung 2020 (132)	Hongkong	Case series	2020/01/26–2020/02/28	50	23 (46.0)	55.2±19.5*

*, mean SD; **, median (IQR); ***, range; –, not report.

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Table S2 Case series

Study ID	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Scores[††]
Luo 2020 (11)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Ng 2020 (21)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Jung 2020 (22)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	6
Hong 2020 (23)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Husain 2020 (24)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Dreher 2020 (26)	No	Yes	Yes	No	No	Yes	Yes	Yes	5
Imai 2020 (27)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Mahévas 2020 (28)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	6
Gao 2020 (58)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	6
Fu 2020 (59)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Liu 2020 (31)	No	Yes	No	Yes	No	Yes	Yes	Yes	5
Liu 2020 (60)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Huang 2020 (61)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Liu 2020 (40)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Liu 2020 (62)	No	No	No	Yes	No	Yes	Yes	No	3
Han 2020 (44)	Yes	Yes	No	No	No	No	Yes	No	3
Yu 2020 (63)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Xia 2020 (64)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Chen 2020 (41)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Ye 2020 (33)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Yang 2020 (65)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Li 2020 (66)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Cao 2020 (67)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Yuan 2020 (46)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Zeng 2020 (68)	Yes	Yes	No	Yes	No	Yes	Yes	No	5
Chen 2020 (69)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Hu 2020 (70)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Zhang 2020 (71)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Yang 2020 (72)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
An 2020 (73)	No	Yes	No	Yes	No	Yes	Yes	Yes	5
Liu 2020 (74)	No	Yes	No	Yes	No	Yes	Yes	No	4
Li 2020 (29)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Shi 2020 (75)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Lei 2020 (76)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Sun 2020 (77)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Bai 2020 (78)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Chen 2020 (79)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Zhong 2020 (80)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Zhu 2020 (81)	No	Yes	No	Yes	No	Yes	Yes	Yes	5
Li 2020 (45)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Zhang 2020 (82)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Zhang 2020 (83)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Xia 2020 (84)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Zheng 2020 (85)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Sun 2020 (86)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Sun 2020 (87)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Xu 2020 (54)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Tian 2020 (88)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Chen 2020 (89)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Yin 2020 (90)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Yu 2020 (91)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Cui 2020 (92)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Shang 2020 (93)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Hao 2020 (94)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	6
Wang 2020 (95)	No	Yes	Yes	No	No	Yes	Yes	No	4
Tian 2020 (96)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6

Table S2 (*continued*)

Table S2 (*continued*)

Study ID	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Scores††
Xu 2020 (37)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Zhu 2020 (97)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Huang 2020 (47)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Jiang 2020 (48)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Xu 2020 (54)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Huang 2020 (35)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Huang 2020 (2)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Lauer 2020 (98)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Xie 2020 (99)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Shi 2020 (100)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Deng 2020 (36)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Hua 2020 (101)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Lu 2020 (102)	No	No	Yes	Yes	No	Yes	Yes	No	4
Shen 2020 (103)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Tian 2020 (42)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Shi 2020 (104)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Hung 2020 (105)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	6
Zhao 2020 (106)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Yu 2020 (107)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Xia 2020 (108)	No	Yes	No	Yes	No	Yes	Yes	Yes	5
Miao 2020 (109)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Huang 2020 (49)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Lam 2020 (110)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Wang 2020 (111)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Zeng 2020 (112)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Zou 2020 (113)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Ding 2020 (114)	No	Yes	No	Yes	No	Yes	Yes	No	4
Li 2020 (115)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Wu 2020 (30)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Wang 2020 (116)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Zhai 2020 (43)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Tian 2020 (117)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Yu 2020 (118)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Tian 2020 (119)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Shang 2020 (120)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Zeng 2020 (121)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Hong 2020 (122)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Wang 2020 (123)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Lin 2020 (124)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Tu 2020 (125)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Liu 2020 (126)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Chen 2020 (127)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Chen 2020 (128)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Yao 2020 (129)	No	Yes	Yes	Yes	No	Yes	Yes	No	5
Zhang 2020 (130)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	6
Duan 2020 (131)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6
Leung 2020 (132)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7

††, according to the methodology evaluation tool recommended by National Institute for Health and Care Excellence. The risk of bias is evaluated according to eight criteria. The results were summarized by scoring method, for the "Yes" items, the score was 1, and for the "no" items, the score was 0. The maximum score is 8; the higher the score, the lower the risk of bias. The numbers 1 to 8 refer to the items of the tool: 1. case series collected in more than one centre, i.e., multi-centre study; 2. is the hypothesis/aim/objective of the study clearly described? 3. are the inclusion and exclusion criteria (case definition) clearly reported? 4. is there a clear definition of the outcomes reported? 5. were data collected prospectively? 6. is there an explicit statement that patients were recruited consecutively? 7. are the main findings of the study clearly described? 8. are outcomes stratified? (e.g., by disease stage, abnormal test results, patient characteristics).

Table S3 Cohort study

Study ID	Selection				Comparability		Exposure			Scores[†††]
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	
Young 2020 (20)	*	*	*	*	*	*	*	×	*	8
Cummings 2020 (25)	*	×	*	*	×	*	*	*	×	6
Hu 2020 (32)	*	×	*	×	×	*	*	×	×	4
Liang 2020 (34)	*	*	*	*	*	*	*	×	×	7
Qi 2020 (38)	*	*	*	×	*	*	*	×	×	6
Zhou 2020 (39)	*	*	*	×	*	*	*	×	×	6

[†††], according to the methodology evaluation tool of Newcastle-Ottawa Scale. It consists of eight domains, for each, we will grade with stars. The more stars, the lower the risk of bias. The maximum score is 9. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. The numbers 1 to 8 refer to the items of the tool: 1. representativeness of the exposed cohort; 2. selection of the non-exposed cohort; 3. ascertainment of exposure; 4. demonstration that outcome of interest was not present at start of study; 5. comparability of cohorts on the basis of the design; 6. comparability of cohorts on the basis of analysis; 7. assessment of outcome; 8. duration of follow-up; 9. adequacy of follow up of cohorts. *, adequate; ×, not adequate/unclear.

Table S4 Summary of findings

Outcomes	No.of studies	Sample size	Certainty assessment					MD (95% CI)	Certainty
			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Duration from symptom onset to first medical visit of the common patients and severe patients	6	1376	Serious[1]	Not serious	Not serious	Not serious	None	−1.25 (−1.71, −0.80)	⊕○○○ very low
Duration from symptom onset to admission of the common patients and severe patients	7	1593	Serious[1]	Not serious	Not serious	Not serious	None	−1.92 (−2.55, −1.30)	⊕○○○ very low

[1], downgrade one level: the risk of bias is high due to the limitations of study design. MD, mean difference; CI, confidence interval.

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