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Distribution of symptoms, comorbidities, and severity among patients with COVID-19 by age groups, countries, and stages of outbreak: a systematic review and meta-analysis

Running head

Symptoms, comorbidities, and severity of COVID-19

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Declaration of interests

The authors declare that they have no conflicts of interest.

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Authors' contribution

KFC and IY wrote the manuscript. KFC and CCW performed the literature review and the statistical analysis. SHL, CFY, STH, CYM, DH, RR, AP, and KFC revised the text. All authors read and approved the final manuscript.

What is already known on this topic?

Since December 2019, the coronavirus disease (COVID-19) pandemic has changed our daily lives, caused near million deaths, and has resulted in a socio-economic impact worldwide.

What question this study addressed?

In this largest systematic review analysis and meta-analysis including 189 studies consisting of 53,659 patients, we demonstrated satisfactory positive and negative likelihood ratios by combining symptoms to provide direction to front-line clinicians confronting the COVID-19 pandemic outbreak.

What this study adds to our knowledge?

In our quantitative synthesis, approximately one in five test-positive adults was not febrile, and we

found that the sensitivity threshold of fever should be 37.3 °C. Overall, we found a lower prevalence (i.e., sensitivity) of symptoms among COVID-19 patients than in earlier studies, and we demonstrated that the stage of the outbreak is an important factor for the prevalence of the symptoms.

How this is relevant to clinical practice?

We demonstrated satisfactory positive and negative likelihood ratios by combining symptoms to provide direction to front-line clinicians confronting the COVID-19 pandemic outbreak. We further demonstrated that fever should not be used as a single measure to screen for patients with possible COVID-19 infection, and the selection of threshold should be carefully evaluated.

Abstract

Study objective

Since December 2019, the coronavirus disease (COVID-19) pandemic has caused over a million deaths and resulted in adverse socio-economic impacts worldwide. However, predictability and prognostication of clinical features vary among different populations.

Methods

We search PubMed, EMBASE, Cochrane Library, Google Scholar, and WHO Global Health Library from December 2019 to April 2020 for studies reporting the risk factors, clinical features, and outcomes. The random-effect models for transformed prevalence (single-arm) or bivariate random-effect models (sensitivity and specificity) for correlated performance indicators.

Results

Among the 189 included studies representing 53,659 patients, the most sensitive predictor for COVID-19 infection was fever in adults (83%, 95% confidence interval [CI]:73–90%), and the most specific predictor was fatigue (96%, 95% CI: 80–99%). Fever was the most sensitive symptom in predicting the severity (89%, 95% CI:83–92%), followed by cough (71%, 95% CI:63–78%). The most specific predictor of severe COVID-19 was a chronic obstructive pulmonary disease (99%, 95% CI:98–99%). The stage of the outbreak and age significantly affect the prevalence of fever, fatigue, cough, and dyspnea. Fever, cough, fatigue, hypertension, and diabetes mellitus combined have a 3.06 positive likelihood ratio (PLR) and a 0.59 negative likelihood ratio

(NLR) in the diagnosis. Additionally, fever, cough, sputum production, myalgia, fatigue, and dyspnea combined have a 10.44 PLR and a 0.16 NLR in predicting severe COVID-19.

Conclusions

Understanding the different distribution of predictors essential for screening potential COVID-19 infection and severe outcomes and the combination of symptoms could improve the pre-test probability.

Introduction

Background

Since the initial cases were identified in Wuhan, China, the coronavirus disease (COVID-19) has spread worldwide at an alarming rate, changed our daily lives, caused over a million deaths, and resulted in an adverse socio-economic impact worldwide.[1, 2] The World Health Organization (WHO) has declared COVID-19 a global health emergency, and over ten months since its outbreak was first reported, countries across the world are struggling with a rise in the incidence of confirmed cases.[3]

Importance

The data on the incidence, risk factors, case fatality rate, and clinical features of COVID-19 have been growing daily.[4] Interestingly, the reported case fatality rate differs according to clinical characteristics and by country.[5-7] Furthermore, as the number of cases rapidly increases, its clinical features, epidemiological characteristics, and risk factors for mortality are still not completely understood.[8-10]

Goals of this investigation

An increased understanding of the epidemiological and clinical course of COVID-19 could significantly improve public health interventions needed to contain the pandemic. An essential measure to prevent COVID-19 from spreading is the timely recognition of infected patients. However, the predictive value of clinical features could vary among different populations. Therefore, we conducted a systematic review and meta-analysis to provide up-to-date qualitative

and quantitative evidence of the epidemiology, clinical characteristics, laboratory data, and test the hypothesis that the distribution of symptoms, comorbidities, and severity would be different among patients different age groups, countries, and stages of outbreak.

Keywords: COVID-19; sensitivity; specificity; diagnosis; prognosis

Methods

This study was performed in adherence to the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guideline[11] and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[12] The protocol was registered in PROSPERO (CRD42020176289).[13]

Search strategy

We searched PubMed, EMBASE, Cochrane Library, Google Scholar, and WHO Global Health Library for articles published between December 1, 2019 and April 30, 2020. With a combination of Boolean operations, the following keywords were used as search terms: COVID-19, coronavirus disease, novel coronavirus, SARS-CoV-2, 2019-nCoV infection, Wuhan coronavirus, Wuhan pneumonia, clinical characteristics, epidemiology, incidence, physical examination, signs and symptoms, clinical manifestation and diagnosis. Additionally, references of included articles were manually searched to ensure that all relevant articles were included (the ‘snow-ball’ search strategy).[14] The detailed search strategy is presented in Table S1.

Eligibility criteria

We included cohort, cross-sectional, case-control, and case-series studies reporting the risk factors, clinical features, and outcomes of COVID-19 patients confirmed by a positive reverse-transcriptase polymerase chain reaction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To avoid language bias,[15] we included articles published in any language. We also included articles that reported outcomes of patients without restriction to clinical settings (inpatients, outpatients, or the general population). We excluded studies considering pregnant women and neonates, owing to many asymptomatic evaluations. We excluded manuscripts without peer-review, non-human studies, non-original studies, duplicates, reviews, case reports, or case series with fewer than four subjects. Ambiguously described data, such as 'fever or cough', were excluded.

Primary and secondary outcomes

The primary outcomes were the diagnostic performance of symptoms, demographics, comorbidities, and laboratory data in predicting COVID-19 infection. The secondary outcomes were the performance of predictors in prognosticating severe infection (e.g. mortality, pneumonia, and ICU hospitalisation).

Data extraction

We extracted data on study characteristics (e.g. author, country, study design, date of a study conducted, number of participants), patient characteristics (e.g. age, gender, ethnicity, comorbidities), symptoms (e.g. degree of fever, cough), laboratory data (e.g. white blood cell (WBC) and lymphocyte counts), and adverse outcomes (e.g. severity, mortality, hospitalisation). If detailed information was missing in the papers, we contacted the authors of those studies to ask

for the relevant data. We transformed medians and interquartile ranges into means and standard deviations and standard errors to standard deviations.[16] We included the most up-to-date and complete data for overlapping patient populations in the studies identified. Additionally, we examined published systematic reviews on COVID-19 to ensure that no study was missed.

Study quality assessment

We used the National Institute of Health in the U.S. Quality Assessment Tool to assess the quality of studies (Supplementary Table S2).[17] Two reviewers reviewed and assessed article by screening (i.e. title screening, abstract screening, full-text review), followed by data extraction and quality assessment independently. Any discrepancy between the reviewers was resolved by discussion with a senior reviewer (K-F C) to reach a consensus.

Data synthesis

The summary measures estimated in this meta-analysis depending on the outcome were mean, standard deviation, prevalence, and weighted mean differences (WMD). The WMD was used to summarise continuous variables such as WBC and lymphocyte counts between severe and non-severe COVID-19 infections. We used the random-effects models to pool estimates of the prevalence of symptoms with the maximum likelihood methods and variance stabilising transformation.[18-20] Some eligible studies had a prevalence of various predictors equal to zero; hence, we computed the pooled estimates using the Freeman–Tukey double arcsine transformation (PFT).[21] We then used the bivariate random-effect models to synthesise evidence of diagnostic accuracy.[22] We also used the hierarchical summary receiver operating characteristic (HSROC)

models[23] to calculate the pooled sensitivity and specificity, and the area under the summary receiver operating characteristic (AUHSROC) curve.

We further utilised the Fagan nomogram[24-26] to illustrate how clinicians could apply the predictors in their daily practice. A nomogram is a two-dimensional graphical tool that is important in estimating the post-test results given a specific pre-test probability and the likelihood ratio of the predictor. The nomogram was based on the combination of the likelihood ratios of a series of predictors obtained from the meta-analysis.

We examined the statistical heterogeneity by visual inspection of the forest plots and the Cochrane Q chi-squared ($\chi 2$) test, and calculated the I^2 statistics.[27] We considered I^2 values of up to 25%, 50%, and 75% to indicate low, moderate, and high heterogeneity, respectively.[28] We determined the statistical significance of heterogeneity using the Cochrane Q test at $p<0.1$.

Publication bias

We examined the potential publication bias by visual inspection of funnel plots using sample size as a measure of precision on the y-axis while dealing with extremely low or high prevalence, rank correlation test, and Egger's regression test.[29]

Sensitivity analyses

We examined how the estimates changed according to study quality, transformation methods, study designs, country, stage of the outbreak, age of patients, and threshold of fever. The stage of the outbreak was divided into early and later stages (conducted after January). The age of the patients was categorised into adults (>18 years) and children. The study designs were sub-classified into cohort studies, case-series, and case-control studies, and the ethnicity was sub-classified into Chinese and non-Chinese settings. The random-effects Q-test for heterogeneity was used to evaluate the subgroup differences. For between-study heterogeneity, we performed an outlier analysis to explore the source of heterogeneity that may be caused by one or more studies with extreme effect sizes. We performed multivariable meta-regression analyses with bivariate binomial mixed-effect models to explore the sources of heterogeneity.

All statistical analyses were conducted using the 'meta' package for general meta-analysis, and 'meta4diag' or 'HSROC' packages for diagnostic meta-analysis in R (The R Foundation for Statistical Computing, Vienna, Austria; version 3.6.3) and Stata 15.1 (Stata Corporation, College Station, TX, USA).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. The authors had full access to all the data, and the corresponding author was responsible for the decision to submit for publication.

Results

Study selection and characteristics of the included studies

Out of 5,180 reports retrieved from the initial search of different databases, we included 189 articles representing a total of 53,659 patients in the study (Figure 1). Most of the included studies were cohort studies (N=129), followed by case series (N=52) and case-control studies (N=8). We included studies from 11 countries, and 171 studies reported data from China. The average age of the reported adult studies was 50.4 years. The most reported symptoms were fever (N=182), cough (N=169), diarrhea (N=110), dyspnea (N=95), and fatigue (N=94, Supplementary Figure S1). The detailed study characteristics are shown (Supplementary Table S3).

Distribution of symptoms of COVID-19

Variables such as mortality rate, the prevalence of COVID-19 infection, fever, cough, sputum production, sore throat, myalgia, fatigue, dyspnea, headache, nausea, and diarrhea were included in the meta-analyses (Supplementary Table S4). The overall prevalence of fever among COVID-19 cases reported in 182 studies was 76% (95% confidence interval [CI]: 72–79%, Supplementary Table S4 and Figure 2). The prevalence of fever was significantly lower among children and in non-Chinese studies (52% vs. 80% and 53% vs. 78%, both $P<0.001$, Supplementary Table S4 and Figure S2b). After removal of 82 considered outliers, the prevalence of fever significantly increased from 76% to 78% ($P<0.05$, Supplementary Table S5). Moreover, the second common reported symptom, cough, had a prevalence of 56% in 169 studies (95% CI: 52–59%) and was significantly less common among children (44% vs. 57%, $P=0.018$, Supplementary Table S4 and Figure 2). The pooled prevalence of the remaining variables is shown in Supplementary Table S4.

The overall prevalence of severe cases among COVID-19 patients reported in 27 studies was 31% (95% CI: 25–37%). The most common symptom of severe cases was fever (89%, 95% CI: 83–92%), followed by cough (71%, 95% CI: 63–78%). The severe cases had significantly higher white blood cell (WBC) counts and lower lymphocyte counts (WMD) (1.06×10^9/L, 95% CI: 0.36–1.77×10^9/L, P<0.01 and -0.38×10^9/L, 95% CI: -0.47–-0.30×10^9/L, P<0.01, respectively, Figure 3 and Supplementary Figure S3), whereas the pooled WBCs for severe and non-severe cases were 5.89×10^9/L (95% CI: 5.45–6.33×10^9/L) and 5.00×0^9/L (95% CI: 4.75–5.26×10^9/L), respectively, and the pooled lymphocyte counts for severe and non-severe cases were 0.78×10^9/L (95% CI: 0.72–0.84×10^9/L) and 1.16×10^9/L (95% CI: 1.10–1.23×10^9/L), respectively.

Diagnostic and prognostic performance analysis

Only adult patients were included in the studies for diagnostic and prognostic performance analyses. The most sensitive symptom in the diagnosis of COVID-19 was fever, with a fair pooled sensitivity of 83% (95% CI: 73–90%), but a poor overall performance (AUHSROC: 0.55, 95% CI: 0.51–0.60, Figure 4a), followed by cough (39%, 95% CI: 11–76%). The most specific predictor of COVID-19 was fatigue (96%, 95% CI: 80–99%), followed by diabetes mellitus (85%, 95% CI: 77–91%) and hypertension (74%, 95% CI: 60–84%, Figure 4b). The overall positive likelihood ratio (PLR) to predict COVID-19 for the combination of five predictors (fever, cough, fatigue, hypertension, and diabetes mellitus) was 3.06, while the overall negative likelihood ratio (NLR) was 0.59 (Figure 5a).

Furthermore, fever was also the most sensitive symptom in predicting severe COVID-19 (89%, 95% CI: 83–92%), followed by cough (71%, 95% CI: 63–78%). The most specific predictor of

severe COVID-19 was chronic obstructive pulmonary disease (COPD) (99%, 95% CI: 98–99%), followed by diabetes mellitus, hypertension, and dyspnea (93%, 95% CI: 91–95%; 87%, 95% CI: 84–89%; and 87%, 95% CI: 75–93%, respectively, Figure 4b). Moreover, we developed a nomogram to aid in predicting the risk of severe infection. The overall PLR for predicting severe COVID-19 for the combination of six symptoms (fever, cough, sputum production, myalgia, fatigue, and dyspnea) was 10.44, while the overall NLR was 0.16 (Figure 5b).

Adverse outcome assessment

The overall pooled mortality rate among the reported COVID-19 cases was 10% (95% CI: 6–14%, Supplementary Table S4, and Figure 2). In sub-group analyses, mortality rates were lower among children (0% vs. 12%, P<0.0001), Chinese studies (9% vs. 15% P=0.462) and in cohort studies (compared to case series: 9% vs. 17%, P= 0.101, Supplementary Table S4 and Figure S2).

Publication bias

Significant publication bias by Egger's test was found in mortality, severity and the following symptoms: fever, cough, sore throat, myalgia, fatigue, dyspnea, headache, nausea, and diarrhea (Supplementary Table S5 and Figure S5).

Sensitivity analysis

We found that the sensitivity of fever was strongly correlated with the thresholds (75% for 37.3 ^{o}C, 45% for 38 °C, and 16% at 39 °C, Table S6). We found no significant difference among different transformation methods such as logit transformation (PLO), arcsine transformation (PAS), PFT, and generalised linear mixed model (GLMM, Supplementary Table S7). However,

we found substantial heterogeneity with >75% I^2 for mortality, the prevalence of severe COVID-19, and symptoms including fever, cough, sputum production, sore throat, myalgia, fatigue, dyspnea, headache, nausea, and diarrhea (Table S4). Additionally, the prevalence of symptoms among COVID-19 patients ranged widely among different study designs. In case-control studies, the prevalence of fever, cough, myalgia, fatigue, and nausea was found to be higher than that in cohort studies (Supplementary Table S4 and Figure S2a). After the removal of 31 studies by outlier analysis, the pooled mortality rate decreased insignificantly from 10% to 9% (Egger's test: -2–0.375, P=0.145, Supplementary Table S5). We further investigated the potential sources of heterogeneity in the multivariable meta-regression.

Meta-regression results

We identified the correlation between the sensitivity of symptoms such as fever, cough, fatigue, and dyspnea, and potential confounders, such as the stage of the outbreak, age, and comorbidities. The sensitivity of fever in COVID-19 cases decreased significantly with the stage of the outbreak (85% to 50%, P<0.001), with a correlation coefficient of -0.152 (Supplementary Figure S4a and Figure S5). Moreover, the sensitivity of fever was positively correlated with age, ranging from 50% to 80% (P<0.001), with a correlation coefficient of 0.283 for the adult age (Supplementary Figure S4b and Figure S5). Cough was negatively correlated with the stage of the outbreak (80% to 60%, P<0.001, Supplementary Figure S4a), while it was positively correlated with age (sensitivity: 45% to 60%, P<0.001, Supplementary Figure S4b), with a correlation coefficient of 0.121 for age in adults (Figure S5). Similarly, fatigue was negatively correlated with the stage of the outbreak but positively correlated with age (sensitivity: 60–10% and 10–45%, respectively; both P<0.001, Supplementary Figure S4). After multivariable meta-regression adjusting for the potential

confounders, the prevalence of dyspnea, myalgia, and headache among COVID-19 patients increased slightly, while that of fever, cough, fatigue, diarrhea, and nausea decreased slightly (Supplementary Figure S5).

Quality assessment

The risk of bias assessment is illustrated in Supplementary Figure S6 and Table S2. Most of the studies lacked adequate justification of sample size and blinding of the outcome assessment. The other common risks of bias were the lack of confounder adjustment, prospective measurement of exposure, sample size justification, and blinding of the outcome assessment (Supplementary Figure S7). In the subsequent sensitivity analysis, we found that predictors such as fever, headache, and sore throat could be over-estimated in non-prospectively measured exposures and that there was a lack of concurrent controls (Supplementary Tables S8 and S9).

Limitations

Our study has several limitations. First, to maximise the sample size to deliver the most confident estimates of the predictors, we pooled different kinds of studies together. However, in the subsequent sensitivity analyses, we provided further detailed results for clinicians. Second, at the beginning of the outbreak, patients included in these studies could have had severe disease manifestation, considering the lack of medical resources, attention, and consistent screening and diagnostic criteria. Nevertheless, we also provided adjusted pooled sensitivity of these predictors in the meta-regression, attempting to minimise the influence of age, comorbidities, and the stage of the outbreak. Third, although we attempted to evaluate the influence of the risk of bias in the subgroup analyses, it is not possible to incorporate different risks of bias in different study designs. Accordingly, we could only provide the potential influence in the sensitivity analyses. Fourth, few studies reported the control group results, which could have influenced the precision of specificity in our study. Fifth, smell and taste dysfunctions, or olfactory and gustatory dysfunctions, were discussed in various articles as important symptoms of COVID-19. Previous systematic reviews indicated that the prevalence of olfactory and gustatory dysfunctions was 41.0% (95% CI: 28.5–53.9%) and 38.2% (95% CI: 24.0–53.6%), respectively.[30] However, since these symptoms remained unrecognised during the early stages of the pandemic, most reports did not consider these symptoms and thus we do not have sufficient data for an accurate analysis. Lastly, the composite criteria of severe COVID-19 used in different studies might have influenced the predictor performance.

Discussion

To the best of our knowledge, this is the largest systematic review analysis and meta-analysis, including 189 studies consisting of 53,659 patients, to evaluate predictors for COVID-19 and severe COVID-19 infection. In our quantitative synthesis, approximately one in five test-positive adults was not febrile, and we found that the sensitivity threshold of fever should be 37.3 ºC. Overall, we found a lower prevalence of symptoms among COVID-19 patients than in earlier studies, and also that the outbreak stage was an important confounding factor. We also demonstrated two nomograms with satisfactory PLR and NLR by combining symptoms to provide direction to front-line clinicians in their daily practice.

We found a lower prevalence of symptoms among COVID-19 patients than earlier studies.[31, 32] The most reported predictors were fever, cough, diarrhea, dyspnea, and fatigue.[33] A previous small-scale study indicated fever as the most prevalent clinical symptom (91.3%, 95% CI: 86–97%), followed by cough (67.7%, 95% CI: 59–76%), fatigue (51.0%, 95% CI: 34–68%), and dyspnea (30.4%, 95% CI: 21–40%).[31] The findings of another larger study that considered patients with more severe infection were similar (fever: 88.7%, 95% CI: 84.5–92.9%, cough: 57.6%, 95% CI: 40.8–74.4%).[32] Furthermore, a previous systematic review of 16 studies identifies fever, myalgia or arthralgia, fatigue, and headache as having clear predictive value (defined as having a PLR of at least 5) for COVID-19 as their specificity was above 90%.[9] However, meta-analyses could not be performed due to the small number of studies, heterogeneity across studies, and the high risk of bias. They also identified incorporation bias, which may increase the sensitivity of the symptoms used to screen patients as well as spectrum bias caused by including participants with only pneumonia for imaging in five of the included studies. However, a recent study found 10% lower estimates from prior systematic reviews and meta-analyses, similar to our results.[34]

Nonetheless, the authors did not examine the risk of bias in the included studies, and they only used fever for dichotomisation.

Another important reason that might result in different prevalence of fever among COVID-19 patients could be due to the thresholds selected in different studies. As we indicated in our study, the prevalence of fever of patients ranged largely from 75% for 37.3 °C to 45% at 38 °C. Since a thermal detector may be used as the only measure to screen patients in many resource-limited settings, the understanding of different thresholds and their related sensitivities is important.

The effect of different stages of the outbreak could be the reason for these discrepancies. We found a lower prevalence of fever and fatigue among studies conducted in later stages of the outbreak, which may be due to different patient selection, different definitions of the disease syndrome, and different resource utilisation. The clinical features of COVID-19 patients might differ in different outbreak stages.[35] The insufficient understanding of the virus, shortage of medical resources, and the spectrum of the patients reported could be the reason patients in different outbreak stages could have different manifestations.[36] Further, fever and cough occurred in the early stage of the infection. Accordingly, clinicians should pay attention to the stage of the pandemic or epidemic in their practice locations as well as the infection stage of the patients.

We also found a lower prevalence of fever, cough, fatigue, dyspnea, and severe cases among younger infected populations. Similar to an updated meta-analysis,[37] we found that only half of the pediatric COVID-19 patients had fever. It is thought that children might have an underdeveloped immune system, which may inversely prevent the likelihood of severe infection induced by an over-reacting immune response.[38]

The pooled mortality rates and prevalence of severe infection were found to be 10% and 31%, respectively. Fever was the most sensitive predictor, and COPD was the most specific predictor for severe COVID-19 infection. These two predictors are less reported, whereas other comorbidities such as hypertension, respiratory system disease, and cardiovascular disease are found to be associated with disease severity.[31, 39] Similar to previous studies, we found that leucocytosis and lymphopenia were associated with severe infection.[40, 41] We provided pooled WBC and lymphocyte counts, along with the WMD between severe and non-severe patients in 27 studies. This phenomenon occurs because T lymphocyte cells, including CD4 and CD8 cells, might be killed by viruses such as influenza in severe cases and result in profound lymphopenia.[42, 43]

Furthermore, many other confounders could influence the diagnostic and prognostic performance of the predictors in the observational studies included. One of the most important factors is the selection of study populations. As we indicated in our subgroup analyses, case-control studies tend to give overestimated prevalence of symptoms among COVID-19 patients. Furthermore, age and many comorbidities could influence the performance of these predictors. The multivariable meta-regression results reveal that the prevalence of dyspnea, myalgia, and headache among patients increased slightly, while that of fever, cough, fatigue, diarrhea, and nausea decreased slightly. Therefore, clinicians should consider different sensitivities in different patient populations.

We provided two nomograms to assist front-line clinicians in predicting and prognosticating COVID-19 in their daily practice. Assuming the independence of these symptoms, patients with

fever, cough, sputum production, sore throat, myalgia, and fatigue would be three-fold more likely to have a positive COVID-19 infection, which could increase a presumed 10% pre-test probability to 25% post-test probability (Figure 5). Similarly, clinicians could use a combination of another six predictors, including fever, cough, sputum production, sore throat, myalgia, and fatigue, to increase their post-test likelihood to ten-fold from a presumed 10% pre-test probability to 54% post-test probability for severe infection.

In conclusion, understanding the different distributions of predictors is essential to screen for potential COVID-19 infection and severe outcomes. Researchers should consider these potential confounders in future studies conducted to evaluate the distribution of symptoms, comorbidities, and severity. The combination of symptoms could improve the pre-test probability before screening for potential infection and severe outcomes.

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Declaration of interests

The authors declare that they have no conflicts of interest.

Authors' contribution

KFC and IY wrote the manuscript. KFC and CCW performed the literature review and the statistical analysis. SHL, CFY, STH, CYM, DH, RR, AP, and KFC revised the text. All authors read and approved the final manuscript.

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Ethical statement

This meta-analysis study is exempt from ethics approval since the study authors were collecting and synthesising data from previous clinical studies in which informed consent has already been obtained by the investigators.

Role of the funding source

The funder of this study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit this paper publication. The authors had full access to all the data, and the corresponding author was responsible for the decision to submit for publication.

Patient and public involvement

Our study contained no direct patient or public involvement; however, the research question was informed by front line health care providers who need accurate biomarkers to detect patients with systemic infection or sepsis.

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Table

Table 1. Sensitivity analysis of different thresholds for fever. Each study could report results from more than one threshold

Definition	Number of Studies	Proportion (%, 95% C.I.)	Q	I^2
Without temperature	126	76 (72-80)	6362.54	98.0%
Temperature >37.3°C	42	75 (68-81)	444.94	90.8%
Temperature >38°C	47	45 (38-52)	979.58	95.3%
Temperature >39°C	35	16 (11-22)	525.80	93.5%

Figure Legends

Figure 1. Flow chart of study identification, screening, inclusion, and exclusion in the systematic review.

Figure 2. Forest plot for the proportion of symptoms and outcomes in COVID-19 patients among the overall and different age groups.

Figure 3a. Forest plot of weighted mean differences of white blood cell counts between severe and non-severe COVID-19 patients.

Figure 3b. Forest plot of weighted mean differences of lymphocyte counts between severe and non-severe COVID-19 patients.

Figure 4a. Performance for predictors in detecting COVID-19 infection.

Figure 4b. Performance for predictors in prognosticating severe COVID-19 infection.

Figure 5a. Fagan's nomogram plot of the combination fever, cough, fatigue, hypertension, and diabetes mellitus to detecting COVID-19 infection.

Figure 5b. Fagan's nomogram plot of the combination fever, cough, sputum production, myalgia, fatigue, and dyspnoea to prognosticate severe COVID-19 infection.

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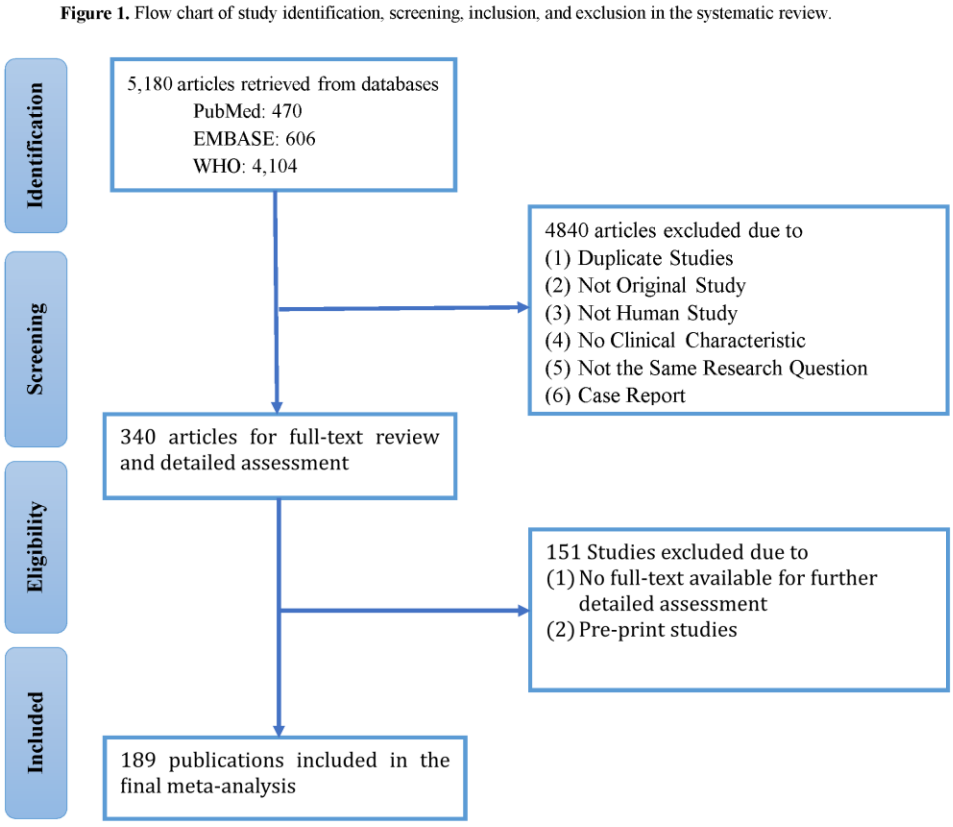

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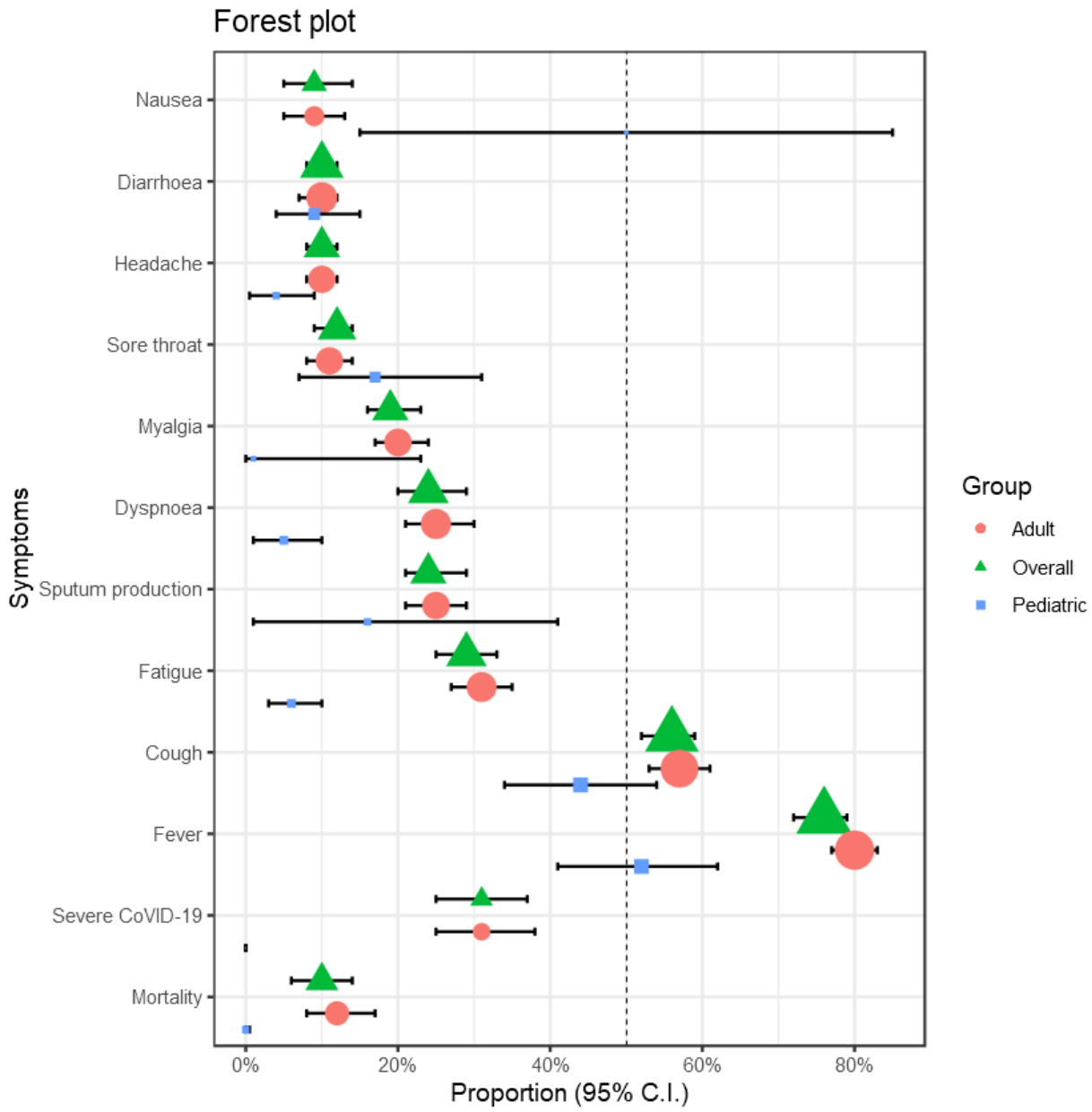

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Figure 3a

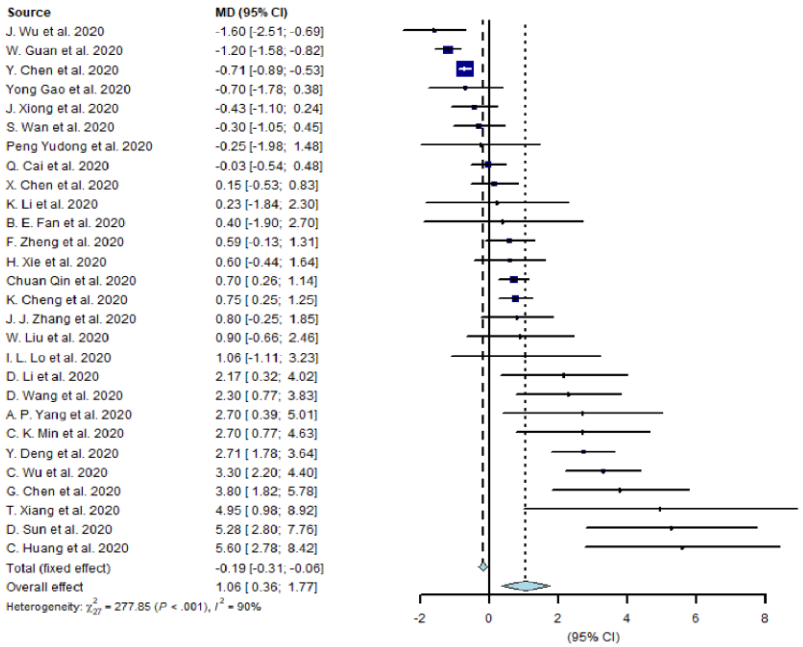

Figure 3b

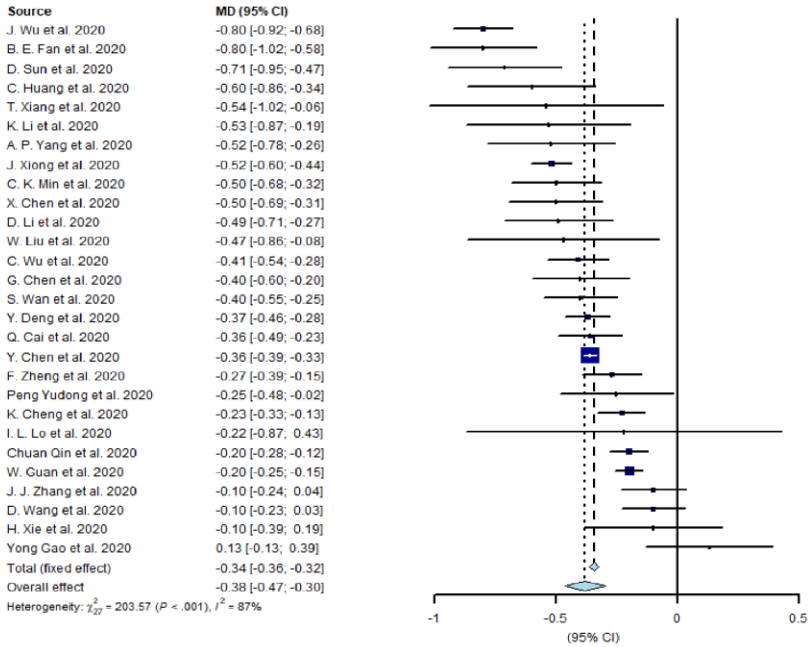

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Figure 4a

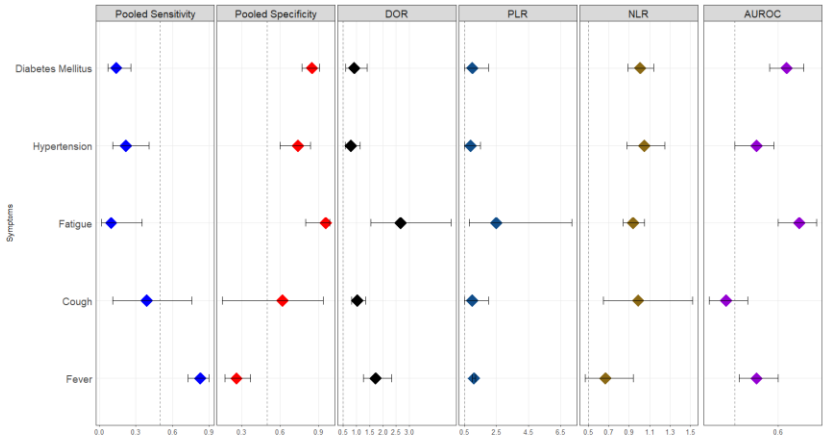
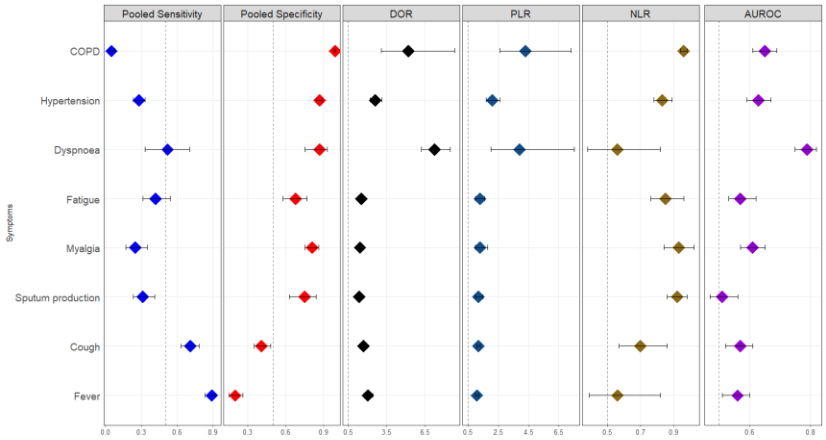


Figure 4b



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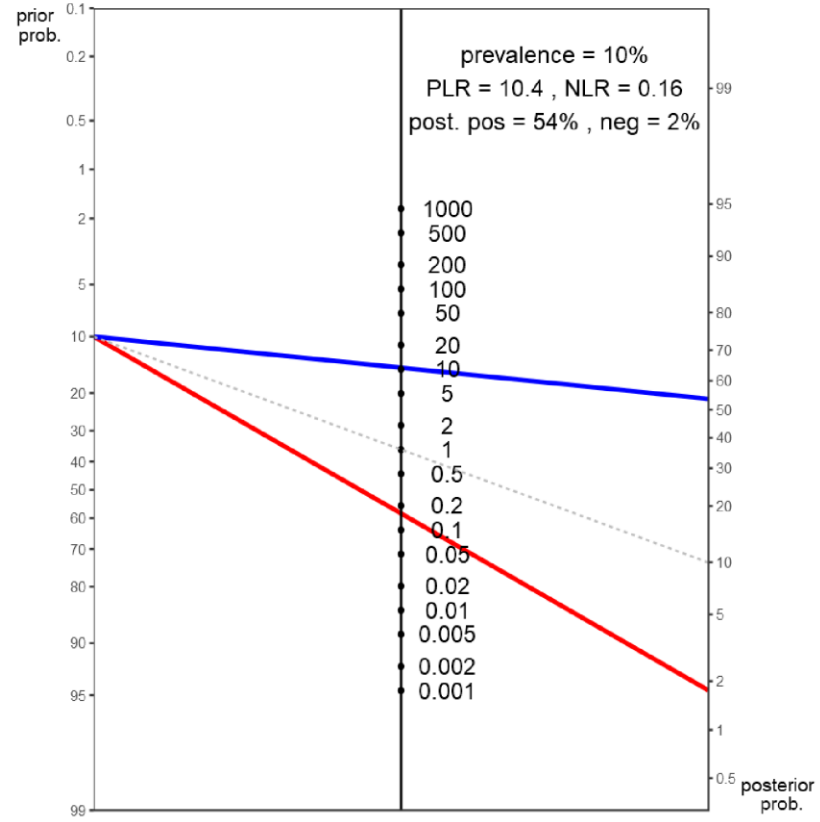

Figure 5b