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Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis

Running title: Predictors of clinical prognosis of COVID-19

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Abstract

Background: Recently, Coronavirus Disease 2019 (COVID-19) outbreak started in Wuhan, China. Although the clinical features of COVID-19 have been reported previously, data regarding the risk factors associated with the clinical outcomes are lacking.

Objectives: To summary and analyze the clinical characteristics and identify the predictors of disease severity and mortality.

Methods: The PubMed, Web of Science Core Collection, Embase, Cochrane and MedRxiv databases were searched through February 25, 2020. Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations were followed. We extracted and pooled data using random-e□ects meta-analysis to summary the clinical feature of the confirmed COVID-19 patients, and further identify risk factors for disease severity and death. Heterogeneity was evaluated using the I^2 method and explained with subgroup analysis and meta-regression.

Results: A total of 30 studies including 53000 patients with COVID-19 were included in this study, the mean age was 49.8 years (95% CI, 47.5-52.2 yrs) and 55.5% were male. The pooled incidence of severity and mortality were 20.2% (95% CI, 15.1-25.2%) and 3.1% (95% CI, 1.9-4.2%), respectively. The predictor for disease severity included old age (≥ 50 yrs, odds ratio [OR] = 2.61; 95% CI, 2.29-2.98), male (OR =1.348, 95% CI, 1.195-1.521), smoking (OR =1.734, 95% CI,

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1.146-2.626) and any comorbidity (OR = 2.635, 95% CI, 2.098-3.309), especially chronic kidney disease (CKD, OR = 6.017; 95% CI, 2.192-16.514), chronic obstructive pulmonary disease (COPD, OR = 5.323; 95% CI, 2.613-10.847) and cerebrovascular disease (OR = 3.219; 95% CI, 1.486-6.972). In terms of laboratory results, increased lactate dehydrogenase (LDH), C-reactive protein (CRP) and D-dimer and decreased blood platelet and lymphocytes count were highly associated with severe COVID-19 (all for $P < 0.001$). Meanwhile, old age (≥ 60 yrs, RR = 9.45; 95% CI, 8.09-11.04), followed by cardiovascular disease (RR = 6.75; 95% CI, 5.40-8.43) hypertension (RR = 4.48; 95% CI, 3.69-5.45) and diabetes (RR = 4.43; 95% CI, 3.49-5.61) were found to be independent prognostic factors for the COVID-19 related death.

Conclusions: To our knowledge, this is the first evidence-based medicine research to explore the risk factors of prognosis in patients with COVID-19, which is helpful to identify early-stage patients with poor prognosis and adapt effective treatment.

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Introduction

Coronaviruses are a family of viruses that widely exist in nature and can infect both humans and animals[1]. At present, there are six recognized types of coronavirus that can cause infection in humans, leading to pneumonia, injury in the digestive tracts, kidney failure and even death. Two of the coronavirus family have been reported to cause deadly infections including Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS)[2,3]. Recently, pneumonia caused by a novel coronavirus (SARS-CoV-2), also termed as Coronavirus Disease 2019 (COVID-19) was first reported in China's Wuhan City, Hubei Province in December 2019 and the disease spread rapidly in China and even around the world[4].

Compared with two other types of coronaviruses, the present new coronavirus is spreading far more quickly and has higher contagiousness[5]. As of March 17, 2020, a total of 187, 361 COVID-19 cases in 151 countries have been confirmed, which almost 22.2 times the number of people infected by the SARS in 2003. Although COVID-19 has a relatively low mortality rate, it can be highly deadly and lethal, especially in high-risk patients[6]. The reported incidence of COVID-19 accompanied with underlying comorbidities in the literature were up to 26.0%, and most of them (65.3%) had cardiovascular and cerebrovascular diseases. Patients infected with SARS-CoV-2 who already have

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underlying diseases were at increased the risk of severe illnesses and death[7].

And more worrying, there is no vaccine and specific treatment available for this novel coronavirus as of now[8]. Therefore, it is necessary to identify potential risk factors for predicting the disease progression and severity for COVID-19. Meanwhile, early monitoring the predictive indicators may also increase the efficiency of treatment and improve the prognosis of COVID-19. Thus, the aim of our study is to perform a systematic review and meta-analysis of clinical characteristics to explore the risk factors of COVID-19-associated severe illness and death, and first time to compare the differences of those predictors between COVID-19, SARS and MERS.

Methods

Our study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines[9,10]. In eMethods in the Supplement, we describe the detailed definitions of COVID-19 laboratory confirmed cases and severe illness.

Search strategy and study selection

PubMed, Embase, Cochrane, the Web of Science Core Collection

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(Clarivate Analytics), and MedRxiv databases were used for searching articles published until February 25, 2020 using the following keywords: "coronavirus", "nCoV", "HCoV", "Wuhan", "2019" "SARS-CoV-2", "COVID*", "NCP*", "China", "clinical", "outcome", "sever*", "death", "fatali*" and "mortalit*" alone and in combination. Detailed search strategies were presented in eMethods in the Supplement. After removing duplicates, three reviewers (C.M. & J.G. & P. H) were assigned to independently screen the titles and abstracts and then examine the full text, and any questions with conflict were resolved by the senior authors (P. L. and X. Z.). Inclusion criteria were as follows: (1) any study that gives information about the clinical characteristics or demographic or outcome of the infectious disease, (2) restriction language to English only, and (3) studies that allowed us to stratify the risk of severe or fatal COVID-19 by demographic or medical condition were preferred. Exclusion criteria were (1) data that could not be reliably extracted, (2) editorials, comments, expert opinions, case reports or articles with number of patients ≤ 10, (3) studies with special populations (eg, only focused on family clusters or severe or death cases).

Data extraction and quality assessment

Two authors (C.M. and J.G.) independently extracted the data using a predesigned spreadsheet, including author's name, publication year, study period, geographical region, study design, epidemiological information,

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sample size, baseline and clinical characteristics, laboratory results, severity and outcomes. For the study cohort divided according to disease severity, data of all patients, severe and non-severe patients were collected, respectively. For further meta-analysis, categorical variables like sex, comorbidities, symptoms or endpoint events, number were dealt with as dichotomous variables, while for continuous variables such as age, laboratory results or timelines of illness, different types of measurement including median (range) or median (IQR, interquartile range) were transferred to the form of mean (SD, standard deviation)[10].

Along with data extraction, study quality was assessed using the Quality Assessment Forms recommended by Agency for Healthcare Research and Quality (AHRQ) for cross-sectional study (eMethods in supplement)[11]. Conflicts on the assessments were resolved either by consensus or by the adjudicator (P.L. and X. Z.).

Data analysis

Firstly, to obtain summary e□ect estimate for each clinical variable, including case severity rate (CSR), case fatality rate (CFR), male proportion, mean age, pooled value of lymphocyte count and timeline of COVID-19 confirmed patients, random e□ects meta-analysis was used because high variability between studies was expected. Heterogeneity was evaluated using the I^2 statistic. Cut-off values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively[12]. We

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visualized the results with forest plots. Secondly, to identify the risk factors for severity, pooled odds ratios (ORs) with 95% CIs were estimated with the dichotomous method, and mean difference (MD) with 95% CIs between severe and non-severe cases were calculated with continuous method, Fixed effects model was used when $I^2 < 50\%$, and random effects models otherwise. Regarding the COVID-19 related death, we conducted logistic regression model to calculate relative risks (RR) with 95% CIs using the data of Chinese Center for Disease Control, which included 44672 laboratory confirmed patients. Thirdly, to explore potential sources of heterogeneity, we conducted subgroup analysis and random-e□ects meta-regression. Variables significant in univariable meta-regression ($P < 0.05$) were included in multivariable meta-regression. Next, sensitivity analyses were performed by systematically removing each study in turn to explore its effect on outcome[13].

Finally, to investigate the risk of publication bias, we applied the Begger test, Egger test and the test used by Peters et al and visually inspected the funnel plots[14]. All analyses were performed using Review Manager (version5.3), Stata (version 15) and R (version 3.5.3), RStudio (version 1.2.1335) and Comprehensive Meta-analysis (version 3.3).

Results

Literature Search and Study Characteristics

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We identified 854 studies, of which 30 were eligible for our analysis including 53,000 COVID-19 confirmed patients (Figure *1*)[1,7,15-38]. All of them were retrospective, observational studies (19 single-center and 11 multi-center studies), which were performed between December 2019 and February 19, 2020. The majority of studies were conducted in Wuhan (13, 43.3%) and other cities in China (11, 36.7%), 2 from nationwide and 3 from other countries including United States, Australia and Korea. To avoid any overlap of cases, the nationwide study of Chinese Centers for Disease Control (CDC) including 44672 confirmed cases was only used for identifying COVID-19 related death risk factors. The male to female sex ratio was 1.25, with an overall average age of 49.8 years (95% CI, 47.5-52.2). Five studies included the information of COVID-19 infected medical staff (Table *1*).

Case Severity Rate and Case Fatality Rate

18 studies listed the number of severe cases, with pooled CSR 20.2% (95% CI, 15.1-25.2%, n = 18, I^2 = 92%). The proportion of severe illness in Wuhan subgroup was higher than outside of Wuhan in China (36.9%; [95% CI, 26.7-47.0%]; n = 7 vs. 10.9%; [95% CI, 6.7-15.1%]; n = 7, P < 0.001]). Of note, the overall case fatality rate (CFR) was 3.1% (95% CI, 1.9-4.2%, n = 23, I^2 = 75%). Subgroup analysis showed a significantly higher CFR in Wuhan than outside Wuhan (9.5%; [95% CI, 5.2-13.8%]; n = 10 vs. 0.2%; [95% CI, 0-0.5%]; n = 8, P < 0.001) (Figure *1*).

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Univariate meta-regression showed that compared with Wuhan, CSR and CFR in other areas were significantly lower (all for $P < 0.0001$), which was consistent with the subgroup analysis. Although not statistically significant, CSR and CFR showed a decreasing trend over time. In addition, onset-to-admission time were identified closely correlation with CSR (4.99% per increase in days, $P = 0.0047$) and CFR (1.97% per increase in days, $P < 0.0001$), suggesting shortening the onset-to-admission time favored COVID-19 related outcomes. Multivariate meta-regression confirmed the close correlation between onset-to-admission time and CFR (1.27% per increase in days, $P = 0.0263$). (Table *2* and Figure *3*).

Clinical characteristics and laboratory results

Clinical and laboratory data from 26 studies, including 1374 severe and 4326 non-severe patients, were extracted for meta-analysis. Of this, 7.7% patients (95% CI, 3.6-11.8%) were medical staff. The pooled CFR of severe patients was significantly higher than non-severe patients (6.0%; [95% CI, 4.6-7.3%] vs. 0.1%; [95% CI, 0-0.2%], $P < 0.001$). The mean incubation period was 7.10 days (95% CI, 6.06-8.14 d), with no statistically difference between severe and non-severe cases. The mean time from symptom onset to hospital admission was 6.18 days (95% CI, 5.23-7.12 d), which is longer in severe cases than that in non-severe cases (6.56 d vs. 4.81d, P = 0.023) and in Wuhan than outside (7.23 d vs.4.86 d,

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P = 0.027).

Severe cases presented with older age (54.5 yrs; [95% CI, 55.5-61.4 yrs] vs. 44.5 yrs; [95% CI, 42.0-47.1 yrs], $P < 0.001$) and higher ratio of male (59.7%; [95% CI, 55.0-64.3%] vs. 51.9; [95% CI, 46.6-57.2%], $P < 0.001$), as compared with non-severe cases. Similarly, patients in Wuhan were older than those outside Wuhan (55.7 yrs vs. 41.6 yrs, $P < 0.001$). Fever (79.1%; 95% CI, 68.0-90.3%), cough (58.0%; 95% CI, 42.0-74.0%) and fatigue (29.3%; 95% CI, 23.4-35.3%) were the dominant symptoms, whereas digestive symptoms such as diarrhea (5.7%; 95%CI 3.9-7.5%), nausea or vomiting (2.0%; 95% CI, 1.0-2.9%) were relatively rare. The overall prevalence of any comorbidity was 37.1% (95% CI, 28.1-46.1%), with higher incidence rate in severe cases than non-severe cases (54.9% vs. 27.6%, P = 0.006), and higher in Wuhan than other areas (45.1% vs. 28.8%, $P = 0.01$). The most common comorbidities were hypertension (19.0%, 95% CI, 13.2-24.9%), followed by diabetes (8.2%, 95% CI, 6.3-10.0%) and cardiovascular diseases (CVD, 2.7%, 95% CI, 1.4-4.1%). Moreover, hypertension, diabetes, CVD, cerebrovascular diseases, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) were significantly more common in severe cases as compared with non-severe cases (all for $P < 0.05$). The overall proportion of bilateral radiologic abnormalities was 87.2% (95% CI, 82.1-92.3%), with significant difference between inside and outside Wuhan (91.6% vs.

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82.6%, $P = 0.018$).

In terms of the laboratory index, several elevated indicators were observed as follows: C-reaction protein (CRP, 26.07 mg/L; 95% CI, 20.69-31.44 mg/L), erythrocyte sedimentation rate (ESR, 46.54 mm/h; 95% CI, 33.31-59.78 mm/h), lactate dehydrogenase (LDH, 287.48 U/L; 95% CI, 260.76-314.20 U/L), cardiac troponin I (cTnI, 4.54 pg/mL,; 95% CI, -1.17-10.24 pg/mL) and ferritin (724.44 ng/mL; 95%CI, 356.28-1092.60 ng/mL). In contrast, the level albumin (37.31 g/L; 95% CI, 34.33-40.28 g/L) and lymphocytes count (1.18 × 10□/L; 95% CI, 1.00-1.36 × 10□/L) were below normal level. Of note, obvious differences in laboratory index were identified between severe and non-severe cases, as well as between Wuhan and outside Wuhan. Elevated level of CRP, LDH and D-dimer, together with reduced level of lymphocytes count and PLT count were the prominent features of severe cases (all for $P < 0.001$). Likewise, more elevated CRP, myoglobin, aspartate aminotransferase (AST) and ferritin, followed by decreased lymphocyte count and hemoglobin were observed in Wuhan patients than outside (all for $P < 0.001$) (Table 2).

Risk factors for severity of COVID-19

Among the baseline characteristics, disease severity was highly associated with old age (≥ 50 yrs, OR = 2.609; 95% CI, 2.288-2.976; n = 5; I^2 = 37%), male (OR =1.348; 95% CI, 1.195-1.521; n = 13; I^2 = 0%), smoking (OR =1.734; 95% CI, 1.146-2.626; n = 4; I^2 = 0%) and any

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comorbidity (OR = 2.635; 95% CI, 2.098-3.309; n = 7; I^2 = 12%). Comorbidities with pooled OR larger than 2 included CKD (6.02; 95% CI, 2.19-16.51; n = 4; I^2 = 0), COPD (5.32; 95% CI, 2.61-10.85; n = 6; I^2 = 0%), cerebrovascular diseases (3.19; 95% CI, 1.51-6.77; n = 6; I^2 = 0%), tumor (3.21; 95% CI, 1.42-7.24; n = 4; I^2 = 30%), diabetes (2.49; 95% CI, 1.82-3.4; n = 10; I^2 = 44%) and hypertension (2.06; 95% CI, 1.61-2.62; n = 10; I^2 = 36%) (Figure *4*, eFigure *5*).

In terms of laboratory results, there were obvious difference between severe and non-severe cases in PLT (MD = -30.654 × 10^9/L, 95% CI, -38.7 to -22.61, n = 8), lymphocyte count (MD = -0.376 × 10^9/L , 95% CI, -0.467 to -0.285, n = 11), LDH (MD = 150.702 U/L, 95% CI, 82.569 to 218.836, n = 5), D-dimer (MD = 0.715 mg/L, 95% CI, 0.562 to 0.868, n = 7) and CRP (MD = 30.395 mg/L, 95% CI, 20.006 to 40.784, n = 10). Meanwhile, the ORs were calculated for several index including lymphocytopenia (OR = 4.23; 95% CI, 3.03-6.03; I^2 = 33%), thrombocytopenia (OR = 2.84; 95% CI, 2.00-4.04; I^2 = 49%), elevated D-dimer (OR = 3.17; 95% CI, 1.86-5.41; I^2 = 69%) and elevated CRP (OR = 4.23; 95% CI, 2.94-6.08; I^2 = 25%). (Figure *5*, eFigure *6-7*).

Comparison of Clinical Characteristics and risk factors among COVID-19, SARS and MERS

The most common comorbidity was diabetes for both SARS (24.0%) and

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MERS (68.0%), while hypertension for COVID-19 (19.0%). Fever and cough were the dominant symptoms for all three viruses, whereas digestive symptoms and chill were relatively rare for COVID-19. Regarding laboratory index, elevated LDH was common for three coronaviruses; higher incidence of lymphopenia, elevated AST or ALT was observed in COVID-19 and SARS than MERS[39,40]. (Table 4).

Both old age and comorbidity proved the common risk factors for predicting death among three coronaviruses. In support, COVID-19 related death was associated with old age ($\geq$ 60 yrs, RR = 9.45; 95% CI, 8.09-11.04), male (RR = 1.67, 95% CI, 1.47-1.89) and any comorbidity (5.86; 95% CI, 4.77-7.19), most notably CVD (6.75; 95% CI, 5.40-8.43) followed by hypertension (4.48; 95% CI, 3.69-5.45) and diabetes (4.43; 95% CI, 3.49-5.61). Similar with COVID-19, male (RR = 1.6; 95% CI, 1.2-2.1) and CVD (OR = 3.5; 95% CI, 3.1-4.8) were also risk factors for MERS related death[41,42]. In contrast, the most predominant risk factor for SARS related death was CKD (9.02; 95% CI, 3.81-21.36), and the risk of male gender was not statistically significant[3,43,44]. In addition, medical staff had a lower fatality rate than non-clinical staff for COVID-19 (RR = 0.12; 95% CI, 0.05-0.30) and MERS (RR = 0.1; 95% CI, 0.02-0.20), whereas the difference was not significant for SARS (RR = 0.76; 95% CI, 0.52-1.15). (Table *5*).

Sensitivity Analysis and Publication Bias

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Leaving each trial out of the analysis one at a time revealed no meaningful differences in CSR and CFR (eFigure *8* in supplement). We observed no evidence of publication bias with inspection of the funnel plot or with the Begger test or the test used by Peters et al (eFigure *9* in supplement).

Discussion

The main findings of this present analysis are that: (1) Despite the high incidence rate, the distinctive feature of COVID-19 was low severity and mortality, showing a significant difference on the incidence of severity and mortality between Wuhan and outside of Wuhan; (2) The onset-to-admission time was closely related to mortality, which will be increased about 1.27% with every day of delay in admission; (3) Older age is a common risk factor for poor prognosis of the three coronavirus diseases; Hypertension and cardiovascular diseases are the most relevant clinical predictors for the death caused by both COVID-19 and MERS-CoV, while chronic kidney disease is for SARS; (4) The five main laboratory indicators of severe illness included lymphocytopenia, thrombocytopenia and the rise of LDH, CRP and D-dimer.

SARS-CoV-2 has been reported to be higher contagious than previously discovered human coronaviruses[45]. Until now, more than 187, 361 confirmed cases and caused 7, 485 deaths in 151 countries on six continents were identified. Despite its high prevalence of COVID-19, the

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pooled severe incidence and fatality rate is significantly lower compared with SARS and MERS, which may explain why the novel coronavirus has spread so widely[46]. Of note, there are regional and spatial differences in the incidence rate of COVID-19. In our research, the pooled severity rate and mortality caused by COVID-19 was found significantly higher in Wuhan than that of the infected outside of Wuhan (all for $P < 0.01$). On the other hand, disease incidence at the early stage of outbreak was higher than that at the late stage, which may be caused by the lack of recognitions and treatment experience for COVID-19. Moreover, the longer time from symptoms to hospitalization, the higher incidence rate of the mortality related to COVID-19, highlighting the importance of timely medical treatment[30]. In addition, among the patients with 2019-nCoV, the pooled infection rate of medical staff was 7.7%, which was lower than that of SARS (23%) and MERS (9.8%)[39].

SARS-CoV-2, SARS-CoV and MERS-CoV belong to high pathogenic coronaviruses, whereas each of which has its own clinical manifestation. In comparison to SARS-CoV (4.6 days) and MERS-CoV (5.2 days)[47], COVID-19 has a longer latent period (7.1 days) and the initial manifestations are non-specific, making it more difficult to prevent and control at early stage. Similar to SARS and MERS, persons with COVID-19 often present initially with lower respiratory signs, including fever, coughing and fatigue. In the late

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course of illnesses, infected persons are characterized by progressive breathing difficulty, tachypnea, acute respiratory distress syndrome, or life-threatening complications. In fact, SARS-CoV-2 has been isolated from respiratory secretions, feces, urine, blood, tears, and conjunctival secretions[48], indicating that SARS-CoV-2 infection is not confined to the respiratory tract. Indeed, in our analysis, the pooled incidences rate of respiratory symptom was present in 79.1% of patients, followed by 7.7% with gastrointestinal disorders and 6.1% with neurological symptoms. Therefore, the patients with COVID-19 whose initial symptom were out of the lung should also be paid more attention, especially for those with the contact history of COVID-19. It should be noted that the pooled incidence of diarrhea symptoms (5.7%) is lower than previous data of patients with MERS-CoV (25%) or SARS-CoV (26%) infection. In terms of laboratory tests, the most common hematological abnormalities in patients with COVID-19 were lymphopenia (54.7%), suggesting aggressive effect on lymphocytes by COVID-19, which is similar to those previously observed in patients with SARS (68-85%). In addition, elevated levels of liver enzymes, LDH, myocardial enzymes, and depressed platelet count concomitant with the rise of D-dimer was observed in our study. Compare with MERS (36%) and SARS (45%), thrombocytopenia was relatively less frequent in patients infected with SARS-CoV-2 (12.8%)[39,47].

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Given the fact that the rapid progression to end-organ failure and even death was occurred in some patients, it is therefore essential to paid more attention to susceptible population of COVID-19[49]. Our results showed the majority of the SARS-CoV-2 infection were male patients (55.5%) similarly to the gender distribution of MERS (64.5%), while the predominance of female patients (43.0%) was observed in SARS. It is believed that the sex difference is probably related to the higher expression of ACE2 receptor in male than that in female and the lack of the protection of estrogen and X chromosome[50]. COVID-19 has affected persons in all age groups; in particular, 53.5% patients were found after more than 50 years, suggesting that the elderly patients are more likely to have weak immune function. Moreover, 10-30% of patients in SARS and 37.1% of patients in COVID-19 had at least one underlying disorder; patients with comorbidities such as diabetes mellitus, cardiovascular diseases, renal failure and chronic respiratory diseases are especially vulnerable to SARS-CoV-2 infection[7]. Owning to the pro-inflammatory state and the reduced immune response, the chronic conditions were also noted to have similar effects in the other two coronaviruses. Although the comorbidities identified in our study has been described previously, their value to predict the severity of COVID-19 has not yet been evaluated.

A focus on risk factor affecting clinical outcome is critically important to identify high-risk patients and mitigate COVID-19

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complications. In the present study, people with old age, male, smoking, presence of comorbidity, CKD, COPD, cancer, hypertension, and diabetes were identified as predictors of severe disease from COVID-19 infection. Importantly, old age, male gender and presence of comorbidity, including hypertension, diabetes, cancer and respiratory disease, were identified predictor of disease severity as well as mortality related to COVID-19, suggesting that elderly patients with these underlying comorbidities should be given more attention and care. In line with previously published studies, the laboratory indicators including lymphocytes, CRP, LDL, PLT, D-dimer, ALT and CK levels were closely related to a poor prognosis, which provided key reference index of the prognosis of COVID-19. In particular, lymphopenia, thrombocytopenia and elevated D-dimer could act as effective predictors of the COVID-19 severity. However, it was worth noting that increased level of myoglobin and ferritin were observed in severe cases, but the predictive value could not be estimated limited by the number of related studies and further in-depth research is needed.

Limitation

Our meta-analysis has several potential limitations. Firstly, there was obvious heterogeneity among studies regarding CSR and its subgroups, because of differences in medical condition, study period, public

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awareness and others. Nevertheless, we conducted meta-regression based on the observation duration and symptom onset to hospital admission time, which explained a large percent of heterogeneity. Secondly, studies published before February 25, 2020 and articles published in English only were included in our study, therefore there was lack of data from other countries. However, our meta-analysis involved 53000 confirmed patients based on the data during the early-to-mid period of disease outbreak in China, which will provide great referential value for global epidemic control. Thirdly, meta-analysis was conducted on the level of the studies and the characteristics of individual patients could not be retrieved, thus it was hard to provide reference for individualized diagnosis and treatment of COVID-19. Finally, all included studies were retrospective, as no randomized control trials and prospective studies related to 2019-nCoV finish till now, thus our results require to be confirmed by more high-quality clinical researches.

Conclusions:

COVID-19 is emerging all over the world and spreading at an unprecedented rate, resulting in significant impacts on global economies and public health. The present study successfully and systematically evaluated the prognostic predictors of COVID-19 by collecting published information on risk factors of the outcomes related to SARS-CoV-2 infections. Nevertheless, more investigations are needed to further

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objectively confirm the clinical value of prognostic factors related to COVID-19.

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Figure legend

Figure 1. PRISMA Diagram of Study Selection.

N, the number of COVID-19 confirmed patients; ICU, intensive care unit.

a EndNote software (Clarivate Analytics) was used to remove duplicates.

Figure 2. Subgroup analysis of CSR (A) and CFR (B) by geographical region.

CSR, case severity rate; CFR, case fatality rate.

Figure 3. Meta-regression analysis for CSR and CFR. (A) meta-regression of Logit CSR on geographical region (Wuhan, outside Wuhan in China, nationwide). (B) meta-regression of Logit CSR on duration from Dec 1, 2019 to the middle time of study period. (C) meta-regression of Logit CSR on mean time from symptom onset to

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hospital admission (D) meta-regression of Logit CFR on geographical region (Wuhan, outside Wuhan in China, nationwide). (E) meta-regression of Logit CFR on duration from Dec 1, 2019 to the middle time of study period. (F) meta-regression of Logit CFR on mean time from symptom onset to hospital admission. The size of the circle represent the population size of each study. The red line in A&D represent the pooled incidence of CSR or CFR in each region, and the red line in B-C, E-F represent the regression equation from meta-analysis.

Figure 4. Clinical risk factors for severe cases. A, old age (> 50 yrs) ; B, male gender; C, any comorbidity; D, hypertension; E, diabetes; F, cerebrovascular diseases; G, chronic kidney diseases (CKD); H, chronic obstructive pulmonary diseases (COPD).All factors were dealt as dichotomous variables and odds ratios (ORs) were showed using fixed effect model (all for $I^2 < 50\%$).

Figure 5. Mean Difference (MD) in main laboratory index between severe and non-severe patients with COVID-19. A, blood platelet count (PLT, $\times 10^9$/L); B, lymphocyte count ($\times 10^9$/L); C, lactate dehydrogenase (LDH, U/L); D, D-dimer (mg/L); E, C-reaction protein (mg/L); F, aspartate aminotransferase (AST, U/L).

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Table 1. Study Characteristics

Study	Study period	Location	N	CSR, n (%)	CFR, n (%)	Mean age (SD)	Male, n (%)	Healthcare worker, n (%)	Quality score[a]
Chaolin Huang et al.	Dec 6, 2019 - Jan 2, 2020	Wuhan	41	NA	6 (15.0)	49.0 (5.2)	30 (73.0)	NA	9
Qun Li et al.	Dec 10, 2019 - Jan 04, 2020	Wuhan	425	NA	NA	59.0 (12.3)	238 (56.0)	15 (3.5)	6
Nanshan Chen et al.	Jan 1-20, 2020	Wuhan	99	NA	11 (11.0)	55.5 (13.1)	67 (68.0)	NA	8
Jing Liu et al.	Jan 5-24, 2020	Wuhan	40	13 (32.5)	2 (5.0)	48.7 (13.9)	15 (37.5)	NA	9
Guang Chen et al.	Dec 19, 2019 - Jan 27, 2020	Wuhan	21	11 (52.4)	4 (19.0)	56.3 (14.3)	17 (81.0)	NA	10
Dawei Wang et al.	Jan 1-28, 2020	Wuhan	138	NA	6 (4.3)	56.0 (11.7)	75 (54.3)	40 (29.0)	9
Yanli Liu et al.	Jan 2 - Feb 1, 2020	Wuhan	109	NA	31 (28.4)	54.7 (17.0)	59 (54.1)	NA	10
Jinjin Zhang et al.	Jan 16 - Feb 3, 2020	Wuhan	140	58 (41.4)	NA	56.5 (10.3)	71 (50.7)	3 (2.1)	9
Jiatao Lu et al.	Jan 21 - Feb 5, 2020	Wuhan	75	15/72 (20.8)	1 (1.3)	60.3 (17.0)	37 (49.3)	NA	9
Zhen Li et al.	Dec, 2019 - Feb 7, 2020[b]	Wuhan, Huangshi, Chongqing[c]	59	28 (47.5)	3 (5.1)	53.8 (13.8)	34 (57.6)	NA	6
Qilin Li et al.	Feb 3-7, 2020	Wuhan	52	NA	NA	58.3 (14.8)	26 (50.0)	NA	9

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Yichun Cheng et al.	Jan 28 - Feb 11, 2020	Wuhan	710	252 (35.5)	89 (12.5)	61.7 (14.8)	374 (52.7)	NA	8
Luwen Wang et al.	Jan 14 - Feb 13, 2020	Wuhan	116	46 (39.7)	7 (6.0)	53.7 (23.0)	67 (57.8)	NA	9
Xiaowei Xu et al.	Jan 10 - Jan 26, 2020	Zhejiang	62	NA	0	43.3 (14.8)	36 (58.1)	NA	9
De Chang et al.	Jan 16-29, 2020	Beijing	13	NA	0	35.3 (3.0)	10 (77.0)	NA	8
Jingyuan Liu et al.	Jan 13-31, 2020	Beijing	61	3 (4.9)	0	40.0 (14.2)	31 (50.8)	NA	10
Zhichao Feng et al.	Jan 17 - Feb 1, 2020	Hunan	141	15 (10.6)	NA	44.3 (15.6)	72 (51.1)	NA	10
Lei Liu at al.	Jan 20 - Feb 3, 2020	Chongqing	51	7 (13.7)	1 (2.0)	42.7 (12.6)	32 (62.7)	NA	9
Qingxian Cai et al.	Jan 11- Feb 6, 2020	Shenzhen	298	58 (19.4)	0	47.0 (20.7)	149 (50.0)	NA	8
Jinwei Ai et al.	Dec, 2019 - Feb 9, 2020[b]	Xiangyang, Hubei	102	NA	3 (2.9)	50.4 (16.9)	52 (51.0)	NA	6
Jingwen Ai et al.	Jan 22 - Feb 9, 2020	Shanghai	20	3 (15.0)	NA	40.4 (12.4)	10 (50.0)	NA	9
Jie Li et al.	Jan 22 - Feb 10, 2020	Dazhou, Sichuan	17	NA	0	45.1 (12.8)	9 (52.9)	NA	9
Hongzhou Lu et al.	Jan 20 - Feb 19, 2020	Shanghai	265	22 (8.3)	1 (0.4)	NA	NA	NA	10
Yishan Zheng et al.	NA	Nanjing	103	8 (7.8)	NA	44.4 (18.9)	55 (53.4)	NA	8
Yang Yang et al.	Dec, 2019 - Jan 26, 2020[b]	Nationwide	4021	935 (25.5)	58 (1.4)	48.0 (16.0)	2213 (55.04)	247 (6.14)	7

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Weijie Guan, et al.	Dec, 2019 - Jan 29, 2020[b]	Nationwide	1099	173 (15.7)	15 (1.4)	47.0 (3.8)	649 (59.1)	NA	10
Chinese CDC	Dec, 2019 - Feb 11, 2020 [b]	Nationwide	44672	8255 (18.6)	1023 (2.3)	NA	22981 (51.4)	1716 (3.8)	9
Moran Ki1, et al.	Jan 20 - Feb 8, 2020	South Korea	24	0	0	41.8 (10.3)	14 (58.3)	NA	7
Kristina L. Bajema, et al	Jan 17-31, 2020	America	11	0	0	NA	NA	NA	7
Liz J Walker, et al.	Jan 10 - Feb 8, 2020	Australia	15	NA	0	NA	NA	NA	5

N, number of COVID-19 confirmed patients; CSR, case severity rate; CFR, case fatality rate; CDC, centers for disease control; NA, data not available.

[a] Study quality was assessed using the Quality Assessment Forms recommended by Agency for Healthcare Research and Quality (AHRQ).

[b] Studies without specific beginning time mentioned, were taken as beginning since Dec, 2019.

[b] The study recruited patients at Tongji Hospital and Wuhan Pulmonary Hospital in Wuhan, Huangshi Central Hospital in Huangshi, and Southwest Hospital in Chongqing, China. The multi-center study was categorized into Wuhan subgroup after a discussion.

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Table 2. Meta-regression Analysis for CSR and CFR

	Univariate meta-regression			Multivariate meta-regression[a]		
	Coefficient (95% CI)	z value	p value	Coefficient (95% CI)	z value	p value
CSR						
Geographic region						
Wuhan	Reference	10.1055	Reference	Reference	3.3328	Reference
Outside Wuhan in China	-0.2472 (-0.3417 to -0.1528)	-5.1316	**<0.0001**	-0.1317 (-0.3150 to 0.0517)	-1.4074	0.1593
Nationwide	-0.1516 (-0.2813 to -0.0219)	-2.2909	**0.0220**	-0.0122 (-0.2162 to 0.2405)	0.1044	0.9169
Outside China	-0.3581 (-0.5004 to -0.2159)	-4.9355	**<0.0001**			
Observation duration[b]	-0.0048 (-0.0102 to 0.0006)	-1.7499	0.0801	-	-	-
Onset-to-admission time[c]	0.0499 (0.0153 to 0.0845)	2.8289	**0.0047**	0.0275 (-0.0189 to 0.0739)	1.1606	0.2458
CFR						
Geographic region						
Wuhan	Reference	8.5225	Reference	Reference	1.0729	Reference
Outside Wuhan in China	-0.0712 (-0.0935 to -0.0488)	-6.2345	**<0.0001**	-0.0450 (-0.0922 to 0.0022)	-1.8686	0.0617
Nationwide	-0.0627 (-0.0894 to -0.0359)	-4.5955	**<0.0001**	-0.0381 (-0.0949 to 0.0187)	-1.3156	0.1883

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Outside China	-0.0767 (-0.1264 to -0.0269)	-3.0214	**0.0025**			
Observation duration[b]	-0.0002 (-0.0013 to 0.0009)	-0.3710	0.7106	-	-	**-**
Onset-to-admission time[c]	0.0197 (0.0133 to 0.0260)	6.0555	**<0.0001**	0.0127 (0.0015 to 0.0239)	2.2217	**0.0263**

[a]Multivariate meta-regression was performed when the univariate meta-regression P value was < 0.05.

[b]Duration from December 1, 2019 to the middle time of study period.

[c]Mean time from symptom onset to hospital admission.

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Table 3. Clinical and laboratory data of the included COVID-19 patients.

	Overall	Severity			Region		
		Severe	Non-severe	P value	Wuhan	Outside Wuhan in China	P value
CSR, % (95%CI)	20.2 (15.1-25.2)	-	-	-	36.9 (26.7-47.0)	10.9 (6.7-15.1)	**<0.001**
CFR, % (95%CI)	3.1 (1.9-4.2)	6.0 (4.6-7.3)	0.1 (0-0.2)	**<0.001**	9.5 (5.2-13.8)	0.2 (0.0-0.5)	**<0.001**
Healthcare worker, % (95%CI)	7.7 (3.6-11.8)	0 (0-2.3)	3.7 (0-7.7)	0.101	10.1 (2.2-18.0)	NA	NA
Timeline of illness, d							
Incubation time	7.10 (6.06-8.14)`	7.00 (6.40-7.60)	7.50 (7.24-7.76)	0.133	NA	NA	NA
Days from symptom onset to hospital admission	6.18 (5.23-7.12)	6.56 (5.35-7.77)	4.81 (3.90-5.72)	**0.023**	7.23 (5.80-8.65)	4.86 (3.32-6.40)	**0.027**
Mean age, y (95% CI)	49.8 (47.5-52.2)	54.5 (55.5-61.4)	44.5 (42.0-47.1)	**<0.001**	55.7 (53.2-58.2)	41.6 (38.8-44.4)	**<0.001**
Male, % (95% CI)	55.5 (53.2-57.7)	59.7 (55.0-64.3)	51.9 (46.6-57.2)	**<0.001**	56.3 (52.2-60.4)	52.7 (49.4-56.0)	0.197
Current smoking, % (95% CI)	6.4 (0.0-12.9)	7.8 (0-16.5)	5.5 (0-12.5)	0.663	1.4 (0.0-3.4)	5.4 (2.3-8.5)	**0.027**
Sign & Symptom, % (95% CI)							
Fever	79.1 (68.0-90.3)	88.4 (73.1-100.0)	81.4 (62.6-100.0)	0.552	81.0 (63.4-98.5)	81.2 (72.4-90.0)	0.984
Cough	58.0 (42.0-74.0)	71.1 (59.6-82.7)	65.7 (57.8-73.5)	0.449	57.6 (38.2-77.0)	57.2 (41.5-72.9)	0.975
Fatigue	29.3 (23.4-35.3)	60.3 (39.9-80.8)	44.2 (32.6-55.9)	0.181	36.1 (27.3-44.9)	21.2 (13.0-29.5)	**0.016**

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Expectoration	11.5 (9.2-13.9)	37.6 (22.7-52.6)	28.0 (19.0-37.0)	0.281	2.7 (0.8-4.6)	20.6 (10.6-30.6)	**0.001**
Headache	6.0 (4.0-7.9)	11.3 (7.4-15.2)	13.5 (7.6-19.4)	0.542	2.0 (0.5-3.5)	8.8 (4.8-12.7)	**0.002**
Diarrhea	5.7 (3.9-7.5)	5.7 (3.1-8.4)	5.8 (3.3-8.3)	0.957	5.6 (2.6-8.6)	6.6 (3.8-9.3)	0.63
Myalgia	3.8 (2.4-5.2)	26.0 (11.1-40.9)	13.1 (8.4-17.8)	0.107	4.7 (2.1-7.3)	1.9 (0.2-3.5)	0.075
Shortness of breath	3.5 (2.2-4.9)	35.7 (17.8-53.7)	12.8 (4.7-20.9)	**0.023**	2.2 (0.4-3.9)	1.9 (0.2-3.7)	0.812
Sore throat/Pharyngalgia	3.2 (1.7-4.6)	7.8 (0-16.1)	9.7 (4.0-15.4)	0.706	1.5 (0.1-2.9)	2.1 (0.4-3.7)	0.587
Nausea or vomiting	2.0 (1.0-2.9)	5.9 (3.1-8.7)	5.7 (2.3-9.0)	0.928	2.5 (0.7-4.2)	1.3 (0.1-2.6)	0.274
Chill	1.1 (0.3-1.9)	26.0 (8.9-43.1)	10.9 (9.0-12.9)	0.087	0.1 (0.0-0.8)	0.4 (0.0-1.4)	0.466
Nasal congestion/Rhinorrhoea	1.1 (0.3-1.9)	2.8 (0.4-5.2)	5.1 (3.8-6.3)	0.097	0.0 (0.0-0.2)	1.6 (0.0-3.3)	0.058
Dyspnea	1.0 (0.3-1.7)	44.2 (7.8-80.6)	5.7 (0-10.7)	**0.042**	7.5 (4.6-10.5)	0.6 (0.0-1.6)	**<0.001**
Anorexia	1.0 (0.4-1.7)	14.9 (8.3-21.5)	8.2 (2.4-13.9)	0.135	2.5 (0.5-4.5)	3.5 (0.9-6.1)	0.55
Dizziness	0.1 (0.0-0.5)	16.1 (3.5-28.8)	12.1 (5.0-19.2)	0.591	0.9 (0.0-2.1)	0.0 (0.0-2.4)	0.269
Any comorbidity, % (95% CI)	37.1 (28.1-46.1)	54.9 (37.2-72.6)	27.6 (19.4-35.8)	**0.006**	45.1 (36.2-53.9)	28.8 (20.2-37.5)	**0.01**
Specific comorbidity, % (95% CI)							
Hypertension	19.0 (13.2-24.9)	29.4 (24.8-34.1)	16.1 (11.5-20.7)	**<0.001**	25.3 (11.3-39.3)	13.1 (9.4-16.9)	0.099
Diabetes	8.2 (6.3-10.0)	17.2 (13.4-20.9)	5.8 (3.4-8.1)	**<0.001**	11.8 (9.5-14.1)	5.4 (3.9-6.9)	**<0.001**
CVD	2.7 (1.4-4.1)	6.9 (3.9-9.8)	2.1 (1.4-2.9)	**0.002**	4.4 (1.7-7.1)	2.0 (0.4-3.6)	0.134
Cerebrovascular disease	1.0 (0.3-1.6)	3.0 (1.2-4.9)	0.9 (0.4-1.3)	**0.031**	2.2 (0.5-3.9)	0.2 (0.0-0.6)	**0.023**
COPD	0.6 (0.3-0.9)	4.1 (1.8-6.3)	0.7 (0.2-1.1)	**0.004**	0.8 (0.1-1.6)	1.2 (0.0-2.4)	0.58

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CKD	0.4 (0.1-0.7)	2.5 (0.8-4.2)	0.6 (0.1-1.0)	**0.035**	1.5 (0.1-2.9)	0.1 (0.0-0.5)	0.054
CLD	1.1 (0.3-1.8)	0.8 (0-1.9)	1.6 (0-3.7)	0.451	0.2 (0.0-0.7)	1.8 (0.3-3.4)	**0.049**
Cancer	0.8 (0.1-1.5)	5.6 (0-12.6)	2.3 (1.5-3.1)	0.309	1.7 (0.1-3.2)	0.6 (0.0-1.2)	0.195
Radiologic findings, % (95% CI)							
Bilateral lung involvement	87.2 (82.1-92.3)	87.5 (81.3-93.8)	72.6 (50.9-94.2)	0.195	91.6 (88.5-94.6)	82.6 (75.9-89.4)	**0.018**
Laboratory findings, mean (95% CI)							
WBC, × 10□/L	5.33 (5.03-5.62)	5.52 (4.79-6.24)	4.74 (4.55-4.92)	**0.041**	5.81 (5.13-6.50)	4.87 (4.61-5.13)	**0.012**
N, × 10□/L	3.43 (2.96-3.90)	4.23 (3.33-5.13)	3.03 (2.73-3.32)	**0.013**	3.87 (2.15-5.25)	3.16 (2.25-4.07)	0.439
L, × 10□/L	1.18 (1.00-1.36)	0.74 (0.67-0.82)	1.14 (1.05-1.23)	**<0.001**	0.87 (0.83-0.91)	1.39 (0.98-1.83)	**0.017**
M, ×□10□/L	0.39 (0.34-0.43)	0.31 (0.26-0.36)	0.55 (0.38-0.72)	**0.007**	0.39 (0.37-0.42)	0.40 (0.32-0.48)	0.815
NLR	NA	4.25 (3.42-5.08)	2.61 (1.85-3.48)	**0.007**	NA	NA	NA
Hb, g/L	133.16 (129.72-136.60)	132.81 (126.82-138.80)	134.81 (132.01-137.60)	0.554	125.30 (119.67-130.92)	139.51 (136.74-142.29)	**<0.001**
PLT, × 10□/L	185.56 (175.13-195.98)	147.14 (39.88-154.40)	176.58 (173.66-179.49)	**<0.001**	188.50 (165.34-211.66)	180.76 (175.74-185.78)	0.522
CRP, mg/L	26.07 (20.69-31.44)	54.37 (41.12-67.62)	16.74 (12.00-21.48)	**<0.001**	35.87 (28.75-43.00)	18.63 (14.26-23.01)	**<0.001**
ESR, mm/h	46.54 (33.31-59.78)	48.51 (36.50-60.51)	32.07 (11.72-52.43)	0.173	49.90 (45.29-54.51)	44.87 (22.14-67.61)	0.671
PCT, ng/mL	0.07 (0.05-0.08)	0.11 (0.07-0.16)	0.05 (0.03-0.06)	**0.007**	0.13 (0.07-0.19)	0.04 (0.04-0.05)	**0.004**

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LDH, U/L	287.48 (260.76-314.20)	378.47 (307.86-449.07)	228.68 (222.62-234.75)	**<0.001**	322.26 (276.49-368.04)	238.30 (225.61-250.99)	**0.001**
cTnI, pg/mL	4.54 (-1.17-10.24)	0.05 (0.03-0.07)	0.02 (0.02-0.03)	**0.026**	6.87 (2.26-11.48)	0.02 (0.02-0.03)	**0.004**
CK, U/L	101.13 (87.22-115.03)	109.80 (72.67-146.92)	110.50 (80.69-140.31)	0.977	109.56 (88.27-130.85)	91.08 (71.51-110.65)	0.211
CKMB, U/L	13.23 (10.83-15.63)	NA	NA	NA	12.00 (8.05-15.51)	14.65 (13.3-15.97)	0.191
Mb, ng/mL	35.99 (5.36-66.61)	76.0 (27.99-124.01)	6.98 (6.08-7.87)	**0.01**	60.83 (51.12-70.55)	23.84 (-6.77-54.46)	**<0.001**
NT-proBNP, pg/mL	NA	269.27 (66.12-472.41)	38.77 (35.17-42.36)	**0.037**	NA	NA	NA
ALT, U/L	26.78 (24.17-29.38)	29.12 (225.57-32.67)	22.02 (20.17-23.87)	**0.001**	29.54 (25.53-33.54)	23.37 (22.20-24.54)	**0.004**
AST, U/L	31.61 (28.10-35.11)	39.91 (31.02-48.43)	24.23 (23.38-25.08)	**0.001**	36.48 (33.93-39.04)	25.41 (23.13-27.68)	**<0.001**
Albumin, g/L	37.31 (34.33-40.28)	35.53 (33.08-37.98)	40.11 (37.16-43.06)	**0.019**	32.70 (31.45-33.95)	40.76 (38.35-43.16)	**<0.001**
TBil, μmol/L	10.51 (9.25-11.76)	10.95 (9.06-12.84)	9.25 (8.03-10.46)	0.138	11.04 (9.86-12.23)	8.16 (6.55-9.77)	**0.005**
Scr, μmol/L	69.99 (67.22-72.75)	68.48	66.05	0.297	72.71	66.95	**0.048**

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		(65.58-71.38)	(62.53-69.58)		(68.85-76.57)	(62.75-71.14)	
BUN, mmol/L	4.94 (4.20-5.68)	5.02 (3.41-6.63)	4.00 (3.58-4.43)	0.237	5.04 (4.19-5.90)	4.37 (3.88-4.86)	0.183
eGFR, ml/min/1.73m^2	98.48 (73.98-122.98)	97.09 (89.89-104.29)	113.98 (111.69-116.28)	**<0.001**	86.00 (84.24-87.77)	111.00 (108.24-113.77)	**<0.001**
Potassium, mmol/L	3.90 (3.78-4.03)	3.80 (3.75-3.86)	3.85 (3.77-3.93)	0.316	4.09 (3.81-4.36)	3.77 (3.70-3.84)	**0.027**
Sodium, mmol/L	135.53 (138.03-139.03)	137.28 (136.43-138.13)	139.21 (138.58-139.85)	**<0.001**	138.69 (138.01-139.36)	138.61 (137.85-139.37)	0.878
PT, s	12.67 (12.19-13.15)	13.43 (12.68-14.18)	13.21 (12.76-13.66)	0.628	12.83 (12.09-13.57)	12.34 (11.43-13.25)	0.413
APTT, s	33.89 (30.00-37.79)	39.37 (36.19-42.54)	40.91 (38.2-43.62)	0.47	33.31 (28.90-37.71)	35.30 (27.10-43.50)	0.675
D-dimer, mg/L	1.00 (0.42-.1.52)	1.07 (0.92-1.22)	0.35 (0.27-0.44)	**<0.001**	1.43 (0.51-2.35)	0.40 (0.20-0.57)	**0.032**
SF, ng/mL	724.44 (356.28-1092.60)	1370.94 (654.26-2087.63)	524.49 (43.01-1005.97)	0.061	845.05 (623.56-1066.54)	269.86 (202.01-337.77)	**<0.001**

CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CLD, chronic liver disease; WBC, white blood cell count; N, neutrophil count; L, lymphocyte count; M, monocyte count; NLR, The ratio of neutrophils to lymphocytes; Hb, hemoglobin; PLT, platelet count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; LDH, lactate dehydrogenase; cTnI, hypersensitive troponin I; CK, creatine kinase; Mb, myoglobin; ALT,

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alanine aminotransferase; AST, aspartate aminotransferase; Tbil, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen; PT, prothrombin time; APTT, activated partial thromboplastin time; SF, serum ferritin.

P <0.05 was considered as statistically significant.

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Table 4. Comparison of clinical characteristics among COVID-19, SARS and MERS.

Clinical Characteristics	**COVID-19**	**SARS**	**MERS**
CFR, %	3.1	9.6	40
Mean age, y	49.8	39.9	50
Male, %	55.5	43	64.5
Health care worker, %	7.7	23	9.8
Current smoking, %	6.4	17	23
Any comorbidity, %	37.1	10-30	76
Diabetes	8.2	24	68
Chronic renal disease	0.4	2-6	49
Chronic heart disease	2.7	10	28
Cancer	0.8	3	2
Hypertension	19	19	34
Presenting symptoms, %			
Fever	79.1	99-100	98
Cough	58	62-100	83
Diarrhea	5.7	20-25	26
Myalgia	3.8	45-61	32
Shortness of breath	3.5	40-42	72
Chill	1.1	15-73	87
Laboratory results, %			
Leucopenia ($<4.0 \times 10^9$ /L)	22.2	25-35	14
Lymphopenia ($<1.5 \times 10^9$ /L)	54.7	68-85	32
Thrombocytopenia ($<140 \times 10^9$ /L)	12.8	40-45	36
High LDH (>245 U/L)	42.9	50-71	48

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High ALT (>40 U/L)	20	20-30	11
High AST (>40 U/L)	23.8	20-30	14

Table 5. Comparison of risk factors for death among COVID-19, SARS and MERS.

		COVID-19			SARS			MERS		
Predictive factors		N	CFR, n (%)	RR (95%CI)	N	CFR, n (%)	RR (95%CI)	N	CFR, n (%)	RR (95%CI)
Age	≥ 60 y	13909	829 (6.0)	9.45 (8.09-11.04)	548	135 (24.6)	7.18 (5.66-9.12)			
	< 60 y	30763	194 (0.6)		4777	208 (4.4)				
Sex	Male	22981	653 (2.8)	1.67 (1.47-1.89)	2720	196 (7.2)	0.81 (0.64-1.02)	888	203 (22.9)	1.6 (1.2-2.1)
	Female	21691	370 (1.7)		2607	147 (5.6)		359	52 (14.5)	
Any comorbidity	Present	5446	273 (5.0)	5.86 (4.77-7.19)	359	164 (45.5)	7.61 (5.80-9.98)	796	201 (25.3)	3.0 (2.2-3.9)
	Absent	15536	133 (0.9)		1396	139 (10.0)		271	23 (8.5)	
Health care worker	Yes	1716	5 (0.3)	0.12 (0.05-0.30)	1021	34 (3.3)	0.76 (0.52-1.15)	150	2 (1.3)	0.1 (0.02-0.2)
	No	42956	1018 (2.4)		4306	309 (7.2)		1064	236 (22.2)	
Hypertension	Yes	2683	161 (6.0)	4.48 (3.69-5.45)						2.6 (2.2-3.5)[a]
	No	18299	245 (1.3)							
Diabetes	Yes	1102	80 (7.3)	4.43 (3.49-5.61)	72	25	6.48 (3.82-10.99)			1.8 (1.5-2.1)[a]
	No	19880	326 (1.6)		1239	94				

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CVD	Yes	873	92 (10.5)	6.75 (5.40-8.43)	47	18	7.15 (3.84-13.32)	3.5 (3.1-4.8)[a]
	No	20109	314 (1.6)		1264	101		
Cancer	Yes	107	6 (5.6)	2.93 (1.34-6.41)	14	3	2.78 (0.76-10.1)	
	No	20875	400 (1.9)		1297	116		
Other factors		Respiratory disease 3.43 (2.42-4.86)			Cerebrovascular disease 5.34 (2.34-12.16); CKD 9.02 (3.81-21.36)			Respiratory disease 3.1 (2.6-4.2)[a]; CKD 2.2 (1.7-2.9)[a]

RR, relative risk

[a] Odds ratio (OR) retrieved from published meta-analysis of MERS.

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Search

618 Records identified through database searching

- **331** PubMed
- **147** Embase
- **132** Web of science
- **8** Cochrane

236 Records identified through MedRxiv

147 Duplicate records excluded[a]

Identification

707 Records induced for title and abstract screening

649 Excluded for the following reasons:

- Basic research or molecular research
- Comments, editorials or expert opinions
- Case reports or case series
- Unrelated topic/not relevant
- Studies with N ≤ 10
- Studies not in English

58 Full-text atricles selected

28 Excluded for the following reasons:

- **13** Epidemiological studies
- **6** Lacking enough clinical information for meta-analysis
- **3** Did not meet inclusion criteria
- **3** Studies with special but not random populations (including only severe or death cases)
- **2** Publication with overlapping data
- **1** Family clusters

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30 Studies included for meta-analysis

- **19** Single-center studies
- **11** Multi-center studies

Analysis

22 Studies divided the patients cohort according to

- **13** the severity of the illness
- **3** the result of nucleic acid test
- **2** whether admitted to ICU or not
- **2** the serum creatine level or renal function
- **1** time since symptom onset
- **1** whether discharged or not

8 Studies without cohort division

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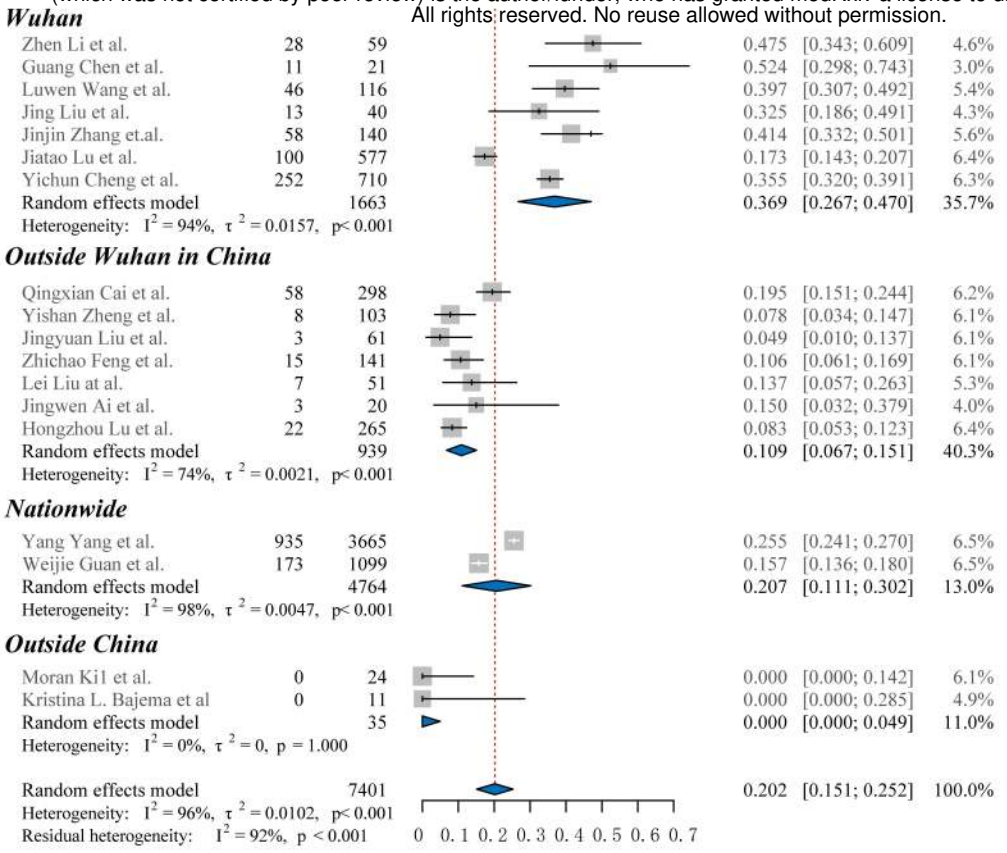
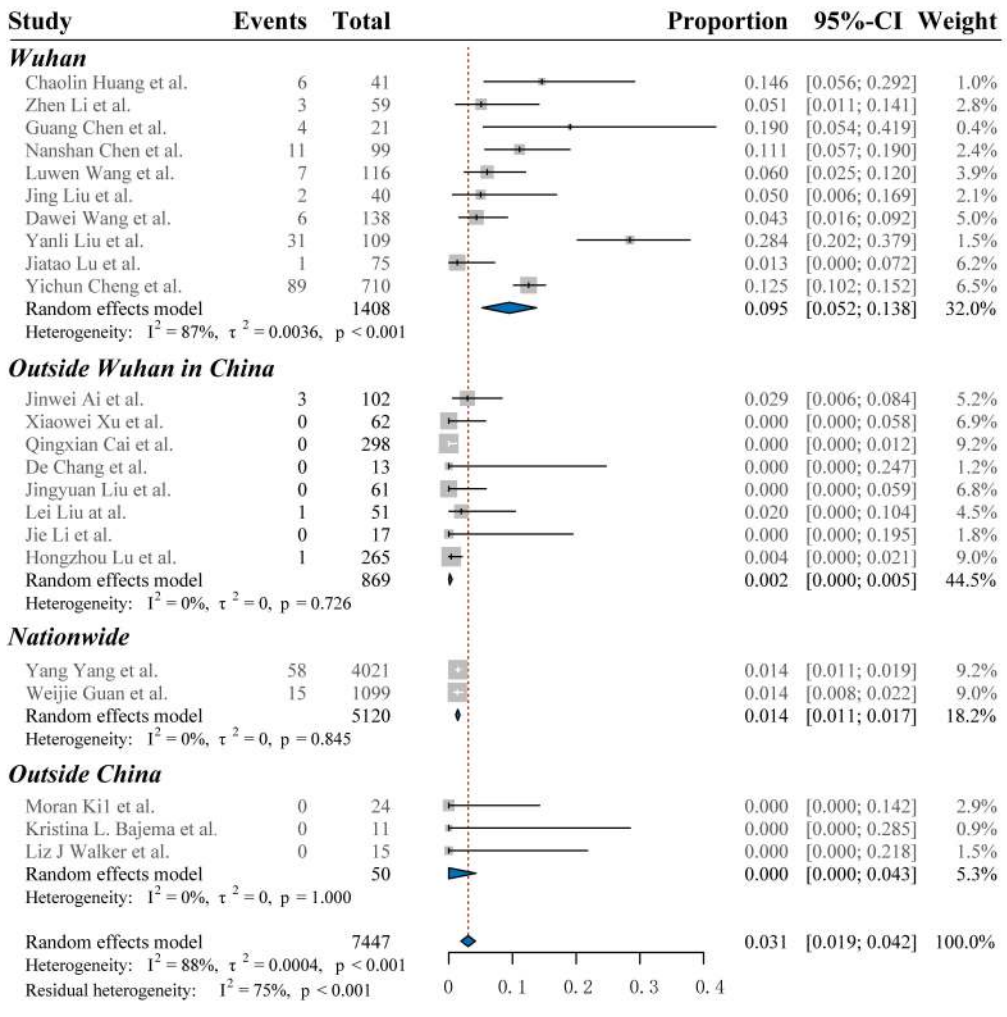
A CSR



B CFR



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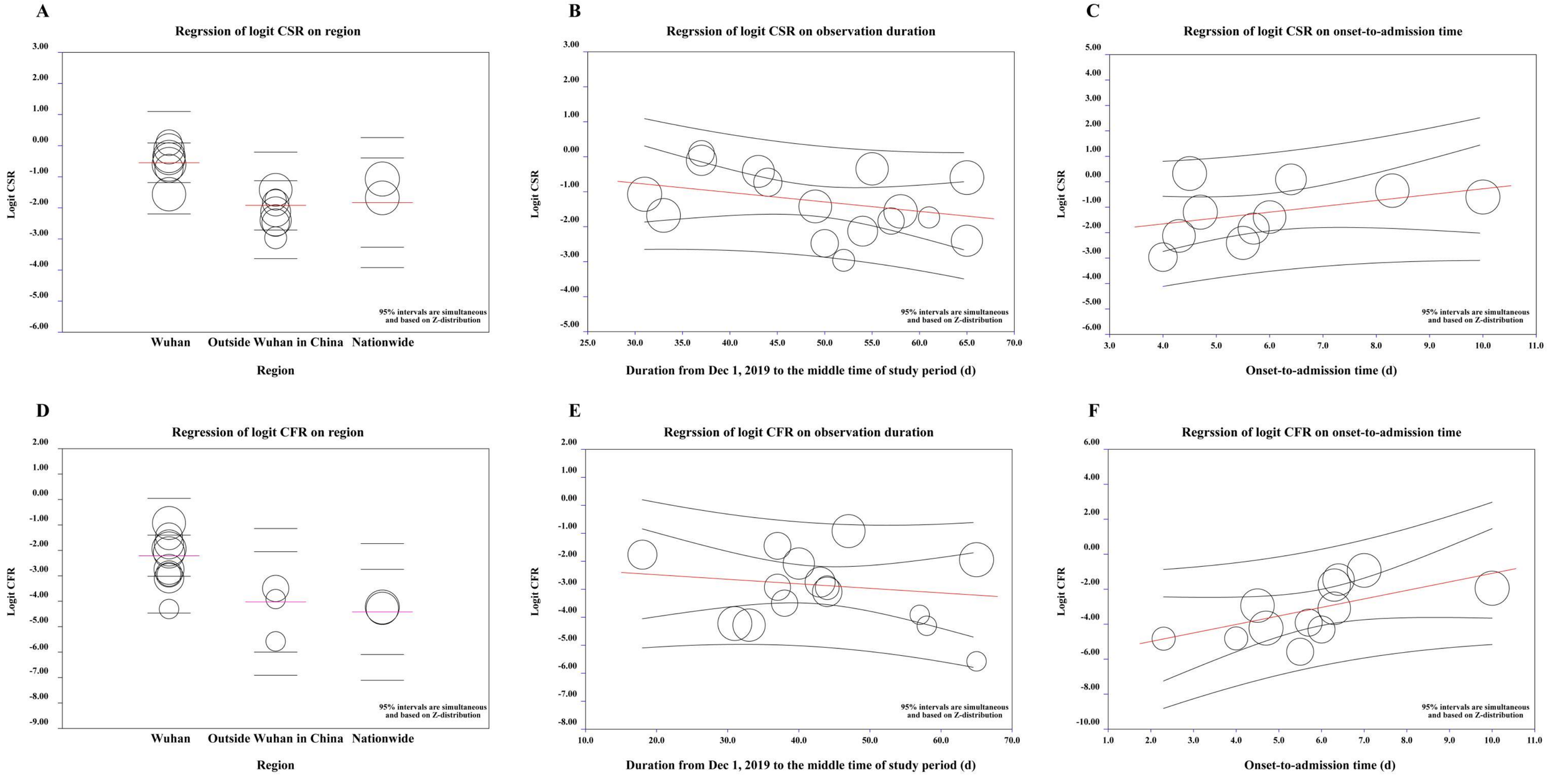
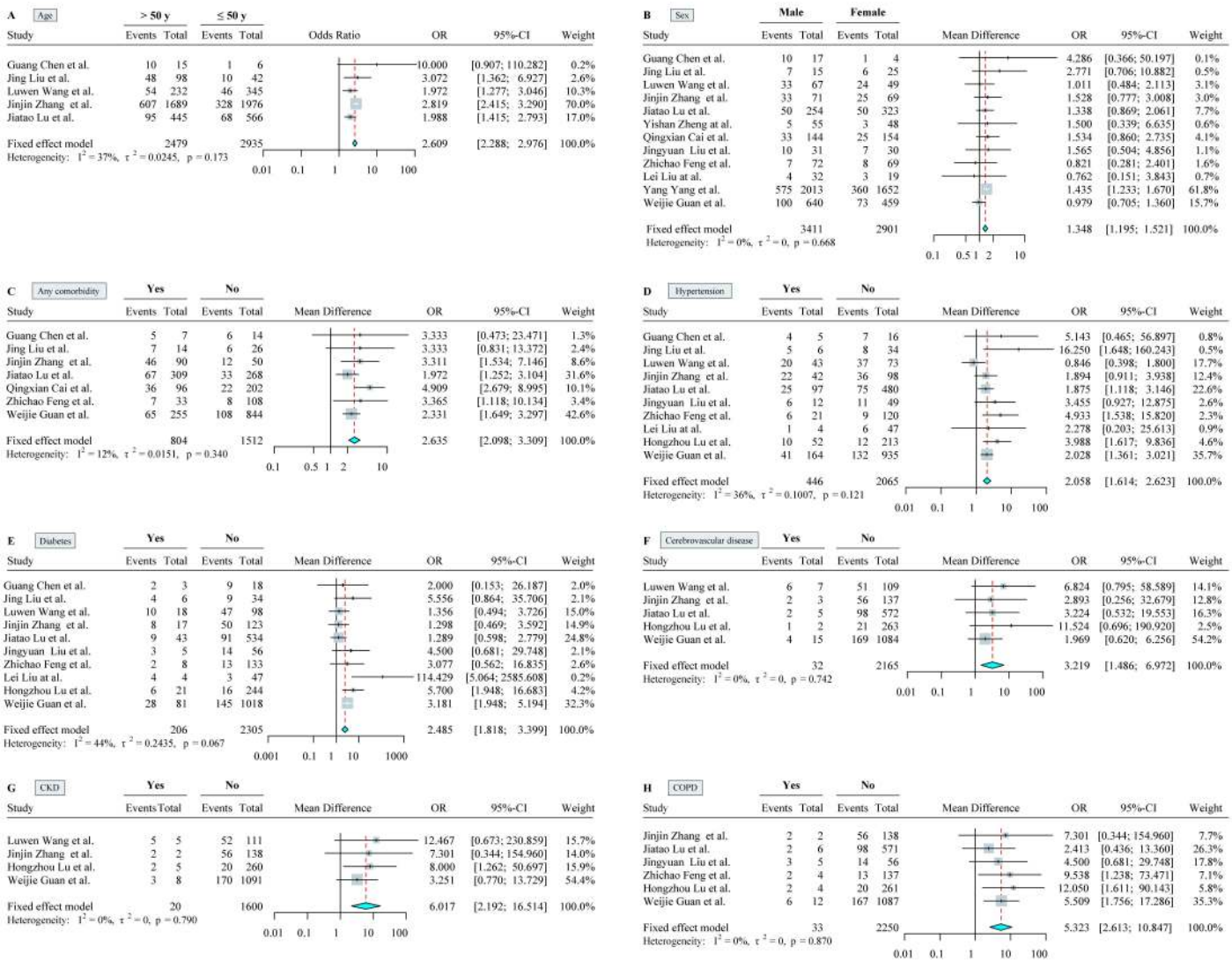
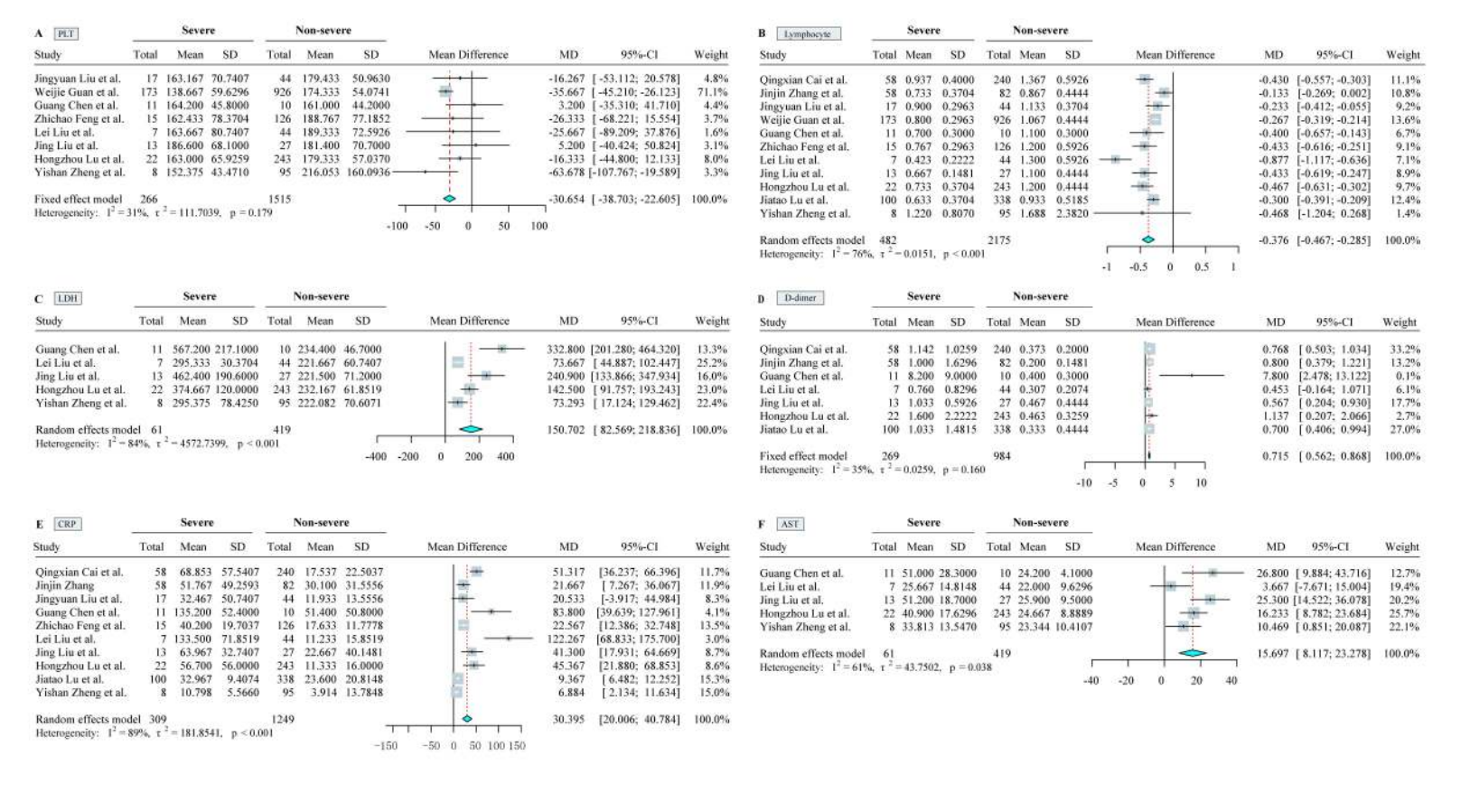



A
Age
> 50 y
≤ 50 y
Study
Events Total
Events Total
Odds Ratio
OR
95%-CI
Weight
Guang Chen et al. 10 15 1 6 10.000 [0.907; 110.282] 0.2%
Jing Liu et al. 48 98 10 42 3.072 [1.362; 6.927] 2.6%
Luwen Wang et al. 54 232 46 345 1.972 [1.277; 3.046] 10.3%
Jinjin Zhang et al. 607 1689 328 1976 2.819 [2.415; 3.290] 70.0%
Jiatao Lu et al. 95 445 68 566 1.988 [1.415; 2.793] 17.0%
Fixed effect model 2479 2935 2.609 [2.288; 2.976] 100.0%
Heterogeneity: I^2 = 37%, τ^2 = 0.0245, p = 0.173
0.01 0.1 1 10 100
B
Sex
Male
Female
Study
Events Total
Events Total
Mean Difference
OR
95%-CI
Weight
Guang Chen et al. 10 17 1 4 4.286 [0.366; 50.197] 0.1%
Jing Liu et al. 7 15 6 25 2.771 [0.706; 10.882] 0.5%
Luwen Wang et al. 33 67 24 49 1.011 [0.484; 2.113] 3.1%
Jinjin Zhang et al. 33 71 25 69 1.528 [0.777; 3.008] 3.0%
Jiatao Lu et al. 50 254 50 323 1.338 [0.869; 2.061] 7.7%
Yishan Zheng at al. 5 55 3 48 1.500 [0.339; 6.635] 0.6%
Qingxian Cai et al. 33 144 25 154 1.534 [0.860; 2.735] 4.1%
Jingyuan Liu et al. 10 31 7 30 1.565 [0.504; 4.856] 1.1%
Zhichao Feng et al. 7 72 8 69 0.821 [0.281; 2.401] 1.6%
Lei Liu at al. 4 32 3 19 0.762 [0.151; 3.843] 0.7%
Yang Yang et al. 575 2013 360 1652 1.435 [1.233; 1.670] 61.8%
Weijie Guan et al. 100 640 73 459 0.979 [0.705; 1.360] 15.7%
Fixed effect model 3411 2901 1.348 [1.195; 1.521] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.668
0.1 0.5 1 2 10
C
Any comorbidity
Yes
No
Study
Events Total
Events Total
Mean Difference
OR
95%-CI
Weight
Guang Chen et al. 5 7 6 14 3.333 [0.473; 23.471] 1.3%
Jing Liu et al. 7 14 6 26 3.333 [0.831; 13.372] 2.4%
Jinjin Zhang et al. 46 90 12 50 3.311 [1.534; 7.146] 8.6%
Jiatao Lu et al. 67 309 33 268 1.972 [1.252; 3.104] 31.6%
Qingxian Cai et al. 36 96 22 202 4.909 [2.679; 8.995] 10.1%
Zhichao Feng et al. 7 33 8 108 3.365 [1.118; 10.134] 3.4%
Weijie Guan et al. 65 255 108 844 2.331 [1.649; 3.297] 42.6%
Fixed effect model 804 1512 2.635 [2.098; 3.309] 100.0%
Heterogeneity: I^2 = 12%, τ^2 = 0.0151, p = 0.340
0.1 0.5 1 2 10
D
Hypertension
Yes
No
Study
Events Total
Events Total
Mean Difference
OR
95%-CI
Weight
Guang Chen et al. 4 5 7 16 5.143 [0.465; 56.897] 0.8%
Jing Liu et al. 5 6 8 34 16.250 [1.648; 160.243] 0.5%
Luwen Wang et al. 20 43 37 73 0.846 [0.398; 1.800] 17.7%
Jinjin Zhang et al. 22 42 36 98 1.894 [0.911; 3.938] 12.4%
Jiatao Lu et al. 25 97 75 480 1.875 [1.118; 3.146] 22.6%
Jingyuan Liu et al. 6 12 11 49 3.455 [0.927; 12.875] 2.6%
Zhichao Feng et al. 6 21 9 120 4.933 [1.538; 15.820] 2.3%
Lei Liu at al. 1 4 6 47 2.278 [0.203; 25.613] 0.9%
Hongzhou Lu et al. 10 52 12 213 3.988 [1.617; 9.836] 4.6%
Weijie Guan et al. 41 164 132 935 2.028 [1.361; 3.021] 35.7%
Fixed effect model 446 2065 2.058 [1.614; 2.623] 100.0%
Heterogeneity: I^2 = 36%, τ^2 = 0.1007, p = 0.121
0.01 0.1 1 10 100
E
Diabetes
Yes
No
Study
Events Total
Events Total
Mean Difference
OR
95%-CI
Weight
Guang Chen et al. 2 3 9 18 2.000 [0.153; 26.187] 2.0%
Jing Liu et al. 4 6 9 34 5.556 [0.864; 35.706] 2.1%
Luwen Wang et al. 10 18 47 98 1.356 [0.494; 3.726] 15.0%
Jinjin Zhang et al. 8 17 50 123 1.298 [0.469; 3.592] 14.9%
Jiatao Lu et al. 9 43 91 534 1.289 [0.598; 2.779] 24.8%
Jingyuan Liu et al. 3 5 14 56 4.500 [0.681; 29.748] 2.1%
Zhichao Feng et al. 2 8 13 133 3.077 [0.562; 16.835] 2.6%
Lei Liu at al. 4 4 3 47 114.429 [5.064; 2585.608] 0.2%
Hongzhou Lu et al. 6 21 16 244 5.700 [1.948; 16.683] 4.2%
Weijie Guan et al. 28 81 145 1018 3.181 [1.948; 5.194] 32.3%
Fixed effect model 206 2305 2.485 [1.818; 3.399] 100.0%
Heterogeneity: I^2 = 44%, τ^2 = 0.2435, p = 0.067
0.001 0.1 1 10 1000
F
Cerebrovascular disease
Yes
No
Study
Events Total
Events Total
Mean Difference
OR
95%-CI
Weight
Luwen Wang et al. 6 7 51 109 6.824 [0.795; 58.589] 14.1%
Jinjin Zhang et al. 2 3 56 137 2.893 [0.256; 32.679] 12.8%
Jiatao Lu et al. 2 5 98 572 3.224 [0.532; 19.553] 16.3%
Hongzhou Lu et al. 1 2 21 263 11.524 [0.696; 190.920] 2.5%
Weijie Guan et al. 4 15 169 1084 1.969 [0.620; 6.256] 54.2%
Fixed effect model 32 2165 3.219 [1.486; 6.972] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.742
0.01 0.1 1 10 100
G
CKD
Yes
No
Study
Events Total
Events Total
Mean Difference
OR
95%-CI
Weight
Luwen Wang et al. 5 5 52 111 12.467 [0.673; 230.859] 15.7%
Jinjin Zhang et al. 2 2 56 138 7.301 [0.344; 154.960] 14.0%
Hongzhou Lu et al. 2 5 20 260 8.000 [1.262; 50.697] 15.9%
Weijie Guan et al. 3 8 170 1091 3.251 [0.770; 13.729] 54.4%
Fixed effect model 20 1600 6.017 [2.192; 16.514] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.790
0.01 0.1 1 10 100
H
COPD
Yes
No
Study
Events Total
Events Total
Mean Difference
OR
95%-CI
Weight
Jinjin Zhang et al. 2 2 56 138 7.301 [0.344; 154.960] 7.7%
Jiatao Lu et al. 2 6 98 571 2.413 [0.436; 13.360] 26.3%
Jingyuan Liu et al. 3 5 14 56 4.500 [0.681; 29.748] 17.8%
Zhichao Feng et al. 2 4 13 137 9.538 [1.238; 73.471] 7.1%
Hongzhou Lu et al. 2 4 20 261 12.050 [1.611; 90.143] 5.8%
Weijie Guan et al. 6 12 167 1087 5.509 [1.756; 17.286] 35.3%
Fixed effect model 33 2250 5.323 [2.613; 10.847] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.870
0.01 0.1 1 10 100


A PLT
Severe
Non-severe
Study Total Mean SD Total Mean SD Mean Difference MD 95%-CI Weight
Jingyuan Liu et al. 17 163.167 70.7407 44 179.433 50.9630 -16.267 [-53.112; 20.578] 4.8%
Weijie Guan et al. 173 138.667 59.6296 926 174.333 54.0741 -35.667 [-45.210; -26.123] 71.1%
Guang Chen et al. 11 164.200 45.8000 10 161.000 44.2000 3.200 [-35.310; 41.710] 4.4%
Zhichao Feng et al. 15 162.433 78.3704 126 188.767 77.1852 -26.333 [-68.221; 15.554] 3.7%
Lei Liu et al. 7 163.667 80.7407 44 189.333 72.5926 -25.667 [-89.209; 37.876] 1.6%
Jing Liu et al. 13 186.600 68.1000 27 181.400 70.7000 5.200 [-40.424; 50.824] 3.1%
Hongzhou Lu et al. 22 163.000 65.9259 243 179.333 57.0370 -16.333 [-44.800; 12.133] 8.0%
Yishan Zheng et al. 8 152.375 43.4710 95 216.053 160.0936 -63.678 [-107.767; -19.589] 3.3%
Fixed effect model 266 1515 -30.654 [-38.703; -22.605] 100.0%
Heterogeneity: I^2 = 31%, τ^2 = 111.7039, p = 0.179
-100 -50 0 50 100
B Lymphocyte
Severe
Non-severe
Study Total Mean SD Total Mean SD Mean Difference MD 95%-CI Weight
Qingxian Cai et al. 58 0.937 0.4000 240 1.367 0.5926 -0.430 [-0.557; -0.303] 11.1%
Jinjin Zhang et al. 58 0.733 0.3704 82 0.867 0.4444 -0.133 [-0.269; 0.002] 10.8%
Jingyuan Liu et al. 17 0.900 0.2963 44 1.133 0.3704 -0.233 [-0.412; -0.055] 9.2%
Weijie Guan et al. 173 0.800 0.2963 926 1.067 0.4444 -0.267 [-0.319; -0.214] 13.6%
Guang Chen et al. 11 0.700 0.3000 10 1.100 0.3000 -0.400 [-0.657; -0.143] 6.7%
Zhichao Feng et al. 15 0.767 0.2963 126 1.200 0.5926 -0.433 [-0.616; -0.251] 9.1%
Lei Liu et al. 7 0.423 0.2222 44 1.300 0.5926 -0.877 [-1.117; -0.636] 7.1%
Jing Liu et al. 13 0.667 0.1481 27 1.100 0.4444 -0.433 [-0.619; -0.247] 8.9%
Hongzhou Lu et al. 22 0.733 0.3704 243 1.200 0.4444 -0.467 [-0.631; -0.302] 9.7%
Jiatao Lu et al. 100 0.633 0.3704 338 0.933 0.5185 -0.300 [-0.391; -0.209] 12.4%
Yishan Zheng et al. 8 1.220 0.8070 95 1.688 2.3820 -0.468 [-1.204; 0.268] 1.4%
Random effects model 482 2175 -0.376 [-0.467; -0.285] 100.0%
Heterogeneity: I^2 = 76%, τ^2 = 0.0151, p < 0.001
-1 -0.5 0 0.5 1
C LDH
Severe
Non-severe
Study Total Mean SD Total Mean SD Mean Difference MD 95%-CI Weight
Guang Chen et al. 11 567.200 217.1000 10 234.400 46.7000 332.800 [201.280; 464.320] 13.3%
Lei Liu et al. 7 295.333 30.3704 44 221.667 60.7407 73.667 [44.887; 102.447] 25.2%
Jing Liu et al. 13 462.400 190.6000 27 221.500 71.2000 240.900 [133.866; 347.934] 16.0%
Hongzhou Lu et al. 22 374.667 120.0000 243 232.167 61.8519 142.500 [91.757; 193.243] 23.0%
Yishan Zheng et al. 8 295.375 78.4250 95 222.082 70.6071 73.293 [17.124; 129.462] 22.4%
Random effects model 61 419 150.702 [82.569; 218.836] 100.0%
Heterogeneity: I^2 = 84%, τ^2 = 4572.7399, p < 0.001
-400 -200 0 200 400
D D-dimer
Severe
Non-severe
Study Total Mean SD Total Mean SD Mean Difference MD 95%-CI Weight
Qingxian Cai et al. 58 1.142 1.0259 240 0.373 0.2000 0.768 [0.503; 1.034] 33.2%
Jinjin Zhang et al. 58 1.000 1.6296 82 0.200 0.1481 0.800 [0.379; 1.221] 13.2%
Guang Chen et al. 11 8.200 9.0000 10 0.400 0.3000 7.800 [2.478; 13.122] 0.1%
Lei Liu et al. 7 0.760 0.8296 44 0.307 0.2074 0.453 [-0.164; 1.071] 6.1%
Jing Liu et al. 13 1.033 0.5926 27 0.467 0.4444 0.567 [0.204; 0.930] 17.7%
Hongzhou Lu et al. 22 1.600 2.2222 243 0.463 0.3259 1.137 [0.207; 2.066] 2.7%
Jiatao Lu et al. 100 1.033 1.4815 338 0.333 0.4444 0.700 [0.406; 0.994] 27.0%
Fixed effect model 269 984 0.715 [0.562; 0.868] 100.0%
Heterogeneity: I^2 = 35%, τ^2 = 0.0259, p = 0.160
-10 -5 0 5 10
E CRP
Severe
Non-severe
Study Total Mean SD Total Mean SD Mean Difference MD 95%-CI Weight
Qingxian Cai et al. 58 68.853 57.5407 240 17.537 22.5037 51.317 [36.237; 66.396] 11.7%
Jinjin Zhang 58 51.767 49.2593 82 30.100 31.5556 21.667 [7.267; 36.067] 11.9%
Jingyuan Liu et al. 17 32.467 50.7407 44 11.933 13.5556 20.533 [-3.917; 44.984] 8.3%
Guang Chen et al. 11 135.200 52.4000 10 51.400 50.8000 83.800 [39.639; 127.961] 4.1%
Zhichao Feng et al. 15 40.200 19.7037 126 17.633 11.7778 22.567 [12.386; 32.748] 13.5%
Lei Liu et al. 7 133.500 71.8519 44 11.233 15.8519 122.267 [68.833; 175.700] 3.0%
Jing Liu et al. 13 63.967 32.7407 27 22.667 40.1481 41.300 [17.931; 64.669] 8.7%
Hongzhou Lu et al. 22 56.700 56.0000 243 11.333 16.0000 45.367 [21.880; 68.853] 8.6%
Jiatao Lu et al. 100 32.967 9.4074 338 23.600 20.8148 9.367 [6.482; 12.252] 15.3%
Yishan Zheng et al. 8 10.798 5.5660 95 3.914 13.7848 6.884 [2.134; 11.634] 15.0%
Random effects model 309 1249 30.395 [20.006; 40.784] 100.0%
Heterogeneity: I^2 = 89%, τ^2 = 181.8541, p < 0.001
-150 -50 0 50 100 150
F AST
Severe
Non-severe
Study Total Mean SD Total Mean SD Mean Difference MD 95%-CI Weight
Guang Chen et al. 11 51.000 28.3000 10 24.200 4.1000 26.800 [9.884; 43.716] 12.7%
Lei Liu et al. 7 25.667 14.8148 44 22.000 9.6296 3.667 [-7.671; 15.004] 19.4%
Jing Liu et al. 13 51.200 18.7000 27 25.900 9.5000 25.300 [14.522; 36.078] 20.2%
Hongzhou Lu et al. 22 40.900 17.6296 243 24.667 8.8889 16.233 [8.782; 23.684] 25.7%
Yishan Zheng et al. 8 33.813 13.5470 95 23.344 10.4107 10.469 [0.851; 20.087] 22.1%
Random effects model 61 419 15.697 [8.117; 23.278] 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 43.7502, p = 0.038
-40 -20 0 20 40