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Clinical Features of COVID-19 and Factors Associated with Severe Clinical Course: A Systematic Review and Meta-analysis

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Abstract:	SUMMARY Background COVID-19 is a new disease which has become a global pandemic, and is caused by a novel coronavirus, SARS-CoV-2. The disease is still not very well characterized, and factors associated with severe clinical course are not well known. Methods The main objectives were to determine the demographic, clinical and laboratory manifestations of COVID-19 and to identify the factors associated with severe clinical course. We searched the PubMed for studies published between Jan 1, 2020 and Mar 17, 2020, and included them if they were in English language, published in full, were retrospective or prospective observational or case control study with data on clinical, laboratory and imaging features of adult patients with COVID-19 disease from single or multiple centers. Studies that included exclusively pediatric patients were excluded. The demographic, clinical and laboratory data was displayed as n (%) or mean (SD). The meta-analysis on factors associated with severe clinical course was performed using the random effects model, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated as the effect sizes. Findings We included 58 studies (6892 patients) for the systematic review on clinical manifestations and 21 studies (3496 patients) for meta-analysis on factors associated with severe clinical course. The mean age of patients with COVID-19 is 49.7±16.3 years with a male to female ratio of 1.2:1. Common symptoms and their frequency are: fever (83.4%), cough (60.5%), fatigue (33.8%), sputum (28.9%), dyspnea (22.1%), myalgia (20.6%), chest tightness / pain (16.3%), sore throat (13.5%), headache (11.2%), diarhhea (7.5%), nasal congestion / rhinorrhea (6.7%), nausea / vomiting (5.6%), pain abdomen (4.6%), and hemoptysis (1.7%). The comorbidities associated with COVID-19 are: hypertension (18.4%), diabetes mellitus (9.8%), cardiovascular

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	diseases (8.8%), endocrine diseases (5.8%), gastrointestinal diseases (5%), CLD (3%), and COPD (2.8%). Among the laboratory parameters WBC was low in 27%, high in 9%, platelets were low in 22.9%, creatinine was high in 6.5%, AST was high in 25.3%, ALT was high in 22.7%, bilirubin was high in 8.8%, albumin was low 60.1%, CT chest was abnormal in 89%, CRP was high in 67.5%, LDH was high in 52%, D-dimer was high in 34.8%, CK was high in 14.4%, and procalcitonin was high in 15.4%. Factors significantly associated severe clinical course (with their ORs) are as follows: High CRP (5.78), high procalcitonin (5.45), age >60 (4.82), dyspnea (4.66), high LDH (4.59), COPD (4.37), low albumin (4.34), high D-dimer (4.03), cardiac disease (3.88), low lymphocyte count (3.22), any associated comorbidity (3.16), diabetes mellitus (3.11), high WBC count (2.67), high bilirubin level (2.55), high creatinine (2.34), high AST (2.31), hypertension (2.30), low platelets (1.78), High ALT (1.69), high CK (1.66), fever spikes ≥39°C (1.59), diarrhea (1.55), male gender (1.47), and sputum (1.35). Interpretation Identification of these factors associated with severe COVID-19 will help the physicians working at all levels of healthcare (primary, secondary, tertiary and ICU) in determining which patients need home care, hospital care, HDU care, and ICU admission; and thus, prioritize the scarce healthcare resource use more judiciously. Many of these identified factors can also help the public at large in the current COVID-19 epidemic setting, to judge when they should seek immediate medical care.

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Clinical Features of COVID-19 and Factors Associated with Severe Clinical Course: A Systematic Review and Meta-analysis

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SUMMARY

Background:

COVID-19 is a new disease which has become a global pandemic, and is caused by a novel coronavirus, SARS-CoV-2. The disease is still not very well characterized, and factors associated with severe clinical course are not well known.

Methods:

The main objectives were to determine the demographic, clinical and laboratory manifestations of COVID-19 and to identify the factors associated with severe clinical course. We searched the PubMed for studies published between Jan 1, 2020 and Mar 17, 2020, and included them if they were in English language, published in full, were retrospective or prospective observational or case control study with data on clinical, laboratory and imaging features of adult patients with COVID-19 disease from single or multiple centers. Studies that included exclusively pediatric patients were excluded. The demographic, clinical and laboratory data was displayed as n (%) or mean (SD). The meta-analysis on factors associated with severe clinical course was performed using the random effects model, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated as the effect sizes.

Findings:

We included 58 studies (6892 patients) for the systematic review on clinical manifestations and 21 studies (3496 patients) for meta-analysis on factors associated with severe clinical course. The mean age of patients with COVID-19 is 49.7±16.3 years with a male to female ratio of 1.2:1. Common symptoms and their frequency are: fever (83.4%), cough (60.5%), fatigue (33.8%), sputum (28.9%), dyspnea (22.1%), myalgia (20.6%), chest tightness / pain (16.3%), sore throat (13.5%), headache (11.2%), diarhhea (7.5%), nasal congestion / rhinorrhea (6.7%), nausea / vomiting (5.6%), pain abdomen (4.6%), and hemoptysis (1.7%). The comorbidities associated with COVID-19 are: hypertension (18.4%), diabetes mellitus (9.8%), cardiovascular diseases (8.8%), endocrine diseases (5.8%), gastrointestinal diseases (5%), CLD (3%), and COPD (2.8%). Among the laboratory parameters WBC was low in 27%, high in 9%, platelets were low in 22.9%, creatinine was high in 6.5%, AST was high in 25.3%, ALT was high in 22.7%, bilirubin was high in 8.8%, albumin was low 60.1%, CT chest was abnormal in 89%, CRP was high in 67.5%, LDH was high in 52%, D-dimer was high in 34.8%, CK was high in 14.4%, and procalcitonin was high in 15.4%. Factors significantly associated severe clinical course (with their ORs) are as follows: High CRP (5.78), high procalcitonin (5.45), age >60 (4.82), dyspnea (4.66), high LDH (4.59), COPD (4.37), low albumin (4.34), high D-dimer (4.03), cardiac disease (3.88), low lymphocyte count (3.22), any associated comorbidity (3.16), diabetes mellitus (3.11), high WBC count (2.67), high bilirubin level (2.55), high creatinine (2.34), high AST (2.31), hypertension (2.30), low platelets (1.78), High ALT (1.69), high CK (1.66), fever spikes ≥39°C (1.59), diarrhea (1.55), male gender (1.47), and sputum (1.35).

Interpretation:

Identification of these factors associated with severe COVID-19 will help the physicians working at all levels of healthcare (primary, secondary, tertiary and ICU) in determining which patients need home care, hospital care, HDU care, and ICU admission; and thus, prioritize the scarce healthcare resource use more judiciously. Many of these identified factors can also

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help the public at large in the current COVID-19 epidemic setting, to judge when they should seek immediate medical care.

Funding:
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KEYWORDS
Coronavirus; 2019-nCoV; nCoV-2019; novel coronavirus; SARS-CoV-2; COVID-19

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RESEARCH IN CONTEXT

Evidence before this study

COVID-19 is a new disease which has become a global pandemic, and is caused by a novel coronavirus, SARS-CoV-2. Knowledge of this disease is still incomplete and evolving. We searched the PubMed for studies published between Jan 1, 2020 and Mar 17, 2020 and found that many retrospective case series have been published on clinical, laboratory and imaging manifestations of COVID-19. However, most of these case series have small sample size, and the data in them are heterogenous and conflicting. A few meta-analyses have also been published on clinical manifestations of COVID-19, however, these meta-analyses have either included small number of studies with limited number of patients or have included overlapping patients from other studies. In addition, since many patients with COVID-19 have rapid course and within days may require ICU admission and mechanical ventilation, hence, it is essential to identify early which patients are likely go into severe clinical course. To the best of our knowledge, no meta-analysis has been published so far studying the factors associated with severe clinical course of COVID-19.

Added value of this study

This systematic review of 6892 patients (58 studies) described the demographic, clinical and laboratory manifestations of COVID-19. Since we included a large number of studies and avoided overlapping data, our estimate of these data is robust and reliable. Our meta-analysis of 3496 patients (21 studies), determined with high-certainty evidence, the demographic, clinical and laboratory factors associated with severe clinical course of COVID-19. The factors (in order of theirs ORs) can be categorized into 4 groups: Vulnerable populations (age >60 years, COPD patients, cardiac patients, patient with comorbidities, diabetes patients, hypertension patients, and male gender); symptoms indicating potential severe disease (dyspnea present, spiking fever with temp ≥39°C, diarrhea present, and productive cough); routine laboratory parameters indicating potential severe disease (low albumin level, low lymphocyte level, high WBC count, high serum bilirubin level, high creatinine level, high AST level, low platelet count, and high ALT level); and patients who may need intensive care (high CRP level, high procalcitonin level, high LDH level, high D-dimer level, and high creatine kinase level).

Implications of all the available evidence

During the midst of COVID-19 pandemic, the findings from our study has several potential implications for multiple stakeholders: the general public, healthcare policy makers, governments, patients of COVID-19, physicians at the primary care facilities, physicians managing COVID-19 patients in hospitals, and critical care specialists of ICUs. Our study clearly elucidated the list of vulnerable populations and symptoms which indicate potential severe COVID-19 disease. This information should be disseminated to the general public at places where COVID-19 epidemic is ongoing. This information will help the public in understanding whether they are at risk of severe COVID-19, and which of their symptoms should make them seek immediate in-hospital medical care and which patients can be safely managed at home by just telephonic consultation. This self-triage by the patients will prevent hospitals from getting overwhelmed by thousands of patients, most of whom do not need hospital care. Physicians working at the primary care facilities and hospitals managing COVID-19 patients can learn from our meta-analysis derangement of which of

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the routine laboratory parameters (such as albumin level or WBC count) indicate potentially severe disease requiring admission or referral to specialized centers. Physicians and critical care specialists working at tertiary care centers and ICUs can be guided from this meta-analysis, based on the inflammatory and infection markers, which patients need intensive care, and which be managed at less intensive settings.

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INTRODUCTION

COVID-19 is a new disease, which within three months of its origin, has now spread to more than 177 countries around the world, affecting more than 724,000 people and caused more than 34,000 deaths, as of 30th March, 2020[1]. The World Health Organization (WHO) has declared COVID-19 a pandemic because of alarming levels of its spread and severity[2]. It is caused by SARS-CoV-2, which is sufficiently genetically divergent from SARS-CoV to be considered a new human-infecting betacoronavirus[3]. It mainly affects the respiratory tract and the illness ranges in severity from asymptomatic or mild to severe or critical disease. Although the current estimate of the case fatality rate of COVID-19 is <5%, up to 15-18% of patients may become severe or critically ill, some of them requiring ICU care and mechanical ventilation[4].

Knowledge of this disease is still incomplete and evolving. Many retrospective case series have been published on clinical, laboratory and imaging manifestations of COVID-19. However, most of these case series have small sample size, and the data in them are heterogenous and conflicting. A few meta-analyses have also been published on clinical manifestations of COVID-19, however, these meta-analyses have either included small number of studies with limited number of patients[5–7], or have included patients from the database of Chinese Center for Disease Control and Prevention[8], which has a significant overlap of patients from other studies[4,9]. In addition, since many patients with COVID-19 have rapid course and within days may require ICU admission and mechanical ventilation, so, it is essential to identify early which patients are likely go into severe clinical course. To the best of our knowledge, no meta-analysis has been published studying the factors associated with severe clinical course.

Hence, this systematic review and meta-analysis was conducted with following objectives: (1) to study the demographic, clinical and laboratory manifestations of COVID-19; and (2) to determine the factors associated with severe clinical course of COVID-19.

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MATERIALS AND METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and guidelines were consulted during the stages of design, analysis, and reporting of this systematic review[10,11]. Since, this is a systematic review and meta-analysis, therefore an ethics committee and/or institutional board approval was not required.

Study Selection

Relevant papers in English language were searched in PubMed database using the following keywords: “2019-nCoV”, “nCoV-2019”, "Novel Coronavirus 2019", “SARS-CoV-2”, “COVID-19”, “coronavirus”, “coronavirus covid-19”, and “corona virus”. The last search was performed on March 17, 2020. Since the first report of COVID-19 disease was published on 31st December, 2019[12], we limited our search to articles published only in 2020. Since there is a high likelihood of duplicate publications on COVID-19[13], especially, same set of patients being reported in English as well as Chinese or other languages, hence we restricted our search to papers published in English language only. For the same reason we restricted our search to PubMed database only and did not search other databases.

The eligibility criteria for inclusion of studies were as follows:

(1) The studies should be in English language;

(2) The studies should be published in full; studies published only in abstract form (such as conference abstracts) were excluded;

(3) the study design should be retrospective or prospective observational or case control study with data on clinical, laboratory and imaging features of COVID-19 disease from single or multiple centers; meta-analyses and systematic reviews were excluded;

(4) the participants should be adult patients with COVID-19 disease. Studies describing exclusively pediatric population were excluded, however, studies which had both adult and pediatric patients were included.

Data extraction

The following data were extracted from each study: date of online publication, number of patients, study setting, demographic data, comorbidities, presenting symptoms, laboratory and imaging features, number of patients having severe and good clinical course. Following criteria was used to identify patients having ‘severe clinical course’:

1. Patients requiring ICU care; or
2. Patients developing ARDS, shock, respiratory failure, or those requiring mechanical ventilation as defined according to the guidance of WHO for COVID-19[14];
3. Patients categorized as severe or critical groups according to the diagnostic and treatment guideline for SARS-CoV-2 issued by the National Health Commission of the People’s Republic of China (version 3-5)[15,16]; or
4. Patients not surviving.

Patients not having any of the feature of ‘severe clinical course’ were categorized into ‘good clinical course’. The baseline clinical and laboratory features of patients with severe clinical course and good clinical course were tabulated separately and compared using appropriate statistical methods. For studies with missing data, the corresponding authors of those studies were contacted with a request to provide the missing data.

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Assessment of quality of studies

For the assessment of quality of studies, the National Institute of Health (NIH) tools were used, which were developed jointly by the National Heart, Lung and Blood Institute (NHLBI) and the Research Triangle Institute International[17]. For the first objective of this meta-analysis, i.e. to study the demographic, clinical and laboratory manifestations of COVID-19, the NIH tool for case series was used. It uses nine domains and based on them each study was given an overall rating of good, fair or poor, depending on 'yes' response in ≥7 domains, 4-6 domains, and <4 domains, respectively. For the second objective of this meta-analysis, i.e. to determine the factors associated with severe clinical course of COVID-19, the NIH tool for case-control studies was used. It uses twelve domains and based on them each study was given an overall rating of good, fair or poor, depending on 'yes' response in ≥8 domains, 6-7 domains, and <6 domains, respectively.

Statistical analysis

The demographic, clinical and laboratory data was displayed as n (%) or mean (SD). For data with median, IQR or range, the method described by Wan et al was used to calculate mean and SD[18]. The meta-analysis was performed using odds ratios (ORs) with 95% confidence intervals (CIs) as the effect sizes of dichotomous data. To assess the heterogeneity among studies I^2 statistic was calculated. An I^2 value >50% indicated substantial heterogeneity. The ORs were pooled using only the random effects model to calculate a more conservative result and to take care of heterogeneity among the studies. In addition, if the heterogeneity among the studies was ≥50%, a sensitivity analysis was also performed after removing the outlier studies. To obtain odds ratios from continuous data (from standardized mean difference) Hasselblad and Hedges' method was used[19]. A p value of <0.05 was considered statistically significant to show a meaningful difference in the outcomes. Review Manager version 5.3.5 software (The Nordic Cochrane Centre, Copenhagen, Denmark), OpenMetaAnalyst software (version 10.12)[20] and Microsoft Excel (version 16.35) were employed for the meta-analysis and statistical analyses.

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RESULTS

Study selection and data collection

Using the keywords “2019-nCoV”, “nCoV-2019”, "Novel Coronavirus 2019", “SARS-CoV-2”, “COVID-19”, “coronavirus”, “coronavirus covid-19”, and “corona virus” and limiting the Entrez date from 01-Jan-2020 to 17-Mar-2020 in the PubMed database, initially 1155 publications in English language were retrieved, which were screened for relevance (Figure 1). After carefully going through the abstracts and full texts of these publications only 69 potentially relevant studies were evaluated in detail for potential inclusion. Of these 11 studies were excluded because of the following reasons: (1) The study by Chung M et al[21] was excluded because of possible overlap with patients in the study by Bernheim et al[22]; (2) The study by Ki M et al[23] was excluded because of possible overlap with patients in the study by CNERC[24]; (3) The study by Chen H et al[25] was excluded because it included only pregnant patients; (4) The study by Yoon SH et al[26] was excluded because there was no clinical data; (5) The study by Liu H et al[27] was excluded as its primary focus was pregnant women and children; (6) The study by Xu T et al[28] was excluded as it was a comparative study between imported, secondary and tertiary cases; (7) The study by Qu R et al[29] was excluded as it was comparison of platelet-to-lymphocyte ratio between severe and non-severe patients; (8) The study by To KK et al[30] was excluded as the main focus of the study was detection of novel coronavirus in saliva; (9) The study by Pan Y et al[31] was excluded as its main focus was CT scan findings with no clinical data; (10) The study by Pan F et al[32] was excluded because it included only recovered patients, and had excluded patients with severe disease; and (11) The study by Liang W et al[33] was excluded because it included only cancer patients. Hence, remaining 58 studies were included in the systematic review. Figure 1 summarizes the systematic review flow.

Characteristics and quality of the included studies

The study characteristics of the included 58 studies are given in Table 1. The total number of included patients in these 58 studies was 6892. Thirty-five out of 58 (60%) studies were from single centres, while remaining 23 (40%) were multi-centre studies. Most studies (53/58, 91%) were from mainland China, and of the remaining 5 studies, one (1.7%) each was from Hong Kong, Singapore, South Korea, Australia and Europe, respectively. Thus 97.5% (6723/6892) of included patients were from mainland China.

The online publication date of the studies was from January 24, 2020 through March 17, 2020. The median number of patients included in the studies were 70 (IQR: 31-137). The largest study was by Guan WJ et al[34], which recruited 1099 patients from 552 hospitals in 30 provinces, autonomous regions, and municipalities of mainland China.

The quality of study was assessed using the NIH tool[17] and the results are shown in table 1. Fifty out of 58 studies were of good quality, while rest 8 were of fair quality. None of the included study was judged poor.

Demographic data of the patients and their baseline comorbidities

The Table 2 shows the demographic data of the included patients. The total number of patients was 6892, and of these 3709 (54%) were males. Thus the male : female ratio was approximately 1.2:1. The combined mean age of patients was 49.7±16.3 years.

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Table 2 also shows the data on underlying comorbidities in included patients. This data was present in 39 studies. The highest frequency of comorbidity was hypertension, which was present in 620/3368 (18.4%) patients. The next most common comorbidities were diabetes mellitus (9.8%), cardiovascular diseases (8.8%), endocrine diseases (5.8%), and gastrointestinal diseases (5%). Since COVID-19 mainly affects respiratory system, presence of underlying respiratory diseases, especially COPD, is relevant. Out of 3847 patients 108 (2.8%) had COPD.

Presenting symptoms of patients

Fifty-three studies had data on symptoms of the patients, which is shown in Table 3. The most common symptom was fever which was present in 4082/4895 (83.4%). This was followed by cough, which was present in 3008/4968 (60.5%), fatigue in 1355/4007 (33.8%), sputum in 908/3146 (28.9%), dyspnea in 856/3879 (22.1%), myalgia in 757/3683 (20.6%), chest tightness / pain in 233/1424 (16.3%), sore throat in 354/2056 (13.5%), and headache in 387/3449 (11.2%). Notably, nasal congestion or rhinorrhea were present in minority (6.7%). Only 1.7% had hemoptysis. Gastro-intestinal symptoms of diarrhea, nausea / vomiting, and pain abdomen were present in 7.5%, 5.6% and 4.6%, respectively.

Laboratory and imaging features of patients

Table 4 shows the routine laboratory and CT features of the patients. Among the hematological parameters, lower than normal WBC count was found in 818/3030 (27%) patients while higher than normal WBC count was found in 264/2918 (9%) patients. Lower than normal platelet count was found in 464/2023 (22.9%). The hemoglobin remained largely within normal range (mean 132±20 g/L). Serum creatinine was deranged in 123/1894 (6.5%). Among the liver function parameters, AST was abnormal in 529/2091 (25.3%), ALT was abnormal in 473/2084 (22.7%), bilirubin was abnormal in 130/1471 (8.8%), serum albumin was low in 491/817 (60.1%) and prothrombin time was high in 55/750 (7.3%). CT scan of chest was abnormal in 3119/3503 (89%) patients.

The table 5 shows various inflammatory and infection markers in the patients. High CRP was the most common finding, present in 1755/2601 (67.5%) patients. LDH was high in 1041/2001 (52%) patients, D-dimer was high in 322/1853 (17.4%) and procalcitonin was high in 278/1806 (15.4%) patients.

Clinical outcome

Since, at the time of publication of most of these studies, many of the included patients were still admitted in the hospital, with many in the ICUs, so it was not possible by many studies to provide the mortality data. However, many studies did classify the patients into severe and non-severe groups based on predefined criteria[14–16]. Overall, 28 studies reported that 3119/3984 (78.3%) of their patients had good clinical course, while the remaining 865/3984 (21.7%) patients had severe clinical course, including admission to ICU, development of ARDs, ventilatory requirement, mortality or pre-defined severity criteria[14–16] (Figure 2).

Factors associated with severe clinical course

A total of 21 studies evaluated factors associated with severe clinical course using univariate analysis as shown in Table 6. The quality of these studies as assessed by the NIH tool for case-control studies[17] is also given in the table. Notably all the included studies were of good

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quality. Of the twelve domains in the quality assessment tool, all the included studies were marked as 'yes' in nine domains. The only domains in which the studies were marked 'no' were: sample size justification, blinding of assessors, and adjusting for confounding variables.

Of the 3496 patients in these twenty-one studies, 817 (23%) patients had severe clinical course and 2679 (77%) patients had good clinical course. The important demographic, clinical and laboratory factors associated with severe clinical course are discussed below.

Demographic factors associated with severe clinical course

Age was compared between patients with severe clinical course and good clinical course in 21 studies. The mean age in patients with severe clinical course was found to be significantly higher than in patients with good clinical course (59.4 [95% CI: 56.1-62.8] versus 46.5 [95% CI: 43.8-49.2] years; p<0.01) (Figure 3). The pooled odds ratio of patients of advanced age (>60 years) having severe clinical course was 4.82 (95% CI: 2.83-8.24; p<0.01) (Figure 4). The heterogeneity among studies was significant with an I^2 of 94%. A sensitivity analysis after removing 4 outlier studies still revealed a significant pooled odds ratio of 4.42 (95%CI: 3.27-5.95) and an I^2 of 47%.

Gender was assessed as a factor associated with severe clinical course in 20 studies. Although most studies individually could not associate gender with severe clinical course, however, meta-analysis of the studies revealed that male gender was significantly associated with severe clinical course with a pooled odds ratio of 1.47 (95% CI: 1.21-1.79; p<0.01) (Figure 5). The heterogeneity among studies was not significant with an I^2 of 12%.

Comorbidities associated with severe clinical course

Presence of any comorbidity was assessed as a factor associated with severe clinical course in 12 studies. The pooled odds ratio of 3.16 (95% CI: 2.32-4.29) suggested that presence of any comorbidity was significantly associated with severe clinical course (Figure 6). The heterogeneity among studies was not significant with an I^2 of 29%.

Presence of diabetes mellitus was assessed as a factor associated with severe clinical course in 14 studies. The pooled odds ratio of 3.11 (95% CI: 1.99-4.88) suggested that presence of diabetes mellitus was significantly associated with severe clinical course (Figure 7). The heterogeneity among studies was not high with an I^2 of 48%.

Presence of hypertension was assessed as a factor associated with severe clinical course in 13 studies. The pooled odds ratio of 2.30 (95% CI: 1.84-2.89) suggested that presence of hypertension was significantly associated with severe clinical course (Figure 8). The heterogeneity among studies was not significant with an I^2 of 3%.

Presence of cardiovascular disease was assessed as a factor associated with severe clinical course in 13 studies. The pooled odds ratio of 3.88 (95% CI: 2.30-6.54) suggested that presence of cardiovascular disease was significantly associated with severe clinical course (Figure 9). The heterogeneity among studies was not significant with an I^2 of 26%.

Presence of COPD was assessed as a factor associated with severe clinical course in 13 studies. The pooled odds ratio of 4.37 (95% CI: 2.52-7.59) suggested that presence of COPD was

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significantly associated with severe clinical course (Figure 10). There was no heterogeneity among studies with an I^2 of 0%.

Symptoms associated with severe clinical course

Fever is the most common symptom of COVID-19, being present in 83.4% of cases. Whether presence of fever was associated with severe clinical course was assessed in 16 studies. The pooled odds ratio for patients with fever progressing to severe clinical course was 1.10 (95% CI: 0.80-1.52) (Figure 11), indicating that fever was equally common in patients with good and severe clinical course. The heterogeneity among studies was not significant with an I^2 of 5%.

Many studies reported that patients having high temperatures had severe disease. Patients having fever spike with temperatures ≥39°C as a factor associated with severe clinical course was evaluated in 10 studies. It was found that patients having temperatures ≥39°C were more likely to have severe clinical course than patients with temperatures <39°C (pooled odds ratio 1.59 [95% CI: 1.10-2.30]) (Figure 12).

After fever, the second most common symptom of COVID-19 is cough, being present in 60.5% of cases. Cough was assessed as a factor associated with severe clinical course in 16 studies and it was not found to be significantly associated. The pooled odds ratio was 1.19 (95% CI: 0.97-1.45) (Figure 13). There was no heterogeneity among studies with an I^2 of 0%.

Sputum production was assessed as a factor associated with severe clinical course in 9 studies. It was found to be significantly associated with severe clinical course with a pooled odds ratio of 1.35 (95% CI: 1.02-1.79) (Figure 14). The heterogeneity among studies was not significant with an I^2 of 17%.

Presence of shortness of breath or dyspnea was assessed as a factor associated with severe clinical course in 14 studies and it was found to be significantly associated with a pooled odds ratio of 4.66 (95% CI: 3.12-6.95) (Figure 15). The heterogeneity among studies was significant with an I^2 of 61%. A sensitivity analysis after removing one outlier study still revealed a significant pooled odds ratio of 4.03 (95%CI: 2.85-5.69) and an I^2 of 46%.

Among the gastro-intestinal symptoms, diarrhea was found in 7.5% cases. Whether it was associated with severe clinical course was assessed in 11 studies. A pooled odds ratio of 1.55 (95% CI: 1.03-2.34) indicated that it was significantly associated with severe clinical course (Figure 16). There was no heterogeneity among studies with an I^2 of 0%.

Laboratory features associated with severe clinical course

Most patients of COVID-19 have either normal (64%) or lower than normal values of WBC count (27%). Only 9% of patients had higher than normal values of WBC count. Whether higher than normal values of WBC count was associated with severe clinical course was assessed in 16 studies. Higher than normal value of WBC count was found to be significantly associated with severe clinical course with a pooled odds ratio of 2.67 (95% CI: 1.73-4.11) (Figure 17). The heterogeneity among studies was significant with an I^2 of 80%. A sensitivity analysis after removing two outlier studies still revealed a significant pooled odds ratio of 3.39 (95%CI: 2.44-4.71) and an I^2 of 41%.

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Lymphocyte count as a factor associated with severe clinical course was evaluated in 17 studies. Lower than normal value of lymphocyte count was found to be significantly associated with severe clinical course with a pooled odds ratio of 3.22 (95% CI: 2.32-4.47) (Figure 18). The heterogeneity among studies was significant with an I^2 of 50%. A sensitivity analysis after removing one outlier study still revealed a significant pooled odds ratio of 3.52 (95%CI: 2.64-4.68) and an I^2 of 33%.

Twelve studies evaluated platelet count and found that lower than normal values of platelet count was significantly associated with severe clinical course with a pooled odds ratio of 1.78 (95% CI: 1.15-2.75) (Figure 19). Since the heterogeneity among the studies was high with an I^2 value of 69%, a sensitivity analysis was done after removing two outlier studies, which again revealed a significant pooled odds ratio of 2.25 (95% CI: 1.52-3.33) with an I^2 value of 47%.

Hemoglobin levels were compared between patients with good and severe clinical course in 8 studies. Patients with severe clinical course had significantly lower haemoglobin levels than patients with good clinical course (127 [95% CI: 125-129] versus 132 [95% CI: 129-134] g/L; $p<0.01$) (Figure 20).

Serum creatinine as a factor associated with severe clinical course was evaluated in 12 studies. High serum creatinine was found to be significantly associated with severe clinical course with a pooled odds ratio of 2.34 (95% CI: 1.71-3.22) (Figure 21). The heterogeneity among studies was not significant with an I^2 of 30%.

Transaminases AST and ALT values were reported to be associated with severe clinical course by many studies. AST was evaluated in 11 studies and higher than normal values of AST was found to be significantly associated with severe clinical course (pooled odds ratio 2.31 [95% CI: 1.38-3.86]) (Figure 22). The heterogeneity among studies was high (I^2 of 90%) so a sensitivity analysis was done after removing two outlier studies, which again revealed a significant pooled odds ratio of 2.96 (95% CI: 2.12-4.13) and a non-significant I^2 of 44%. ALT was evaluated in 12 studies and higher than normal values of ALT was found to be significantly associated with severe clinical course (pooled odds ratio 1.69 [95% CI: 1.24-2.31]) (Figure 23). Since the heterogeneity among the studies was high (I^2 74%), a sensitivity analysis was done after removing one outlier study, which still revealed a significant pooled odds ratio of 1.83 (95% CI: 1.47-2.27) and an I^2 of 7%.

Serum bilirubin was assessed in 6 studies and higher than normal values of serum bilirubin was found to be significantly associated with severe clinical course with a pooled odds ratio of 2.55 (95% CI: 1.83-3.54) (Figure 24). The heterogeneity among the studies was non-significant with an I^2 of 25%.

Serum albumin was assessed in 8 studies and lower than normal values of serum albumin was found to be significantly associated with severe clinical course with a pooled odds ratio of 4.34 (95% CI: 2.18-8.63) (Figure 25). Since the heterogeneity among studies was high with an I^2 of 91%, a sensitivity analysis was done after removing one outlier study, which again revealed a significant pooled odds ratio of 5.00 (95% CI: 3.50-7.15) and I^2 of 33%.

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Inflammatory and infection markers associated with severe clinical course

CRP as a factor associated with severe clinical course was evaluated in 13 studies. Higher than normal value of CRP was found to be significantly associated with severe clinical course with a pooled odds ratio of 5.78 (95% CI: 2.79-11.99) (Figure 26). Since the heterogeneity among studies was significant with an I^2 of 94%, a sensitivity analysis was done after removing two outlier studies, which again showed a significant pooled odds ratio of 5.06 (95% CI: 3.52-7.28) and I^2 of 42%.

Serum D-dimer level as a factor associated with severe clinical course was evaluated in 11 studies. Higher than normal values of serum D-dimer was found to be significantly associated with severe clinical course with a pooled odds ratio of 4.03 (95% CI: 2.62-6.18) (Figure 27). The heterogeneity among studies was significant with an I^2 of 66%. A sensitivity analysis was done after removing two outlier studies, which also revealed a significant pooled odds ratio of 3.13 (95% CI: 2.19-4.46) and an I^2 of 44%.

LDH was evaluated in 10 studies and high LDH was found to be significantly associated with severe clinical course with a pooled odds ratio of 4.59 (95% CI: 2.16-9.76) (Figure 28). Since the heterogeneity among the studies was high with an I^2 of 95%, a sensitivity analysis was done after excluding 4 outlier studies, which again revealed a significant pooled odds ratio of 2.32 (95% CI: 1.63-3.31) and I^2 of 22%.

Serum procalcitonin was evaluated in 9 studies and high serum procalcitonin values were found to be significantly associated with severe clinical course (pooled odds ratio 5.45 [95% CI: 3.23-9.21]) (Figure 29). The heterogeneity among the studies was not high with an I^2 of 36%.

Serum creatine kinase was evaluated in 7 studies and high serum creatine kinase values were found to be significantly associated with severe clinical course (pooled odds ratio 1.66 [95% CI: 1.12-2.45]) (Figure 30). The heterogeneity among the studies was not high with an I^2 of 44%.

Summary of all factors associated with severe clinical course

A summary forest plot was created to depict all the factors associated severe clinical course along with their odds ratios (95% CI) (Figure 31). In addition, based on the results of this meta-analysis a summary table was created (Table 7) categorizing factors into four groups: Vulnerable population for severe COVID-19, symptoms indicating potential severe COVID-19, routine laboratory parameters indicating potential severe COVID-19, and factors that indicate patients in need of intensive care.

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DISCUSSION

To summarise the results of this systematic review and meta-analysis, the mean age of patients with COVID-19 is 49.7±16.3 years with a male to female ratio of 1.2:1. Common symptoms and their frequency are: fever (83.4%), cough (60.5%), fatigue (33.8%), sputum (28.9%), dyspnea (22.1%), myalgia (20.6%), chest tightness / pain (16.3%), sore throat (13.5%), headache (11.2%), diarhhea (7.5%), nasal congestion / rhinorrhea (6.7%), nausea / vomiting (5.6%), pain abdomen (4.6%), and hemoptysis (1.7%). The comorbidities associated with COVID-19 are: hypertension (18.4%), diabetes mellitus (9.8%), cardiovascular diseases (8.8%), endocrine diseases (5.8%), gastrointestinal diseases (5%), CLD (3%), and COPD (2.8%). Among the laboratory parameters WBC was low in 27%, high in 9%, platelets were low in 22.9%, creatinine was high in 6.5%, AST was high in 25.3%, ALT was high in 22.7%, bilirubin was high in 8.8%, albumin was low 60.1%, CT chest was abnormal in 89%, CRP was high in 67.5%, LDH was high in 52%, D-dimer was high in 34.8%, CK was high in 14.4%, and procalcitonin was high in 15.4%. Factors significantly associated severe clinical course (with their ORs) are as follows: High CRP (5.78), high procalcitonin (5.45), age ≥60 (4.82), dyspnea (4.66), high LDH (4.59), COPD (4.37), low albumin (4.34), high D-dimer (4.03), cardiac disease (3.88), low lymphocyte count (3.22), any associated comorbidity (3.16), diabetes mellitus (3.11), high WBC count (2.67), high bilirubin level (2.55), high creatinine (2.34), high AST (2.31), hypertension (2.30), low platelets (1.78), High ALT (1.69), high CK (1.66), fever spikes ≥39°C (1.59), diarrhea (1.55), male gender (1.47), and sputum (1.35).

The strengths of this systematic review and meta-analysis is that it included large number of studies: 58 studies involving 6892 for the data on demographic and clinical features, and 21 studies involving 3496 for data on factors associated with severe clinical course. This is the first meta-analysis on factors associated with severe clinical course. The results of this meta-analysis will help in early differentiation of patients who are likely to progress to severe clinical course and develop adverse outcome from those who are likely to remain stable and have better outcome. The healthcare resources such as hospital admission, HDU and ICU care, intensive monitoring, and organ support can be prioritized towards these potentially sicker patients which will help in saving their lives; while patients who are likely to have good clinical course can be managed at home or with minimal resource utilization.

The first objective of our systematic review was to study the clinical and laboratory manifestations of COVID-19, and our results confirm findings from previous other meta-analyses. According to a meta-analysis of 10 studies involving 1994 patients by Li LQ et al[5] the main clinical symptoms of COVID-19 patients were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), dyspnea (21.9%). In addition to common respiratory symptoms, the symptoms of headache or dizziness (12.1%) diarrhea (4.8%), nausea, and vomiting (3.9%) were also obvious in some patients[5]. Another meta-analysis by Rodriguez-Morales AJ et al[7] revealed that of 656 patients, fever (88.7%), cough (57.6%) and dyspnea (45.6%) were the most prevalent manifestations. Among the patients, 20.3% required ICU, 32.8% presented with ARDS, 6.2% with shock, and 13.9% of hospitalized patients had fatal outcomes. In another metanalysis by Sun P et al[4] of 10 studies including 50,466 patients, the incidence of fever was 89.1%, cough 72.2%, and muscle soreness or fatigue 42.5%. The incidence of ARDS was 14.8%, abnormal chest CT 96.6%, the percentage of severe cases in all infected cases was 18.1%, and the case fatality rate of patients with SARS-CoV-2 infection was 4.3%. In another meta-analysis of six studies with 1527 patients by

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Li B et al the proportions of hypertension, cardia-cerebrovascular disease and diabetes in patients with COVID-19 were 17.1%, 16.4% and 9.7%, respectively[6]. According to a meta-analysis by Yang J et al[9] on eight studies with 46,248 patients the most prevalent clinical symptom was fever (91%), followed by cough (67%), fatigue (51%) and dyspnea (30%). The most prevalent comorbidities were hypertension (17%) and diabetes (8%), followed by cardiovascular diseases (5%) and respiratory system disease (2%). Both the meta-analyses, by Sun P et al[4] and Yang J et al[9], had included 44,672 patients from the database of Chinese Center for Disease Control and Prevention[8], and a significant overlap between these 44,672 patients and patients from other studies is expected. It has been pointed out that reporting of the same patients of COVID-19 in different articles (without clear indication of the duplicate reporting) creates an inaccurate scientific record, may affect the accuracy of subsequent estimates of prevalence of the disease or outcomes, and may preclude valid meta-analyses, unless authors of the meta-analyses are able to obtain individual patient data to ensure that patients are not being counted more than once in any publication[13]. We in our meta-analysis have tried our best to avoid this flaw by excluding papers with potential overlap of patients, limiting our search to single database (PubMed), and limiting our search to English language only. This makes the results from our meta-analysis more robust and reliable.

Among the demographic factors, we found that advanced age was a very important predictor for severe clinical course. The mean age of patients who had severe clinical course was close to 60, which was at least one decade more than those who had better clinical course. The pooled odds ratio for patients with advanced age developing severe clinical course was 4.82. The implication of this finding is that the elderly population needs to be especially protected from contracting this virus, as they are about 5 times more likely to have a severe clinical course.

Patients with comorbidities, such as hypertension, cardiovascular disease, diabetes mellitus, and COPD among others were found have severe clinical course with odds ratios ranging from 2.3 to 4.37. Among all the comorbidities, COPD had the highest odds ratio for developing severe clinical course which is an expected finding, as development of pneumonia or ARDS on already compromised lungs could be detrimental in these patients. The vulnerability of patients with cardiac disease and hypertension developing severe clinical course is a surprising finding. Guo et al[35] recently showed that 27.8% of severe COVID-19 patients had evidence of myocardial injury as indicated by elevated troponin levels, and they had higher mortality. According to a meta-analysis by Lippi G et al[36] the values of cardiac troponin I were found to be significantly elevated in COVID-19 patients with severe disease compared to non-severe disease. Another study by Shi S et al[37] found that cardiac injury was a common complication occurring in 19.7% patients of COVID-19, and there was a statistically significant association between cardiac injury and mortality. In patients with underlying cardiovascular diseases such as coronary artery disease, hypertension, and cardiomyopathy, viral illnesses such as COVID-19 can further damage myocardial cells through several mechanisms including direct damage by the virus, systemic inflammatory responses, destabilized coronary plaque, and aggravated hypoxia[35]. Whether SARS-CoV-2 directly damages cardiomyocytes is not known, however, it has been shown previously that the closely related virus SARS-CoV can mediate myocardial inflammation and damage by down-regulation of myocardial ACE2 system, which may be responsible for the myocardial dysfunction and adverse cardiac outcomes in patients with SARS[38].

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Among the presenting symptoms of COVID-19, presence of dyspnea, fever spikes ≥39°C, diarrhea, and productive cough indicate impending severe clinical course. Dyspnea, high fever and sputum production indicates likely presence of pneumonia, and these are the patients who might develop respiratory failure. This finding from our meta-analysis, along with finding of vulnerable comorbidities, holds a lot of significance from public health perspective in the epidemic setting of COVID-19. This information needs to be conveyed to the general public that if they are elderly with comorbidities, and notice symptoms of dyspnea, high fever above 39°C, and productive cough, they should seek medical help immediately as their disease is likely to progress.

Among the laboratory parameters, we found certain routine parameters such as low albumin, low lymphocyte count, high WBC count, high bilirubin level, high creatinine level, high AST/ALT, and low platelets to be significantly associated with severe clinical course. A meta-analysis by Lippi G et al[39] had also suggested that low platelet count was associated with increased risk of severe disease and mortality in patients with COVID-19. These simple laboratory parameters such as CBC, renal, and liver function tests can be done even at primary healthcare level, even in resource poor settings, and help in triaging vulnerable patients to more specialized care,

Among the inflammatory and infection markers, high CRP, high procalcitonin, high LDH, high D-dimer, and high CK were found to be significantly associated with severe clinical course. While CRP is not only a marker of increased cardiovascular events and infection, it plays important roles in inflammatory processes and host responses to infection including the complement pathway, apoptosis, phagocytosis, nitric oxide (NO) release, and the production of cytokines, particularly interleukin-6 and tumor necrosis factor-α[40]. Procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients[41]. LDH is an indicator of tissue damage. D-dimer not only serves as a valuable marker of activation of coagulation and fibrinolysis, it also is a significant prognostic factor in patients with infection and sepsis[42]. Elevated serum levels of CK have been used as a sensitive, but nonspecific, test for myocardial injury. All these markers indicate activation of systemic inflammatory response syndrome with or without super-added bacterial sepsis. These markers have important prognostic significance and are associated with higher mortality. Lippi G et al[43] had also shown that increased procalcitonin values was associated with a nearly 5-fold higher risk of severe SARS-CoV-2 infection. Elevated procalcitonin level indicates super-added bacterial sepsis, and might also help in guiding antibiotic use in these critically ill patients. All these markers are routinely done in tertiary care settings, especially in patients admitted in HDUs and ICUs. The results on these markers from our meta-analysis will guide physicians and critical specialists managing these sick patients in prioritizing intensive care resources to patients who are likely to have a severe clinical course.

Our meta-analysis had a few limitations. The first limitation was that several of the identified factors may be confounding variables, and which of these factors are independently associated with severe clinical course could not be determined. Since our meta-analysis included only retrospective case series with a lot of heterogeneity, identification of independent factors was not possible. Only a well-designed prospective study can identify independent factors associated with severe clinical course or mortality. Second limitation was

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the heterogeneity among the studies with regards to the clinical endpoints. For example, clubbing studies that compared patients with and without ICU admission with studies that used mortality as endpoint may not be statistically justified. However, many of the included studies had patients which were still admitted and a sufficient follow-up time has still not elapsed to determine their final outcome. Hence our use of 'severe clinical course' as an endpoint in our meta-analysis was the best approximation for clubbing the varied endpoints in all these studies.

In conclusion, during the midst of COVID-19 pandemic, the findings from our study has several potential implications for multiple stakeholders: the general public, healthcare policy makers, governments, patients of COVID-19, physicians at the primary care facilities, physicians managing COVID-19 patients in hospitals, and critical care specialists of ICUs. Our study clearly elucidated the list of vulnerable populations and symptoms which indicate potential severe COVID-19 disease. We also determined routine and specialized laboratory parameters associated with severe clinical course of COVID-19. The information on vulnerable population and potentially severe symptoms should be disseminated to the general public, healthcare policy makers and governments at places where COVID-19 epidemic is ongoing. This information will help the public in understanding whether they are at risk of severe COVID-19, and whether their symptoms merit immediate hospital care. This self-triage by the patients will prevent hospitals from getting overcrowded by thousands of patients, most of whom do not need hospital care. Physicians working at the primary care facilities and hospitals managing COVID-19 patients can learn from our meta-analysis derangement of which of the routine laboratory parameters indicate potentially severe disease requiring admission or referral to specialized centers. Physicians and critical care specialists working at tertiary care centers and ICUs can guide their treatment from this meta-analysis, based on the laboratory, inflammatory and infection markers.

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Contributors

AK, PS, and SK did the literature search, screened records, evaluated full texts. AK, PS, SAA, NB, VS, SK and AS extracted the data. AK and SAA evaluated the quality of studies. AK designed the literature search, did the statistical analyses, and wrote the first draft of the manuscript. PS and AA provided critical input for the methods. All authors reviewed the manuscript and provided critical intellectual contributions to the analysis and interpretation of the data, and revision of the manuscript.

Declaration of interests

We declare no competing interests.

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TABLES

Table 1: Characteristics and quality of included studies.

Author	Date of publication	Number of patients	Study setting	Study quality
Huang C et al[44]	Jan 24, 2020	41	Single centre in Wuhan, Hubei Province, China	Good
Chan JF et al[45]	Jan 24, 2020	6	Single centre in Shenzhen, Guangdong Province, China	Good
Li Q et al[46]	Jan 29, 2020	425	Multi-centre in Wuhan, Hubei Province, China	Good
Chen N et al[47]	Jan 30, 2020	99	Single centre in Wuhan, Hubei Province, China	Good
Song F et al[48]	Feb 6, 2020	51	Single centre in Shanghai, China	Good
Wang D et al[49]	Feb 7, 2020	138	Single centre in Wuhan, Hubei Province, China	Good
Liu K et al[50]	Feb 7, 2020	137	Nine tertiary hospitals in Hubei Province, China	Good
Chang et al[51]	Feb 7, 2020	13	Three hospitals in Beijing, China	Good
Liu Y et al[52]	Feb 9, 2020	12	Single centre in Shenzhen, Guangdong Province, China	Good
Ren LL et al[53]	Feb 11, 2020	5	Single centre in Wuhan, Hubei Province, China	Good
Tang N et al[54]	Feb 19, 2020	183	Single centre in Wuhan, Hubei Province, China	Good
Zhang JJ et al[55]	Feb 19, 2020	140	Single centre in Wuhan, Hubei Province, China	Good
Xu XW et al[56]	Feb 19, 2020	62	Seven hospitals in Zhejiang Province, China	Good
Bernheim A et al[22]	Feb 20, 2020	121	Four hospitals in four provinces in China	Good
Wu J et al[57]	Feb 21, 2020	80	Two hospitals in Chongqing, China	Good
COVID-19 National Emergency Response Center (CNERC)[24]	Feb 21, 2020	28	Multi-centre in South Korea	Fair
Kwok KO et al[58]	Feb 21, 2020	14	Single centre in Hong Kong	Fair
Shi H et al[59]	Feb 24, 2020	81	Two centres in Wuhan, Hubei Province, China	Good
Yang X et al[60]	Feb 24, 2020	52	Single centre in Wuhan, Hubei Province, China	Good
Xu YH et al[61]	Feb 25, 2020	50	Single centre in Beijing, China	Good
Ai T et al[62]	Feb 26, 2020	1014	Single centre in Wuhan, Hubei Province, China	Good
Yang W et al[63]	Feb 26, 2020	149	Three tertiary hospitals in Wenzhou City, Zhejiang Province, China	Good
Tian S et al[64]	Feb 27, 2020	262	Designated hospitals of Beijing Emergency Medical Service in Beijing, China	Good
Huang Y et al[65]	Feb 27, 2020	34	Single centre in Wuhan, Hubei Province, China	Good
Guan WJ et al[34]	Feb 28, 2020	1099	552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China	Good
Xu X et al[66]	Feb 28, 2020	90	Single centre in Guangdong Province, China	Good
Liu W et al[67]	Feb 28, 2020	78	Three tertiary hospitals in Wuhan, Hubei Province, China	Good
Li K et al[68]	Feb 29, 2020	83	Single centre in Chongqing, China	Good
Wu J et al[69]	Feb 29, 2020	80	Multi-centre in Jiangsu Province, China	Good

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Cao J et al[70]	Mar 2, 2020	102	Single centre in Wuhan, Hubei Province, China	Good
Ruan Q et al[71]	Mar 3, 2020	150	Two centres in Wuhan, Hubei Province, China	Good
Zhao W et al[72]	Mar 3, 2020	101	Four institutions in Hunan Province, China	Good
Xiao F et al[73]	Mar 3, 2020	73	Single centre in Guangdong Province, China	Fair
Xiong Y et al[74]	Mar 3, 2020	42	Single centre in Wuhan, Hubei Province, China	Good
Young BE et al[75]	Mar 3, 2020	18	Four hospitals in Singapore	Good
Zhang J et al[76]	Mar 3, 2020	14	Single centre in Jinhua, Zhejiang Province, China	Fair
Li Y et al[77]	Mar 4, 2020	51	Single centre in Wuhan, Hubei Province, China	Good
Hu Z et al[78]	Mar 4, 2020	24	Single centre in Nanjing, Jiangsu Province, China	Good
Yao Y et al[79]	Mar 5, 2020	195	Patients reported by the Health Commission of Shaanxi Province, China	Fair
Zhou S et al[80]	Mar 5, 2020	62	Single centre in Wuhan, Hubei Province, China	Good
Spiteri G et al[81]	Mar 5, 2020	38	WHO European region except UK	Fair
Wang L et al[82]	Mar 5, 2020	18	Single centre in Zhengzhou, Henan Province, China	Fair
Zhang S et al[83]	Mar 5, 2020	17	Single centre in Sichuan Province, China	Good
Zhou F et al[84]	Mar 11, 2020	191	Two hospitals in Wuhan, Hubei Province, China	Good
COVID-19 National Incident Room Surveillance Team (CNIRST)[85]	Mar 11, 2020	71	Multi-centre in Australia	Fair
Liu K et al[86]	Mar 11, 2020	56	Single centre in Hainan Province, China	Good
Chen J et al[87]	Mar 11, 2020	249	Single centre in Shanghai, China	Good
Zhao D et al[88]	Mar 12, 2020	19	Two hospitals in Anhui Province, China	Good
Chen Q et al[89]	Mar 12, 2020	9	Single centre in Anhui Province, China	Good
Wu C et al[90]	Mar 13, 2020	201	Single centre in Wuhan, Hubei Province, China	Good
Zhu W et al[91]	Mar 13, 2020	32	Two emergency departments in Anhui Province, China	Good
Cheng Z et al[92]	Mar 14, 2020	11	Single centre in Shanghai, China	Good
Mo P et al[93]	Mar 16, 2020	155	Single centre in Wuhan, Hubei Province, China	Good
Wang Z et al[94]	Mar 16, 2020	69	Single centre in Wuhan, Hubei Province, China	Good
Wang Y et al[95]	Mar 17, 2020	55	Single centre in Shenzhen, Guangdong Province, China	Good
Han R et al[96]	Mar 17, 2020	108	Single centre in Wuhan, Hubei Province, China	Good
Qian GQ et al[97]	Mar 17, 2020	91	Five hospitals in Zhejiang Province, China	Good
Gao Y et al[98]	Mar 17, 2020	43	Single centre in Fuyang, Anhui Province, China	Good

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Table 2: Demographic data of the patients and their baseline comorbidities.

		Age (years)		Gender		Comorbidities									
Author	**N**	**Mean**	**SD**	**Male (n)**	**Male (%)**	**COPD**	**DM**	**HT**	**CAD**	**GI Dis**	**CLD**	**CKD**	**Neuro**	**Cancer**	**Endocrine**
Huang C et al[44]	41	49.3	13.1	30	73	1	8	6	6		1			1	
Chan JF et al[45]	6	46.2	22.5	3	50										
Li Q et al[46]	425	55.5	12.4	240	56										
Chen N et al[47]	99	55.5	13.1	67	68	1			40	11			1	1	13*
Song F et al[48]	51	49.0	16.0	25	49	1	3	5	1		1				
Wang D et al[49]	138	55.3	19.5	75	54	4	14	43	20		4	4	7	10	
Liu K et al[50]	137	54.2	12.1	61	45	2	14	13	10					2	
Chang et al[51]	13	38.7	11.6	10	77										
Liu Y et al[52]	12	53.7	18.0	8	67	1	2	3	4		0	2		0	
Ren LL et al[53]	5	53.6	9.5	3	60			1			1				
Tang N et al[54]	183	54.1	16.2	98	54										
Zhang JJ et al[55]	140	56.5	11.8	71	51	2	17	42	7	7	8	2	3		5
Xu XW et al[56]	62	41.7	15.2	35	56	1	1	5			7	1	1		
Bernheim A et al[22]	121	45.0	15.6	61	50										
Wu J et al[57]	80	44.0	11.0	42	53	3	4	4	1						
CNERC[24]	28	42.6	13.2	15	54										
Kwok KO et al[58]	14	59.8	13.4	9	64										
Shi H et al[59]	81	49.5	11.0	42	52	9	10	12	8		7	3	6	4	
Yang X et al[60]	52	59.7	13.3	35	67	4	9		5				7	2	
Xu YH et al[61]	50	43.9	16.8	29	58										
Ai T et al[62]	1014	51.0	15.0	467	46										
Yang W et al[63]	149	45.1	13.4	81	54	1			28		8		0	2	9*
Tian S et al[64]	262	47.5	16.5	127	48										
Huang Y et al[65]	34	56.2	17.1	14	41	2	4	8	6		1			3	2
Guan WJ et al[34]	1099	46.7	17.1	640	58	12	81	165	27		23	8	15	10	
Xu X et al[66]	90	51.0	13.8	39	43	1	5	17	3					2	
Liu W et al[67]	78	42.7	18.1	39	50	2	5	8						4	
Li K et al[68]	83	45.5	12.3	44	53	5	7	5	1						
Wu J et al[69]	80	46.1	15.4	39	49	1			25	3	1	1	1	1	5*
Cao J et al[70]	102	52.7	22.6	53	52	10	11	28	5		2	4	6	4	
Ruan Q et al[71]	150	57.7	12.5	102	68	3	25	52	13		4	2	12	3	

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Zhao W et al[72]	101	44.4	11.6	56	55	5			16	6					3*
Xiao F et al[73]	73	41.2	16.2	41	56					0				7	
Xiong Y et al[74]	42	49.5	14.1	25	60										
Young BE et al[75]	18	49.5	11.5	9	50										
Zhang J et al[76]	14	46.8	20.2	7	50										
Li Y et al[77]	51	58.0	12.7	28	55										
Hu Z et al[78]	24	36.2	29.9	8	33	0	2	2	1		0	1	1	0	
Yao Y et al[79]	195	44.1	15.8	129	66										
Zhou S et al[80]	62	52.8	12.2	39	63		4	4				1	1		
Spiteri G et al[81]	38	41.8	18.5	25	66				1/7						
Wang L et al[82]	18	41.0	20.9	10	56		3	5	3				2	1	
Zhang S et al[83]	17	48.6	14.2	8	47	2		2	1	2					
Zhou F et al[84]	191	56.3	15.7	119	62	6	36	58	15			2		2	
CNIRST[85]	71	46.0	19.8	36	51										
Liu K et al[86]	56	52.1	14.7	31	55		3	10	2		1	1			
Chen J et al[87]	249	50.3	20.9	126	51	5			55	9	2			1	25
Zhao D et al[88]	19	43.7	23.2	11	58			2			1				
Chen Q et al[89]	9	42.1	15.3	5	56										
Wu C et al[90]	201	51.3	12.7	128	64	5	22	39	8		7	2	7	1	2
Zhu W et al[91]	32	44.3	13.2	15	47	2	4	7	2		2	1	2	2	
Cheng Z et al[92]	11	50.4	15.5	8	73										
Mo P et al[93]	155	54.0	18.0	86	55	5	15	37	15		7	6	7	7	
Wang Z et al[94]	69	46.3	20.4	32	46	4	7	9	8		1			4	
Wang Y et al[95]	55	42.2	14.7	22	40						1				1
Han R et al[96]	108	45.0	13.6	38	35										
Qian GQ et al[97]	91	47.8	15.4	37	41		8	15	3						
Gao Y et al[98]	43	43.7	12.1	26	60	8	7	13	3						
All patients	**6892**	**49.7**	**16.3**	**3709**	**54%**	**108/ 3847**	**331/ 3379**	**620/ 3368**	**343/ 3872**	**38/ 766**	**90/ 3011**	**41/ 2592**	**79/ 2651**	**74/ 3361**	**65/ 1115**
						2.8%	**9.8%**	**18.4%**	**8.8%**	**5.0%**	**3.0%**	**1.6%**	**3.0%**	**2.2%**	**5.8%**

In these studies diabetes was included in endocrine diseases.

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Table 3: Presenting symptoms of patients.

Author	N	General				Respiratory							Gastro-intestinal		
		Fever	Headache	Fatigue	Myalgia	Cough	Sore throat	Nasal congestion / rhinorrhea	Sputum	Hemoptysis	Chest tightness / pain	Dyspnea	Diarrhea	Nausea / vomiting	Pain abdomen
Huang C et al[44]	41	40	3/38	18	18	31			11/39	2/39		22/40	1/38		
Chan JF et al[45]	6	5		3		4	1	1	1		1		2		
Li Q et al[46]	425														
Chen N et al[47]	99	82	8		11	81	5	4			2	31	2	1	
Song F et al[48]	51	49	8	16	16	24	3	2	10		7	7	5	3	
Wang D et al[49]	138	136	9	96	48	82	24		37			43	14	14	3
Liu K et al[50]	137	112	13	44	44	66			6	7		26	11		
Chang et al[51]	13	12	3		3	6		1	2				1		
Liu Y et al[52]	12	10	0		4	11							2	2	
Ren LL et al[53]	5	5	1	3	3	5			1			4	0		
Tang N et al[54]	183														
Zhang JJ et al[55]	140	110/120		90/120		90/120					44/120	44/120	18/139	24/139	8/139
Xu XW et al[56]	62	48	21	32	32	50			35	2			3		
Bernheim A et al[22]	121	74				58			20						
Wu J et al[57]	80	61	8		13	58	9		11	3	5	7	7		7
CNERC[24]	28	9	3	3	4	5	9		5						
Kwok KO et al[58]	14	12			1	5		1				2			
Shi H et al[59]	81	59	5	7		48		21	15		18	34	3	4	
Yang X et al[60]	52	51	3	18	6	40		3			1	33		2	
Xu YH et al[61]	50	43	5	8	8	20	4		7		4	4	1		
Ai T et al[62]	1014														
Yang W et al[63]	149	114	13		5	87	21	5	48		21	2	11	2	
Tian S et al[64]	262	215	17	69		120						18			
Huang Y et al[65]	34	32	2	22	22	17			8			5	5		
Guan WJ et al[34]	1099	975	150	419	164	745	153	53	370	10		205	42	55	
Xu X et al[66]	90	70	4	19	25	57	23		11				5	5	
Liu W et al[67]	78	57				34									
Li K et al[68]	83	72	9		15	65	6		15		5	9	7		7
Wu J et al[69]	80	63	13		18	51	11	5			3	30	1	1	
Cao J et al[70]	102	83		56	35	50							11		
Ruan Q et al[71]	150	127		37	19	110			54	3		110			
Zhao W et al[72]	101	79		17	17	63	12					1	3	2	

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Xiao F et al[73]	73					53							26		
Xiong Y et al[74]	42	36		14		27						8	10		
Young BE et al[75]	18	13				15	11	1				2	3		
Zhang J et al[76]	14	13				10							0	0	
Li Y et al[77]	51	46		3		1									
Hu Z et al[78]	24	5		2	1	2		1							
Yao Y et al[79]	195														
Zhou S et al[80]	62	54		14	20	28			28			15	9		
Spiteri G et al[81]	38	20/31	6/31	8/31		14/31	2/31	2/31				2/31	1/31	1/31	
Wang L et al[82]	18	17	1		2	10	1			1		4	3	1	
Zhang S et al[83]	17	12		6	7	9	1		7			1			
Zhou F et al[84]	191	180		44	29	151			44				9	7	
CNIRST[85]	71	22/34	12/34		6/34	24/34	17/34	10/34			3/34	3/34	9/34	2/34	
Liu K et al[86]	56	44		5		21		3	21		4	4		10	
Chen J et al[87]	249	217	28	39		91	16	17				19	8		
Zhao D et al[88]	19	15	2	2		9	4				1		1		
Chen Q et al[89]	9	8				7					2		2		0
Wu C et al[90]	201	188		65	65	163			83			80			
Zhu W et al[91]	32	27	1	5	5	21			5	0	3		1		
Cheng Z et al[92]	11	8			3	7	1		3			1	1		
Mo P et al[93]	155	126	8	60	50	97					61	50	7	3	3
Wang Z et al[94]	69	60	10	29	21	38	6		20		14	20	10	3	
Wang Y et al[95]	55	7				7									
Han R et al[96]	108	94	14	42	12	65	14				17		15		
Qian GQ et al[97]	91	65	7	40	5	55			30		17	10	21	11	
Gao Y et al[98]	43														
All patients	**6892**	**4082/ 4895**	**387/ 3449**	**1355/ 4007**	**757/ 3683**	**3008/ 4968**	**354/ 2628**	**138/ 2056**	**908/ 3146**	**28/ 1617**	**233/ 1424**	**856/ 3879**	**291/ 3875**	**153/ 2750**	**28/ 604**
	%	**83.4%**	**11.2%**	**33.8%**	**20.6%**	**60.5%**	**13.5%**	**6.7%**	**28.9%**	**1.7%**	**16.3%**	**22.1%**	**7.5%**	**5.6%**	**4.6%**

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Table 4: Routine laboratory and CT features of patients.

Author	N	Low WBC	High WBC	Low PLT	Hb		High Creat	High AST	High ALT	High Bilirubin	Low Albumin	High PT	Abnormal CT Chest
					Mean	SD							
Huang C et al[44]	41	10/40	12/40	2/40	128	17	4	15					
Chan JF et al[45]	6	0	1	2	144	11	2	0	0	0	0	0	
Li Q et al[46]	425												
Chen N et al[47]	99	9	24	12	130	15	3	35	28	18	97	5	99
Song F et al[48]	51												
Wang D et al[49]	138												138
Liu K et al[50]	137	51	26										
Chang et al[51]	13				147	12							
Liu Y et al[52]	12	0	1	1			2	2	2	0	6		
Ren LL et al[53]	5	1	2	1			1		1			1	5
Tang N et al[54]	183												
Zhang JJ et al[55]	140	27/138	17/138										134/135
Xu XW et al[56]	62	19	1	3	139	18	3	10					
Bernheim A et al[22]	121												117
Wu J et al[57]	80	7	10										76
CNERC[24]	28												
Kwok KO et al[58]	14												
Shi H et al[59]	81		26	0	124	12		43					
Yang X et al[60]	52							15	15				
Xu YH et al[61]	50												41
Ai T et al[62]	1014												888
Yang W et al[63]	149	33	2	20			43	27	18	4	9	17	132
Tian S et al[64]	262												
Huang Y et al[65]	34	6	4	9			6	7	8	3	25	17	33
Guan WJ et al[34]	1099	330/978	58/978	315/869	134	22	12/752	168/757	158/741	76/722			840/975
Xu X et al[66]	90	19	3										72
Liu W et al[67]	78												
Li K et al[68]	83	10	9										
Wu J et al[69]	80	36	5	11	125	13	2	3	3	1	2	0	55
Cao J et al[70]	102												
Ruan Q et al[71]	150	61/147		29/149				54/147	43/146	18/147	114/148		
Zhao W et al[72]	101												93
Xiao F et al[73]	73												66
Xiong Y et al[74]	42	10/37	1/37										
Young BE et al[75]	18				140	15							

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Zhang J et al[76]	14												13
Li Y et al[77]	51												
Hu Z et al[78]	24	4	0		132	19	2	0	2	0			17
Yao Y et al[79]	195												
Zhou S et al[80]	62	6/30											
Spiteri G et al[81]	38												
Wang L et al[82]	18	3/16						4/16	4/16				
Zhang S et al[83]	17												
Zhou F et al[84]	191	32	40	13	129	16	8/186		59/189			11/182	
CNIRST[85]	71												
Liu K et al[86]	56	11	4		120	23							56
Chen J et al[87]	249												
Zhao D et al[88]	19	7	0					5/18	5/18				
Chen Q et al[89]	9	3	1										
Wu C et al[90]	201						9/198	59/198	43/198	10/198	195/198	4/195	
Zhu W et al[91]	32	7	1		135	24							
Cheng Z et al[92]	11				139	08							11
Mo P et al[93]	155	44	11	36			23	54	54				
Wang Z et al[94]	69	36/67	1/67		129	17		19	23				
Wang Y et al[95]	55	11	1										39
Han R et al[96]	108	11	0										108
Qian GQ et al[97]	91	14	3	10	135	15	3	9	7		43		86
Gao Y et al[98]	43												
All patients	**6892**	**818/ 3030**	**264/ 2918**	**464/ 2023**	**132**	**20**	**123/ 1894**	**529/ 2091**	**473/ 2084**	**130/ 1471**	**491/ 817**	**55/ 750**	**3119/ 3503**
	%	**27.0%**	**9.0%**	**22.9%**			**6.5%**	**25.3%**	**22.7%**	**8.8%**	**60.1%**	**7.3%**	**89.0%**

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Table 5: Inflammatory and infection markers of patients.

Author	N	High CRP	High LDH	High D-dimer	High CK	High Procal
Huang C et al[44]	41		29/40		13/40	3/39
Chan JF et al[45]	6	3	3	2/3	0	
Li Q et al[46]	425					
Chen N et al[47]	99	63	75	36	13	6
Song F et al[48]	51	41				
Wang D et al[49]	138					49
Liu K et al[50]	137	115				
Chang et al[51]	13					
Liu Y et al[52]	12	10	11		1	1
Ren LL et al[53]	5			3		2
Tang N et al[54]	183					
Zhang JJ et al[55]	140	125/136		35/81	4/60	41/118
Xu XW et al[56]	62		17		5	7
Bernheim A et al[22]	121					
Wu J et al[57]	80	37				32
CNERC[24]	28					
Kwok KO et al[58]	14					
Shi H et al[59]	81					
Yang X et al[60]	52					
Xu YH et al[61]	50	26				
Ai T et al[62]	1014					
Yang W et al[63]	149	82	45	21	12	
Tian S et al[64]	262					
Huang Y et al[65]	34			5	1/12	13/31
Guan WJ et al[34]	1099	481/793	277/675	260/560	90/657	35/633
Xu X et al[66]	90	38				
Liu W et al[67]	78					
Li K et al[68]	83	50				44
Wu J et al[69]	80	62	17	3	18	1
Cao J et al[70]	102					
Ruan Q et al[71]	150	119/149	109/148		59/137	
Zhao W et al[72]	101					

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Xiao F et al[73]	73					
Xiong Y et al[74]	42	27/32	15/26			3/30
Young BE et al[75]	18					
Zhang J et al[76]	14					
Li Y et al[77]	51					
Hu Z et al[78]	24	4/23	4	4/22		5
Yao Y et al[79]	195					
Zhou S et al[80]	62	27/27				
Spiteri G et al[81]	38					
Wang L et al[82]	18	12/16				4/16
Zhang S et al[83]	17	17				
Zhou F et al[84]	191		123/184	117/172	22/168	14/164
CNIRST[85]	71					
Liu K et al[86]	56					
Chen J et al[87]	249					
Zhao D et al[88]	19	18	6		1/18	
Chen Q et al[89]	9	3	4/8	4/8		0/7
Wu C et al[90]	201	166/194	194/198	44/189	9/198	
Zhu W et al[91]	32	21		3		0
Cheng Z et al[92]	11					
Mo P et al[93]	155		74	25	74	
Wang Z et al[94]	69	42/63	25/61			4/62
Wang Y et al[95]	55	10	13			
Han R et al[96]	108	107				
Qian GQ et al[97]	91	49		22		14
Gao Y et al[98]	43					
All patients	**6892**	**1755/ 2601**	**1041/ 2001**	**584/ 1680**	**322/ 1853**	**278/ 1806**
	%	**67.5%**	**52.0%**	**34.8%**	**17.4%**	**15.4%**

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Table 6: Factors associated with severe clinical course on univariate analysis in various studies.

Author	Total number of patients	Patients with severe clinical course	Patients with good clinical course	Quality of study
Huang C et al[44]	41	13	28	Good
Wang D et al[49]	138	36	102	Good
Tang N et al[54]	183	21	162	Good
Zhang JJ et al[55]	140	58	82	Good
Yang X et al[60]	52	32	20	Good
Xu YH et al[61]	50	13	37	Good
Tian S et al[64]	262	46	216	Good
Guan WJ et al[34]	1099	173	926	Good
Liu W et al[67]	78	11	67	Good
Li K et al[68]	83	25	58	Good
Cao J et al[70]	102	18	84	Good
Ruan Q et al[71]	150	68	82	Good
Zhao W et al[72]	101	14	87	Good
Young BE et al[75]	18	6	12	Good
Zhou F et al[84]	191	54	137	Good
Chen J et al[87]	249	22	227	Good
Wu C et al[90]	201	84	117	Good
Mo P et al[93]	155	85	70	Good
Wang Z et al[94]	69	14	55	Good
Qian GQ et al[97]	91	9	82	Good
Gao Y et al[98]	43	15	28	Good
Number of patients	**(n=3496)**	**(n=817)**	**(n=2679)**	

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Table: 7: Summary table of factors associated with severe COVID-19 in order of their importance under various categories, useful for various stakeholders.

Information useful for general public, healthcare policy makers, governments and patients of COVID-19		*Information useful for physicians at primary care facilities and hospitals*	*Information useful for physicians and critical care specialists managing COVID-19 patients in hospitals and ICUs*
Vulnerable population for severe COVID-19	**Symptoms indicating potential severe COVID-19**	**Routine laboratory parameters indicating potential severe COVID-19**	**Patients in need of intensive care**
Age >60 years COPD patients Cardiac patients Patient with comorbidities Diabetes patients Hypertension patients Male gender	Dyspnea present Spiking fever with temp ≥39°C Diarrhea present Productive cough	Low albumin level Low lymphocyte level High WBC count High serum bilirubin level High creatinine level High AST level Low platelet count High ALT level	High CRP level High procalcitonin level High LDH level High D-dimer level High creatine kinase level

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FIGURES

Figure 1: PRISMA flow diagram depicting the flow of information through different phases of a systematic review.

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Figure 2: Clinical course of the patients.

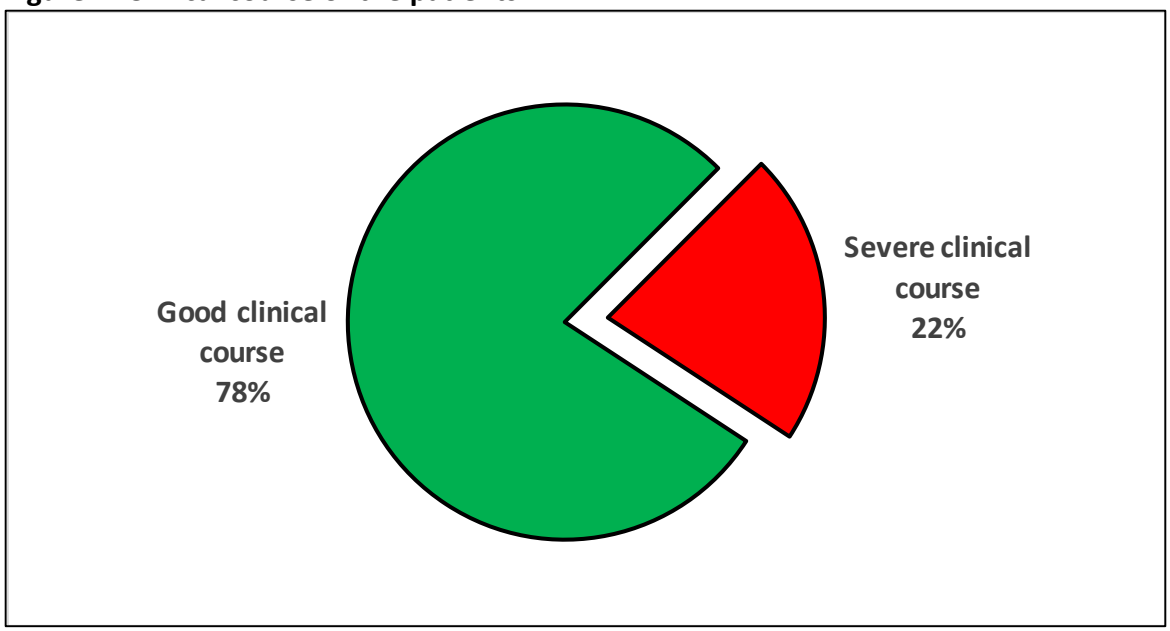

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Figure 3: Mean age of patients with good and severe clinical course.

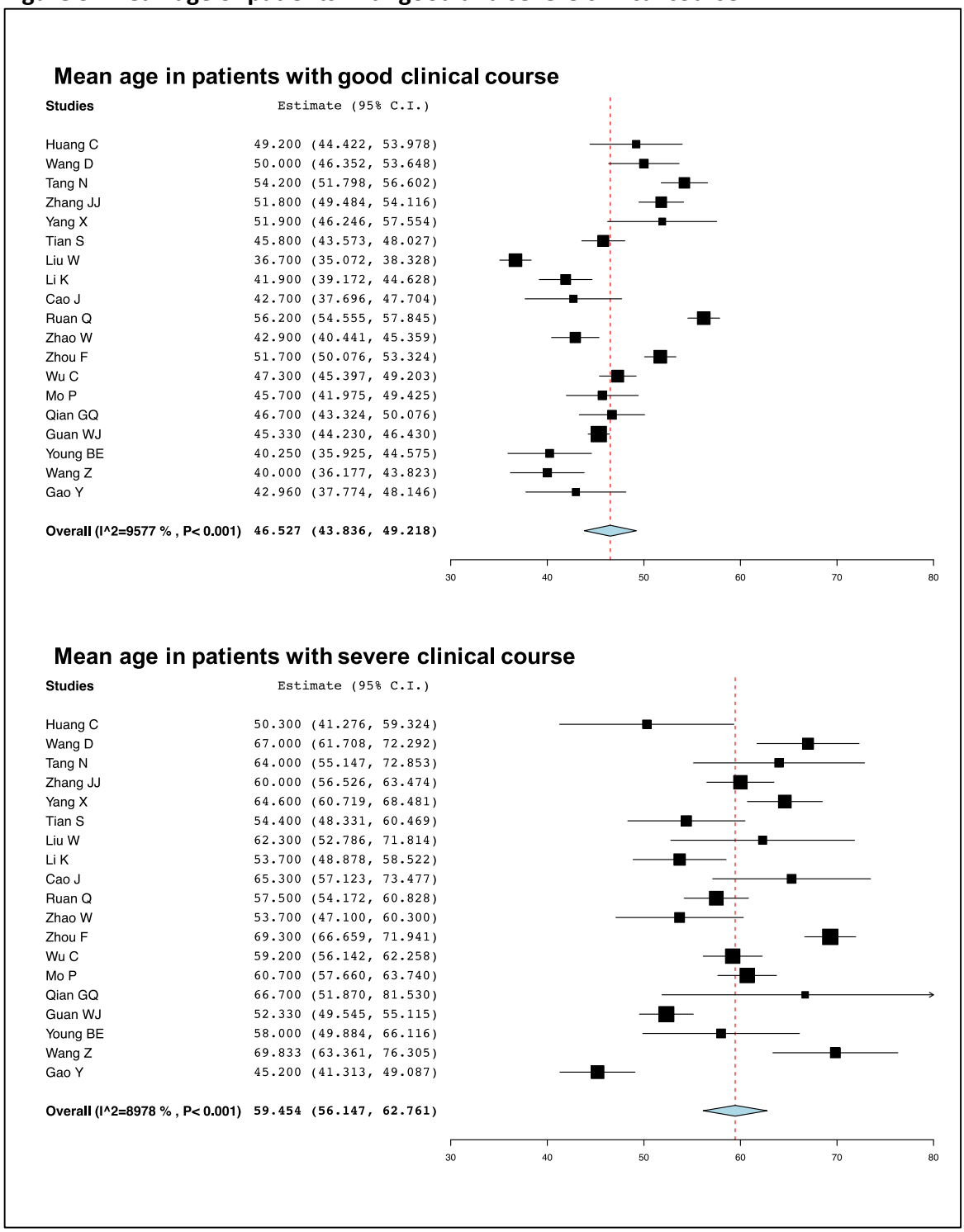

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Figure 4: Forest plot showing pooled odds ratio for patients with higher age (≥60 years) developing severe clinical course.

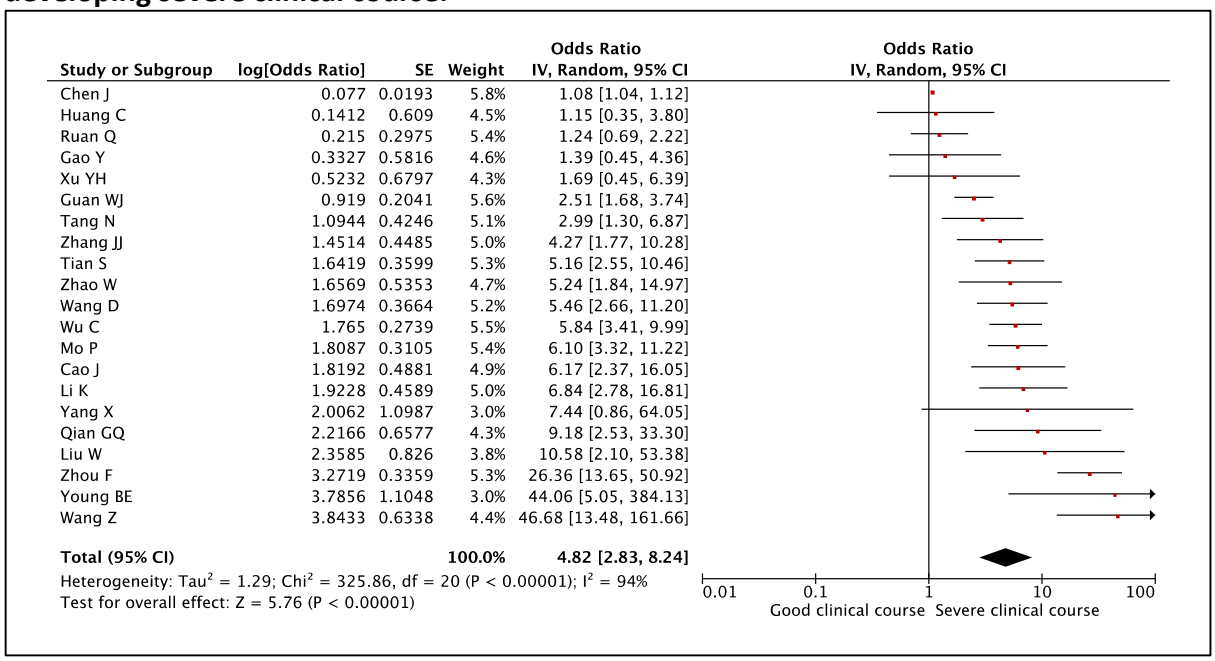

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Figure 5: Forest plot showing pooled odds ratio for male gender developing severe clinical course.

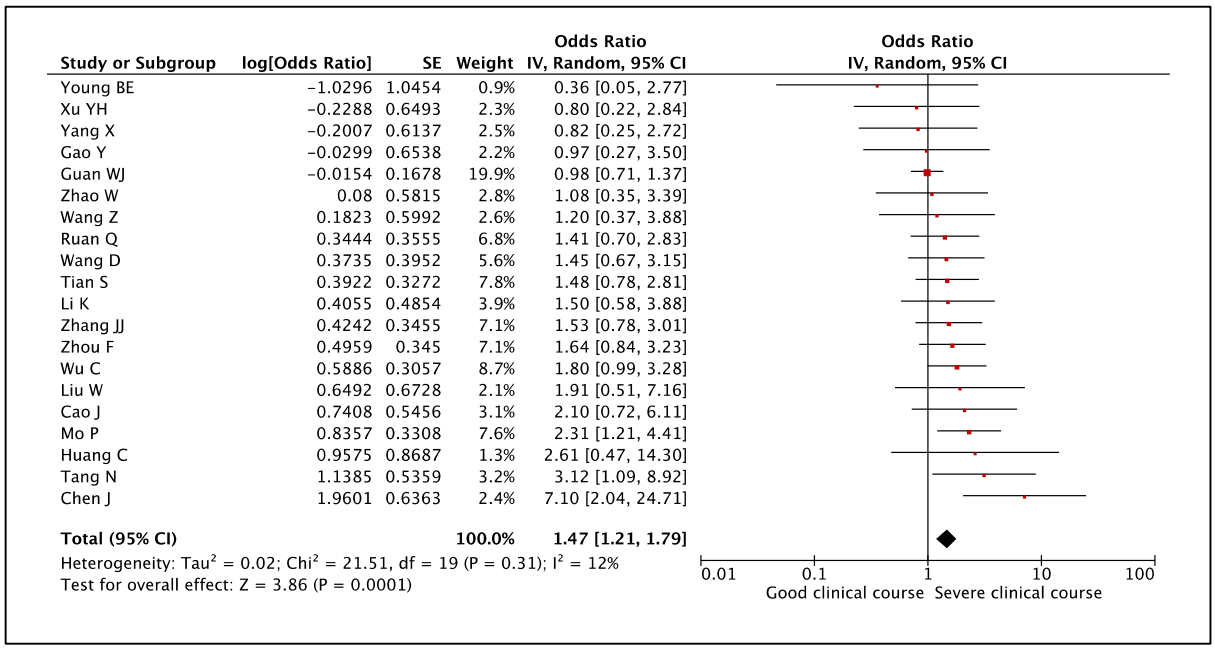

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Figure 6: Forest plot showing pooled odds ratio for patients having any comorbidity developing severe clinical course.

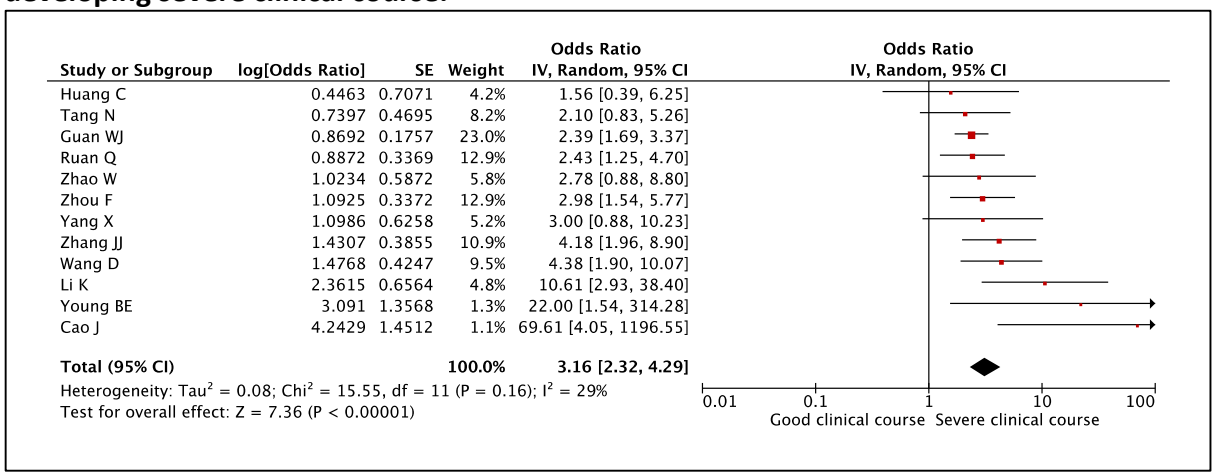

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Figure 7: Forest plot showing pooled odds ratio for patients with diabetes mellitus developing severe clinical course.

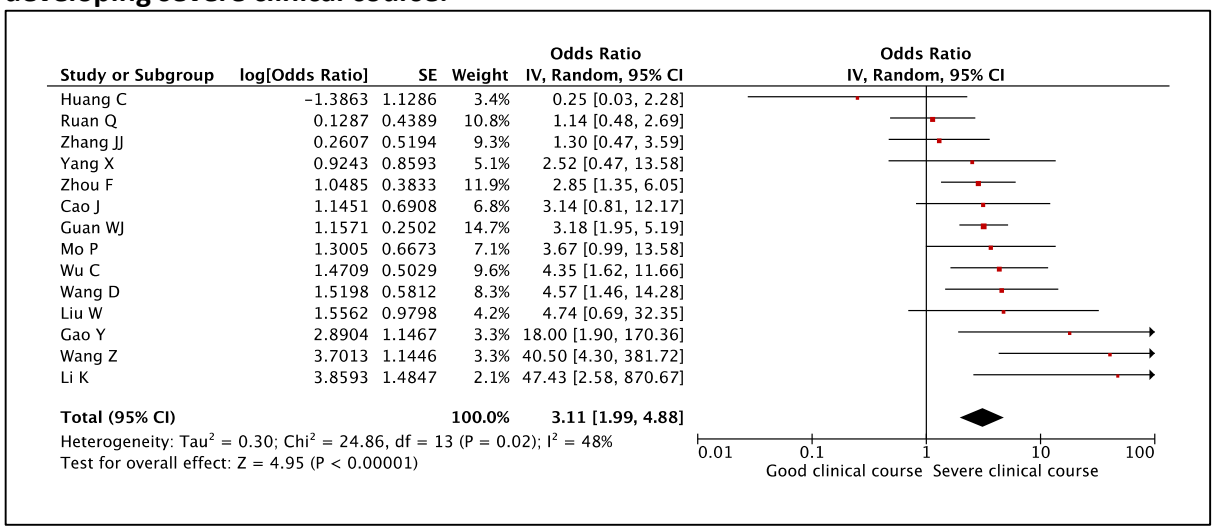

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Figure 8: Forest plot showing pooled odds ratio for patients with hypertension developing severe clinical course.

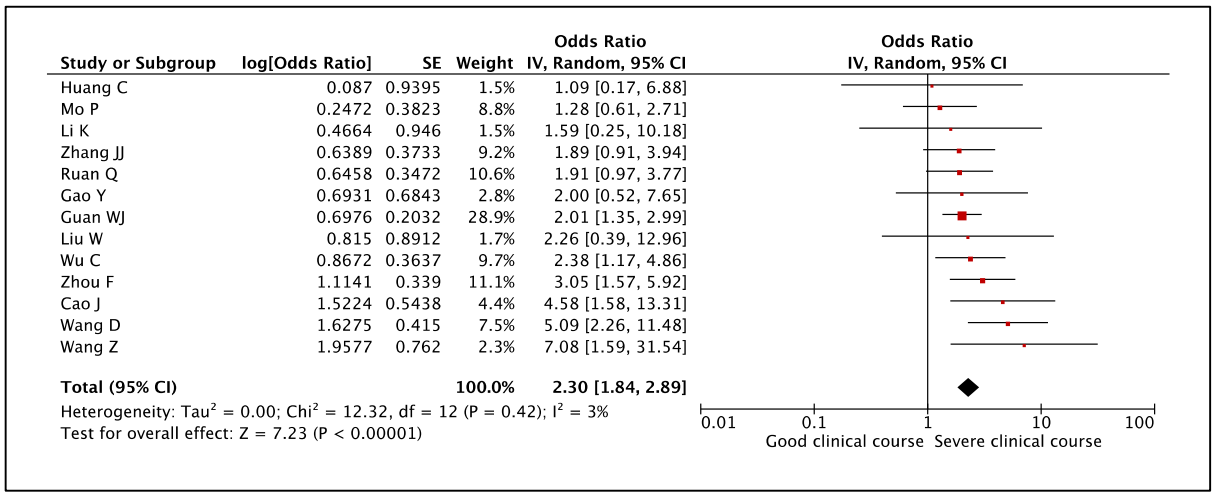

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Figure 9: Forest plot showing pooled odds ratio for patients with cardiovascular disease developing severe clinical course.

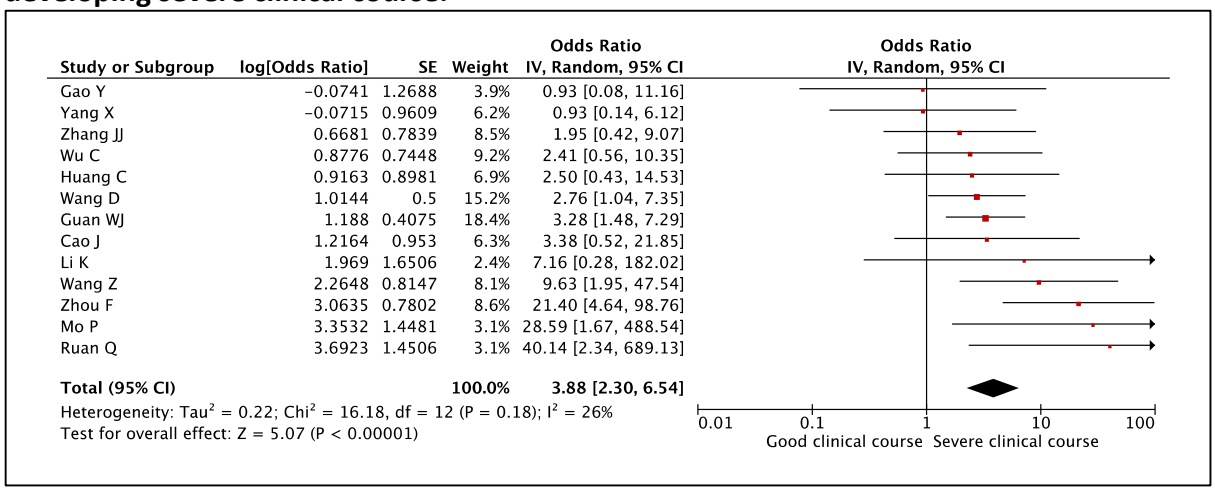

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Figure 10: Forest plot showing pooled odds ratio for patients with COPD developing severe clinical course.

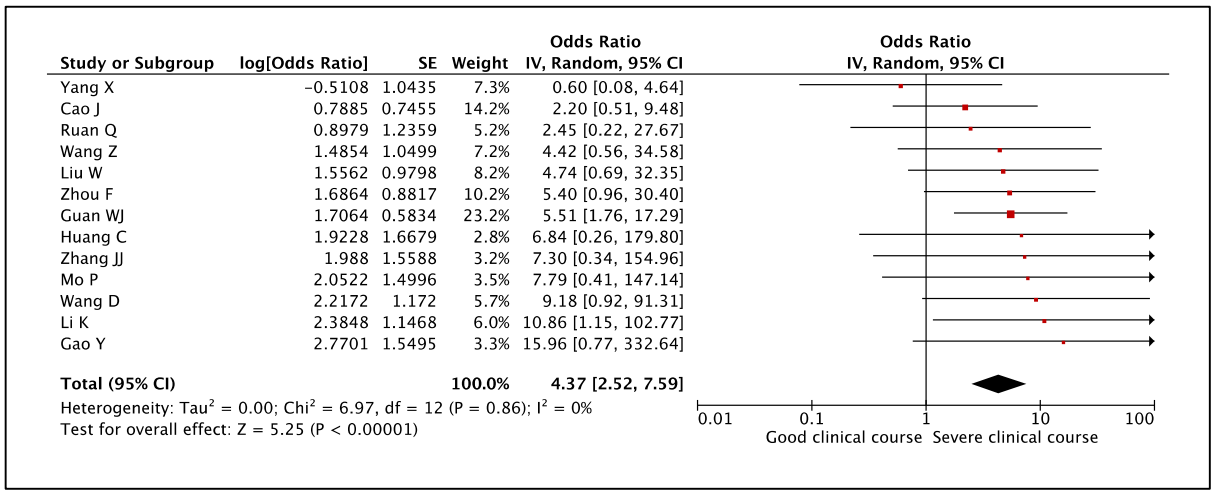

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Figure 11: Forest plot showing pooled odds ratio of fever being associated with severe clinical course.

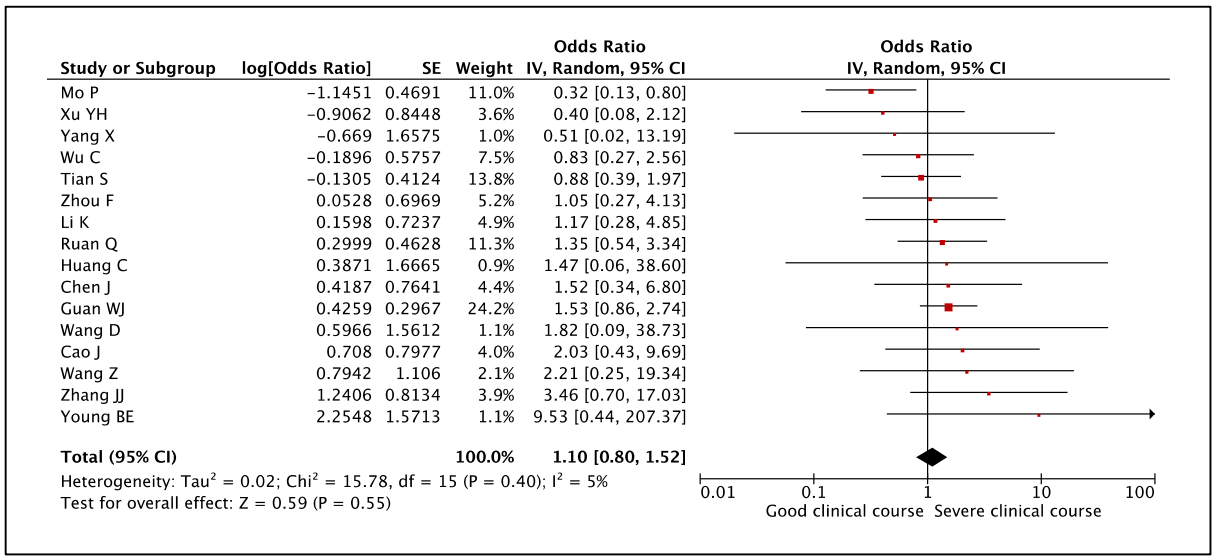

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Figure 12: Forest plot showing pooled odds ratio of high temperature (≥39°C) being associated with severe clinical course.

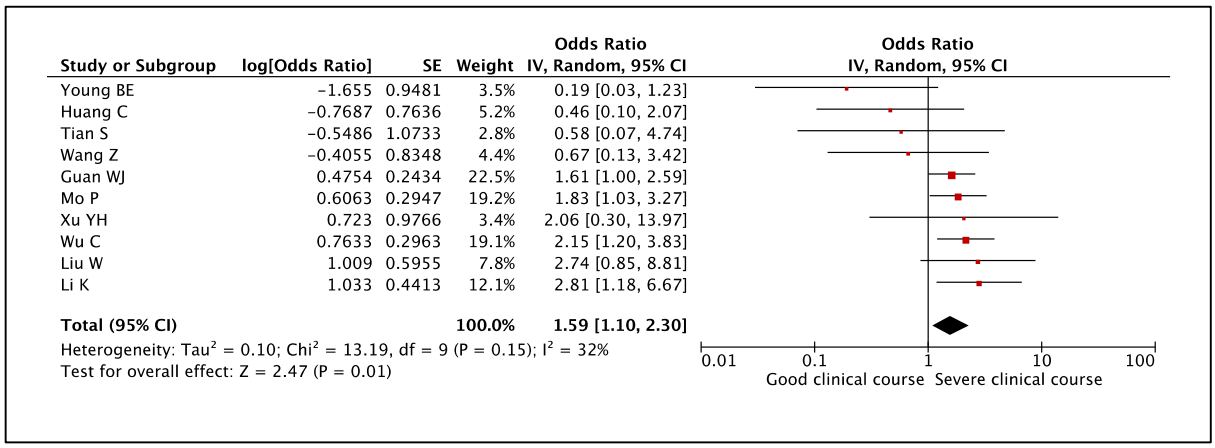

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Figure 13: Forest plot showing pooled odds ratio of cough being associated with severe clinical course.

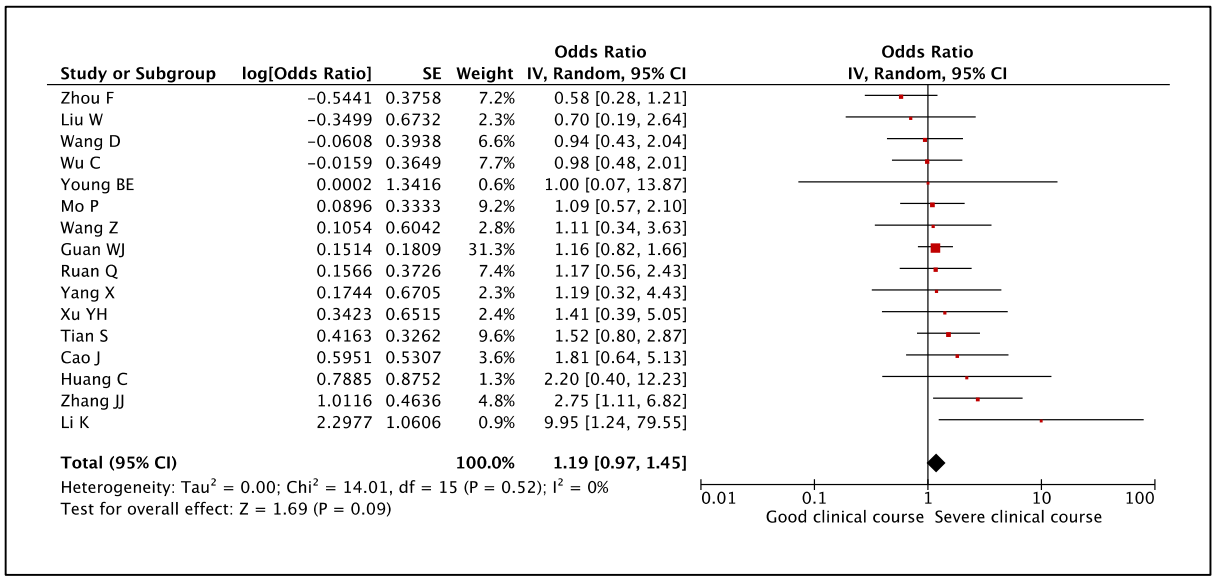

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Figure 14: Forest plot showing pooled odds ratio of sputum production being associated with severe clinical course.

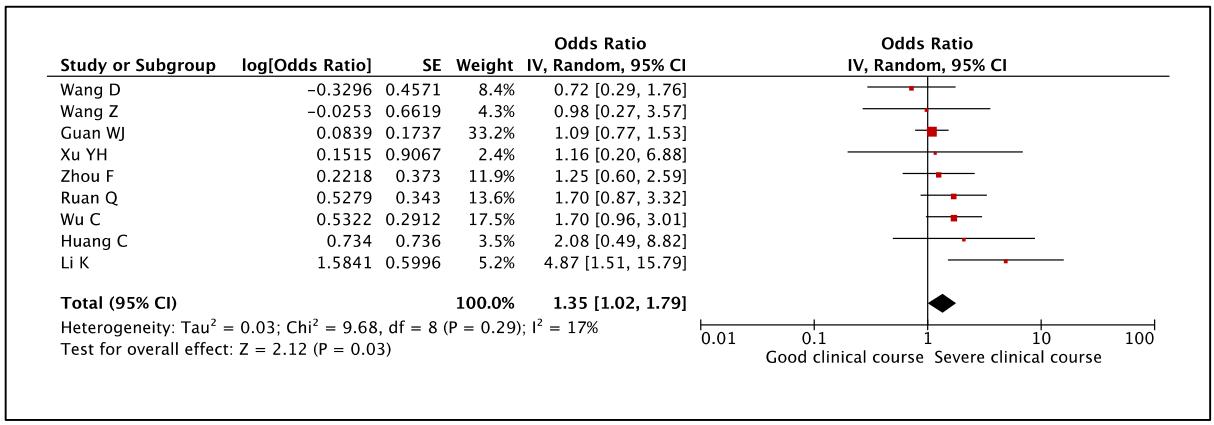

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Figure 15: Forest plot showing pooled odds ratio of dyspnea being associated with severe clinical course.

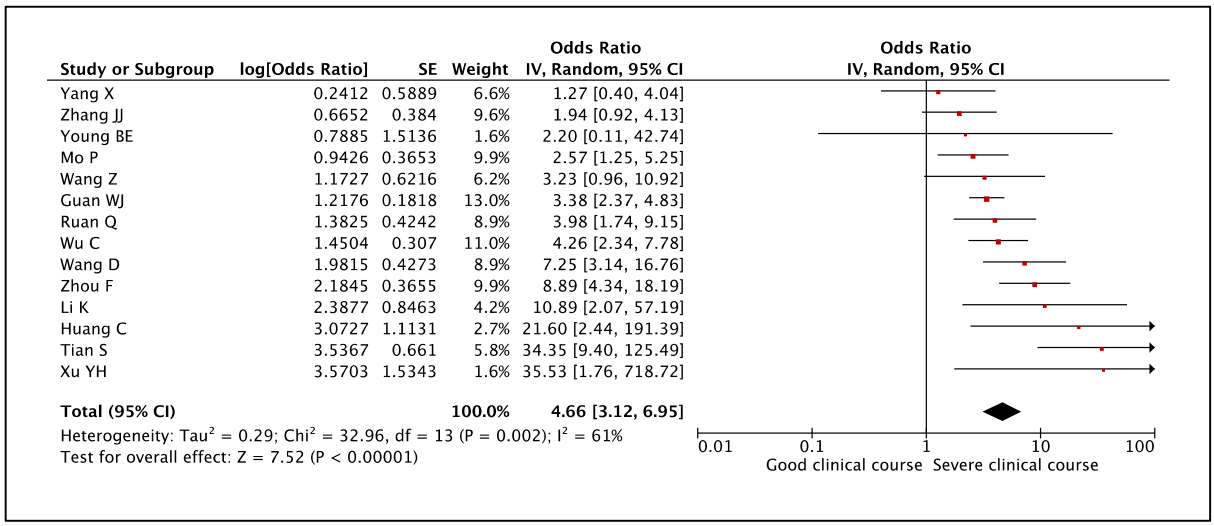

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Figure 16: Forest plot showing pooled odds ratio of diarrhea being associated with severe clinical course.

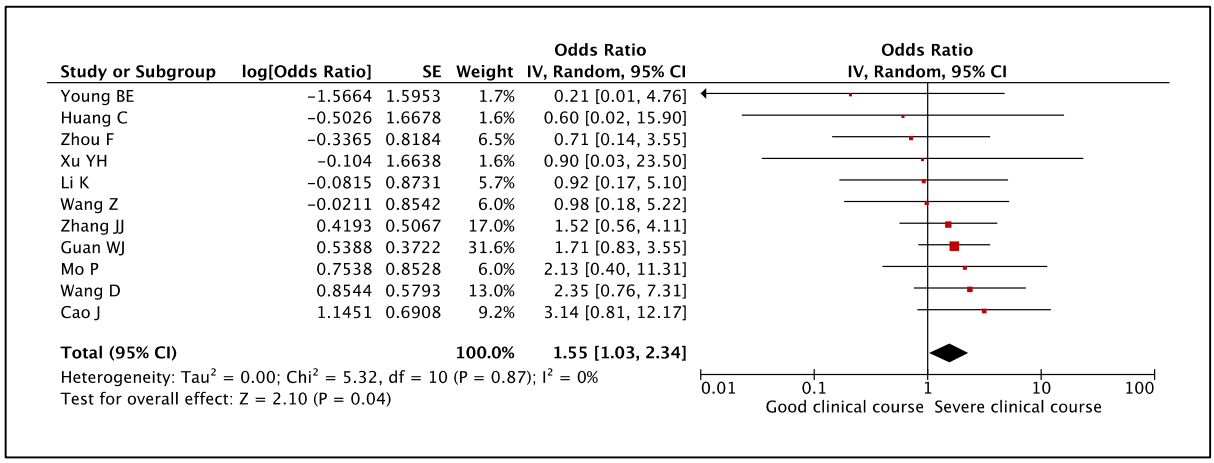

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Figure 17: Forest plot showing pooled odds ratio of higher than normal values of WBC count being associated with severe clinical course.

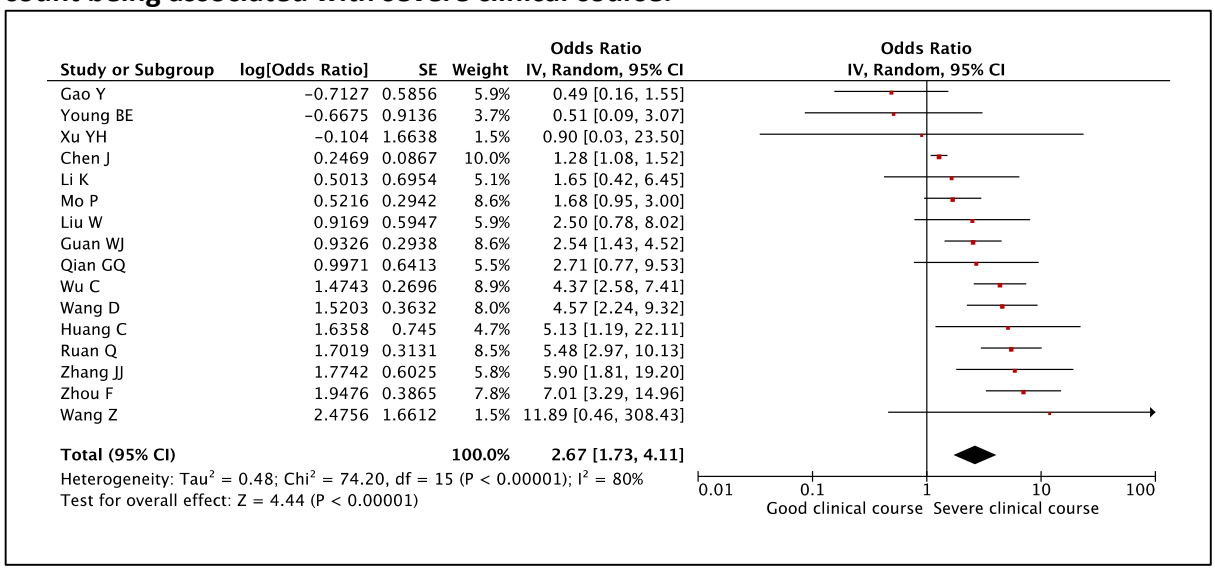

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Figure 18: Forest plot showing pooled odds ratio of lower than normal values of lymphocyte count being associated with severe clinical course.

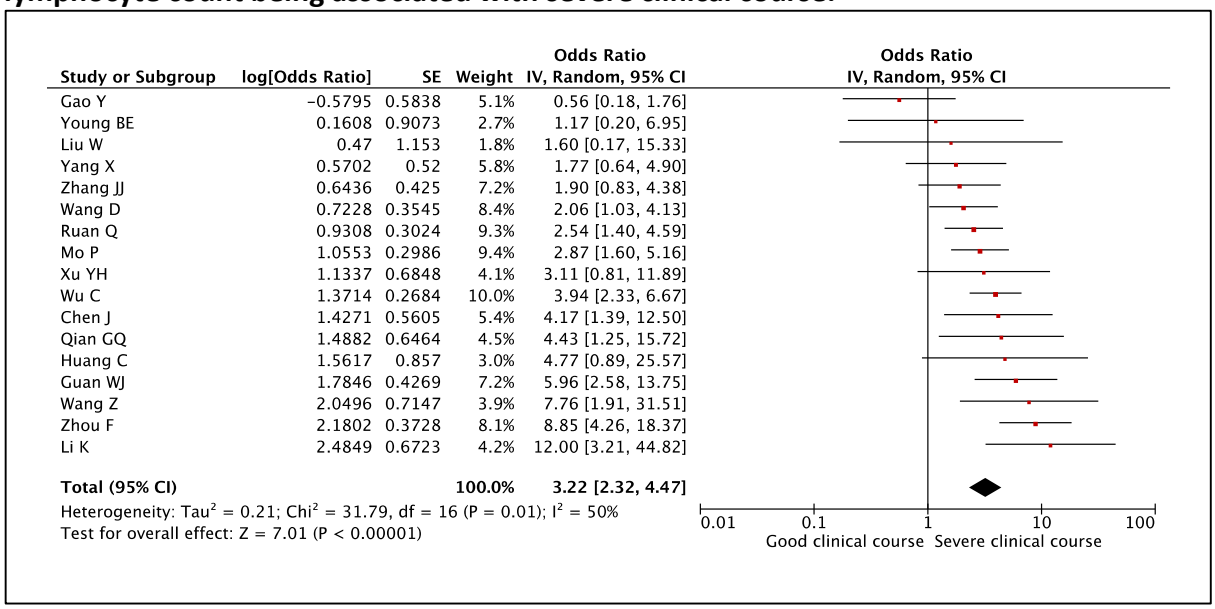

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Figure 19: Forest plot showing pooled odds ratio of lower than normal values of platelet count being associated with severe clinical course.

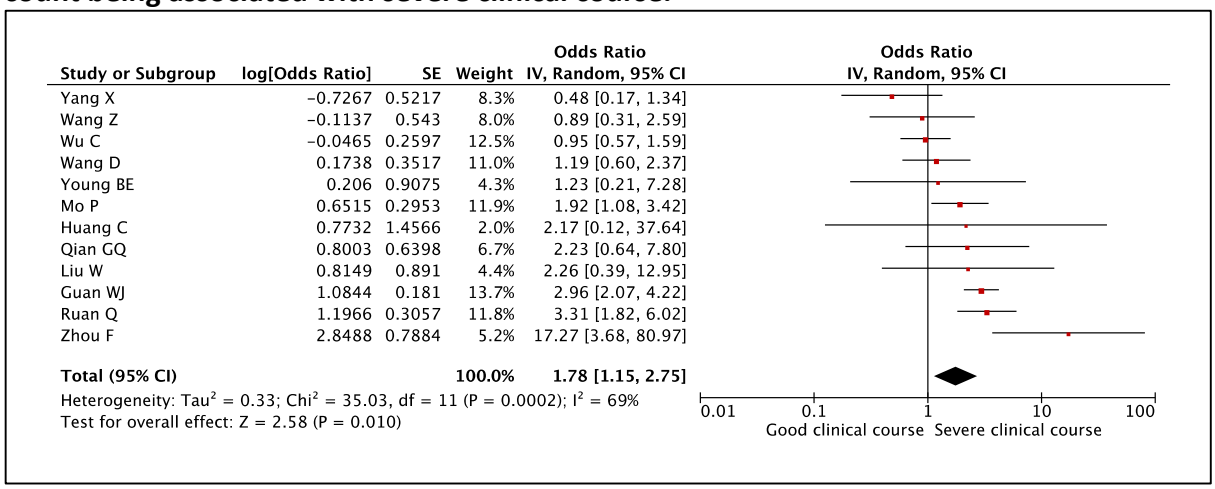

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Figure 20: Comparison of mean hemoglobin values between patients with good and severe clinical course.

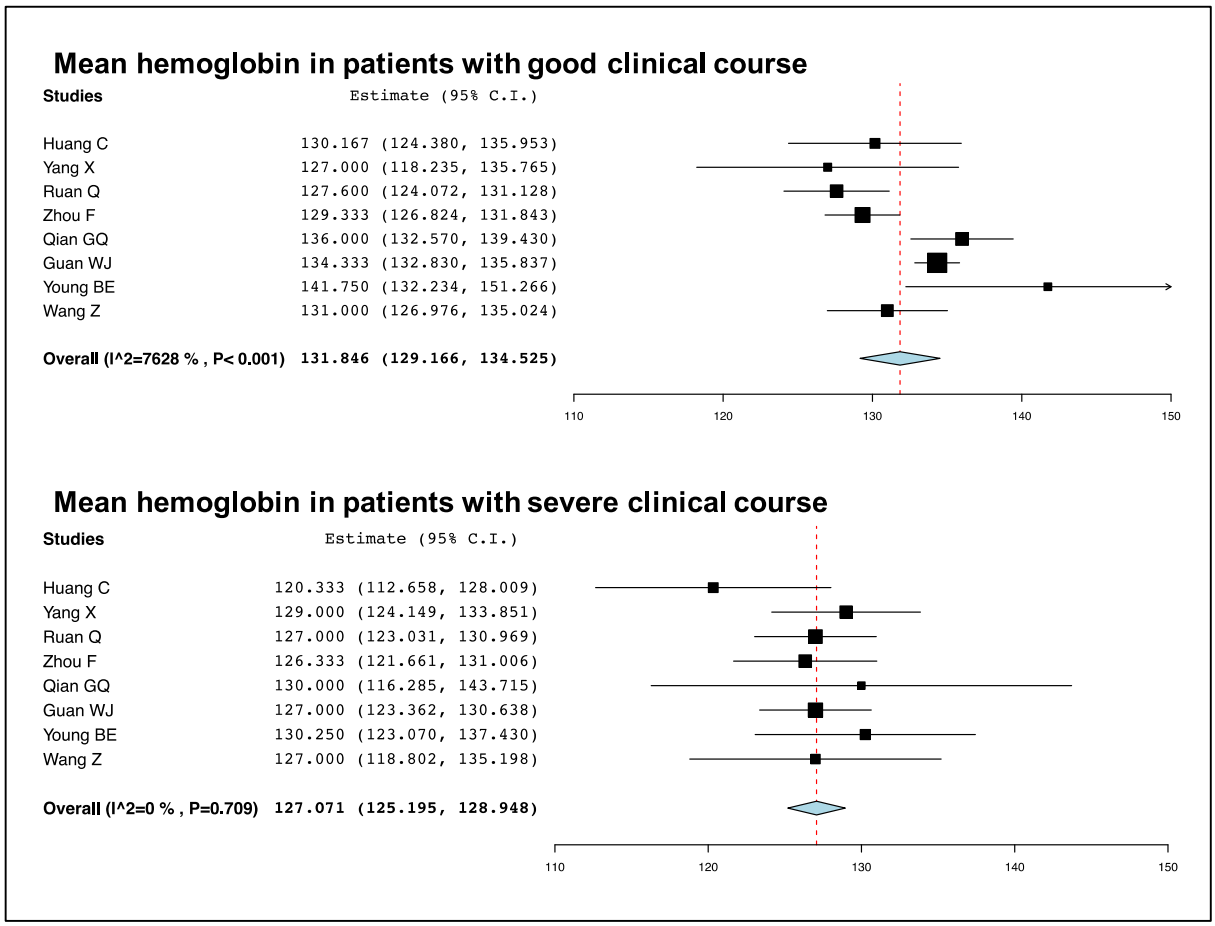

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Figure 21: Forest plot showing pooled odds ratio of high creatinine values being associated with severe clinical course.

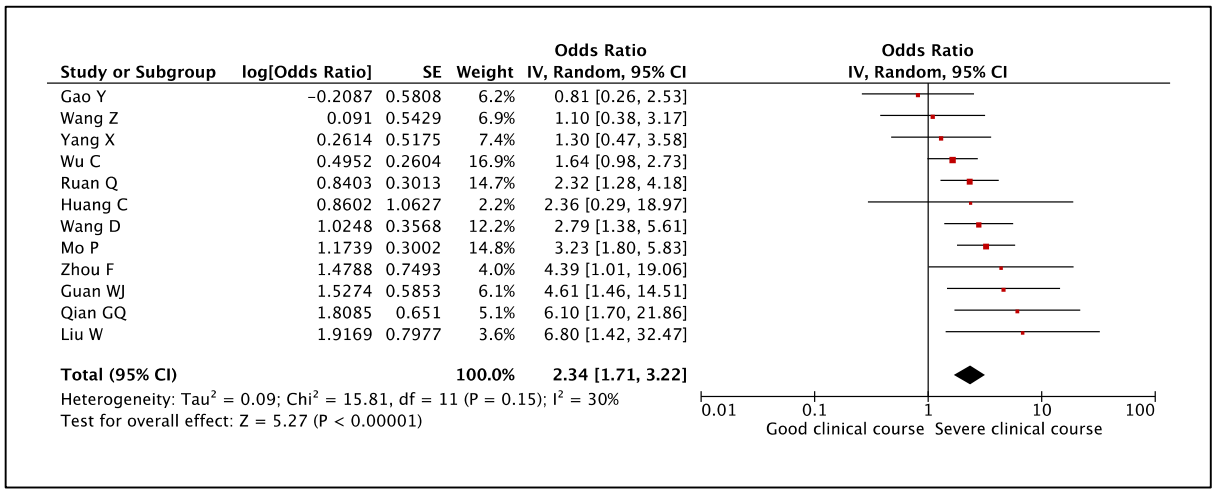

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Figure 22: Forest plot showing pooled odds ratio of higher than normal values of AST being associated with severe clinical course.

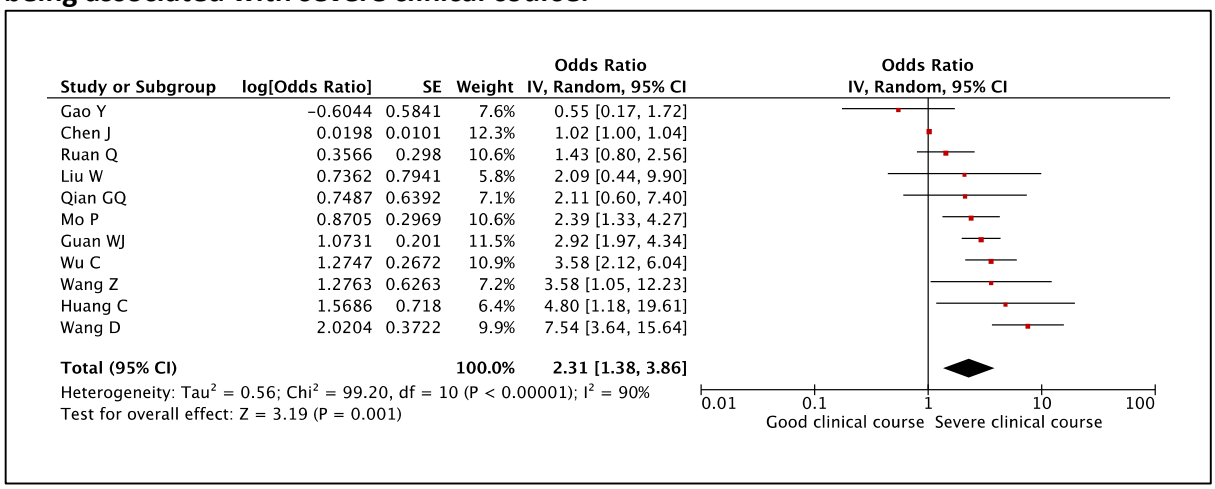

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Figure 23: Forest plot showing pooled odds ratio of higher than normal values of ALT being associated with severe clinical course.

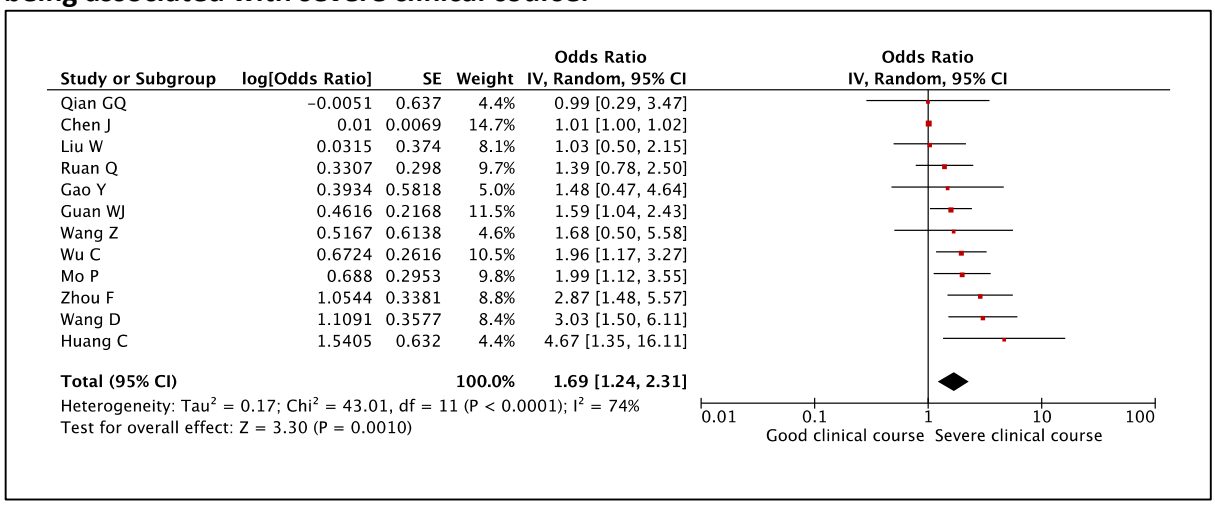

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Figure 24: Forest plot showing pooled odds ratio of higher than normal values of serum bilirubin being associated with severe clinical course.

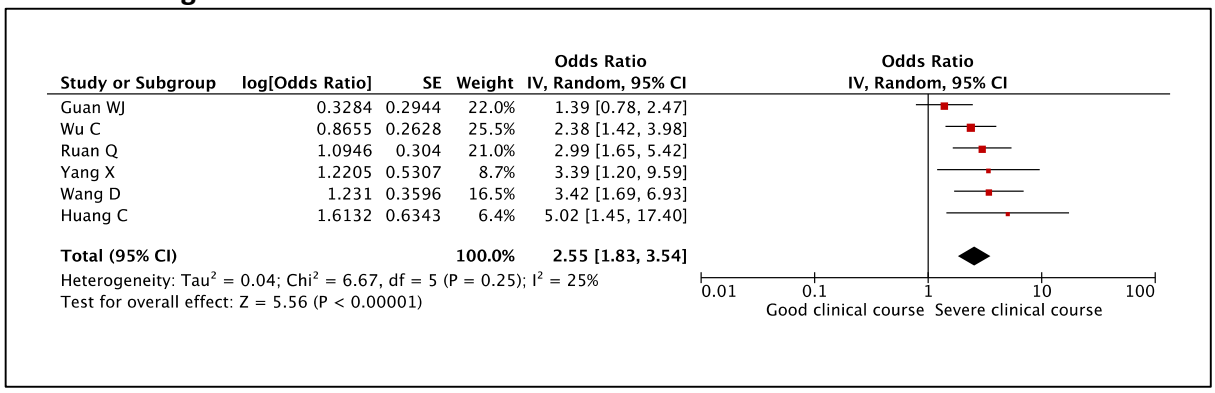

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Figure 25: Forest plot showing pooled odds ratio of lower than normal values of serum albumin being associated with severe clinical course.

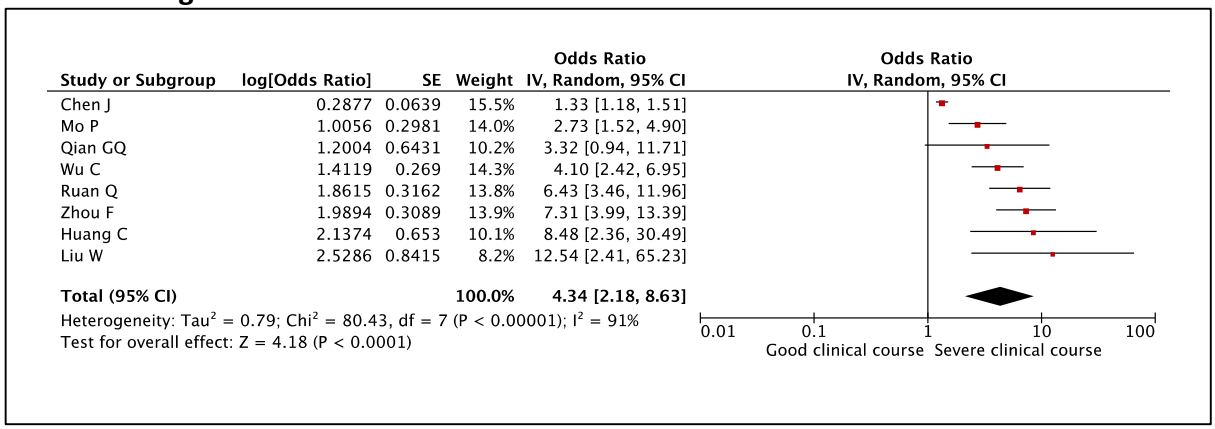

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Figure 26: Forest plot showing pooled odds ratio of higher than normal values of C-reactive protein being associated with severe clinical course.

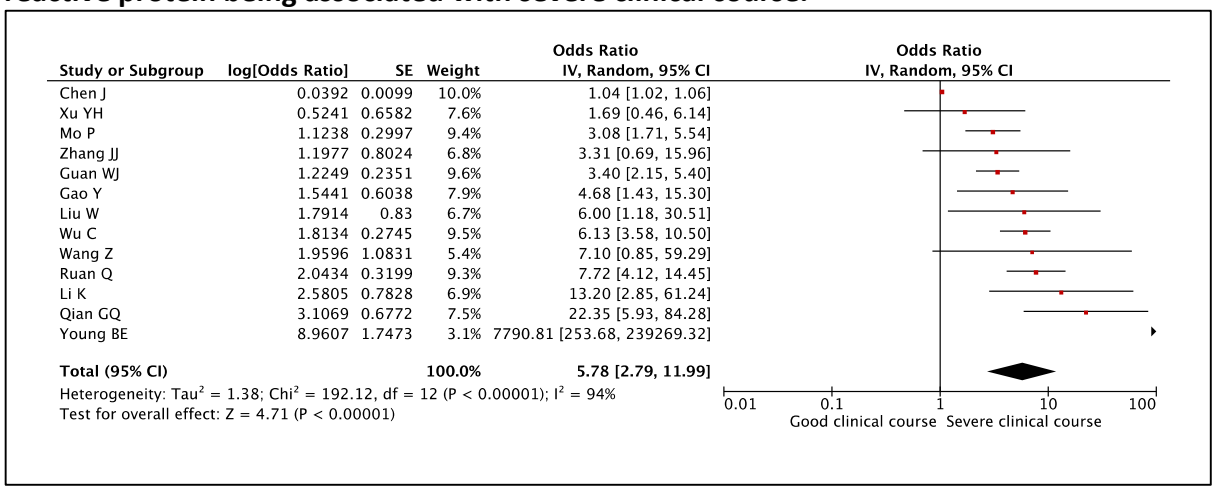

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Figure 27: Forest plot showing pooled odds ratio of higher than normal values of D-dimer being associated with severe clinical course.

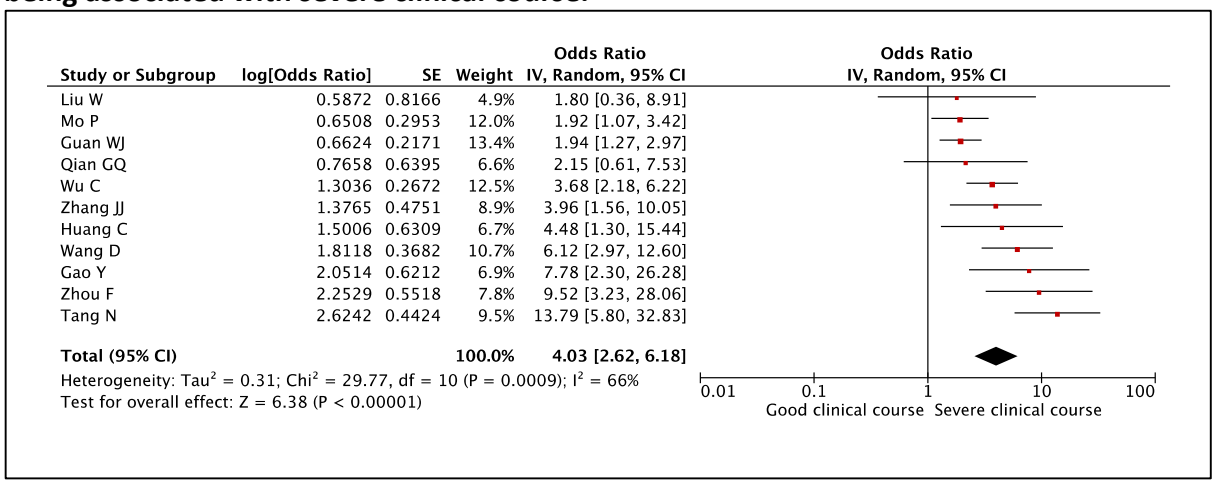

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Figure 28: Forest plot showing pooled odds ratio of high LDH being associated with severe clinical course.

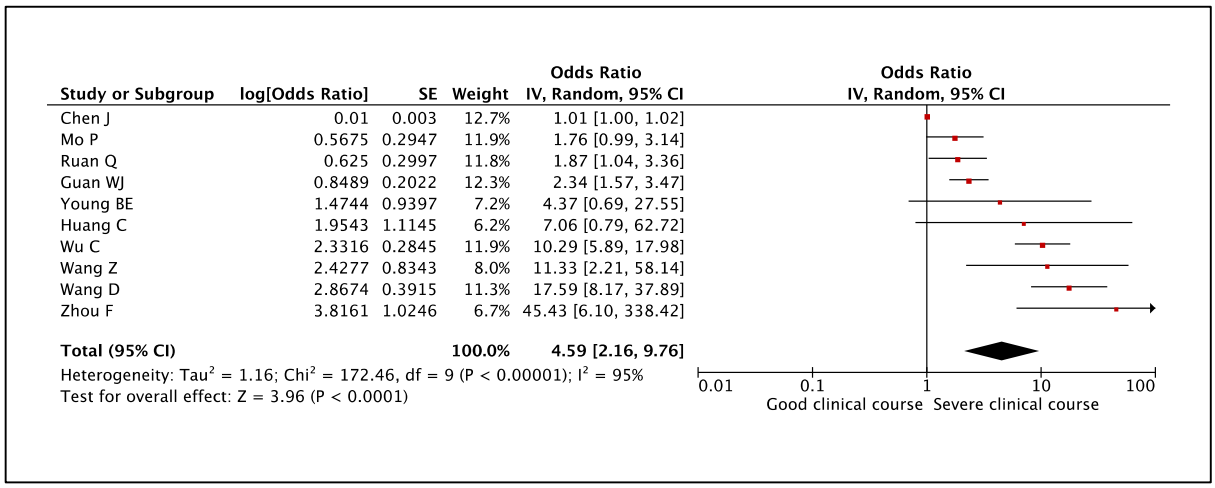

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Figure 29: Forest plot showing pooled odds ratio of high serum procalcitonin being associated with severe clinical course.

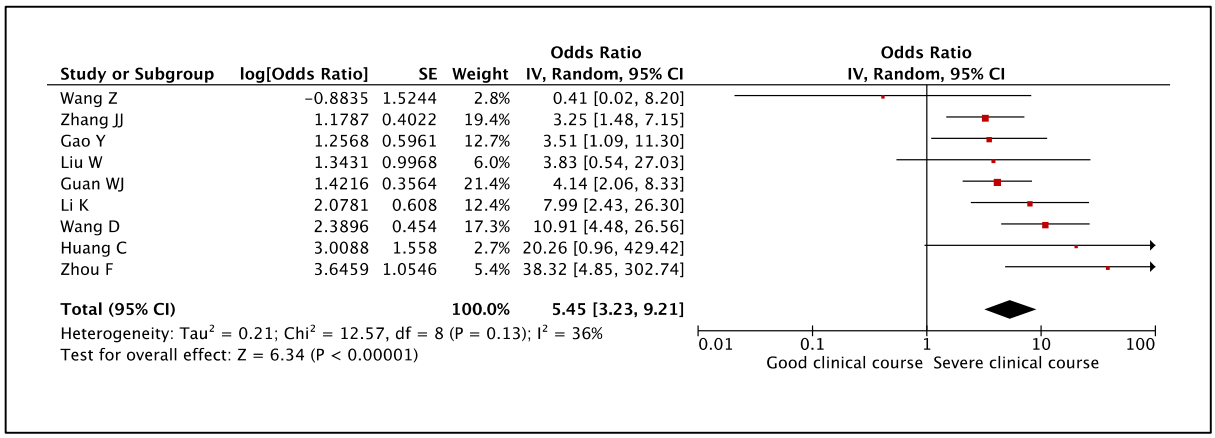

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Figure 30: Forest plot showing pooled odds ratio of high serum creatine kinase being associated with severe clinical course.

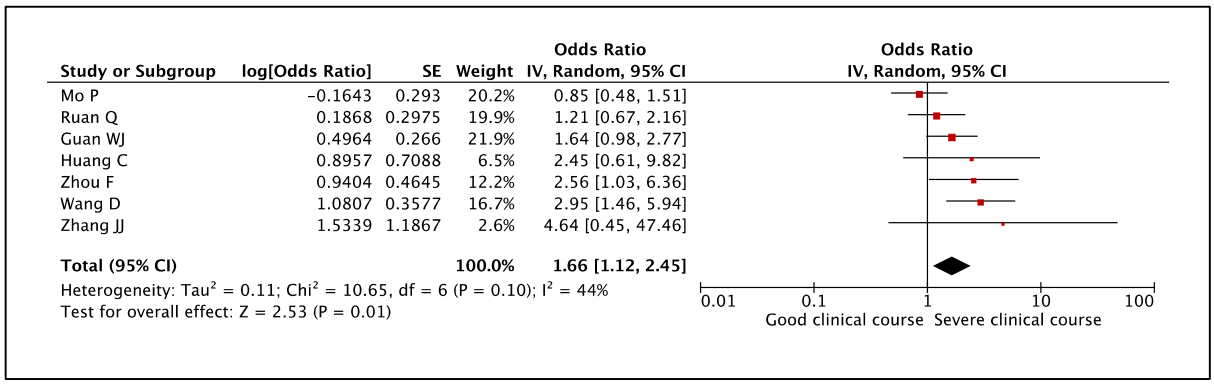

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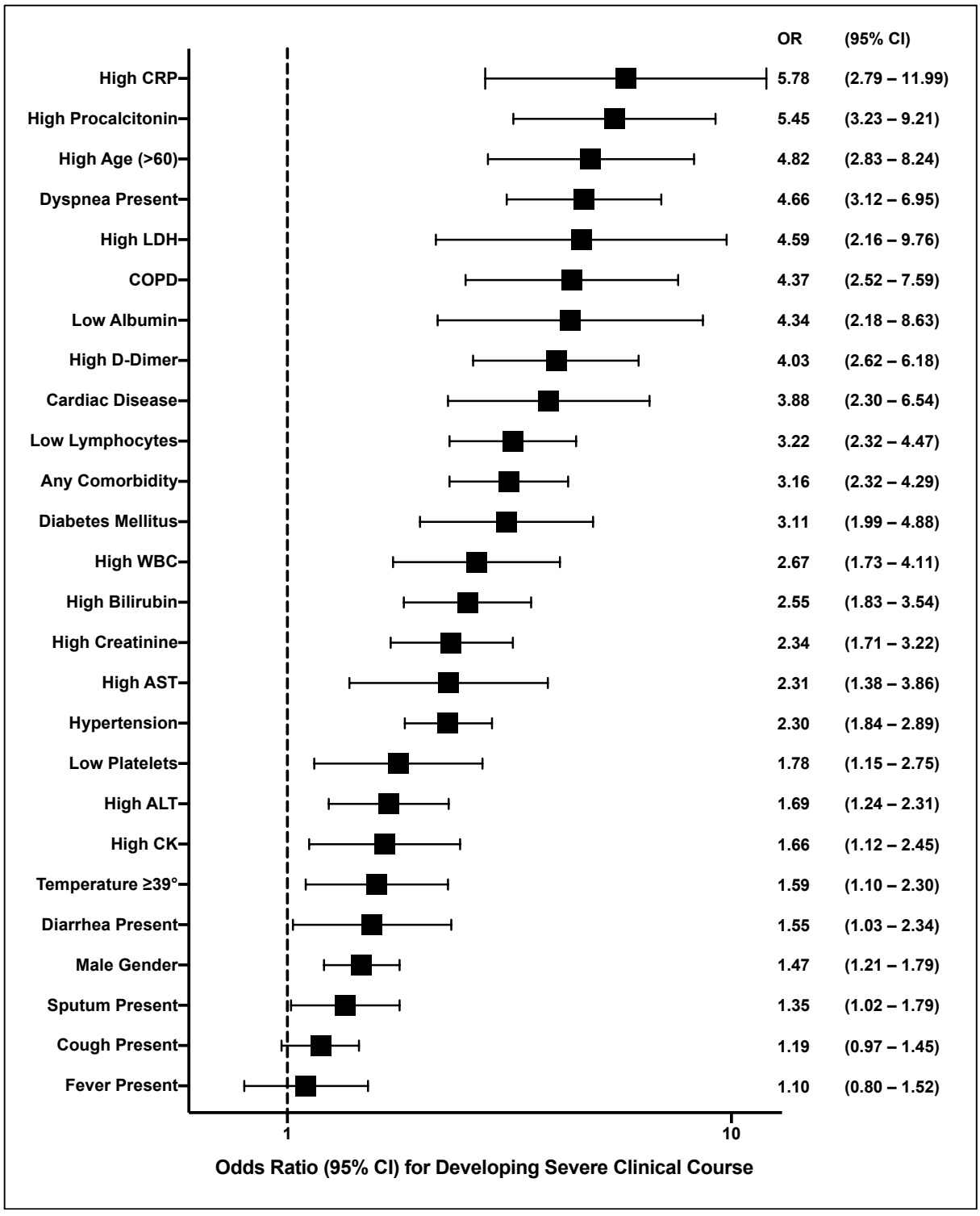
Figure 31: Summary forest plot showing odds ratios of all the factors associated with severe clinical course.



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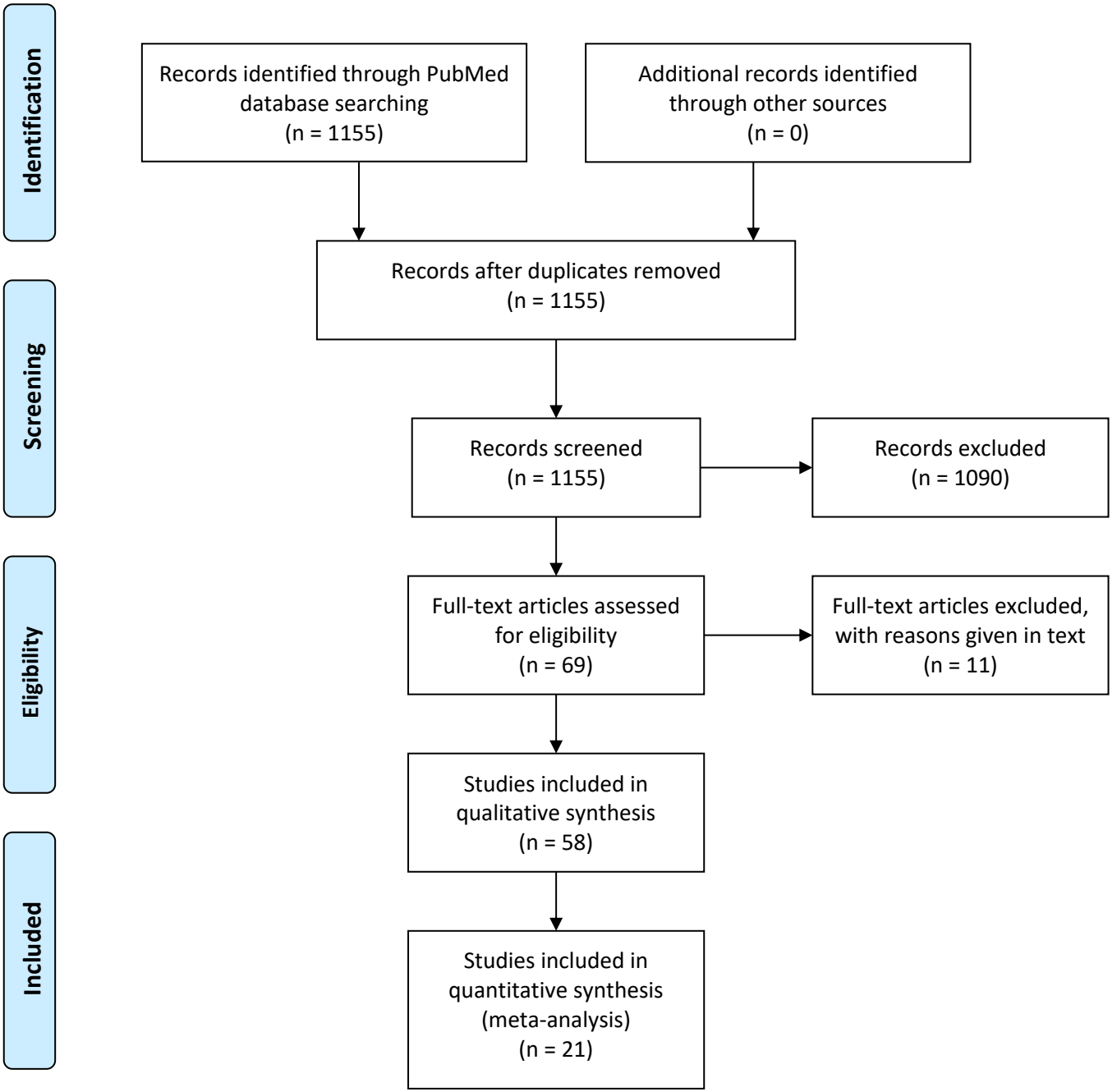
Identification
Screening
Eligibility
Included
Records identified through PubMed database searching (n = 1155)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 1155)
Records screened (n = 1155)
Records excluded (n = 1090)
Full-text articles assessed for eligibility (n = 69)
Full-text articles excluded, with reasons given in text (n = 11)
Studies included in qualitative synthesis (n = 58)
Studies included in quantitative synthesis (meta-analysis) (n = 21)