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[Li He](#), [Rundong Qin](#), [Zhaowei Yang](#), [Nan Jia](#) ...+11 more authors

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Identification of immunological, inflammatory, hematological, and coagulation abnormalities associated with severity and mortality of COVID-19: a meta-analysis of 64 observational studies

Li He

Guangzhou Medical College First Affiliated Hospital <https://orcid.org/0000-0002-8782-7793>

Rundong Qin

Guangzhou Medical College First Affiliated Hospital

Zhaowei Yang

Guangzhou Medical College First Affiliated Hospital

Nan Jia

Guangzhou Medical College First Affiliated Hospital

Ruchong Chen

Guangzhou Medical College First Affiliated Hospital

Jiaying Xie

Guangzhou Medical College First Affiliated Hospital

Wanyi Fu

Guangzhou Medical College First Affiliated Hospital

Hao Chen

Guangzhou Medical College First Affiliated Hospital

Xinliu Lin

Guangzhou Medical College First Affiliated Hospital

Renbin Huang

Guangzhou Medical College First Affiliated Hospital

Tian Luo

Guangzhou Medical College First Affiliated Hospital

Yukai Liu

Guangzhou Medical College First Affiliated Hospital

Siyang Yao

Guangzhou Medical College First Affiliated Hospital

Mei Jiang

Guangzhou Medical College First Affiliated Hospital

Jing Li (✉ lijing@gird.cn)

Guangzhou Medical College First Affiliated Hospital

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Abstract

Background

Laboratory abnormalities associated with disease severity and mortality in patients with coronavirus disease 2019 (COVID-19) have been reported in many observational studies. However, there are significant heterogeneities in patient characteristics and research methodologies in these studies.

Objectives

We aimed to provide an updated synthesis of the association between laboratory abnormalities and COVID-19 prognosis.

Methods

We conducted an electronic search of PubMed, Scopus, Ovid, Willey, Web of Science, and the China National Knowledge Infrastructure (CNKI) for studies reporting hematological, coagulation, inflammatory, and immunological results during hospital admission of COVID-19 patients with different severities and outcomes.

Results

A total of 64 studies were included in the current meta-analysis, with 8 hematological, 3 coagulation, 5 inflammatory, and 23 immunological variables reported. Of them, white blood cell (WBC) and neutrophil counts (Neu), D-dimer level, procalcitonin (PCT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, serum amyloid A (SAA), interleukins (ILs)–2R, IL-6, and IL-10 were significantly increased in severely ill patients and non-survivors. Meanwhile, non-severely ill patients and survivors presented significantly higher counts of eosinophils, lymphocytes, and CD4⁺ and CD8⁺ T cells. A majority of included variables presented with significant heterogeneity, some of which resulted from differing disease severities and ages of included patients.

Conclusions

The current meta-analysis provides a comprehensive and updated synthesis of the association between admission laboratory abnormalities with severity and mortality of COVID-19. Our results highlight that increases in the levels of PCT, ESR, CRP, ferritin, SAA, IL-2R, IL-6, and IL-10 were associated with disease deterioration, whereas elevated eosinophils, lymphocytes, and T-cell subsets might serve as indicators of favorable outcomes.

Introduction

As of August 5, 2020, the outbreak of coronavirus disease 2019 (COVID-19) has affected more than 200 countries, with 15,785,641 confirmed cases and 640,016 deaths worldwide.¹ The disease is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which results in a large number of severe/critical ill patients who require rigorous managements in intensive-care units (ICUs).^{2–4} Until now, there is no consensus on an effective method to eradicate SARS-CoV-2. Prompt recognition and supportive care for potentially severe/critical ill patients are the main stay treatments to save lives.

Our previous study⁵ showed that lymphocyte, T-cell subset, eosinophil, and platelet counts decreased markedly in severely and fatally ill patients. Non-survivors maintained high levels of or showed an upward trend in neutrophils (Neu), interleukin-6 (IL-6), procalcitonin (PCT), D-dimer, serum amyloid A protein (SAA), and C-reactive protein (CRP), while these markers held stable or showed a downward trend in survivors. Studies from other research groups have also investigated the correlation between abnormal laboratory results, including leukocyte, lymphocyte (Lym), and eosinophil counts (Eos), infection-related variables, and serum inflammatory-cytokine levels, and severity or mortality of the disease.^{5–7} D-dimer and, to a lesser extent, lymphopenia demonstrated the largest prognostic associations.⁸ Therefore, identifying abnormal hematological and immunological laboratory results might provide a method to predict the disease progression and potential fatal outcomes.

The increasing body of published studies on the laboratory findings of COVID-19 patients allows for a more comprehensive analysis of the associations between the laboratory abnormalities and prognosis in the disease. However, there are marked heterogeneities in the demographic and clinical characteristics of included patients, detected time of laboratory parameters, and treatment interventions among these studies. Therefore, we systematically reviewed the effects of hematological, immunological, infection-related, and coagulation variables on the prognosis of COVID-19 patients. The study's purpose was to provide strong evidence for risk stratification that can warn health professionals of the disease severity and mortality.

Materials And Methods

Search strategy and selection criteria

We conducted an electronic search of PubMed, Scopus, Ovid, Willey, Web of Science, and the China National Knowledge Infrastructure (CNKI) by using the keywords “laboratory” OR “hematological” OR “coagulation” OR “inflammatory”, OR “immunological” AND “coronavirus 2019” OR “COVID-19” OR “2019-nCoV” OR “SARS-COV-2”, from January 1, 2020 to May 13, 2020, without any language restrictions. Two independent reviewers assessed the title, abstract, and full text of each article identified in the search for eligibility. Any disagreements were solved by a discussion with a third reviewer to reach a consensus. Studies included were those that were retrospective in design and reported available data on hematological, coagulation, inflammatory or immunological variables and included patients (a) with different severity levels of COVID-19 or (b) both patients who died or survived from SARS-CoV-2 infection. Reviews, case reports, editorials, correspondences, letters, data papers, comments, notes and erratum were excluded. Included publications were assessed using the Newcastle–Ottawa Scale (NOS).

Data collection

Two reviewers independently extracted data, which included authors, year of study, country, language, study design, sample size (case number/control number), groups, time of laboratory tests performed, and the results of hematological, coagulation, inflammatory, or immunological tests. For the meta-analysis, we transformed the format of laboratory variables presented as “median [interquartile range (IQR)]” into that of “mean [standard deviation (SD)]”.^{9,10} As the originally reported clinical groups were highly diverse among the included publications, we attempted to combine them into two groups, severe COVID-19 and non-severe COVID-19, based on the classifications of the *Guidelines on the Diagnosis and Treatment of COVID-19*, 7th edition,¹¹ by the National Health Commission of China. The strategy for this combination was as follows: (1) groups consisting of severe or critical cases, cases treated in ICUs, aggravations, refractory disease, ARDS cases, and/or cases requiring supplemental oxygen were placed into the severe COVID-19 group; and (2) groups consisting of non-severe, mild, moderate, common, ordinary, or general cases; cases not treated in ICUs; cases without ARDS; and/or cases not requiring supplemental oxygen were placed into the non-severe COVID-19 group. Raw published/publicly available data were extracted, verified in duplication, and combined into a single database. The value of “mean (SD)” of each included variable in the combined groups was calculated with the raw data from the originally reported groups using the formula proposed by Zhang et al.¹²

Statistical analysis

We divided studies into two separate cohorts for analysis: a severity cohort and a mortality cohort. Standardized mean differences (SMDs) and 95% confidence intervals (95% CIs) were calculated as the primary metrics for each laboratory variable. Laboratory data was pooled whenever two or more publications reported a given variable. We quantified the variations in observed laboratory variables across studies attributable to heterogeneity using the I^2 statistic, a metric ranging from 0% (indicating that all the heterogeneity was spurious) to 100% (indicating that all the heterogeneity was “real” and required further examination or explanation). To probe the sources of heterogeneity, when $I^2 > 50\%$, we performed subgroup analysis by grouping studies with their original reported clinical groups by average age of severely ill patients and patients who had died of COVID-19. In addition, meta-regression analysis was further performed to confirm the contribution of the potential source of heterogeneity. All analyses were performed using R software version 3.6.2 (package: meta/metafor; R Project for Statistical Computing, <https://www.r-project.org>).

Results

Identification of studies and characteristics of included studies

Figure 1 shows the flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We identified a total of 1257 studies through our database searches. Of these, we screened the title and abstract of 967 articles, and assessed 344 full-text articles in this meta-analysis. We excluded 280 publications, mainly due to ineligible study designs ($n = 69$) or lack of laboratory data on patients with versus without severe COVID-19 or survivors versus non-survivors ($n = 211$). Ultimately, we included 64 eligible publications in this review.^{5,6,8,13-73} Most studies were from China, with only five studies from Iran, South Korea, the United States, and Singapore. All studies reported that laboratory variables were measured on admission or early on during the hospitalization, and one study on the day of COVID-19 onset. There were 47 studies published in English and 17 studies published in Chinese. The characteristics of the included studies are presented in **Table 1**.

Hematological results

Eight hematological variables, white blood cell (WBC), neutrophil (Neu), lymphocyte (Lym), eosinophil (Eos), and platelet counts, monocyte and basophil absolute counts, and hemoglobin level, were included in the meta-analysis for comparisons between patients with severe and non-severe COVID-19. Except for basophils, all hematological variables were available for comparisons between non-survivors and survivors of COVID-19. The summarized results are presented in **Figure 2**.

1. Severe versus non-severe COVID-19

WBC and neutrophil counts were significantly increased in patients with severe versus those with non-severe COVID-19 (WBCs = 0.51 [95%CI, 0.37-0.65], $P < 0.001$, $I^2 = 81\%$; neutrophils = 0.69 [95%CI, 0.48-0.90], $P < 0.001$, $I^2 = 88\%$), whereas lymphocyte, eosinophil, monocyte, and platelet counts, as well as hemoglobin levels, were significantly decreased in patients with severe versus those with non-severe COVID-19 (lymphocytes = -0.73 [95%CI, -0.17 to -0.01], $P < 0.001$, $I^2 = 79\%$; eosinophils = -0.31 [95%CI, -0.48 to -0.13], $P < 0.001$, $I^2 = 61\%$; monocytes = -0.09 [95%CI, -0.17 to -0.01], $p = 0.024$, $I^2 = 27\%$; platelets = -0.40 [95%CI, -0.63 to -0.16], $p = 0.001$, $I^2 = 91\%$; hemoglobin = -0.20 [95%CI, -0.34 to -0.06], $P < 0.001$, $I^2 = 51\%$). There was no difference in the basophil count between the two groups.

2. Non-survivors versus survivors of COVID-19

Similarly, WBC and neutrophil counts were significantly increased in non-survivors versus survivors of COVID-19 (WBCs = 0.95 [95%CI, 0.73-1.16], $P < 0.001$, $I^2 = 64\%$; neutrophils = 1.29 [95%CI, 0.95-1.63], $P < 0.001$, $I^2 = 82\%$), whereas lymphocyte and platelet counts were significantly decreased in non-survivors versus survivors (lymphocytes = -0.91 [95%CI, -1.10 to -0.71], $P < 0.001$, $I^2 = 58\%$; platelets = -0.53 [95%CI, -0.65 to -0.41], $P < 0.001$, $I^2 = 3\%$). There were no differences in eosinophil count, monocyte count, or hemoglobin level between the two groups.

Coagulation results

Three coagulation variables, activated partial thromboplastin time (APTT), prothrombin time (PT), and D-dimer, were included for comparisons between patients with severe and non-severe COVID-19 and between non-survivors and survivors infected with SARS-CoV-2. The summarized results are presented in **Figure 3**.

1. Severe versus non-severe COVID-19

PT and D-dimer values were significantly increased in patients with severe versus those with non-severe COVID-19 (PT = 0.58 [95%CI, 0.40–0.76], $P < 0.001$, $I^2 = 70\%$; D-dimer = 0.84 [95%CI, 0.70–0.97], $P < 0.001$, $I^2 = 74\%$). There was no difference in APTT between the two groups.

2. Non-survivors versus survivors of COVID-19

All three coagulation parameters were significantly increased in non-survivors versus survivors of COVID-19 (aPPT = 0.15 [95%CI, 0.02–0.28], $P < 0.001$, $I^2 = 0\%$; PT = 0.79 [95%CI, 0.53–1.05], $P < 0.001$, $I^2 = 74\%$; D-dimer = 1.16 [95%CI, 0.95–1.36], $P < 0.001$, $I^2 = 54\%$).

Inflammatory results

Five inflammatory variables, procalcitonin (PCT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferretin, and serum amyloid A (SAA), were included for comparisons between patients with severe and those with non-severe COVID-19 and between non-survivors and survivors infected with SARS-CoV-2. The summarized results are presented in **Figure 4**.

1. Severe versus non-severe COVID-19

Levels of all five inflammatory variables were significantly increased in patients with severe versus those with non-severe COVID-19 (PCT = 0.63 [95%CI, 0.22–1.04], $P < 0.001$, $I^2 = 96\%$; ESR = 0.50 [95%CI, 0.27–0.74], $P < 0.001$, $I^2 = 83\%$; CRP = 1.27 [95%CI, 1.05–1.49], $P < 0.001$, $I^2 = 90\%$; ferretin = 0.93 [95%CI, 0.67–1.20], $P < 0.001$, $I^2 = 68\%$; SAA = 1.14 [95%CI, 0.54–1.74], $P < 0.001$, $I^2 = 93\%$).

2. Non-survivors versus survivors of COVID-19

Similarly, levels of all five inflammatory variables were significantly increased in non-survivors versus survivors of COVID-19 (PCT = 1.08 [95%CI, 0.81–1.34], $P < 0.001$, $I^2 = 72\%$; ESR = 0.36 [95%CI, 0.16–0.56], $P < 0.001$, $I^2 = 0\%$; CRP = 0.89 [95%CI, 0.57–1.20], $P < 0.001$, $I^2 = 76\%$; ferretin = 1.22 [95%CI, 1.07–1.37], $P < 0.001$, $I^2 = 8\%$; SAA = 0.35 [95%CI, 0.16–0.55], $P < 0.001$, $I^2 = 0\%$).

Immunological results

A total of 23 immunological variables were included for comparisons between patients with severe and those with non-severe COVID-19: IL-1 β , IL-2, IL-2R, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-alpha (TNF- α), interferon (IFN), CD3-positive T-lymphocyte absolute count (CD3⁺ T[ab]), CD3⁺ T percentage (CD3⁺ T%), CD4⁺ T(ab), CD4⁺ T%, CD8⁺ T(ab), CD8⁺ T%, CD4⁺ T(ab)/CD8⁺ T(ab) ratio, CD19-positive B-lymphocyte absolute count (CD19⁺ B[ab]), natural-killer (NK) cells, complement C3 (C3), complement C4 (C4), immunoglobulin A (IgA), IgM, and IgG. Of these, IL-2R, IL-6, IL-8, IL-10, TNF- α , CD3⁺ T(ab), CD4⁺ T(ab), and CD8⁺ T(ab) were available for comparisons between non-survivors and survivors infected with SARS-CoV-2. The summarized results are presented in **Figure 5**.

1. Severe versus non-severe COVID-19

IL-2R, IL-6, IL-8, IL-10 and CD4⁺ T(ab)/CD8⁺ T(ab) ratio were significantly increased in patients with severe versus those with non-severe COVID-19 (IL-2R = 1.03 [95%CI, 0.53–1.52], $P < 0.001$, $I^2 = 88\%$; IL-6 = 1.31 [95%CI, 0.93–1.69], $P < 0.001$, $I^2 = 95\%$; IL-8 = 0.49 [95%CI, 0.32–0.66], $P < 0.001$, $I^2 = 4\%$; IL-10 = 0.64 [95%CI, 0.52–0.75], $P < 0.001$, $I^2 = 41\%$; CD4⁺ T(ab)/CD8⁺ T(ab) ratio = 0.30 [95%CI, 0.17–0.44], $P < 0.001$, $I^2 = 0\%$), whereas CD3⁺ T(ab), CD4⁺ T(ab), CD4⁺ T%, CD8⁺ T(ab), CD8⁺ T%, NK cells, and IgM were significantly decreased in patients with severe versus those with non-severe COVID-19 (CD3⁺ T[ab] = -0.98 [95%CI, -1.24 to -0.71], $P < 0.001$, $I^2 = 84\%$; CD4⁺ T[ab] = -1.72 [95%CI, -1.31 to -0.90], $P < 0.001$, $I^2 = 93\%$; CD4⁺ T% = -0.19 [95%CI, -0.34 to -0.04], $P = 0.012$, $I^2 = 14\%$; CD8⁺ T[ab] = -1.00 [95%CI, -1.24 to -0.71], $P < 0.001$, $I^2 = 77\%$; CD8⁺ T% = -0.52 [95%CI, -0.67 to -0.36], $P < 0.001$, $I^2 = 40\%$; NK = -0.93 [95%CI, -1.58 to -0.27], $P = 0.031$, $I^2 = 89\%$; and IgM = -0.24 [95%CI, -0.39 to -0.10], $P < 0.001$, $I^2 = 45\%$).

2. Non-survivors versus survivors of COVID-19

IL-2R, IL-6, IL-10, and TNF- α were significantly increased in non-survivors versus survivors of COVID-19 (IL-2R = 1.58 [95%CI, 1.10–2.09], $P < 0.001$, $I^2 = 20\%$; IL-6 = 1.17 [95%CI, 0.77–1.56], $P < 0.001$, $I^2 = 87\%$; IL-10 = 1.56 [95%CI, 1.03–2.09], $P < 0.001$, $I^2 = 59\%$; TNF- α = 0.79 [95%CI, 0.57–1.01], $P < 0.001$, $I^2 = 0\%$). CD3⁺ T(ab), CD4⁺ T(ab), and CD8⁺ T(ab) were significantly decreased in non-survivors versus survivors (CD3⁺ T[ab] = -0.96 [95%CI, -1.16 to -0.76], $P < 0.001$, $I^2 = 0\%$; CD4⁺ T[ab] = -0.81 [95%CI, -0.97 to -0.65], $P < 0.001$, $I^2 = 32\%$; CD8⁺ T[ab] = -0.86 [95%CI, -1.02 to -0.69], $P < 0.001$, $I^2 = 0\%$).

Investigation of heterogeneity

A majority of included variables in the current review presented significant heterogeneity ($I^2 > 50\%$). The heterogeneity might have come from various factors, such as demographic and clinical characteristics of included patients, time of the laboratory parameters measured, and treatment intervention before the admission. However, we could extract data only on the originally reported disease severity and ages of included patients. We identified five subgroups according to reported disease severity, severe and critical (severe/critical), severe alone, critical alone, other, and unknown, for the subgroup analysis of the comparison between severe and non-severe COVID-19. Based on the average age of severely ill patients and non-survivors of COVID-19, we classified the

studies into three (average age of severe patients with COVID-19 >60 years (y), >70y, and unknown) and six (average age of non-survivors <18y, >40y, >50y, >60y, >70y, and unknown) subgroups, respectively. The included variables presenting high heterogeneity ($I^2 > 50\%$) and reported by an adequate number of studies ($n > 5$) were applied in our subgroup analysis.

The main findings of our heterogeneity analysis were as follows: (1) a portion of variables reported only in studies of patients with critical COVID-19 presented low heterogeneity; (2) a portion of variables reported in studies comprising non-survivors of COVID-19 whose average age was >70 y presented low heterogeneity; and (3) meta-regression showed that neither disease severity nor average age was the main source of heterogeneity. The detailed results are presented in **Appendix S4-S7** and **Appendix Table S1–S3**.

Publication bias analysis

Data on WBC, PCT, ESR, and IL-6 showed evidence of publication bias analysis. The results are presented in **Appendix S5**.

Discussion

Many studies have suggested that clinical and laboratory variable abnormalities are associated with disease severity and mortality in COVID-19 patients. However, these studies had a significant heterogeneity in patient characteristics, sites, and therapeutic intervention before the laboratory tests. A systematic comparison of differences in these clinical indicators in either a severity or mortality cohort is urgently required to provide comprehensive evidences for risk stratification and clinical managements. Our meta-analysis of 64 cross-sectional studies found significant abnormalities in hematological, coagulation, inflammatory or immunological results detected on admission in patients with severe COVID-19 and in those who died from the disease. In summary, on admission, WBC, Neu, PT, D-dimer, PCT, ESR, CRP, ferritin, SAA, and cytokines, including IL-2R, IL-6, and IL-10, were significantly increased in severely ill patients and in non-survivors. Meanwhile, patients with non-severe COVID-19 and survivors presented significantly higher levels of Eos, Lym, and T-cell subsets including CD3⁺ T, CD4⁺ T, and CD8⁺ T.

A dramatically increased WBC count is a prominent hematological abnormality in patients with severe COVID-19 and has prognostic value in determining fatal outcomes. Increased WBC count might be driven by elevated neutrophil count, which is caused by SARS-CoV-2 infection of airway endothelial cells to release neutrophil extracellular traps (NETs), with subsequent initiation and propagation of inflammation and thrombosis.^{74,75} However, co-infection with bacteria might be another crucial contributor to high neutrophil count. In this new pandemic pneumonia, levels of inflammatory variables, including PCT, ESR, CRP, ferritin, and SAA, were significantly increased in both patients with severe COVID-19 and non-survivors.^{76–79} Our current evidence synthesis greatly coincides with the findings of previous individual studies. PCT was produced in response to bacterial infections and strongly correlated with the extent and severity the disease.⁸⁰ However, as shown previously, PCT did not increase during the viral infection, which strongly indicated that superimposed bacterial infection could occur in patients with COVID-19 who were at a high risk of developing the severe illness.⁸¹ Our data showed that the increased levels of the above mentioned infectious indicators were general characteristics of patients with severe COVID-19 and of non-survivors. This implies that the complication from bacterial infection might play an important role in progression of COVID-19. Prompt antibiotic therapy should be considered once increases in these indicators are detected.

Inflammatory and immune response against COVID-19 leading to a subsequent cytokine storm is a crucial contributor to severe disease and fatal outcome. Our data showed that, in the included cytokines, levels of IL-2R, IL-6, and IL-10 were significantly increased in both the severe-disease and mortality cohorts, which has been previously reported in SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).^{82–88} IL-6 is one of the most important pro-inflammatory cytokines and a key driver of cytokine dysregulation, which can cause hyperinflammation in the lungs of patients infected with SARS-CoV-2.⁸⁹ Anti-IL-6 treatment approaches, including tocilizumab, sarilumab, and siltuximab, have an increasing application worldwide.⁹⁰ IL-10, an acknowledged anti-inflammatory cytokine related to T_H2 response,⁹¹ is also significantly increased in severe COVID-19 and have favorable capability of predicting severity in many clinical-observation studies. Similarly, the IL-2R/lymphocyte ratio was reported to be well associated with clinical progression of COVID-19.⁹² However, cytokine storm occurring in SARS-CoV-2 infection involves a significant number of cytokines with a complex interaction network.⁹³ Even though the number of studies adequately focusing on the cytokine profile was limited, our current synthesis data still highlighted that IL-2R, IL-6, and IL-10 were all associated with the disease severity and fatal outcome during the SARS-CoV-2 infection. The underlying mechanisms of these cytokines in an inflammatory and immune mediator network still require further research.

Notably, we observed substantial decreases in lymphocytes and their subsets, including T cells, B cells, and NK cells, in our systematic review. This was in line with the results from a recent meta-analysis targeting lymphocytes and their subset counts.⁹⁴ We found that a decline in CD8⁺ T cells was more significant in severe than in non-severe patients. We further demonstrated that a significantly higher ratio of CD4⁺ to CD8⁺ T cells was associated with disease severity, indicating a greater reduction of CD8⁺ T cells than of CD4⁺ T cells in patients with severe COVID-19. Although not identified as a prognostic factor in the present meta-analysis, possibly due to the small number of included studies, eosinopenia was associated with COVID-19 severity on admission. Our previous study also suggested that dynamic changes in blood eosinophil counts might predict COVID-19 progression and recovery.⁹⁵ Overall, our findings indicated that lymphopenia, in particular decreased CD8⁺ T-cell and NK cell counts, could be a risk factor related to severe disease and fatal outcomes that should be closely monitored over the course of hospitalization.

Studies in COVID-19 coagulopathy showed decreased platelet counts and fibrinogen levels, as well as elevated PT/international normalized ratio (INR), APTT, and D-dimer.^{40,96} Several retrospective analyses^{97–99} have revealed that venous thromboembolism contributed to poor prognosis in COVID-19 patients. An autopsy study¹⁰⁰ found that thrombosis with microangiopathy and alveolar capillary microthrombi were nine times as prevalent in patients with COVID-19 as in those with influenza. Our meta-analysis showed that levels of PT and D-dimer were significantly increased in patients with severe versus those with non-

severe COVID-19. Similarly, the levels of APTT, PT, and D-dimer were significantly increased in non-survivors versus survivors. The mechanism behind this coagulopathy is not well understood. More studies are required to understand the role of anti-coagulation and its effect on morbidity and mortality associated with COVID-19-associated coagulopathy.

Our meta-analysis has limitations. In line with the heterogeneity that characterized these observational studies,¹⁰¹ a majority of included variables presented large I^2 values, indicating significant variations in terms of outcomes observed. Although we attempted to manage this by performing subgroup analysis and meta-regression by patient age and disease severity, the results could not fully explain the source of heterogeneity. We were confined by the methodologies of the studies included, as well as the heterogeneity in characteristics of included patients, such as comorbidity, treatment before admission, and time of symptom onset, which were not provided in the included studies. However, the observed heterogeneity did not impair our main conclusion that severe COVID-19 and mortality were associated with significant abnormalities in the hematological, coagulation, inflammatory, and immunological variables. What the heterogeneity suggests is that these abnormalities might show some variation from one country to another, from one city to another, and from one clinical setting to another.

Conclusions

In conclusion, our meta-analysis provides an updated evidence synthesis showing the associations between the abnormal hematological, coagulation, inflammatory, and immunological results with the severity and mortality of COVID-19. Increased WBC and neutrophil counts, elevated levels of PT, D-dimer, and inflammatory indicators and cytokines, and decreased numbers of immune cells (including eosinophils, lymphocytes, and their subtype CD4⁺ and CD8⁺ T cells) were risk factors contributing to the disease severity and increased mortality in patients infected with SARS-CoV-2. COVID-19 is a worldwide pandemic. Factors associated with its severity and mortality could vary depending on many factors in addition to the laboratory test results. Future longitudinal studies are warranted to further explore the predictive factors in guiding clinical management.

Abbreviations

APTT
activated partial thromboplastin time
COVID-19
coronavirus disease 2019
CNKI
China National Knowledge Infrastructure
CRP
C-reactive protein
CD3⁺ T[ab]
CD3-positive T-lymphocyte absolute count
CD19⁺ B[ab]
CD19-positive B-lymphocyte absolute count
C3
complement
CIs
confidence intervals
ESR
erythrocyte sedimentation rate
Eos
eosinophil
ICUs
intensive-care units
IL-6
interleukin-6
IFN
interferon
IgA
immunoglobulin A
IQR
interquartile range
INR
international normalized ratio
Lym
lymphocyte
MERS-CoV
Middle East respiratory syndrome coronavirus
NOS

Newcastle–Ottawa Scale
NK cells
natural-killer cells
Neu
neutrophil
NETs
neutrophil extracellular traps
PCT
procalcitonin
PT
prothrombin time
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SARS-CoV-2
severe acute respiratory syndrome coronavirus 2
SAA
serum amyloid A protein
SD
standard deviation
SMDs
Standardized mean differences
TNF- α
tumor necrosis factor-alpha
WBC
white blood cell

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data collected or analysed during this study are included in this published article (and its supplementary information files).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All the authors conceived and designed the study project. Li He and Rundong Qin performed the literature search and evaluated the study quality. Jing Li, Mei Jiang and all the other authors assessed study details. Li He, Rundong Qin, Xinliu Lin, Renbin Huang, Tian Luo, Yukai Liu, Siyang Yao completed the data extraction. Rundong Qin performed the statistical analyses. This study was drafted by Rundong Qin, Li He, Zhaowei Yang, Nan Jia, Ruchong Chen, Jiaying Xie, Wanyi Fu, Hao Chen, Jing Li. It was revised following critical review initially by Jing Li, Rundong Qin, Li He and all the co-authors. All the authors gave final approval of the version to be submitted and agreed to be accountable for the whole paper.

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Tables

Table 1 Characteristic of included studies							
Study	Country	Language	Study type	Original reported groups	Groupst	Sample size‡	Case gro Age (y)
Mostafa Javanian 2020	Iran	English	Retrospective	Non survivors/Survivors	Non survivors/Survivors	100(19/81)	69.3
JH.Fu 2020	China	English	Retrospective	Severe/Mild/Moderate	Severe/Non severe	75(16/59)	51.8
Kyung Soo Hong 2020	South Korea	English	Retrospective	ICU/Non-ICU	Severe/Non severe	98(13/85)	63.2
D.Li(a) 2020	China	Chinese	Retrospective	Critical/Severe/Moderate	Severe/Non severe	62(44/18)	54.5
J.Xu 2020	China	Chinese	Retrospective	Severe/Moderate	Severe/Non severe	155(30/125)	51
Jerry Y.Chao 2020	America	English	Retrospective	Admitted to PICU/ Admitted to medical unit	Severe/Non severe	46(13/33)	14
Barnaby Edward Young 2020	Singapore	English	Retrospective	Required supplemental O2/ Did not require supplemental O2	Severe/Non severe	18(6/12)	59.1
H.Yang 2020	China	Chinese	Retrospective	Death/Survival	Non survivors/Survivors	94(13/81)	77
Y.Ling 2020	China	Chinese	Retrospective	Severe/Non severe	Severe/Non severe	292(21/271)	65.5
RC.Chen 2020	China	English	Retrospective	A. Non survivors/ Survivors B. Critical/Severe/Moderate/Mild	A. Non survivors/ Survivors B. Severe/Non severe	575(103/445;203/345)	66.9/61
ZL.Lu 2020	China	Chinese	Retrospective	Severe/Non severe	Severe/Non severe	101(34/67)	61.4
SX.Wan(a) 2020	China	English	Retrospective	Severe/Moderate	Severe/Non severe	123(21/102)	61.3
YL.Wang 2020	China	English	Retrospective	Severe/Non severe	Severe/Non severe	43(8/35)	6.8
F.Zhou 2020	China	English	Retrospective	Non survivors/Survivors	Non survivors/Survivors	191(54/137)	69.4
Y.Liu 2020	China	English	Retrospective	Severe/Mild	Severe/Non severe	76(30/46)	NA
C.Qin 2020	China	English	Retrospective	Severe/Moderate	Severe/Non severe	452(286/166)	60.3
YL.Zheng 2020	China	English	Retrospective	Critical/Moderate	Severe/Non severe	99(67/32)	63.8

J.Liu 2020	China	English	Retrospective	Severe/Mild	Severe/Non severe	40(13/27)	59.7
J.Zhang 2020	China	English	Retrospective	Severe/ Moderate	Severe/Non severe	111(18/93)	63.6
F.Liu 2020	China	English	Retrospective	Severe/Mild	Severe/Non severe	140(33/107)	76.6
YL.Zhou 2020	China	English	Retrospective	Aggravation group/ Non aggravation group	Severe/Non severe	17(5/12)	42.2
YL.Yan 2020	China	English	Retrospective	Non survivors/Survivors	Non survivors/Survivors	193(108/85)	70
F.Wang 2020	China	English	Retrospective	ICU/Non-ICU	Severe/Non severe	28(14/14)	71.4
Y.Yang 2020	China	English	Retrospective	Critical/Severe/Moderate	Severe/Non severe	50(36/14)	58.9
RH.Du 2020	China	English	Retrospective	Deceased/Survivors	Non survivors/Survivors	179(21/158)	70.2
GC.Pei 2020	China	English	Retrospective	Critical/Severe/Moderate	Severe/Non severe	333(189/144)	59.6
L.Chen 2020	China	Chinese	Retrospective	Critical/Severe/Moderate	Severe/Non severe	29(14/15)	NA
TL.Chen 2020	China	English	Retrospective	Non survivors/Survivors	Non survivors/Survivors	55(19/36)	77
F.Yang 2020	China	English	Retrospective	Critical/Severe/Mild	Severe/Non severe	52(19/33)	NA
XH.Chen 2020	China	English	Retrospective	Critical/Severe/Moderate	Severe/Non severe	48(27/21)	73.8
B.Xu 2020	China	English	Retrospective	Critical/Severe/Mild	Severe/Non severe	187(107/80)	64.1
TX.Xiang 2020	China	Chinese	Retrospective	Severe/Moderate	Severe/Non severe	49(9/40)	53
G.Chen 2020	China	English	Retrospective	Severe/Moderate	Severe/Non severe	21(11/10)	61.2
T.Chen 2020	China	English	Retrospective	Dead/Survive	Non survivors/Survivors	274(113/161)	69.1
PZ.Mo 2020	China	English	Retrospective	Refractory/General	Severe/Non severe	155(85/70)	60.6
SX.Wan 2020	China	English	Retrospective	Severe/Mild	Severe/Non severe	135(40/95)	60.6
ZL.Wang 2020	China	English	Retrospective	Severe/Mild	Severe/Non severe	69(14/55)	69.8
L.Wang 2020	China	English	Retrospective	Death/Survival	Non survivors/Survivors	339(65/274)	76.4
Y.Feng 2020	China	English	Retrospective	Critical/Severe/Moderate	Severe/Non severe	476(124/352)	58.5
CM.Wu 2020	China	English	Retrospective	ARDS/Without ARDS	Severe/Non severe	201(84/117)	59.2
XW.Fang 2020	China	Chinese	Retrospective	Critical/Severe/General	Severe/Non severe	79(24/55)	56.7

FT.Zuo 2020	China	Chinese	Retrospective	Severe/Non severe	Severe/Non severe	50(11/39)	53.7
J.Xiong 2020	China	Chinese	Retrospective	Critical/Severe/Moderate/Mild	Severe/Non severe	89(31/58)	NA
Y.Lei 2020	China	Chinese	Retrospective	Critical/Severe/Ordinary	Severe/Non severe	51(19/32)	NA
W.Gao 2020	China	Chinese	Retrospective	Critical/Severe/Moderate/Mild	Severe/Non severe	90(33/57)	66.6
W.An 2020	China	Chinese	Retrospective	Non survivors/Survivors	Non survivors/Survivors	110(11/99)	72.4
XY.Ai 2020	China	Chinese	Retrospective	Severe/Moderate/Mild	Severe/Non severe	128(10/128)	62.2
YD.Peng 2020	China	Chinese	Retrospective	Critical/Moderate	Severe/Non severe	112(16/96)	58.2
D.Li(b)2020	China	Chinese	Retrospective	Critical/Severe/Moderate/Mild	Severe/Non severe	80(17/63)	56
J.Wu 2020	China	English	Retrospective	Critical/Severe/Moderate/Mild	Severe/Non severe	280(83/197)	63
YB.Ouyang 2020	China	English	Retrospective	Critical/Severe/Moderate/Common	Severe/Non severe	11(6/5)	63.2
QQ.Chen 2020	China	English	Retrospective	Severe/Non severe	Severe/Non severe	145(43/102)	52.8
SQ.Lei 2020	China	English	Retrospective	ICU/Non ICU	Severe/Non severe	34(15/19)	57.9
W.Guan 2020	China	English	Retrospective	Severe/Non severe	Severe/Non severe	1099(173/926)	52.4
JJ.Zhang 2020	China	English	Retrospective	Severe/Non severe	Severe/Non severe	140(58/82)	58
DW.Wang 2020	China	English	Retrospective	ICU/Non ICU	Severe/Non severe	138(36/102)	67.1
GQ.Qian 2020	China	English	Retrospective	Severe/Mild	Severe/Non severe	91(9/82)	66.7
QX.Cai 2020	China	English	Retrospective	Severe/Non severe	Severe/Non severe	298(58/240)	61.4
F.Zheng 2020	China	English	Retrospective	Severe/Non severe	Severe/Non severe	161(30/131)	56.5
CL.Huang 2020	China	English	Retrospective	ICU/No ICU	Severe/Non severe	41(13/28)	50.5
HS.Xie 2020	China	English	Retrospective	Severe/Moderate/Mild	Severe/Non severe	79(28/51)	60.1
Iek Long Lo 2020	China	English	Retrospective	Severe/Moderate/Mild	Severe/Non severe	10(4/6)	61
JP.Zhang 2020	China	English	Retrospective	Non survivors/Survivors	Non survivors/Survivors	19(8/11)	78.1
YJ.Chen 2020	China	Chinese	Retrospective	Critical/Severe/Moderate	Severe/Non severe	143(36/107)	51.3

Data of age are presented as Mean.

NA: Not available.

Combined groups*: Case group(Non survivors/ Severe)/ Control group(Survivors/ Non severe) .

Sample size*: Total sample(Case group sample/ Control group sample).

Quality score*: The Newcastle-Ottawa Scale was used for the assessing the Quality score of each article, with more stars higher score.

Figures

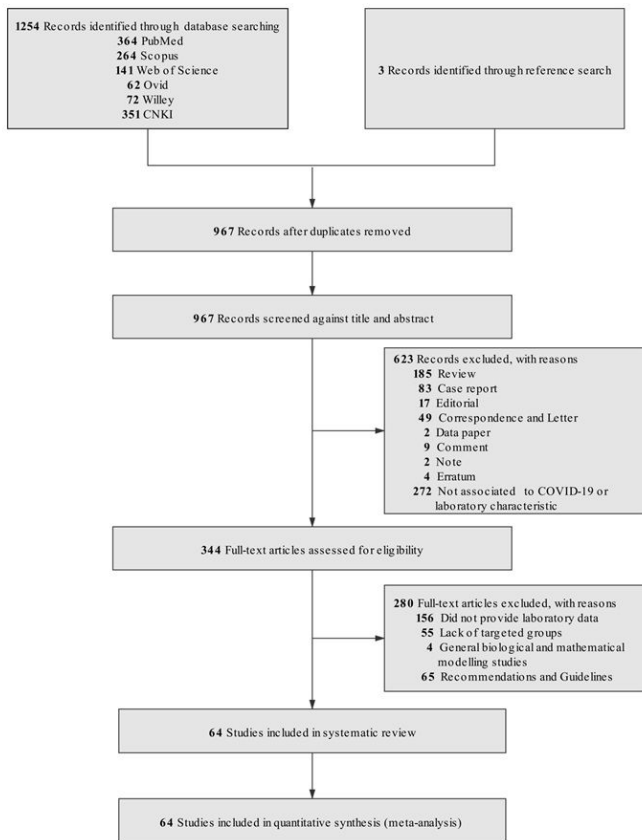


Figure 1

Study flowchart.

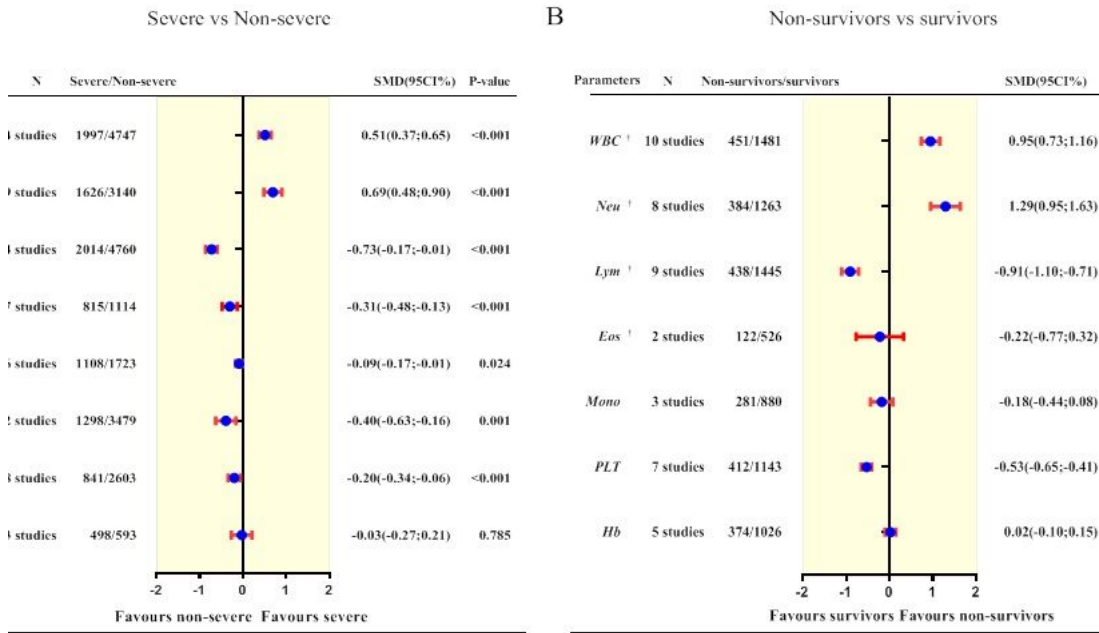


Figure 2
 Summary results of the comparisons of hematological variables (A) between patients with severe and non-severe COVID-19 and (B) between non-survivors and survivors of COVID-19. † indicates the I2 value > 50%.

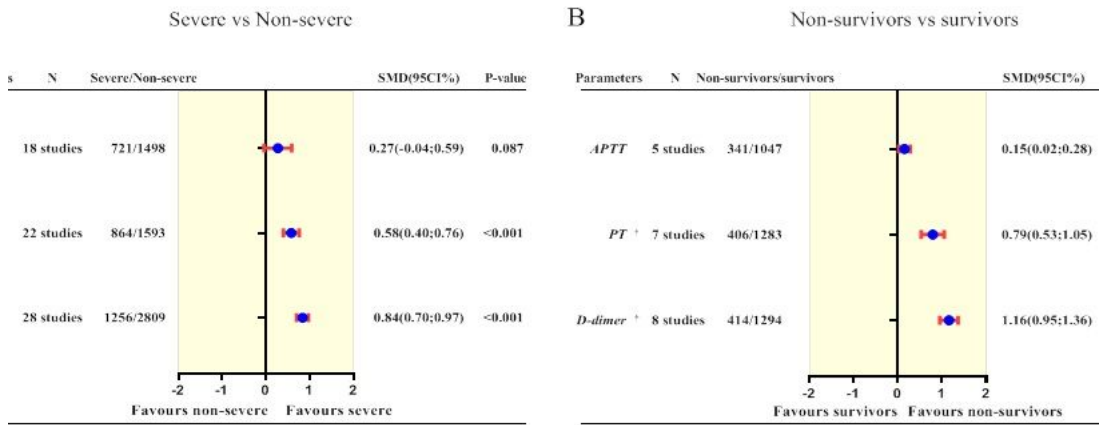


Figure 3
 Summary results of the comparisons of coagulation variables (A) between patients with severe and non-severe COVID-19 and (B) between non-survivors and survivors of COVID-19. † indicates the I2 value > 50%.

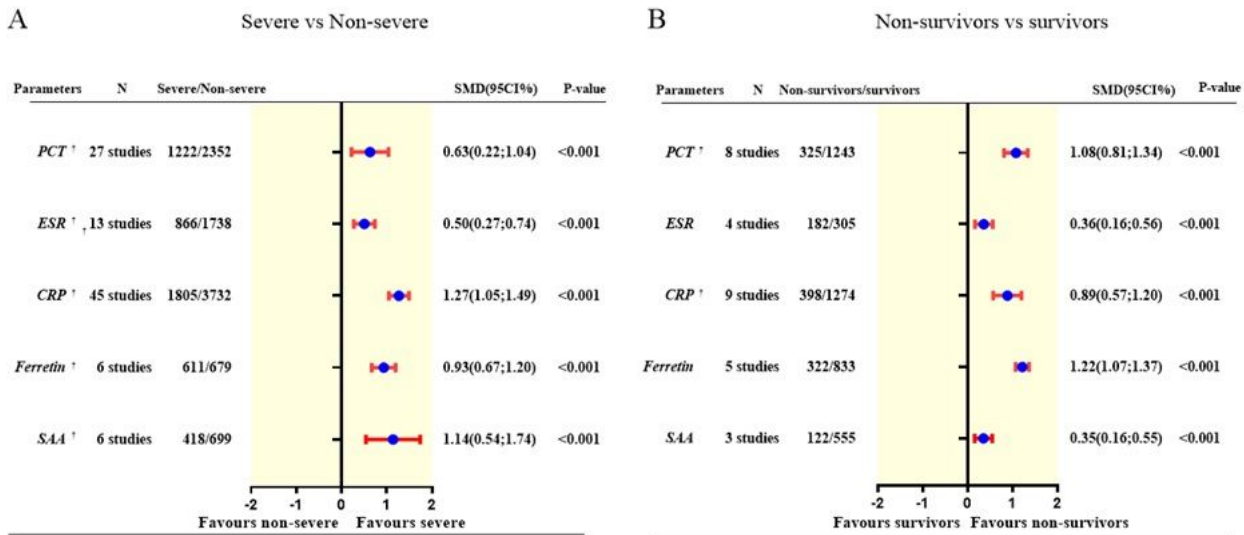


Figure 4 Summary results of the comparisons of inflammatory variables (A) between patients with severe and non-severe COVID-19 and (B) between non-survivors and survivors of COVID-19. † indicates the I2 value > 50%.

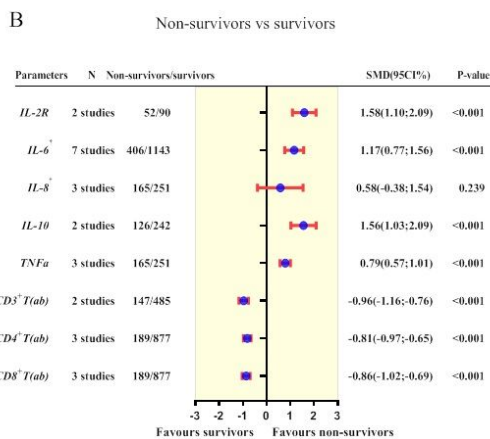
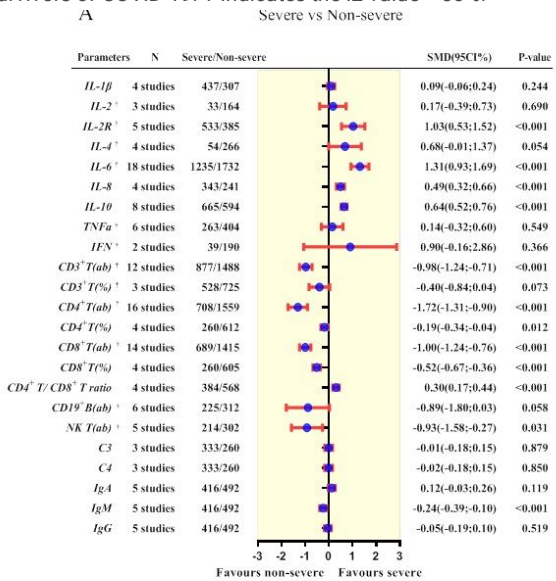


Figure 5 Summary results of the comparisons of immunological variables between (A) patients with severe and non-severe COVID-19 and (B) between non-survivors and survivors of COVID-19. † indicates the I2 value > 50%.

Supplementary Files

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