WITHDRAWN:
The Association of HScore Parameters with Severe COVID-19: a Systematic Review and Meta-Analysis

Elham Roshandel
Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Terhan, Iran.
Mohammad Hossein Kazemi
Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Terhan, Iran. https://orcid.org/0000-0002-2899-9755
Bentolhoda Kuhestani Dehaghi
Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Terhan, Iran.
Hossein Bonakchi
Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Terhan, Iran.
Sayeh Parkhideh
Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Terhan, Iran.
Mahshid Mehdizadeh
Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Terhan, Iran.
Abbas Hajifathali
hajifathali@yahoo.com

Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Terhan, Iran.

Systematic Review

Keywords: COVID-19, hemophagocytic lymphohistiocytosis, HScore, meta-analysis

Posted Date: August 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-54490/v1

EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Several reports associated the severe Coronavirus disease-2019 (sCOVID-19) with secondary-haemophagocytic lymphohistiocytosis (sHLH) and proposed the HScore table for sCOVID-19 patients. We conducted a meta-analysis to found the possible association of HScore parameters with severity in COVID-19 patients. Systematic search was performed in Medline (PubMed), EMBASE, and Cochrane databases using all HScore and COVID-19 keywords. The records were screened based on inclusion/exclusion criteria. Random/fixed-effect models were employed. The pooled mean differences were estimated for continuous parameters. The pooled odds-ratio was estimated for fever. Eighteen studies met the criteria and included in the meta-analysis (2459 patients). Significant higher levels of leukocyte, neutrophil, aspartate-transaminase (AST), ferritin, and fibrinogen, as well as lower level of lymphocyte, platelet, and hemoglobin were found in sCOVID-19 patients compared to non-severe ones. Fever was nearly associated with 2 times increased odds of sCOVID-19 (p-value = 0.051). Lymphopenia, thrombocytopenia, hypohemoglobinemia, hyperferritinemia, high levels of AST, and fever are common features of both sCOVID-19 and HLH. However, leukocytosis, neutrophilia, and hyperfibrinogenemia found in sCOVID-19 contrast with HScore. Conclusively, HScore parameters could be risk factors for the severity of COVID-19. However, some parameters' roles are contradictory, suggesting further investigation and a new way of HScore interpretation for sCOVID-19 patients.

Introduction

The pandemic coronavirus disease 2019 (COVID-19) has involved 18,354,342 cases with a mortality of 696,147 by August 5th, 2020 [1]. There is a wide range of clinical and laboratory findings in COVID-19 patients such as fever, dry cough, myalgia, changes in white blood cell (WBC), lymphocytopenia, high levels of c-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin, ferritin, aspartate/alanine transaminase (AST/ALT), inflammatory cytokines, along with coagulative disorders manifested with high levels of fibrinogen, D-dimer, prothrombin time (PT), and international normalized ratio (INR) [2].

National Health Commission of China released guidelines that stratified COVID-19 patients into four categories: mild, moderate, severe, and critical [3]. The majority of patients are asymptomatic or show mild/moderate symptoms. However, a considerable part of cases develops severe/critical manifestations with a high mortality rate emphasizing the importance of biomarkers for better managing this group. A subset of COVID-19 patients is observed to develop acute respiratory distress syndrome (ARDS) threatening their lives. These severe/critical patients experienced fever, hyperferritinemia, and a massive release of inflammatory cytokines known as cytokine storm [4]. Identification of clinical and laboratory parameters associated with severe disease could help the clinicians to manage the outcomes.

Recently, the HScore application has been suggested to detect hyperinflammatory syndrome in severe COVID-19 (sCOVID-19) patients to identify the patients for whom immunosuppressive agents could decrease mortality [5]. The primary application of HScore is in diagnosing secondary hemophagocytic lymphohistiocytosis (sHLH), which is rare but could be triggered by viral infections and resembles the cytokine profile and clinical features of sCOVID-19 [5–7].

A key laboratory finding in sHLH is hyperferritinemia [8,9], which is found in many sCOVID-19 cases [4–6]. Moreover, abnormal liver function and coagulopathy being in both COVID-19 and sHLH suggest that a subgroup of COVID-19 pneumonia cases also have sHLH [10,11]. However, there are still controversies in the association of COVID-19 and sHLH, highlighting the necessitate to find out the possible association between HScore parameters and the severity of COVID-19 patients.

The HScore is comprised of several clinical and laboratory factors, including fever, one- or multi-lineage cytopenias, organomegaly, triglyceridemia, hyperferritinemia, hypofibrinogenemia, hypohemoglobinemia, high aspartate transaminase (AST), hemophagocytosis on bone marrow aspirate, and prolonged use of immunosuppressants [12].

In this meta-analysis, we attempted to find the possible association between parameters listed in the HScore with the severity of the COVID-19 patients.

Materials And Methods

Search strategy

The conducted meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic electronic search was carried out separately by two independent authors (MHK and BHKD) in Medline (PubMed), EMBASE, and Cochrane using the keywords listed in Table 1. Keywords for COVID-19 were searched in title/abstract while the keywords related to HScore were searched in full-text/all fields. Regarding the date of COVID-19 occurrence, the records published between January 1st - June 22nd, 2020, were imported to the reference manager software EndNote X8 for further management, including removal of duplicates and identification of potentially eligible records. References of selected articles were reviewed to prevent the loss of data sources.

Eligibility criteria

We systemically reviewed the studies that investigated the association of each HScore variables with severity in COVID-19 patients. Two reviewers (MHK and BHKD) independently screened the abstracts and full text according to the eligibility criteria. A consensus or a third reviewer resolved disagreements.

The inclusion criteria were: 1. Types of studies: retrospective, prospective, descriptive, or observational research articles reported the relationship between HScore variables (fever, any cytopenias, hemoglobin, ferritin, AST, organomegaly, triglyceride, fibrinogen, and any immunosuppressive conditions) and severity of patients with COVID-19; 2. Subjects: patients diagnosed with COVID-19; 3. Exposure/intervention: studies classified COVID-19 patients in severe (critical or severe) versus non-severe (moderate or mild) condition according to the National Health Commission of China guidelines for COVID-19 diagnosis [3]; 4.

Outcome indicator: the odds ratios (OR) with 95% confidence intervals (CI) for fever, and the mean or median with standard deviation (SD) or interquartile range (IQR)/simple range (SR), respectively for other variables were included.

The exclusion criteria were: 1. Case reports/series, reviews, editorials, letters, commentaries, guidelines, perspectives; 2. Studies with insufficient data; 3. Studies without stratification on severity; 4. Studies enclosed less than two of indicators (e.g., only fever).

Data extraction

Data extraction was performed by two authors who searched and screened records. The mean or median values (with SD and IQR/SR, respectively) of all HScore variables were extracted. After reviewing the final records, the variables such as eosinophil, basophil, monocyte, triglyceride, and immunosuppression, which are available in less than five studies, were not entered the analysis. Therefore, the following variables were included: fever, WBC, lymphocyte, neutrophil, platelet, AST, ferritin, fibrinogen, and hemoglobin. Due to the higher frequency of mean/median of indicators rather than OR, and variation in cut-off values used for laboratory indices, the mean/median with SD/IQR(or SR) were included for variables. Only the data for fever was included as OR with CI.

The outcome of interest was severity status, based on which the patients were stratified as severe and non-severe groups. Severe groups comprised of severe and/or critical patients with any of the following criteria: respiratory rate (RR) ³ 30 breaths/min; oxygen saturation at rest ≤ 93%; arterial partial oxygen pressure (PaO2)/ fraction of inspired oxygen (FiO2) £ 300 mmHg; respiratory failure requiring mechanical ventilation; patients with shock and organ failure requiring ICU care. The non-severe group consisted of mild and/or moderate patients with one of the following criteria: mild clinical symptoms, and no radiological sign of pneumonia; fever and respiratory symptoms with pneumonia signs in radiological imaging.

Statistical analysis

The meta-analysis was performed using STATA software version 16. We used the inverse variance method to estimate the pooled mean differences (MDs) with 95% CI for cell blood parameters, AST, ferritin, and fibrinogen. Also, the Mantel-Haenszel method was used to estimate the pooled OR with 95% CI for dichotomous fever variable. I^2 and Tau^2 measures and Q test based on Chi^2 were applied to assess the heterogeneity. Based on the I^2 index (>50% and <50%), the random-effects model using restricted maximum likelihood method and the fixed-effects model were employed, respectively. Publication bias was assessed using the funnel plot; the Egger and the Begg tests for continuous variables and the Harbord test for binary outcomes were used. The significance level was set at 0.05. Due to the unavailable of the effect size of interest, the mean and SD of variables were estimated from sample size, median and IQR/SR according to Lou et al. [13] and Wan et al. [14].

Results

Study selection and baseline characteristics

Based on the described search strategy, a total of 26151 studies were identified in the three searched online databases. Following the removal of duplicates and screening all records, 18 studies meeting the predetermined eligibility criteria were imported in the meta-analysis [15–31]. The article number and reason for exclusion in each screening steps are depicted in Fig 1. Accumulatively, 2459 patients were included in the quantitative analysis, among which 710 patients were in severe/critical condition, and the rest (1737 cases) classified as mild/moderate disease. The baseline characteristics of the studies are presented in Table 2.

Meta-analysis

Blood cell parameters

The I^2 index showed that there was a heterogeneity for WBC (I^2 = 73.52%, p-value=0.0006), lymphocyte count (I^2 = 66.83%, p-value = 0.001), and neutrophil count (I^2 = 64.53%, p-value < 0.0001) variables. Therefore, a random-effects model was used for these variables. There was no heterogeneity for hemoglobin and platelet variables and the fixed-effects model was performed (I^2 = 0%, p-value = 0.52 and I^2 = 0%, p-value = 0.51, respectively). The results of random-effects meta-analysis showed that in twelve studies [15,16,18,19,22–24,26,28–30,32], patients with sCOVID-19 had higher WBC compared to patients with non-severe COVID-19 which it was significant (MD = 1.23 [0.29,2.17], p-value = 0.01) (Fig 2A). For lymphocyte, although one of the studies [19] showed that patients with sCOVID-19 had higher lymphocyte count compared to non-severe COVID-19 ones (MD = 0.01 [-0.34,0.36]), the pooled results of thirteen studies [15,16,18,19,22–26,28–30,32] showed that lymphocyte count in patients with sCOVID-19 was significantly lower compared to non-severe COVID-19 patients (MD = -0.38 [-0.47,-0.29], p-value < 0.0001) (Fig 2B). In twelve studies [15,18,19,22–26,28–30,32], patients with severe conditions had significantly higher neutrophil count than those with non-severe complications (MD = 2.01 [1.22,2.80], p-value = 0.005) (Fig 2C). The results of fixed-effects meta-analysis on the ten studies [15,16,18,19,22–24,26,28,30] showed that platelet count in patients with sCOVID-19 was significantly lower compared to patients with non-severe COVID-19 (MD = -11.7 [-23.03,-0.38], p-value = 0.042) (Fig 2D). Finally, in eleven studies [15,16,18,19,22–24,26,28,30,32] those categorized as severe patients had lower hemoglobin compared to non-severe patients which it was significant (MD = -4.95 [-7.48,-2.41], p-value = 0.0001) (Fig 2E).

Fever

The results of random-effects meta-analysis (I^2 = 70.71%, p-value < 0.0001) on twelve studies [15,16,18,19,22–26,28,30,32] showed that fever was nearly associated with 2 times increased odds of sCOVID-19 (OR = 2.01 [0.99,4.09], p-value = 0.051) (Fig 3A).

AST

There was no heterogeneity for AST and a fixed-effects model was employed (I^2 = 45.09%, p-value = 0.06). The results of meta-analysis on ten studies [15,16,18,19,21–23,25,30,32] showed that AST in patients with sCOVID-19 was significantly higher than non-severe ones (MD = 13.85 [11.16,16.53], p-value = <0.0001) (Fig 3B).

Ferritin

There was heterogeneity for ferritin and a random-effects model was used (I^2 = 68.20%, p-value = 0.02). The results of meta-analysis on five studies [19,22,29,30,32] showed that ferritin in patients with sCOVID-19 was significantly higher than those with non-severe disease (MD = 437.25 [100.37,774.13], p-value = 0.01) (Fig 3C).

Fibrinogen

The results of random-effects meta-analysis (I^2 = 68.80%, p-value = 0.009) on six studies [15,20,22,23,30,31] showed that fibrinogen in patients with sCOVID-19 was significantly higher compared to patients with non-severe COVID-19 (MD = 0.96 [0.46,1.54], p-value = 0.0001) (Fig 3D).

Publication bias

Regression-based Egger test showed small-study effects for fibrinogen and lymphocyte count (p-values = 0.002 and 0.001, respectively) and no small-study effects for AST, hemoglobin, neutrophil count, platelet count and WBC (p-values = 0.28, 0.16, 0.70, 0.83, and 0.29, respectively). For ferritin, regression-based Egger test showed that there were small-study effects (p-value = 0.01), but the Begg test showed no small-study effects (p-value = 0.08). The Harbord test showed that there were no small-study effects for fever (p-value = 0.56) (Fig S1).

Discussion

Fatal multi-organ failure, hyper-inflammation, cytokine storm, and coagulative disorders suggest that COVID-19 is not only an airways disease but an air-borne systemic complication [2]. Daily increasing the disease and mortality statistics with the growing evidence of severe infection in youngsters and even children emphasize the necessitate of developing preventive and curative approaches. The interesting hypothesis of using HLH score (HScore) in treatment of COVID-19 patients stems from sHLH manifestation in sCOVID-19 patients including hemophagocytosis in bone marrow (BM) aspirates, hyperferritinemia, and cytopenia [5]. Although some evidence reported that sCOVID-19 could cause sHLH, it might be soon to associate the sCOVID-19 with sHLH [6,7,33]. However, the hyper-inflammatory condition such as the release of a massive amount of cytokines/chemokines, including interleukin (IL)-6, IL-1b, tumor-necrosis factor (TNF)-a, IL-7, IL-8, granulocyte/monocyte colony-stimulating factor (GM-CSF), G-CSF, interferon gamma-induced protein (IP-10 / CXCL10), monocyte chemoattractant protein-1 (MCP-1 / CCL2), and macrophage inflammatory protein 1(MIP-1a / CCL3) is seen in both sHLH and sCOVID-19. Besides, the promising result of using immunosuppressive agents in both diseases, it could be concluded that the current therapeutic approaches for sHLH could be beneficial for sCOVID-19 [2]. Hence, it has been proposed that the HScore table might be applicable to determine the subgroup of COVID-19 patients for whom immunomodulators and immunosuppressants are propitious [5,33]. Although recent comments have questioned the application of HScore in the COVID-19 due to its limitation and low sensitivity [34], the new results suggest the overlap between the HScore clinical/laboratory parameters and those found in sCOVID-19 patients [2,5–7]. Therefore, the evaluation of HScore parameters as biomarkers for severity in COVID-19 will facilitate future decisions on COVID-19 managements. To the best of our knowledge, no meta-analysis yet explicitly focused on the relationship between HScore parameters and severity in COVID-19 patients.

There was heterogeneity in most of the variables and the outcome of interest (lymphocyte and neutrophil counts, fever, ferritin, and fibrinogen), so the random-effects meta-analysis approach was used to obtain a pooled estimate. This approach allows us to address heterogeneity that cannot be easily expressed by other factors. Regression-based Egger and nonparametric Begg tests were employed to assess the publication bias. Only two parameters, fibrinogen and lymphocyte, had publication bias. However, ferritin showed publication bias based on the Egger method, and no publication bias is seen in ferritin, based on the Begg method. When the number of studies is small, the power of Egger test to detect bias is low [35]. The heterogeneity of studies might be due to the other numerous causes which are not well investigated yet in COVID-19. On the other hand, the aim of our study was to evaluate the effect of HScore parameters on the severity of COVID-19. The effects of other clinical and laboratory factors were investigated in other meta-analyses [36–38].

Our results indicated that the sCOVID-19 patients had leukocytosis and neutrophilia, as well as lymphopenia and thrombocytopenia. Lymphopenia and thrombocytopenia are in common with sHLH and also reported previously to have an association with sCOVID-19 [39,40]. Though, leukocytosis and neutrophilia that are seen in sCOVID-19 is in contrast with HScore [5,38]. Moreover, lower hemoglobin is found in sCOVID-19 and sHLH as well [5]. The other parameters found in our study that are parallel to sHLH is the high fever and high levels of AST and ferritin. We found that hyperfibrinogenemia is associated with sCOVID-19, while the hypofibrinogenemia is a sHLH biomarker [5,12].

There are some points which should be considered: 1. The HScore is based on the criteria with specific cut-offs and scores. The sum of scores leads us to HLH diagnosis. Due to the lack of data on COVID-19, our study is not based on the cut-off defined in HScore. Further investigations are required to precisely calculate the HScore in COVID-19 patients; 2. Some HScore parameters, such as ferritin, should be at a very high level to be associated with HLH, while this high level is not common in COVID-19; 3. According to the high heterogeneity of included studies, the results should be interpreted cautiously and further confirmed by including other confounders; 4. We have searched all keywords related to the HScore parameters in COVID-19 patients and retrieved the records. Evidence on some of the parameters such as triglyceride, organomegaly, history of immunosuppressive therapy, or immunocompromised conditions as well as monocyte-, basophil-, eosinophil-, and red blood cell (RBC)-related cytopenia in COVID-19 is limited. Hence, they were not included in the meta-analysis. By progression the studies on these parameters in COVID-19, future meta-analyses could comprise all HScore parameters to elucidate the possible relationship with severity in COVID-19.

In conclusion, our study indicated that the majority of HScore parameters are associated with severity in COVID-19; Some of which such as lymphopenia, thrombocytopenia, low hemoglobin level, fever, as well as high levels of AST and ferritin, are associated with sCOVID-19 and HLH. However, leukocytosis, neutrophilia, and hyperfibrinogenemia, which are observed in sCOVID-19 had contradictory effect on HLH. HScore parameters could be risk factors for the severity of COVID-19. However, some parameters' roles are contradictory, suggesting further investigation and a new way of HScore interpretation in sCOVID-19 patients.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgment

The authors would like to thank Hematopoietic Stem Cell Research Center and Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for providing the possibility of performing the study.

Conflict of Interest: The authors declare that they have no conflict of interest.

Authors' contribution: ER. Contributed in study concept and design, conducting the study and manuscript writing; MHK. Wrote the manuscript, contributed in systematic search, literature review, screening records, and table preparation; BHKD. Contributed in systematic search, literature review, screening records, and table preparation; HB. Performed statistical analysis and prepared plots; SP. and MM. critical evaluation of the study, data interpretation, and revise the manuscript; AH. Supervised the project and revise the manuscript; All authors approved final draft of manuscript.

References

[1] WHO Coronavirus Disease (COVID-19) Dashboard.

[2] Skevaki C, Fragkou PC, Cheng C, Xie M, Renz H. Laboratory characteristics of patients infected with the novel SARS-CoV-2 virus. J Infect. 2020;

[3] Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) [Internet]. Available from: http://en.nhc.gov.cn/2020-03/29/c_78469.htm. accessed on July 12 2020.

[4] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475–81.

[5] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Vol. 395, Lancet. 2020. p. 1033–4.

[6] Prilutskiy A, Kritselis M, Shevtsov A, Yambayev I, Vadlamudi C, Zhao Q, et al. SARS-CoV-2 Infection Associated Hemophagocytic Lymphohistiocytosis: An autopsy series with clinical and laboratory correlation. medRxiv. 2020.

[7] Faguer S, Del Bello A, Abravanel F, Nicolau-Travers M-L, Kamar N. Tocilizumab for Hemophagocytic Syndrome in a Kidney Transplant Recipient With COVID-19. Ann Intern Med. 2020.

[8] Sharif K, Vieira Borba V, Zandman-Goddard G, Shoenfeld Y. Eppur Si Muove: ferritin is essential in modulating inflammation. Clin Exp Immunol. 2018;191(2):149–50.

[9] Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med. 2013;11(1):185.

[10] Bracaglia C, Prencipe G, De Benedetti F. Macrophage activation syndrome: different mechanisms leading to a one clinical syndrome. Pediatr Rheumatol. 2017;15(1):1–7.

[11] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar;

[12] Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613–20.

[13] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785–805.

[14] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14(1):135.

[15] Zhou Y, Han T, Chen J, Hou C, Hua L, He S, et al. Clinical and Autoimmune Characteristics of Severe and Critical Cases of COVID-19. Clin Transl Sci. 2020 Apr;

[16] Chen Q, Zheng Z, Zhang C, Zhang X, Wu H, Wang J, et al. Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China. Infection. 2020 Apr;1–9.

[17] Zhao X-Y, Xu X-X, Yin H-S, Hu Q-M, Xiong T, Tang Y-Y, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study. BMC Infect Dis. 2020 Apr;20(1):311.

[18] Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. Diagnosis (Berl). 2020 May;7(2):91–6.

[19] Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am J Transplant . 2020 Apr;

[20] Zou Y, Guo H, Zhang Y, Zhang Z, Liu Y, Wang J, et al. Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. Biosci Trends. 2020 Apr;

[21] Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int. 2020 Apr;

[22] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020 May;55:102763.

[23] Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med. 2020 Jun;201(11):1380–8.

[24] Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. 2020 Mar;323(15):1488–94.

[25] Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol. 2020;31(6):1157–65.

[26] Yao Q, Wang P, Wang X, Qie G, Meng M, Tong X, et al. Retrospective study of risk factors for severe SARS-Cov-2 infections in hospitalized adult patients. Polish Arch Intern Med. 2020;

[27] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;

[28] Zheng Y, Zhang Y, Chi H, Chen S, Peng M, Luo L, et al. The hemocyte counts as a potential biomarker for predicting disease progression in COVID-19: a retrospective study. Clin Chem Lab Med. 2020 Jun;58(7):1106–15.

[29] Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI insight. 2020 May;5(10).

[30] Medetalibeyoğlu A, Şenkal N, Çapar G, Köse M, Tükek T. Characteristics of the initial patients hospitalized for COVID-19: a single-center report. Turkish J Med Sci. 2020 Jun;

[31] Di Micco P, Russo V, Carannante N, Imparato M, Rodolfi S, Cardillo G, et al. Clotting Factors in COVID-19: Epidemiological Association and Prognostic Values in Different Clinical Presentations in an Italian Cohort. J Clin Med. 2020 May;9(5).

[32] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020 May;130(5):2620–9.

[33] Loscocco GG. Secondary hemophagocytic lymphohistiocytosis, HScore and COVID-19. Vol. 112, Int J Hem. 2020. p. 125–6.

[34] Leverenz DL, Tarrant TK. Is the HScore useful in COVID-19? Lancet. 2020;395(10236):e83.

[35] Fagerland MW. Evidence-based medicine and systematic reviews. Res Med Biol Sci. 2015;431–61.

[36] Zhang Z-L, Hou Y-L, Li D-T, Li F-Z. Laboratory findings of COVID-19: a systematic review and meta-analysis. Scand J Clin Lab Invest. 2020 May;1–7.

[37] Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.

[38] Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020 Jun;58(7):1021–8.

[39] Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020 Jul;506:145–8.

[40] Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J intensive care. 2020;8:36.

Tables

Table 1. Keywords used for search in databases

	Searched field	Keywords
1	Laboratory and Clinical general findings	Laborator*, Clinic*
2	Temperature	Temperature*, Fever*, Heat*
3	Cytopenia	Cytopenia*, Pan-cytopenia*, Pan cytopenia*, Leukopenia*, Anemia*, Neutropenia*, Thrombocyto*, Lymphopenia*, White blood cell*, "WBC", leukocyt*, lymphocyt*, neurophil*, monocyt*, eosinophil*, basophil*, platelet*
4	Hemoglobin	Hemoglobin,
5	Ferritin	Ferritin*, Isoferritin*
6	Serum aspartate aminotransferase	Glutamate Aspartate Transaminase*, glutamic oxaloacetic transaminase*, glutamat oxaloacetate transaminase*, "SGOT", Aspartate Aminotransferase*, Aspartate Transaminase*, Transaminase*, "AST"
7	Organomegaly	Organomegal*, Hepatomegal*, Splenomegal*, Hepatosplenomegal*
8	Triglycerides	Triglyceride*, Triglyceridemia*, Hypertriglyceridemia*, Triacylglycerol*, Triacylglyceride*
9	Fibrinogen	Fibrinogen*, Factor I, Factor 1, Factor-I, Factor-1
10	Known Immunosuppressant	Immune deficiency*, Immune-deficiency*, Immunodeficiency*, Immune-deficient*, Immunodeficient*, Immune-compromised*, Immune compromised*, mmunocompromised*, Immunosuppressive*, Immune suppressive*, Immune-suppressive*, Immunosuppressant*, Immunosuppression*, Immune suppression*, Immune-suppression*, HIV, AIDS*, Chemotherap*, Methotrexate*, Glucocorticoids*, Cortone* Cortisone*, Hydrocortisone*, Prednisone*, Deltasone*, Orasone*, Budesonide*, Entocort*, Prednisolone*, Millipred*, Methylprednisolone*, Dexamethasone*, Cyclosporine*, Neoral*, Sandimmune*, SangCya*, Azathioprine*, Azasan*, Imuran*, Mycophenolate*, Mycophenolate mofetil*, CellCept*, Myfortic*, Sphingosine 1, Sphingosine-1-Phosphate*, Sphingosine-1 Phosphate*, Phosphate inhibitor*, Fingolimod*, FTY720*, Tacrolimus*, Astagraf*, Envarsus*, Prograf*, Tofacitinib*, Xeljanz*, Sirolimus*, Rapamune*, Everolimus*, Afinitor*, Zortress*, Leflunomide*, Arava*, Abatacept*, Orencia*, Adalimumab*, Humira*, Anakinra*, Kineret*, Certolizumab*, Cimzia*, Etanercept*, Enbrel*, Golimumab*, Simponi*, Infliximab*, Remicade, Ixekizumab*, Taltz*, Natalizumab*, Tysabri*, Rituximab*, Rituxan*, Secukinumab*, Cosentyx*, Tocilizumab*, Actemra*, Ustekinumab*, Stelara, Vedolizumab*, Entyvio*, Basiliximab*, Simulect*, Daclizumab*, Zinbryta*, Antilymphocyte serum*, Antilymphocyte antibod*, Antilymphocyte Globulin*, Antithymphocyte Globulin*, Anti-thymphocyte Globulin*, Anti thymphocyte Globulin*, Antilymphocyte immunoglobulin*, Anti-rejection therap*, Anti rejection therap*, Antirejection therap*, Transplantation, Transplant*, Graft*
11	COVID-19	Covid*, sars-cov-2*, corona virus*, coronavirus*, cv 19, cv-19 2019-ncov, ncov*, Wuhan coronavirus*, Wuhan pneumonia*,

All words were searched by an star in ending to cover all the possible variants of words. The keywords in sections 1-10 were searched with "OR" together and the keywords for COVID-19 (section 11) were searched with "OR" separately. The results of these two searches are then retrieved with "AND".

Table 2. The baseline characteristics for included studies

Study	Country	Sample size	Male %	Severe/non-severe patient	Age (median or mean years)	Severe cases in fever/total fever cases (%)	WBC ´10^9/L (severe/non-severe)	Lymphocyte ´10^9/L (severe/non-severe)	Neutrophil ´10^9/L (severe/non-severe)	Platelet ´10^9/L (severe/non-severe)
Chen et al. (32)	China	21	81	11/10	56	10/20 (50)	8.3/4.5	0.7/1.1	6.9/2.7	157/175.6
Zhang et al. (21)	China	115	42.6	31/84	49.52	-	-	-	-	-
Liu et al. (22)	China	40	37.5	13/27	48.7	13/36 (36.1)	6.6/3.9	0.6/1.1	4.7/2.0	186.6/181.4
Zou et al. (20)	China	303	52.1	26/277	51	-	-	-	-	-
Zhou et al. (15)	China	21	61.9	13/8	66.1	12/19 (63.1%)	10.68/9.3	0.66/0.79	9.47/7.83	204.23/219.25
Chen et al. (16)	China	145	54.5	43/102	47.5	39/109 (35.7)	6/5	0.9/1.3	-	192/204.5
Zhao et al. (17)	China	91	53.8	30/61	46	-	-	-	-	-
Aggarwal et al. (18)	USA	16	75	8/8	67	8/15 (53.5)	13.46/6.4	0.84/0.88	6.7/3.8	209.5/211.5
Pereira et al. (19)	USA	90	59	27/63	57	13/63 (20.6)	4.4/5.66	0.84/0.7	3.64/4.1	186/174
Feng et al. (23)	China	422	56.4	70/352	53	64/341 (18.7)	7.19/5.15	0.82/1.13	5.99/3.39	181/185
Young et al. (24)	Singapore	18	50	6/12	47	6/13 (46.1)	3.4/4.6	1.1/1.2	1.8/2.8	156/159
Pei et al. (25)	China	200	51.5	56/144	56.3	52/178 (29.2)	-	0.55/1.01	5.79/2.99	-
Yao et al. (26)	China	96	37.5	13/83	52	11/72 (15.2)	5.57/4.65	0.79/1.41	3.33/2.53	145/195
Li et al. (27)	China	548	50.9	269/279	60	228/476 (47.9)	-	-	-	-
Zheng et al. (28)	China	141	52.4	29/112	47	25/98 (25.5)	6.1/4.9	0.7/1.3	5.1/3.2	158/203
Wang et al. (29)	China	45	57	30/15	57.11	-	8.7/5.2	0.5/0.9	7.7/3.8	-
Medetalibeyoğlu et al. (30)	Turkey	68	69.1	11/57	55.8	13/45 (28.8)	5.58/5.67	0.56/1.04	4.66/4.04	189.5/186.68
Di Micco et al. (31)	Italy	67	70	24/43	-	-	-	-	-	-
Total	-	2459	-	710/1737	-	-	-	-	-	-

WBC. White blood cells; AST. Aspartate-aminotransferase

Figures

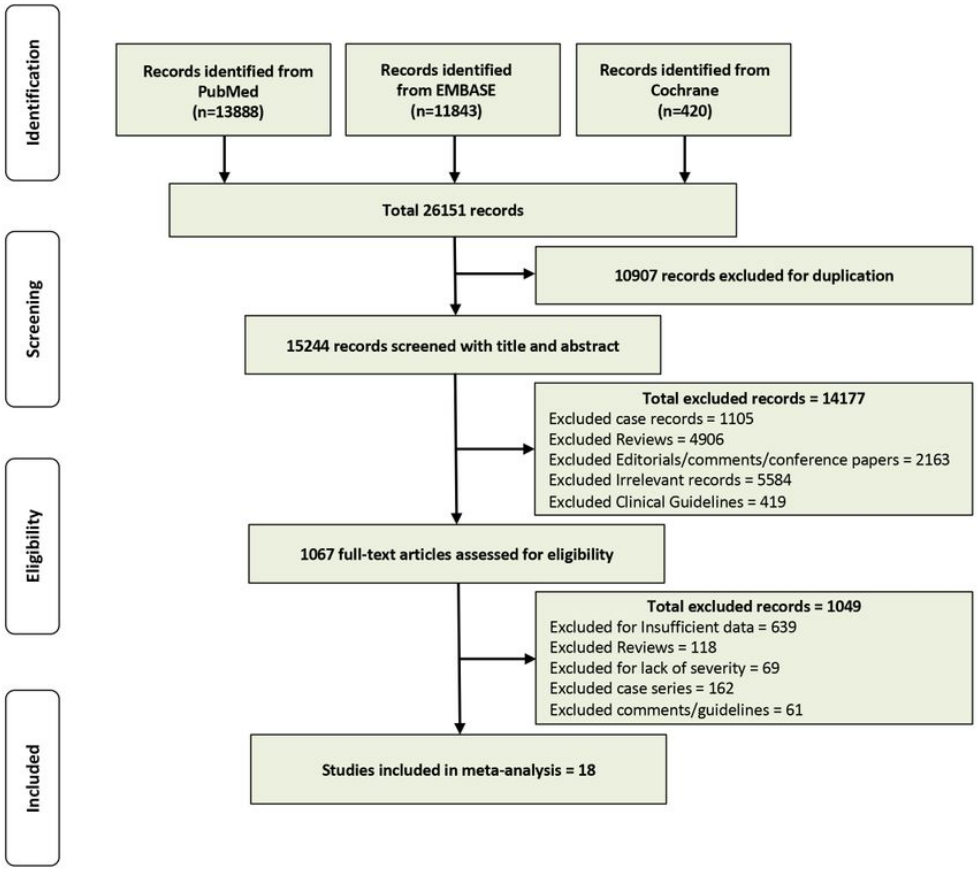

Figure 1

The PRISMA study flow diagram

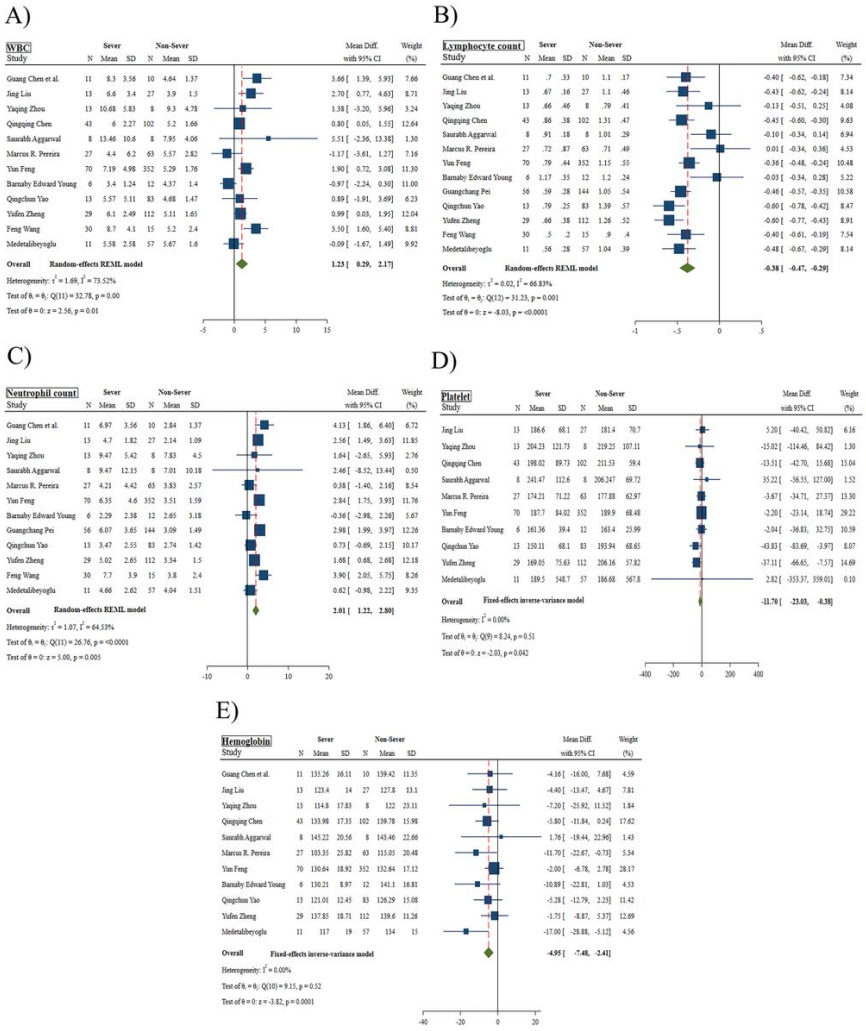

Figure 2

Forest plots of blood cell parameters

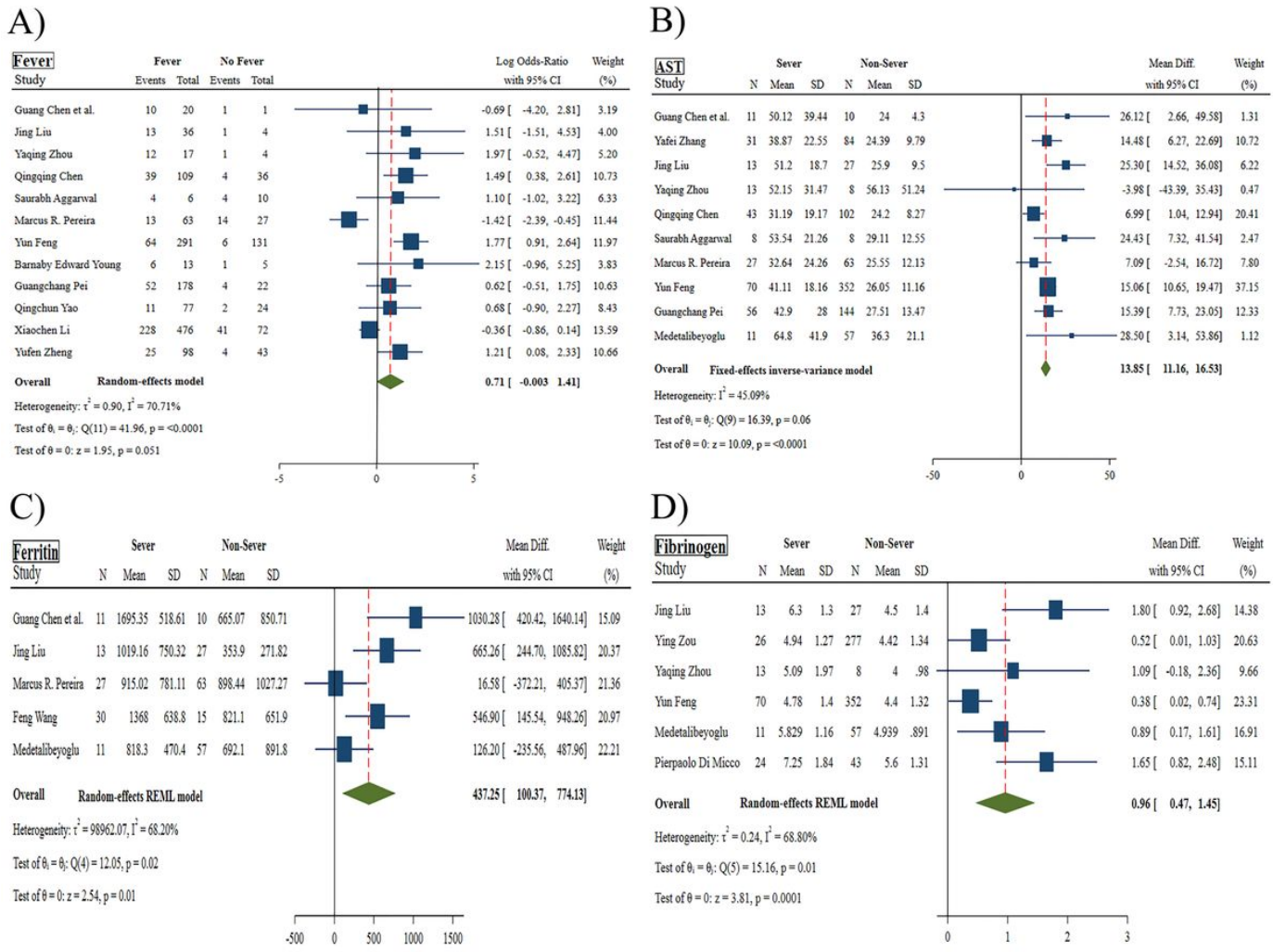

Figure 3

Forest plots of fever, AST, ferritin, and fibrinogen

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SuplementaryFigure1.jpg