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

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Systematic Review

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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 necessity 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, triglycerideremia, 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) ≥ 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 variable fever. I² and Tau² measures and Q test based on Chi² were applied to assess the heterogeneity. Based on the I² 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 I² index showed that there was a heterogeneity for WBC (I² = 73.52%, p-value=0.0006), lymphocyte count (I² = 66.83%, p-value = 0.001), and neutrophil count (I² = 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 I² = 0%, p-value = 0.52 and I² = 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 [15,16,18,19,22–24,26,28,30,32] 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 (I² = 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 = 0.001) (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 necessity 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 sCOVID-19 with sHLH [6,7,33]. However, the hyper-inflammatoriy condition such as the release of a massive amount of cytokines/chemokines, including interleukin (IL)-6, IL-1β, tumor-necrosis factor (TNF)-α, IL-7, IL-8, granulocyte/moноocyte 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-1α / 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 management. 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

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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


Tables

Table 1. Keywords used for search in databases

<table>
<thead>
<tr>
<th>Searched field</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory and Clinical general findings</td>
<td>Laborator*, Clinic*</td>
</tr>
<tr>
<td>Temperture</td>
<td>Temperature*, Fever*, Heat*</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Hemoglobin,</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Ferritin*, Isoferritin*</td>
</tr>
<tr>
<td>Serum aspartate aminotransferase</td>
<td>Glutamate Aspartate Transaminase*, glutamic oxaloacetic transaminase*, glutamat oxaloacetate transaminase*, SGOT*, Aspartate Aminotransferase*, Aspartate Transaminase*, Transaminase*, AST*</td>
</tr>
<tr>
<td>Organomegalaly</td>
<td>Organomegal*, Hepatomegal*, Splenomegal*, Hepatosplenomegal*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Triglyceride*, Triglyceridemia*, Hypertriglyceridemia*, Triacylglycerol*, Triacylglyceride*</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Fibrinogen*, Factor I, Factor 1, Factor-I, Factor-1</td>
</tr>
</tbody>
</table>

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

- SupplementaryFigure1.jpg