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Hematological Changes in Patients with Severe COVID-19: Systematic Review and Meta-Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. Authors LGC and PIMS designed the study, wrote the protocol, wrote the first draft of the manuscript and managed the literature searches. Authors MMSN and MP managed the analyses of the study. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Aims: To produce a systematic review with meta-analysis on the hematological manifestations of COVID-19, comparing the changes among the clinical severity groups.
Study Design: We conducted a systematic review with meta-analyses.
Methodology: A systematic review was carried out based on the PRISMA 2020 protocol in Medline/Pubmed, Embase, LILACS and SciElo databases. A standardized mean difference was calculated to assess the differences between the groups, with a confidence interval of 95%. Heterogeneity was calculated using the Chi-square test and the I^2 test. Significant heterogeneity was defined as $p<0.10$ or $I^2>50\%$.

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Results: The systematic review search identified a total of 2682 articles, and at the end of the screening, 55 were selected for review and 16 for meta-analysis. The selected articles enrolled 13,289 participants, 10,312 with a mild to moderate clinical condition and 3977 with a severe to critical clinical condition. When comparing the severe disease group with the mild disease group, it was found that the mean values of leukocytes, neutrophils, C-reactive protein (CRP), ferritin, fibrinogen, and prothrombin time (PT) were significantly higher, and the lymphocyte count was significantly lower in the severe group.
Conclusions: Individuals with severe COVID-19 had reduced lymphocyte count and elevated leukocytes, neutrophils, CRP, ferritin, fibrinogen, and PT.

Keywords: COVID-19; SARS-CoV-2; hematological tests.

1. INTRODUCTION

In December 2019, the city of Wuhan, capital of the Chinese province of Hubei, became the center of an outbreak of pneumonia of unknown cause. Initial reports pointed out that the first cases were associated with the seafood market in Huanan, where live birds and wild animals were traded. However, the cases spread quickly between people and other provinces and countries [1,2].

In January 2020, the novel coronavirus was identified and genetically sequenced from a patient's oropharyngeal sample. Initially, the virus was named "novel coronavirus 2019" (2019-nCov) by the World Health Organization (WHO), and its infection was named "coronavirus disease 2019" (COVID-19). Nevertheless, a study group of the International Committee on Taxonomy of Viruses (ICTV) proposed the name SARS-CoV-2 due to its multiple similarities with the virus that causes Severe Acute Respiratory Syndrome (SARS) [3].

Due to the severity of the outbreak and the potential for the disease to spread globally, the WHO declared a state of emergency in late January and a pandemic in March 2020. Compared to other emerging viruses such as Ebola, H7N9, SARS-CoV and MERS-CoV, the SARS-CoV-2 has lower pathogenicity and medium transmissibility [4].

In a few months, COVID-19 spread to all countries in the world. Until May 2022, there were more than 510 million confirmed cases and over six million deaths worldwide [5].

Common symptoms in hospitalized patients with COVID-19 include fever (70%-90%), dry cough (60%-86%), dyspnea (53%-80%), fatigue (38%), myalgia (15%-44%), nausea/vomiting or diarrhea (15%-39%), headache, asthenia (25%) and rhinorrhea (7%). Anosmia and ageusia may be the only symptoms in approximately 3% of the cases [6].

Differentiating patients according to the severity of the condition is useful and essential to improve the cure rates of COVID-19 [7]. However, the criteria used to make such differentiation are mostly of respiratory factors, such as respiratory rate, oxygen saturation and progression of lung injury on imaging tests.

Although COVID-19 is primarily a respiratory system disease, cardiovascular, gastrointestinal and hematologic manifestations also occur. Among the most frequent hematological changes in patients with COVID-19, lymphopenia, elevation of inflammatory markers, coagulation abnormalities, and thrombocytopenia stand out [7,8].

Therefore, risk stratification allows for adequate targeting of human and technical resources. Thus, laboratory findings from the hematological investigation may represent a good alternative to determine the severity and prognosis of COVID-19, since they are simple, economical, quick and commonly available tests.

The systematic review and meta-analysis aimed to determine the main hematological manifestations of COVID-19, comparing the changes between the clinical severity groups.

2. METHODOLOGY

2.1 Search Strategy and Selection Criteria

A systematic literature review and meta-analysis was performed based on the MOOSE (Meta-analysis of Observational Studies in Epidemiology) [9], and the study protocol was elaborated and registered on PROSPERO website under the number CRD42022316654.

2.2 Eligibility Criteria

To define the eligibility criteria, the PECO structure was adopted. Thus, the population (P) was individuals diagnosed with COVID-19, the exposure (E) was individuals with severe illness, the comparator (C) was individuals with mild or moderate illness, and the outcome (O) was changes in hematological parameters.

Inclusion criteria were: (1) articles in Portuguese or English; (2) study with a population over 18 years old; (3) primary studies containing hematologic laboratory values of COVID-19 patients.

For this study, patients with mild to moderate conditions were considered to be those with pneumonia and other disease symptoms but without hypoxemia (SpO2 < 92%). Patients with severe or critical conditions were those with pneumonia and hypoxemia and/or SARS, shock, encephalopathy, myocardial injury, coagulation dysfunction, acute kidney injury, and heart failure.

Exclusion criteria were: (1) articles not available in the full version; (2) literature review studies, systematic review, expert opinion or editorials; (3) *in vitro* or animal research; (4) articles that did not compare parameters between severity groups; (5) articles with specific groups such as children, elderly or pregnant women.

2.3 Screening Process and Study Selection

The search was performed in Medline/PubMed, Cochrane Library, Embase, LILACS and SciElo databases, using articles published between 2020 and May 2022. It was used MeSH/DeCs descriptors and recurrent keywords in studies on the topic: (1) “COVID-19” or “SARS -CoV-2"; (2) “Hematological Tests”; (3) “Erythrocyte Count”, “Red Blood Cell Count”, “Leukocyte Count”, “Platelet Count”, “Ferritin”, “Coagulopathy”, “Prothrombin Time”, “Partial Thromboplastin Time”, “C-reactive protein", “Fibrinogen”.

The search strategy (Table S1) was not restricted to subject descriptors. It encompassed uncontrolled vocabulary, such as synonyms, acronyms, related terms and spelling variations, to increase search sensitivity and retrieve more articles. The terms were combined with the Boolean operators (OR, AND, NOT), and a record of the search strategy was carried out in each database.

The first step in evaluating the eligibility of articles consisted of reading the title and abstract. Two evaluators independently screened the works, and, in case of divergence, it was only necessary for one reviewer to judge the article eligible for it to move on to the next step, full-text reading. The second stage was also performed by two evaluators, using a standardized form containing the established eligibility criteria. For articles excluded at this stage, the reason for exclusion was described in the form.

2.4 Data Extraction

The data collected in a clinical record were: (1) name of the first author, (2) year of publication, (3) the country of origin of the study, (4) size of the study population, (5) a number of severe or critical cases (6) several, mild or moderate cases (7) the mean and standard deviation of the patients' laboratory parameters, such as of leukocytes, neutrophils, lymphocyte, C-reactive protein (CRP), ferritin, fibrinogen, prothrombin time (PT), Partial thromboplastin time (PTT), monocytes, platelets, D-dimer, hemoglobin and hematocrit.

2.5 Risk of Bias Assessment

The quality of cross-sectional studies was assessed using the Joanna Briggs Institute (JBI) scale for cross-sectional studies, in which the maximum score is 8 [10]. Cohort studies were evaluated using the Newcastle-Ottawa scale in which 6-9 points are considered low risk of bias and 4-5 points are regarded as medium risk of bias [11].

2.6 Data Analysis

To assess the difference between the parameters measured in patients in each group, a standardized mean difference was calculated, with a 95% confidence interval (CI) for continuous data. The random effects models to estimate the summary measure and the heterogeneity between studies was calculated using the chi-square test and the I^2 test. Significant heterogeneity was defined as $p<0.10$ or I^2 >50% [12].

The publication evaluation was carried out using the Egger test and funnel plot [13]. To evaluate

Table 1. Distribution of the number of participants, age and gender according to severity groups

Variable	Mild to moderate	Severe to critic
Number of participants	10,312	3977
Mean age	49.8	61.3
Gender		
Female	4589 (44,5%)	1310 (32,9%)
Male	4847 (47,0%)	2296 (57,7%)
No identification	876 (8,5%)	371 (9,3%)

the publication bias, we considered a minimum of 10 studies for the Egger regression model and funnel graph evaluation. [14] Stata software version 17.0 was used to perform the statistical analysis.

3. RESULTS AND DISCUSSION

3.1 Study Identification

The systematic search identified a total of 2682 articles in the main databases, including PubMed (n= 1142), Cochrane (n= 836), Embase (n= 573), LILACS (n= 98) and SciElo (n= 33). Of these, 118 articles were selected after reading the title and abstract. Therefore, 63 articles were excluded after full-text reading, of which three were duplicated, and sixty did not meet the inclusion criteria. Twenty-six articles did not compare hematological parameters between the clinical severity criteria groups, and thirty-three did not have adequate laboratory data. One article was in a language other than Portuguese or English. Ultimately, 55 eligible articles were included in the quantitative synthesis of this study (Fig. 1), and 16 were eligible for meta-analysis.

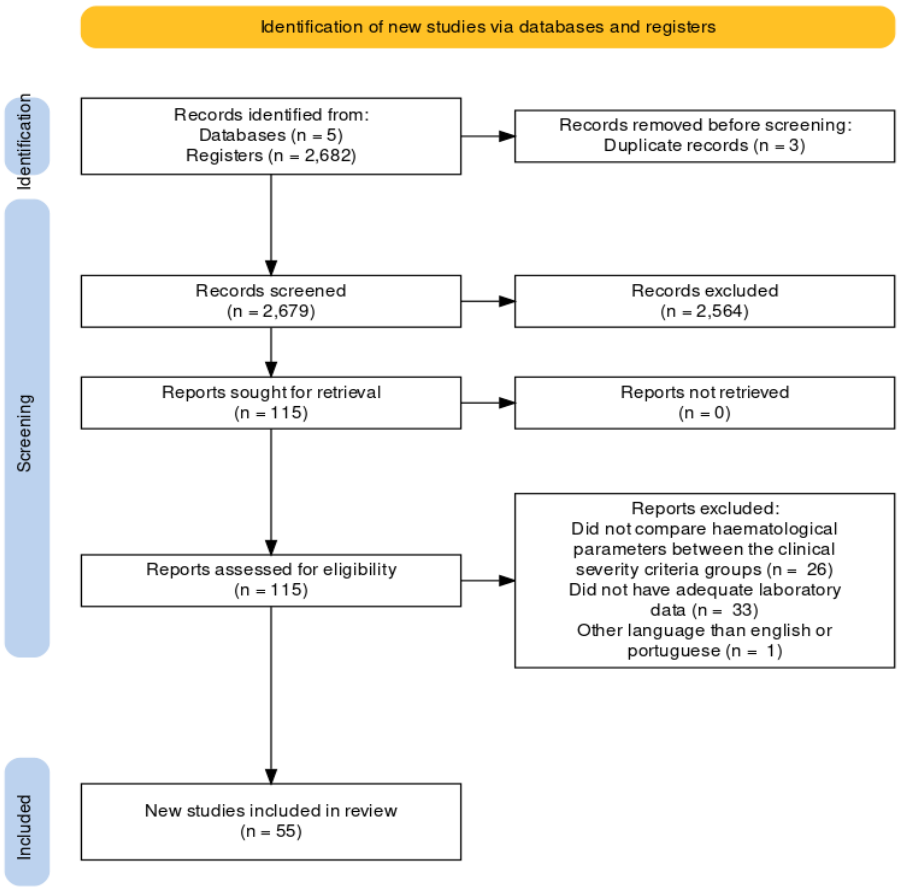


Fig. 1. Flow diagram for study selection

3.2 Study Characteristics

The selected studies were published in the years 2020 (n= 25) and 2021 (n= 30) and were mostly conducted in hospitals in China (n= 36), but also in Türkiye (n= 7), Pakistan (n= 2), Japan (n= 2), USA, Netherlands, India, Ecuador, Egypt, Qatar, Iran and Spain (all with n= 1). As for the design of the selected studies, 46 were retrospective studies, in which information was collected from medical records, and 9 were prospective cohort studies (Table S2).

In 25 studies, the clinical classification of participants regarding severity followed the guidelines for diagnosis and classification of COVID-19 proposed by the National Health Council of China [3], which: (1) mild: they have mild symptoms but no signs of pneumonia; (2) moderate: fever, respiratory symptoms, and radiological findings of pneumonia; (3) severe: oxygen saturation ≤ 92%, respiratory rate ≥ 30 ipm, arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg and pulmonary involvement of more than 50%; (4) critical: respiratory failure, pulmonary involvement >75%, need for mechanical ventilation, admission to the Intensive Care Unit (ICU), shock or multiple organ failure.

However, there was a variation in the cutoff point for oxygen saturation in severe cases, ranging from 85-94%. In addition, some studies considered only oxygen saturation (n= 2), the need for oxygen supplementation (n= 2) or ICU admission (n= 2) as the only severity classification criterion. In 6 studies, it was not possible to identify the clinical severity criteria used.

Regarding the form of grouping, most studies (n= 38) allocated participants into two groups: severe, non-severe (n= 20); mild, severe (n= 10); mild and moderate, severe and critical (n= 7) and; moderate, severe (n= 1). In 8 studies, participants with severe and critical clinical conditions were allocated to only one group called severe.

Studies report differences between groups about cell group counts and laboratory levels and parameters. Changes in some parameters are often described as potential biomarkers of severity.

Increased leukocyte and neutrophil counts, increased CRP levels, pro-inflammatory cytokines, D-dimer, fibrinogen degradation products, and ferritin are risk factors for progression to severity. Likewise, the reduction in the count of lymphocytes, eosinophils and platelets is also highlighted as the worsening of the clinical picture. Other prognostic predictors also mentioned are aspartate aminotransferase (AST), alanine aminotransferase (ALT), neutrophil-lymphocyte ratio (NRL), advanced age, presence of comorbidities, reduced blood pH and oxygen saturation.

3.3 Demographic Data

The selected articles enrolled 13,289 participants, 10,312 with a mild to moderate clinical condition and 3977 with a severe to critical clinical condition. The mean age was 49.8 years old for participants with mild to moderate illness (group 01) and 61.3 years old for the severe to critical illness group (group 02).

As for the distribution between sexes, women represented 44.5% of individuals in group 01 (n= 4589) and 32.9% (n= 1310) of individuals in group 02. Some articles did not stratify the gender according to severity groups. Therefore, there is a percentage in which it was impossible to identify the sex (Table S1).

3.4 Quality Analysis and Risk of Bias

The percentage of risk of bias for each item is demonstrated in Fig. 2. Most of the cross-sectional studies (93%) had a high risk of bias for the evaluation criteria (Fig. 2A). The requirements that scored most negatively among the selected studies included strategies to deal with confounding factors stated (93%) and appropriate confounding factors identified (18%). All cohort studies had a high risk of bias for the evaluation criteria (Fig. 2B).

3.5 Meta-analysis Results

The meta-analysis results, which included 16 studies, are presented according to the leukocyte count, lymphocyte counts, neutrophil counts, platelet counts, fibrinogen levels, D-dimer, active partial thromboplastin time, prothrombin time, hemoglobin, hematocrit, ferritin and CRP in COVID-19 patients.

3.5.1 Leukocyte count

It was observed that people with severe COVID-19 had higher leukocyte means than people with

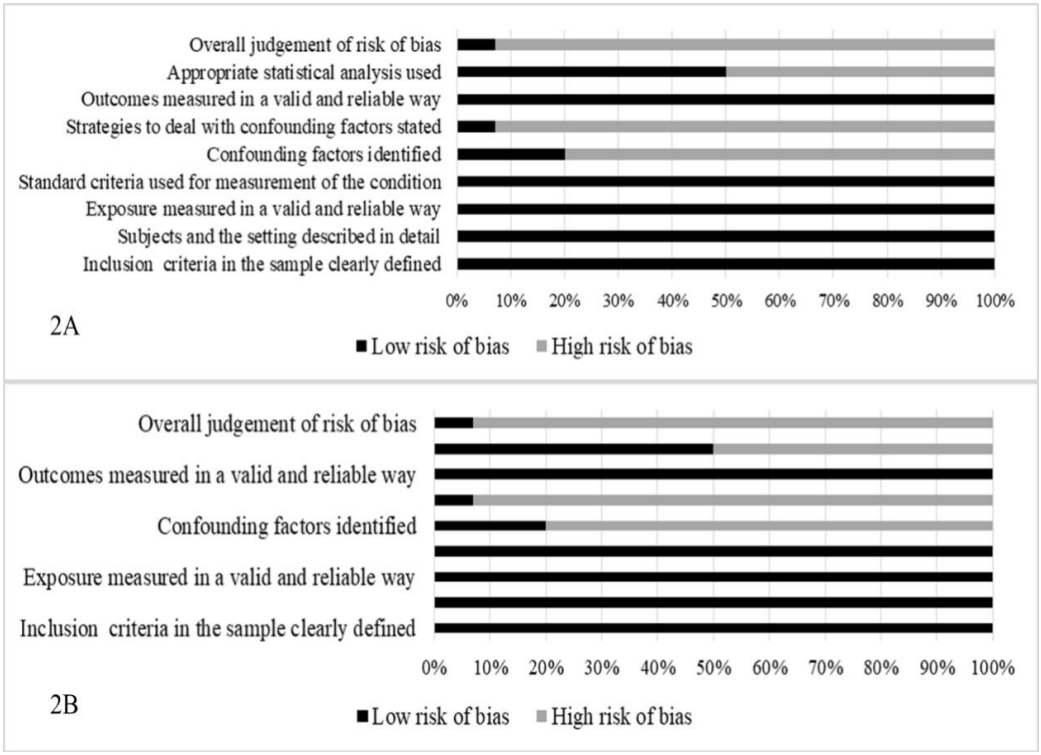


Fig. 2. Risk of bias for cohorts and cross-sectional studies. JBI scale for cross sectional studies (2A) and NewCastle-Ottawa scale for Cohort studies (2B)

mild COVID-19 (SMD: 0.47; 95% CI: 0.24 − 0.70; I2: 86.2%) (Fig. 3A). In the funnel plot analysis (Fig. 3A), there is a symmetric distribution of the included studies related to a lower publication bias risk.

3.5.2 Lymphocyte count

It was observed that people with severe disease had lower means of lymphocytes than people with mild disease (SMD: -1.25; 95% CI: -1.67 − -0.83; I^2: 95.7%) (Fig. 3B). In the funnel plot for lymphocytes (Fig. 3B), the distribution observed is asymmetric, associated with a more considerable publication bias risk.

3.5.3 Platelet count

There was no statistically significant difference in the comparison between the severe and mild groups (SMD: -0.16; 95%CI: -0.50 − 0.18; I^2: 79.2%) (Fig. 3C).

3.5.4 Neutrophil counts

Subjects with severe COVID-19 (SMD: 1.44; 95% CI: 0.92 − 1.96; I^2: 0.0%) had higher neutrophil averages when compared to individuals with mild disease (Fig. 4A).

3.5.5 Monocyte count

There was no statistically significant difference between the mild and severe groups (SMD: 0.14; 95% CI: -0.09 − 0.37; I^2: 77.7%) (Fig. 4B).

3.5.6 Fibrinogen levels

People with severe COVID-19 were shown to have higher means of fibrinogen compared to people with mild COVID-19 (SMD: 0.55; 95%CI: 0.16 − 0.93; I^2: 40.5%) (Fig. 4C).

3.5.7 D-dimer

There was no statistically significant difference between the severe and mild groups (SMD: 0.26; 95%CI: -0.19 − 0.71; I^2: 87.42%) (Fig. 4D).

3.5.8 Activated partial thromboplastin time

There was no statistically significant difference when comparing the severe group with the mild group (SMD: -0.20; 95% CI: -1.45 − 1.04; I^2: 92.8%) (Fig. 4E).

3.5.9 Hemoglobin

There was no statistically significant difference between the severe and mild group (SMD: -0.89; 95% CI: -2.32 − 0.53; I^2: 98.4%) (Fig. 4E).

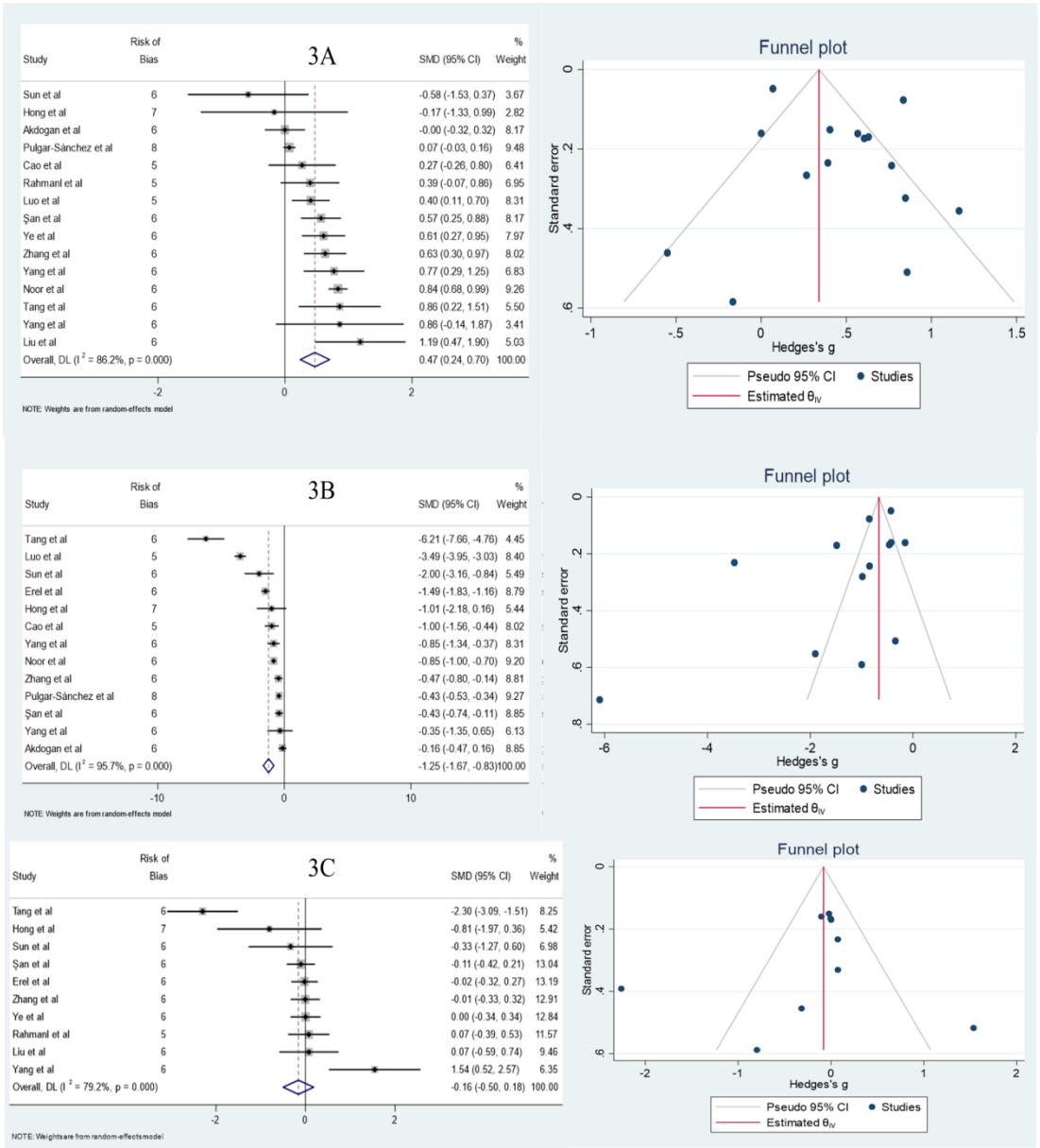


Fig. 3. Meta-analysis of mean values of leukocytes (3A), lymphocytes (3B) and platelets (3C) grouped between patients with severe and mild COVID-19. Forest Plot and Funnel chart showing the mean values of leukocytes grouped between patients with severe and mild COVID-19

3.5.10 Hematocrit

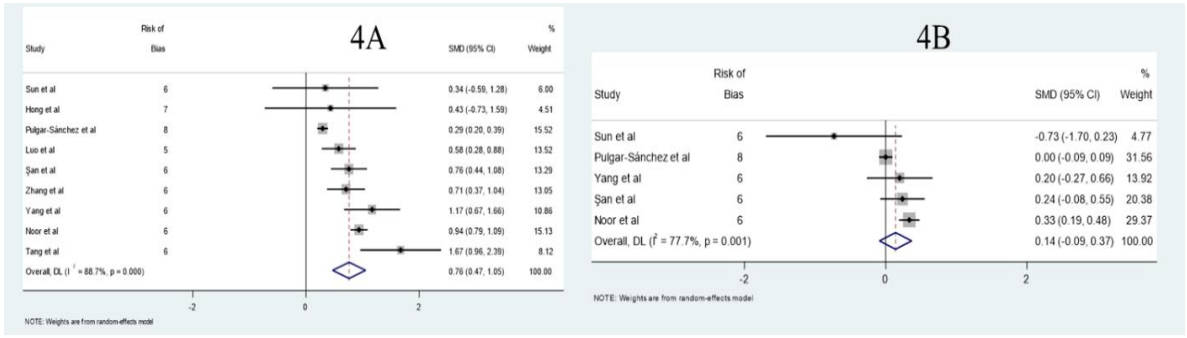
There was no statistically significant difference between the means of participants in the severe group compared with the mild group (SMD: 0.06; 95%CI: -0.10 − 0.31; I²: 20.5%) (Fig. 5A).

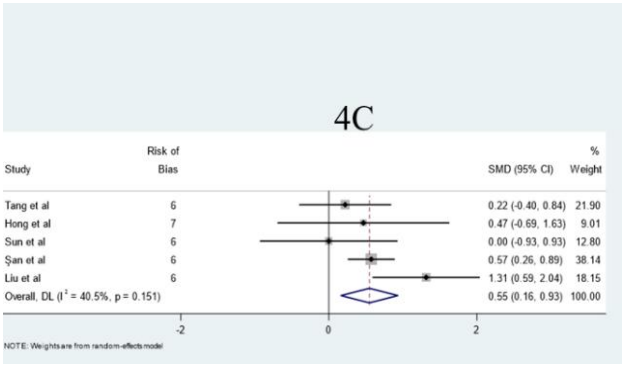
3.5.11 Ferritin

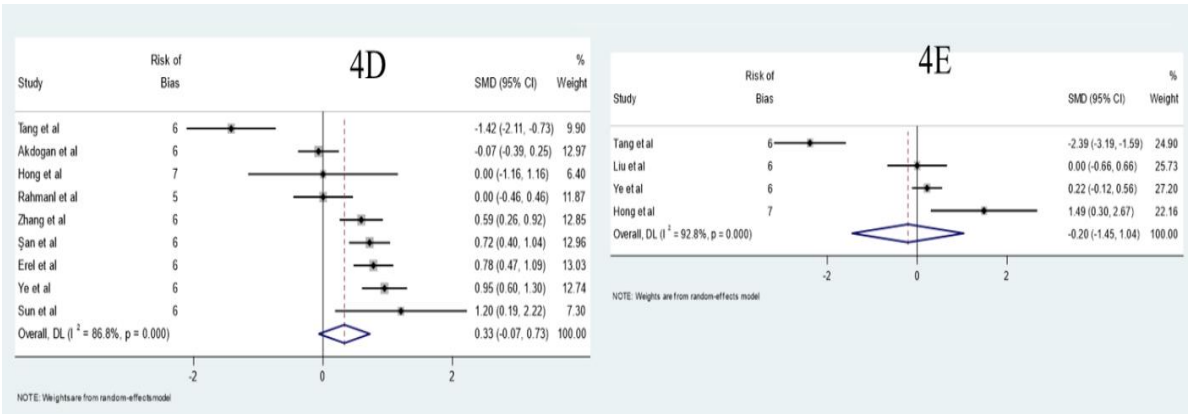
Individuals with severe COVID-19 had higher means of ferritin when compared to participants with mild disease (SMD: 1.13; 95%CI: 0.57 − 1.69; I²: 72.6%) (Fig. 5B).

3.5.12 CRP

Significant differences were observed between the groups. Individuals with severe COVID-19 had higher means when compared to individuals with mild disease (SMD: 3.98; 95%CI: 2.16 − 5.80; I²: 98.2%) (Fig. 5C).







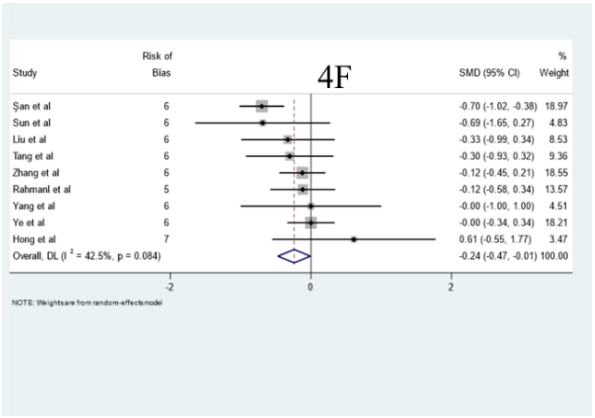


Fig. 4. Forest Plot showing the mean values of neutrophils (4A), monocyte count (4B), fibrinogen levels (4C), D-Dimer (4D), Thromboplastin time (4E) and Hemoglobin (4F) grouped between patients with severe and mild COVID-19

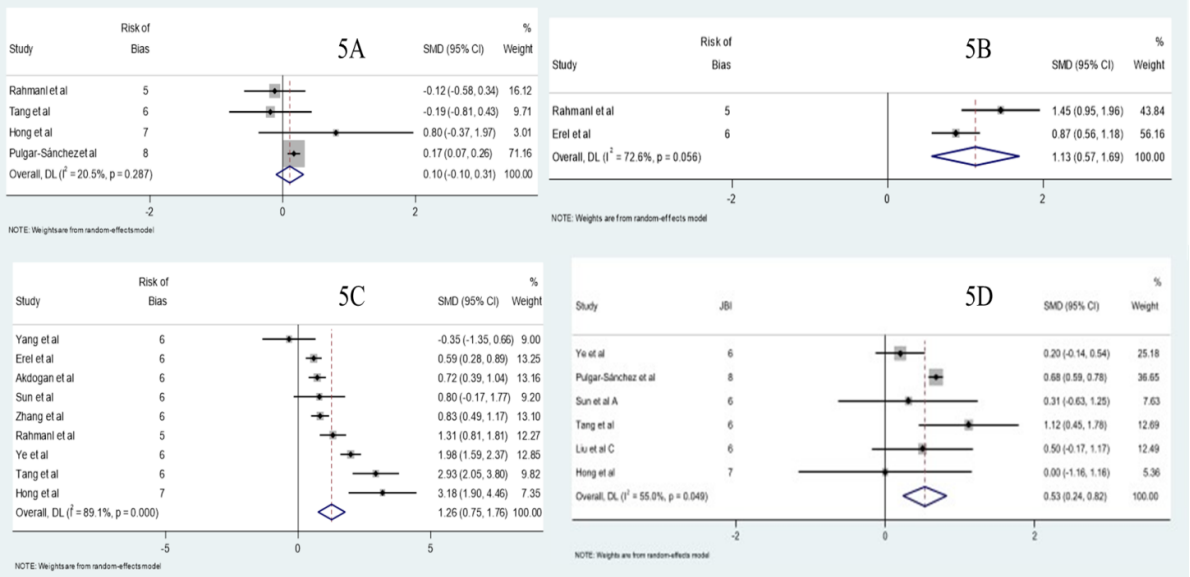


Fig. 5. Forest Plot showing pooled mean hematocrit (5A), ferritin (5B), CRP (5C) and Prothrombin time (5D) values between patients with severe and mild COVID-19

3.5.13 Prothrombin time

Participants with severe COVID-19 had higher mean prothrombin time when compared with participants with mild disease (SMD: 0.53; 95%CI: 0.24 − 0.82; I²: 55.0%) (Fig. 5D).

COVID-19 has a broad spectrum of presentations, from asymptomatic forms to critical illness, characterized by acute respiratory failure requiring mechanical ventilation, septic shock and multiple organ failure. The proportion of individuals in each clinical group shows high heterogeneity between studies [15,16].

A report by the Chinese Center for Disease Control and Prevention looked at 44,672 confirmed cases, and among those with symptoms, it found a rate of 81% mild illness, 14% severe illness, and 5% critical illness. The overall mortality rate was 2.3%, and no deaths were reported among non-critical cases [17].

A meta-analysis found a rate of 0.25% asymptomatic among the entire population tested and 40.5% among the population with a confirmed diagnosis. On the other hand, a review before the introduction of COVID-19 vaccination estimated that 33% of people infected with SARS-CoV-2 do not develop symptoms [18,19].

SARS-CoV-2 infection induces a number of changes in routine blood tests, and some of them can be used to monitor and predict the severity and prognosis of COVID-19 [20]. The results of this work suggest that an increase in leukocyte count, neutrophils, CRP, fibrinogen, PT and ferritin and a reduction in lymphocyte count are associated with progression to severe conditions.

A quantitative analysis performed on a total of 6,320 patients showed that severe cases were more likely to have elevated blood leukocyte levels (OR: 1.75; 95% CI: 1.21 − 2.54, p=0.002), neutrophil count (OR: 2.62; 95% CI: 1.72 − 3.97; p <0.001) and prothrombin time (OR: 1.82; 95% CI: 1.00 − 3.33, p= 0.047), in agreement with the present paper. The increase in these indicators was also associated with greater probability of being admitted to the ICU [21].

Another meta-analysis performed in 2020 had results similar to our pool; a significant increase in leukocyte count was noted among patients with severe COVID-19 (WMD: 1.25×10^9/L; 95% CI: 0.91 − 1.59). When compared within the severe group, between survivors and non-survivors, they noted that non-survivors had greater increases in WBC count, total bilirubin, creatine kinase, serum ferritin, and IL-6, and more significant decreases in platelet and lymphocyte counts [22].

As well as this meta-analysis, Kazemi et al. also observed the inverse relationship between lymphocyte count and disease severity. In their analysis, the mean number of lymphocytes in the mild and moderate group (mean value: 1.32; CI:

1.21 − 1.43, p< 0.001) was higher than that of the critical and severe groups [23]. Likewise, Zhao et al. also observed a significant reduction in lymphocytes of 0.31×10^9/L in the severe group compared to the non-severe group (random effects model, CI: -0.42−0.19), which was also observed in the present study [24].

Several studies point to the occurrence of neutrophilia in severe cases of the disease. Elshazli et al. (2020) performed an analysis in a decision tree model and found high performance in neutrophil count as a predictor of severity. The parameter identified critically ill patients with 100% sensitivity and 81% specificity [21]. However, in contrast to the literature and the results of this review, Xu et al. found no differences between neutrophil counts between severe and mild cases (WMD: 2.92; CI: -1.33 − 7.17) [25].

The alterations in coagulation parameters observed were mainly an increase in PT and fibrinogen. In a meta-analysis that compared values between severity groups, the severe group had a higher value of fibrinogen (WMD: 1.02; 95% CI: 0.50 − 1.54; p < 0.001) and PT (WMD: 0.19 95% CI: -0.13−0.51; p= 0.243, I2: 65.2%), and for the last one, the difference was not significant [26].

The meta-analysis performed by Len et al., identified in the severe group, in addition to a significant increase in PT and fibrinogen, also an increase in D-dimer (WMD: 0.6985; CI: 0.5155 − 0.8815), aTPP (WMD: 0.2683; CI: 0.1357 - 0.4009) and platelet reduction (WMD: -0.1684; IC: -0.2826 − -0.0542) [27]. On the other hand, about aPTT, the work carried out by Lin et al (2020) in line with this review, did not find a significant difference between the groups (WMD: -1.56; CI: -5.77 − 2.64).

Elevated serum D-dimer values may be present in up to 45% of patients and are an independent risk factor for death. A meta-analysis of 16 studies shows that high D-dimer values are associated with an almost three-fold increased risk of poor outcomes. When values are above 1,000 ng/mL, patients with lower D-dimer values are nearly 20 times more likely to die from infection [26,28,29,30].

Hariyanto et al. demonstrated that serum D-dimer provides good discrimination between serious and non-serious infections, with an optimal cutoff of 0.635 µg/L, yielding a sensitivity of 75% and a specificity of 90% [31]. However, in contrast to the literature, no significant differences were observed between the levels of D-dimer of the evaluated groups in this study.

Although the present work did not demonstrate an association between platelet levels and disease severity, several studies suggest that thrombocytopenia is significantly associated with severe disease, the possibility of developing intravascular coagulopathy, and increased mortality [32]. The meta-analyses performed by Lippi et al. and Lin et al. found a significantly lower platelet count in patients with more severe COVID-19 (WMD:31×10^9/L; 95% CI: -35 − -29×109/L) and (WMD: -24.83; 95% CI: -34.12 − -15.54; p< 0.001), respectively [26,33].

On the other hand, the analysis performed by Kazemi et al showed that the mean platelet count in the critical group was higher than in the other groups (WMD: 205.96 $\times10^9$/L CI: 85.86 – 226.05, p. < 0.001) [23]. Urbano et al. also found higher platelet values in ICU patients, which is consistent with studies that state that the higher the platelet count, the greater the cytokine storm and the worse the clinical condition [34].

In line with this study, Lino et al., also found a significant increase in ferritin levels in patients with moderate and severe disease compared with patients with mild disease (p: 0.006 and 0.005, respectively) [35]. A second study found an increased frequency of death in patients with higher ferritin values. Among those with ferritin values between 3,345 – 14,660ng/mL, 75% died [36].

Similarly, the analyzes performed by Cheng et al. and Kaushal et al. also found higher ferritin values in the group with severe COVID-19 when compared with individuals with mild disease (WMD: 397.77; 95% CI: 306.51 – 489.02; p<.001) and (WMD: 0.882 CI: 0.738 – 1.026, I2: 85%), respectively [37,38].

A meta-analysis of 20 studies with 4,843 patients with COVID-19 showed an almost fourfold increased risk of poor outcomes in patients with elevated CRP (pooled OR: 3.97; 95% CI: 2.89 – 5.45; p<0.00001). A second retrospective cohort study showed that the likelihood of progressing to severe disease increased from CRP levels >41.8 mg/L. Like this work, both studies suggest that the CRP level is a potential indicator of severity [30,39].

Most of the studies included in this pool had a cross-sectional design. Laboratory values were measured at admission or at an early point in hospitalization, which represents a limitation as they may not reflect the clinical course and worsening of the disease. There was also heterogeneity in the clinical classification parameters and the measurement units used in the results. Many studies were excluded from the meta-analysis due to insufficient data.

In addition, comorbidities, clinical manifestations or factors that play an important role in pathogenesis such as secondary infection, treatment and immunological status were not evaluated.

4. CONCLUSION

SARS-COV-2 infection has a broad spectrum of presentations and its severity may vary from an asymptomatic patient to a high mortality outcome. From our analyses, COVID-19 presents important changes in the hematopoietic system that can be identified through laboratory tests, which are common and worldwide-distributed parameters in the healthcare systems. Futhermore, their results, could determine the disease's severity and prognosis and help establish a therapeutic plan.

The articles included in this systematic review indicate that during SARS-CoV-2 infection in individuals with severe or critical illness, there is an increase in leukocyte count, neutrophils, CRP, fibrinogen, PT and ferritin levels, and a reduction in the lymphocytes count. Our results link this laboratory changes with acute onset COVID-19, mainly because the laboratory values on most studies only were measured at admission. Further analyses are needed for a better understanding of other alterations and their relationship with the patient's clinical status and evolution through the infection.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Table S1. Databases, search strategy

Databases	Search Strategy
Medline/Pubmed	**#1** ((COVID-19) OR (COVID 19)) OR (COVID-19 Virus Disease)) OR (COVID 19 Virus Disease)) OR (COVID-19 Virus Diseases)) OR (Disease, COVID-19 Virus)) OR (Virus Disease, COVID-19)) OR (COVID-19 Virus Infection)) OR (COVID 19 Virus Infection)) OR (COVID-19 Virus Infections)) OR (Infection, COVID-19 Virus)) OR (Virus Infection, COVID-19)) OR (2019-nCoV Infection)) OR (2019 nCoV Infection)) OR (2019-nCoV Infections)) OR (Infection, 2019-nCoV)) OR (Coronavirus Disease-19)) OR (Coronavirus Disease 19)) OR (2019 Novel Coronavirus Disease)) OR (2019 Novel Coronavirus Infection)) OR (2019-nCoV Disease)) OR (2019 nCoV Disease)) OR (2019-nCoV Diseases)) OR (Disease, 2019-nCoV)) OR (COVID19)) OR (Coronavirus Disease 2019)) OR (Disease 2019, Coronavirus)) OR (SARS Coronavirus 2 Infection)) OR (SARS-CoV-2 Infection)) OR (Infection, SARS-CoV-2)) OR (SARS CoV 2 Infection)) OR (SARS-CoV-2 Infections)) OR (COVID-19 Pandemic)) OR (COVID 19 Pandemic)) OR (COVID-19 Pandemics)) OR (Pandemic, COVID-19)) NOT (COVID-19 Vaccines[MeSH Terms])) NOT (COVID-19 serotherapy[MeSH Terms])) NOT (COVID-19 Nucleic Acid Testing[MeSH Terms])) NOT (COVID-19 Serological Testing[MeSH Terms])) NOT (COVID-19 Testing[MeSH Terms]) **#2** ((((((((((Hematologic Tests) OR (Hematological Tests)) OR (Hematological Test)) OR (Test, Hematological)) OR (Tests, Hematological)) OR (Test, Hematologic)) OR (Tests, Hematologic)) OR (Blood Tests)) OR (Blood Test)) OR (Test, Blood)) OR (Tests, Blood)) OR (Hematologic Test) **#3** (((((Prognosis) OR (Prognoses)) OR (Prognostic Factors)) OR (Factor, Prognostic)) OR (Factors, Prognostic)) OR (Prognostic Factor)) OR (Clinical outcome) ((#1) AND (#2)) AND (#3)
SCIELO	(("testes hematológicos") OR ("alterações laboratoriais") OR ("alterações hematológicas") OR ("Exames laboratoriais") OR ("Contagem de Células Sanguíneas") OR ("Contagem de Eritrócitos") OR ("Contagem de Leucócitos") OR ("Contagem de Plaquetas") OR ("Tempo de Protrombina") OR ("Tempo de Tromboplastina Parcial") OR ("Proteína C-Reativa") OR ("Fibrinogênio") OR ("Hemograma") OR ("Leucograma") OR ("Coagulograma") OR ("Plaquetograma")) AND ((COVID-19) OR (SARS-COV-2) OR (2019-nCoV) OR (Novo Coronavírus) OR ("Novo Coronavírus de 2019") OR (“SARS Coronavirus 2”) OR (“Vírus SARS-CoV-2”) OR (“Infecção Viral COVID-19”) OR (“Infecção pelo SARS-CoV-2”))
COCHRANE	#1 (COVID-19) OR (COVID 19) OR (COVID-19 Virus Disease) OR (COVID 19 Virus Disease) OR (COVID-19 Virus Diseases) #2 (Hematologic Tests) OR (Hematological Tests) OR (Hematological Test) OR (Blood Tests) OR (Blood Test) #3 (#1) AND (#2)
LILACS	(("testes hematológicos") OR ("alterações laboratoriais") OR ("alterações hematológicas") OR ("Exames laboratoriais") OR ("Contagem de Células Sanguíneas") OR ("Contagem de Eritrócitos") OR ("Contagem de Leucócitos") OR ("Contagem de Plaquetas") OR ("Tempo de Protrombina") OR ("Tempo de Tromboplastina Parcial") OR ("Proteína C-Reativa") OR ("Fibrinogênio") OR ("Hemograma") OR ("Leucograma") OR ("Coagulograma") OR ("Plaquetograma")) AND ((COVID-19) OR (SARS-COV-2) OR (2019-nCoV) OR (Novo Coronavírus) OR ("Novo Coronavírus de 2019") OR (“SARS Coronavirus 2”) OR (“Vírus SARS-CoV-2”) OR (“Infecção Viral COVID-19”) OR (“Infecção pelo SARS-CoV-2”))
EMBASE	#1 'coronavirus disease 2019' OR 'COVID-19' OR 'COVID 19' OR 'COVID 19 Virus Disease' #2 'blood examination' OR 'hematologic test' OR 'hematological test' OR 'blood test' #3 #1 AND #2

Table S2. General characteristics of the articles selected for analysis

Autores	Year	Country	N	Type of study
Yang et al. [40]	2020	China	103	Retrospective
Tahtasakal et al. [41]	2020	China	534	Retrospective
Lei et al. [42]	2020	China	297	Retrospective
Zhao et al. [43]	2021	China	172	Retrospective
Shi et al. [44]	2020	China	90	Retrospective
Waris et al. [45]	2021	Pakistan	61	Retrospective
Ye et al. [46]	2021	China	196	Retrospective
Pulgar-Sanchez et al. [47]	2021	Ecuador	4009	Retrospective
Akdogan et al. [48]	2021	Türkiye	175	Retrospective
Cao et al. [49]	2021	China	58	Retrospective
Henry et al. [50]	2021	USA	52	Prospective
Foaud et al. [51]	2021	Egypt	338	Retrospective
Karakoyun et al. [52]	2021	Türkiye	197	Retrospective
Huang et al. [53]	2021	China	33	Retrospective
Cheng et al. [54]	2021	China	213	Retrospective
Chen et al. [55]	2020	China	113	Retrospective
Zheng et al. [56]	2020	China	141	Retrospective
Sun et al. [57]	2020	China	18	Retrospective
Xu et al. [58]	2020	China	79	Retrospective
Yang & Chen [59]	2020	China	108	Retrospective
Li et al. [60]	2020	China	215	Retrospective
Liao et al. [61]	2020	China	294	Retrospective
Sun et al. [62]	2020	China	57	Retrospective
Gómez et al. [63]	2020	Spain	540	Retrospective
Okuma et al. [64]	2021	Japan	63	Retrospective
Luo et al. [65]	2021	China	196	Prospective
Ding et al. [66]	2021	China	311	Retrospective
Güçlü et al. [67]	2021	Türkiye	215	Retrospective
Şan et al. [68]	2021	Türkiye	388	Retrospective
Horiuchi et al. [69]	2021	Japan	194	Retrospective
Sun et al. [70]	2020	China	116	Retrospective
Xie et al. [71]	2020	China	97	Retrospective
Kaya et al. [72]	2021	Türkiye	141	Retrospective
Erel et al. [73]	2021	Türkiye	517	Prospective
Tang et al. [74]	2021	China	71	Retrospective

Autores	Year	Country	N	Type of study
Eijmael et al. [75]	2021	Netherlands	230	Retrospective
Zhang et al. [76]	2021	China	172	Retrospective
Rahmanl et al. [77]	2021	India	306	Prospective
Xu et al. [78]	2021	China	98	Prospective
Kilercik et al. [79]	2021	Türkiye	82	Retrospective
Cyprian et al. [80]	2021	Qatar	66	Prospective
Li et al. [81]	2021	China	254	Retrospective
Liu et al. [82]	2020	China	308	Retrospective
Noor et al. [83]	2020	Pakistan	735	Prospective
Liu et al. [84]	2021	China	122	Retrospective
Taghiloo et al. [85]	2021	Iran	61	Prospective
He et al. [86]	2020	China	204	Retrospective
Yang et al. [87]	2020	China	136	Retrospective
Yang et al. [88]	2020	China	93	Retrospective
Han et al. [89]	2020	China	154	Retrospective
Liu et al. [90]	2020	China	40	Retrospective
Li et al. [91]	2020	China	69	Prospective
Hong et al. [92]	2020	China	67	Retrospective
Song et al. [93]	2020	China	41	Retrospective
Liu et al. [94]	2021	China	408	Retrospective

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