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Hematological characteristics of patients in coronavirus 19 infection: a systematic review and meta-analysis

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ABSTRACT

Background COVID-19 infection has become a pandemic and a global health issue since its origin in Wuhan, China in December 2019. The present systematic review and meta-analysis aim to assess hematological changes seen in COVID-19 infection and their association with the severity of the disease.

Methods Pooled proportions were calculated using both fixed effects model and random effects model. Weighted mean difference and 95% CI were calculated and reported.

Results Initial search identified 84 reference articles, 23 relevant articles were selected and reviewed. Compared to general population, the weighted mean difference of WBC count in all COVID-19 patients was lower by 0.97 × 10^9 mm^3 (95% CI = −1.29 to −0.66). In severe COVID-19 patients, the weighted mean difference of platelet count was lower by 23.85 × 10^9/liter (95% CI = −35.18 to −9.53), as compared to general population. The weighted mean difference of prothrombin time, D-Dimer, and fibrinogen in severe COVID-19 patients was higher by 1.92 seconds (95% CI = 0.01 to 3.84), 6.23 mg/liter (95% CI = 0.11 to 12.36) and 1.88 g/liter (95% CI = 1.18 to 2.48) respectively, as compared to general population. Pooled proportion showed D-Dimer to be elevated in 80.00% (95 % CI = 50.00 to 99.00) of severe patients.

Conclusions Our meta-analysis shows that patients with COVID-19 have significant thrombocytopenia, leukopenia along with elevated D-dimer, fibrinogen and prothrombin time. These laboratory findings are marked in severe COVID–19 infections and could be helpful in early recognition of severe infection.

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1. Introduction

COVID-19 is a disease caused by SARS-CoV-2, a novel coronavirus related to the virus that caused the SARS (severe acute respiratory distress syndrome) outbreak in 2002 (SARS-CoV) and MERS (Middle East respiratory syndrome) outbreak in 2012. Initially believed to originate from Wuhan seafood Market in December 2019, when individuals with exposure to seafood market presented with a new type of pneumonia without an identifiable cause. By the end of January 2020, the USA (US) experienced its first case of COVID-19, and as of 19 May 2020, the number of cases in the US has reached 1,504,830 and has surpassed all the other countries in the world. While the fatality of SARS-CoV-2 is lower than that of SARS or MERS, there is a much larger rate of person to person transmission due to its wide spectrum of disease manifestations in individuals.

Like SARS and MERS, COVID-19 is known to have catastrophic complications such as ARDS (acute respiratory distress syndrome), severe pneumonia, acute respiratory failure, acute cardiac events, and ischemic events related to prothrombotic state as reported out of China [1]. Less severe symptomatology includes sore throat, cough, low-grade fevers, and malaise. The symptom complex while still being further evaluated, currently the CDC recommends a high index of suspicion for COVID-19 in patients presenting with fever, chills, cough, shortness of breath, sore throat, muscle pain, headache, and new loss of taste or smell.

Characteristics of patient population and presentation including symptomatic and laboratory findings continue to evolve with numerous publications initially out of China, and currently from Europe and the USA. Although primary symptoms in people infected with COVID-19 are respiratory, but there are increasing reports of symptoms related to GI tract [2–5], venous and arterial thrombotic complications associated with the infection including ischemic strokes, myocardial infarction, deep vein thrombosis (DVT), and pulmonary emboli being reported [6–10]

Hematological parameters have recently gained more attention due to reports of thrombocytopenia, impaired oxygen transport, and hypercoagulable state in these patients. Currently, there is a paucity of

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literature on COVID-19, while it continues to spread all around the world. It remains crucial for us to understand its symptoms and various presentations to assist with early identification and help in disease containment.

The objective of this review and meta-analysis was to review available literature since the onset of disease with special focus on hematological characteristics including WBC count, hemoglobin, platelet count, D-dimer, prothrombin time, and fibrinogen in patients presenting with COVID-19 and to assess the differences in these parameters if any between severe and non-severe patients.

2. Methods

A literature search was conducted using the electronic database engines MEDLINE through PubMed, Ovid, Cochrane Library, EMBASE, DARE, International Pharmaceutical Abstracts, and Google Scholar from 2019 to March 31st, 2020 to identify published articles using keywords 'Novel Coronavirus', 'Coronavirus 2019′, 'COVID-19′, 'SARS-CoV-2′, 'laboratory findings' 'D-Dimer, 'Prothrobmin time', or 'Fibrinogen'. The reference list of all eligible studies was reviewed to identify additional studies. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. Titles and abstracts selected from the initial search were first scanned, and the full papers of potentially eligible studies were reviewed.

3. Study eligibility

We included peer-reviewed studies, case series with RT-PCR confirmed COVID-19 infection. Studies were eligible for inclusion if they reported COVID-19 related hematological and coagulation profile results in patients with confirmed COVID-19 infection. Articles were excluded if [1] they were not written in English [2], no outcomes were reported, or [3] they represented review articles or studies published as abstracts only. Two reviewers (MA, HS) independently performed study selection according to eligibility criteria.

4. Data extraction and quality assessment

The following data were independently abstracted onto a standardized form: study characteristics (Primary author, year of publication, and country of the population studied), study design, baseline characteristics of the study population (number of patients included, sex, age of patients, risk stratification if mentioned into mild/moderate or severe disease), and outcomes (WBC count, hemoglobin, platelet count, prothrombin time, D-dimer, and fibrinogen)

5. Outcomes of interest

We assessed the weighted mean difference of WBC count, hemoglobin, platelet count, D-dimer, prothrombin time, and fibrinogen in all COVID-19 positive patients and patients with severe COVID-19 as compared to the general population. Severe COVID-19 was defined as severe community-acquired pneumonia based on American Thoracic Society (ATS) guidelines, or patients requiring admissions to intensive care unit (ICU) due to COVID-19, or respiratory distress, respiratory rate>30 breaths per minute, oxygen saturation <93% at rest, the partial pressure of oxygen/FIO2 < 300, acute respiratory distress syndrome (ARDS), shock arrhythmia, multiorgan failure, or non-survivors all other cases were classified as non-severe infection.

6. Statistical analysis

Microsoft Excel was used for data collection and meta-analysis was performed using Stata version*12* (StataCorp. College Station, TX). The meta-analysis was performed, with a calculation of weighted mean difference and 95% confidence interval (CI) of hemoglobin, WBC count, platelet count, prothrombin time, D-dimer, and fibrinogen in patients with COVID-19 and patients with severe COVID-19 compared to the general population. Mean and standard deviations were calculated for continuous variables. If unavailable, mean and standard deviations were calculated from sample size, median, and interquartile range according to Hozo et al. [11].

Pooled proportions and 95% CI were used to summarize the weighted effect size for each subgroup proportions. Forrest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forrest plots indicates the assigned weight to that study. The heterogeneity among studies was tested using I^2 statistic and Cochran Q test based upon inverse variance weights [12]. I^2 of 0% to 39% was considered as non-significant heterogeneity, 40% to 75% as moderate heterogeneity, and 76% to 100% as considerable heterogeneity. If P-value is >0.05, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested by both Harbord–Egger bias indicator and Begg–Mazumdar bias indicator [13,14]. Also, funnel plots were constructed to evaluate potential publication bias [15,16].

7. Results

The initial search identified 84 articles based on our search criteria. After thorough screening and removal of abstracts, review papers, and duplicates 23 articles were included in our meta-analysis with a total of 4977 cases, 1107 patients with severe COVID-19. Preferred reporting items for Systematic Reviews and Meta-analyses flow diagram for detail of the review process are shown in Figure 1. All studies were published as full-text articles. All pooled estimates given are estimates calculated by the random effect model. The random-effect model was preferred to fixed effects model for better accuracy based on the nature of individual study characteristics and heterogeneity.

Among the included studies, twenty-one were based in China, one in USA, and one in France. The mean age of all COVID-19 patients was 49 years, while that of patients afflicted with severe COVID-19 was 59.1 years. The P for Chi-squared heterogeneity for all the pooled accuracy estimates was significant if <0.05. The agreement between reviewers for the collected data gave a Cohen κ value of 1.0.

8. Outcomes of interest

8.1. White blood cell count

The weighted mean difference of WBC count in all COVID-19 patients was lower than the general population by 0.97 × 10^9 mm^3 (95% CI = – 1.29 to – 0.66). In severe COVID-19 patients, weighted mean difference of WBC count was non-significant (0.35 X 10^9 mm^3, 95% CI = – 0.56 to 1.27) as compared to the general population.

In our pooled patient population, the percentage of patients with leukocytosis was 7.00% (95% CI 4.00 to 11.00) in all COVID-19 patients, and in32.00% (95% CI 0.00 to 63.00) in severe COVID-19 patients. Begg-Mazumdar indicator gave a Kendall tau value of 2.48 (p = 0.449).

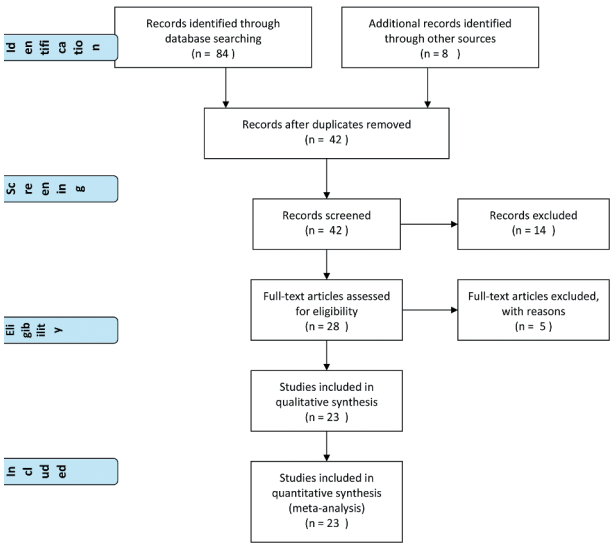

Figure 1. Preferred reporting items for Systematic Reviews and Meta-analysis flow diagram for detailing the review process.

8.2. Hemoglobin

The weighted mean difference of hemoglobin in all COVID-19 patients was higher by 0.67 g/dl (95% CI = 0.41 to 0.93) as compared to the general population. While, in severe COVID-19 patients, the weighted mean difference of hemoglobin was non-significant (0.35 g/dl, 95% CI = –0.03 to 0.72) as compared to the general population.

8.3. Platelet count

The weighted mean difference of platelet count in COVID-19 patients was found to be lower by 13 × 10^9/liter (95% CI = –19.36 to –8.28) as compared to the general population. While, in severe COVID-19 patients, the weighted mean platelet count was lower by 23.85 x 10^9/liter (95% CI = –35.18 to –9. 53) as compared to the general population. The Forrest plot representing Platelet count in severe COVID-19 infections is shown in Figure 2.

In our pooled cohort, the proportion of patients with thrombocytopenia was 15.00% (95% CI 5.00–-24.00) in all COVID-19 patients and 37.00% (95% CI 20.00–55.00) in severe COVID-19 patients.

8.4. Prothrombin time

The weighted mean difference of prothrombin time in all COVID-19 patients was non-significant (0.41 seconds, 95% CI = –0.35 to 1.17) as compared to the general population. In severe COVID-19 patients, the weighted mean difference of prothrombin time was higher by 1.92 seconds (95% CI = 0.01 to 3.84) as compared to the general population.

8.5. D-Dimer

The weighted mean difference of D-dimer in all COVID-19 patients was higher by 0.35 mg/L (95% CI = 0.13 to 0.23) as compared to the general population. While in severe COVID-19 patients the

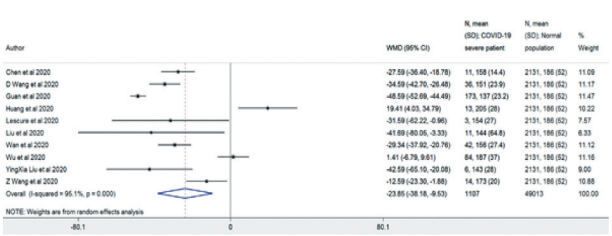

Figure 2. Forrest plot representing platelet count in severe COVID-19 patients.

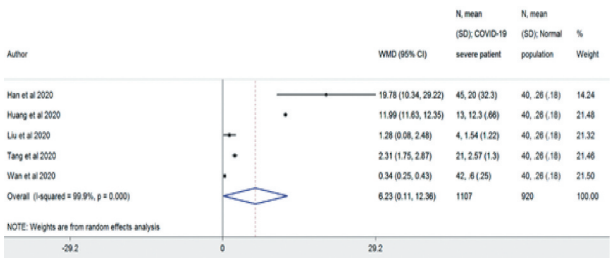

Figure 3. Forrest plot representing D-dimer in severe COVID-19 patients.

weighted mean difference of D-dimer was higher by 6.23 mg/liter (95% CI = 0.11 to 12.36) when compared to the general population. The Forrest plot representing D-dimer in severe COVID-19 patients is shown in Figure 3.

In our pooled patient population, percentage of patients with elevated D-dimer was 19.00% (95% CI = 8.00–29.00) in non-severe COVID-19 infection and 80.00% (95% CI = 50.00 to 99.00) in severe COVID-19 patients.

8.6. Fibrinogen

The weighted mean difference value of fibrinogen was higher by 1.33 g/liter (95% CI = 0.33 to 2.33) in COVID-19 patients as compared to the general population. In severe COVID-19 patients, the weighted mean difference was higher by 1.88 g/liter (95% CI = 1.18 to 2.48) as compared to the general population.

9. Discussion

COVID–19 which started a cluster of novel pneumonia cases in December 2019seen in Wuhan, China, currently has involved almost entire humanity and brought life to a standstill. Our ability to combat this pandemic is limited by our finite understanding of this novel virus. While pulmonary symptoms are reported in more than 90% of the patient population, more data seem to be emerging about gastrointestinal symptoms [2–5], vascular, and thrombotic complications of the novel coronavirus infection [6–10]. In this meta-analysis, we analyzed and evaluated laboratory characteristics including a coagulation profile of more than 4,000patients to further improve our understanding and to mitigate risks. Our findings are robust and important as our study is one of the largest meta-analysis performed so far assessing the hematological parameters of COVID-19 patients.

Leukocytosis or leukopenia is commonly seen in patients with COVID-9, with lymphopenia being the most pronounced laboratory finding [17,18]. The reason for this lymphopenia while exactly unclear is thought to be related to lymphocyte expression of angiotensin-converting enzyme 2 (ACE 2) receptors, which are in turn utilized by the virus to infect and cause destruction of CD-4 and CD −8 cells [19]. Another explanation for lymphopenia is increased bone marrow production of macrocytes to enhance the phagocytic process as explained by Liu et al. [20]. In our meta-analysis, while we did not directly assess lymphopenia, the trend towards leukopenia was noticed in non-severe COVID-19 patients. White cell count was found to be higher in severe disease as compared to the general population; however, the difference was non-significant. While the reason for this pattern is not exactly clear, trends towards leukocytosis in severe patients could be multifactorial due to superimposed bacterial infection or pneumonia in severe patients, steroid use, multiple medications being trialed, enhanced stress response. Analysis of pooled patient population also demonstrated that severe COVID-19 patients were more likely to have leukocytosis as compared to non-severe patients; these results are in accordance with previously reported results [18].

Recently, COVID–19 patients have been reported to develop microangiopathy and complications related to it including hemolysis [21]. Also, it has been reported that COVID-19 attacks the beta chain of hemoglobin, thus disrupting the heme and acquiring its porphyrin ring and releasing free iron into circulation [20]. One would expect to see anemia or lower hemoglobin in COVID-19 patients if this were true. Our results in contrast show the weighted mean difference of hemoglobin to be significantly higher in non-severe COVID-19 patients and non-significantly elevated in severe COVID-19 patients. These patterns of increased hemoglobin could be reflective of increased bone marrow production of red cells to counteract the severe hypoxemia or hemoconcentration in the setting of sepsis.

Severe COVID-19 infection has been associated with thrombocytopenia in previous studies [21,22]. Our results support these findings, the weighted mean difference of platelet count was found to be lower by 13×10^{9}/liter in non-severe and by 23.85 x 10^{9}/liter in severe COVID-19 patients compared to the general population. The previously weighted mean difference of platelet count has been reported to be lower by 31 X 10^{9}/liter in severe COVID-19 patients [23]. In our pooled patient population, the percentage of patients with thrombocytopenia was 15.00% in all COVID-19 patients and was 37.00% in severe COVID-19 patients indicating thrombocytopenia to be a marker of severe disease. The etiology of thrombocytopenia is likely multifactorial in the setting of infection including consumptive coagulopathy, ITP, DIC, or bone marrow response as described above [24].

COVID-19 infection is thought to generate a profound prothrombotic state and various

publications have recently supported this notion [6–10]. The pathophysiology of the thrombotic state remains unclear. It has been postulated that virus attaches to ACE-2 receptors on endothelial cells causing endothelitis and activation of thrombotic cascade causing a prothrombotic state [25]. In addition to the loss of protective endothelium, the acute phase reactants produced in the setting of severe infection also contribute to hypercoagulability and microvascular thrombosis [26]. Case reports of ischemic digits and cerebral infarcts along with elevated anticardiolipin and antiphospholipid antibodies have also been reported [27]. Han et al. reported significantly increased D-dimer and fibrinogen values in COVID-19 patients as compared to controls. Tang et al. [10] also reported similar findings and their correlation with mortality, elevated D-dimers have been associated with increased mortality [19]. The result of our meta-analysis supports these findings; however, we did not assess mortality. The weighted mean difference of D-dimer in all Covid-19 patients and patients with severe COVID-19was found to be higher by 0.35 mg/dl and 6.23 mg/dl, respectively, as compared to the general population. The pooled proportion of patients showed D-dimer to be elevated in 19% of the total population and 80% of patients with severe COVID-19 infection. Previously D-dimer levels have been elevated in up to 25% of patients with COVID-19 infection [28]. Fibrinogen also showed similar trends, the weighted mean difference value of fibrinogen was higher by 1.33 g/l in all COVID-19 and significantly by 1.88 in severe patients as compared to the general population.

The weighted mean difference of prothrombin time in all COVID-19 patients was higher by only 0.41 seconds while by 1.92 seconds in severe COVID-19 patients as compared to the general population. Prothrombin time in the previous studies has also been found to be near normal or slightly elevated. These combinations of findings with elevated D-dimer along with elevated fibrinogen and near-normal clotting times have also been observed in previous studies [25–27]. These findings support the notion that while COVID-19 patients may have a cytokine-mediated hypercoagulable state, but they do not have typical findings of DIC [29].

Anticoagulation for severe COVID −19 patients is recommended based on the above findings. The Laboratory markers of D-dimer, prothrombin time, and fibrinogen levels as described in our meta-analysis can act as surrogate markers to help with identifying patients at risk for thrombotic complications and possible interventions.

International Society of thrombosis and hemostasis (ISTH) and American Society of Hematology (ASH) recommend daily trending of these four parameters as described in our meta-analysis, namely, platelet count, D-dimer, prothrombin time, and fibrinogen levels in patients admitted to the hospital. If elevated, prophylactic LMWH is recommended. According to the society guidelines, therapeutic anticoagulation is not warranted at this time and the role of intermediate or full therapeutic anticoagulation for critically ill COVID-19 patients without documented VTE is being studied. Case series published by Wang et al. [30] have reported transient improvement in the oxygenation in patients given tPA, suggesting the possible role of lytic therapy.

Our meta-analysis had several limitations, most of our studies were single-center observational or retrospective case series, the definition of severe disease differed amongst various studies, different cut-offs for WBC count, hemoglobin, platelet count, D-dimer, prothrombin time, and fibrinogen may limit interpretation of the analysis. Duration of symptoms upon presentation was unclear. There was significant heterogeneity and no subgroup analysis is performed which will affect the accuracy of our meta-analysis. Moreover, most of the studies included were from China and future studies from USA and Europe may help to further characterize the disease.

In conclusion, clinicians must be aware of early and late hematological findings of COVID-19 infection. Our results suggest that leukocytosis and thrombocytopenia may reflect severe disease and warrant close monitoring. Similarly, our findings of elevated fibrinogen, D-dimer, and prothrombin support the hypothesis of a prothrombotic state promoting ischemic events in COVID-19. Our findings do not support hemolysis or anemia in these patients. However, our results must be interpreted in caution in light of significant heterogeneity, and further large-scale clinical studies are needed to draw more concrete conclusions.

Disclosure statement

No potential conflict of interest was reported by the authors.

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