Clin. Lab. 2021;67:XXX-XXX

REVIEW ARTICLE

Hematological Parameters Predict Disease Severity and Progression in Patients with COVID-19: a Review Article

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SUMMARY

Background: **In December 2019, an outbreak of pneumonia of no identifiable cause had been widely spreading in Wuhan, Hubei Province, China. In late December 2019, the pathogen was identified as a new strain of coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its associated disease, named Coronavirus disease-19 (COVID-19). As of July 3, 2020, 10,906,822 cases have been confirmed worldwide, with 522,112 deaths, as reported by the World Health Organization. Given the developing situation with COVID-19, extensive studies are urgently needed that determine indicators of severity to provide evidence for health policymakers. This study aimed to review the currently available data on hematological parameters to predict disease severity in patients of COVID-19.**

Methods: **We performed a review using three electronic databases. Fourteen papers are included. In this review, we summarized the latest research highlighting the clinical features, pathogenesis, and diagnosis, with a concentration on hematological parameters that predict severity to help identify patients with severe disease. These indicators will help doctors know earlier which patients may need intensive care unit (ICU) care to manage their patients with an evidence-based protocol.**

Results: **Most reviewed studies report hematological parameters that predict disease severity, including lymphopenia and elevated fibrin fragment D.**

Conclusions: **We recommend using these indicators in addition to others, like respiratory failure, shock, or multiple organs dysfunction syndrome, for disease classification in situations where there are insufficient ventilators or ICU beds to prioritize advanced medical services accordingly and to ensure the maximum provision of sufficient medical care.**

(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2020.200655)

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Review Article accepted July 13, 2020

KEY WORDS

COVID-19, lymphopenia, fibrin fragment D, SARS-CoV-2 infection, hematological parameters

INTRODUCTION

Coronaviruses are viruses that cause diseases in birds and mammals. These viruses target the lungs and cause mild respiratory illness. Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS-Co-V) were associated with higher mortality rates in comparison to other coronaviruses [1]. In December 2019, an outbreak of pneumonia of no identifi-

able cause had been widely spreading in Wuhan, Hubei Province, China [2]. In late December 2019, the pathogen of this pneumonia was identified as a new strain of coronavirus, named novel coronavirus (2019-nCoV) by the World Health Organization (WHO), and later renamed Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. Some researchers linked the origin of this outbreak to seafood and wet animal wholesale in Wuhan [2,3]. As of July 3, 2020, 10, 906,822 confirmed cases worldwide and 522,112 deaths had been reported by WHO for the coronavirus pneumonia pandemic. Given the developing situation with the COVID-19, extensive studies are urgently needed to produce evidence for the health policymakers that determine indicators of severity and progression.

Objectives

The purpose of this study was to review the currently available data on hematological parameters to predict disease severity and progression in patients of COVID-19. These indicators will help health practitioners know earlier which patients may need intensive care unit (ICU) care or a ventilator to manage patients with an evidence-based protocol.

METHODS

Search strategy and selection criteria

We reviewed currently available literature about hematological parameters that predict disease severity and progression using three electronic databases (PubMed, Web of Science, and MEDLINE) using the keywords SARS-CoV-2, COVID-19, and hematological parameters. For studies to be included in this review, they had to report on primary research, be published in peer-reviewed journals, and be written in the English language. Any article that did not meet the inclusion criteria was excluded. Fourteen papers are included in this review. In this review, we summarized the latest research highlighting the clinical features, pathogenesis, and diagnosis, with a concentration on hematological parameters that predict severity to help identify patients with severe disease. These indicators will help doctors know earlier which patients may need intensive care unit (ICU) care to manage their patients with an evidence-based protocol. As this is a review, Institutional Review Board approval was not sought.

RESULTS AND DISCUSSION

Clinical features

The clinical spectrum of COVID-19 appears to be broad, including asymptomatic infection, mild flu-like illness, and acute respiratory distress syndrome (ARDS) [4-6]. The most common clinical features include fever, dry cough, arthralgia, and/or myalgia, fatigability, and dyspnea [4-9]. Some patients rapidly developed ARDS, metabolic acidosis, coagulation abnormalities, septic shock, and ultimately multiple organ dysfunction syndrome [4,6,10]. Other less common clinical features included sputum production, headache, nausea or vomiting, and diarrhea [4,5,9-13]. However, a small proportion of cases present initially with atypical features like sore throat, anorexia, chills, nasal and or pharyngeal congestion, hemoptysis, abdominal pain, conjunctival congestion, rash, tonsil swelling, lymph node enlargement [10], and dizziness [5]. The American Academy of Otolaryngology-Head and Neck Surgery and the WHO have proposed adding anosmia and dysgeusia (loss of smell and taste, respectively) as a screening symptom for potential COVID-19. According to the COVID-19 diagnosis and treatment plan issued by the National Health Committee of China [14], COVID-19 classified clinically into mild, moderate, severe, and critical. Fortunately, most patients have mild flu-like symptoms [4] or are asymptomatic, especially with young adults and children [15].

Pathogenesis

The primary pathology of COVID-19 has been severe pneumonia [4]. The pathogenesis of COVID-19 is related to a virus-induced inflammatory response [16-18]. Angiotensin-converting enzyme 2 (ACE2), located in the lower respiratory system, acts as a cell receptor for SARS-CoV-2 [19,20]. The binding of virion S-glycoprotein on the surface of the SARS-CoV-2 and ACE2 receptor on the surface of lower respiratory tract cells is a vital step for virus entry [21]. Once entry occurs, SARS-CoV-2 particles invade the respiratory mucosa and induce a series of immune reactions that result in a cytokine storm [22,23]. Markedly elevated pro-inflammatory cytokines have been observed in the blood of COVID-19 patients, especially in severe cases. These cytokines included interleukin (IL)1-β, IL2, IL1RA, IL4, IL7, IL8, IL9, IL10, IL12, IL13, IL17, hematopoietic growth factor (HGF), interferon-gamma (IFNγ), tumor necrosis factor-alpha (TNFα), macrophage inflammatory proteins (MIP1α and MIP1β), granulocyte colony-stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GMCSF), IP10, monocyte chemotactic protein 1 (MCP1), vascular endothelial growth factor A (VEGFA), platelet-derived growth factor subunit B (PDGFB), and basic fibroblast growth factor 2 (FGF2) [4,24]. The severity of COVID-19 is directly related to the cytokine storm, which is related to the discharge of abundant cytokines by the immune system [4,10].

Diagnosis

The standard method for diagnosing COVID-19, according to the WHO recommendation, is real-time reverse transcription-polymerase chain reaction (rRT-PCR) [25]. The WHO established the protocol of the RT-PCR assay. The most common specimens used for this test are nasopharyngeal swab and sputum [26]. The

results are usually obtained within a couple of hours to two days [27]. Blood test results have little immediate value because it requires two blood samples taken two weeks apart [28]. Scientists from China released the genetic sequence of the coronavirus after isolation of the strain for further confirmation by next-generation sequencing [29]. In March 2020, the Food and Drug Administration (FDA) confirmed the use of a point-of-care test [30]. According to an American-Singaporean panel, the computed tomography (CT) scan findings is not confirmatory for COVID-19 [31]. However, the CT scan has been used by some as an alternative diagnostic test [32-34]. The typical CT finding is ground-glass opacities, is initially confined to one lung, but as the disease progresses, it becomes bilateral. Additional CT findings include air space consolidation, linear opacities, and reverse halo sign [8,35].

Hematological parameters that predict disease severity and prognosis

Hematological parameters reviewed in this article included coagulation profile and complete blood count (CBC). Coagulation parameters that were evaluated include prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized time (INR), thrombin time (TT), antithrombin (AT), fibrinogen (FIB) and fibrin/fibrinogen degradation products (FDP). CBC parameters addressed in this review were hemoglobin (Hb) and white blood cells (WBC) with differential and platelet count. There were numerous differences in the coagulation profile and CBC results between mild, severe, and non-survivor cases. Most studies concluded that patients of COVID-19 with severe disease showed significantly higher levels of fibrin fragment D than patients with the milder disease [4,5,9, 19,22,23,36-38]. Liu Y et al. found the same findings. The level of fibrin fragment D also was noted to be higher in the intensive care unit (ICU) patients than in non-ICU patients [2] and in non-survivors than in survivors [5,9,37]. Patients with severe disease [4,37] and non-survivors [37] had higher FDP values. Similarly, PT was longer among patients with severe disease [36, 37] and in non-survivors [9,37]. The FIB concentration was found to be higher in severely ill patients compared with patients of mild disease [21]. Overall, approximately three-fourths (71.4%) of COVID-19 patients who pass away diagnosed with disseminated intravascular coagulation (DIC) compared to only 0.6% of those who survived [38], so regular evaluation for DIC should be considered during the patients follow up. The values of AT and TT in the COVID-19 patients were lower and shorter, respectively, than those in the control group; however, no significant difference could be found between mild and severe cases [36,37] (Table 1).

Regarding CBC, Zhou F et al. and Qu R et al. concluded that patients with lymphopenia [9,10] and thrombocytopenia [10] became more seriously ill, suffered more severe disease, and were admitted for a longer period. Wang et al. found the percentage of lymphocytes was lower than 20% in severe cases. When the disease progresses, this percentage continues to fall below 5% in non-survivor cases [5]. This finding is similar to the study reported by Fan, who found that severe cases usually had severe lymphopenia in addition to neutrophilia and reduced hemoglobin levels [39]. COVID-19 patients who require ICU care had leukocytosis [4,5], neutrophilia [4,5,23,37,39,40], and lymphopenia [4,5,8,23, 39,40]. Leucopenia was reported only in one study [9] (Table 2).

Flow cytometry performed on peripheral blood of ICU patients demonstrated marked lymphopenia, with significantly lower CD45+, CD3+, CD4+, CD8+, CD19+, and CD16/56+ counts [39]. Leucocytes and neutrophils were found to be higher in non-survivors than in survivors; despite that, non-survivors developed severe lymphopenia [5,9]. No significant difference could be observed for other hematological parameters between severe and non-severe cases. The findings of this review indicate that disease severity and progression can be anticipated mainly by increasing values of fibrin fragment D, FDP, and lymphopenia. So, monitoring these parameters may help healthcare providers identify patients with severe disease at an early stage.

CONCLUSION

Given the developing situation with COVID-19, extensive studies are urgently needed to produce evidence for health policymakers to determine indicators of severity and progression. These indicators may help treating doctors know earlier which patients will need ICU care or a ventilator so they can manage their patients with an evidence-based protocol. In this review, we summarized the latest research highlighting clinical features, pathogenesis, diagnosis, and findings of hematological parameters. This review may be helpful for the early identification of severe cases in patients with COVID-19. Among CBC parameters, most confirmed cases of COVID-19 showed lymphopenia; the lymphocyte count was markedly reduced in severe cases and moderately reduced in moderate and mild cases. Thus, the degree of lymphopenia can be used as a valid and reliable indicator for disease progression, classification, and prognosis [41]. Currently, lymphopenia is considered as one of the diagnostic criteria for COVID-19 [42,43]. Patients with COVID-19 showed abnormal coagulation findings, particularly elevated fibrin fragment D, FDP, PT, and DIC features. Patients with severe disease and non-survivors usually presented with higher levels on these tests. Elevated fibrin fragment D at admission has been shown to be a risk factor for death. Elevation of fibrin fragment D and FDP was found to be a reliable indicator of COVID-19 severity and prognosis. So, regular monitoring would appear advisable in patients with COVID-19. Using elevation in fibrin fragment D and lymphopenia together for predicting the severity likely more accurate. Monitoring hematological parameters are advisable for

Table 1. Coagulation parameters of the study patients according to disease severity, ICU admission, and survival status.

Coagulation parameters	Severe cases	ICU patients	Non-survivors
D-dimer	increased	increased	increased
FDP	increased	-	increased
PT	prolonged	-	prolonged
FIB	increased	-	-
DIC findings	-	-	showed

Abbreviations: FDP - fibrin/fibrinogen degradation products, PT - prothrombin time, FIB - fibrinogen, DIC - disseminated intravascular coagulation, ICU - intensive care unit.

Table 2. CBC parameters of the study patients according to disease severity, ICU admission, and survival status.

CBC parameters	Severe cases	ICU patients	Non-survivors
Leucocytosis	-	√	√
Lymphopenia	√	√	√
Thrombocytopenia	√	√	-
Neutrophilia	√	√	√
Reduced Hb level	√	-	-

Abbreviations: CBC - complete blood count, ICU - intensive care unit.

identifying patients with severe disease and patients who may need ICU care to improve outcomes in this pandemic. We recommended using these indicators in addition to the others, like respiratory failure, shock, or multiple organ dysfunction syndrome, for disease classification in situations where there are insufficient ventilators or ICU beds to prioritize advanced medical services accordingly and to ensure the maximum provision of sufficient medical care.

Authors' Contributions:

Alamin AA: conceptualization (equal), formal analysis (equal), methodology (equal), project administration (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal), writing-review & editing (equal); Yahia AIO: conceptualization (equal), data curation (equal), project administration (equal), supervision (equal), validation (equal), writing-original draft (equal), writing-review & editing (equal). All authors approved the final version of the manuscript for publication.

Declaration of Interest:

The authors declare that they have no conflicts of interest.

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