Evaluation of Prognostic/Diagnostic Value of Hematological Markers in the Detection of Inflammation in Coronavirus Disease: A Review Study

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ABSTRACT

The Coronavirus infectious disease 2019 (COVID-19) has recently emerged as a pandemic and has endangered the lives of thousands of people worldwide. No specific treatment has been identified so far. However, the identification of diagnostic and prognostic factors in patients can be valuable for the application of preventive strategies. Increased platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), prothrombin time (PT), and D-dimer indices have been found in patients with increased inflammation and thrombosis and can lead to heart disease. Also, an increase in these indices is accompanied by worsening of the disease and impairment of the respiratory tract, which necessitates ventilation for the patients eventually. The evaluation of NLR, PLR, and coagulation parameters can be useful for identifying high-risk individuals who need to be intubated. Patient survival will improve by the timely identification and the use of appropriate treatment strategies.

Keywords: COVID-19, Diagnosis, Inflammation, Lymphocyte, Neutrophil, Platelet

Introduction

Coronavirus infectious disease 2019 (COVID-19) is an enveloped virus from the Coronaviridae family, and its genome is a single-stranded RNA (1). The virus has a high pandemic potential and has infected many people around the world in 2020 (2). The importance of the virus came to light when some patients showed symptoms of pneumonia in Wuhan, China, in 2019; after many investigations, the World Health Organization (WHO) introduced the COVID-19 as the cause of pneumonia (3). The COVID-19 causes severe acute respiratory syndrome (SARS) by inflammation of the respiratory tract. It activates immune cells by stimulating the immune system and producing a large amount of pro-inflammatory cytokines (4,5). The occurrence of inflammatory responses not only damages the respiratory system, but also leads to autoimmune diseases and disrupts the function of many organs, including liver, heart, and lungs (6,7). Therefore, identifying inflammatory markers in infected patients is essential for preventing these

disorders and their progression. In this study, we evaluated the diagnostic value of inflammatory markers in COVID-19-infected patients and identified associated organ disorders. This review article provides an overview of the published papers on COVID-19. The relevant literature was searched in the PubMed database (from December 2019 to April 2020); the search was limited to the English language and the terms "COVID-19", "Inflammation", "Platelet", "Lymphocyte", "Neutrophil" and "Diagnosis" were used.

Platelet-to-lymphocyte Ratio (PLR)

Inflammatory responses play an important role in the prognosis and treatment of COVID-19 patients (8). Some inflammatory indices, especially blood cell counts, are important for monitoring COVID-19 progression. The PLR is an index used in many diseases as a prognostic/diagnostic factor (9). The lung

is one of the sites of mature megakaryocytes accumulation which releases a large number of platelets. COVID-19-infected patients with severe clinical conditions have increased platelet production, in addition to inflammatory cytokine production. The platelets are also destroyed by these cytokines; therefore, the severity of the inflammatory responses induces thrombocytopenia (10,11). Another point to note is a T helper type 2 (Th2) cell differentiation increment in COVID-19-infected patients, unlike SARS cases, which is a good prognostic event (12).

Lymphocytes decrement is associated with poor prognosis in many diseases and is a common finding in cancers and cardiovascular disorders (CVD) (13,14). According to the role of lymphocytes in the immune function, its decrement is not known as a good prognostic marker. PLR is a hematological index which shows the ratio of absolute platelet count to absolute lymphocyte count. Increased PLR is associated with the progression of the disease and severity of inflammatory responses; it is also related to the immune responses' modulation and uncontrolled inflammation prevention (5,10).

PLR increment is characterized by high platelet production. On one hand, platelets increase inflammatory responses and, on the other, stimulate coagulation pathways. Finally, this condition causes thrombosis and heart failure. Therefore, PLR evaluation can be useful for the appraisement of disease course and response to treatment as well as the identification of people with underlying diseases, including high-risk cardiovascular individuals.

Neutrophil-to-lymphocyte Ratio (NLR)

Neutrophils are one of the key components of the innate immune system. These cells move to the site of inflammation as the first immune cell (15). Evidence suggests that the NLR index can be used as an independent prognostic factor in many maladies (16). COVID-19-infected patients have increased NLR which is associated with disease progression and poor prognosis (17, 18). Increased neutrophil counts are associated with an increased expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1); these adhesions are present on the surface of many cells, including endothelial cells (ECs). The adhesion molecules bind neutrophils to the EC surface and cause EC dysfunction (19), which is one of the significant risk factors for CVD. Neutrophils' binding to EC leads to platelet activation, and the rest of the process occurs as mentioned earlier (20).

 The neutrophils increase as the COVID-19 infection progresses. This increase is in line with the rise in the NLR index (17). Previous studies have shown that increased neutrophil count is associated with a decreased blood oxygen level and the need for oxygen therapy (21). Therefore, it can be hypothesized that said event is due to the neutrophil attachment to the EC. The mentioned process worsens patients' clinical symptoms. Generally, it can be concluded that elevated NLR in COVID-19 patients can help identify high-risk individuals who need intubation.

Coagulation Parameter

D-dimer is another marker associated with inflammation and increases in blood after fibrinolysis (22,23). The presence of D-dimer indicates increases clot formation and its destruction by fibrinolytic agents. An increased level of D-dimer is reported in cardiovascular disorders and infections (24,25), and is more important in infectious diseases. An elevated level of D-dimer is associated with severe pneumonia and poor prognosis in COVID-19 cases (26), and it also increases the risk of CVD. It seems that D-dimer increment increases the mortality of these patients due to simultaneous inflammation and cardiac disorders (26,27).

Prothrombin time (PT) is a coagulation test that detects the external coagulation pathway factors' deficiency (28). As it was mentioned before, inflammation activates the platelets and induces blood clot formation, so the amount of coagulation factors is reduced, thereby prolonging the PT test (29). Prolonged PT is also reported in cases of severe pneumonia as a result of COVID-19 and indicates a poor prognosis. PT prolongation has some consequences:

- The amount of coagulation factors is reduced and the risk of bleeding is increased;

- The incidence of thrombosis and the CVD risk are increased;

- The activation of coagulation pathways can be associated with the activation of inflammatory responses, the stimulation of immune cells, and EC dysfunction disorders, which may increase patients' need for intubation (26,30).

Finally, in COVID-19 patients, coagulation markers not only show thrombosis but also indicate inflammatory responses' activation and disease progression. Therefore, these markers can identify high-risk individuals and prevent disease progression.

Conclusion

Recently, the use of hematological markers has become a significant research topic because of the diagnostic

and, occasionally, prognostic role for identifying high-risk individuals. It seems that these markers' evaluation is inexpensive and of high value in the diagnosis and response to treatment. Identifying and monitoring COVID-19 patients, which requires aggressive methods to track patients' clinical status, is a significant problem, and the timely detection and identification of high-risk individuals can help reduce the use of aggressive therapies such as intubation. Evaluating said parameters at the time of diagnosis can increase patient survival by identifying high-risk individuals who need to be intubated.

Study Limitations

One of the limitations of the present study is the small sample size. Also, all participants were patients of a single health center.

Acknowledgments

Ethical approval

This article does not contain any studies on human participants or animals performed by any of the authors.

Funding

Conflict of Interest

Authors declared no conflict of interest.

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