Review Article

The Hemotological Profile in COVID-19 Infection: A Mini-Review

Olufunto Olufela Kalejaiye, Babatunde M Duduyemi[1]

Department of Medicine, College of Medicine, University of Lagos and Lagos University Teaching Hospital, Lagos, Nigeria, [1]Department of Pathology, University of Sierra Leone Teaching Hospitals Complex/College of Medicine and Allied Health Sciences, Freetown, Sierra Leone

Abstract

The report of clusters of pneumonia-like cases in Wuhan, China, on December 31, 2019, began a tumultuous cascade of health, social, and economic disruptions globally. Consequently, this resulted in the coronavirus disease-2019 (COVID-19) pandemic, described as one of the most lethal pandemics the world has had to face. Several aspects of infection and its implications on different organ systems have been reported in formal literature, with more studies generated daily. Although the infection is reported to be dominantly respiratory, it may result in multisystem dysfunction. In this review, we discuss the hematological abnormalities induced by COVID-19 infection. These findings could contribute to a better understanding of the disease pathophysiology and ultimately guide in prognostication, guide assessment, monitoring, and treatment approaches and help develop targeted adjuvant therapies.

Keywords: Coronavirus disease-2019, hematological profile, review

Received on: 26-03-21 **Review completed on:** 23-12-21 **Accepted on:** 25-12-21 **Published on:** ***

Introduction

Coronaviruses (CoVs) are a group of viruses that co-infect humans and other vertebrate animals. CoV infections result in multisystemic damaging affecting the respiratory, gastrointestinal, and central nervous systems of humans, livestock, birds, bats, mice, and many other wild animals.[1] For example, CoVs caused severe acute respiratory syndrome (SARS) emergence in 2002 and the Middle East respiratory syndrome emergence in 2012 when transmission occurred from animals to humans.[2-4] The disease caused by SARS-CoV-2 was called "coronavirus disease 2019" (COVID-19).[5-7] Hematological profiling is an essential component of the management of many conditions.[8] In infections caused by other viruses such as the arboviruses, the hematological parameters of the patients are a useful marker of detection, diagnosis, and monitoring treatment response.[9]

Method

We performed a literature search of online databases including Google, Google Scholar, and PubMed from January 2020 to January 2021, using the following search terms: COVID-19 infection and Hematological profile. Thirty-three articles were found eligible and were used for our review.

Coronavirus Disease-2019 and the Peripheral Blood Cells

Changes in hematological parameters during the COVID-I9 infection have been reported in a few studies carried out worldwide, focusing mainly on white blood cells and platelets.[10] This is not surprising, changes in white cell count remain a focus in the diagnosis, management, and monitoring of other viral infections.[11] However, unlike other viral infections, significantly lower levels of total lymphocyte count and proportions of lymphocytes, thrombocytes, eosinophil, and monocytes have been reported

Address for correspondence: Dr. Olufunto Olufela Kalejaiye, Department of Medicine, College of Medicine, University of Lagos and Lagos University Teaching Hospital, Idi Araba, Lagos, Nigeria.
E-mail: okalejaiye@unilag.edu.ng

Access this article online

Quick Response Code:

Website: www.atpjournal.org

DOI: 10.4103/atp.atp_5_21

How to cite this article: Kalejaiye OO, Duduyemi BM. The hemotological profile in COVID-19 infection: A mini-review. Ann Trop Pathol 2022;XX:XX-XX.

in COVID-19 patients.[12,13] In many reports, these changes in leukocyte count in COVID-19 infection were linked to disease severity, with many COVID-19 patients who did not survive the illness having considerably lower levels of lymphocytes and higher leukocytes levels than patients who survived.[14] In contrast, neutrophils have been noted to be significantly higher in severe cases.[15] A meta-analysis of potential biomarkers associated with severity of COVID-19 infection by Danwang *et al.* in 2020 revealed that severe cases of COVID-19 were more likely to present lymphopenia and thrombocytopenia but not leukopenia.[16] These findings represented a useful marker of differentiation of COVID-19 infection from other causes of febrile illness in the early days of the pandemic, especially in countries like Nigeria where infectious diseases (like malaria) are endemic, and the capacity for testing was limited.[17]

Although the pathophysiology of lymphopenia in COVID-19 infection is still largely unclear, it has been postulated that SARS CoV2 may directly induce cytotoxicity via active viral replication within the lymphocyte pool or indirectly cause lymphocyte damage via cytokine release, which can induce programmed cell death.[18] High levels of glucocorticoids seen in severe COVID-19 cases can also result in downregulation of lymphokine, which is necessary for lymphocyte activation.[16]

In any chronic infection, especially in instances of infectious diseases, it is not uncommon to anticipate a reduction in the mean hemoglobin levels; in COVID-19 infection, minimal to no changes in mean hemoglobin values have been reported.[19] In a recent study by Goel *et al.*, who conducted a systematic review of 3231 COVID-19 cases, it was reported that the mean hemoglobin values were mostly normal. This finding was attributed to the acute course of the disease.[20] Platelet levels are also dysregulated during COVID-19 infection.[21] Goel *et al.*reported thrombocytopenia in about one-third of patients with COVID-19 infection reviewed.[20] This is attributable to infection at the site of blood production (the bone marrow), resulting in a subsequent reduction in platelets' production. It may also increase peripheral destruction of platelets by generating autoantibodies. The inflammation cascade in the lungs can result in platelet activation and formation of microthrombi, rapidly consuming available platelets and resulting in thrombocytopenia. Thrombocytopenia makes patients susceptible to coagulopathy and must be addressed promptly.[16]

The peripheral blood cell parameters are, therefore, useful guide for the prediction of outcomes in COVID-19 patients as reported in the United Kingdom by Abdul-Jawad *et al*.[22] It was reported that neutrophil-to-lymphocyte ratios, platelet-to-lymphocyte ratios, basophil, and lymphocyte counts, and hemoglobin were significant correlates of COVID-19 severity, with lymphopenia having one of the highest predictive accuracies for COVID-19 severity.[22] Similarly, in a multivariable Cox regression model, Chen *et al*. [2] reported that the restored levels of lymphocytes, eosinophils, and platelets could serve as predictors for recovery. In contrast, increased levels of neutrophils and basophils are associated with poorer outcomes.[23]

Therefore, in practice, lymphopenia is the most useful peripheral hematological marker of disease severity and is useful for early identification and stratification of patients who might require admission to the intensive care unit (ICU).[9]

Coronavirus Disease-2019 Infection and Inflammatory Markers

COVID-19 has been linked to a severe systemic immune response driven by a cytokine storm.[24] After the virus enters into the pneumocytes via the angiotensin-converting enzyme 2 receptor, it triggers a systemic inflammatory response and the release of pro-inflammatory cytokines such as interleukin (IL)-2, IL-6, IL-7, monocyte chemoattractant protein -1 (MCP1), and tissue necrosis factor alpha (TNFα) which, in turn, stimulates the production of inflammatory markers such as procalcitonin (PCT) and C-reactive protein (CRP).[16]

Immunological studies that were done on COVID-19-infected patients who were hospitalized show hyperinflammation in about 25%–30% of cases.[22] Cellular and tissue damage primarily results from the hyperinflammation induced by COVID-19 and not necessarily the virus itself. Inflammation at the respiratory tract results in increased capillary permeability, pulmonary edema, and respiratory distress. Inflammation can also trigger reactions around the body and lead to multisystemic organ dysfunction, linked to worsened prognosis regardless of treatment.[16]

Inflammatory markers have been reported to be higher in patients with severe COVID-19 disease. In 2020, Huang *et al.* reported that patients requiring ICU admission had higher concentrations of ILs – IL2, IL7, and IL10, granulocyte colony-stimulating factor, interferon-gamma-induced protein 10, MCP1 macrophage inflammatory protein 1 alpha, and TNFα when compared to those who did not require ICU care.[23] Similarly, Danwang *et al.* in a meta-analysis of 16 studies aimed to summarize the available data on the severity of COVID-19 and common hematological, inflammatory, and biochemical parameters. The studies comprised one cross-sectional survey and 15 case series. The patients had a mean age of 9 to 70.5 years in severe cases and 7.5 to 59.7 years nonsevere cases. They reported that inflammatory (PCT, CRP), hematologic (lymphocyte, thrombocytes), and biochemical (CK-MB, troponin I, D-dimer, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and gamma-glutamyl transferase) biomarkers are significantly associated with severe COVID-19 and suggested that these biomarkers might be helpful in prognostic risk stratification of patients with COVID-19. Severe cases had a threefold higher risk of having higher PCT levels and IL-6 was significantly higher in nonsurvivors compared to survivor cases.[16]

A systematic review of over 3000 COVID-19 cases carried out by Goel *et al.* in 2021 explored the clinical features and related laboratory parameters in COVID-19 infection and evaluated critical factors that may affect the disease course and prognosis. CRP, TNF, and erythrocyte sedimentation rates levels were increased compared to universally accepted laboratory reference values in 59.51%, 58.26%, and 57.14% of cases, respectively. IL-6 and IL-2 levels were elevated in 54.52% and 52.54% of cases, respectively. PCT level was increased by only 6.59% of cases.[20] Thus, early measurement of inflammatory markers can help delineate the severity index of cases and guide the institution of appropriate therapy. Recognized treatment options for the management of cytokine storm include the use of corticosteroids, nonsteroidal anti-inflammatory drugs, (NSAIDS) immunosuppressive, and immunomodulatory therapies (such as tocilizumab, etoposide, and ruxolitinib). There are still controversies over the use of corticosteroids and NSAIDS in the management of cytokine storms in COVID-19 patients.[16-25]

Coronavirus Disease-2019 Infection and Coagulopathy

COVID-19 can result in coagulopathy and has been associated with an increased risk of abnormal bleeding and thromboembolism. Asides earlier explained mechanism of causing thrombocytopenia, COVID-19 has also been linked to liver injury resulting in altered production of clotting factors.[16] Disseminated intravascular coagulation triggered by sepsis in infected patients has also been linked to higher D-dimer levels. Coagulopathy and thrombocytopenia likely result from consumption coagulopathy caused by activation of procoagulant pathways.[16]

Venous thromboembolic events have been reported in COVID-19 patients who are acutely or critically ill and the American Society of Hematology 2021 guidelines have advised that prophylactic-intensity anticoagulation over intermediate-intensity anticoagulation or therapeutic-intensity anticoagulation be used for COVID-19 patients with acute illness or critical illness who are not confirmed or suspected to have venous thromboembolism (VTE). At present, there is no direct high-certainty evidence comparing different types of anticoagulants. The selection of a specific agent (e.g., low-molecular-weight heparin, unfractionated heparin, etc.) may be based on availability, resources required, familiarity, and the aim of minimizing personal protective equipment use or staff exposure to COVID-19-infected patients as well as patient-specific factors (e.g., renal function, history of heparin-induced thrombocytopenia, and concerns about gastrointestinal tract absorption).[26] Danwang *et al.,* in a meta-analysis of potential biomarkers associated with severity of COVID-19 in 2020, found significant differences in D-dimer and prothrombin time (PT) between COVID-19 patients with severe and nonsevere cases, with the former exhibiting higher levels of D-dimer and longer PT. Activated thromboplastin time and fibrinogen levels did not differ significantly between severe and nonsevere cases.[16] Patients with severe COVID-19 diseases are also more likely to have increased serum D-dimers.

D-dimer, a fibrin degradation product, is a widely used initial screening test to diagnose patients with signs or symptoms suggestive of VTE.[27] High levels are suggestive of VTE, but it can also be elevated in other inflammatory conditions such as sepsis.[27] Therefore, it is not surprising that high levels have been found in patients with COVID 19, especially in cases of severe disease, which is associated with cytokine storm, a phenomenon in which there is an overproduction of pro-inflammatory cytokines.[28,29] D-dimer has also been found to predict clinical outcomes in COVID-19 patients.[30] A study by Wang *et al.*, in Wuhan China, found that higher D-dimer levels were seen in nonsurvivors of COVID 19 and were associated with a prolonged hospital stay.[31]

Coagulopathy results in a poorer prognosis in patients with COVID-19. Tang *et al.,* in Wuhan China in a study of the coagulation profile of patients with COVID-19, found that nonsurvivors of COVID infection had significantly higher D-dimer, fibrin degradation product levels, longer PT, and activated partial thromboplastin time than the survivors.[32]

Disseminated intravascular coagulation was also seen in 71.4% of nonsurvivors, unlike in 0.6% of survivors.[32] Regular monitoring of coagulation profile of cases with severe form and prompt correction of noted abnormalities is vital in COVID management to improve prognosis.

Controversy still surrounds the association between blood types and COVID-19. However, some studies have reported that patients with blood type A were more likely to have COVID-19 infection than when compared to patients with blood type O.[33]

Conclusion

Hematological profiling should be incorporated as a routine component of diagnosis, prognostication, and management of COVID-19 patients, especially in low-resources settings like Nigeria.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, *et al.* Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect 2020;9:221-36.
2. Chen Y, Guo D. Molecular mechanisms of coronavirus RNA capping and methylation. Virol Sin 2016;31:3-11.
3. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019;17:181-92.
4. Cauchemez S, Van Kerkhove MD, Riley S, Donnelly CA, Fraser C, Ferguson NM. Transmission scenarios for Middle East Respiratory

Syndrome Coronavirus (MERS-CoV) and how to tell them apart. Euro Surveill 2013;18:20503.
5. Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, *et al.* Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013;503:535-8.
6. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536-44.
7. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020;92:401-2.
8. Etim NN, Williams ME, Akpabio U, Offiong EE. Haematological parameters and factors affecting their values. Agric Sci 2014;2:37-47.
9. Duarte FB, Lemes RP, Duarte IA, Duarte BA, Duarte JV. Hematological changes in COVID-19 infections. Rev Assoc Med Bras (1992) 2020;66:99.
10. Letícia de Oliveira Toledo S, Sousa Nogueira L, das Graças Carvalho M, Romana Alves Rios D, de Barros Pinheiro M. COVID-19: Review and hematologic impact. Clin Chim Acta 2020;510:170-6.
11. Warny M, Helby J, Nordestgaard BG, Birgens H, Bojesen SE. Lymphopenia and risk of infection and infection-related death in 98,344 individuals from a prospective Danish population-based study. PLoS Med 2018;15:e1002685.
12. Wang C, Deng R, Gou L, Fu Z, Zhang X, Shao F, *et al.* Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. Ann Transl Med 2020;8:593.
13. Chen J, Pan Y, Li G, Xu W, Zhang L, Yuan S, *et al.* Distinguishing between COVID-19 and influenza during the early stages by measurement of peripheral blood parameters. J Med Virol 2021;93:1029-37.
14. Zhao Y, Nie HX, Hu K, Wu XJ, Zhang YT, Wang MM, *et al.* Abnormal immunity of non-survivors with COVID-19: Predictors for mortality. Infect Dis Poverty 2020;9:108.
15. Tomar B, Anders HJ, Desai J, Mulay SR. Neutrophils and neutrophil extracellular traps drive necroinflammation in COVID-19. Cells 2020;9:1383.
16. Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res 2020;8:37.
17. Hussein MI, Albashir AA, Elawad OA, Homeida A. Malaria and COVID-19: Unmasking their ties. Malar J 2020;19:457.
18. Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. Immunol Lett 2020;225:31-2.
19. DeMartino AW, Rose JJ, Amdahl MB, Dent MR, Shah FA, Bain W, *et al.* No evidence of hemoglobin damage by SARS-CoV-2 infection. Haematologica 2020;105:2769-73.
20. Goel H, Gupta I, Mourya M, Gill S, Chopra A, Ranjan A, *et al.* A systematic review of clinical and laboratory parameters of 3,000 COVID-19 cases. Obstet Gynecol Sci 2021;64:174-89.
21. Koupenova M. Potential role of platelets in COVID-19: Implications for thrombosis. Res Pract Thromb Haemost 2020;4:737-40.
22. Abdul-Jawad S, Baù L, Alaguthurai T, Del Molino Del Barrio I, Laing AG, Hayday TS, *et al.* Acute immune signatures and their legacies in severe acute respiratory syndrome coronavirus-2 infected cancer patients. Cancer Cell 2021;39:257-75.e6.
23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
24. Mangalmurti N, Hunter CA. Cytokine storms: Understanding COVID-19. Immunity 2020;53:19-25.
25. Patel M, Dominguez E, Sacher D, Desai P, Chandar A, Bromberg M, *et al.* Etoposide as salvage therapy for cytokine storm due to coronavirus disease 2019. Chest 2021;159:e7-11.
26. Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, *et al.* American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021;5:872-88.
27. Pulivarthi S, Gurram MK. Effectiveness of d-dimer as a screening test for venous thromboembolism: An update. N Am J Med Sci 2014;6:491-9.
28. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 2020;80:607-13.
29. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al.* COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
30. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, *et al.* D-dimer levels on admission to predict in-hospital mortality in patients with COVID-19. J Thromb Haemost 2020;18:1324-9.
31. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
32. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-7.
33. Urgessa F. Biochemical, Hematological and Immunological Parameters among Covid19 Infected Patients. Int Aca. J App Biomed Sci.2020;1:1-5.