Review Article

A Narrative Review; Relation of Coronavirus Disease 2019 (COVID-19) with Several Hematological Disorders

Amirmohsen Mahdavian [1], Fatemeh Pouran [1], Hossein Aghazadeh [1], Elina Rahimi Zamani [1], Masoumeh Navidinia [2, *]

[1] Student Research Committee, Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding author: Department of Laboratory Sciences, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Quds Sq., Tehran, Iran . Tel/Fax: +98-2126850560, Email: m.navidinia@yahoo.com

Abstract

Context: It's crucial to monitor hematologic biomarkers in patients with coronavirus disease 2019 (COVID-19) to identify abnormalities and guide treatment decisions. These biomarkers provide valuable information about the severity of the disease and assist healthcare providers in making informed decisions about patient care.

Evidence Acquisition: The present study reviewed the most recent literature on hematologic biomarker abnormalities in patients with COVID-19 and considered their clinical significance.

Results: Various abnormalities were observed in hematologic biomarkers, including prothrombin time (PT), partial thromboplastin time (PTT), red blood cell indices, interferon regulatory factor (IRF-7), and white blood cell (WBC) count. Notably, significant lymphocytopenia, thrombocytopenia, and leukocytosis were reported in patients with severe and fatal COVID-19 compared to those with non-severe disease and survivors.

Conclusions: Hematologic biomarkers play a crucial role in understanding COVID-19 pathogenesis and guiding clinical management. Utilizing these markers allows clinicians to assess disease severity, predict prognosis, and tailor treatment strategies to improve patient outcomes. Continued research in this area is essential to fully realize the potential of hematologic biomarkers for COVID-19 management.

Keywords: Hematological Abnormalities, Coronavirus Disease 2019 (COVID-19), Neutropenia, Thrombocytopenia, Leukopenia

1. Context

Coronaviruses (CoVs) are zoonotic viruses belonging to the single-stranded RNA viruses family. Coronaviruses can infect a variety of animals and are associated with a range of diseases, including respiratory, cardiovascular, enteric, hematologic, and neurologic disorders. They frequently cause a range of symptoms, including respiratory and gastrointestinal tract diseases, common cold, pneumonia with symptoms such as cough, dyspnea, tachypnea, and chest pain, bronchitis, and severe acute respiratory distress syndrome (ARDS) with arterial hypoxemia and dyspnea. Other symptoms can include coagulopathy, multi-organ failure, cystic fibrosis, asthma, chronic obstructive pulmonary disease, and even death in humans (1).

Coronaviruses were previously known to primarily cause lower respiratory tract infections, but it is now understood that they can affect multiple systems. Several hematological abnormalities have been observed, including changes in hemoglobin, platelets, white blood cells, and coagulation/fibrinolytic factors. Thrombocytopenia, lymphopenia, and elevated D-dimer levels are common hematological abnormalities in coronavirus disease 2019 (COVID-19). These changes are notably more frequent and pronounced in patients with severe COVID-19 and could be used as biomarkers to identify individuals requiring hospitalization and intensive care. Monitoring coagulation abnormalities

closely and taking appropriate actions to prevent or mitigate their adverse effects is crucial (2). Based on these observations, we have decided to examine the abnormalities related to hematologic biomarkers in patients with COVID-19.

2. Evidence Acquisition

COVID-19, caused by the SARS-CoV-2 virus, can significantly impact the hematologic system, leading to various abnormalities that serve as valuable biomarkers for disease severity, prognosis, and therapeutic monitoring. In this narrative review, we identify hematologic biomarker abnormalities in patients with COVID-19 and discuss their clinical significance based on the most recent information.

3. Results

COVID-19 is classified as an infectious-inflammatory disease that primarily affects the lungs. According to a retrospective analysis, dry cough (60%) and fever (89%) were the most prevalent clinical symptoms (3). Recently, multi-organ involvement with various injury pathways has been identified. Disruptions in the balance between an effective antiviral response and an uncontrolled immune response are key determinants of the severity of COVID-19 progression. Comorbidities have been correlated with hematological, immunological, and biochemical parameters. When CoVs infect endothelial and monocyte cells, a complex cytokine storm and eventual intravascular thrombosis can result (1, 2). In this context, we examined some of the most prevalent hematologic abnormalities in patients with COVID-19.

3.1. Hemoglobin Variants and Diabetic Patients

Diabetes is a risk factor for the development and prognosis of COVID-19. There is limited information about the relationship between inflammation, glycated hemoglobin (HbA1c) levels, and the prognosis of COVID-19 patients. In the study by Wang et al. (4), 73% of the patients had comorbid conditions, including hypertension and diabetes, followed by cardiovascular, cerebrovascular, and chronic kidney diseases. At the time of admission, oxygen saturation (SaO_2) varied between 59% and 99%. Significant differences were observed in parameters such as C-reactive protein (CRP), ESR, IL-6 levels, SaO_2, serum ferritin, and fibrinogen (FBG). Glycated hemoglobin levels had a linear negative correlation with SaO_2, while serum ferritin, FBG, CRP, and ESR levels had a linear positive correlation with HbA1c.

In COVID-19 patients, high HbA1c levels were associated with lower arterial SaO_2, inflammation, and hypercoagulability, and patients with diabetes had a higher mortality rate. Therefore, determining HbA1c levels after hospital admission could help evaluate the prognosis of COVID-19 patients, as well as assess hypercoagulability and inflammation (4). Additionally, in patients with diabetes who developed ARDS, levels of D-dimer and lactate dehydrogenase were increased (5).

Hemoglobinopathy, hypoxia, and iron overload in cells could also play a role. Different studies have identified two possible pathophysiological mechanisms: One involves the interaction of SARS-CoV-2 with the hemoglobin molecule via the CD26 or CD147 receptors found on erythrocytes and/or blood cell precursors. The other mechanism involves a viral spike protein that mimics hepcidin, resulting in the induction of ferroportin blockage. Cavezzi et al. emphasized the pathological metabolic pathways resulting from iron metabolism dysregulation and hemoglobin denaturation. The following factors contribute to decreased hemoglobin function: (a) iron overload in cells and tissues (hyperferritinemia); (b) hypoxia and systemic hypoxia; (c) release of free toxic heme; (d) decreased nitric oxide levels; (e) activation of the clotting cascade; (f) ferroptosis with lipoperoxidation and oxidative stress; and (g) mitochondrial apoptosis and degeneration (6).

Several clinical syndromes have been reported, including arterial vasoconstriction, altered alveolar-capillary barriers, arteriovenous thromboembolism, endothelitis, vasospastic acrosyndrome, and sideroblastic-like anemia. A more thorough diagnosis and treatment plan for COVID-19 was suggested, including potential adjuvant treatments for hemoglobin dysfunction, iron overload, and generalized hypoxia (7, 8).

Diabetes is a risk factor for COVID-19 development, but there is limited information on the relationship between HbA1c levels, inflammation, and the prognosis of COVID-19 patients. Some inflammatory markers, such as ESR, CRP, serum ferritin, and FBG, were positively correlated with HbA1c levels, whereas SaO_2 was negatively correlated with HbA1c levels. Interestingly, in patients with elevated HbA1c but without diabetes,

levels of inflammatory markers and FBG were also significantly increased. In COVID-19 patients, elevated HbA1c was associated with inflammation, low SaO_2, and hypercoagulability. It has also been reported that the mortality rate is higher in patients with diabetes. Based on previous studies, measuring HbA1c levels is useful for assessing hypercoagulability and inflammation in the prognosis of COVID-19 patients after hospital admission (4, 9, 10). Low hemoglobin (Hb) levels significantly predicted ICU admission and mortality (P = 0.004) (11).

3.2. Coagulation Abnormalities (Prothrombin Time, Partial Thromboplastin Time) and Platelet Reactivity

Patients with COVID-19 must receive prophylactic anticoagulation due to the disease's impact on the coagulation system, which is associated with high rates of morbidity and mortality. Pulmonary microthromboses and pulmonary embolism can result from arterial and venous thromboses. Identifying these complications and promptly initiating therapeutic anticoagulation is crucial for effective management. Although less common, virus-induced disseminated intravascular coagulation (DIC) shares some similarities with traditional DIC. Poor outcomes are associated with elevated levels of hematologic biomarkers such as D-dimer, C-reactive protein, lactate dehydrogenase, and ferritin. Understanding the pathophysiology of COVID-19 and identifying factors linked to poor prognosis are essential for improving patient outcomes (3).

The high frequency of thrombosis in COVID-19 is a concerning feature, particularly among patients admitted to the intensive care unit due to respiratory complications. Thrombotic events are widespread and include deep vein thrombosis (DVT), arterial thrombotic events, in situ pulmonary arterial thrombosis (PAT), and pulmonary embolism (PE). There have also been reports of unusual thrombotic events such as mesenteric artery and vein thrombosis, cerebral venous sinus thrombosis, neutrophilia, lymphopenia, thrombocytosis, and mild thrombocytopenia. Elevated levels of prothrombin time (PT), activated partial thromboplastin time (aPTT), von Willebrand factor, fibrin D-dimer, and hyperfibrinogenemia are among the hematological abnormalities observed in COVID-19 patients. Many of these abnormal hematological parameters are indicative of a poor prognosis, including a higher likelihood of developing severe respiratory disease and death, even at the time of initial hospitalization. Some studies have reported progression to diffuse intravascular coagulation in fatal COVID-19 cases. It has been demonstrated that, during the prevention and treatment of COVID-19 thrombosis using low molecular-weight heparin or unfractionated heparin, vigilance for heparin-induced thrombocytopenia (HIT) is necessary (12). Elevated D-dimer levels have also been reported among COVID-19 patients. There is some evidence linking high rates of venous thromboembolism (VTE) and DIC with COVID-19. Parameters such as procalcitonin, fibrinogen, ESR, ferritin, and CRP are typically higher in patients with thrombotic complications compared to those without. Clinically, while DIC rarely presents with reduced fibrinogen and thrombocytopenia, it is associated with significant bleeding manifestations. Therefore, to determine the potential benefit of intensified anticoagulant prophylaxis in COVID-19 patients, randomized trials are needed, given the observed bleeding rates (13, 14).

It was also discovered that COVID-19 was associated with rates of thrombosis and bleeding comparable to those observed in hospitalized patients with similar levels of critical illness. Elevated D-dimer levels at the time of initial presentation indicated a higher likelihood of thrombotic complications, severe illness, and death. In addition to D-dimer, inflammatory markers, rather than coagulation parameters, were more frequently associated with thrombosis (12).

3.3. Leukocyte Morphology and Count

White blood cell levels were found to be significantly correlated with mortality. Using the second quartile threshold ($> 6.16 \times 10^9$/L), regression analysis revealed a significant correlation between WBC levels and death. Kaplan-Meier survival analysis indicated a significantly lower cumulative survival rate for patients with leukopenia (P = 0.001) below 6.16×10^9/L. Liu et al. (15) reported that about 80% of patients had either a normal or reduced number of white blood cells, with 72.3% exhibiting lymphocytopenia. Conversely, all patients with negative PCR results had mostly normal peripheral white blood cell counts. However, patients with higher WBC counts were at greater risk of mortality (15-17).

It was also demonstrated that neutrophil (NEU) count, lactate dehydrogenase (LDH), CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum urea levels were all significantly higher in patients with positive reverse transcriptase PCR (RT-PCR) results. Additionally, these patients had lower serum

albumin levels and WBC counts compared to others. C-reactive protein, ALT, LDH, NEU count, and urea all demonstrated excellent accuracy in predicting positive RT-PCR cases for COVID-19 [18].

It has been reported that leukopenia, lymphopenia, high-sensitivity CRP (hsCRP), ESR, and fibrinogen concentrations are elevated in COVID-19 patients. Additionally, after treatment, levels of AST, hsCRP, and LDH decreased, while the numbers of RBCs, platelets, and pre-albumin increased significantly [19].

In severe and critical cases, the total number of lymphocytes, CD3, and CD4 T-cell levels were reduced in patients who developed ARDS. However, IL-6 levels were high in both mild and severe cases. Regardless of disease severity or the presence of comorbid conditions, ESR, WBC count, and CRP levels increased. In patients with severe and critical COVID-19, procalcitonin levels varied, showing either an increase or decrease, but $CD3^+$, $CD4^+$ T cells, and the total lymphocyte count were found to be low. Elevated levels of CRP, ESR, and IL-6 were noted. Understanding the inflammatory response in COVID-19 patients is essential for developing better therapeutic and management approaches [2, 20].

Hemocytometric changes in COVID-19 infection, both early and throughout the course of the disease, have been examined in numerous studies. The most common abnormalities reported include lymphopenia and an increased neutrophil/lymphocyte ratio. These alterations become more pronounced over time, especially in patients with advanced disease [21].

It has been demonstrated that patients with severe COVID-19 exhibit lymphopenia and decreased levels of B cells, $CD4^+$ T cells, $CD8^+$ T cells, and natural killer (NK) cells compared to patients with mild COVID-19. Notably, $CD8^+$ T cells and the $CD4^+/CD8^+$ ratio showed a significant correlation with the inflammatory status of COVID-19. In non-responsive cases, no significant changes were observed in these subsets. Multivariate analysis identified an increased $CD4^+/CD8^+$ ratio and a decrease in $CD8^+$ T cells and B cells post-treatment as independent predictors. Additionally, alterations in peripheral lymphocyte subsets were associated with COVID-19 severity and treatment effectiveness, with $CD8^+$ T cells frequently serving as an independent predictor [22]. On the other hand, the average number of neutrophils was significantly higher in patients who died ($P = 0.032$) [11].

Granulocyte colony-stimulating factors (G-CSFs) promote cytokine production and neutrophil proliferation. Neutropenia has frequently been treated with G-CSFs, despite limited efficacy data. A relationship has been reported between respiratory distress and neutropenia, but not with G-CSFs. In most clinical settings, G-CSFs have a history of being safe and well-tolerated. However, there is limited information about the effects of G-CSFs in severe inflammatory conditions like COVID-19. Taha et al. reported a case where COVID-19 with neutropenia deteriorated quickly after receiving G-CSF. They observed a faster recovery from neutropenia following G-CSF administration. The rapid recovery from neutropenia and the active inflammatory response in COVID-19 patients present a significant challenge regarding the positive effects of G-CSF in these patients [23]. Figure 1 shows the mechanisms of hematological abnormalities in COVID-19 [24].

3.4. Immunological Markers

In patients infected with COVID-19, ω-3 polyunsaturated fatty acids (n3-PUFAs) can have beneficial effects on the immune system. It has been established that ω-3 PUFA supplementation may improve clinical outcomes in patients with COVID-19, including promising effects on acidosis and renal function. ω-3 PUFA supplementation resulted in significantly higher levels of arterial pH and HCO_3, and lower levels of BUN, Cr, and K. However, ω-3 PUFA supplementation did not significantly affect blood glucose, Ca, P, Na, HCT, mean arterial blood pressure (MAP), SaO_2, PO_2, PCO_2, WBCs, Glasgow Coma Scale (GCS), Hb, platelet (Plt) count, PTT, or albumin. Despite this, some parameters related to respiratory and kidney function in patients with acute COVID-19 showed improvement with ω-3 supplementation. Additionally, ω-3 supplementation may potentially increase lymphocyte count and GCS. It has been reported that patients with severe COVID-19, possibly due to microcirculation dysfunction, experience severe metabolic and respiratory acidosis [25-29].

Cellular metabolism has been found to be activated during viral infection and the replication of SARS-CoV-2. A serine-threonine kinase that contributes to cell proliferation is mammalian targets of rapamycin (mTOR). During viral replication, the mTOR pathway facilitates the efficient synthesis of ribosomes and proteins by activating downstream genes such as the
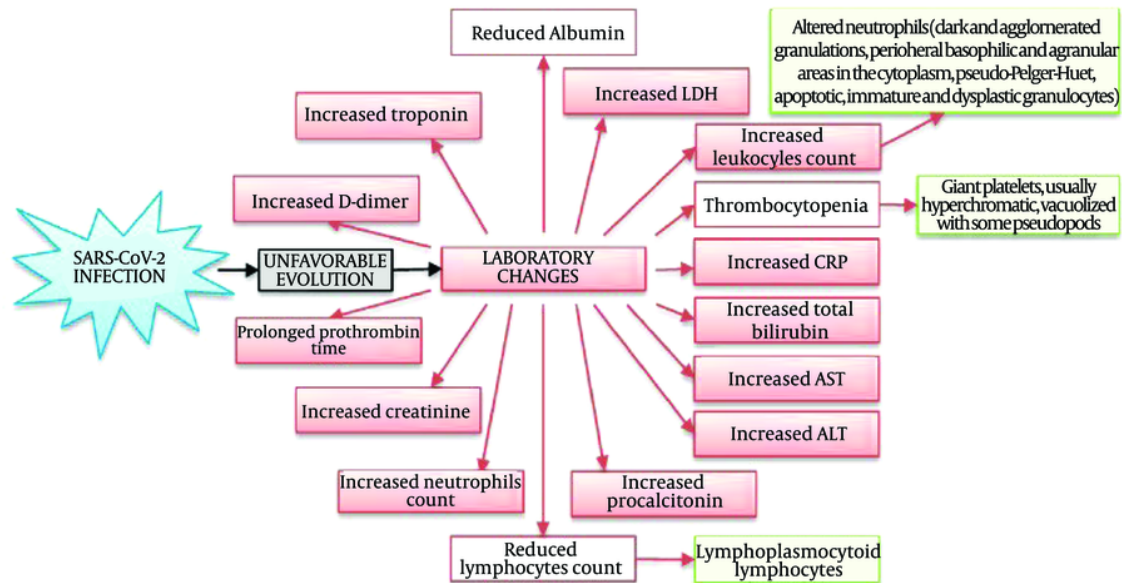
Figure 1. Main laboratory changes in patients with an unfavorable evolution of SARS-CoV-2 infection (24)

eukaryotic translational initiation factor 4E-binding protein 1 (4-E-BP1) and the ribosomal protein S6 kinase beta 1 (S6K1). Mammalian targets of rapamycin also enables the activation of type-I interferon (IFN) genes by mediating the association of the adapter protein MyD88 and the interferon regulatory factor (IRF-7) in plasmacytoid dendritic cells (pDCs). Additionally, viruses can deactivate the IFN pathway by disrupting the IRF-7-mediated activation of IFN-gene transcription. Consequently, mTOR inhibitors could help prevent viral infection and replication in their early stages. Intriguingly, viral survival in host cells may be increased because the virus-encoded E3 ubiquitin ligase ring-finger and CHY zinc-finger domain-containing 1 (RCHY1) degrades the important tumor-suppressor protein p53. Therefore, microRNAs can act as p53 activators and mTOR inhibitors, targeting the 3'-UTR of mTOR RPS6KB1. Both mechanisms may effectively inhibit viral replication in human respiratory tract and lung cells (30).

In response to the coronavirus, host immune responses vigorously attempt to combat the infection using all available cells and cytokines. Chronic SARS-CoV-2 infections can exhaust T cells and natural killer cells, leading to lymphopenia and a reduced cell count. The inability to clear the infected organs causes the

immune system to become hyperinflamed, resulting in the release of excessive inflammatory cytokines to compensate for the depleted immune system and lower lymphocyte counts. This results in cytokine storm syndrome (31).

Several indices in patients with acute COVID-19 were significantly higher compared to those in mild cases ($P \leq 0.05$), including neutrophil count, eosinophil count (EOs), WBC count, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), red blood cell distribution width-standard deviation (RDW-SD), lymphocyte count (Lym), and high fluorescent cell percent (HFCP). Assessing combined NLR and RDW-SD parameters can be a useful indicator to help clinicians anticipate the severity of COVID-19 in patients (32).

A higher NLR was significantly associated with mortality. Non-surviving patients had notably lower Plt counts ($P = 0.023$). Compared to survivors, non-survivors had significantly lower Plt and Hb counts ($P = 0.001$ for both). The PLR was also significantly higher among non-survivors ($P = 0.034$) and correlated with mortality. It has been suggested that hematological laboratory parameters are crucial for developing effective diagnosis and treatment plans for infectious diseases. In hospitalized COVID-19 patients, parameters such as PLR,

NLR, Hb, low Plt, prolonged PT, and elevated d-dimer, along with inflammatory markers, can serve as hematologic predictors of severe outcomes (31).

3.5. XGBoost Algorithm Scoring

According to the feature importance scoring of the XGBoost algorithm (a gradient-boosting decision tree method used globally by data scientists and researchers to optimize machine-learning models), MCHC, INR, albumin, EOs, and PT were identified as the five most useful routine blood parameters for diagnosing COVID-19.

Changes in blood parameters in severe COVID-19 patients resemble those seen in bacterial infections more than in viral infections, as indicated by T-distributed stochastic neighbor embedding (t-SNE) visualization. The t-SNE technique is a dimensionality reduction method that helps visualize high-dimensional data. The reported diagnostic accuracy of this approach is likely supportive of RT-PCR and chest CT studies, if not at least comparable to them. Patients exhibiting symptoms such as fever, coughing, and myalgia could have their preliminary routine blood tests evaluated using this diagnostic tool. Those with positive COVID-19 indications would then undergo standard RT-PCR tests for confirmation. The outcomes of this approach are claimed to significantly aid in the diagnosis of COVID-19 (33).

3.6. Age-Dependent Differences in the COVID-19 Intensity

There are several studies on age-dependent differences in COVID-19 intensity. Explanations for the disparity between the intensity of COVID-19 in children and adults include risk factors for adults and protective factors for children. It has been shown that many parameters are age-dependent, including:

- Changes in clotting function

- Endothelial damage

- Higher density, greater affinity, and different distribution of transmembrane serine protease 2 and angiotensin-converting enzyme 2 receptors

- Pre-existing coronavirus antibodies (including antibody-dependent enhancement) and T cells

- Immunosenescence and inflammation, including the effects of chronic cytomegalovirus infection

- A higher prevalence of comorbidities associated with diabetes

Children may be protected by factors such as different microbiota, distinct innate and adaptive immune systems, pre-existing immunity to coronaviruses, more frequent recurrent infections, higher levels of melatonin, less intense SARS-CoV-2 exposure, and protective off-target effects of live vaccines (34, 35).

It has been demonstrated that both PLR and NLR are readily available measurements linked to inflammation and prognosis in various conditions. The relationship between PLR and NLR and the severity of COVID-19 has been identified using available data. PLR and NLR can serve as separate prognostic markers of disease severity (36).

3.7. Abnormal Red Blood Cells

Red blood cell distribution width, which has previously been shown to be a helpful prognostic parameter in various serious diseases and infectious illnesses, was examined by Henry et al. (35) in patients with COVID-19. As COVID-19 severity increased, a progressive rise in RDW was observed. In multivariate analysis, elevated RDW was associated with 9-fold and 16-fold increased odds of severe COVID-19 and acute kidney injury (AKI), respectively. Based on these findings, RDW should be included in the routine laboratory assessment and monitoring of COVID-19 (35).

Figure 2 illustrates COVID-19-associated hematologic manifestations, including changes in blood cell counts (lymphopenia, neutrophilia, thrombocytopenia), coagulation disorders (DIC, increased risk of VTE), and abnormal levels of D-dimer, CRP, LDH, and clotting factors. These issues highlight the complex interplay between the virus, immune response, and blood clotting (23). Figure 3 presents the mechanisms of hematological abnormalities in COVID-19 (36).

4. Conclusions

According to our study, several biomarkers for predicting severe and fatal COVID-19 were identified, which may potentially aid in risk stratification models. These findings could delineate a new etiological pathway for future exploration. Therefore, clinicians should be aware of the potential paraclinical indicators in COVID-19 patients to avoid neglecting or overdiagnosing cases.
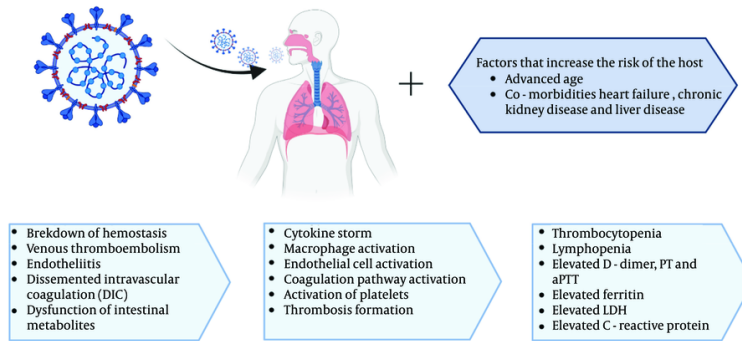
Figure 2. Coronavirus disease 2019 (COVID-19)-associated hematologic manifestations in patients (23)
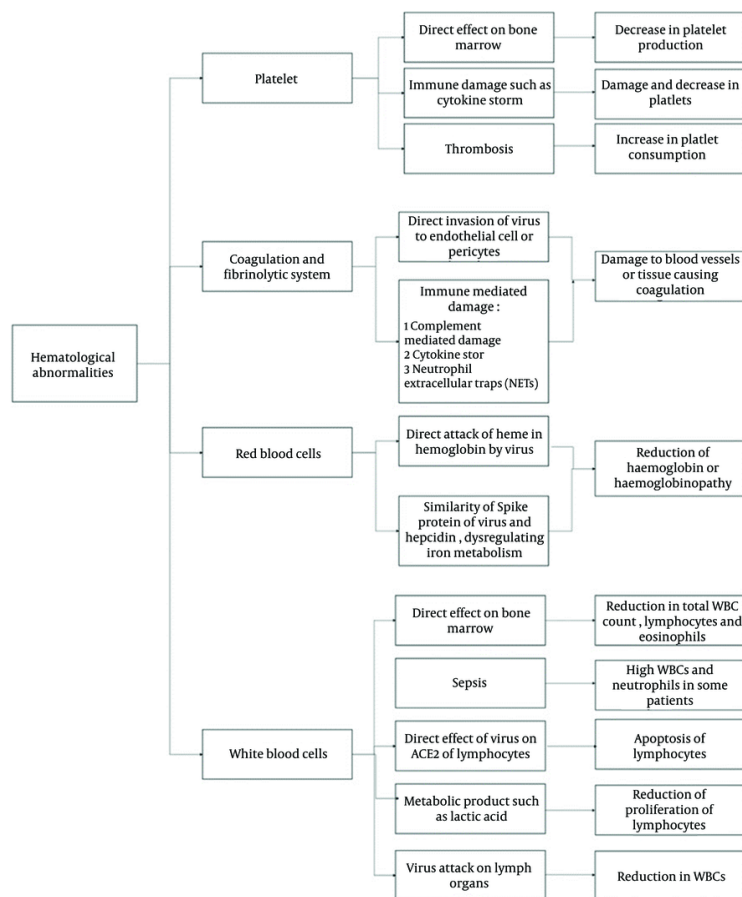

Figure 3. Mechanisms of hematological abnormalities in coronavirus disease 2019 (COVID-19) (36)

I would like to express my special thanks of gratitude

to medical laboratory staff, who gave us the golden opportunity to do this wonderful project.

References

1. Navidinia M, Goudarzi M. The Main Associated Symptoms Related to COVID-19 (Coronavirus Disease 2019) Among Pediatric Patients. *Arch Adv Biosci*. 2020;**11**(3):64-72. https://doi.org/10.22037/aab.v11i3.30707.

2. Rahman A, Niloofa R, Jayarajah U, De Mel S, Abeysuriya V, Seneviratne SL. Hematological Abnormalities in COVID-19: A Narrative Review. *Am J Trop Med Hyg*. 2021;**104**(4):1188-201. [PubMed ID: 33606667]. [PubMed Central ID: PMC8045618]. https://doi.org/10.4269/ajtmh.20-1536.

3. Rahi MS, Jindal V, Reyes SP, Gunasekaran K, Gupta R, Jaiyesimi I. Hematologic disorders associated with COVID-19: a review. *Ann Hematol*. 2021;**100**(2):309-20. [PubMed ID: 33415422]. [PubMed Central ID: PMC7789889]. https://doi.org/10.1007/s00277-020-04366-y.

4. Wang Z, Du Z, Zhu F. Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. *Diabetes Res Clin Pract*. 2020;**164**:108214. [PubMed ID: 32416121]. [PubMed Central ID: PMC7233217]. https://doi.org/10.1016/j.diabres.2020.108214.

5. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci*. 2020;**57**(6):389-99. [PubMed ID: 32503382]. [PubMed Central ID: PMC7284147]. https://doi.org/10.1080/10408363.2020.1770685.

6. Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. *Clin Pract*. 2020;**10**(2):1271. [PubMed ID: 32509258]. [PubMed Central ID: PMC7267810]. https://doi.org/10.4081/cp.2020.1271.

7. Pittman RN. Chapter 7, Oxygen Transport in Normal and Pathological Situations: Defects and Compensations. *Regulation of Tissue Oxygenation*. San Rafael, CA: Morgan & Claypool Life Sciences; 2011.

8. Landa N, Mendieta-Eckert M, Fonda-Pascual P, Aguirre T. Chilblain-like lesions on feet and hands during the COVID-19 Pandemic. *Int J Dermatol*. 2020;**59**(6):739-43. [PubMed ID: 32329897]. [PubMed Central ID: PMC7264591]. https://doi.org/10.1111/ijd.14937.

9. Philips BJ, Meguer JX, Redman J, Baker EH. Factors determining the appearance of glucose in upper and lower respiratory tract secretions. *Intensive Care Med*. 2003;**29**(12):2204-10. [PubMed ID: 14647890]. https://doi.org/10.1007/s00134-003-1961-2.

10. Klekotka RB, Mizgala E, Krol W. The etiology of lower respiratory tract infections in people with diabetes. *Pneumonol Alergol Pol*. 2015;**83**(5):401-8. [PubMed ID: 26379004]. https://doi.org/10.5603/PiAP.2015.0065.

11. Mousavi SA, Rad S, Rostami T, Rostami M, Mousavi SA, Mirhoseini SA, et al. Hematologic predictors of mortality in hospitalized patients with COVID-19: a comparative study. *Hematology*. 2020;**25**(1):383-8. [PubMed ID: 33124971]. https://doi.org/10.1080/16078454.2020.1833435.

12. Warkentin TE, Kaatz S. COVID-19 versus HIT hypercoagulability. *Thromb Res*. 2020;**196**:38-51. [PubMed ID: 32841919]. [PubMed Central ID: PMC7416717]. https://doi.org/10.1016/j.thromres.2020.08.017.

13. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;**136**(4):489-500. [PubMed ID: 32492712]. [PubMed Central ID: PMC7378457]. https://doi.org/10.1182/blood.2020006520.

14. Zhu B, Feng X, Jiang C, Mi S, Yang L, Zhao Z, et al. Correlation between white blood cell count at admission and mortality in COVID-19 patients: a retrospective study. *BMC Infect Dis*. 2021;**21**(1):574. [PubMed ID: 34126954]. [PubMed Central ID: PMC8202964]. https://doi.org/10.1186/s12879-021-06277-3.

15. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. 2020;**133**(9):1025-31. [PubMed ID: 32044814]. [PubMed Central ID: PMC7147277]. https://doi.org/10.1097/CM9.0000000000000744.

16. Zhang MQ, Wang XH, Chen YL, Zhao KL, Cai YQ, An CL, et al. [Clinical features of 2019 novel coronavirus pneumonia in the early stage from a fever clinic in Beijing]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;**43**(0). E013. Chinese. [PubMed ID: 32061066]. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.0013.

17. Mardani R, Ahmadi Vasmehjani A, Zali F, Gholami A, Mousavi Nasab SD, Kaghazian H, et al. Laboratory Parameters in Detection of COVID-19 Patients with Positive RT-PCR; a Diagnostic Accuracy Study. *Arch Acad Emerg Med*. 2020;**8**(1). e43. [PubMed ID: 32259132]. [PubMed Central ID: PMC7130449].

18. Yu S. Comparison of Clinical Characteristics and Peripheral Blood Tests of COVID-19 and Influenza B Patients. *Am J Trop Med Hyg*. 2023;**108**(5):1028-30. [PubMed ID: 36913928]. [PubMed Central ID: PMC10160907]. https://doi.org/10.4269/ajtmh.22-0620.

19. Khartabil TA, Russcher H, van der Ven A, de Rijke YB. A summary of the diagnostic and prognostic value of hemocytometry markers in COVID-19 patients. *Crit Rev Clin Lab Sci*. 2020;**57**(6):415-31. [PubMed ID: 32568604]. https://doi.org/10.1080/10408363.2020.1774736.

20. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. *J Infect Dis*. 2020;**221**(11):1762-9. [PubMed ID: 32227123]. [PubMed Central ID: PMC7184346]. https://doi.org/10.1093/infdis/jiaa150.

21. Doaei S, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F, Bagheri SE, et al. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. *J Transl Med*. 2021;**19**(1):128. [PubMed ID: 33781275]. [PubMed Central ID: PMC8006115]. https://doi.org/10.1186/s12967-021-02795-5.

22. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. *CNS Neurosci Ther*. 2020;**26**(5):499-501. [PubMed ID: 32266761]. [PubMed Central ID: PMC7163592]. https://doi.org/10.1111/cns.13372.

23. Taha M, Sharma A, Soubani A. Clinical deterioration during neutropenia recovery after G-CSF therapy in patient with COVID-19.

Respir Med Case Rep. 2020;**31**:101231. [PubMed ID: 32999856]. [PubMed Central ID: PMC7515585]. https://doi.org/10.1016/j.rmcr.2020.101231.

24. Leticia de Oliveira Toledo S, Sousa Nogueira L, das Gracas Carvalho M, Romana Alves Rios D, de Barros Pinheiro M. COVID-19: Review and hematologic impact. *Clin Chim Acta*. 2020;**510**:170-6. [PubMed ID: 32659224]. [PubMed Central ID: PMC7351669]. https://doi.org/10.1016/j.cca.2020.07.016.

25. Vasil'ev AP, Strel'tsova NN, Sekisova MA. [Effect of omega-3 fatty acids on the serum lipid profile and microcirculation in patients with metabolic syndrome and hypertensive disease]. *Klin Med (Mosk)*. 2009;**87**(4):37-41. Russian. [PubMed ID: 19514319].

26. Weitzel LR, Mayles WJ, Sandoval PA, Wischmeyer PE. Effects of pharmaconutrients on cellular dysfunction and the microcirculation in critical illness. *Curr Opin Anaesthesiol*. 2009;**22**(2):177-83. [PubMed ID: 19307892]. https://doi.org/10.1097/ACO.0b013e328328d32f.

27. Ramaiah MJ. mTOR inhibition and p53 activation, microRNAs: The possible therapy against pandemic COVID-19. *Gene Rep*. 2020;**20**:100765. [PubMed ID: 32835132]. [PubMed Central ID: PMC7324924]. https://doi.org/10.1016/j.genrep.2020.100765.

28. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. *Cell Biol Int*. 2020;**44**(9):1792-7. [PubMed ID: 32458561]. [PubMed Central ID: PMC7283672]. https://doi.org/10.1002/cbin.11403.

29. 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**(9):593. [PubMed ID: 32566620]. [PubMed Central ID: PMC7290538]. https://doi.org/10.21037/atm-20-3391.

30. Kukar M, Guncar G, Vovko T, Podnar S, Cernelc P, Brvar M, et al. COVID-19 diagnosis by routine blood tests using machine learning. *Sci Rep*. 2021;**11**(1):10738. [PubMed ID: 34031483]. [PubMed Central ID: PMC8144373]. https://doi.org/10.1038/s41598-021-90265-9.

31. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child*. 2021;**106**(5):429-39. [PubMed ID: 33262177]. https://doi.org/10.1136/archdischild-2020-320338.

32. Chan AS, Rout A. Use of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in COVID-19. *J Clin Med Res*. 2020;**12**(7):448-53. [PubMed ID: 32655740]. [PubMed Central ID: PMC7331861]. https://doi.org/10.14740/jocmr4240.

33. Heller A, Koch T. [Immunonutrition with omega-3-fatty acids. Are new anti-inflammatory strategies in sight?]. *Zentralbl Chir*. 2000;**125**(2):123-36. German. [PubMed ID: 10743032].

34. Mahmood A, Mehmood S, Zhang W; Shama. Pathological Effects of SARS-CoV-2 Associated with Hematological Abnormalities. *Curr Issues Mol Biol*. 2023;**45**(9):7161-82. [PubMed ID: 37754237]. [PubMed Central ID: PMC10528388]. https://doi.org/10.3390/cimb45090453.

35. Henry BM, Benoit JL, Benoit S, Pulvino C, Berger BA, Olivera MHS, et al. Red Blood Cell Distribution Width (RDW) Predicts COVID-19 Severity: A Prospective, Observational Study from the Cincinnati SARS-CoV-2 Emergency Department Cohort. *Diagnostics (Basel)*. 2020;**10**(9). [PubMed ID: 32825629]. [PubMed Central ID: PMC7554711]. https://doi.org/10.3390/diagnostics10090618.

36. Wang C, Zhang H, Cao X, Deng R, Ye Y, Fu Z, et al. Red cell distribution width (RDW): a prognostic indicator of severe COVID-19. *Ann Transl Med*. 2020;**8**(19):1230. [PubMed ID: 33178762]. [PubMed Central ID: PMC7607068]. https://doi.org/10.21037/atm-20-6090.