Pathological changes of biochemical, hematological and coagulation analyses in patients with COVID-19 disease

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ABSTRACT

The identification of patients with poor prognosis and early detection of COVID-19 disease complications are made possible by pathological analyses of routine hematological, coagulation, and biochemical tests. Interpreting analyses needs to be done within the framework of each patient's unique clinical picture. It's also critical to keep an eye on changes at the individual parameter level. From May 20th, 2021, to March 30th, 2024, a comprehensive search of literature was carried out using international databases, such as PubMed, Embase, Web of Science, Scopus, and the Cochrane Library, in compliance with the PRISMA guidelines. The research question was formulated using the PICO strategy. The following terms were used: biochemical parameters in COVID-19, hematological parameters in COVID-19, blood coagulation parameters in COVID-19, indicators of inflammation, and indicators of tissue damage in SARS-CoV-2. Routine hematological, coagulation, and biochemical tests are primarily used to monitor the progression of the disease and the effectiveness of treatment rather than being utilized for the established diagnosis of COVID-19 due to their low specificity. Molecular genetics and immunological techniques should be used to determine the COVID-19 disease diagnosis.

Introduction

On March 13th, 2020, the Ministry of Health in Kosovo announced that two of the samples for microbiological PCR analysis were positive for SARS-CoV-2. One was a 20-year-old female with Italian citizenship, a temporary resident in Kosovo in a humanitarian organization, and a male over 77 years of age with Kosovar citizenship, from two different regions in Kosovo.[1] The following three years, starting in March 2020, the Ministry of Health in Kosovo implemented the World Health Organization's May 5, 2023, declaration for the lifting of the public health emergency, while also considering the epidemiological situation in Kosovo. The Kosovo Ministry of Health declared on May 24, 2023, that the COVID-19 pandemic had ended and the Public Health Emergency was closed.[2]

Hematological, biochemical and coagulation data that were requested were most frequently analyzed during the SARS-CoV-2 pandemic (Tables 1-2). Hematological blood tests, including erythrocyte sedimentation rate (ESR), white blood cells, red blood cells, hemoglobin (Hb), packed cell volume, mean cell volume, mean cellular hemoglobin, mean cellular hemoglobin concentration, red cell distribution width coefficient variations. Cagulation tests; platelets (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), disseminated intravascular coagulation (DIC), and D-dimer. Biochemical tests included: fibrinogen, C-reactive protein (CRP), ferritin, procalcitonin, troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP), fasting blood sugar, hemoglobin A1c, high-density lipoprotein, low-density lipoprotein, triglycerides, total cholesterol, creatinine (CR), sodium, chloride, potassium, calcium, magnesium, albumin (ALB), total protein, alkaline phosphatase, alanine transaminases, aspartate transaminases, total bilirubin, direct bilirubin, creatine phosphokinase, creatine kinase-myoglobin binding (CK-MB), lactate dehydrogenase (LDH), and tests of acid-base status.[3]

Pathological findings of routine hematological, coagulation, and biochemical tests enable the identification of patients with a poor prognosis and the early detection of complications of the COVID-19 disease. Findings must be

interpreted in the context of the overall clinical picture of an individual patient, and longitudinal monitoring of changes in the magnitude of individual parameters is also extremely important.[4,5] Khourssaji *et al.*,[6] in a retrospective study of COVID-19 patients, reported that a panel of readily available biomarkers can aid in diagnosis and risk stratification. This panel consists of early biomarkers such as CRP, ferritin, fibrinogen, lymphopenia and eosinopenia. These biomarkers were consistently found in all patients, and some could also be used for risk stratification [CRP, ferritin, lymphocyte count, eosinophilia count, neutrophil to lymphocytes (NLR)]. Other biomarkers that can be used are NT-proBNP, high-sensitivity troponin T (hs-TnT), neutrophilia and D-dimers. NLR also correlates well with severity throughout the hospital stay. Late markers for COVID-19 are elevated liver and heart enzymes and a drop in hemoglobin.[6]

Hematological analyses: leukocyte changes in COVID-19

Laboratory abnormalities, particularly hematological changes, allow checking the status of SARS-CoV-2 infection, since the hematopoietic system and hemostasis suffer significant impacts during the evolution of COVID-19.[7]

The majority of symptomatic persons suffering from COVID-19 disease in early infection has a total leukocyte count within the limits of the reference interval with a differential blood count disorder present, which manifests as lymphopenia, eosinopenia, and neutrophilia. An increase in the total number of leukocytes and an increase in the number of neutrophil granulocytes is a bad prognostic marker for the development of a severe form of the disease and its complications, daily longitudinal monitoring is extremely important in hospitalized patients.[8]

Lymphopenia

Lymphopenia is one of the earliest findings that is present in almost all symptomatic individuals. It is caused by the interaction of several mechanisms that include the direct lytic action of the novel coronavirus SARS-CoV-2 on lymphocytes by binding to receptors for angiotensin-converting enzyme 2 (ACE2) on the cell surface and the secretion of pro-inflammatory cytokines that cause lymphocyte apoptosis, atrophy of lymphoid organs and decreased proliferation of lymphocytes. Lymphopenia was strongly correlated to the inflammatory biomarkers of COVID-19 and was significant. Lymphopenia was observed as an indicator of prolonged duration of hospitalization but was not significant. The majority of patients who died from COVID-19 had significantly lower lymphocyte counts.[9,10]

Eosinopenia

Eosinopenia is caused by the migration of eosinophils to the site of inflammation, a decrease in their production in the bone marrow and the action of cytokines, apoptosis of eosinophils is increased by the activation of Fas pathways induced by Th1 cytokines (TNF-α, interferon γ) and the activation and eosinophil production decreases due to lymphopenia resulting from a decrease in interleukin (IL) 5 secretion by Th2 lymphocytes. Eosinopenia is an early sign of infection that is present in almost all symptomatic patients during the first week of symptom onset.[11] Eosinopenia – <10/μL – and eosinophil/polymorphonuclear ratio are useful, low-cost, reproducible tools to help diagnose COVID-19, during an epidemic period, in a population of hospitalized patients admitted for suspicion of COVID-19.[12]

Neutrophilia

In early infection, there is an increased percentage of neutrophil granulocytes compared to other leukocyte populations, with an absolute number within the reference range. In patients with an inadequate immune response to SARS-CoV-2, in the later course of the disease, as a result of the hyperinflammatory response, there is an increase in the absolute number of neutrophil granulocytes, which can lead to a cytokine storm. In the initial phase, the cytokine storm is localized in the lungs and appears as acute respiratory distress syndrome (ARDS), and in the advanced phase of the disease it turns into a systemic reaction, the consequence of

Table 1. Hematological parameters of the disease COVID-19.

Parameter	Discovery	Clinical significance
Differential blood count	Decrease in the number of lymphocytes. Decrease in the number of eosinophils. Increase in the number of neutrophils	An increase in the number of neutrophil granulocytes and an increase in NLR indicates a poor prognosis of the disease
Platelet count	Decrease in the number of platelets	Bad prognosis of the disease

NLR, neutrophil granulocytes to lymphocytes ratio.

Table 2. Coagulation parameters in COVID-19 disease.

Parameter	Discovery	Clinical significance
PT	High	Monitoring of coagulation disorders
APTT	High	Assess for coagulation disorders
Fibrinogen	Up or down	High in coagulopathy, and low in DIC
D-dimer	High	Bad prognosis of the disease

PT, prothrombin time; APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation.

which is often the failure of many organs. The increase in the number of neutrophil granulocytes could also be caused by bacterial co-infection. In addition to the absolute increase in the number of neutrophil granulocytes, an important prognostic marker is the ratio of the number of NLR, which has a high diagnostic sensitivity and specificity in assessing the severity of the disease. The increase in NLR during hospitalization is associated with deterioration of the clinical picture and according to previous researches, it is considered a risk indicator as important as old age, the presence of concomitant diseases related to the cardiovascular system and the increase in the concentration of CRP.[13,14] Na Rong *et al*. (2024) concluded that more studies are needed to investigate the effects of degranulation and the release of NETs (NETs are network structures composed of histone proteins, elastase, myeloperoxidase, and cathepsin G and are located on the decondensed chromatin scaffold) from activated neutrophils in the antiviral response to infection. How to prevent damage caused by excessive neutrophil activation while ensuring their normal recruitment to sites of inflammation remains a challenge.[15]

Platelet changes and coagulation tests

Thrombocytopenia develops in most patients with a severe clinical picture of the disease. It is strongly associated with multiorgan failure and death, and any drop in PLT count, whether it is thrombocytopenia or the PLT count is still within the reference interval, is an independent risk factor for misdiagnosis of clinical status and the development of serious complications. There are several samples of thrombocytopenia and they can be divided into samples generated by the direct effect of the new coronovirus SARS-CoV-2 on PLT or hematopoietic stem cells to samples generated by damage to the pulmonary endothelium caused by the virus.[16] The new SARS-CoV-2 coronavirus binds to ACE2 receptors located on CD34+ stem cells, PLT and megakaryocytes, after which the virus is internalized into cells, its rapid replication and cell apoptosis occur. Through the interaction of the virus and host cells, specific autoantibodies are formed that coat PLT, hematological progenitors and other blood cells and thus lead to their destruction. Due to the effect of the virus on the immune system, there is a disruption of the secretion of cytokines involved in the formation and maturation of PLT, with a decrease in the secretion of thrombopoietin and an increase in the secretion of TGF-β and interferon-α, which leads to a decrease in the formation of megakaryocytes.[16-17]

Damage to the lung tissue and endothelium due to the action of the virus results in the activation, aggregation and encapsulation of PLT in the lungs and increases their consumption. In addition to the effect of viruses on the body, thrombocytopenia can also be iatrogenic, caused by the use of antiviral drugs that interfere with the functioning of the hematopoietic system.[18]

The prognostic marker of the course of the disease is the ratio of PLT to lymphocytes ratio (PLR), an indicator that reflects the extent of systemic inflammation and is particularly important in acute inflammatory and prothrombotic states. When following the findings of patients, it is not the size of the PLR that is important, but its change, which shows a linear correlation with the duration of hospital treatment.[19]

Coagulation tests

The evaluation of the Wuhan data suggests that the coagulopathy with COVID-19 is a result of the inflammatory response to SARS-CoV-2 infection resulting in thrombo-inflammation and driving thrombosis.[20] Disturbed values of coagulation tests and DIC are the most common causes of deterioration of the clinical condition and death of persons suffering from the disease COVID-19.[21]

The intracellular presence of the SARS-CoV-2 virus leads to direct damage to the endothelial cells of blood vessels, mainly in the lungs, causing morphological changes in the cells, their swelling and loss of the basal membrane. An injury to a blood vessel leads to the exposure of the endothelium to the circulating blood, which is followed by the process of primary hemostasis and the formation of a PLT clot. Secondary hemostasis begins with the entry of tissue factor into the circulation and is released by virus-damaged cells, vascular endothelial cells, monocytes, and macrophages. The expression of tissue factors in cells of the mononuclear-macrophage system increases due to the secretion of pro-inflammatory cytokines, mainly IL-6.[21,22]

The increased secretion of pro-inflammatory cytokines and activation of the coagulation cascade is a trigger for immunothrombosis and results in vessel wall damage, bleeding, and pulmonary embolism. In addition to dysregulated systemic and local thrombin generation, impairment of coagulation status also contributes to impairment of the fibrinolytic system. The loss of hemostatic balance in the most severe cases leads to the spread of DIC, which ultimately results in thrombosis of small blood vessels and failure of the affected organs with simultaneous bleeding due to the consumption of PLT and coagulation factors.[22,23]

In patients suffering from COVID-19, the results of blood coagulation tests such as PT and APTT values in the early stages of the disease are more often within the range of reference. The prolongation of PT and APTT occurs when the disease worsens associated with associated coagulopathy.[6,8] In a study by Araya *et al*., the authors reported that prolonged PT and elevated INR were detected in more than 50% of severe and critical patients with COVID-19. Thrombocytopenia and prolonged APTT were predominant in patients with COVID-19 older than 55 years.[24]

Fibrinogen

Fibrinogen is a positive reactant of the acute phase of inflammation and its concentration is elevated in almost all individuals affected with COVID-19. In expressed DIC, due to consumption (eating), the concentration of fibrinogen can decrease, but considering that its concentration in inflammation increases as long as the synthetic function is preserved, it is not useful to compare the concentration measured with the limit of the reference interval, but the dynamics of changes in the values obtained in the longitudinal determination should be followed.[25]

D-dimer

The coagulation dysfunction is closely related to the severity of COVID-19 cases and affects the prognosis of COVID-19 patients. Low PLT, high D-dimer and fibrinogen may serve as risk indicators for the progression of COVID-

19 severity in the early screening of severe and nonsevere COVID-19 patients.[26] An increased concentration of D-dimer is an indicator of the activation of the coagulation cascade and the fibrinolytic system. More than 50% of patients have a concentration of D-dimer above the threshold value at the time of diagnosis, and in almost all patients an increase in concentration is observed in proportion to the severity of the disease. When assessing the onset of the disease and determining the prognosis for the development of complications, it is necessary to take into account the longitudinal changes in the concentration of D-dimer and the initial value measured during the diagnosis.[27,28]

Indicators of inflammation

The immune response plays a major role in overcoming the COVID-19 disease. New SARS-CoV-2 replication and cell damage lead to the initiation of an inflammatory response and increased secretion of pro-inflammatory cytokines and chemokines that accelerate the migration of immune cells to the site of inflammation, trigger an immune response and ultimately lead to a cytokine storm leaving its consequences in the body of the infected person. Several inflammatory parameters are key in monitoring disease progression, mainly ESR, CRP, ferritin and procalcitonin concentrations.[29]

Erythrocyte sedimentation rate

ESR is a non-specific indicator used to determine the inflammatory reaction and mainly indicates the increase of acute phase proteins. ESR values are elevated in people suffering from the disease of COVID-19 in proportion to the severity of the clinical picture and the higher values are a consequence of the fact that ESR directly depends on the severity of the inflammation. Considering the low sensitivity and specificity of the test, it is recommended, when possible, to determine other inflammatory parameters, mainly CRP.[30]

C-reactive protein

CRP is a sensitive systemic indicator of acute inflammation, infection and tissue damage. It is an acute-phase protein whose synthesis depends on the release of inflammatory mediators and its serum concentration is proportional to the strength of the inflammatory response. Almost 100% of people suffering from the disease COVID-19 have an elevated concentration of CRP at diagnosis, and the initial concentration and its increase during the development of the disease are useful prognostic indicators of the severity of the disease and the development of complications.[31,32]

Ferritin

Ferritin is a positive reactant of the acute phase and its concentration increases proportionally with the intensity of inflammation. The increase in ferritin concentration is mainly the result of the inflammatory process, but it also acts as a modulator of inflammation, because its effect on lymphocytes and macrophages increases the synthesis of pro-inflammatory cytokines. The initial concentration measured at the time of diagnosis is higher in patients with a higher risk of developing serious complications of the disease and death, and significantly higher concentrations were recorded in patients with one or more comorbidities. A high concentration is a prognostic marker that warns of the severity of all diseases whose basis is inflammation, including the disease of COVID-19. Conversely, a decrease in concentration is associated with control of inflammation and a favorable outcome.[33,34]

Procalcitonin

In patients with acute respiratory symptoms, procalcitonin serves to differentiate the causes of bacterial from viral infection. In bacterial infections, due to the action of pro-inflammatory cytokines such as IL-6 and TNF-α, the secretion of procalcitonin increases, while viral infections are characterized by the synthesis of interferon-γ, which acts as a suppressor of TNF-α. Therefore, the viral agent does not affect the release of procalcitonin and its values are below the limit values or slightly elevated. Bacterial co-infection is a frequent complication of the disease COVID-19, which is the most common cause of the development of sepsis and death. Given that in the severe form of the disease COVID-19, procalcitonin is elevated due to a generally bad condition even in the absence of bacterial co-infection, so its negative predictive values are higher than 90%. The results of Cowman *et al.* suggest that elevated baseline procalcitonin (PCT) levels in hospitalized patients with COVID-19 may mislead physicians into prescribing antibiotics in the absence of co-infections. Antibiotic overuse and the rise of antibiotic-resistant infections have been well documented in many countries throughout the COVID-19 pandemic.[35,36]

Indicators of tissue damage

The main site of entry of SARS-CoV-2 into cells is the ACE2 receptor, which is highly expressed in cells of the lungs, testes, heart, kidneys, small intestine and cholangiocytes in the liver. The binding of the virus to the receptors leads to a direct cytological effect on the organs and their damage and also occurs due to the deterioration of the balance between the coagulation and fibrinolytic systems, which ultimately leads to thrombosis of blood vessels and blockage of the organs of the body. affected. The majority of diagnosed symptomatic persons have high levels of LDH, which is not specific for white tissue damage, and findings of other biochemical parameters within the limit of the reference interval. In the further course of the disease, due to the deterioration of the clinical picture, an increase in cardiac markers, liver enzymes, bilirubin, urea and CR and a decrease in ALB concentration is observed.[37,38]

Lactate dehydrogenase

LDH is found in all human cells, due to damage to the integrity of the cell membrane, it is released from the cell and its concentration in the serum increases. LDH is slightly increased in cases of patients with the disease COVID-19 already in the early stage of the disease, and the increase is more pronounced with the deterioration of the clinical picture of the patients, which warns of a greater degree of organ

damage due to of the direct cytopathological effect of the virus on the affected organs and due to hypoxia caused by lung damage. LDH is not only an indicator of organ damage, but also of immune status. Namely, increased LDH activity leads to increased lactate production, which leads to inhibition of cells such as natural killer cells and cytotoxic T-lymphocytes, and increased activation of immunosuppressive cells, including macrophages and dendritic cells. Therefore, LDH is a prognostic marker of the disease with a sensitivity higher than 90%, and a specificity higher than 70%.[39] Abnormal values of liver enzymes and bilirubin in the early stages of the disease are mostly found in patients with liver disease and other risk factors such as old age and obesity. The increase in liver enzymes during hospitalization is an important prognostic indicator as it warns of liver tissue damage that can be caused by the direct action of the virus, but also assisted by cells of the immune system, hypoxia or antiviral therapy. Hepatocyte dysfunction leads to damage to all fractions of the liver, which leads to the accumulation of toxic compounds in the body and a decrease in protein synthesis, which weakens the body's ability to respond to infections, *i.e.*, to primary infection caused by SARS-CoV-2 and secondary bacterial infections. Weakening of excretory function is monitored by laboratory analysis with the help of increased bilirubin concentration, while weakened synthetic function is more pronounced through prolonged PT and reduced ALB concentration.[40,41]

Cardiac biomarkers

The use of biomarkers has been particularly important in COVID-19 patients, as they can help clinicians stratify patients based on their risk for developing cardiovascular disease and lower mortality rates. For example, levels of biomarkers of acute myocardial injury such as TnT, CK-MB, and NT-proBNP have been found to correlate with more severe symptoms of COVID-19. These biomarkers can also be used to guide therapeutic management based on drugs that prevent the activation of coagulation processes.[42]

Troponin and N-terminal pro-B-type natriuretic peptide

Damage to the cardiac system is a prominent symptom that appears in cases with a severe clinical picture. Intensive care unit patients have significantly higher high-sensitivity troponin and NT-proBNP values, and acute myocardial injury or heart failure accounts for more than 50% of fatal outcomes.[43] Cardiac injuries are caused by a variety of direct and indirect mechanisms. The direct mechanism is the direct infiltration of the myocardium by the virus, which leads to inflammation and death of cardiomyocyte cells. The binding of SARS-CoV-2 to ACE2 receptors in the myocardium leads to a decrease in ACE2 activity, which impairs its role in the regulation of the angiotensin-aldosterone-renin system (RAAS), which also contributes to cardiac dysfunction and causes disturbances in regulation of blood pressure. Indirect mechanisms of cardiac injury include increased cardiac stress due to respiratory failure and hypoxemia and myocardial injury via the systemic inflammatory response.[44,45]

Tests of acid-base status and electrolytes

The deterioration of the patient's clinical condition and ARDS are associated with hypoxemia and he development of acidosis. Abnormal laboratory findings include decreased oxygen partial pressure and hemoglobin oxygen saturation, increased carbon dioxide partial pressure, decreased pH, and increased lactate values. A decrease in saturation below 90% is considered a poor prognostic marker. Electrolyte imbalance in people suffering from the disease COVID-19 is related to this clinical picture of the order and serves as a prognostic marker for the development of complications. It manifests as a reduced concentration of sodium, potassium, and calcium. Increased electrolyte loss occurs primarily through the gastrointestinal system, while hypokalemia also occurs due to increased renal loss caused by RAAS dysregulation caused by virus binding to ACE2 receptors.[46] Furthermore, patients with hypernatremia displayed a more severe course of COVID-19 and the mortality rate was higher in this group compared to the patients not developing hypernatremia. This makes hypernatremia a possible indicator of severe disease and highlights the importance of sodium monitoring.[47]

Conclusions

Due to insufficient specificity, routine hematological, coagulation and biochemical tests are not used for the established diagnosis of the disease COVID-19 but are mainly used to assess the severity of the disease and to monitor the course of the disease and the effect of treatment. To establish the diagnosis of the disease of COVID-19, the methods of molecular genetics and immunological methods should be applied. In conclusion, we have identified many candidate variables for risk prognostic models that may serve as clinical predictors of severe and fatal COVID-19 disease. In hospitalized patients with respiratory distress, we recommend that physicians carefully monitor leukocyte count, lymphocyte count, PLT count, IL-6, and serum ferritin as markers for possible progression to critical illness. PCT should be measured regularly to serve as a marker of secondary bacterial infection, which is often found in non-survivors, thus reflecting earlier evidence collected for SARS-CoV-2.

References

1. BalkanWeb.com. Coronavirus arrives in Kosovo, the first two cases are confirmed, a 20-year-old Italian and an elderly person. 2020. Available from: https://www.balkanweb.com/koronavirusi-mberrin-ne-kosove-konfirmohen-dy-rastet-e-para-nje-20-vjecare-dhe-nje-e-moshuar/
2. Hoti I. Qeveria e Kosovës zyrtarisht mbyll COVID-19 [The Government of Kosovo officially closes COVID-19]. 2023. Available from: https://kallxo.com/lajm/qeveria-e-kosoves-zyrtarisht-mbyll-COVID-19/
3. Haroon Hasanat HA, Mohammed Saghir SA, Al-Areefi M. Hematological and biochemical parameter changes among healthy individuals infected with COVID-19 ac-

cording to sex and age: A hospital based study. Electron J Gen Med 2023;20:em527.

4. Thompson S, Bohn MK, Mancini N, et al. IFCC interim guidelines on biochemical/hematological monitoring of COVID-19 patients. Clin Chem Lab Med 2020;58: 2009-16.

5. Kurstjens S, van der Horst A, Herpers R, et al. Rapid identification of SARS-CoV-2-infected patients at the emergency department using routine testing. Clin Chem Lab Med 2020;58.

6. Khourssaji M, Chapelle V, Evenepoel A, et al. A biological profile for diagnosis and outcome of COVID-19 patients. Clin Chem Lab Med 2020;58:2141-50.

7. Debuc B, Smadja DM. Is COVID-19 a new hematologic disease? Stem Cell Rev Rep 2021;17:4-8.

8. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020;95:834-47.

9. El Aidouni G, Merbouh M, El Kaouini A, et al. Lymphopenia in COVID-19: a single center retrospective study of 589 cases. Ann Med Surg (Lond) 2021;69:02816.

10. Niu J, Sareli C, Mayer D, et al. Lymphopenia as a predictor for adverse clinical outcomes in hospitalized patients with COVID-19: a single center retrospective study of 4485 cases. J Clin Med 2022;11:700

11. Ndieugnou Djabgang N, Peluso L, Talamonti M, et al. Eosinopenia in COVID-19 patients: a retrospective analysis. Microorganisms 2020;8:1929.

12. Outh R, Boutin C, Gueudet P, et al. Eosinopenia <100/µL as a marker of active COVID-19: An observational prospective study. J Microbiol Imunol Infect 2021;54:61-8.

13. Anurag A, Jha PK, Kumar A. Differential white blood cell count in the COVID-19: A cross-sectional study of 148 patients. Diabetes Metab Syndr 2020;14:2099-102.

14. Taghavi-Farahabadi M, Mahmoudi M, Hashemi SM, Namaki S. Neutrophils to lymphocytes ratio and the prognosis of the COVID-19 patients. Immunoregulation 2020;3:89-96.

15. Rong N, Wei X, Liu J. The role of neutrophil in COVID-19: positive or negative. Innate Immun 2024;16:80-95.

16. Zhang Y, Zeng X, Jiao Y, et al. Mechanisms involved in the development of thrombocytopenia in patients with COVID-19. Thromb Res 2020;193:10-5.

17. Kichloo A, Dettloff K, Aljadah M, et al. COVID-19 and hypercoagulability: a review. Clin Appl Thromb Hemost 2020;26:1-9.

18. Xu SW, Ilyas I, Weng JP. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacol Sin 2023;44:695-709.

19. Qu R, Ling Y, Zhang YH, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol 2020;92:1533-41.

20. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135: 2033-40.

21. Hakobyan N, Ilerhunmwuwa N, Wasifuddin M, et al. COVID-19-associated disseminated intravascular coagulopathy presenting as inferior st-segment elevation myocardial infarction. Cureus 2023;15:e39308.

22. Katrien MJ. Devreese.COVID-19–related laboratory coagulation findings. Int Soc Lab Hematol 2021;43:36-42.

23. Ceriz T, Lagarteira J, Alves SR, et al. Disseminated intravascular coagulation in COVID-19 setting: a clinical case description. Cureus 2023;15:e39941.

24. Araya S, Mamo MA, Tsegay YG, et al. Blood coagulation parameter abnormalities in hospitalized patients with confirmed COVID-19 in Ethiopia. PLoS ONE 2021;16:e0252939.

25. Sui J, Noubouossie DF, Gandorta S, Cao L. Elevated plasma fibrinogen is associated with excessive inflammation and disease severity in COVID-19 patients. Front Cell Microbiol 2021;11.

26. Lin J, Yan H, Chen H, et al. COVID-19 and coagulation dysfunction in adults: a systematic review and meta-analysis. J Med Virol 2021;93:934-44.

27. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care 2020;8:49.

28. Short S, Gupta S, Brenner S, et al. D-dimer and death in critically ill patients with Coronavirus disease 2019. Crit Care Med 2021;E500-E511.

29. Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. Int J Infect Dis 2020;96:467-74.

30. Bray C, Bell LN, Liang H, et al. Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. WMJ 2016;115:317-21.

31. Li F, He M, Zhou M, et al. Association of C-reactive protein with mortality in COVID-19 patients: a secondary analysis of a cohort study. Sci Rep 2023;13:20361.

32. Avihai B, Sundel EP, Lee E, et al. CRP Monitoring in Early Hospitalization: Implications for Predicting Outcomes in Patients with COVID-19. Pathogens 2023;12:1315.

33. Cheng L, Li H, Li Let al. Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. J Clin Lab Anal 2020:34:e23618.

34. Kaushal K, Kaur H, Sarma P, et al. Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. J Crit Care 2022;67:172-81.

35. Dolci A, Robbiano C, Aloisio E, et al. Searching for a role of procalcitonin determination in COVID-19: a study on a selected cohort of hospitalized patients. Clin Chem Lab Med 2021;59:433-40.

36. Cowman K, Rossi J, Gendlina I, et al. Elucidating the role of procalcitonin as a biomarker in hospitalized COVID-19 patients. Diagn Microbiol Infect Dis 2022;103:115721.

37. Lu Y, Sun K, Guo S, et al. Early Warning indicators of severe COVID-19: a single-center study of cases from Shanghai, China. Front Med (Lausanne) 2020;7:432.

38. Wang Q, Cheng J, Shang J, et al. Clinical value of laboratory indicators for predicting disease progression and death in patients with COVID-19: a retrospective cohort study. BMJ Open 2021;11:e043790.

39. Han Y, Zhang H, Mu S, et al. Lactate dehydrogenase, an independent risk factor of severe COVID-19 patients: a retrospective and observational study. Aging 2020;12: 11245-58.

40. Boregowda U, Aloysius MM, Perisetti A, et al. Serum activity of liver enzymes is associated with higher mortality in COVID-19: a systematic review and meta-analysis. Front Med 2020;7:431.

41. Vidal-Cevallos P, Higuera-De-La-Tijera F, Chávez-Tapia NC, et al. Lactate-dehydrogenase associated with mortality in hospitalized patients with COVID-19 in Mexico: a multi-centre retrospective cohort study. Ann Hepatol 2021;24.

42. Yaluri N, Stančáková Yaluri A, Žeňuch P, et al. Cardiac biomarkers and their role in identifying increased risk of cardiovascular complications in COVID-19 patients. Diagnostics (Basel) 2023;13:2508.

43. Caro-Codón J, Rey JR, Buño A, et al. Characterization of NT-proBNP in a large cohort of COVID-19 patients. Eur J Heart Fail 2021;23:456-64.

44. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system. Circ Res 2020;126.

45. Akhmerov A, Marban E. COVID-19 and the heart. Circ Res 2020;126:1443-55.

46. Taheri M, Bahrami A, Habibi P, Nouri F. A review on the serum electrolytes and trace elements role in the pathophysiology of COVID-19. Biol Trace Elem Res 2020:8:1-7.

47. Sjöström A, Rysz S, Sjöström H, Höybye C. Electrolyte and acid-base imbalance in severe COVID-19. Endocr Connect 2021;10:805-14.