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Review article

Pathophysiological and Laboratory Aspects of Hemostatic Disorders in Patients with COVID-19

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SUMMARY

Introduction/Aim. Although coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily affects the respiratory system, the possibility of multisystem tissue and organ damage is not excluded. In severe forms of the disease, hematological disorders with the accompanying laboratory derangements often occur. The aim of the review was to describe and further improve our understanding of the possible pathophysiological mechanisms involved in hemostatic derangements in COVID-19 patients with accompanying laboratory findings.
Material and Methods. A comprehensive investigation was conducted using keywords "COVID-19", "SARS-CoV-2", "hemostatic disturbances in COVID-19", "laboratory findings in COVID-19", in the PubMed, Google Scholar and Science Direct databases to determine the eligible studies.
Results. The most recognizable laboratory findings of these disorders include increase in the concentration of D-dimer values, prolonged prothrombin time with or without slight changes in the activated partial thromboplastin time, changes in the number of platelets according to thrombocytopenia or thrombocytosis (rarely), as well as an increase in the concentration of fibrinogen, usually in the initial stages of the disease.
Conclusion. The importance of COVID-19 coagulopathy is reflected in an increased mortality rate due to the high frequency of thromboembolic episodes, which can be the reason for multiorgan dysfunction syndrome.

Keywords: **COVID-19, hemostatic disorders, laboratory findings, SARS-CoV-2**

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that first broke out in Wuhan, China (1). After the appearance of sporadic cases, in a short period of time the disease spread and took on a pandemic character (2). High virulence capacity and rapid transmissibility, primarily through aerosol droplets, are the basic characteristics of SARS-CoV-2 (3). The entry of enveloped viruses into host cells is mediated by binding the SARS-CoV-2 spike protein to the receptor angiotensin converting enzyme 2 (ACE2) on susceptible cells (4). The expression of these receptors is detected in type II alveolar cells, respiratory epithelial cells, myocardial cells, enterocytes, neurons, renal proximal tubule cells, as well as vascular endothelial cells (5, 6).

An excessive inflammation during viral infection results in local tissue damage, with a tendency to spread and cause systemic inflammatory response syndrome and multiorgan dysfunction. In the other words, the initial phase of the disease is a consequence of viral replication in the cells, while the progression is associated with an uncontrolled immune response and the so-called "cytokine storm" (7). Consequently, COVID-19 disease has a wide spectrum of clinical presentations (8). Clinical manifestations of COVID-19 range from asymptomatic to mildly symptomatic (in 80% of cases), including fever, myalgia, fatigue and dry cough (9). A severe clinical picture with acute respiratory distress syndrome (ARDS) could be developed in about 10% of patients (10).

The studies published so far have indicated that COVID-19 could disrupt the coagulation and homeostasis cascades which results in the occurrence of thrombotic events with laboratory alteration of hemostatic parameters (11 - 15). Overt signs of hypercoagulability have been reported in patients with COVID-19, including prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), elevated levels of D-dimer and other fibrinogen breakdown products, while antithrombin activity was decreased (14). Although the pathophysiological aspects of the COVID-19 coagulopathy remain unclear, vascular endothelial damage with abnormal clot formation appears to be the initial step in the pathogenesis of COVID-19 coagulopathy. Simultaneous activation of an inflammatory and hemostatic responses (overactivation of coagulation system, increased platelet activity with the alterations in fibrinolytic and anticoagulant mechanisms) could lead to disseminated intravascular coagulation (DIC) and poor outcome (13, 16, 17).

The aim of this review was to describe and further improve our understanding of the possible pathophysiological mechanisms involved in hemostatic changes in COVID-19 patients. We also evaluated hemostatic laboratory findings to identify potential predictors of poor outcome in COVID-19 subjects. A comprehensive investigation was conducted using keywords “COVID-19“, “SARS-CoV-2“, “hemostatic disturbances in COVID-19“, “laboratory findings in COVID-19“, in the PubMed, Google Scholar and ScienceDirect databases to determine the eligible studies.

PATHOPHYSIOLOGY OF HEMOSTATIC DISORDERS IN COVID-19

Undoubtedly, hemostatic function is significantly altered in patients with COVID-19 and it is associated with unfavorable disease outcome.

Post-mortem histopathological investigations indicated an increased incidence of venous and arterial thrombosis - pulmonary microthrombosis, acute myocardial infarction and stroke in COVID-19 subjects (18, 19). The SARS-CoV-2 virus does not appear to have intrinsic procoagulant effects itself, but the coagulopathy likely results from a profound inflammatory response and endothelial activation during COVID-19 (14).

The close interrelationship between the inflammation and thrombosis have been described in many pathological conditions including COVID-19 (20). It is thought that severe inflammation and the action of certain inflammatory mediators promote thrombosis through endothelial dysfunction and microcirculatory disturbances (21). Endothelian dysfunction is preceded by SARS-CoV-2 binding to ACE2 receptors on endothelial cells. In this way, SARS-CoV-2 induces ACE2 downregulation and thus a higher concentration of angiotensin II which could stimulate the synthesis of plasminogen activator inhibitor-1 (PAI-1), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), while P selectin from the cells induces the syntesis of tissue factor (TF) (22). As known, TF is the primary cellular initiator of blood coagulation as a transmembrane receptor for factor

VII (FVII). The formation of TF- FVIIa complex triggers blood coagulation via proteolytically cleavage of serine protease FIX and FX, which leads to fibrin deposition and the activation of platelets. Activated endothelial cells release variety of molecules that increase platelet adhesion such as von Willebrand factor (VWF), which is essential for platelet adhesion to collagen at sites of vascular injury. Additionally, it is necessary for stabilization of circulating FVIII (23).

On the other side, direct effects of the virus on ACE2 could increase the kallikrein–kinin system activity resulting in a "kinin storm"with elevated vascular permeability and inflammation (24).

However, it seems that TF upregulation plays one of the main roles in COVID-19 coagulopathy. TF expression is additionally stimulated by neutrophil leukocytes, complement cascade components as well as COVID-19 related hypoxemia.

An excessive activation with reverse transendothelial migration of neutrophil leukocytes in COVID-19 patients causes the release of free oxygen species and the appearance of COVID-19 endothelitis, which explains diffuse microvascular thrombosis in critically ill patients (25). Neutrophils are stimulated by pro-inflammatory cytokines such as interleukin 6 (IL-6), interleukin 8 (IL-8) and tumor necrosis factor alpha (TNF-α), secreted in response to SARS-CoV-2 presence (26). These cytokines change the endothelial properties from an anticoagulant to a procoagulant state through glycocalyx disruption and VWF expression (27). In turn, neutrophils also enhance the effect of ACE2 downregulation in the sense of TF expression and an initiation of coagulation cascade by the release of neutrophil extracellular traps (NETs). NETs are extracellular webs of chromatin, microbicidal proteins and oxidant enzymes released from neutrophils and they capture blood cells and form the procoagulant and prothrombotic scaffold (28).

Complement cascade over-activation has been well demonstrated in COVID-19 patients. A number of studies highlight the potential importance of the complement system in COVID-19 coagulopathy. Earlier, it has been established that coagulation abnormalities, endothelial injury and microvascular thrombotic complications in COVID-19 might be mediated by an intense complement activation and deposition of complement terminal complexes, the so-called membrane attack complex (MAC, C5b-9) (29). Furthermore, patients with severe COVID-19 showed an increased circulating levels of C3 and C5a complement components, which have been reported to induce TF-dependent coagulation pathway (30). Complement and coagulation pathways are closely related, so that hyperactivation of complement may contribute to the disturbance of the coagulation system, and vice versa (31).

Hemostastic disorders in COVID-19 subjects are contributed by the impaired oxygen exchange, too. There is evidence that hypoxic pulmonary vasoconstriction, reduced lung perfusion, as well an increased blood viscosity, causes the endothelial dysfunction in ARDS (32). Secondly, hypoxia may change the endothelium towards a procoagulant and proinflammatory phenotype, by the alteration of some transcriptional factors, as hypoxia-inducible factor 1 (HIF-1). Such altered endothelium binds circulating cells: neutrophils which release NETs and cause further damage of the endothelial cells and platelets which are activated and involved in hemostasis through VWF (33).

Finally, some authors suggested that hemostatic disorders in COVID-19 patients are associated with low serum calcium (Ca^{2+}) concentrations (34 - 37). Qi X and contributors showed that the level of Ca^{2+} was significantly reduced in patients with severe COVID-19 infection, and that it corresponded to significantly increased levels of procalcitonin and calcitonin. There was also a significant relationship of decreased Ca^{2+} and coagulation dysfunction with inflammation (34). Furthermore, it was reported that patients with severe prothrombotic status always have lower Ca^{2+} levels (35). A potential explanation for the association of low serum Ca^{2+} with a higher incidence of hemostatic complications and poor outcome in COVID-19 patients is that Ca^{2+} was shown to be essential for SARS-CoV-2 entry into host cells (36). This "consumption" of Ca^{2+} for the virus entry into cells might contribute to hypocalcemia and more pronounced inflammation, which further stimulates the activity of the coagulation cascade. Expectedly, multiple studies have shown significant association between hypocalcemia and inflammatory markers that reflect the severity of COVID-19 (37).

On the other side, the reduced anticoagulant activity was elucidated in COVID-19 patients, including the activity of tissue factor pathway inhibitor (TFPI), antithrombin (AT) and activated protein C (APC) (38). Increasingly, AT depletion and worsening of coagulopathy with COVID-19 progress

were shown (39). It seems to be the consequence either of an intense inflammation or hypofibrinolysis caused by the release of PIA-1 (40, 41).

Similarly, literature data indicate that severe COVID-19 was linked with a hypercoagulable disturbances rather than consumptive coagulopathy and bleeding complications (42). An extreme state of hypercoagulability in COVID-19 patients is mainly presented as venous thromboembolism (VTE) in about 20% of patients with pneumonia (43). Thus Helms et al. estimated a significantly higher risk of thromboembolic complications in patients with ARDS due to COVID-19, compared to non-COVID-19 ARDS subjects (44). Additional factors that contribute to this condition, besides an altered hemostatic balance, are diffuse alveolar damage after infection and reduced removal capacity of fibrin deposits with its abnormal accumulations in alveolar spaces (Figure 1).

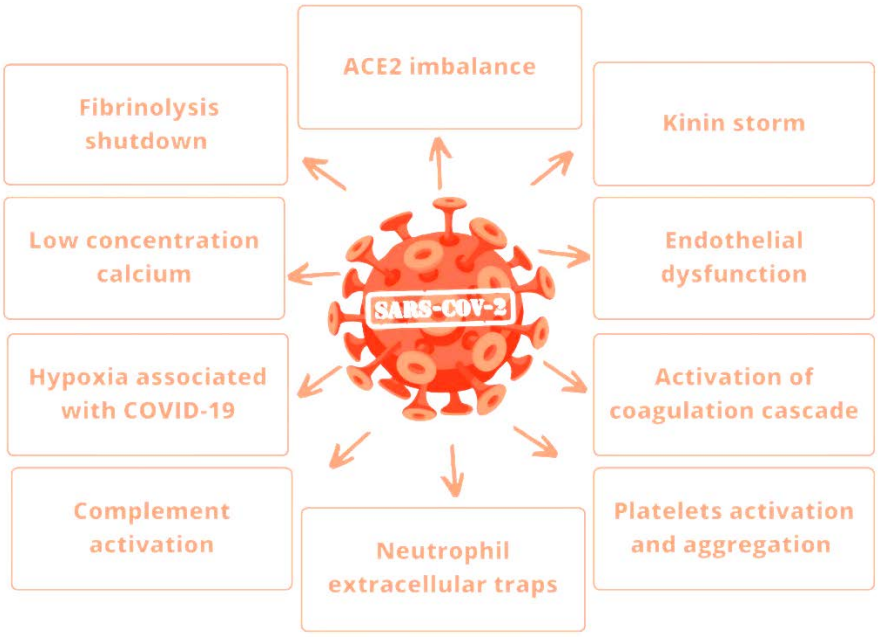

Figure 1. *Illustration of the pathophysiological mechanisms responsible for the occurrence of hemostasis disorders in SARS-CoV-2 virus infection*

LABORATORY CHARACTERISTICS OF HEMOSTATIC DISORDERS IN COVID-19

As mentioned above, clinical significance of laboratory changes due to hematologic abnormalities, which have been reported in COVID-19 patients, is reflected in prognosis of disease course (45). Namely, abnormal coagulation parameters are associated with poor outcomes in COVID-19 patients.

The elevated level of D-dimer, fibrin-degradation product, and fibrinogen are the two most common laboratory abnormalities found in COVID-19 patients. Han et al. estimated that D-dimer and fibrinogen were elevated in all COVID-19 patients, so that the concentrations were higher in patients with severe SARS-CoV-2 infection than those in patients with milder forms (46). Similarly, Nopp pointed out that COVID-19 patients developing venous thromboembolism had higher D-dimer levels (47). Several studies described that elevated D-dimer levels correlate with adverse outcomes, and that COVID-19 patients with high values of this parameter should be hospitalized, even if they have no other symptoms, because of the potential risk of thrombosis (48 - 50). It seems that COVID-19 coagulopathy mimics other systemic coagulation abnormalities, but the level of D-dimer is found to be more abnormally elevated in SARS-CoV-2 infection than in an ordinary disseminated intravascular coagulation (51).

Proceeding from the multifaceted role of fibrinogen in tissue injury and inflammation, many authors indicated that fibrinogen concentrations are commonly elevated in COVID-19 patients (52). There is a positive correlation of the concentration of

fibrinogen with the degree of excessive inflammation and disease severity. Thus, a significant association of fibrinogen with IL-6 concentration in COVID-19 subjects was established (53). Actually, the concentration of fibrinogen reflected the degree of lung tissue injury induced by direct viral effects on pulmonary tissue, and by the action of free oxygen radicals and inflammatory mediators. Meanwhile, in the late stage of the disease, thrombolysis reduces fibrinogen levels and increases fibrin degradation products (54). In that light, Tang et al. reported differences in fibrinogen levels between survivors and non-survivors (14). A decrease in fibrinogen concentration was found in a number of patients just before death (55), which might imply a higher degree of fibrinogen consumption in final stages of COVID-19 (56).

When it comes to fibrinolysis, fibrinolysis shutdown in severe COVID-19 infection was reported by some investigators, and its occurrence correlated with thrombotic events (57, 58). Unlike the early stages of the disease where there is a balance between activators (plasminogen) and inhibitors of fibrinolysis (α-2 antiplasmin and PAI-1), COVID-19 progression leads to plasminogen consumption and an increase in PAI-1, resulting in hypofibrinolysis (39). However, the presence of elevated D-dimer in patients with COVID-19 contradicts the role of PAI-1, which is expected to cause hypofibrinolysis with low D-dimer levels. It remains to be answered whether the process of fibrinolysis is really reduced in these patients (59, 60).

According to the International Society of Thrombosis and Hemostasis interim guidance (15), PT is the second most important parameter in laboratory investigations of COVID-19 coagulopathy. It was found that PT was significantly longer in COVID-19 patients compared to healthy subjects, and that the PT values were more pronounced in severe patients (10, 14). Although some previously conducted studies showed mild changes in aPTT (60, 61), it is assumed that PT is a better predictor of disease severity, given that aPTT could be prolonged due to heparin therapy, presence of lupus anticoagulant, or elevated CRP value. Finally, Lu and associates (62) found no significant difference in aPTT values between different groups of COVID-19 patients.

Dynamic changes in routine blood parameters of severe COVID-19 patients also include blood platelet count and platelet activation (63). Platelets play one of the key roles in maintaining hemostasis and contribute to thromboinflammatory processes (64). At different stages of viral infection, changes in the dynamics of platelets production as well as platelets function could result in either prothrombotic events or the risk of bleeding (65). There are numerous studies that reported the presence of thrombocytopenia in COVID-19 subjects, which corresponds to the severity of the disease (66, 67). In line with that, Arachchillage (16) concurred that platelets monitoring might signify imminent clinical improvement in COVID-19, and that the mortality increased with the decreasing of platelets count. Additionally, megakaryocyte, the precursor cell of platelets, dysfunction in COVID-19 have been described by some investigators. Elevated and abnormal megakaryocytes were found in postmortem and autopsy cases in the lungs, heart, brain and bone marrow (68 - 71). Recently, the concept that megakarycytopoiesis also takes place in the lung parenchyma with a significant contribution of the lungs in platelet biogenesis has emerged (72). Inflammation and hypoxia induced by SARS-CoV-2 can lead to changes in the capillary bed of the lung parenchyma, interfering with the fragmentation steps of megakaryocytes and ultimately affecting megakryocytopoiesis, which contributes to thrombocytopenia (73). Other possible mechanism of thrombocytopenia implies a fall in primary platelet production by an inhibition of hematopoiesis, increase in platelet destruction (by antibodies or immune complexes) as well as an increase in platelet consumption due to lung injury and, consequently, an elevated platelet activation (68, 74).

It is assumed that the changes in platelets count depend on the stage of the disease, i.e. whether the development of consumptive coagulopathy or the stimulation of megakaryocytes by cytokine storm has occurred. For these reasons, platelet count is currently considered a less important marker compared to D-dimer and PT time in COVID-19 diagnosis and prognosis of the course of the disease (56).

Bazan et al. estimated that increased levels of VWF and FVIII are significant features of COVID-19 coagulopathy (75). The observed increase in VWF in COVID-19 patients might be explained by the activation and damage of endothelial cells that release Weibel-Palade bodies. These bodies are small storage granules located in endothelial cells that store two principal molecules, VWF and P-selectin (11).

Also, an increased level of VWF might be associated with a concomitant decrease in the level of ADAMTS-13 (a disintegrin-like metalloproteinase with a thrombospondin type 1) activity (75), which is known to regulates primary hemostasis by proteolyzing VWF. Different studies noted abnormal VWF-ADAMTS-13 ratios in COVID-19 patients, decreased ADAMTS-13 and increased VWF levels, which reflected the disease severity (76, 77).

Lastly, a markedly elevated value of FV was stated in early COVID-19 (78). It was noticed that FV levels decrease with the disease progression so that its activity is significantly lower in the final phase of COVID-19 (79). In a similar pattern, higher levels of FVII, FVIII, FXI, XVII and FVIII were observed in patients with asymptomatic and mild COVID-19, while lower levels of the mentioned factors were noted with the onset coagulation and worsening of the disease (39).

The results of previously conducted studies on hemostatic disorders in COVID-19 patients are summarized in Table 1.

Table 1. *Systematic review of certain studies concerned with hemostatic disorders in COVID-19 patients*

Study	Hemostatic disorders	Laboratory findings
Wu Z et al. (1)	Venous thromboembolism (DVT, PE), arterial thromboembolism, DIC	high D-dimer, high fibrinogen, high FDP thrombocytopenia, prolonged or normal PT and aPTT, low antithrombin III
Asakura H et al. (7)	Venous thrombosis (DVT, PE), arterial thrombosis (cerebral infraction, myocardial infarction and limb arterial trimbosis), hemorrhage	high D-dimer, prolonged aPTT, thrombocytopenia, lupus anticoagulant
Srivastava S et al. (11)	Venous thromboembolism (DVT, PE)	high D-dimer, low fibrinogen, high FDP, thrombocytopenia, prolonged PT and aPTT, low antithrombin III
Salamanna F et al. (12)	Microthrombosis of lungs and other organs	high D-dimer, prolonged PT, thrombocytopenia
Long H et al. (13)	Thromboembolism, DIC	high D-dimer, high or low fibrinogen, prolonged PT and aPTT
Tang N et al. (14)	Thromboembolism, DIC	high D-dimer, low fibrinogen, high FDP, prolonged PT, low antithrombin III
Thachil J et al. (15)	Venous and arterial thromboembolism	high D-dimer, thrombocytopenia or thrombocytosis, prolonged PT and aPTT,
Arachchillage DRJ et al. (16)	Thromboembolism, DIC	high D-dimer, high FDP thrombocytopenia, prolonged PT and aPTT
Miesbach et al. (17)	Venous thromboembolism (DVT, PE), arterial thromboembolism, hemorrhage	high D-dimer, low fibrinogen, thrombocytopenia, prolonged PT and aPTT, normal antithrombin III
Ahmed S et al. (18)	Venous thromboembolism (DVT, PE, venous sinus thrombosis), arterial thromboembolism (stroke, myocardial infarction)	high D-dimer, prolonged aPTT, thrombocytopenia, antiphospholipid antibodies
Panigada M et al. (21)	Hypercoagulability (DVT of the lower limbs, PE)	high D-dimer, high fibrinogen, normal platelet count, normal or slightly prolonged PT and aPTT, high FVIII, high VWF
Robba C et al. (22)	Thromboembolism (DVT), hemorrhage (muscular and	high D-dimer, low fibrinogen, thrombocytopenia, prolonged PT

	retroperitoneal hemorrhage)	
Joly BS et al. (32)	Venous and arterial macrothrombosis	high D-dimer, high fibrinogen high FV and FVIII, low antithrombin III
Qi X et al. (34)	Thromboembolism	high D-dimer, low fibrinogen, low antithrombin III, low calcium, prolonged PT
Helms J et al. (43)	Venous thromboembolism (DVT, PE), arterial thromboembolism (myocardial infarction, cerebral ischemic attack)	high D-dimer, high fibrinogen, normal platelet count, prolonged PT, normal aPTT, high FV and FVIII, high VWF antigen, normal antithrombin III
Jandial A et al. (44)	Venous and arterial macrothrombosis	high D-dimer, thrombocytopenia, prolonged PT and aPTT
Levi M et al. (50)	Thromboembolism, DIC	high D-dimer, thrombocytopenia, prolonged PT and aPTT, low antithrombin III
Devreese KMJ et al. (54)	Venous thromboembolism	high D-dimer, high or low fibrinogen, thrombocytopenia, prolonged PT, high FV and FVIII, high VWF
Wright FL et al. (56)	Venous and arterial thromboembolism, hemorrhage	high D-dimer, high fibrinogen, thrombocytopenia, prolonged PT and aPTT, high FVIII, high VWF
Soni M et al. (60)	Thromboembolism	high D-dimer, high fibrinogen, prolonged PT
Violi F et al. (63)	Hypercoagulability	high D-dimer, thrombocytopenia, prolonged PT and aPTT

DIC – disseminated intravascular coagulation; DVT – deep vein thrombosis; PE – pulmonary embolism; PT – prothrombin time; aPTT – activated partial thromboplastin time; FDP – fibrin degradation product; FV - coagulation factor V; FVIII - coagulation factor VIII; VWF - von Willebrand factor

CONCLUSION

COVID-19 associated coagulopathy is an important part of clinical presentation of the disease which can significantly contribute to mortality and morbidity. It is mainly expressed as thrombo-embolism, more rarely as bleeding. A review of the available evidence suggests that SARS-CoV-2 has multiple impact on the hemostatic system: from ACE2 downregulation, endothelial dysfunction, TF overexpression and stimulation of coagulation cascade, platelets activation and aggregation, kallikrein-kinin dyregulation, to fibrinolysis shutdown. In that sence, certain laboratory parameters (D-dimer, fibrinogen, PT, aPTT, platelets, coagulation factors, complement components, plasminogen) have been recognized as the important predictors of disease progression or adverse outcome. Considering the risk of fatal complications, some further studies should investigate COVID-19 coagulation puzzle for early identification of disorders, an adequate stratification of subjects and the application of appropriate therapeutic strategies.

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Conflict of interest

Authors declare no conflict of interest.

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Patofiziološki i laboratorijski aspekti poremećaja hemostaze kod bolesnika sa COVID-19

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SAŽETAK

Uvod/Cilj. Iako koronavirusna bolest 2019 (COVID-19), uzrokovana teškim akutnim respiratornim sindromom koronavirus 2 (SARS-CoV-2), prvenstveno pogađa respiratorni sistem, nije isključena mogućnost multisistemskog oštećenja tkiva i organa. U teškim oblicima bolesti često se javljaju hematološki poremećaji sa pratećim laboratorijskim abnormalnostima. Cilj ovog pregleda bio je da se opiše i dodatno unapredi razumevanje mogućih patofizioloških mehanizama uključenih u hemostatske poremećaje kod bolesnika sa COVID-19, sa pratećim laboratorijskim nalazima.

Materijal i metode. Sveobuhvatno istraživanje sprovedeno je korišćenjem ključnih reči „COVID-19", „SARS-CoV-2", „poremećaji hemostaze u COVID-19" i „laboratorijski nalazi u COVID-19" u bazama podataka *PubMed, Google Scholar* i *ScienceDirect*, kako bi se odabrale relevantne studije.

Rezultati. Najprepoznatljiviji laboratorijski nalazi koji reflektuju ove poremećaje jesu povećanje koncentracije vrednosti D-dimera, produženo protrombinsko vreme sa blagim promenama aktiviranog parcijalnog tromboplastinskog vremena ili bez njih, promene broja trombocita po tipu trombocitopenije ili trombocitoze (ređe), kao i povećanje koncentracije fibrinogena, obično u početnim stadijumima bolesti.

Zaključak. Značaj COVID-19 koagulopatije ogleda se u povećanju stope mortaliteta zbog velike učestalosti tromboembolijskih epizoda, što može biti razlog nastanka sindroma multiorganske disfunkcije.

Ključne reči: **COVID-19, poremećaji hemostaze, laboratorijski nalazi, SARS-CoV-2**