Review article:

Biomarkers associated with coagulation in COVID-19 patients: A literature review.

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Abstract

The coronavirus disease (COVID-19), a highly contagious illness, has resulted in one of the worst pandemics in history. COVID-19, unlike other pandemics, has novel transmission mechanisms and produces diverse health-related issues. Severe acute respiratory syndrome coronavirus 2 infection has been associated with thrombocytopenia, neutropenia, and lymphopenia, all of which disrupt the coagulative system and may lead to potentially fatal consequences, including pulmonary embolism. In this review of the oft-documented complications of COVID-19, including venous thromboembolism and pulmonary embolism, coagulative and inflammatory markers, such as ferritin, D-dimer, C-reactive protein, and lactate dehydrogenase have been evinced and the therapeutic options are discussed briefly. It is crucial to detect potential issues early and initiate anticoagulant-based treatments, such as low-molecular-weight heparins and unfractionated heparins to optimize patient outcomes. Therefore, a thorough understanding of COVID-19 pathophysiology and the ability to recognize coagulation abnormalities that are linked to a poor prognosis are necessary to improve patient outcomes.

Keywords:

thrombotic complications, D-dimer, patient outcome, SARS-CoV-2.

Introduction

In December 2019, the severe acute respiratory syndrome coronavirus [2] (SARS-CoV-2) emerged in Wuhan, China, which subsequently led to a substantial public health crisis, known as the coronavirus disease (COVID-19) pandemic. SARS-CoV-2 mostly affects the respiratory system and may induce various symptoms, ranging from mild influenza-like symptoms to the development of the severe acute respiratory distress syndrome (ARDS) and potentially multiorgan failure [1]. The global COVID-19 pandemic has affected more than 14 million individuals and has a mortality rate of 600,000, which makes

it the most lethal pandemic in recent times [2]. COVID-19 has been linked to a range of unusual and diverse complications, including cardiovascular problems, neurological symptoms, and coagulative disorders, in addition to respiratory symptoms[3]. In the People's Republic of China, a case series reported the hematologic manifestations that were observed in COVID-19 patients, and these currently constitute the generally recognized signs of COVID-19 and have considerable prognostic impact although the pathogenesis is unelucidated. Patients who severely infected with COVID-19 are more susceptible to have venous thromboembolism (VTE), pulmonary embolism (PE), and deep vein thrombosis (DVT), as well as other complications, which are primary causes of increased mortality [3, 4].

Despite heparin thromboprophylaxis, VTE remains prevalent and microthrombi have been found in several organs, including the pulmonary vasculature, during autopsy investigations. There is an evident need to provide efficient treatment of thrombotic complications for COVID-19 patients who require intensive care. A higher severity of thrombocytopenia, lymphopenia, and coagulation panel abnormalities has been noticed in patients who died from COVID-19. These findings signify the need for early intervention for hematologic complications to improve the overall outcomes [4, 5].

This review was conducted with the objective to undertake a comprehensive examination of the hematologic occurrences that are associated with coronaviruses, elucidate their root cause, identify biomarkers associated with these events, and provide suitable therapeutic strategies to effectively alleviate the adverse consequences of the complications associated with COVID-19.

Materials and Methods

In this review, we used PubMed, Embase, Cochrane and Medline to investigated biomarkers associated with coagulation in COVID-19 patients.

Thrombosis, Thrombocytopenia, and Disseminated Intravascular Coagulation

Thrombosis, thrombocytopenia, and disseminated intravascular coagulation (DIC) are all hemostatic abnormalities and have a significantly higher prevalence among COVID-19 patients. Due to the systemic inflammation and immobility caused by critical illnesses, including endothelial dysfunction, sepsis, acute pancreatitis, dehydration, and stasis, critically ill patients are more likely to experience VTE. Patient-related factors that confer a higher likelihood of VTE include metabolic syndrome, peripheral arterial disease, coronary artery disease, and hereditary

thrombophilia [5, 6]. Patients who are critically ill may develop infections that can lead to DIC through the activation of intravascular coagulation and endothelial damage. Patients with DIC can experience earlier-onset, less severe sepsis-induced coagulopathy (SIC), which if untreated can progress to DIC [6].

Hematologic disorders associated with COVID-19 are more analogous to those of thrombotic microangiopathy [7]. Both macrovascular and microvascular thrombotic complications are associated with COVID-19 and arterial thrombotic events, DVT, and PE have been observed. The exact mechanism of these thrombotic complications is not yet entirely comprehended due to the logistic difficulties of acquiring CT scans and the clinical aim to reduce exposure of transportation employees and ultrasound technologists. Studies in China have shown that 25% of patients who were analyzed had VTE; however, the specifics of thromboprophylaxis were not described [5, 8]. Autopsy studies in China have shown microvascular thrombi in multiple organs. Further autopsy-related investigations of 21 COVID-19 patients revealed microthrombi in the alveolar capillaries in five patients and significant PE in four, with three patients showing signs of glomerular thrombotic microangiopathy [9, 10]. A Dutch study found that the cumulative 31% incidence of thromboembolic events among 184 intensive care unit (ICU) COVID-19 patients who all received thromboprophylaxis [11]. The most prevalent thrombotic consequence was PE. Further research from the Dutch population showed that 46.6% of 75 patients with thromboembolic events were admitted to the ICU with COVID-19 [7].

COVID-19 and Coagulopathy

The etiopathogenesis of COVID-19-associated coagulopathy is not completely comprehended, although it is attributed to an inflammatory hyperresponse to SARS-CoV-2 infection. Severe COVID-19 infection can cause a substantial inflammatory state through the interaction between monocytes and endothelial activation [11,12, 13]. It was posited that the spike protein of SARS-CoV-2, the viral agent responsible for the onset of COVID-19, has an affinity for angiotensin-converting enzyme-2 receptors that are located on endothelial cells and trigger the release of inflammatory cytokines. The activation of endothelial cells is accompanied by the activation of adhesion molecules, including P-selectin. Subsequently, blood monocytes undergo activation in response to circulating damage-associated molecular proteins (DAMP), viral pathogen-associated molecular proteins (PAMP), and cytokines.

As a consequence, microvesicles (MV) are generated from monocytes and the tissue factor (TF) expressed on the membrane [14, 15]. The instigation of the intrinsic coagulation pathway arises subsequent to the production of TF and the shedding of MVs from endothelial cells and activated monocytes. The SIC/DIC pathway and hypercoagulation mechanism have similarities as they both include the upregulation of TF expression and the initiation of coagulation [16]. Nevertheless, the etiology of this activation varies between COVID-19 and other pathological states.

Furthermore, empirical studies have shown a clear and intricate correlation between the complement and coagulation systems. The activation of the complement system is initiated by neutrophil extracellular traps (NET), which are intricate structures that ensnare pathogens. SARS-CoV-2 infection results in the upregulation of the complement system, which triggers the activation of platelets, membrane attack complexes (MAC), and thrombosis [14, 17]. Thrombosis may manifest in severely sick COVID-19 patients secondary to a syndrome characterized by severe microvascular damage, which encompasses a procoagulant state and the activation of the complement system. Several investigations have shown that thrombosis may manifest in a subset of critically sick COVID-19 patients because of the complex interaction between the complement and coagulation systems [16, 18].

Biomarker Findings

Millions of individuals worldwide have been afflicted by the COVID-19 epidemic, and several biomarkers have been identified to detect and predict the disease severity. Many biomarkers are considered beneficial and significant indicators of prognosis, including procalcitonin, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer. Typical results in coagulation tests in COVID-19 include an activated plasma thromboplastin time (aPTT) and a normal prothrombin time (PT) in moderate disease as well as a substantial lengthening of PT and aPTT in severe disease. In moderate sickness, platelet counts can range from normal to slightly higher whereas, in severe disease, they can be significantly lower [19]. D-dimer and fibrinogen levels that range from mild to significantly elevated reflect the severity and mildness of COVID-19. Despite the limited evidence, a few studies have provided significant prognostic markers. Individuals with severe ARDS and COVID-19 had higher D-dimer levels [19]. Patients with ARDS who did not survive had higher D-dimer levels compared to those who recovered [20]. Furthermore, 36% of patients

in a descriptive examination of 99 cases from China showed increased D-dimers, and 12% developed thrombocytopenia. In 41 patients, another study revealed that those who required ICU admission had higher D-dimers and PT values than those who did not require ICU-level care. Only 5% of patients had thrombocytopenia [21].

An investigation among 81 patients showed that a D-dimer cutoff value of 1.5 g/mL accurately predicted VTE with specificity, sensitivity, and negative predictive value (NPV) of 88.5%, 85.0%, and 94.7%, respectively [21]. Another retrospective investigation of 1449 COVID-19 patients from China revealed greater PT, D-dimer, and aPTT baseline and maximal values among COVID-19 patients who died. Changes in platelet count, fibrinogen, and baseline D-dimer level were linked to higher mortality rates [22, 23]. In another investigation of 19 studies, which included 3383 individuals, patients with severe COVID-19 had more severe thrombocytopenia than those with less severe illness. The total fatality was 11.5% in a report of 183 patients during the early stages of the pandemic. For 2 weeks, coagulation parameters were monitored. Both 0.6% of survivors and 71.4% of non-survivors had overt DIC. The PT, aPTT, and D-dimer values of patients who died were noticeably greater than that of those who survived [24, 25].

The CRP is an acute-phase reactant that is triggered by IL-6 and is a sensitive biomarker for various inflammatory diseases, including COVID-19 [26, 27]. Many individuals with severe illness have increased CRP levels. Numerous studies have demonstrated that a spike in blood CRP levels is a good indication of the presence and severity of SARS-CoV-2 infection [25, 28]. A study from Wuhan, China, found that illness development accelerates when CRP levels are >41.8 g/mL, and there is a favorable correlation between early-stage CRP levels and lung-lesion diameter and the COVID-19 severity [29].

LDH is an enzyme that is expressed in almost all human cells, including the heart, lungs, kidneys, liver, and bone marrow [25]. LDH catalyzes pyruvate production to lactate, and serum LDH levels are increased when any of the many different cell types that express LDH are damaged. LDH elevation is frequently observed in patients with severe COVID-19 and is considered a sign of poor outcome. Higher LDH levels correspond with the severity of SARS-CoV-2 pneumonia and poor prognosis in COVID-19 [25, 26].

Procalcitonin is downregulated after a viral infection and is upregulated during severe bacterial infections. Procalcitonin levels often stay within the standard range in COVID-19 patients without complica-

tions, but an increase might be a sign of a concurrent bacterial infection and the emergence of the disease's most severe form [30]. Individuals who have severe illness have increased procalcitonin, which can aid distinguishing between SARS-CoV-2-negative and -positive patients [31, 32].

Ferritin is one of the most significant biomarkers to store iron, and its composition consists of subunits H and L. Ferritin is an acute-phase reactant that is induced by various inflammatory stimuli such as cytokines [33]. It has been shown that the H subunit of ferritin has both immunosuppressive and proinflammatory properties. Higher ferritin levels, along with many other biomarkers, including D-dimer, CRP, neutrophilia, LDH, and lymphocytopenia, among others, were related to an increased risk of ARDS. Patients with COVID-19 who had serum ferritin levels <500 g/L at admission as well as high lymphocyte count and elevated CRP levels which indicated an independent risk for disease severity [34,35,36].

Table 1. Biomarkers associated with COVID-19

Coagulation Biomarker	Increase D-Dimer and fibrinogen Prolonged PT and aPTT
Biochemical Biomarkers	Increased Creatinine kinase and tropine Increased AST, ALT, and total bilirubin
Inflammatory Biomarkers	High CPR, cytokines, ESR and ferritin

Clinical Indication

The detection of thromboembolic occurrences in COVID-19 patients necessitates careful monitoring of coagulation panels and a heightened awareness of changes in platelet count, aPTT, PT, D-dimer, and fibrinogen levels [23]. Patients who are severely ill with COVID-19 are more prone to VTE, DVT, and PE, which can be identified by a sudden and rapid rise in arterial carbon dioxide partial pressure (PaCO2) [23, 24]. Compared to DIC, clotting is more common than bleeding in COVID-19. Although acute DIC is often marked by a predominance of bleeding and a significant decrease in fibrinogen and platelet count, COVID-19's hypercoagulable state is characterized by a somewhat reduced platelet count, whereas high fibrinogen levels characterize chronic DIC. Thus, it is crucial to monitor coagulation parameters closely in COVID-19 patients to identify and manage thromboembolic complications promptly [37].

Diagnosis, Treatment and Management

Early detection of VTE is crucial in COVID-19 patients. For those experiencing respiratory distress, tachycardia, oxy-

genation deterioration, and hypotension, PE should be diagnosed. Dead-space ventilation caused by PE may be indicated by an increase in PaCO2, and a significant increase in the D-dimer level should be investigated [6]. Institutional protocols ought to be in place to support in the diagnosis and management of VTE in COVID-19 patients, as computed tomography pulmonary angiogram (CTPA) or DVT ultrasonography may not easily accessible due to limitations on staff exposure to COVID-19. In diagnosing PE, electrocardiograms (ECG) may be used to analyze right ventricular strain patterns [26].

Hospitalized COVID-19 patients should receive pharmacologic thromboprophylaxis with fondaparinux, LMWH, or UFH to prevent VTE [38, 39]. Fondaparinux and LMWH are preferred due to their once-daily administration [39]. Intermediate or weight-based LMWH doses are no longer recommended, and caution should be exercised when using direct oral anticoagulants (DOACs) due to the risk of fast deterioration, acute kidney injury, and hemodynamic instability. Mechanical thromboprophylaxis with pneumatic compression devices can be used when anticoagulants are contraindicated [39].

To achieve therapeutic anticoagulation for VTE, the use of LMWH, UFH, and DOAC are advocated [39, 40]. Systemic thrombolytic therapy is recommended for patients with hypotension and PE [40]. Apixaban and rivaroxaban are preferred over edoxaban and dabigatran because they do not require initial parenteral anticoagulation [41]. Bleeding is a potential adverse effect of anticoagulation, and the risk of bleeding in anticoagulation-treated patients can be assessed using a scoring system such as HAS-BLED. DOAC-related bleeding issues can be treated with specific reversal medications and prothrombin complex concentrates [38]. During the pandemic, catheter-directed therapy should only be used in life-threatening situations, and the usage of inferior vena cava filters should be evaded. Treatment of the underlying illness is typically the primary focus of DIC management. Blood products such as cryoprecipitate and fresh frozen plasma can be used to treat bleeding in COVID-19-associated DIC. Patients with prolonged aPTT or PT should receive cryoprecipitate and FFP for bleeding [40].

Conclusions

In summary, COVID-19 is a pathological condition that impacts several physiological systems and has a strong association with hematologic illnesses. The phenomenon of increased coagulability is attributed to immune-mediated processes. COVID-19 significantly increases coagu-

lability, and the pathophysiology at play is thought to be immune-mediated. It tends to cause significant morbidity and mortality, somewhat similar to SIC and DIC. Multiple anomalies in hematologic laboratory parameters are caused by COVID-19, and a few of them, like LDH and D-dimer, may be indicative of prognosis. In order to create a customized treatment plan for at-risk patients, a high index of suspicion and close laboratory parameter monitoring are essential. These factors may also help with the triage of high-risk patients to the ICU. As far as venous thromboembolism is concerned, it is crucial and common among all. The ability to quickly intervene to improve patient outcomes depends on the early identification of potentially fatal complications such as PE, DIC, stroke, and limb ischemia. For these issues, it is important to use diagnostic tests carefully. This strategy may lead to better clinical results in COVID-19 patients who are at high risk and in severe conditions to formulate efficacious strategies for intervention. The timely recognition of and intervention for complications are of paramount importance to enhance the overall results for the patient.

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