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Anticoagulant Status Under COVID-19: The Potential Pathophysiological Mechanism

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Abstract:

Coronavirus disease 19 (COVID-19) is a systematic multitropic disease. Sustaining blood homeostasis is a mission of multiple factors includes procoagulant and anticoagulant systems. Subsequently, maintaining a precise equilibrium between these antagonists' systems is crucial to prevent hemostasis. Frequently, during severe forms of COVID-19 patients, studies reported a discrepancy between the procoagulant and anticoagulant that usually results in fatal outcomes through multiorgan ischemia by thrombotic events. The proper interpreting of the anticoagulant status changes in COVID-19 patients is sufficient for effective and safe anticoagulant treatment. Our postulation is the first to address the pathophysiology of anticoagulant status under COVID-19.

Keywords:

Anticoagulant, coagulopathy, coronavirus disease 19, hemostasis, homeostasis, pathogenesis, pulmonary embolism, severe acute respiratory syndrome coronavirus disease 2, thrombosis

Introduction

As of October 8, 2021, the coronavirus disease 19 (COVID-19) confirmed cases exceeded a quarter-billion (236,132,082) with approximately a half million new cases every day (448,770). However, the mortality curve is declining with a total of 4,822,472 death worldwide.[1] The debate has increased about the role of anticoagulant system impairment in the pathogenesis of the mortality rate in COVID-19 patients.[2] The current understanding of the COVID-19-associated mortality depends on the presence of concomitant diseases, age, and immune state. All these factors are involved in hemostasis regulation. Hypercoagulability is a cardinal feature in these groups of patients. Pathophysiological mechanisms of over clotting include increase procoagulant activity and/or decrease in anticoagulant activity. Where, overexpression of procoagulant genes, receptors, and proteins is a fundamental pathophysiological process associated with a reduction in the expression or deactivation of the anticoagulant protein, receptors, and genes even epigenomic markers silencing.

The anticoagulant system is comprised four relevant pathways antithrombin glycosaminoglycan pathway, protein Z-dependent pathway, protein S pathway, and tissue factor pathway. In addition, anticlotting mechanisms involved nonspecific and fibrinolytic systems.[3] The cooperation of the previously mentioned pathways is responsible for maintaining blood hemostasis. Functional impairment of whatever pathway is catastrophic and results either in over clotting or bleeding. However, not only the anticoagulant system can be disrupted but also the coagulation system too. Therefore, a precise physiological balance must be kept between these two antagonistic systems and pharmacologically induced balance in COVID-19 patients.

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Potential Mechanism of Anticoagulant System Disturbance; Novel Insight

Remarkable pathophysiological changes in the hemostatic status have been noticed in COVID-19 patients. Hemostasis impairment returns to the misbalance between anticoagulant and procoagulant systems. In the pathogenesis of hyperclotting and bleeding. Cytokine storm plays the leading role in the pathogenesis of anticoagulant system impairment [Figure 1].[4]

Protein C and S Levels Under Coronavirus Disease 19

Active protein C plays a central role in the anticoagulant system. The available studies showed noticeable hyperactivity in the protein S. Downregulation of the serum levels of protein C, as well as expression levels, indicates the severity of the over clotting and the urgency for anticoagulant therapy.[5] The suggested pathophysiological mechanism involved the cardinal feature of the COVID-19 cytokine storm that involved interleukin (IL) 6, 8, and 1 β as well as tumor necrosis factor α (TNFα). A more pronounced effect is played by IL 6 which directly downregulates the protein S serum level, which is required for the activation of protein C.[6] Protein S is involved in the regulation of hemostasis through its capability to interact with thrombomodulin and activate protein C.[7] Dramatic reduction in the levels of Protein S was recorded in severely ill COVID-19 patients indicates the hypercoagulability state and the poor prognosis.

Physiologically, activated protein C is involved in inflammation regulation, apoptosis regulation, and endothelial cell stabilization and epithelial barrier function regulation.[8] Therefore, COVID-19-induced protein C level reduction plays a key role in the perturbance of cell homeostasis.

Endothelial Protein C Receptor Expression Levels Under Coronavirus Disease 19

The expression of the protein C receptors on endothelial cells increases with the severity of the over clotting. However, no recent studies demonstrated the exact modification in the expression level of the receptors and their intracellular synthesis and storage.

Direct tropism of severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV2) to the endothelial cells and cytokine storm induces endothelial cell dysfunction and endotheliallitis. Consequently, a reduction in the level of the receptors and synthesized protein C by the endothelial cells. Hypercoagulability possesses a poor prognosis in COVID-19 patients.[7]

Antithrombin and Thrombomodulin under Coronavirus Disease 19

Various types of antithrombin are present with antithrombin activity. Crucially, antithrombin II and III are the primary antagonist for thrombin activation. Overactivity of antithrombin II and III has been registered in several studies.

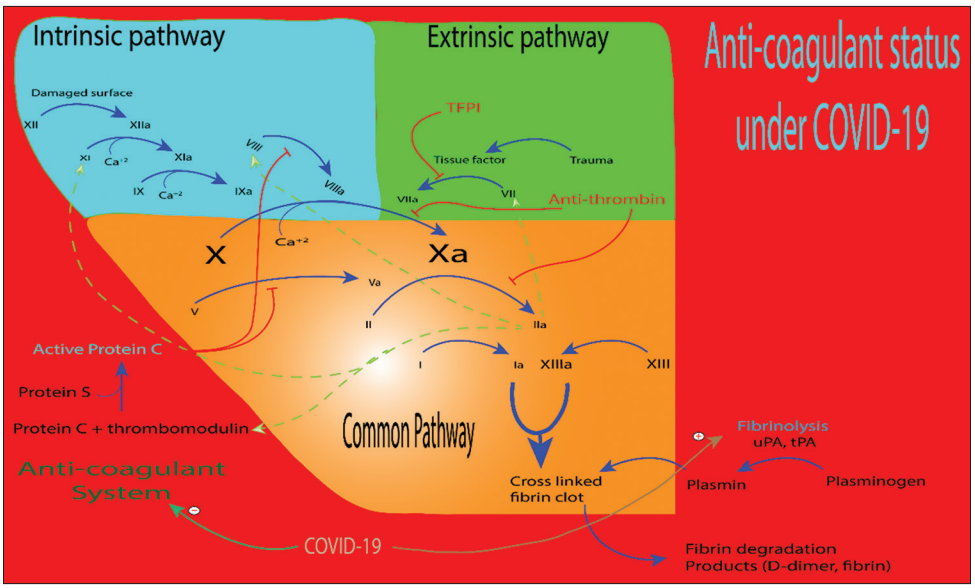


Figure 1: Schematic illustration of the anti-coagulant status under coronavirus disease 19. Coronavirus impairs the anticoagulant system activity through the reduction in the level of Protein C, S, antithrombin, and thrombomodulin. Furthermore, in response to over clotting state and the direct effect of coronavirus disease 19 on the fibrinolysis system, bleeding may occur. Finally, coronavirus disease 19 is a well-known inducer for special disseminated intravascular coagulation syndrome (coronavirus disease 19 induced disseminated intravascular coagulation)

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Thrombomodulin is a receptor for the thrombin expressed on the endothelial cell surface. Hyperclotting induces the overexpression of the thrombomodulin on the cell surface.

A recent study showed that COVID-19 patients have elevated angiopoietin-2 (ANGPT2) levels.[9] The study reported that ANGPT2 is responsible for the reduction of the bleeding time and its knockdown increases bleeding time *in vitro* by inhibition of thrombomodulin-mediated anticoagulation and protein C.

D-Dimer Levels in Coronavirus Disease 19 Patients

Several multicenter studies have demonstrated a remarkable elevation in the D-dimer level in COVID-19 patients' ≥0.5 ml/L, approximately in 43.2%. Whereas, more pronounced elevation in 59.6% of severe patients.[10,11] In addition, the level of D-dimer on average was 0.9 mg/L in 36% COVID-19 patients.[10,12] D-dimer level is severity dependent where severely ill patients had D-dimer level of 2.4 mg/L and mild patients had 0.5 mg/L.[13] COVID-19 survivors in 24% had <1 mg/L D-dimer level, whereas in nonsurvivors, 81% had >1 mg/L.[14] Another study showed that 85% of survivors had D-dimer >3 mg/L.[15]

D-dimer has higher sensitivity for disease progression and mortality rate than fibrin split products (FSP). However, elevation in the FSP level was significantly higher in deceased patients 7.6 μg/mL and 4 μg/mL in survivors.[15]

Fibrinogen Levels in Coronavirus Disease 19 Patients

A simultaneous increase in fibrinolysis and thrombogenesis reduces the level of fibrinogen which is confirmed by the biochemical blood analysis of many patients. A tight association has been found between IL6 and fibrinogen levels.[7,15] Where elevation of IL6 induces fibrinogen overproduction which is a precursor of the coagulation system. Fibrinogen elevation in COVID-19 patients was not correlated with the mortality rate. On average, fibrinogen level was 4.55 g/L in COVID-19 patents. Whereas, in severely ill patients and due to disseminated intravascular coagulation, the fibrinogen level reduced in 29% of patients to <1 g/L.[15] Fibrinogen serum levels possess a low clinical value in determining the prognosis and potential mortality in COVID-19 patients due to their low sensitivity (22%).

Prothrombin Time and Activated Partial Thromboplastin Time Status in Coronavirus Disease 19 Patients

Prothrombin time (PT) reflects the response of the body to external trauma. Prolonged PT indicates impairment of the coagulation system and increases the risk of bleeding. Chinese studies have found that COVID-19 patients have a prolonged PT and activated partial thromboplastin time (aPTT) time only in 5% and 6% of patients, respectively.[11,12,16]

A recent cohort study showed a remarkable elevation in the PT and aPTT related with a dramatic increase in the mortality intensive care unit (41.1%; 168 of 409 patients) versus general care (8.4%; 79 of 942 patients).[17]

Noticed prolongation in the PT time in critically ill patients has been observed.[14] Approximately, PT of critically ill patients is by 1.9 s longer than nonfatal and critical patients. Whereas, 48% in the late course of the disease in fatal cases, the PT prolongation exceeds the 6 s.[15] Therefore, PT is of clinical value in critically ill patients to determine the prognosis of the patients.

Clinical usage of aPTT time is not valuable since their level is nearly the same in critically ill patients and noncritical.[16] Furthermore, aPTT level does not depend on the severity or mortality rate of the disease.[15]

Potential Mechanism of Coronavirus Disease 19 Associated Disseminated Intravascular Coagulation

The scientific community agreed that COVID-19 patients experience a different type of coagulopathy and hemostasis perturbance, which is returned to the different pathophysiological mechanisms that underlie its development. COVID-19 patients have a remarkable increase in the C-reactive protein, thrombocytopenia, and particularly important the cytokine storm (IL1 and 6, TNFα).[18] The inflammatory mediators play a central role in the pathogenesis of over clotting and mortality rate[17,19] [Figure 2].

MicroRNA Dysregulation

The role of special microRNAs in the pathogenesis of anticoagulant system impairment remains under debate. A recent multicenter study demonstrated that critically ill patients were having remarkably elevated miR-148a-3p, miR-451a, and miR-486-5p.[20] Transcription analysis showed that ten microRNAs were different from other nonintensive care units required. More important in the clinical settings is the elevation in these microRNAs miR-192-5p and miR-323a-3p. The study has found that the critically ill patients were having upregulated miR-27b-3p, miR-27a-3p, miR-148a-3p, miR-199a-5p, and miR-491-5p and downregulated miR-16-5p, miR-92a-3p, miR-150-5p, miR-451a, and miR-486-5p. Using microRNAs as a marker of severity and prognosis in COVID-19 patients probably has high sensitivity and

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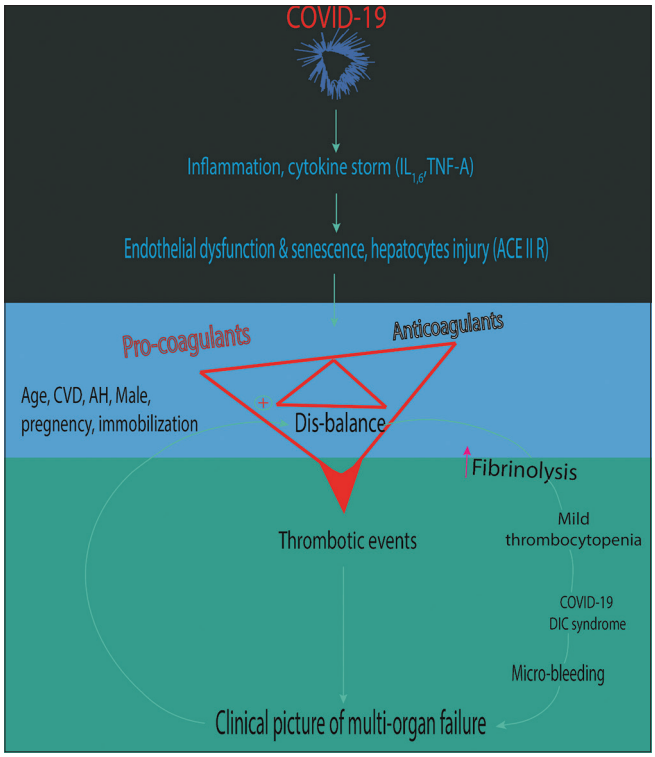


Figure 2: Schematic presentation of the pathogenesis of multiorgan failure due to coagulopathy and anticoagulant system function impairment

specificity. Remains the debate about the origin and the potential role of these microRNAs in the pathogenesis of coagulopathy. The study found that the elevation of these microRNAs is related to the medications used in the treatment of COVID-19 patients such as antibiotics for miR-16-5p, miR-92a-3p, and miR-150-5p, corticoid for miR-92-3p, and hydroxychloroquine for miR-150-5p. Furthermore, the findings excluded the role of age or sex in the modification of the serum level of these markers. Moreover, the microRNAs level was found to be inversely related to the length of hospitalization in the intensive care unit.

Gene Expression Polimorfism

Gene expression modifications involved both sides; virus overexpression of coagulopathy inducing genes nsp14, ORF14, ORF3b, ORF7b, ORF7a, nsp2, nsp8, and nsp13. Whereas, from the human side, overexpression of the Serine/Cysteine Proteinase Inhibitor Clade G Member 1 (SERPING1 or C1 inhibitor) and downregulation of K epOxide Reductase Complex subunit 1 (VKORC1) expression.[21] Consequently, two antagonistic systems are over-functioning, the final effect depends on the predominant system which is also regulated by the inflammation severity and immune response of the patient. Controlling these gene products or the expression of these genes can be recruited to modify coagulopathy.

Discussion

COVID-19-induced disseminated intravascular syndrome differs from the classical coagulopathy of overt sepsis by low or unrecognized elevation in the aPTT and PT.[22-25] Recent investigations suggested the involvement of antiphospholipid antibodies in coagulopathy, where these antibodies bind to the cell surface of the endothelial cell and trigger thrombogenesis.[26]

The strong association between IL6 and fibrinogen level reminds us about the role of cytokine storm role in the anticoagulant system impairment and overproduction of procoagulant factors. The overproduction of IL6 by the local pulmonary inflammatory cells including macrophage induces the macrophage activating syndrome-like that later induces tissue factor expression and increasing production of fibrinogen and platelets.[7,27] Therefore, inhibition of IL 6 with monoclonal antibodies (tocilizumab) is effective in normalizing the hemostasis state. In COVID-19 patients, mechanical ventilation is indicated if the IL6 level exceeds 121–218 pg/mL.[7,28]

Hypoxia-induced transcription factors are probably involved in the pathogenesis of anticoagulant system impairment through upregulation for thrombosis gene expression.[29] Hypoxia is a predominant feature of COVID-19 where microvascular disorders occur due to endothelial cell damage. Furthermore, plasmin/urokinase pathway disbalance may play a role in this pathological cascade of anticoagulant system impairment. Hypoxia is a well-known reducer for protein S level.[30]

The administration of anticoagulants for critically ill patients reduces the risk of mortality rate without adverse outcomes such as bleeding.[13,31,32] The current improvements in the anticoagulant therapy administration protocols effectively enhanced the outcomes and this returns to the advancements in the understanding of the underlying pathophysiological changes of the physiological anticoagulant system.

Conclusion

COVID-19 disease effects continue to affect people despite the development of an effective vaccine. Coagulopathy is a hallmark in the prognosis determination of COVID-19 patients. SARS-CoV2 interferes with coagulopathy through two pathways direct and indirect. The direct pathway involved its binding with the ACEII receptors on the endothelial cells and the hepatocytes that consequently impair their function. Whereas, the indirect pathway is represented by the cytokine storm and the effects of acute-phase inflammatory response [Figure 1]. Recent postmortem findings suggested apoptosis and

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pyroptosis as possible mediators of endotheliitis in deceased patients.[33] The significant difference in IL-6 level in critically ill patients is the hallmark of the severity of anticoagulant system impairment.

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Conflicts of interest

There are no conflicts of interest.

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