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COVID-19 AND COAGULATION DYSFUNCTION: A SYSTEMATIC REVIEW

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Abstract

The mechanism of blood coagulation, which is responsible for maintaining hemostasis, is an intricate process that is carried out by a number of clotting factors. The components I, II, IX, X, XI, and XII are the ones that make up the intrinsic route. The initial processes that set off this cycle of inflammation and thrombosis take place in the alveoli of the lungs. It is in these alveoli that the SARS-CoV-2 virus penetrates the alveolar epithelium through the angiotensin converting enzyme (ACE)-2 receptor. This leads to a significant inflammatory response, which, through a variety of mechanisms, commences the thrombotic stage of the process. Patients who are younger and do not have any other medical conditions can suffer from a serious disease if there is an excessive release of cytokines. Researchers have shown a link between having elevated serum levels of several inflammatory cytokines and chemokines and having a severe disease or even death. Numerous investigations have unequivocally established that there is a causal connection between inflammation and thrombosis, as well as a two-way exchange of information between the two. An increase in high levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, interleukin-6, and D-dimer are proof that COVID-19 creates a hyper pro-inflammatory condition. This is shown by the fact that these levels increase. Patients diagnosed with COVID-19 were shown to have a correlation that went in both directions between the levels of IL-6 and fibrinogen, which lends credence to the concept of inflammatory thrombosis.

Keyword: *Coagulation; COVID-19; Hemostasis; Inflammation*

INTRODUCTION

The coagulation pathway is a cascade of events leading to hemostasis. The complicated pathway allows for rapid healing and prevention of spontaneous bleeding. The two pathways, intrinsic and extrinsic, originate separately but converge at a specific point, leading to fibrin activation. The goal is to stabilize the ends of the platelets with a fibrin mesh.[1,2] The function of the coagulation pathway is to maintain hemostasis which is a blockage of bleeding.[3]

Primary hemostasis is the aggregation of platelets that form a plug at the site of damaged endothelial cells. Secondary hemostasis includes two main coagulation pathways, namely intrinsic and extrinsic which meet at one point to form a common pathway. The common pathway ultimately activates fibrinogen to become fibrin. These fibrin subunits have an affinity for each other and combine to form fibrin strands that bind platelets together, stabilizing the platelet plug.[4]

The coagulation mechanism that enables hemostasis is a complex process that is carried out through a series of clotting factors. The intrinsic pathway consists of factors I, II, IX, X, XI, and XII. Each is named, fibrinogen, prothrombin, Christmas factor, Stuart-Prower factor, plasma thromboplastin, and Hageman factor. The extrinsic pathway consists of factors I, II, VII, and X. Factor VII is called the stable factor. The general pathway consists of factors I, II, V, VIII, X. These factors circulate through the bloodstream as zymogens and are activated into serine proteases.[5,6]

This serine protein acts as a catalyst to break down the next zymogen into more serine proteins and finally activates fibrinogen. The following are serine proteases: factors II, VII, IX, X, XI and XII. These are not serine proteases: factors V, VIII, XIII. The intrinsic pathway is activated via exposed endothelial collagen, and the extrinsic pathway is activated via tissue factors released by endothelial cells following external damage.[5,6]

Correa *et al*[7] demonstrated that aPTT, PT, and INR remained normal throughout the study, whereas fibrinogen was increased in patients with COVID-19. Giannis' report[8] regarding the clinical and laboratory findings of COVID-19 patients that were commonly found were thrombocytopenia (36.2%), increased D-dimer (46.4%), prolonged PT, and disseminated intravascular coagulation (DIC). Coagulation disorders occur in the early stages of COVID-19 infection where 43.5% of patients experience increased D-Dimer and 64.3% of patients experience increased fibrinogen.[9]

The causal and bidirectional relationship between inflammation and thrombosis has been clearly recognized by many studies. COVID-19 causes a hyper pro-inflammatory condition as evidenced by an increase in high levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, interleukin-6 and D-dimer. IL-6 and fibrinogen levels were shown to be bidirectionally correlated in patients with COVID-19, lending credence to the idea of inflammatory thrombosis.[10,11]

The triggering events for this cycle of inflammation and thrombosis originate in the alveoli of the lungs, where SARS-CoV-2 enters the alveolar epithelium via the angiotensin converting enzyme (ACE)-2 receptor. This results in a severe inflammatory response that initiates the thrombotic stage through several mechanisms. Excessive cytokine release causes severe disease in younger patients without comorbidities. Elevated serum levels of several inflammatory cytokines and chemokines have been associated with severe disease and death.[10] This article showed association between COVID-19 and coagulation dysfunction.

METHODS

Protocol

The principles outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist were adhered to throughout the course of this systematic review. The regulations that governed the process of carrying out this systematic review were built on top of these guidelines, which served as the foundation.

Eligibility Criteria

This systematic review was developed to analyze papers on "COVID-19" and "coagulation dysfunction". These are the subjects that were covered in depth in the research that was taken into account. The following requirements have to be met in order for your work to be taken into consideration: 1) Articles have to be written in English. 2) Articles have to have been published after 2012, but before the time this systematic review is created. The following kinds of textual contributions will under no circumstances be considered for inclusion in the anthology: 1) Editorial letters, 2) contributions that do not have a Digital Object Identifier (DOI), and 3) article reviews and submissions that are comparable to those that have previously been published in the journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from November 30th, 2022 using the PubMed and SagePub databases by inputting the words: "COVID-19" and "coagulation dysfunction". Where *("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All*

Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("blood coagulation"[MeSH Terms] OR ("blood"[All Fields] AND "coagulation"[All Fields]) OR "blood coagulation"[All Fields] OR "coagulation"[All Fields] OR "blood coagulation tests"[MeSH Terms] OR ("blood"[All Fields] AND "coagulation"[All Fields] AND "tests"[All Fields]) OR "blood coagulation tests"[All Fields] OR "coagulability"[All Fields] OR "coagulable"[All Fields] OR "coagulants"[Pharmacological Action] OR "coagulants"[MeSH Terms] OR "coagulants"[All Fields] OR "coagulant"[All Fields] OR "coagulate"[All Fields] OR "coagulated"[All Fields] OR "coagulates"[All Fields] OR "coagulating"[All Fields] OR "coagulational"[All Fields] OR "coagulations"[All Fields] OR "coagulative"[All Fields] OR "coagulator"[All Fields] OR "coagulators"[All Fields]) AND ("dysfunctional"[All Fields] OR "dysfunctionals"[All Fields] OR "dysfunctioning"[All Fields] OR "dysfunctions"[All Fields] OR "physiopathology"[MeSH Subheading] OR "physiopathology"[All Fields] OR "dysfunction"[All Fields]) is used as search keywords.

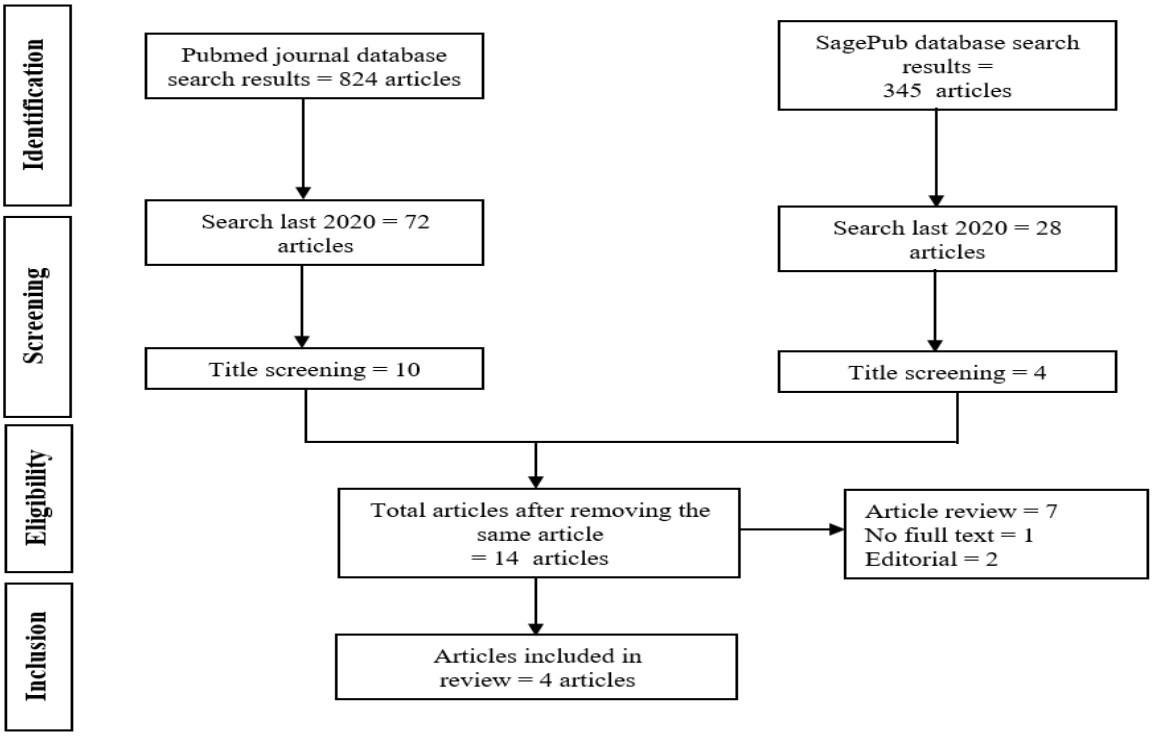

Figure 1. Article search flowchart

Data retrieval

The author of the study updated the criteria for what should and should not be included in the study after doing a literature review and analyzing the titles and abstracts of previously published research. This was done in order to determine what should and should not be included in the study. Following a study of other research that had been previously published, the author made these modifications.

During the process of compiling the systematic review, the only research projects that were considered to be relevant were those that fulfilled each and every requirement. This was done to ensure that the review is as thorough as it possibly can be. It is possible to gather information about each individual study, such as the title of the study, its author, the publication date of the study, the study's place of origin, the research design, and the research variables. The delivery of this information may take place in any one of a number of various formats.

Quality Assessment and Data Synthesis

The authors conducted their own independent reviews of a subset of the research listed in the titles and abstracts of the papers to determine which studies could be considered. Following this, the full texts of the studies that meet the inclusion criteria for the systematic review will be read to determine which studies can be used as final inclusions for the purposes of the review. This will be done in order to answer the question, "Which studies can we use for the review?".

RESULT

A coagulation issue manifested itself early on in the course of the COVID-19 infection, with 50 (43.5%) patients exhibiting increased DD and 74 (64.3%) patients demonstrating increased Fg. There was a correlation between the levels of DD and Fg and the clinical categorization. Out of the 23 patients who passed away, 18 had an elevated DD at the first laboratory test, 22 had an increased DD at the second and third laboratory tests, and 18 had a prolonged PT at the third laboratory test.[9] Other study showed elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and d-dimer were found in a smaller percentage of the patients.[12]

An autopsy report showed the most common reason for death was respiratory failure, which was characterized by exudative widespread alveolar injury and extensive capillary congestion. Despite anticoagulation, this condition was frequently associated by microthrombi. In ten of the instances, bronchopneumonia was found to be overlaid. In addition, there were four patients who had a pulmonary embolism, three patients who had alveolar hemorrhage, and one patient who had vasculitis. The majority of the pathologies found in other organ systems may be attributed to shock; three patients had symptoms of generalized thrombotic microangiopathy, and five patients had pulmonary thrombotic microangiopathy.[13]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size / Characteristic	Parameter	Result
Long, 2020[9]	China	Prospective study	115	D-dimer (DD), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (Fg)	Coagulation disorder developed early in COVID-19 infection, with 50 (43.5%) patients having increased DD and 74 (64.3%) patients having increased Fg. Clinical classification was found to be related to DD and Fg levels. Among the 23 patients who died, 18 had elevated DD on the first lab test, 22 had elevated DD on the second and third lab tests, and 18 had prolonged PT on the third test.
Guan, 2020[12]	China	Retrospecti ve study	1,099 patients	D-dimer	Elevated levels of C-reactive protein were found in the majority of the patients. Elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and d-dimer were found in a smaller percentage of the patients.
Menter, 2020[13]	Switzerland	Reports the autopsy findings	21 COVID-19 patients	Pulmonary embolism, microthrombi	Respiratory collapse with exudative diffuse alveolar injury, severe capillary congestion, and microthrombi despite anticoagulation was the main cause of mortality. Ten had superimposed bronchopneumonia. Pulmonary embolism, alveolar hemorrhage, and vasculitis were found. Shock caused three cases of generalized and five of pulmonary thrombotic microangiopathy in different organ systems.
Smilowitz, 2021[14]	United State	Prospective study	3,334 patients	Thrombosis	Acute MI occurred in 2.8% of hospitalizations, VTE in 1.6%, ischemic stroke in 0.7%, and other systemic embolism in 0.1%. Patients with thrombosis had higher in-hospital mortality (14.9% vs 3.3%, P<0.001) than those without thrombosis. The proportion of hospitalizations complicated by thrombosis was lower in patients with viral respiratory illness in 2002-2014 than in COVID-19 (median age 64; 39.6% female) in 2020 (5% vs 16%; P<0.001)

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DISCUSSION

The coagulation cascade is activated in viral infections as a defense against the spread of pathogens. Initially, there is an adaptive hemostatic response associated with a systemic inflammatory response. The increased inflammatory activity significantly increases the fibrinogen level, and thrombin formation occurs. The increased cytokine production during viral infection also stimulates additional procoagulant reactions by increasing the expression of tissue factor which is the main initiator of coagulation activation.[15]

Other factors such as phosphatidylserine on cellular membranes, neutrophil extracellular trapping, and damage-associated molecular patterns (DAMPs) may also be involved in the procoagulant profile of COVID-19. In some cases, the presence of antiphospholipid antibodies which may cause arterial thrombosis was reported, and its relevance to stroke and acute coronary disease should be examined in future studies. There is an association between bronchoalveolar coagulation/fibrinolysis and the pathogenesis of ARDS with increased intrapulmonary fibrin deposition.[15,16]

Measurement of coagulation factors and fibrinolysis in bronchoalveolar lavage fluid (BALF) in cases of bacterial infection has shown increased intrapulmonary thrombin formation, inadequate physiological anticoagulation, and fibrinolysis suppressing factors mediating the pathogenesis of ARDS. COVID-19 patients experienced increased procoagulant activity through the tissue factor pathway, and suppressed plasmin activity by decreasing urokinase-type plasminogen activator and increasing plasminogen activator inhibitor-1.[15,16]

COVID-19 patients have been shown to have high D-dimer levels, although only mild prolongation of PT, ApTT, mild thrombocytopenia, and increased D-Dimer.[12] Pulmonary histopathology shows only the initial findings seen in COVID-19 including alveolar damage with proteinaceous exudate and alveolar edema, vascular congestion, and focal fibrin

deposition with pneumocytic hyperplasia. These findings suggest that pulmonary coagulopathy begins early in the development of the disease itself.[17]

Table 2. Resume of coagulation profile in patient woth COVID-19

No	Parameter	Level
1	D-dimer	Increased
2	Prothrombin time	Prolonged
3	APTT	Prolonged
4	Thrombin time	Prolonged
5	Fibrinogen	Increased

Measurement of blood coagulation factors showed a greater risk of coagulopathy in patients in the non-survival group. Platelet levels were significantly lower (<35.9 × 109/L, 95% CI, −53.3 to −18.5; P<.0001) in the non-surviving group whereas D-dimer (>4.6 pg/mL, 95 % CI, 2.8 - 6.4; P <.00001) higher. Prothrombin time increased slightly in the non-surviving group (>1.2 seconds, 95% CI, 0.4-1.9; P = 0.002). The investigators found no significant association between partial thromboplastin time and death.[18]

Deaths have been reported early on, but autopsy data from COVID-19 patients is lagging behind. To date, very few studies of histopathological findings are available.[17] Autopsy data showed that there was diffuse exudative alveolar damage with severe capillary congestion. In addition, frequent findings include pulmonary embolism, pulmonary edema, alveolar hemorrhage, and alveolar capillary microthrombi.[13] Pulmonary embolism (PE) is the direct cause of death in 33% of patients.[11,19]

Studies have shown that coagulation factor abnormalities are consistent with CT imaging results, in which increased D-Dimer is associated with CTA-confirmed pulmonary embolism.[9] The overall incidence of pulmonary embolism is 24% in patients with COVID-19 pneumonia.[20] A review of Sakr et al showed that the mean age of patients with PE was 59 years (age range 17-84 years) whereas more than half of the patients were male. No source of PE was detected in the majority of cases (80%).[21]

The diagnosis of PE was made at a median of 11 days (range 4–22 days) from the onset of COVID-19 symptoms, in which 66.7% of patients had bilateral PE and 26.7% of patients had central PE. Two main phenotypes of COVID-19 patients with thrombotic lung injury can be identified, namely venous thromboembolism (VTE) and pulmonary microthrombosis (PMT). Generally, DVT or other sources of VTE are not consistently found in COVID-19 patients with PE, so that PMT is caused by local hypercoagulability due to embolization of the lower extremities.[21]

Thrombus formation in the microvasculature may be part of a physiologic effort to limit viral load. Viral invasion causes intense lung inflammation and can trigger activation of local hemostasis driven by interactions between platelets and endothelium. The start of microthrombi formation during COVID-19 is related to endothelial cell dysfunction. The pattern of coagulation activation in ARDS COVID-19 patients in the ICU is not the same as in non-COVID-19 ARDS patients.[21]

PT, aPTT and AT levels are generally within normal ranges, whereas fibrinogen and D-Dimer are elevated. This pattern is also different from that of patients with septic shock who frequently develop DIC. The mechanisms underlying COVID-19-induced coagulopathy may be different from those reported in other patients with sepsis. This could also explain the phenotypic differences found in patients with COVID-19 who show a predominance of thromboembolic manifestations rather than bleeding tendencies.[21]

Several mechanisms may contribute to the hypercoagulable state and PMT during COVID-19. First, the direct and indirect pathological effects of COVID-19, such as severe hypoxia, pre-existing co-morbidities, and related organ dysfunctions can affect hemostatic disorders, including KID. Hypoxia can affect thrombosis by increasing blood viscosity and through hypoxia-induced transcription factor-dependent signaling pathways.[21]

VTE risk was also associated with age, immobilization, obesity, patient or family history of VTE, cancer, sepsis, respiratory or cardiac failure, pregnancy, stroke, trauma, or history of surgery. ICU-specific risk factors may also contribute to this risk, such as sedation, immobilization, administration of vasopressors, and use of central venous catheters. Second, endothelial dysfunction, increased von Willebrand Factor (vWF), Toll-like receptor activation, and tissue-factor pathway activation which can cause pro-inflammatory and procoagulant effects through complement activation and cytokine release.[21]

This results in dysregulation of the coagulation cascade with formation of systemic or intra-alveolar fibrin clots. This can be proven by increasing levels of plasminogen activator inhibitor 1 (PAI-1) with decreased fibrinolytic activity. The activity of vWF and vWF antigen (vWF: Ag) was drastically increased, as was factor VIII. In addition, 50 of the 57 patients studied (87.7%) had positive circulating lupus anticoagulation during their ICU stay.[21]

Third, the release of proinflammatory cytokines (IL-2, IL-6, IL-7, IL-8, granulocyte colony-stimulating factor, interferon gamma-induced protein 10 (IP10), monocyte chemotactic protein-1 (MCP1), macrophage inflammatory protein 1A (MIP1A) and tumor necrosis factor (TNF-α) overexpression of the so-called "cytokine storm" is a common feature of sepsis leading to the development of hemophagocytic lymphohistiocytosis secondary to activation of blood coagulation.[21]

These conditions increase the risk of intravascular microthrombosis and secondary local consumption coagulopathy leading to VTE. Interactions between different types of blood cells (macrophages, monocytes, endothelial cells, platelets and lymphocytes) may play an important role in the procoagulant effect of viral infections. For example, activation of platelets upon antigen recognition can enhance clearance of pathogens by activation of white blood cells and formation of clots. This can be modulated by platelet-induced neutrophil extracellular traps (NETs) and plays an important role in sepsis-associated hypercoagulability.[21]

CONCLUSION

The causal and bidirectional relationship between inflammation and thrombosis has been clearly recognized by many studies. COVID-19 causes a hyper pro-inflammatory condition as evidenced by an increase in high levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, interleukin-6 and D-dimer. IL-6 and fibrinogen levels were shown to be bidirectionally correlated in patients with COVID-19, lending credence to the idea of inflammatory thrombosis.

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