Review Article

Blood Coagulation: A Potentially Lethal Manifestation in Covid-19 Patients

ABSTRACT:

Blood clotting is a well-known phenomenon which is intended to provide protection in case of any external cellular/ tissue injury. However, their lies a concern due to this phenomenon in Covid-19 patients that is leading to unusual thrombotic presentations. Since the emergence of novel corona virus, World has come across various benign as well as lethal manifestations in COVID-19 patients and one such life-threatening manifestation which needs rigorous attention is the genesis of strange blood clots that can travel and get logged into several parts of the COVID-19 patients leading to various clinical presentations. COVID-19 infection is caused due to interaction of spike glycoproteins of corona virus with ACE 2 receptors of host cell surface. This interaction in the arteries, veins or capillaries could lead to injury in vascular wall of blood vessels that can directly/Indirectly lead to coagulation and clotting cascades activation and subsequent formation of internal blood clots. However, it is undesirable to have the presence of these clots as they could lead to certain fatal complications that need emergency medical intervention or else, they may lead to death of patient. Due to the severity of this manifestation, early detection of these blood clots in covid-19 patients become very important intervention which could be done by observing certain specific signs and symptoms and/or with the help of various laboratory biomarkers like D-dimer, platelet count, erythrocyte sedimentation rate (ESR), ferritin, fibrinogen, etc. Once the early diagnosis is made, patient can be treated appropriately with the help of anticoagulant therapy, which includes use of oral and parenteral anticoagulant drugs. This way the complications of blood coagulation like thrombo-embolism, could be prevented.

KEYWORDS:

- Covid-19
- Blood Clotting
- ACE 2 receptors
- Anticoagulants.

BACKGROUND:

Severe acute respiratory syndrome coronavirus-2, designated as SARS-CoV-2 first recognised in the middle of an outbreak in Wuhan City, Hubei Province, China; is the causative organism of Coronavirus disease 2019 (COVID-19). On 31th December, 2019, it was first conveyed to the World Health Organization (WHO). The World Health Organisation announced this corona virus outbreak as a global health crisis on 30th of January 2020. Then in the same year on 11th of March, the World Health Organisation declared COVID-19 a global pandemic. Since then, over the course of time with the advent of new mutated corona virus strains, dynamics of COVID-19 have kept on evolving.

SARS-CoV-2 is a virus composed of a single strand of Ribonucleic acid (RNA), glycoprotein, spike protein and an envelop. It is a virus of the pulmonary system and so when it enters in the human body, it primarily infects the predominant organ of pulmonary system which is the lung.[1] This access is facilitated by the linking of the receptor-binding domain (RBD) of S1 subunit present on the spike protein of virus with the angiotensin-converting

enzyme-2 (ACE-2) receptor of the host which are principally articulated in type II pneumocytes, serving as a pool for the virus.[2][3]

A major proportion of individuals infected with COVID-19 remain asymptomatic and recover without requiring any medical intervention. However, common clinical presentations in symptomatic patients include dry cough, sore throat, fever and breathlessness.[4] Although a variety of other symptoms have been seen in patients infected with different mutated strains of corona virus over the course of pandemic.

Blood clots have been discovered in the minute blood vessels of various organs like lungs, heart, liver, and kidney, on post mortem examinations of a significant percentage of COVID-19 patients. These blood clots can cause ischemia of the tissues or organs in which they are logged.[5] Thus, this aspect of covid-19 disease has become an area of research and requires adequate concern.

OBJECTIVES:

The main objective of this review article is to collect, summarize and present all the important data and information in regard to blood coagulation which has come out to be a most important hematological appearance in patients suffering from covid-19 disease. This article comprises of the complete story of blood coagulation in covid-19 patients under following heads:

- Introduction
- Pathophysiology
- Clinical picture
- Laboratory findings
- Treatment

INTRODUCTION:

The pandemic of Coronavirus disease 2019 (COVID-19) has been producing substantial mortality and morbidity since its outbreak in December 2019. COVID-19 has been linked up with various coagulative disorders and hypercoagulable states in a growing number of studies. Coronavirus infection could trigger numerous systemic coagulative and inflammatory

reactions, as per the hypothesized mechanism. Increased production of proinflammatory cytokine is a result of host inflammatory responses, which triggers coagulation cascade activation and consumptive coagulopathy.[6] When compared to historical data, numerous observational studies have found a greater prevalence of venous thrombotic events amid the corona virus infected individuals under intensive care unit (ICU) admission.[7] However, some studies have also testified thrombotic events in arteries of individuals infected with corona virus.[8] Experts urge anticoagulant prophylaxis for all corona virus infected patients who are seriously unwell.

METHODOLOGY:

This is a Narrative review article which has been prepared after going through various literature works from sources such as PubMed and Google scholar.

PATHOPHYSIOLOGY:

After primary infection, the virus moves into the systemic circulation and attaches itself to the Angiotensin-converting enzyme-2 (ACE-2) expressing endothelial cells that forms the lining of the blood vessels. This linkage aids the virus, resulting in injury to endothelial cells and harm to the surface of blood vasculature. The injury to the vasculature can also happen because of inflammation in endothelial cells that can lead to cytokine release and subsequent blood vessel injury. Following injury to endothelial cells in blood vessels, recruitment and aggregation of platelets together with collagen takes place at the place of injury. This aggregation is enhanced by release and action of the Von Willebrand factor. Soon coagulation is initiated by activation of coagulation cascade following the intrinsic pathway. The genesis of clots in blood vasculature can be initiated following sequential activation of all the twelve clotting factors, followed by conversion of prothrombin to form thrombin and then conversion of fibrinogen to form insoluble and elongated fibrins. These fibrins cross link with platelets by covalent bonds which results in formation of a firm interlocking network of fibrin clot at location of injury. This leads to formation of haemostatic plugs. This haemostatic plug can lead to various complications, of which thrombosis is one of the most commonly perceived complication among Covid-19 individuals.

Virchow described three primary events which predispose to thrombus formation and are collectively known as Virchow's triad. It includes: -

- ***Endothelium injury***:

It triggers platelet activation and genesis of thrombus by the action of von Willebrand factor (vWF) and tissue factor in the heart and in the arterial circulation, where coagulation is impeded by high rates of blood flow. Activation and adherence of platelets is an important pre-requisite for formation of thrombus and therefore clots in arteries and heart are exclusively rich in platelets. Hence, in cases of coronary artery disease and acute myocardial infarction, platelet-inhibitors like aspirin, etc are brought in use. There are several prothrombotic events that can lead to what is called endothelial activation or dysfunction. These events include varied exposures to infectious agents, physical injury, altered blood flow, mediators of inflammation, abnormalities of metabolism such as hypercholesterolemia or homocystinemia, and toxins assimilated from cigarette smoke.

Following are some important prothrombotic alterations: -

- Procoagulant changes - On activation by cytokines, endothelial cells reduce the thrombomodulin expression, which is a main regulator of thrombin activity. This can cause continuous thrombin activation, causing stimulation of platelets and augmentation of inflammation through Protease-activated receptors (PARs) expressed over platelets and other inflammatory cells. Along with this, the inflamed endothelium also reduces the activity of anticoagulants like protein C and tissue factor protein inhibitors.
- Antifibrinolytic effects - Cells of endothelium on activation release plasminogen activator inhibitors (PAIs), that limit lysis of fibrins.

❖ ***Altered blood flow (Stasis or turbulent)***:

Normally, blood flow in vessels is laminar in a such way that the platelets and other cellular elements flow in the centre in the lumen of vessel, around this central flow of cellular elements is the layer of plasma which moves slowly and separates it from the endothelium. Endothelial injury is caused by turbulent flow which leads to formation of counter-currents that contribute to cardiac and arterial thrombosis. Whereas, major cause behind formation of venous thrombi is stasis.

- Abnormal flow of blood promotes endothelial activation, which enhances procoagulant activity and leukocyte adhesion.
- It disturbs laminar flow and platelets come in contact with endothelium.
- It also safeguards the removal of active clotting factors by and inhibits the inflow of inhibitors of clotting factors.

Altered blood flow aids thrombosis in several clinical syndromes such as aneurysms, acute myocardial infarctions, rheumatic mitral valve stenosis, polycythaemia vera, sickle cell anaemia, etc.

- ***Hypercoagulability of blood***:

  Hypercoagulability also known as thrombophilia is defined as any haematological disorder predisposing to thrombosis. Hypercoagulability particularly contributes in thrombosis of veins. It can be classified as primary disorders that are genetic and secondary disorders that are acquired. The most common events leading to thrombophilia are point mutations in the prothrombin gene and factor V gene.

  - One of the mutations leading to hypercoagulability is mutation of a single nucleotide in factor V, called as factor V Leiden. This mutation leads in substitution of glutamine by arginine at 506 amino acid residue that results in factor V becoming resistant to splitting and deactivation by protein C, resulting in loss of an antithrombotic counterregulatory pathway.
  - Another single nucleotide mutation in the prothrombin gene at 3′- untranslated region can be linked up with hypercoagulability. It leads to raised levels of prothrombin and a threefold increase in venous thrombosis.
  - Apart from above mentioned genetic factors, raised homocysteine levels also aid in thrombosis of arteries and veins. Increased levels of homocysteine could be due to an inherited deficiency of cystathione β-synthetase.[9][10]

CLINICAL PICTURE:

In general, the location of blood clot in the body determines the clinical features a patient suffers:

- A blood clot in heart or lung could cause-
  i. Chest pain
  ii. Shortness of breath
  iii. Upper body discomfort in the arms, back, neck, or jaw
- A blood clot in brain could cause-
  i. Headache
  ii. Paralysis

iii. Dizziness
iv. Trouble in speaking or understanding speech

- A blood clot in deep veins of the leg could cause-
  i. Pain
  ii. Redness
  iii. Warmth
  iv. Swelling

Corona positive individuals can come up with a variety of abnormalities of coagulation as well as complications of thrombosis, some of which are as follows:

- Pulmonary embolism (PE)
- Venous thromboembolism (VTE)
- Sepsis-induced coagulopathy (SIC)
- Disseminated intravascular coagulation (DIC)
- Thrombotic micro-angiopathy
- Microvascular thrombosis
- Micro-thrombosis

LABORATORY FINDINGS:

Following are some of the potentially useful Laboratory findings in COVID-19: -

- **Tests in which levels are likely to increase**:
- C-reactive protein (CRP)
- D-dimer
- Activated partial thromboplastin (aPTT)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Lactate dehydrogenase (LDH)
- Fibrinogen
- Prothrombin time (PT)
- CBC (platelets and lymphocytes)

The levels of above-mentioned markers are usually expected to increase in acute stage of the disease.

- **Tests in which levels are likely to decrease**:

- Albumin
- Activated partial thromboplastin (aPTT)
- CBC (platelets and lymphocytes)
- Fibrinogen
- Prothrombin time (PT)

The levels of above-mentioned markers are usually expected to decrease in late stage of disease.

There are specific laboratory markers which are helpful for diagnosis, treatment and prognosis of blood coagulation and its related disorders in patients with COVID-19. These include: -

- **D-dimer**: D-dimer is an outcome of denaturation of fibrin. It is one of the fragments of protein formed on termination of a blood clot in body. In normal circumstances, it is either undetectable or detectable at a very low level. It is detected only when there is formation and breakdown of blood clots in the body. It's presence in blood indicates fibrinolysis.[11] In patients with COVID-19, raised D-dimer readings are observed to be associated with bad prognosis and increased mortality. In patients with COVID-19, Systemic Inflammatory Response Syndrome (SIRS) lead to coagulation cascade activation which ultimately is responsible for such high D-Dimer levels.[12]
- **Platelet count**: Platelets are also designated as thrombocytes. These are colourless bits of blood cells that prevent or stop bleeding by forming clots. Thrombocytopenia is detected in corona positive patients but the incidence varies as per the severity of disease. Severely diseased patients have a platelet count ranging between 23 ×109/L to 31 ×109/L on average, which is lower as compared to those with non-severe disease. Platelets are involved in inflammatory signals as well as the immune response. Platelets may assist target haemostasis and immunological responses against possible infectious agents to limit microbial invasion by combining thrombotic and immune recruiting roles.

- **C-reactive protein (CRP)**: It is considered to be an "acute stage protein", that is an early marker of any infectious or inflammatory conditions. Normally, the concentration of CRP in blood is less than 10 mg/L. Although within 6 to 8 hours, it rapidly increases and peaks within 48 hours from the disease onset.[13] Half- life of C-reactive protein is about 19 hours and when the inflammatory stage ends, its concentration decreases.
- **Erythrocyte sedimentation rate (ESR)**: It is a procedure or method to evaluate blood by measuring the speed of sinking of erythrocytes (red blood cells) at the lowermost part of a test tube. Raised ESR can lead to various joint abnormalities like osteoarthritis, it can also be seen as a precursor of renal and hepatic dysfunction therefore raised ESR in individuals with COVID-19 could be a sign of bad prognosis.
- **Fibrinogen:** Fibrinogen is a complex of glycoprotein that is synthesized in liver. It is enzymatically converted by thrombin into fibrin as a consequence of any tissue or vascular injury**.** [14] The fibrin clots so formed primarily acts to occlude blood vessels in order to stop bleeding. Several studies have found remarkably higher fibrinogen levels in critically diseased patients.
- **Ferritin:** It is an intracellular iron-storage protein. Various studies have suggested elevated levels of serum ferritin in individuals with severe COVID-19 disease.[15] In autopsies of 12 patients with COVID-19 as a cause of death, raised levels of serum ferritin were found.[16]
- **Procalcitonin:** Procalcitonin is the precursor of calcitonin, which regulates the calcium homeostasis. preprocalcitonin is cleaved by endopeptidase to form procalcitonin. The level of procalcitonin can reflect the severity of disease in corona positive patients.

TREATMENT:

The treatment protocols for Covid-19 disease have kept on changing with the course of pandemic. In general, the treatment for covid-19 is definite and is based on the severity of disease and presence or absence of some risk factors. Currently, a wide range of therapeutic modalities are available for management of COVID-19 under Emergency Use Authorization (EUA) issued by Food and Drug Administration (FDA). These include: -

- Anti-inflammatory drugs
- Anti-SARS-CoV-2 monoclonal antibodies
- Antiviral drugs
- Immunomodulators agents [17]

Anticoagulant drugs are usually used to treat blood clots. These group of drugs not only prevent existing clots from getting bigger but they also keep a check on new clot formation. One observational study examined the effects of anticoagulants in people who were hospitalized with COVID-19. It found that people who were treated with anticoagulants in the hospital had a more positive outcome than those who were not.[18] Therefore, WHO recommends the use of low dose anticoagulants in hospitalized patients for preventing the blood clots formation in blood vessels.

Chart 1. Parenteral anticoagulants: -

INDIRECT THROMBIN INHIBITORS	DIRECT THROMBIN INHIBITORS
Heparin (unfractionated)	Bivalirudin
Low molecular weight heparins (Enoxaparin, Reviparin, Nadroparin, Ardeparin, Parnaparin)	Argatroban
Fondaparinux	
Danaparoid	

Chart 2. Oral anticoagulants: -

VIT K ANTAGONISTS	DIRECT FACTOR Xa INHIBITOR	ORAL DIRECT THROMBIN INHIBITOR
Bishydroxycoumarin (Dicumarol)	Rivaroxaban	Dabigatran-etexilate
Warfarin sod.	Apixaban	
Acenocoumarol (Nicoumalone)		
Ethyl-biscoum-acetate		

[19-25]

There are some measures which are certainly helpful in preventing blood coagulation and associated disorders. These are as follows:

- Stay active- A sedentary lifestyle can increase the risk of developing blood clots therefore been fit and active is very important for which regular exercises are very important.
- Lose weight- Shedding excess weight can help lower your risk for developing blood clots.
- Quit smoking- Smoking can harm the blood vessel lining and lead to formation of blood clots.

CONCLUSION:

Since the time of emergence of noble corona virus, scientists as well as medical professionals around the world have made a lot of progress in unfolding facts related to various aspects of the virus. Based on this study we can state that blood coagulation is indeed a very lethal manifestation of COVID-19 disease. It occurs as a consequence of endothelium injury which can be due to binding of spike proteins with ACE 2 receptors or due to release of Inflammatory cytokines. This leads to formation of blood coagulants that can ultimately cause various abnormalities of coagulation and complications associated with thrombosis. Although timely diagnosis based on various signs and symptoms, and with the help of various laboratory markers; followed by timely medical intervention using anticoagulant therapy can prevent the patient from entering the state of critical condition or even death.

There is lot of scope and requirement of research in areas related to COVID-19 as the corona virus is there to stay with us for a long time and we have to find ways to combat its lethal effects on human beings.

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