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Pathophysiology, management and therapeutic challenges of coagulopathy in COVID-19 patients

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Abstract: The pathophysiology of COVID-19-associated coagulopathy is characterized by a complex of interactions within viral factors, abnormal haemostasis, dysfunction of endothelial cells, and inflammatory reactions, necessitating the research to elucidate underlying mechanisms and identify novel therapeutic targets. Severe COVID-19 conditions are frequently coupled with an increased immunological response, dubbed a cytokine storm, which facilitates the release of pro-inflammatory cytokines (e.g., interleukin-6, tumour necrosis factor-alpha). The cytokine storm contributes to widespread inflammation and endothelial activation, disrupting the balance between pro-coagulant and anticoagulant factors. Additionally, it is capable of being transmitted by contacting surfaces that are contaminated and then rubbing the face. Biomarkers such as D-dimer levels serve as valuable tools in risk assessment and monitoring, yet their interpretation requires careful consideration within the clinical context. Although some COVID-19 patients may not exhibit any symptoms, they can still spread the virus to others, and there is proof that the virus can spread via the air in some environments, especially confined areas with inadequate ventilation. Vaccines have been developed and deployed globally to prevent COVID-19 infection and reduce severe illness, hospitalizations, and deaths. Governments and health authorities worldwide have implemented policies including lockdowns, social isolation, mask-wearing, investigation, contact tracking, and vaccination campaigns to control transmission and reduce the impact of the virus. Data were sorted from PubMed, Google Scholar, Springer, Nature, Tailor and Francis, MDPI, BMC and some other related data. This review provides appreciable information on the pathophysiology, management and therapeutic challenges of coagulopathy in Covid-19 patients.

Keywords: *COVID-19 virus, Pathophysiology, Management and therapeutic challenges.*

1. Introduction

Coronavirus Disease 2019 (COVID-19) is caused by the emerging coronavirus SARS-CoV-2. In several studies, it was described as SARS-CoV-2 due to its resemblance to severe acute respiratory syndrome (SARS) [1]. Since December 2019, a coronavirus disease 2019 (COVID-19) outbreak has spread around the world, originating in the Chinese city of Wuhan in the Hubei province [2]. On February 11, 2020, the International Committee on Taxonomy of Viruses' Coronavirus Study Group formally designated the novel coronavirus that causes COVID-19 as "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)," and on March 11, 2020, the World Health Organisation declared the new COVID-19 to be a pandemic because of its widespread distribution and severity [3]. This virus is a

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member of the coronavirus family, which also contains viruses that cause more serious conditions including MERS (middle east respiratory syndrome) and SARS (severe acute respiratory syndrome).

The single-stranded RNA coronavirus known as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) primarily enters human cells by attaching itself to angiotensin converting enzyme 2 (ACE 2), which is expressed in higher quantities in the lung's alveolar cells, cardiac myocytes, vascular endothelium, and other cells. SARS-CoV-2 is mostly spread by inhaling virus particles, making it possible to get into the respiratory system [4]. On surfaces that permit transmission, this virus can persist for up to 24 to 72 hours [5]. Due to mutations in SARS-CoV-2, variations with distinct traits, such as greater transmissibility or antibody resistance, have emerged. Worldwide, vaccines have been created and implemented to stop COVID-19 infections and lower the number of serious illnesses, hospital stays, and fatalities. The main way that COVID-19 is transmitted is by respiratory droplets released by an infected individual when they cough, sneeze, or speak. Additionally, it can be transmitted by contacting infected surfaces and then rubbing the face.

Fever, coughing, exhaustion, and shortness of breath or trouble breathing are the most typical symptoms. Muscle pains, nausea, diarrhoea, congestion, sore throats, and loss of taste are other symptoms. Mild to severe symptoms are possible, and some people get severe respiratory illnesses that necessitate hospitalisation [6]. An infected individual may not exhibit symptoms throughout the 2–14day incubation period following infection, but they can still transmit the virus during this time. Although some COVID-19 patients may not exhibit any symptoms, they can still spread the virus to others, and there is proof that the virus can spread via the air in specific environments, especially confined areas with inadequate ventilation [7]. To stop the virus's spread and lessen its effects, governments and health authorities throughout the world have put policies in place including lockdowns, social distance, mask wearing, testing, contact tracking, and vaccine programs.

1.2. Coagulopathy (Coagulation Disorder)

Coagulopathy (often referred to bleeding disorder), is a disorder that affects the blood's capacity to coagulate [8]. This disorder can result in bleeding diathesis, a propensity for excessive or protracted bleeding that can happen on its own or after an accident or medical or dental operations.

1.3. Clotting Mechanisms in the Body

1.3.1. Primary Hemostasis:

Vascular spasm**:** When a blood vessel is damaged, platelets stick to the area, activate, and group together to create a transient platelet plug.

1.3.2. Secondary Hemostasis

Coagulation Cascade**:** A series of complex biochemical reactions involving clotting factors (proteins in the blood plasma) are triggered to reinforce the platelet plug and form a stable fibrin clot. This cascade includes activation of clotting factors, formation of thrombin (enzyme that converts fibrinogen to fibrin), and cross-linking of fibrin strands to stabilize the clot.

1.3.3. Fibrinolysis

Clot Removal: Once the injury is healed, fibrinolysis (breakdown of fibrin) occurs to dissolve the excess clot and restore blood flow.

1.4. Types of Coagulation Disorders

1.4.1 Hemophilia

It is typically inherited as X-linked recessive disorders, affecting males more severely than females. It has symptoms of prolonged bleeding, especially into joints and muscles after minor trauma or spontaneously. The two types of haemophilia are haemophilia A and haemophilia B.
Deficits in factor VIII result in Haemophilia A, while deficiencies in factor IX result in Haemophilia B.

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1.4.2. Von Willebrand Disease (VWD)

It is due to deficiency or dysfunction of von Willebrand factor (vWF), a protein that helps platelets adhere to blood vessel walls. It has symptoms similar to hemophilia but generally milder, with mucocutaneous bleeding (nosebleeds, excessive menstrual bleeding).

1.4.3. Disseminated Intravascular Coagulation (DIC)

It is due to widespread activation of clotting factors throughout the body, often due to severe infections, trauma, or certain cancers. Initially it causes excessive clotting (thrombosis) followed by consumption of clotting factors, leading to bleeding tendencies. Clinically, patient can present with both thrombotic and bleeding manifestations, often critically ill.

1.4.4. Thrombophilia

This medical condition increases the risk of venous thromboembolism (pulmonary embolism, deep vein thrombosis) and excessive clot formation (thrombosis). These include acquired illnesses like antiphospholipid syndrome and hereditary abnormalities like Factor V Leiden mutation and prothrombin gene mutation.

1.4.5. Acquired Coagulation Disorders

It may be caused by vitamin K insufficiency, which is necessary for the synthesis of clotting factors II, VII, IX, and X, or liver illness, which hinders the synthesis of clotting factors.

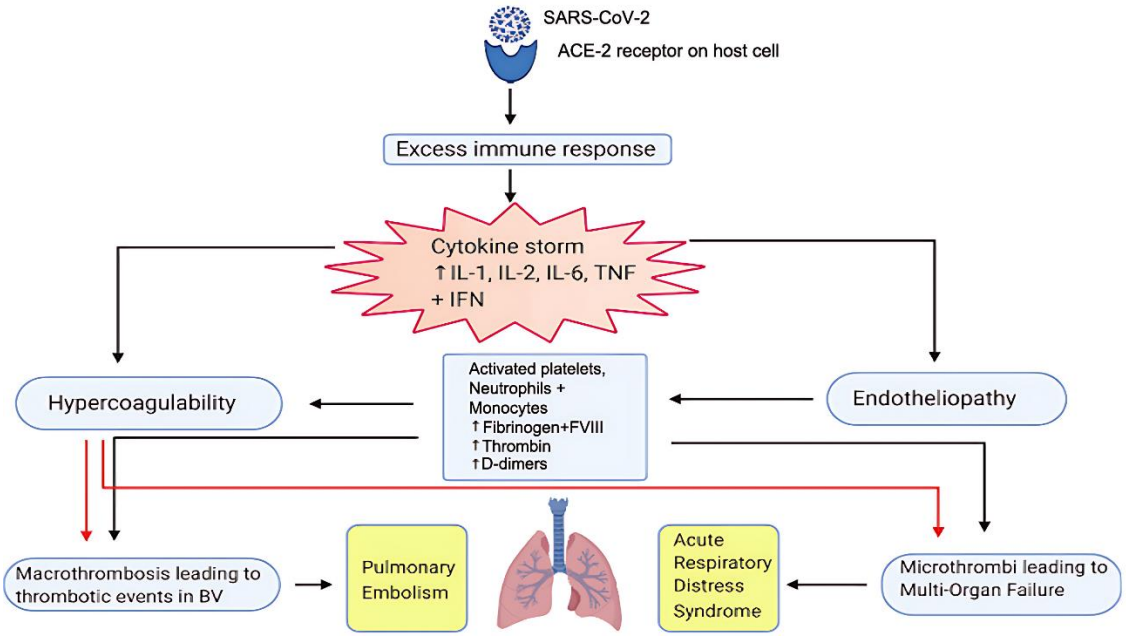

Figure 1.
Mechanism of Covid-19 Associated Coagulopathy [9].

2. Coagulation Disordes in COVID-19 Patients

Coagulopathy in covid-19 patients occur through the following process.

2.1. Endothelial Dysfunction and Thrombosis:

Research has shown that COVID-19 can induce endothelial cell inflammation and dysfunction, leading to increased expression of pro-inflammatory and pro-thrombotic molecules such as von Willebrand factor and tissue factor [10]. Endothelial dysfunction is linked to worse outcomes in COVID-19 patients and is a contributing factor to microvascular thrombosis.

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2.2. Hypercoagulability and Thrombotic Events:

Despite preventative anticoagulation, studies have shown a considerable rate of venous and arterial thrombotic events in severe COVID-19 patients [11]. The coagulation cascade is activated in COVID-19-associated coagulopathy, as shown by increased levels of D-dimer, fibrinogen, and fibrin degradation products [12].

2.3. Inflammatory Response and Coagulation Cascade:

A hyperinflammatory condition that upsets the equilibrium between pro-coagulant and anticoagulant components is a result of the cytokine storm seen in severe COVID-19 patients [13].

Patients with COVID-19 have a higher risk of thrombosis when their levels of interleukin-6 (IL-6) and other inflammatory markers are elevated.

2.4. Antiphospholipid Antibodies (APLAs)

Antiphospholipid antibodies, which are linked to an elevated risk of thrombotic events and sequelae, may develop in some COVID-19 patients, according to new research Zuo, et al. [14]. APLAs may play a part in the pathophysiology of coagulopathy linked to COVID-19, but further study is required to fully understand their function.

3. Pathophysiology

Viral pathogenesis and the host immune response interact intricately in COVID-19-associated coagulopathy, resulting in abnormal coagulation cascade activation and endothelial dysfunction.

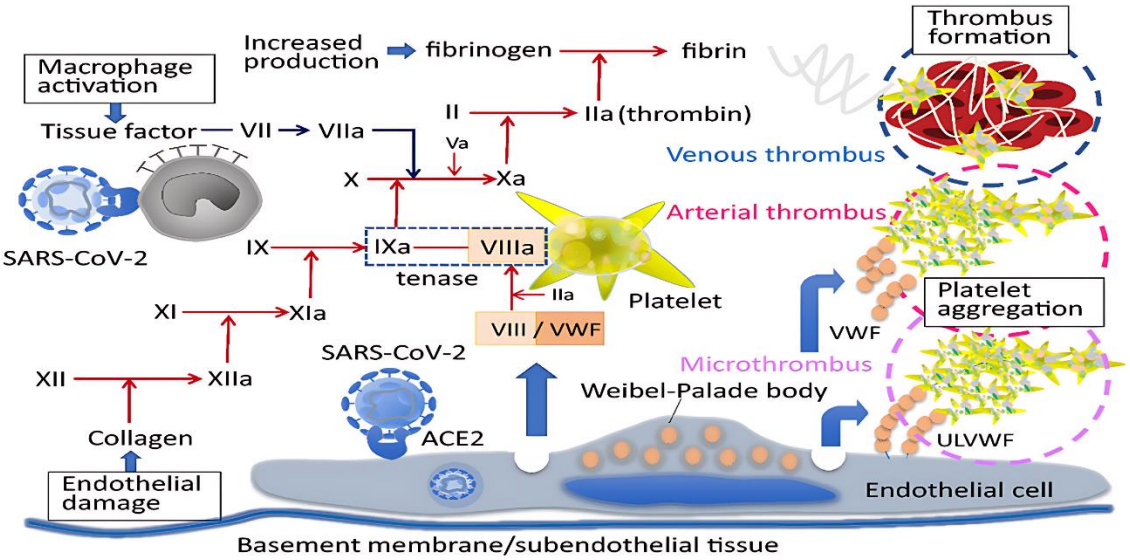

Figure 2.
Mechanism of clot formation in Covid-19 associated Endothelial Dysfunctions [15].

3.1. Viral Entry

The angiotensin-converting enzyme 2 (ACE2) receptor, which is found on respiratory tract epithelial cells, endothelial cells, and other organs, is the main way that SARS-CoV-2, the virus that causes COVID-19, penetrates human cells. Cell death, immune response activation, and the production of inflammatory mediators are all consequences of viral invasion [5].

3.2. Inflammatory Response and Cytokine Storm

A cytokine storm—an excessive immune response that involves the production of pro-inflammatory cytokines including interleukin-6 and tumour necrosis factor-alpha—is frequently a defining feature of

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severe COVID-19 patients. The equilibrium between procoagulant and anticoagulant factors is upset by the cytokine storm, which also causes endothelial activation and extensive inflammation [16].

3.3. Endothelial Dysfunction

Endothelial dysfunction and activation can result from direct endothelial cell infection by SARS-CoV-2. Increased production of adhesion molecules, pro-inflammatory cytokines, and tissue factor, which promote a pro-thrombotic state, are characteristics of endothelial dysfunction [17].

3.4. Activation of Coagulation Cascade

When the coagulation cascade is activated by endothelial dysfunction and systemic inflammation, more fibrinogen, fibrin, and von Willebrand factor are produced, which encourages the development of microthrombi in tiny blood vessels [18].

3.5. Platelet Activation and Aggregation

COVID-19 can induce platelet activation and aggregation through various mechanisms, including direct viral effects and inflammatory mediators. Activated platelets release pro-thrombotic factors, further contributing to thrombus formation and vascular complications. The microthrombi formation in small vessels contributes to tissue ischemia and multi-organ dysfunction, affecting the lungs (acute respiratory distress syndrome, ARDS), heart, kidneys, and brain [19].

3.6. Antiphospholipid Antibodies (APLAs)

Some COVID-19 patients develop antiphospholipid antibodies, which can contribute to thrombotic events. APLAs interfere with phospholipid-dependent coagulation tests and are associated with increased thrombotic risk in affected individuals [14].

3.7. Disseminated Intravascular Coagulation (DIC)

In extreme situations, COVID-19-induced coagulopathy may develop into DIC, which is typified by extensive coagulation cascade activation and clotting factor consumption. DIC results in both thrombotic and hemorrhagic complications, contributing to multi-organ dysfunction and poor clinical outcomes [20].

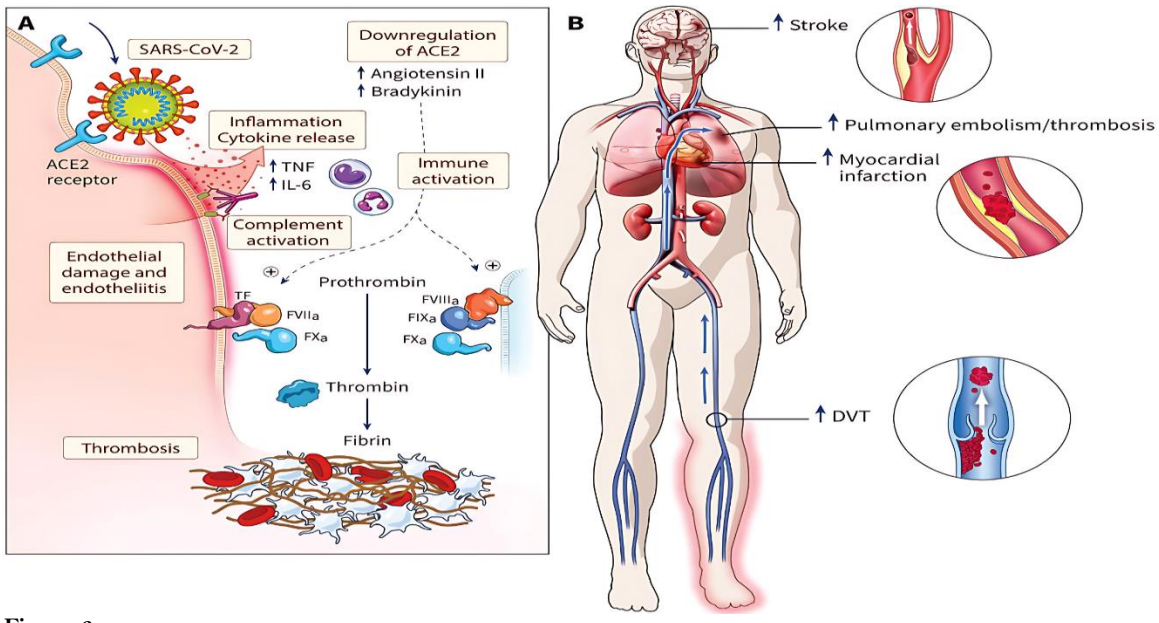

Figure 3.
Potential causes of COVID-19 thrombosis and its clinical implications [21].

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4. Clinical Manifestation

(A) Diffuse endotheliitis is believed to result from endothelium damage brought on by the entrance of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells through the angiotensin-converting enzyme 2 (ACE2) receptor. The inflammatory host response brought on by endothelial injury may be typified by a cytokine storm and excessive immunological activation, which encourages thrombosis and hypercoagulability. (B): potential COVID-19-related venous and arterial thrombotic consequences. Note: TF stands for tissue factor, TNF for tumour necrosis factor α, PE for pulmonary embolism, IL-6 for interleukin 6, DVT for deep vein thrombosis, and FVIIa for factor VIIA.

4.1. Deep Vein Thrombosis (DVT)

Because of their immobility and hypercoagulable status, COVID-19 patients are more likely to develop DVT, especially in the lower extremities [22].

4.2. Pulmonary Embolism (PE)

This is a serious complication where thrombi from peripheral veins migrate to the lungs, causing potentially life-threatening respiratory distress [22].

4.3. Disseminated Intravascular Coagulation (DIC)

Widespread clotting cascade activation, which results in thrombosis and clotting factor consumption, is a hallmark of COVID-19-induced DIC. The systemic aspect of DIC is reflected in the manifestations, which include thrombotic events and bleeding tendencies [20].

4.4. Microvascular Thrombosis

Microthrombi can form in tiny blood arteries all throughout the body as a result of COVID-19, which can lead to multi-organ dysfunction. This can lead to complications such as renal impairment, hepatic dysfunction, and neurological deficits due to impaired blood flow in affected organs [10].

4.5. Stroke and Cardiovascular Complications

Large vascular occlusion or small vessel disease brought on by coagulation disorders can cause ischaemic strokes in COVID-19 patients. Arrhythmias and myocardial damage are also possible, which in extreme situations may exacerbate cardiovascular problems [23].

4.6. Skin Manifestations

Cutaneous manifestations such as livedo reticularis (mottled discoloration of the skin), acral ischemia (bluish discoloration of fingers or toes), and petechiae may indicate underlying coagulation abnormalities [24].

4.7. Elevated D-Dimer level

In COVID-19 patients, elevated D-dimer levels (>1 μg/mL) are linked to a higher risk of thrombosis and a more severe disease. D-dimer by itself, however, is non-specific and may also be raised under other circumstances.

4.8. Prolonged PT/PTTK

Prolonged PT or aPTT may indicate deficiencies in clotting factors or the presence of anticoagulant therapies. In COVID-19, these tests may be prolonged due to consumption of clotting factors in DIC or liver dysfunction.

4.9. Thrombocytopenia

Thrombocytopenia (low platelet count) in COVID-19 patients can indicate DIC or increased consumption due to systemic inflammation and microthrombi formation.

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4.10. Elevated fibrinogen level

In COVID-19 individuals, elevated fibrinogen levels are linked to a hypercoagulable condition and may be a sign of thrombosis and a continuing inflammatory response.

4.11. Image Studies

Pulmonary embolism and deep vein thrombosis [12].

5. Management

Effective management involves a multifaceted approach aimed at preventing thrombotic complications while minimizing bleeding risks:

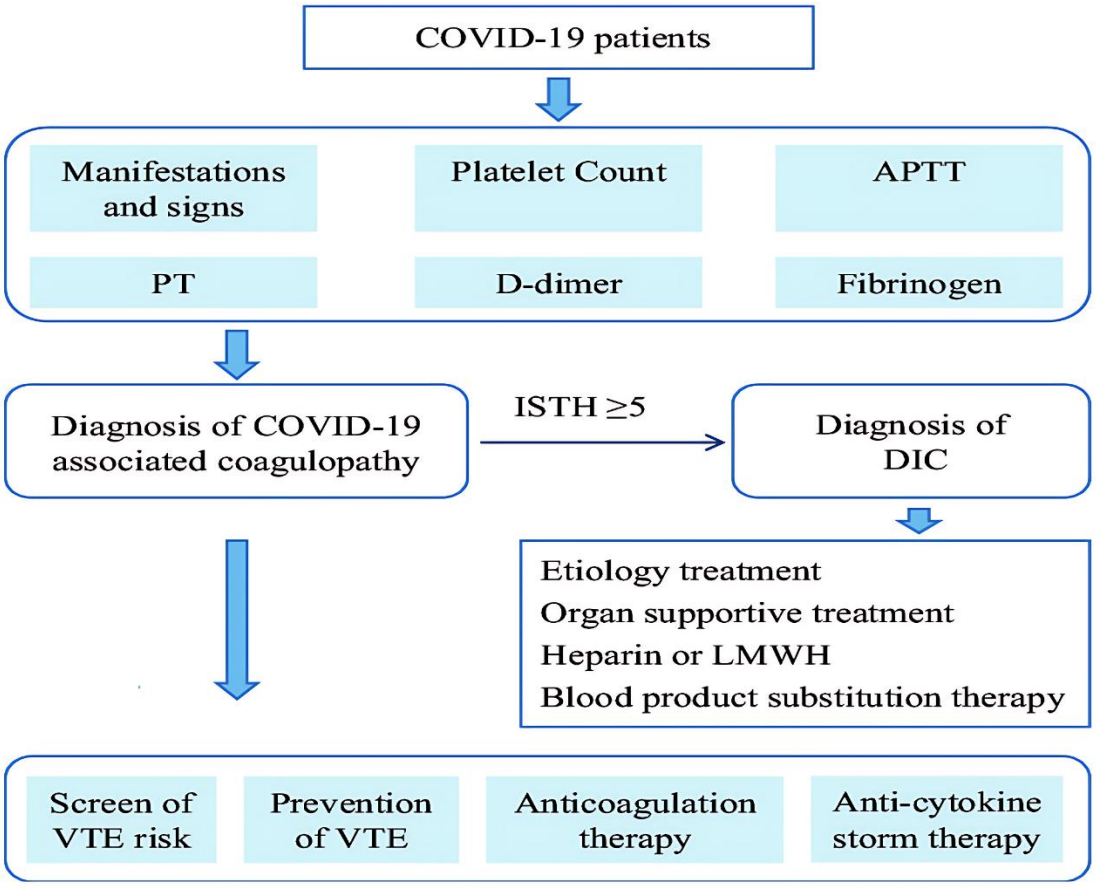

Figure 4.
The COVID-19 Associated Coagulopathy Management Algorithm. LMWH: Low molecular weight heparin; ISTH: International Society of Thrombosis and Haemostasis VTE stands for venous thromboembolism; PLT for platelets; and PT for prothrombin time [25].

5.1. Prophylactic Anticoagulation

Hospitalized COVID-19 patients receive prophylactic anticoagulation to reduce venous thromboembolism (VTE) risk. Guidelines recommend dosing based on risk assessment tools and consideration of patient-specific factors.

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5.2. Therapeutic Anticoagulation

Consideration for therapeutic anticoagulation in COVID-19 patients with confirmed thrombosis or high-risk features despite prophylactic measures. Challenges include balancing benefits with bleeding risks, particularly in critically ill patients.

5.3. Monitoring and Adjustment

Frequent evaluation of clinical state and coagulation measures (such as D-dimer levels) to inform modifications to anticoagulant treatment. Individualized approaches based on evolving clinical data and patient response to treatment.

6. Treatment Approaches

6.1. Anticoagulant Agents

Are a class of drugs that prevent blood from clotting. Heparin and anti-factor Xa medications (rivaroxaban and apixaban) are two examples. Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are the heparins that are utilised [26].

6.1.1. Low Molecular Weight Heparin (LMWH)

Because UFH has a longer duration of competitive spike protein, heparin has a less direct antiviral effect. It is the preferred agent for prophylactic anticoagulation due to its predictable pharmacokinetics and reduced risk of heparin-induced thrombocytopenia (HIT) [27].

6.1.2. Unfractionated Heparin (UFH)

Is the only agent that needs regular lab testing, is less expensive, has a shorter half-life, and is readily eliminated from the body. It is used in hospitalized patients requiring therapeutic anticoagulation, especially in those with renal dysfunction or when rapid reversal is needed [28].

6.2. Direct Oral Anticoagulants (DOACs)

They are the best treatment option for COVID-19 patients who need long-term anticoagulation after being released from the hospital [29]. These medicines are recommended over vitamin K antagonists like warfarin because they do not require routine international normalised ratio monitoring. The most effective DOAVs to use are apixaban, betrixaban, and rivaroxaban [30].

6.3. Adjunctive Therapies

Is a therapy that is given in addition to the primary or initial therapy to maximize its effectiveness.

6.3.1. Antiplatelet Agents

May be taken into consideration in COVID-19 patients who have ischaemic stroke or acute coronary syndrome, weighing the risks of bleeding and thrombosis. For instance, dipyridamole, ticagrelor, clopidogrel, aspirin, and cilostazol.

6.3.2. Immunomodulatory Agents

Are substance that tamp down over-active immune responses (e.g. tocilizumab/sarilumab). New treatments that target inflammation, such as IL-6 inhibitors and corticosteroids, may have an indirect impact on coagulation problems in severe COVID-19 patients.

7. Therapeutic Challenges

7.1. Optimal Anticoagulation Regimens

Determining the optimal timing, dosing, and duration of anticoagulation therapy remains a challenge.

Variability in clinical presentation and coagulation profiles necessitates personalized approaches.

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7.2. Risk-Benefit Assessment

Critically ill patients' thrombotic risk versus bleeding risk must be carefully considered, and multidisciplinary cooperation is frequently required.

There are extra difficulties in managing anticoagulation in individuals who have hepatic or renal impairment.

7.3. Emerging Evidence and Guidelines

Rapidly evolving evidence and guidelines necessitate ongoing updates and adaptation of clinical practices.

Incorporating new data on thrombotic mechanisms and treatment outcomes into clinical decision-making.

8. Conclusion

The pathophysiology of COVID-19-associated coagulopathy involves complex interactions between viral factors, inflammatory responses, endothelial dysfunction, and dysregulated hemostasis, necessitate ongoing research to elucidate underlying mechanisms and identify novel therapeutic targets. Biomarkers such as D-dimer levels serve as valuable tools in risk assessment and monitoring, yet their interpretation requires careful consideration within the clinical context. Looking forward, future research should focus on refining anticoagulation strategies, exploring adjunctive therapies, and investigating long-term implications for survivors, including cardiovascular and pulmonary sequelae. Additionally, interdisciplinary collaboration and integrated care models are essential to optimize outcomes and provide comprehensive support for COVID-19 patients throughout their recovery journey.

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