Thiqar University

Collage of medicine

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Department of medicine

Thromboembolic phenomena in patients with covid 2019

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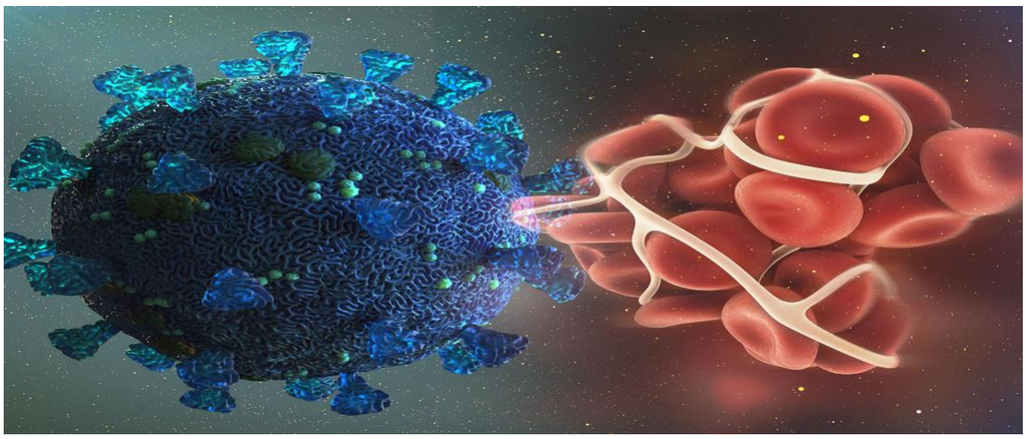

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Introduction :

The current coronavirus pandemic caused by the SARS-CoV2 has rapidly emerged as a global health crisis. To date, over four million people have been affected by coronavirus disease 2019 (COVID-19) worldwide in about 188 countries and the number continues to grow . In the United States alone, confirmed cases and deaths continue to rise, with current estimates at more than 1.9 million positive patients and over 110,000 deaths .

Symptoms range from asymptomatic or mild constitutional symptoms to pneumonia, sepsis and sometimes severe acute respiratory distress syndrome (ARDS) necessitating hospitalization and intensive care unit (ICU) admission.

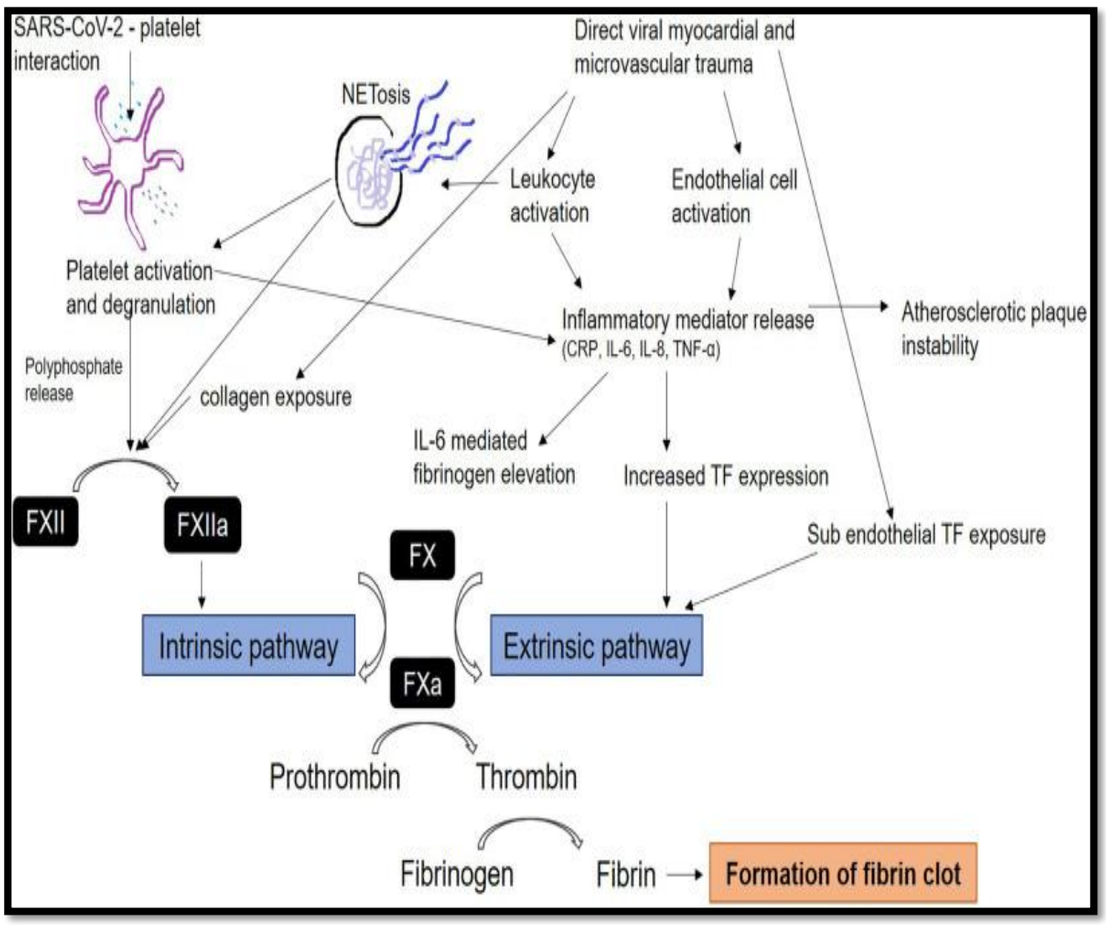
The pivotal role of thrombo-inflammation and endothelial injury in the pathogenesis of the disease is being increasingly recognized. Overproduction of proinflammatory cytokines, including tumor necrosis factor (TNF), Interleukin (IL) -6, IL-8, and IL-1β, is believed To be the cause of what is being termed, "cytokine release syndrome" or "cytokine storm", a phenomenon which is however not unique to this disease and has been noted in sepsis and sterile inflammation as well. This exaggerated cytokine response may lead to multiorgan failure and eventually death in some patients . In addition to elevations in pro-inflammatory markers, hypercoagulability has been identified to be playing a key role determining prognosis in patients with COVID-19 In some observational series, thrombotic complications have been noted to be as high as 31% in patients requiring ICU admission and the risk persists even in patients on anticoagulation .

Pathogenesis and risk factors :

COVID-19 shares multiple similarities with other well defined inflammatory states such as sepsis and sterile inflammation wherein simultaneous rise in pro and anti-inflammatory cytokines are seen. More pertinently, there is evidence of complement activation in COVID-19 by direct endothelial infection which includes release of anaphylotoxin C5a Complement activation as seen in COVID-19 not only drives neutrophil dysfunction leading to susceptibility to secondary infections but also activates the coagulation system thereby propagating a prothrombotic state. Coagulopathy associated with COVID-19 may be explained by the 'two way activation' theory, as seen by thrombocytopenia in critically ill patients (TICP) and the encompassing inflammatory and micro-thrombogenic responses that occur when endothelial insult takes place. While the inflammatory pathway releases cytokines, the activation of microthrombotic pathway is mediated by release of large polymers of Von Willebrand factors (VWF). In the face of sepsis-induced endothelial injury, this reaction is aggravated causing enhanced platelet activation and consumption thrombocytopenia . In contrast to the typical consumptive coagulopathy and disseminated intravascular coagulation (DIC) profile observed in sepsis, patients with COVID-19 typically have relatively normal coagulation and platelet profiles. Progression to DIC occurs in a minority of patients, rarely developing in survivors. Therefore it seems that in keeping with Virchow's triad, thrombosis is driven both by the activation of coagulation factors and endothelium. In-situ immune-thrombosis plays a key role to be the unifying mechanism explaining the micro and macrothrombotic manifestations of the disease. It should however be emphasized that in-situ micro thrombosis has also been demonstrated in pulmonary and systemic tissue beds in

ARDS and sepsis and therefore may not necessarily be unique to this population.

In addition to the factors mentioned above, these patients have additional risk factors for increased thrombosis, most notable among those being hypoxia, and immobility (made worse by frequent use of prone positioning). Although not systematically assessed, reduced staffing coupled with isolation precautions which limit frequent position changes and mobility may further predispose patients to a prothrombotic state.



Risk factors :

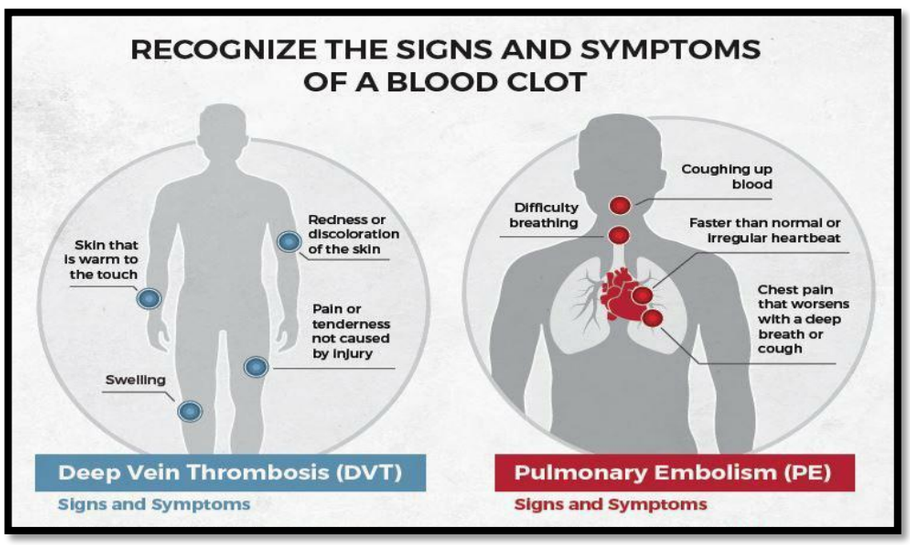
COVID-19-Related Risk Factors	Variables
Age	≥70 year
Gender	Males > females
Obesity	BMI > 30
Cancer	Active or not
Comorbidities	Hypertension, CVD, diabetes, stroke, CKD
Medical ICU admission	18.5%
Inflammation	Existing or not
Cytokine release syndrome (cytokine storm)	High-grade fevers, hypotension, multi-organ dysfunction
Lung injury	Pre-existing or not

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease; ICU, intensive care unit.

Clinical presentation :

Symptoms and signs for the thromboembolic events that might occur:

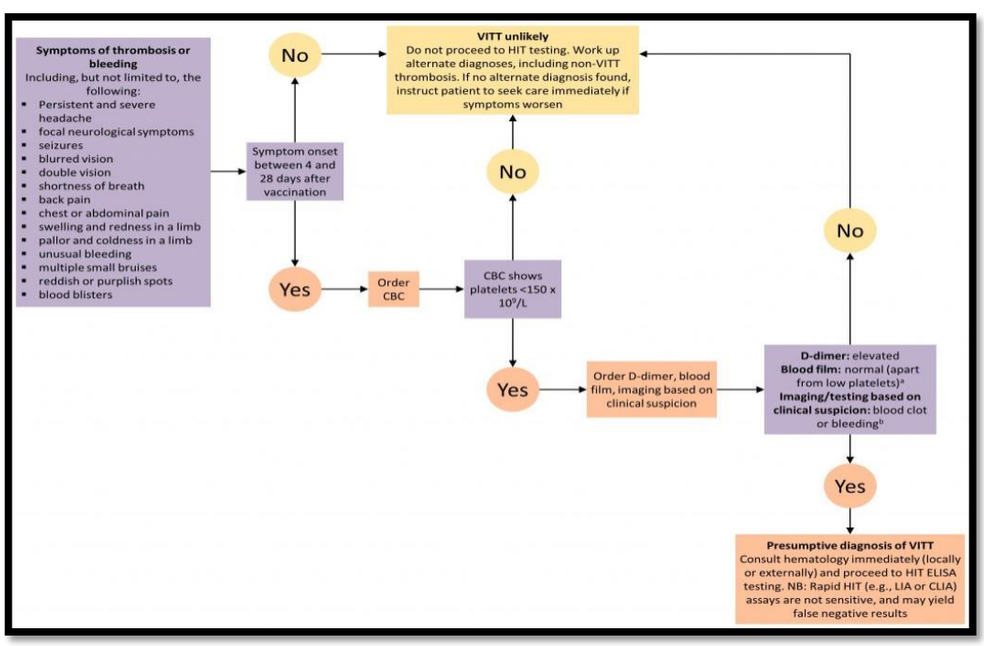
1. Persistent and severe headache .
2. focal neurological symptoms
3. seizures .
4. blurred vision ,double vision
5. shortness of breath
6. back pain chest or abdominal pain
7. swelling and redness in a limb
8. pallor and coldness in a limb
9. unusual bleeding .
10. multiple small bruises reddish or purplish
11. spots blood blisters



Diagnosis

prospective study comparing coagulation parameter derangement among patients with COVID-19 and healthy controls found that the values of d-dimer (10.36 vs 0.26 ng/L; p < 0.001),

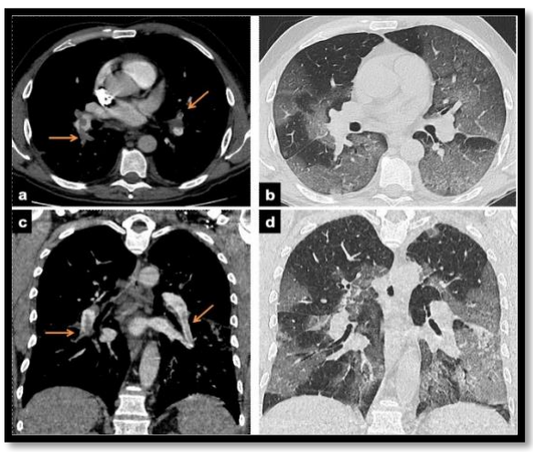
- **fibrin/fibrinogen degradation products (33.83 vs 1.55 mg/L; p < 0.001),**
- **and fibrinogen (5.02 vs 2.90 g/L; p < 0.001) in all SARS-CoV-2 cases were substantially higher than those in healthy controls. Moreover,**
- **d-dimer and fibrinogen degradation product values in patients with severe SARS-CoV-2 infection were higher than those in patients with mild disease .**
- **A meta-analysis showed that patients with severe disease were found to have a significantly lower platelet count (mean difference: − 31 × 109/L, 95% confidence interval − 35 to − 29 × 109/L) and thrombocytopenia**

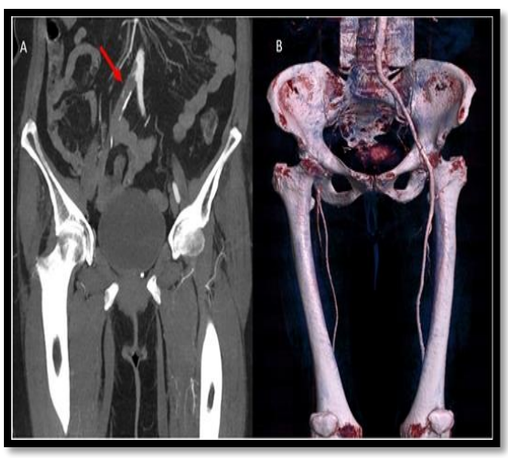


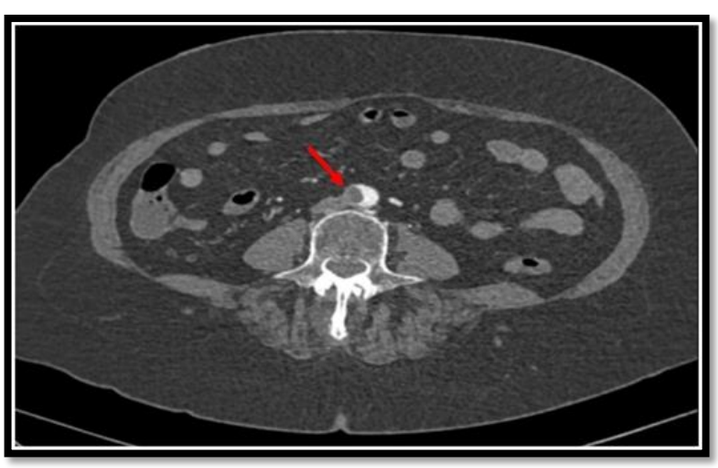
- **Imaging for Diagnosing Venous Thromboembolism**

Imaging studies can help yield a definitive diagnosis of VTE.

Studies have shown the usefulness of compression ultrasonography and CTPA . One study from Italy showed 16 (36%) out of 44 patients had VTE on imaging, and ten (33%) out of 30 patients had a pulmonary embolism on CTPA. More than 50% of VTE events were diagnosed within the first 24 h of hospital admission, highlighting the significance of early diagnosis and treatment in patients with COVID-19 . The decision to perform an imaging study for diagnosing DVT should be based on clinical judgment. Routine screening for DVT in asymptomatic patients is not recommended







Treatment of Thrombotic Complication in COVID-19 :

Prophylactic Anticoagulation :

- **In-Hospital :**

The International Society on Thrombosis and Hemostasis has recommended the use of antithrombotic prophylaxis with low-molecular-weight heparin for all admitted patients unless there is a contraindication. In the setting of heparin-induced thrombocytopenia,fondaparinux is recommended . Routine thromboprophylaxis is not recommended in ambulatory patients with acute medical illness or respiratory symptoms . Interestingly, the use of heparin is not only helpful for the anticoagulant effect, but also for its anti-inflammatory effect in patients with COVID-19

- **Post-Discharge :**

Patients admitted to the hospital for acute medical illness have an increased risk of VTE up to 90 days after discharge. A similar risk should be considered for patients with COVID-19. It may be reasonable to consider extended treatment to prevent thromboembolic events after discharge from the hospitals. A regulatory-approved regimen can be used (betrixaban 160 mg on day 1, followed by 80 mg once daily for 35–42 days, or rivaroxaban 10 mg daily for 31–39 days). Increased bleeding risk should be considered depending on the patient's clinical condition and comorbidities

Therapeutic Anticoagulation:

The treatment with a full dose of AC may be beneficial for patients who are meeting the criteria of a SIC score or who have a markedly elevated d-dimer level

Tissue Plasminogen Activator:

Few preclinical and clinical reports have suggested that fibrinolytic therapy may be useful in improving survival in patients with acute lung injury and ARDS

Summary of the recommendations :

The analysis of the peripheral blood smear, platelet count, PT ,aPTT, fibrinogen and D-dimer levels are recommended for all hospitalized patients at admission. These parameters should

be regularly monitored in critically ill patients. The most adequate time interval between tests is uncertain and testing should be based on clinical indication, assays availability and the local laboratory capacity and facility.

We suggest performing venous compression Duplex scan at admission of ICU patients and then on a regular basis, whenever available and at convenient intervals, to detect DVT and to prevent its complications. We also suggest maintaining vigilance for clinical and echocardiographic signs of PE.

The diagnosis of DIC does not indicate anticoagulation, unless a thrombotic event is present. The use of anticoagulants in COVID-19 should be restricted to prophylaxis of VTE or the treatment of thrombotic events.

All patients hospitalized for suspected or confirmed COVID-19 should receive pharmacologic thromboprophylaxis,

unless there are contraindications . We suggest the use of LMWH. Alternatively, UFH or fondaparinux can be given for thromboprophylaxis. In the case that pharmacologic thromboprophylaxis is contraindicated, mechanical prophylaxis should be used.

We suggest the use of LMWH at a standard dose for thromboprophylaxis, adjusted for body weight and renal function

, for patients admitted to general wards or the ICU,unless there are specific contraindications . We are

aware that the apparent increased incidence of VTE in COVID19 has led physicians to change their practice by increasing the dose of prophylactic anticoagulation to intermediate or therapeutic doses of LMWH in ICU patients or in patients with

high D-dimers or fibrinogen levels. However, the benefit of this approach has not yet been confirmed and trials are needed to address this question.

Prophylaxis for thrombosis should be prescribed during the

entire hospitalization period. It is reasonable to maintain prophylaxis after the hospital discharge for patients at high risk of thrombosis or for those with immobility, unless there are specific contraindications. The risks and benefits of this approach should be reevaluated periodically.

Acute VTE events should be confirmed by imaging tests. In the case this is not feasible, presumptive diagnosis of an acute VTE event may be made based on clinical history, combined

with physical examination, laboratory and other available tests. The diagnosis of VTE should not be based solely on the values of D-dimers.

We recommend the use of LMWH for the treatment of acute VTE. Alternatively, UFH or fondaparinux can be used .

We recommend switching DOAC and AVK to LMWH if the patient is admitted to the ICU or is at risk of significant drug–drug interaction.

Reference :

- **Samhati Mondal, Ashley L. Quintili, Somnath Bose Journal of Intensive Care volume 8, Article number: 70 (2020) Cite this article**
- **World Health O . Coronavirus disease 2019 (COVID-19): situation report, 157. Geneva: World Health Organization; 2020**
- **Zuckier LS, Moadel RM, Haramati LB, Freeman LM. Diagnostic evaluation of pulmonary embolism during the COVID-19 pandemic. Journal of Nuclear Medicine. 2020;61(5):630**

  [PubMed] [Google Scholar]
- **Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497–506. [PMC free article] [PubMed]**
- **Medicine JHU. Corona Virus Resource Center. 04.28.2020 ed. Baltimore, USA 2020.**
- **Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19**
- **Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. JAMA 2020.**
- **Meduri GU, Kohler G, Headley S, Tolley E, Stentz F, Postlethwaite A.**

- **Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. Chest. 1995;108:1303–14.**
- **Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844–7.**
- **Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020.**