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ILLUSTRATED REVIEW

rpth research & practice in thrombosis & haemostasis

Thrombosis and coagulopathy in COVID-19: An illustrated review

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Abstract

This illustrated review discusses the haemostatic changes seen in patients with severe coronavirus disease 2019 (COVID-19) infection and their possible causes. We discuss the crosstalk between inflammation and coagulation resulting in high levels of acute-phase proteins, very high levels of D-dimers, and absence of disseminated intravascular coagulation seen in patients with severe COVID-19. There appear to be high rates of venous thromboembolism and also, what has been poorly described before in acute lung injury, a high rate of pulmonary immunothrombosis (thrombosis secondary to inflammation).

KEYWORDS

COVID-19, novel coronavirus, thrombosis, coagulopathy, coagulation

Essentials

- There are marked increases in coagulation proteins in patients with severe coronavirus disease 2019 (COVID-19) infection, consistent with a profound acute-phase response.
- D-dimer levels are extremely high and reflect activation of fibrinolysis systemically and also in the lungs.
- Disseminated intravascular coagulation is rarely seen in severe COVID-19 infection outside of preterminal multiorgan failure.
- Thrombosis rates appear high due to venous thromboembolism and pulmonary immunothrombosis.

Coagulation laboratory characteristics of COVID-19 infection

	Survivors	Non-survivors
Platelet count <150x10⁹/L	30-70%	45-80%
Platelet count <100x10⁹/L	0-1%	3-5%
Prothrombin time > 3 sec. prolonged	0-5%	15-25%
Fibrinogen < 1.0 g/L	0%	5-10%
Fibrinogen > 4.0 g/L	80-100%	80-100%
D-dimer > 1 mg/L (2x ULN)	15-25%	80-90%
D-dimer > 3 mg/L (6x ULN)	1-5%	50-70%
Antithrombin < 80%	0%	0-2%

The laboratory characteristics of (severe) COVID-19 infection are:[1-3]

a mildly to moderately reduced platelet count in the most severe patients

a mild prolongation of the prothrombin time in a minority of patients

high fibrinogen levels in virtually all patients

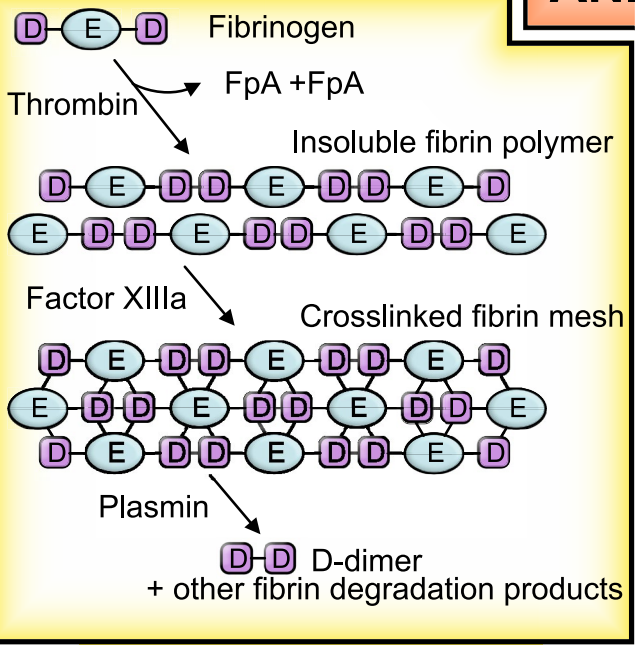
(with very low levels in severely ill patients briefly before death)

(very) elevated D-dimer levels, in particular in non-survivors

normal antithrombin levels

D-dimer is a fibrin degradation product. Why are D-dimer levels increased in COVID-19?

As a result of systemic thrombin generation and subsequent fibrin formation and breakdown



PRO:

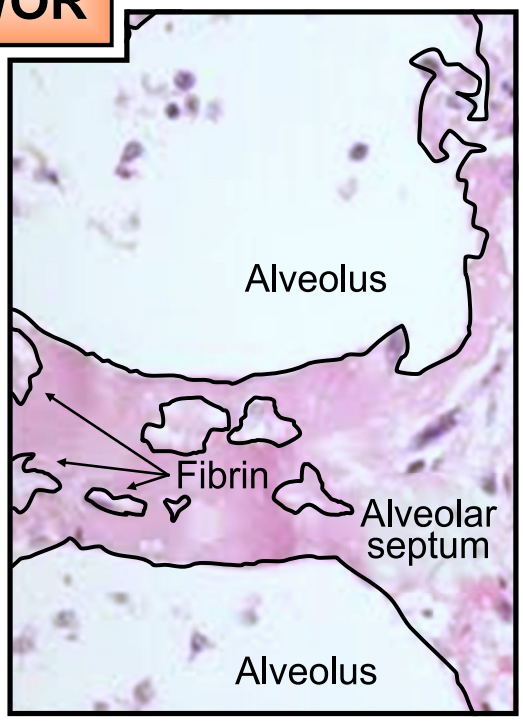
There is some coagulopathy (thrombocytopenia, prolonged prothrombin time) that suggests thrombin generation.[4–5]

CON:

- The D-dimer increase is disproportional to the other markers of coagulation
- The DIC score in most patients is not pointing to overt DIC, as would be expected with such deranged D-dimer.[6–7]

AND/OR

As a result of enhanced fibrin turnover in the lung due to severe lung inflammation



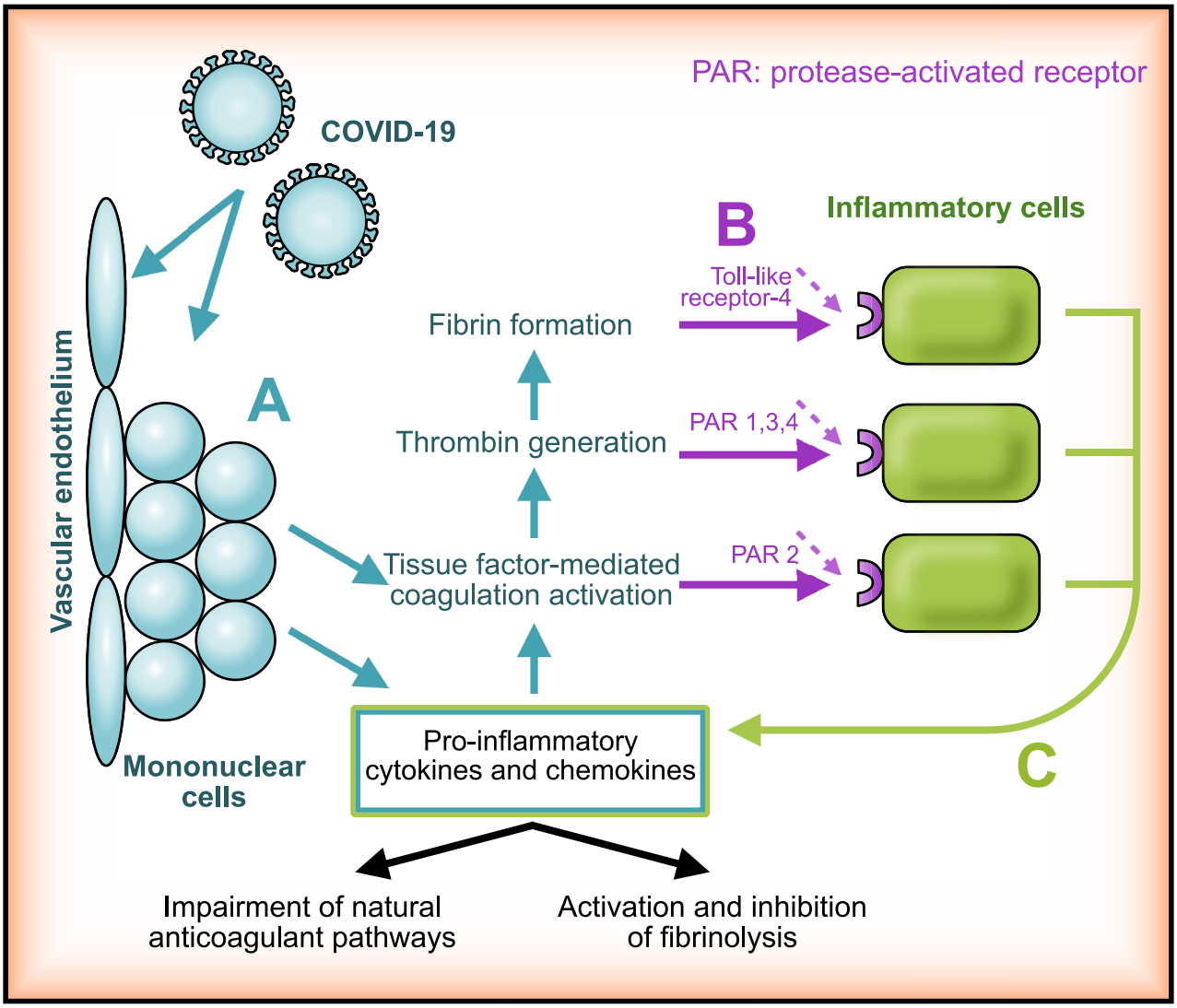
PRO:

Fibrin deposition is a hallmark of Adult Respiratory Distress Syndrome (ARDS) and macrophage activation.[8]

CON:

There is some degree of systemic coagulopathy, albeit mild

Like many other infections, there is significant cross-talk between inflammation and coagulation



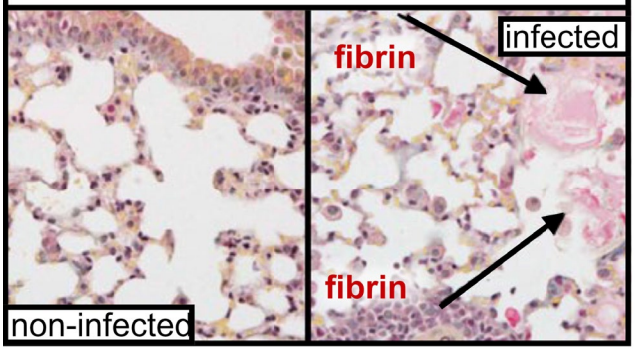
A Severe COVID-19 generates an increase in pro-inflammatory cytokines and activates endothelial cells, neutrophils, mononuclear cells, and platelets leading to tissue factor-mediated activation of coagulation.[2,9]

B Coagulation proteases bind to specific receptors that mediate further pro-inflammatory responses.[10]

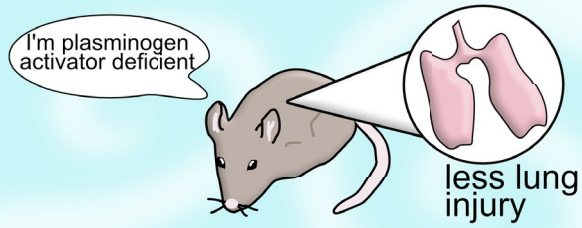
C The inflammatory response to COVID-19 results in activation of coagulation that itself may modulate further inflammatory activity.

In addition, there is a specific effect of coronaviruses on the plasminogen-plasmin system which might be related to lung injury and lethality

Coronaviruses are associated with enhanced plasminogen activator activity which increases lung injury.

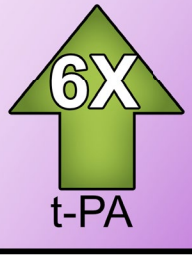


Alveolar pneumocytes produce urokinase and mice injected with SARS had upregulation of this production.[11]



In a coronavirus model, mice deficient in plasminogen activator had less lung injury/fibrin deposition and better survival.[11]

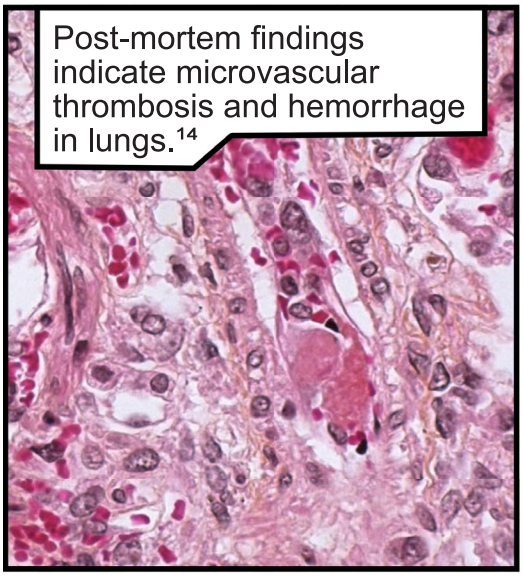
Plasma levels of tissue-type plasminogen activator (t-PA) were 6-fold increased in human SARS-CoV-1 infection.[12]

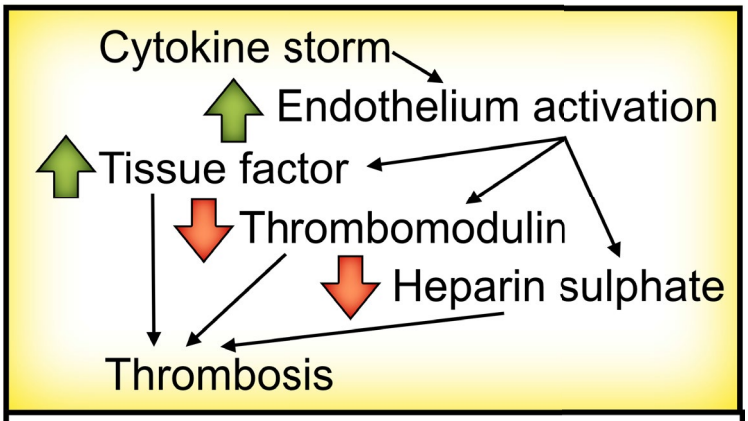


The resulting plasminogen-plasmin system activation may have major implications for extracellular matrix disruption, vascular leakage and pulmonary edema but the exact role of lung fibrinolysis is not fully understood.[13]

There is pulmonary immunothrombosis in COVID-19 infections

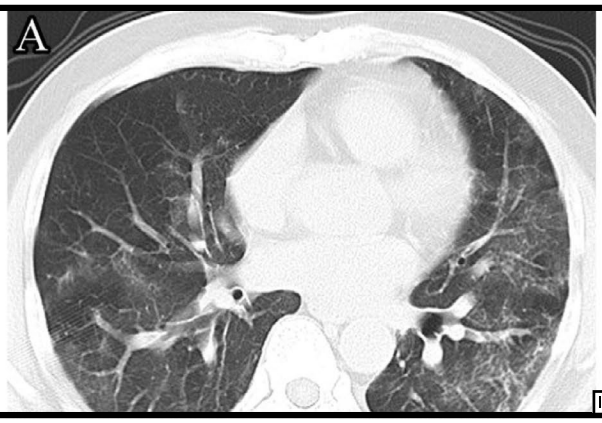
Post-mortem findings indicate microvascular thrombosis and hemorrhage in lungs.[14]

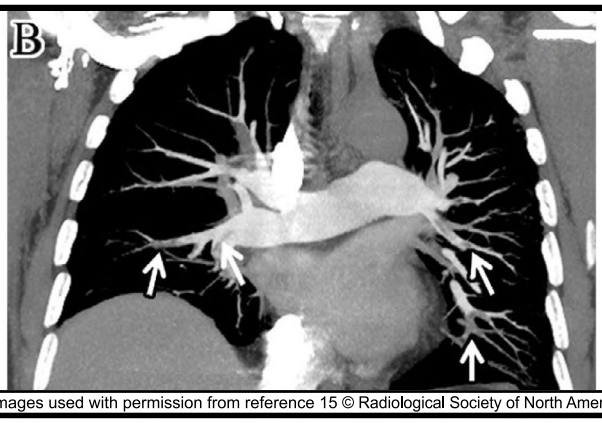




Local thrombosis is due to inflammation and hypoxia leading to endothelial cell activation and tissue factor expression, downregulation of thrombomodulin and loss of heparin sulphate.[10]

There seems to be a high incidence of venous thromboembolism in COVID-19





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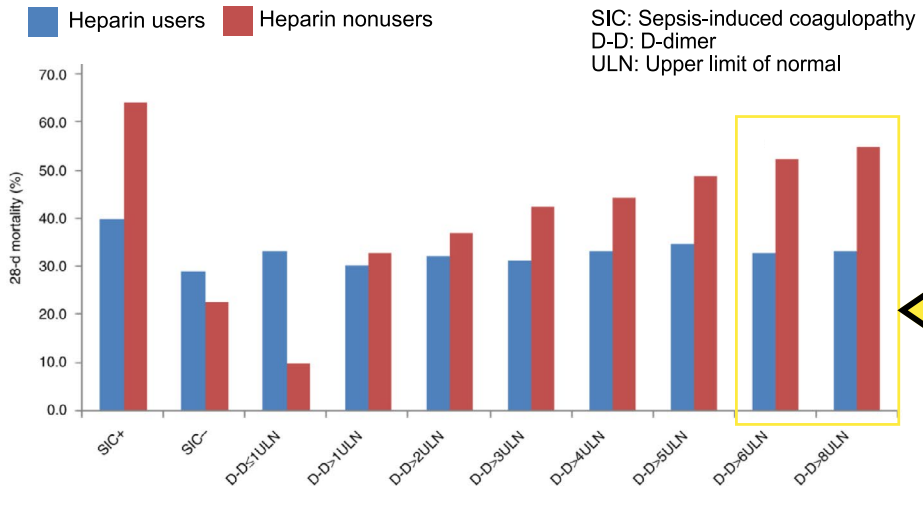
Increasing anecdotal reports and case studies showed a high incidence of venous thromboembolism in COVID-19 patients.[15–17]

Unclear whether this is more than usual in critically ill patients.[18]

Undiagnosed pulmonary embolism could contribute to sudden and unexplained respiratory deterioration.

Does a (very) high D-dimer point to a high risk of venous thromboembolism or is it just a marker of severe inflammatory pulmonary disease?



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D-dimer is a sensitive but not specific marker for venous thromboembolism.

Patients with (very) high D-dimer levels have a concentration-dependent higher 28-day mortality.[3,19]

Anecdotal reports seem to link very high D-dimer levels to an increased risk of venous thromboembolism but it is unclear whether D-dimer is just a marker of higher disease intensity or a link between coagulopathy, thromboembolic events and adverse outcome.

Guidance on diagnostic and therapeutic management related to coagulation and thrombosis in COVID-19

Diagnostic approach[20]

Repeated (every 2-3 days) assessment of:

- D-dimer
- Prothrombin time
- Platelet count

Therapeutic management[20]

Thromboprophylaxis with subcutaneous low dose low molecular weight heparin in all hospitalized patients

Consider pulmonary embolus in case of rapid respiratory deterioration

Perform CT angiography if feasible and/or perform lower extremity venous ultrasound in case of suspected venous thromboembolism

If very high suspicion of pulmonary emboli and diagnostic testing is not possible and low bleeding risk: consider therapeutic anticoagulation (awaiting solid clinical trial evidence)

Other interventions (such as other anticoagulants or full intensity anticoagulation in the absence of thrombosis, plasma exchange, anti-platelet agents or thrombolysis) are experimental and should be considered in clinical trials only

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