Microvascular thrombosis from severe endothelial dysfunction, a new theory of COVID-19's unusual pathophysiological effects

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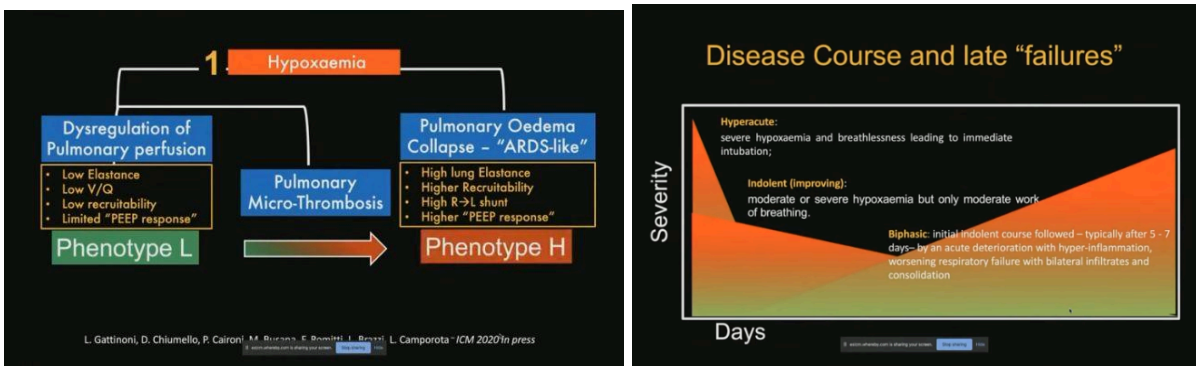
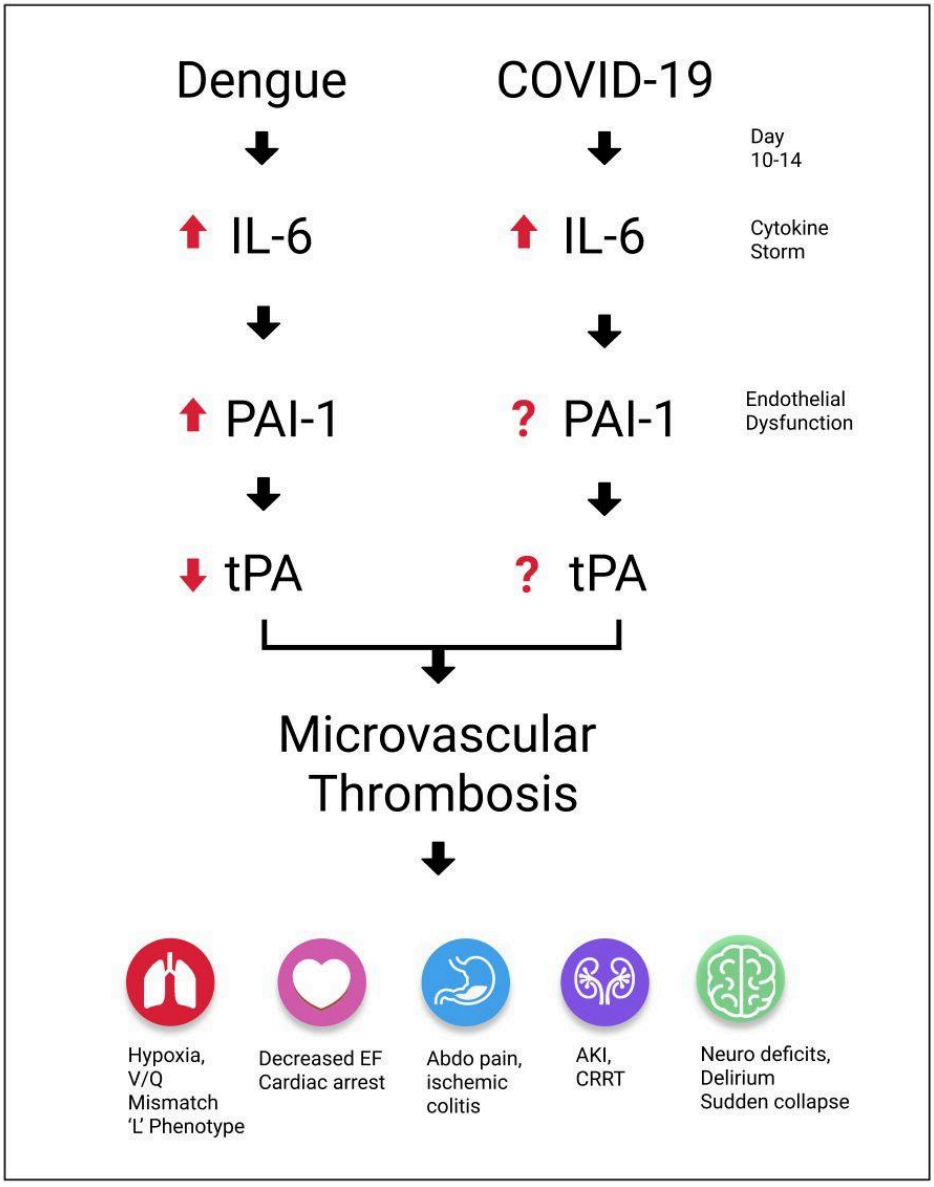
Patients with severe COVID-19 disease proceed through what is described as an ARDS pathway, but there are a number of unusual early findings that indicate that a novel pathway may be at play in this novel virus. Two phenotypes have been described recently, a type 'H' which follows a traditional ARDS picture, and a type 'L' which is described to have high lung compliance, sudden drops in A-a gradients, limited PEEP response and low recruitability (1). This phenotype often follows a biphasic course where, following a period of relative indolence there is an abrupt development of respiratory failure, cardiomyopathy and/or idiopathic acute kidney injury (AKI) along with unexpected neurologic insults(1). We posit that microvascular thrombosis from severe endothelial dysfunction can explain these acute phenomena.



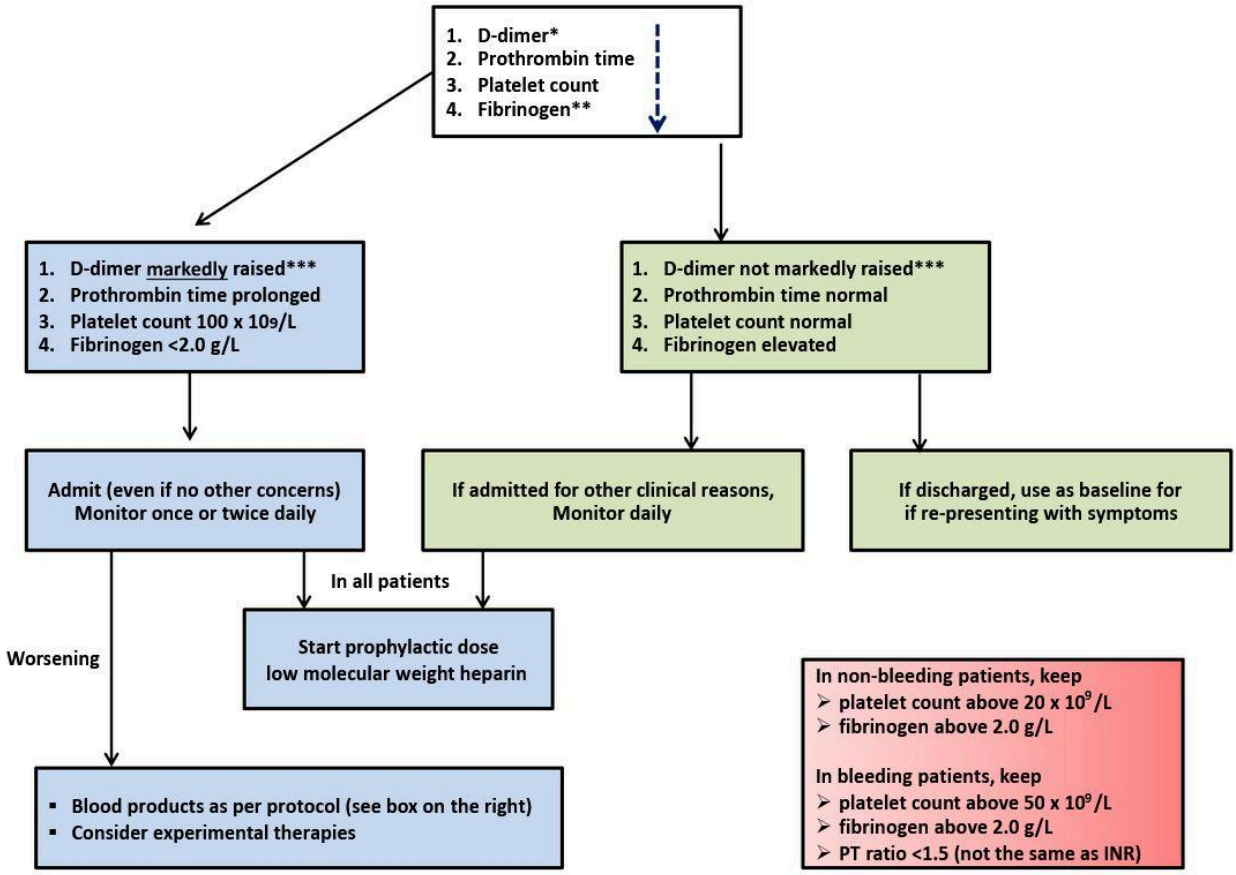
ESICM Webinar (1b)

Dengue virus infections provide an analogy. They have been known to give rise to increased Interleukin-6 (IL-6), which in turn leads to an increase in Plasminogen activator inhibitor-1 (PAI-1)(2), a decrease in tPA which leads to a pro-thrombotic state(3)(4). Severe cases of Covid-19 are associated with increased IL-6 levels (5) and other inflammatory markers, and there have been increased reports of pulmonary embolisms without associated deep venous thrombosis (6). Severe cases of the original SARS virus showed elevated PAI-1 levels and required anticoagulation (7). Severe presentations seem to correlate to traditional Framingham risk factors such as diabetes and obesity, which themselves are correlated to endothelial dysfunction(8). There is evidence of decreased mortality with the use of anti-coagulants in Covid patients with coagulopathies (9).

A difficult task facing physicians has been determining which initially stable patients will enter an end-stage cascade, and then determining the correct time to intervene. This would call for close monitoring of thrombotic markers such as D-dimer, Fibrinogen, anti-factor Xa levels or rapid thromboelastography. Some algorithms are already exploring the use of heparin in mild cases (10), and one could consider even tPA in acute decompensating cases, or medications known to stabilize endothelial dysfunction such as inhaled nitric oxide, N-acetylcysteine, statins and vitamin C (11)(12). Future studies, and possibly early tissue biopsy studies, are necessary to address these questions and better care for our vulnerable COVID19 patients.



Proposed Screening Algorithm



Thachil et.al (10)

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