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Proposal of a new nomenclature for the underlying pathogenetic mechanism of severe Coronavirus Disease-19: "Inflammatory Thrombosis with Immune Endotheliitis—ITIE"

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Dear Editor,

The world is going through an extraordinary period. Science is evolving very rapidly as never seen on planet Earth. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is the causing agent of this pandemic, and the disease caused by this virus is called coronavirus disease-19 (COVID-19). Clinical spectrum of COVID-19 is very wide: ranging from asymptomatic patients to hyperimmune activation with or without apparant thrombosis. About 15–20% of the cases develop moderate-to-severe manifestations and about 5% of all patients admit to critical care unit [1]. Herein, we tried to propose a new nomenclature for the pathophysiological process going on the patients resembling severe COVID-19.

The underlying mechanism of severe disease has been proposed as "the activation of the immune system". At the early stages of pandemic, "hyper-inflammation" caused by SARS-CoV-2 has been thought as a kind of "macrophage activation syndrome (MAS)". However, growing body of data is now supporting that the process triggered by SARS-CoV-2 differs from classical MAS. First, main histopathological feature causing organ dysfunction in COVID-19 is the thrombosis which is quite rare in classical MAS [2]. A recent review of the main histopathological findings of COVID-19 revealed thrombus formation (either macro or micro) nearly in all tissues, especially in the lung and central nervous system [3]. Second, laboratory parameters are somehow different in COVID-19-related hyper-inflammation than classical MAS. For instance, ferritin level is extremely high in classical MAS compared to relatively high levels in COVID-19-related hyper-inflammation. Fibrinogen level is low in classical MAS suggesting the development of disseminated intravascular coagulation (DIC); however, fibrinogen level is extremely high in COVID-19-related hyper-inflammation, supporting the hypothesis of pulmonary intravascular coagulopathy is prominant in COVID-19 patients rather than DIC [4].

Laboratory surrogate of possible thrombotic process (D-Dimer) is also extremely high in COVID-19-related hyper-inflammation state in contrast to classical MAS [5]. "Cytokine release syndrome (CRS)" was another proposed term for the process occurred in COVID-19. However, cytokine profile and laboratory values are somehow different in two entities. Ferritin, interleukin-6 and soluble interleukin-2 receptor-alpha levels are extremely higher in CRS compared to COVID-19-related hyper-inflammation [5]. On the other hand; d-dimer and fibrinogen levels are extremely higher in COVID-19-related hyper-inflammation compared to CRS [5]. Another overlapping but differing situation is the typical acute respiratory distress syndrome (ARDS), and in ARDS, cytokine levels, IL-6,8 and tumor necrosis alpha, are extremely high compared to COVID-19-related hyper-inflammation [6]. Also, necropathological examination of patient with COVID-19 revealed a much higher rate of microvascular injury and microthrombi compared to ARDS related to other infections, and accelerated thrombosis plays a central role in COVID-19 [7, 8]. Besides the cytokine and laboratory parameter differences between COVID-19 and other clinical entities, pulmonary endothelialitis plays a central role in COVID-19. Endotheliitis leads to disruption of vascular integrity and remaining subendothelial substances activate coagulation cascade; VEGF-A, PDGF-AA, PDGF-AB/BB, angiopoietin-2, FLT-3L and PAI-1 are several biomoleculs proposed as a biomarker for endotheliitis [9, 10]. This injury may explain the microthrombi formation and elevation of D-dimer. Also, another clue of the endotheliitis and its involvement in the COVID-19 is the high prevalence of Kawasaki disease in children.

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Current nomenclature of the process occuring in COVID-19 is highly confusing. In clinical aspect, "inflammation"-oriented definitions have promoted anti-cytokine-based treatments and have left aside the treatments targeting coagulation process. However, none of the anti-cytokine-based treatments have been shown to reduce mortality, yet.

Regarding all these data, we are proposing a new name for the COVID-19-related hyper-inflammation "Inflammatory thrombosis with immune endotheliitis [ITIE]" that implicates the underlying process more clearly and combines the pathways that should be targeted with medical therapies.

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Compliance with ethical standards

Conflict of interest None.

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