News

A third of covid-19 patients admitted to UK hospitals die

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Rapid Response:

Pre-existing endothelial dysfunction: a unifying hypothesis for the burden of severe SARS-CoV-2

Dear Editor

There is a common underlying circumstance among people with an increased risk of severe COVID-19: pre-existing endothelial dysfunction. Hypertension, diabetes, obesity, cardiovascular disease, cancer, chronic kidney disease, chronic liver disease, Alzheimer's disease, aging, male sex, and black race increase the risk for a severe SARS-CoV-2 infection. Each of these conditions can be associated with endothelial dysfunction (1). Of note is the fact that vascular endothelial dysfunction is regarded as a primary phenotypic expression of normal human aging (2).

Endothelial cells have very separate and singular functions that are predominant in vascular biology. Blood vessel tone, fluid filtration, hemostasis, neutrophil recruitment, hormone trafficking, and other functions are all under control of endothelial cells. When endothelial dysfunction is present, the ability to perform one or more of these functions results in reduced vasodilation, a proinflammatory state, and prothrombic properties (1).

All endothelial cell function can be greatly altered by virus infection (3). Cytokine storm during viral infection is a prospective predictor of morbidity and mortality and endothelial cells, as central regulators of cytokine storm, have been identified (4).

Elevated levels of inflammation-inducing cytokines in the blood of hospitalized COVID-19 patients have been shown, and disease severity is probably driven by this out of proportion inflammatory response to the virus (5). There is evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation (6), secondary

dysregulated immune response resulting in excessive activation of the endothelium by enhancing antibodies and memory T cells could result in a cytokine “tsunami” (7). Endothelium appears to be the battlefield of COVID-19.

Blood clot forming is only one of several complications of endothelial dysfunction. It is recognized that clotting is a major feature of severe COVID-19 and subtle clotting might begin early in the lungs, perhaps due to an inflammatory reaction in their fine web of blood vessels, which could set off a cascade of proteins that prompts blood to clot and prevents it from getting properly oxygenated (8). However, a report on 3200 COVID-19 positive deceased patients in Italy reported atrial fibrillation as one of the most common comorbidities (9); consequently, many patients at the beginning of COVID-19 were using oral anticoagulant and nevertheless they died. Prior anticoagulation was not protective unless the cause of death was independent by their coagulation state in all deceased patients. Clotting is one important severity risk factor in COVID-19, but systemic inflammatory vasculitis secondary to endotheliitis appears to be the most feared complication in SARS-CoV-2 infection. This explains why anticoagulant therapy even started at the beginning of the disease does not always result in a striking effect on mortality.

We speculate that the degree of pre-existing endothelial dysfunction could be a condition sine qua non for developing moderate-severe SARS-CoV-2 infection. During the COVID-19 pandemic, the deaths of so many older adults could be caused by a common underlying circumstance: the progressive decline of endothelial function with age (2) further complicated by other coexisting comorbidities associated with endothelial dysfunction such as hypertension, cardiovascular diseases, diabetes or cancer.

An effective endothelial dysfunction treatment might change the disease course.

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Competing interests: No competing interests

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