Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome

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Interleukin-6 and the COVID-19 cytokine storm syndrome

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The concept of coronavirus disease 2019 (COVID-19)-related cytokine storm syndrome (COVID-CSS) emerged early in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic to explain why some patients exposed to this virus become critically ill with acute respiratory distress syndrome, multi-organ failure, and death. A seminal study from Wuhan, China reported higher serum concentrations of inflammatory cytokines in patients requiring critical care compared to those with milder disease, and the authors postulated that "cytokine storm was associated with disease severity" [1]. COVID-19 hypercytokinaemia initially invited comparisons to other respiratory viral infections that cause a dysregulated immune response, namely severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Subsequently, similarities between COVID-CSS and other cytokine storm syndromes such as haemophagocytic lymphohistiocytosis (HLH) [2], autoinflammatory syndromes, and chimeric antigen T-cell therapy cytokine release syndrome (CAR T-cell CRS) became apparent [3–5]. The proposition that hypercytokinaemia is pathological in some patients with COVID-19 catalysed numerous clinical trials of immunomodulatory and cytokine-inhibitor therapy. However, critics contend that CSS is a misleading conceptual framework in COVID-19 and two prominent editorials have raised significant doubt about COVID-CSS [6, 7]. In brief, these authors contend that:

there is no definition of cytokine storm syndrome;