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Commentary

A glimpse into the eye of the COVID-19 cytokine storm

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The pathogenesis of pandemic coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) likely depends heavily on disruption of immune and inflammatory processes. Thus far, the precise immune mechanisms have not been fully elucidated or studied in detail. In this issue of *EBioMedicine*, Liu and colleagues [1] showed that patients with severe COVID-19 had lymphopenia and increased neutrophil counts along with high levels of circulating pro-inflammatory cytokines compared to patients with mild COVID-19 illness. The investigators used flow cytometry to investigate immune phenotype and function of peripheral blood mononuclear cells (PBMC), as well as quantified plasma cytokine levels, from 40 COVID-19 patients. In particular, substantial depletion of CD8+ *T* cells were associated with disease severity, and both the ratios of neutrophils to CD8+ *T* cells (N8R) and neutrophils to lymphocytes (NLR) were predictive of COVID-19 outcome. These data suggest that depletion of lymphocytes, particularly cytotoxic T lymphocytes that function by eliminating infected cells, coupled with neutrophils capable of mediating a proinflammatory "cytokine storm" may be key players in COVID-19 pathogenesis.

While "cytokine storms" have long been associated with acute respiratory distress syndrome (ARDS) caused by SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV) [2], pro-inflammatory cytokine dynamics in the context of cellular immune responses in COVID-19 have not been well-characterized. This study clearly demonstrates that severe COVID-19 is associated with significant increases in pro-inflammatory cytokines such as IL-6 as well as significant reductions in CD8+ *T* cells. Th1 antiviral responses appear to be suppressed, which is supported by increases in the Th2 cytokine IL-10. A recent study in 21 patients also demonstrated that COVID-19 induced increases in IL-6 and IL-10 with corresponding lymphopenia [3]. These data indicate that cytokine storms may, in concert with suppressed Th1 antiviral adaptive responses, underlie the pathogenesis of severe COVID-19 disease.

These findings are valuable for clinicians as it further supports the significant effect SARS-CoV-2 has on the systemic inflammatory response and gives insight on how to identify patients at risk for severe disease. It demonstrates potentially critical roles for IL-2, IL-6, IL-10, and IFN-γ in severe disease, suggesting that the magnitude of the cytokine storm is associated with severity of disease. Mean IL-6 concentrations have been shown to be 2.9 times higher in patients with severe disease and maximal IL-6 highly predictive of respiratory failure [4,5]. These data also suggest that monitoring N8R and NLR over time could be a way to identify patients early on at risk for developing severe disease [6].

Understanding how to identify which patients who present with COVID-19 will go on to develop severe disease is of paramount importance to clinicians. Monitoring N8R and NLR over time may assist frontline clinicians in identifying those at greatest risk for developing severe COVID-19 and prompt them to institute supportive care earlier or initiate transfer to a higher level of care [6]. Appreciating the role of pro-inflammatory cytokines in the pathogenesis of the disease is important as the scientific community develops therapeutics to treat patients. IL-6 inhibitors such as tocilizumab and siltuximab are already being used in the treatment of patients with severe COVID-19 in hopes of suppressing inflammatory responses and have been adopted in the most recent Chinese National Health Commission Novel Coronavirus Pneumonia guidelines [5,7].

Additionally, levels of fibrinogen, D-dimer, C-reactive protein, and ferritin were found to be significantly higher in patients with severe diseases compared to mild patients and are other potential laboratory markers clinicians can monitor over time to assess how individuals are responding [8]. This is consistent with prior reports that higher levels of C-reactive protein, ferritin and D-dimer were associated with severe COVID-19 [3].

This study was limited to 40 COVID-19 patients, thus limiting the applicability to larger populations. Furthermore, five of the severe patients had fungal or bacterial co-infections, which likely confound associations of inflammatory dysfunction with specific features of COVID-19 disease. Although N8R and NLR remained significant predictors of COVID-19 outcome when the patients with fungal infections were removed, larger studies that can account for variables introduced by co-infections are needed. A subset of patients received methylprednisolone, a corticosteroid with known

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immunomodulatory effects, further complicating interpretations of COVID-19-specific effects on inflammatory cytokine production and immune cell function. To confirm that lymphocyte depletion and increased numbers of neutrophils are associated with cytokine storms and COVID-19 severity, further data from other cohorts of COVID-19 patients must be obtained.

Animal models and samples from patients will be crucial tools for studying the interplay between lymphocytes, neutrophils, and other key cellular mediators of host immunity. In particular, detailed functional studies of immune cells infiltrating the lungs are needed to better understand mechanisms of immune-mediated lung injury. This is particularly relevant in immunocompromised patients, such as those with HIV, cancer, organ transplant recipients, or genetic immune deficiencies.

Declaration of Competing Interest

The authors declare no conflict of interest.

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