

CORRESPONDENCE

Cytokine Storm

TO THE EDITOR: In their review article on cytokine storm, Fajgenbaum and June (Dec. 3 issue)¹ include a discussion of signaling by mitogen-activated protein kinase (MAPK), nuclear factor κ B, and mammalian target of rapamycin. We feel compelled to point out one major omission that has a clear therapeutic effect for cytokine storm in general and for therapies for coronavirus disease 2019 (Covid-19) in particular: the p38 MAPK–MAPKAPK2 pathway. This pathway is a master regulator that controls the expression of many proinflammatory cytokines in myeloid and lymphoid cells, including interleukin-6, interleukin-1 β , interferon- γ , and tumor necrosis factor α , through both transcriptional and post-transcriptional mechanisms after tissue damage or exposure to pathogen-associated molecular patterns or other stimuli.²⁻⁴ Covid-19 infection has been shown to lead to phosphorylation and activation of p38 MAPK.⁵ Therefore, small-molecule inhibitors of p38 MAPK (e.g., losmapimod) and of the p38 MAPK–MAPKAPK2 signaling complex (e.g., ATI-450) are currently in clinical trials as anti-Covid-19 therapeutics (ClinicalTrials.gov numbers, NCT04511819 and NCT04481685, respectively). These two drugs are expected to show efficacy that extends beyond that seen with single monotherapies directed at individual cytokines alone.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In their discussion of cytokine storm, Fajgenbaum and June provide an enlightening overview of the background and therapeutic approaches. However, we suggest that cytokine storm after cardiac arrest should also be considered in further discussions.¹ Intensivists observe full-blown and often fatal cytokine storm in patients with the postcardiac arrest syndrome, particularly after prolonged cardiopulmonary resuscitation. In addition, the authors largely neglect extracorporeal hemoadsorption as a promising treatment option, although they acknowledge specific treatments, such as cytokine-receptor blockade and direct cytokine neutralization. In a pathogen-associated cytokine storm (bacterial sepsis or severe viral infection), the immune response is indispensable for recovery. Extracorporeal hemoadsorption aims at reducing levels of particularly elevated cytokines in order to restore equilibrium while avoiding complete clearance or receptor blockage.² Furthermore, such therapy effectively clears other disease-promoting substances, such as damage-associated molecular patterns and pathogen-associated molecular patterns, which trigger and maintain the cytokine storm.³ Although data from retrospective analyses encourage further research into this field, there is a need for randomized, controlled trials to investigate clinical end points.⁴

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that Fajgenbaum and June propose will create some difficulty in the classification of the disorder in patients who have serious infections with viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza. Nearly all these patients who are hospitalized for respiratory failure and require oxygen administration will meet the three criteria for cytokine storm in the proposed definition. We recently described a low incidence of dysregulated systemic cytokine expression in patients with Covid-19¹: only 7 of 168 patients in our cohort had systemic cyto-

TO THE EDITOR: The definition of cytokine storm

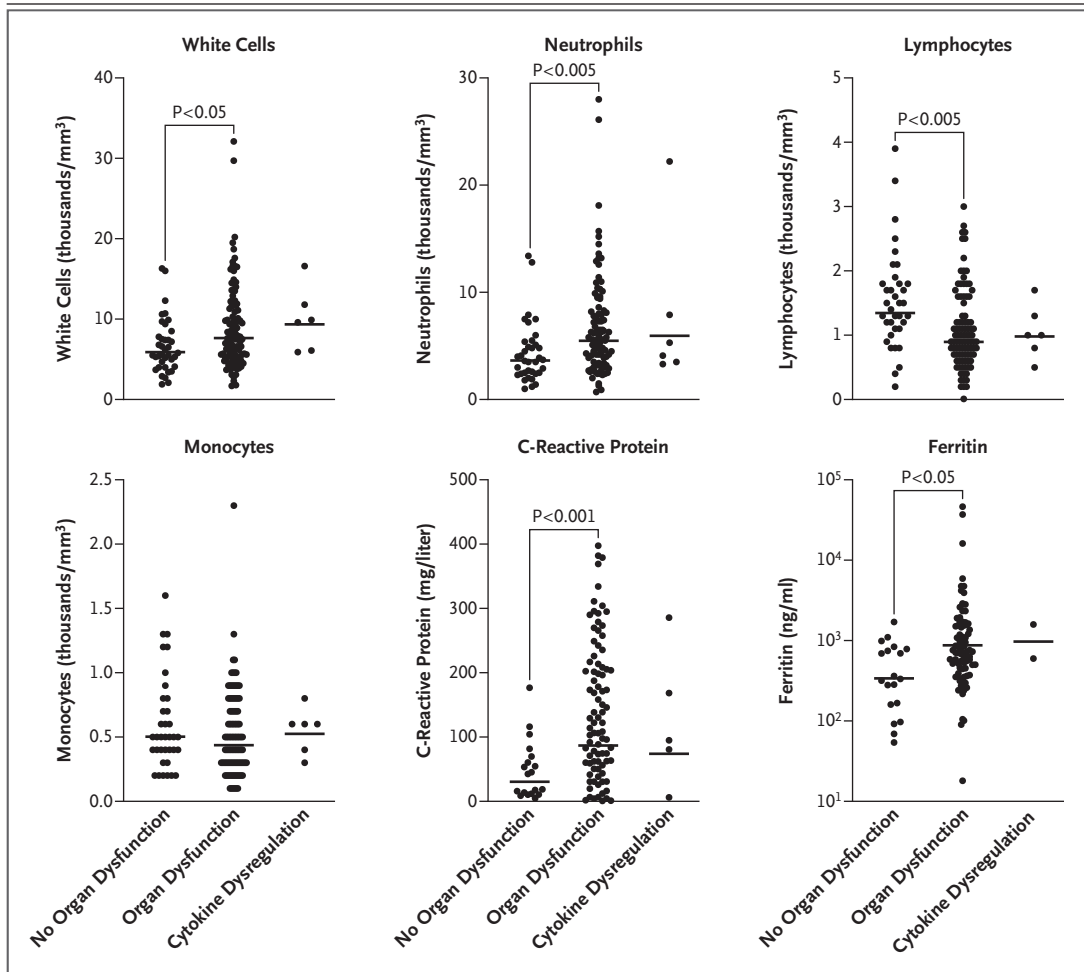


Figure 1. Clinical Laboratory Studies in Patients with Covid-19.

Common clinical laboratory studies do not discriminate between patients with Covid-19 who have secondary organ dysfunction and appropriately elevated cytokines and those with cytokine dysregulation or cytokine storm. In a cohort of 168 patients, we identified 7 patients who had systemic cytokine dysregulation that exceeded the normal variation associated with acute Covid-19 infection using principal component analysis of the levels of 35 separate plasma cytokines.¹ Shown here are the results of common clinical laboratory studies that were performed in the study patients within 24 hours after cytokine measures were obtained. Included are data obtained from all the patients in the study cohort who had available clinical laboratory measurements. Statistical comparisons were performed by means of Kruskal–Wallis analysis of variance followed by Dunn’s multiple comparison test. The horizontal lines indicate the geometric mean.

kines that were broadly dysregulated and expressed beyond the normal cytokine up-regulation that is associated with acute viral infection. Blood counts, C-reactive protein levels, and ferritin values did not seem to discriminate between patients with a dysregulated systemic cytokine response and those without such a response (Fig. 1). We propose that any formal definition of cytokine storm during acute viral infection must include a direct assessment of circulating cytokines and outline relative thresholds for these values.

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1. Mudd PA, Crawford JC, Turner JS, et al. Distinct inflammatory profiles distinguish COVID-19 from influenza with limited contributions from cytokine storm. *Sci Adv* 2020;6(50):eabe3024.
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THE AUTHORS REPLY: We agree with Gaestel et al. that further discussion is warranted related to the role of MAPK and MAPK inhibitors in cytokine storm. Given the limited data on MAPK inhibitors for treating cytokine-storm disorders, we mentioned MAPK only briefly, but we did include it as one of the four signaling pathways.

We agree with the comment by Supady et al. that cytokine storm after cardiac arrest and extracorporeal hemoadsorption could have been discussed further.¹ Although we did not discuss hemoadsorption of cytokines in detail, we mentioned that it was under evaluation for cytokine-storm disorders. This is a promising area that we hope will be found to be effective in numerous patients with this disorder.

Mudd et al. highlight a very important issue with our proposed unifying definition of cytokine storm: it does not specify precisely which cytokines must have elevated levels or thresholds for how elevated these cytokines must be to constitute a cytokine storm. We would also like to include specific cytokines and thresholds in our unifying definition, but unfortunately requisite data do not currently exist.

In this regard, Mudd et al. refer to their elegant immunophenotyping study² in Covid-19 versus influenza to identify a small subgroup of pa-

tients with Covid-19 who had strikingly elevated cytokine profiles. They concluded that these patients had “cytokine dysregulation” and all other patients with Covid-19 who did not cluster separately from those with influenza had “normal variation” in cytokines, despite the fact that these patients often had highly elevated cytokine levels, proinflammatory markers, and organ dysfunction. Although we agree that only a fraction of patients with Covid-19 have a cytokine storm, we disagree with their method for determining which cases had “appropriate elevation” versus “cytokine dysregulation” by principal component analysis. The patients with influenza who were presumed to represent a normal immune response included those who required mechanical ventilation and died, potentially because of cytokine dysregulation. We also disagree with their assessment of the figure that they included with their letter. The large positive effect size of immunosuppression with dexamethasone in hospitalized patients who are receiving supplemental oxygen and the trend toward negative outcomes in hospitalized patients who are treated with immunostimulatory intravenous interferon suggest that many of these patients with organ dysfunction probably have excessive inflammation.^{3,4} We think that data provided by the correspondents reveal the challenges of selecting specific analytic methods or thresholds for specific cytokines in serum to define the level above which there is “appropriate elevation” versus “cytokine dysregulation” when sufficient data are not yet available.

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Since publication of their article, the authors report no further potential conflict of interest.

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