EDITORIAL

Is a "Cytokine Storm" Relevant to COVID-19?

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In its most severe form, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), leads to a life-threatening pneumonia and acute respiratory distress syndrome (ARDS). The mortality rate from COVID-19 ARDS can approach 40% to 50%.[1,2] Although the mechanisms of COVID-19–induced lung injury are still being elucidated, the term *cytokine storm* has become synonymous with its pathophysiology, both in scientific publications and the media. Absent convincing data of their effectiveness in COVID-19, drugs such as tocilizumab and sarilumab, which are monoclonal antibodies targeting interleukin (IL)-6 activity, are being used to treat patients; trials of these agents typically cite the cytokine storm as their rationale (NCT04306705, NCT04322773). A critical evaluation of the term *cytokine storm* and its relevance to COVID-19 is warranted.

Cytokine storm has no definition. Broadly speaking, it denotes a hyperactive immune response characterized by the release of interferons, interleukins, tumor-necrosis factors, chemokines, and several other mediators. These mediators are part of a well-conserved innate immune response necessary for efficient clearance of infectious agents. *Cytokine storm* implies that the levels of released cytokines are injurious to host cells. Distinguishing an appropriate from a dysregulated inflammatory response in the pathophysiology of critical illness, however, has been a major challenge. To add further complexity, most mediators implicated in cytokine storm demonstrate pleotropic downstream effects and are frequently interdependent in their biological activity. The interactions of these mediators and the pathways they inform are neither linear nor uniform. Further, although their quantified levels may suggest severity of responses, they do not necessarily imply pathogenesis. This complex interplay illustrates the limitations of interfering in the acute inflammatory response based on single mediators and at indiscriminate time points.

Why has the "cytokine storm" been so closely associated with COVID-19? During the SARS epidemic caused by SARS-CoV-1, the term *cytokine storm* was described as a feature and associated with adverse outcomes.[3] Several early case series in COVID-19 reported levels of some plasma cytokines elevated above the normal range. In most cases, however, they are lower than plasma levels in previous cohorts of patients with ARDS. Interleukin-6, a proinflammatory cytokine, is a key mediator in the acute inflammatory response and the purported cytokine storm. The **Table** summarizes reported IL-6 levels in 5 cohorts of patients with COVID-19,[1,2,4-6] each with more than 100 patients, and 3 cohorts of patients with ARDS.[7-9] Although the median values are above the normal range in many (but not all) cases, they are lower than the median values typically reported in ARDS. The median values in random-

Table. Plasma Levels of Interleukin-6 Reported in COVID-19 Compared With Levels Previously Reported in ARDS[a]

	Total population				Severe disease		
COVID-19	No.	IL-6 levels, pg/mL			No.	IL-6 levels, pg/mL	Measurement platform
Zhou et al[4]	191	7 (5-11)			54[b]	11 (8-14)	CL
Wu et al[1]	123	7 (6-9)			84[c]	7 (6-11)	CL
Mo et al[5]	155	45 (17-96)			85[d]	64 (31-165)	CL
Qin et al[2]	452	21 (6-47)			286[e]	25 (10-55)	CL
Cummings et al[6]	NR	NR			237[f]	26 (11-69)	CL
	Total population		Hypoinflammatory		Hyperinflammatory		
ARDS	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	Measurement platform
ALVEOLI[7]	521	238 (94-741)[f]	386	154 (67-344)	135	1525 (584-3802)	ELISA
FACTT[8]	884	130 (46-411)[f]	638	86 (34-216)	246	578 (181-2621)	ELISA
SAILS[9]	720	443 (173-1513)[f]	451	282 (115-600)	269	1618 (517-3205)	ELISA

Abbreviations: ALVEOLI, Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury; ARDS, acute respiratory distress syndrome; CL, clinical laboratory; CLIA, chemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; FACTT, Fluids And Catheters Treatment Trial; ICU, intensive care unit; IL-6, interleukin-6; NR, not reported; SAILS, Statins for Acutely Injured Lungs From Sepsis.

[a] Presented values are the medians with interquartile ranges. The top segment of the Table reports data from selected COVID-19 cohorts (n > 100) and their corresponding severe subgroups. The bottom segment reports data from 3 National Heart, Lung, and Blood Institute ARDS network randomized clinical trials. Values are reported for the total cohorts and in subgroups stratified by ARDS phenotypes (hypoinflammatory and hyperinflammatory). The mean (SD) IL-6 levels for the ARDS trials were as follows: ALVEOLI, 2051 (8208) pg/mL; FACTT, 1048 (3348) pg/mL; and SAILS, 2363 (10 940) pg/mL.

[b] Nonsurvivors.

[c] ARDS.

[d] Refractory hypoxemia.

[e] Acute hypoxemic respiratory failure.

[f] Requiring ICU admission.

ized clinical trials conducted by the National Heart, Lung and Blood Institute's ARDS Network are approximately 10- to 40-fold higher, even when only patients with severe COVID-19 are considered.[7-9] The hyperinflammatory phenotype of ARDS is characterized by elevated proinflammatory cytokines, an increased incidence of shock, and adverse clinical outcomes.[7-9] The characteristics of this phenotype could be considered as most consistent with those expected with the cytokine storm. However, median IL-6 levels in patients with the hyperinflammatory phenotype of ARDS are 10- to 200-fold higher than levels in patients with severe COVID-19 (Table).

Putting the unsubstantiated theory of the cytokine storm aside, the more intriguing question to ask is why are clinical outcomes in COVID-19 so unfavorable despite relatively low levels of circulating IL-6? One hypothesis is that severe viral pneumonia from COVID-19 produces primarily severe lung injury, without the same magnitude of systemic responses in most patients with COVID-19 as reported in prior studies of the hyperinflammatory phenotype in ARDS.[7-9] For example, a recent postmortem report of patients with COVID-19 ARDS identified severe vascular injury, including alveolar microthrombi that were 9 times more prevalent than found in postmortem studies of patients with influenza ARDS.[10] Ongoing research may identify more specific mechanisms of COVID-19–mediated lung injury.

There are some limitations to these observations. Almost all the COVID-19 IL-6 data are from clinical laboratory tests. In most studies, details of the exact methods used are not available; calibration issues could lead to underestimating IL-6 levels compared with measurements based on enzyme-linked immunosorbent assay used in prior ARDS studies.[7-9] Furthermore, plasma levels of cytokines may not be representative of lung inflammation. Given the number of COVID-19 cases worldwide, the data on IL-6 levels are from a very small fraction of patients. Nevertheless, the theory of the cytokine storm is based on these data, and the case for its presence in COVID-19 seems weak. A more appropriate conclusion would be that in comparison to other causes of ARDS, COVID-19 is characterized by lower levels of circulating cytokine responses. Perhaps the most valid conclusion, however, is that the current data are insufficient to ascertain the precise role and scope of dysregulated cytokine responses in COVID-19.

Widespread acceptance of the term *cytokine storm* in COVID-19 has motivated the use of potent immunomodulatory therapies both in the setting of clinical trials and on a compassionate basis. These drugs, such as IL-6 inhibitors and high-dose corticosteroids, block pathways critical to host immune responses. Many monoclonal antibody drugs are being repurposed from treating patients with chronic inflammatory conditions where optimal pharmacokinetics demand prolonged half-lives. Long-lasting and indiscriminate suppression of inflammation in the acute critical care setting raises concerns about impaired clearance of SARS-CoV-2 and increased risk for secondary infections. Enthusiasm for the use of immunomodulatory approaches in COVID-19 seems to derive in large part from clinical experience with *cytokine release syndrome* (CRS), a term frequently interchanged with *cytokine storm*. In the 2016 study of CRS by Maude and colleagues, patients who developed CRS following treatment with chimeric antigen receptor T cells were effectively treated with tocilizumab.[11] Notably, the peak plasma IL-6 level in patients who developed CRS was approximately 10 000 pg/mL—almost 1000-fold higher than that reported in severe COVID-19. Conceivably, these therapies could be effective in COVID-19, but the likelihood for success would be enhanced by selecting the right patients with predictive enrichment and the right timing for intervention.[7]

Given reports that dexamethasone may improve survival for patients with COVID-19 and ARDS, it should be determined whether these effects differ between ARDS phenotypes and if they occur despite the absence of a circulating hyperinflammatory cytokine response. If so, the additional information about dexamethasone would further substantiate the importance of studying local inflammatory responses to COVID-19 in the lungs.

For these reasons, the term *cytokine storm* may be misleading in COVID-19 ARDS. Incorporating a poorly defined pathophysiological entity lacking a firm biological diagnosis may only further increase uncertainty about how best to manage this heterogeneous population of patients. The manifestations of elevated circulating mediators in the purported cytokine storm are likely to be endothelial dysfunction and systemic inflammation leading to fever, tachycardia, tachypnea, and hypotension. This constellation of symptoms already has a long history in critical care, known as systemic inflammatory response syndrome, and was used to define sepsis for decades. Interventions targeting single cytokines in sepsis, unfortunately, also have a long history of failure. Although the term *cytokine storm* conjures up dramatic imagery and has captured the attention of the mainstream and scientific media, the current data do not support its use. Until new data establish otherwise, the linkage of cytokine storm to COVID-19 may be nothing more than a tempest in a teapot.

ARTICLE INFORMATION

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Letters

RESEARCH LETTER

Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions

An abnormally strong proinflammatory response known as "cytokine storm" may play an important role in the pathophysiology of coronavirus disease 2019 (COVID-19), although cytokine storm remains ill defined.[1] Sinha and colleagues[2] reported that although IL-6 levels are elevated in severe COVID-19, they are lower than levels usually observed in (non-COVID-19) acute respiratory distress syndrome (ARDS). However, this comparison is limited by the use of different assays, which are not well standardized.[3] We compared cytokine levels in critically ill patients with COVID-19 vs levels in patients with other critical illnesses.

Methods | All patients in this study were admitted to the intensive care unit (ICU) of Radboud University Medical Center. Plasma concentrations of the proinflammatory cytokines tumor necrosis factor (TNF), IL-6, and IL-8 were determined in consecutive mechanically ventilated patients with COVID-19 with ARDS (partial pressure of oxygen/fraction of inspired oxygen ratio <300; sampled within 48 hours after ICU admission), bacterial septic shock with or without ARDS (sampled within 24 hours after septic shock diagnosis), out-of-hospital cardiac arrest (OHCA; sampled within 24 hours after ICU admission), and multiple traumas (sampled within 24 hours after trauma). The patients with sepsis and trauma are part of larger published cohorts,[4,5] whereas data of 14 patients with OHCA were previously published.[6] Sampling occurred between 2010 and 2020 (**Table**). Patients with immunological insufficiencies were excluded, defined as chronic/concomitant use of immunosuppressive medication, chemotherapy/radiotherapy in the last year or in the past for (non-)Hodgkin lymphoma, or humoral/cellular deficiencies. Cytokines in all cohorts were determined using the same methodology (Milliplex assay, Millipore, on a MAGPIX instrument, Luminex Corporation) by the same technician using the same protocol.

Patient characteristics were analyzed using Fisher exact or Kruskal-Wallis tests followed by Dunn post hoc tests. Cytokine data are presented as geometric means (95% CIs) and analyzed using 1-way analysis of variance on log-transformed data followed by Dunnett post hoc tests.

Table. Patient Characteristics[a]

Characteristic	COVID-19 with ARDS, March 11 to April 27, 2020 (n = 46)	Septic shock, March 15, 2013, to March 28, 2017		Out-of-hospital cardiac arrest, February 5, 2010, to December 12, 2013 (n = 30)	Trauma, March 19, 2011, to May 30, 2013 (n = 62)
		With ARDS (n = 51)	Without ARDS (n = 15)		
Sex, No. (%)					
Male	34 (74)	36 (71)	6 (40)	22 (73)	44 (71)
Female	12 (26)	15 (29)	9 (60)	8 (27)	18 (29)
Age, median (IQR), y	67 (57-71)	62 (53-72)	73 (64-78)	65 (52-75)	58 (37-72)
BMI, median (IQR)	27.5 (25.0-29.3)	26.4 (23.8-30.5)	25.0 (21.5-30.3)	25.1 (23.4-26.9)[b]	24.7 (23.2-27.4)[c]
Medical history, No. (%)					
Cardiovascular insufficiency	12 (26)	2 (4)[c]	2 (13)	1 (3)[b]	1 (2)[d]
Respiratory insufficiency	3 (7)	1 (2)	0	0	0
COPD	3 (7)	5 (10)	0	0	0
Kidney insufficiency	0	5 (10)	0	0	0
Metastatic neoplasm	4 (9)	1 (2)	2 (13)	1 (3)	0[b]
Diabetes	13 (28)	8 (16)	1 (7)	1 (3)[c]	4 (6)[c]
Hematologic malignancy	0	0	0	0	0
APACHE II score, median (IQR)[e]	14 (12-18)	21 (17-26)[d]	24 (18-31)[d]	27 (20-34)[d]	20 (14-25)[c]
Pao_2/Fio_2 ratio, median (IQR)	139 (107-171)	206 (162-260)[d]	354 (328-424)[d]	246 (159-370)[d]	253 (201-361)[d]
Leukocytes, median (IQR), $\times 10^9$/L	8.2 (6.4-11.1)	14.0 (9.8-20.8)[d]	15.4 (7.2-24.4)[c]	12.9 (10.0-16.7)[d]	11.8 (8.9-14.0)[c]

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; Fio_2, fraction of inspired oxygen; IQR, interquartile range; Pao_2, partial pressure of oxygen.

[a] Data were obtained on the same day that blood was obtained for cytokine determination.

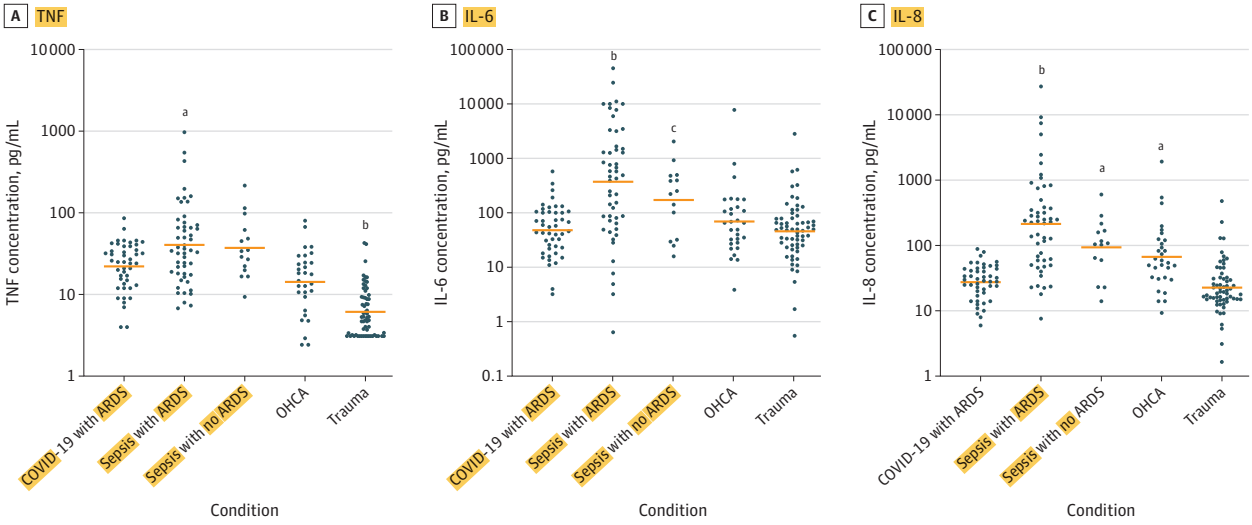
[b] $P < .05$ vs COVID-19 with ARDS.

[c] $P < .01$ vs COVID-19 with ARDS.

[d] $P < .001$ vs COVID-19 with ARDS.

[e] Intensive care unit score of overall disease severity ranging from 0-71; a higher score indicates more severe disease.

Figure. Cytokine Levels in Critically Ill Patients With Coronavirus Disease 2019 (COVID-19) and Other Conditions



Plasma concentrations of tumor necrosis factor (TNF) (A), IL-6 (B), and IL-8 (C) in patients with COVID-19 and acute respiratory distress syndrome (ARDS) (n = 46), septic shock with ARDS (n = 51), septic shock without ARDS (n = 15), out-of-hospital cardiac arrest (OHCA; n = 30), and multiple traumas (n = 62). Data are presented as scatter plots with red horizontal bars indicating the geometric mean levels.

[a] $P < .01$ vs COVID-19 with ARDS.

[b] $P < .001$ vs COVID-19 with ARDS.

[c] $P < .05$ vs COVID-19 with ARDS.

Data were analyzed using Graphpad Prism version 8.3.0 (Graphpad Software). A 2-sided $P < .05$ was considered statistically significant. The study was carried out in accordance with the applicable rules concerning the review of research ethics committees and informed consent in the Netherlands. All patients or legal representatives were informed about the study details and allowed to abstain from participation. Patients who consented to participate or their next of kin provided oral consent.

Results | There were 46 patients with COVID-19 with ARDS, 51 with septic shock with ARDS, 15 with septic shock without ARDS, 30 with OHCA, and 62 with multiple traumas. There were no significant differences in sex or age between patients with COVID-19 and other patient groups (Table). Patients with COVID-19 had a higher body mass index and prevalence of diabetes than patients with OHCA and trauma. In COVID-19, cardiovascular insufficiency was more common, overall disease severity and leukocyte counts were lower, and lung injury was more severe compared with the other groups.

Levels of all 3 cytokines were significantly lower in patients with COVID-19 than in patients with septic shock with ARDS; the geometric means were 22 pg/mL (95% CI, 18-27) vs 40 pg/mL (95% CI, 30-55) ($P < .01$) for TNF; 48 pg/mL (95% CI, 35-66) vs 376 pg/mL (95% CI, 190-744) ($P < .001$) for IL-6; and 27 pg/mL (95% CI, 23-33) vs 215 pg/mL (95% CI, 133-347) ($P < .001$) for IL-8 (depicted in the **Figure** on a log scale). Patients with COVID-19 also displayed significantly lower IL-6 and IL-8 concentrations compared with patients with septic shock without ARDS (Figure). TNF levels in patients with COVID-19 were higher than those in trauma patients, whereas no differences between patients with COVID-19 and OHCA or trauma were present for IL-6. For IL-8, lower concentrations were found in patients with COVID-19 compared with patients with OHCA, while no differences vs the trauma group were observed.

Discussion | In this study, critically ill patients with COVID-19 with ARDS had circulating cytokine levels that were lower compared with patients with bacterial sepsis and similar to other critically ill patients. These findings are in line with lower leukocyte counts observed in patients with COVID-19, and are possibly due to lower overall disease severity, despite the presence of severe pulmonary injury. The findings of this preliminary analysis suggest COVID-19 may not be characterized by cytokine storm. Whether anticytokine therapies will benefit patients with COVID-19 remains to be determined. Limitations of the study include the small sample sizes, single center involved, and the use of different lots of the same assays without data on lot-to-lot variability.

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