Editorial

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Cytokine "storm", cytokine "breeze", or both in COVID-19?

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The ongoing coronavirus disease 2019 (COVID-19) pandemic outbreak, which has seemingly emerged in Wuhan (China) at the end of 2019, has now spread all around the world, causing dramatic clinical consequences (in terms of morbidity, disability or mortality), a collapse of worldwide economies, raising also serious threats to human society [1]. Although several pathogenic features of this infectious disorder still need to be unraveled, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory pathogen, whose virulence extends far beyond what is commonly seen in patients with infections caused by other similar microorganisms. The evidence garnered so far allows us to conclude that COVID-19 is not a narrow respiratory disorder, though it principally manifests with low respiratory tract infection (i.e., bilateral interstitial pneumonia, eventually progressing to acute respiratory distress syndrome; ARDS), but shall rather be considered an evolving systemic pathology, which may affect many organs and tissues, characterized also by relevant risk of developing capillary, venous and arterial thrombosis, inside and outside the lung tissue [2].

Beside evidence of systemic dissemination of SARS-CoV-2 in patients with severe and especially critical forms of illness [3], an abnormal, often exaggerated inflammatory response has been reported, since the beginning of this outbreak, in patients at risk of unfavorable disease progression. This phenomenon, defined "cytokine storm" [4], resembles that seen in other hyperinflammation syndromes, falling into the broader definition of cytokine release syndrome (CRS) (Table 1) [5]. Irrespective of the specific causes, the underlying mechanisms leading to CRS have usually been identified with an abnormal, supraphysiologic response to specific (immune) triggers, then accompanied by exaggerated activation and/or engagement of lymphocytes, monocytes/macrophages, dendritic and other immune effector cells, culminating with development and persistence of a self-reinforcing inflammatory loop.

This conclusion has mostly emerged from observations that the circulating values of many proinflammatory biomarkers, especially C reactive protein (CRP), ferritin, interleukin (IL)-6, IL-8, IL-10 and even the erythrocyte sedimentation rate, were considerably increased over their upper limit of reference range in COVID-19 patients, being magnified in those with adverse clinical progression [6]. Nonetheless, despite the onset of a "cytokine storm" has hence been considered quite a hallmark of SARS-CoV-2 infection, recent evidence would instead suggest that hyperinflammation may not be as ubiquitous as earlier purported.

Sinha et al. conducted a prospective observational study, where clinical and laboratory correlates of COVID-19 patients with ARDS were compared to those of patients with COVID-19 unrelated ARDS [7]. The IL-6 and soluble tumor necrosis factor receptor 1 (sTNFR1) concentrations were found to be similar or even lower in COVID-19 patients than in those with ARDS triggered by other causes, whilst a hyperinflammatory phenotype could be identified in less than one-fourth of all COVID-19 cases (i.e., 21%). Nonetheless, the death rate was found to be nearly 20% higher in COVID-9 patients with hyperinflammatory than in those with hypoinflammatory phenotype. In another study Kox et al. found that circulating cytokine levels (i.e., those of tumor necrosis factor, IL-6 and IL-8) of COVID-19 patients with critical disease and ARDS were comparable or even lower than those observed in patients with other critical illnesses such as bacterial septic shock, out-of-hospital cardiac arrest and severe trauma [8]. In another cross-sectional investigation, Salvagno et al. reported that the values of CRP and IL-6 in patients testing positive for

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Table 1: Pathological conditions frequently associated with cytokine release syndrome (CRS).

– Macrophage activation syndrome.
– Haemophagocytic lymphohistiocytosis.
– Viral infections.
– Sepsis with or without systemic inflammatory response syndrome (SIRS).
– Drugs (e.g., protein-based cancer drugs and immunotherapy).
– Chimeric antigen receptor (CAR)-T cell therapy.
– Haploidentical hematopoietic cell transplantation.
– Graft-versus-host disease (GVHD).
– Massive tissue injury.

COVID-19 at hospital admission were globally comparable to those of patients urgently admitted for acute respiratory symptoms triggered by other conditions [9]. To summarize the findings that have been published so far, Leisman et al. carried out a meta-analysis of all COVID-19 studies reporting IL-6 concentration in patients with severe or critical SARS-CoV-2 infections, which were then compared to those observed in studies of patients with CRS, sepsis or COVID-19 unrelated ARDS [10]. Despite the pooled analysis conformed that IL-6 values were frequently elevated in patients with SARS-CoV-2 infection, the concentration of this biomarker was found to be approximately 100-fold lower than in patients with CRS, 27-fold lower than in those with sepsis, and even 12-fold lower than in patients COVID-19 unrelated ARDS.

In an article published in this issue of the *Journal*, Martens et al. provide additional useful insights on the inflammatory response in COVID-19. Briefly, the authors measured many hematological and biochemical parameters in a large cohort of patients presenting with suggestive COVID-19 symptoms, 553/1140 of whom (48.5%) tested positive for SARS-CoV-2 [11]. At hospital admission, CRS could be diagnosed in 166/553 (30%) of COVID-19 patients, who also showed a paradigmatic hematological fingerprint, characterized by reactive and higher permeability monocytes, activated or immature granulocytes, as well as by antibody-synthesizing lymphocytes.

The convincing evidence that the inflammatory response frequently seen in patients with severe or critical SARS-CoV-2 infections may at least partially differ from that observed in other hyperinflammatory conditions has persuaded Webb and colleagues to construct a COVID-19-specific hyperinflammatory syndrome (cHIS) score, based on six different parameters, and encompassing the presence of fever (body temperature >38 °C), macrophage activation (ferritin ≥700 μg/L), hematological dysfunction (neutrophil-to-lymphocyte ratio ≥10, or hemoglobin ≤92 g/L, or platelet count $\leq 110 \times 10^9$), hepatic injury (lactate dehydrogenase ≥400 U/L, or aspartate aminotransferase ≥100 U/L), coagulopathy (D-dimer ≥1.5 μg/mL) and cytokinaemia (IL-6 ≥15 pg/mL, or triglycerides ≥1.69 mmol/L, or CRP ≥0.15 g/L) [12]. In a cohort of 299 COVID-19 patients, a cHIS score ≥2 was associated with 92% accuracy, 95% sensitivity and 59% specificity for predicting mechanical ventilation, as well as with 81% accuracy, 96% sensitivity and 49% specificity for predicting mortality, thus corroborating the principle that hyperinflammation is probably a major driver of adverse clinical evolution in patients with SARS-CoV-2 infection, along with direct cytopatic injury, functional immunoparalysis and thrombosis.

Nonetheless, several lines of evidence now contribute to downsize the perhaps overrated presence of a cytokine "storm" in COVID-19. Although it is unquestionable that the values of proinflammatory cytokines are frequently elevated in patients with SARS-CoV-2 infection, their levels remain relatively modest in the vast majority of cases [13]. The elevations of many biomarkers of tissue injury are also relatively mild compared to those seen in patients with other COVID-19 unrelated ARDS and/or CRS [13]. Finally, the effectiveness of cytokine blockade by means of tocilizumab and other similar agents has been disputed for preventing the need of mechanical ventilation or mortality in COVID-19 patients with moderate illness [14].

Therefore, concluding as to whether COVID-19 is accompanied by a cytokine "storm", or just by a modest cytokine "breeze", is indeed not so straightforward, whereby the clinical spectrum of this pathology is so broad than can span from a totally asymptomatic condition to a catastrophic systemic disease, characterized by multiple organ failure, leading to an almost inevitable death. It seems hence more reasonable to hypothesize that the outcome of SARS-CoV-2 infection may be strongly influenced by a variable individual response, and that progression of COVID-19 towards a "cytokine storm" phenotype, and thereby to more severe/critical illness, may be dependent on multiple factors, i.e., genetic (e.g., ABO blood group, polymorphisms in host cell receptors, immune response and inflammatory pathways), phenotypic (e.g., age, sex, ethnic origin, body weight, smoking status, presence of co-morbidities, frailty, nutritional deficiencies, viral strain and load, and so forth) and even environmental (e.g., social inequalities, timeliness and quality of care) (Figure 1) [15]. However, what seems to clearly emerge from recent evidence on this matter, and as also brilliantly highlighted in the article of Martens and colleagues [11], is that an accurate and early recognition of the "hyperinflammatory phenotype" shall be regarded as an essential element for addressing the triage and managed care of

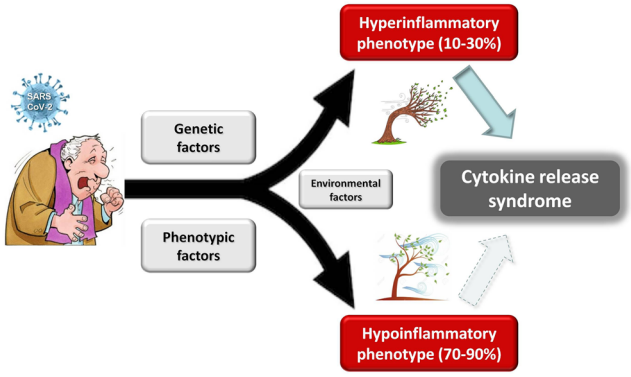

Figure 1: Phenotypes of inflammatory response in patients with coronavirus disease 2019 (COVID-19).

patients with SARS-CoV-2 infection, either symptomatic or not. In fact, early treatment with specific cytokine antagonists, macrophage-targeted cell-signalling modifiers, corticosteroids and perhaps also anticoagulant drugs, may be much more effective in COVID-19 patients with hyperinflammatory response, while these agents may be almost worthless, or even detrimental, in those with no or low grade inflammation, thus strengthening the concept that patient selection and timing of therapy administration are essential elements in the managed care of SARS-CoV-2 infections [1].

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