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Commentary

Biomarkers for severe COVID-19

Xin Li[a,b], Kelvin K.W. To[a,b,*]

[a] State Key Laboratory for Emerging Infectious Diseases, Carol Yu Centre for Infection, Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong Special Administrative Region, People's Republic of China
[b] Department of Microbiology, Queen Mary Hospital, Hong Kong Special Administrative Region, People's Republic of China

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Coronavirus Disease 2019 (COVID-19) has a wide spectrum of clinical severity. Studies have estimated that while 30–60% of COVID-19 cases are asymptomatic or mildly symptomatic, 5% of symptomatic cases are critically ill [1]. Severe COVID-19 is usually characterized by respiratory compromise and multiorgan failure. Clinical or demographic risk factors for severe disease include older age, male sex, and chronic health conditions, especially diabetes mellitus, cardiovascular disease, immunosuppression and obesity [1]. Genetic variations in the immune pathways or autoantibodies against type I interferon, are associated with severe COVID-19.

Host response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can be beneficial or deleterious, and plays an important role in the pathogenesis of COVID-19. For example, a rare Kawasaki-like multisystem inflammatory syndrome in children (also known as paediatric inflammatory multisystem syndrome) is believed to be caused by an improper autoimmune response [2]. But unlike other severe respiratory virus infections, severe SARS-CoV-2 infection invokes a more limited inflammatory response, wherein cytokine storm is not a major feature [3]. To identify host factors or pathways that are associated with poor outcome, van de Beek et al. analysed the changes of 64 blood biomarkers that are related to endothelial activation, inflammation, neutrophil activation and neutrophil extracellular traps (NET) formation, activation of the complement, coagulopathy and epithelial barrier disruption [4]. As reported in this issue of *EBioMedicine*, they compared the expression profiles of these factors in two cohorts of COVID-19 patients. The first cohort included patients admitted to the general ward, and the outcome measure was admission to intensive care unit (ICU) or mortality. The second cohort included patients admitted to the ICU, and the outcome measure was 12-week mortality. While some factors/pathways were common to both cohorts, there were several factors that demonstrated characteristic changes unique to either the general ward or ICU cohort. The strongest predictors for poor outcome in the general ward were endothelial activation and chemotaxis. On the other hand, the markers of poor prognosis in the ICU included those involved in enhanced inflammation, activation of complement system and coagulation. The authors concluded that interventions in the general ward should focus on strategies that enhance endothelial integrity and limit chemotaxis, while ICU patients require interventions on multiple pathways.

The unique feature of the study by van de Beek et al., as compared with other studies on host response of COVID-19 patients, is the determination of deleterious markers in two distinct cohorts with different clinical severity. The biological insights of the immune response based on the patients' clinical severity are especially relevant for clinicians, as previous studies showed that the efficacy of treatment is associated with disease severity. For example, dexamethasone is most efficacious among patients requiring oxygen supplementation but not among those with mild disease [5]. On the other hand, the monoclonal antibody LY-CoV555 was only efficacious among out-patients but not hospitalized patients [6]. Hence, instead of a one-size-fits-all approach, clinicians should treat their patients according to the different stages of patients' illness.

Endothelial dysfunction is of particular concern in COVID-19, which can be caused by direct endothelial cell infection by SARS-CoV-2, or by the immune response towards SARS-CoV-2. Endotheliitis can trigger the innate immune response, and can contribute to thromboembolism and multisystem involvement of COVID-19. The prevalence of alveolar capillary microthrombi was found to be 9 times higher for patients with COVID-19 than those with influenza [7]. In this study, a heightened endothelial activation among more severe patients in the general ward suggested that the endothelial dysfunction occurs early in the disease course, even before the development of clinical deterioration. Therefore, early intervention that ameliorates endothelial dysfunction can theoretically prevent the progression of COVID-19. Several such interventions, such as defibrotide and heparanase inhibitors, have been proposed [8].

The study by van de Beek et al. can help researchers in finding potential host-directed treatment targets. However, it should be noted that inhibitors against these biomarkers or pathways may or may not be clinically useful. For example, interleukin 6 (IL-6) was found to be a biomarker for unfavourable outcome in both general ward and ICU cohorts. However, there are conflicting data regarding the use of IL-6 receptor antagonist in COVID-19 patients, including several well-conducted randomized clinical trials. While the REMAP-

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* Corresponding author.
E-mail address: kelvinto@hku.hk (K.K.W. To).

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CAP Investigators showed that IL-6 receptor antagonists improved the survival of critically ill COVID-19 patients, Salama et al. did not find any survival benefit for IL-6 receptor antagonists [9,10]. Hence, these inhibitors must be evaluated carefully in animal studies and clinical trials. Furthermore, as multiple pathways lead to unfavourable outcome, a combination of these host factor inhibitors may provide additive or synergistic benefit.

Contributors

XL and KKWT co-wrote this commissioned Commentary.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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