Future directions

According to the current guidelines, the efficacy and benefits of syncope units have not been established yet.1,2 Initiatives such as the SUTHC across the world can respond to this question. We are going to systematically answer this issue; however, we think that the SUTHC results in better organization of the patients with VVS and decreases unnecessary emergency room visits. Moreover, we are going to develop a website for the education of these patients. Although Syncopaedia currently addresses this concern admirably,7 we think that providing educational content in Persian with a special focus on patient education is needed and helpful for our community.

The referral nature of Tehran Heart Center in addition to the appropriate organization of patients with VVS in the SUTHC has enabled us to build a unique registry of these patients. We have carried out some studies by virtue of this organization.8,9 Furthermore, we are working to determine the efficacy of lifestyle modifications and compliance of patients in the SUTHC. These insights will aid us in performing well-designed randomized controlled trials.9

We are cordially inviting researchers from all over the world for international collaboration on joint projects. Moreover, we appreciate the opinions of colleagues and experts worldwide to improve the quality of the SUTHC more than before.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References

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Weekly Journal Scan

COVID 19: in the eye of the cytokine storm

Comment on ‘An inflammatory cytokine signature predicts COVID-19 severity and survival’ was published in Nature Medicine 2020; 26: 1636–1643 (https://doi.org/10.1038/s41591-020-1051-9).

Key points

• The study examined data from 1484 patients hospitalized for suspected or confirmed (n = 1257) COVID-19 at the Mount Sinai Health System in New York between 21 March and 28 April 2020. Serum levels of four inflammatory cytokines were analysed upon admission with a rapid multiplex test: interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)-α, and IL-1β. These results were correlated with clinical and laboratory markers of disease severity and with clinical outcome.
• Patients were followed from the day of hospitalization to the day of discharge or death (median 8 days). IL-6, IL-8, and TNF-α were significantly (P < 0.0001) elevated in COVID-19 patients compared to healthy donors (n = 9) or patients with cancer treated with chimeric antigen receptor-modified (CAR)-T cells with no cytokine release syndrome (CRS) (n = 151), but lower than in patients with CRS induced by CAR-T cell therapy (n = 121). The vast majority of COVID-19 patients presented with elevated cytokines or cytokine storm.
• Serum levels above the median value of IL-6 [hazard ratio (HR) 2.23; 1.61–3.09], IL-8 (HR 1.41; 1.05–1.89), and TNF-α (HR 1.50; 1.09–2.07) at the time of hospitalization were strong and independent predictors of decreased survival after adjusting for demographics and comorbidities.
• When adjusting for disease severity, common inflammation markers, hypoxia, and other vitals (temperature, O2 saturation, respiratory rate, and severity score), IL-6, and TNF-α serum levels remained independent and significant predictors of disease severity and mortality.

Comment

This study focused on four cytokines known to contribute to pathogenic inflammation in CRS of patients receiving CAR-T cells, with clinically available or experimental blocking drugs. The clinical picture of the cytokine storm in COVID-19 was different from that of the coordinated increase during traditional CRS, showing different patterns of cytokine expression, and potentially distinct clinical presentations based on the
relative profile of each cytokine. Accordingly, serum levels of IL-6 and TNF-α were lower in COVID-19 compared to classical CRS. The plasma cytokine cluster of COVID-19 recalls the cytokine pattern associated with acute coronary syndromes (ACS). In ACS, IL-6 levels are correlated with prognosis, and IL-6 blockade by tocilizumab quenches the acute inflammatory response of ACS patients undergoing percutaneous coronary intervention. In COVID-19, the cytokine storm might evoke and/or potentiate existing or new cardiac functional abnormalities, as well as trigger ACS through a thrombo-inflammatory response.

Previous studies have demonstrated that higher serum concentrations of IL-6 are associated with higher levels of SARS-CoV-2 viremia, prolonged viral RNA shedding, progression to mechanical ventilation, and death. Although IL-6-receptor blockade might theoretically interrupt the COVID-19 inflammatory cascade at an early stage, there has been a limited success so far with drugs blocking IL-6. Evidence from non-randomized trials and open-label studies has been contradictory, and recently published results from a randomized, double-blind, placebo-controlled trial failed to demonstrate the efficacy of IL-6 receptor blockade in the treatment of hospitalized patients with COVID-19.

One potential explanation is that IL-6 and other inflammatory proteins elevated in patients with COVID-19 represent a physiological host response to the infection, rather than components of a self-amplifying, pathogenic inflammatory loop. In general, the higher risk of severe COVID-19 disease in diabetes mellitus, obesity, and heart disease might be attributable to synergistic activation of macro- and micro-vascular thrombo-inflammatory pathways associated with both COVID-19 and cardiometabolic disease. It is also plausible that other anti-inflammatory approaches, including anti-TNF-α, may be effective in the course of COVID-19 disease.

The therapeutic window in CRS is narrow, and timely control of the cytokine storm is crucial to reduce short-term mortality. Premature use of immunosuppressants could indeed further compromise viral shedding with the risk of increasing viral replication and tissue damage directly induced by the virus. The RECOVERY trial has clearly shown that benefits from dexamethasone are restricted to patients with at least 7 days of symptoms and those requiring invasive or non-invasive ventilation, suggesting that only a late phase of COVID-19 is dominated by pathogenic inflammation. Notably, in a subset of 244 patients enrolled in the current study with more than one assay performed, those treated with corticosteroids showed a rapid reduction in IL-6, with no effect on TNF-α. IL-6 suppression might represent an important mechanism underlying the beneficial effects of dexamethasone in this setting.

In conclusion, the present study convincingly demonstrated that early cytokine increases, in particular IL-6 and TNF-α, were reliable predictors of COVID-19 severity and mortality, independently of demographics, comorbidities, and clinical biomarkers of disease severity. Multiple cytokine profiling could be used to determine which individuals are likely to develop respiratory failure and end-organ damage, in order to prioritize treatment in those at highest risk. Moreover, the predictive value of these cytokines might help guide resource allocation, as well as the design of prospective interventional studies.

Theoretically, patients with moderate disease severity and high IL-6 or TNF-α levels might benefit the most from cytokine blockade.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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