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Cytokine storm with rapidly elevated interleukin-6 indicates sudden death in patients with critical COVID-19

Dear Editor

Few mild patients with coronavirus disease 2019(COVID-19) have the potential to suddenly deteriorate in the early stages of diseases and the process of recovery, meanwhile some critical patients may rapidly develop acute respiratory distress syndrome (ARDS), multiple-organ failure (MOF) or even death [1]. This phenomenon may be attributed to excessive immune response induced by cytokine storm manifested by elevated interleukin-6 (IL-6). In the current edition of Cytokine & Growth Factor Reviews, Sun and his colleagues detailed review the role of cytokine storm in the pathogenesis and progression of COVID-19 pneumonia and the current understanding of cytokine storm intervention in the early stages of COVID-19 pneumonia [2]. As an addition, we estimate its association between cytokine storm and sudden death in patients with critical COVID-19 in the hope that this will help clinicians better manage critical patients.

From Jan 21 to April 15, Yichang Central People's Hospital admitted a total of 25 critical COVID-19 patients confirmed by sputum or nasopharyngeal swab real-time reverse transcriptase polymerase-chain-reaction (RT-PCR) SARS-CoV-2 test. According to the guidelines of National Health Commission of the People's Republic of China [3], critical COVID-19 patients must meet one of the following criterias: (1) the occurrence of respiratory failure required mechanical ventilation; (2) septic shock or failure of other organs need care in the intensive care unit (ICU). All 19 fatal patients were included into this study. We gathered all related data from electronic medical records, which mainly included demographic, epidemiological, clinical symptoms, laboratory findings, chest computed tomography (CT) scan, therapeutic processes, and outcome (Supplementary Table 1). Potential cause of death of fatal patients was confirmed through the discussion of expert groups from Yichang and Fujian.

Among 19 fatal patients with 69 years (interquartile range (IQR): 63.5–77.5 years) of median age ranged from 51 to 85 years, there was predominant male (63 %), 8 patients with hypertension and 5 with diabetes. The median duration from onset to hospital admission was 5 days (IQR: 4.5–8.5 days). There were 19 patients with fever and 18 patients with dyspnea, followed by cough, fatigue and sputum. Meanwhile, there were 16 patients with lymphocytopenia and 18 patients with eosinophilopenia. All patients occurred elevated C-reactive protein (CRP) with 15 elevated procalcitonin and 11 abnormal D-dimer. Myocardial damage was presented in ten patients. The common imaging in chest CT scan were diffuse round-glass opacities and consolidation with involving five lung lobes (100 %) and subplerual area (94.7 %). On admission, the median CURB-65 was 3 (IQR:2−3) with the range from 1 to 5. Two critical patients had a CURB-65 score of 1, 2 (31.6 %) patients had a score of 2 and 7 (36.8 %) patients harbored a score of 3. The majority of patients received combined treatments, including lopinavir/ritonavir (73.7 %), interferon-α (63.2 %), arbidol (94.7 %), herbs(63.2 %), intravenous immunoglobulin (89.5 %), corticosteroid (89.5 %), thymosin (26.3 %) and antibiotics(100 %). 15 patients received the treatment of noninvasive mechanical ventilation with 10 treatments of invasive mechanical ventilation. Continuous renal replacement therapy was performed in four patients. From Feb 20, three patients received plasma exchange and transfusion of COVID-19 convalescent plasma. Case 18 was performed venous-venous extra corporeal membrane oxygenation (vv-ECMO) treatment due to refractory hypoxia. This patients also received the treatment of high-dose corticosteroid (120 mg) and pirfenidone for treating fibrosis. Considering persistent cytokine storm, case 17 was treated with tocilizumab injection (400 mg) after three sections of therapeutic plasma exchange and three transfusions of COVID-19 convalescent plasma. Case 17 and 18 occurred viral shedding at 30 days after hospital admission. The median hospital stays among all patients were 12 days (IQR: 7.5–17.5 days) with the range from 2 to 72 days.

Because case 14 rejected all examinations and treatments after hospital admission, we did not speculate his death cause. After light activity, case 4 suddenly occurred cardiopulmonary arrest and was speculated to be pulmonary embolism. In the remaining 17 patients, the major death cause was attributed to MOF (6) and respiratory failure (6), followed by cardiac arrest (3), septic shock (2). We found 11 patients with two tests of IL-6 during three days before death (Table 1). All 8 patients with rapid elevated IL-6 were associated with sudden death at 24 h. Among the remaining 3 patients without significantly elevated IL-6, case 15 and case 16 were attributed to cardiac arrest secondary to refractory heart failure and case 8 was MOF. In addition, case 12 with one test occurred high level of IL-6 before death (176ng ml).

In this retrospective study about fatal patients with critical COVID-19, we found significantly higher prevalence of lymphocytopenia and eosinophilopenia than mild patients. Persistent immunodepression manifested by lymphocytopenia and eosinophilopenia were identified to have a poor prognosis of COVID-19 [4]. More complications occurred in critical patients, including bacterial infection, myocardial damage, liver damage, and renal damage. In addition, the risk of thromboembolism secondary to SARS-CoV-2 infection also deserves our full attention. As above mentioned, death cause of case 4 was attributed to pulmonary embolism and 11 patients had elevated D-dimer. High prevalence (69 %) of thromboembolic events still was presented in critical COVID-19 patients even though therapeutic anticoagulation [5]. Cardiac damage was another main concern in patients with critical COVID-19 [6]. Our study harbored ten patients with abnormal manifestations of myocardial enzyme spectrum and three patients with cardiac arrest. Our study observed that cytokine storm manifested by rapidly elevated IL-6 in a short time maybe the main cause of sudden death. All 8 patients with

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Table 1
The last two levels of IL-6 before death.

	Next-to-last level of IL-6 (ng/mL)	Last level of IL-6 (ng/mL)
Case 1	534.9	4556
Case 2	16.57	560.4
Case 3	6.31	> 5000
Case 7	435.7	709.7
Case 8	31.57	17.87
Case 10	29.99	186.8
Case 11	47.65	310.9
Case 15	9.74	22.94
Case 16	14.97	10.2
Case 17	1824	3276
Case 18	80.92	936.5

cytokine storm died at 24 h. SARS-CoV-2 infection seemingly have the ability to induce long-term cytokine storm. We performed corticosteroid, plasma exchange, COVID-19 convalescent plasma and tocilizumab to manage persistent cytokine storm of Case 17. Unfortunately, his death still was attributed to cytokine storm with rapidly elevated IL-6 (from 1824 pg/mL to 3276 pg/mL) at 37 days after admission. Case 18 died at 72 days after admission, who also was associated with cytokine storm before death(IL-6 from 80.92 pg/mL to 936.5 pg/mL). A recent study showed that SARS-CoV-2 infection not only impaired innate immune response [7], but also induced persistently strong expression of chemokines and interleukins [8]. Even after the reduction of viral load and viral shedding, this strong cytokine storm still was presented [8]. Our study observed that case 17 still occurred cytokine storm after viral shedding (three negative SARS-CoV-2 testings and normal SARS-CoV-2 IgM and IgG). Tocilizumab, as anti-human IL-6 receptor monoclonal antibody, was observed to have the ability to immediately improve the clinical outcome in patients with severe and critical COVID-19 [9].

In conclusion, our study showed that SARS-CoV-2 infection can induce long-term immunodepression and cytokine storm. Cytokine storm manifested by rapidly elevated IL-6 has the potential to result in sudden death in patients with critical COVID-19. Continuous monitoring of IL-6 is essential, even after SARS-CoV-2 viral shedding. Tocilizumab potentially decrease the mortality of patients with critical COVID-19.

Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Ethics approval

All patients gave written informed consent and the study was approved by the ethics committee of Yichang Central People's Hospital.

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Declaration of Competing Interest

This was not an industry supported study. The authors have declared that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.08.001.

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