IL-10 served as an indicator in severe COVID-19 patients

To the Editor,

Recently, the coronavirus disease 2019 (COVID-19) pandemic has reached more than 32,730,000 confirmed cases and over 991,000 deaths worldwide. Accumulated evidence suggests that severe COVID-19 patients have an immune response disorder, leading to excessive inflammation. Moreover, recent studies have reported that inflammatory cytokines are associated with the severity of COVID-19. However, there is limited systemic analysis to clarify the role of various inflammatory cytokines in the assessment of COVID-19 severity. Therefore, we performed a literature analysis to investigate the association of cytokines and lymphocyte subsets between severe and nonsevere COVID-19 patients.

Databases of Medline (PubMed), Embase, Cochrane, and Web of Sciences from January 1 to September 1, 2020, were systematically analyzed to identify all published studies in the English language, using the following keywords: "2019-nCoV" OR "SARS-CoV-2" OR "COVID-19" OR "new corona virus" OR "novel coronavirus" OR "nCoV" OR "coronavirus 2019." The title, abstract, and full text of all the documents meeting these search criteria were scrutinized by two independent investigators, and only those containing data on cytokines and lymphocyte subsets of COVID-19 patients with and without severe disease (i.e., those requiring intensive care unit admission, mechanical ventilation, vital life support, or those who died) were included in our analysis. The reference lists of relevant literature were also manually screened to identify other eligible studies.

Overall, 18 studies were considered in the final analysis. Mean and standard deviation of lymphocyte subsets and cytokines values were extrapolated from the sample size, median, and interquartile range for statistical homogeneity. Meta-analysis was performed using Stata 12.0 (StataCorp), calculating the standardized mean difference (SMD) and the 95% confidence interval (95% CI) of lymphocyte subsets and cytokines levels in COVID-19 patients with or without severe disease. Statistical heterogeneity was evaluated using $I^2$ statistic, and a random-effects model was used when the value exceeded 50%. Otherwise, a fixed-effects model was used. The clinical and the immunological data from 3004 patients were collected, including 1119 (37.25%) severe patients. The sample size ranged from 8 to 334 patients. The SMD of the 18 studies used for each parameter is summarized in Figure 1.

The cytokine levels, especially IL-10, were increased significantly in severe patients (SMD, 1.56; 95% CI, 0.97–2.15; Figure 1A). IL-10 was associated with the severity of the disease and was primarily involved in the suppression of inflammatory responses. Thus, this hypothesis further advanced the idea that both inflammatory and anti-inflammatory responses may occur simultaneously. High IL-10 levels in severely infected patients may be responsible for the negative feedback of systemic and local inflammation. In addition, the lymphocyte counts, as well as their subsets T, B, NK, CD4+ T, CD8+ T, CD28+ Ts cells values were found to decrease significantly in patients with COVID-19 with severe disease, while severe patients had a more clinically significant decrease in CD8+ T cells (SMD, −1.57; 95% CI, −2.09 to −1.05; Figure 1B). Based on these analyses, this study has enhanced the significance of lymphocytes and cytokines in the severity of COVID-19 coronavirus disease.

Activated by antigen-presenting cells, T cells can proliferate and differentiate into specific effector T cells, producing a variety of pro-inflammatory cytokines. Here, we find that severe COVID-19 was associated with the elevated cytokines, in particular IL-10. There were reduced T, B, NK, CD4+ T, CD8+ T, and CD28+ Ts cells, while activated Ts cells percentages were increased. Thus, monitoring the changes of IL-10 has an important implication for the prediction and treatment of severe COVID-19 patients who may get critically ill.

This study has several limitations. First, studies included were mainly retrospective cohorts. The interpretation of some findings may be limited by the sample size. However, with appropriate statistical tools, we were able to identify several indicators to indicate disease severity in patients with COVID-19. In addition, only the articles containing both lymphocyte subsets and cytokines were included to ensure the two sets of data from the same cohort of patients.

DOI: 10.1002/jmv.26580
FIGURE 1  Risk factors associated with disease severity in COVID-19 patients. Standardized mean difference (SMD) and 95% confidence interval (95% CI) of (A) cytokines and (B) lymphocyte subset values in COVID-19 patients with or without severe disease. IFN, interferon; IL, interleukin; Lym, lymphocyte; NK cells, natural killer cells; no., number; Th cells, helper T cells; TNF, tumor necrosis factor; Treg, regulatory T cells; Ts cells, suppressor T cells.
ACKNOWLEDGMENTS

We thank all the researchers involved in this study.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

Fei Huang MM1,2
Xu Liu MD1
Xiaolin Sun PhD1
Zhanguo Li MD, PhD1

1Department of Rheumatology and Immunology,
Peking University People’s Hospital, Beijing, China
2Department of Nephrology and Rheumatology,
Affiliated Hospital of Zunyi Medical University, Zunyi, China

Correspondence
Zhanguo Li, MD, PhD, Department of Rheumatology and Immunology, Peking University People’s Hospital, 11 Xizhimen South St, 100044 Beijing, China.
Email: li99@bjmu.edu.cn

ORCID
Fei Huang http://orcid.org/0000-0001-6954-3036
Zhanguo Li http://orcid.org/0000-0002-2590-6242

REFERENCES
1. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762–768. https://doi.org/10.1093/cid/ciaa248
2. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763. https://doi.org/10.1016/j.ebiom.2020.102763
3. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620–2629. https://doi.org/10.1172/JCI137244
4. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):1–11. https://doi.org/10.1001/jamainternmed.2020.0994
5. Xu B, Fan C, Wang A, et al. Suppressed T cell-mediated immunity in patients with COVID-19: a clinical retrospective study in Wuhan, China. J Infect. 2020;81(1):e51–e60. https://doi.org/10.1016/j.jinf.2020.04.012
6. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71(15):769–777. https://doi.org/10.1093/cid/ciaa272
7. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;80(6):639–645. https://doi.org/10.1016/j.jinf.2020.03.019
8. He R, Lu Z, Zhang L, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol. 2020;127:104361. https://doi.org/10.1016/j.jcv.2020.104361
9. Liu Y, Liao W, Wan L, Xiang T, Zhang W. Correlation between relative nasopharyngeal virus RNA load and lymphocyte count disease severity in patients with COVID-19. Viral Immunol. 2020. https://doi.org/10.1089/vim.2020.0662
10. Wan S, Yi Q, Fan S, et al. Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. Br J Haematol. 2020;189(3):428–437. https://doi.org/10.1111/bjh.16659
11. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091. https://doi.org/10.1136/bmj.m1091
12. Wei YY, Wang RR, Zhang DW, et al. Risk factors for severe COVID-19: evidence from 167 hospitalized patients in Anhui, China. J Infect. 2020;81(1):e89–e92. https://doi.org/10.1016/j.jinf.2020.04.010
13. Yang P, Wang P, Song Y, Zhang A, Yuan G, Cui Y. A retrospective study on the epidemiological characteristics and establishment of an early warning system of severe COVID-19 patients. J Med Virol. 2020;92:2173–2180. https://doi.org/10.1002/jmv.26022
14. Chen R, Sang L, Jiang M, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol. 2020;146(1):89–100. https://doi.org/10.1016/j.jaci.2020.03.003
15. Zeng YL, Zhang C, Gao F, et al. Analysis of clinical characteristics of 49 cases of COVID-19. Zhonghua Jie He He Xi Za Zhi. 2020;43(8):654–658. https://doi.org/10.3760/cma.j.cn112147-20200225-00184
16. Liu F, Ji C, Luo J, et al. Clinical characteristics and corticosteroids application of different clinical types in patients with corona virus disease 2019. Sci Rep. 2020;10(1):13689. https://doi.org/10.1038/s41598-020-70387-2
17. Gan J, Li J, Li S, Yang C. Leucocyte subsets effectively predict the clinical outcome of patients with COVID-19 pneumonia: a retrospective case-control study. Front Public Health. 2020;8:299. https://doi.org/10.3389/fpubh.2020.00299
18. Li S, Jiang L, Li X, et al. Clinical and pathological investigation of patients with severe COVID-19. JCI Insight. 2020;5(12):e138070. https://doi.org/10.1172/jci.insight.138070
19. He S, Zhou C, Lu D, et al. Relationship between chest CT manifestations and immune response in COVID-19 patients. Int J Infect Dis. 2020;98:125–129. https://doi.org/10.1016/j.ijid.2020.06.059
20. Wan X, Wang W, Liu J, Tang T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135. https://doi.org/10.1186/1471-2288-14-135
21. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39(5):517–528. https://doi.org/10.1007/s00281-017-0639-8