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## Letter to the Editor

## Low serum CCL17 as a marker for severe/critical COVID-19: A pathogenic link

## ARTICLE INFO



Sir,

Sugiyama et al. (2021) report lower serum levels of CCL17 and higher serum levels of IL6, CXCL9, IP-10 (CXCL10) and IFN- $\lambda$ 3 (IFNL3) in severe/critical patients than mild/moderate patients of coronavirus disease 2019 (COVID-19). Of these chemokines and cytokines, CCL17, CXCL9 and CXCL10 were associated with COVID-19 alone, not other, mostly non-infectious, immune diseases examined. Highly robust statistical association of CCL17 with development of COVID-19 related pneumonia supported use of this chemokine as a first triage marker, with the other cytokines and chemokines serving as subsequent markers for predicting onset of severe COVID-19. For how these markers could relate to severe/critical pneumonia in COVID-19, the authors hypothesized, based on findings from mouse models of pulmonary inflammation, a possible role of regulatory T cells expressing the CCL17 receptor CCR4. Here, it is interesting to note that previously reported gene expression and immunohistochemical findings in severe/critical COVID-19 are also consistent with a pathogenic role of CCL17 in the illness. A study (Ackermann et al., 2020) that compared gene expression levels of inflammation-associated genes in autopsy lung samples of patients who died from COVID-19 or from influenza A infection related pneumonia, with that in age-matched, uninfected control lungs showed down-regulation of CCL17 and upregulation of IL6 and CXCL10 in COVID-19 alone, not influenza. What is more, the same study also found that between COVID-19 and influenza there is a differential abundance of T cell subset in the precapillary and postcapillary vessel walls in the lungs. With CCL17 as a ligand for T-lineage cell migration, and CCR4 as a dominant-type chemokine receptor for regulatory and helper T cells (Yoshie and Matsushima, 2015), this finding is consistent with a role of CCL17 in COVID-19 lung pathology. Finally, on a different note, Sugiyama et al. mentions that theirs is a first report of low CCL17

expression in a disease state. Here, it may be noted that low tumor tissue levels of CCL17 has previously been identified as an adverse prognostic biomarker in clear cell renal cell carcinoma (Xiong et al., 2017).

## Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

- Ackermann, M., Verleden, S.E., Kuehnel, M., Haverich, A., Welte, T., Laenger, F., Vanstapel, A., Werlein, C., Stark, H., Tzankov, A., Li, W.W., Li, V.W., Mentzer, S.J., Jonigk, D., 2020. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N. Engl. J. Med.* 383 (2), 120–128.
- Sugiyama, M., Kinoshita, N., Ide, S., Nomoto, H., Nakamoto, T., Saito, S., Ishikane, M., Kutsuna, S., Hayakawa, K., Hashimoto, M., Suzuki, M., Izumi, S., Hojo, M., Tsuchiya, K., Gatanaga, H., Takasaki, J., Usami, M., Kano, T., Yanai, H., Nishida, N., Kanto, T., Sugiyama, H., Ohmagari, N., Mizokami, M., 2021. Serum CCL17 level becomes a predictive marker to distinguish between mild/moderate and severe/critical disease in patients with COVID-19. *Gene* 766, 145145. <https://doi.org/10.1016/j.gene.2020.145145>.
- Xiong, Y., Liu, L., Xia, Y., Wang, J., Xi, W., Bai, Q., Qu, Y., Xu, J., Guo, J., 2017. Low CCL17 expression associates with unfavorable postoperative prognosis of patients with clear cell renal cell carcinoma. *BMC Cancer* 17, 117.
- Yoshie, O., Matsushima, K., 2015. CCR4 and its ligands: from bench to bedside. *Int. Immunol.* 27 (1), 11–20.

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Abbreviations: COVID-19, Coronavirus Disease 2019.

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