Correspondence on 'Lung involvement in macrophage activation syndrome and severe COVID-19: results from a cross-sectional study to assess clinical, laboratory and artificial intelligence–radiological differences' by Ruscitti *et al*

Our research team read Ruscitti *et al*'s article regarding lung involvement in coronavirus disease 2019 (COVID-19) and macrophage activation syndrome (MAS) with great interest.[1] This topic not only addresses the current pandemic, but also is of concern in our team's expertise—rheumatology. As we thoroughly examined the details of this research study, we noticed a few points we would like to address and discuss: the definition of patient selection criteria, the necessity of differentiating among COVID-19 CT patterns, the pathogenic mechanism differences between MAS and COVID-19, and the potential relationship between COVID-19 and vasculopathy.

First of all, this article states that age matching is not reliable. However, we contemplate that age is crucial in disease pathogenesis, such as immunosenescence, age-related inflammatory disease and periodontal disease, all of which could contribute to COVID-19 and MAS. Thus, "age" should still be an important factor to be considered and controlled as a confounding variable.[2 3] In addition, we doubt about the accuracy of diagnosis based on Yamaguchi criteria, as they simply serve as preliminary criteria for adult-onset Still's disease (AOSD),[4] which may led to misclassification. Furthermore, this article reports differences in H-scores between patients with MAS and COVID-19. If original diagnosis of MAS is preliminary, crosschecking with differential diagnoses may be preferable, especially through CT imaging.

Dai and Zhang reported cases from China in January 2020 that unenhanced CT scans showed (1) lateral basal ground-glass opacities (GGOs), (2) interlobular septal thickening with interlobar pleural thickening, and (3) patchy and partially consolidated lung tissues that gradually developed into reticular patterns and lesions.[5] Another study by Ye *et al* demonstrates chest CT manifestations of COVID-19 with disease progression. Initial degeneration of lung tissues originates with GGO in unilateral or bilateral lower lobes. As the hazing continuously develops, alveolar air starts being substituted by abnormal fluids, resulting in consolidation. Once consolidation could no longer be contained in a certain area of the lung, reticular patterns, namely, interlobular septa and intralobular lines, begin developing and are manifested by lesions. Consequently, thickening of such abnormality could demonstrate crazy paving patterns.[6] By close examination of CT scans from patients with MAS and COVID-19 from this paper and other previous studies, we could differentiate the two diseases prior to further comparison and contrast, thus improving current clinical practice.

Another area of our interest is the pathogenic mechanism differences between MAS and COVID-19, especially from the cytokine storm point of view. MAS inflammatory infiltrate was originally discovered to consist predominately of CD4 T cells and macrophages. Hence, scientists classified MAS as a secondary form of haemophagocytic lymphohistiocytosis.[7] Investigation into animal models of MAS reports that IL-6 overproduction results in autoinflammation or autoimmunity and suggests that interferon (IFN)-γ level is exceptionally elevated in experimental knockout mice. Since IFN-γ is a crucial cytokine that activates macrophages, we could infer that the primary cause of cytokine storm in MAS is IFN-γ.[7] On the other hand, for COVID-19, while IL-6 is continuously secreted by patients, high levels of other cytokines, such as IL-1β, TNF-α, CCL-2, CCL-3 and CCL-5, are also detected. However, the decisive difference between the two diseases is low levels of type I IFNs, an important factor for viral clearance, which may potentially be used as a differential diagnosis in the future.[8 9]

In continuation, our last point of comment is the correlation between COVID-19 and vasculopathy. Mondal *et al*'s research team stated that with an elevated level of IL-1β, cell pyroptosis, an inflammatory form of apoptosis, is indicated in the lymphocyte and macrophage cascade, leading to vasculopathy similarly to the previous studies of coronavirus family (severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus).[10] COVID-19 has an inhibiting effect on human haeme synthesis, which may trigger haemolysis, causing oxidative stress and leading to endothelial vasculature damage. With further evidence that shows a positive correlation between IL-6 and fibrinogen, this would raise the possibility of thrombosis in patients with COVID-19.[10] Another case series with regard to patients with COVID-19 originated from the intensive care unit (ICU) in Northern France drew our team's attention: 22 patients experienced pulmonary embolism (PE) among the first 107 confirmed COVID-19 cases, a statistically significant increase in comparison to other ICU patients. More shockingly, 20 of the 22 patients were already under prophylactic heparin at the time of PE diagnosis.[11] This wound lead to the fact that COVID-19 indeed has a positive correlation with vasculopathy.

In conclusion, the exact pathophysiology and mechanism of COVID-19 to lung and autoimmune injury are not well known yet. Ruscitti *et al* compare and contrast with MAS, opening up further discussions with various perspectives. We would like to contribute our share of knowledge to clinical science to improve patients' welfare.

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