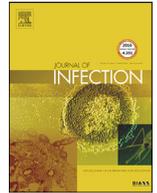




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Letter to the Editor

Lymphopenic community acquired pneumonia as signature of severe COVID-19 infection

As recently commented by Tang and colleagues in this Journal, the novel Coronavirus emerged at the end of 2019 from Wuhan has already spread beyond China [1], which led WHO to declare a public health emergency of international concern by Jan 30, 2020. Infection caused by this virus (COVID-19) courses with severe community acquired pneumonia (CAP) in a minority of the cases, but given its transmission characteristics, this is a further cause of alarm.

In two recent articles from Huang C et al. and Yang X in *The Lancet* [2,3], 85% of critically ill patients with COVID-19 showed lymphopenia. The presence of lymphopenia as a signature of severe COVID-19 was confirmed by Wang D et al., who, in their study published in *JAMA*, reported that ICU patients suffering this infection had a median lymphocyte count of 800 cells/mm [3], with non survivors exhibiting persistent lymphopenia [4]. ICU patients present also with high levels of plasma cytokines [2]. The existence of hyper-cytokinaemia in COVID-19 patients with lymphopenia could indicate a poor control of the pathogen, as showed in severe patients infected with the 2009 Pandemic Influenza virus. Interestingly, hypercytokinaemia and lymphopenia were also evident in critical patients with Severe Acute Respiratory Syndrome due to the Coronavirus emerged in 2003 (SARS-CoV) [5,6]. These features (lymphopenia + hypercytokinaemia) fit the characteristics of a particular immunological phenotype of community acquired pneumonia (CAP), lymphopenic CAP (L-CAP), which, as we recently demonstrated in an article published in the *Journal of Infection*, is associated with increased severity, mortality and a dysregulated immunological response [7].

In their works, Yang X et al. and Chen N et al. propose a direct cytotoxic action of the virus to explain the low lymphocyte counts observed in the severe cases of COVID-19 [3,8]. But, in our opinion, host factors could also contribute to induce lymphopenia in these cases. Compared with those patients not requiring intensive care, COVID-19 patients admitted to the ICU are older and are more likely to have hypertension, diabetes, cardiovascular and cerebrovascular disease [4]. Aging and chronic diseases induce chronic endothelial dysfunction. As we recently reviewed in *J Clin Med*, endothelial dysfunction induces disassembly of intercellular junctions, endothelial cell death and blood-tissue barrier disruption, along with enhanced leukocyte adhesion and extravasation, which could contribute to explain the lymphopenia observed in severe COVID-19 patients [9]. Recent findings from our group have evidenced the interconnection between lymphopenia and endothelial dysfunction in patients with CAP and organ failure [10]. Endothelial dysfunction induces also increased oxidative stress and systemic inflammation, glycocalyx degradation and shedding along with a pro-coagulant and anti-fibrinolytic state [9]. In aged

individuals with chronic diseases, these features could represent predisposing factors for presenting a severe respiratory failure following COVID-19 infection.

In the Huang et al. report, 32% of the hospitalised patients required admission to the ICU [2], and 26% in the study of Wang D et al. [4]. Co-circulation of the novel Coronavirus in China is coincident with the winter season, a period of high demand for ICU resources due to influenza and other respiratory infections. Finding new biomarkers that can be used at the earliest stages of hospitalization to identify those individuals with COVID-19 who will become critically ill will be important for efficient management of ICU resources. Lymphocyte count can easily be obtained at admission to the emergency room. In areas with sustained circulation of the new Coronavirus, evaluation of lymphocyte counts in patients with CAP could help to identify and prioritize those individuals who require or will shortly require critical care.

In conclusion, there is growing evidence suggesting that severe infection caused by the novel Coronavirus emerged in 2019 induces L-CAP. The presence of L-CAP suggests the existence of immunological dysregulation as an accompanying event of the critical illness caused by this virus. Early recognition of this immunological phenotype could be useful to assist prompt recognition of severe patients. Should lymphopenia play a role in the pathogenesis of the disease, drugs targeting lymphocyte proliferation or apoptosis (IL-7, PD1/PD-L1 inhibitors) could help to prevent lymphopenia or restore lymphocyte counts in severe patients suffering COVID-19. The potential role of endothelial dysfunction as predisposing and pathogenic actor in this disease merits investigation. Biomarkers / tests assessing endothelial function could also help to early identify severe cases of COVID-19. Drugs improving endothelial dysfunction such as adrenergic agonists could play a role in its treatment. Preclinical works on animal models should contribute to elucidate the true role of lymphopenia and endothelial dysfunction in this disease.

Declaration of Competing Interest

none

Authors' contributions

All the authors participated in generating the idea. Jesús F Bermejo-Martin wrote the initial version of the letter. Raquel Almansa, Rosario Menéndez, Raúl Mendez, David J Kelvin and Antoni Torres critically reviewed and edited it with their comments.

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