Response to: '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*' by Chen *et al*

Dear Editor,

We read with interest the correspondence by Chen *et al*[1] about our recent article on the comparison of clinical, laboratory and artificial intelligence–radiological findings in patients with lung involvement either from macrophage activation syndrome (MAS), a secondary form of haemophagocytic lymphohistiocytosis (HLH) or severe coronavirus disease 2019 (COVID-19).[2]

Age is one of the most common confounding factors in any observational study since it is associated with an increased risk of comorbidities, which may influence the outcome. In our study, the matching for age was not reliable because of higher prevalence of severe COVID-19 in elderly patients, who were admitted to intensive or subintensive care units of our hospital. These results mirror what was already observed in other observational studies,[3 4] in which the incidence and severity of COVID-19 are generally higher in elderly patients due to higher frequency of comorbidities, increased frailty and immunosenescence.[5] Conversely, MAS complicating adult-onset Still's disease (AOSD), as patients assessed in our study, usually affects young adults.[6] Considering the scientific debate behind our study,[2] about the possibility that severe COVID-19 could be considered or not part of HLH spectrum, the age of occurrence may further differentiate the clinical pictures between these diseases.

Furthermore, Chen *et al*[1] questioned the use of Yamaguchi criteria in classifying AOSD patients .[7] Although the classification criteria of AOSD may be considered an accessory part of our study, which evaluated patients with a fully developed MAS, we would like to point out that these criteria are widely used in the context of clinical research. Yamaguchi *et al* derived a set of major and minor criteria by a multicentre survey involving 90 AOSD patients and 267 controls.[7] Requiring five or more criteria, with at least two major ones, these provide 96.2% sensitivity and 92.1% specificity.[8] In addition, such criteria have been used as inclusion criteria in recent clinical trials on AOSD.[9–11]

Instrumental assessment by chest CT represents a key point for the staging and follow-up process in both COVID-19 pneumonia and MAS lung involvement. During the recent COVID-19 outbreak, CT examinations, due to the wide availability and rapid execution, also played a crucial role in the screening of many patients, along with the clinical laboratory data.[12] Several studies considered CT findings as a primary tool for the detection of COVID-19 in epidemic areas to optimise patient management, due to the high sensitivity and the important prognostic value.[13] In particular, the most typical findings in COVID-19 pneumonia, especially at the onset when most patients are examined, are represented by the presence of ground-glass opacities (GGOs) with bilateral peripheral localisation.[14] In our study, standard analysis of CT findings showed that peripheral, basal and bilateral GGOs were the most frequent findings in COVID-19 pneumonia when compared with MAS lung involvement. Nevertheless, CT findings of COVID-19 show overlapping features with other viral pneumonia (influenza and parainfluenza viruses, adenovirus and respiratory syncytial virus), as well as with other pulmonary conditions, such as pulmonary oedema, pulmonary haemorrhage, bronchiolitis obliterans and drug-induced lung disease.[15] Due to the cross-sectional design of our study,[2] we did not evaluate the evolution of radiological findings over time, but we assessed COVID-19 patients in the most severe phases, which led to the admission of the patients to intensive or subintensive care units, before the administration of any immunosuppressive therapy. In this context, a further analysis using dedicated artificial intelligence software could be an added value for a proper quantitative evaluation, crucial in disease staging, for quantitative correlation with clinical laboratory data at the time of diagnosis and during follow-up.[16]

As far as pathogenetic mechanisms of both diseases are concerned, it has been suggested that MAS and severe COVID-19 may share a similar cytokine profile.[17] As described in patients affected by MAS or primary HLH,[18] severe COVID-19 patients are burdened by a cytokine storm syndrome, a virally induced one, associated with a large release of proinflammatory cytokines.[5 17] According to Chen *et al*,[1] low levels of type I interferons (IFNs) could be a crucial pathogenic difference between MAS and severe COVID-19. This is an interesting topic deserving further investigations, probably able to differentiate these diseases, since a specific phenotype was observed in severe COVID-19 patients, consisting of no IFN-β and low IFN-α production and activity, associated with a persistent blood viral load and exacerbated proinflammatory response.[19]

Chen *et al*[1] also pointed out that COVID-19 may be associated with a relevant cardiovascular involvement, including myocardial injury, arrhythmias, acute coronary syndrome and thromboembolism.[20] Although we focused our interest on the differences concerning radiological findings and some laboratory biomarkers,[2] this is a relevant point, which should be addressed in the future. In any case, there are some important features differentiating the specific cardiovascular involvement in COVID-19 from what has been observed in MAS. In fact, during COVID-19, after having directly been infected by SARS-COV-2, the endothelial cells could attract proinflammatory cells, which lead to an endotheliitis and drive endothelial cell death.[20] Conversely, the cardiovascular involvement in MAS is usually associated with the multiple organ dysfunction syndrome, the leading cause of death of more severe patients.

In conclusion, despite overlapping clinical features, some differences could be recognised comparing patients with lung involvement either with MAS or severe COVID-19. Additional studies are needed to entirely elucidate these issues, furtherly investigating differences between these diseases, from a clinical as well as a pathogenic point of view.

Piero Ruscitti,[1] Federico Bruno,[1] Onorina Berardicurti ,[1] Chiara Acanfora,[1] Viktoriya Pavlych,[1] Pierpaolo Palumbo,[1] Alessandro Conforti,[1] Francesco Carubbi ,[2] Ilenia Di Cola,[1] Paola Di Benedetto ,[1] Paola Cipriani,[1] Davide Grassi,[3] Carlo Masciocchi,[1] Annamaria Iagnocco,[4] Antonio Barile,[1] Roberto Giacomelli [1]

[1]Department of Clinical Sciences and Applied Biotechnology, University of L'Aquila, L'Aquila, Abruzzo, Italy
[2]Department of Medicine, ASL 1 Avezzano Sulmona L'Aquila, L'Aquila, Abruzzo, Italy
[3]Department of Clinical Medicine Life Health and Environmental Sciences, University of L'Aquila, L'Aquila, Abruzzo, Italy
[4]Dipartimento Scienze Cliniche e Biologiche, Università degli Studi di Torino, Torino, Italy

Correspondence to Dr Roberto Giacomelli, Department of Clinical Sciences and Applied Biotechnology, University of L'Aquila, L'Aquila 67100, Abruzzo, Italy; roberto.giacomelli@cc.univaq.it

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ORCID iDs
Onorina Berardicurti http://orcid.org/0000-0002-2808-1581
Francesco Carubbi http://orcid.org/0000-0003-1958-5136
Paola Di Benedetto http://orcid.org/0000-0003-2927-8703
Roberto Giacomelli http://orcid.org/0000-0003-0670-9638

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