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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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COVID-19, chronic inflammatory respiratory diseases and eosinophils—Observations from reported clinical case series

To the Editor,

Currently, the world is facing a global pandemic with a new coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2) causing infectious disease named COVID-19 (coronavirus infectious disease 2019). Comparing the clinical presentation and epidemiological characteristics of COVID-19 with previous coronavirus-associated respiratory diseases (SARS-CoV1 and MERS) revealed some remarkable findings and differences. Moreover, the clinical course of SARS-CoV-2 infection showed the complexity of COVID-19 profile with the variable clinical presentations.¹ Recently published clinical reports tried to identify possible risk factors resulting in a higher incidence of COVID-19 infection associated with complications and a severe disease. It seems that elderly people and/or immune-compromised individuals are at the highest risk while males showed higher mortality rate.² Other important risk factors include various comorbidities affecting 34.9 to 79.3% of COVID-19 patients.^{3,4} Several authors observed that the severity of its clinical manifestation is associated with certain individual characteristics

of the infected patients. In general, pre-existing chronic respiratory conditions (including bronchial asthma, COPD, bronchiectasis) are reported only in a small proportion of patients.^{3,5-8} This is in contrast with the other respiratory viral infections (eg influenza, rhinovirus), which are typically affecting allergic patients and those with chronic respiratory diseases. In a group of 140 patients from Wuhan (China), comorbidities were noted in 79.3% of severe patients (hypertension in 37.9%; diabetes mellitus in 13.8%; liver diseases in 6.9%; coronary heart diseases in 6.9%; and COPD in 3.4%) and in 53.7% of non-severe patients (hypertension in 24.4%; diabetes mellitus in 11.0%; liver disease in 5.0%; and coronary heart diseases in 3.7%; COPD in 0%).⁴ Other chronic diseases (eg chronic gastritis, arrhythmia and thyroid disease) were observed in less than 5.7% of all the patients. Interestingly, none of the COVID-19 patients in Wuhan, regardless the disease severity, reported bronchial asthma, allergic rhinitis or atopic dermatitis,⁴ while the prevalence of allergic airway diseases in Wuhan is 4.2% (asthma) and 9.7% (allergic rhinitis), respectively [S9,S10].

TABLE 1 Summary of reported changes in immune/inflammatory parameters during COVID-19 infection

Parameter	References
Lymphopenia (in 3-75% of COVID-19 patients)	2,4-6,8,9 [S26,S33,S34]
Eosinopenia (in 52.9-90% of COVID-19 patients)	4,6 [S26,S33,S34]
↓ CD3 ⁺ T cells, CD4 ⁺ T helpers, CD8 ⁺ T cytotoxic cells	8 [S26,S27,S28]
↓ memory T helper and ↑ naïve T helper cells	[S26]
↓ T regulatory cells	[S26]
↑ IL-10 and IL-6	[S26,S27]
↑ IL1β, IL1RA, IL7, IL8, IL9, IL10, FGF, GCSF, GM-CSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, VEGF	2

This lack of susceptibility to COVID-19 in patients with pre-existing asthma and allergic airway disease appears in contrast with the established link between these chronic respiratory conditions and susceptibility to common respiratory viruses, especially rhinoviruses [S11,S12]. However, rhinovirus uses the ICAM-1 molecule as an entrance into respiratory epithelial cells [S13], which is overexpressed in allergic airways as a marker of allergic inflammation [S14]. In contrast, COVID-19 uses another host cell receptor abundantly present in the oral mucosa and within the (healthy) airways, that is the angiotensin-converting enzyme2 (ACE2) [S15,S16], which plays a crucial role in the disease development and associated lung injury [S17,S18]. ACE2 is a homologue of angiotensin-converting enzyme (ACE). ACE activity and certain gene polymorphisms are positively correlated with clinical manifestations of asthma or COPD. As compared with those on maintenance therapy with inhaled corticosteroids (ICS), lower expression of ACE has been found within the airways of

asthmatic patients not treated with ICS. Moreover, low ACE expression within the bronchial epithelium was inversely associated with eosinophilic infiltration within asthmatic airways [S19]. Previous data showed that the homeostasis between ACE and ACE2 is crucial for lung damage and ACE2 probably could represent a protective factor under certain conditions [S20]. Hence, ACE2 probably has a double effect on SARS-induced lung injury: initially, it serves as a receptor for invading coronavirus, while its subsequent down-regulation promotes lung injury [S18]. Expression of ACE2 is increased in patients with type 1 and type 2 diabetes mellitus and patients with hypertension treated with ACE inhibitors (ACEi)—that is ACE2-stimulating drugs. This could explain the increased risk of COVID-19 in patients with diabetes or hypertension reported in some publications,⁴ [S21]. On the other hand, recently published reports suggested also possible protective role of the inhibitors of renin-angiotensin system [S22]. In a recent trial, these agents increased CD3⁺ and CD8⁺ T cell counts and decreased the peak viral load compared to other antihypertensive drugs in patients with hypertension and COVID-19 [S23]. Currently, the theoretically increased risk for COVID-19 in patients treated with ACEi was not proven by clinical studies and is based only on a hypothesis. Therefore, professional societies strongly recommend to continue the treatment of ACEi.

Another remarkable finding is the high proportion of COVID-19 patients (in general but especially in the severe cases) with leukopenia and lymphopenia (including eosinopenia)^{2,4,6} [S26,S33,S34]. Guan et al found leukopenia ($<1.5 \times 10^9/L$) in 83.2% patients on admission.⁵ Patients with severe COVID-19 disease had more prominent laboratory abnormalities including lymphopenia and leukopenia compared to those with nonsevere disease.⁵ The proportion of leukopenic patients varied across studies from 3% to 83.2%, but usually was found in more than 50% of patients [S34]. The number of T cells was significantly decreased, especially T helper (Th) cells in severe patients [S26]. Another group also reported decreased CD8⁺ and CD4⁺ T cells in COVID-19 patients with pneumonia [S27], while low numbers of

TABLE 2 Summary results of eosinopenia in the reported trials (based on the availability of the data in the publications)

References	Normal reference range [$\times 10^9/L$]	Eosinophils [$\times 10^9/L$]			<i>P</i> ^a
		All	Nonsevere patients	Severe patients	
4	0.02-0.52 $\times 10^9/L$	0.01 (0.0-0.05)	0.02 (0.008-0.05)	0.01 (0.0-0.06)	.451
	Proportion of patients	73/138 (52.9%)	39/82 (47.6)	34/56 (60.7%)	.165
6	0.02-0.52 $\times 10^9/L$	0.01 (0.01-0.01)	—	—	—
	Proportion of patients	7/10 (70%)	—	—	—
[S26]	0.02-0.52 $\times 10^9/L$	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	<.001
	0.4-8.0%	0.0 (0.0-0.4)	0.2 (0.0-0.7)	0.0 (0.0-0.2)	<.001
[S33]	0.02-0.52 $\times 10^9/L$	Eosinopenia in 9/10 (90%)	—	—	—
[S34]	0.02-0.52 $\times 10^9/L$	0.013 $\pm$ 0.025 ^b	—	0.013 $\pm$ 0.025	—
	Proportion of patients	69/85 (81.2%)	—	69/85 (81.2%)	—

^aComparison between severe and nonsevere cases.^bSeries of 85 fatal cases of COVID-19.

CD4⁺ T lymphocytes were associated with prolonged detection of viral RNA in patients' stool [S28]. CD4⁺ Th cells are more important in the control of COVID-19 than CD8⁺ T cytotoxic lymphocytes [S29]. The major changes in immune system parameters observed during COVID-19 infection so far are summarized in Table 1.

Considering the antiviral effects of eosinophils [S30-S32], the reported eosinopenia in COVID-19 patients is of special interest. So far, at least five studies reported on blood eosinopenia in a majority of the COVID-19 patients,^{4,6} [S26,S33,S34]: that is 52.9% (73/138),⁴ 70% (7/10),⁶ 90% (9/10) [S33] and 81.2% (69/85) [S34], respectively (Table 2), while no data on this topic have been presented by other available literature. In the study of Zhang et al (2020), blood eosinopenia was observed in more than half of the patients, both in severe and less severe cases.⁴ Normalization of the eosinophil number signalled the improvement of the clinical status in another case series [S33]. Conversely, in a series of 85 fatal COVID-19 cases, a substantial number of the patients showed profound and persistent eosinopenia [S34]. As suggested by the authors, decreased blood eosinophil counts may serve as a potential indicator of COVID-19 infection and may have an important diagnostic value, especially in patients with respiratory symptoms and radiological changes such as ground-glass opacities in the lung bilaterally [S4]. In the context of recent evidence of antiviral effects of eosinophils, the observed eosinopenia could be either the sign of host exhaustion due to clearance of invaded COVID-19 or the primary risk factor for severe and invasive infection with this virus. On the other hand, among the cytokine profile pattern associated with COVID-19 (especially severe cases), classic eosinophil-driving cytokines are missing (eg IL-5) [S2]. Whether the eosinopenia is the consequence of Th1/Th2 imbalance or induces it remains unclear. However, increased production of TNF- α shifts the spectrum of cytokines produced by eosinophils towards Th1 response (eg antiviral IFN- γ) with the lack of classical Th2 cytokines [S35]. It could be speculated that this could be one of the reasons of low incidence of asthmatics among COVID-19-infected patients. Moreover, the reported Th17 inflammatory signature in severe COVID-19 patients [S36] could be the result of the lack of the suppressing effect of the missing or dysfunctional eosinophils [S37].

Based on the current evidence and clinical observations, it could be suggested that allergic airway disease associated with eosinophilic infiltration and down-regulation of ACE2 does not represent a risk factor for COVID-19 infection. Further investigations are highly needed to confirm mechanisms underlying the low prevalence of allergies and chronic inflammatory/respiratory diseases in COVID-19 patients and to clarify the clinical meaning and therapeutic consequences of eosinopenia in these patients.

KEYWORDS

asthma, biomarkers, eosinophils, inflammation, virus

CONFLICTS OF INTEREST

MJ received honoraria, consultancy and speaker fees from ALK, Stallergenes-Greer, MSD, Sanofi-Genzyme, Sanofi-Pasteur,

Angelini, GSK, Novartis, Nutricia, Nestle, Mundipharma, Berlin-Chemie, CSL Behring and Hero. PB declared no conflict of interests. ZD acts as Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies and received honoraria, consultancy and speaker fees from Acucort, AstraZeneca, ALK, Aquilon, Boehringer Ingelheim, CSL, HAL Allergy, MSD and Sanofi-Genzyme.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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SARS-CoV-2 immunogenicity at the crossroads

To the Editor,

The outbreak of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a global health emergency and became a worldwide pandemic. We summarize the recent findings with respect to the function, structure, and immunogenicity of the spike (S) protein, arising mutations, and implications on vaccine development and therapeutics.

The novel coronavirus can cause pneumonia leading to severe respiratory failure driven by immune dysregulation.¹ SARS-CoV-2 belongs to the Betacoronavirus genus and is closely related to SARS-CoV, which had caused a previous outbreak in 2002-2003.

Cell entry of coronaviruses requires the concerted action of receptor binding and proteolytic processing of the trimeric surface spike glycoprotein. S protein priming is mediated by cellular proteases into S1 and S2 subunits, harboring the receptor-binding domain (RBD) and the fusion machinery, respectively. Upon receptor binding, conformational changes lead to exposure of a second cleavage site (S2') allowing fusion of viral and cell membrane. SARS-CoV-2 employs the cellular protease TMPRSS2 for S protein priming like SARS-CoV.² Strikingly, SARS-CoV-2 S possesses a polybasic furin cleavage site at the boundary of S1/S2 in contrast to SARS-CoV S that harbors only a monobasic site² (Figure 1). This suggests that ubiquitously expressed furin-like proteases might contribute in addition to TMPRSS2 to cell entry leading to an expanded tissue tropism

or even altered pathogenicity of the novel SARS-CoV-2 relative to SARS-CoV.

Both SARS-CoV-2 and SARS-CoV use angiotensin-converting enzyme 2 (ACE2) as their host entry receptor.^{2,3} Several recent publications resolved the structural basis of the interactions between ACE2 and the RBD of SARS-CoV-2, located in the C-terminal portion of S1 (CTD).^{3,4} Interestingly, most reports indicate that SARS-CoV-2 S binds to human ACE2 with higher affinity than the SARS-CoV S protein,^{3,4} which may impact viral infectivity for SARS-CoV-2.

Based on studies on SARS-CoV and the Middle Eastern respiratory syndrome coronavirus (MERS-CoV), the S protein is the main target for neutralizing antibodies and an ideal candidate target for vaccination studies (Table 1). Interestingly, S-reactive CD4 + T cells have been reported in more than 80% of COVID-19 patients, targeting both N- and C-terminal epitopes of S.⁵ Strikingly, CD4 + T cells in 34% of seronegative healthy donors did react, but only to the C-terminal part of S containing the S2 subunit but not the RBD.⁵ This suggests a potential preexisting cross-reactive cellular immunity to SARS-CoV-2 directed to S2. Although the S proteins of SARS-CoV-2 and SARS-CoV share a high degree of sequence similarity and use the same receptor, they seem not to share cross-reactive neutralizing epitopes within S1 or the RBD. Monoclonal and polyclonal antibodies targeting the S1 or RBD of SARS-CoV did not recognize SARS-CoV-2 or poorly neutralized SARS-CoV-2 entry.^{3,4} In line with this observation, Ju et al reported on RBD-specific monoclonal

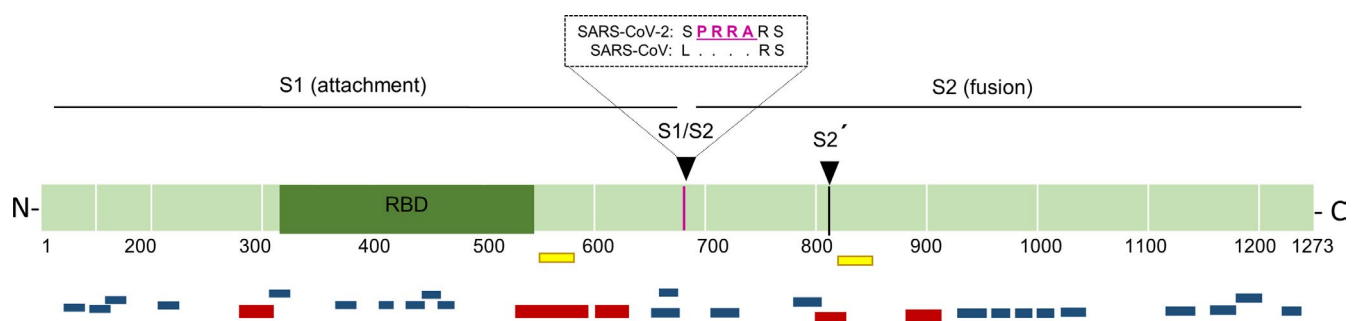


FIGURE 1 Schematic of SARS-CoV and SARS-CoV-2 spike protein. Coronavirus spike protein harbors the S1 and S2 subunits, which are cleaved at the S1/S2 boundary and the S2' cleavage site, as indicated by arrows. SARS-CoV-2 spike protein harbors a polybasic furin cleavage sequence (PRRAR) with an insertion of four amino acid residues distinct from SARS-CoV and other SARS-like viruses. The receptor-binding domain (RBD) is indicated in dark green. Predicted dominant B- and T-cell epitope regions are indicated as red and blue bars, respectively, adapted from Grifoni et al.⁷ The two immunodominant B-cell linear epitopes identified by Poh et al are indicated as yellow bars⁸

Online supplementary material:

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