Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Very low reporting rate of connective tissue diseases among coronavirus disease 2019 (Covid-19) patients and the renin-angiotensin system – An overlooked association?

Severe cases of Covid-19 are strongly associated with pre-existing comorbidities, specifically cardiovascular disease (CVD), diabetes, obesity and hypertension [1]. These conditions are commonly found in elderly persons and in those with connective tissue diseases (CTDs) at higher frequency than the general population.

We interrogated PubMed, Embase and Medline databases for reports of CTDs at 12th April 2020 among published studies on Covid-19. Surprisingly, only five confirmed cases of Covid-19 in CTDs patients have been recorded so far [2,3]. This is remarkable, considering that the estimated prevalence of CTDs is 4•5% in the United States [4], and infections are important risk factors for both hospitalization and mortality in active CTDs [5].

Several reasons could justify the very low reporting rate of CTDs among severe Covid-19 cases. First, CTDs are mostly found in women, and female sex is associated with less severe Covid-19 [6]; secondly, there is paucity of data of patients with less severe disease who do not require hospital admission; thirdly, the diagnosis of CTDs may have been under-reported; fourthly, hydroxychloroquine, an antimalaric drug with some in-vitro efficacy against SARS-CoV, is commonly used for CTDs treatment, though reports concerning its preventive effects of Covid-19 are contrasting [7]; and last, many CTDs patients may be less exposed to contagion because of social retirement. Nevertheless, we believe there are also mechanistic reasons about patients with CTDs might get less critically severe Covid-19.

The key event in the infection of SARS-CoV-2 is the invasion of human tissues through the angiotensin-converting enzyme 2 (ACE2) receptor expressed on the surface of alveolar epithelial cells and other target cells (e.g. intestinal tract, kidney or myocardium) [8]. In physiological conditions, ACE2 is a critical system for endothelial homeostasis, as a counter-regulatory mechanism opposing the action of angiotensin II. ACE2 cleaves angiotensin II to form 2 smaller peptides, angiotensin 1-7 and angiotensin 1-9 (which is also formed by cleavage of angiotensin I) Angiotensin 1-7 binds a specific Mas receptor and has vasodilator and anti-proliferative effects, Angiotensin 1-9 has the same activity, but through binding on the AT2 receptor, the counter-regulatory receptor of the renin-angiotensin system [8]. CTDs patients with clinically evident endothelial dysfunction expressed significantly higher amounts of ACE2 than controls, but exhibited reduced ACE2 activity due to circulating autoantibodies attenuating enzyme activity *in vitro* [9].

SARS-CoV2-infected or recombinant SARS-spike protein-treated wild-type mice exhibited significantly reduced ACE2 expression and function in the lungs. These mice showed increased severity of pathological conditions in acute lung injury [8]. Therefore, downregulation of ACE2 function in SARS-CoV2 infection could lead to toxic angiotensin II over-accumulation and local renin-angiotensin system (RAAS) unrestricted activation, which may play a causal role in the progression of Covid-19 from the viral invasion to the stage of hyper inflammation characterizing the advanced phase up to acute respiratory distress syndrome (ARDS) or fulminant myocarditis.

Noteworthy, endothelial dysfunction can be reversed by effective immune-modulating treatment against the disease [10], and ACE2 activity can be restored after intense immune-suppression in patients with CTDs [9]. The possibility has been raised that ACE2 down-regulation induced by viral invasion may be particularly detrimental in individuals with baseline ACE2 deficiency [11]. These data suggest that an increased expression of ACE2 receptors in CTD patients could in some way protect from inflammatory complications of Covid-19.

Interestingly, the administration of ACE2 appeared to ameliorate lung damage by influenza infection in mice [12], and safely reduced angiotensin II levels in human ARDS [13]. Recombinant ACE2 is being tested in patients with SARS-CoV-2 as well [14,15].

All these observations together suggest that restoration of the ACE2 system downregulated by SARS-CoV-2 has a strong potential to mitigate the effects of RAAS hyper-activation.

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Authors' contributions

A.G.: provided the conception of the study, literature search, and interpretation of data, drafting the article, revised it critically for important intellectual content, and final approval of the version to be submitted; G.D.S: provided interpretation of data, drafting the article, revised it critically for important intellectual content, and final approval of the version to be submitted; G.C., M.R, O.V.: provided the revised the article critically for important intellectual content and gave final approval of the version to be submitted.

Declaration of Competing Interest

All authors have no conflict of interest to report.

Patient and public involvement statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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