Review of: "Role of Nicotine in RAS and Fibrosis Linked to Severe COVID-19 Manifestations"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

Sir,

this referee read with interest the paper in object, but did not find reasons to appreciate it very much. Moreover, the English language employed in the paper is often very poor.

Strictly speaking, the title of the paper promises some opinionated statements, at present never provided definitely in literature, about the (otherwise expected) aggravating effects of cigarette smoking on the clinical course of Covid-19. This promise goes completely unfulfilled in the paper by Xiaoli et al.

Actually, the paper remarkably lists well known reasons not to smoke, and describes a plethora of mechanisms through which nicotine exerts its damage on heart, lung, CNS and systemic circulation, something already stated and repeatedly read. But when it comes to discussing the interactions between smoking (or, at least, nicotine effects) and SARS-CoV-2 infection, the paper does not go beyond the statement that nicotine stimulates cell expression of ACE (and therefore Ang II synthesis) and reduces cell expression of ACE2 (and therefore Ang1-7 synthesis). No news here. So much so that this paper might better be titled ‘Reappraisal of the bad effects of nicotine on body function’, or some such, rather than ‘Role of nicotine in RAS and fibrosis linked to severe Covid-19 manifestations’.

As a matter of fact, the topic presumably dealt with by the authors is, indeed, rather tough because it leads to the central clinical conundrum of Covid-19: for instance, ACE inhibitors and angiotensin receptor blockers may generally improve outcomes in patients with ARDS through reduced Ang II content or function, but both classes of drugs potentially increase susceptibility to SARS-CoV-2 infection and viral spread through cellular upregulation of ACE2; conversely, nicotine increases ACE expression (and therefore organ and vessel damage by Ang II) but reduces expression of ACE2 (the cell membrane receptor of SARS-CoV-2) and therefore might reduce cellular infection or spread of this coronavirus.

Here are some examples of the lack of certainties displayed in literature about the topic of nicotine and Covid-19: A) ever since 2015 it has been known that chronic smoking reduces ACE2 protein expression, and therefore susceptibility to coronavirus infection in the airways (J Renin-Angiotensin-Aldosterone Syst 2015; 16: 249-53); B) compared with never smokers, current smokers appear to be at reduced risk of SARS-CoV-2 infection while former smokers appear to be at increased risk of hospitalisation, increased disease severity and mortality from COVID-19 (Addiction 2020 Oct 2 :

10.1111/add.15276. doi: 10.1111/add.15276); C) for COVID-19, one review did not report on smoking as a risk factor for infection, but did report an increased risk of severe disease and need for mechanical ventilation or death for current smokers. Another meta-analysis did not find an association between current smoking and disease severity (Lancet Respir Med. 2020 Jul; 8(7): 664–665); D) higher number of cigarettes smoked per day was associated with higher risks of all outcomes (infection OR 2.51, 95% CI 1.20 to 5.24; hospitalisation OR 5.08, 95% CI 2.04 to 12.66; and death OR 10.02, 95% CI 2.53 to 39.72) (Thorax 2022 Jan;77(1):65-73).
Of course, the paper by Xiaoli et al. cannot contribute to clarity in the area of research it seems to address.

When all is said and done, the world should aim to be tobacco free, but given the intricate web of finance, taxes, jobs, lobbying, and payments made to officials, this is unlikely to happen in the near future. However, the battle against tobacco use should continue: avoiding COVID-19 now, but having lung cancer or COPD later on, is not a desired outcome.