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Letter to the Editor

Active smoking and severity of coronavirus disease 2019 (COVID-19): Differences in measurement of variables could cause errors in the results



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In this letter to the editor, we would like to address some main points presented in the manuscript by Lippi G, and Henry BM. [1] regarding smoking as a risk factor for SARS-CoV-2. Even though the author suggested that ACE2 receptors are diminished in severe acute respiratory syndrome patients (SARS-CoV-1), this does not seem to apply to SARS-CoV-2 patients. Actual studies reporting the molecular characteristics of the lungs of smokers indicate that ACE2 receptors seem to be upregulated in both current and former smokers with SARS-CoV-2. This data gathered from both Asian and European patients also suggests otherwise, and supports that since ACE2 receptors promote viral entry into epithelial lung cells via a spike glycoprotein, and smokers show an upregulation of this receptor into the lung tissue, smoking could therefore be increasing the risk of infection in this population [2,3]. About disease progression, it has been proposed that smoking combined with ACE2 deficiency promotes lung injury through inflammation and vascular permeability, which clearly is not compatible with the author's ideas [4].

It is important to highlight that, in the elaboration of the meta-analysis some limitations of the included articles were ignored. The authors of the meta-analysis, to identify the role of active smoking as a predictor of progress to severe disease in COVID-19, did not mention the following limitations (See Table 1): **A.** In a publication by Guan W et al, 2020 [5], current smokers were found 29 / 137 (21.17%), ex-smokers 9/21 (42.86%), and never smokers 134/927 (14.46%). These authors mention the recall bias by the participants and the generation of the data was not systematic, in such a way that the questions were not standardized for the collection of information. Furthermore, data extraction was affected by the variability of the included databases. **B.** In the study by Huang C et al, 2020 [6], of the total of 41 patients evaluated, only 3 were current smokers, and the authors specified that it is difficult to assess the host's risk factors for the severity and mortality of the disease. However, it is mentioned that standardizing data collection with a larger cohort would help to redefine natural history and risk factors more and better. **C.** Liu et al, in 2020 [7], found that among the factors that led to the progression of pneumonia was smoking history 3/5 (27.3%) compared to 2/5 (3.0%) in those who did not have a smoking history with a statistically significant value of

$P = 0.018$. However, the measured variable was smoking history, current non-smoker, this measure being dichotomous, yes or no. **D.** Yang X et al, 2020 [8], meanwhile, measured the variable smoking in a study population of 52 critically ill participants, with only 2 current smokers participating, and the response variable was survivor or non-survivor, which is a different progression of the disease assessed in other studies. **E.** In the study by Zhang JJ et al, 2020 [9], the limitation with current smokers is mentioned, being 2/140 (1.4%) current smokers and 7/140 (5.0%) ex-smokers. The 2 current smokers had severe disease.

We agree with the information provided in the letter to the editor prepared by Loe E, Lasnier B and Benoit L [10] where the high variability in the meta-analysis of Lippi et al (1) is highlighted, this being reflected in the wide intervals of confidence, preventing the ruling out of a clinical association. Authors indicate that a more appropriate conclusion for this study is that, due to lack of sample size, the effect of smoking on COVID-19 severity remains highly possible.

Non-significant P values in the evaluated studies and the results of the meta-analysis do not necessarily rule out the association between the use of tobacco products and COVID-19 severity. Moreover, pooled OR analysis shows potential bias since the risk factor assessed within the individual data is categorized using different criteria. These results motivate us to analyze the different studies considering the limited number of current smokers in each study, the discrepancies in which the main variable "current smoker" was measured (See Table 1) and multivariable analysis to estimate the effect of smoking exposure. Furthermore, the response variables were not the same in the different studies, since some assessed disease severity and others survival. Another restraint not mentioned in the articles included, is the frequency of tobacco use and the time being a current smoker, as an important indicator used to predict disease severity, since an occasional user is not to be compared to a frequent user with a history 20 years of tobacco use in terms of morphological and pathophysiological modifications.

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Table 1
Smoking history variable for each study.

Study	Sample size	Smoking history variable	Outcome	Potential bias
Guan W et al (2020) [5]	1099	Never smoker Former smoker Current smoker	Smoking history vs Disease Severity* NS (n=913); S (n=172) Never smoker (n=927) NS (86.9%) vs S (77.9%) Former smoker (n=21) NS (1.3%) vs S (5.2%) Current smoker (n=137) NS (11.8%) vs S (16.9%)	Many patients remained hospitalized; hence data cutoff might leave out some relevant changes on clinical outcomes. Criteria for smoking history classification was not display.
Huan C et al (2020) [6]	41	Current smoking	Smoking history vs ICU care* NIC (n=28); IC (n=13) Current smoking (n=3) NIC (11%) vs IC (0%)	Former smokers were not measure.
Liu W et al (2020) [7]	78	History of smoking (Yes or No)	Smoking history vs Patient clinical course* ISG (n=67); PG* (n=11) History of smoking (Yes) (n=5) ISG (3.0%) vs PG (27.3%) *OR = 12.19; p = 0.011	Smoking history does not differentiate between former and current smokers.
Yang X et al (2020) [8]	52	Smoking (Yes or no)	Smoking history vs Survivors (n=20) or Non-Survivors (n=32) Survivors with smoking history 2 (10%). Non-survivors with smoking history (0%).	Category 'smoking' does not specify whether it refers to former, current smoking, or both. Disease severity status of 'survivors' is not stated.
Zhan JJ et al (2020) [9]	140	Past smokers Current smokers Smoking Index* < 400 ≥ 400	Smoking history vs Disease Severity* NS (n=82); S (n=58) Past smokers (n=7) NS (3.7%) vs S (6.9%) Current smokers (n=2) NS (0%) vs S (3.4%) Smoking Index < 400 (n=3) NS (1.3%) vs S (3.4%) Smoking Index ≥ 400 (n=6) NS (2.4%) vs S (6.9%)	-

*Disease Severity = Nonsevere (NS); Severe (S). *ICU care = No ICU care (NIC); ICU care (IC). *Patient clinical course = Improvement/stabilization group (ISP); Progression group (PG) includes two cases of death. *Odds Ratio of Yes vs No history of smoking was calculated. *Smoking index = Cigarettes smoked per day multiply by year of smoking.

Declaration of Competing Interests

The authors declare they have no conflict of interest.

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