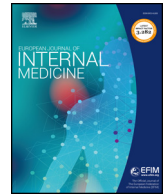




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## Commentary

## No double-edged sword and no doubt about the relation between smoking and COVID-19 severity

Silvano Gallus<sup>a,\*</sup>, Alessandra Lugo<sup>a</sup>, Giuseppe Gorini<sup>b</sup><sup>a</sup> Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Mario Negri 2, 20156 Milan, Italy<sup>b</sup> Oncologic network, prevention and research Institute (ISPRO), Florence, Italy

At the beginning of March 2020, with the publication of the first Chinese epidemiological studies on the determinants of a severe form of COVID-19, tobacco smoking consistently appeared as one of the most important avoidable risk factors for a poorer prognosis [1,2]. COVID-19 was going to be added to the long list of diseases caused by smoking and was becoming the latest key argument to recommend avoiding tobacco use and quitting smoking [1,3,4]. However, Lippi and Henry [5] published in the European Journal of Internal Medicine a meta-analysis with an unequivocal title: “Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19)”. In this meta-analysis, based on five Chinese studies, the authors reported a pooled odds ratio (OR) for COVID-19 progression of 1.69 (95% confidence interval, CI, 0.41-6.92) for smokers versus non-smokers. This study enjoyed widespread visibility in the scientific literature, as well as the lay press and various online social networks. It has been cited, posted or tweeted, particularly by researchers or subjects financially supported by the tobacco industry.

On 30 April 2020, Guo [6] published a commentary on Tobacco Induced Diseases, showing that the meta-analysis by Lippi and Henry [5] contained several mistakes in data collection. Guo did a meta-analysis using correct figures from the same five studies and obtained an OR of 2.20 (95% CI, 1.31-3.67).

We double-checked the two meta-analyses and agree with all the criticism raised by Guo [6]. We feel justified in drawing attention to a number of mistakes and debatable choices made by Lippi and Henry in their review [5], which were only partially addressed by Guo [6]. With reference to the study by Guan and colleagues [7], Lippi and Henry's meta-analysis considered the OR for severity at admission, but, as shown in Table 1, they misreported that they had considered the OR for a composite outcome, i.e. requiring intensive care unit (ICU) admission or mechanical ventilation, or death (mistake 1). The decision to consider the OR for severity at admission (OR: 1.51; 95% CI 0.97-2.36) instead of for the composite outcome (OR: 2.60; 95% CI 1.45-4.66) is highly debatable (debatable choice 1), since the composite outcome, not surprisingly defined as the primary endpoint by Guan and colleagues [7], seems a more reliable and objective measure of the progression of the disease.

Then too, Lippi and Henry [5] considered the OR for current smokers versus non-smokers (former and never smokers combined; debatable choice 2). However - at least when the information is available - it is preferable to compare the risk of ever (current and former smokers) versus never smokers (from information provided by Guan et al. [7] one can estimate an OR of 1.87; 95% CI 1.25-2.82) or current versus never smokers (OR: 1.59; 95% CI, 1.01-2.49). In fact, given that a large proportion of ex-smokers quit smoking because of smoking-related conditions [8], the inclusion of ex-smokers in the reference category would bias any possible effect of current smokers.

For the same reason, the inclusion in the meta-analysis of the study by Huang and colleagues [9], providing estimates for current versus non-smokers, is debatable too (debatable choice 3). For this study the correct number of non-severe patients is 28 (not 31; mistake 2) and the corresponding OR is 0.27 (95% CI, 0.01-5.62), not 0.30 (95% CI, 0.01-6.26; mistake 3) [9]. The choice of univariate estimate for Liu and colleagues' study [10] (OR: 12.19; 95% CI, 1.76-84.31) instead of multivariate estimate (OR: 14.29; 95% CI, 1.58-25.00) is also debatable (debatable choice 4). It is not by chance, in fact, that the multivariate result was reported by Liu and colleagues in the Abstract [10]. The study by Yang and colleagues [11] gives the number of non-severe patients (i.e. survivors) as 20, not 18 (mistake 4). More importantly, the correct OR - also reported by Guo [6] - is 0.11 (95% CI, 0.01-2.50) not 3.03 (95% CI, 0.14-68.71; mistake 5). Finally, in the study by Zhang and colleagues [12], the number of severe patients is 58 not 60 (mistake 6). Thus, the corresponding OR is 7.30 (95% CI, 0.34-154.96) not 7.05 (95% CI, 0.33-149.60; mistake 7).

The worrying number of mistakes and debatable choices in the Lippi and Henry paper [5] is not the only problem. The main concern is their use of a non-standard method to compute meta-analytic figures [13,14]. As well explained also in a rebuttal letter by Lo and Lasnier [14], the model Lippi and Henry used [5] has fundamental flaws which result in incorrect uncertainty intervals. We re-analyzed the same (incorrect) ORs used in their meta-analysis [5] but with standard procedures in R (*metagen* package) and found the same fixed-effects point estimate for the OR. However, we found a slimmer 95% CI, giving a significant figure (OR: 1.69; 95% CI, 1.11-2.58). Also excluding the

\* Corresponding author.

E-mail address: [silvano.gallus@marionegri.it](mailto:silvano.gallus@marionegri.it) (S. Gallus).

study by Guan and colleagues [7] from the meta-analysis, we still found a significant pooled estimate (OR: 4.59; 95% CI, 1.23-17.15). Accordingly, Carmona-Bayonas [15] used a Bayesian random-effects model to find a 95% posterior probability of the disease following a worse course in a smoker compared to a non-smoker.

Moreover, the comments of other researchers on the Lippi and Henry meta-analysis [5], including the warning to be cautious, taking published data as only preliminary [16] and recommending a correct interpretation of pooled estimates from studies with potential limitations [17], are common sense. However, in this case they are superfluous since they rely on properly conducted meta-analyses.

Lippi and colleagues replied to the comments by Garufi and colleagues [16], with a letter to the editor entitled “Active smoking and COVID-19: a double-edged sword” [18]. The letter reported the results from two additional studies [19,20], apparently in favor of the hypothesis that there was no relation between smoking and COVID-19 progression. However, Lippi and colleagues overlooked some other findings from the same studies which contrast with their hypothesis. For instance, from the article by Petrilli et al. [19], Lippi and colleagues reported the crude OR for current versus non-smokers as 0.63 (95% CI, 0.40-1.00), without mentioning that the study found inconclusive results for ever smokers, with a multivariate OR of 0.89 (95% CI, 0.65-1.21) [19]. In addition, Lippi et al. [18] reported that in the Centers for Disease Control and Prevention (CDC) COVID-19 Response Team study [20] the proportion of current smokers among ICU patients was nearly half that among non-ICU patients, the crude OR of ICU for current versus non smokers being 0.51 (95% CI, 0.19-1.36). But again they did not mention that former smokers were 7.2% of ICU patients and 4.4% of non-ICU patients, corresponding to a crude OR of 1.70 (95% CI, 1.07-2.70). More importantly, when considering all the participants in that study (not only hospitalized, but also non-hospitalized patients, who were excluded in Lippi and colleagues’ estimates [18]), the OR for ever versus never smokers from the CDC COVID-19 Response Team study [20] was 2.60 (95% CI, 1.82-3.73) [13].

The latest systematic review, published in pre-print on 23 May 2020, clarified the role of smoking in COVID-19 severity and mortality, summarizing the main findings so far [21]. It examined 22 studies reporting disease severity in hospitalized patients according to smoking status. The meta-analysis included only three fair-quality studies. Current smokers were at higher risk of more severe disease than never smokers (RR: 1.37; 95% CI, 1.07-1.75). There was no significant difference between former and never smokers (RR: 1.51; 95% CI, 0.82-2.80).

Another recent meta-analysis included 19 studies for a total of 11,590 COVID-19 patients [13]. Of these, 30% of ever smokers experienced disease progression, compared with 18% of non-smokers (OR: 1.91, 95% CI, 1.42-2.59). Results were similar for current versus never smokers (OR: 1.91; 95% CI, 1.10-3.29), but based on only five studies [13].

In conclusion, the meta-analysis by Lippi and Henry [5] suffers from a surprising number of errors, resulting in misleading conclusions. It is the only review so far indicating no relation between smoking and COVID-19 severity. There are now at least 17 further studies in subsequent meta-analyses [13,21] that provide definite evidence of a direct relationship between tobacco smoking and COVID-19 severity and progression.

Given the self-declared lack of competing interest of these authors, we are confident that the paper is the result of an unfortunate series of honest errors, with no intentional misconduct. The authors, not experts in tobacco control, were probably not aware of the serious, far-reaching potential consequences of their erroneous results, statements and conclusions. In fact, they were – and are still – giving the tobacco industry and its advocates a chance to raise doubts about the evidence that smoking worsens COVID-19 progression and prognosis. Unfortunately, this has substantially reduced the efficacy of the tobacco control community’s claims to support smoking cessation in the COVID-19 era.

## Declaration of Competing Interest

None to declare.

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