Association between Smoking and Progression to Severe Disease in COVID-19 Patients

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Associação entre Fumar e Progressão para Complicações Respiratórias Graves em Pacientes com Covid-19

Asociación entre Tabaquismo y Progresión a Enfermedad Grave en Pacientes con Covid-19

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INTRODUCTION

Smoking is considered a severe public health problem[1] and one of its complications is the reduction of the individual respiratory capacity. In addition, smoking increases the risk of bacterial and viral infections such as invasive pneumococcal pulmonary disease, influenza and tuberculosis. Still, smoking is the main risk factor associated to the development of chronic obstructive pulmonary disease (COPD), responsible, in Brazil, for 88% of the deaths by COPD among males and 81% of deaths among females[2]. Smoking behavior is also associated to other non-communicable diseases (NCD) such as cardiopathies, diabetes, arterial hypertension and cancer[1].

These comorbidities are important risk factors for complications and death by coronavirus 2019 (COVID-19). This text attempts to present a critical summary of the available data and published in indexed journals about the association between smoking and evolution of COVID-19-related respiratory complications.

DEVELOPMENT

All the studies published so far (April 3, 2020) come from China, where the epidemics started first.

A literature review conducted in middle March 2020 (March 17, 2020) found five relevant articles[3]. Three of the five papers did not show statistically significant differences among smokers and non-smokers in terms of progression of the disease[4-6] and one study, regrettably, failed to report the p value encountered for the statistic comparison among smokers and non-smokers in the progression of the disease[7]. Finally, one study that analyzed 78 patients diagnosed with COVID-19-associated pneumonia and who were hospitalized for two weeks verified that the odd of negative progression of the disease (including death) was nearly 14 times higher among individuals with smoking history in comparison with those who did not smoke[8]. This was the strongest risk factor among all the factors of progression analyzed in this study.

Regardless of one study having failed to show the statistical comparison and three published articles having found statistically inconclusive results, their findings suggest worse diagnosis among smokers (*vs* non-smokers). For example, the study that evaluated 1,099 patients and did not report the p value of statistical comparison, found that smokers had nearly triple the odds of evolving to worse prognosis (including death) when compared to non-smokers[7]. Another study that evaluated the prognostic variables of death among 191 individuals hospitalized with COVID-19 and that did not find statistical association with smoking showed that smokers had two times more odds of dying than non-smokers[6].

In short, despite the reduced number of studies available so far, the systematic review of the literature[3] indicated a probable association between smoking and negative progression of COVID-19-related respiratory complications.

A meta-analysis[9] conducted with articles published until March 9, 2020 and published in the same period of the systematic review mentioned before[3] included an article that was not addressed in this review[10]. In this article, among 53 patients analyzed, there were only two smokers, and both had better evolution of the disease. On the other hand, in the systematic review[3] there is another article published on March 12 presenting a more unfavorable scenario for 11 smokers of a total of 191 patients analyzed[6].

The result of the meta-analysis did not find a statistically significant relation between active smoke and severity of COVID-19. Nevertheless, the most robust study with more than one thousand patients included in this meta-analysis found odds ratio – OR for severity of COVID-19 of 1.51 (0.97 – 2.36)[7] among smokers and

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non-smokers. That is, the lower limit of the measure of association is well close to one and, in addition, the set of most probable values based in the distribution curve clearly indicates a worse scenario for smokers.

More recently, another article published on March 26[11] appeared. Actually, it is the same study referenced previously[7]: "the study that evaluated 1,099 patients and concluded that smokers had nearly triple the odds of evolving to worse prognosis (including death) when compared to non-smokers[7]", with the following complements: 1) 1,599 hospitalized patients *vs* 1,099 hospitalized patients; 2) patients from 575 hospitals in 31 China provinces *vs* patients from 552 hospitals in 30 provinces; 3) the most recent article was basically concerned in analyzing the relation between the presence of comorbidities and evolution for worse outcome and concluded, for example, the independent effect of the presence of COPD, hypertension, diabetes or cancer over the worsening of the diagnosis (necessity of mechanic ventilation, Intensive Care Unit – ICU or death). Moreover, this study evaluated the independent negative effect of the individual presenting at least one comorbidity (or two or more comorbidities) over the evolution of its health condition. Further to the specific analysis already referenced, there is information about cardiovascular, kidney, auto-immune diseases and hepatitis; 4) the most interesting and new was that the authors adjusted all the analyzes by age and smoking status of the patient. That is, despite the authors having addressed the smoking status only as a confounding variable of the main analysis, they also obtained the independent effect of the patient being a smoker or not (i.e., without considering age differences and presence or not of comorbidities among smokers and non-smokers) over the evolution to a more negative outcome (necessity of mechanic ventilation, ICU or death). In other words, it is possible to understand if the smoker will evolve worse not only because, as it is known, it has high frequency of comorbidities than the non-smoker. The results obtained indicate that, considering the different follow up period of the patients, regardless of age, of having or not COPD, diabetes, hypertension or cancer, ever smokers have in average a 67% higher risk of evolving to a worse outcome than non-smokers (hazard ratio - HR 1.67 (1.01-2.76)). In addition, independently of having some comorbidity (one, two or more comorbidities) or not, again, the smoker has in average a risk 73% higher of worse prognosis when compared to non-smokers (hazard ratio - HR 1.73 (1.05-2.87)).

Most of the studies published so far have found high percentage of males among patients with COVID-19, which could suggest also that, as men smoke well more than women in China, tobacco use would also be associated to higher incidence of the disease among smokers[12].

However, the proportion of smokers among the ill is much lower than anticipated for the Chinese population in general. In a recent study, for example, nearly 7% were smokers/ex-smokers, when the expected proportion of smokers would have been of almost 30% (50% in males and 2% in females)[13], if smokers had the same likelihood of getting infected than non-smokers[11]. In other words, based on the data presented/collected, many men who were hospitalized with COVID-19 were non-smokers.

Why are smokers not being infected? Right now, we are unable to answer, since great part of the prognostic factors of the disease evolution could be more or less related with those associated to the predisposition to be infected.

Is it possible that not all the smokers with COVID-19 are being identified? For instance, maybe the smokers, usually much more socioeconomically underprivileged, not even succeed in being hospitalized before getting ill and/or die and fail to be included as hospitalized patients enrolled in studies to be published later ("survival bias").

Or are COVID-19 patients not being classified correctly in relation to their "smoking status" and this is happening more frequently among smokers than with non-smokers (differential misclassification of exposure)?

Or would it be a more behavioral explanation such as, for instance, smokers are more attentive to not exposing themselves to the virus for knowing they will have worse prognosis for evolution of the disease? Or yet that smokers are less frequently in confined places or with great number of persons because they cannot smoke indoors (according to China's Smoke Free Places Law - "*Smoking is completely prohibited in at least 28 indoor public places, including medical facilities, restaurants, bars, and most public transportation. Designated smoking areas are permitted in other specified places, such as long-distance transport. Sub-national jurisdictions have the authority to implement local smoke free policies*")[14]?

Still in relation to the theme of proportion of smokers among infected patients, on March 24, 2020 a meta-analysis with studies published until February 15 (that is, did not use the most recent studies) to estimate the prevalence of diseases (including smoking) among COVID-19 patients[15] was published. Obviously, there was much heterogeneity among the six studies included[4-5,7,11,15], and the result found was of combined prevalence of smoking of 7.63% (3.83-12.43).

The results of the meta-analysis article published on March 24, 2020[15] reinforce the necessity of continuing to study the profile of patients with COVID-19 in other countries to understand to what extent the incidence of this disease would be related not only to the noxious

effects of the compounds present in tobacco by-products (article published on March 20 presenting a biological justification of this association, since smokers present higher expression of ACE2 enzyme, receptor recognized as associated to COVID-19)[16], but also to behavioral issues of the smoker because of different cultural realities and/or different legislative tobacco control scenarios. In order to facilitate this evaluation, it would be fundamental to include the risk/disease factor "smoking" in the list of comorbidities presented in the COVID-19 National Notification Card.

CONCLUSION

Finally, it is worth reinforcing that, since the decade of 1980, Brazil develops innumerous structured actions for tobacco control. However, COVID-19 epidemics and its several impacts to the individual such as increased stress because of uncertainty in relation to the future (including economic recession) and social isolation at home represent a potential challenge for the effective implementation of actions targeted for the prevention of initiation, of relapse among millions of Brazilian ex-smokers, and stimuli to quitting[17].

CONTRIBUTION

The author contributed substantially in all the stages of the manuscript and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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