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Review Article

Smoking is Associated with Higher Mortality and Hospitalization Secondary to Novel Coronavirus: A Systematic Review

Valéria Mata de Duarte Ferreira Ribeiro[1], Gabriel de Souza Quirino[1], Guilherme Gouveia Hollunder[1], Ramon José Moreira Silva[1], Alberto Barceló[2, 3] and Arise Garcia de Siqueira Galil[4]*

[1]*Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil*

[2]*Department of Public Health Science, University of Miami, Florida, USA*

[3]*Medical School, Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil*

[4]*Internship Department–Medical School, Federal University of Juiz de Fora, Juiz de Fora, Brazil*

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ABSTRACT

Aim: The aim of the present study was to assess whether there is an association between smoking and higher mortality and hospitalization due to the disease of the new coronavirus (COVID-19).

Methods: A systematic review of studies on the novel coronavirus containing information on smoking and its association with COVID-19 mortality was carried out. The bibliographic search was performed using six databases, with the search terms: ['novel coronavirus' OR 'COVID- 19'] AND ['smoking' OR 'tobacco'] AND ['mortality']. Studies published from December 2019 until April 8, 2020 were included. As an inclusion criterion, studies targeting humans, adults, infected with Sars-Cov-2 were selected, and as the chosen language, English.

Results: From the total of researched studies, 65 articles were selected, one being presented in two databases simultaneously. As a final result of this review, 11 articles were included, with a population total estimated at 84.050 patients, with the prevalence of smokers ranged from 1.4% to 27.3% and it was observed that the impact of smoking on fatal outcomes was described in four publications, with unfavourable repercussions on hospitalization rates and more serious conditions secondary to COVID-19 (9 out of the 11 publications evaluated).

Conclusion: The presence of smoking can worsen infectious conditions by COVID-19 and increase the prevalence of hospitalizations and fatal outcomes, especially in men, the elderly and those with multimorbidities. Smoking status should be used in the screening of patients infected with the novel coronavirus given the evidence of poorer outcomes among smokers.

Introduction

The novel coronavirus is a pathogen causing an infectious disease (COVID-19) that was detected for the first time in early December 2019 in Wuhan, China [1, 2]. The epidemic rapidly spread throughout China and has been followed by numerous countries around the world causing a global pandemic in a short period of time. On April 6th 2020, the COVID-19 had already spread to the majority of countries around the globe, affecting more than 1.1 million people and causing almost 63.000 deaths. The speed of Sars-Cov-2 dissemination and the number of fatal cases reveals the urgency to explore effective prevention strategies. In addition to clinical conditions, the scientific community was focused on finding best diagnosis means, treatments and the identification of risk factors associated with higher mortality, with the aim to save the highest number of lives possible [1, 2].

Smoking is recognized as one of the most important risk factors for preventable deaths. Smoking is responsible for the development and worsening of some diseases, especially chronic pneumopathies and

Correspondence to: Arise Garcia de Siqueira Galil, Internship Department–Medical School, Universidade Federal de Juiz de Fora, Rio Branco Avenue 2001, 603, Center, Zip Code: 36015510, Juiz de Fora, Minas Gerais, Brazil; E-mail: galilarise@gmail.com; ORCID: 0000-0001-6161-5963

cardiovascular diseases, among others [1-5]. This notorious relationship between tobacco use and the predisposition to respiratory tract infections had been related to an increase in the frequency and the severity of diseases as well as with decreased efficacy of anti-infective therapy [6]. Tobacco use is deemed to result in decreased airway host defences, especially suppressing the protective functions of mucociliary epithelium and alveolar macrophages, leading to chronic systemic activation of neutrophils [6]. In a previous epidemic, secondary to MERS-CoV, tobacco use was associated with higher mortality [7]. Regarding the current pandemic, secondary to SARS-CoV-2 infection, Leug JM *et al.* (2020) claim that active smoking leads to the upregulation of ACE-2 receptors in lower airways, which is the key receptor used by SARS-CoV-2 to invade host mucosa. This suggests that smokers may have an increased risk of novel coronavirus infection and a predisposition to more severe presentations of COVID-19 disease [8, 9]. Pre-existing respiratory diseases, cardiovascular diseases and other comorbidities are recognized risk factors for worse outcomes. The presence of frequent arrhythmias and varied levels of myocardial ischaemia, due to inflammatory cytokine storm seen in the novel coronavirus infection, seems to lead to toxic injury of cardiomyocytes [2, 10].

Tobacco use represents, *per se*, a chronic dependency disorder. This dependency frequently couple with high morbimortality, as result of its unfavourably impact on various domains such as respiratory, cardiovascular and metabolic systems often associated with coexistent chronic conditions [11]. Therefore, because of the gap on this topic, the objective of this study was to carry out a systematic review, looking for articles studying the effect of tobacco smoking on the novel coronavirus morbidity as well as its associated risk of hospitalizations.

Methods

A systematic review was conducted to identify studies regarding the novel coronavirus COVID-19 infection and its associated mortality and its relation to tobacco smoking. The bibliographic research has been made until April 8th, 2020, using the following databases: PubMed, Scopus, Lilacs, VHL Regional Portal Information and Knowledge for Health, Wikipedia and Portal Regional BVS, with the search terms: ['novel coronavirus' OR 'COVID-19'] AND ['smoking' OR 'tobacco'] AND ['mortality']. We included studies published during the period 2019-2020 (due to the appearance of the novel coronavirus dating from December 2019). As inclusion criteria we selected studies that concerned about human beings, adults, infected by Sars-Cov-2, and as chosen language, English. As exclusion criteria, we defined animal studies and studies relating to children and adolescents. With respect to study designs included, due to the current gap in the literature, we selected controlled randomized studies, experimental studies without randomization, observational studies, cohort studies, cross-sectional studies, and case series. Under the nature review study, no approval by the Research Ethics Committee was required.

Results

For the proposed review, the search for articles in Lilacs and Portal Regional BVS database did not show any reference to studies with the descriptors presented. Of the total researched studies list, we selected 65 articles, being one presented in two databases concomitantly. In an initial evaluation, 13 articles were eligible, have undergone a further re-

evaluation on account of the date of publication and two articles being excluded for being dated 2019, but before December. As a final result of this review, 11 articles were included. About half of the studies on the included reference list were from China, and the others were from Italy, Sweden, the United Kingdom, Iran, Australia, and The United States of America, one publication each. In all studies, the population was patients with COVID-19 and the sample size ranged from 41 to a final sample of 84.050 patients evaluated, with the prevalence of smokers ranged from 1.4% to 27.3%. Concerning the study design, it has been analysed four systematic reviews (one with meta-analysis associated) and seven retrospectives studies (five cohort studies and three described as case series), covering the period from December 2019 to April 08th, 2020.

Among the studies evaluated, the review from Vardavas *et al.* (2020), demonstrated consistent data relating smoking with the novel coronavirus and fatal outcomes. The authors evaluated the association between smoking and outcomes in COVID-19 infection, such as hospitalization, severity of the disease, need for mechanical ventilation and intensive care, as well as mortality. They used two databases (PubMed and ScienceDirect), with 77 initial articles, reaching the selection of 5 finals studies, all Chinese, with the inclusion period from December 2019 to January 2020. After analysis of the articles, the authors stated that smokers were 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more prone to be admitted in the intensive care unit, need mechanical ventilation, or evolve to death, compared to non-smokers. Hence, smoking would be associated with negative progression and unfavourable outcomes in COVID-19 [12].

The meta-analysis of Amir *et al.* (2020), with PubMed, Scopus, Web of Science and Google Scholar as databases, and with articles published until February 15, 2020, included hospitalized patients with COVID-19. Ten articles were included, and it was found that systemic arterial hypertension (SAH), cardiovascular diseases, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), neoplasms, chronic renal disease, and smoking (i.e., the presence of comorbidities) were the most prevalent factors among hospitalized COVID-19 patients. The combined prevalence of infection by COVID-19 in hospitalized patients with a history of smoking was estimated at 7.63%, without any publication bias found. Smoking alone did not present an association with higher mortality, different from when it was associated with two or more comorbidities [13]. In the review of Harris *et al.* (2020), the authors cited smoking as a risk factor for death and severe presentations of COVID-19, whereas in the review of Lupia *et al.* (2020), the lack of data on smoking was highlighted [14, 15].

Little attention has been paid to the role of smoking in the transmission of the novel coronavirus, in severe acute respiratory syndrome secondary to the virus (SARS-CoV-2, real virus) or in the mortality rate by COVID-19. In China, with a high rate of male and adult smokers, most deaths secondary to COVID-19 occurred among men, elderly, and with the presence of associated comorbidities [16]. Lupia *et al.* (2020), selected publications from two databases (PubMed and COCHRANE), with COVID-19 descriptors or similar, and observed similar results concerning the characteristics of the patients, referring to gender, age-range and the presence of comorbidities, also similar to the results of Chen *et al.* (2020) [15, 17]. This last study, also Chinese, showed a mortality rate of 11.11%, while 27.3% of these deaths were related to smokers [17]. Shi *et al.* (2020), in a retrospective cohort in the Chinese province, developed a score to assess the susceptibility of those infected

with the coronavirus to present a more severe clinical picture during hospital admission. It was observed that 10.1% of the sample configured as severe cases at admission and no deaths were reported at the end of follow-up. Although the study did not focus on smoking, it was noted that, among the demographic and epidemiological features, tobacco use was seen in 8.2% of the studied population, 12.2% in the high severity population, compared to 7.8% among those of moderate severity (p non-significant value) [18].

Guan *et al.* (2020), evaluated the risk of severe adverse outcomes in patients with COVID-19 stratifying the quantitative status of comorbidities. Among the confirmed cases of COVID-19, patients with any comorbidity presented worse clinical outcomes than those without it. A greater number of comorbidities also correlated with worse clinical outcomes among hospitalized patients confirmed in a laboratory, from provincial hospitals in mainland China, between December 11, 2019, and January 31, 2020. Smoking was included among the studied comorbidities, along with SAH, DM, cancer, COPD [19]. In another observational study, between the end of December 2019 and the end of January 2020, were evaluated patients infected with pneumonia by COVID-19, and of those with severe symptoms (7.32%), 61.5% had fatal outcomes. It was observed that between those considered more

severe, such as the elderly, with comorbidities and severe disease, smoking did not present statistical significance in isolation [20]. Zhang *et al.* (2020) studied hospitalized patients with COVID-19 in Wuhan, China, with clinical, imaging and laboratory confirmation, with data collected from January 16 to February 3, 2020. The most relevant findings were the 1:1 prevalence among men and women, SAH (30.0%) and DM (12.1%), as the most common comorbidities. Patients with COPD (1.4%) and current smokers (1.4%) were scarcely prevalent, and there was a higher prevalence of smokers (3.4%) among those with more severe disease (without statistical significance) [21]. Tao Guo *et al.* (2020) conducted an observational study, also in China, between January 23, 2020, and February 23, 2020. Patients infected by Sars-CoV-2 were included, with 22.99% of fatal outcomes, but reported that the influence of smoking on mortality was not evaluated [1].

Therefore, we observed that the impact of smoking on fatal outcomes was described in four publications and that the presence of smoking had unfavourable repercussions for outcomes of hospitalization rates and more severe conditions secondary to COVID-19 among 9 of the 11 publications evaluated. Table 1 lists the studies evaluated and their main information.

Table 1: Characteristics of the studies included in the analysis.

Publication Date	Authors	Journal	Location	Type of Study	No. participants	Males	Smokers	Mortality
24032020	Emami A; *et al.* [13]	Arch Acad Emerg Med 2020;8(1): e35	Shiraz, Iran	Systematic review and meta-analysis	3403	57,97%	7.63%	&
21022020	Lupia T; *et al.* [15]	Viruses. 2020 Feb; 12(2): 135.	Turin, Italy	Systematic review	76993	56%	2%	&&
2020	Harris C; *et al.* [14]	J Global Health 2002 Jun 10(1):011001	Edinburgh, UK	Systematic review				&&
20032020	Vardavas CI, *et al.* [12]	Tob Induc Dis 2020; 18:20	Boston, USA	Systematic review	1099		&&&	Uninformed
2020	Guan W; *et al.*[19]	Eur Respir J 2020 Mar 26:2000547	Wuhan, China	Retrospective study	1590	59,30%	3,10%	&*
29012020	Chen N; *et al.* [17]	Lancet 2020; 15-21Feb;395(10223):507-513	Wuhan, China	Retrospective study	99	67,67%	11%	58%
27032020	Guo T; *et al.* [1]	J Glob Antimicrob Resist 2020 Mar 7	Wuhan, China	Retrospective study	187	48,66%	10,38%	22,90%
21022020	Yang X; *et al.* [20]	Lancet respir Med 2020; Feb 28; 8(4): e26	Wuhan, China	Retrospective study	52	67,30%	3,84%	32%
2020	Shi Y; *et al.* [18]	Crit Care 2020; 24:108	Hangzhou, China	Retrospective study	487	53,18%	8,21%	61,50%
20032020	Brake SJ; *et al.* [16]	J. Clin. Med. 2020, 9(3), 841	Tasmania, Australia	Retrospective study				&**
18022020	Zhang J; *et al.* [21]	Allergy. 2020 Feb 19	Wuhan, China; Davos, Switzerland	Retrospective study	140	50,70%	1,40%	Uninformed

&: smoking was not directly related to increased mortality, but rather to the occurrence of more severe COVID-20 pictures; &&: It mentions smoking as a risk factor for deaths by COVID-19; &&&: 2.4 times (RR=2.4, 95% CI: 1.43-4.04) more likely to be admitted to the intensive care unit, need mechanical ventilation or die; &*: It refers to the association between the increase in the number of comorbidities and the increase in mortality and hospitalization outcomes by COVID-19; &**: It refers to the association of men, elderly and the presence of comorbidities as unfavourable factors for mortality and hospitalization outcomes by COCID-19.

Discussion

The present systematic review revealed to us that smoking is associated with fatal outcomes and increased hospitalization among patients infected by the novel coronavirus, through a consistent sample, and with high scientific taxonomy reviews, with a longer evaluation compared to the selected publications [12, 13, 15-17].

The novel coronavirus belongs to a family of viruses that cause infections of the human respiratory system. They are viruses enveloped with a positive RNA genome and were named after the crown look of their microscopy in the 1960s. Three human coronaviruses were studied in detail before this current pandemic in 2020. HCoV-229E and HCoV-OC43 were identified as causing the common cold. In 2002, SARS-COV was identified as a causative agent of severe life-threatening pneumonia and had been the most pathogenic human coronavirus identified so far [22]. However, in 2019, in Wuhan, China, a new member of the human coronavirus family was identified as causing an acute respiratory distress syndrome in some patients and due to this was named by the Commission on Taxonomy of Viruses (ICTV) as SARS-CoV-2. Contagious among humans, it is believed that its main form of transmission is through direct human contact with droplets produced in the respiratory system that is contaminated with viruses expelled after coughing or indirect contact through contaminated surfaces [16, 23].

Smoking, in turn, is the most frequent component in coexistence for the population with multimorbidities, a fact that the present review has shown to be an important risk factor for COVID-19 [24]. Carriers of multimorbidities are characterized by a progressive increase following the increase in the age group, greater severity of their coexisting conditions in isolation, increased drug interaction, increased health complications and expenses, worsened quality of life and worse survival [25]. The presence of smoking among patients with multimorbidities has been prevalent and has been associated with worse clinical profiles, compared to non-smokers [26]. In a recent publication about the clinical features of those with COVID-19 in New York, United States of America, it was likewise observed the greater presence of males, the elderly, and those with multimorbidities, highlighting among them, in that country, obesity. Smoking was present but did not have an unfavourable effect on the sample studied [27]. Patwardhan (2020), points out that in the ascending phase of the pandemic, with increased mandatory social isolation, and consequent increase in emotional stress, it is necessary to think with priority on current smokers, due to the risk of increased smoking load and therefore worse outcomes related to COVID-19, as well as on former smokers, given the high risk of relapses [28].

As a limitation of this review, it was noticeable that in selected publications there were frequent references with the term "comorbidities", often including chronic diseases such as SAH, DM, COPD, neoplasms and also smoking. This data has limited the analysis of the disease "smoking" in isolation, in several publications. Another limitation was the short time of evaluation of the great majority of the articles, encompassing approximately 2 months, in most of the evaluations.

In conclusion, the presence of smoking can worsen infectious conditions by COVID-19 and increase the prevalence of hospitalizations and fatal outcomes, especially in men, the elderly and those with multimorbidities. It is reasonable to add smoking status in the screening of patients infected with the novel coronavirus and, in the days of COVID-19, to reinforce interventions for smoking cessation, as well as those for maintaining abstinence among those who have ceased addiction.

Author Contributions

Ribeiro VMDF and Quirino GS, developed the details of the introduction, presentation of results and discussion, in addition to the detailed selection of articles, data collection and analysis. Hollunder GG and Silva RJM were responsible for reading all the selected articles and judging those that were included, with a sequential review by Ribeiro VMDF, Quirino GS and Galil AGS, together with the writing of the discussion. Barceló A was responsible for being the third examiner of the work, with the final choice of the works included, with revision and refining of the manuscript. Galil AGS developed the idea of the study, collaborated in the selection, collection, data analysis and writing of the initial draft of the manuscript, in contribution with the other authors, as well as assuming the role of second examiner, collaborating in the final writing of the work. The authors state that the manuscript is an honest, accurate and transparent account of the study had being reported; that no important aspect of the study was omitted; and that any study discrepancies as planned have been explained. All rights reserved.

Ethical Approval

It was not necessary.

Data Sharing Statement

All data used to prepare this article are available from the sources cited.

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Competing Interests

All authors declare that they have no financial relationships with any organization that may have an interest in the work submitted in the previous three years and no other relationship or activity that may appear to have influenced the work submitted.

Conflicts of Interest

None.

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