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Tobacco smoking and COVID-19 pandemic: old and new issues. A summary of the evidence from the scientific literature

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Summary. *Introduction*: COVID-19 pandemic burst onto the international scene as a new disease disproportionately affecting certain patient groups; hence it has risen many questions yet to be clarified. The aim of this study was to outline the main issues that led tobacco smoking being discussed as a potential risk factor associated with COVID-19. *Methods:* articles from MEDLINE and pre-prints published from January to April 2020 were identified. *Results:* data from China showed that men had more severe outcomes of COVID-19 than women. Since smoking prevalence is very high among Chinese men in comparison to women, it was hypothesized that smoking could be a risk factor for poor prognosis. This was also supported by the higher prevalence of comorbidities, many of which tobacco-related diseases, in patients with severe COVID-19, who were also more likely to have a smoking history. A meta-analysis confirmed these results, reporting an OR=2.25 (95% CI: 1.49-3.39) for developing severe COVID-19 among patients with a smoking history. Some authors, noticing that reported smoking prevalence among hospitalized patients was substantially lower than smoking prevalence in the source populations, speculated a protective role of nicotine. However, it is likely that low prevalence among hospitalized patients are partially due to many smokers misclassified as nonsmokers. Tobacco smoking seems to cause a dose-dependent upregulation of angiotensin-converting-enzyme-2 (ACE2), the virus cellular entry receptor, which could explain the higher risk of severe COVID-19 in smokers. *Conclusions*: There is need for further independent studies to clarify the role of smoking on COVID-19 incidence, progression and mortality. (www.actabiomedica.it)

Key words: COVID-19, tobacco smoking, risk factors, smoking cessation

Acronims

ACE2 – Angiotensin-Converting Enzyme 2
CFR – Case-Fatality Ratio
CI – Confidence Interval
COPD – Chronic Obstructive Pulmonary Disease
COVID-19 – Coronavirus Disease 2019
CVD – Cardiovascular Diseases
DIC – Disseminated Intravascular Coagulation
FEV1 – Forced Expiratory Volume in the 1st second
HCW – Health Care Workers
MERS-CoV – Middle East Respiratory Syndrome coronavirus (2012)
OR – Odds Ratio
PHS – Public Health Scientists
SARS-CoV – Severe Acute Respiratory Syndrome coronavirus (2003)
SARS-CoV-2 – Severe Acute Respiratory Syndrome coronavirus-2 (2019)
RR – Relative Risk

Introduction

COVID-19 pandemic has put the world into a public health emergency of international concern (1) and has raised new questions for Health Care Workers (HCW) and Public Health Scientists (PHS).

COVID-19 (acronym for "coronavirus disease 2019") is a severe acute respiratory syndrome caused by a novel strain of coronavirus (SARS-CoV-2) which has some similarities to the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV, 2003) and to the Middle East respiratory syndrome coronavirus (MERS-CoV, 2012) (2).

COVID-19 can cause null or mild to severe symptoms, but, in some individuals, can trigger a life-threatening pneumonia (2-5). This is an acute respiratory distress syndrome (ARDS), which could be characterized by distinctive features with near-normal respiratory system compliance despite severe hypoxemia (6). Consequently, the existence of two distinct COVID-19 phenotypes (Type Low - L and Type High - H) (7) has been hypothesized depending on the interaction of several factors including severity of the infection, host response, physiologic reserve, comorbidities. Pneumonia may be associated with disseminated intravascular coagulation (DIC) which is a strong predictor of mortality. The pathophysiology of DIC is complex and multifactorial involving host and virus issues (8)

The COVID-19 does not seem to affect patients uniformly, not only from a clinical and prognostic point of view, but also from an epidemiological one. From this latter perspective, some patients' characteristics, including gender, age, comorbidities and smoking, raised the interest of the scientific community.

Aim of this paper is to outline main the issues that led tobacco smoking to be indicated as a potential risk factor associated with COVID-19, and to summarize the evidence from observational studies, systematic reviews, and meta-analyses published so far, on the relationships between smoking history and COVID-19.

Material and Methods

Published articles from MEDLINE and preprints were identified in order to identify systematic reviews, meta-analyses and observational studies on the relationship between tobacco smoking and COVID-19, published from January to April 2020.

For observational studies, we included those with community-dwelling or hospitalized adults who had been tested for SARS-CoV-2 or were diagnosed with COVID-19, providing that data on smoking status were reported.

Results and Discussion

In order to better clarify how the issues about tobacco smoking and COVID-19 emerged and progressed in the literature, the results are preceded by few considerations on some related epidemiological aspects, i.e. gender, age, comorbidities.

Gender

Men and women are infected by SARS-Cov-2 in nearly equal numbers, but severe outcomes and mortality rate seem to be significantly and substantially higher in men than in women, as it was in SARS and MERS (2-5, 9-11).

Some possible explanation for this difference may be sexual dimorphism, higher prevalence of smokers among males, higher female personal hygiene.

Sexual dimorphism in innate and adaptive immunity has been well studied (12). Estrogen has an immune-stimulating effect on the immune system, while testosterone an immunosuppressive one (13); the X chromosomes contain more immune-related genes: the X chromosome contains 10% of the microRNA (miRNA) in the human genome compared to 2% miRNA in the Y chromosome (14, 15).

Another reason that has been hypothesized lies in the more frequent smoking habit among men than women (see the section on Smoking).

Also, women generally dedicate more time and attention to personal hygiene during their daily lives in comparison to men (16).

Age

COVID-19 epidemic seems to mainly affect middle-aged and old adults (2-5).

In China, the median age of hospitalized COV-

ID-19 subjects was around 50 years varying according to patient samples, being, 47 years in the study by Guan (3), 49 years in that by Huang (4) and 57 years in that by Zhang (5).

In Italy, more than 70% of hospitalized cases had 50 years or more and the median was 62 years in the update of 24/April/2020 (17).

The reported case-fatality ratio (CFR) for COVID-19 (April 13, 2020) among Chinese and Italian patients increases progressively with age, being 8.0% and 14.8% among patients aged 70-79 years and 80+ years respectively in China and 9.7% and 21.4% among those aged 70-79 years and 80+ years respectively in Italy (2, 18).

Comorbidities

Comorbidities reported in hospitalized patients affected by COVID-19 were mainly hypertension, cardiovascular diseases, diabetes mellitus, smoking, chronic obstructive pulmonary disease (COPD), overweight and obesity, asthma, cerebrovascular diseases, malignancy, and chronic kidney disease (2-5, 19). The prevalence of comorbidities varies according to patient samples; in the meta-analysis of Emami and coauthors, hypertension (16.4%), cardiovascular diseases (CVD) (12.1%), Diabetes (7.9%) and smoking (7.6%) were the most prevalent underlying diseases (19).

Less than half of hospitalized patients had an underlying disease. However, the presence of comorbidities substantially increased the risk of severe prognosis (2-5).

Chinese men have higher rates of type 2 diabetes, hypertension, COPD and lung cancer compared to women (3-5).

Many comorbidities, including COPD, lung cancer and cardiovascular diseases are tobacco-related diseases.

Tobacco smoking

Tobacco smoking is recognized to increase the susceptibility to infections in a multifactorial way, including the alteration of the host's mechanical (muco-ciliary) and immunological defenses and the likely increased virulence of virus and bacteria (20). In addition, tobacco smoking has a significant impact on the immune system and activates inflammation; moreover, the smoke-related structural and immunological alterations found in chronic bronchitis, COPD and emphysema patients represent ideal attachment areas for bacterial and viral infections (21).

It was surprising that the first confirmed Italian case of COVID-19, known worldwide, was a 38-year-old young healthy male who regularly participated in running events and soccer games. He experienced an extremely short time-lapse between onset of symptoms and pneumonia (only 2 days) and was admitted to the intensive care unit for respiratory failure, required intubation and supportive treatment for many weeks and finally recovered (18).

Intensive fatiguing works, including sport as well as smoking, that imply high respiratory volumes, deep inhalation, change of breathing from nose to mouth, progressive cooling and drying of the respiratory tract mucous, decrease movement of ciliated cells and increase mucosal viscosity which impairs filtering of microorganisms from the upper respiratory tract system. These mechanisms are hypothesized to allow the virus to spread to lower airways and alveoli, bypassing the natural immune response in the oral cavity and upper respiratory airways and facilitating penetration of virus to lower airways at a stage in which an adaptive immune response is still not initiated (18).

When the first articles about COVID-19 epidemic in China were published, data became available to investigate the role of smoking in COVID-19.

Since in China smoking habit differs according to gender (52.1% of men and only 2.7% of women regularly smoke (22)), Chinese men have higher prevalence of comorbidities and a higher rate of severe or fatal outcomes in COVID-19 pandemic, tobacco smoking has been hypothesized to be an important risk factor for poor prognosis (3, 4).

Indeed, several studies, as happened in MERS, reported that smokers are more likely than non-smokers to have severe symptoms and need for mechanical ventilation and intensive care unit. Mortality too was observed to be higher among infected smokers compared with infected never smokers (23).

Guan and colleagues examined 1,099 Chinese COVID-19 patients, showing that 32% of patients with a history of smoking (smokers and ex-smokers) at the time of hospitalization had a severe form of

COVID-19 pneumonia, compared to 15% of never smokers. In addition, 16% of smokers required hospitalization in intensive care units or died, compared to 5% of never smokers (3).

In another study from China, on patients diagnosed with COVID-19-associated pneumonia, Liu and colleagues reported that 27% of smokers worsened (including death) within two weeks of hospitalization, compared to 3% of non-smokers (23). A multivariate analysis confirmed the statistically significant association between history of smoking and severe/fatal outcome (23).

Two preliminary systematic reviews, investigating the role of smoking on severity of COVID-19, reported opposite results: Lippi reported that active smoking was not found to be a significant predictor of COVID-19 severity, despite a trend towards higher risk was appreciable, while Vardavas and Nikitara reported that smoking is most likely associated with negative progression and adverse outcomes of COVID-19. Each of these systematic reviews evaluated 5 studies, (some, but not all, were included in both analyses), but available data were scanty and the analysis provided failed to show estimates adjusted for other potential important confounding factors, including gender, age and comorbidities (24, 25).

A meta-analysis based on 15 studies and recently published in pre-print (i.e., without having received a peer-review), showed that 63% of COVID-19 patients with COPD had a severe form of the disease compared to 33% among patients without COPD; the relative risk (RR) was 1.9 (95% CI: 1.4– 2.4). The authors also reported that 22% of current smokers and 46% of ex-smokers had severe complications (26).

A systematic review and meta-analysis (published in pre-print in April, 2020), focusing on smoking and COVID-19 progression, evaluated 12 studies (but not their quality on smoking data) and reported severe disease progression in 17.8% of smokers in comparison to 9.3% of non-smokers and a statistically significant association between smoking and disease severity (OR = 2.25, 95% confidence interval, CI: 1.49-3.39); nevertheless, out of 9025 patients only 495 (5.5%) were ever smokers (27). In many studies, reported smoking prevalence among hospitalized patients was substantially below smoking prevalence in the corresponding populations.

In 10 Chinese studies, smoking prevalence in hospitalized patients ranged from 3.8% to 14.6% while in the Chinese population it is 27.7% (52.1% for men and 2.7% for women). Low smoking prevalence among hospitalized patients was observed also in Korean and in the US patients (27).

Some researchers recently explained - in articles published in pre-print - these relatively low prevalences of smokers among COVID-19 hospitalized patients, in terms of a protective role of nicotine on COVID-19 infection (28-30).

A very recent systematic review (also published in pre-print in April 2020), tried to clarify the role of smoking on infection, hospitalization, disease severity and mortality from COVID-19 and summarized the main findings emerged so far (31). First, still the majority of articles come from China and ethnicity may be a variable to be taken into consideration. Indeed, this systematic review included 28 articles: 22 conducted in China, 3 in the United States, 1 in South Korea, 1 in France and 1 in multiple countries. Second, the quality of the recorded data on smoking habit is very low: 25 of the 28 studies did not register the smoking habit for many patients and did not explicitly indicate whether the patients who were not included in the group of smokers or ex-smokers were confirmed never smokers. Moreover, in some studies smoking habit was classified as "smokers", "ex-smokers" and "non-smokers plus missing values about smoking". The latter is a "misleading category" which could have brought authors to erroneously interpret their results. All the 28 studies included in the systematic review were carried out in the context of an emerging epidemic; therefore, the collection of smoking habit was not considered a priority. This may have led to an underestimation of the prevalence of smokers and former smokers may have been conflated with never smokers. Moreover, smokers with severe symptoms of COVID-19 may have quit smoking prior to hospitalization and therefore may not have been recorded as current smokers (i.e. reverse causality). WHO definition of "ex-smoker" implies to have quit smoking for at least 6 months (32).

This supposed misclassification of smokers as nonsmokers is highly likely to have lowered prevalences and biased the risk estimates toward the null.

The results of this systematic review showed that there was no significant difference between ever

and never smokers according to hospital admission for COVID-19 (this result is based on the only two studies where smoking status had been adequately collected) (31). The same systematic review showed, (among the 1370 hospitalized people across the two high-quality studies), that there was greater disease severity in ever compared with never smokers (RR=1.43, 95% CI: 1.15-1.77, p = 0.002), while mortality, evaluated only in three studies, could not give any pooled estimate due to the high number of missing data (i.e. >90% of individuals with no collection of smoking history) (31).

The hypothesis that nicotine may have a protective role in COVID-19 patients, has also contributed to the debate on the angiotensin-converting enzyme 2 (ACE2). This enzyme has been identified as the cellular entry receptor for SARS-CoV-2 (33). ACE-2 is expressed in a variety of different tissues: upper and lower respiratory tract (including goblet cells, club/Clara cells, and alveolar type 2 cells), myocardium, kidneys and gastrointestinal mucosa, reflecting the target organs involved in the disease (the virus was detected in stool samples from patients with COVID-19 gastrointestinal symptoms) (34, 35).

A study by Smith and colleagues (34) reported high levels of ACE2 receptors in the respiratory tract and in oral epithelial cells of smokers, but not in those of never-smokers or ex-smokers. The authors also found that tobacco smoking (expressed as pack-years) causes a dose-dependent upregulation of ACE2, that chronic smoking exposure increases ACE2 expression and that quitting smoking results in a decrease in lung ACE2 levels.

Multivariate linear regression further confirmed that smoking history was a significant predictor of ACE2 expression even when controlling for a patient's age, sex, race, and body-mass index.

According to the authors, these results may partially explain why smokers are particularly predisposed to a severe form of SARS-CoV-2 infection, and why quitting smoking could lessen coronavirus susceptibility (34).

A dose-dependent regulation of ACE 2 expression was also reported by Leung and colleagues in COPD patients undergoing bronchoscopy. In this study, ACE-2 expression in the bronchial epithelial cells (especially in lower respiratory tract) was significantly increased in COPD versus non-COPD subjects. A significant inverse relationship was found between ACE-2 gene expression and levels of Forced Expiratory Volume in the 1st second (FEV1); smoking status was also significantly related to ACE-2 gene expression, with current smokers having a significantly higher gene expression than never smokers, and ex-smokers having level between those of never and current smokers (35).

Both these last two studies reported the presence of a dose-response effect and the study by Smith and colleagues also reported that the upregulation of ACE2 is reversible with quitting smoking; these findings are important elements in the assessment of the causality relationship.

Other Authors, however, have speculated that there is an inhibiting effect of nicotine on the ACE2 receptor, suggesting a protective effect of nicotine (30). This "nicotinic hypothesis" proposes that the virus could enter the body through neurons of the olfactory system and/or through the lung, leading to different clinical features with different outcome. In fact, nicotine, besides increasing the expression and/or activity of renin, ACE and Angiotensin II receptor type 1, may in a compensatory way, downregulate the expression and/or activity of ACE2 and Angiotensin II receptor type 2. This second possibility has not yet been explored in the framework of viral neuro-infections (30).

Conclusion

The role of smoking on COVID-19 is highly controversial due to the lack of reliable data.

COVID-19 is a new disease that has different clinical presentations and affects patients with a wide range of symptoms; our knowledge about it is still incomplete.

Further independent studies, not funded by the tobacco industry nor by electronic cigarette companies, could contribute to better clarify how smoking contributes to COVID-19.

Longitudinal studies should be performed to interview patients, or family members for deceased pa-

tients, in order to collect good quality data about patient smoking status.

Also, smoking status should be systematically, routinely and accurately collected in clinical records, in all countries (37).

So far, there is some evidence that smokers and ex-smokers have anincreased risk of more severe outcomes.

Even if the role of smoking in COVID-19 has to be confirmed, there is evidence that hypertension, cardiovascular diseases, diabetes mellitus, COPD, cancer, and chronic kidney disease were among the most prevalent underlying diseases among hospitalized COVID-19 patients (19). Since many of these underlying health conditions are tobacco-related diseases, smoking is likely to negatively influence COVID-19 outcomes.

Thus, since the pandemic is still under progression, tobacco smoking, having highly negative consequences on health, may represent the most important avoidable risk factor. We recommend quitting smoking, besides the other well-known health benefits, also to protect smokers in case of SARS-Cov-2 infection (36, 37).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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