Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Internal Medicine 77 (2020) 121–122

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the editor

Smoking habit and hospitalization for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related pneumonia: The unsolved paradox behind the evidence.

ARTICLE INFO

Keywords:
Smoking
Covid-19
Sars-CoV-2
Pneumonia

Since the beginning of the SARS-CoV-2 pandemic earthquake (more than 1.8 million infected subjects worldwide as of mid-April), differences across countries with regard to hospitalization and death rate are currently emerging, and a series of hypotheses reporting to dissimilarities according to clinical features of patients have been carried out. Given that smoking habit prevalence actually differs according to countries exposed to infection, we explored the prevalence of smoking among hospitalized individuals affected by Coronavirus Disease 2019 (COVID-19).

Vardavas CI et al. performed a systematic review of studies on COVID-19 that included information on patients' smoking status to evaluate its with COVID-19 outcomes. To this purpose, they identified five Chinese studies (4 out of 5 conducted in Wuhan region), with a sample size ranging from 41 to 1099 patients. They concluded that smoking is most likely associated with a rapid progression and adverse outcomes of COVID-19 [1]. In the meta-analysis conducted by *Lippi G* et al., despite a trend towards a higher risk of poor prognosis was appreciable, no significant association have been found between active smoking and severity of COVID-19 [2].

While there is preliminary (and apparently logical) evidence of a relationship between smoking and severity of the disease, it remains to be clarified: 1) whether the impact of smoking on COVID-19-outcome is rather linked to the smoking-related comorbidities, and 2) which comorbidities are associated with a worse clinical course of SARS-CoV-2 infection.

It is noteworthy that the studies included in the above-mentioned meta-analyses incorporate hospitalized patients, with unexpectedly few of them smokers (4–14,6%) [3,4]. With regard to the largest series, *Guan W* et al. reported the clinical features of COVID-19 in 1099 hospitalized patients in 552 sites as of January 29, 2020 throughout China. The great majority of patients (85.4%) were non-smokers and have never smoked, despite the smoking habit is widespread in China [4].

Even if the pathophysiology of the other two (beta)-Coronaviruses, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), has not been completely understood, a series of studies have shown that high levels of proinflammatory cytokines in serum were associated with pulmonary inflammation and extensive lung damage in symptomatic patients for SARS [5].

Following the virus invasion of the respiratory tract, the elevation of the plasma chemokines can induce the hyper-innate inflammatory response. This leads to the recruitment and accumulation of alveolar macrophages and polymorphonuclear neutrophil, as well as the activation of Th1 cell-mediated immunity by the stimulation of natural killer and cytotoxic T lymphocytes [5,6]. This cascade of events generates an over-production of immune cells and cytokines, known as cytokine release syndrome, that can lead to a rapidly progressing disease with an acute respiratory distress syndrome (ARDS) and septic shock, eventually followed by multiple organ failure [7].

A recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, showed that elevated inflammatory indicators in the blood, including interleukin-6 (IL-6), could be predictors of a fatal outcome in COVID-19, suggesting that mortality might be due to virus-activated '*cytokine-storm syndrome*' [6]. In a cohort of 41 patients with laboratory-confirmed COVID-2019, it was reported that intensive care unit (ICU) patients had higher plasma levels of proinflammatory cytokines in serum, such as IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα, in comparison with non-ICU patients [8]. According to such pathogenetic mechanism, 21 patients with SARS-CoV-2 infection in China have been treated with Tocilizumab, a humanized IgG1 monoclonal antibody against the IL-6 receptor, achieving promising results. This led to a series of randomized, controlled trial for the efficacy and safety of tocilizumab in the treatment of COVID-19 in Europe and China, confirming the importance of turning off the excessive immune response that occurs in the later stages of the disease.

The exposure to smoke has been shown to modulate immune and adaptive immune responses and reduce systemic levels of several immune/inflammation markers, when compared with never smokers. Thus, smoking could attenuate the normal defensive function of the immune system [9,10], which becomes tolerant of a continuous inflammatory insult, while the immune system of never smokers may be more suitable for a cytokine release syndrome. Paradoxically, a provocative hypothesis could be that the cytokine storm with excessive production of pro-inflammatory molecules could possibly more easily be triggered in a perfectly immunocompetent individual rather than in smokers.

In this regard, we may assume that the immune system of a current smoker is more tolerant and less reactive, compared to patients who have never smoked, whose immune system may be more suitable for

https://doi.org/10.1016/j.ejim.2020.04.042
Received 14 April 2020; Accepted 20 April 2020
Available online 23 April 2020

triggering a cytokine release syndrome, that could be associated to COVID-19-related high mortality. This can contribute to partially explain the data observed in the studies published so far, reporting the great majority of COVID −19 hospitalized patients as non-smokers.

In addition, it should be considered that the prevalence of smoking in the studies published so far refers only to hospitalized patients, with more severe symptoms of the disease than individuals who not admitted to hospital. The hospitalized patients represent only a (hopefully small) part of the COVID-19 positive population. Indeed, it is likely that the SARS-CoV-2 infection occurs asymptomatically or with mild symptoms that do not require hospitalization; the prevalence of smoking in these cases is unknown and actually it does not help the clarify the association between smoking and severity of pneumonia.

Therefore, it is not currently possible to establish the real prevalence of smoking among all individuals affected with COVID-19. However, according to the studies published so far, smokers represent a minority among hospitalized patients. It would be interesting to investigate the spread of smoking among asymptomatic individuals or those with few symptoms, in order to clarify whether smoking is a real risk factor not only for the clinical course but also for contracting and manifesting the infection.

In light of the recent onset of the COVID-19 pandemic, it is necessary to consider the data published so far as preliminary and to be confirmed. Collaborative and international efforts between multiple health agencies are needed, so that more reliable data on the epidemiological and clinical characteristics of the COVID-19, including smoking status, will be available and more reliably interpreted. Matching the associations between the clinical characteristics on the one hand and the prevalence and clinical course of the disease on the other, even in asymptomatic or with mild symptoms individuals, could allow to implement the most appropriate prevention and containment strategies.

Declaration of Competing Interest

E.B. received speakers' and travels' fee from MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche. E.B received consultant's fee from Roche, Pfizer. E.B. received institutional research grants from Astra-Zeneca, Roche.

Acknowledgments

E.B. is currently supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) under Investigator Grant (IG) No. IG20583. GT is supported by AIRC, IG18599, AIRC 5 × 1000 21052. EB is currently supported by Institutional funds of Università Cattolica del Sacro Cuore(UCSC-project D1-2018/2019).

References

[1] Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. Tob. Induc. Dis. 2020;18:20.
[2] Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). Eur. J. Intern. Med. 2020. https://doi.org/10.1016/j.ejim.2020.03.014.
[3] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir. Med. 2020.
[4] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 2020.
[5] Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin. Exp. Immunol. 2004;136:95–103.
[6] Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020.
[7] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
[8] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[9] Qiu F, Liang CL, Liu H, et al. Impacts of cigarette smoking on immune responsiveness: up and down or upside down? Oncotarget 2017;8:268–84.
[10] Shiels MS, Katki HA, Freedman ND, et al. Cigarette smoking and variations in systemic immune and inflammation markers. J. Natl. Cancer Inst. 2014:106.

Giovanna Garufi[a,b,*], Luisa Carbognin[c], Armando Orlandi[b], Giampaolo Tortora[a,b], Emilio Bria[a,b]
[a] *Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy*
[b] *Medical Oncology, Università Cattolica del Sacro Cuore, Roma, Italy*
[c] *Division of Gynecologic Oncology, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy*
E-mail address: giovanna.garufi@unicatt.it (G. Garufi).

* Corresponding author at: