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Early View

Correspondence

COVID-19 and the nicotinic cholinergic system

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Title. COVID-19 and the nicotinic cholinergic system

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Short synopsis

The prevalence of smoking among hospitalized COVID-19 patients is low. COVID-19 manifestations could be linked to impairment of the cholinergic anti-inflammatory pathway. Nicotinic cholinergic agonists should be examined as potential therapeutic options.

To the Editor –

We have read with great interest the paper by Leung et al. published in European Respiratory Journal [1], the correspondence by Russo et al. [2] and also the subsequent comment by the first group [3]. Both research teams are reporting increased ACE-2 expression in airways of current smokers and those with COPD with important implications for COVID-19 patients. Since ACE-2 has been shown to be the main receptor utilized by SARS-CoV-2 to enter the host cells [2], the authors conclude that nicotine is a risk factor for COVID-19 pandemic. Russo et al. [2] have shown that nicotine up-regulates ACE-2 through alpha7 nAChRs which are present in neuronal and non-neuronal cells. Leung et al. [3] provided further evidence in support of this hypothesis and propose the repurposing of alpha7-nAChR antagonists for the pandemic (e.g. methyllycaconitine, alpa-conotoxin), expecting that such treatment will alter ACE-2 expression and prevent SARS-CoV-2 entry.

While this hypothesis is based on laboratory experiments, it is not supported by clinical data. Recent observations on the prevalence of smoking among hospitalized COVID-19 patients have

raised some important issues. Many studies, while based on preliminary data and subject to several limitations (e.g. lack of adjustment for confounding factors, possibility for inability to report, inaccurate recording or under-reporting of the smoking status, etc.), suggest that the proportion of hospitalized COVID-19 patients who are current smokers is by far lower than expected based on population smoking rates [4,5]. In one study, smoking was associated with lower odds of hospitalization for COVID-19 after adjusting for covariates [6].

To further address this issue, we calculated the pooled prevalence of current smoking in 11 published case series (Table 1), 9 from China and 2 from the US [5,7-16], and compared it to the expected prevalence based on gender-adjusted and gender and age-adjusted population smoking rates in each country by estimating the prevalence odds ratio (POR) using random effects meta-analysis. Due to the lack of data on patients' age distribution, the age-adjustment for the expected smoking prevalence was calculated by assuming that all patients were aged $\geq$ 65 years since lower smoking prevalence is observed in the elderly compared to younger adult age groups. Population smoking prevalence information was derived from the WHO 2018 GATS [17] for China, and from the US CDC (for gender-adjustment) [18] and Statista (for gender and age-adjustment) [19]. The pooled prevalence of smoking was 5.4% (95%CI: 3.5-7.7%), while the POR was 0.17 (95%CI: 0.12-0.25, P<0.001) compared with gender-adjusted and 0.20 (95%CI: 0.13-0.31, P<0.001) compared with gender and age-adjusted expected prevalence. Despite the many limitations, these observations need to be taken into consideration. Recently, a hypothesis that the nicotinic cholinergic system may be involved in COVID-19 infection was presented, based on the fact that several of the symptoms and clinical signs of COVID-19, including the cytokine storm, could be explained by dysfunction of the cholinergic anti-inflammatory pathway [20]. Alpha7 nAChRs are potentially involved in modulating pro-inflammatory cytokine secretion and suppressing the cytokine storm [21,22]. Additional clinical manifestations of COVID-19 (such as anosmia and thromboembolic complications) can also be associated with dysfunction of the nicotinic cholinergic system [20].

In conclusion, the observations of a low smoking prevalence among hospitalized COVID-19 patients, despite the important limitations, together with the hypothetical links between dysfunction of the nicotinic cholinergic system and clinical manifestations of the disease raise some important research questions, considering that nicotine is a cholinergic agonist. The interaction between SARS-CoV-2 and the nicotinic cholinergic system should be further examined and any proposal for the repurposing of

alpha7-nAChR antagonists should be approached with caution, since it could potentially propagate the cytokine storm and adversely affect the prognosis. Obviously, smoking cannot be considered protective for COVID-19 (or any other disease), but pharmaceutical nicotine products are widely available and their role in COVID-19 should be explored.

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Table 1. Studies used to estimate the pooled prevalence and the prevalence odds ratio of current smoking among hospitalized COVID-19 patients. Random-effects meta-analysis was used.

* No data about patients' gender was available; thus, the gender-unadjusted population prevalence of smoking in the US was used to calculate the expected number of smokers.

	Country	**Patients** N	**Age mean (SD) or median (IQR)**	**Males %**	**Females %**	**Smokers** n	**Smokers** % (95% CI)	**Expected smokers (%) gender-adjusted**	**Expected smokers (%) gender and age-adjusted ****	**Prevalence Odds Ratio (gender-adjusted)**	**Prevalence Odds Ratio (gender and age-adjusted) ****
CDC [5]*	USA	1494				27	1.8 (1.2-2.6)	13.7%	8.8%	0.12 (0.08-0.17)	0.19 (0.13-0.29)
Guan et al. [7]	China	1085	47 (35-58)	58.1%	41.9%	137	12.6 (10.6-14.6)	30.2%	27.3%	0.36 (0.28-0.44)	0.39 (0.31-0.48)
Chen et al. [8]	China	274	62 (44-70)	62.4%	37.6%	12	5.4 (2.4-8.3)	32.3%	29.0%	0.10 (0.05-0.19)	0.11 (0.06-0.21)
Zhou et al. [9]	China	191	56 (46-67)	62.3%	37.7%	11	5.8 (2.5-9.1)	32.3%	29.0%	0.14 (0.07-0.27)	0.15 (0.08-0.30)
Mo et al. [10]	China	155	54 (42-66)	55.5%	44.5%	6	3.9 (0.9-6.9)	29.0%	26.2%	0.11 (0.04-0.26)	0.11 (0.05-0.28)
Zhang et al. [11]	China	140	57 (25-87)	50.7%	49.3%	2	1.4 (0.0-3.3)	26.6%	24.3%	0.04 (0.01-0.18)	0.05 (0.01-0.19)
Wan et al. [12]	China	135	47 (36-55)	53.3%	46.7%	9	6.7 (2.5-10.9)	27.9%	25.4%	0.20 (0.09-0.43	0.21 (0.10-0.46)
Liu et al. [13]	China	78	38 (33-57)	50.0%	50.0%	5	6.4 (0.1-11.8)	26.3%	24.1%	0.20 (0.07-0.58)	0.22 (0.08-0.61)
Huang et al. [14]	China	41	49 (41-58)	73.2%	26.8%	3	7.3 (0.0-15.3)	37.5%	33.3%	0.14 (0.04-0.54)	0.16 (0.04-0.61)
Zhang, Cai et al. [15]	China	645	35 (14.2) 47 (14)	50.9%	49.1%	41	6.4 (4.6-8.5)	26.7%	24.4%	0.20 (0.14-0.28)	0.21 (0.15-0.30)
Mehra et al. [16]	USA	8910	48 (17) 56 (15)	59.9%	40.1%	491	5.5 (5.1-6.0)	14.2%	9.1%	0.35 (0.32-0.39)	0.58 (0.52-0.65)
Total (pooled)		**11654**				**717**	**5.4 (3.5-7.7)**			**0.17 (0.12-0.25)**	**0.20 (0.13-0.32)**

*No data about patients' age and gender was available; thus, the unadjusted population prevalence of smoking in the US was used to calculate the expected number of smokers.

** Since the age distribution of patients was not available, age-adjusted smoking prevalence was calculated for all studies by assuming that all patients were aged ≥ 65 years.

Data on population smoking prevalence were derived from the WHO GATS 2018 survey for China and from the CDC for gender-specific smoking prevalence and Statista for gender specific smoking prevalence in adults aged ≥ 65 years for the US.