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META-ANALYSIS: COVID-19 DISEASE SEVERITY CORRELATES WITH SMOKING STATUS

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ABSTRACT

The novel COVID-19 disease is a contagious acute respiratory infectious disease whose causative agent has been demonstrated to be a new virus of the coronavirus family, SARS-CoV-2. Multiple studies have already reported that risk factors for severe disease include older age and the presence of at least one of several underlying health conditions. However, a recent physiopathological report and the French COVID-19 scientific council have postulated a protective effect of tobacco smoking.

Thanks to a meta-analysis, we have been able to demonstrate the statistical significance in this regard of twelve series from China, France and in the US, reporting three different smoking status (current smoker,former smoker, with a smoking history) as well as disease severity (with respectively odds-ratio of 1.78 [1.08-3.10], 4.60 [3.13-7.17], 2.74 [0.63-5.89]). Subsequently and using a Bayesian approach we have established that past, and present smoking is associated with more severe COVID-19 outcomes. Finally, we refute claims linking general population smoking status ($N=O(10^8)$ or $O(10^9)$) to much smaller disease course series ($N=O(10^4)$). The latter point in particular is presented to stimulate academic discussion, and must be further investigated by well-designed studies.

IMPLICATIONS

Recent preliminary estimates of the prevalence of selected underlying health conditions among patients with COVID-19, in China, France and in the United States, show that individuals with underlying health conditions appear to be at higher risk for more severe COVID-19.Thanks to a meta-analysis, we have concluded that the only significant findings that can be confidently asserted from the series discussed in this article, is that past, and present smoking is associated with more severe COVID-19 outcomes.

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INTRODUCTION

The novel coronavirus pneumonia (COVID-19) is a contagious acute respiratory infectious disease whose causative agent has been demonstrated to be a new virus of the coronavirus family, SARS-CoV-2. This illness was first evinced in December 2019 in the Seafood Market of Wuhan, Hubei Province, in southern China[1,2]. Patients with the coronavirus pneumonia have a fever, and the temperature above 38 degrees Celsius with symptoms such as dry cough, fatigue, dyspnea, difficulty breathing, and diarrhea[1-5]. There is a high transmission for this disease, which, as result of this and other factors such as international travel and trade, has now turned into a pandemic, with hundred thousands of individuals confirmed to be infected worldwide – and most likely millions of unreported cases[5].

Recent preliminary estimates of the prevalence of selected underlying health conditions among patients with COVID-19, in China as well as in the United States, show that individuals with underlying health conditions appear to be at higher risk for more severe COVID-19[3,6]. A recent Greek epidemiological review suggests that smoking is most likely associated with the negative progression and adverse outcomes of COVID-19[7]. Meanwhile, a recent physio-pathology study has formulated the hypothesis that the effectiveness of ACE inhibitors/angiotensin II receptor blockers and nicotine in patients infected with COVID-19[8].

The smoking prevalence in China, in France and in the U.S. have been previously and broadly documented: these are, respectively, of 26.6%, 30% and 19.7%[9,10,11]. Furthermore, the president of the COVID-19 Scientific Council of France recently postulated that nicotine may have a protective role against COVID-19 infection[12]. Thanks to a meta-analysis based upon twelve studies[3,6,13-22], we can observe that the prevalence of past/current smokers is higher in COVID-19 severe infected patients. In this context, we would like to know whether the past/current smoking status entails higher probability of a severe course of COVID-19 illness, as compared to having never smoked.

METHODS

Study and Participants

We conducted a systematic search using ReseachGate on May 15, 2020, with the search term: ((smoking) OR (characteristics) OR (risk factors) OR (outcomes) OR (smoker*)) AND ((COVID-19) OR (COVID) OR (coronavirus) OR (sars cov-2) OR (sars cov 2) OR (severity)) for studies published between January 1, 2020 and May 15, 2020. One author extracted information for each study, screened the abstract or the full text, with questions resolved through discussion among both authors. There were no language restrictions. The source and targeted populations are the whole humanity in view of the ongoing COVID-19 pandemic. The eligible population is constituted by all Chinese, French and American already included in previous papers.

The study was conducted by a consortium of two data analysts, a MD-PhD specialized in radiology, and a medical student in clinical years. NexGen Analytics had no role in designing the study, nor in making the decision to submit manuscript to the publication, nor did it receive any fee or compensation in the context of this work. The first author vouches for the data and analyses, as well as for the fidelity of this report to the study protocol.

Enrollment

The studied and included population gathers patients from all studies upon COVID-19 with informations concerning the smoking status. The inclusion criteria were observationnal studies with as outcomes smoking status and the COVID-19 infection severity. The exclusion criteria were: incomplete data upon COVID-19 infection severity or smoking status, meta-analysis.

Outcome Measures

Our null hypothesis (H_0) was the orthogonality between two variables: the smoking status (X) and the COVID-19 Symptoms Severity (Y). Each variable can take different values: for the smoking status (X), it was a never smoker (X_1) or a current smoker (X_2) or a former smoker (X_3) or a patient with a smoking history (X_4); for the COVID-19 Symptoms Severity (Y), it was a mild (non-hospitalised) (Y_1) or a severe (hospitalised, ICU or not) (Y_2) symptoms severity.

Statistical Analysis

Each sample was analysed separately. First, we had to calculate for each sample (if they haven't been calculated by the authors) : the odds ratio with the never smoker as reference for current smokers, former smokers and patients with a smoking history. We then calculated, for each observed sample, the expected odd ratios assuming H_0 expected sample: in each case, we multiplied the two corresponding sums and subsequently divided by the actual total. In this way, we were able to apply a χ^2 test to compare the observed table to the expected table, for each sample. The p-value was subsequently computed in order to evince a statistically significant difference between the observed and the expected tables.

RESULTS

Populations

We found 79 studies on ResearchGate. Thirty-seven studies met the inclusion and exclusion criteria. A total of 29 observational studies and eight meta-analyses were identified. All observational studies reported the prevalence of smoking amongst hospitalized COVID-19 patients. Twelve of the 29 observational studies containing data on smoking status by severity of COVID-19 outcomes. After a short treatment of the initial data from both series (*Table 1*), in particular to eliminate incomplete data and studies outside our inclusion criteria, we have obtained the observed data for each study *(Table 2*).

Outcomes

We estimated the expected data on each case by multiplying the two corresponding sums and then by dividing by the total effective, for each sample. In these conditions, thanks to the χ^2 test, we were able to estimate, for both samples, trust interval and the p-values where the difference between observed and expected data are significant (*Table 3*). Indeed, the association between COVID-19 severity infection and the

smoking status for current and former smoker is significant with respectively odds ratio of 1.78 [1.08-3.10] and 4.60 [3.13-7.17], with a p-value of $1.22*10^{-1}$ and $1.87*10^{-2}$. The smoking history is linked to the COVID-19 severity infection by an odds ratio of 2.74 [0.63-5.89] with a p-value of $6.11*10^{-2}$ *(Table 4)*. Subsequently and using a Bayesian approach we have established that past and present smoking is associated with more severe COVID-19 outcomes.

DISCUSSION

Subsequently, by computing the empirical probability distributions conditioned on smoking status, we have established that past and present smoking is associated with more severe COVID-19 outcomes, in those samples. Nevertheless, our study has some limitations:

1. The difference between smoking status as observed across populations, and the same observed in our small clinical datasets (*Table 2*) is significant. As a result, the previously claimed relationship between former/current smoking status and a COVID-19 disease severity may not be confidently estimated from a global population.

2. Only adults were considered to compute smoking prevalence[10].

However, regarding the first limitation above, we contend that claims linking general population smoking status, computed across populations with cardinalities N in the order of $O(10^8)$ or even $O(10^9)$ with broadly varying smoking habits (e.g. already rural vs urban divide in this regard), to much smaller disease course series ($N = O(10^4)$), are at best imprudent and at worst marred by selection bias, especially as the latter regard a fraction of patients from the same urban area. We therefore claim that specific smoking status data, relevant to the concerned geographic areas, is required to evince a statistically significant under-representation of smokers among COVID-19 patients. An alternative argument could be made from a physio-pathological standpoint as well: indeed, previous studies and assertions describe a hypothetical protector role of nicotine against COVID-19 infection[8], but these are largely speculative at this point and require laboratory confirmation. We therefore conclude that the only significant findings that can be confidently asserted from the series discussed in this article, is that past and present smoking is associated with more severe COVID-19 outcomes.

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The authors declare no conflicts of interest.

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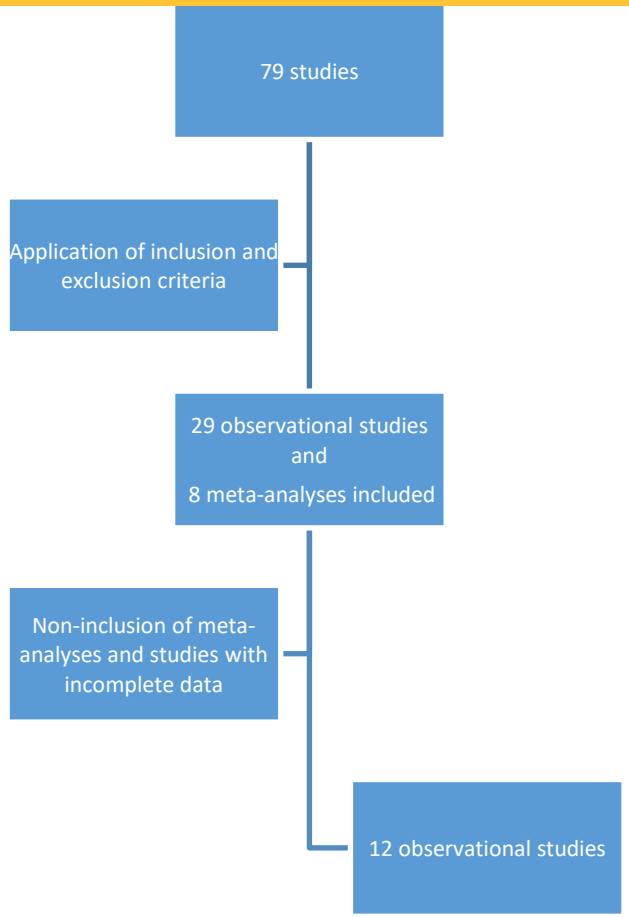

Table 1. Flow-chart of selected studies

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Table 2. Data obtained from the twelve selected articles

Authors	Setting	Sample size	Type of study	Outcome	Severe patients				Non severe patients				Univariate analysis			Multivariate ajusted analysis		
					N	Current (%)	Former (%)	Never smoke (%)	N	Current (%)	Former (%)	Never smoke (%)	OR	IT 95%	P-Value	OR	IT 95%	P-Value
S.S.A., 2020.	G.A.N. militaries, France	999	Retrospective cohort study between 21/02-13/04/20	Asymptomatic, Aspecific symptomatic, Symptomatic, Severely ill	25	1 (4.0%)	24 (96.0%)		974	322	652		0.16	0.04-0.67	0.01	0.19	0.04-0.83	0.03
Chen et al., 2020.	Medical Center, Zhejiang, China.	145	Single center retrospective observationnal study between 01/01-11/03/20.	Disease severity	43	3 (7%)		40 (93%)	102	12 (11.8%)		90 (88.2%)	Data unavailable in the article					
Chow N. et al., 2020.	U.S.A	6,637	Retrospective study from 12/02- 28/03/20	Non hospitalized, hospitalized without ICU admission, hospitalized with ICU admission	1,094	27 (3%)	78 (7%)	989 (90%)	5,143	61 (1%)	80 (2%)	5,002 (97%)	Data unavailable in the article					
Guan W. et al, 2020.	552 hospitals in mainland China	1,099	Retrospective study until 29/01/2020	Severity and admission to an ICU, the use of mechanical ventilation, or death	172	29 (16.9%)	9 (5.2%)	134 (77.9%)	913	108 (11.8%)	12 (1.3%)	793 (86.9%)	Data unavailable in the article					
Huang C. et al., 2020.	Hospital in Wuhan, China	41	Prospective study from 16/12-31/01/20	Admission in ICU or not	13	0	13 (100%)		28	3 (11%)	25 (89%)		Data unavailable in the article					
Li J. et al., 2020.	Dazhou Central Hospital, Sichuan, China	17	Retrospective single-center case serie from 17/01- 08/02/20	Discharged or not	12	1 (8.3%)		11 (91.7%)	5	2 (40.0%)		3 (60.0%)	Data unavailable in the article					
Liu W. et al.,	Three tertiary hospitals in	78	Retrospective multicentre cohort	Disease	11	3	8		67	2		65	12.187	1.762-84.306	0.011	14.285	1.577-25.000	0.018

2020.	Wuhan, China		study from 30/12-15/01/20	progression		(27.3%)	(72.7%)			(3%)	(97%)							
Miyara M. et al., 2020.	APHP Pitié-Salpêtrière Hospital, Paris, France	547	Cross sectionnal survey from 28/02-23/03/20 for outpatients and from 23/03- 09/02/20 for inpatients	Inpatients VS Outpatients	338	18 (5%)	111 (33%)	209 (62%)	132	14 (11%)	41 (31%)	77 (58%)	Data unavailable in the article					
Mo P. et al., 2020.	Zhongman Hospital of Wuhan University, Wuhan, Hubei, China	155	Retrospective single-center study from 01/01-05/02/20	Refractory COVID-19 patients compared to general COVID-19 patients	85	4 (5%)		81 (95%)	70	2 (2.86%)	68 (97.14%)		Data unavailable in the article					
Shy Y. et al., 2020.	Province of Zhejiang, China	474	Retrospective single-center cohort followed-up to 17/02/20	Mild or severe ill	49	6 (12.2%)	43 (87.8%)		425	34 (8%)		391 (92%)	Data unavailable in the article					
Wan S. et al., 2020.	Chongqing University Three Georges Hospital, Chongqing, China	135	Prospective single-center cohort study between 23/01-08/02/20	Mild or Severe cases	40	1 (2.5%)		39 (97.5%)	95	8 (8.4%)	92 (91.6%)		Data unavailable in the article					
Zhang J.J. et al., 2020.	No.7 Hospital of Wuhan, China	140	Retrospective study 16/01- 03/02/20	Disease severity	58	2 (3%)	4 (6%)	52 (91%)	82	0 (0%)	3 (4%)	79 (96%)	Data unavailable in the article					
Zhang X. et al., 2020.	Province of Zhejiang, China	645	Retrospective single-center study from 17/01-08/02/20	Abnormal imaging findings	573	37 (6.5%)	536 (93.5%)		72	4 (5.6%)	68 (94.4%)		Data unavailable in the article					

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Table 3. Odds-ratio comparison table

Authors	Country	Outcome	Odds-Ratio	95% TI lower born	95% TI higher born	P-Value	Sample weight	Part of total outcome sample (%)		
								Current smoker	Former smoker	Smoking history
S.S.A.	**France**	**Current smoker**	**0.19**	**0.04**	**0.83**		999	9.866		
Chen T. et al.	China	Smoking history	0.563	0.150	2.103		145			20.308
Chow N. et al.	U.S.A	Current smoker	2.239	1.416	3.540		6,637	65.544		
		Former smoker	4.931	3.583	6.785				79.657	
Guan W. et al.	China	Current smoker	1.589	1.014	2.489		1,085	10.715		
		Former smoker	4.439	1.835	10.739				13.022	
Li J. et al.	China	Smoking history	0.136	0.009	2.062		17			2.381
Liu W. et al.	China	Smoking history	14.285	1.577	25.000		78			10.924
Myiara M. et al.	France	Current smoker	0.474	0.225	0.999		470	4.641		
		Former smoker	0.997	0.640	1.553				5.641	
Mo P. et al.	China	Current smoker	1.679	0.298	9.449		155	1.530		
Shy Y. et al.	China	Smoking history	1.604	0.637	4.038		474			66.387
Wan S. et al.	China	Current smoker	0.294	0.036	2.430		135	1.333		
Zhang J.J. et al.	China	Former smoker	2.026	0.435	16.750		140		1.680	
Zhang X. et al.	China	Current smoker	1.173	0.406	3.393		645	6.370		
							TOTAL	100	100	100
Global outcomes		*Smoking history*	2.743	0.626	5.888	0.06112	714			
		Current smoker	1.783	1.082	3.109	0.1225	10,126			
		Former smoker	4.596	3.137	7.173	0.01869	8,332			

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Table 4. Odds Ratio Comparison chart