Review

What is Happening with Smokers and COVID-19? A Systematic Review and a Meta-Analysis

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Abstract: SARS-CoV-2 is a new coronavirus that has caused a worldwide pandemic. It produces severe acute respiratory disease (COVID-19), which is fatal in many cases, characterised by cytokine release syndrome (CRS). According to the World Health Organization, those who smoke are likely to be more vulnerable to infection. Here, in order to clarify the epidemiologic relationship between smoking and COVID-19, we present a systematic literature review until 28 April 2020 and a meta-analysis. It includes 18 recent COVID-19 clinical and epidemiological studies based on smoking patient status from 720 initial studies in China, USA, and Italy. The percentage of hospitalised current smokers was 7.7% (95%CI: 6.9-8.4) in China, 2.3% (95%CI: 1.7-2.9) in the USA and 7.6% (95%CI: 4.2-11.0) in Italy. These percentages were compared to the smoking prevalence of each country and statistically significant differences were found in them all ($p < 0.0001$). By means of the meta-analysis, we offer epidemiological evidence showing that smokers were statistically less likely to be hospitalised (OR=0.18, 95%CI: 0.14-0.23, $p<0.01$). CRS and exacerbated inflammatory response are associated with aggravation of hospitalise patients. In this scenario, we hypothesise that nicotine, not smoking, could ameliorate the cytokine storm and severe related inflammatory response through the cholinergic-mediated anti-inflammatory pathway.

Keywords: COVID-19; SARS-CoV-2; current smoker; smoking; smoker; hospitalized; nicotine; cytokine storm.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the new coronavirus that first broke out in Wuhan (Hubei Province, China) in December 2019, has quickly spread and become a global pandemic [1,2]. SARS-CoV-2 is the third coronavirus outbreak of this century, following severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [3]. Coronavirus disease 2019 (COVID-19) causes clinical manifestations that range from mild respiratory symptoms to severe pneumonia, can be fatal in many cases, and is aggravated by cytokine release syndrome (CRS) or cytokine storm [4].

It has been well established that smokers are at a significantly high risk of chronic respiratory disease and acute respiratory infections, and current smokers are at more risk of developing

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influenza than non-smokers [5]. Smoking is also closely associated with MERS-CoV [6], but there is no clear evidence for this association with SARS-CoV-2 [7].

In today's pandemic caused by coronavirus 2019 (COVID-19), some clinical characteristics have been described, but not without controversy about the effects of tobacco [8–12]. All this suggests that a smoking habit background is a poor prognosis factor in infected patients [13], or smokers could be more prone to contagion [13–15]. As evidence is lacking, the effect that tobacco has on contagions, number of hospital admissions and the seriousness of smoking patients is unclear [15].

It is worth remembering that smoking kills around eight million people worldwide every year [16], irrespectively of any interaction with COVID-19, which is why smoking cessation is an urgent priority. Nonetheless, clinical data published until the time of the COVID-10 outbreak in China, as well as the first date made public in the USA [17,18] and Italy [19], indicate that the number of smokers hospitalised for COVID-19 was perceptibly lower than expected if we bear in mind the prevalence of smoking in these countries, and even despite the possible biases in reports [17,20,21].

In China, the mean proportion of smokers is 26.1%. Among males, 54.0% are current smokers, and only 2.6% among women [22]. In the USA, the proportion of smokers is 15.6% in males and 12.0% in females, with a combined proportion of 13.7% [23]. the proportion of smokers in Italy is 19%, with 23.3% in males and 15.0% in females [24]. So, a similar or higher percentage of current smokers hospitalised with SARS-CoV-2 is expected to appear, with males predominating.

As this virus has only recently appeared, very few studies have evaluated possible risk factors, including the effect of tobacco. Given the existing gaps in evidence, we carried out a systematic review and a meta-analysis of studies about COVID-19, which includes information about the smoking habit (current smokers) of patients hospitalised in China, USA, and Italy to evaluate the relation between smoking and COVID-19.

2. Methods

2.1. Literature search strategy

The systematic review was carried out according to the Referred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) and MOOSE guidelines [25,26]. A flow chart is provided in Figure 1. A systematic searched was made of the ISI Web of Science (http://www.webofknowledge.com) for the relevant works published until 28 April, 2020.

The following search terms were used: ['COVID 19' OR 'NCOV 19' OR 'sars cov-2' OR 'sars cov 2' OR 'novel coronavirus'] AND ['smoking' OR 'tobacco' OR 'smoker*' OR 'risk factor' OR 'clinical features' OR 'clinical characteristics'].

2.2. Inclusion and exclusion criteria

In a first phase, any duplicated works and those not written in English were excluded. Then the studies that did not provide clinical characteristics were removed, or those describing diagnosis techniques, therapies, modelling, strategic response, imaging, genetics, biology, transmission mechanisms, healthcare workers protection, surveillance, scenarios, animal, genomics, those about asymptomatic patients, skin lesions and lesions specific of other organs, data on children or breastfed infants, among others. In the next phase, the works that provided no details about smokers were removed, especially those with no data on "current smokers". Finally, certain types of articles were excluded from the meta-analysis, e.g. comments, letters, editorial, viewpoint, correspondence, etc., which included no detailed data about smoking patients. However, they were considered to perform the qualitative analysis along with three systematic reviews and meta-analyses.

2.3. Data Extraction

Records were checked for duplicates using Zotero 5.0.85 (http://www.zotero.org). Two independent reviewers (AN and JGR) screened the literature search and assessed each study to be included by reading titles, abstracts and full texts. Any disagreement was solved in conference with the support of a third author (JN). Relevant data were acquired from each eligible study by means of a

structured extraction sheet, which was prepared and approved by all the reviewers' by reaching a consensus after screening the eligible studies.

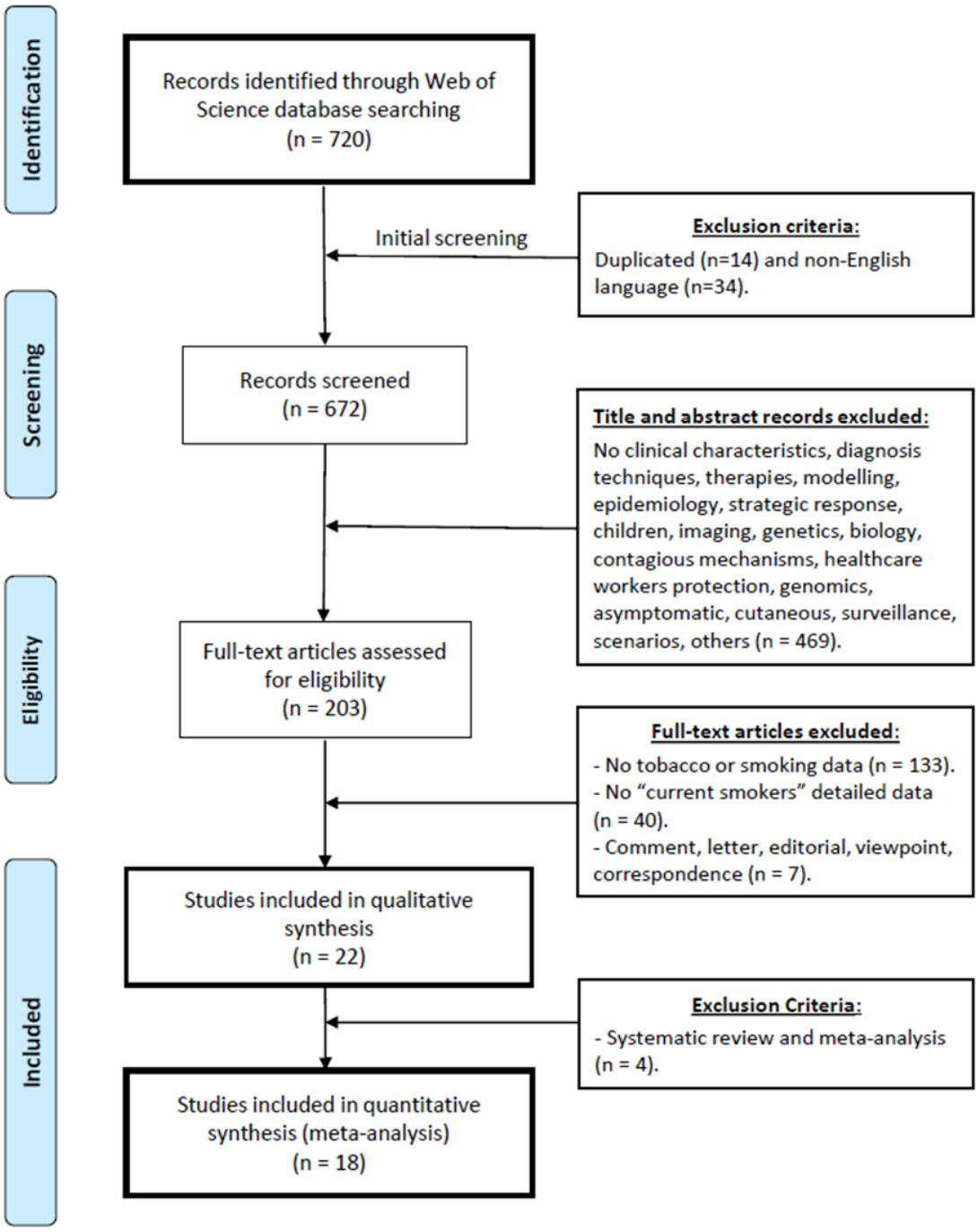

Figure 1. Flow chart showing how studies were identified and selected.

2.4. Statistical analysis

Data analyses were performed using the meta packages in R (Software R-3.6.3). A random-effects meta-analysis was used to calculate the pooled estimated prevalence with 95% confidence intervals (95%CI). A Chi-square test or Fisher's exact test was carried out to compare the differences between the observed and expected current smokers for all the studies individually and by combining all the data.

Heterogeneity between studies was assessed by the Cochran Chi-square test and I2. Depending on the I2 value, a fixed-effects (less than 50%) or a random-effects (more than 50%) model was used.

3. Results

3.1. Literature retrieval

The literature search gave 720 articles. Removing duplicate documents (n=14) and those not written in English (n=34) left 672 items. Then selection was performed by reading titles and abstracts (469 were excluded). Finally, publications were selected by applying the final selection criteria (detailed current smoker data and hospitalised patients). Of the remaining 203 works, 41 included data about smoking habit or a smoking background with the last inclusion criterion: the work should provide details of the proportion of smokers by specifying current smokers and hospitalised patients.

This procedure gave 18 experimental documents: 15 papers with data on the China outbreak [27–41], one official report with preliminary data on the USA outbreak [17], in New York city [18] and the Italian outbreak [19]. We provide more details in Tables 1 and 2 and in the flow chart (Fig. 1) to make this search repeatable in the future.

Table 1. Comparison of the hospitalised current smokers in the Chinese COVID-19 outbreak. The combined analysis is the result of adding all the individual studies. The expected current smokers were estimated using 54% and 2.6% for males and females, respectively [22].

	N (male/female)	current smokers	95%CI	expected current smokers (male/female)	Sig.
Chen et al., 2020	274 (171, 103)	12 (4·4%)	[2·0-6·8]	95· 0 (92·3, 2·7)	p<0·0001
Guan et al., 2020	1085 (631, 454)	137 (12·6%)	[10·7-14·6]	352·5 (340·7, 11·8)	p<0·0001
Han et al. 2020	17 (6, 11)	3 (17·6%)	[-0·5-35.8]	3·5 (3·2, 0·3)	p=0·9999
Huang et al., 2020	41 (30, 11)	3 (7·3%)	[-0·7-15·3]	16·5 (16·2, 0·3)	p=0·0006
Jin et al., 2020	651 (320, 331)	41 (6·3%)	[4·4-8·2]	181·4 (172·8, 8·6)	p<0·0001
Li et al., 2020	548 (279, 269)	41 (7·5%)	[5·3-9·7]	157·7 (150·7, 7·0)	p<0·0001
Lian et al., 2020	788 (407, 381)	54 (6·9%)	[5·1-8·6]	229·7 (219·8, 9·9)	p<0·0001
Mo et al., 2020	155 (86, 69)	6 (3·9%)	[0·8-6·9]	48·2 (46·4, 1·8)	P<0·0001
Wan et al., 2020	135 (72, 63)	9 (6·7%)	[2·5-10·9]	40·5 (38·9, 1·6)	p<0·0001
Wang et al. 2020	125 (71, 54)	16 (12·8%)	[6·9-18·7]	39·7 (38·3, 1·4)	p=0·0003
Yao et al., 2020	108 (43, 65)	4 (3·8%)	[1·0-7·3]	24·9 (23·2, 1·7)	p<0·0001
Zhang, Dong et al., 2020	140 (69, 71)	2 (1·4%)	[-0·5-3·4]	39·1 (37·3 ,1·9)	p<0·0001
Zhang, Cai et al., 2020	645 (328, 317)	41 (6·4%)	[4·5-8·2]	185·4 (177·2, 8·2)	p<0·0001
Zhang, Ouyang et al., 2020	120 (43, 77)	6 (5·0%)	[1·1-8·9]	25·2 (23·2, 2·0)	p=0·0004
Zhou et al., 2020	191 (119, 72)	11 (5·8%)	[2·5-9·1]	66·2 (64·3, 1·9)	p<0·0001
Combined	5,023 (2675, 2348)	386 (7·7%)	[6·9-8·4]	1,505·6 (1444·5, 61·0)	p<0·0001

3.2. China

As previously mentioned, all the studies included in the analysis contained detailed data about hospitalised current smokers. All the patients had been diagnosed with COVID-19 by PCR tests. Most studies were conducted in the Hubei province [27,29,31,33,36,39–42], three in the Zhejiang province [30,32,38], one in the Anhui province [35] and another in the Chongqing province [34]. One study had collected data from 30 provinces [28] and from 522 hospitals. In general, most of the studies collected data from patients in only one hospital. Almost all the works included in the meta-analysis were retrospective, one was prospective [40] and one was ambispective [31]. Their collected data were taken between 11 December, 2019 and 12 February, 2020. Data were generally

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taken from electronic medical records, except one work, which collected them directly by personally communicating with patients [35]. The studies homogeneously reported clinical and epidemiological data, and included patients, for example, in the order in which they arrived at hospital. However, one of the studies included 17 patients who had been discharged from hospital [29] and included the highest percentage of current smokers (12.6%). Three other studies recruited patients according to some selection criterion, or because they presented abnormal imaging findings [38], had previously visited the Huanan seafood market [40] or were older patients [43].

Table 1 presents the data that correspond to the 15 included studies. They all provide details of the total proportion of males and females, and the number of current smokers. The expected smokers values were calculated with these details, the proportion of males and females in each study and the smoking prevalence in China [22]. The 95% confidence interval (95%CI) of the percentage of smokers estimated with the observed values was also included. In all cases, statistically significant differences ($p<0.001$) appeared between the observed and expected values, except for the study by Han et al. 2020, whose sample included only 17 patients ($p=0.9999$). The combined values were obtained by adding all the patients in each study to consider a total sample of 4,795 patients, of whom 376 were current smokers. The prevalence percentage of current smokers was 7.7% (95%CI: 6.9-8.4%). Once again, the observed difference was very significant ($p<0.0001$) compared to the expected values. This value was much lower than the expected one when considering the prevalence in China (54% in males, 2.6% in females, and a combined 26.1%).

3.2.1. Meta-analysis in China

Figure 2 offers the meta-analysis results. The obtained heterogeneity (I2) was 64%, so the selected model was the random model ($p<0.01$), which gave an odds ratio value of 0.17 and a 95%CI of 0.13-0.22.

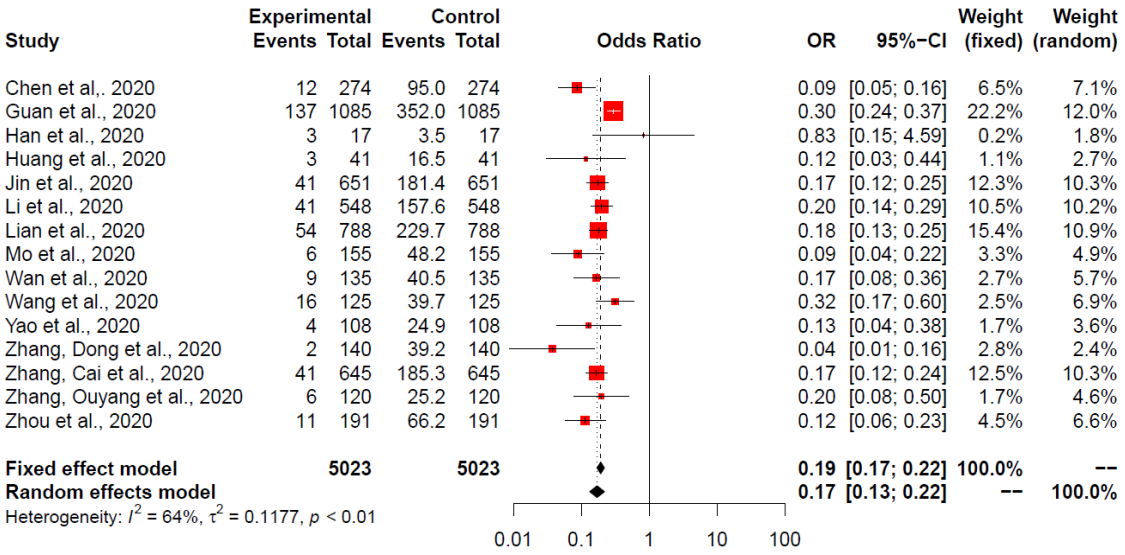

Figure 2. Meta-analysis of the Chinese studies.

3.3. USA and Italy

Only three studies not conducted in China were included: two from the USA with official data from Centers for Disease Control and Prevention (CDC) and New York city [17,18]; one from Italy [19]. As numbers are small, they are all presented in this section (Table 2). In all, the two US studies included 2,412 hospitalised patients, of whom 55 were current smokers (1.7% and 5.1%, respectively), although no gender proportions were provided in the CDC study. The Italian study recruited 236 patients, of whom 18 were current smokers (7.6%). All the patients' COVID-19 diagnosis had been

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confirmed by laboratory tests, in which case the US studies employed an official report [17] and a comment to the Editor [18], but provided detailed information about current smokers.

Table 2. Comparison of the hospitalised current smokers in the COVID-19 outbreaks in the USA and Italy. To calculate the expected current smokers values in the USA, 15·6% in males and 12·0% in females were taken, which gave a combined 13·7% [23]. In Italy, 23.3% in males and 15.0% in females were taken [24].

	N (male/female)	current smokers	95%CI	expected current smokers (male/female)	Sig.
CDC, 2020	2019[1]	35 (1·7%)	[1·2-2·3]	278·6	p<0·0001
Goyal et al., 2020	393 (238, 155)	20 (5·1%)	[2·9-7·3]	55·7 (37·1, 18·6)	p<0·0001
USA, combined	2,412	55 (2·3%)	[1·7, 2·9]	334·3	p<0·0001
Colombi et al., 2020	236 (177, 59)	18 (7·6%)	[4·2-11·0]	50·1 (41·2, 8·9)	p<0·0001

[1] Gender proportions not specified.

When comparing the observed and expected values according to smoking prevalence in each country, the differences were very statistically significant in all cases (p<0.0001). This result was also obtained when the expected proportion was analysed by considering the combination of the two US studies.

3.4. Global meta-analysis

Figure 3 provides the meta-analysis results of the 18 studies included in the systematic review. The resulting heterogeneity was I2=69% (p<0.01), so the random model that provided an odds ratio of 0.18 and a 95%CI of 0.14-0.22 was selected.

The meta-analysis results (OR) revealed statistically significant differences in 17 of the 18 studies and in the combined total (p<0.01). Only one study did not show these differences, that by Han et al. (2020).

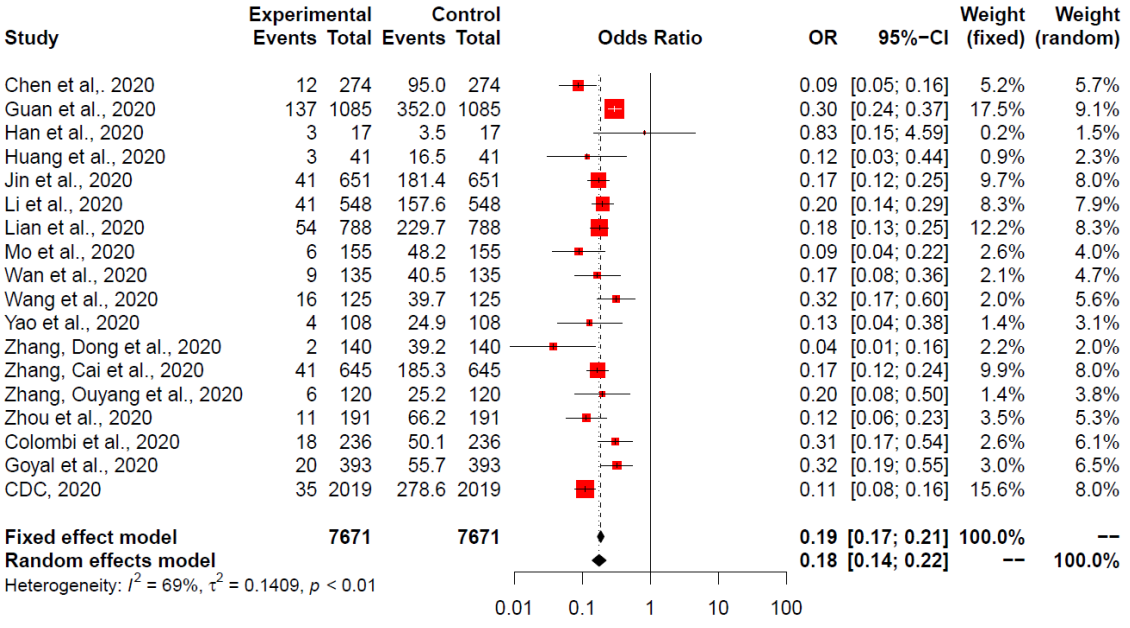

Figure 3. Global Meta-analysis.

4. Discussion

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This work takes data from 18 studies conducted in different parts of the world, but mainly China. They describe the number of current smokers hospitalised and with a confirmed COVID-19 diagnosis. All the studies included in the meta-analysis provide details of patients' smoking background, which allowed the number of current smokers. This is very important because the other studies excluded from the analysis, despite having recruited lots of patients, did not provide information about smoking background [20].

In each case, these data were compared to the prevalence of smokers in each country by considering the proportion of males and females whenever possible. In every case except one, which had the fewest patients, very statistically significant differences were observed ($p<0.001$) and would indicate that something is happening with COVID-19 incidence in smokers.

Both the systematic review and the presented meta-analyses have some limitations. The heterogeneity in the meta-analysis was determined as I2=64% in the Chinese studies and as I2=69% when summing the US and Italian works. The effect of some studies on heterogeneity was explored. Heterogeneity considerably lowered when the work by Guan et al. (2020) was eliminated (I2=36% for the set of Chinese works and I2=56% in the global meta-analysis). This analysis is not provided in the results.

It was not possible to perform a detailed study using the age groups of current smokers, although all patients were adults. As smoking habit prevalence changes with age, mean values were used. With males, this value could vary with age from 41.5% (males aged 70 years) and 60.3% (males between 40-49 years old) in China [21]. Conversely, these values for females were much lower, and varied between 1.2% (aged 18-29 years) and 5.8% (older than 70). The number of males and females was similar in practically all the studies. Generally speaking, more male patients were included in all the studies, they smoked more heavily and were at higher risk of suffering the disease [44]. In females, if tobacco, some of its components or smoking habit had some protective effect, more females would be expected to be hospitalised, but this was not the case. Some confounding factors could exist and would condition the number of hospitalised females. What we doubtlessly observed was that the difference between smokers hospitalised for COVID-19 and the expected values was very significant. Another interpretation could be that smokers were more likely to catch the disease from their habits: touching cigarettes and cigarette packets, exchanging tobacco, touching their face or placing cigarettes in their mouths, etc. Other factors or artefacts could bias this study. For instance, as smokers know they are an at-risk population, they could have been more aware of taking social distancing and hygiene measures. Nonetheless, as the time frame within which the studies were conducted was an early stage of today's pandemic and no differences were observed among them, this would not appear to be a plausible hypothesis.

Another possible bias may have something to do with data quality. We believe that smokers could have attempted to hide this characteristic given the alarm of these characteristics, and the threat of hospitals and ICUs being overcrowded. Nonetheless, most data were taken from electronic medical records, which meant that we had access to patients' smoking background in many cases. Given the serious nature of the pandemic, in other cases we could presume that many smoking patients had stopped smoking before being hospitalised and were, thus, included in the groups of non-smokers or former smokers. So, it would be very interesting to specify the exact time when these data were collected, for example during a medical interview when admitted to hospital or from patients' previous medical records. Moreover, the definition of smoker in such studies is not clear because heavy smokers are not distinguished from occasional smokers.

In any case, it is necessary to remember that tobacco causes 20,000 deaths a day all over the world [16] and, with COVID-19 patients, it generally comes with comorbidities, which means a worse prognosis [15].

4.1. Physiological substrate for anti-inflammatory pulmonary effect

SARS-CoV-2 causes varying degrees of illness. Fever and cough are dominant symptoms, but severe disease also occurs. When COVID-19 patients' aggravation takes place, lung hyperinflammation may appear due to virus-activated "cytokine storm" or CRS [45]. Of the different

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cytokines that increase and reach such an exacerbated response [46], Interleukin-6 (IL-6) in serum is mainly expected to predict SARS-CoV-2 pneumonia severity as the suppression of pro-inflammatory IL-6 has been demonstrated to have a therapeutic effect on many inflammatory diseases, including viral infections [47]. In severe cases, SARS-CoV-2 has been shown to activate both innate and adaptive immune systems in alveolar tissue by inducing the release of many cytokines and subsequent cytokine release syndrome [48]. During this response, levels of pro-inflammatory cytokines (include TNFα, interleukin (IL)-1b, IL-6, and IL-8) rise [46], which is an important cause of death [49]. Therefore, it is believed that controlling such crucial inflammatory factors could be a successful approach to reduce mortality in severe patients.

The existence of a cholinergic anti-inflammatory pathway has been demonstrated, which modulates inflammatory responses during systemic inflammation [50]. α7-nicotinic acetylcholine receptors (α7nAChR) are known to be expressed in macrophages and are essential for attenuating the inflammatory response by their activation during systemic inflammation [51]. The underlying mechanism conveys that α7nAChR activation in infiltrated inflammatory cells, including macrophages and neutrophils, induces not only the suppression of NF-kB activation [52], but also the secretion of pro-inflammatory cytokines and chemokines from inflammatory cells, including alveolar macrophages [53]. In lungs, this process involves a physiological feedback mechanism as it has been demonstrated that pulmonary injury signals produced by inflammation are transmitted by vagal sensory neurons to the central nervous system [54], where they are integrated and transformed into a vagal reflex [55]. This response activates the parasympathetic neurons innervated by the efferent vagus nerve, which results in a higher ACh concentration in lungs [56]. Interestingly, it has been reported that nicotine, an α7nAChR agonist, exerts an anti-inflammatory effect of acute lung injury in a murine model [51]. In other inflammatory diseases, such as ulcerative colitis (UC), smoking or treatment with nicotine has been demonstrated to significantly reduce the risk of developing the disease [52]. Indeed, nicotine has been shown to reduce acute colonic inflammation severity with the concomitant inhibition of IL-6 mRNA expression [57–59]. So, nicotine, an exogenous α7nAchR agonist, has already been demonstrated to selectively down-regulate the inflammatory response in a number of infection and inflammatory t has also been suggested that smoking could interact with susceptibility to SARS-CoV-2 infection through the renin-angiotensin system [60]. It is believed that SARS-CoV-2 uses the angiotensin-converting enzyme-2 (ACE2) receptor to enter cells [14]. However, while smoking would induce chronic lung damage that would, in turn, increase susceptibility to severe COVID forms, evidence suggests that nicotine down-regulates compensatory ACE2 [60,61]. These results support the data included in Table 1 and could explain why smoking is either harmful or presents an unexpected protective effect by reducing the virus entry pathway.

5. Conclusions

The number of hospitalised smokers was smaller than expected based on the smoking prevalence in the different countries. The meta-analysis results obtained in China, US and Italy indicated that smoking habit lowers the likelihood of being hospitalised by COVID-19.

Currently, the most promising trial under run to treat severe COVID-19 patients is the one using Tocilizumab, a blocker of IL-6 receptor for the treatment of cytokine storm [47]. However, very strict criteria for clinical use limits its availability, mainly due to price and adverse effects. Another recent strategy has proposed the use of Baricitinib, which is predicted to reduce the ability of the virus to infect lung cells through ACE2 receptor [62], although drugs with similar action mechanism used in oncology bring serious side-effects [62,63]. Nevertheless, to our knowledge, no clinical trials of nicotine in COVID-19 patients are currently being run. We suspect that nicotine could be contribute to an amelioration of the cytokine storm and severe related inflammatory response through the α7nAChR-mediated cholinergic anti-inflammatory pathway during patient's aggravation. Hence, therapeutic strategies probably should consider the combination of antiviral and anti-inflammatory treatments [64] in order to reduce viral infectivity, viral replication, exacerbated inflammatory response, and to limit side effects.

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Conflicts of Interest: "The authors declare no conflict of interest."

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