

Smoking is independently associated with an increased risk for COVID-19 mortality: A systematic review and meta-analysis based on adjusted effect estimates

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Abstract

Introduction: Smoking can cause muco-ciliary clearing dysfunction and poor pulmonary immunity, leading to more severe infection. We performed this study to explore the association between smoking and mortality of coronavirus disease 2019 (COVID-19) patients utilizing a quantitative meta-analysis on the basis of adjusted effect estimates.

Methods: We conducted a systematic search of the online databases including PubMed, Web of Science, Scopus and Embase. Only articles reporting adjusted effect estimates on the association between smoking and the risk of mortality among COVID-19 patients in English were included. Newcastle-Ottawa scale (NOS) was fitted to assess the risk of bias. A random-effects model was applied to calculate the pooled effect with the corresponding 95% confidence interval (CI).

Results: A total of 73 articles with 863,313 COVID-19 patients were included in this meta-analysis. Our results indicated that smoking was significantly associated with an increased risk for death in patients with COVID-19 (pooled relative risk = 1.19, 95% CI = 1.12-1.27). Sensitivity analysis indicated that our results were stable and robust.

Conclusion: Smoking was independently associated with an increased risk for mortality in COVID-19 patients.

Keywords: COVID-19, smoking, mortality, adjusted effect estimates, meta-analysis

Implications: This present study may contribute to summarizing the association between smoking and the risk of COVID-19 mortality based on adjusted effect estimates. More detailed and complete data on smoking status should be collected to more accurately estimate the effect of smoking on COVID-19 mortality.

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Introduction

Recently, Karanasos et al.¹ have performed a systematic meta-analysis to explore the impact of smoking status on mortality of patients with coronavirus disease 2019 (COVID-19). The authors concluded that smoking was not significantly associated with increased mortality of COVID-19 on the basis of five studies with 838 cases (odds ratio (OR) = 1.45, 95% confidence interval (CI) = 0.78-2.72). However, the pooled effect in this meta-analysis was synthesized on the basis of un-adjusted effect estimates. It has been reported that several risk factors including gender, age and underlying diseases (hypertension, diabetes, chronic obstructive pulmonary disease and chronic kidney diseases, etc.) have significant influences on clinical progression of COVID-19 patients²⁻⁵, suggesting that these risk factors might modulate the association between smoking and the risk of COVID-19 mortality. Moreover, multiple studies have reported that the effect estimates on the association of smoking with COVID-19 mortality were markedly reduced in multivariable analyses compared with univariate analyses⁶⁻⁸. Therefore, this present meta-analysis aimed to clarify whether smoking (current/former) increased the risk of death in patients with confirmed COVID-19 compared to never smoking using a quantitative meta-analysis based on adjusted effect estimates.

Methods

This meta-analysis rigorously adhered to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (<http://www.prisma-statement.org/PRISMAStatement/>). We conducted a systematic search of the online databases including PubMed, Web of Science, Scopus and Embase from January 15th, 2020 to April 12th, 2021. The search terms and key words we used were as follows: “coronavirus disease 2019” or “COVID-19” or “SARS-CoV-2” or “2019-nCoV” or “novel coronavirus” and “smoking” or “smoker” or “tobacco” or “cigarette” or “clinical characteristics” and

“mortality” or “fatality” or “death” or “non-survivor” or “deceased”. The detailed search strategies of various databases are available in Supplementary Table S1. The eligibility criteria were as follows: (1) articles published in English as of April 12th, 2021; (2) studies that examined inpatients and (or) outpatients diagnosed COVID-19 according to World Health Organization (WHO) criteria; (3) articles reporting adjusted effect estimates on the association between smoking and the risk of mortality among COVID-19 patients; (4) observational studies, retrospective studies, prospective studies, cross-sectional studies and case series. The exclusion criteria were the following: (1) non-English-language studies; (2) studies reporting only un-adjusted effect estimates on the association between smoking and COVID-19 mortality; (3) review articles, errata, comments or repeated articles (For studies based on the same data sources, we included only the articles with the most complete data); (4) studies without the adjusted effect sizes for the impact of smoking on COVID-19 mortality. Newcastle-Ottawa scale (NOS) was fitted to assess the risk of bias.

Data from the included studies were extracted independently by two authors (Hongjie Hou and Yang Li). Disagreements were resolved by consensus. The main information included: first author’s name, country, study design, sample size, adjusted risk factors, smoking status, age, percentage of male and effect estimates. The definitions of the extracted variables are reported in Supplementary Table S2. Our study defined the exposed group as those with a history of smoking (former or current smokers) and the control group as never smokers. The study outcome was death (deceased, died, dead, death, mortality, non-survival and fatal) in patients diagnosed with COVID-19. Stata 11.2 (StataCorp LP, College Station, Texas, USA) was applied to calculate the pooled effect and 95% CI on the association between smoking and COVID-19 mortality using a random (Inverse-Variance heterogeneity) model. Heterogeneity was assessed using I^2 statistic. We performed subgroup analyses based on age, country, study design and effect estimate to detect the major sources of heterogeneity

for the reason that differences in the age distributions and regional distributions of study subjects are often an important source of clinical heterogeneity. Similarly, methodological heterogeneity is often induced by the differences in study designs and effect estimates of the included studies. Sensitivity analysis by omitting studies one by one was conducted to examine the stability of our results using R software (version 3.6.3, The R Foundation). We evaluated publication bias with Begg's rank correlation test and Egger's linear regression test to draw more robust conclusions (We regarded publication bias existence if the two tests do not provide a similar result). $P \leq 0.05$ was considered statistically significant.

Results

A total of 25,117 studies were retrieved through initial search. After removing duplications and screening titles and abstracts, 138 records remained for full-text evaluation. 65 articles were subsequently excluded due to lack of adjusted effect estimates on the association of smoking with the risk of mortality in COVID-19 patients. Finally, 73 studies with 863,313 COVID-19 patients were included in this meta-analysis. The flow diagram of study selection is shown in Supplementary Figure S1. The primary characteristics of the included studies are presented in Supplementary Table S3. And the results of the risk of bias assessment are displayed in Supplementary Table S4.

Overall, smoking was significantly linked to an increased risk of mortality in patients with COVID-19 (pooled relative risk = 1.19, 95% CI = 1.12-1.27, random-effects model) (Figure 1). When we restricted analysis in studies presenting data on former smoking explicitly, there was a significant association between former smoking and the increased risk for mortality (18 studies, pooled relative risk = 1.15, 95% CI = 1.05-1.26) (Supplementary Figure S2A), whereas in studies reporting current smokers explicitly, there was no significant association between current smoking and the risk for mortality (17 studies, pooled relative

risk = 1.06, 95% CI = 0.90-1.26) (Supplementary Figure S2B). This significant association was also observed in subgroup analyses based on age (23 studies, pooled relative risk = 1.19, 95% CI = 1.05-1.35 for ≤ 60 years old and 42 studies, pooled relative risk = 1.32, 95% CI = 1.17-1.48 for > 60 years old) (Supplementary Figure S3) and effect estimates (27 studies, pooled hazard ratio (HR) = 1.29, 95% CI = 1.17-1.42; 44 studies, pooled OR = 1.16, 95% CI = 1.05-1.29) (Supplementary Figure S4). Subgroup analysis by study design revealed that there was a significant association between smoking and the increased risk for mortality of COVID-19 patients among retrospective study (49 studies, pooled relative risk = 1.30, 95% CI = 1.18-1.43), but not among prospective study (22 studies, pooled relative risk = 1.08, 95% CI = 0.93-1.25) (Supplementary Figure S5). As we implemented subgroup analysis by countries, the association was still significant in the subgroups of China (6 studies, pooled relative risk = 1.78, 95% CI = 1.44-2.19), Spain (4 studies, pooled relative risk = 1.49, 95% CI = 1.01-2.21) and USA (30 studies, pooled relative risk = 1.18, 95% CI = 1.05-1.34), while no significant association was found in the subgroups of Italy (6 studies, pooled relative risk = 1.49, 95% CI = 0.94-2.35), England (7 studies, pooled relative risk = 1.11, 95% CI = 0.96-1.29) and Mexico (6 studies, pooled relative risk = 0.96, 95% CI = 0.93-0.99) (Supplementary Figure S6). Sensitivity analysis demonstrated that our results were robust and reliable (Supplementary Figure S7). Publication bias existed in Begg's test ($P = 0.025$, Supplementary Figure S8A) and Egger's test ($P < 0.001$, Supplementary Figure S8B).

Discussion

There have been four meta-analyses investigating the association between smoking and the mortality of COVID-19 patients^{1,9-11}. But the findings from all these previous meta-analyses were based on un-adjusted effect estimates. Our present meta-analysis based on adjusted effect estimates demonstrated that smoking was significantly associated with an increased risk for mortality of COVID-19 patients. This association could be explained by several

potential mechanisms. Firstly, Smoking can cause muco-ciliary clearing dysfunction and poor pulmonary immunity, leading to more severe infection^{12,13}. Secondly, smoking can impair redox balance and increase the expression and release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-6 and interleukin-8. And this process might promote cytokine storm marked by overproduction of similar inflammatory mediators, which is closely linked to adverse outcomes in patients with COVID-19^{14,15}. Additionally, recent studies have reported that smoking may upregulate the expression of angiotensin converting enzyme 2 (ACE2), which serves as a receptor when severe acute respiratory syndrome coronavirus 2 enters cells¹⁶⁻¹⁸. Although the relationship between ACE2 expression and disease severity in COVID-19 patients remains unclear, it can be assumed that the upregulated expression of ACE2 might play a role in poor prognoses of smokers through vascular dysfunction or pro-inflammatory response.

In further subgroup analysis by smoking status, the significant association was observed in former smoking, but not in current smoking. The inconsistent results between former smoking and current smoking might be partly explained by longer exposure times and higher prevalence of smoking-related conditions such as cardiovascular and respiratory illness in former smokers. Our finding that current smoking was not significantly associated with the increased mortality of COVID-19 patients agreed with previous finding by Reddy RK and co-workers¹⁰. This insignificant association might be due to the inaccurate records of smoking status during the global pandemic, which resulted in the misclassification of smokers as non-smokers and biased the pooled effect of current smoking towards a null result. Furthermore, self-isolation and lockdown restrictions during the pandemic, combined with increased unemployment and excessive fear caused by the pandemic, might increase relapse of former smokers and initiation of smoking in nonsmokers, which could potentially dilute the smokers with healthy individuals with less cumulative exposure to tobacco. These

speculations need to be validated by the further prospective studies which report the duration of exposure precisely.

In our study, subgroup analysis by effect estimate indicated that the significant association between smoking and COVID-19 mortality was found in OR-reported studies and HR-reported studies, but not in risk ratio (RR)-reported studies. Our study finally included 73 articles, of which 44 reported ORs and 27 reported HRs. In particular, the only two RR-reported articles presented that there was no significant association between smoking and COVID-19 mortality. Likewise, there were 49 retrospective studies, 22 prospective studies and 2 retrospective-prospective studies according to the stratification by study design. Results indicated that there was a significant association between smoking and the increased risk for mortality of COVID-19 patients among retrospective study, but not among prospective study and retrospective-prospective study. Similar pictures emerged in the analysis of subgroup based on country. Thus, our results need to be verified by further studies based on large sample sizes.

Several limitations should be acknowledged in this current meta-analysis. Firstly, smoking status varied among studies included in our analysis. Some studies reported smoking status as “current” or “former” separately, while other studies reported as a history of smoking generally. And most of studies included in our analysis didn't present the data on either duration of smoking or any special smoking habits such as electronic cigarette, water pipe and passive smoking. Secondly, although we searched as much literature as possible, there was publication bias in this study. Thirdly, there was obvious heterogeneity assessed through I^2 . To detect the major source of heterogeneity, we performed subgroup analyses of age, countries, study design and effect estimates, respectively. Whereas, no clear heterogeneity source was identified. Fourthly, although the included studies reported adjusted effect estimates, the adjusted confounding factors varied across studies. Fifthly, the included

studies were mainly retrospective, further prospective studies with large sample sizes are needed to verify the findings.

In conclusion, this present meta-analysis based on adjusted effect estimates showed that smoking was independently associated with an increased risk for mortality in COVID-19 patients. These preliminary findings might contribute to the risk stratification of patients with COVID-19. Policymakers, physicians and public health professionals should take effective measures to promote smoking cessation in order to reduce the mortality in patients with COVID-19. The COVID-19 pandemic should serve as an incentive for patients and at-risk populations to quit smoking. More detailed and complete data on smoking status should be collected to more accurately estimate the effect of smoking on COVID-19 mortality. The mechanisms by which smoking increases the risk of poor prognoses in COVID-19 patients are not fully understood yet, especially regarding ACE2, which warrants further study. Smoking cessation is one of the most immediately modifiable factors for reducing the heavy burden associated with the disease, especially in countries with higher tobacco burdens and higher numbers of vulnerable populations.

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Conflicts of interest: All authors report that they have no potential conflicts of interest.

Author contributions: Haiyan Yang and Yadong Wang conceptualized the study. Hongjie Hou and Yang Li performed literature search and data extraction. Hongjie Hou, Peihua Zhang, Jian Wu, Li Shi, Jie Xu and Jie Diao analyzed the data. Hongjie Hou, Haiyan Yang and Yadong Wang wrote and reviewed the manuscript. All the authors approved the final manuscript.

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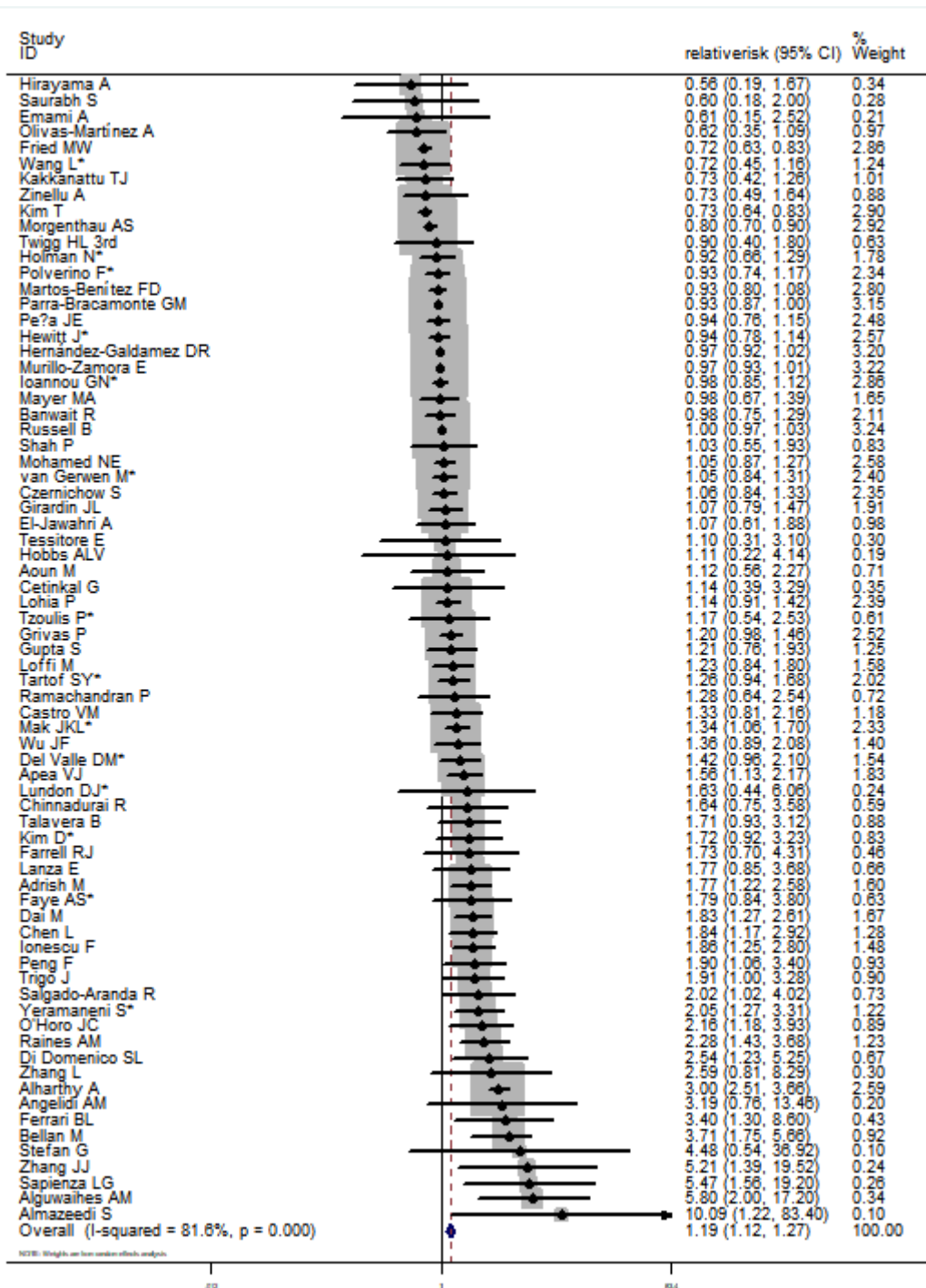


Figure caption

Figure 1. Forest plot with pooled effect and 95% confidence interval (CI) indicating the association between smoking and the risk of mortality in coronavirus disease 2019 (COVID-19) patients. * indicates combined effects based on subgroups.