Smoking is Associated with COVID-19 Progression: A Meta-Analysis

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INTRODUCTION

COVID-19, the coronavirus-transmitted infectious disease, has caused a worldwide pandemic. Smoking[1,2] and e-cigarette use[3] increases risk and severity of pulmonary infections because of damage to upper airways and a decrease in pulmonary immune function. In particular, smokers have a higher risk of infection and mortality from Cov-MERS.[4] Two reviews[5,6] of the first 5 papers presenting data on smoking and COVID-19 reached different conclusions. Another review described 6 published case series presenting data on smoking among COVID-19 patients but did not draw a conclusion about the association of severity of COVID-19 with smoking.[7] We reviewed and summarized 19 peer-reviewed papers presenting data on the association between smoking and severity of COVID-19.

METHODS

We conducted a systematic search using PubMed on April 28, 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)) for studies published between January 1, 2020 and April 28, 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. A total of 907 studies were retrieved through the search, of which 19,[8-26] 16 from China, 1 from Korea, and 2 from the U.S., included data on smoking behavior and COVID-19 disease progression (Table S1). Seventeen studies[9-12,14-26] were based on hospitalized patients and two[8,13] included both hospitalized patients and outpatients.

The exposure group for our analysis were those who had a history of smoking (current smokers or former smokers) and unexposed group was never smokers. Nine studies[10,12,14,18,20,21,23,25,26] assessed whether the patient was a "current smoker," five studies[8,9,13,16,24] assessed whether the patient was a current or former smoker (as separate

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categories), and five studies[11,15,17,19,22] assessed whether the patient had a "history of smoking" (current or former).

Outcomes were progression of COVID-19 to more severe or critical conditions or death. Six studies[11,16,20,21,23,24] categorized the outcome as severe or critical (respiratory distress with respiratory rate ≥ 30/min, or oxygen saturation ≤ 93% at rest, or oxygenation index ≤ 300 mmHg, based on the diagnostic and treatment guideline for SARS-CoV-2 issued by Chinese National Health Committee or the American Thoracic Society guidelines for community acquired pneumonia[23,24]) or non-severe, three[10,17,18] categorized the outcome as progression or improvement, two[8,14] categorized the outcome as ICU admission or non-ICU admission, one[13] categorized the outcome as the primary composite end point (ICU admission, the use of mechanical ventilation, or death) or not, three[9,22,26] categorized the outcome as death or survivor, one[19] categorized the outcome as the occurrence of severe cases (without defining severe) or death or mild, one study[15] categorized the outcome as clinical deterioration during the hospitalization and needed supplemental oxygen therapy, one[12] categorized the outcome as a need of intensive mechanical ventilators, and one[25] categorized the outcome as abnormal chest imaging findings.

We also conducted sensitivity analysis using the 5 studies[8,9,13,16,24] that we were able to compare the association of severity of COVID-19 between current smokers and never smokers.

We computed unadjusted odds ratios (OR) and 95% confidence interval (CI) for each study using the number of smokers (current and former) and never smokers with and without disease progression. Random effects meta-analysis was performed using the Stata version 14.0 *metan* command and using *metabias* command with Harbord and Peters to test for the presence of publication bias.

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RESULTS

A total of 11,590 COVID-19 patients included in our meta-analysis, 2,133 of whom (18.4%) experienced disease progression and 731 (6.3%) with a history of smoking. A total of 218 patients with a history of smoking (29.8%) experienced disease progression, compared with 17.6% of non-smoking patients. The meta-analysis showed an association between smoking and COVID-19 progression (OR 1.91, 95% CI 1.42-2.59, p=0.001) (Figure 1). There was moderate heterogeneity among the studies (I^2=38%, *p*=0.048) and no significant evidence of publication bias (Harbord's *p*=0.813, Peters' *p*=0.941).

Sensitivity analysis of the five studies[8,9,13,16,24] of current smokers vs. never smokers yielded a similar result (OR 1.91, 95% CI 1.10-3.29, p=0.021). There was no evidence of significant heterogeneity (I^2=53.5%, *p*=0.072) or publication bias (Harbord's *p*=0.382, Peters' *p*=0.512) among the studies.

DISCUSSION

Our analysis confirms that smoking is a risk factor for progression of COVID-19, with smokers having 1.91-times the odds of progression in COVID-19 severity than never smokers. This finding contrasts with an earlier meta-analysis,[6] which included only 5 studies and used a non-standard method to compute the meta-analysis. The finding that smoking is associated with COVID-19 progression is not surprising because of the adverse effects of smoking on pulmonary immune function.[1,2]

Some [27,28] have argued that the fact that reported smoking prevalence in COVID patients is lower than has been reported in the general population as evidence for a protective effect of smoking. As noted above, the low prevalence reported among COVID patients may be due to under-assessment of smoking, especially in the difficult conditions present when caring for people in overwhelmed health systems.[29,30] In any event, our analysis shows that

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among those people assessed as smokers risk of disease progression is significantly increased.

Limitations

Our study has several limitations.

The definition of "smoking" sometimes includes former smokers and sometimes does not. Only three studies[8,13,24] separated current and former smokers in different categories, which was not enough data to do a meta-analysis for current and former smokers separately. Because the lung recovers after someone stops smoking, including former smokers in the exposed group may bias the effect estimate to the null. Reported smoking prevalence in the 16 studies in China ranged from 3.7% to 16.8%, which was substantially lower than 27.7% (52.1% for men and 2.7% for women) smoking prevalence in 2015.[31] Reported smoking prevalence in the U.S. (3.6-5.1%) and Korea (18.5%) studies were also lower than the countries' smoking prevalence; U.S. smoking prevalence in 2018 was 13.7% (15.6% for men and 12.0% for women)[32] and Korea in 2017 was 21.1% (37.0% for men and 5.2% for women).[33] It is highly likely that many smokers were misclassified as nonsmokers, which would bias the risk estimate toward the null.

This analysis is based on unadjusted ORs that were either reported in the studies[17] or that we calculated based on counts in the studies.[8-16,18-26] Only one[17] of the studies reported unadjusted and adjusted ORs using multivariate analysis; after adjusting for confounding by age, maximum temperature at admission, respiratory failure, severe illness, albumin, creatinine, procalcitonin, and C-reactive protein level, the effect of smoking on disease severity increased (unadjusted: OR 12.19, 95% CI 1.76-84.31, p=0.011; adjusted: OR 14.29, 95% CI 1.58-25.0, p=0.018). Three peer-reviewed meta-analysis papers[6,34,35] on association between smoking and COVID-19 were also based on unadjusted odds ratios, but with fewer studies included.

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None of these studies assessed e-cigarette use.

All these limitations suggest that this analysis underestimates the risk of smoking in terms of increasing COVID-19 severity.

All 19 studies were of patients who had already developed COVID-19, so the risk estimate we report does not represent the effect of smoking on the risk of contracting COVID-19 in the general population. As population-level testing ramps up, it would be useful to collect data on smoking and e-cigarette use to determine what risks these behaviors impose in terms of infection.

Conclusions

Smoking is associated with COVID-19 disease progression. Physicians and public health professionals should collect data on smoking and, given the pulmonary effects of e-cigarettes,[3] e-cigarette use as part of clinical assessments and add smoking (and, to be health protective, e-cigarette) cessation to the list of practices to blunt the COVID-19 pandemic.

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COMPETITING INTERESTS

Nothing to report.

CONTRIBUTORSHIP

RP developed the idea for the study, collected, analyzed the data, and wrote the first draft of the manuscript. SAG assisted with revising and refining the manuscript.

DATA SHARING STATEMENT

All data used to prepare this paper are available from the cited sources.

DISCLOSURE

The authors have nothing to disclose.

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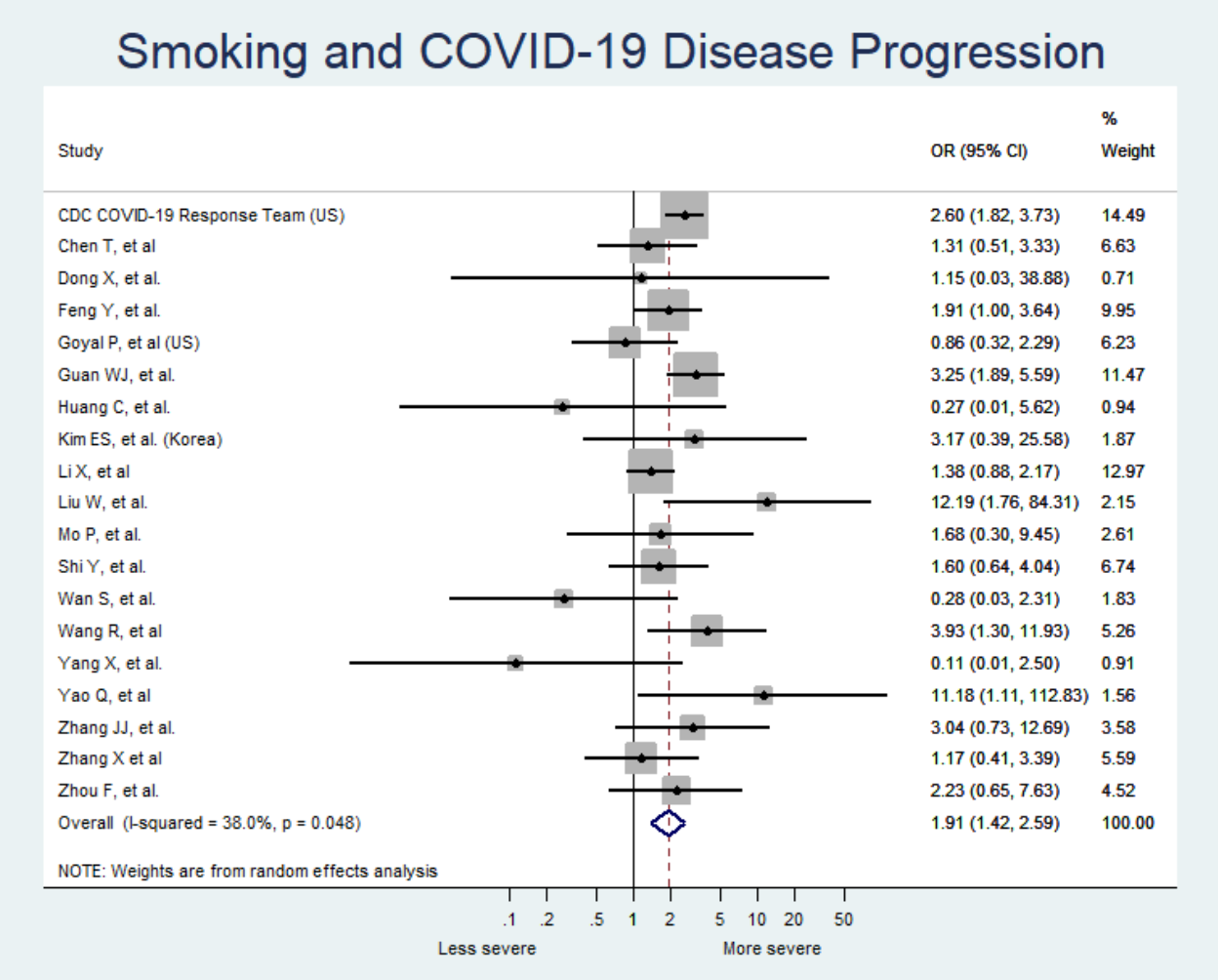

Figure 1. Smoking is associated with COVID-19 progression. All papers from China unless otherwise indicated.

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