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Commentary
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Commentary

# Impact of Smoking Status on Disease Severity and Mortality of Hospitalized Patients With COVID-19 Infection: A Systematic Review and Meta-analysis

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The recent COVID-19 pandemic has raised concern regarding risk factors associated with disease severity and case fatality. In this context, the association of smoking with severity and mortality of COVID-19 infection remains controversial.[1] We conducted this systematic review and meta-analysis to summarize relevant studies and quantify the impact of smoking on disease severity and mortality of hospitalized COVID-19 patients.

The primary outcome was a composite for disease severity including severe disease (including critical cases), ICU admission or invasive ventilation, and adverse disease progression or refractory disease. The secondary outcome was death. Inclusion criteria were as follows: (1) full-length original research publications in peer-reviewed journals in English; (2) inclusion of hospitalized adult patients with COVID-19 infection; (3) reported incidence of smoking stratified by a component of the primary outcome or mortality status; and (4) sample size > 20 patients. Details of literature search, data extraction, and statistical analysis are available in online Supplementary Material. Briefly, a systematic review of literature from September 1, 2019 to May 4, 2020 was performed, and additional data sources were identified through manually searching references. Two independent reviewers (A.K. and K.A.) recorded the incidence of smoking per group and performed an assessment of study quality using seven indicators (see online Supplementary Material for details).

The initial search identified 652 results. After screening titles and/or abstracts, 166 articles remained for full-text assessment from which 146 were subsequently excluded. Two additional studies were identified by searching references. Overall, 22 studies met our inclusion criteria, 17 reporting on severity,[2–18] 4 on mortality,[19–22] and 1 on both[23] (Supplementary Table). Study quality was generally low (Figure 1; online Supplementary Material). For the primary outcome of disease severity, 18 studies were included with 6310 patients.[2,4–19,21] Smoking modestly increased the risk for the combined end point of disease severity (odds ratio [OR] = 1.34, 95% confidence intervals [CI] = 1.07–1.67, $I^2$ = 45%) (Figure 1A). Sensitivity analyses were consistent (online Supplementary Material). After restricting the analysis in studies explicitly reporting current smoking, the association of smoking with disease severity was not statistically significant (10 studies with 4152 patients; OR = 1.12, 95% CI = 0.84–1.50, $I^2$ = 38%).

There was a difference ($p$ = .03) between Chinese studies (16 studies—4423 patients; OR = 1.48, 95% CI = 1.17–1.87; $I^2$ = 40%)[2,4,6–12,14–19,21] and US studies (2 studies—1887 patients; OR = 0.65, 95% CI = 0.33–1.29; $I^2$ = 0%).[5,13] Visual inspection of the funnel plot did not reveal publication bias.

Meta-regression analyses are reported in online Supplementary Material. Age ($Z$ = –0.91, $p$ = .05) and diabetes ($Z$ = –2.81, $p$ = .005) had significant negative associations with log-OR of smoking for disease severity (Supplementary Figure). In studies with low (<15%) prevalence of diabetes, smoking increased the risk for severe disease (OR = 1.66, 95% CI = 1.26–2.18, $I^2$ = 34%), whereas in studies with high (≥15%) prevalence of diabetes, there was a trend for a negative association (OR = 0.70, 95% CI = 0.46–1.08, $I^2$ = 0%) ($\chi^2$ for subgroup differences = 10.82, $p$ = 0.001) (Supplementary Figure).

For mortality, five studies with 838 patients were included.[3,9,20,22,23] Smoking was not significantly associated with increased mortality (OR = 1.45, 95% CI = 0.78–2.72, $I^2$ = 18%) (Figure 1B). Results were similar for studies explicitly reporting current smoking (2 studies—465 patients; OR = 1.57, 95% CI = 0.75–2.31, $I^2$ = 0%).

Our main findings were (1) that smoking modestly increases the risk of severe disease in hospitalized COVID-19 patients, whereas

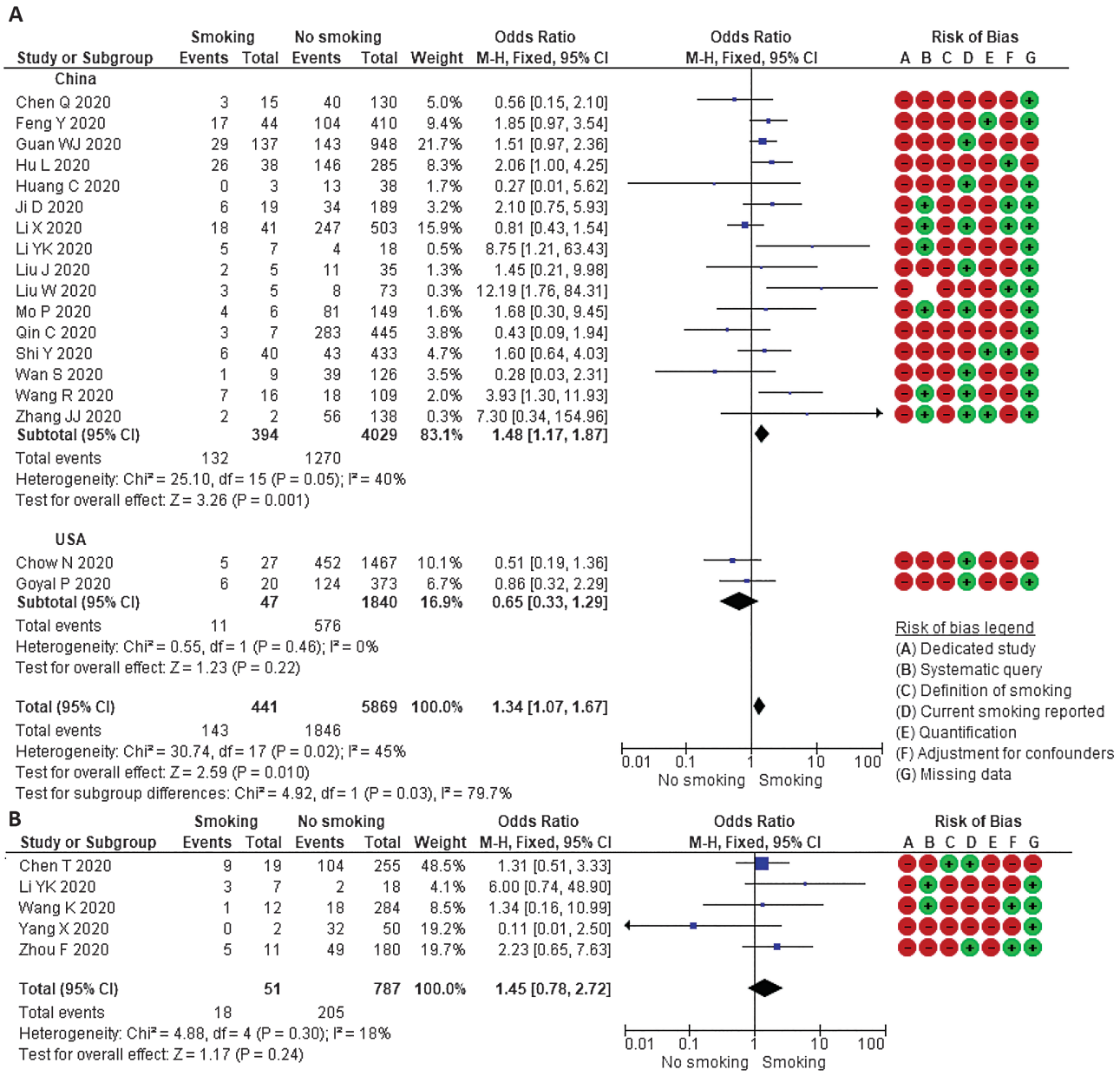


**Figure 1.** Forest plot and risk of bias tables examining in hospitalized COVID-19 patients the association of smoking with (A) the composite end point of disease severity in China and in US regions and (B) mortality. Boxes represent odds ratio (OR) and lines represent the 95% confidence interval [CI] for individual studies. Diamonds and their width represent pooled ORs and the 95% CI, respectively.

mortality data suggest a similar effect size but are currently inconclusive due to a low sample size and (2) that this increased risk for disease severity is more prominent in younger patients without diabetes.

Although smoking may enhance lung inflammation, increase epithelial cell permeability, and cause mucus overproduction and impaired mucociliary clearance,[24] its specific impact on COVID-19 disease is controversial. Hypotheses support both a potentially hazardous impact via overexpression of the ACE2 receptor gene[24] and a potentially protective effect via attenuation of the commonly observed in critically ill patients with COVID-19 infection excessive immune response.[1] Our findings demonstrate an adverse impact for smoking on disease severity of hospitalized COVID-19 patients, which was more pronounced in younger patients without diabetes. Thus, our study provides evidence supporting the utilization of smoking cessation programs, especially in younger populations, as part of a strategy to minimize the adverse consequences of COVID-19 pandemic. Although smoking increased the risk of severe disease in hospitalized COVID-19 patients, it is not clear whether this hazard derives from nicotine itself or from other toxic components of tobacco smoke; therefore, a positive or neutral impact of nicotine alone on disease severity cannot be excluded based on the present study.

Although most patients were from China, a considerable number of US patients were included, notably with evidence of regional differences. This difference may be explained by the higher age and diabetes ratio of the non-Chinese population, which we showed to be important risk moderators, or could be due to further differences

in comorbidities and care. Therefore, updated studies more representative of the global population are urgently needed.

Our study had several limitations. This meta-analysis is prone to bias attributed to the included retrospective studies, which relied on poor-quality data and did not specifically investigate the impact of smoking. However, due to the nature of the analysis and the need to quickly gain insights into COVID-19 infection mechanisms, it is unlikely that prospective, high-quality studies will be available soon. Moreover, study heterogeneity was low-to-moderate and sensitivity analyses were consistent. The number of included studies and patients for the end point of mortality is small and more data are required to properly examine this association. Finally, despite screening included studies for duplicate patients, we cannot exclude the possibility that some patients, especially in nationwide registries, were reported twice.

In summary, current data suggest a possible adverse impact of smoking on disease severity and mortality of hospitalized COVID-19 patients, which is more pronounced in younger patients without diabetes. Further data more representative of the global population are required to corroborate these preliminary findings.

## Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, is available online at https://academic.oup.com/ntr.

## Declaration of Interests

None declared.

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