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# What Is the Risk of Developing a Severe Form of COVID-19 Infection Among Adults Who Currently Smoke Compared to Ex-smokers? Protocol for a Systematic Review and Meta-analysis

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**Abstract**

**Introduction**: Smoking is associated with an increased risk of chronic diseases and poorer outcomes in patients with COVID-19. Although lung function improves after smoking cessation, evidence directly comparing COVID-19 severity between current and former smokers remains limited.
**Objective**: This systematic review aims to synthesize available evidence on the risk of developing severe COVID-19 among current smokers compared with former smokers.
**Methods and Analysis**: This review will follow the PRISMA-P 2015 guidelines. Non-randomized studies published from December 2019 onward will be systematically searched in PubMed, Cochrane CENTRAL, Embase, and Epistemonikos. Additional studies will be identified through grey literature sources, relevant journals, and reference list screening. Eligible studies must report outcomes for both current and former smokers and include at least one marker of severe COVID-19: ICU admission, assisted ventilation, or death. Two reviewers will independently screen studies and extract data. Risk of bias will be assessed using the Newcastle–Ottawa Scale, and the GRADE framework will be applied to evaluate the certainty of the evidence. Statistical analyses will be conducted using R version 4.3.2. Heterogeneity will be quantified using the $I^2$ statistic; a fixed-effect model will be used when heterogeneity is low, and a random-effects model will be applied otherwise. As this review will use published data, ethical approval is not required. PROSPERO Registration Number: CRD42022368552.

Keywords: COVID-19; Sars-CoV-2; Severity, Negative progression; Ex-Smokers; Current smoking, Review.

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## Introduction

The pathogen responsible for the coronavirus disease first identified in Hubei Province, China, in 2019 (COVID-19) is the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1,2). COVID-19 rapidly posed a substantial risk of international spread, threatened global trade, and had profound public health consequences (3). As a result, it was designated a *Public Health Emergency of International Concern (PHEIC)* by the World Health Organization (WHO) due to its ability to cross international borders, cause mortality, and disrupt global systems (4). It is one of six PHEIC declarations issued by the WHO to date, alongside the 2009 influenza pandemic, wild poliovirus (2014), the West African Ebola outbreak (2014), the Zika virus (2016), and the 2018 Ebola outbreak (4). On 11 March 2020, the WHO officially declared COVID-19 a pandemic (5), and it has since affected nearly every country worldwide, hindering socioeconomic development (6).

Risk factors for COVID-19 severity include demographic characteristics such as age and sex, as well as lifestyle factors, underlying medical conditions, and laboratory parameters (7). Most infected individuals experience mild to moderate illness, predominantly affecting the respiratory tract, and recover at home (8). However, a subset progress to severe disease requiring hospital admission, intensive care, mechanical ventilation, or other forms of organ support, with potential progression to multi-organ failure and death (9).

Smoking is a well-established lifestyle risk factor for chronic diseases associated with adverse COVID-19 outcomes (18). It is the leading preventable cause of death globally and is strongly associated with numerous respiratory conditions (11–13). Public health measures remain essential to prevent smoking initiation and support cessation efforts (10). Smoking alters both cellular and humoral immune responses (12), impairs the function of polymorphonuclear leukocytes critical for host defense (12), and compromises respiratory immunity by promoting peribronchiolar inflammation, fibrosis, impaired mucociliary clearance, and epithelial damage (13). These mechanisms increase susceptibility to systemic infections (11).

During the pandemic, concerns were raised regarding whether current smokers have worse clinical outcomes or heightened susceptibility to SARS-CoV-2 infection (14). The virus gains entry into cells via the angiotensin-converting enzyme 2 (ACE-2) receptor (15). Evidence suggests that current smokers exhibit increased ACE-2 gene expression in the airway and oral epithelium (13,16), potentially elevating infection risk (17). SARS-CoV-2 may also infect T-lymphocytes through ACE-2 receptors and the CD147-spike protein pathway, contributing to lymphopenia (18,19), a biomarker of severe disease (20–22). Conversely, some studies have suggested that nicotine may inhibit ACE-2 receptor activity (23). Despite these conflicting findings, both former and current smoking status have been associated with respiratory viral and bacterial infections (24) and worse outcomes when infected (25).

Importantly, the increased risk associated with smoking declines substantially after cessation and eventually normalizes (26). A recent review (27) reported limited evidence that disease severity among hospitalized COVID-19 patients is higher in current or former smokers compared with never-smokers, and evidence remains insufficient to conclude whether infection, hospitalization, or mortality rates are increased in these groups (28). Many studies evaluating smoking status and COVID-19 progression have small sample sizes, and confounding may obscure true associations (29).

**Rationale for This Systematic Review and Meta-analysis**

Evidence regarding the relationship between smoking and COVID-19 outcomes remains inconsistent. Misclassification of smoking status in earlier studies, as identified in a previous meta-analysis, likely underestimated the true effect of current smoking on COVID-19 severity and mortality (16). As the lungs recover following smoking cessation (30), including former smokers in the "exposed" group may bias effect estimates toward the null.

No previous review has directly compared the risks of severe COVID-19 between current and former smokers. Several studies have reported a higher likelihood of severe respiratory disease among smokers than non-smokers (27). Understanding these differences is crucial for clinical risk assessment, strengthening public health messaging, and identifying intervention targets. Most early studies were conducted in China during 2020, and updated evidence is needed as the pandemic evolves. Additionally, one of the global non-communicable disease targets for 2025 is a 30% reduction in tobacco use among adults; findings from this review can support ongoing global tobacco-control efforts (31).

**Objectives of the Review**

1. **To determine the risk of severe COVID-19 disease** (ICU admission, mechanical ventilation, or death) in current smokers compared with former smokers.
2. **To examine the effect of comorbidities** on COVID-19 severity among current and former smokers.

## Methods

This systematic review and meta-analysis protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 checklist (32) and other established guidelines (33,34). It is registered with PROSPERO (2022).

**Eligibility Criteria**

Studies published in any language involving adult current and former smokers diagnosed with COVID-19 using RT-PCR (35) will be included. The PICOS framework guides inclusion and exclusion criteria.

**Inclusion Criteria**

**Population:** Adults ≥18 years who smoke, **Exposure:** Current smoking, **Comparator:** Former smokers, **Outcome:** Severe COVID-19, defined as ICU/HDU admission, mechanical ventilation, or death (16) and **Design:** Observational studies (retrospective, prospective, case series, descriptive studies) from December 2019 onward.

**Exclusion Criteria**

Systematic reviews, opinion pieces, laboratory studies, studies not reporting on current or former smokers, pediatric studies, and studies on other coronaviruses will be excluded. Reasons for exclusion will be documented in the PRISMA flow diagram.

**Patient and Public Involvement**

As this is a systematic review protocol, no individual-level patient data will be collected, and patients will not be involved in the planning, analysis, or dissemination processes.

**Information Sources**

A comprehensive search will be conducted in PubMed, CINAHL, Embase, Web of Science, Cochrane CENTRAL, Scopus, and Epistemonikos from December 2019 to the present.

**Grey Literature**

Grey literature will be searched through the British National Bibliography for report literature, the Science Citation Index, OpenGrey, and ProQuest Dissertations. Reference lists of included studies and relevant journals (SAGE, AJOL, *The Lancet*) will also be searched.

**Search Strategy**

A combination of keywords and controlled vocabularies will be used, linked by Boolean operators. Wildcards/truncation will capture variations in terminology. A sample search strategy includes: *COVID-19 OR SARS-CoV-2 OR coronavirus infection AND severity OR progression OR ICU admission OR mechanical ventilation OR death AND smoking status OR current smoker OR smok* OR tobacco smoking AND adult AND observational studies.*Search terms will be adapted for each database.

**Data Management and Study Selection**

All retrieved articles will be imported into ZOTERO for de-duplication. Screening will occur in three stages; title, abstract, and full text, by two independent reviewers (AJT and ANP), with disagreements resolved by a third reviewer (OJC).

**Data Extraction**

A standardized data extraction form will be piloted on four studies. Two reviewers will independently extract data on

study characteristics, PICOS variables, and outcomes. Disagreements will be resolved through discussion.

**Handling Missing Data**
Study authors will be contacted for clarification when necessary. If missing data cannot be retrieved, the affected data will be excluded and reasons documented.

**Outcomes**
The primary outcome is severe COVID-19, defined as ARDS, $SpO_2$ <94%, need for mechanical ventilation, ICU admission, or death (16). Secondary outcomes include the influence of comorbidities on disease progression among current and former smokers.

**Risk of Bias Assessment**
The Newcastle–Ottawa Scale will assess risk of bias in included observational studies across selection, comparability, and outcome domains.

**Data Synthesis**
Qualitative and quantitative syntheses will be undertaken. For dichotomous outcomes, odds ratios with 95% CIs will be extracted. A fixed-effect model will be used if heterogeneity is low ($I^2$ <50%) (36); otherwise, a random-effects model will be applied (37). Sensitivity analyses will assess robustness.
Subgroup analyses will include: studies from China versus other regions and other studies with sufficiently similar study designs.

Statistical analyses will be conducted using **R** (version 4.3.2).

**Assessment of Meta-biases**
Given sufficient eligible studies, publication bias will be assessed using funnel plots.

**Certainty of Evidence**
The GRADE framework (38) will be used to rate the certainty of evidence as high, moderate, low, or very low. Observational evidence may be upgraded for large effects, dose–response relationships, or if confounders would reduce but not negate the observed effect (39,40). Downgrading will occur for risk of bias, inconsistency, imprecision, indirectness, and publication bias (41,42).

**Dissemination**
Findings will be presented at national and international conferences and submitted to a peer-reviewed journal. Any protocol amendments will be documented.

**Ethical Considerations**
As the study synthesizes data from published literature, ethical approval is not required.

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**Author Contributions**
AJT conceptualized and designed the protocol and was written, revised and final version approved by AJT and ANP.

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**Competing Interests**
None declared.

**Patient and Public Involvement**
No involvement.

**Patient Consent for Publication**
Not applicable.

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