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Original Article

Does Tobacco Use Enhance the Risk of SARS-CoV-2 Infection: Evidence from Eastern Indian Population

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Abstract

Background: Tobacco consumption causes altered immune and inflammatory responses which lead to various respiratory diseases such as asthma and chronic obstructive pulmonary disease, as well as cardiovascular and cerebrovascular disorders. Studies have only confirmed the harmful effects of tobacco consumption on the severity of COVID-19. The present study aimed to explore the association between tobacco consumption and the initiation of COVID-19.

Methods: This retrospective cohort study was conducted to explore the relationship between tobacco consumption and COVID-19. A brief closed-ended, self-structured questionnaire was prepared to record participants' responses. The Participants included the individuals who visited Rajendra Institute of Medical Sciences (RIMS), Ranchi, India for the COVID-19 diagnostic test. The statistical analysis was performed using SPSS software (version 24). The chi-square test and logistic regression analysis were also used to predict the odds of getting infected with COVID-19.

Findings: A total of 521 valid responses were obtained and subjected to analysis. Moreover, 256 participants (49.13%) were COVID-19 positive and 57 participants (10.94%) were tobacco users. The odds ratio of tobacco consumption was higher in COVID-19-positive patients compared to COVID-19-negatives (OR = 1.78; 95% CI 1.01, 3.13). The current tobacco users had a higher risk of developing COVID-19 as compared to the former users (OR = 4.8; 95% CI 1.39, 16.61). The frequency and duration of tobacco use also affected the COVID-19 infectivity rate but these were statistically insignificant.

Conclusion: The COVID-19 positivity rate was significantly higher in tobacco users, especially in current tobacco users as compared to former users. Nevertheless, gender and occupation had no significant effect on COVID-19 incidence in this study.

Keywords: Tobacco, COVID-19, Smokeless tobacco, Smoking, Nicotine

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Introduction

Worldwide efforts have been made to identify effective treatments for COVID-19 infection and reduce the effects of the disease. Tobacco use is an established risk factor for several illnesses such as cancer, cardiovascular disease, and cerebrovascular disease. Tobacco use is mainly divided into two broad categories i.e., smoking tobacco and smokeless tobacco (SLT). The latter refers to unburned tobacco products that are inhaled nasally or chewed orally. In Asian countries, different forms of SLT products are used, e.g., *gutkha* (mixture of tobacco, crushed areca nut, spices, and other ingredients), *khaini* (sun-dried and coarsely cut fermented tobacco plant leaves), snuffs, *mawa* (prepared through mixing the areca nut, slaked lime, and processed tobacco), *mishri* (a chewing form which contains roasted tobacco leaves powder), *jarda* (a locally used form of chewing tobacco), tobacco tooth powders, and tobacco paste.[1] The use of tobacco products causes altered immune responses leading to inflammatory and allergic reactions, asthma, and chronic obstructive pulmonary disease, atherosclerotic events, aortic aneurysms, coronary heart disease, and cerebrovascular disorders. All of these are the risk factors for severe COVID-19.[2] The smokers are expected to be more susceptible to COVID-19 infection with angiotensin converting enzyme 2 (ACE2) being a possible explanation for this association.[3] However, few earlier studies found contradicting results and suggested

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beneficial effects of various forms of tobacco usage on COVID-19 disease severity and adverse outcomes. This assumption of the beneficial effect of tobacco use has been reported by initial studies in hospital settings in China. It was noted that the smoking prevalence in the general population of these Chinese locales was higher than that in hospitalized patients.[4,5] The possible mechanism of the protective effect of tobacco on disease progression through alteration of the renin-angiotensin-aldosterone system (RAAS) was proposed. Nicotine may downregulate ACE2 receptors and maintain the cholinergic anti-inflammatory function.[6] Several studies reported decreased odds of testing positive for COVID-19 among smokers. However, the results of these studies had methodological limitations and were biased.[7] It may be postulated that nicotine can decrease cytokine storm and maintain a balanced immune response against COVID-19.[8] However, nicotine or other tobacco products cannot be recommended for the above-said effect because these products contain hundreds of chemicals with carcinogenic properties and are linked to developing several respiratory and cardiovascular diseases.[1,9]

Well-planned case-control studies have reported the harmful effects of tobacco consumption. It has been observed that smokers experience more severe outcomes and a higher progression rate of COVID-19.[3,10] Recent meta-analyses have reported that tobacco use worsens COVID-19 leading to the increase in hospitalization, requirement for critical care services, mechanical ventilation support, or death as compared with non-smokers.[10,11] However, these studies could not confirm the association of tobacco use with the onset of COVID-19. The World Health Organization (WHO) has also pointed out the need to know whether tobacco consumption is related to the initiation of COVID-19.[12]

A retrospective study on the association of tobacco use, in smoking and smokeless forms, with COVID-19 disease might be advantageous. Moreover, the previous studies on the relationship between COVID-19 and tobacco use focused on smoking tobacco forms. Hence, the present study was conducted to examine the association between tobacco use and the initiation of COVID-19 infection.

Methods

This was a retrospective cohort study conducted at the Department of Pharmacology, Rajendra Institute of Medical Sciences (RIMS), Ranchi, India. The study population consisted of individuals who provided nasal and throat swab samples for COVID-19 diagnostic purposes at the Department of Pharmacology, RIMS, Ranchi, India. Data collection started after ethical approval from Institute Ethics Committee, RIMS, Ranchi, India. The study was conducted from May 2021 to September 2021 and followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. The individuals with a Truenat test (for COVID-19) cut-off value below 32 were classified as COVID-19 diagnosed/positive cases. The study included participants who met the following criteria: (i) age 18 years and above, (ii) both genders, and (iii) undergoing COVID-19 testing at the Department of Pharmacology, RIMS, Ranchi. The participants who did not have telephone access were excluded from the study. A list of phone numbers, COVID-19 test results, and Truenat CT values for all individuals was obtained from the department. Separate lists of COVID-19 confirmed positive and confirmed negative individuals were prepared and every individual was given a unique number. A random computer-generated sequence was made, and the individuals were contacted telephonically based on their sequence order in the list till the desired sample size was achieved. Two research staff were trained for data collection and made the calls. The objectives of the study, the anonymity of the responses, and the voluntary nature of telephonic surveys were explained to the participants. Verbal consent was obtained before administering the questionnaire telephonically. The responses were marked with a pen on the questionnaire proforma. If a candidate did not receive the phone on the first instance, a repeat call was made the next day before moving on to the next individual from the list. A brief closed-ended, self-structured questionnaire was prepared to record the responses of the participants regarding the demographics as well as the type, form, frequency, and duration of tobacco use. The severity of tobacco use was assessed by the habit index calculated by multiplying duration and frequency. The content validity of the questionnaire was ensured with the help of experts. Before actual data collection, a pilot study with a small sample (10 participants) was done to check the acceptability and comprehensibility of the questionnaire. The questionnaire's reliability was also measured by obtaining responses from the same participants after a 10-day gap and was found to be acceptable (alpha value = 0.86). The participants whose responses did not match the previous ones were excluded from the analysis. The STROBE flow chart showing the number (n) of patients involved in different stages of the study is presented in Figure 1.

The sample size was estimated based on a study by Miyara et al on the association between tobacco use and the COVID-19 infection severity.[13] The calculations were done via Epi-Info software (version 3.01) using the following parameters: two-sided confidence level (1-alpha) = 95, power = 80, case-control ratio = 1, the fraction of controls with exposure = 25.4, the proposed fraction of cases with exposure = 6.1, and minimum value of extreme odds ratio to be detected = 0.23. The calculated sample size was 150 (75 cases and 75 controls). The sample size was inflated by four times anticipating complete/partial/incomplete responses from the participants,

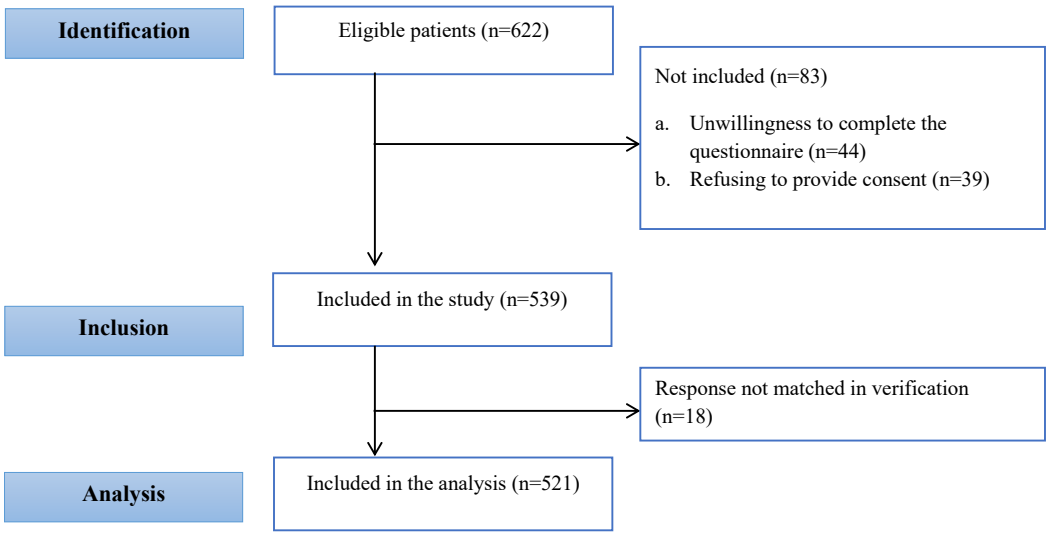

Figure 1. STROBE Flow Chart showing the number (n) of patients involved in different stages of the study

commonly done in telephonic surveys.

For statistical analysis, the responses of the participants were entered into Microsoft Excel and IBM SPSS Statistics software (version 24) was used for data analysis. The incidence of COVID-19 was taken as the dependent variable, while age, gender, occupation, tobacco habit, tobacco use history, type of tobacco, frequency of tobacco use, and duration of tobacco use were considered as the independent variables. Using the chi-square test, the independent variables were grouped into binary categories to determine the association between the study variables. Logistic regression analysis was used to predict the odds of being infected with COVID-19. A *P* value of < 0.05 was considered to be significant. If a participant did not answer all questions, the statistical association was determined only for the valid responses.

Results

A total of 521 participants gave their responses. The mean age of the participants was 40.43 ± 17.42 years. Moreover, 256 participants (49.13%) were confirmed COVID-19-positive cases and 57 participants (10.94%) were tobacco users. Complete responses were not obtained for many of the questions e.g., 15 (2.8%), 11 (2.1%), and 56 (10.74%) participants preferred not to reveal their age, gender, and current tobacco use history, respectively.

Table 1 shows the association of demographics and different study variables with the incidence of COVID-19. No significant association was found between gender and occupation for COVID-19 positivity. The odds of tobacco consumption were higher in participants with positive COVID-19-infection compared to that for negative ones (OR = 1.78; 95% CI 1.01, 3.13) (Table 1). Both current and past tobacco users had a high possibility of getting COVID-19 infection. However, the current tobacco users showed a significantly higher risk of being affected by COVID-19 disease compared to the former users (OR = 4.8; 95% CI 1.39, 16.61). The frequency of tobacco use also affected the COVID-19 infectivity rate but that was statistically insignificant. The odds ratio for the frequency of tobacco use was 1.36 (95% CI 0.42, 4.39). Similarly, the duration of tobacco use affected the COVID-19 infectivity rate, but the odds ratio for the duration of tobacco use was statistically insignificant (OR = 1.24; 95% CI 0.42, 3.65). For the severity of tobacco use, the habit (gutkha) index was calculated by multiplying duration and frequency. The odds ratio for the habit index was statistically insignificant (OR = 0.77; 95% CI 0.23, 2.54).

A forest plot was generated to model the combined effect of the variables on the occurrence of COVID-19 (Figure 2). Tobacco use, either past or present, significantly increased the chances of getting COVID-19. The value of the Nagelkerke R square model was 31.6%.

Discussion

This single-center retrospective study investigated the association between tobacco use and COVID-19 disease. Several studies have reported an inconsistent relationship between smoking and COVID-19 infection.[10] The SARS-CoV-2 virus invades the host cells through the angiotensin converting enzyme 2 (ACE2) receptors. Certain studies have indicated that smokers may have an increased susceptibility to COVID-19 infection due to elevated gene expression and subsequent receptor levels in the airway and oral epithelial cells. Nonetheless, some studies reported that nicotine downregulates the activity of ACE2 receptors.[5]

ACE2 receptors are present in type II alveolar cells, bronchial cells, and neurons, including tissues of the heart, kidney, and uterus.[14] ACE2 is an important regulator for the renin-angiotensin-aldosterone (RAAS) mechanism. The RAAS regulates human physiological functions like systemic vascular resistance and blood

Table 1. Association of different study variables with the incidence of COVID-19

Variables	COVID-19 positive cases	COVID-19 negative cases	Total number of responses received[a]	*P* value	Unadjusted odds ratio [95% CI]
Age					
Below 50 years	154 (42.9%)	205 (57.1%)	359 (100%)	<0.001[b]	0.39 [0.26-0.58]
Above 50 years	97 (66.0%)	50 (34.0%)	147 (100%)		
Gender					
Male	154 (50.5%)	151 (49.5%)	305 (100%)	0.71	1.07 [0.75-1.53]
Female	100 (48.8%)	105 (51.2%)	205 (100%)		
Occupation					
Skilled	141 (47.0%)	159 (53.0%)	300 (100%)	0.246	0.81 [0.56-1.16]
Unskilled	98 (52.4%)	89 (47.6%)	187 (100%)		
Tobacco habit					
Yes	34 (59.6%)	23 (40.4%)	57 (100%)	0.048[b]	1.78 [1.01-3.13]
No	185 (45.3%)	223 (54.7%)	408 (100%)		
Tobacco use history					
Current user	18 (78.3%)	5 (21.7%)	23 (100%)	0.01[b]	4.8 [1.39-16.61]
Former user	12 (42.9%)	16 (57.1%)	28 (100%)		
Type of tobacco					
Smokeless tobacco	26 (61.9%)	16 (38.1%)	42 (100%)	0.60	1.39 [0.4-4.89]
Smoking tobacco	7 (53.8%)	6 (46.2%)	13 (100%)		
Frequency of tobacco use					
<3 times a day	11 (64.7%)	6 (35.3%)	17 (100%)	0.77	1.36 [0.42-4.39]
>3 times a day	23 (57.5%)	17 (42.5%)	40 (100%)		
Duration of tobacco use					
<5 years	21 (61.8%)	13 (38.2%)	34 (100%)	0.69	1.24 [0.42-3.65]
>5 years	13 (56.5%)	10 (43.5%)	23 (100%)		
Habit Index					
≤15	25 (59.52%)	17 (40.48%)	42 (100%)	0.92	0.77 [0.23-2.54]
>15	8 (53.33%)	7 (46.66%)	15 (100%)		

CI, Confidence Interval.
[a] The total number of responses was different for the variables presented as some participants did not answer some questions.
[b] Statistically significant.

volume management.[15] The binding of SARS-CoV-2 with ACE2 receptors potentially alters its function leading to cardiorespiratory failure. In addition, the SARS-CoV-2 causes ACE/ACE2 imbalance and RAAS activation, which worsens COVID-19.[14]

Smoking appears to reduce susceptibility to infection, but it increases the threat of serious illness.[16] Studies suggest that smoking weakens immunity leading to an increased risk for various infectious diseases.[17] The association of COVID-19 with ACE2 and tobacco is a bit complex. Several significant changes occur in the lungs of smokers, including compromised mucociliary activity, increased permeability of airway epithelial cells, and inflammation in the respiratory airways. The systemic inflammation induced by smoking causes the release of several chemokines and inflammatory cytokines which may lead to severe forms of COVID-19.[17]

Various studies reported that nicotine suppresses ACE2 activity, thus reducing entry points of SARS-CoV-2 and the infectivity of the virus.[18] Another mechanism suggested that nicotine acts as an anti-inflammatory and neurotransmitter agent which influences COVID-19 initiation and progression. Nicotine has cholinergic agonist activity that regulates RAAS. It also inhibits interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF-α) via cholinergic anti-inflammatory activity with the help of alpha7 nicotinic acetylcholine receptor (α7-nAChR). It may be postulated that nicotine can decrease cytokine storm and maintain a balanced immune response against COVID-19.[8] A recent hypothesis proposed about nicotine described that the nAChR plays a major role in the pathogenesis of COVID-19 and therefore, it becomes a crucial target for the treatment of COVID-19 infection.[19] Contrarily, Russo et al reported some opposite effects of nicotine enhancing the ACE2 level. An in-vitro study on the epithelial cells

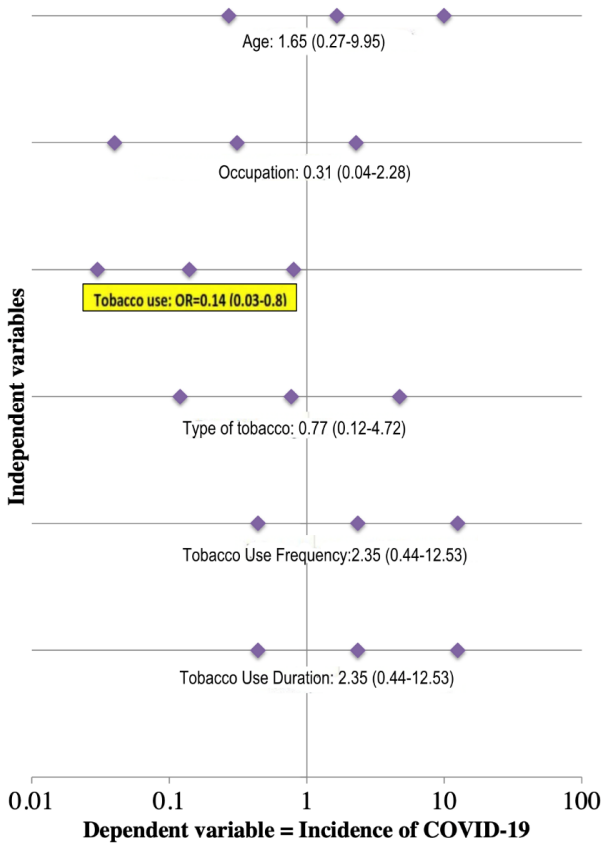

Figure 2. Forest plot model representing the odds ratio (95% CI) of different variables for getting infected with COVID-19

of human lung alveoli reported that nicotine enhances ACE2 activity through the α7-nAChR mechanism.[20] This increased ACE2 activity may enhance virus invasion into host cells, but it also prevents the harmful effect of angiotensin-II on organ damage.

The data in this study revealed that the COVID-19 incidence was significantly high in people aged over 50 years. However, gender and occupation had no significant effect on COVID-19 incidence. This was similar to the results of the study by Paleiron et al.[16] Tobacco use was higher in COVID-19-positive cases compared to COVID-19-negative ones (OR = 1.78; 95% CI 1.01, 3.13). The current tobacco users had a significantly higher risk for COVID-19 initiation as compared to the former users (OR = 4.8; 95% CI 1.39, 16.61). This was similar to the findings reported in other studies assessing the association of tobacco use with COVID-19 infection. A meta-analysis by Sanchez-Ramirez et al. indicated that smokers (current smokers OR = 1.98, 95% CI: 1.16, 3.39; and former smokers OR = 3.46, 95% CI: 2.46, 4.85) showed higher odds of severe outcomes of COVID-19.[21] The study by Oelsner et al reported that all smoking patterns including former smokers and current smokers with low-intensity were more prone to develop progressive damage to the lungs, thus worsening COVID-19 outcomes.[22] Unlike most of the previous studies on the association of COVID-19 and tobacco use that were confined to smoking tobacco forms, this study also included the effect of tobacco use on COVID-19 SLT users.

Some limitations are notable in this study which are also an inherent part of telephone-based surveys e.g., incomplete responses obtained from participants for many questions, recall bias, etc. In addition, the tobacco use status in this study was only assessed in the individuals who came for a diagnostic test for COVID-19, whereas a part of tobacco users who did not develop any symptoms could not get their test done. Therefore, the present study could predict the incidence of symptomatic COVID-19 infection.

Conclusion

This study explored the association between tobacco use and the initiation of COVID-19 infection. The positivity rate for COVID-19 was significantly higher in tobacco users, especially in current tobacco users as compared to former users. Nevertheless, gender and occupation had no significant effect on COVID-19 incidence. The frequency and duration of tobacco use affected the COVID-19 infectivity rate, but the odds ratio for the same was statistically insignificant. Health professionals should collect data on tobacco consumption in their clinical assessments of COVID-19 patients, and advise tobacco cessation practices to reduce COVID-19 infectivity rate.

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Authors' Contribution

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Investigation: Arpita Rai, Pratik Verma, Priyanka Singh.
Methodology: Arpita Rai, Nishant Mehta, Lakhan Manjhi.
Project administration: Arpita Rai.
Resources: Arpita Rai, Lakhan Manjhi.
Software: Nishant Mehta, Zeya ul Haque.
Supervision: Arpita Rai, Ansul Kumar, Lakhan Majhee.
Validation: Arpita Rai, Nishant Mehta, Zeya ul Haque.
Visualization: Arpita Rai, Nishant Mehta, Zeya ul Haque.
Writing–original draft: Nishant Mehta, Zeya ul Haque.
Writing–review & editing: Arpita Rai, Nishant Mehta, Ansul Kumar, Lakhan Majhee, Pratik Verma, Priyanka Singh, Zeya Ul Haque.

Competing Interests

None.

Consent for publication

All the participants have consented to the submission of their findings and report to the journal. No identifying information about participants is mentioned in the manuscript.

Consent to participate

Verbal consent was obtained before administering the questionnaire telephonically.

Data Availability Statement
The research data will be provided on special request with valid justifications.

Ethical Approval
The study was approved by the Institute Ethics Committee, RIMS, Ranchi vide Letter No. 233 dated 20 May 2021.

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