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ORIGINAL ARTICLE

Tobacco, alcohol use and other risk factors for developing symptomatic COVID-19 vs asymptomatic SARS-CoV-2 infection: a case–control study from western Rajasthan, India

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Background: Understanding risk factors of symptomatic coronavirus disease 2019 (COVID-19) vis-à-vis asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, severe disease and death is important.

Methods: An unmatched case–control study was conducted through telephonic interviews among individuals who tested positive for SARS-CoV-2 in Jodhpur, India from 23 March to 20 July 2020. Contact history, comorbidities and tobacco and alcohol use were elicited using standard tools.

Results: Among 911 SARS-CoV-2-infected individuals, 47.5% were symptomatic, 14.1% had severe COVID-19 and 41 (4.5%) died. Older age, working outside the home, cardiac and respiratory comorbidity and alcohol use were found to increase the risk of symptomatic disease as compared with asymptomatic infection. Current tobacco smoking (odds ratio [OR] 0.46 [95% confidence interval {CI} 0.26 to 0.78]) but not smokeless tobacco use (OR 0.81 [95% CI 0.55 to 1.19]) appeared to reduce the risk of symptomatic disease. Age ≥60 y and renal comorbidity were significantly associated with severe COVID-19. Age ≥60 y and respiratory and cardiac comorbidity were found to predispose to mortality.

Conclusions: The apparent reduced risk of symptomatic COVID-19 among tobacco smokers could be due to residual confounding owing to unknown factors, while acknowledging the limitation of recall bias. Cross-protection afforded by frequent upper respiratory tract infection among tobacco smokers could explain why a similar association was not found for smokeless tobacco use, thereby being more plausible than the 'nicotinic hypothesis'. Those with comorbidities and age ≥60 y should be prioritized for hospital admission.

Keywords: alcohol, case-control, COVID-19, cross-protection, nicotine hypothesis, tobacco

Introduction

Coronavirus disease 2019 (COVID-19) has emerged as a pandemic with 83.3 million confirmed cases and 1.8 million deaths worldwide as on 5 January 2021.[1] The humanitarian and economic toll of this disease has been unprecedented. It emerged in China, where the first case was reported from Wuhan in early December 2019.[2] With >10 million cumulative COVID-19 cases, India is now the second most affected country in the world after the United States.[1]

Asymptomatic infection has been implicated in undetected transmission and the large size of COVID-19 outbreaks.[3] The risk factors for severe COVID-19 disease resulting in the requirement for ventilation and death have been studied among patients admitted to hospitals.[4,5] These include comorbidities such as diabetes, heart disease, chronic obstructive pulmonary disease and age >65 y.[4,5] Similarly, it is important to find the risk factors that lead to an individual developing symptomatic COVID-19 disease vis-à-vis those who are infected but remain completely asymp-

tomatic. It could be useful to identify those contacts who are at a higher risk of developing symptomatic disease and would be more likely to benefit from focused monitoring and follow-up in the community. This could also help in developing better strategies of symptomatic screening of COVID-19. Therefore we aimed to study the factors predisposing to symptomatic disease among the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected individuals, especially with regards to age, gender, comorbidities, tobacco smoking, smokeless tobacco use, alcohol use and other epidemiological factors.

Methods

Study setting and eligibility for inclusion

Our institute covers Jodhpur and its adjoining districts in the western part of Rajasthan state in India (Figure 1). As per national guidelines, all symptomatic individuals with influenza-like illness who had a history of foreign travel within the past 14 d, a history of domestic migration within the past 7 d, were residing in hotspot or containment zones, had contact with a confirmed COVID-19 case and health workers involved in the care of COVID-19 cases were considered as suspected COVID-19 and were eligible for SARS-CoV-2 testing.[6] Those with severe acute respiratory infection and asymptomatic contacts of COVID-19 cases were also eligible for testing.[6] These individuals suspected of COVID-19 were being tested at our institute with nasopharyngeal and oropharyngeal swab real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 prior to admission.[6] Additionally, field-level swab samples from among inbound travellers, contacts of confirmed COVID-19 cases and from areas designated by administration as having COVID-19 transmission (hotspot areas) were also being sent for testing at our institute.

Study design and data collection procedure

A prospective observational study with unmatched case–control design was conducted among those individuals who had tested positive for SARS-CoV-2 and were admitted at our institute from 23 March to 20 July 2020. Owing to the introduction of guidelines for home isolation, we expanded our eligibility criteria to all those testing positive instead of only those being admitted during 16 May–8 June 2020. In order to minimize the risk of infection to interviewers, all eligible individuals were contacted by telephone and were interviewed upon providing verbal informed consent, usually 2–3 d after real-time RT-PCR test results were available. Telephone interviews provided a uniform data collection procedure for all study participants, whether admitted at our institute or undergoing isolation at home or an institutional facility. Information pertaining to individuals <18 y of age was provided by parents after they provided verbal informed consent. The study was approved by the institutional ethics committee (AIIMS/IEC/2020-21/1099).

Definition of cases, controls and severe COVID-19

All individuals detected as infected with SARS-CoV-2 and reporting at least one symptom were taken as symptomatic and were enrolled as 'cases' in the case–control study. A standard case investigation form developed by the National Centre for Disease Control, New Delhi, India was used for recording symptoms, comorbidities and epidemiological data of COVID-19 cases.[7] Symptoms specifically assessed as per the format were fever, cough, sore throat, running nose, breathlessness, general weakness, headache, pain (muscular, chest, abdominal, joint), nausea/vomiting, diarrhoea and irritability/confusion. Any other symptoms reported by the patient but not specified in the format, such as anosmia, were also recorded and were considered for ascertainment as 'cases'. Those ascertained as asymptomatic SARS-CoV-2-infected individuals were taken as 'controls'.

Of the SARS-CoV-2-infected individuals, those admitted with clinical signs of pneumonia plus respiratory rate >30 breaths/min, severe respiratory distress or peripheral capillary oxygen saturation <90% on room air were defined as having severe COVID-19 as per in national clinical management protocol.[8] Comorbidities were self-reported by study participants at the time of telephonic interview, which reflected diagnoses prior to admission or isolation as well as those made during the initial days of hospital admission. Additional data related to plausible risk factors such as tobacco smoking, smokeless tobacco and alcohol use were collected using a structured questionnaire adopted from the World Health Organization (WHO) STEPwise Approach to Surveillance instrument.[9] Smoking was further quantified into cigarette pack-years. Bidi smoking was also converted to equivalent cigarette pack-years using a conversion factor of 2.64 bidis equalling 1 commercial filtered cigarette, based on nicotine content.[10] Occupational history was obtained and was broadly classified as those requiring movement outside the home and those mostly staying home, such as homemakers and retirees.

Outcome assessment

The outcomes of the patients were subsequently obtained from the official report provided on a daily basis to the state government by our institute. Additionally, all individuals, whether admitted or in isolation, were followed up by telephone 30 d after detection of SARS-CoV-2 infection to have their final outcome updated and to cross-check their history of tobacco smoking, smokeless tobacco use and alcohol use. Death in the study was defined as death in a SARS-CoV-2-infected individual within 30 d of diagnosis. The availability of tobacco products and alcohol remained restricted after the first countrywide lockdown of 25 March 2020. Therefore a 1-month period prior to lockdown was taken as the reference period for assessing current tobacco or alcohol use.

Sample size calculation

We considered a proportion of approximately 60% asymptomatic individuals among those testing positive, yielding an asymptomatic: symptomatic ratio of 1.5, based on a previous report.[11] Related to the primary outcome of interest, a tobacco use prevalence of 28.6% was used for controls, similar to that of the Indian population as per the Global Adult Tobacco Survey 2016–17.[12] In the absence of prior estimates, we assumed that tobacco use increased the odds of symptomatic disease among SARS-CoV-2-infected individuals by 1.5 times. This yielded

Figure 1. Location of the All India Institute of Medical Sciences and the approximate catchment area of Jodhpur and surrounding districts in western Rajasthan, India. (Modified from source file https://commons.wikimedia.org/wiki/File:India_districts_map.svg, Creative Commons Attribution-Share Alike 4.0 International license).

a total sample size of 900 individuals with 80% power and an α error of 5% using the OpenEpi tool.[13] We attempted to universally sample each eligible individual until the required sample size was reached.

Data analysis

Continuous variables were described using mean and standard deviation (SD) or median and interquartile range (IQR), where appropriate. Categorical variables related to risk factors were tabulated and odds ratios (ORs) were calculated both using univariate analysis and multivariate logistic regression in order to adjust for potential confounding. Analysis was done separately for all three dependent variables—symptomatic vs asymptomatic, severe COVID-19 vs mild or moderate COVID-19 and dead vs alive outcome. Multivariate analysis was done with model 1 taking all plausible risk factors together and model 2 taking all risk factor together with tobacco smoking categorized in

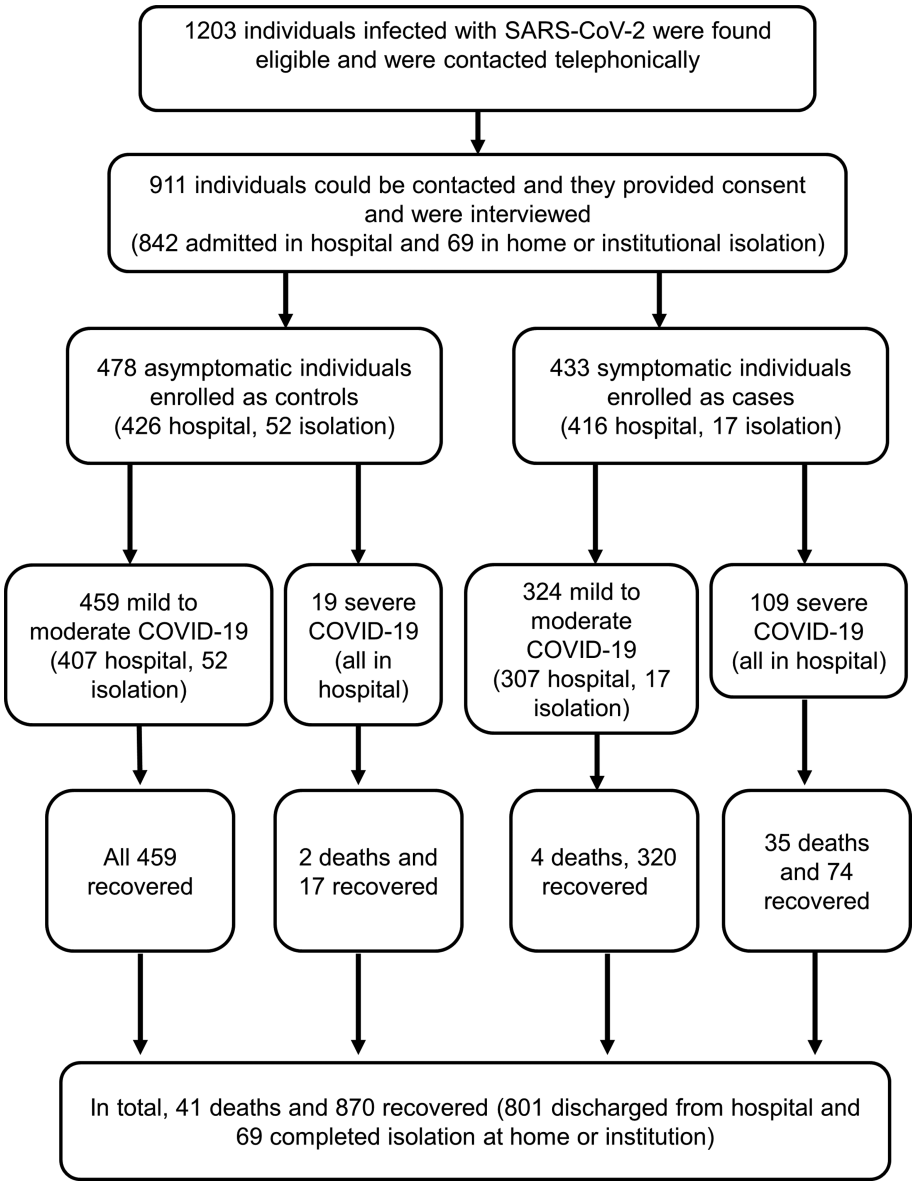

Figure 2. Flowchart of recruitment of SARS-CoV-2-infected individuals for the case–control study, their clinical severity and outcomes.

pack-years instead of a binary variable. For multivariate models, similar variables were not analysed together to avoid collinearity. Data analysis was conducted using Stata version 16 (StataCorp, College Station, TX, USA). A p-value <0.05 was considered significant.

Results

Clinical and epidemiological characteristics

Of a total of 1203 eligible SARS-CoV-2-infected individuals whom we attempted to contact, 911 provided consent and could be interviewed. Around half (433 [47.5%]) were symptomatic and 128 (14.1%) were classified as having severe COVID-19. From among the symptomatic COVID-19 patients, fever was the most common self-reported symptom in almost two-thirds (280 [64.7%]), followed by cough (146 [33.7%]), sore throat (89 [20.6%]), breathlessness (72 [16.6%]), generalized weakness (59 [13.6%]), myalgia (34 [7.9%]), runny nose (32 [7.4%]), headache (22 [5.1%]), anosmia (14 [3.2%]) and other symptoms (32 [7.4%]).

Of the 911 study participants, 41 (4.9%) died of COVID-19-related complications and 870 (95.1%) recovered and were alive at the 1-month follow-up (Figure 2). Among the recovered, 801 patients were discharged from the hospital and 69 successfully completed isolation at their home or institutional facility (Table 1 and Figure 2). The age and gender of symptomatic and asymptomatic individuals were similarly distributed (Table 1). The median duration from symptom onset to COVID-19 testing was

Table 1. Demographic and clinical characteristics of asymptomatic and symptomatic SARS-CoV-2-infected individuals

Characteristics	Asymptomatic (n=478)	Symptomatic (n=433)	Total (N=911)
Demographic details			
Age (years), mean (SD)	42.1 (19.8)	44.2 (18.4)	43.1 (19.2)
Age group (years), n (%)			
0–9	22 (4.6)	12 (2.8)	34 (3.7)
10–19	39 (8.2)	18 (4.2)	57 (6.3)
20–29	93 (19.5)	77 (17.8)	170 (18.7)
30–39	70 (14.6)	70 (16.2)	140 (15.4)
40–49	57 (11.9)	79 (18.2)	136 (14.9)
50–59	80 (16.7)	70 (16.2)	150 (16.5)
60–69	66 (13.8)	73 (16.9)	139 (15.3)
≥70	51 (10.7)	34 (7.9)	85 (9.3)
Gender, n (%)			
Female	170 (34.6)	151 (34.9)	321 (35.2)
Male	308 (64.4)	282 (65.1)	590 (64.8)
Comorbidities, n (%)			
Any comorbidity	134 (28.0)	165 (38.1)	299 (32.8)
Diabetes	64 (13.4)	66 (15.2)	130 (14.3)
Hypertension	70 (14.6)	79 (18.2)	149 (16.4)
Diabetes or hypertension	105 (22.0)	116 (26.8)	221 (24.3)
Diabetes and hypertension	29 (6.1)	29 (6.7)	58 (6.4)
Respiratory	5 (1.0)	22 (5.1)	27 (3.0)
Cardiac	14 (2.9)	28 (6.5)	42 (4.6)
Renal	3 (0.6)	6 (1.4)	9 (1.0)
Gastrointestinal	1 (0.2)	2 (0.5)	3 (0.3)
Malignancy	3 (0.6)	7 (1.6)	10 (1.1)
Health services and outcomes			
Facility of care, n (%)			
Home isolation	31 (6.5)	10 (2.3)	41 (4.5)
Non-hospital institutional isolation	21 (4.4)	7 (1.6)	28 (3.1)
Hospital	426 (89.1)	416 (96.1)	842 (92.4)
Symptom onset to COVID-19 testing (days), median (IQR)	–	2 (0–3)	2 (0–3)
Testing to admission (days), median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)
Symptom onset to interview (days), median (IQR)	–	7 (5–10)	7 (5–10)
Testing to interview (days), median (IQR)	5 (3–7)	5 (4–7)	5 (3–7)
COVID-19 severity, n (%)			
Mild to moderate	459 (96.0)	324 (74.8)	783 (85.1)
Severe	19 (4.0)	109 (25.2)	128 (14.9)
Outcomes, n (%)			
Completed isolation	52 (10.9)	17 (3.9)	69 (7.6)
Discharged from hospital	424 (88.7)	377 (87.1)	801 (87.9)
Death	2 (0.4)	39 (9.0)	41 (4.5)
Time to discharge (days), median (IQR)	8 (6–11)	8 (7–10)	8 (6–10)

2 d and testing to admission was 1 d. The median duration from COVID-19 testing to interview was 5 d (IQR 3–7) and 5 d (IQR 4–7) among asymptomatic and symptomatic individuals, respectively (Table 1).

Epidemiological history revealed that those having contact with a confirmed COVID-19 case, belonging to a known cluster or hotspot of COVID-19 cases and having a history of travel were more likely to contribute to detection of asymptomatic SARS-CoV-2 infection as compared with symptomatic disease (Table 2). Nearly four-fifths of the SARS-CoV-2-infected individuals did not report any contact with a confirmed COVID-19 case (Table 2). The most common contact with another confirmed COVID-19 case was within the household setting for both symptomatic and asymptomatic individuals. Current smoking, the use of smokeless tobacco and the use of any form of tobacco was 8.1%, 15.3% and 22.1%, respectively, among all infected individuals. Current alcohol use was reported by 3.8%. The full study data set is also provided (supplementary file 1).

Table 2. Epidemiological characteristics of asymptomatic and symptomatic SARS-CoV-2-infected individuals

Characteristics	Asymptomatic (n=478)	Symptomatic (n=433)	Total (N=911)
Epidemiological history, n (%)			
Occupation requiring movement outside the home	250 (52.3)	268 (61.9)	518 (56.9)
Contact with a laboratory-confirmed COVID-19 case	107 (22.4)	72 (16.6)	179 (19.6)
Type of contact with a confirmed COVID-19 case (among N=179), n (%)			
From another member of the same household	84 (78.5)	39 (54.2)	123 (68.7)
From neighbourhood	10 (9.3)	18 (25.0)	28 (15.6)
During clinical care or visit to a place of sample collection	7 (6.5)	6 (8.3)	13 (7.3)
At workplace or with a friend	3 (2.8)	8 (11.1)	11 (6.1)
During travel	3 (2.8)	1 (1.4)	4 (2.2)
Self-reporting of belonging to a COVID-19 cluster or hotspot area	124 (25.9)	85 (19.6)	209 (22.9)
Attended mass gathering in the past month	5 (1.0)	11 (2.5)	16 (1.8)
Any travel history in the past month	100 (20.9)	57 (13.2)	157 (17.2)
Domestic travel outside district in the past month	43 (9.0)	52 (12.0)	95 (10.4)
Foreign travel in the past month	57 (11.9)	5 (1.2)	62 (6.8)
Tobacco and alcohol use, n (%)			
Ever tobacco smoker (both current and past smokers)	50 (10.5)	30 (6.9)	80 (8.8)
Past tobacco smokers	3 (0.6)	3 (0.7)	6 (0.7)
Median duration of stopping tobacco smoking for past smokers (years)	20	20	20
Current tobacco smoker (both daily and occasional)	47 (9.8)	27 (6.2)	74 (8.1)
Daily tobacco smoker	44 (9.2)	25 (5.8)	69 (7.6)
Occasional tobacco smoker (less than daily)	3 (0.6)	2 (0.5)	5 (0.5)
Type of product smoked among current tobacco smokers (N=74), n (%)			
Cigarette	26 (55.2)	17 (63.0)	43 (58.1)
Bidi	20 (42.6)	10 (37.0)	30 (40.5)
Chillum	1 (2.1)	0 (0)	1 (1.4)
Pack-years among current smokers (N=74), n (%)			
<1	18	10	28
1–5	16	10	26
>5	12	6	18
Not applicable (for chillum)/data missing	1	1	2
Current user of smokeless tobacco	74 (15.5)	65 (15.0)	139 (15.3)
Current user of any form of tobacco	113 (23.6)	87 (20.1)	201 (22.1)
Currently smoker as well as using smokeless tobacco	8 (1.7)	4 (0.9)	12 (1.3)
Current use of alcohol (at least once in the past month)	12 (2.5)	23 (5.3)	35 (3.8)
Current regular use of alcohol (at least once a week)	10 (2.1)	21 (4.8)	31 (3.4)
Current user of both tobacco and alcohol	9 (1.9)	9 (2.1)	18 (2.0)

Risk factors of symptomatic COVID-19

Upon univariate analysis, having an occupation requiring outdoor movement, the presence of any comorbidity, the presence of respiratory or cardiac comorbidity and the use of alcohol were found to be significantly associated with symptomatic COVID-19 as compared with asymptomatic SARS-CoV-2 infection. On the other hand, residing in a cluster or hotspot area and having a history of travel in the past month were associated with greater asymptomatic infection as compared with symptomatic disease.

Upon multivariate analysis with model 1, older age, especially the 40–49 and 60–69 y age groups, occupation requiring movement outside the home, respiratory comorbidity and alcohol use were found to increase the risk of symptomatic disease as compared with asymptomatic infection (Table 3). A history of travel in the past month and tobacco smoking appeared to reduce the risk of symptomatic disease, while the apparently protective association with residing in a cluster or hotspot area disappeared completely (Table 3). Multivariate analysis with model 2 additionally showed an association of asymptomatic course among those with >5 pack-years of tobacco smoking as compared with non-smokers. No significant association was found for an asymptomatic course among those smoking <1 pack-year or 1–5 pack-years as compared with non-smokers.

Risk factors for severe COVID-19

Older age and comorbidities such as diabetes, hypertension and cardiac and renal disease were significantly associated with

Table 3. Univariate and multivariate analysis of plausible risk factors for developing symptomatic COVID-19 as compared with asymptomatic SARS-CoV-2 infection (N=911)

	Univariate analysis		Multivariate analysis (model 1)		Multivariate analysis (model 2)	
Characteristics	OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Demographic and epidemiological characteristics						
Male gender (vs female)	1.02 (0.78 to 1.34)	0.865	0.78 (0.56 to 1.11)	0.401	0.79 (0.56 to 1.12)	0.185
Age (years)	1.006 (0.999 to 1.012)	0.111	–	–	–	–
Age group (years)						
0–9	Reference	–	Reference	–	Reference	–
10–19	0.85 (0.34 to 2.08)	0.715	0.68 (0.27 to 1.69)	0.401	0.67 (0.27 to 1.69)	0.400
20–29	1.52 (0.71 to 3.26)	0.285	1.58 (0.72 to 3.45)	0.250	1.58 (0.72 to 3.44)	0.253
30–39	1.83 (0.84 to 3.99)	0.127	2.11 (0.95 to 4.66)	0.066	2.10 (0.95 to 4.66)	0.067
40–49	2.54 (1.16 to 5.55)	0.019	2.48 (1.11 to 5.88)	0.028	2.45 (1.09 to 5.48)	0.029
50–59	1.60 (0.74 to 3.48)	0.231	1.83 (0.81 to 4.13)	0.145	1.83 (0.81 to 4.13)	0.145
60–69	2.03 (0.93 to 4.42)	0.075	2.55 (1.11 to 5.88)	0.028	2.58 (1.12 to 5.96)	0.026
≥70	1.22 (0.53 to 2.79)	0.064	1.86 (0.77 to 4.53)	0.170	1.88 (0.77 to 4.59)	0.163
Residing in a cluster or hotspot area	0.70 (0.51 to 0.96)	0.029	1.00 (0.67 to 1.50)	0.983	1.00 (0.67 to 1.49)	0.996
Any travel in the past month	0.58 (0.40 to 0.82)	0.002	0.57 (0.36 to 0.90)	0.015	0.57 (0.36 to 0.89)	0.015
Occupation requiring movement outside the home	1.48 (1.14 to 1.93)	0.004	2.02 (1.41 to 2.90)	<0.0001	2.01 (1.40 to 2.89)	<0.0001
Comorbidities						
Any comorbidity	1.61 (1.22 to 2.12)	0.001	–	–	–	–
Diabetes	1.19 (0.82 to 1.73)	0.359	1.06 (0.69 to 1.63)	0.775	1.08 (0.70 to 1.66)	0.725
Hypertension	1.33 (0.93 to 1.89)	0.113	1.09 (0.71 to 1.68)	0.702	1.07 (0.69 to 1.65)	0.765
Diabetes or hypertension	1.32 (0.98 to 1.79)	0.071	–	–	–	–
Respiratory	5.1 (1.91 to 13.55)	0.001	4.43 (1.62 to 12.11)	0.004	4.68 (1.69 to 12.95)	0.003
Cardiac	2.30 (1.20 to 4.43)	0.013	2.08 (0.99 to 4.35)	0.052	2.10 (1.00 to 4.42)	0.050
Renal	2.23 (0.56 to 8.99)	0.258	1.69 (0.39 to 7.22)	0.481	1.66 (0.39 to 7.12)	0.495
Tobacco and alcohol use						
Current tobacco smoking	0.61 (0.37 to 1.00)	0.051	0.46 (0.26 to 0.78)	0.005	–	–
Pack-years of tobacco smoking among current smokers						
0 (non-smoker)	Reference	–			Reference	–
<1	0.59 (0.27 to 1.29)	0.187			0.50 (0.21 to 1.15)	0.101
1–5	0.66 (0.30 to 1.48)	0.316			0.51 (0.21 to 1.22)	0.130
>5	0.53 (0.20 to 1.43)	0.209			0.31 (0.10 to 0.95)	0.041
Current smokeless tobacco use	0.97 (0.68 to 1.39)	0.745	0.81 (0.55 to 1.19)	0.284	0.81 (0.55 to 1.19)	0.277
Current use of any form of tobacco	0.83 (0.60 to 1.14)	0.242	–	–	–	–
Current alcohol use	2.19 (1.08 to 4.45)	0.031	2.42 (1.12 to 5.24)	0.024	2.39 (1.10 to 5.17)	0.027

Model 1 parameters: log likelihood=593.75, minus 2 log likelihood difference vs intercept=73.19, df=19, p<0.0001, pseudo-R^2=0.0581. Model 2 parameters: log likelihood=593.45, minus 2 log likelihood difference vs intercept=73.79, df=21, p<0.0001, pseudo-R^2=0.0585.

severe COVID-19 on univariate analysis. Furthermore, older age, especially the 60–69 and ≥70 y age groups, and renal comorbidity remained as risk factors for severe COVID-19 upon multivariate analysis with model 1 (Table 4). Residing in a cluster or hotspot area was associated with reduced severity of COVID-19. The magnitude of association of tobacco smoking with reduced severity of COVID-19 became non-significant (OR 0.47 [95% CI 0.21 to 1.08], p=0.074) as compared its significant association with reduced symptomatic COVID-19 (OR 0.46 [95% CI 0.26 to 0.78], p=0.008). The association of smokeless tobacco use with severe COVID-19 (OR 0.98 [95% CI 0.57 to 1.70], p=0.952) remained close to 1 as well as statistically non-significant, which was nearly similar to that for its association with symptomatic COVID-19 (OR 0.81 [95% CI 0.55 to 1.19], p=0.284). Model 2 showed similar results while also showing a marginally significant association of reduced severity of COVID-19 for those with tobacco smoking of ≥1 pack-years. Reduced severity of COVID-19 was not significantly associated with those smoking <1 pack-year.

Risk factors for mortality in COVID-19

Univariate analysis revealed that older age, especially ≥60 y, hypertension, the presence of diabetes or hypertension and respiratory, cardiac and renal comorbidity were associated with mortality (Table 5). Upon multivariate analysis, only older age and respiratory and cardiac comorbidity were found to be the risk factors of mortality among COVID-19 patients (Table 5). No significant association of tobacco smoking either as a binary variable or categorized as pack-years, smokeless tobacco use or alcohol use was seen with risk of mortality on either univariate or multivariate analysis. A significant association of those working outside the home and a history of travel in the past month with a lower risk

Table 4. Univariate and multivariate analysis of plausible risk factors for developing severe COVID-19 as compared with mild or moderate disease (N=911)

	Univariate analysis		Multivariate analysis (model 1)		Multivariate analysis (model 2)	
Characteristics	OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Demographic and epidemiological characteristics						
Male gender (vs female)	1.28 (0.86 to 1.92)	0.224	1.59 (0.93 to 2.71)	0.087	1.61 (0.94 to 2.74)	0.082
Age (years)	1.051 (1.039 to 1.064)	<0.001	-	-	-	-
Age group (years)						
0–9	Reference	–	Reference	–	Reference	–
10–19	0.59 (0.36 to 9.74)	0.900	0.61 (0.04 to 10.24)	0.734	0.60 (0.04 to 10.08)	0.725
20–29	0.80 (0.09 to 7.34)	0.840	0.90 (0.10 to 8.38)	0.927	0.87 (0.09 to 8.10)	0.903
30–39	2.27 (0.28 to 18.53)	0.445	2.55 (0.31 to 21.00)	0.385	2.50 (0.30 to 20.64)	0.395
40–49	4.71 (0.60 to 36.74)	0.139	4.36 (0.55 to 34.52)	0.163	4.20 (0.53 to 33.28)	0.174
50–59	7.24 (0.95 to 55.30)	0.056	7.61 (0.97 to 59.64)	0.053	7.48 (0.95 to 58.66)	0.055
60–69	16.32 (2.16 to 123.11)	0.007	16.02 (2.05 to 125.00)	0.008	16.15 (2.07 to 126.15)	0.008
≥70	12.24 (1.58 to 94.73)	0.016	12.18 (1.51 to 98.49)	0.019	12.33 (1.52 to 99.77)	0.019
Residing in a cluster or hotspot area	0.28 (0.15 to 0.53)	<0.001	0.38 (0.18 to 0.83)	0.015	0.37 (0.17 to 0.81)	0.012
Any travel in the past month	0.28 (0.14 to 0.59)	0.001	0.42 (0.17 to 1.03)	0.058	0.42 (0.17 to 1.02)	0.056
Occupation requiring movement outside the home	0.61 (0.42 to 0.88)	0.009	1.09 (0.64 to 1.86)	0.737	1.08 (0.64 to 1.84)	0.767
Comorbidities						
Any comorbidity	3.32 (2.05 to 5.37)	<0.001	-	-	-	-
Diabetes	3.17 (2.05 to 4.91)	<0.001	1.45 (0.87 to 2.42)	0.149	1.48 (0.89 to 2.47)	0.135
Hypertension	3.70 (2.44 to 5.62)	<0.001	1.34 (0.80 to 2.24)	0.259	1.35 (0.81 to 2.25)	0.253
Diabetes or hypertension	3.41 (2.31 to 5.02)	<0.001	-	-	-	-
Respiratory	2.21 (0.91 to 5.33)	0.078	1.67 (0.63 to 4.39)	0.300	1.75 (0.66 to 4.64)	0.259
Cardiac	4.16 (2.16 to 8.00)	< 0.001	1.52 (0.69 to 3.35)	0.301	1.52 (0.68 to 3.37)	0.305
Renal	12.79 (3.16 to 51.80)	< 0.001	6.34 (1.32 to 30.49)	0.021	5.93 (1.19 to 29.47)	0.030
Tobacco and alcohol use						
Current tobacco smoking	0.84 (0.41 to 1.72)	0.626	0.47 (0.21 to 1.08)	0.074	-	-
Pack-years of tobacco smoking among current smokers			-	-		
0 (non-smoker)	Reference	–			Reference	–
<1	0.73 (0.22 to 2.44)	0.605			1.26 (0.29 to 5.53)	0.761
1–5	1.82 (0.71 to 4.61)	0.210			0.37 (0.14 to 0.97)*	0.044
>5	0	-			NA	-
Current smokeless tobacco use	1.18 (0.72 to 1.95)	0.513	0.98 (0.57 to 1.70)	0.952	0.99 (0.57 to 1.71)	0.970
Current use of any form of tobacco	1.10 (0.70 to 1.71)	0.686	-	-	-	-
Current alcohol use	0.78 (0.27 to 2.26)	0.650	0.56 (0.17 to 1.77)	0.322	0.51 (0.16 to 1.65)	0.264

*For model 2, pack-year categories 1–5 and >5 were combined and the OR for the combined category is presented here as ≥1 pack-years.
Model 1 parameters: log likelihood=295.84, minus 2 log likelihood difference vs intercept=147.83, df=19, p<0.0001, pseudo-R^2=0.1999.
Model 2 parameters: log likelihood=295.19, minus 2 log likelihood difference vs intercept=149.13, df=20, p<0.0001, pseudo-R^2=0.2017.

of death disappeared on multivariate analysis, probably owing to confounding by older individuals staying at home and also being at risk of a fatal outcome.

Discussion

Epidemiological factors

Prompt symptom onset to diagnosis in COVID-19 was in contrast to the long delay observed in the diagnosis of centuries-old infectious diseases such as tuberculosis and visceral leishmaniasis.[14,15] This could be attributed to widespread awareness of COVID-19 symptoms in the community as well as rapid deployment of testing facilities. The short duration from testing to admission could be explained by admission of a substantial number of suspected COVID-19 cases while awaiting test results.

The present study adds to the evidence that older age and comorbidities increase the risk of severe COVID-19 and mortality, which appears biologically plausible.[4,5] Greater risk of severe disease and death was associated with comorbidities even after adjusting for age and other possible confounders. The relative abundance of asymptomatic SARS-CoV-2-infected individuals among travellers, those having contact with lab-confirmed COVID-19 and those residing in a cluster or hotspot area could be attributed to aggressive household contact testing of confirmed COVID-19 cases, community testing in hotspot areas and testing among travellers. This was in accordance with the prevailing COVID-19 case-finding strategy.[6] Thus a larger number of asymptomatic individuals were detected among these groups as compared with the general population, who would have likely approached the health facility only upon emergence of symptoms.

Table 5. Univariate and multivariate analysis of plausible risk factors for mortality in COVID-19 (N=911)

	Univariate analysis		Multivariate analysis (model 1)		Multivariate analysis (model 2)	
Characteristics	OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Demographic and epidemiological characteristics						
Male gender (vs female)	1.05 (0.54 to 2.04)	0.881	1.15 (0.50 to 2.64)	0.736	1.15 (0.50 to 2.65)	0.737
Age (years)	1.079 (1.055 to 1.103)	<0.001	1.078 (1.051 to 1.107)	<0.001	1.079 (1.051 to 2.648)	<0.001
Age group (years)						
0–9	0					
10–19	0					
20–29	0					
30–39	0					
40–49	1 (reference)	-				
50–59	1.38 (0.38 to 4.98)	0.63				
60–69	5.55 (1.84 to 16.69)	0.002				
≥70	4.91 (1.51 to 15.95)	0.008				
Residing in a cluster or hotspot area	0.45 (0.18 to 1.17)	0.102	0.76 (0.24 to 2.37)	0.634	0.76 (0.24 to 2.39)	0.642
Any travel in the past month	0.24 (0.06 to 0.99)	0.048	0.28 (0.05 to 1.50)	0.138	0.28 (0.05 to 1.50)	0.137
Occupation requiring movement outside the home	0.38 (0.20 to 0.73)	0.004	0.91 (0.39 to 2.13)	0.827	0.91 (0.39 to 2.13)	0.823
Comorbidities						
Any comorbidity	3.79 (1.98 to 7.27)	<0.001	-	-	-	-
Diabetes	2.02 (0.96 to 4.22)	0.063	1.18 (0.52 to 2.70)	0.693	1.16 (0.51 to 2.68)	0.720
Hypertension	3.55 (1.84 to 6.82)	<0.001	0.91 (0.41 to 2.02)	0.812	0.95 (0.42 to 2.12)	0.892
Diabetes or hypertension	3.17 (1.68 to 5.97)	<0.001	-	-	-	-
Respiratory	3.98 (1.31 to 12.10)	0.015	3.62 (1.08 to 12.12)	0.037	3.65 (1.08 to 12.34)	0.037
Cardiac	7.90 (3.46 to 18.02)	<0.001	3.46 (1.28 to 9.38)	0.015	3.41 (1.25 to 9.29)	0.017
Renal	6.87 (1.38 to 34.26)	0.019	1.96 (0.27 to 14.30)	0.507	1.64 (0.19 to 13.81)	0.651
Tobacco and alcohol use						
Current tobacco smoking	1.24 (0.43 to 3.57)	0.696	0.60 (0.18 to 2.00)	0.407	-	-
Pack-years of tobacco smoking among current smokers						
0 (non-smoker)	1 (reference)	-			1 (reference)	-
<1	0.80 (0.11 to 6.07)	0.831			1.28 (0.09 to 17.88)	0.856
1–5	0.87 (0.11 to 6.57)	0.890			0.34 (0.04 to 2.91)	0.325
>5	2.71 (0.60 to 12.22)	0.195			0.74 (0.14 to 4.01)	0.730
Current smokeless tobacco use	1.37 (0.62 to 3.03)	0.440	1.30 (0.55 to 3.10)	0.549	1.31 (0.55 to 3.11)	0.543
Current use of any form of tobacco	1.49 (0.75 to 2.98)	0.258	-	-	-	-
Current alcohol use	0.61 (0.08 to 4.60)	0.636	0.80 (0.10 to 6.71)	0.840	0.81 (0.09 to 6.91)	0.847

Model 1 parameters: log likelihood=127.19, minus 2 log likelihood difference vs intercept=80.02, df=13, p<0.0001, pseudo-R^2=0.2393.
Model 2 parameters: log likelihood=126.88, minus 2 log likelihood difference vs intercept=80.64, df=13, p<0.0001, pseudo-R^2=0.2411.

Tobacco and alcohol use

We also found alcohol use as a risk factor for developing symptomatic disease, which was retained on multivariate analysis. This appears plausible given the harmful effect of alcohol in supressing immunity and thereby predisposing to a greater risk of infectious respiratory diseases.[16]

Current tobacco smoking was found to be associated with reduced symptomatic COVID-19, even after adjusting for possible confounders on multivariate analysis. Further, some evidence of a dose–response relationship was seen with greater pack-years of tobacco smoking associated with an apparently reduced risk of symptomatic and severe disease. Earlier studies using the approach of comparing smoking prevalence among hospitalized patients with that of population surveys found a protective effect of smoking on the risk of testing positive for SARS-CoV-2 and being hospitalized with COVID-19.[17,18] However, this approach could lead to information bias due to the better effectiveness of smoking-related information collection in population-level surveys as compared with hospital settings.[19] In the present study we attempted to eliminate this information bias by collecting the smoking-related data in the asymptomatic and symptomatic groups in a similar manner through telephone interviews.

'Nicotine hypothesis' of protection against COVID-19

The reduced risk of SARS-CoV-2 infection among tobacco smokers has been hypothesized to be due to the effect of nicotine on the nicotinic acetylcholine receptor (nAChR). This has been proposed to act through a reduction of potential sites for viral entry in the pulmonary alveolar epithelium and through inhibition of pro-inflammatory cytokines.[17,19–21] As seen in other viral diseases such as cytomegalovirus, factors reducing the risk of infection could also reduce the possibility of symptomatic disease due to lesser primary viremia.[22]

The nAChR receptors are located in the brain, where nicotine dissolved in blood crosses the blood–brain barrier.[23] It could reach the bloodstream through absorption in the lung, gut or transdermally.[23] Theoretically, any association of tobacco smoking with reduced SARS-CoV-2 infection or severity through the nicotinic mechanism should also be seen with regard to smokeless tobacco use. In this regard, India provides an appropriate opportunity to test this hypothesis, as smokeless tobacco use is twice as prevalent as tobacco smoking.[12] Since we did not observe an association of smokeless tobacco use with either reduced symptomatic COVID-19 or reduced severity of COVID-19, the 'nicotine hypothesis' may need to be re-examined. Further, if we consider smokeless tobacco use in the present study as a proxy for pharmaceutical nicotine patches, suggestions regarding their use to explore protection against COVID-19 seem implausible.[17,19]

Several studies have found that tobacco smoking increases the risk of progression to severe disease, the requirement for mechanical ventilation and mortality among COVID-19 patients.[24,25] Further, the biological plausibility of respiratory pathogenesis suggests that smoking leads to severe lung disease in influenza and tuberculosis.[26,27] However, we did not find a statistically convincing effect of tobacco use on severe disease and death, possibly because our study was underpowered to detect these effects due to the lower overall proportion of severe disease and deaths among all infected individuals.

Alternative explanations

We suggest an alternative hypothesis for explaining the possible association of tobacco smoking with the low risk of SARS-CoV-2 infection. A recent immunological study detected SARS-CoV-2-reactive $CD4^+$ T cells among 40–60% of unexposed individuals. This suggests cross-reactivity between commonly circulating low-pathogenic coronaviruses causing the common cold and SARS-CoV-2, mainly targeting the viral 1AB polyprotein and S protein regions.[28] Genetically, these regions also consistently show high sequence similarity between the common cold coronaviruses (229E, NL63, OC43 or HKU1) and SARS-CoV-2.[29] Further, cross-reactivity of SARS-CoV-2 antibodies has been shown with the full spike proteins of common cold coronaviruses using enzyme-linked immunosorbent assays.[30] Exposure to cigarette smoke has been known to lead to more frequent and serious upper respiratory tract infections, including the common cold.[26,31,32] Therefore we propose that cross-protection afforded by frequent upper respiratory tract infection among tobacco smokers could explain the association of tobacco smoking with the lower risk of SARS-CoV-2 infection. Studies assessing cell-mediated and humoral cross-reactivity of SARS-CoV-2 with common cold coronaviruses among tobacco smokers as compared with non-smokers may be conducted to further explore this hypothesis.

Further, variations in host genetic factors are known to modulate susceptibility to SARS-CoV-2 and can influence the severity of symptoms.[33] Single-nucleotide polymorphisms of a variety of genes, including *ACE2*, *TMPRSS2*, *HLA*, *CD147*, *MIF*, *IFNG* and *IL6*, have been implicated in the pathological and immunological response to COVID-19.[33] The pseudo-R^2 value of only 5% in the multivariate analysis suggests that the 13 plausible risk factors taken together failed to provide a substantial association explaining the risk of symptomatic COVID-19 vis-à-vis asymptomatic infection. Therefore the presence of residual confounding factors such as host genetic or environmental factors should also be considered to fully explain the risk of development of symptomatic COVID-19.

Due to the harmful effect of smoking on respiratory and cardiac health and its effect on increasing mortality, we support the WHO guidance that tobacco smoking should be discouraged during the COVID-19 pandemic and afterwards.[34] Also, owing to the presence of silent hypoxemia in a subset of patients, an asymptomatic course of disease does not necessarily mean the absence of pathogenesis in COVID-19.[35] Contradictory and confusing findings emphasizing the protective effect of smoking on COVID-19 could potentially reverse the gains made in anti-tobacco messaging. Consequently, smokers on the verge of quitting could delay or abandon such plans owing to the perception of a reduction in potential harm.

The majority of infected individuals diagnosed at our institute had no history of contact with a laboratory-confirmed COVID-19 case. Similar epidemiological data are being collected country-wide by the Integrated Disease Surveillance Programme through the Integrated Health Information Platform portal. Basic information related to the age and gender distribution of COVID-19 patients is already being displayed in an online dashboard.[36] If similar findings emerge from the country-level data of India, then the current transmission classification of 'clusters of cases' might need to be revised to 'community transmission'.[1]

Limitations

We elicited the symptomatic history only once after the lab confirmation of SARS-CoV-2 infection. This could lead to misclassification of cases and controls owing to the study design for some of the individuals who might have been in a pre-symptomatic phase of their illness during the telephone interview. We interviewed individuals a median of 5 d (IQR 3–7) after testing, whereas the median pre-symptomatic phase is known to be <1–4 d.[37] This could have allowed sufficient time to elapse for most of the pre-symptomatic individuals to develop symptoms, thus the effect of misclassification based on symptom elicitation only once is not expected to be large. However, some amount of misclassification due to recall errors from the patients' side was possible.

Furthermore, around 25% of the eligible individuals could not be contacted for inclusion in the study. This could have led to a possible selection bias in the study population. We cross-checked the distribution of key risk factors in the study population, such as the prevalence of tobacco use, which was found similar to that of population estimates for Rajasthan in the Global Adult Tobacco Survey 2016–17.[12] In the worst-case scenario, this suggested a non-differential bias with regard to tobacco use–related risk factors, which could have influenced the key OR estimates to move towards null. This could have some implication with regard to the validity of our findings that smokeless tobacco use was not associated with either a protective or harmful effect for symptomatic or severe COVID-19. The possibility of underrepresentation of some other plausible risk factors such as comorbidities also remained. Further, the possibility of some recall bias existed for alcohol and tobacco use, especially when their availability had been reduced recently due to lockdown. We also did not

collect data on household size, factors influencing social mixing and other predisposing factors for respiratory illness.

Conclusions

Earlier and more aggressive case-finding among household contacts of confirmed cases and travellers resulted in a greater representation of asymptomatic cases. Older age and the presence of comorbidities were associated with symptomatic disease, severe symptomatic disease and death. Alcohol use was found to be associated with symptomatic disease. Tobacco smoking was found to be associated with reduced risk of symptomatic disease and severe disease to some extent, while no association was found with mortality. However, the lack of a similar association with smokeless tobacco use goes against the 'nicotine hypothesis' of protection against COVID-19. Both smoking and smokeless tobacco use should be strongly discouraged during the COVID-19 pandemic due to the known effect of increasing morbidity and mortality through multiple pathways. We propose that cross-protection afforded by frequent upper respiratory tract infections among tobacco smokers could possibly explain its association with a lower risk of symptomatic COVID-19. Genetic factors influencing host immunity should be further explored for symptom development and severity of COVID-19. The evidence of risk factors of symptomatic and severe symptomatic disease could be useful for prioritizing measures of prevention in the community and clinical care in the hospital. We recommend that older SARS-CoV-2-infected individuals, especially those ≥60 y of age, and those with comorbidities be prioritized for hospital admission due to a greater risk of severe disease and fatal outcome.

Supplementary data

Supplementary data are available at *Transactions* online.

Authors' contributions: MKV, VG, NK and SS collected, curated and entered the data. SS conducted the analysis with input from PPS and wrote the draft manuscript with input from MKV, VG, ADG, VJ, PPS, MKGupta, KS, PB and MKGarg. VJ and VLN coordinated the laboratory testing and MKGarg coordinated the clinical care of COVID-19 patients. SM provided overall supervision of the laboratory testing, clinical care and research related to COVID-19 at the All India Institute of Medical Sciences. All authors approved the final manuscript.

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