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Research Paper

Mumbai mayhem of COVID-19 pandemic reveals important factors that influence susceptibility to infection

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ABSTRACT

Background: COVID-19 severity is disproportionately high in the elderly and people with comorbidities. However, other factors that predispose individuals to increased chances of infection are unclear.
Methods: Data from 18,600 people screened for COVID-19 in Mumbai during the outbreak's initial phase, March 7 to June 30, 2020, were used to assess risk factors associated with COVID-19 using the odds ratio analysis.
Findings: Males aged ≥60 years having both diabetes and hypertension were at the highest risk of COVID-19 infection (M vs. F OR=2.5, 95% CI=1.34−4.67, p = 0.0049). People having both diabetes and hypertension in ≥20 years (OR=4.11, 95% CI=3.26−5.20, p <0.0001), diabetes and hypertension independently in 20−39 (OR=4.13, 95% CI=2.22−7.70, p <0.0001, OR=4.32, 95% CI=2.10−8.88, p = 0.0001) and ≥60 years (OR=2.69, 95% CI=1.87−3.87, p <0.0001, OR=2.03, 95% CI=1.46−2.82, p <0.0001), chronic renal disease in 20−39 years (OR=5.38, 95% CI=1.91−15.09, p = 0.0007) age groups had significantly higher risk of COVID-19 infection than those without comorbidity. Quarantined people had significantly lower positive odds (OR=0.59, 95% CI=0.53−0.66, p <0.001) than non-quarantined people.
Interpretation: Our research indicates that the risk of getting COVID-19 disease is not equal. When considering sex, age, and comorbidity together, we found that males aged ≥60 years and having both diabetes and hypertension had a significantly high risk of COVID-19 infection. Therefore, remedial measures such as vaccination programs should be prioritized for at-risk individuals.
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1. Introduction

On February 11, 2020, the World Health Organization (WHO) declared "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)" as the causative agent of Coronavirus disease 2019 (COVID-19) [1]. The virus belongs to the β-genus of the coronavirus family [2]. With a confirmed caseload of 10,286,709 people and 148,994 deaths as of December 31, 2020, India has been the second worst-affected country globally [3]. However, the proportion of the total population infected is low compared with other countries [4].

Mumbai, a metropolitan city home to 23.598 million [5] people, is India's financial capital, home to one of the busiest Indian seaports [6], airports [7], and a big manufacturing hub. Being the hub of multiple economic activities [8], Mumbai is densely populated, with most of its inhabitants living in congested conditions. Mumbai also has a sizeable slum-dwelling population [9]. All these factors lay the ground for the fast spread of any infectious disease. The ports of entry led to high international exposure during the advent of the pandemic. This perhaps fueled a significant upsurge in the COVID-19 pandemic cases turning Mumbai into a hotspot of infection [10].

The lack of preparedness [11], limited availability of preventives like facial masks [12], and poor sanitation led to the spread, as many people were exposed to the virus. The city was thus a hotspot of COVID-19 infection since the beginning of the pandemic [10]. However, an unprecedented countrywide lockdown imposed by the Indian government [13] in late March stopped almost all human activities. Coupled with scaled-up RT-PCR based testing, efforts for

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Research in context

Evidence before this study

The COVID-19 pandemic has exposed the elderly and patients with comorbidities to severe forms of the disease. We searched PubMed for COVID-19 associated articles that reported the vulnerability to COVID-19 infection between January 2020 and November 2020. However, a detailed population study on the susceptibility to COVID-19 infections has been lacking.

Added value of this study

The present study is a comprehensive analysis of COVID-19 susceptibility across age groups, sex, comorbidities, and symptoms. The present study unravels risk factors for COVID-19 in an Indian cohort. Further, it can also help clinicians and policymakers make decisions related to vaccination and even help scientists understand the infection's biology.

Implications of all the available evidence

COVID-19 does not affect us all with equal aggressiveness. Our research is one of the very few studies conducted globally to assess the risk of contracting COVID-19 disease. With vaccination programs underway, this study shall help both clinicians and policymakers arrive at an informed decision on prioritizing such programs.

controlling the pandemic began. However, multiple factors such as non-compliance of advisories to prevent the spread and infected people sharing cramped living spaces with family members, especially during the asymptomatic phase, the spread continued in families and immediate neighborhoods [14]. These factors made the population of Mumbai an ideal population model to study SARS-CoV-2 exposure risks. Although many studies have looked into the severity of infection vis-à-vis the age and comorbidity [15–19], very few studies evaluated patients' susceptibility to SAR-CoV-2 infection, especially in the Indian sub-continent.

In this study, we assess the epidemiological data for a population tested for COVID-19 using RT-PCR from March 7 to June 30, 2020, which constituted the initial outbreak. We divided the cohorts based on sex, age, disease symptoms, and comorbidities. Further, we statistically computed the odds ratio of COVID-19 infection among distinct groups. The findings are exciting and reveals important risk factors of infection in an ethnically homogenous Asian dataset comprising Indians.

2. Methodology

Test results and metadata of all samples tested for COVID-19 at the Kasturba Hospital for Infectious Diseases, Mumbai were retrieved from the ICMR portal by clinicians from Kasturba Hospital for Infectious Diseases. A total of 18,600 people got tested for possible SARS-CoV-2 infection using RT-PCR over the four months, from March 7 to June 30, 2020, which were considered the initial wave of the outbreak. A small subset of these patients was admitted to the same hospital (Table 1). The Institutional Review Board of Kasturba Hospital for Infectious Diseases, Mumbai, approved the use of the data for secondary analysis.

2.1. Testing strategy

The selection of people for RT-PCR-based tests was primarily based on advisories issued by the Indian Council of Medical Research (ICMR), Department of Health Research, Government of India [20].

Table 1.
Summary of patients admitted to Kasturba Hospital for Infectious Diseases after COVID-19 testing.

No. of patients	1652
Males	1106
Females	546
Age Group	
0–19	67
20–39	481
40–59	727
≥ 60	373
Death (Total)	211
Males	143
Females	68
Survival	1013
Males	688
Females	325
Transfer*	428
District of residence	
Mumbai	1554
Thane	67
Others	31

*no records available for patients after transfer from hospital.

The tested population included symptomatic people who had undertaken international travel in the previous 14 days, symptomatic contacts of laboratory-confirmed cases, symptomatic healthcare workers who were previously managing COVID-19 patients were tested regardless of symptoms. Samples were collected at multiple COVID-19 hospitals and primary healthcare centers spread across the Mumbai metropolitan area by a dedicated team of healthcare workers. Information about patients was collected based on the questionnaire contained within the mandatory ICMR Specimen Referral Form for COVID-19 (SARS-CoV-2). All samples were transported to Kasturba Hospital for Infectious Diseases for diagnosis. RT-PCR assays that were positive for at least two genes specific to the SARS-CoV-2 and one internal control for a human gene were taken as positive COVID-19 outcome. Information regarding the primary patient data, symptoms and comorbidities related information and RT-PCR outcome were stored in a national database maintained by the ICMR. The information was accessible to the clinicians at Kasturba Hospital (J.S. and S.A.) during the period of the study. The data uploaded in this database were collected for our analysis along with the test results.

2.2. Data cleaning and preprocessing

For the study, we considered COVID-19 test outcomes of 18,600 people and the following variables: age, sex, comorbidities, symptom status (symptomatic or asymptomatic), COVID-19 symptoms, whether under 14-day quarantine or not, and whether or not the individuals were healthcare workers involved in managing COVID-19 patients. The numerical variable (age) and the categorical variables with more than 50 categories (comorbidities and COVID-19 symptoms) were categorized into different groups. Categories were selected so that each group had at least 30 SARS-CoV-2 positive and negative cases. Those comorbidities that were highly prevalent (accounted for 75% of all the comorbidities) were considered categories of their own. The remaining 25% were grouped into a separated category called 'other'. The same method was used for defining categories of symptoms. People were classified into the following age groups: 0–19, 20–39, 40–59 years, and ≥ 60 years. The various comorbidities such as hypertension, diabetes, chronic renal disease, heart disease, and other malignancies were considered. These, as well as the co-occurrence of multiple comorbidities such as diabetes along with hypertension, diabetes along with heart disease and hypertension, heart disease and hypertension, diabetes and heart disease, chronic lung disease, chronic renal disease and hypertension, chronic renal disease along with diabetes and hypertension, chronic obstructive pulmonary disorder, chronic renal disease and diabetes, diabetes along with malignancy, chronic liver disease, chronic lung disease along with diabetes and hypertension, other and hypothyroidism, were also considered (Supplementary Table 2.5). Additionally, symptoms were classified into a fever with cough and breathlessness, fever with breathlessness, fever and cough, cough and breathlessness, breathlessness, fever alone, cough alone, cough along with sore throat, and sore throat alone, and asymptomatic (Supplementary Table 2.6).

2.3. Data analysis

The $\chi 2$ test with Yates' correction was used for 2 × 2 contingency data, and Pearson's $\chi 2$ test was used for contingency data for variables with more than two categories. Further, to explore risk factors or their interactions associated with odds of COVID-19 infection, odds ratios (ORs) and 95% confidence intervals (CIs) were computed from the contingency tables, where sex, age, comorbidities, and symptoms were taken as confounding variables. Fisher's exact test was used to determine the significance of the association between the risk factors and positive odds of COVID-19 infection (OR=1 vs. OR≠1). p <0.05 was considered to be statistically significant. All statistical analysis was done using Python, and the charts were created in MS Excel. The concept and interpretation of odds ratios are described in detail with an example in Supplementary Section 1.

2.4. Role of the funding source

This study was funded by the Science and Engineering Research Board (SERB), Government of India (SB/S1/COVID-2/2020), and a seed grant RD/0520-IRCCHC0-006 from IRCC, IIT Bombay to SS. These funding sources had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results. All authors had full access to the full data in the study and accepted the responsibility to submit for publication.

Table 2.
Features of study population based on COVID-19 test outcome.

Characteristics	Total Tests	COVID-19 Test Outcome	
		Positive	Negative
	(*N* = 18,600)	(*N* = 8103)	(*N* = 10,497)
Age			
Median (IQR)	39 (28–54)	47 (32–58)	33 (26–48)
Distribution			
0–19 years	1582 (8.51%)	371 (23.45%)	1211 (76.55%)
20–39 years	7822 (42.05%)	2593 (33.15%)	5229 (66.85%)
40–59 years	6042 (32.48%)	3237 (53.57%)	2805 (46.43%)
≥60 years	3154 (16.96%)	1902 (60.3%)	1252 (39.7%)
Sex			
Female	7130 (38.33%)	2791 (39.14%)	4339 (60.86%)
Male	11,470 (61.67%)	5312 (46.31%)	6158 (53.69%)
Healthcare worker involved in managing COVID-19 patient			
No	17,578 (94.51%)	7865 (44.74%)	9713 (55.26%)
Yes	1022 (5.49%)	238 (23.29%)	784 (76.71%)
Quarantine status			
No	16,989 (91.34%)	7583 (44.63%)	9406 (55.37%)
Yes	1611 (8.66%)	520 (32.28%)	1091 (67.72%)
Symptom category			
Fever + Cough + Breathlessness	1091 (5.87%)	815 (74.7%)	276 (25.3%)
Fever + Breathlessness	528 (2.84%)	385 (72.92%)	143 (27.08%)
Fever + Cough	910 (4.89%)	600 (65.93%)	310 (34.07%)
Cough + Breathlessness	707 (3.8%)	457 (64.64%)	250 (35.36%)
Breathlessness	829 (4.46%	524 (63.21%)	305 (36.79%)
Fever	1283 (6.9%)	748 (58.3%)	535 (41.7%)
Other	4549 (24.46%)	2323 (51.07%)	2226 (48.93%)
Cough	905 (4.87%)	396 (43.76%)	509 (56.24%)
Cough + Sore throat	431 (2.32%)	120 (27.84%)	311 (72.16%)
Asymptomatic	6605 (35.51%)	1577 (23.88%)	5028 (76.12%)
Sore throat	762 (4.1%)	158 (20.73%)	604 (79.27%)
Underlying medical condition			
Diabetes + Hypertension	390 (2.1%)	294 (75.38%)	96 (24.62%)
Hypertension	453 (2.4%)	320 (70.64%)	133 (29.36%)
Diabetes	506 (2.72%)	348 (68.77%)	158 (31.23%)
Other	521 (2.8%)	278 (53.36%)	243 (46.64%)
Chronic Renal Disease	81 (0.44%)	43 (53.09%)	38 (46.91%)
N/A	16,649 (89.51%)	6820 (40.96%)	9829 (59.94%)

Abbreviations: N/A, Not applicable.

3. Results

3.1. General features of the dataset

Out of the 18,600 people (Table 2), 11,470 (61.67%) were males, 11,995 (64.49%) showed influenza-like illness symptoms, and 1611 (8.66%) were quarantined, while only 8103 (43.56%) tested positive for SARS-CoV-2. Although the test positivity rate was low at only 6.13% in March, at the beginning of the pandemic, it gradually picked pace to reach 58.39% in May while decreasing marginally to 51.69% in June (Fig. 1a). The median age of the population was 39 years. Among the 8103 (43.56%) COVID-19 patients (Fig. 1b), 65.56% were males (Fig. 1d). The majority (64.49%) of the surveyed population were symptomatic (Fig. 1 f). Significant associations were found between older age (≥ 60 vs < 60 years: OR=2.26, 95% CI=2.09–2.45, p <0.001), sex (males vs females: OR=1.34, 95% CI=1.26–1.42, p <0.001) and risk of contracting COVID-19 infection (Supplementary Tables 3.2 and 4). Overall, 1951 (10.49%) people had comorbidities, and their odds of having COVID-19 infection were significantly higher (OR=2.77, 95% CI=2.51–3.05, p < 0.001) than those without comorbidities (Fig. 1e) (Supplementary Table 5.2). About 5.49% of the surveyed population were healthcare workers involved in managing COVID-19 patients. Quarantined people had significantly lower positive odds (OR=0.59, 95% CI=0.53–0.66, p <0.001) than non-quarantined people. (Fig. 1d) (Supplementary Section 2, Tables 2.1–2.5, Supplementary Section 7, and Supplementary Section 11, Tables 11.1 and 11.2)

3.2. Age

While the median age of the population sampled was 39 years, it was 47 for the group which tested positive for SARS-CoV-2. Although 83.04% of all people included in the study fell in the < 60 years' age group, old age (≥ 60 years) significantly raised the odds of infection (OR=2.26, 95% CI=2.09–2.45, p <0.001) (Fig. 1c; Supplementary Section 3, Tables 3.1 and 3.2).

3.3. Sex

Among the population which tested positive, 65.56% were males. In general, males were significantly more likely to have COVID-19 (OR=1.34, 95% CI=1.26–1.42, p <0.001) than females with positive odds of 0.86 and 0.64, respectively (Supplementary Table 4). For ≥20 years' age group, males were significantly more susceptible to COVID-19 infection (OR=1.33, 95% CI=1.25–1.41, p <0.001) than females. However, this does not hold true for people in the 0–19 years' age group (Supplementary Table 8.1). Moreover, pre-existing medical conditions and symptoms show male preponderance (Supplementary Fig 1a and b). COVID-19 positive odds do not differ significantly based on sex for any comorbidity (hypertension, diabetes, both diabetes and hypertension, and chronic renal disease) or symptom (fever, breathlessness, cough, sore throat, fever along with cough and breathlessness, both fever and breathlessness, both fever and cough, both cough and breathlessness, both cough and sore throat) considered individually (Supplementary Tables 8.2 and 8.3). The

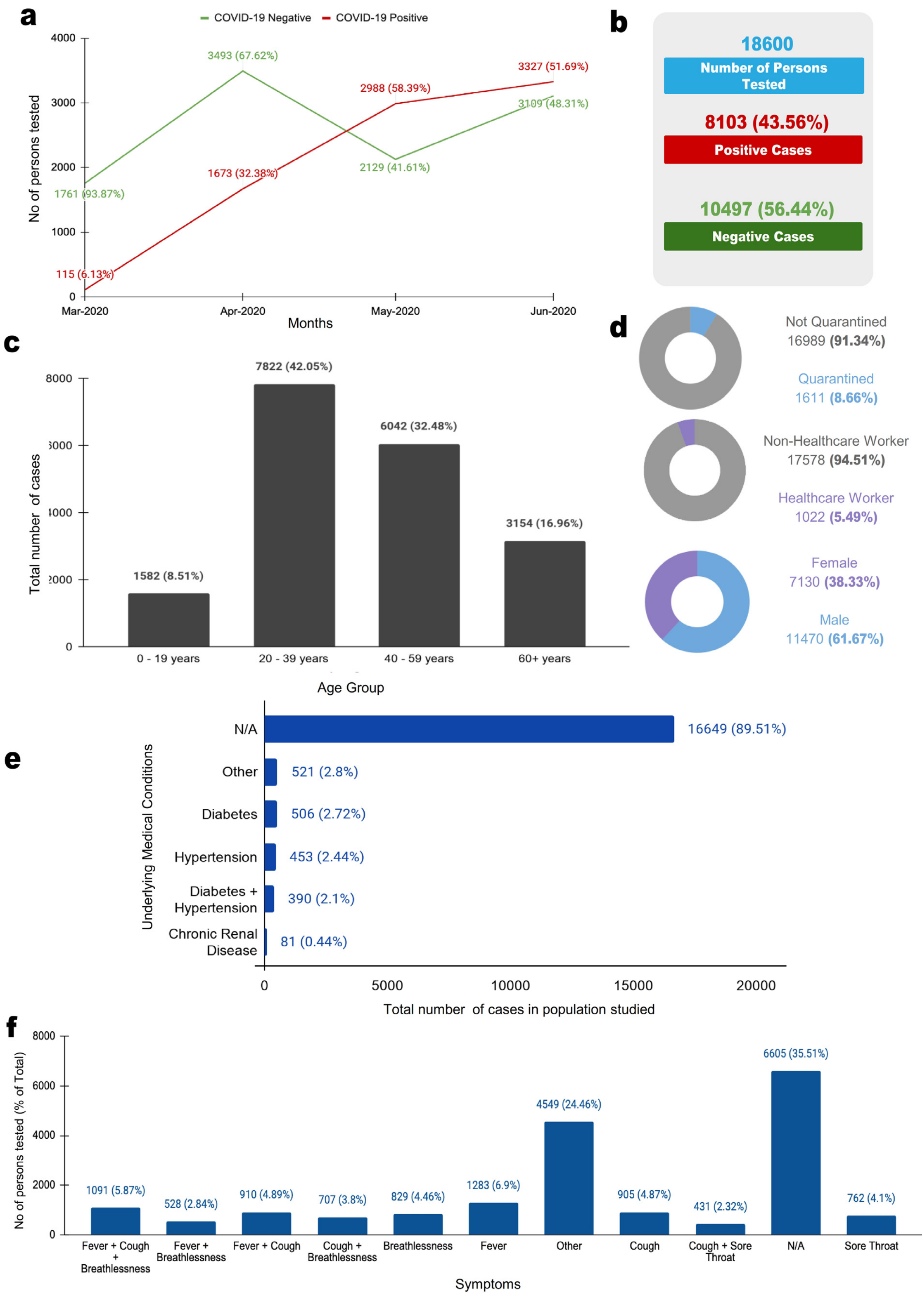

Fig. 1. Features of the study population.

RT-PCR test summary-(a) distribution across months and (b) overall test positivity rate. (c) Age-wise distribution of the study population. (d) Distribution of study population based on gender, quarantine status, and occupation (healthcare worker involved in managing COVID-19 patients). (e) Distribution of comorbidities reported across the study population. (f) Distribution of symptoms reported across the study population.

impact of sex and associated symptoms on the susceptibility to COVID-19 infection varied across age groups. For the 20−39 years' age group, males having both cough and breathlessness as symptoms were significantly more likely to test positive for COVID-19 infection (OR=2.60, 95% CI=1.26−5.37, p = 0.01) than females showing these symptoms. However, this does not hold true for other age groups and symptoms (Supplementary section 8, Tables 8.1−8.4; Supplementary Table 12.1).

3.5. Symptoms

We found that the symptomatic individuals (64.49%) were significantly more likely to test positive for COVID-19 infection (OR=3.80, 95% CI=3.56−4.07, p <0.001) than asymptomatic individuals (Supplementary Table 6.1). The odds of testing positive for COVID-19 infection were the highest for people having fever, cough, and breathlessness, or both fever and breathlessness as symptoms, with odds being 2.95 (fever, cough, and breathlessness vs. no symptoms: OR=9.41, 95% CI=8.12−10.91, p <0.001) and 2.69 (both fever and breathlessness vs. no symptoms: OR=8.58, 95% CI=7.03−10.49, p <0.001), respectively (Supplementary Tables 6.8 and 6.12). Positive odds of COVID-19 infection were the lowest for people having both cough and sore throat (odds=0.39, both cough and sore throat vs. no symptoms: OR=1.23, 95% CI=0.99−1.53, p = 0.0632) or sore throat (odds=0.26, sore throat vs. no symptoms: OR=0.83, 95% CI=0.69−1.00, p = 0.0527) as symptoms (Supplementary Tables 6.7 and 6.11). Fever, cough, and breathlessness or both fever and breathlessness as symptoms were also identified as the high-risk factors (fever, cough, and breathlessness or fever and breathlessness vs. all other symptoms: OR=2.72, 95% CI=2.41−3.05, p <0.001). However, cough and sore throat both or sore throat were identified as the low-risk factors (cough and sore throat both or sore throat vs. all other symptoms: OR=0.22, 95% CI=0.19−0.25, p <0.001) for COVID-19 infection as compared to all the other symptoms (Supplementary Tables 6.13 and 6.14).

The impact of symptoms on the test positivity for COVID-19 infection varied significantly across different age groups. Among people in the 40−59 or ≥ 60 years' age group, those having the following symptoms were at a significantly higher risk of contracting COVID-19 than those showing no symptoms: fever, cough and breathlessness (40−59 years: positive odds=3.86, OR=9.52, 95% CI=7.48−12.11, p <0.0001, ≥ 60 years: positive odds=3.67, OR=7.46, 95% CI=5.48−10.16, p <0.0001), both fever and breathlessness (40−59 years: positive odds=3.29, OR=8.12, 95% CI=5.84−11.29, p <0.0001, ≥60 years: positive odds=3.16, OR=6.42, 95% CI=4.43−9.30, p <0.0001), both fever and cough (40−59 years: positive odds=2.86, OR=7.04, 95% CI=5.42−9.14, p <0.0001, ≥60 years: positive odds=3.56, OR=7.25, 95% CI=4.92−10.69, p <0.0001), both cough and breathlessness (40−59 years: positive odds=2.35, OR=5.8, 95% CI=4.43−7.59, p <0.0001, ≥60 years: positive odds=1.52, OR=3.08, 95% CI=2.28−4.18, p <0.0001), fever (40−59 years: positive odds=2.16, OR=5.32, 95% CI=4.23−6.69, p <0.0001, ≥60 years: positive odds=2.6, OR=5.3, 95% CI=3.77−7.45, p <0.0001), breathlessness (40−59 years: positive odds=2.08, OR=5.13, 95% CI=4.0−6.58, p <0.0001, ≥60 years: positive odds=2.12, OR=4.32, 95% CI=3.24−5.76, p <0.0001), and cough (40−59 years: positive odds=1.16, OR=2.86, 95% CI=2.2−3.71, p <0.0001, ≥ 60 years: positive odds=1.26, OR=2.56, 95% CI=1.71−3.84, p <0.0001). For 20−39 years' age group, people having fever, cough, and breathlessness (positive odds=2.06, OR=7.15, 95% CI=5.32−9.61, p <0.0001), or both cough and breathlessness (positive odds=1.81, OR=6.29, 95% CI=4.44−8.91, p <0.0001) as symptoms had significantly higher positive odds of COVID-19 infection than those without symptoms. People in only two age groups having both cough and sore throat together as symptom had significantly higher odds of COVID-19 infection than the asymptomatic individuals: 0−19 (positive odds=0.6, OR=3.9, 95% CI=1.39−10.92, p = 0.0147) and ≥ 60 years' age group (positive odds=1.3, OR=2.64, 95% CI=1.14−6.12, p = 0.0244). Positive odds of COVID-19 infection among people having sore throat alone as a symptom were as low as 0.47. However, in the 0−19 years' age group, it was significantly higher (OR=3.06, 95% CI=1.29−7.23, p = 0.0147) than those without any symptom. Interestingly, among the people in the 40−59 years' age group, the odds of having COVID-19 infection for those having no symptom were significantly higher (positive odds=0.41, OR=1.58, 95% CI=1.09−2.29, p = 0.0161) than those having sore throat alone as a symptom (Fig. 2a) (Supplementary Section 9, Tables 9.1− 9.6).

Age and sex considered together, males aged 20−39 years having both cough and breathlessness as symptoms were significantly more likely to test positive for COVID-19 infection (M vs. F: OR=2.60, 95% CI=1.26−5.37, p = 0.01) than females in the same age group and having these symptoms (Supplementary Section 6, Tables 6.1−6.14; Supplementary Table 12.1).

3.6. Comorbidities

A total of 1951 people (10.49%) out of the study cohort had comorbidities. People with comorbidities have reported severe symptoms of COVID-19 [15]. However, whether they also were more susceptible to COVID-19 infection was unknown. To check this, we performed an odds ratio analysis of comorbidities along with age and gender as confounding variables. It was found that the odds of having COVID-19 infection were significantly higher for comorbid patients (odds=1.92, OR=2.77, 95% CI=2.51−3.05, p <0.001) than for those without any comorbidities (Supplementary Table 5.2). People with diabetes and hypertension or hypertension alone had significantly higher odds of COVID-19 infection than those having any other medical condition (odds=2.68, OR=1.76, 95% CI=1.45−2.14, p <0.001) (Supplementary Table 5.8). As compared to the asymptomatic individuals, the odds of having COVID-19 infection were significantly more likely for the following comorbidities: both diabetes and hypertension (odds=3.06, OR=4.41, 95% CI=3.5−5.57, p <0.001), hypertension (odds=2.41, OR=3.47, 95% CI=2.83−4.25, p <0.001), diabetes (odds=2.2, OR=3.17, 95% CI=2.62−3.84, p <0.001), and chronic renal disease (odds=1.13, OR=1.63, 95% CI=1.05−2.53, p = 0.0311) (Supplementary Tables 5.3, 5.4, 5.6, and 5.7). Males aged ≥60 years and having both diabetes and hypertension were significantly more likely to have COVID-19 infection (odds=3.83, OR=2.5, 95% CI=1.34−4.67, p = 0.0049) than females aged ≥60 years having these comorbidities (Fig. 2b) (Supplementary Table 12.2).

Furthermore, if taken together with age, the story becomes more fascinating. There was no statistically significant impact of comorbidity on COVID-19 positive odds for the 0−19 years' age group. People having both diabetes and hypertension were significantly more likely to have COVID-19 infection than those without comorbidities for the following age groups: 20−39 years (odds=6, OR=12.4, 95% CI=2.77−55.46, p <0.0001), 40−59 years (odds=4.03, OR=3.83, 95% CI=2.62−5.59, p <0.0001) and ≥60 years (odds=2.42, OR=1.83, 95% CI=1.33−2.5, p <0.0001). Interestingly, the odds of COVID-19 infection for people with both diabetes and hypertension decreased with an increase in age. The odds of COVID-19 infection for people having hypertension alone increased with age and were significantly higher than those for people without comorbidities in 20−39 (odds=2.09, OR=4.32, 95% CI=2.1−8.88, p <0.0001), 40−59 (odds=2.28, OR=2.16, 95% CI=1.62−2.89, p <0.0001) or ≥60 years (odds=2.69, OR=2.03, 95% CI=1.46−2.82, p<0.0001) age groups. As compared to people without any comorbidity, the COVID-19 positive odds were significantly higher for people with diabetes in 20−39 (odds=2, OR=4.13, 95% CI=2.22−7.7, p <0.0001), 40−59 (odds=1.8, OR=1.71, 95% CI=1.33−2.21, p <0.0001) or ≥ 60 years (odds=3.56, OR=2.69, 95% CI=1.87−3.87, p <0.0001) age groups. Chronic renal disease was identified as a significant high-risk factor only for those in the 20−39

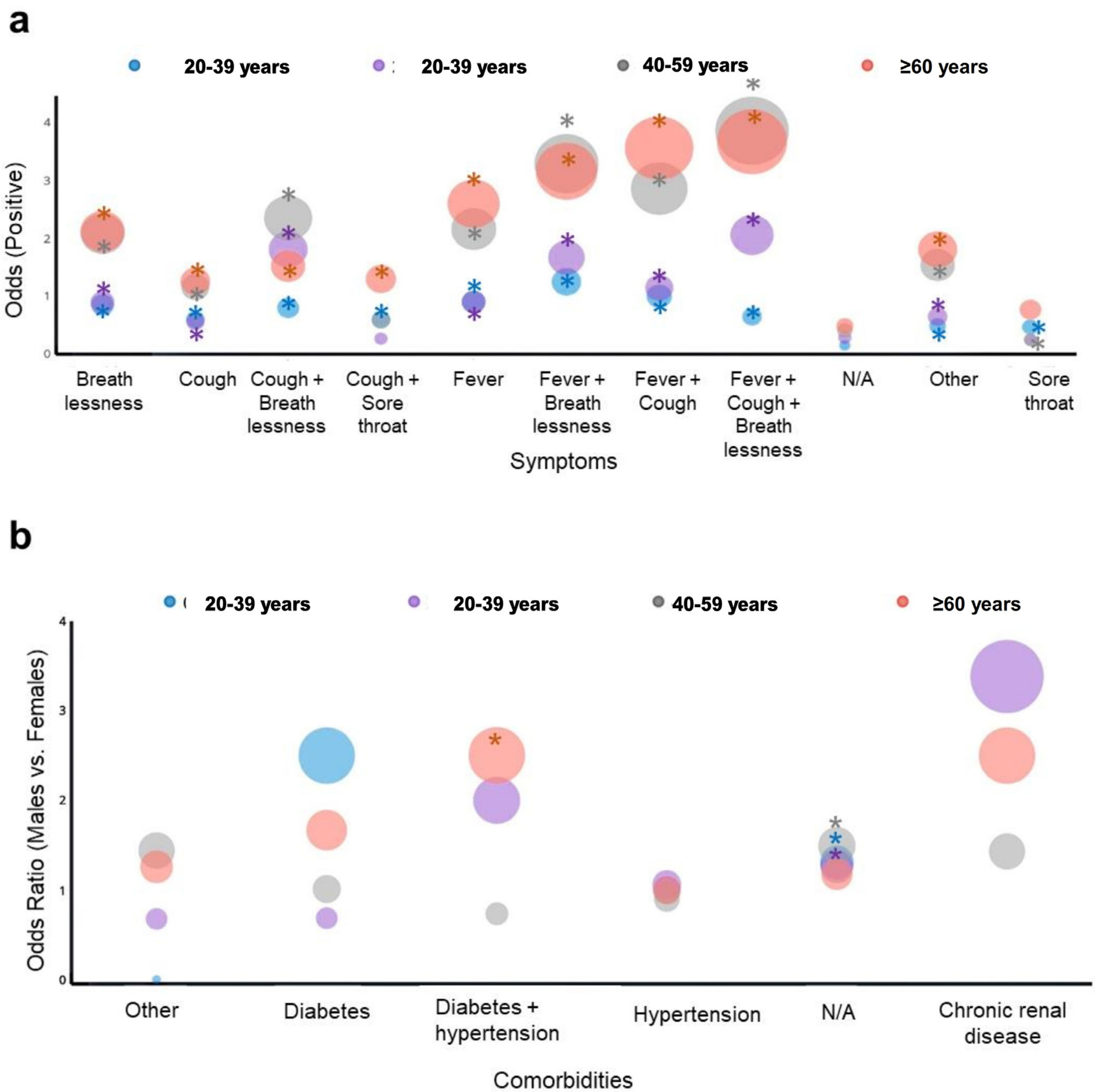

Fig. 2. Odds of age on COVID-19 infection with symptoms, sex, and comorbidities

(a) The odds of test positivity and symptoms across age groups. The cytokine and interferon response-driven symptoms of fever, cough, and breathlessness appear to increase with age, with a marked preponderance in patients aged more than 40. An asterisk marks the significant groups. (b) The odds ratio of males vs. females and comorbidities across age groups. Diabetes alone and in combination with hypertension appear to be high-risk factors for getting infected with COVID-19 in the younger population, while renal diseases elevate the risk on elderly males.

years' age group (odds=2.6, chronic renal disease vs. no comorbidity: OR=5.38, 95% CI=1.91−15.09, p = 0.0007) (Fig. 2b; Supplementary Table 9.6; Supplementary section 5, Tables 5.1−5.8, and Supplementary Section 10, Tables 10.1−10.3).

4. Discussion

COVID-19 has been a pandemic [21] with no parallels in recent history. The insufficient knowledge of the disease and its unclear pathobiology during the early days led to a rapid spread. Nonetheless, the knowledge about the causative agent and its genome [22] paved the way for molecular diagnostics [23] and various 'omics' platforms enhanced our understanding of disease pathobiology [24−28]. SARS-CoV-2 attacks the lungs primarily during the early stages of the disease, and it triggers a cytokine-mediated inflammation as evidenced by the dysregulated IL6, IL17, and CCL2 [29] in patient blood. Clinically, COVID-19 manifests itself through an array of symptoms. While most patients experience very mild-to-moderate symptoms, around one in five patients develops pneumonia coupled with severe respiratory distress. These patients require treatment in hospital intensive care units (ICU). COVID-19 can aggravate and lead to multi-organ dysfunction, failure, and sometimes death [30−32].

Using patient data from Mumbai during the early phase of the pandemic, we studied the odds ratio of COVID-19 susceptibility in the general populace. The initial phase of the pandemic saw a massive surge in the number of infected patients. Even as the number of

Table 3.
Total positive cases by age, sex, symptoms, and medical conditions.

Variables and Categories	World	India*	Mumbai#
Gender			
Male	17,500,931 (50.67)	18,57,758 (64.54)	11,470 (61.67)
Female	17,036,424 (49.33)	10,20,025 (35.44)	7130 (38.33)
Age			
0–19	N/A	27,392 (14.21)	1582 (8.51)
20–39	N/A	93,569 (48.55)	7822 (42.05)
40–59	N/A	53,784 (27.91)	6042 (32.48)
≥ 60	N/A	17,991 (9.33)	3154 (16.96)
Symptoms			
Fever	N/A	10,512 (25.22)	1283 (6.9)
Cough	N/A	6770 (16.24)	905 (4.87)
Breathlessness	N/A	2004 (4.81)	829 (4.46)
Sore throat	N/A	2907 (6.98)	762 (4.1)
Fever + cough	N/A	N/A	910 (4.89)
Fever + breathlessness	N/A	N/A	528 (2.84)
Cough + breathlessness	N/A	N/A	707 (3.8)
Cough + sore throat	N/A	N/A	431 (2.23)
Fever + cough + breathlessness	N/A	N/A	1091 (5.87)
Other	N/A	19,483 (46.75)	4549 (24.46)
Asymptomatic	N/A	N/A	6605 (35.51)
Comorbidities			
Diabetes	N/A	1870 (5.04)	506 (2.72)
Hypertension	N/A	2056 (5.54)	453 (2.44)
Diabetes	N/A	N/A	390 (2.1)
Chronic Renal Disease	N/A	219 (0.59)	81 (0.44)
Other	N/A	24,633 (66.39)	521 (2.8)
N/A	N/A	8323 (22.43)	16,649 (89.51)

All the values are presented as n (%); N/A, Not available.
#data from Mumbai collected from March 7, 2020, to June 30, 2020.
* data from India as on, data as of December 17, 2020 Source: https://ncdc.gov.in/dashboard.php.

patients kept increasing during our study period, the test positivity rate was high at 48.31% in June. This demonstrates that the disease had spread far and wide in the city. The high odds of fever with cough and breathlessness and fever with breathlessness as symptoms result from the innate immune response to the infection. Further, a robust anti-viral interferon response precipitates as fever in COVID-19 patients [33]. We compared our results with data from India and the world (Table 3). The preponderance of males getting infected was true across all datasets from India. However, globally, there was no difference between males and females. The most affected age group seems to be 20–39 years. It has been hypothesized that age-related decline and dysregulation of the immune function can lead to susceptibility to severe COVID-19 outcomes in older adults [34]. The least chances of catching COVID-19 appear in the young population. Angiotensin converting enzyme 2 (ACE2) receptor expression variability can explain this finding since it has been reported that ACE2 gene expression [35] was ominously higher in grown-up children(10–17 years) (p = 0.01), young adults (aged 18–24 years) (p <0.001), and adults (>25 years) (p = 0.001), therefore, allowing the young children to escape the virus. Serum levels of ACE2 receptors and CTSL1(cathepsin L)-the protease essential for internalizing the virus-also positively correlated to increasing age hence making age a risk factor. Moreover, males express these proteins in higher amounts, thus, increasing the chances of infection [36]. Nevertheless, data from Israel suggests that children can catch COVID-19 with high rates [37] when schools reopened.

The comorbidities affecting the population across the nation are diabetes and hypertension, which are the most prevalent comorbidities across all Indian datasets. Geldsetzer et al. [38] identified that the crude prevalence of diabetes and hypertension in India was 7.5% and 25.3%, respectively. Given this high prevalence and effect of therapies to treat the comorbid conditions discussed previously, more studies need to be conducted with even larger datasets. Elderly patients with renal diseases showed elevated risks. While no studies have looked into the odds of COVID-19 infection in such patients, Wu et al. reported that patients with renal failure have a more severe form of COVID-19 than the general population. Moreover, they had a higher chance of fatality (14% vs. 4%) [39]. Radzikowska et al. [40] reported that the expression of infection-related molecules, namely ACE2 and TMPRSS2, CD147 (BSG), cyclophilins (PPIA and PPIB), and CD26 (DPP4) related genes correlated with patient age in the PBMCs and T cells. Additionally, CD147-related genes correlated positively with age and BMI. These reports can explain at least part of our observations on the age and comorbidities that lead to higher infection odds.

Diabetes is also known to upregulate the ACE2 expression [41]. Moreover, therapeutic management of diabetes using drugs such as ACE inhibitors, GLP-1 agonists, and statins may further increase ACE2 levels [18]. For many years, ACE-2 inhibitors have been targeted for drug therapy in patients with hypertension. They act by reducing systemic vascular resistance in patients with hypertension, diabetes, and chronic renal disease. Prolonged use of ACE inhibitors might lead to over-expressed ACE-2 by a retrograde feedback loop [42]. However, whether the high odds of infection in these patients directly result from the pre-existing drug therapies needs to be considered further. Male immunogenetics and the hormonal profile might drive the increased susceptibility of the group. Globally, it has been found that males are predisposed to COVID-19 infection [43]. It is most likely because they are monoallelic to *X*-chromosome linked genes related to the immune response [44]. These observations uphold our results and place comorbid males at the highest risk of contracting COVID-19.

Understanding the most vulnerable populations should be the guiding principle of all decisions taken during pandemic management. Age, sex, and comorbidities such as diabetes, hypertension, and chronic renal failure have significant fallout on the prevalence of the disease in specific populations. Undoubtedly, effective vaccination against SARS-CoV-2 is the best strategy to stop the pandemic at its tracks. In a country as large and diverse as India, prior knowledge is essential for targeting prevention programs like vaccination, screening for infection in case of a local upsurge, and finally, drafting treatment procedures. However, to our knowledge, there has been no prior study on these factors, especially using a robust dataset. Mumbai, a large metropolitan city with its teeming population, is a model city to study the risk factors of infection of the novel virus. Our study definitively proves that preventive measures such as quarantine and lockdown work well to prevent the spread of COVID-19. Preventive measures such as quarantine lowered the odds of infection (OR=0.59, 95% CI=0.53–0.66, p <0.001).

Our study identified the elderly males aged ≥ 60 years, people with both diabetes and hypertension or hypertension alone as underlying medical conditions, and the people presenting fever, cough, and breathlessness or fever and breathlessness as symptoms as independent high-risk groups for COVID-19 infection. Considering age and comorbidity, diabetes and hypertension together, or diabetes or hypertension alone as pre-existing medical conditions for people aged ≥ 20 years, and chronic renal disease for those aged 20–39 years are high-risk factors. Interestingly, the COVID-19 positive odds increase for people having both diabetes and hypertension, whereas the odds decrease for people having hypertension alone with an increase in age. Considering age and symptoms, fever, cough, and breathlessness, or both fever and breathlessness, or both fever and cough, or both cough and breathlessness, or fever or breathlessness, or cough are high-risk factors for all age groups. Further, both cough and sore throat as symptoms only significantly impacted those aged 0−19 and ≥ 60 years, while sore throat alone as a symptom only significantly impacted those aged 0−19 years.

Curiously though, the odds of COVID-19 infection for people with a sore throat in the 40−59 years' age group are significantly lower than those with no symptoms in this age group [45]. Although no biological evidence of such an observation could be found, this might be due to this age group's variable immune response to viral infection. Finally, considering sex, age, and comorbidity, males aged ≥ 60 years and having both diabetes and hypertension are at the most risk. However, we argue that being the primary drivers of the economy, the younger age group, especially those with comorbidities like diabetes and hypertension, should be protected against the virus on priority. Most people in this age group would need to travel for work and other essential activities, thus increasing their exposure risks. Moreover, with evidence [16,46] of increased chances of a lethal infection in comorbid patients, we find it is only natural to priortise this group for the vaccination.

However, our data has some limitations within which the results of this investigation should be interpreted. Patients self-reported the comorbidities to the attending clinicians and healthcare workers. Thus, we do not have access to their medical history or past medications prescribed to the patients before the testing, potentially altering the study's baseline characteristics. Despite this, our study identified the at-risk groups, and thus these findings should be of significance to clinicians and policymakers alike. Vaccination strategies should target the at-risk groups outlined above on priority to reduce mortality and to minimize the virus's circulation in the population, and take steps towards herd immunity.

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Data sharing statement

We have shared the odds ratio analysis results associated with the study as supplementary files. Clinical records maintained by the hospital can be shared upon reasonable request to the corresponding authors after anonymization for patient privacy.

Authors' contributions

Study conceptualized and designed by SVS, JS, and SS. SS did the funding acquisition. Data collected from the COVID-19 testing center by SA, RB, VP, and AS. RY, SS, and SVS curated the data. RY and SVS did the formal statistical analysis and draft data visualization. AA wrote the draft manuscript. RY, AA, AS, and SS prepared final figures. SS, SVS, JS, AA, AS, and RY revised the final draft. All data were independently verified by RY, SVS, SS, SA, JS, AS, RB, VP, and AA. RY and AA contributed equally to the work. All authors discussed the results and commented on the manuscript. All authors went through the final version of the manuscript.

Declaration of Competing Interest

Dr. Srivastava reports grants from DST SERB and from IRCC, IIT Bombay, during the conduct of the study.The other authors have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100841.

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