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The COVID-19 havoc and clues from Sex disaggregated data in the Indian population

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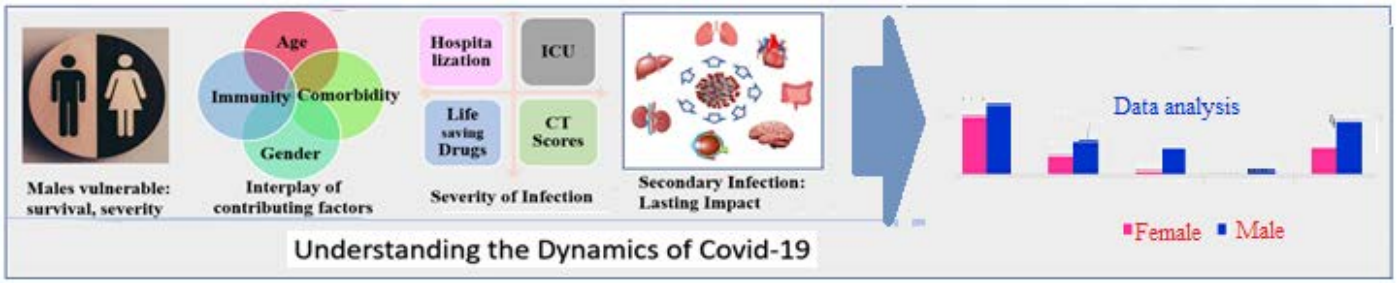
ABSTRACT



The coronavirus infectious disease (COVID-19) has created a turmoil across the globe, with India emerging as one of the worst-hit countries. The Global scenario indicates a gender bias with a higher COVID-19 Case fatality rate (CFR) in males as opposed to females. However, countries like India, Nepal, Vietnam and Slovenia have reported a reverse trend in mortality. Real-time disaggregated data empowers countries to design more effective, sustainable, and people-centered approaches to treat and prevent COVID-19. Our study aimed to procure sex-disaggregated data in the Indian population by using a google form based online health survey. We have analyzed parameters like age, gender, occupation, sex and severity of infection based on CT score, steroid dependence, need for hospitalization, etc. The responses were evaluated by descriptive statistics by excluding arbitrary correlation. We found that the males were at a significantly greater risk of severe disease and mortality (~ twice) than females. We also found that the males as compared to females, presented almost eighteen times the odds of requiring intensive care unit (ICU) admission; reflecting severity of the infection. A sex-informed approach to COVID-19 research would reveal novel responses of the host immune system to SARS-CoV-2, which can then be utilized in formulation of policies for equitable health outcomes.

Keywords: COVID-19, Sex disaggregation, gender, severity, Case fatality Rate

INTRODUCTION

Recurrent waves of infection with evolving coronavirus strains have posed an unprecedented challenge to the entire world. With a global death toll of more than 59.3 lakh,[1] the eradication/mitigation of this virus seems like an uphill struggle. Collective efforts in understanding the dynamics of COVID-19 infection, from across the continents can contribute to development of a comprehensive and tailored approach for combating this global public health emergency. The entire world needs to be aware and prepared in all capacities to face the worst consequences of any future waves.[2] With some countries getting ready to brace the fifth wave of the pandemic, the ongoing chaos highlights the need for all countries to step up their response, gear up for pandemic preparedness and understand the various factors which could be playing a crucial role in the progression of this disease. This study aims to contribute towards the understanding of the interplay of various contributing factors of Covid -19, through the gender lens.

BACKGROUND & SUMMARY

With over 42.9 million confirmed cases, India is unfortunately one of the worst hit nations with respect to the global burden of COVID-19.[1] The COVID-19 death toll in India has currently crossed 5.13 lakh accounting for as high as ~10 % of the global COVID-19 deaths.[1] The global data indicates an elevated proportion of deaths among identified, confirmed COVID-19 cases. Sex of the individual is also an important factor in occurrence of COVID-19 disease.[3] Epidemiological studies suggest that clinical severity of COVID-19 and mortality associated with it, may be higher in males, especially in chronically ill older males.[4,5] Gender

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differences in clinical outcomes have also been observed in other coronavirus induced diseases.[6] Susceptibility to SARS-CoV and case fatality rate was higher in males as compared to females. In MERS-CoV infected individuals, females exhibited higher morbidity and mortality than males.[7]

On the basis of sex chromosome complement, reproductive tissues (ovaries or testes) and sex steroid hormone (estrogen, progesterone and testosterone) concentrations, human gender is designated as male, female or intersex, and is considered as a multidimensional aspect that shapes infectious disease pathogenesis. The difference in disease severity has usually been attributed to the difference in sex hormones, or copies of immune response genes found on X chromosomes[8] along with cultural and behavioral factors.[9]

The COVID-19 has presented a heterogeneous outcome in different countries of the world. The reported COVID-19 CFR in countries like India, Nepal, Vietnam and Slovenia shows a trend opposite to the global scenario and needs further inspection. This study aims to present the role of sex/gender in COVID-19 infection and mortality risk in humans in India in the light of other factors like age, comorbidities, and immune response. To contribute to the understanding of the interactions and associations between COVID-19 infection and associated biological factors, this study presents an analysis conducted on a dataset, collected through an online survey.

MATERIALS AND METHODS

This study was performed using a google form based online survey (open to participants above 18 years with informed consent) in the month of June-October 2021. The questionnaire was structured to obtain information on socio-demographic parameters like gender, age, occupation and city of residence (Section A) and on symptoms of COVID-19, disease severity (intensive care and oxygen cylinders and concentrators), comorbidity, vaccination, post-covid infection and recovery time. Participation in the survey was limited to one response per individual (ascertained by necessary logging in with the email ID) to avoid duplicated or exaggerated data. The participants were requested to fill out the form and encouraged to assist in sharing the questionnaire with their family members, relatives and friends. The questionnaire also sought information about relatives of participants. For such cases, the data was manually checked to remove any repeated reporting of mortality. The survey was designed in English as well as Hindi to facilitate easy comprehension of questions among participants.

Parameters like infection rate, death rate, recovery rate and comorbidity rate were calculated. Infection rate for each gender, and each age interval was calculated by dividing the number of individuals contracting the infection from the total number of individuals, multiplied by 100 (Figure 1). The death rate for each gender was calculated by dividing the number of deceased individuals from the total number of individuals and multiplied by 100 (Figure 1). Recovery rate was plotted as the number of individuals falling in a particular recovery window divided by the total number of individuals who tested positive for each gender, multiplied by 100 (Figure 3). Comorbidity rate was calculated by dividing the number of individuals reporting a particular type of comorbidity divided by the total number of individuals who contracted infection, multiplied by 100. Comorbidity rate was also calculated gender-wise in the same manner for both males and females. Secondary infection Rate was calculated by dividing the number of individuals reporting a particular type of secondary infection divided by the total number of individuals who contracted the infection, multiplied by 100.

STATISTICAL ANALYSIS

Descriptive statistical analysis was carried out for the data using the Statistical Package for Social Sciences (SPSS) version 23, adopting a confidence interval (CI) of > 95%. The results including means, frequencies and standard deviations (SD) are reported in descriptive statistics. Statistical differences between the various analyzed parameters, were determined by Two-tailed student's t-test. Significant associations and correlations between univariate sociodemographic variables and awareness subscales were evaluated using Pearson's correlations and Pivot tables. Multivariate analysis was performed using Regression analysis (using ANOVA). A p-value of < 0.05 was considered statistically significant.

Pivot tables and charts were constructed to compare and summarize the data variables to explore the trends based on the available information. Pearson's correlation analysis was performed to understand the relationship between the various factors under consideration. Regression analysis was performed, where linear regression models were built to understand the strength of relationship between the multiple variables in order to highlight the predictors in the model that are statistically significant, along with analyzing the confidence levels.

The data was analyzed for sampling errors by removing the variables which did not have a considerable sample size pertaining to unequal coverage among people from different age groups, gender, city of residence etc. Response bias was minimized by opting for a diversified set of questions while framing the questionnaire and processing errors were eliminated by a data cleaning step where each response was studied for any inconsistencies.

Descriptive statistics like measures of central tendencies, frequencies and proportions were used for response evaluation using SPSS software. Data wrangling, cleaning and visualization were performed using Microsoft Excel 2016 and SPSS.

Informed Consent: All the participants answering the survey were above 18 years of age and voluntarily consented to participate in the study, where, data shared by them would only be used and published for the purpose of scientific study.

RESULTS AND DISCUSSION

Socio-Demographic Variables:

The survey received 1078 responses from various states across India including Delhi, Punjab, Bihar, West Bengal, Maharashtra, Kerala, Uttar Pradesh, Haryana, Madhya Pradesh, Rajasthan, Andhra Pradesh, Telangana, Karnataka, Himachal Pradesh and Tamil Nadu.

Analyzing the interplay of various factors through the gender lens:

The survey was undertaken by 516 (47.87%) female and 562 (52.13%) male participants. 256 females and 307 males reported the contraction of COVID-19. The infection rate and death rate reported by the respondents is presented in Figure 1. Affliction with COVID-19 was significantly higher in the males (64%) than in females (54%) ($P < 0.05$). Figure 1a shows the distribution of infection rate among individuals of various age groups in the male and female participants.

A total of 1130 deaths among their family and extended family members were reported by respondents, with the death toll being more than two-fold in the males (68.1%) as compared to females (31.9 %). The death rate reported by participants is presented in Figure 1b. It indicates that the deaths were not restricted to a particular age group, but it was observed that most of the deaths were reported in the age group above 46 years in both the genders, however in the 36–45-year age group 22.8 % deaths were reported in the males as compared to 0.03 % in the females. Though the infection rate for males as well as females is comparable (as assessed by respondent's data), there is marked difference in death rates between two genders (as reported by respondents for their family members).

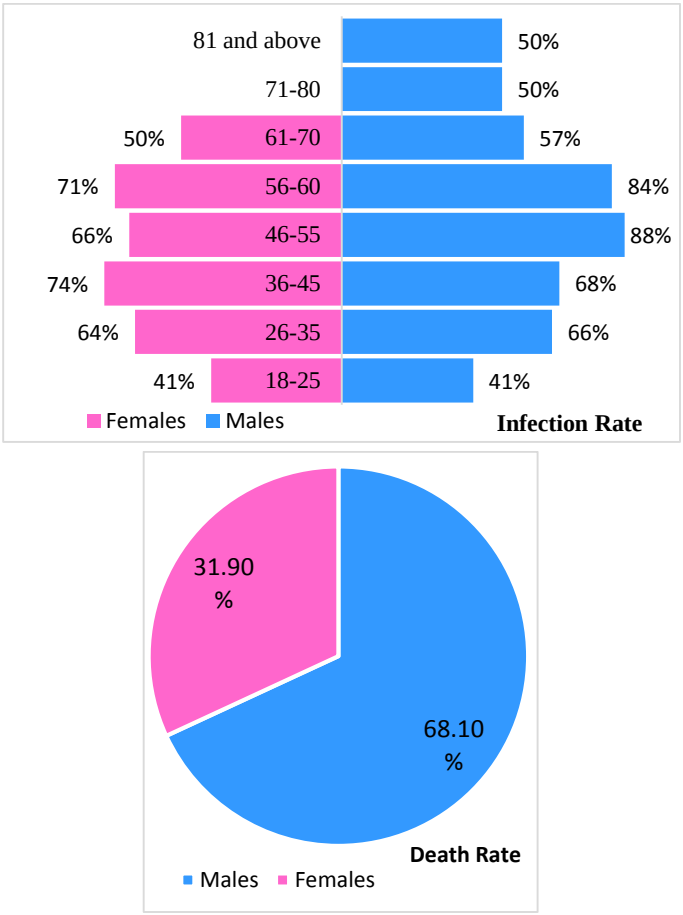


Figure 1 a) Age wise Infection rate among the male and female participants. b) Death rate among the family members of the participants.

Infection Rate accounts for individuals who contracted the infection or tested COVID-19 positive. The gender-wise distribution is shown for the different age groups. The infection rate was more or less comparable in the males and females in the younger age groups. Above 46 years of age, males displayed a higher incidence of infection as compared to the females.

Death Rate accounts for the individuals who succumbed to COVID-19. Among the individuals reported to succumb to the COVID-19, the number of males was more than two times that of females.

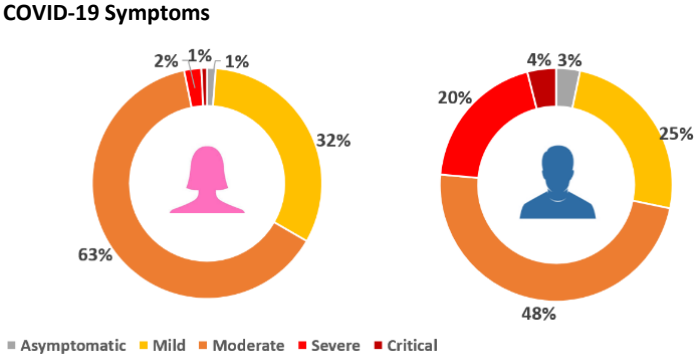
Globally, males have been reported to have a higher overall burden of infection, however, it is not certain if the males experience a higher incidence of mortality across the age-spectrum or there exists a sex-differential survival rate. The global sex ratio of confirmed cases is M:F = 1.03:1,[4] however, the reported case fatalities in India indicate a greater disadvantage for females as compared to males. COVID-19 cases in India are found to have a non-uniform ratio for mortality among men and women across different age groups. The mortality risk is reported to be significantly higher in women as compared to men, specifically in the 40–49-year age group.[4] Interaction between factors like gender and age can be a key factor in the observed gender related differences in case fatality.[4] Further, this can be attributed to a decline in estradiol levels post menopause. A high mortality risk is displayed by elderly males and females who require special care after getting infected.

However, our study indicates higher incidences of infection and mortality among males as compared to females. In the 30–60 years age group, the death rate was significantly lower in females, thus, highlighting a protective role of sex steroids (Figure 1b). Our hypothesis in support of the gender bias in COVID-19 related CFR suggests a protective role of estrogen against COVID-19. A study reported higher mortality in ovariectomized/estrogen receptor antagonist administered mice in comparison to normal female mice. A study proposed sex differences in the susceptibility to SARS-CoV-2.[10] A study from China also reported greater severity of symptoms in women having low estrogen levels.[11] A protective role for reproductive steroids against the COVID-19 infection was first suggested in another study.[12] Circulating female reproductive steroids, namely estrogen and progesterone and its metabolite allopregnanolone, are anti-inflammatory in nature and are found to increase the competence of immune cells, stimulate antibody production, and enhance proliferation and repair of respiratory epithelial cells, indicating that they could confer protection against the COVID-19 infection.[12] The females of reproductive age are therefore better equipped to face the viral attack as compared to marginal age females or males.

However, in a contrasting report, the underlying biological factors like viral and host genetic variations instead of reproductive steroids have been reported to play a role in the disparity of COVID-19 severity and deaths among men and women.[13] The role of genetics and inborn errors of immunity which are more prevalent in males, is significant in contributing towards COVID-19 related mortality among men as compared to women, instead of the circulating sex steroid hormone levels.[13] The male sex hormone testosterone, contrastingly, is known to suppress the immune

system: high levels of inflammatory cytokines, antibody titres, CD4/CD8 ratios, natural killer cells, and, a decline in the numbers of regulatory T cells are reported to be associated with hypo-androgenism.[14]

Among the respondents affected with COVID-19, the infection manifested from mild symptoms to critical illness and death. Moderate symptoms defined by fever, body ache, fatigue, congestion, loss of taste and smell were reported by 63% females as compared to 48% males (Figure 2). The occurrence of severe symptoms, defined by breathing trouble, severe lung damage, dependence on oxygen cylinders and concentrators was significantly higher in the males (24%) as compared to females (3%). The recovery period (days taken to recover) was also found to be significantly shorter in the females (less than 14 days in 72% females) as compared to the males (more than 15 days in 53% males) ($P < 0.05$) (Figure 3). This may be attributed to female hormones.



- Asymptomatic: Tested positive, no symptoms
- Mild: Fever, body ache, fatigue
- Moderate: Fever, body ache, fatigue, loss of taste and smell, congestion
- Severe: Breathing trouble, oxygen given and lungs impacted
- Critical: Severe lung damage, oxygen cylinders and concentrators administered

Figure 2: Description of COVID-19 symptoms among the male and female participants. Symptoms reported by participants were categorized as mild, moderate, severe and critical. A percentage score of these categories was calculated and plotted on SPSS software. Most females showed mild to moderate symptoms, whereas the symptoms in males ranged mainly between mild, moderate and severe. Females were found to show significantly higher instances of mild to moderate symptoms in contrast to the males ($P < 0.05$). The difference between females exhibiting severe/critical symptoms in contrast with males was also significant ($P < 0.05$). Severe symptoms were reported by 2% of the female participants, as compared to 20% of the male participants.

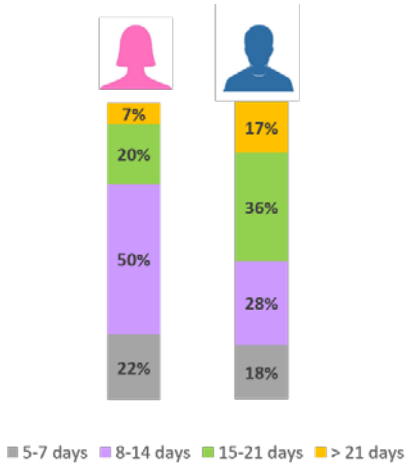
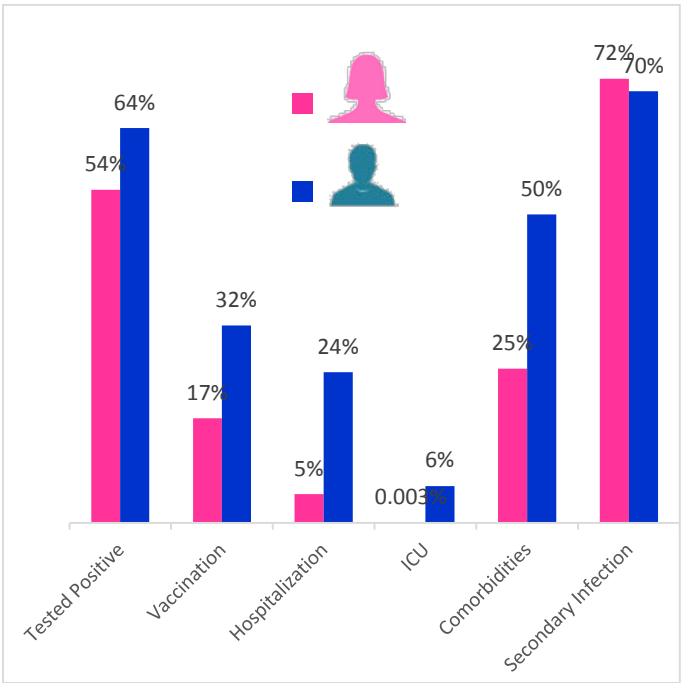


Figure 3: Recovery time Female Vs Male- Time taken to recover from the infection.

The recovery time directly affects the severity of the disease. There were significant differences in the recovery time and a clear gender bias was visible where females were seen to be recovering significantly faster than the males ($P < 0.05$). Seventy-two percent of the females who contracted the infection recovered before 14 days, whereas, 53% of the males took more than 15 days to recover, out of which 17% took more than 22 days representing critical illness (7% in females). The recovery time was significantly shorter in the females ($P < 0.05$).

The severity of infection was reflected by the acquisition of symptoms like ARDS (acute respiratory distress syndrome), a life-threatening condition causing severe damage, injury and fluid accumulation in the lungs, a need for oxygen concentrators and medical care (Figure 4). Severity in symptoms showed gender bias' with 94.7% of the total patients requiring ICU admission for treatment being males as compared to 5.3% females. The requirement of oxygen cylinders and concentrators was also significantly higher for the males as compared to the females. This observation was also reported by other authors who found that in most of the age groups (less than 80 years), more males as compared to females, were hospitalized and required intensive care.[15]



Note: Vaccination amongst total population:

Female: 10% (n=474) Male: 22% (n=482)

Note: Base for Vaccination, Hospitalization, Comorbidities & Secondary Infections is COVID Positive individuals.

Figure 4: Gender differences could impact severity and progression of COVID-19.

The figure 4 (from left to right) indicates gender-wise rate of contraction of infection, vaccination status, reflecting the immune preparedness in terms of antibody repertoire, need for hospitalization, requirement of intensive care (ICU), pre-existing comorbidities (which could be age related) and development of long-lasting secondary infection. The male related gender bias is clearly evident when it comes to disease severity represented by need for hospitalization and intensive care. Occurrence of higher number (two – times) of pre-existing comorbidities also predisposes the males to greater chances of contraction of the infection.

A gender-wise analysis of parameters related to disease progression indicated a many-fold difference in the requirement of hospitalization and intensive care (ICU) among males (Figure 4). It highlights various components that could be governing the appearance of severe symptoms in the two genders. Critical illness was identified on the basis of need for hospitalization and intensive care (ICU). Among the total number of individuals who contracted the infection, comorbidity was reported by twice the number of males as compared to females (Figure 4).

The drugs administered to COVID-19 patients also reflect the severity of infection. Most patients were administered steroids, antibiotics and antiallergics (data not shown). Our respondent data indicates a marked difference in administration of the steroids/ Oxygen supplementation/ tocilizumab and/or Remdesivir to males as compared to females ($P < 0.05$). The drugs administered for treatment of COVID-19 symptoms were broadly categorized as antibiotics, antiallergics, steroids and use of oxygen concentrators was also factored in. The drugs for COVID-19 treatment were analyzed with the gender lens, and we found that while most of the participants were administered antibiotics and antiallergics, male participants showed a significant ($P< 0.05$) dependence on steroids and oxygen concentrators, thus reflecting the severity of disease.

The patients displayed broad spectrum secondary infections post COVID-19 and were presented with respiratory, neurological and/or digestive problems, fatigue, anemia, anxiety, lack of sleep, depression, and many other problems (Figure 6). Respiratory trouble and lung damage was found to be more prevalent in the males. Though the recovery time post infection showed a slight male bias (Figure 3), most of the secondary infection symptoms except respiratory problems were more prevalent in females (Figure 6). This is in sync with another study,[15] which predicted worse long-term outcomes among females, albeit with a higher probability of surviving severe acute disease. Studies suggest an association between COVID-19 severity/deaths and pre-existing comorbidities. In our study, 75 % female respondents did not display any comorbidity whereas 50 % of the male respondents contracting the infection were found to be comorbid (Figure 5b). Nature of comorbidity in these individuals included diabetes, hypertension, arthritis, bronchitis, neurological problems, heart problems, high cholesterol, etc. (Figure 5a). Pre-existing comorbidities coupled with other factors like presence of multiple comorbidities, age, gender, immunity etc. could therefore predispose individuals to COVID-19 infection, severity and progression.

The COVID-19 data indicates a greater risk of COVID-19 related mortality in individuals with pre-existing comorbidities. The individuals with comorbidities which interfere or suppress the function of the immune system, are at a greater risk of severe COVID-19. Disease etiology and common therapies along with the drugs prescribed for the treatment of these conditions influence the COVID-19 progression.[16–19] The expression of angiotensin converting enzyme 2 (ACE 2) receptors – the key players in SARS-CoV-2 viral entry and human to human transmission is more in the males. ACE2 gene is located on the X chromosome, therefore, it could escape X- inactivation observed in women, also, Estrogen could influence ACE2 expression. Elevated expression of angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane protease serine 2 (TMPRSS2) receptors, the entry points of SARS-CoV-2 virus, throughout the body on account of

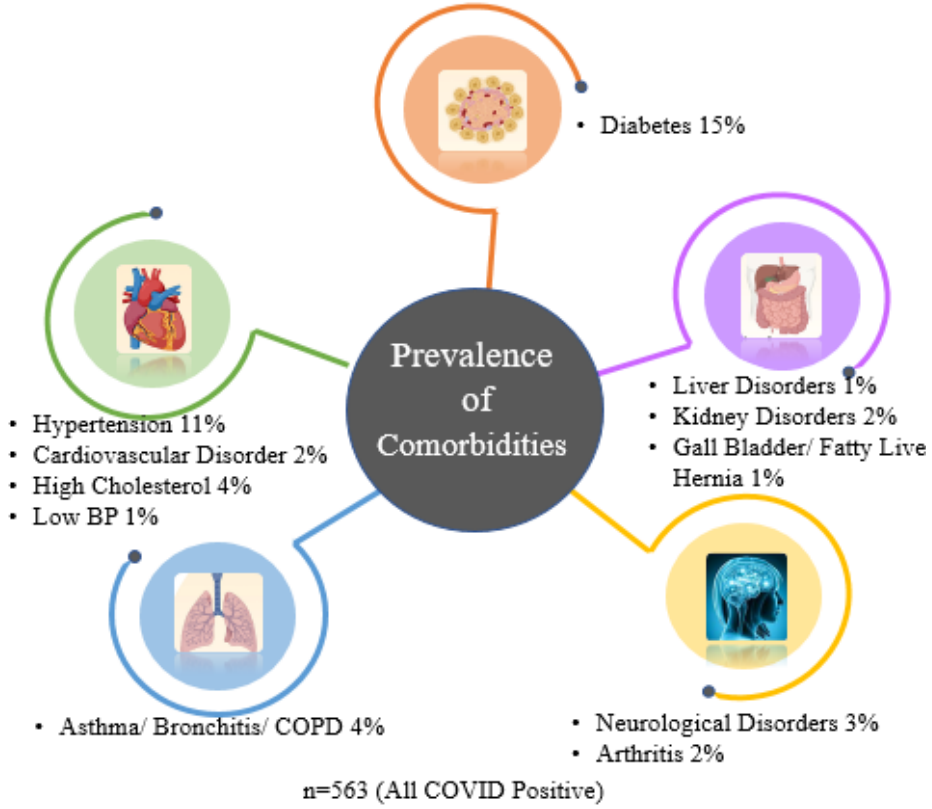


Figure 5a: Prevalence of pre-existing comorbidities among the recovered COVID-19 participants.

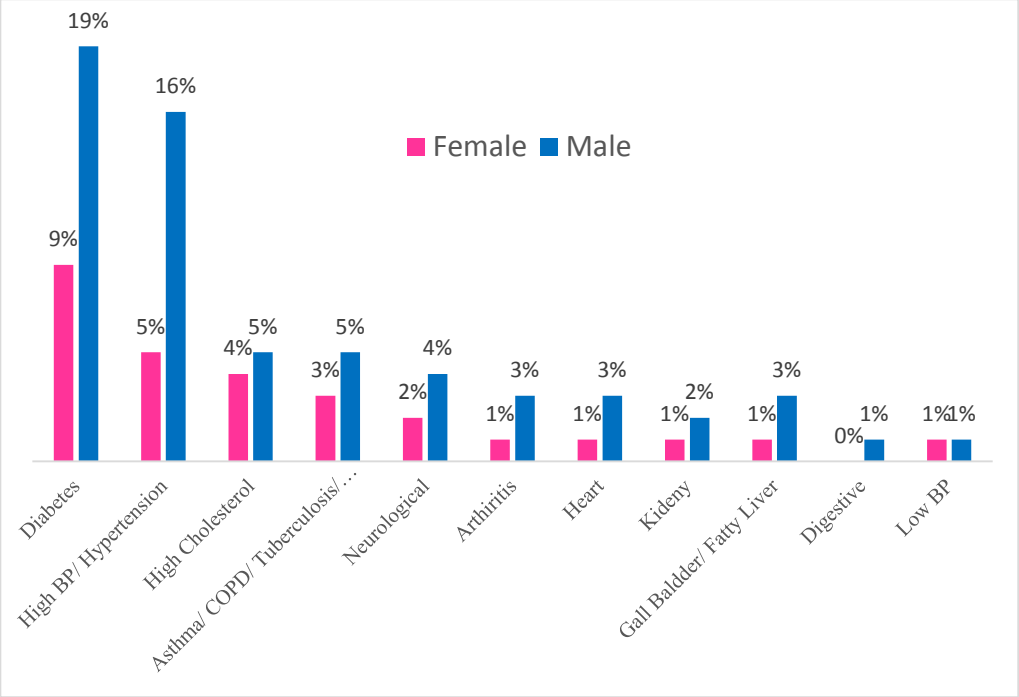


Figure 5b: Gender-wise presentation of comorbidities in the respondents.

sex hormones, may increase vulnerability to COVID-19 infection and fatality, thereby elucidating the sex differences in COVID-19 outcomes.[20]

Our results also indicate that advanced age is the most significant risk factor for mortality and disease severity on elimination of factors like demography and comorbidity. Comorbidity is found to be associated with a compromised immune response. For instance, in diabetic patients, the natural immune function was found to reduce markedly, thus restricting antibody generation against any infection.[21,22] The immune system is a vital player in context of COVID-19, and the extent of immune dysfunction is proportional to disease severity.[18] The COVID-19 infection triggers an immune response leading to local inflammation, recruitment of monocytes, natural killer (NK), dendritic cells (DCs), T and B cells.[23,24] In case of severe infection, extreme lymphopenia and infiltration of functionally exhausted T and NK cells occurs, which when unable to clear the virus, mount an overwhelming systemic hyperinflammation. This response sometimes leads to critical and potentially life-threatening complications like pneumonia, ARDS, septic shock and multiple organ failure. Basic gender-based differences in both the innate and adaptive immune system are already established and could be responsible for the female advantage in COVID-19.[25] Another

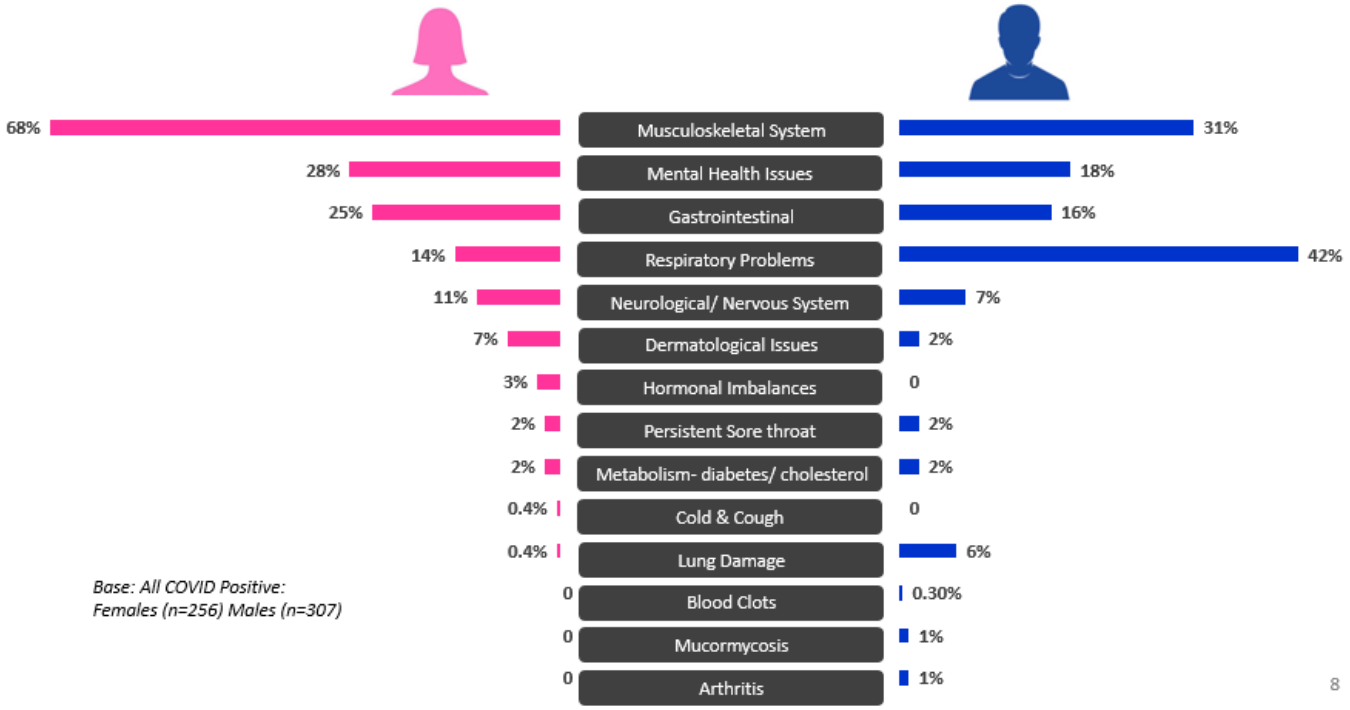
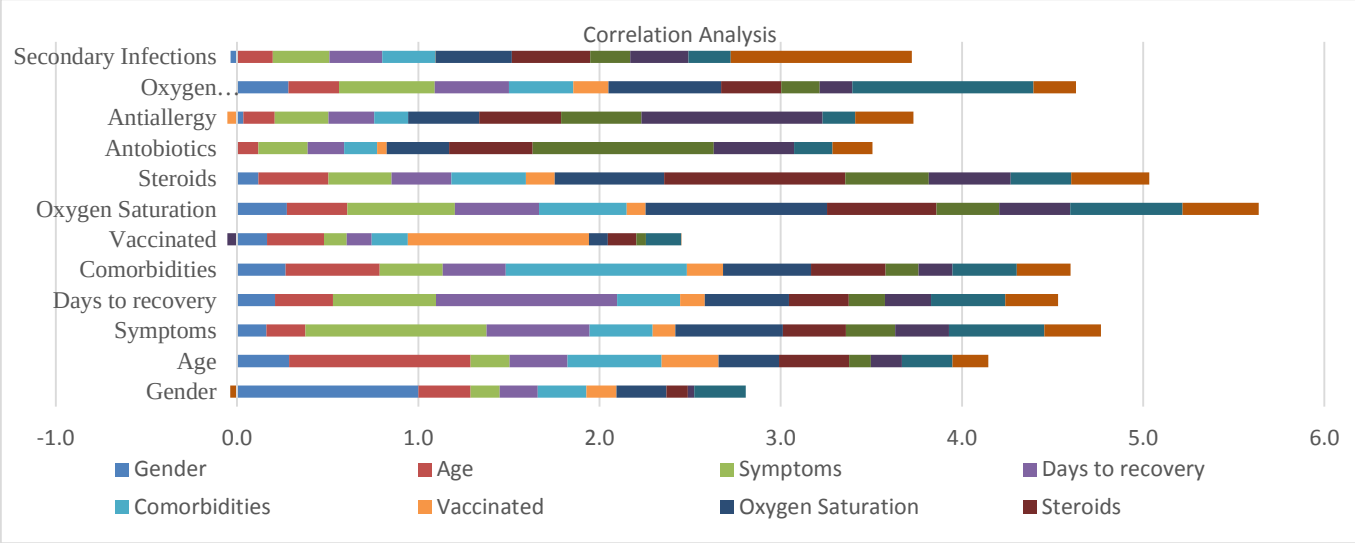


Figure 6: Gender-wise description of secondary infections reported by the participants after recovering from COVID-19.



Data Variables	Gender	Age	Symptoms	Days to recovery	Comorbidities	Vaccinated	Oxygen Saturation	Steroids	Antobiotics	Antiallergy	Oxygen Concentrat	Secondary Infections
Gender	1.0	0.3	0.2	0.2	0.3	0.2	0.3	0.1	0.0	0.0	0.3	0.0
Age	0.3	1.0	0.2	0.3	0.5	0.3	0.3	0.4	0.1	0.2	0.3	0.2
Symptoms	0.2	0.2	1.0	0.6	0.3	0.1	0.6	0.3	0.3	0.3	0.5	0.3
Days to recovery	0.2	0.3	0.6	1.0	0.3	0.1	0.5	0.3	0.2	0.3	0.4	0.3
Comorbidities	0.3	0.5	0.3	0.3	1.0	0.2	0.5	0.4	0.2	0.2	0.4	0.3
Vaccinated	0.2	0.3	0.1	0.1	0.2	1.0	0.1	0.2	0.1	-0.1	0.2	0.0
Oxygen Saturation	0.3	0.3	0.6	0.5	0.5	0.1	1.0	0.6	0.3	0.4	0.6	0.4
Steroids	0.1	0.4	0.3	0.3	0.4	0.2	0.6	1.0	0.5	0.5	0.3	0.4
Antobiotics	0.0	0.1	0.3	0.2	0.2	0.1	0.3	0.5	1.0	0.4	0.2	0.2
Antiallergy	0.0	0.2	0.3	0.3	0.2	-0.1	0.4	0.5	0.4	1.0	0.2	0.3
Oxygen Concentrators	0.3	0.3	0.5	0.4	0.4	0.2	0.6	0.3	0.2	0.2	1.0	0.2
Secondary Infections	0.0	0.2	0.3	0.3	0.3	0.0	0.4	0.4	0.2	0.3	0.2	1.0

Figure 7: Interplay of several factors important for analyzing the dynamics of COVID-19.

difference between the sexes is the age-associated changes in the immune system. A significant correlation between advancing age and morbidity/mortality in COVID-19 has been reported.[26] For instance, it is known that males show an age-related reduction in B cells and an accelerated immune ageing pattern, which could be a contributing factor for the male bias found in COVID-19.

Diabetes (15%), cardiovascular complications (2%) comprising hypertension (11%), high cholesterol (4%), hypotension (1%) and asthma/ bronchitis/ COPD (4%) were among the most commonly reported pre-existing comorbidities.

Gender distribution was analyzed for each type of comorbidity. Male bias was observed for almost all disease types reported; predisposing the males to a higher chance of contraction of the infection.

The participants displayed broad spectrum secondary infections; some of which were new-onset with no previous history. Musculoskeletal problems, mental health issues, gastrointestinal disorders, respiratory problems and neurological disorders were the top five secondary infections reported by the respondents. Females were found to be affected more than males for most types of infections except respiratory problems which were significantly higher in the males ($P<0.05$).

The dynamics of COVID-19 are defined by an interplay of several variables. For a better understanding of the inter-relationship of these variables, correlation analysis was performed between several variables chosen for our study (Figure 7). We found that 'age' exhibits moderate correlation with comorbidities and 'symptoms' show moderate correlation with days to recovery, oxygen saturation and oxygen concentration ($P < 0.05$). 'Gender' showed moderate correlation (0.3) with 'age', 'comorbidity' and oxygen requirement. The results of multivariate linear regression analysis are presented in figure 8 and figure 9. These indicate that 'days to recovery' were strongly driven by the severity of infection as indicated by oxygen saturation levels, need for oxygen concentrators, age, followed by consumption of antiallergics, pre-existing comorbidities, gender, vaccination status, administration of antibiotics and steroids to the respondents (in this order).

Real-time sex disaggregated data allows valuable cognizance into the differential infection, differences in undertaking care and treatment and variation in the fatality rate of COVID-19 which is

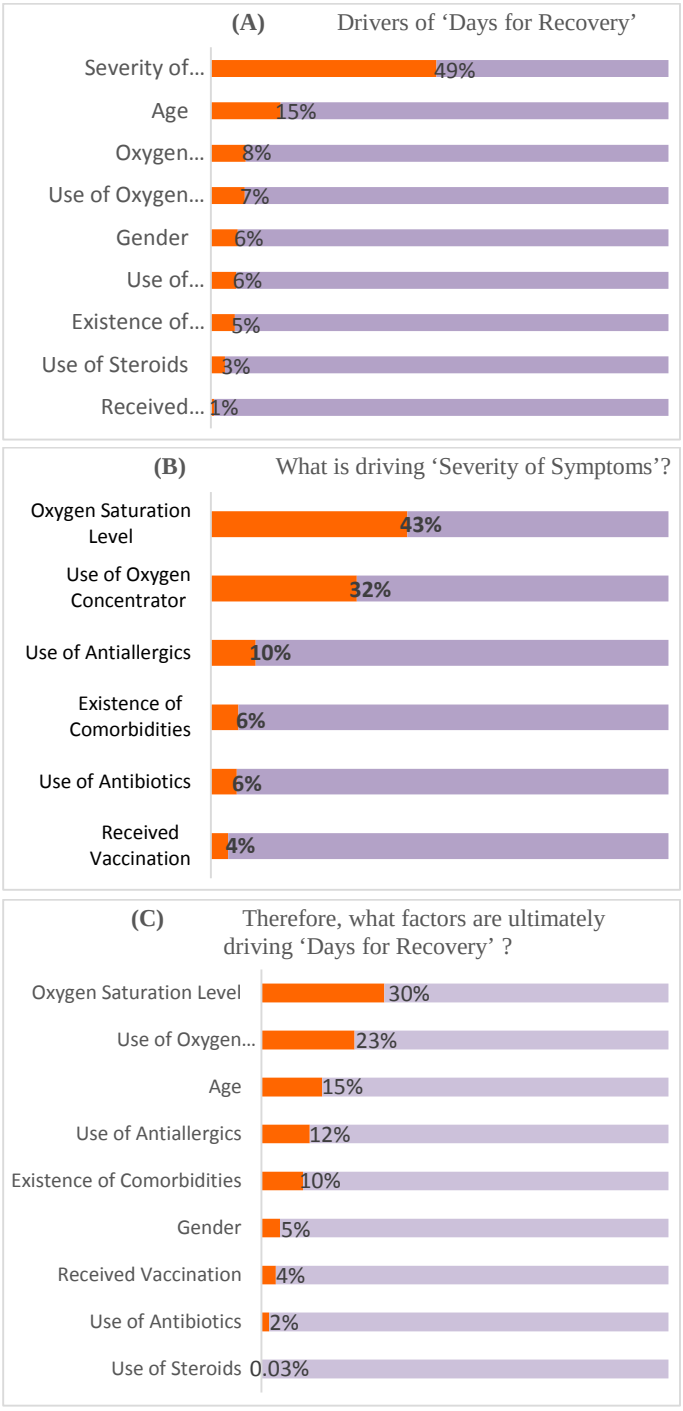


Figure 8. Final Drivers for 'Days to Recovery' - Statistical Linear Regression Analysis performed for building the Model representing multivariate data analysis. (A) Statistical Linear Regression Analysis has been done with 'Days for Recovery' as the dependent variable. Statements are represented in the order of importance which are derived through Beta coefficient. Model Strength is moderate (R2 = 0.4). (B) Statistical Linear Regression Analysis has been done with 'Severity of Symptoms' as the dependent variable. Statements are represented in the order of importance which are derived through Beta coefficient. Model Strength is moderate (R2 = 0.41). (C) Statistical Linear Regression Analysis has been done with 'Days for Recovery' as the dependent variable. Statements are represented in the order of importance which are derived through Beta coefficient.

evidently instrumental and much needed for developing gender-equitable solutions to this disease.

The figure represents correlation analysis using Pearson's coefficient to understand the relationship between the different factors under consideration using a two-way linear data analysis. The strength of linear relationships can be described by a higher correlation value. For the analysis, correlation values less than 0.3 were considered weak, 0.3-0.7 as moderate and more than 0.7 as strong. The significant data points are highlighted in green in the table shown above. Age shows moderate correlation with comorbidities. Symptoms show moderate correlation with days to recovery, oxygen saturation and oxygen concentration ($P< 0.05$).

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The strength between the outcome (dependent variable) which is 'Days to recovery' and predictor (independent) variables like oxygen saturation, oxygen concentrators, age, consumption of antiallergics, antibiotics and steroids, comorbidity, gender and vaccination status, was analyzed by multivariate analysis. The first model was built with 'Days for Recovery' as the dependent variable. Statements which are derived through Beta coefficient, are represented in the order of importance. Model Strength is moderate (R^2=0.4). The second model includes Statistical Linear Regression Analysis done with 'Severity of Symptoms' as the dependent variable. (Model 1 and 2 are presented as Supplementary data – Supplementary figure 1 and Supplementary figure 2) Statements which are derived through Beta coefficient, are represented in the order of importance. Model Strength is moderate (R^2=0.41). The final model incorporates Statistical Linear Regression Analysis done with 'Severity of Symptoms' as the dependent variable. Linear Regression Analysis has been run to show or predict the strength of the relationship between the Dependent (Outcome) variable and the Independent (predictor) variables. Through this regression model, we have attempted to analyze the final key drivers/ predictors for Days for Recovery, post identifying the key drivers/ predictors of Severity of Symptoms which is the key variable impacting Days for Recovery, as seen earlier. Here, Days for Recovery is the Dependent Variables while Gender, Age, Presence of Comorbidities, Vaccination Status, Oxygen Saturation levels along with administration of Steroids, Antiallergics, Antibiotics and Oxygen Concentrators are the Independent Variables. All the predictor variables have been entered in the regression model at once (Enter Method). R Square value of the model is 0.280 which indicates that 28.0% of the total variability observed in Days for Recovery is explained by the independent variables collectively in the dataset under examination. Standardized Coefficients (beta) have been used to analyze the relative importance or strength of each coefficient in the regression model. In this case, Oxygen Saturation levels has the highest beta (0.230), which indicates that Severity of Symptoms is the top predictor of Days for Recovery, accounting for 30% of the

Oxygen Saturation	30%
Oxygen Concentrators	23%
Age	15%
Antiallergic	12%
Comorbidities	10%
Gender	5%
Vaccinated	4%
Antibiotics	2%
Steroids	0.03%

Model 3 : Dependent Variable: Days for Recovery

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.529[a]	0.280	0.268	0.830

a. Predictors: (Constant), Oxygen Concentration, Antiallergic, Vaccinated, Gender, Comorbidities, Antibiotics, Age, Steroids, Oxygen Saturation

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	1.463	0.109		13.452	0.000
	Gender	0.068	0.077	0.035	0.881	0.379
	Age	0.072	0.029	0.114	2.516	0.012
	Comorbidities	0.156	0.092	0.078	1.688	0.092
	Vaccinated	0.060	0.087	0.027	0.691	0.490
	Oxygen Saturation	0.113	0.028	0.230	3.996	0.000
	Steroids	0.000	0.100	0.000	0.005	0.996
	Antibiotics	0.035	0.106	0.014	0.330	0.741
	Antiallergic	0.177	0.085	0.091	2.085	0.037
	Oxygen Concentration	0.434	0.117	0.175	3.725	0.000

a. Dependent Variable: Days for Recovery

	Total	529.723	562			

a. Dependent Variable: Days for Recovery

b. Predictors: (Constant), Oxygen Concentration, Antiallergic, Vaccinated, Gender, Comorbidities, Antibiotics, Age, Steroids, Oxygen Saturation

Figure 9. Regression analysis data

variability observed in Days for Recovery in the regression model, followed by use of Oxygen Concentrators with beta value 0.175.

COVID-19 impacts different genders in variable ways. Approximately equal number of men and women have been diagnosed with COVID-19 globally,[27] making the infection contraction rate more or less unbiased, however, in most of the countries, men are at a higher risk of severe illness. Our study reinforces that, males present a considerably higher risk of severe disease and death as compared to females. Similar findings have been reported in other studies.[28] Fever, respiratory, digestive and neurological symptoms were reported as the most common initial clinical manifestations in the patients who succumbed to the infection.[24]

In our study, broad spectrum secondary infections were reported by the participants, where some infections were new-onset with no previous history. Among the top five secondary infections reported were musculoskeletal system, mental health issues, gastrointestinal disorders, respiratory problems and neurological disorders. Cardiovascular disease has been reported to be highly prevalent among the COVID-19 survivors and is also thought to be responsible for COVID-19 related mortalities. Cardiovascular conditions such as thromboembolic events, acute coronary syndrome, myocarditis, arrhythmia, cardiogenic shock and heart failure, have been reported in COVID-19 patients without any prior history of cardiovascular disease,[29] demonstrating a noticeable impact of COVID-19 infection on the heart. COVID-19 is now established as a multi-organ disease displaying a broad spectrum symptoms. Falling in line with the survivors of previous virulent coronavirus epidemics, reports of persistent and long-lasting effects, even after recovering from acute COVID-19 are on the rise.

India's COVID-19 vaccination drive initiated by the government was launched on January 16, 2021. Having side effects from a vaccine is a common occurrence. It generally does not pose any serious threats. It has come to the fore that women are at a higher risk of experiencing side effects of the vaccine as compared with men. Studies have revealed that the number of women who have complained of mild to severe side effects is significantly higher than their male counterparts. This might sound alarming for women, but it is interesting to note that it is actually attributed to a better immune system of women compared to men. Research has also shown that women produce significantly more potent antibodies as opposed to men. Women are known to generate greater antibody titers in response to most pathogenic vaccines like the trivalent inactivated seasonal influenza vaccination (TIV)100, and hence the case with the current vaccine.

In our study, a higher death toll was reported for the age group of 46 year and above in comparison with the age group 36-45 year, also showing male bias mortality in the older age group. Similar observations have been reported by CDC where the rate of death was four times higher in 30–39-year-olds as compared to 18–29-year-olds, and 570 times higher in those who are 85 years and older. The infection rate in females is higher than males in the younger age group (pre-menopausal), but the females are clearly doing better than males in terms of coping with the disease and not developing acute/critical symptoms which are showing a male bias along with need for critical care and death. We therefore propose that the advantage offered by the female reproductive hormones (higher in premenopausal women as compared to post-menopausal women) is reflected in better disease management evidenced by the shorter recovery rate, restricted disease progression (lower, terminal and critical illness) and higher survival (lower death rate). Many studies have previously reported that the females display less severe symptoms for viral infections and therefore shorter recovery periods.[25] There is a powerful role of estrogen in immunomodulation against Covid-19 in females and modulation of cellular ACE2/TMPRSS2 axis expression, hence limiting the entry of the COVID-19 virus into the cells. The secondary infections being more pronounced in the females in our study is again

consistent with earlier reports,[15] which have highlighted worse long-term COVID-19 related after effects in females below 50 years of age.

In the context of current pandemic outbreak, several factors like the evolution of the virus leading to the generation of variant strains or the nuances of the contagion and its spread accompanied by the uncertainty of disease reinfections are at play.[30] Also, various other associated factors like age, gender, comorbidities, nutrition levels, socio economic status need to be taken into consideration in order to develop a fool-proof strategy to counter any new wave of mutant SARS-CoV2 infection. Analyzing the COVID-19 data through a gender lens can help reveal larger social dynamics that may be driving people's risk of infection and illness - and thus could be addressed to reduce the impact of COVID-19 for everyone.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

SUPPLEMENTARY INFORMATION

The supplementary data for Model 1 and Model 2 have been provided and can be downloaded from article page online.

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