Gender Disparity in Risk Factors of COVID-19 Mortality Rates

Abstract

Incidence and mortality rates due to COVID-19 have varied widely in different parts of the world and placed a huge strain on hospital resources. Understanding the underlying reasons behind such variation is crucial to developing population-specific or even individual-specific management strategies. This paper presents a comprehensive analysis of incidence and mortality rates from data collected over a cumulative period of approximately 6.5 months from February to August 2020 across 411 districts of India, totalling over 2 million individuals. We identify the health factors which have both positive as well as negative correlates with high mortality rates, using data obtained from district-wise aggregated COVID-19 incidence and mortality rates and health data obtained from National Family Health Survey (NFHS).

To obtain robust indicators, we apply both machine learning techniques as well as classical statistical methods and show that the same factors are identified by both methods. We also identify positive and negative correlates at multiple population scales by dividing the cohort into sub-cohorts formed from two Indian states which were further segregated by gender.

We show that there is a disparity of risk factors among males and females. While obesity is the highest risk factor for men, anaemia is the highest risk factor for women.

Hence, to better manage the health of a specific group of people, it is important to consider gender-wise heterogeneity in health risk factors which could contribute to differing vulnerabilities.

Keywords: COVID-19, Gender Disparity, Mortality Rates, Risk Factors.

1 Introduction

Coronavirus disease 2019 (COVID-19) has been a subject of intense study since its outbreak in December 2019. Incidence and mortality rates of the disease have varied widely, both across regions and time-periods. Understanding the underlying risks, especially of mortality due to the disease could help in developing better management strategies at population and individual levels. The rapid spread of the disease has put enormous stress on the healthcare system, including hospitals and health workers and has precluded the
gathering of detailed statistics of affected individuals. This is seen in the pattern of data collection in countries like India where details such as longitudinal follow-up of affected individuals and extensive contact tracing were carried out from March to May by most of the states [1]. However, as the number of cases began to spike, this was stopped. The advisory guidelines released by the Indian Council of Medical Research (ICMR) on 23rd of June, 2020 [2] touch on the need to increase the outreach of testing by deploying rapid antigen Point-of-Care (PoC) tests in all containment zones and hospitals while maintaining the previous methods of testing. This indicates a shift of focus from contact tracing towards mass testing coupled with follow-ups on high-risk contact cases.

Population risk factors for COVID-19 have so far been studied from small cohorts or case studies under hospitalization conditions or isolation centres where parameters can be collected and monitored in a controlled environment [3, 4, 5, 6].

Due to India’s large and diverse population, it has been the centre for several prediction and containment strategies related to COVID-19. As of October 1, India has a cumulative total of 6,388,010 positive cases and a death toll of 99,720. India has been one of the few countries which had enforced early lockdown and large scale restrictions. Given the geographic spread and the number of affected individuals, this is one of the largest exercises in the world, impacting the most number of people. Hence, it is important to understand the risk factors underlying mortality from COVID-19, especially in vulnerable populations, which can help plan effective distribution of healthcare resources.

Prior studies on risk factors associated with COVID-19 have considered the impact on mortality rates of a single risk factor such as obesity [7, 8, 9, 10] or nutrition [11, 12]. In a first gender-wise study, Nakeshbandi et al. [13] showed with data collected from hospitalized patients over a month, that obesity is associated with higher mortality in men but not in women.

In India, maternal and child health is an area of concern. The government has focused efforts on monitoring and providing interventions for women in the age group of 15-49 and children. Gender-wise data of both men and women in this age group has been collected periodically by the National Family Health Survey (NFHS) [14] on several health parameters. Health data aggregated over districts are published under the stewardship of the Ministry of Health and Family Welfare (MoHFW), coordinated by the International Institute for Population Sciences (IIPS), Mumbai, and implemented by a group of survey organizations and Population Research Centres, following a rigorous selection procedure.
In this observational study, the impact of the health parameters as obtained from the NFHS data on the
mortality rate of COVID-19 in the reproductive age group of 15-49 at different population levels is studied.
The analysis of positive and negative correlates is performed on data spanning 411 districts across 23 states
and 3 union territories. We also repeat the analysis on a sub-cohort of two Indian states to analyze possible
heterogeneity of risk factors in different states. We perform aggregated as well as gender-wise analysis
on these two states and show that there are disparities in the positive and negative correlates of COVID-19
among men and women. We also discuss how these compare with gender-related risk and protective factors
in other diseases.

To our knowledge, this is the first study that considers both positive and negative correlates of mortality
rates, which could correspond to the risk and protective factors. This is also the first study that considers a
population at multiple levels of aggregation. Moreover, this is also the first time such an analysis has been
carried out on a large aggregate, totalling about 2,350,000 individuals.

2 Methods

The data processing pipeline for this study consists of the collection, cleaning, and analysis. Data extraction
from multiple sources constituted a significant portion of the effort. The Scikit-learn [15] and SciPy[16]
module in Python was used for the analysis.

2.1 Data Sources

Data related to incidence and mortality of COVID-19 was collected from multiple sources since no single
published source of such data is available. The data collected from the period of January 30 to August 18
include those put out by the government agencies, crowd-sourced data and daily media bulletins. Gender-
wise data related to COVID-19 incidence and mortality is not published by the Ministry of Health and Family
Welfare, Government of India. However, some state governments issue official daily bulletins through formal
releases to the media. Data from these media bulletins were extracted for the period of April 15 to August
18, 2020 for the state of Karnataka and for the period of May 1 to August 18, 2020 for the state of Tamil
Nadu. A sample data of such a bulletin can be found in [17, 18]. The sources from which data for this study
was sourced include:
• The Open Government Data Platform India website [19] contains data officially published by the Government of India. Serial follow up of people who tested positive for COVID-19 was done and details of age, sex and status (hospitalized, discharged, tested negative) was captured for a few selected cities[20, 21, 22, 23, 24, 25]. This site was last updated on July 30, 2020 and contains details of a total of 16,981 cases and 683 deaths.

• COVID-19 India [26] is a crowd-sourced initiative to extract and update data related to COVID-19 cases and deaths across India. The data collected here contains district-wise numbers of confirmed cases, active cases, recovered cases and deceased cases for 800 districts across India starting from 30th of January, 2020. We have used the data available until the 18th of August, 2020.

• Media bulletins issued by the states of Karnataka and Tamil Nadu : Details of incidence in the state of Karnataka were curated by Siva Athreya et al. [27]. This data contains details of 71,068 positive cases extracted from the Karnataka government media bulletins. Additionally, district-wise numbers for 3763 deaths in Karnataka were collected by manually going through the official media bulletins. Similarly, the details of 20,731 positive cases and 5161 deaths were extracted for the state of Tamil Nadu. Of these, the data related to the age group 15-49 was extracted and resulted in 47,213 cases, 756 deaths from Karnataka and 14,174 cases, 677 deaths from Tamil Nadu. Gender information for positive cases was available until 31st of May, 2020 for Tamil Nadu media bulletins and 20th of July, 2020 for Karnataka media bulletins. Thereafter, only total infected cases related to COVID-19 cases were published, and gender-wise segregation was not available.

• National Family Health Survey Data : The National Family Health Survey (NFHS) is a large-scale, multi-round survey conducted in a representative sample of households throughout India. In 2014-2015, India implemented the fourth National Family Health Survey (NFHS-4). NFHS-4 had a sample size of approximately 568,200 households and a total sample of 625,014 women and 93,065 men eligible for the interview. The NFHS [14, 28] data provides updates and evidence of trends in key population, health and nutrition indicators. The data spans across 29 states and 6 union territories, a total of 640 districts across India. For each of these districts, 93 key indicators are recorded ranging from various issues during pregnancy, nutrition, population, literacy and more.
2.2 Data Curation

Details of total confirmed cases (which included the number of active, recovered, and deceased cases) and the number of deaths were available for 800 districts. Of these, 535 districts overlapped with the 640 districts for which NFHS data was available. We considered the subset of these districts which had at least 5 deaths, resulting in a total of 411 districts, spanning across 23 states and 3 union territories of India on which final analysis was done. These 411 districts represent a geographical extent of more than 3 million square kilometres and a cumulative total of 2,331,363 cases and 46,239 deaths.

In the sub-cohort of the states of Karnataka and Tamil Nadu, gender-wise numbers of COVID-19 positive cases was available only until 20th of July and 31st of May, 2020 respectively. Thereafter, only total positive cases related to COVID-19 cases were published, and gender-wise segregation was not available. We compute the gender-wise fraction in the age group 15-49 from this initial data, estimate the gender-wise numbers for each district for later periods using this fraction and the total number of positive cases published in the bulletins as of August 18, 2020.

Among the 93 key indicators included in the NFHS data, we selected the ones corresponding to adult health indicators and further limited it to factors discussed in case reports and medical opinions in literature. We also took into account chronic conditions that are unlikely to have changed in the period between the collection of the health data and the COVID-19 pandemic. The broad categories of factors considered were those related to low BMI, obesity, anaemia, blood pressure and diabetes. The set of health factors chosen for analysis are enumerated in Table 1.

The health factors extracted from the NFHS data are published gender-wise. To obtain the gender-desegregated population value, the weighted average of each factor was computed according to the sex ratio of each district. Through this process, aggregated health factors corresponding to the gender-desegregated population of each district was obtained.

2.3 Analysis

A Lasso regression[29] of the health factors on mortality rates calculated from the COVID-19 India data was conducted on districts that reported at least 5 deaths. The health data was standardized before the regression. For each Lasso test, the $\lambda$ (regularisation parameter) with the best $R^2$ value was taken through
a search of the results from the Lasso_path function. Residual plots corresponding to this value of $\lambda$ were inspected visually to ensure there was no bias.

Independently, factors which differed significantly between the districts with high mortality rates and those with low mortality rates were identified via the Mann-Whitney U test with a significance level of 0.05 corrected by the Bonferroni criterion for each health factor. The districts were classified into two categories of low and high mortality, depending on whether they fell below or above the second quartile in mortality rates. The effect size was also calculated for all the factors between the two sub-groups using Cohen’s d effect size and interpreted according to the thresholds defined in [30] i.e. $|d|\leq 0.2$ is ‘negligible’ effect size, $0.2<|d|\leq 0.5$ is ‘small’, $0.5<|d|\leq 0.8$ is ‘medium’ and otherwise ‘large’.

The factors obtained from the Mann-Whitney U test and the Lasso test were compared and common factors identified as the risk and protective factors of the population. The same procedure was also followed in the sub-cohort of the two states of Karnataka and Tamil Nadu.

Further, each state was analyzed independently and positive and negative correlative factors were identified. For the gender-wise correlates using the Mann-Whitney U test, the data of each gender across the two states were combined to yield significant numbers.

3 Results

A preliminary two-tailed test performed on the Open Government Data, results of which presented in Table 2, shows that there is a significant difference between male and female mortality rates in some regions while other regions do not show a significant difference. Further, though female mortality rates are higher than male mortality rates in many regions, it is not possible to infer that this is uniformly true for all regions.

3.1 Aggregated population across the country

The distribution of the aggregated health factors in the 411 districts is presented in Figure 1. District-wise counts of 2,331,363 COVID-19 cases and 46,239 deaths are used to draw correlations between the health factors and mortality from these districts.

The Lasso plot on this data (Figure 2) indicates that the most positive correlates are overweight or obesity and BMI below normal. Anaemia, high blood sugar level and very high blood pressure show a negative
correlation with mortality, with anaemia having the highest negative correlation at higher values of $\lambda$.

The results of the Mann-Whitney U test on the same data between the two categories of districts of high and low values of mortality rates are shown in Table 3. Anaemia and obesity emerged as statistically significant with small effect sizes.

By considering the factors that were identified by both the tests, we conclude that obesity (DM=-3.2, 95%CI (-4.8,-1.7), $P<0.0001$, ES=0.2026) is positively correlated and anaemia (DM=4.00, 95%CI (2.3,5.6), $P<0.0001$, ES=0.2306) is negatively correlated with high mortality on the cohort of nation-wide population.

3.2 Sub-cohort of two Indian states

A sub-cohort of 29 districts, consisting of 16 districts from the state of Karnataka and 13 districts from the state of Tamil Nadu was analysed. Using available case data from the bulletins for the age group of 15-49, we estimated the number of cases for 240,912 cases from Karnataka and 298,046 cases from Tamil Nadu. Only those districts that had reported at least 5 deaths for each gender in the age group 15-49 from the death data was considered for this analysis. This resulted in a total of 667 deaths from Karnataka and 556 deaths from Tamil Nadu. The distribution for the aggregated health factors in these districts can be seen in Figure 3.

From the Lasso plot in Figure 4, BMI below normal, high blood sugar level, very high blood pressure are the positive correlates while obesity and anaemia are the negative correlates.

The results of the Mann-Whitney U test on the same data between the two categories of districts of high and low values of mortality rates are shown in Table 4. Obesity, BMI below normal and anaemia were found to be statistically significant with medium effect sizes.

By considering the factors that were identified by both the tests, it is seen that BMI below normal (DM=-6.4, 95%CI (-9.9,-2.4), $P=0.013$, ES=0.5836) is positively correlated while Obesity (DM=7.4, 95%CI (2.7,11.6), $P=0.013$, ES=0.5836) and Anaemia (DM=5.4, 95%CI (1.8,8.8), $P=0.02$, ES=0.5570) are negatively correlated with high mortality in the sub-cohort.

3.3 Gender-wise analysis of the sub-cohort

A gender-segregated analysis was performed on the districts of Karnataka and Tamil Nadu to determine the association between gender-wise mortality and health factors from these two states. The gender-wise
distribution of each district was estimated for 240,912 cases from Karnataka and 298,046 cases from Tamil Nadu using the initial case data. From the data on deaths in Karnataka and Tamil Nadu, we considered only districts with at least 5 deaths separately for each gender. Karnataka had 224 female deaths across 16 districts and 496 male deaths across 23 districts. Tamil Nadu data had 186 female deaths across 13 districts and 434 male deaths across 21 districts.

The distribution of the gender-wise health factors across districts of Karnataka and Tamil Nadu is presented in Figure 5. The results of the gender-segregated Lasso tests on Karnataka and Tamil Nadu can be seen in Figure 6 and Figure 7 respectively. In the case of males, overweight or obesity is positively correlated and anaemia is negatively correlated with the high mortality rate in both the states. In the case of females, anaemia and high blood sugar level show a positive correlation while obesity shows a strong negative correlation, and very high blood pressure a weak negative correlation. In order to ascertain that the correlations were not due to multi-collinearity effects, the slope from the linear fit of scatter plots was examined for each factor separately.

The Mann-Whitney U test was performed by combining the data of both the states to improve the sample size. 44 districts for male and 29 districts for female were considered for analysis based on the condition that the number of deaths for the gender under consideration was at least 5. From the results presented in Table 5 for females and Table 6 for males, none of the factors showed statistical significance. However, the factors of BMI below normal, obesity and anaemia for women and anaemia for men had non-negligible effect sizes.

By considering the factors that were identified by both the tests, it is seen that Anaemia (DM=4.3, 95%CI (0.3,8.5), P=0.2275, ES=0.3891) is positively correlated and Obesity (DM=6.05, 95%CI (0.2,11.5), P=0.163, ES=0.4156) is negatively correlated with high mortality in females. Conversely, Anaemia (DM=2.4, 95%CI (-1.0,5.6), P=0.6495, ES=0.2327) is negatively correlated with high mortality in males.

3.4 Summary of Results

The factors identified by each test and the common factors at each level of population aggregation is shown in Figure 8.
4 Conclusion

In this paper, we have reported the first large scale analysis of health factors correlated positively as well as negatively with mortality rates of COVID-19 in India. The factors affecting mortality rates show a distinct difference among males and females in the age group of 15-49. Among males, obesity has been shown to be a risk factor in both regression as well as statistical analysis. Other studies investigating obesity have also concluded that there is difference in the impact of obesity in males and females on COVID-19 mortality [13]. Pre-menopausal obesity has been shown to be associated with a lower risk of breast cancer [31, 32], thus suggesting that fat distribution could play a significant role in health conditions [33] and pre-menopausal obesity could serve as a protective factor.

We conclude through this study that anaemia is positively correlated with COVID-19-related mortality in women, but negatively correlated with mortality in men. The difference in the role played by anaemia in women vs. men can be explained by the fact that anaemia, when present in men, is mild or moderate, whereas the prevalence of severe anaemia is higher in women [34]. It is also evident from the gender-wise distribution in Figure 5 that anaemia is twice as prevalent in females as in males. Recent estimates of iron-deficiency anaemia (IDA) show that 52% of women aged 15-49 are anaemic [35]. This difference in prevalence could be significantly higher during menstruation and pregnancies. Severe anaemia has been associated with higher maternal mortality [36]. Severe anaemia has also been associated with higher rates of ICU admission in COVID-19 [37, 38, 39]. This first study of the effect of anaemia in COVID-19 suggests that haemodilution could play a role in COVID-19 mortality.

The findings indicate that risk factors for COVID-19 mortality are by themselves heterogeneous, and their effects need to be investigated in conjunction with gender, menopausal status, and severity of the condition to understand them better.
Competing Interests Statement

The authors declare no competing interests.

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Table 1. Selected health factors from NFHS data.

| Factor (%)                                      | Characteristic                                      |
|------------------------------------------------|-----------------------------------------------------|
| Men whose Body Mass Index (BMI) is below normal | BMI < 18.5 kg/m²                                     |
| Women whose Body Mass Index (BMI) is below normal| BMI < 18.5 kg/m²                                     |
| Men who are overweight or obese                 | BMI ≥ 25.0 kg/m²                                     |
| Women who are overweight or obese                | BMI ≥ 25.0 kg/m²                                     |
| Men who are anaemic                              | <13.0 g/dl                                          |
| Women who are anaemic                            | <12.0 g/dl (Non-pregnant) and <11.0 g/dl (Pregnant) |
| Men who have a high blood sugar level            | >140 mg/dl                                          |
| Women who have a high blood sugar level          | >140 mg/dl                                          |
| Men who have very high blood pressure            | Systolic ≥ 180 mm of Hg and/or Diastolic ≥ 110 mm of Hg |
| Women who have very high blood pressure          | Systolic ≥ 180 mm of Hg and/or Diastolic ≥ 110 mm of Hg |
Table 2. Results of the hypothesis tests on gender-wise mortality rates across different regions in India.

| Region    | Difference in mortality rates (%) | 95 % CI                  | P Value |
|-----------|-----------------------------------|--------------------------|---------|
| Surat     | 0.8613                            | (-0.0837, 1.8063)        | 0.362   |
| Thane     | -0.8337                           | (-1.2795, -0.3880)       | 0.0614  |
| Jabalpur  | 3.6054                            | (1.5874, 5.6234)         | 0.074   |
| Rajkot    | 2.5332                            | (0.6437, 4.4227)         | 0.18    |
| **Indore**| -1.6341                           | (-2.1142, -1.1540)       | < 0.001 |
| Varanasi  | 1.0449                            | (-0.2144, 2.3041)        | 0.4067  |
| **Karnataka** | -0.3217                        | (-0.3737, -0.2698)       | < 0.001 |
| **Tamil Nadu** | -0.5387                      | (-0.5849, -0.4924)       | < 0.001 |

Significant regions are marked in bold.
Table 3. Results of Mann-Whitney U test on aggregated health parameters across India.

| Aggregated Factor (%)                | Difference in Median | 95% CI          | P Value  | Effect size |
|--------------------------------------|----------------------|-----------------|----------|-------------|
| Body Mass Index (BMI) below normal   | 1.9                  | (0.4, 3.4)      | 0.0675   | 0.1221      |
| **Overweight or obese**             | -3.2                 | (-4.8, -1.7)    | <0.0001  | 0.2026      |
| Anaemia                              | 4.0                  | (2.3, 5.6)      | <0.0001  | 0.2306      |
| High blood sugar level               | 0.2                  | (-0.2, 0.7)     | 1.0      | 0.0472      |
| Very high blood pressure             | -0.03                | (-0.1, 0.05)    | 1.0      | 0.0299      |

Significant regions are marked in bold.
Table 4. Results of Mann-Whitney U test on aggregated health parameters across Karnataka and Tamil Nadu.

| Aggregated health Factor (%)          | Difference in median | 95% CI     | P Value | Effect size |
|---------------------------------------|----------------------|------------|---------|-------------|
| Body Mass Index (BMI) below normal    | -6.4                 | (-9.9, -2.4) | 0.013   | 0.5836      |
| Overweight or obese                   | 7.4                  | (2.7, 11.6)  | 0.013   | 0.5836      |
| Anaemia                               | 5.4                  | (1.8, 8.8)   | 0.02    | 0.5570      |
| High blood sugar level                | 0.6                  | (-0.6, 1.8)  | 1.0     | 0.1415      |
| Very high blood pressure              | 0.08                 | (-0.4, 0.5)  | 1.0     | 0.0530      |

Significant regions are marked in bold.
Table 5. Results of Mann-Whitney U test on female health parameters across Karnataka and Tamil Nadu.

| Female health Factor (%)                  | Difference in median | 95% CI        | P Value | Effect size |
|------------------------------------------|----------------------|---------------|---------|-------------|
| Body Mass Index (BMI) below normal        | -4.1                 | (-8.1, 0.2)   | 0.2975  | 0.3670      |
| Overweight or obese                       | 6.05                 | (0.2, 11.5)   | 0.163   | 0.4156      |
| Anaemia                                   | 4.3                  | (0.3, 8.5)    | 0.2275  | 0.3891      |
| High blood sugar level                    | 0.45                 | (-0.8, 2.0)   | 1.0     | 0.1503      |
| Very high blood pressure                  | 0.0                  | (-0.4, 0.3)   | 1.0     | 0.0354      |
Table 6. Results of Mann-Whitney U test on male health parameters across Karnataka and Tamil Nadu.

| Male health Factor (%)          | Difference in median | 95% CI      | P Value | Effect size |
|---------------------------------|----------------------|-------------|---------|-------------|
| Body Mass Index (BMI) below normal | -1.45                | (-5.5, 2.7) | 1.0     | 0.1271      |
| Overweight or obese            | 1.0                  | (-3.4, 4.3) | 1.0     | 0.0913      |
| Anaemia                         | 2.4                  | (-1.0, 5.6) | 0.6495  | 0.2327      |
| High blood sugar level          | -0.35                | (-1.9, 1.4) | 1.0     | 0.0501      |
| Very high blood pressure        | 0.2                  | (-0.4, 0.8) | 1.0     | 0.1020      |
Figure 1. Distribution of aggregated health factors on pan India data.
Figure 2. Lasso regression on pan India data. $R^2 = 0.1035$; Teal - BMI below normal, Orange - Overweight or obese, Green - Anaemia, Blue - High blood sugar level, Pink - Very high blood pressure.
Figure 3. Distribution of aggregated health factors on sub-cohorts of Karnataka and Tamil Nadu.
Figure 4. Lasso regression on aggregated sub-cohorts of Karnataka and Tamil Nadu. $R^2 = 0.3509$; Teal - BMI below normal, Orange - Overweight or obese, Green - Anaemia, Blue - High blood sugar level, Pink - Very high blood pressure.
Figure 5. Distribution of gender-wise health factors on sub-cohorts of Karnataka and Tamil Nadu. Red - Female; Blue - Male;
Figure 6. Lasso regression on gender-wise sub-cohorts of Karnataka. (a) $R^2 = 0.1917$ (b) $R^2 = 0.1529$; Teal - BMI below normal, Orange - Overweight or obese, Green - Anaemia, Blue - High blood sugar level, Pink - Very high blood pressure.
Figure 7. Lasso regression on gender-wise sub-cohorts of Tamil Nadu. (a) $R^2 = 0.1567$ (b) $R^2 = 0.2270$; Teal - BMI below normal, Orange - Overweight or obese, Green - Anaemia, Blue - High blood sugar level, Pink - Very high blood pressure.
Figure 8. Summary of influencing factors across regions and gender.