Title: Comparison of risk factors of mortality during the two COVID-19 waves in Delhi, India.

ABSTRACT

Objective: To determine the risk factors of mortality (in terms of age, gender and comorbidities) among hospitalized patients in an Indian tertiary care hospital during the first and second waves.

Methods: A retrospective observational study where the patients' mortality data was collected over two COVID-19 periods, and their characteristics were compared. The first phase was from May 2020 to January 2021 and the second wave was from March 2021 to August 2021.

Results: A mortality rate of 23.84% (874 deaths among 3666 patients) and 1.36% (232 deaths among 17000 patients) was noted in the second and first wave of COVID-19 respectively. Compared to the first wave, second wave deaths had comparable age (65.82 ± 14.82 vs. 67.63±13.78, P=0.094); comparable gender (P=0.094); and significantly lower comorbidities like hypertension (10.18% vs. 27.59%, P<0.0001), diabetes (10.41% vs. 31.47%, P<0.0001) and chronic kidney disease (5.38% vs. 17.67%, P<0.0001). Multivariate regression showed that age, male gender, hypertension, diabetes, chronic kidney disease were independent significant risk factors of mortality with adjusted odds ratio (aOR) of 1.050, 2.754, 2.389, 3.891, 6.358, in the first wave; while age, male gender, hypertension, and diabetes were independent significant risk factors of mortality (aOR 3.124, 3.412, 5.428, and 6.731) in the second wave.

Conclusion: In comparison to the first wave, the second wave had a higher overall mortality rate and more severe disease even among the patients without significant comorbidities. Higher age
and male gender were unanimous significant risk factors of mortality in both the COVID-19 waves.

**Key words:** COVID-19, first wave, pandemic, SARS-COV-2, second wave
Introduction:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused Coronavirus Disease-19 (COVID-19), which evolved as pandemic, presenting a significant health risk globally. Many nations have seen a two-wave pattern of COVID-19 affected patients, with the first wave occurring in the spring and the second wave occurring in the late summer and autumn.\textsuperscript{1,2,3,4}

In spite of isolated cases being reported in February, the first outbreak of COVID-19 cases in India began in early March 2020.\textsuperscript{5} During the outbreak of first wave, strong prophylactic measures were taken by the Indian government, which included lockdown from March 13th to May 4th and thereafter 3-month duration of progressively increasing social interaction, work, and commercial activities. These measures prevented the early occurrence of first wave.\textsuperscript{5}

As of July 2020, life in the country was almost normal, with the requirement of wearing a face mask and maintaining safe social distance. The first wave peaked in September 2020. The world’s largest vaccination drive for eligible beneficiaries was initiated on 16th January 2021.\textsuperscript{6} However, an increase in the patients was seen by the end of March, 2021 initiating the second wave, which peaked in March 2021. Different parts of the country experienced different stages of the outbreak.

This forced the government to reintroduce strong restrictions, including local and regional lockdowns, shutdown of hotels, restaurants, cultural and sports events, and a nighttime curfew in containment zones.

Till date of writing the article, i.e. 23rd February 2022, total 42732820 patients affected by COVID-19, with the rate of mortality being 1.2\% (n = 512924). The empirical evidence reveals
that in terms of age range and disease severity, this second wave differs from the first. As Delhi, India, has system for reporting death statistics, this study aimed to compare COVID-19 mortality data from the first and second waves in the city, which is one of India's COVID-19 epicentres.

**Methods:**

This retrospective observational study was conducted at tertiary care hospital in Delhi, India. The first phase was from May 2020 to January 2021 and the second wave was from March 2021 to August 2021, during which the data was recorded.

The consent from patients was not required as it was a retrospective observational study. The study did not require ethical approval because there was no intervention.

**Sample size:** The study of Iftimie S et al\(^2\) observed that mortality rate in first wave was 24\% and second wave was 13.2\%. Taking these values as reference, the minimum required sample size with 80\% power of study and 5\% level of significance is 200 patients in each study group. Total sample size taken is 1106 (232 in first wave and 874 in second wave).

Formula used is:

\[
n > \frac{(pc*(1-pc)+pe*(1-pe))*(Z_\alpha + Z_\beta)^2}{(pc-pe)^2}
\]

with

- pc = mortality in first wave
- pe = mortality in second wave

Where \(Z_\alpha\) is value of Z at two sided alpha error of 5\% and \(Z_\beta\) is value of Z at power of 80\%.
The patients' demographic information was acquired. A detailed clinical history of respiratory, cardiovascular, renal, and/or multiorgan dysfunction was recorded. Although the absence of pinpointer history was considered to be non-specific, only minor symptoms were reported. The gold standard considered for labeling patients as COVID-19 positive was the RT-PCR test. The government's healthcare system of India plays an important role in offering free RT-PCR testing. In addition, routine lab tests performed in all patients were complete hemogram, prothrombin time/international normalized ratio, renal function test, IL6 determination, serum ferritin, and lactate dehydrogenase. Other tests were performed depending on the disease profile of the patients.

The primary outcomes were to find out in-hospital mortality in first and second waves. The secondary outcomes were to compare the association of age, gender and co-morbidities like hypertension (HTN), diabetes mellitus (DM) and chronic kidney disease (CKD) with mortality in first and second waves. The study flow in shown in Figure 1.

Statistical analysis: The data was entered in Microsoft EXCEL and analyzed using SPSS version 21.0. The data presentation was done as number (%). All qualitative variables i.e. gender, co-morbidities were associated using Chi-Square test. Independent t test was used to associate age. Univariate and multivariate logistic regression was used to find out significant risk factors of COVID-19 mortality in 2020 and 2021. P value<.05 was considered as statistically significant.

Results
A total of 17,000 COVID-19 positive patients were admitted during the first wave during which 232 patients died (1.36%). A total of 3,666 COVID-19 positive patients were admitted during the second wave during which 874 patients died (23.84%). (Figure 2).

Compared to the first wave, second wave deaths had comparable age (65.82 ± 14.82 vs. 67.63±13.78, P=0.094); comparable gender (P=0.094); and significantly lower HTN (10.18% vs. 27.59%, P<0.0001), DM (10.41% vs. 31.47%, P<0.0001) and CKD (5.38% vs. 17.67%, P<0.0001) (Table 1).

During the first wave of COVID-19 pandemic, on performing univariate logistic regression, age, gender, hypertension, DM, CKD were significant risk factors of mortality. With the increase in age, risk of mortality significantly increases with odds ratio of 1.042(1.026 to 1.059). Males and patients with hypertension, DM, CKD had significantly higher risk of mortality with odds ratio of 1.585(1.185 to 2.120), 2.214(1.655 to 2.961), 2.928(2.211 to 3.876), 6.133(4.333 to 8.683) respectively. On performing multivariate logistic regression, age, gender, hypertension, DM, CKD were independent significant risk factors of mortality. With the increase in age, risk of mortality significantly increases with adjusted odds ratio of 1.050(1.033 to 1.068). Males and patients with hypertension, DM, CKD had significantly higher risk of mortality with adjusted odds ratio of 2.754(1.579 to 4.802), 2.389(1.465 to 2.982), 3.891(2.059 to 5.392), 6.358(5.675 to 10.564) respectively (Table 2).

During the second wave of COVID-19 pandemic, on performing univariate logistic regression, age, gender, hypertension, DM were significant risk factors of mortality. With the increase in age, risk of mortality significantly increases with odds ratio of 3.217(1.098 to 4.235). Males and
patients with hypertension, DM had significantly higher risk of mortality with odds ratio of 2.653(2.013 to 4.531), 4.576(2.341 to 5.638), 5.672(3.761 to 8.913) respectively. On performing multivariate logistic regression, age, gender, hypertension, and DM were independent significant risk factors of mortality. With the increase in age, risk of mortality significantly increases with adjusted odds ratio of 3.124(2.314 to 3.998). Males and patients with hypertension, DM had significantly higher risk of mortality with adjusted odds ratio of 3.412(2.317 to 5.615), 5.428(4.761 to 9.361), 6.731(4.516 to 10.871) respectively (Table 3).

Discussion

The COVID-19 pandemic led to a high rate of mortality in the world, demonstrating the severity of the problem. We observed that the mortality rate was higher in the second wave (23.84%) than the first wave (1.36%). The primary causes of death in COVID-19 were acute failure, which included respiratory, renal, cardiovascular, and/or multiorgan involvement. Similar findings were reported in North Indian study by Budhiraja et al, who observed 40% higher mortality rate in second wave than first wave. Consistently, Kumar et al evaluated data of patients enrolled in National Clinical Registry for COVID-19 and reported that in second wave, mortality increased by 3.1%.

In another Indian study, Nath et al reported that the number of deaths in the first wave and second wave were 35% and 65%, respectively, with case fatality rate (CFR) in first wave and second wave being 19.2% and 24.18%, respectively.

Jain et al found that death rate was not significantly different in first and second waves; however because of higher number of infections, mortality rate was high. The reason for the non-significance can be the fact that study was conducted in April when COVID-19 was at peak.
In a South African study, Jassat W et al.\textsuperscript{13} also found that in-hospital mortality was higher in the second wave than the first wave.

On the contrary, Iftimie et al\textsuperscript{2} reported that there were few deaths the second wave at Spain, although hospital admission rates were higher. The lesser death rates in developed countries could be due to advanced healthcare system. Developed countries were more prepared and experienced when it came to patient treatment. Furthermore, more diagnostic tests were performed, allowing for early identification and successful treatment of serious cases.

The higher number of cases in India's second wave could be due to many factors. The mutant virus was discovered to have a higher transmission potential and a shorter incubation period. The public demonstrated reluctance for "Covid Appropriate Behaviors," or CAB, and the masks utilized vary greatly in quality. N-95 masks are not frequently utilized in India due to their greater costs, and the majority of the patients preferred to use either local cotton masks or the same old worn-out masks.\textsuperscript{14}

The high increase in number of affected cases could be attributed to increased testing. But, there are concerns about the quality of testing, because several patients with symptoms of COVID-19 were found to have negative RT-PCR test.\textsuperscript{11-14}

We observed that age and gender of patients who died in second wave were similar as that of first wave deaths. Overall, elderly individuals were affected more by COVID-19. Also, there were more male patients in both the waves. The age, gender, hypertension, DM, and CKD were independent significant risk factors of mortality in both waves, while CKD was only an additional risk factor of mortality in first wave.
The presence of comorbid metabolic conditions such as diabetes mellitus, hypertension, and chronic kidney disease weakens immunity resulting in greater susceptibility and disease severity; reduced clearance of airway and mucus; restrictions of medicine treatment and cross drug interactions are linked to an increased risk of infection and death in the elderly.\textsuperscript{10}

Treatment preference is not given at the onset of disease symptoms to non-earning, dependent elderly in developing countries, usually because of family financial constraints. This causes symptoms to worsen, and the disease may progress to systemic, irreversible complications before people seeking medical treatment.\textsuperscript{8}

Males have a higher risk of infection and death because of more outside exposure because they are still the family's primary earner, implying more exposure of social gathering, longer travel stretches, and weakened immunity related to smoking and alcohol consumption.\textsuperscript{8}

This is accordance with the findings by Nath et al,\textsuperscript{11} as age and gender were similar in both groups. Similarly, Budhiraja S et al\textsuperscript{9} found that age was comparable in both waves; however, females were admitted slightly more in second wave.

However, Kumar et al\textsuperscript{10} found that among the deceased patients in second wave, there was an increased mortality among all age groups with the exception of those under the age of 20, where mortality declined. There were lesser number of males in second wave (63.7% vs. 65.4%, \textit{P}=0.02).

Iftimie et al,\textsuperscript{2} reported that patients of the second wave were younger than those of first wave. Other previous studies from different countries found similar findings reported.\textsuperscript{3,4,15} The reason for the difference in the two waves is still not known.
Aleta et al\textsuperscript{16} and Fan G et al\textsuperscript{3} reported that there was more infection in young, healthy adults, and children, which could be due to reluctance of young age individuals to follow norms of social distancing.

We found that nonsurvivors in second wave deaths had significantly lesser cases of hypertension, DM and CKD.

Similarly, Kumar et al\textsuperscript{10} reported that the second wave non-survivors had significantly less number of comorbidities. However, in another Indian study,\textsuperscript{9} second wave cases were found to have significantly more comorbidities such as diabetes or HTN (59.7\% vs. 54.8\%, P<0.001).

However, concomitant diseases were comparable in both waves in the study by Iftimie et al,\textsuperscript{2} which was similar in another study by Iftimie S et al.\textsuperscript{17} In contrast, Saito S et al\textsuperscript{4} reported cerebrovascular and cardiovascular diseases to be present in lesser number of COVID-19 patients in Japan. Di Castelnuovo A et al\textsuperscript{18} reported that impaired renal function, but not obesity, CVD or cancer were the main predictors of in-hospital mortality.

These chronic illnesses have also been identified by the World Health Organization as the greatest cause of death.\textsuperscript{19} In the case of diabetes mellitus, persistently high blood sugar levels weaken the immune system, making it more susceptible to infection. Although there is no established mechanism for diabetes related to COVID-19 severity, the possibility of angiotensin-converting enzyme 2 (ACE2) overexpression in diabetes mellitus has been suggested.

COVID-19 patients are reported to have the highest rate of hypertension of any cardiovascular disorders. The exact mechanism of myocardial damage in COVID-19 patients is unknown, however it is possible that the virus causes myocarditis and pericarditis, which leads to
arrhythmias as well as heart failure; damage caused by ACE2 expression in cardiac tissue; and acute cardiac injury leading to cardiac failure. In the presence of hypertension, additional pressure is placed on cardiac muscle pumps, resulting in cardiac collapse. Though the specific mechanism by which the COVID-19 virus affects renal tissue is unknown, the kidney's expression of ACE2 may play a major role.8 COVID-19-related mortality was more common in elderly males with comorbidities. Thus the immunization campaign was being prioritized to reach the high-risk population first. To combat the pandemic in the future, this vulnerable group should exercise extreme vigilance, and vaccination programs should be accelerated to reach nearly 70% of the population. Future research is needed to improve diabetes treatment and find new approaches to manage patients through technological advancements like telecare.8

Limitations: One of the limitations was that research was limited to a single center and particular geographic area, thus its findings cannot be generalized. However, the study's findings are important because they could represent patients in India and other developing nations, about which there is currently little information.

Conclusion: To sum up, the second wave had higher overall mortality and severe disease than the first wave; however, it afflicted a demographic population that was similar in age and gender in comparison to the first wave. Higher age, male gender and presence of comorbidities like hypertension and diabetes holds a significantly higher risk in COVID-19 mortality and thus demands a watchful monitoring of such patients.
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REFERENCES


