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COVID−19 mortality and its risk factors: A single−center observational study

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ABSTRACT

Objectives: To determine COVID-19 mortality and its risk factors in hospitalized patients at of a tertiary care center in north India.

Methods: A retrospective observational study was conducted of patients who were hospitalized from May 2020 to January 2021. The in-hospital mortality was assessed, and demographic variables and comorbidities between COVID-19 deaths and survivors were compared.

Results: A total of 24 000 patients were admitted during the study period, among which 17 000 had shown positive results of the RT-PCR test for COVID-19. The total mortality was 329 patients (1.37%), among which 232 (70.52%) succumbed due to COVID-19, and 97 (29.48%) died due to other illnesses. The mean age of the patients was (64.09±16.99) years. The mean age was significantly higher in COVID-19 related deaths [(67.63±13.78) years] as compared to that of the survivors [(60.52±19.5) years] (P<0.001). Compared to COVID-19 survivors, there were more males (72.41% *v.s.* 61.5%) and less females (27.59% *v.s.* 38.5%) in COVID-19 related deaths (P=0.001). Comorbidities such as hypertension, diabetes mellitus, and chronic kidney disease showed a significant correlation with COVID-19 mortality with an adjusted odds ratio of 2.389 (95% *CI*: 1.465-2.982), 3.891 (95% *CI*: 2.059-5.392), and 6.358 (95% *CI*: 5.675-10.564), respectively.

Conclusions: Elderly males with comorbidities have higher risk for mortality related to COVID-19. Ongoing vaccination drive is rightfully prioritised to serve the high-risk category first.

KEYWORDS: COVID-19; Mortality; Comorbidities; Elderly

1. Introduction

Coronavirus disease 2019 (COVID-19), an infectious disease caused by the SARS-CoV-2 virus, swept over the whole world rapidly and is making a recurrence. To date, cases and mortality

Significance

This study was conducted of 17 000 COVID-19 hospitalized patients to determine the mortality rate and its risk factors. The results show that advanced ages, male gender and comorbidity are risk factors of COVID-19 mortality. Therefore, preventative measures should give priority to the at-risk population.

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due to COVID-19 are on the rise, even though the vaccine has been developed for quite a long time. Statistics released by the World Health Organization show that globally, as of October 2021, there have been over 246 million confirmed cases with around 4.9 million deaths. In India, there have been 34.2 million confirmed cases with over 457 thousand deaths[1].

The association of demographic characteristics such as age, gender, and comorbidities with mortality of COVID-19 has been much explored[2-4]. Qiu *et al.*[5] found highest mortality rates in COVID-19 patients among elderly males with comorbidities like hypertension, diabetes[6], cardiovascular and neurovascular disease.

Because of the pertinent association of comorbidities with COVID-19 morbidity and mortality, the vaccine drive has focused on this subset of the population, that is, senior citizens>60 years or individuals>45 years with long-standing (>10 years) comorbidities such as hypertension and diabetes[7].

As the pandemic is ongoing, the research on the risk factors of mortality continues. As we are aware of the fact that there is a huge difference across the globe in COVID-19 infection rate, clinical presentation, recovery rate, and complications; so we did this study to report COVID-19 related mortality rate and the factors (age, gender, comorbidities) affecting the mortality from tertiary care center in north India. Worldwide, there is an urgent need to identify risk factors relevant in a specific geographical location so that the local population falling in the high-risk category should exercise extra caution.

2. Patients and methods

2.1. Study design

We conducted a retrospective observational study for 9 months (May 2020 to January 2021), where we retrieved the data of all patients who were admitted to the tertiary care hospital in North India.

2.2. Ethical consideration

Considering the retrospective observational nature of the study, consent was waived off. Ethical clearance was also not required for the study as there was no intervention.

2.3. Sample size

The sample size calculation of the study was done based on the survey by Qiu *et al.*[5] who observed that the prevalence rate of underlying diseases among COVID-19 dead patients was 72.21%. Taking this value as reference, the minimum required sample size with a 5% margin of error and 5% level of significance is 309 patients. To reduce the margin of error, the total sample size taken is 329.

2.4. Data collection

We obtained the demographic details of the patients. Detailed clinical history related to dysfunction of respiratory, cardiovascular, renal, and or multiorgan involvement was noted. Though we kept in mind the possibility of absence of pinpointer history as non-specific, minimal symptoms were reported[8]. RT-PCR test was taken as the gold standard to label cases as COVID-19 positive. In India, government healthcare service has a significant role in providing free access to reliable RT-PCR testing. Besides, routine lab investigations included complete hemogram, prothrombin time/international normalized ratio, kidney function tests, determination of IL6, serum ferritin, lactate dehydrogenase were deployed; additional tests per individual disease profile were recorded. The records of the patients for oxygen saturation, chest X-ray, computerized tomography, coagulation profile, and management mainly with oxygen support with or without ventilators and drugs like azithromycin, hydroxychloroquine, ivermectin, zinc, vitamin C, steroids, low molecular weight heparin, direct thrombin inhibitors, remdesivir, and tocilizumab were obtained.

2.5. End points

The primary outcomes were in-hospital mortality. The secondary outcomes were the association of demographic variables and comorbidities between COVID-19 deaths and survivors.

2.6. 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 were associated using *Chi* square test/ Fisher's Exact test was used to determine the association between qualitative variables. Independent *t*-test was used to determine the association between age and in-hospital mortality. Univariate and multivariate logistic regression was used to find out significant risk factors of COVID-19 mortality. Point-biserial correlation coefficient was used to determine the correlation between COVID-19 mortality and age, hypertension, diabetes (DM) and chronic kidney disease (CKD). The significant level of this study was set at α=0.05.

3. Results

A total of 24 000 patients were admitted during the study period, among which 17 000 were COVID-19 positive. The total mortality was 329 patients, among which 232 (70.52%) died of COVID-19, and 97 (29.48%) died due to other causes (Figure 1).

The mean age (SD) of the study patients was (64.09±16.99) years. The mean age was significantly higher in COVID-19-related deaths (67.63±13.78) years as compared to the survivors (60.52±19.50) years, (t=5.540, P<0.001). Table 1 shows the age-wise distribution concerning mortality. There was a significant

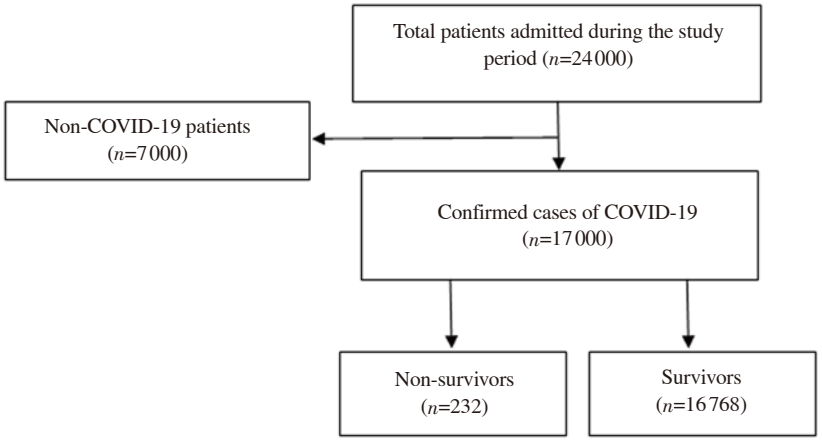

Figure 1. The study flowchart.

Table 1. Age distribution between COVID-19 mortality and survivors

Age, years	Non-survivors, *n* (%)	Survivors, *n* (%)	Total
≤10	1 (0.43)	870 (5.19)	871 (5.12)
11-20	0 (0)	345 (2.06)	345 (2.03)
21-30	0 (0)	518 (3.09)	518 (3.05)
31-40	6 (2.59)	1211 (7.22)	1217 (7.16)
41-50	9 (3.88)	2074 (12.37)	2083 (12.25)
51-60	59 (25.43)	3630 (21.65)	3689 (21.70)
61 -70	44 (18.97)	3458 (20.62)	3502 (20.60)
71-80	69 (29.74)	3625 (21.62)	3694 (21.73)
81-90	39 (16.81)	864 (5.15)	903 (5.31)
≥91	5 (2.16)	173 (1.03)	178 (1.05)

difference in the age distribution among COVID-19 deaths and COVID-19 survivors (P<0.05). In the age group of 71 years and above, more COVID-19 related deaths were recorded (48.7% *v.s.* 27.8%, P<0.001), while COVID-19 survivors predominated in the age group of <70 years. A significant positive correlation was observed between age and the COVID-19 mortality (r=0.310, P<0.001).

There was a significant association of gender with COVID-19 related mortality. Compared to non-COVID-19 associated deaths, there were more males (72.41% *v.s.* 61.5%) and fewer females (27.59% *v.s.* 38.5%) in COVID-19 related deaths (P=0.001).

The distribution of comorbidities among COVID-19 deaths and COVID-19 survivors were significantly different (Table 2). The common comorbidities recorded were hypertension, diabetes mellitus, and chronic kidney disease; all of which were significantly different related to COVID-19 mortality (P<0.001). A significant positive correlation was seen of COVID-19 mortality with all the comorbidities like hypertension (r=0.213, P<0.001), diabetes mellitus (r=0.256, P<0.001) and chronic kidney disease (r=0.185, P<0.001).

On performing multivariate regression, age and males were significant independent risk factors of the COVID-19 mortality after adjusting for confounding factors. With the increase in age, the risk of COVID-19 mortality significantly increases with an odds ratio of 1.05 (95% *CI*: 1.033-1.068). Male had a significantly high risk of COVID-19 mortality with an odds ratio of 2.754 (95% *CI*: 1.579-4.802). Comorbidities such as hypertension, diabetes mellitus, and chronic kidney disease also showed a higher odds of COVID-19 mortality with an adjusted odds ratio of 2.389, 3.891, and 6.358 respectively (Table 3).

Table 2. Association of comorbidities with mortality.

Co-morbidities	Non-survivors, *n* (%)	Survivors, *n* (%)	Total	χ^2	*P*
Hypertension	64 (27.59)	2462 (14.68)	2526	30.117	<0.001
Diabetes mellitus	73 (31.47)	2273 (13.56)	2346	61.705	<0.001
Chronic kidney disease	41 (17.67)	567 (3.38)	608	135.521	<0.001

Table 3. Univariate and multivariate logistic regression to find out significant risk factors of COVID-19 mortality.

Variables	Univariate		Multivariate	
	P	Odds ratio	*P*	Adjusted odds ratio
Age, years	<0.001	1.042 (1.026-1.059)	<0.001	1.050 (1.033-1.068)
Gender				
Female	Reference	-	-	-
Male	0.002	1.585 (1.185- 2.120)	<0.001	2.754 (1.579-4.802)
Hypertension	<0.001	2.214 (1.655- 2.961)	<0.001	2.389 (1.465-2.982)
DM	<0.001	2.928 (2.211-3.876)	<0.001	3.891 (2.059-5.392)
CKD	<0.001	6.133 (4.333- 8.683)	<0.001	6.358 (5.675-10.564)

4. Discussion

COVID-19 pandemic has resulted in a heavy death toll worldwide, indicating the significance of the problem. We reported a COVID-19 mortality rate of 1.36% against the overall mortality rate of 1.37%. Similarly, a study shows a high COVID-19 mortality rate of 23.6% against the overall mortality rate of 27.3% in a total of 1018 patients in 3 months[9].

As seen in other studies, reasons for mortality in COVID-19 were primarily due to acute failure: respiratory, renal, cardiovascular, and or multiorgan involvement.

It has been seen that the elderly population is at high risk, which was observed in the present study as well [(67.63 ±13.78) years *v.s.* (60.52±19.50) years, $P<0.001$]. Among other studies[10,11] similar results of elderly persons at high risk were observed. Suleyman *et al.* reported a higher death rate in older>60 years[12], likewise Gili *et al.*[13] and Nikpouraghdam *et al.*[14] reported it to be (66.8±16.4) years and 65 years, respectively.

Reason for increased chances of infection and deaths in the elderly are attributed to a more often presence of comorbid metabolic conditions like diabetes mellitus, hypertension, chronic kidney disease; waning immunity leading to increased susceptibility and disease severity; decreased airway and mucus clearance; psychological fear of getting the disease; weak will power to fight the infection; medicine treatment restrictions and cross drug interactions in patients already on medications for cardiovascular, central nervous system, endocrine disorders. In developing countries, often due to family financial constraints, treatment preference is not given to non-earning, dependent elderly at the beginning of disease symptoms. This leads to worsening symptoms, and disease could progress to systemic, irreversible complications before people try to seek medical help at hospitals.

We also observed that COVID-19 related deaths were more in males than in females (72.41% *v.s.* 61.5%, $P<0.05$). Our findings were in line with the study by Biswas *et al.*[15].

Among other studies, though most of them show male preponderance, some studies from the USA showed contrasting results[16]. Two Chinese[17,18] studies showed that the increased chances of infection and deaths in males are attributed to more outdoor exposure as still the main earning member of the family is male, indicating more social gathering exposure, more travel stretches, and weak immunity due to smoking, alcohol intake.

The comorbidities observed in the present study patients were hypertension, diabetes mellitus, and chronic kidney disease. WHO has also recognized these chronic conditions as the leading cause of mortality[19]. Similar to our observation, in other studies[20,21] hypertension, diabetes, and cardiovascular reasons diseases are the most common comorbid conditions associated.

As for diabetes mellitus, sustained high blood sugar levels weaken the immune system, leading to increased infection susceptibility. No established pathway for diabetes linked with COVID-19 severity has been published, the feeble possibility of angiotensin-converting enzyme 2 (ACE2) overexpression in diabetes mellitus is proposed. ACE2 is the primary binding site of the COVID-19 virus, thus leading to increased viral load[22].

Among all cardiovascular conditions, studies have reported hypertension is found in a maximum number of COVID-19 patients. Although the exact mechanism of myocardial damage in COVID-19 patients is still uncertain, possibilities include COVID-19 virus causing myocarditis, pericarditis eventually resulting in arrhythmias and heart failure[23,24]; damage due to cardiac tissue expression of ACE2[25]; acute cardiac injury resulting in cardiac failure[26]. Copresence of hypertension results in extra pressure load on cardiac muscle pumps and cardiac collapse. Though the exact mechanism by which the COVID-19 virus damages renal tissue is not well established, ACE2 expression by the kidney could play the culprit[27].

Worldwide studies (China[17], Italy[28], USA[29], UK[30]) have found a vast disease spectrum associated: chronic obstructive pulmonary disease; chronic kidney disease; liver disease, GI disorders, immunosuppression, neurological disorders, psychiatric disorders, metabolic disorders, blood disorders, transplant, chronic pancreatitis, connective tissue disorder, smoking, obesity, and hyperlipidemia. So, the graveness of the COVID-19 pandemic is being depicted by its poor prognosis with any of these comorbidities associated, and the comorbidity inclusion list is still on the rise.

Statistically, we also supported that the presence of comorbidities (hypertension, diabetes mellitus, and chronic kidney disease) carry higher odds of mortality with an adjusted odds ratio of 2.389, 3.891 and 6.358 respectively. Our findings are in line with the study by Biswas *et al.*[15]. who also found that comorbidities showed increased risk of mortality; kidney disease (*RR*: 4.90, 95% *CI*: 3.04-7.88; $P<0.001$), cerebrovascular disease (*RR*: 4.78; 95% *CI*: 3.39-6.76; $P<0.001$), cardiovascular disease (*RR*: 3.05, 95% *CI*: 2.20-4.25; $P<0.001$), respiratory disease (*RR*: 2.74; 95% *CI*: 2.04-3.67; $P<0.001$), diabetes (*RR*: 1.97, 95% *CI*: 1.48-2.64; $P<0.001$), hypertension (*RR*: 1.95; 95% *CI*: 1.58-2.40; $P<0.001$), and cancer (*RR*: 1.89; 95% *CI*: 1.25-2.84; $P=0.002$) but not liver disease (*RR*: 1.64; 95% *CI*: 0.82-3.28; $P=0.16$). Another recent systematic review support this notion of increased COVID-19 mortality with the presence of co-morbidities[31].

As COVID-19 has emerged as a new pandemic disease, the medical fraternity was not ready with set treatment protocols to deal with such grave systemic illness. At the beginning of the pandemic, with a sudden high number of COVID-19 cases, shrinking medical infrastructure compared to prevalence, fear of self-protection, over-running treatment capacity, and daily new emerging fatality rate took a toll on humanity, and we couldn't do justice to required medical care. However, after knowing the predisposing factors, we are more aware and take greater care of the comorbid population allowing for a better outcome.

The study must be interpreted under certain limitations. First, we enrolled a small set of patients from a single institute. Second, we were not able to evaluate hematological or biochemical investigations as the risk for mortality. It might be possible that uncontrolled glycemic levels of the diabetes mellitus patients, the

raised blood pressure in hypertensives, or deranged creatinine levels in CKD might influence the prognosis of admitted patients.

Given this, more extensive, multicentric studies are required to identify high-risk populations, facilitating improved, individualized treatment protocols for this subset of the population.

Elderly males with comorbidities fell in a higher risk group for mortality related to COVID-19. Ongoing vaccination drive is rightfully prioritized to serve the high-risk category first. This vulnerable group should exercise extra caution to fight the pandemic in the future, and simultaneously, vaccination programs should be stepped up to include almost 70% of the population at the fastest pace. Future research is required to optimize the management of patients with diabetes and develop new ways to manage them *via* technological developments such as telecare.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

A.K.G., N.K., R.G., V.K.: Concept, design, literature search, data analysis, manuscript preparation; A.K.G., S.S., K.G.: Design, data acquisition, manuscript review; A.K.G., V.K., S.S., K.G.: Design, data acquisition, manuscript review.

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