Demographic and clinical factors associated with early hospital Coronovirus disease 2019 deaths in a low middle income setting: A record-based analysis of 20,641 deaths from India

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Abstract

Understanding the demographic and clinical characteristics of cases and deaths is essential for better clinical and public health management of coronavirus disease-2019 (COVID-19) in resource-limited settings. We analyzed the COVID-19 deaths reported from India, to describe the demographic and clinical characteristics and identify the factors associated with early hospital deaths (within one day of hospitalization) and survival duration. We conducted a record review of the publicly available data on COVID-19 deaths reported between January 30th and November 30th, 2020. After imputation for missing data, we calculated unadjusted and adjusted prevalence ratios, and regression coefficient for factors associated with early hospital deaths and survival duration. Of the 20,641 COVID-19 deaths analyzed: a) 14,684 (71.1%) were males; b) 10,134 (50.9%) were aged <65 years; c) 9,722 (47.1%) treated at public hospitals and d) 5405 (27.1%) were early hospital deaths. Breathlessness was the most common presenting complaint. Diabetes (11,075,53.7%), hypertension (95,77,46.5%) and coronary artery disease (2,821,13.7%) were the common comorbidities. After adjustment, early hospital death was significantly higher among patients aged <65 years, without severe acute respiratory illness (SARI) at admission, non-diabetics, and cared at public hospitals compared to their counterparts. Similarly, the survival duration was at least one day higher among patients presented with SARI, chronic liver disease and cared at a private hospital. The analysis covered >10% of India's COVID-19 deaths, providing essential information regarding the COVID-19 epidemiology. The characteristics associated with early hospital death and survival duration among the COVID-19 fatalities may be deliberated as markers for prognosis and compared with survivors.

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Ethical approval: We used anonymized data available in the public domain, hence an exemption from the ethical review board was obtained from the Institute Ethics Committee, PGIMER, Chandigarh, India.

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Introduction

Coronavirus disease 2019 (COVID-19) is one of the most rapid and newest communicable diseases in the public health history affecting the livelihoods, globally. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 83.33 million people and killed 1.83 million people across the world within a year of its identification [1]. Although the countries worldwide have taken multiple preemptive and simultaneous non-pharmacological, and pharmacological interventions, the case fatality rate has remained fairly high at 2.2% [1], reaching even up to 29% in Yemen [2],

The respiratory and febrile symptoms are considered the cardinal symptoms of COVID-19. Severe acute respiratory infection (SARI) is defined as an acute respiratory illness of recent onset (within ten days) manifested by cough and fever (≥38°C) or having history of fever and requires hospitalization [3]. Since COVID-19 is an important cause of SARI, it was made mandatory to notify SARI for COVID-19 testing strategy [4]. However there are gaps remaining in our understanding of the impact and burden of SARI on COVID-19 deaths. With the evolution of the pandemic and the accumulation of the case data, it is evident that the initial patient presentation to the health system can be with extensive non-respiratory symptoms [5]. A differential rate of infection and mortality has been observed across the world regarding sex and age groups, which generated various hypotheses for such differences [6,7]. Though <50% of the SARS-CoV-2 infected people have one or more comorbidities, comorbidities have been found to aggravate the fatalities in COVID-19 [8].

The emerging non-communicable disease burden in low-and-middle-income countries (LMICs) presents a challenge to the public health system. These comorbidities have been identified as a risk factor for hospitalization during the COVID-19 pandemic [9,10]. Male sex, elderly age, respiratory, diabetes, cardiovascular, and cerebrovascular diseases are reported as risk factors for increased severity and criticality of the COVID-19 infection and mortality [7,8,11-13]. However, the role of these risk factors in the pathophysiology of the COVID-19 is still under study. Due to the high burden of COVID-19, most countries focus on identifying severe disease among high-risk populations to reduce mortality. COVID-19 fatality characteristics have been reported across the world from multiple countries [13-18], but none from the LMICs.

India had reported its first case of COVID-19 on January 30th, 2020. A total of 11.6 million cases and 159,755 deaths have been reported from India till March 21st, 2021 [1]. Such a high volume of patients presenting to health systems during this pandemic overwhelms the human and mechanistic capacities available, especially the need for critical care support. Though the country's case fatality rate is lower than that of other worst-affected countries [2], the characteristics of the deceased in the second most populous and COVID-19 affected country remained to be studied. Elsewhere, publicly available data has been used in studying the epidemiology of COVID-19 hospitalizations and deaths [19]. Hence, we conducted an analysis of COVID-19 deaths reported from India, based on the data available in the public domain, to bring out the clinico-demographic characteristics of COVID-19 fatalities. We also aimed to identify the factors associated with early hospital deaths and survival duration, which may guide preventive action for better pre-hospital and in-hospital management of COVID-19 in resource-limited settings.

Materials and Methods

We conducted a record review of the COVID-19 deaths reported from India between January 30th and November 30th, 2020. All the 36 Indian states and union territories publish health/news bulletin for media and public, at regular intervals, wherein details about the new COVID-19 cases and deaths are provided. Two authors independently searched COVID-19 related websites and daily media bulletins of all states and union territories. The states publishing/reporting the demography, clinical presentation, comorbidities with or without hospital-related characteristics at individual patient level were chosen [20,21]. The states or central bulletin/websites providing only the summary numbers (cases and deaths) were excluded.

For the media bulletins available in text format, we used Epicollect5 (https://five.epicollect.net/) for data capture (double entered and validated) and merged with the media bulletin available (converted) in excel format. The merged datasheet was exported to STATA version 16 (Copyright 1985-2019 StataCorp LLC) for analysis. Median and interquartile range (IQR) were calculated for continuous variables like age, treatment-seeking time (between the onset of symptom and hospital admission), hospitalization (between hospital admission and death) and survival (between onset symptom and death) durations since these were not normally distributed (tested using Kolmogorov smirnov test of normality). Frequencies and proportions were summarized as categorical variables. Mann-Whitney U test was used for comparing the difference of treatment-seeking time and duration of hospitalization between various categories of demographic, and clinical characteristics except for the time of lockdown period and age group where Kruskal Wallis test was used. After imputation of missing data using multiple imputation by chained equation (predictive mean matching with nearest neighbors method, 50 imputations), the association of various characteristics with SARI vs Non-SARI (logistic regression) and survival time (linear regression) was assessed. Adjusted prevalence ratio (aPR) using multiple logistic regression and adjusted regression coefficient (aRC) using multiple linear regression along with 95% confidence interval (CI) were calculated to assess the independent effect of variables on early hospital death and the survival time, respectively. Kaplan-Meier survival curves were plotted to assess the difference in survival between various demographic and clinical characteristics. A p-value of <0.05 was considered statistically significant. Since we used anonymized data available in the public domain, an exemption from the ethical review was obtained from the Institute Ethics Committee, PGIMER, Chandigarh.

Results

We found only two states, namely Tamil Nadu and Karnataka, publishing details of the patients who died of COVID-19. No Indian state is publishing detailed data on all COVID-19 cases. The case fatality rate (CFR) was 1.5% for Tamil Nadu and 1.3% for Karnataka, which showed a deviant distribution over the period (Figure 1). During the same period, India observed a CFR of 1.5% which varied between 0.1% in Mizoram to 3.2% in Punjab (Supplementary Table 1). Of the reported 23,490 deaths from both the states, complete details were available for 95.5% (11,190/11,712) and 80.2% (9,451/11,778) deaths from Tamil Nadu and Karnataka, respectively. Of the total 20,641 COVID-19 deaths analyzed, a) 14,684 (71.1%) were males; b) 101,134 (50.9%) were aged <65 years; c) 9,722 (47.1%) were treated at public hospitals, and d) 492 (2.4%) died out of hospital (Table 1). Over the months, the proportion of deaths shared by people aged <65 years and females has decreased (Figure S1). The proportion of deaths from private hospitals has increased compared to public hospitals.

Symptom profile was available for 14181 (68.7%) patients. Of the 13598 symptomatic patients, a total of 10,302 (75.8%) presented with SARI. Gastrointestinal symptoms, myalgia and neurological symptoms were present in 321 (2.4%), 179 (1.6%) and 107 (0.8%), respectively. Of the deceased, 16,599 (77.5%) had one or more comorbidities. Diabetes (11075, 53.7%), hypertension (9,577, 46.5%) and coronary artery disease (2821, 13.7%) were the common comorbidities (Table 1). Over the period, the proportion of deceased with symptoms, SARI, comorbidities and to a certain extent, the long treatment-seeking time (≥7days) has increased (Figure S2).

The median (IQR) days taken for treatment-seeking (n=4,085), and hospitalization (n=19,933) were 4.0 (2.0, 6.0) and 4.0 (1.0, 8.0) days, respectively (Table 2). The treatment-seeking time was significantly longer among males (p-0.026) and with SARI (p<0.001), and shorter among people who died at private hospitals (p<0.001) compared to their respective counterparts. Similarly, duration of hospitalization was significantly longer among males (p<0.001), aged ≥65 years (p<0.001), symptomatic at the time of admission (p<0.001), with comorbidity (p<0.001), patients from Tamil Nadu (p<0.001) and in private hospitals (p<0.001). Presence of SARI was significantly high among patients a) diagnosed after unlock 2.0 (aPR:1.42, 95%CI-1.30, 1.54); b) from Karnataka (aPR:1.58, 95%CI-1.44, 1.72); c) treated in public hospitial (aPR:1.76, 95%CI-1.56, 1.98); and among patients without CAD, CKD, CLD and Cancers. Similarly, increasing treatment seeking time was significantly associated with presence of SARI (Table 3).

A total of 5405 (27.1%) patients died within 24 hours (early deaths) of hospitalization (Table 4). After adjustment, early hospital death was significantly higher among patients a) aged <65 years (<45 years-aPR:1.29, 95%CI-1.15, 1.45 and 45-64 years-aPR:1.15, 95%CI-1.07, 1.23); b) non-SARI at admission (aPR:1.19, 95%CI-1.08, 1.31); c) non-diabetics (aPR:1.13, 95%CI-1.06, 1.21); d) from Karnataka (aPR:1.75, 95%CI-1.64, 1.88), and e) cared at public hospitals (aPR:1.75, 95%CI-1.64, 1.88) than their respective comparators.

The median (IQR) duration of survival of the deceased (n-4079) was 10.0 (7.0, 16.0) days (Supplementary Table 2). The survival duration of the deceased persons was at least one day higher among patients presented with SARI (aRC: 2.00, 95%CI-1.67, 2.34), chronic liver disease (aRC: 1.75, 95%CI-0.90, 2.60), and cared at private hospitals (aRC: 3.94, 95%CI-3.63, 4.25) after adjustment to other factors compared to their respective counterparts. Patients with chronic kidney disease (aRC:-1.22, 95%CI-(-1.71), (-0.72)) had more than one day lower survival duration compared to their counterparts. The survival curves are significantly different between the lockdown periods and type of hospital cared (Figure S3). However, it was not significantly different for other demographic and clinical characteristics (Figure S4).

Discussion

To our knowledge, this is the first study from India that provides insights into the key demographic, clinical and survival duration related characteristics covering >10% of reported COVID-19 deaths. Enumerating the clinical and demographic characteristics of the COVID-19 fatalities aides the clinicians to be vigil towards the patients with poor prognostic features and assisting the public health specialists in prioritizing action and targeting communication for population groups at greater risk [11,13]. The majority of the deceased in our analysis were male, aged <65 years, presented with breathlessness, SARI at admission, and had underlying one or more comorbidities.

The CFR varied over a period and stabilized between 1.3-1.5% nearly at the end of unlock 2.0 in Tamil Nadu and Karnataka. The observed CFR is lower than or equal to the nation-

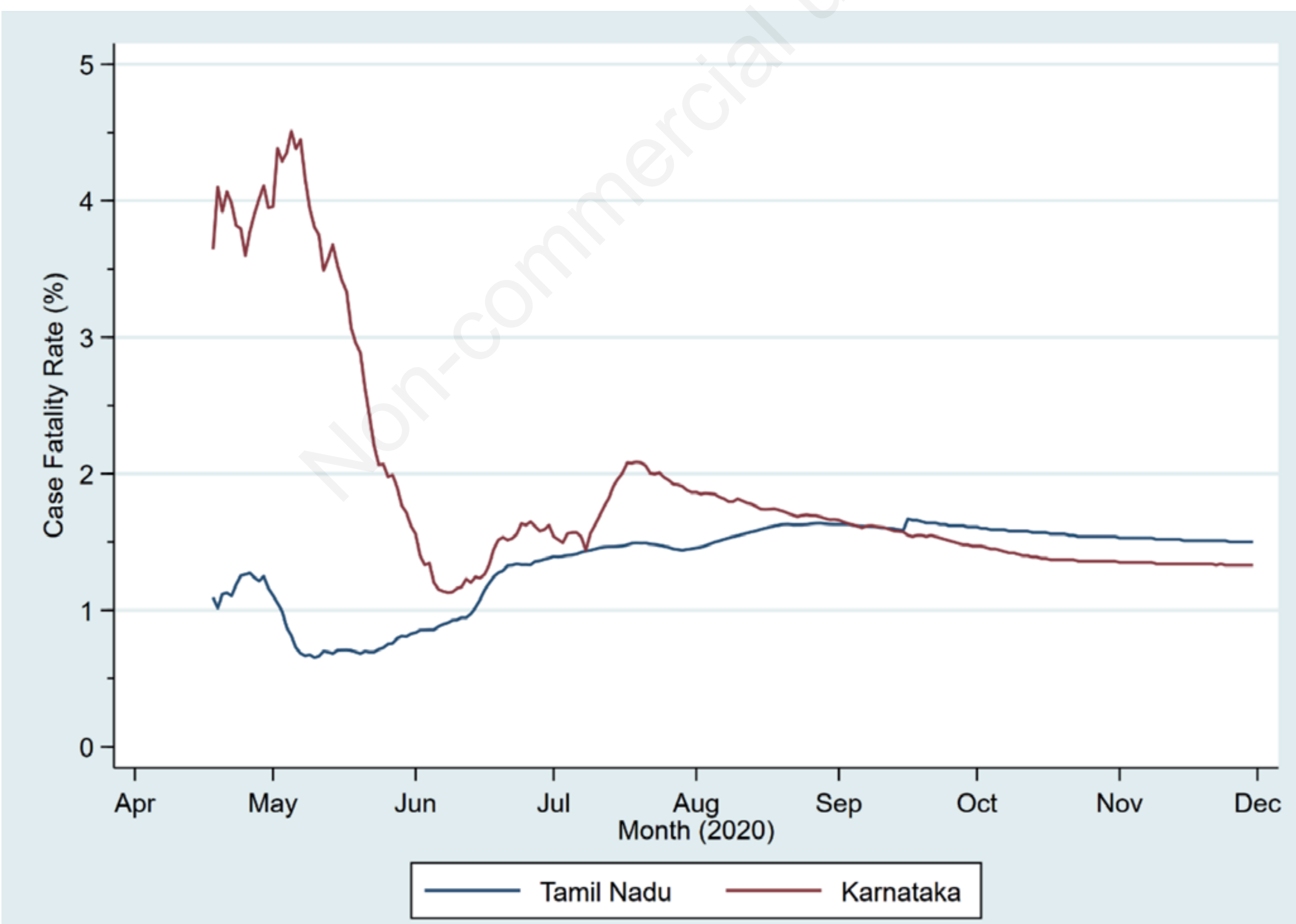

Figure 1. Time trend of case fatality rate due to COVID-19 in Tamil Nadu and Karnataka of India between January 30 and November 30, 2020.

al average, i.e., 1.5% during the same period. However, the CFR varied from 0.1 to 3.2% across the Indian states. The differential CFR over the period, between the states, might be due to non-uniform system of diagnosis and management, (under-) reporting of cases and deaths and healthcare inequities that exists between the states, as health is a state subject [22,23]. Similarly, the high CFR during the initial stage of the pandemic in the studied states might be due to poor and differential health system preparedness [24].

Table 1. Demographic and clinical profile of patients deceased due to coronavirus disease-2019 (COVID-19) in India.

Characteristics	Male [n (%)][a]	Female [n (%)][a]	Total [n (%)][a]
Total	14,684	5,957	20,641
Admission period			
Complete lockdown	207 (1.4)	111 (1.9)	318 (1.6)
Up to unlock 2.0	4,888 (33.3)	2,074 (34.8)	6,962 (33.7)
After unlock 2.0	9,589 (65.3)	3,772 (63.3)	13,361 (64.7)
State of residence			
Tamil Nadu	8,149 (55.5)	3,041 (51.0)	11,190 (54.2)
Karnataka	6,535 (44.5)	2,916 (49.0)	9,451 (45.8)
Median age in years (IQR)	64 (55,72)	63 (54,71)	64 (55,72)
Age group (in years)			
≤12	15 (0.1)	15 (0.3)	30 (0.1)
13-44	1278 (8.7)	564 (9.5)	1,842 (8.9)
45-64	6,051 (41.2)	2,584 (43.4)	8,635 (41.8)
≥65	7,340 (50.0)	2,794 (46.9)	10,134 (49.1)
Symptom status			
Symptomatic	9,687 (66.0)	3,911 (65.7)	13,598 (65.9)
Asymptomatic	398 (2.7)	185 (3.1)	583 (2.8)
Not known	4,599 (31.3)	1,861 (31.2)	6,460 (31.3)
Presence of any respiratory symptoms[b]	8,923 (92.1)	3,597 (92.0)	12,520 (92.1)
Breathlessness	7,592 (78.3)	3,079 (78.7)	10,671 (78.5)
Cough	4,829 (49.9)	1,785 (45.6)	6,614 (48.6)
Other respiratory symptoms[c]	54 (0.6)	22 (0.6)	76 (0.6)
Presence of fever[b]	8,018 (82.8)	3,209 (82.1)	11,227 (82.6)
Presence of severe acute respiratory illness[b]	7,357 (75.9)	2,945 (75.3)	10,302 (75.8)
Other symptoms[d]	461 (4.8)	217 (5.5)	593 (5.0)
Presence of one or more comorbidities[d]	11,309 (77.0)	4,690 (78.8)	16,599 (77.5)
Presence of endocrine comorbidity	7,892 (53.8)	3,331 (56.0)	11,223 (54.4)
Diabetes mellitus	7,831 (53.4)	3,244 (54.5)	11,075 (53.7)
Other endocrine diseases[d]	187 (1.3)	251 (4.2)	438 (2.1)
Presence of cardivascular comorbidity (CVS)	7,606 (51.9)	3,161 (53.1)	10,767 (52.2)
Hypertension	6,659 (45.4)	2,918 (49.1)	9,577 (46.5)
Coronary artery disease	2,195 (15.0)	626 (10.5)	2,821 (13.7)
Other CVS disease[d]	196 (1.3)	97 (1.6)	293 (1.4)
Presence of respiratory system (RS) comorbidity	711 (4.8)	297 (5.0)	1,008 (4.9)
Asthma	184 (1.3)	122 (2.1)	306 (1.5)
Chronic obstructive pulmonary disease	360 (2.5)	112 (1.9)	472 (2.3)
Other RS disease[d]	187 (1.3)	74 (1.2)	261 (1.3)
Presence of genitourinary comorbidity	1,861 (12.7)	680 (11.4)	2,541 (12.3)
Chronic kidney disease	1623 (11.1)	601 (10.1)	2,224 (10.8)
Acute kidney disease	168 (1.1)	55 (0.9)	223 (1.1)
Other genitourinary disease[d]	126 (0.9)	41 (0.7)	167 (0.8)
Presence of chronic liver disease	176 (1.2)	48 (0.8)	224 (1.1)
Presence of central nervous system (CNS) comorbidity	491 (3.3)	164 (2.8)	655 (3.2)
Cerebro vascular accident	312 (2.1)	109 (1.8)	421 (2.0)
Other CNS disease[d]	191 (1.3)	63 (1.1)	254 (1.2)
Presence of cancer[d]	131 (0.9)	92 (1.6)	223 (1.1)
Presence of obesity	127 (0.9)	86 (1.4)	213 (1.0)
Other diseases[d]	236 (1.6)	133 (2.5)	396 (1.9)
Place of care/death			
Public hospital	6,899 (47.0)	2,823 (47.4)	9,722 (47.1)
Private hospital	4,534 (30.9)	1,628 (27.3)	6,162 (29.8)
Out of hospital	336 (2.3)	156 (2.6)	492 (2.4)
Not known	2,915 (19.9)	1,350 (22.7)	4,265 (20.7)

IQR, interquartile range; [a]all are column percentages; [b]of the symptomatic patients (n=13,599); [c]other respiratory symptoms: sore throat (65), cold (9), hemoptysis (2), nasal symptoms (1), running nose (1), and purulent expectoration and wheeze (1); [d]details in Supplementary files.

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Table 2. Time (in days) taken for seeking treatment and duration of hospitalization across various socio-demographic and clinical profile of deceased due to COVID-19 in India.

Characteristics	Treatment seeking time (n=4,085) Median (IQR)	p-value[a]	Duration of hospitalization (n=19,933) Median (IQR)	p-value[a]
Total	4 (2, 6)		4 (1, 8)	
Admission period				
Complete lockdown	4.5 (3, 7)	<0.001	4 (2, 9)	<0.001
Up to unlock 2.0	3 (2, 6)		3 (1, 8)	
After unlock 2.0	4 (2, 7)		4 (1, 7)	
State of residence				
Tamil Nadu	4 (2, 6)	NA	4 (2, 8)	<0.001
Karnataka	NA		3 (1, 7)	
Type of hospital				
Public	3 (2, 5)	<0.001	3 (1, 6)	<0.001
Private	4 (2, 7)		6 (2, 10)	
Age group (in years)				
<45	4 (3, 6)	0.001	3 (1, 7)	<0.001
45-64	4 (2, 7)		3 (1, 7)	
≥65	4 (2, 6)		4 (2, 8)	
Sex				
Male	4 (2, 7)	0.026	4 (1, 8)	<0.001
Female	4 (2, 6)		3 (1, 7)	
Symptom status				
Symptomatic	4 (2, 6)	NA	4 (1, 8)	<0.001
Asymptomatic	NA		2 (1, 6)	
Presence of any respiratory symptoms				
Yes	4 (2, 7)	<0.001	4 (1, 8)	0.104
No	3 (2, 5)		5 (1, 9)	
Presence of fever				
Yes	4 (3, 7)	<0.001	4 (1, 8)	0.001
No	3 (2, 5)		4 (1, 8)	
Presence of SARI				
Yes	4 (3, 7)	<0.001	4 (1, 8)	0.021
No	3 (2, 5)		4 (1, 8)	
Comorbidity status				
Present	4 (2, 6)	0.251	4 (1, 8)	<0.001
Absent	4 (3, 6)		3 (1, 7)	
Diabetes mellitus				
Yes	4 (2, 6)	0.393	4 (2, 8)	<0.001
No	4 (2, 6)		3 (1, 7)	
Hypertension				
Yes	4 (2, 7)	0.830	4 (1, 8)	<0.001
No	4 (2, 6)		3 (1, 7)	
Coronary artery disease				
Yes	3.5 (2, 6)	0.037	4 (1, 8)	0.637
No	4 (2, 6)		4 (1, 7)	
Asthma				
Yes	3 (4, 7)	0.198	5 (2, 8.5)	0.006
No	4 (2, 6)		4 (1, 7)	
COPD				
Yes	4 (2, 6.5)	0.747	3 (1, 7)	0.953
No	4 (2, 6)		4 (1, 8)	
Chronic kidney disease				
Yes	3 (2, 6)	0.002	4 (1, 7)	0.003
No	4 (2, 7)		4 (1, 8)	
Chronic liver disease				
Yes	3.5 (2, 7)	0.885	4 (1, 7)	0.973
No	4 (2, 6)		4 (1, 8)	
Cerebrovascular accident				
Yes	3 (2, 7)	0.792	4 (2, 8)	0.341
No	4 (2, 6)		4 (1, 8)	
Cancer				
Yes	3 (2, 6)	0.106	4 (2, 8)	0.082
No	4 (2, 6)		4 (1, 8)	

IQR, interquartile range; [a]Mann-Whitney U test was used for testing the difference between the groups except for admission period and age group where Kruskal Wallis test was used; SARI, severe acute respiratory illness (fever with at least one respiratory symptom namely cough or breathlessness); COPD, chronic obstructive pulmonary disease.

The observed proportion of elderly, symptomatic and severe cases, and comorbidity among deceased during initial period was low compared to post-lockdown. Further, the duration of hospitalization/survival was also higher during the initial period than the later study period.

The median age of the deceased reported in our study was lower than the ones reported in other countries [11,13-17,25,26]. While the majority of Indian fatalities were <65 years old, the elderly ≥65 years constituted the major deceased in other studies. It could be due to the longer life expectancy, in general, in these countries than India.

Table 3. Demographic and clinical characteristics associated with presence of SARI among patients died with coronavirus disease-2019 (COVID-19) in India.

Characteristics	Total N	SARI n (%)	Unadjusted prevalence ratio[a] (95% CI)	Adjusted prevalence ratio[a] (95% CI)
Total	20,641	10,302 (49.9)		
Admission period				
Complete lockdown	318	66 (20.8)	1.13 (0.83, 1.53)	1.17 (0.84, 1.62)
Up to unlock 2.0	6,962	2754 (39.6)	1	1
After unlock 2.0	13,361	7,482 (56.0)	1.53 (1.42, 1.66)	1.42 (1.30, 1.54)
State of residence				
Tamil Nadu	11,190	3,081 (27.5)	1	1
Karnataka	9,451	7,221 (76.4)	1.69 (1.56, 1.83)	1.58 (1.44, 1.72)
Type of hospital (n=15,884)				
Public	9,722	2,780 (28.6)	1.33 (1.20, 1.47)	1.76 (1.56, 1.98)
Private	6,162	4,427 (71.8)	1	
Age group (in years)				
<45	1,872	900 (48.1)	1.04 (0.91, 1.19)	Not included
45-64	8,635	4,306 (49.9)	1.07 (0.99, 1.16)	
≥65	10,134	5,096 (50.3)	1	
Sex				
Male	14,684	7,357 (50.1)	1.02 (0.94, 1.10)	Not included
Female	5,957	2,945 (49.4)		
Diabetes mellitus[b]				
Yes	11,075	5,507 (49.7)	1	1
No	9,539	4,793 (50.2)	1.16 (1.07, 1.25)	0.99 (0.90, 1.09)
Hypertension[b]				
Yes	9,577	5,025 (52.5)	1	Not included
No	11,037	5,275 (47.8)	1.03 (0.95, 1.12)	
Coronary artery disease[b]				
Yes	2,821	1,282 (45.4)	1	1
No	17,793	9,018 (50.7)	1.51 (1.35, 1.69)	1.18 (1.04, 1.34)
Asthma[b]				
Yes	306	121 (39.5)	1	Not included
No	20,308	10,179 (50.1)	1.16 (0.81, 1.64)	
COPD				
Yes	472	266 (56.4)	1	Not included
No	20,142	10,034 (49.8)	1.09 (0.86, 1.38)	
Chronic kidney disease[b]				
Yes	2,224	865 (38.9)	1	1
No	18,390	9,435 (51.3)	2.38 (2.12, 2.67)	1.91 (1.65, 2.12)
Chronic liver disease[b]				
Yes	224	107 (47.8)	1	1
No	20,390	10,193 (50.0)	1.52 (1.06, 2.16)	1.55 (1.02, 2.35)
Cerebrovascular accident[cb]				
Yes	421	158 (37.5)	1	Not included
No	20,193	10,142 (50.2)	1.14 (0.82, 1.59)	
Cancer[b]				
Yes	223	69 (30.9)	1	1
No	20,391	10,231 (50.2)	2.04 (1.46, 2.86)	1.62 (1.11, 2.37)
Treatment seeking time (days) (n=4,085)				
≤2	1,131	596 (52.7)	1	1
3-4	1,325	943 (71.2)	1.95 (1.65, 2.30)	1.99 (1.68, 2.35)
5-6	614	472 (76.9)	3.06 (2.41, 3.89)	3.15 (2.49, 3.98)
>6	1,015	760 (74.9)	4.13 (3.34, 5.12)	4.18 (3.36, 5.21)

SARI, severe acute respiratory illness (fever with at least one respiratory symptom namely cough or breathlessness); [a]all unadjusted and adjusted analysis was carried out after multiple imputation by chained equation using predictive mean matching nearest neighbors method; [b]n=20,614; COPD, chronic obstructive pulmonary disease.

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Table 4. Demographic and clinical characteristics associated with early (≤1 day) hospital deaths among patients died with coronavirus disease-2019 (COVID-19) in India.

Characteristics	Total n	Early hospital death (≤1 day) n (%)	Unadjusted prevalence ratio[a] (95% CI)	Adjusted prevalence ratio[a] (95% CI)
Total	19,933	5,405 (27.1)		
Admission period				
Complete lockdown	289	68 (23.5)	1	1
Up to unlock 2.0	6,690	2,006 (30.0)	1.36 (1.04-1.79)	1.21 (0.91-1.60)
After unlock 2.0	12,954	3,332 (25.7)	1.10 (0.83-1.44)	1.03 (0.77-1.36)
State of residence				
Tamil Nadu	11,126	2,549 (22.9)	1	1
Karnataka	8,807	2,856 (32.4)	1.61 (1.51-1.71)	1.75 (1.64-1.88)
Type of hospital (n=15819)				
Public	9,670	2,822 (29.2)	1.94 (1.77-2.12)	1.94 (1.76-2.14)
Private	6,149	1,047 (17.0)	1	
Age group (in years)				
<45	1,783	599 (33.6)	1.56 (1.40-1.74)	1.29 (1.15-1.45)
45-64	8,330	2,400 (28.8)	1.24 (1.17-1.33)	1.15 (1.07-1.23)
≥65	9,820	2,406 (24.5)	1	1
Sex				
Male	14,203	3,768 (26.5)	1	1
Female	5,730	1,637 (28.6)	1.11 (1.04-1.19)	1.06 (0.98-1.13)
Symptom status (n=13537)				
Symptomatic	13,078	3,466 (26.5)	1	1
Asymptomatic	459	179 (39.0)	1.59 (1.29-1.95)	1.20 (0.97-1.49)
Presence of SARI (n=13078)				
Yes	9936	2,568 (25.8)	1	1
No	3,142	898 (28.6)	1.13 (1.04-1.23)	1.19 (1.08-1.31)
Diabetes mellitus (n=19913)				
Yes	10814	2695 (24.9)	1	1
No	9,099	2,708 (29.8)	1.28 (1.20-1.36)	1.13 (1.06-1.21)
Hypertension (n=19913)				
Yes	9321	2382 (25.6)	1	1
No	10,592	3,021 (28.5)	1.16 (1.09-1.24)	1.04 (0.98-1.12)
Coronary artery disease (n=19913)				
Yes	2429	774 (28.2)	1	Not included
No	17,170	4,629 (27.0)	0.93 (0.85-1.02)	
Asthma (n=19913)				
Yes	301	62 (20.6)	1	1
No	19,612	4,933 (27.2)	1.43 (1.08-1.89)	1.13 (0.85-1.50)
COPD (n=19913)				
Yes	461	120 (26.0)	1	Not included
No	19,452	5,283 (27.2)	1.06 (0.86-1.31)	
Chronic kidney disease (n=19,913)				
Yes	2156	620 (28.8)	0.91 (0.83-1.01)	0.96 (0.86-1.06)
No	17,757	4,783 (26.9)	1	
Chronic liver disease (n=19,913)				
Yes	210	54 (25.7)	1	Not included
No	19,703	5,349 (27.1)	1.07 (0.79-1.46)	
Cerebrovascular accident (n=19,913)				
Yes	410	97 (23.7)	1	1
No	19,503	5,306 (27.2)	1.22 (0.97-1.53)	1.10 (0.87-1.39)
Cancer (n=19,913)				
Yes	219	49 (22.4)	1	Not included
No	19,694	5,354 (27.2)	1.31 (0.95-1.80)	
Treatment seeking time (days) (n=4,079)				
≤2	1,128	222 (19.7)	1.29 (1.08-1.55)	1.15 (0.95-1.38)
3-4	1,323	214 (16.2)	1.10 (0.96-1.26)	1.03 (0.90-1.18)
5-6	614	81 (13.2)	0.94 (0.80-1.10)	0.93 (0.80-1.09)
>6	1,014	157 (15.5)	1	1

[a]All unadjusted and adjusted analysis was carried out after multiple imputation by chained equation using predictive mean matching nearest neighbors method; SARI, severe acute respiratory illness (fever with at least one respiratory symptom namely cough or breathlessness); COPD, chronic obstructive pulmonary disease.

Yet, the proportion of COVID-19 mortality has been skewed towards the elderly in India, with 49.1% among the total deaths, while the population aged ≥65 years constitutes only 4.8% of India's general population [27]. This disproportionate fatal effect of COVID-19 on the elderly is in line with the reports from the United States of America (USA) and Norway [13,17].

Though most of the patients presented with respiratory symptoms suggestive of COVID-19, they were admitted late to the hospital after four days, despite an ongoing active and passive surveillance. In addition, 2.4% of the deaths happened out of hospital (brought dead or at home). These could be due to poor accessibility, availability, and affordability of COVID-19 services/facilities, the stigma associated with COVID-19 [28], or vigilance gaps in the health system, which needs further investigation. Studies from South Korea and Norway reported a higher proportion (14.8%) of out-of-hospital deaths [17,18], while supplementary surveillance from the USA reported 2.4% home deaths, similar to our findings [13].

Breathlessness was the most common presenting complaint in our study. However, fever has been the most common clinical presentation of COVID-19 elsewhere [11,29,30]. This differential presentation may be due to admitting the patients to prevent worsening of prognosis. The clinical progression and role of risk factors among deceased without symptoms and non-respiratory symptoms at presentation needs further study.

The median treatment-seeking time was four days in our analysis, while Palmieri et al reported a higher duration (mean-six days) [15] .The duration of hospitalization was lower in our deceased patients compared to other countries. The early hospital deaths (≤1 day) were significantly higher during the unlock period (June 1st onwards) than India's lockdown period (March 24th- May 31st). It might be due to the high volume of patients with severe disease, and low availability of advanced supportive care during post-lockdown. A higher proportion of the deceased aged <65 years had early hospital deaths, similar to those reported from the USA [13].The higher early hospital deaths in the younger age group might be due to the differential health seeking behavior, i.e., ignorance or neglect and hesitancy in testing for COVID-19 during mild symptoms and reaching the health facility with severe disease. Further, the health systems had a focused and active case detection strategy among elderly and people with comorbidities compared to younger and people without comorbidities in India [31]. High proportion of early hospital deaths in public hospitals might be due to referral bias, i.e., referral of patients with advanced disease at terminal stage from the private to public hospitals, a practice observed in India even before COVID-19 pandemic [32]. Importantly, the public hospitals were admitting most of the COVID-19 cases, which might have also overstretched the resources causing the increased early hospital deaths.

The median duration of survival (10 days) was the same as that reported from the USA and South Korea [13,18], but less than that of China and Itlay [11,15,25]. We observed a higher survival duration in lockdown period than unlock 1.0 (June 1st-July 31st) and unlock 2.0 (August 1st onwards). It is in contrast to the observations from Italy. It can be due to differential treatment-seeking in two countries, the volume of patients and the treatment protocol, including the institutionalization for advanced support care. The low survival time among patients without SARI could be due to inadequate attention given to patients presenting with non-respiratory symptoms and *vice versa*.

The majority of the deceased were males and had one or more comorbidity, in line with the COVID-19 deaths analyzed from other countries [11-13,15,16,18,25,33]. Females had significantly shorter survival time and higher out of hospital deaths than males, thus indicating the possibility of gender disparity in accessing COVID-19 services. However, the longer duration taken by men to reach the hospital might have confounded the overall association between gender and survival duration in our study. It could be due to the social construct of hiding the fear by men and early treatment-seeking by women as observed in other health conditions [34-37]. In the wake of nationwide lockdown in India, the impact on the individual's economic and employment status might have made the men prioritize searching for livelihood over approaching hospitals for illness at an earlier and/or milder stage. Differential immune response, genetics, hormones, and habits have also been hypothesized as the reason for better survival among females [33,38,39]. Further evaluation of the clinical and biological aspects of sex on the differential effect towards COVID-19 might help us formulating gender targeted potential therapeutics [40]. Our observation of higher out-of-hospital deaths among females indicates inequity in mortally critical women accessing the healthcare services, as observed in the past health emergencies across the world [41].

A significantly higher proportion of the deceased aged ≥65 years had comorbidities. Such a high proportion of comorbidities was also observed among the elderly COVID-19 fatalities in Romania [14]. Cardiovascular diseases, hypertension and diabetes have been associated with increased severity and mortality in COVID-19.[30,42,43] We have found diabetes mellitus as the most prevalent comorbidity in the Indian COVID-19 fatalities, in contrast to hypertension reported in other studies [13,14,25,26]. Every second COVID-19 fatality in the two states of India had diabetes, with or without other comorbidities. Moreover, diabetes and hypertension burden among studied COVID-19 deaths were higher than the reported general population estimates, nationally and globally [44].

There was a higher proportion of SARI among the patients which was seen in Brazil, too [45-47]. This high figure was more so among the deceased without any comorbidity. It could be due to the a) low attention or late presentation of patients without any comorbidity as the country adopted a high-risk approach for COVID-19 surveillance, i.e., among patients with comorbidity and b) Failure of systematic assessment for comorbidities among critically ill patients. The best practices for SARI including infection prevention and control and optimized supportive care for severely ill patients are essential. Sentinel surveillance for COVID-19 among SARI patients may be used to control the pandemic [48]. Along with this we need to initiate comprehensive workshops for training healthcare professionals for management of SARI in COVID-19 suspected cases to fill in the knowledge gap regarding its identification and management at primary healthcare level [49].

Our analysis is not without limitations. Firstly, it is a record-based study. However, analysis of existing programmatic or record-based data is essential for a better understanding of the disease and prioritize future action during any new pandemic or otherwise. Secondly, the non-uniform reporting between states and data from only two states. As health is a state subject in India, there will be certain differences in the planning, implementation and reporting of healthcare services between states. The non-availability of data from other states could be due to various health system factors. Thirdly, we observed a high proportion of missing data, including some key variables like survival time. It could be due to differential reporting between states and the type of health facilities. However, we did impute all missing data and used the imputed data for adjusted analysis. Fourthly, absence of disease course, control status of comorbidities and treatment data, which may be available with the respective states and can be used in the future analysis if access is provided. Non-validation of the cause of death and the possibility of underreporting COVID-19 deaths are the other limitations of our study. Though the symptomatic 'tested negative' or died while results 'awaited' or 'inconclusive' are to be declared as 'clinically-epidemiologically diagnosed', 'suspected', and 'probable' COVID-19 deaths [50], most of the Indian states including the ones in our analysis, report only the confirmed COVID-19 cases [23]. Thus, underreporting COVID-19 deaths either due to not testing or attributing it towards the comorbidities could have been recorded [23].

Publicly available data can be a valuable tool for providing supplementary information regarding the COVID-19 epidemiology. The characteristics associated with early hospital death and survival duration among the COVID-19 fatalities may be deliberated as markers for prognosis and compared with survivors. Further prospective studies on duration and control status of comorbidities and clinical progression of COVID-19 among various subgroups is the need of the hour. Strengthening the existing surveillance system and establishing a behaviour change communication system to reduce treatment-seeking time is urgently needed. A uniform COVID-19 death reporting and scrutinizing system and periodic review may be established across India.

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