BMJ Open

Clinicodemographic profile and predictors of poor outcome in hospitalised COVID-19 patients: a single-centre, retrospective cohort study from India

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To cite: Tiwari L, Gupta P, N Y, *et al*. Clinicodemographic profile and predictors of poor outcome in hospitalised COVID-19 patients: a single-centre, retrospective cohort study from India. *BMJ Open* 2022;**12**:e056464. doi:10.1136/bmjopen-2021-056464

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-056464).

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Received 16 August 2021
Accepted 03 May 2022

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ABSTRACT

Objectives Primary objective was to study the clinicodemographic profile of hospitalised COVID-19 patients at a tertiary-care centre in India. Secondary objective was to identify predictors of poor outcome.

Setting Single centre tertiary-care level.

Design Retrospective cohort study.

Participants Consecutively hospitalised adults patients with COVID-19.

Primary and secondary outcome measures Primary outcome variable was in-hospital mortality. Covariables were known comorbidities, clinical features, vital signs at the time of admission and on days 3–5 of admission, and initial laboratory investigations.

Results Intergroup differences were tested using χ^2 or Fischer's exact tests, Student's t-test or Mann-Whitney U test. Predictors of mortality were evaluated using multivariate logistic regression model. Out of 4102 SARS-CoV-2 positive patients admitted during 1-year period, 3268 (79.66%) survived to discharge and 834 (20.33%) died in the hospital. Mortality rates increased with age. Death was more common among males (OR 1.51, 95% CI 1.25 to 1.81). Out of 261 cases analysed in detail, 55.1% were in mild, 32.5% in moderate and 12.2% in severe triage category. Most common clinical presentations in the subgroup were fever (73.2%), cough/coryza (65.5%) and breathlessness (54%). Hypertension (45.2%), diabetes mellitus (41.8%) and chronic kidney disease (CKD; 6.1%) were common comorbidities. Disease severity on admission (adjusted OR 12.53, 95% CI 4.92 to 31.91, p<0.01), coagulation defect (33.21, 3.85–302.1, p<0.01), CKD (5.67, 1.08–29.64, p=0.04), high urea (11.05, 3.9–31.02, p<0.01), high prothrombin time (3.91, 1.59–9.65, p<0.01) and elevated ferritin (1.02, 1.00–1.03, p=0.02) were associated with poor outcome on multivariate regression. A strong predictor of mortality was disease progression on days 3–5 of admission (adjusted OR 13.66 95% CI 3.47 to 53.68).

Conclusion COVID-19 related mortality in hospitalised adult patients at our center was similar to the developed countries. Progression in disease severity on days 3–5 of admission or days 6–13 of illness onset acts as 'turning point' for timely referral or treatment intensification for optimum use of resources.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To the best of our knowledge, this study represents the first large study of hospitalised adult COVID-19 patients from Eastern India during the peak of coronavirus pandemic.
⇒ Unlike previous studies from the region, the mortality rate of 20.3% was in agreement with studies from developed countries.
⇒ Severity progression on days 3–5 of admission, corresponding with days 6–13 from symptom onset, emerged as a strong predictor of poor outcome and as a 'turning point' to upscale clinical management of patients.
⇒ The sample size calculated for the research question is small to address some additional complex questions on predictors of poor outcome and effect of treatment variables.
⇒ Due to potential for type I error, findings should be interpreted as exploratory and descriptive.

INTRODUCTION

More than 30 million cases and 400 000 COVID-19 deaths reported from India[1 2] are comparable to the total healthy Indian lives lost from all respiratory infections combined in 2017.[3] The spectrum of COVID-19 illness varies across age groups from asymptomatic infection to life-threatening multiorgan dysfunction.[4–6] Most of the studies and meta-analyses suggest that older age, male sex and presence of comorbidities are strongly associated with severity of illness and risk of death in COVID-19 patients.[7 8] In the studies from USA and Italy, median age of hospitalised patients is reported >60 years and mortality rates of 21%–39%.[9–12] Community

and hospital-based studies from developing countries have reported mortality rates up to 50% among probable and suspected COVID-19 patients.[13 14] Studies from India during the early phase of the pandemic reported disease in the younger population of 33–40 years, with mortality rates as low as 1.4%–2.6%.[15–17] Reported difference in the pattern, severity and outcome of disease could be due to complex interplay of population demographics, prevalence of comorbidities and intensive care infrastructure with geopolitical and socioeconomic factors resulting in under-reporting of the disease.[18 19] There was lack of clinical data from India especially during the peak of first wave of COVID-19 pandemic. We planned this study to describe the clinicodemographic profile, identify predictors of poor outcome and understand effect of treatment variables on outcome in hospitalised COVID-19 patients from the region that ranks at the bottom of the list of Indian states on the human development index.[20] It will help identifying the cost-effective and time-critical interventions to adapt in the triaging and clinical management for optimum utilisation of limited resources.

METHODOLOGY

Study design

A single-centre, retrospective cohort study was designed to study a subset of adult population admitted at a tertiary-care dedicated COVID-19 hospital during the peak of first wave of COVID-19 pandemic in Bihar. To have homogeneity in the data, we started case recruitment 1 month after implementation of institutional COVID-19 management protocol V.3.0.[21] As per the prevalent hospital mortality rate of 20% during COVID-19, and assuming a population size of 5000, the sample size of 261 was derived for estimating the expected mortality rate with 5% absolute precision and 95% confidence. Case sheets of 261 COVID-19 positive patients aged 18 years or above, consecutively admitted from 10 August 2020 were included. Admissions in the day-care, patients transferred out within 24 hours or case sheets that were non-traceable, damaged or had insufficient information to identify study variables were excluded (figure 1). Detailed clinical and laboratory parameters for these 261 patients were retrospectively collected. Patients discharged alive were telephonically followed up on the registered mobile number for survival outcomes 28 days after hospital discharge. Selection bias was tested by comparing the sampled 261 patients for key demographic variables (age, sex and proportion of elderly patients with an age of 60 years or more with a high mortality rate) available on the hospital information system for all (4102) patients.

Patient and public involvement

Research question, study variables and outcome measures were based on observed patients' apprehensions regarding their prognosis. However, they were not involved in the design of the study.

Objectives

Primary objective was to study the clinicodemographic profile of hospitalised COVID-19 patients at a tertiary-care centre in India. Secondary objectives were to identify predictors of poor outcome.

Study variables

Demographic information, comorbidities, clinical features, vital signs at the time of admission and on days 3–5 of admission and laboratory investigations typically done within 24 hours of admission were collected (tables 1 and 2). Organ dysfunction at the time of

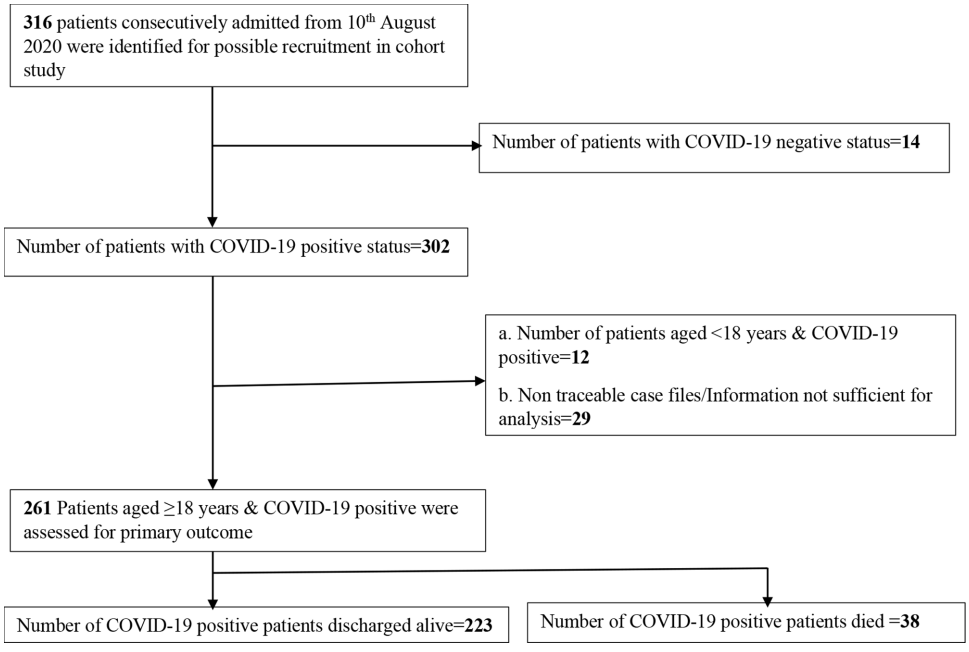

Figure 1 Flow diagram describing patient recruitment, and timeline for statistical analysis.

Table 1 Demographic and clinical profile of survivors and non-survivors

Sl no.	Variables	Normal value	Total N, M, IQR	Alive N, M, IQR	Death N, M, IQR	P value
A.	Demographic details					
1.	Age (years)		261, 54, 40–65	223, 52, 40–62	38, 63, 52–70	<0.01
3.	Hospital stay (days)		261, 11, 8–14	223, 11, 8–14	38, 8.5, 3–17	0.03
B.	Vitals at the time of admission					
1.	Heart rate (/min)	60–100	261, 89, 80–104	223, 88, 80–102	38, 101, 88–120	<0.01
2.	RR (/min)	12–20	261, 22, 20–24	223, 22, 20–24	38, 24, 22–28	<0.01
3.	SpO_2 (%)	95–100	261, 97, 94–98	223, 97, 95–98	38, 94, 88–97	<0.01
4.	Temperature (F)	96.8–98.6	260, 98, 97.8–98.5	222, 98, 97.7–98.4	38, 98.1, 98–98.7	0.2
5.	SBP (mm Hg)	90–120	258, 128, 120–142	221, 127, 119–140	37, 135, 124.5–149	<0.01
6.	DBP (mm Hg)	60–80	258, 80, 72–86	221, 80, 72–86.5	37, 80, 72–85	0.93
C.	Laboratory investigations on admission					
1.	Hb (g/dL)	13–17	243, 12, 10.4–13.2	210, 12, 10.6–13.2	33, 11, 9.1–12.4	0.03
2.	TLC (x1000 per mm^3)	4–10	243, 7.7, 5.4–11.8	210, 7.5, 5.4–10.9	33, 10.7, 5.9–18.1	0.02
3.	N:L ratio	<3.5	243, 6.1, 3.3–11.7	210, 5.5, 3.1–9.9	33, 19.2, 8.7–28.8	<0.01
4.	Platelet count (x1000 per mm^3)	150–450	241, 179, 118.5–249.5	209, 180, 119–246	32, 160, 101–255	0.4
5.	S urea (mg/dL)	13–43	243, 33.6, 23.1–52.2	208, 31.3, 22.4–45.2	35, 71.1, 49–133.1	<0.01
6.	S creatinine (mg/dL)	0.7–1.3	243, 0.82, 0.69–1.02	208, 0.8, 0.67–0.94	35, 1.2, 0.9–2.46	<0.01
7.	S calcium (mg/dL)	8.6–10	237, 8.77, 8.33–9.13	202, 8.83, 8.43–9.17	35, 8.42, 7.77–8.69	<0.01
8.	S albumin (g/dL)	3.4–4.8	243, 3.55, 3.24–3.89	207, 3.6, 3.33–3.94	36, 3.26, 2.91–3.52	<0.01
9.	Corr s calcium (mg/dL)	8.6–10	236, 9.1, 8.8–9.4	201,9.1, 8.8–9.4	35, 9.1, 8.7–9.3	0.35
10.	Total bilirubin (mg/dL)	0.3–1.2	243, 0.95, 0.73–1.2	207, 0.94, 0.72–1.2	36, 1.0, 0.8–1.3	0.35
11.	AST:ALT		240, 0.9, 0.67–1.41	205, 0.9, 0.67–1.31	35, 1.31, 0.6–1.97	0.04
12.	PT (s)	<14	212, 13, 12.2–13.9	182, 12.9, 12.2–13.7	30, 14.3, 13.3–16.5	<0.01
13.	INR	1.0	212, 0.98, 0.9–1.1	182, 0.96, 0.9–1.04	30, 1.07, 1–1.24	<0.01
14.	aPTT (s)	30–40	153, 29, 24.63–34.59	131, 28.9, 24.1–34.2	22, 33.2, 28–42	0.02
D	Inflammatory markers on admission					
1	CRP (mg/L)	0–5	176, 44, 6–105	152, 41, 4–89	24, 136, 29–229	0.01
2.	D-dimer (mcg/mL)	<0.2	194, 0.74, 0.48–1.8	168, 0.67, 0.46–1.37	26, 2.79, 0.8–3.97	<0.01
3.	S ferritin (ng/mL)	22–322	211, 443, 239–755	179, 420, 202–696	32, 748, 551–863	<0.01
4.	S LDH (U/L)	230–460	161, 769, 595–1052	135, 718, 566–1009	26, 1252, 777–1706	<0.01
5.	S procalcitonin (ng/mL)	<0.2	170, 0.5, 0.29–0.82	142, 0.43, 0.23–0.69	28, 1.005, 0.66–2.23	<0.01
6.	IL-6	<6.4	57, 24.8, 5.82–76.29	41, 16.2, 4.5–40.09	16, 57.8, 20.8–150.6	0.02
E.	Vital signs on days 3–5 of admission					
1.	HR (bpm)	60–100	252, 86, 78–98	218, 84, 78–94	34, 98, 86–114	<0.01
2.	RR (per min)	12–20	253, 22, 20–23	219, 22, 20–22	34, 25, 22–28	<0.01
3.	SpO_2 (%)	95–100	253, 97, 95–98	219, 97, 95–98	34, 90, 88–96	<0.01
4.	Temperature (F)	96.8–98.6	253, 98.2, 97.8–98.6	219, 98.2, 97.8–98.6	34, 98.2, 97.4–99	0.6
5.	SBP (mm Hg)	90–120	252, 125, 114–138	218, 122.5, 115–136	34, 134, 100–146	0.43
6.	DBP (mm Hg)	60–80	252, 79, 70–83.5	218, 80, 72–84	34, 74, 60–80	<0.01

Continued

Table 1 Continued

Sl no.	Variables	Normal value	Total N, M, IQR	Alive N, M, IQR	Death N, M, IQR	P value
F.	Severity class on admission					
	Mild		144 (55.2%)	142 (63.6%)	2 (5.3%)	<0.01
	Moderate		85 (32.6%)	68 (30.5%)	17 (44.7%)	
	Severe		32 (12.3%)	13 (5.8%)	19 (50%)	
G.	Severity class on days 3–5 of admission		n=253	n=223	n=30	
	Mild		141 (54%)	141 (63.2%)	0 (0%)	<0.01
	Moderate		83 (31.8%)	72 (32.3%)	11 (36.7%)	
	Severe		29 (11.1%)	10 (4.5%)	19 (63.3%)	
	Death		8 (3.1%)	–	–	

aPTT, activated partial thromboplastin time; AST:ALT, aspartate aminotransferase:alanine aminotransferase ratio; Corr s calcium, corrected serum calcium; CRP, C-reactive protein; DBP, diastolic blood pressure; Hb, haemoglobin; HR, heart rate; IL-6, interleukin-6; INR, international normalised ratio; LDH, lactate dehydrogenase; M, median; N, number of observations; N:L ratio, neutrophil:lymphocyte ratio; PT, prothrombin time; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, oxygen saturation; TLC, total leucocyte count.

admission was assessed based on the definitions adapted from surviving sepsis campaign and sequential organ failure assessment score.[22 23] Need of oxygen support was labelled as respiratory dysfunction, mean arterial pressure below 70 mm Hg as cardiovascular dysfunction and serum creatinine>1.3 mg/dL or need of dialysis due to acute or chronic kidney disease (CKD) as renal dysfunction. Liver, haematological and coagulation dysfunction were defined as total serum bilirubin>4 mg/dL, platelet count<1 00 000/µL and international normalised ratio (INR)>1.5 or activated partial thromboplastin time (aPPT)>60 s, respectively. Treatment variables such as the use of investigational therapies like remdesivir, convalescent plasma and tocilizumab were also recorded. The disease was classified as mild, moderate and severe adapted from the guidelines of the Ministry of Health and Family Welfare India. Patients with SpO_2≥94% on room air were labelled as mild, those with SpO_2 90%–93% on room air or requiring nasal prongs, face mask or non-rebreathing mask to maintain SpO_2≥94% were moderate. The patients with SpO_2<90% on room air or requiring non-invasive ventilation or invasive mechanical ventilation were labelled as severe. As the inflammatory phase starts in the second week of symptom onset, coinciding with 3–5 days of hospital admission, clinical and laboratory status at this time was likely to suggest the turning point for disease progression. Thus, severity status on admission and on days 3–5 of hospitalisation was recorded. Worsening from mild to severe class or death in any class was defined as progression in severity. Progression would alert the treating team to identify the turning point and upscale or intensify the clinical management. The primary outcome variable was in-hospital mortality. Information bias due to the retrospective nature of the study was minimised by excluding the health records with missing critical information on clinical or laboratory details. The statistician was blind to the exposure condition at the time of analysis.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics for Windows, V.22.0. Qualitative variables were described as proportions and quantitative variables were described as median with IQR. Two groups based on outcome at the time of hospital discharge (survival and death) were compared. Intergroup differences were tested using χ^2 or Fischer's exact tests (categorical variables), Student's t-test (normally distributed continuous variables) or Mann-Whitney U test (continuous variables with skewed distribution). Binary logistic regression was done to identify predictors of mortality, and multivariable regression analysis was done to control potential confounders. Adjusted ORs with 95% CI were estimated. Missing observations and loss to follow-up were excluded from analysis. Kaplan-Meier cumulative survival curve was plotted for the groups showing progression and no progression in severity by days 3–5 of admission.

RESULTS

As per the medical records department data, 4102 SARS-CoV-2 positive patients were admitted at AIIMS Patna during 1 year period between 1 April 2020 and 31 March 2021, excluding day-care admissions. Out of this, 3268 (79.66%) survived to discharge and 834 (20.33%) died in the hospital. The peak number of admissions was noted in the month of July 2020 (965 (23.5%)) (figure 2). The median age of admitted COVID-19 patients was 55 years. The median age of non-survivors was significantly higher than those of survivors (63 (54–70) vs 52 (39–62), p-value<0.01). The maximum number of admitted patients (1024; 25%) were in the 51–60 year age group,

Table 2 Demographic and clinical profile of survivors and non-survivors (categorical variables)

Sl no.	Variables	Total (n=261)	Alive (n=223)	Death (n=38)	P value	OR for death (CI=95%)		
						Value	Lower limit	Upper limit
A.	Gender (male)	177 (67.8%)	150 (67.2%)	27 (71.1%)	0.39	1.19	0.54	2.82
B.	Clinical features							
1.	Fever	191 (73.2%)	159 (71.3%)	32 (84.2%)	0.1	2.15	0.86	5.38
2.	URTI	171 (65.5%)	144 (64.6%)	27 (71.1%)	0.44	1.35	0.63	2.86
3.	Shortness of breath	141 (54%)	112 (50.2%)	29 (76.3%)	<0.01	3.19	1.45	7.06
4.	GI symptoms	32 (12.3%)	30 (13.5%)	2 (5.3%)	0.16	0.36	0.08	1.56
5.	Myalgia	31 (11.9%)	25 (11.2%)	6 (15.8%)	0.42	1.49	0.57	3.90
6.	Asymptomatic	23 (8.8%)	23 (10.3%)	0 (0%)	0.04	0.9	0.86	0.94
7.	Chest pain	17 (6.5%)	15 (6.7%)	2 (5.3%)	0.74	0.77	0.17	3.51
8.	Headache	6 (2.3%)	6 (2.7%)	0 (0%)	0.31	0.97	0.95	0.99
9.	Palpitation	3 (1.1%)	3 (1.3%)	0 (0%)	0.47	0.99	0.97	1.00
10.	Anosmia	3 (1.1%)	3 (1.3%)	0 (0%)	0.47	0.99	0.97	1.00
11.	Ageusia	2 (0.8%)	2 (0.9%)	0 (0%)	0.56	0.99	0.98	1.00
C.	Comorbidities							
1.	Hypertension	118 (45.2%)	95 (42.6%)	23 (60.5%)	0.04	2.07	1.02	4.17
2.	Diabetes	109 (41.8%)	88 (39.5%)	21 (55.3%)	0.68	1.89	0.95	3.79
3.	CAD/CVA	16 (6.1)	14 (6.3%)	2 (5.3%)	0.81	0.83	0.18	3.80
4.	Chronic kidney disease	16 (6.1%)	9 (4%)	7 (18.4%)	<0.01	5.37	1.87	15.45
5.	Hypothyroidism	14 (5.4%)	12 (5.4%)	2 (5.3%)	0.98	0.98	0.21	4.55
6.	COPD/asthma	9 (3.4%%)	8 (3.6%)	1 (2.6%)	0.77	0.73	0.09	5.98
D.	Disease progression by days 3–5	37 (14.2%)	18 (8.1%)	19 (50%)	<0.01	11.39	5.13	25.29
E.	Disease improvement by days 3–5 (117*)	21 (17.9%)	19 of 81 (23.5%)	2 of 36 (5.6%)	0.02	0.2	0.04	0.87
F	Investigational therapies							
1.	Remdesivir	104 (39.8%)	76 (34%)	28 (73%)	<0.01	5.4	2.4	11.7
2.	Convalescent plasma	27 (10.3%)	14 (6.2%)	13 (34.2%)	<0.01	7.76	3.28	18.37
3.	Tocilizumab	30 (11.5%)	17 (7.6%)	13 (34.2%)	<0.01	6.3	2.74	14.49

n=117 after exclusion of mild cases.
CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular attack; GI symptoms, gastrointestinal tract symptoms (vomiting/loose stool); URTI, upper respiratory tract infections (cough, cold and sore throat).

but the highest number of deaths (263) were seen in the age group 61–70 years (24.3%). The mortality rate consistently increased with increasing age groups in adults (table 3 and figure 3). The female to male ratio was 0.36:1. Deaths were significantly more in males as compared with females (661 (22.01%) vs 173 (15.7%), p<0.01; OR 1.51 (95% CI 1.25 to 1.81)). The median length of hospital stay was 10 (8–14) days and significantly longer in survivors as compared with non-survivors (10 (8–14) vs 8 (4–13), p-value<0.01).

As per the study protocol, 261 cases aged 18 years or above consecutively admitted from 10 August 2020 were analysed in detail. A comparison of the key demographic variables of sampled patients (261) with the total admitted patients (4102) suggested that the sample was representative. Mean age in the two groups had no statistical difference (52.18 (SD 15.6) vs 52.51, (SD 16.5) years p=0.75) on the independent t-test. The proportions of the male sex did not differ (X^2=3.576, p=0.06) between the two groups. The proportion of the elderly population in overall 4102 and sample population of 261 patients was 37.86% and 35.63%, respectively. A X^2 goodness of fit test did not show a statistically significant difference between the two groups (X^2=0.552, p=0.46). Out of 261 cases, 223 (85.4%) patients survived to discharge and 38 (14.6%) died in the hospital. The median duration from the appearance of the first symptom to hospital admission was 6.0 (IQR 3.25–8) days. At the time of admission, 144 (55.1%) patients were in mild, 85 (32.5%) in moderate and 32 (12.2%) in severe triage category with mortality

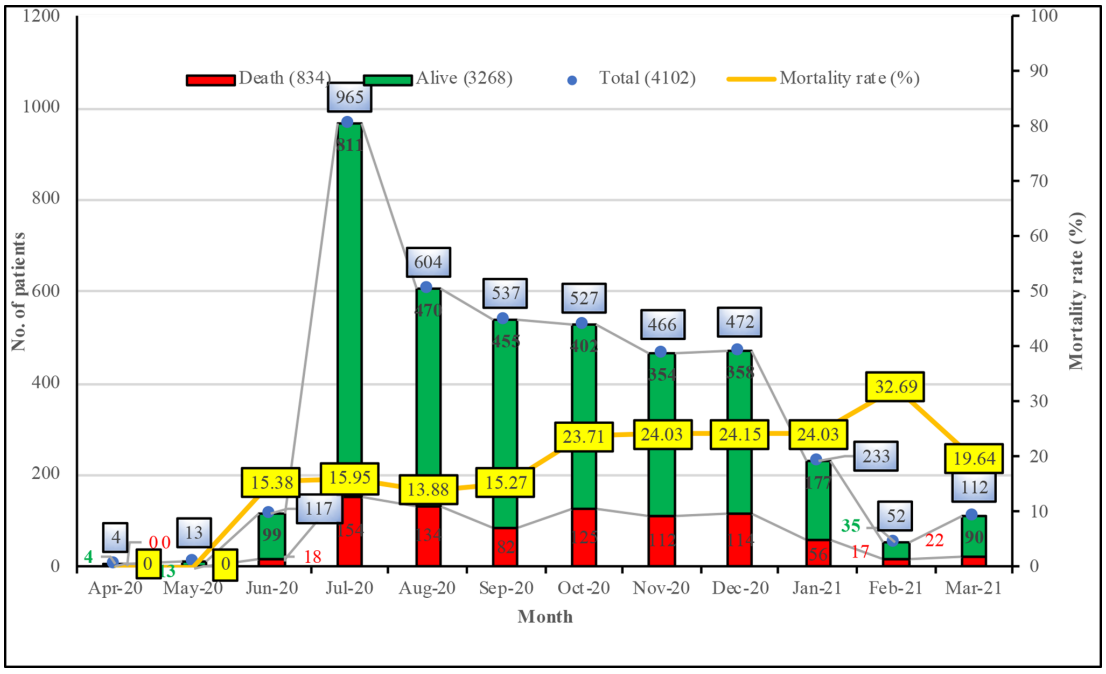

Figure 2 Trend of monthly hospital admissions and deaths during first wave of COVID-19.

rate of 1.4%, 20.0% and 59.4%, respectively. The most common clinical presentation was fever (73.2%) followed by upper respiratory tract infection (65.5%), shortness of breath (54%) and gastrointestinal tract symptoms (12.3%). Other less common symptoms were myalgia (11.9%), chest pain (6.5%) and headache (2.3%); 8.8% patients had asymptomatic presentation. Shortness of breath at the time of admission was significantly associated with mortality. Heart rate, respiratory rate and systolic blood pressure (SBP) were high and oxygen saturation (SpO_2) was low at the time of admission in non-survivors as compared with survivors.

Comorbidities

Hypertension was the most common comorbidity (118, 45.2%) followed by diabetes mellitus (109, 41.8%), CKD (16, 6.1%) and coronary artery or cerebrovascular disease (16, 6.1%). On binary logistic regression analysis, hypertension and CKD were significantly associated with mortality. However, on multivariable regression analysis, CKD was the only comorbidity significantly associated with death.

Laboratory parameters within first 24 hours

As depicted in table 1, total leucocyte count (TLC), neutrophils and neutrophil to lymphocyte ratio were high in non-survivors. Inflammatory markers such as C-reactive protein (CRP), serum ferritin, serum lactate dehydrogenase (LDH) and serum procalcitonin were significantly raised in non-survivors. Serum urea, creatinine and potassium were deranged in both the groups but more in non-survivors. Non-survivors had low serum albumin, raised aspartate aminotransferase, alanine aminotransferase, prothrombin time (PT), INR, aPTT and D-dimer.

Organ dysfunction

Of note, 118 (45.2%) patients had no organ-dysfunction, 104 (39.8%) had single organ-dysfunction and 39 (14.9%)

Table 3 Age-specific mortality rate, absolute risk and relative risk of death in hospitalised COVID-19 patients

Sl no.	Age group (year)	Total n=4102	Alive n=3268	Death n=834	Mortality rate (%) (20.33)	Age-specific absolute risk of mortality	Age-specific relative risk of mortality
1	0–18	91	86	5	5.4	−15.17	0.26
2	19–30	413	394	19	4.6	−17.49	0.21
3	31–40	479	432	47	9.8	−11.91	0.45
4	41–50	714	614	100	14.0	−7.66	0.65
5	51–60	1024	821	203	19.8	−0.67	0.97
6	61–70	878	615	263	29.9	12.24	1.69
7	71–80	404	248	156	38.6	20.28	2.10
8	>80	99	58	41	41.4	21.60	2.11

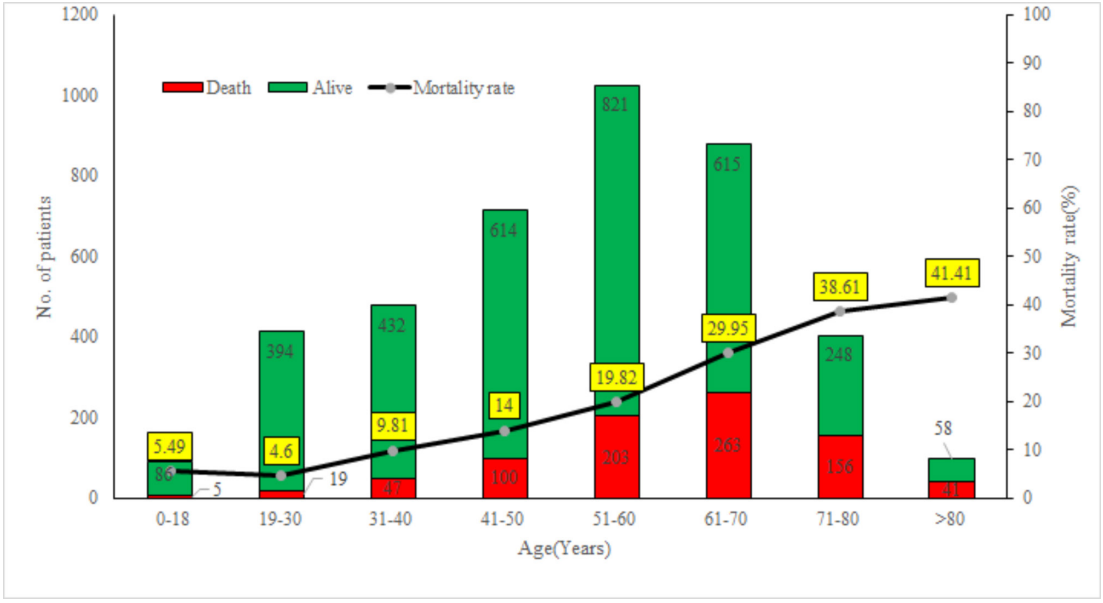

Figure 3 Age-specific hospital admissions and mortality rate in COVID-19 patients.

had two or more organ-dysfunction detected within first 24 hours of admission. Most common organ affected was respiratory system in 109 (41.8%) patients. Other organ systems affected were haematological in 35 (13.4%), renal system in 34 (13%), coagulation defects in 8 (3.1%) and cardiovascular dysfunction in 4 (1.5%) patients. Presence of multiorgan dysfunction was seen in 39 (14.9%) cases and was significantly associated with death. Coagulation defect was independently associated with poor outcome on multivariable regression analysis (table 4).

Investigational therapies

104 (39.8%) patients received remdesivir; 27 (10.3%) plasma therapy and 30 (11.5%) tocilizumab. There was significantly higher odds of death among those who received remdesivir (OR 5.4; 95% CI 2.4 to 11.7), convalescent plasma (OR 7.76; 95% CI 3.28 to 18.37) and tocilizumab (OR 6.3; 95% CI 2.74 to 14.49).

Disease progression on 3–5 days of admission

High respiratory rate, low SpO_2, high heart rate and low DBP on days 3–5 of admission were significantly associated with non-survival. Odds of death were significantly higher in those who showed progression in severity from admission to days 3–5 of hospital stay. Total 37 (14.2%) patients had progressed on disease severity with significantly higher proportion in those who died in hospital (19 (50%) vs 18 (8.1%); OR 11.39 (5.1–25.3)). To record improvement in severity, mild cases were excluded as it is not possible to record improvement in this class of least severity. Out of remaining 117 cases, 21 showed improvement with significantly lower odds of death as compared

Table 4 Risk factors for hospital mortality on multivariable regression analysis

Sl. no.	Variables	Adjusted OR (95% CI)	P value	R^2
A.	Clinical variables			
1.	Disease severity on admission	12.53 (4.92 to 31.91)	0.0001	0.49
2.	Progression in severity by 3–5 days	13.66 (3.47 to 53.68)	0.0001	
3.	Systolic blood pressure (>120 mm Hg)	6.92 (1.64 to 29.22)	0.008	
4.	Coagulation dysfunction (yes)	33.21 (3.85 to 302.1)	0.002	
5.	CKD (yes)	5.67 (1.08 to 29.64)	0.040	
B.	Laboratory variables			
1.	Serum urea (>43 mg/dL)	11.05 (3.94 to 31.02)	0.0001	0.26
2.	Prothrombin time (>14 s)	3.91 (1.59 to 9.65)	0.003	
C.	Inflammatory markers			
1.	Serum ferritin (>322 ng/mL)	1.02 (1.00 to 1.03)	0.019	0.16
2.	LDH (>460 U/L)	1.01 (1.00 to 1.02)	0.030	

CKD, chronic kidney disease; LDH, lactate dehydrogenase.

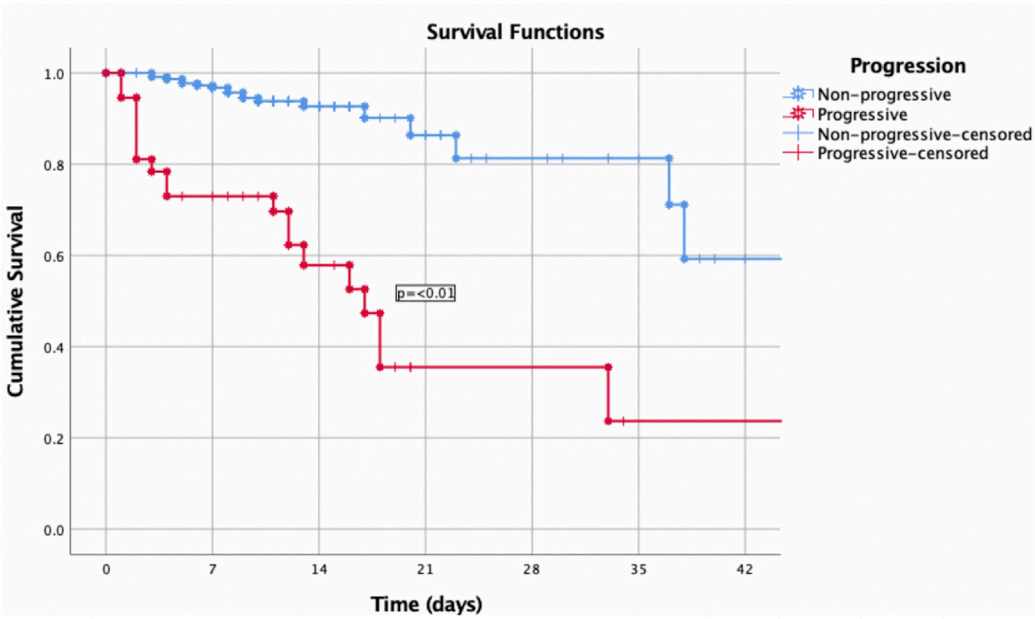

Figure 4 Kaplan-Meier cumulative survival curve for progressive and non-progressive severity of illness by 3–5 days of hospital admission.

with those who remained in the same class of severity or deteriorated (2 (5.6%) vs 19 (23.5%); OR 0.20 (95% CI 0.04 to 0.87)). As depicted in figure 4, we plotted Kaplan-Meier cumulative survival curve for COVID-19 patients showing severity progression and non-progression by 3–5 days of hospital admission. Cumulative survival for the group showing progression in severity by days 3–5 was 48.6% as compared with 91.9% in the group showing no progression in severity. Difference was statistically significant on log rank test with p value<0.01. Estimated median survival time for the progressive group was 17 (SE 2.22) days.

Predictors of mortality

Variables found significantly associated with mortality on binary logistic regression analysis in each category were further analysed on multivariable regression after dropping clinically associated variables to avoid collinearity. Among clinical variables disease severity on admission, progression in severity by 3–5 days of hospitalisation, SBP above 120 mm Hg on admission, coagulation defect and CKD on admission were significantly associated with mortality. High urea (>43 mg/dL), PT (>14 s), ferritin (>322 ng/mL) and LDH (>460 U/L) were the laboratory variables significantly associated with poor outcome (table 4).

Follow-up

Out of the 261 patients, 223 patients who were discharged were telephonically followed-up to assess for 28-day survival outcome; 28 did not respond and there were five additional deaths within 28 days from discharge.

DISCUSSION

This study represents hospitalised adult COVID-19 patients from India during the peak of first wave of COVID-19 pandemic witnessed in August 2020 in Bihar state and in September 2020 all over the India.[2] The overall mortality rate of 20.3% (n=4102) among total hospitalised COVID-19 population is in contrast to previous smaller studies from tertiary-care centres in India with reported mortality rates of 1.4%–2.6%.[15 16] Other developing countries have reported hospital mortality rates of up to 50% in COVID-19 patients.[13] Overall mortality rate comparable to USA and Italy (20%–21%) highlights the importance of development of a predefined COVID-19 management protocol during such disasters.[9 11] Our findings of additional 2.5% mortality rate within 28 days of hospital-discharge highlights the need of robust follow-up of COVID-19 patients discharged from hospital.

The median age of hospitalised adult COVID-19 patients in our study is 55 years as compared with 62–63 years reported from the developed nations and 40–42 years from other developing countries, reflective of the population pyramids of these countries.[9 10 12–15 24 25] As previously reported, the mortality rate progressively increased with age.[9 11] Skewed female:male ratio and higher odds of death in males is in confirmation to other studies, irrespective of geographical and socioeconomic boundaries.[9 11 15 26] This biological difference in outcome has been attributed to behavioural differences, prevalence of comorbidities and protective effect of female reproductive hormones. As the pandemic spread and healthcare resources were strained, hospital admission policies became stringent and triage-based. In the detailed analysis of 261 patients,

8.8% were asymptomatic as compared with 44.4%–57.8% in previous studies conducted while the pandemic was still unfolding in India;[15 16] 12.3% patients had severe COVID-19 at admission needing intensive care, similar to other bacterial or viral community-acquired pneumonia.[27] In the wake of a pandemic, the absolute number is high enough to overwhelm any healthcare facility. Compared with 60% mortality in the severe category, survival of 80% in moderate and 98.6% in mild category reiterates the role of timely referrals particularly in resource-limited settings.

Fever, upper respiratory tract symptoms and fatigue were the common clinical presentations of COVID-19 in our cohort similar to previous studies.[8] As previously reported, shortness of breath and requirement for oxygen supplementation at presentation were early warning signs of poor outcome.[9 10] SBP was higher and DBP was normal at the time of admission but SBP became normal, while DBP fell below normal range among non-survivors on days 3–5. This is consistent with the trends of systemic inflammatory response syndrome progressing to circulatory organ dysfunction. In our study, 61% of the patients had at least one comorbidity in contrast to 94% in developed countries[9 10] and 16%–30% reported in previous studies from India.[15 16] Hypertension and diabetes mellitus were the two most common presenting comorbidities consistent with previous reports.[11 28] The odds of death were five times more in patients with CKD in our study confirming other reports.[7 13] Contrary to previous reports, we did not find difference in COVID-19 related mortality in patients with coronary artery disease, cerebrovascular accidents, COPD and asthma.[7 29] Earlier believed to be a single-organ (respiratory) dysfunction, COVID-19 triggers systemic inflammation leading to multiorgan dysfunction which is important to be recognised early for triaging and timely referral.[8] At least one organ dysfunction at presentation was seen in 40% of our patients and it was not limited to only respiratory system. Rather, 20% of them had haematological derangement. Presence of two or more organ dysfunctions at presentation was significantly associated with mortality. In accordance to works of previous authors, non-survivors in our study had higher inflammatory markers, serum urea, creatinine, PT, INR, aPTT and D-dimer compared with survivors.[7 10] Of these, serum ferritin (>322 ng/mL), LDH (>450 IU/L), elevated serum urea (>43 mg/dL) and PT (>14 s) were significantly associated with mortality on multivariable regression analysis. Renal dysfunction may be explained by direct cytopathic effect of SARS-CoV-2 virus due to expression of angiotensin converting enzyme-2 receptor on renal tubular cells.[30] SARS-CoV-2 can infect vascular endothelial, a seabed for both haemostasis and thrombosis. Early reports from China were suggestive of minimal elevations in PT and significant elevations in D-dimer among critically-ill COVID-19 patients.[31 32] An elevated D-dimer was not found to be a significant predictor of poor outcome in our study. This may be due to early initiation of low molecular weight heparin at admission in moderate–severe cases as a standard protocol at our centre. Higher odds of death in patients receiving remdesivir, tocilizumab or convalescent plasma therapy support WHO recommendation against remdesivir and plasma therapy.[33 34] The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial supported the use of tocilizumab in severe COVID-19 patients.[35] Our findings suggesting increased mortality with the use of tocilizumab could be due to small sample size, more severity at presentation or delayed administration of drug due to lack of widespread availability.

This study attempts to provide statistical evidence for clinical indicators of poor outcome. The odds of death were 13 times higher among patients who progressed in illness severity on days 3–5 of admission. On the Kaplan-Meier survival curve, the cumulative survival frequency was almost double for patients who did not show severity progression. Cummings *et al* found 3 days as the median time to clinical deterioration following admission.[10] Few studies have evaluated the prognostic role of laboratory parameters on days 3–5 of admission.[36 37] To the best of our knowledge, no other study has statistically demonstrated the role of progression of disease severity by 3–5 days in predicting outcome and identifying the 'turning point' to intensify clinical management of COVID-19 patients. Having 3.25–8 days as the range of duration of symptom onset to the hospitalisation, this turning point may be visible between 6 and 13 days from the onset of symptoms. This study serves as a preliminary assessment of clinicodemographic profile of COVID-19 patients with some limitations. The sample size calculated for primary research question is small to address some additional complex questions on predictors of poor outcome and effect of treatment variables. Due to the retrospective nature of the study, not all laboratory tests were available for all patients and missing values were excluded from analysis. Hence, due to potential for type I error, findings should be interpreted as exploratory and descriptive. This was a tertiary-care level hospital-based study in Eastern India, thus, potentially limiting generalisability to other clinical and geographical settings.

In conclusion, this study was conducted at a time when the incidence and mortality from COVID-19 were at their highest in India. We found that the mortality rate was more with increasing age, male sex, CKD, shortness of breath, severe disease and presence of two or more organ dysfunctions at presentation. Elevated ferritin, LDH, serum urea and PT were statistically significant predictors of poor outcome. But a stronger predictor of mortality was progression in disease severity on days 3–5 of admission, highlighting the need for identifying early warning signs and 'turning point of disease progression' for timely referral or treatment intensification.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval Ethical clearance was granted by institutional ethics committee, under approval number AIIMS/Pat/IEC/2020/599. Written informed consent was waived being a retrospective data collection from case records.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. No additional data available.

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