Original Article

Demographic comparison of the first, second and third waves of COVID-19 in a tertiary care hospital at Jaipur, India

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) infection in India demonstrated three peaks in India, with differences in presentation and outcome in all the three waves. The aim of the paper was to assess differences in the epidemiological, clinical features and outcomes of patients with COVID-19 presenting at a tertiary care hospital in the three waves at Jaipur, India. **Methods:** This was a retrospective study conducted at a tertiary care hospital at Jaipur, India. Demographic, clinical features and outcomes were compared of confirmed COVID-19 cases admitted during the first wave (16-7-2020 to 31-1-2021), second wave (16-3-2021 to 6-5-2021) and third wave (1-1-22 to 20-2-22) of the outbreak. **Results:** There were 1006 cases, 639 cases and 125 cases admitted during the three waves, respectively. The cases presenting in the second wave were significantly younger, with significantly higher prevalence of symptoms such as fever, cough, sore throat, nausea, vomiting, headache, muscle ache, loss of appetite and fatigue ($P < 0.05$). A significantly higher proportion of patients received Remdesivir in the second wave ($P < 0.001$). However, in the second wave, the use of low molecular weight heparin, plasma therapy, non-invasive and invasive ventilator were higher ($P < 0.001$). Co-morbid conditions were significantly higher in the admitted patients during the third wave ($P < 0.05$). Radiological scores were similar in second and third wave, significantly higher than the first wave. Lymphopenia and rise of inflammatory markers including C-reactive protein and interleukin-6 were more evident in the second wave ($P < 0.001$). The mean mortality, hospital stay and air-leak complications were also significantly higher in the second wave ($P < 0.001$). **Conclusions:** The second wave was more vicious in terms of symptoms, inflammatory markers, radiology, complications, requirement of ventilation and mortality. Mutation in the virus, lack of immunity and vaccination at the time point of second wave could have been the possible causes. The ferocity of the second wave has important implications for the government to formulate task forces for effective management of such pandemics.

KEY WORDS: COVID-19, invasive ventilator, mortality, non-invasive ventilator, Remdesivir

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) began in late 2019 in Wuhan, China, and spread across the world causing a pandemic and a global shutdown around the world. The infection was novel; thus, there was uncertainty regarding its duration, complications and future of the disease.[1] In India, significant number of confirmed cases and deaths related to the disease have been reported. The first case of the disease was reported on 30 January 2020 in Kerala and subsequently spread to other parts of the country.[2] India has one of the highest crude numbers of patients, improved patients and deaths due to COVID-19 in the world.[3]

In Jaipur, Rajasthan, the first COVID-19 patient was reported on 2 March 2020. This city experienced three waves of COVID pandemic disease. In an earlier report describing the clinical pattern of patients during first wave, most patients presented with anorexia, dry cough, dyspnoea, fever and fatigue.[4] Those who had associated co-morbid diseases such as diabetes mellitus, hypertension, coronary heart diseases and chronic kidney disorders had poor outcomes.[4]

The disease presentation varied during the first and second wave in terms of clinical pattern, severity and outcome of the disease.[5] In India, number of COVID cases increased slowly during later part of 2020, subsided in early part of 2021 and during late part of March 2021 the second wave of COVID-19 spread with more virulence and infectivity. As of January 2022, the third wave stuck which was unique in clinical presentation and natural history. The third wave also occurred post the massive vaccination campaign in the country. The current study was planned to describe the epidemiologic features of the disease and compare the features in the three waves of COVID-19 outbreak. The comparison of different epidemiological dimensions of these waves will be useful in health policymaking for the prevention and control of disease in India and beyond.

MATERIAL AND METHODS

The current study was a retrospective observational study conducted at a tertiary level private 250-bedded hospital at Jaipur, India. The study has been approved by the Ethics Committee of Asthma Bhawan, with reference ID IECAB/2022/187 dated 7th April 2022. The demographic, clinical and laboratory characteristics of the patients who were confirmed cases of COVID-19, during the period from 1-1-22 to 20-2-22 (considered as the third wave) and 16-3-2021 to 6-5-2021 (considered as the second wave of the epidemic in this region) were compared with data of confirmed COVID-19 patients admitted in the same hospital from 16-7-2020 to 31-1-2021 (during the first wave of the epidemic). Collected data included the patient's age and gender, clinical symptoms, underlying disorders, need for intensive care unit (ICU) admission and tracheal intubation, and the outcome of the disease at the time of hospital discharge. The patients whose nasopharyngeal or oropharyngeal specimens were positive for severe acute respiratory syndrome (SARS-CoV-2) RNA using real-time polymerase chain reaction (RT-PCR) were considered as confirmed cases. The computed tomography (CT) severity was assessed by using the CT severity score.[6] In addition, for patients admitted during the third wave, data regarding their vaccination status were also procured from the electronic data collection software. The treatment was adopted as per the Ministry of Health and Family Welfare (MoHFW) guidelines.[7,8] Dose of Remdesivir used was 200 mg on day 1 followed by 100 mg/day for days 2–5. Steroids were used in the form of Dexamethasone 6 mg/day for 7–10 days, depending on efficacy and side effects. They were tapered sooner in case of side effects. Antibiotics were used according to source of infection – in case of community-acquired ceftriaxone or amoxicillin plus clavulanic acid was used. For hospital-acquired infection, antibiotic was decided by culture and sensitivity reports. COVID-19 immunoglobulin G (Ig G) antibody levels were assessed in the three waves to gauge the level the immunity the patients developed after infection. The source for data collection was the hospital-based electronic medical records of the COVID-19 patients. Data analysis was performed using SPSS-20 software package. Chi-square and logistic regression tests were used for data analysis. A P value less than 0.05 was considered as significant. Stepwise multivariate logistic regression was applied to calculate the odds ratio for non-invasive ventilation and death after adjusting for various factors.

RESULTS

There were 1006, 639 and 125 confirmed cases with COVID-19 who were admitted during the first, second and third wave, respectively, at RHL, Jaipur, a tertiary care 250-bedded hospital.

Among the 1006 confirmed cases with COVID-19, 692 (68.8%) individuals were males and 314 (31.2%) were females in the first wave. However, this proportion for male gender was 431 (66.6%) in the second wave ($P = 0.290$). Mean age of patients in the first, second and third waves were 58.21 ± 13.63 years, 56.38 ± 15.89 years and 63.11 ± 18.03 years, respectively ($P < 0.001$).

Clinical manifestations that were common among patients with confirmed COVID-19 during the three waves of the disease have been summarized in Table 1. This table shows that fever ($P < 0.001$), cough ($P < 0.001$), sore throat ($P < 0.000$), headache ($P < 0.000$), fatigue (OR = 4.19; CI = 3.87–5.18; $P = 0.000$), loss of appetite ($P < 0.001$) and fatigue ($P < 0.000$) were more incidental in the second wave of the disease compared to the first and third one. Runny nose and chest pain were predominant in the third wave compared to the first and second wave ($P < 0.001$, respectively). Underlying disorders co-morbid to COVID-19 among

Table 1: Demographic and clinical characteristics of patients admitted with COVID-19 during the first and second outbreak

Characteristics	First wave *n*=1006	Second wave *n*=639	Third wave *n*=125	*P*
Age				
Mean±SD	58.21±13.63	56.38±15.89	63.11±18.03	0.000
Median (IQR)	60 (50-67.25)	57 (43-69)	66 (54-77)	
Age group				
<40	104 (10.3)	117 (18.1)	18 (14.3)	0.000
40-59	397 (39.5)	247 (38.2)	24 (19.2)	
60+	505 (50.2)	283 (43.7)	83 (66.4)	
Male	692 (68.8)	431 (66.6)	78 (62.4)	0.290
Symptoms				
Fever	816 (81.1)	547 (84.5)	63 (50.4)	0.000
Cough	788 (78.3)	544 (84.1)	79 (63.2)	0.000
Breathlessness	666 (66.2)	413 (63.8)	79 (63.2)	0.550
Sore throat	30 (3.0)	74 (11.4)	10 (8.0)	0.000
Running nose	8 (0.8)	19 (2.9)	7 (5.6)	0.000
Nausea	28 (2.8)	47 (7.3)	9 (7.2)	0.000
Vomiting	34 (3.4)	40 (6.2)	9 (7.2)	0.012
Diarrhoea	21 (2.1)	12 (1.9)	4 (3.2)	0.628
Headache	60 (6.0)	91 (14.1)	6 (4.8)	0.000
Muscle ache	67 (6.7)	61 (9.4)	8 (6.4)	0.102
Joint pain	24 (2.4)	19 (2.9)	5 (4.0)	0.517
Loss of appetite	116 (11.5)	172 (26.6)	21 (16.8)	0.000
Chest pain	32 (3.2)	57 (8.8)	13 (10.4)	0.000
Fatigue	256 (25.4)	377 (58.3)	30 (24.0)	0.00
Physical examination				
Blood pressure (systolic)	130.1±14.66	129.96±16.21	128.50±20.17	0.565
Blood pressure (diastolic)	78.34±10.24	79.12±11.24	75.13±11.66	0.001
Pulse rate	87.17±13.08	88.52±15.29	91.85±17.96	0.001
Respiratory rate	26.15±13.10	23.44±13.85	22.58±3.67	0.836
Pharmacotherapy				
Remdesivir*	897 (61.1)	485 (75.0)	87 (69.6)	0.000
Antibiotic**	957 (95.1)	629 (97.2)	116 (92.8)	0.030
Steroid***	958 (95.2)	626 (96.8)	80 (64.0)	0.000
Inj. LMWH	929 (92.3)	617 (95.4)	52 (41.6)	0.000
Tocilizumab	961 (95.5)	633 (97.8)	117 (93.6)	0.015
Plasma therapy	17 (1.7)	72 (11.1)	0 (0.0)	0.000
Oxygenation	570 (56.7)	425 (65.7)	75 (60.0)	0.001
Non-invasive ventilator	126 (12.5)	190 (29.4)	8 (6.4)	0.000
Invasive ventilator	3 (0.3)	66 (10.2)	4 (3.2)	0.000
Hospital stay (days)				
Mean±SD	6.65±4.08)	8.52±6.60	5.97±4.84	0.000
Median (IQR)	6 (5-7)	7 (5-7)	5 (5-7)	0.000
<5 days	226 (22.5)	121 (18.7)	62 (49.6)	
5-7 days	544 (54.1)	275 (42.5)	33 (26.4)	
≥8 days	236 (23.5)	251 (38.8)	30 (24.0)	
Avg. day on ventilator	1.33±0.58	4.97±4.67	4.75±2.87	0.403
Avg. day on oxygen	3.71±2.54	5.70±5.19	4.08±3.14	0.000
Avg. day on non-invasive ventilation	3.78±3.54	4.76±3.87	4.63±6.28	0.080
Air-leak complications**** due to COVID-19	11 (1.1)	49 (7.7)	0 (0.0)	0.000

*200 mg day 1, 100 mg days 2-5. **For community-acquired infections Ceftriaxone/Amoxycillin + Clavulenic acid, for hospital-acquired infections according to sensitivity of bacteria grown on culture. The antibiotics were administered for 5-7 days depending on clinical response. ***Dexamethasone 6 mg/day for 7-10 days, depending on tolerability and response. In case of hyperglycaemia or infection, a lower dose was used in some patients. ****Pneumothorax/Hydropneumothorax/Pneumomediastinum. *P* value of less than 0.05 was significant. LMWH: Low molecular weight heparin

confirmed cases have been presented in Table 2. Heart disease ($P < 0.001$), chronic obstructive pulmonary disease ($P < 0.001$) and thyroid disorders ($P < 0.001$) were the most common co-morbidities in the admitted patients during the third wave. Laboratory parameters showed lymphopenia defined as lymphocyte count of < 1000/mcL ($P = 0.009$), and lower lymphocyte-to-neutrophil ratio ($P = 0.000$) in second wave as compared to first and third wave [Table 3]. During the second wave, the inflammatory markers and antibody titres were significantly higher, that is IL-6 ($P = 0.073$), serum ferritin ($P = 0.000$) and C-reactive protein (CRP; $P = 0.001$), then the first and third waves [Table 3]. d-Dimer ($P < 0.001$) and COVID antibody titre ($P < 0.05$) were significantly higher in the third wave compared to the previous two waves. However, severe respiratory conditions and need to non-invasive ($P < 0.001$) and invasive ventilation ($P < 0.001$) were significantly higher during the second wave of the disease [Table 1]. Mean duration of hospital stay was more in the second wave and

two-fifth stayed more than seven days in second wave as compared to first and third waves ($P = 0.000$) [Table 1]. Complications due to COVID-19 like pneumothorax, hydropneumothorax and pneumomediastinum were more common in the second wave (7.7%) compared to the other two waves ($P < 0.001$) [Table 1]. Ten patients (8%) with confirmed COVID-19 during the third wave, 112 patients (17.3%) during the second wave and 4 (0.4%) during the first wave expired [Table 4]. Crude mortality rate was higher and recovery rate was lower in the second wave of the disease ($P < 0.000$) [Table 4]. The correlation of vaccination status with the disease outcome in terms of oxygenation, non-invasive and invasive ventilation, and mortality was done in Table 5. The risk of non-invasive ventilation, mechanical ventilation and death in waves 1 and 2 compared to third wave is elaborated in Table 6; a stepwise unadjusted odd's ratio is described followed by adjustments for age, gender, co-morbidities, investigations, inflammatory markers, hospital stay, oxygen and treatment.

Table 2: Co-morbid disorders in hospitalized patients with confirmed COVID-19 during the two COVID-19 outbreaks

Co-morbidities	First wave *n*=1006	Second wave *n*=647	Third wave *n*=125	*P*
Systemic hypertension	422 (41.9)	245 (37.9)	64 (51.2)	0.015
Type 2 diabetes mellitus	356 (35.4)	194 (30.0)	46 (36.8)	0.055
Chronic obstructive pulmonary disease	49 (4.9)	14 (2.2)	23 (18.4)	0.000
Bronchial asthma	61 (6.1)	31 (4.8)	10 (8.0)	0.293
Heart disease	103 (10.2)	59 (9.1)	32 (25.6)	0.000
Thyroid disease	46 (4.6)	23 (3.6)	15 (12.0)	0.000

P value of less than 0.05 was significant

DISCUSSION

The current study demonstrates the ferocity of the second wave of COVID-19 pandemic at a single tertiary care centre in a metropolitan city of India. This research describes the three waves of COVID-19 pandemic; only hospitalized RT-PCR-confirmed COVID-19 patients were included; and the demographic characteristics, co-morbidities, laboratory inflammatory markers on admission and outcomes between the three waves were compared. As compared to the first and third waves, the cases during the second wave of the pandemic presented at a younger age group with symptoms of fever, cough, sore throat, headache, loss of appetite and fatigue ($P < 0.001$). The use of Remdesivir, low molecular weight heparin, steroids, plasma therapy, invasive and non-invasive ventilator were higher in the second wave compared to the other two waves ($P < 0.001$). Air-leak complications, hospital stay and mortality were also higher in the second wave ($P < 0.001$). There was no significant association of morbidity and mortality due to

Table 3: Laboratory parameters of the COVID-19 cases in the first and second wave

Investigator parameters	Normal values	First wave *n*=1006	Second wave *n*=647	Third wave *n*=125	*P*
Haematology parameter					
WBC (10^9 cells/L)	4.5-11×10^3 cells/mcL	7.21±4.10	7.06±7.98	8.35±5.42	0.085
Neutrophil count (10^9 cells/L)	2.6-0.5×10^3 cells/mcL	5.35±3.73	5.57±5.99	6.10±4.91	0.219
Lymphocyte count (10^9 cells/L)	0.77-4.5×10^3 cells/mcL	1.25±0.82	0.95±3.05	1.06±0.86	0.009
Monocyte count (10^9 cells/L)	0.14-1.3×10^3 cells/mcL	0.46±0.34	0.35±0.35	0.43±0.35	0.000
Eosinophil count (10^9 cells/L)	0-0.55×10^3 cells/mcL	0.08±0.16	0.04±0.10	0.08±0.11	0.000
L: N ratio	0.78-3.53	0.32±0.33	0.20±0.59	0.25±0.54	0.000
Hb	>12-14 g/dL	13.14±1.88	12.50±2.0	12.35±2.33	0.000
Biochemical parameters					
SGOT	<35 U/L	44.94±96.87	52.78±71.84	40.24±56.13	0.226
SGPT	<35 U/L	43.44±56.19	43.75±53.11	32.13±32.01	0.146
Serum creatinine	<1.2 mg/dL	1.05±0.48	1.11±0.79	1.24±0.0.85	0006
Serum bilirubin	<1.2 mg/dL	0.61±8.64	0.30±0.65	0.39±0.73	0.735
HbA1c	4.7-8.5%	7.38±1.94	7.32±2.14	7.60±2.01	0.786
Blood urea	8-20 mg/dL	36.78±25.08	40.27±29.88	43.70±36.86	0.015
HRCT values at time admission*	0	10.48±2.51	11.47±4.91	11.76±4.38	0.000
Inflammatory marker					
d-Dimer					
IL-6	<500 ng/mL	726.96±1024.82	1659.42±2168.25	2031.89±2668.35	0.000
Serum ferritin	<7 pg/mL	87.07±235.44	471.72±4510.83	155.90±621.63	0.073
LDH	<300 ng/mL	430.10±477.41	682.13±583.42	429.66±508.98	0.000
CRP	<160 U/L	51.56±61.14	90.48±323.82	75.63±82.01	0.001
COVID antibody titre	<10 mg/L	10.60±16.52	14.28±45.34	29.44±30.57	0.030
CURB 65 criteria					
0-1 Score		645 (64.1)	379 (58.6)	91 (72.8)	0.000
2 Score		334 (33.2)	191 (29.5)	30 (24.0)	
3-4 Score		27 (2.7)	77 (11.9)	4 (3.2)	

All the continuous variables are reported as median and 25-75th interquartile range. Numbers in parentheses are percentages for categorical variables and IQR for continuous variables. *P* values derived using χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables. *P* value of less than 0.05 was significant. BP: Blood pressure, HRCT: high resolution computed tomographic scan, WBC: white blood count; L:N ratio: lymphocyte:neutrophil ratio; Hb: haemoglobin; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; AG ratio: albumin/globulin ratio; IL-6: interleukin 6; HbA1c: haemoglobin A1c; LDH: lactate dehydrogenase; CRP: C-reactive protein. *Kunwei Li, Yijie Fang, *et al*. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). *Eur Radiol* 2020;30 (8):4407-4416

third wave of COVID-19 with the vaccination status of the patient.

The cause of higher mortality rate during the second wave could be multi-factorial. The air-leak complications were significantly more common in the second wave. The delta variant of the virus which was primarily responsible for the second wave had predisposition to involve mucus membranes and, thus, cause pneumothorax and similar complications.[9] Another possible reason for higher mortality rate could be the higher disease burden and hospitalization of only severe cases, thereby facing a higher mortality amongst those with severe disease. Factors associated with higher mortality include age, gender, co-morbidities, laboratory work, hospital stay, oxygen and treatment. The outcomes were worse in second wave compared to third wave, and in third wave compared to the first wave [Table 6].

The patients admitted during the second wave were younger and the ones admitted in the third wave had significantly more co-morbid conditions. The patient population being admitted were older with more co-morbids in the first and third wave. Mean age was lower in the second wave as compared to the other waves. A systematic review and meta-analysis reported a median age of 46.2 years among the patients with a confirmed COVID-19 diagnosis.[10] Our patient population was much older with mean age of 58.21 years, 56.38 years and 63.11 years in the three waves, respectively. Although the exact cause for the difference of the patients' age between the three waves is unknown, the probable virulence of the delta variant predominant in the second wave may be a possible explanation. Omicron variant during the third wave has been associated with milder disease which could attribute the milder disease in the third wave. Furthermore, COVID vaccination campaign that was conducted prior to third wave provided immunity against serious disease, contributing to milder disease.

In our study, amongst the cases, men predominated in all three waves. It may be due to lifestyle behaviours such as smoking, health-related self-care, active socialization or other factors that can potentially impact gender predisposition of the virus.[11,12] Several studies reported that disease severity and mortality is worse in men.[13-16] In our study, the proportion of men among the patients with severe or critical illness was similar in the three waves; however, there were more men among the deceased patients in the second wave than in the first and third waves. A similar finding was noted in a comparative study from Spain wherein gender was associated with mortality in the second wave but not in the first wave.[5]

Gastrointestinal manifestations were more common in the second and third waves. Literature review shows that GI features can be present in more than a fourth of patients with COVID-19.[17] The incidental GI symptoms akin to other viral illnesses in these patients have been reported as loss of appetite, nausea and/or vomiting.[17-20] It is important to be aware of gastrointestinal symptoms in both adult and paediatric populations, for early diagnosis and treatment.

Inflammatory markers such as d-dimer, CRP, IL-6 and serum ferritin were amongst the most important biomarkers showing the severity of COVID-19. They are independent predictors of severe illness and mortality.[1,21,22] In our study, we found that levels of inflammatory markers such as CRP, IL-6 and ferritin were significantly higher in the second wave compared with the first and third wave. This demonstrates that patients with severe/critical illness who were hospitalized in the second wave had more severe disease compared with the other two waves. The antibody levels though the highest in the third wave were not significantly different. These data are consistent with the latest guidelines, which suggest that antibody levels does not assess immunity or protection to infection.[23] The CURB-65 index was higher in the second wave compared to the other two waves [Table 3], this proved that the disease was more severe in the second wave. According to the COVID-19 guide published by the MoHFW, non-severe patients were hospitalized for at least 3–7 days to see if the disease has worsened, and discharge criteria were stricter in the first wave than in the second wave. In the second wave, our national guidelines for the management of COVID pneumonia had changed, and Remdesivir was administered to hospitalized patients who worsened despite outpatient management.[24] In other words, mild-to-moderate cases were managed in out-patient during the second wave. This could explain why inflammatory levels were higher in patients in the second wave than in the first wave.

Table 4: Outcome in first and second wave in terms of mortality, recovery and referrals

Outcomes	First wave *n*=1006	Second wave *n*=647	Third wave *n*=125	*P*
Mortality	4 (0.4)	112 (17.3)	10 (8.0)	0.000
Recovery	981 (97.5)	523 (80.8)	101 (80.8)	0.000
Referred/LAMA/ Discharge on request	21 (2.1)	12 (1.9)	14 (11.2)	0.000

Table 5: Vaccination* and outcomes of third wave

Characteristics	No vaccination *n*=19	One-dose COVID *n*=12	Two-dose COVID *n*=89	Two doses and one booster *n*=5	*P*
Invasive ventilation	0 (0.0)	0 (0.0)	4 (0.0)	0 (0.0)	0.643
Oxygenation	9 (47.4)	6 (50.0)	25 (28.1)	0 (0.0)	0.078
Non-invasive ventilation	1 (5.3)	2 (16.7)	5 (5.6)	0 (0.0)	0.460
Death	1 (5.3)	1 (8.3)	8 (9.0)	0 (0.0)	0.862
Recovery	14 (73.7)	9 (75.0)	73 (82.0)	5 (100.0)	0.541

*Either COVID shield or Covaxin vaccine

Table 6: Stepwise multivariate logistic regression analyses and odd's ratio (95% CIs) for adverse outcomes in first COVID wave and second COVID wave compared with third COVID wave

COVID status in third wave	UOR (95%CI)	Age- and sex -adjusted	Plus co-morbidities	Plus clinical factors, routine investigations	Plus Inflammatory markers	Plus hospital stay	Plus oxygenation	Plus treatment[¥]
Death								
First COVID wave	0.05 (0.01-0.15)***	0.07 (0.02-0.23)***	0.07 (0.02-0.29)***	0.09 (0.01-0.52)**	0.02 (0.00-0.75)*	0.02 (0.00-1.00)	0.01 (0.0-0.88)*	0.01 (0.0-0.85)*
Second COVID wave	2.41 (1.22-4.74)*	3.20 (1.59-6.47)**	3.72 (1.84-7.52)***	3.35 (1.22-9.27)*	4.46 (0.90-21.98)	4.53 (0.89-22.98)	4.49 (0.89-22.78)	3.06 (0.50-18.62)
Bi-Pap								
First COVID wave	2.09 (0.99-4.39)	2.51 (1.18-5.34)*	2.83 (1.29-6.16)**	4.76 (1.74-13.02)**	19.16 (2.95-124.64)**	7.39 (1.12-48.65)*	6.51 (0.99-42.64)	6.01 (0.80-45.20)
Second COVID wave	6.08 (2.91-12.69)***	6.33 (3.01-13.29)***	6.80 (3.22-14.39)***	8.27 (3.04-22.44)***	16.92 (3.19-89.73)**	13.95 (2.19-88.59)**	14.43 (2.16-96.49)**	9.69 (1.26-74.36)*
Ventilator								
First COVID wave	0.09 (0.02-0.41)**	0.13 (0.03-0.65)*	0.11 (0.02-0.72)*	0.16 (0.02-0.13)	0.08 (0.01-3.16)	0.01 (0.00-2.19)	0.01 (0.00-2.79)	0.01 (0.00-5.58)
Second COVID wave	3.44 (1.23-9.61)*	0.16 (0.34-0.67)*	0.17 (0.04-0.75)*	0.17 (0.01-0.18)**	0.11 (0.01-3.28)	0.10 (0.01-3.09)	0.10 (0.01-3.08)	0.07 (0.01-2.61)

*Treatment included steroid + antibiotic + Remdesivir + LMW heparine. *<0.05; **<0.001; ***<0.000

Since number of cases were more during the second wave, only severe cases were admitted. Thereby higher inflammatory markers, complications, use of non-invasive and invasive ventilation, higher doses of corticosteroids, usage of enoxaparin and plasma therapy administration were administered. The mean time from hospitalization to ICU admission was longer in the second wave, which again indicates the severity of the disease, the disease burden and insufficient resources including drugs such as Remdesivir and Tocilizumab during the second wave.

Viral mutation to the more devastating delta strain which caused rapid infection of young and naive populations was the possible explanation to the second-wave phenomenon. The mutation in the virus had resulted in some of the most dangerous variants detected in India (UK strain: 20I/501Y.V1 or B.1.1.7, South African 20I/501Y.V2 or B.1.351, Brazilian strain P. 1 and double mutant Indian variant B.1.617).[25,26] The double mutant variant is highly infectious and contributed to the exponential increase of cases in the second wave. Subsequently in November 2021, another heavily mutated variant was defined as concerning was the B1.1.1.529, also called as the Omicron.[27] This was first identified in Botswana and South Africa. This strain was highly infective and escaped the immunity provided by the previous COVID-19 infection or vaccination.

Recent studies have suggested that, in addition to direct viral damage, uncontrolled inflammation contributes to disease severity in COVID-19.[21,22] Consistent with this hypothesis, high levels of inflammatory markers, including CRP, ferritin, low neutrophil-to-lymphocyte ratio and increased levels of inflammatory cytokines and chemokines, have been observed in patients with severe diseases.[28-30] Pathogenic inflammation, also referred to as cytokine storm, shares similarities with what was previously seen in patients infected with other severe coronaviruses, including SARS-CoV and Middle East respiratory syndrome coronavirus, and bears similarities to cytokine release syndrome observed in patients with cancer treated with chimeric antigen receptor-modified T cells.[31] Interestingly, though the IL-6 levels were above the baseline in all three waves, there was no significant difference. IL-6 inhibitors such as Tocilizumab have also not shown to be effective in cytokine storm induced by COVID.[32] Thereby, the correlation of IL-6 with disease severity is uncertain, a finding also noted in our study.

Our study had several limitations. First, it was a single-centre and retrospective study. Second, we did not collect data on secondary infections. Early initiation and more frequent use of corticosteroid therapy could cause more secondary infections including bacterial and fungal, leading to increased mortality in the second wave. Third, data on causes of death, such as venous thromboembolism, which affects the course of the disease were not collected. Finally, previous studies from India have reported varying mortality rates in the first wave. This variation was possibly driven by differences in study settings and patient

population characteristics. However, currently there are no studies from Western India which have compared the disease characteristics including mortality rate between the three waves. This and the lack of detailed information provided by national authorities were the reasons we could not compare our results with previous findings from Jaipur.

The study has provided valuable insights into the viciousness of the second wave of the COVID-19 pandemic in a tertiary care centre in India. The cases during the second wave of COVID-19 had more symptoms, higher inflammatory markers, requirement for non-invasive ventilator, invasive ventilator, higher mortality rate and more air-leak complications. The implication of these findings is huge as the health policy makers need to be prepared to deal with these pandemics in terms of resources.

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Conflicts of interest

There are no conflicts of interest.

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