BMJ Open Retrospective study of comparison of clinical severity and outcome of hospitalised COVID-19 patients during the first and second waves of the pandemic in India

Abhilash Paul Prabhakar Kundavaram,1 Saravanan Selvan,1 Vivek Raja,1 Ponnivalavan Mathiyalagan,3 Rohini Kanagarajan,1 Narmadha P Reddy,1 Natarajan Rajendiran,1 Darpanaryan Hazra,1 Karthik Gunasekaran,1 2 Mahesh Moorthy,3 Audrin Lenin,2 Divya Mathew,2 Ramya Iyyadurai,2 George M Varghese,4 Christopher DJ,5 Melvin Joy,6 John Victor Peter2

ABSTRACT

Objectives To compare the clinical severity and outcome of hospitalised patients during the two waves of the COVID-19 pandemic in India.

Setting A tertiary care referral hospital in South India.

Participants Symptomatic SARS-CoV-2 reverse transcriptase PCR positive patients presenting to the emergency department during the two waves were recruited. The first wave spanned between April and December 2020 and the second wave between April and May 2021.

Primary and secondary outcome measures The primary outcome of interest was mortality. Secondary outcomes included illness severity at presentation, need for oxygen therapy, non-invasive ventilation (NIV) and hospital or intensive care unit admission.

Results The mean (SD) age of the 4971 hospitalised patients in the first wave was similar to the 2293 patients in the second wave (52.5±15.4 vs 52.1±15.1 years, p=0.37). When compared with the first wave, during the second wave, a higher proportion of patients presented with critical illness (11% vs 1.1%, p<0.001) and needed supplemental oxygen therapy (n=2092: 42.1% vs n=1459: 63.6%, p<0.001), NIV (n=643: 12.9% vs n=709: 30.9% p<0.001) or inotropes/vasoactive drugs (n=108; 2.2% vs n=77: 3.4%; p=0.004). Mortality was higher during the second wave (19.2% vs 9.3%; p<0.001). On multivariable regression analysis, age >60 years (risk ratio, RR 2.80; 95% CI 1.75 to 4.40), D-dimer >1000 ng/mL (RR 1.34; 95% CI 1.15 to 1.55), treatment with supplemental oxygen (RR 14.6; 95% CI 8.98 to 23.6) and presentation during the second wave (RR 1.40; 95% CI 1.21 to 1.62) were independently associated with mortality.

Conclusion The second wave of the COVID-19 pandemic in India appeared to be associated with more severe presentation and higher mortality when compared with the first wave. Increasing age, elevated D-dimer levels and treatment with supplemental oxygen were independent predictors of mortality.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large cohort of patients during the first and second waves of the pandemic from India.
⇒ Study comparing the two waves fills the gap in scientific literature from low-income and middle-income countries.
⇒ This was a single-centre retrospective study and hence limited by information that was recorded during hospital admission.
⇒ The cohort of patients who successfully completed home isolation was not included in the study.
⇒ The outcome of 507 patients (6.9%) who were discharged against medical advice was unknown and hence not included in the outcome analysis.

INTRODUCTION

In December 2019, the emergence of SARS-CoV-2 in Wuhan, China resulted in a global pandemic of an unprecedented scale with India being one of the most affected countries. This forced the government to implement regional and national lockdown measures and mandate wearing of face masks and social distancing and personal protection. Despite these measures, COVID-19 spread at an alarming pace. Several countries had to deal with two to three waves of COVID-19 at different times.1–3 In India, the first case of COVID-19 was reported on 27 January 2020, in the state of Kerala.4 When community transmission became prevalent by the middle of June 2020, most states of India had large surges in the number of cases. The epidemiological trends in India showed two waves in the first 2 years of the pandemic. The first wave in India was between March
and December 2020 with a peak incidence in August and September and was largely driven by the alpha and beta variants. The delta variant predominant second wave was much larger and steeper and spanned the months of April, May and June 2021. There has been speculation that the two waves differ in terms of age, severity of presentation, need for supplemental oxygen therapy and mortality. This study was undertaken to compare the demographic profile, illness severity and outcome of reverse transcriptase PCR (RT-PCR) confirmed COVID-19 patients during the two waves of the pandemic in India.

PATIENTS AND METHODS
Study design and setting
This was a retrospective cohort study of COVID-19 patients who presented to the emergency department (ED) during the first and second waves of the pandemic. The study was conducted in a 2800-bed tertiary care referral hospital in South India.

Study period
Patients were included from two time periods: between April 2020 and December 2020, defined as the first wave and the months of April 2021 and May 2021, defined as the second wave when the delta variant was dominant.

Participants
All symptomatic patients who presented to the ED during the two waves and confirmed to have COVID-19 infection were included in the analysis. SARS CoV-2 RNA was detected in respiratory samples using RT-PCR assays (Altona RealStar SARS CoV-2) and/or Cartridge Based Nucleic Acid Amplification Test (CBNAAT) assay (Xpert Xpress SARS CoV-2).

Treatment and outcomes
Patient data were collected from the hospital electronic database and the ED triage database and included demographic data, comorbidities, need for supplemental oxygen therapy, non-invasive ventilation (NIV), inotropes/vasoactive drugs and need for hospital admission or intensive care unit (ICU) care. All staff working in the hospital as well as medical, nursing and allied health students were included in the category of healthcare workers.

Patients were managed according to the treatment guidelines developed by the institution based on recommendations of the national and state governments. During the first 3 months of the first wave, the state government mandated institutional isolation regardless of severity, while home isolation (HI) for mild cases was recommended during the latter half of the first wave and throughout the second wave. These government recommendations on HI were strictly implemented in our institution (online supplemental file). The guidelines were reviewed periodically, revised based on new evidence and made available on the institutional intranet. Mildly symptomatic patients were managed under a monitored HI programme that was run by the institution. Mandatory criteria for recruitment to the HI programme included heart rate <110/min, systolic blood pressure (SBP) >100 mm Hg, respiratory rate (RR) <24/min and pulse oximetry SpO2 >94%. Other important prerequisites for enrolment in the HI programme were the availability of caretakers to provide food and a separate room with attached bathroom for the patient.

The inpatient treatment protocol included antiviral agents, anticoagulation and corticosteroids. Remdesivir was part of the treatment protocol for inpatients during the second wave of the pandemic and this was based on the available evidence at that time of a possible benefit in moderately ill patients who received oxygen therapy. Prophylactic or therapeutic anticoagulation was prescribed based on illness severity. Corticosteroids were used as per published guidelines. The choice of the corticosteroid was left to the treating physician.

Patients were initiated on NIV if they had evidence of respiratory failure with increasing tachypnoea (RR >24/min) and/or signs of increased work of breathing with accessory muscle use and were haemodynamically stable, conscious and cooperative. Patients who failed trial of NIV were intubated unless there was a directive for non-escalation of care either from the patient or the next of kin. Patients who were intubated and ventilated received analgesedation and other organ support as indicated. Nosocomial infections and ventilator related adverse events were diagnosed and managed as per guidelines.

Every effort was made to provide ICU beds for those who were invasively ventilated. At the peak of the pandemic, particularly during the second wave, when there was a critical shortage of beds, NIV was provided in level 2 wards which were upgraded to semi-ICU facilities with the provision of additional manpower and monitoring equipment. Data on the number of patients who could not be admitted to the hospital due to lack of beds or other reasons were not available and hence excluded from the study.

The primary outcome of interest was mortality. Secondary outcomes included illness severity at presentation, need for supplemental oxygen therapy, NIV and hospital or ICU admission. The severity of illness at presentation was assessed using the National Institute of health guidelines as mild illness, moderate illness, severe illness or critical illness.

Statistical analysis
The primary analysis assessed the difference in clinical severity at presentation and outcomes of hospitalised COVID-19 patients during the first and the second waves of the pandemic. Descriptive statistics were used to summarise the data; results were reported as mean and SD or median and IQR for continuous variables, as appropriate. Categorical variables were summarised as counts and percentages. We compared the baseline characteristics between the two groups of patients (first wave...
vs second wave) using χ² tests for categorical variables, unless the expected number of subjects in any one category was less than five, in which case Fisher’s exact test was used. To find the mean difference across the groups, independent t-test was used. Similarly, Mann-Whitney U test was used to compare median difference.

We used multivariable Poisson regression with log-link in the generalised linear model to identify the predictors of mortality with COVID-19. Associations were reported as risk ratio (RR) with 95% CIs. Two-sided p<0.05 was considered statistically significant. The following variables were used in the multivariable analysis: age >60 years, male gender, d-Dimer >1000 ng/mL, presentation during the second wave and receiving oxygen supplementation. Statistical analyses were performed using Stata software, V.16.0 (StataCorp).

**Patient and public involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**RESULTS**

During the two waves of the pandemic, the ED received a total of 54,125 patients in the COVID-19 suspect zone of the ED, of which 9,426 (17.4%) patients tested positive for COVID-19. The remainder were either negative or not willing to be tested. In this study cohort, 5,213 RT-PCR positive patients were screened during in the first wave (April–December 2020) of whom 4,971 (95.4%) were admitted and 242 (4.6%) patients were managed in the HI programme. During the second wave (April–May 2021), 4,213 patients were screened, of whom 2,293 (54.4%) were hospitalised and 1,920 (45.6%) were managed by HI (figure 1). The decision on HI was partly determined by the ministry of health services policy, which for the early part of the first wave mandated hospitalisation for isolation, regardless of severity.

The baseline characteristics of hospitalised patients in both waves are shown in table 1. The mean (SD) age of hospitalised patients in both waves was similar (52.5±15.4 years vs 52.1±15.1 years, p=0.37). A greater male preponderance was noted in the first wave when compared with the second wave (67.5 vs 62.8%; p<0.001). Patients presenting during the second wave had longer duration of symptoms and higher prevalence of fever, cough and breathlessness. The SBP and the oxygen saturation were lower and RR higher during the second wave. The comorbidity profile was similar in both waves (table 1).

When the clinical severity at presentation was assessed using the NIH clinical spectrum, (table 2), it was observed that a higher proportion of patients presented with critical illness in the second wave (11% vs 1.1%; p<0.001) when compared with the first wave. A significantly higher proportion of patients were treated with supplemental oxygen therapy, NIV and inotropes/vaso-active drugs during the second wave of the pandemic (table 2). The mortality among hospitalised patients was significantly higher during the second wave (19.2% vs 9.3%; p<0.001).

On multivariable Poisson regression analysis (table 3), the following risk factors were independently associated with mortality: age >60 years (RR 2.80; 95% CI 2.12 to 3.70), D-dimer >1000 ng/mL (RR 1.34; 95% CI 1.15 to 1.55), treatment with supplemental oxygen (RR 14.6; 95% CI 8.98 to 23.6) and presentation during the second wave (RR 1.40; 95% CI 1.21 to 1.62).

**Figure 1** STROBE diagram showing the outcome among COVID-19 patients during the first and second waves of the pandemic in India of the 54,125 patients who presented to the COVID-19 suspect zone of the ED, 9,426 (17.4%) tested positive for COVID-19 19. In this study cohort, 5,213 patients were screened in the first wave (April–December 2020) of which 4,971 (95.4%) were admitted and 242 (4.6%) patients managed by HI. In the second wave (April–May 2021), 4,213 patients were screened of whom 2,293 (54.4%) were hospitalised and 1,920 (45.6%) were managed by HI. ED, emergency department; HI, home isolation; RT-PCR, reverse transcriptase PCR; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.
This large study of patients presenting to a tertiary care hospital in India during the two waves of the COVID-19 pandemic demonstrated significant differences in the demographic characteristics, clinical severity and hospital outcome of patients admitted with symptomatic COVID-19 infection. The key findings were increased severity of illness at presentation, a higher proportion treated with respiratory support and higher mortality during the second wave of the pandemic in India when compared with the first wave of the pandemic.

The mean age of hospitalised patients during the second wave was similar to that during the first wave of the pandemic. This was surprising since there was an

<table>
<thead>
<tr>
<th>Variable</th>
<th>First wave N=4971</th>
<th>Second wave N=2293</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH clinical spectrum of SARS CoV2 infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild illness</td>
<td>3125 (62.8)</td>
<td>959 (41.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>1101 (22.1)</td>
<td>605 (26.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe illness</td>
<td>691 (13.9)</td>
<td>477 (20.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Critical illness</td>
<td>54 (1.1)</td>
<td>252 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated with supplemental oxygen</td>
<td>2092 (42.1)</td>
<td>1459 (63.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>643 (12.9)</td>
<td>709 (30.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inotrope/vasoactive drugs support</td>
<td>108 (2.2)</td>
<td>77 (3.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Needed ICU admission</td>
<td>1910 (38.4)</td>
<td>902 (39.3)</td>
<td>0.236</td>
</tr>
<tr>
<td>Mortality</td>
<td>463 (9.3)</td>
<td>440 (19.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time interval from admission to death (median: IQR)</td>
<td>7 (3–15)</td>
<td>6 (3–12)</td>
<td>0.334</td>
</tr>
</tbody>
</table>

All values are expressed as number (n) and percentage unless indicated. ICU, intensive care unit; NIH, National Institute of Health.
assumption that younger patients were more affected during the second wave of the pandemic when compared with the first wave. However, our observations are consonant with a study of ICU patients in Maharashtra where the mean age was found to be similar (57.6±14.6 and 56.7±15.7 years). In contrast, an ICU-based study from Pakistan showed that patients admitted during the second wave were older (65±18.5 years) when compared with the first wave (56±19 years). A secondary analysis of more than 0.5 million RT-PCR tests conducted in a laboratory in North India in Uttar Pradesh reported an overall lower mean age, but again with an older mean age in the second wave (46.1±16.8 years) compared with the first (35.1±15.9 years). In South Africa, where the peaks of the first two waves preceded the waves in India by 2 months, a similar pattern of a higher age was noted among hospitalised patients during the second wave.

The second wave of India was widely perceived to be steeper and larger compared with the first wave and largely driven by the newly emerged delta variant at that time. In this study, the second wave was associated with a higher proportion of people with critical illness as determined by the NIH clinical spectrum of SARS CoV2 infection. Treatment with supplemental oxygen and NIV were also significantly higher in the second wave as was the mortality rate (19.2% vs 9.3%). The higher proportion of patients presenting with increased severity of presentation resulted in a demand-supply mismatch of oxygen during the second wave and the need to source oxygen concentrators.

A study from South Africa comparing their first wave (June 2020 to August 2020) and second wave (November 2020 to February 2021) showed an increased rate of hospitalisation, especially among the elderly and increased mortality rate during the second wave. This was attributed to the new beta lineage that was prevalent during their second wave. A comparative study of hospitalised patients in the first (27 February 2020 to 28 July 2020; n=174) and second (29 July 2020 to 31 December 2020; n=331) waves in Germany showed a higher proportion of patients treated as outpatients (20% vs 11%) in the second wave with similar mortality rates (16%) in both the waves. This can probably be explained by the fact that the highly transmissible variants of concern were detected in Germany only during the end of 2020 and hence did not impact the comparative study of the two waves. In Iran, the in-hospital mortality rate was lower in the second wave (8%) considered between 21 May 2020 and 21 September 2020, than in the first wave (23.4%) considered between 19 February, 2020 and 20 May 2020. Here too, in the mentioned time periods, the likely variants in circulation were the alpha and beta variants and not the delta variant as seen during the second wave period of our study. As seen with the above data, the periods of the first and second waves in other countries do not coincide with the first two waves in India and hence the differences in disease severity and outcome could purely be due to the different variants in circulation at that time.

Existing literature on the comparison of clinical presentation and outcomes during the first two waves in India with similar periods is scant. A large multicentric study on hospitalised patients across 41 centres in India, with similar time periods, recruited 12,059 patients in the first wave and 6903 patients in the second wave. In that study, the second wave had a significantly higher proportion of patients presenting with shortness of breath (48.6% vs 42.8%), the requirement of supplemental oxygen (50.3% vs 42.7%), mechanical ventilation (15.9% vs 11.1%) and mortality (13.3% vs 10.2%). An ICU-based study from Maharashtra that included 1921 patients in the first wave and 1577 patients in the second wave reported a significantly higher in-hospital mortality of 29.9% in the second wave compared with 18.2% during the first wave. The findings of the two Indian studies corroborate that the clinical presentation and outcome of COVID-19 patients was worse during the second wave in India.

### Table 3 Univariate and multivariate analysis of predictors of mortality with COVID-19

<table>
<thead>
<tr>
<th>Values</th>
<th>Non-survivor (N=903)</th>
<th>Survivor (N=5854)</th>
<th>Univariate analysis* (RR, 95% CI)</th>
<th>P value</th>
<th>Multivariate analysis (RR, 95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>546 (60.5)</td>
<td>1766 (30.2)</td>
<td>4.78 (3.79 to 6.04)</td>
<td>&lt;0.001</td>
<td>2.80 (2.12 to 3.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>637 (70.5)</td>
<td>3801 (64.9)</td>
<td>1.25 (1.08 to 1.44)</td>
<td>0.002</td>
<td>1.10 (0.94 to 1.28)</td>
<td>0.25</td>
</tr>
<tr>
<td>Non HCW</td>
<td>902 (99.9)</td>
<td>5565 (95.1)</td>
<td>40.5 (5.69 to 288)</td>
<td>&lt;0.001</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥2 Comorbidities</td>
<td>417 (46.2)</td>
<td>1752 (29.9)</td>
<td>1.81 (1.59 to 2.07)</td>
<td>&lt;0.001</td>
<td>1.05 (0.90 to 1.21)</td>
<td>0.54</td>
</tr>
<tr>
<td>D-Dimer &gt;1000 ng/mL†</td>
<td>407 (52.6)</td>
<td>1139 (22.8)</td>
<td>3.04 (2.64 to 3.50)</td>
<td>&lt;0.001</td>
<td>1.34 (1.15 to 1.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second wave</td>
<td>440 (48.7)</td>
<td>1650 (28.2)</td>
<td>2.12 (1.86 to 2.42)</td>
<td>&lt;0.001</td>
<td>1.40 (1.21 to 1.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Received supplemental oxygen</td>
<td>873 (96.7)</td>
<td>2374 (40.6)</td>
<td>31.5 (21.9 to 45.3)</td>
<td>&lt;0.001</td>
<td>14.6 (8.98 to 23.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

© Excluded 507 patients who left against medical advice as their outcome was not known.

*Poisson regression with log link.; HCW was not incorporated into the model due to the huge CI in the univariate estimate; values in parentheses indicate percentages unless indicated otherwise.

1979 missing values in D-Dimer

HCW, healthcare worker; n, number of patients; RR, risk ratio.
Multivariate logistic regression analysis identified age >60 years, presentation with D-dimer >1000 ng/mL, treatment with supplemental oxygen and presentation during the second wave to be significant predictors of mortality. In a large cohort of ICU patients, Zirpe et al. identified male gender, admission during the second wave, increasing high-resolution CT score and the need for mechanical ventilation as significant predictors of mortality.13

Countries experienced multiple waves of COVID-19 at different time periods. Published literature from developed countries like Spain, Italy, South Africa and Germany highlighted differences in the pattern and severity of the waves. Such comparative studies have been few from developing countries such as India, where factors such as delayed presentation and constraints such as resource limitation may influence illness severity at presentation and outcome. Systematic study and documentation of the clinical presentation, course in hospital, outcomes and factors predicting outcome during the different waves of a pandemic helps understand and plan not only for future waves of the COVID-19 pandemic, but also for other pandemics.

The following limitations merit mention. This was a single-centre retrospective study in a tertiary care referral hospital and hence limited by information that was recorded during hospital admission as well as referral bias. The comparison of factors between the two waves was significantly influenced by the differences in the HI policy in the two waves, the accelerated kinetics of wave 2 compared with wave 1, the pressure on hospital beds during the second wave which may have resulted in a selection bias of sicker patients being admitted to a tertiary care centre, as well as the use of corticosteroids during the second wave. The effects of societal and medical advice that accrued between the waves and the early effects of the vaccination programme, which started in India in January 2021, may also be significant. The outcome of 507 patients (6.9%) who were discharged against medical advice was unknown and hence not included in the outcome analysis. This could have potentially underestimated the mortality due to COVID-19. Despite these limitations, this large study from a developing country, adds to the body of evidence from developed countries that patients presented with more severe illness and had a higher mortality during the second wave of the pandemic when compared with the first wave.

CONCLUSIONS
The second wave of COVID-19 in India was associated with a higher proportion of patients presenting with critical illness, a higher proportion requiring respiratory supports and a higher mortality rate compared with the first wave of 2020. Higher age, elevated D-dimer levels and treatment with supplemental oxygen were found to be independent predictors of mortality.

REFERENCES
Supplementary material 1: Home isolation

All symptomatic patients presenting to the hospital and confirmed to have COVID-19 infection using reverse transcriptase polymerase chain reaction (RT-PCR) were screened for eligibility to be enrolled into the Home Isolation (HI) program.

**Criteria for HI:** Mandatory criteria for recruitment to the HI program included heart rate (HR) <110/min, Systolic Blood Pressure (SBP) >100 mm Hg, Respiratory rate (RR) <24/min and pulse oximetry SpO2 >94%. Other important pre-requisites for enrolment in the HI program were the availability of caretakers to provide food and a separate room with attached bathroom for the patient. Patients enrolled in the program were dispensed a “Home isolation kit” which contained basic items such as a pulse oximeter, thermometer, sanitizer and masks. They were taught the use of these monitors and educated on the measurement of their vital signs. All patients were monitored through tele-consultation twice a day by a designated healthcare worker (HCW) for 10 days or until hospitalization.

The home isolation criteria remained unchanged during both waves of the pandemic except during the initial 3 months during the first wave of the pandemic where government regulations mandated admission for ALL patients diagnosed to have COVID-19 infection.