JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Clinico-demographic profile of COVID-19 positive patients – first wave versus second wave – an experience in north-east India

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Abstract

Introduction: India witnessed two distinct COVID-19 waves. We evaluated the clinico-demographic profile of patients infected during first wave (FW) and second wave (SW) in a hospital in north-east India.

Methodology: Patients who tested positive for severe acute respiratory syndrome-coronavirus-2 specific gene by reverse transcriptase polymerase chain reaction across FW and SW were diagnosed as COVID-19 positive. The clinico-demographic data of these positive patients were retrieved from the specimen-referral-form. Vital parameters including respiratory rate, SpO_2, data on COVID-19-associated mucormycosis (CAM), COVID-19-associated acute respiratory distress syndrome (CARDS) were obtained from hospital records for in-patients. Patients were categorized based on disease severity. The data obtained in both waves were analyzed comparatively.

Results: Out of a total of 119,016 samples tested, 10,164 (8.5%) were SARS-CoV-2 positive (2907 during FW, 7257 during SW). Male predominance was seen across both waves (FW: 68.4%; SW:58.4%), with more children infected during SW. Patients with travel history (24%) and contact with laboratory confirmed cases (61%) were significantly higher during SW relative to FW (10.9% and 42.1% respectively). Healthcare worker infection was higher in SW (5.3%). Symptoms like vomiting [14.8%], diarrhea [10.5%], anosmia [10.4%] and aguesia [9.4%] were more in SW. More patients developed CARDS in SW (6.7%) compared to FW (3.4%) with 85% and 70% patients expiring across FW and SW respectively. No case of CAM is documented in our study.

Conclusions: This was probably the most comprehensive study from north-east India. Industrial oxygen cylinder usage may have been the source of CAM in the rest of the country.

Key words: COVID-19; north-east India; associated ARDS; wave, associated mucormycosis; clinico-demographic profile.

J Infect Dev Ctries 2023; 17(2):166-177. doi:10.3855/jidc.16607

(Received 22 March 2022– Accepted 05 December 2022)

Introduction

The world was faced with an unexpected onslaught by a novel coronavirus –severe acute respiratory syndrome (SARS-CoV-2) leading to the coronavirus disease -19 (COVID-19) pandemic just over two years ago. SARS-CoV-2 belongs to the Coronaviridae family, genus Betacoronavirus, subgenus Sarbecovirus and species severe acute respiratory syndrome-related coronavirus [1]. Devoid of a precise technical definition, the term 'wave' is used to signify the rising and falling trends of a disease over a long period of time. In India, there were two distinct waves of COVID-19 infections over the last two years. The first wave (FW) reached its peak in September 2020. The second wave (SW) started in March-April, 2021 and peaked in the first week of May, 2021. According to the World

Health Organization (WHO), India reported an average of 390,000 new cases during the first week of May 2021 with the peak of 414,188 cases reported on May 7th, 2021. Thereafter, there had been a steep fall in the number of new cases from June onwards with only 7,495 cases reported on 20th December, 2021 until a fresh surge in cases started in the first week of January which possibly was the third wave and weaned rapidly [2].

Considering the novelty and ever evolving dynamic nature of this virus it is pertinent to determine the difference between clinico-demographic profile of patients affected during FW and SW. This study also evaluates the demographic characteristics, co-morbid conditions, clinical course and outcomes amongst admitted COVID-19 patients across both waves. The data generated from this study may be used in various mathematical models to make reliable future projections of the timings of possible surge of infection and identifying the vulnerable population proportions, in addition to understanding the disease trend. Our study will add to existing knowledge and may further aid the local health authorities to make data driven north-east (NE)-centric guidelines and ramp up preparedness to tackle this pandemic, especially with the 'stealth omicron' variant causing explosive outbreaks in China and Korea [3].

Methodology

Study settings and design

This was a retrospective hospital-based observational study conducted at a premiere tertiary healthcare centre of NE India which caters to the people from the north-east region of the country. The study was approved by institute's Ethics Committee (Project No. P20/2022/22). All the required data were analyzed anonymously after removing all personal identifiers.

Sampling strategy and inclusion criteria

The sampling strategy employed was non-probability convenience sampling method where all non-duplicate consecutive patients who tested positive for SARS-CoV-2 specific gene by real time-Reverse Transcriptase-Polymerase Chain Reaction (qRT-PCR) assay on throat and/or nasopharyngeal swab samples since the 13th of April, 2020, when the first case was reported from Meghalaya state, until 31st October, 2021were included in the study. The selected patients were then segregated into two cohorts - patients who tested positive for SARS-CoV-2 during FW (13th April, 2020 to 31st March, 2021) formed the first cohort while those who tested positive during SW (1st April, 2021 to 30th October, 2021) formed the second cohort.

Exclusion criteria

All duplicate samples of patients who tested positive within a 3 month period from testing positive were excluded from the study as they fell into the Centres for Disease Control and Prevention (CDC) case definition of an existing case [4]. This was done to avoid including duplicate results of same patients in COVID-19 positive group since many patients from this group were re-tested as a protocol to meet the discharge criteria particularly in the FW. In addition, patients with incompletely filled specimen referral form (SRF) were excluded from the study.

Data collection

The epidemiological and clinical data of all patients were retrieved from the SRF of COVID-19 designed by the Indian Council of Medical Research (ICMR). The form was duly filled for all patients who underwent test for SARS-CoV-2 and included information such as personal details including age, gender, occupation of patients, testing strategies, clinical signs and symptoms, history of contact with COVID-19 patients, medical history including co-morbidities, quarantine and travel history. This form was revised and updated several times during the course of the pandemic to include newly emerging testing strategies, clinical signs and symptoms, and the latest version recorded the vaccination status [5]. In addition, the vital parameters of in-patients including respiratory rate and oxygen saturation recorded at the time of admission were obtained from the hospital database and patient records. Any other COVID-19 associated emerging co-infection such as mucormycosis and aspergillosis were also recorded.

Classification of COVID-19 infected patients

The categorization of all patients was done based on the latest guidelines issued by WHO and Ministry of Health and Family Welfare (MoH&FW) [6] (Supplementary Table1). Patients having no symptoms were labeled as asymptomatic. Furthermore, for the purpose of comparison of patients with severe disease, those patients who were asymptomatic or categorized as mild and moderate disease were clubbed together as non-severe COVID-19.

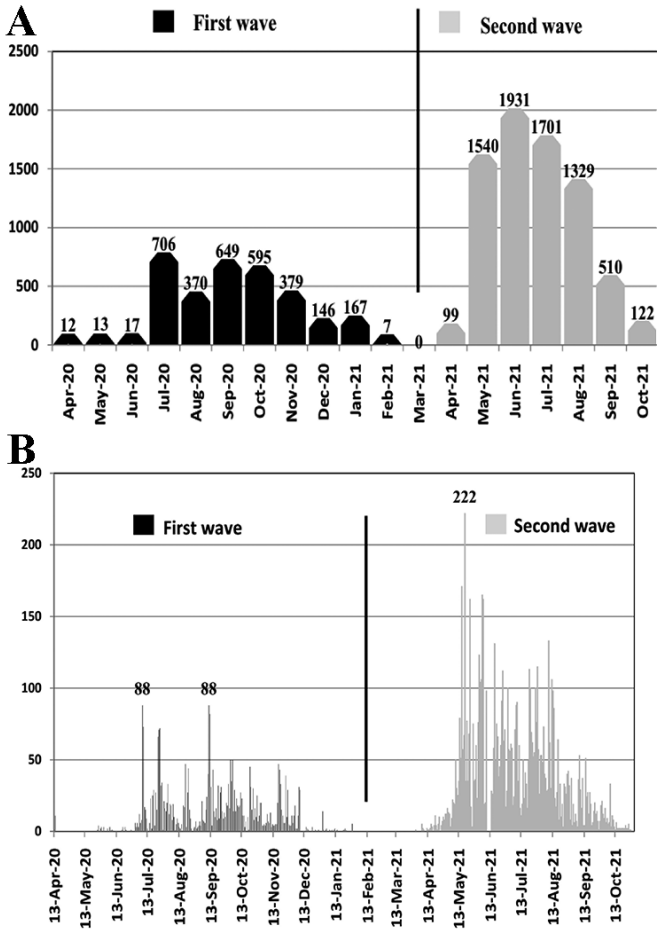
Specimen collection and processing of samples

Throat and/or nasopharyngeal samples were collected using standard techniques, inserted into a

single viral transport medium (VTM) and transported to the microbiology laboratory maintaining cold chain where it was stored at -20 °C until processed. Ribonucleic acid (RNA) was extracted from the samples in the laboratory using various ICMR approved kits during the course of the pandemic. The manufacturer's instructions were stringently adhered to during extraction procedure.

The RNA elute was subjected to multiplex qRT-PCR assay to detect SARS-CoV-2 specific targets using various ICMR approved kits [7]. The SARS-CoV-2 specific genes that were amplified included *E* gene, *ORF 1ab*, *N* gene and *RdRp* gene. During the major part of the FW, primer probes, reverse transcriptase enzyme and master mix was provided by the ICMR. However, in the later stages, the kits were procured by the institute. Preparation of the master mix and programming of the real-time PCR thermocycler (HIMEDIA, Mumbai, India; BiORAD, Hercules, USA; Qiagen, Hilden, Germany) and subsequent assay run validation and interpretation of the result strictly followed the manufacturer's instructions. The cycle threshold (Ct) of samples showing exponential amplification trace for the target genes was labeled as positive and recorded.

Figure 1. Distribution of COVID cases during first wave (FW) (13th April, 2020 to 31st March, 2021) and second wave (SW) (1st April, 2021 to 30th October, 2021).



A: Month-wise distribution of COVID cases during FW and SW; **B**: Day-wise distribution of COVID cases during FW and SW. FW peak: 11th Sep & 8th Jul 2021 (88 cases on each day); SW peak: 21st Jul 2021 (222 cases)

Data on sequencing

Samples from patients with severe illness, vaccine breakthrough infections, long healers, patients with other atypical clinical presentation or patients with history of international travel were sequenced. A representative number of samples from these patients were sent for sequencing to designated regional genome sequencing laboratories (RGSL) as per direction of local health authorities [8]. The sequencing data were updated on the government portal according to the region. The institute or local laboratories were not individually provided with sequencing data.

Statistical analysis

The data were collected and recorded using MS-Excel for Windows v2013® and the basic descriptive statistics were computed. Summary statistics and analysis of significance were calculated using MedCalc® v12.5.0 for Windows (MedCalc Software, Ostend, Belgium). All quantitative data such as age and days admitted in hospital were estimated using measures of central location (mean, median). Qualitative or categorical variables were described as proportions. Comparison of two proportions (first cohort and second cohort) was done using the Chi square test. The unadjusted logistic regression of developing severe COVID-19 infection in patients with certain comorbid conditions was expressed as prevalence ratio (PR) with 95% confidence interval (CI) by comparing to an internal group of non-severe COVID-19 patients. The threshold for significance was considered at $p < 0.05$.

Results

Patients whose samples amplified SARS-CoV-2 specific gene by qRT-PCR were designated as COVID-19 infected patients. Out of a total of 119,016 (FW: 61,507 + SW: 57,509) non-duplicate samples tested, 10,164 (8.5%) were found to be positive for SARS-CoV-2 specific target gene. Among the positives, 2,907 (4.7%) samples tested positive during FW while 7,257 (12.6%) tested positive during SW. Figure1 summarizes the month-wise and day-wise breakup of

Table 1. Comparison of demographic profile of COVID-19 infected patients during FW and SW.

Variables	Sub-variables	Total		*p* value[#]
		FW (n = 2907)	SW (n = 7,257)	
Age	< 1 yr	5 (0.1%)	17(0.23%)	0.1770
	≥ 1 yrs ≤ 5 yrs	68 (2.5%)	335 (4.6%)	< 0.0001*
	≥ 6 yrs ≤ 12 yrs	126 (4.3%)	724 (9.9%)	< 0.0001*
	≥ 13 yrs ≤ 59 yrs	2573 (88.6%)	5697 (78.5%)	< 0.0001*
	≥ 60 yrs	135 (4.6%)	431 (5.9%)	0.0096*
	Not mentioned	0	53(0.73%)	-
	Mean (± SD) yrs	34.3 ± 14.6	29.6 ± 16.8	< 0.0001*
	Median (yrs)	33	28	-
	Range (yrs)	48 days to 98 yrs	27 days to 100 yrs	-
Gender	Male	1988 (68.4%)	3982 (54.8%)	< 0.0001*
	Female	919 (31.6%)	3246 (44.7%)	< 0.0001*
	Transgender	0	2 (0.02%)	-
	Not mentioned	0	27 (0.37%)	-
Category (based on collection site)	Armed forces	961 (33%)	71 (0.97%)	< 0.0001*
	Hospital collection site	688 (25.3%)	2371 (32.6%)	< 0.0001*
	Others	1258 (43.2%)	4815 (66.3%)	< 0.0001*
HCW		58 (1.9%)	385 (5.3%)	< 0.0001*
Symptoms	Present	349 (12 %)	1370 (18.8%)	< 0.0001*
	Absent	2558 (88 %)	5887 (81.1%)	< 0.0001*
Comorbidities	Present	94 (3.2%)	186 (2.5%)	0.0491
Travel history	Present	318 (10.9%)	1778 (24.5%)	< 0.0001*
Contact with lab-confirmed case	Present	1228 (42.2%)	4426 (61%)	< 0.0001*

n: number of patients; yrs: years; FW: First wave; SW: Second wave; *p*: probability; HCW: Health care workers; [#]Chi-squared test for the comparison of two proportions from independent samples performed; *When $p < 0.05$, the two proportions differ significantly.

COVID-19 patients during the FW and SW respectively.

Demographic profile of all COVID-19 infected patients tested at the hospital screening point

The demographic profiles of all COVID-19 infected patients tested at the hospital's screening point during FW and SW together with their statistical significance are listed in Table 1. History of travel reported by the patients acted as a surrogate marker for potential exposure to COVID-19 infected patients.

Clinical profile of patients tested at hospital screening point and admitted patients

All symptoms associated with COVID-19 infection during the SW occurred with increased frequency except for symptoms of hemoptysis and chest pain which were more common during the FW. However, on comparing symptoms between FW and SW, all were found to be statistically significant except abdominal pain. The details pertaining to clinical presentation are listed in Table 2. Among admitted patients, more patients developed COVID-19-associated acute respiratory distress syndrome (CARDS) during the SW

Table 2. Comparison of clinical profile of symptomatic COVID-19 infected patients during FW and SW[@].

Symptoms	FW (%) n = 349	SW (%) n = 1370	*p* value[#] (Comparison of proportions)
Fever	172 (49.2)	1074 (78.3)	< 0.0001*
Body ache	94 (26.9)	832 (60.7)	< 0.0001*
Sore throat	94 (26.9)	863 (62.9)	< 0.0001*
Nasal discharge	22 (6.3)	174 (12.7)	0.0008*
Cough	152 (43.5)	922 (67.2)	< 0.0001*
Aguesia	5 (1.4)	130 (9.4)	< 0.0001*
Anosmia	8 (2.2)	143 (10.4))	< 0.0001*
Vomiting	27 (7.7)	203 (14.8)	0.0005*
Diarrhea	16 (4.5)	144 (10.5)	0.0006*
Pain abdomen	8 (2.2)	45 (3.2)	0.9
SOB	21 (6)	864 (63)	< 0.0001*
SARI	138 (39.5)	869 (63.4)	< 0.0001*
Haemoptysis	19 (5.4)	5 (1.3)	< 0.0001*
Chest pain	11 (3.1)	17 (1.2)	< 0.0001*

@: Each of symptomatic patients had one or more symptoms; n: number of patients; FW: First wave; SW: Second wave; SOB: Shortness of breath; [#]Chi squared test for the comparison of two proportions from independent samples performed; *When $p < 0.05$, the two proportions differ significantly.

Table 3. Comparison of demographic data between COVID-19 infected patients admitted during FW and SW.

Variables	Sub-variables	Total		*p* value
		FW (%)	SW (%)	
Patients admitted	n	**292**	**894**	-
Age	< 1 yr	2 (0.6)	6 (0.6)	1
	≥ 1 yrs ≤ 5 yrs	3 (1)	8 (0.8)	0.74
	≥ 6 yrs ≤ 12 yrs	1 (0.3)	18 (2)	0.04*
	≥ 13 yrs ≤ 59 yrs	229 (78.4)	667 (74.6)	0.18
	≥ 60 yrs	57 (19.5)	195 (21.8)	0.40
	Mean (± SD) yrs	43.1 (± 17.5)	44.7 (± 17.9)	-
	Median (yrs)	41	43	-
	Range (yrs)	0.66-98	0.16-97	-
Gender	Male	175 (59.9)	461 (51.6)	0.01*
	Female	117 (40.1)	433 (48.4)	0.01*
Ward admitted to at the time of admission	ICU	18 (6.2)	50 (5.6)	0.70
	Non ICU	274 (93.8)	844 (94.4)	0.70
Classification (Based on disease severity)	Asymptomatic	107 (36.6)	119 (13.3)	< 0.0001*
	Mild	80 (27.3)	283 (31.6)	0.16
	Moderate	73 (25)	364 (40.7)	< 0.0001*
	Severe	32 (10.9)	128 (14.3)	0.13
Co-morbidities	Present	135 (46.2)	427 (47.7)	0.6
Patients expired		37 (12.6)	196 (21.9)	0.0005*
COVID-19 related complications	ARDS	10 (3.4)	60 (6.7)	0.03*
	AKI	8 (2.7)	22 (2.4)	0.77
	Lung fibrosis	2 (0.68)	4 (0.44)	0.61
	Pulmonary embolism	2 (0.68)	6 (0.67)	0.91
Days in hospital	Mean (± SD) (days)	12.7 (±13.4)	11 (±9.5)	0.01*
	Median (days)	10	9	-
	Range (days)	1-119	1-84	-
	95% CI for mean (days)	11.2 – 14.3	10.4 – 11.6	-

n: number of patients; yrs: years; FW: First wave; SW: Second wave; p: probability; ARDS: Acute Respiratory Distress Syndrome; AKI: Acute Kidney Injury; CI: Confidence interval;[#]Chi-squared test for the comparison of two proportions from independent samples performed; *When p<0.05, the two proportions indeed differ significantly.

(6.7%) compared to the FW (3.4%) with 85% and 70% patients expiring across SW and FW respectively. The case fatality rate (CFR) in FW and SW among patients tested at screening point was 1.27% and 2.7% respectively ($p < 0.0001$). The other details of admitted patients in FW and SW are listed in Table 3. The presence of comorbid conditions among patients admitted during FW and SW and their associated prevalence ratio (PR) of developing severe COVID-19 infection is detailed in Table 4.

Clinical profile of expired COVID-19 infected patients

The clinical profile of expired COVID-19 infected patients is presented in Table 5. There were 11 (5.6%) patients who were diagnosed with mild COVID-19 disease and expired during the course of stay at the hospital during the SW. They apparently had serious comorbid conditions such as cardiac-related [dilated cardiomyopathy (2 nos.), trifascicular block (1 no), paroxysmal supraventricular tachycardia], chronic kidney disease (CKD) on haemodialysis (4 nos.),

Table 4. Presence of co-morbid condition in COVID-19 infected patients admitted during FW and SW.

Comorbid condition	FW (%) n = 292	Severe disease FW (%) n = respective co-morbid disease	PR, 95% CI, *p* value	SW (%) n = 894	Severe disease SW (%) n = respective co-morbid disease	PR, 95% CI, *p* value
Diabetes mellitus	59 (20.2)	16 (27.1)	3.7, 1.9 to 6.9, < 0.0001*	173 (19.3)	35 (20.2)	1.5, 1.1-2.2, 0.01*
Hypertension	71 (24.3)	16 (22.5)	2.9, 1.5-5.4, < 0.0008*	202 (22.5)	31 (15.3)	1.09, 0.7-1.5, 0.6
CKD	23 (7.8)	8 (34.7)	2.8, 1.4-5.7, 0.0032*	58 (6.4)	10 (17.2)	1.2, 0.6-2.1, 0.50
CHD	18 (6.1)	6 (33.3)	3.3, 1.6-7.1, 0.0013*	44 (4.9)	6 (13.6)	0.95, 0.4-2.03, 0.8
Malignancy	6 (2)	2 (33.3)	3.0, 0.94 to 10.0, 0.06	13 (1.4)	1 (7.6)	0.54, 0.08-3.6, 0.53
Hypothyroidism	14 (4.8)	4 (28.5)	2.7, 1.1-6.7, 0.02*	38 (4.2)	5 (13.1)	0.9, 0.3-2.1, 0.83
CVD	12 (4.1)	2 (16.6)	1.5, 0.4-5.5, 0.5	33 (3.6)	1 (3.0)	0.2, 0.02-1.4, 0.1
CNS related diseases	10 (3.4)	1 (10)	0.9, 0.15-6.4, 0.9	22 (2.4)	2 (9.0)	0.77, 0.2-2.8, 0.42
Chronic lung disease	7 (2.4)	2 (28.5)	2.6, 0.77-8.8, 0.12	19 (2.1)	5 (26.3)	1.7, 0.8-3.8, 0.13
Co-infection with TB	8 (2.7)	1 (12.5)	1.1, 0.17-7.14, 0.91	13 (1.4)	5 (38.4)	2.7, 1.3-5.5, 0.005*
CLD	7 (2.4)	1 (14.2)	1.11, 0.17-7.1, 0.91	6 (0.6)	1 (16.6)	1.16, 0.19-7.0, 0.8
Autoimmune diseases	4 (1.3)	None	0.8, 0.06-12.1, 0.9	8 (0.8)	None	0.3, 0.02-5.6, 0.48
Anaemia	5 (1.7)	None	0.7, 0.04-10.3, 0.80	27 (3.0)	2 (7.4)	0.5, 0.13-1.9, 0.32

n: number of patients; yrs: years; FW: First wave; SW: Second wave; *p*: probability; *$p < 0.05$ is considered as significant; CKD: Chronic Kidney Disease; CHD: Chronic Heart Disease; CVD: Cerebrovascular Disease; CNS: Central Nervous System; CLD: Chronic Liver Disease; ARDS: Acute Respiratory Distress Syndrome; TB: Tuberculosis; CI: Confidence interval; PR: Prevalence ratio.

chronic liver disease (CLD) (4 nos.), pre-existing tuberculosis infection (2 nos.), cerebrovascular disease (CVD) (2 nos.) and one patient with past history of caesarean section presented with uterine rupture. These conditions may have acted as an antecedent cause while COVID-19 may have been only the contributing condition.

Vaccine breakthrough infection during SW

The number of patients who received vaccine were 10,156 of which 4,734 (46.6%) patients received double dose and only 4,633 patients were fully protected (> 14 days since the second dose of vaccine). Vaccine breakthrough infection was noted in 299 patients (Supplementary Table 2) based on CDC definition [9]. Among them, 22 required admissions. The remaining 277 patients who did not require admission were categorized into asymptomatic (n = 135) and mild (n = 142) (Supplementary Table 3) [6,9]. Among the 22 admitted patients, seven were asymptomatic while 11 had mild symptoms. Only three of the patients were diagnosed with moderate COVID-19 infection while only one of them had severe symptoms and recovered later.

Results of sequencing

A total of 98 samples were sent for sequencing during FW and SW. The week-wise NE region sequencing data uploaded at Indian SARS-CoV-2 Genomics Consortium (INSACOG) website indicated the delta variant [B.1.617.2] to be the predominant strain circulating in this region during the SW. During the peak months (May-June-July 2021) of the SW, almost 100% strains were found to be delta variant [10]. The predominant strain circulating during the FW belonged to the 'other lineage' group which includes strains other than those labeled as Variant of Concern (VoC) and Variant of Interest (VoI) by WHO [10]. This data is representative of the samples sent from our centre.

Discussion

In summary, there had been an unprecedented surge in the number of cases (12.6%), deaths (2.7%), healthcare workers (HCWs) infected (5.3%), patients developing CARDS (6.7%), and cases with history of travel (24.5%) and contact with laboratory confirmed cases (61%) during the SW relative to FW. India is a country with a large population with regional variations in health literacy, health care inequity, and poor risk perceptions among the general people which underlines

Table 5. Details of admitted COVID-19 infected patients who expired during FW and SW.

Variables	Sub-variables	Total		*p* value
		FW (%) n = 37	SW (%) n = 196	
Age of expired patients	< 1 yr	0	2 (1.0)	0.54
	≥ 1 yrs ≤ 5 yrs	0	1 (0.5)	0.66
	≥ 6 yrs ≤ 12 yrs	0	1 (0.5)	0.66
	≥ 13 yrs ≤ 59 yrs	19 (51.3)	76 (38.7)	0.15
	≥ 60 yrs	18 (48.6)	116 (59.1)	0.23
	Mean (± SD) yrs	57.5 (± 14.8)	56.4 (± 18.2)	0.34
	Median (yrs)	58	60	-
	Range (yrs)	27-98	0.16-97	-
Gender	Male	26 (70.3)	112 (57.1)	0.13
	Female	11 (29.7)	84 (42.8)	0.13
HCW	Expired	0	2 (1.02)	0.53
Ward admitted to at the time of admission	ICU	15 (40.5)	41 (20.9)	0.01*
	Non-ICU	22 (59.5)	155 (79.1)	0.01*
Classification (Based on disease severity)	Asymptomatic	0	0	-
	Mild	5 (13.5)	11 (5.6)	0.08
	Moderate	7 (18.9)	79 (40.3)	0.01*
	Severe	25 (67.5)	99 (50.5)	0.05*
Comorbidities	Present	35 (94.5)	136 (69.3)	0.001*
COVID-19 related complications	ARDS	7 (18.9)	51 (26)	0.01*
	AKI	4 (10.8)	15 (7.6)	0.51
	Lung fibrosis	0	2 (1.02)	0.53
Days in hospital	Mean (± SD) (days)	11.4 (± 12.9)	8.8 (± 7.4)	0.08
	Median (days)	9	6	-
	Range (days)	1-69	1-31	-
	95% CI for mean (days)	7.1-15.7	7.7-9.8	-

n: number of patients; yrs: years; FW: First wave; SW: Second wave; p: probability; HCW: Health Care Worker; #Chi-squared test for the comparison of two proportions from independent samples performed; *When $p < 0.05$, the two proportions differ significantly.

the importance of availability of region-specific epidemiological data that will aid the local health authorities in formulating guidelines and policies to preempt and control future surge in COVID-19 infection. In addition, NE India stands out conspicuously to the rest of the country in their genetic makeup, environment, tradition and geography. It is the eastern-most region of the country and shares its international border with several neighboring countries - Tibet (north), Myanmar (east), and Bangladesh, Bhutan and Nepal in the west. All of the neighboring countries, along with Bangladesh with which the Indian state of Meghalaya shares a relatively porous long border, have been affected by the ongoing pandemic [11–14]. This makes NE India vulnerable to future outbreaks.

There are a large number of people from the state of Meghalaya who are working in metro cities where COVID-19 has spread like a tsunami [15]. The unprecedented surge during the SW in the NE, including Meghalaya, occurred a fortnight after the peak was recorded in most parts of the country [15]. This sudden surge in infection coincided with the migrant workers returning to their native state in anticipation of re-imposing of nationwide lockdown as was observed in our study [16]. The returnees coming from hotspot regions may have mainly contributed to the spurt of infection. The patients with history of travel were significantly higher in the SW (24.5%) relative to the FW (10.9%). While most of our efforts in curbing spread of COVID-19 have concentrated on international migrants, this study highlights the increased attention that needs to be paid to the internal migrants who may have acted as vectors in spreading COVID-19 across the country, especially in NE India. The internal migrant crisis was exposed explicitly during the FW when a nationwide blanket lockdown was announced on 25th March, 2020. In a resource poor country like India, this issue needs to be tactfully addressed with compassion as the majority of people working in the country are engaged in the informal economy [17]. They are left to fend for themselves in the event of crisis as they are not monitored by the state.

In our study, the months of June and July were the worst affected months whereas the cumulative data of India suggests May to be the worst affected month [18]. Similar trend was observed during the FW. However, it was much lesser in intensity due to stricter quarantine rules imposed by the state government where all returnees were tested for SARS-CoV-2 infection and if found positive were isolated and if negative were quarantined in government designated centers, thus limiting contact with susceptible family members. This may have accounted for increased no. of asymptomatic individuals (36.6%) admitted during the FW relative to SW (13.3%) (Table 3). Most asymptomatic patients during the SW were admitted due to reasons other than COVID-19 such as for elective surgery and infections unrelated to COVID-19. During the SW, only patients diagnosed with moderate, severe or critical COVID-19 disease were admitted while mild, asymptomatic and those who tested negative for SARS-CoV-2 infection were allowed home quarantine. This resulted in the rapid spread of infection among family members and community at large as evidenced by the increased no. of patients (61%) with history of contact with a laboratory confirmed case in our study. This may also have resulted in increased proportion of pre-school and school children (14.8%) being infected during the SW as against only 6.8% of infected children in the FW even though schools were closed for the most part of the SW surge [19].

The patients in our study group were younger (median FW: 33yrs, SW: 28yrs). Most Indian studies have similar age as ours [20]. The severity of COVID-19 is known to increase with age due to waning immunity and presence of comorbid conditions which may have resulted in higher median age observed among admitted patients (FW: 41yrs; SW: 43yrs).

Higher male predominance seen during the FW was due to increased proportions of patients tested from armed forces (33%) relative to SW (0.97%) as ours was the only laboratory testing for SARS-CoV-2 during early phase of the pandemic which may have resulted in selection bias. However, towards the end of the FW, the number of laboratories in the state increased many folds which resulted in lower proportions of patients being tested from armed forces and hence lower gender disparity in the SW.

There was almost a 3-fold increase in the number of COVID-19 infected HCWs in the SW. This may be attributed to increased hospital admissions experienced during the SW which increased exposure frequency and burden on the HCWs. Probability of lapses in infection control practices due to fatigue, extended duty hours and use/reuse of doubtful quality mask in the wake of unprecedented demand cannot be ruled out. Our study also reported two HCWs who expired due to COVID-19 during the SW (0.51%) while there were none during the FW. Globally thousands of deaths have been reported amongst HCWs [21]. The national registry of Indian Medical Association (IMA) reports that 747 doctors have died of COVID-19. Most doctors were from the states of Maharashtra and West Bengal [22].

The SW saw an increased percentage of symptomatic patients (18.8%) as against 12% in the FW. This may be attributed to the delta strain which was the predominant strain circulating in the country including NE India during the SW [23]. It has been designated as a VoC by WHO as it was found to be more transmissible and virulent with some atypical clinical presentation as evidenced in our study where symptoms such as vomiting (14.8%), diarrhea (10.5%), anosmia (10.4%) and ageusia (9.4%) occurred with increased frequency. These findings were concordant with studies from Europe and India while discordant with some [24–26]. Our study showed increased predominance of shortness of breath (SOB) (63%) during SW which may be ascribed to dominant VoC delta strain circulating in the community which is known to cause severe disease in unvaccinated individuals [27]. In addition, due to the stigma attached to COVID-19, it is possible that many of the patients under-reported their symptoms accounting for large number of asymptomatic cases across both waves. Apparently, patients with more distressing symptoms such as SOB reported proper history which may have resulted in their predominance in our study during the SW.

It is postulated that SARS-CoV-2 binds to the angiotensin converting enzyme-2 (ACE-2) receptor on target cells to gain entry, possibly with the assistance of transmembrane serine protease-2. ACE2 is recognized as an important regulator of intestinal inflammation and many hypothesize that this is the mechanism by which diarrhea associated with COVID-19 is caused [28]. It is also envisaged to play a potential role in trans-neuronal spread of the virus to the olfactory bulb resulting in anosmia [26]. The increased incidence of hemoptysis in the FW may be related to co-presence of pulmonary embolism. During the earlier part of the FW when very little information was available about the virus, anticoagulation therapy was not instituted routinely resulting in possible increased incidence of COVID-induced pulmonary embolism [29]. This may also have accounted for increased proportion of patients with chest pain during the FW.

Another finding of note was the higher mortality [21.9%] observed during the SW among admitted patients relative to the FW. If mortality was to gauge the severity of the FW and SW, then it can be unambiguously concluded that the SW was far more devastating than the FW. This may be attributed to the circulating VoC delta strain which accounted for increased proportion of patients diagnosed with moderate/severe disease requiring admission during the SW which was concordant with a study in Scotland [10,30]. The global case fatality rate (CFR) is 1.9 whereas that of the nation and state were 1.3 and 1.7 respectively [2]. These numbers do not reflect the true reality of the catastrophe caused by the SW. Another conspicuous finding was the death of two infants of two and three months age respectively during the SW as against FW where no children expired. They were diagnosed with COVID-19 pneumonia and later succumbed to it. One infant was diagnosed with multisystem inflammatory disorder in children (MIS-C) as per CDC definition while the other suffered from seizure disorder. Both of their mothers were COVID-19 positive (primary source) who recovered later. Death among infants was rare and there are very few studies reporting the same [31,32].

Eighty five percent of the patients who developed CARDS finally succumbed to it during the SW which was much higher relative to other studies from Italy (22.2%) and Iran (25%) [33,34]. However, there are studies from Poland [73%] and China [97.8%] which have data concordant with our finding [35,36]. The difference in mortality estimates of CARDS among countries may be explained by the setting where patients with ARDS were receiving care since the management of ARDS requires a well-organized and advanced level of care. Indeed, the mortality data from Italy and Iran were derived exclusively from ARDS patients admitted to the intensive care units (ICUs) which may have contributed to the relatively lower mortality estimate due to more organized management of CARDS. On the contrary, the exceptionally high mortality estimate observed in Poland and China may be due to pan-hospital centric data where the majority of the patients were initially admitted in wards where possibility of receiving suboptimal care loomed high. In our study too, 42 of 60 patients diagnosed with CARDS during their stay in hospital were initially admitted in ward. The possibility of delaying in shifting patients to the ICU due to unavailability/overburden of ICUs cannot be ruled out.

The possibility of the disease having a more acute onset, disease progression and recovery/death in the SW as against the FW may be suggested due to observation of shorter hospital stay by 1.7 days. In addition, it was observed the hospital stay duration reduced by 2.6 days among the expired patients, which suggests rapid progression of disease in vulnerable patients. This finding supports the claims of the delta strain being more virulent and fatal relative to its predecessors [37].

On assessing the PR associated with comorbid condition in developing severe/critical COVID-19 infection, the mean of pooled range difference of 95% CI obtained in the SW (2.7) was significantly lower relative to FW (6.94). This may be attributed to a bigger sample size during the SW which proportionately increases the confidence of the findings obtained during the SW. A systemic review and meta-analysis by Singh *et. al.* across 18 studies including 14,558 individuals with comorbidities found hypertension (11.5%), diabetes (9.7%), chronic heart disease (CHD) (3.1%), chronic obstructive pulmonary disease (COPD) (3.1%), CKD (3%) and malignancy (3.9%) as the most common comorbidities associated with COVID-19 infection. These comorbid conditions were also associated with an increased risk of having severe COVID-19 relative to individuals without them [38]. These findings were concordant with findings in our study except for malignancy (PR = 0.54) and autoimmune diseases (PR = 0.3) (Table 4) which apparently had a negative association with developing severe COVID-19. Invariably, such patients were on immunomodulatory therapy which impedes the triggering of cytokine release syndrome (CRS) that may eventually cause development of CARDS - a life threatening condition with extremely poor prognosis [39]. However, the number of such patients across both waves was very few to consider this finding clinically significant.

Another observation of note, though a negative finding, is that none of the patients across both waves especially during SW reported COVID-19 associated mucormycosis (CAM). This happened at a time when the rest of the country was reeling under the cloud of CAM. According to a recent study, approximately 71% of the world CAM was reported from India [40]. Among the NE states, only Assam, Manipur and Tripura have reported few cases of CAM [41–43]. One obvious reason for the very low burden of CAM on NE states may be attributed to low prevalence of diabetes (most important risk factor for mucormycosis infection) in NE India [5·9%, 95% CI 5·5-6·2] as against mainland India [8·3%, 95% CI 7·9-8·7] [44]. In addition, unlike the rest of the country, the health infrastructure in NE did not collapse due to relatively lower burden of COVID-19 patients requiring admissions which allowed more regulated use of steroids - another major risk factor for CAM. Moreover, the comparatively clean, cool climate of NE India makes the environment less conducive for Mucorales to thrive efficiently. Also, due to acute shortage of oxygen in the rest of the country, industrial cylinders were used to deliver oxygen to hospitals. The quality checks for these cylinders were not as stringent as it is for medical purpose cylinders. This may be one of the many risk factors responsible for causing the explosive outbreak of CAM in all of the country but not in NE India where there was no shortage of oxygen.

Vaccine had no role to play in the FW as vaccination against COVID-19 in India started on 16th January 2021 in phases while it had minimal role in SW as very few of the general public were fully vaccinated and protected as seen in our study population. The sample size of fully vaccinated individuals was scarce to draw any meaningful inference. Hence, further in-depth analysis of data on vaccination was aborted. However, the preliminary data on vaccination generated from our study looks promising as only 6.4% of fully vaccinated individuals vs 13.2 % of unvaccinated/partially/fully vaccinated but unprotected went on to contract the infection. The proportion of patients developing COVID-19 in partially/fully vaccinated but unprotected (15.3%) was almost similar to unvaccinated (12.9%) people (Supplementary Table 2). This gives an indication that completion of vaccination schedule and 14 days post the second dose is essential for protection. Including data from the third wave may have given complete insight on the protection offered by vaccination due to the large proportion of the population that was vaccinated. This remains a glaring drawback. In addition, due to lack of funds, reagents, manpower and technical expertise, we could not perform sequencing at our Institute and had to depend on RGSL (where our samples were sent) for data on sequencing. There was often a delay in getting the results due to sample overload at the RGSL which eventually delayed the control measures taken to contain the viruses with VoI/VoC potentiality.

Conclusions

To the best of our knowledge, this is the most comprehensive study from the NE region of the country which would assist in making NE centric advisories. The findings from this study where we have seen spike in cases coinciding with the return of the migrant population bears causal relationship to community transmission in the state. It may be recommended to have more stringent quarantine and isolation practices like the ones that were in place during the FW whenever a fresh influx of migrants are anticipated especially when the 'stealth omicron' variant, a sub-lineage for the omicron variant is causing the worst COVID outbreak after Wuhan in China and South Korea and is a threat to cause the fourth outbreak in India [3]. It has already caused explosive outbreaks in South Africa and the UK

and is threatening to do the same in India [45]. In anticipation of subsequent waves, it is necessary to ramp-up preparedness and critical-care-unit infrastructure and training of ICU personnel so that moderate/severe and CARDS cases receive an advance level of care early which may change the outcome of such patients towards betterment.

Acknowledgements

We are extremely indebted to Department of Health Research, Government of India for setting up of viral research & diagnostic laboratory in the state of Meghalaya at Department of Microbiology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS) where all COVID-19 related tests were performed. We thank them for their constant guidance and logistics support offered during the course of the pandemic. We also thank UNICEF for supplying PCR thermocycler (CFX96 Touch real-time PCR Detection System, BiORAD) and Department of Biochemistry, NEIGRIHMS for transferring their PCR thermocycler (Rotor-Gene Q, Qiagen) to the Microbiology Department for SARS-CoV-2 testing. We would like to express gratitude to our laboratory technical staff – Mrs Merinda Marbaniang, Mr Golap Baishya, Mrs Juban Ksiar Sunabi and Ms Sony Gandhi who worked tirelessly during the pandemic and were extremely helpful in accumulating and documenting data related to the study. The authors also thank the data entry operators – Mr George Kevin Syiemlieh and Mr Wanjoplang Wansaiand, the Medical Records Department (MRD), NEIGRIHMS for their relentless effort in documenting and mining study related data across both waves.

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Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Classification of COVID-19 based on disease severity.

COVID-19 infection			
Asymptomatic	**Mild disease**	**Moderate disease**	**Severe disease**
Real-time RT-PCR positive for SARS-CoV-2 infection andasymptomatic	Upper respiratory tract infection (and/or fever) WITHOUT shortness of breath or hypoxia	**Any one of: -** 1. Respiratory rate ≥ 24/minute, breathlessness; 2. SpO_2: 90% to ≤ 93% in room air	**Any one of: -** 1. Respiratory rate > 30/minute, breathlessness; 2. SpO_2: ≤ 90% in room air

Supplementary Table 2. Vaccination status of patients who were tested in SW.

COVID-19	Vaccination status			
	Vaccinated and protected (%)	**Vaccinated but not protected [A]*(%)**	**Unvaccinated [B] (%)**	**Unprotected against COVID-19 [A + B] (%)**
Present	299 (6.4%)	838 (15.3%)	6,120 (12.9%)	6,958 (13.2%)
Absent	4,334 (93.6%)	4,631 (84.7%)	41,287 (87.1%)	45,918 (86.8%)
Total (n)	4,633	5,469	47,407	52,876

*Includes people who have received only single shot of vaccine or have received both the doses but are not protected due to of less than 14 days elapse since last dose at the time of testing.

Supplementary Table 3. COVID-19 breakthrough infection classification based on disease severity.

COVID-19 breakthrough infection*	n = 299 (%)	COVID-19 classification based on disease severity	n
Requiring admission	22 (7.3)	Asymptomatic	7
		Mild	11
		Moderate	3
		Severe	1
Not requiring admission	277 (92.7)	Asymptomatic	135
		Mild	142
		Moderate	0
		Severe	0

n: number.