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Coronavirus Pandemic

Real-world effect of casirivimab and imdevimab cocktail in patients infected with SARS-CoV-2 delta and omicron variants

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Abstract

Introduction: The casirivimab and imdevimab antibody cocktail has proven to be extremely effective against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) delta variant. Currently, no data on the clinical outcomes of antibody cocktail with the newer omicron form is available. This retrospective study evaluated the effectiveness of casirivimab and imdevimab antibody cocktail in patients infected with SARS-CoV-2 delta and omicron variants.

Methodology: Data of 85 patients of age < 60 years, with comorbid conditions and BMI > 25 kg/m^2 were identified from a database of 871 patients.

Results: Most of the patients in both delta and omicron groups were administered 600 mg casirivimab + 600 mg imdevimab intravenously. SARS-CoV-2 symptoms started resolving from the 3rd day and by the end of the 14th day most patients in both groups did not report any symptoms. There was no significant difference between delta and omicron group with respect to average symptom onset days, number of hospitalized days post cocktail and number of days post cocktail administration to reverse transcription polymerase chain reaction (RT-PCR) negative status. Forty (58%) patients in the delta group and 16 (94%) patients in the omicron group had the high-resolution computed tomography (HRCT) score of zero. No patient required oxygen support during hospitalization and no mortality was reported.

Conclusions: There was no difference in effectiveness and safety of casirivimab and imdevimab antibody cocktail in the patients infected with SARS-CoV-2 delta or omicron.

Key words: Casirivimab; imdevimab; cocktail; SARS-CoV-2; delta; omicron.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of coronavirus disease-2019 (COVID-19) that has sparked concern due to its high morbidity and mortality [1]. There have been 44,670,075 confirmed cases of COVID-19 in India, with 530,596 deaths reported to the World Health Organization (WHO) till November 23, 2022. A total of 2,198,226,412 vaccine doses have been delivered as of November 15, 2022 [2].

COVID-19 is a contagious disease caused by a novel virus, SARS-CoV-2 [3]. The virus is transmitted through respiratory droplets and aerosols from person to person. The virus binds to host receptors inside the body and enters host cells through endocytosis or membrane fusion [4]. SARS-CoV-2 infection may be asymptomatic or symptomatic. Symptoms include upper respiratory tract infection and life-threatening sepsis [5]. The common symptoms noted in COVID-19 patients during the acute stage are fever, dyspnea and cough, while minor symptoms include anosmia, dysgeusia, gastrointestinal symptoms, headache and skin lesions [3,6-8]. Since the beginning of COVID-19 in 2019 from Wuhan city in China, several mutations have been observed, and certain variants of concern (VOC) such as delta (B.1.617.2) and omicron (B.1.1.529) have evolved and propagated dominantly [1,9]. The delta VOC was identified in late 2020 and has since become the most common lineage worldwide, accounting for 99.8% of COVID-19 cases in Europe in September 2021 [1]. The delta VOC has caused higher rates of hospitalization than other VOC, even among vaccinated people; thus requiring immediate action to avoid more serious diseases and increased burden on intensive care units (ICUs) [9]. After the second wave of the delta variant, the world was on the verge of entering into a third wave due to the highly divergent VOC omicron [10-11]. The omicron VOC arose in late November 2021, only a few months after the delta VOC was identified, and quickly became the dominant strain globally. This variation had an extremely high number of spike protein mutations, 15 of which are in the

receptor-binding domain (RBD) [12]. The rising number of COVID-19 cases in India was a major concern, and experts already projected a third wave related to omicron in the beginning of 2022 [13].

People infected with the omicron variant are significantly less likely to develop smell and taste loss compared to the delta variant [14]. The omicron variant had a higher affinity for human angiotensin-converting enzyme 2 (ACE2) than the delta variant due to a significant number of mutations in the SARS-CoV-2 receptor-binding domain (RBD), indicating a higher potential for transmission [15]. A prospective observational study concluded that the more-frequent symptoms with delta variant included loss or altered sense of smell, sneezing, runny nose, brain fog, eye soreness, headache, fever, and dizziness, while symptoms such as sore throat and hoarse voice were commonly observed with omicron. The duration of acute symptoms was longer with the delta variant than with omicron, although the difference was less marked for vaccinated individuals [16].

Due to the lack of clinically proven treatment options, the treatment of COVID-19 is symptomatic, and clinical management includes infection prevention, control measures, and supportive care. Available therapy include antiviral drugs (remdesivir, favipiravir, molnupiravir) and supportive measures (vitamin C, azithromycin, IL-6 antagonists, corticosteroids). Some vaccines are also approved by the health authorities for the prevention of COVID-19 [17]. In particular, many treatments have been studied both as a measure to prevent the progression and to prevent deaths. Regarding the prevention of progression, three antivirals have been approved: molnupiravir, nirmatrelvir and ritonavir with a 3 days course [3,18-19]. Further, monoclonal antibodies (mAbs) may be required for those who are not protected by vaccination [2,20]. The use of antibody cocktail has piqued interest since the start of the COVID-19 pandemic, due to decreased virus replication and mortality owing to its antibodies neutralizing effect [1,21]. Antibody cocktail is reported to prevent COVID-19 progression during early disease presentation [22]. Two most common monoclonal antibodies currently used are casirivimab/imdevimab and sotrovimab [23]. Casirivimab and imdevimab antibody cocktail is a mixture of two neutralizing immunoglobulin gamma-1 (IgG-1) human mAbs against the SARS-CoV-2 spike protein [24]. Casirivimab and imdevimab prevent the virus from infecting host cells by binding to the epitopes of the receptor-binding domain of the SARS-CoV-2 and thereby reducing viral load, shortening the duration of symptoms, reducing the requirement for hospitalization, and lowering the risk of mortality [11,13].

The antibody cocktail received its first emergency use licence in the United States (US) for the treatment of COVID-19 in November 2020, with similar authorizations in India, Canada, and Switzerland soon after. The casirivimab and imdevimab cocktail received a favorable scientific opinion in the European Union (EU) in February 2021 for the treatment of COVID-19. On September 24, 2021, the casirivimab and imdevimab antibody cocktail was recommended for emergency use by WHO, in mild or moderate patients with elevated risk of severe disease, as well as severe patients with seronegative status [25]. The recommended dose for the prevention and treatment of COVID-19 is casirivimab 600 mg + imdevimab 600 mg. In the case of patients requiring continuous prophylaxis, a repeat-dose regimen is recommended comprising of a single dose of casirivimab 600 mg + imdevimab 600 mg, followed by subsequent doses of 300 mg casirivimab + 300 mg imdevimab once every 4 weeks [24]. The casirivimab and imdevimab antibody cocktail has been administered to more than 16,000 people in clinical trials which included both hospitalized and non-hospitalized patients [26]. The cocktail's capacity to preserve effectiveness against delta VOC has been demonstrated in COVID-19 patients [1,22,27]. Recent in vitro investigations however indicated that the omicron VOC escapes neutralization by imdevimab and casirivimab antibody cocktail [28-29]. Little is known about the effectiveness of the casirivimab and imdevimab antibody cocktail in SARS-CoV-2 patients infected by the omicron VOC.

There are few studies published on real-world clinical evidence of the effectiveness and safety of casirivimab and imdevimab antibody cocktail in SARS-CoV-2 patients. The present retrospective, single centre, observational study was designed to evaluate the real-world effectiveness of casirivimab and imdevimab antibody cocktail in patients infected with delta and omicron VOC.

Methodology

Data collection

The study included patients treated for SARS-CoV-2 infection with casirivimab and imdevimab antibody cocktail between December 2021 to January 2022 when India experienced the third COVID-19 wave. During this period, omicron was prevalent in India, along with the presence of the delta variant. However, during this time genomic sequencing was the only available means

of detection of variant and the actual variant was identified to be omicron or delta after 4-5 days. Patients received the casirivimab and imdevimab at the time of admission as per the approved indication in India. Historical patient data for delta was used for comparison to study the safety and effectiveness.

Patients data inclusion criteria

Patients with age < 60 years and body mass index (BMI) >25 kg/m^2 was selected; case-control matching was performed to match the cases according to age, BMI and comorbid conditions. The case control matching was performed to avoid confounding factors ensuring an equal distribution among those who were exposed and unexposed to the variables. A total of 85 matched cases were identified from a database of 871 patients (delta: 757 and omicron: 114), out of which 68 had delta variant and 17 had omicron variant infection (4:1 ratio). The inclusion criterion for the participants were: (a) reverse transcription-polymerase chain reaction (RT-PCR) confirmed mild to moderate COVID-19 patients (>12 years) who were stable in room air; and (b) patients who had received single dose intravenous (IV) administration of casirivimab and imdevimab during the treatment.

The primary objectives of the study were to evaluate: (a) the time to COVID-19 symptom resolution; and (b) the proportion of patients with disease progression defined in terms of oxygen requirement. The time to COVID-19 symptoms resolution was defined as number of days from administration to resolution of symptoms. The secondary objectives of the study were to evaluate (a) the safety and (b) all cause mortality. The safety was assessed by recording the incidence and severity of treatment emergent adverse events (TEAEs) (infusion related reactions) during the study.

The patient characteristics such as infection status, vaccination status and comorbid conditions were recorded. The presence of COVID-19 symptoms during drug administration and symptom resolution at different timepoints (3rd, 7th and 14th day) for delta and omicron groups were recorded. The pre and post-treatment biomarker levels in delta and omicron group from time of drug administration to 3rd day of treatment were recorded. The number of days of hospitalization and high-resolution computed tomography (HRCT) severity score was also recorded.

Table 1. Characteristics of SARS-CoV-2 infected patients treated with casirivimab and imdevimab antibody cocktail.

Characteristics	Delta (n = 68)	Omicron (n = 17)	*p* value
Age (years), mean ± SD	42.29 ± 11.15	42.29 ± 11.41	0.990
BMI (kg/m^2)	30.02 ± 4.12	28.89 ± 2.50	0.598
Gender (M/F)	39 (57.35%) / 29 (42.65%)	14 (82.35%) / 3 (17.65%)	0.091
Infection status at time of drug administration			
Mild	68 (100%)	17 (100%)	-
Drug route (IV)	68 (100%)	17 (100%)	-
Dose (1200 +1200 / 600 + 600 mg)	1 (1.47%) / 67 (98.53%)	0 (0%) / 17 (100%)	-
Vaccination status			
Vaccinated	32 (47.05%)	16 (94.12%)	-
Unvaccinated	36 (52.94%)	1 (5.88%)	-
Vaccine			
AstraZeneca / Covishield	28 (41.18%)	11 (64.71%)	-
Covaxin	3 (4.41%)	2 (11.76%)	-
Janssen / Johnson	1 (1.47%)	1 (5.88%)	-
Pfizer	0	1 (5.88%)	-
Vaxveria	0	1 (5.88%)	-
Comorbid conditions			
Presence of any one of comorbid condition	26 (38.23%)	4 (23.53%)	0.395
No comorbidities	42 (61.76%)	13 (76.47%)	0.395
Comorbidities details			
Hypertension	14 (20.59%)	3 (17.65%)	0.999
Diabetes mellitus	9 (13.23%)	0	0.194
Ischemic Heart Disease (IHD)	2 (2.94%)	1 (5.88%)	0.493
Hypothyroidism	5 (7.35%)	0	0.578
Other			
Bronchial asthma	1 (1.47%)	1 (5.88%)	-
Hyper triglyceridaemia	1 (1.47%)	0	-
Koch's disease	1 (1.47%)	0	-
Scleroderma	0	1 (5.88%)	-

BMI: Body mass index; IV: intravenous; M: male; F: female; SD: standard deviation; IHD: ischemic heart disease.

Statistical analysis

The descriptive statistics including means and standard deviation (SD) for continuous data and frequencies, and percentages for categorical data were calculated. The distribution of data was checked for normality using Kolmogorov-Smirnov (K-S) test prior performing comparative analysis. The mean differences between delta vs. omicron group for various parameters were assessed using independent sample t-test or Mann Whitney U test depending upon the distribution of the data. Two sample proportion test was used to compare symptom proportion between groups at different timepoints. Pearson Chi-square test was used to assess the association between presence of comorbid condition and SARS-CoV-2 VOC.

Statistical analysis was performed with SPSS version 27.0 (SPSS Inc., Chicago, IL, USA). p value of < 0.05 was considered as statistically significant for comparative analysis.

Results

Patients' characteristics

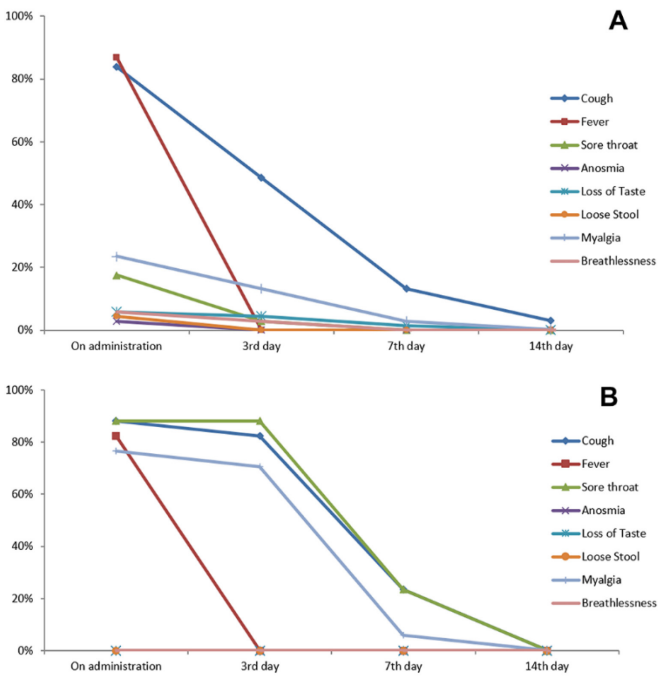
The characteristics of SARS-CoV-2 infected patients treated with casirivimab and imdevimab antibody cocktail are presented in Table 1. The average age (± SD) of the patients from delta and omicron groups were 42 ± 11 years. The average BMI for patients from delta group was 30.02 ± 4.12 kg/m^2 and from omicron group was 28.89 ± 2.50 kg/m^2. No statistically significant difference was observed for age (p = 0.990) and BMI (p = 0.598) between delta and omicron groups. In the delta group, 39 (57%) patients were males while in omicron group 14 (82%) patients were males. There was no significant difference in gender distribution between both the groups (p = 0.091). Out of 85 patients, 32 (47%) patients with delta variant and 16 (94%) patients with omicron variant were vaccinated. Twenty eight (41%) patients with delta variant and 11 (64%) patients with omicron variant were vaccinated with covishield (Serum Institute of India Pvt Ltd., Pune, India). Three (4%) patients with delta variant and 2 (11.8%) patients with omicron variant were vaccinated with covaxin (Bharat Biotech, Hyderabad, India). One patient each with delta and omicron variant (1% and 5.9%) was vaccinated with Janssen/Johnson (Janssen, Leiden, Netherlands). Two patients with omicron variant (5.9% each) were vaccinated with Pfizer (Pfizer, Puurs, Belgium) and Vaxveria (AstraZeneca AB, Sodertalje, Sweden). Out of 32 patients in the delta group, 16 received 1 dose, 13 received 3 doses and details were not available for 3 patients. All the 16 patients in the omicron group received two doses of vaccine. All the patients at the time of drug administration had mild infection. The IV route was used to administer casirivimab and imdevimab antibody cocktail to all patients, and the preferred dose for both the groups was 600 mg casirivimab + 600 mg imdevimab. Only one patient in the delta group received the dose of 1200 of casirivimab +1200 mg of imdevimab. All the doses were administered based upon the physicians' discretion.

Twenty six (38%) patients from the delta group and 4 (23%) from omicron group had at least one comorbid condition. The most common comorbid conditions were hypertension, diabetes mellitus, ischaemic heart disease (IHD) and hypothyroidism. No statistically significant difference was observed between the proportion of patients with presence of comorbid conditions in both the groups (Table 1).

Treatment outcomes on progression of disease

The presence of COVID-19 symptoms during drug administration and at different timepoints for delta and omicron group are presented in Figure 1. COVID-19 symptoms started resolving from the 3rd day and by the end of the 14th day none of the patients reported any symptoms in both the delta and omicron groups; except two patients with cough on the 14th day in the delta group. There was significant difference seen between the delta and omicron groups in the proportion of subjects with presence of cough on the 3rd day (48.53%

Figure 1. Presence of COVID-19 symptoms at different timepoints in (**A**) delta group, and (**B**) omicron group.



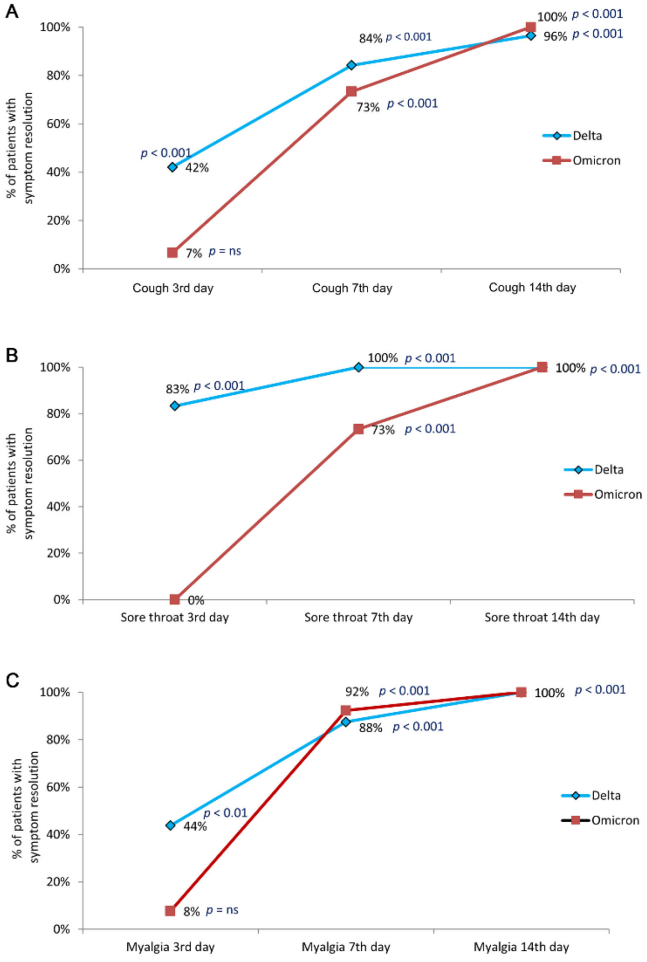
vs. 82.35%; $p < 0.014$), presence of sore throat on administration (17.65% vs. 88.23%; $p < 0.001$) and 3rd day (2.94% vs. 88.23%; $p < 0.001$) and presence of myalgia on administration (23.53% vs. 76.47%; $p < 0.001$) and 3rd day (13.23% vs. 70.59%; $p < 0.001$).

The percentage of patients with resolution of cough, sore throat and myalgia from drug administration to subsequent visits in delta and omicron groups are presented in Table 2 and Figure 2. There was significant difference in symptoms resolution of cough, sore throat and myalgia from drug administration to subsequent visits (i.e., on the 3rd, 7th and 14th day) ($p < 0.001$) in delta as well as the omicron group; except the resolution of cough and myalgia on 3rd day (*p* = Not Significant, NS) in the omicron group.

There was no significant difference (*p* = NS) between pre and post treatment white blood cells (WBC) count (6.20 ± 1.97 vs. 6.63 ± 2.00), C-reactive protein (CRP; 8.08 ± 11.04 vs. 7.28 ± 15.27) and ferritin (357.35 ± 375.94 vs. 269.58 ± 258.48) among levels patients with delta variant. In the case of patients with the omicron variant, a significant ($p = 0.049$) difference was observed between pre and post treatment CRP (9.00 ± 6.19 vs. 5.48 ± 4.24) levels only.

There was no significant (*p* = NS) difference between delta vs. omicron groups for symptom onset days (3.82 ± 1.56 vs. 3.76 ± 2.19), total number of hospitalized days (8.34 ± 3.27 vs. 7.76 ± 2.22), number of hospitalized days post cocktail (6.94 ± 2.89 vs. 7.18 ± 2.18) and number of days post cocktail administration to being RT-PCR negative (7.82 ± 4.14 vs. 8.59 ± 3.10) (Table 3).

Figure 2. Percentage of patient with resolution of (**A**) cough, (**B**) sore throat, and (**C**) myalgia from drug administration to subsequent visits in delta and omicron groups.



p values calculated for % of patients with resolution of symptoms from drug administration. *p* values indicate the % of patients with symptom resolution as compared to baseline (i.e. from administration of a drug).

Table 2. Percentage of patients with symptom resolution from drug administration to subsequent visits.

Symptom progression	Delta (n = 68)			Omicron (n = 17)		
	Patients with presence of symptoms	Patients with symptom resolution after drug administration	*p* value	Patients with presence of symptoms	Patients with symptom resolution after drug administration	*p* value
Cough						
Cough on administration	57 (83.82%)	-	-	15 (88.23%)	-	-
Cough 3rd day	33 (48.53%)	24 (42.10%)	< 0.001	14 (82.35%)	1 (6.67%)	*p* = NS
Cough 7th day	9 (13.23%)	48 (84.21%)	< 0.001	4 (23.53%)	11 (73.33%)	< 0.001
Cough 14th day	2 (2.94%)	55 (96.49%)	< 0.001	0	15 (100%)	< 0.001
Sore throat						
Sore throat on administration	12 (17.65%)	-	-	15 (88.2%)	-	-
Sore throat 3rd day	2 (2.94%)	10 (83.33%)	< 0.001	15 (88.23%)	0	-
Sore throat 7th day	0	12 (100%)	< 0.001	4 (23.53%)	11 (73.33%)	< 0.001
Sore throat 14th day	0	12 (100%)	< 0.001	0	15 (100%)	< 0.001
Myalgia						
Myalgia on administration	16 (23.53%)	-	-	13 (76.47%)	-	-
Myalgia 3rd day	9 (13.23%)	7 (43.75%)	< 0.01	12 (70.59%)	1 (7.69%)	*p* = NS
Myalgia 7th day	2 (2.88%)	14 (87.50%)	< 0.001	1 (5.88%)	12 (92.31%)	< 0.001
Myalgia 14th day	0	16 (100%)	< 0.001	0	13 (100%)	< 0.001

NS: Non-significant.

Safety

There was no disease progression in both delta and omicron groups after casirivimab and imdevimab cocktail administration. None of patients reported any adverse drug reaction (ADR) and no-one required oxygen support during the hospitalization period. No mortality was reported in either group. None of the patients in either group required remdesivir or favipiravir. Forty (58%) patients in delta and 16 (94%) in omicron group reported HRCT score as zero. HRCT score of > 5 was reported in 25% of patients with delta variant.

Discussion

SARS-CoV-2 continues to pose new challenges due to genetic mutations that arise during genome replication resulting in the rapid spread of new VOC. The evolution of resistant forms of SARS-CoV-2 during treatment with antiviral agents or by circulation among the global community will continue to be a concern in the development of efficient COVID-19 therapeutics and vaccines [30]. The majority of current therapy options are supportive, implying that efforts should be focused on preventing disease progression. The monoclonal antibodies (mAbs) are recombinant proteins that target the S glycoprotein of SARS-CoV-2 and prevent it from binding to its corresponding receptor ACE-2 on host cells, avoiding the disease from progressing to more severe symptoms. Since the spread of SARS-CoV-2 VOC may limit the effectiveness of vaccination and containment programmes, the changing scenario necessitates a better understanding of mAb potential. Therefore, this retrospective observational study was planned to evaluate the real-world effectiveness of casirivimab and imdevimab antibody cocktail in patients infected with SARS-CoV-2, delta and omicron VOC.

Antibody cocktail therapy has been found to reduce the requirement for additional medical interventions by 70% compared to those who did not receive the therapy. Casirivimab and imdevimab cocktail has the potential to reduce the burden of care in mild to moderate COVID-19 patients who have high-risk factors from receiving additional treatments such as supplemental oxygen, steroids, or antiviral therapies [27]. Casirivimab and imdevimab cocktail has been used effectively on delta variant vaccine breakthrough patients, resulting in a reduction in viral load in 10 days and the absence of viral load by nucleic acid amplification test (NAAT) on nasopharyngeal swab by the 30th day without any adverse effects [31].

COVID-19 patients with a history of hypertension, obesity, chronic lung disease, diabetes and cardiovascular disease (CVD) had the worst prognosis and are more likely to develop acute respiratory distress syndrome (ARDS) or pneumonia [32]. A retrospective descriptive study evaluated the comorbidities in 78 cases of death due to COVID-19. Hypertension, CVD and diabetes were observed to be the most common comorbidities in more than 25% of patients' death due to COVID-19 [33]. In line with this report, the most common comorbidities observed in delta and omicron groups in the current study were hypertension, diabetes, IHD followed by hypothyroidism.

According to a phase 1-2 trial interim analysis data, the casirivimab and imdevimab cocktail treatment in 275 COVID-19 patients was found to reduce the viral load, the need for medical treatment, and was strongly suggestive of a lower risk of hospitalization [34]. The phase 3 clinical trial data revealed that early treatment with casirivimab and imdevimab cocktail in outpatients with high-risk factors for severe COVID-19 reduced the chance of hospitalization or all cause mortality by more than 70%, the resolution of symptom duration by 4 days and reduced the viral load quicker than placebo at equivalent dosages of 600 mg of each mAbs [30]. Casirivimab and imdevimab cocktail IV infusion was also found to reduce the 28 day mortality rate in 3,153 baseline seronegative hospitalized patients [21]. In our observations, no mortality was seen in individuals infected with SARS-CoV-2 delta or omicron VOC who had a casirivimab and imdevimab cocktail administered; indicating increased probability of being discharged alive during hospitalization as well as absolute risk reductions.

As per earlier reports, no differences have been found in the occurrence of severe illness outcome between unvaccinated and vaccinated patients who

Table 3. Number of hospitalized days.

Variables	Delta			Omicron			*p* value
	N	N*	Mean ± SD	N	N*	Mean ± SD	
Days since symptoms onset	68	0	3.82 ± 1.56	17	0	3.76 ± 2.19	NS
Total number of days hospitalized	68	0	8.34 ± 3.27	17	0	7.76 ± 2.22	NS
Hospitalization days post cocktail	68	0	6.94 ± 2.89	17	0	7.18 ± 2.18	NS
Number of days post cocktail administration to RT-PCR negative	34	34	7.82 ± 4.14	17	0	8.59 ± 3.10	NS

N*: number of missing observations; NS: non-significant; N: number of patients.

received casirivimab and imdevimab therapy and those who did not [11]. Casirivimab and imdevimab cocktail treatment was associated with lower rates of hospitalization among 403 vaccinated and unvaccinated patients [35]. The mAb recipients have shown a similar all cause 30 day admission rate independent of vaccination status, supporting FDA in vitro evidence suggesting maintained action of casirivimab and imdevimab antibodies against delta VOC [22,26]. In our observations, 47% of the patients with delta variant and 94% of patients with omicron variant were vaccinated. In the current assessment, despite difference in vaccination status, the treatment with casirivimab and imdevimab antibody cocktail did not show any significant difference in treatment outcomes between delta and omicron groups; suggesting the clinical outcomes of antibody cocktail are independent of vaccination status in COVID-19 patients.

In a phase 3 trial for the prevention of COVID-19 in affected individuals' household contacts, casirivimab and imdevimab cocktail, was found to lower the likelihood of symptomatic COVID-19 infections by more than 80% [20]. Treatment with a casirivimab and imdevimab antibody cocktail considerably sped up the recovery from COVID-19 related fever, with a median time of just 1 day after injection, which is likely an additional benefit for COVID-19 patients [27]. In our assessment, COVID-19 symptoms (cough, fever, sore throat, and myalgia) started resolving from the 3rd day and by the end of the 14th day, none of the patients reported any symptoms in both the delta and omicron groups, except for 2 patients who had cough in the delta group on the 14th day after treatment with casirivimab and imdevimab antibody cocktail. Reduced progression to symptomatic infection, as observed here, showed the possible benefit of a faster recovery from COVID-19 related symptoms and could have clinical implications for the use of mAbs for COVID-19 therapy in the initial stages.

Antibody cocktail therapy has been linked to a lower risk of hospitalization or mortality in high-risk COVID-19 patients [27]. In our assessment, there was no significant difference between delta or omicron groups for symptom onset days, number of hospitalized days, hospitalized days post cocktail and number of days post cocktail administration to RT-PCR negative; indicating similar effectiveness in lowering the risk of hospitalization in both VOC.

The severity indicators of COVID19 (i.e., elevated CRP, WBC and ferritin) were observed in our population. There was no significant difference between pre and post WBC count, CRP, and ferritin levels in the delta group while a significant difference was observed between pre and post CRP levels in the omicron group. The reduction of CRP levels after casirivimab and imdevimab cocktail administration indicates a reduction of disease severity. In addition, none of the patients were needed to shift on other treatments like remdesivir or favipiravir.

In this study, the majority of patients reported HRCT score as 0 from delta and omicron group while the HRCT score of > 5 was reported in 25% of patients with delta variant; indicating that most of the patients had no lung involvement and no severe disease progression after casirivimab and imdevimab antibody cocktail administration.

In an Indian retro-prospective comparative observational study, treatment with casirivimab and imdevimab antibody cocktail was clinically beneficial in 79 high-risk COVID19 patients, with lesser need for mechanical ventilation, high flow oxygen, and no death [13]. In our assessment also, none of patient reported any ADR and no-one required oxygen support during the hospitalization period in both delta and omicron groups; supporting the use of antibody cocktail therapy in reducing absolute risk and the need for additional therapy which may reduce the burden of healthcare costs in the early cases of COVID-19. No mortality was reported in delta and omicron patients treated with cocktail.

A recent in vitro study studied the efficacy of antiviral agents against the SARS-CoV-2 omicron subvariant BA.2 and reported that the combination of REGN10987 (marketed as imdevimab) and REGN10933 (marketed as casirivimab) also inhibited omicron/BA.2 [36].

As new SARS-CoV-2 VOCs may emerge in the future, additional well designed clinical studies will be required to assess the efficacy of this antibody cocktail.

The limitations of the study are as follows: (a) this was a retrospective study with a smaller sample size for omicron infected patients; (b) comparison involved using historical data for delta VOC; (c) standard of care comparison was not available; and (d) genome sequencing of historical data was not available.

Conclusions

Overall, the casirivimab and imdevimab antibody cocktail seems to be promising in improving the outcome of COVID-19 patients with SARS-CoV-2 delta and omicron VOC. In the initial stages of the disease, casirivimab and imdevimab antibody cocktail appears to be a viable strategy to reduce COVID-19's serious impact. No progression of disease, adverse

reactions and mortality was recorded in both delta and omicron patients presenting no differences in the treatment outcomes. A prospective, randomized study needs to be designed to validate the clinical benefits from casirivimab and imdevimab antibody cocktail against emerging SARS-CoV-2 VOC variants.

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Research quality and ethics statement

The study was approved by the Institutional Review Board (IRB) with waiver of informed consent since analyses were based on retrospective data collection via electronic health record. All methods were performed in accordance with the relevant guidelines and regulations as stated in the Declarations of Helsinki.

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