Effectiveness of Regdanvimab in Patients With Mild-to-moderate COVID-19: A Retrospective Cohort Study

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Abstract

Background

Monoclonal antibodies are a treatment option for patients with mild-to-moderate coronavirus disease (COVID-19). We investigated the effectiveness of regdanvimab, an anti-SARS-CoV-2 monoclonal antibody approved in South Korea, in the treatment of patients with mild-to-moderate COVID-19.

Methods

Medical records of mild-to-moderate COVID-19 patients admitted to a COVID-19 designated hospital were reviewed to assess baseline characteristics (age, gender, BMI, and comorbidities) and clinical outcomes such as supplemental oxygen requirements, mortality, and length of hospitalization.

Results

Four hundred seventy-four COVID-19 patients were included in the study, and 66 of them were administered regdanvimab. The proportion of patients requiring supplemental oxygen was significantly lower in the regdanvimab group than in control group without statistical significance (6.1% vs. 22.8%, $P = 0.001$). There was no significant difference in mortality (0% vs 1.2%, $P > 0.999$) and the length of hospitalization (median: 10.5 days vs. 7.5 days, $P = 0.067$) between both groups. Increasing age, male sex, chest X-ray abnormality, underlying chronic kidney disease and administration of regdanvimab were found to have a significant univariate association with oxygen requirement. The multivariate analysis demonstrated that increasing age (OR: 1.03, 95% CI: 1.01-1.05, $P < 0.001$) and chest X-ray abnormality (OR: 4.40, 95% CI: 2.49-8.21, $P < 0.001$) were independently associated with higher requirement of oxygen and administration of regdanvimab was independently associated with lower oxygen supplement (OR: 0.17, 95% CI: 0.05-0.47, $P < 0.002$).

Conclusions

Regdanvimab reduced the need for supplemental oxygen and fatalities in mild-to-moderate COVID-19 patients who matching the indications for administration of regdanvimab.

Background

The coronavirus disease (COVID-19) pandemic that started in December 2019 continues to affect millions of people worldwide [1, 2]. The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is diverse. Although most people with SARS-CoV-2 infection experience mild disease with spontaneous resolution, some individuals, particularly those who have risk factors such as older age, obesity, diabetes, cardiovascular disease, and chronic lung disease, develop critical illness that requires intensive care, including mechanical ventilation [3–6].

Comprehensive efforts have been made to develop therapeutic agents for treating COVID-19. Currently, there are two categories of antiviral medications that have been approved for the treatment of COVID-19, antiviral agents and anti-SARS-CoV-2 antibody. The choice of therapeutic strategies and agents depends on the stage and severity of the disease. Remdesivir, which binds the viral RNA-dependent RNA polymerase and inhibits viral replication, has been shown to reduce the time to clinical recovery in individuals with moderate to severe COVID-19 [7, 8]. For individuals with mild-to-moderate COVID-19, the World Health Organization (WHO) recommends treatment with the anti-SARS-CoV-2 monoclonal antibodies [9].

Neutralizing monoclonal antibodies is one of the treatment options for infections with viruses such as respiratory syncytial virus and Ebola virus [10–12]. Although it is not clear how a neutralizing antibody treatment affects natural adaptive immunity, recent advances in antibody engineering have enabled large-scale production of high-affinity monoclonal antibodies with fewer adverse effects. Neutralizing monoclonal antibodies against SARS-CoV-2 have been rapidly developed and are in clinical use.

There are three anti-SARS-CoV-2 monoclonal antibody products that have been granted Emergency Use Authorization by the United States Food and Drug Administration (US FDA) for use in non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk of developing severe disease. Use of the combination of bamlanivimab plus etesevimab (Eli Lilly and Co., USA), which bind to different but overlapping epitopes in the receptor-binding domain (RBD) of SARS-CoV-2, has been reported to be associated with a 70% reduction in the risk of COVID-19-related hospitalization or death compared to placebo [13]; however, this product is currently not authorized because it has limited effectiveness against the Beta (B.1.351) and Gamma (P.1) variants of SARS-CoV-2 [14]. Sotrovimab (GlaxoSmithKline, United Kingdom) administered on its own without other neutralizing monoclonal antibodies, has been reported to reduce the risk of all-cause hospitalization and death and has been approved in many countries, including the United States, Canada, Singapore, Australia and Japan, for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 [15]. Sotrovimab is thought to be effective against variants of SARS-CoV-2 because it targets conserved epitopes in the RBD shared by SARS-CoV-1 and SARS-CoV-2 [16]. The combination of casirivimab plus imdevimab (Regeneron Pharmaceuticals, USA), which binds to non-overlapping epitopes of RBD of SARS-CoV-2, has been reported to reduce the risk of hospitalization and all-cause death by approximately 70% [17, 18].

Regdanvimab (Celltrion, Republic of Korea) is an anti-SARS-CoV-2 monoclonal antibody that has been approved in South Korea, Indonesia, and Brazil for the treatment of mild-to-moderate COVID-19. In an interim analysis of a clinical trial published as a preprint, treatment with regdanvimab was associated with a decreased risk of hospitalization or death in non-hospitalized COVID-19 patients compared to placebo [19]. Based on this result, the South Korean Ministry of Food and Drug Safety granted conditional marketing authorization for the emergency use of regdanvimab for the treatment of mild-to-moderate COVID-19 on February 5, 2021.

To date, there have been no studies on the effectiveness of regdanvimab other than clinical trials. In this study, we investigated the effectiveness of regdanvimab in hospitalized patients with mild-to-moderate COVID-19.

Methods

Patients and data collection

In this retrospective cohort study, we analyzed data from the medical records of patients with COVID-19 who were admitted to a COVID-19 designated hospital with 765 inpatient beds including 195 nationally designated negative pressure isolation units in Seoul, South Korea, between February 1 and June 31, 2021. This hospital, which can accommodate 180 patients, admits all high-risk patients, regardless of their age and symptoms, and also admits low-risk patients if hospitalization is necessary. Some low-risk patients are admitted to COVID-19 designated community centers for isolation and transferred to this hospital when hospitalization is required. Among the patients hospitalized during the study periods, patients administered regdanvimab during hospitalization were selected. Next, for appropriate comparison, patients who meet the criteria of regdanvimab administration but did not actually receive it were selected as a control group. Regdanvimab (Celltrion, Republic of Korea) was approved to use in South Korea at February, 2020 and indication of regdanvimab administration was COVID-19 patients within 7 days of symptom onset and met at least one of following criteria: were aged 60 years or older, had abnormalities on chest X-ray, or had more than one underlying comorbidity, such as cardiovascular disease, chronic respiratory disease, diabetes mellitus, and hypertension. In addition, we also excluded patients younger than 18 years, pregnant women, patients who required oxygen therapy on the day of admission from control group. The clinical outcome measures used in the analysis were a requirement for supplemental oxygen, mortality during hospitalization, and length of hospitalization.

Statistical analysis

Patients were divided into a regdanvimab group and a control group in the analysis. Patient descriptive characteristics were summarized as counts and percentages or medians and interquartile ranges (IQRs). Baseline characteristics of the regdanvimab group and the control group were compared using chi-square tests or Fisher's exact test for categorical variables, and the Mann-Whitney U-test for continuous variables. Logistic regression was used to identify factors associated with requiring supplemental oxygen. Multivariable logistic regression analysis was performed with the variables that were statistically significant in univariate logistic regression analysis. The results of the logistic regression analyses were reported as odds ratios (ORs) with the 95% confidence intervals (CIs). P -values < 0.05 were considered statistically significant. All analyses were performed using R Version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 1,171 patients with COVID-19 were admitted to the study hospital. We excluded 697 patients who were younger than 18 years, pregnant, received oxygen therapy at the day of hospital admission or did not meet the criteria for regdanvimab administration (Figure 1). A total of 474 patients were eligible for regdanvimab administration. Of the 474 patients, 66 (13.9%) received regdanvimab (Table 1). Patients in the regdanvimab group were significantly older than those in the control group (median age: 66 years vs. 61 years, $P = 0.008$). The majority of patients in both groups were female. The median body mass index did not differ significantly according to group (median 22.82 vs. 22.79 kg/m², $P = 0.364$). Chest X-ray abnormalities were less common among patients in the regdanvimab group than those in the control group (median: 50% vs. 63.5%, $P = 0.051$). There was no significant difference between groups in the prevalence of underlying comorbidities or the use of immunosuppressive drugs. The frequency of supplemental oxygen use was significantly lower in the regdanvimab group than in the control group (6.1% vs. 22.8%, $P = 0.001$). Although, interval from symptom onset to starting supplemental oxygen was longer in the patients in the regdanvimab group than those in the control group, the difference was not statistically significant (median: 10.5 days vs. 7.5 days, $P = 0.067$). Patients in the regdanvimab group all received monoclonal antibodies within 7 days after symptom onset (median: 4 days, IQR: 3–5 days). There were no deaths in the regdanvimab group and five deaths in the control group (0% vs. 1.2%, $P > 0.999$). The median length of hospitalization was 10 days in both the regdanvimab group and the control group.

Table 1

Baseline Characteristics and clinical outcomes of COVID-19 patients who matching the indications of regdanvimab administration

	Regdanvimab (N = 66)	Control (N = 408)	<i>P</i>
Age years [median (IQR)]	66 (56.25-74.75)	61 (50-70)	0.008
Male sex [N (%)]	30 (45.5)	190 (46.6)	0.972
BMI [median (IQR)]	22.82 (20.82-26.72)	22.76 (21.71-26.18)	0.364
Chest x-ray abnormality [N (%)]	33 (50.0)	259 (63.5)	0.051
Comorbidity [N (%)]			
Hypertension	33 (50.0)	160 (39.2)	0.129
Cardiovascular disease	7 (10.6)	40 (9.8)	>0.999
Diabetes	14 (21.2)	91 (22.3)	0.969
Chronic pulmonary disease	6 (9.1)	37 (9.1)	>0.999
Chronic kidney disease	5 (7.6)	12 (2.9)	0.128
Cancer	4 (6.1)	19 (4.7)	0.545
Immunosuppression	2 (3.0)	7 (1.7)	0.363
Oxygen requirement [N (%)]	4 (6.1)	93 (22.8)	0.001
Duration of symptoms before oxygen requirement [median (IQR)]	10.5 (8.75-11.75)	7 (5-8)	0.067
Duration of symptoms before infusion [median (IQR)]	4 (3-5)		
In hospital mortality [N (%)]	0 (0)	5 (1.2)	>.999
Admission duration (days) [median (IQR)]	10 (9-11)	10 (8-11)	0.273
N, number			
IQR, interquartile range			
<i>P</i> , p-value			
BMI, body mass index			

Table 2. Univariate and multivariate logistic regression analyses for supplemental oxygen.						
	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age	1.02	1.00-1.03	0.014	1.03	1.01-1.05	<.001
Sex (male)	1.59	1.02-2.50	0.043	1.60	0.99-2.59	0.056
BMI	1.03	0.97-1.09	0.303			
Chest x-ray abnormality	4.04	2.33-7.40	<.001	4.40	2.49-8.21	<.001
Comorbidity [N (%)]						
Hypertension	1.01	0.64-1.59	0.953			
Cardiovascular disease	0.65	0.26-1.41	0.312			
Diabetes	1.19	0.69-1.98	0.516			
Chronic pulmonary disease	0.87	0.36-1.85	0.735			
Chronic kidney disease	2.83	1.00-7.58	0.040	2.64	0.83-8.31	0.095
Cancer	0.85	0.24-2.35	0.775			
Immunosuppression	1.96	0.41-7.56	0.349			
Regdanvimab administration	0.22	0.07-0.55	0.004	0.17	0.05-0.47	0.002
OR, odds ratio						
CI, confidence interval						
BMI, body mass index						

In the univariate logistic regression analysis to identify variables associated with requiring supplemental oxygen, increasing age, male sex, abnormal findings on chest X-ray, and chronic kidney disease were found to be associated with an increased risk of requiring supplemental oxygen, and administration of regdanvimab was associated with a decreased risk of requiring supplemental oxygen (**Table 2**). In the multivariable logistic regression analysis, older age (OR: 1.03, 95% CI: 1.01-1.05, $P < 0.001$) and chest X-ray abnormalities (OR: 4.40, 95% CI: 2.49-8.21, $P < 0.001$) were associated with a significantly higher risk of requiring supplemental oxygen. After adjustment of age, sex, chest X-ray abnormalities, and chronic kidney disease, administration of regdanvimab remained associated with a significantly lower risk of requiring supplemental oxygen (OR: 0.17, 95% CI: 0.05-0.47, $P < 0.002$).

None of the patients who received regdanvimab experienced hypersensitivity reactions or infusion reactions. One patient reported the urticaria of both arms one day after receiving a regdanvimab infusion. There were no serious adverse reactions recorded in the electronic medical records.

Discussion

This study investigated the effectiveness of regdanvimab for the treatment of COVID-19. Patients in the regdanvimab group were significantly less likely to require supplemental oxygen than patients in the control group, and regdanvimab administration was independently associated with a reduced likelihood of requiring supplemental oxygen during hospitalization after controlling for confounders. However, there was no difference the mortality rate or the length of hospitalization between the two groups.

Older age, male sex and chest X-ray abnormality have previously been identified as risk factors for severe COVID-19 [4–6, 20], and were significantly associated with requiring supplemental oxygen in this study. However, in this study, obesity, which is also known to be a risk factor for severe disease [21], was not significantly associated with requiring supplemental oxygen in this study. Administration of regdanvimab was significantly associated with a reduced likelihood of requiring supplemental oxygen, even after adjusting for age, sex, the presence of chest X-ray abnormalities, and chronic kidney disease.

In South Korea, patients without risk factors for disease progression are primarily admitted to community treatment centers, which are facilities that provide minimum tests and few medications [22]. Patients with worsening symptoms or risk factors for disease progression are admitted or transferred to hospitals. The disease severity of patients in this study is likely to have been more severe than that of patients who participated in clinical trials because we only included hospitalized patients, although most patients who meet the indications for regdanvimab administration are hospitalized. This may explain the higher proportion of patients that required supplemental oxygen in this study than in the clinical trials [19]. As in the clinical trials, there were no deaths among patients in the regdanvimab group in this study. However, the reduction in mortality was not statistically significant in this study because the mortality rate in the control group was low.

The length of hospitalization was similar between patients in the regdanvimab group and in the control group. This may not adequately represent the effects of regdanvimab because a minimum of 10 days hospitalization after symptom onset is a statutory requirement in South Korea. In addition, the control group may have included patients with asymptomatic and relatively mild disease who would not have required additional therapeutics such as regdanvimab. This could have masked any effect of regdanvimab on reducing the length of hospitalization in patients with COVID-19.

This study has some limitations. It was a retrospective cohort study. It was difficult to find an appropriate control group because of the heterogeneity in of the disease manifestations. To overcome this limitation, we restricted the control group to patients who had indications for regdanvimab administration. Nevertheless, patients in regdanvimab group were significantly older than patients in control group and abnormalities on the initial chest X-ray were more common in patients who did not receive regdanvimab. In addition, it is possible that adverse reactions were under-recognized because they may not have been recorded in patients' medical records.

In addition, SARS-CoV-2 variants were not investigated in this study. Mutations of the SARS-CoV-2 spike protein could affect the effectiveness of anti-SARS-CoV-2 monoclonal antibodies. The combination of bamlanivimab plus etesevimab has not been approved because of its limited effectiveness against the SARS-CoV-2 Beta (B.1.351) and Gamma (P.1) variants. In addition, the SARS-CoV-2 Delta (B.1.167.2) variant, first detected in India in December 2020 [23], is estimated to be 40–60% more transmissible than the Alpha (B.1.1.7) variant, and is now spreading worldwide. The Delta variant is currently the cause of most COVID-19 cases in the United States and South Korea [24, 25]. The Delta variant has mutations in the RBD of the spike protein that impair the binding affinity of neutralizing monoclonal antibodies targeting the RBD. Of the monoclonal antibodies approved by the US FDA, bamlanivimab does not bind to the Delta variant [26]. Regdanvimab is a class I neutralizing monoclonal antibody that blocks ACE2 receptors and binds to the RBD [27, 28]. Although regdanvimab has been shown to reduce the death rate and ameliorate weight loss in ACE2-transgenic mice infected with the Delta variant, it showed reduced binding affinity and susceptibility to regdanvimab, and the neutralizing activity of regdanvimab against the Delta variant was lower than that against the original strain of SARS-CoV-2 *in vitro* [29]. The effectiveness of regdanvimab against the Delta variant *in vivo* is uncertain.

Conclusions

This study provides the real-world data about the effectiveness of regdanvimab for the treatment of mild to moderate COVID-19 patients. The administration of regdanvimab reduced the requirement for supplemental oxygen in patients who matched the indications for administration of regdanvimab in our study. Further research is needed to determine the efficacy of regdanvimab in patients infected with the SARS-CoV-2 Delta variant

Abbreviations

COVID-19

Coronavirus disease

SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2

WHO

World Health Organization

US FDA

United States Food and Drug Administration

RBD

Receptor-binding domain

BMI

Body mass index

IQRs

interquartile ranges

ORs
Odds ratios
CIs
Confidence intervals

Declarations

Ethics approval and consent to participate

All methods of this study were performed in accordance with the Declaration of Helsinki and the relevant guidelines and regulations. This study was approved by the Institutional Review Board of the Seoul Metropolitan Government Boramae Medical Center (No. 20-2021-53). The IRB waived the requirement for informed consent from the study participants because of the retrospective study design.

Consent for publication

Not applicable

Availability of data and materials

All relevant data are within the paper. Requests for additional information should be addressed to the corresponding author and data may be provided on reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author's contributions

SJC: data collection and analysis, manuscript writing

SWP: intellectual content, supervision, manuscript editing.

EL: study conception and design, supervision, manuscript editing.

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References

1. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY *et al*: **A new coronavirus associated with human respiratory disease in China.** *Nature* 2020, **579**(7798):265-269.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R *et al*: **A Novel Coronavirus from Patients with Pneumonia in China, 2019.** *N Engl J Med* 2020, **382**(8):727-733.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC *et al*: **Clinical Characteristics of Coronavirus Disease 2019 in China.** *N Engl J Med* 2020, **382**(18):1708-1720.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X *et al*: **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.** *Lancet* 2020, **395**(10223):497-506.
5. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C *et al*: **Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.** *JAMA Intern Med* 2020, **180**(7):934-943.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X *et al*: **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.** *Lancet* 2020, **395**(10229):1054-1062.
7. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S *et al*: **Remdesivir for the Treatment of Covid-19 - Final Report.** *N Engl J Med* 2020, **383**(19):1813-1826.
8. Spinner CD, Gottlieb RL, Criner GJ, Arribas Lopez JR, Cattelan AM, Soriano Viladomiu A, Ogbuagu O, Malhotra P, Mullane KM, Castagna A *et al*: **Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial.** *JAMA* 2020, **324**(11):1048-1057.
9. **Therapeutics and COVID-19: living guideline** [<https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3>]
10. The IMPact-RSV Study Group: **Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMPact-RSV Study Group.** *Pediatrics* 1998, **102**(3 Pt 1):531-537.
11. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH, Jr., Connor EM, Sondheimer HM, Cardiac Synagis Study G: **Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease.** *J Pediatr* 2003, **143**(4):532-540.
12. Mulangu S, Dodd LE, Davey RT, Jr., Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A *et al*: **A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics.** *N Engl J Med* 2019, **381**(24):2293-2303.

13. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, Hebert C, Perry R, Boscia J, Heller B *et al*: **Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19**. *N Engl J Med* 2021.
14. **COVID-19 Treatment Guidelines** [<https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/>]
15. Gupta A, Gonzalez-Rojas Y, Juarez E, Casal MC, Moya J, Falci DR, Sarkis E, Solis J, Zheng H, Scott N *et al*: **Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab**. *medRxiv* 2021:2021.2005.2027.21257096.
16. Cathcart AL, Havenar-Daughton C, Lempp FA, Ma D, Schmid MA, Agostini ML, Guarino B, Di iulio J, Rosen LE, Tucker H *et al*: **The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2**. *bioRxiv* 2021.
17. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, Soo Y, Rofail D, Im J *et al*: **REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19**. *N Engl J Med* 2021, **384**(3):238-251.
18. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Xiao J, Hooper AT, Hamilton JD, Musser BJ *et al*: **REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients**. *medRxiv* 2021.
19. Joong Sik Eom MI, Anca Streinu-Cercel, Oana Săndulescu, Liliana-Lucia Preotescu, Yeon-Sook Kim, Jin Yong Kim, Shin Hyea Cheon, Young Rock Jang, Sang Joon Lee, Sung Hyun Kim, Ilsung Chang, Jee Hye Suh, Seul Gi Lee, Mi Rim Kim, Da Rae Chung, Han Na Kim, Adrian Streinu-Cercel: **Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate SARS-CoV-2 infection**. *PREPRINT (Version 1) available at Research Square* 2021.
20. CDC Covid- Response Team: **Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020**. *MMWR Morb Mortal Wkly Rep* 2020, **69**(13):382-386.
21. Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, He Q, Wang Z, Liu Y, Liu L *et al*: **Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China**. *Diabetes Care* 2020, **43**(7):1392-1398.
22. Lee SY, Song KJ, Lim CS, Kim BG, Chai YJ, Lee JK, Kim SH, Lim HJ: **Operation and Management of Seoul Metropolitan City Community Treatment Center for Mild Condition COVID-19 Patients**. *J Korean Med Sci* 2020, **35**(40):e367.
23. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, Rakshit P, Singh S, Abraham P, Panda S *et al*: **SARS-CoV-2 Spike Mutations, L452R, T478K, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India**. *Microorganisms* 2021, **9**(7).

24. Kim IH, Park AK, Lee H, Kim J, Kim DH, Kim JA, No JS, Lee CY, Woo S, Lee J *et al*: **July 2021 status and characteristics of the COVID-19 variant virus outbreak in the Republic of Korea.** *Public Healthy Weekly Report* 2021.
25. Ryu B, Oh J, Shin M, Kim S, Kim I: **Global trends and characteristics of the SARS-CoV-2 Delta Variant.** *Public Healthy Weekly Report* 2021.
26. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, Planchais C, Porrot F, Robillard N, Puech J *et al*: **Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization.** *Nature* 2021, **596**(7871):276-280.
27. Kim C, Ryu DK, Lee J, Kim YI, Seo JM, Kim YG, Jeong JH, Kim M, Kim JI, Kim P *et al*: **A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein.** *Nat Commun* 2021, **12**(1):288.
28. Barnes CO, Jette CA, Abernathy ME, Dam KA, Esswein SR, Gristick HB, Malyutin AG, Sharaf NG, Huey-Tubman KE, Lee YE *et al*: **SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies.** *Nature* 2020, **588**(7839):682-687.
29. Ryu D-K, Woo H-M, Kang B, Noh H, Kim J-I, Seo J-M, Kim C, Kim M, Kim J-W, Kim N *et al*: **The in vitro and in vivo potency of CT-P59 against Delta and its associated variants of SARS-CoV-2.** *bioRxiv* 2021:2021.2007.2023.453472.

Figures

Figure 1

Flow diagram of patient's selection for retrospective cohort study.