

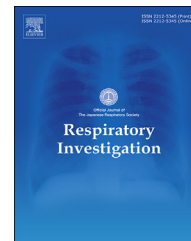


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Original article

Risk factors for progression to acute respiratory failure after casirivimab and imdevimab administration: A retrospective study



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ABSTRACT

Background: Casirivimab and imdevimab are effective in preventing hospitalization in outpatients with coronavirus disease 2019 (COVID-19); however, disease progression after casirivimab and imdevimab administration has been reported. This study aimed to elucidate the risk factors for disease progression after casirivimab and imdevimab administration.

Methods: This retrospective study included patients with COVID-19 who received casirivimab and imdevimab at Hiroshima City Funairi Citizens Hospital between August 6, 2021, and October 10, 2021. All patients had at least one risk factor for severe disease and were treated on admission. The patients' background characteristics and test results at the first visit were analyzed. The patients were divided into two groups (progressed and improved) based on whether they progressed to acute respiratory failure during hospitalization.

Results: Sixty-seven patients were included: 9 patients in the progressed group (median age, 56 years) and 58 patients in the improved group (median age, 51 years). Age, coexistence rate of diabetes, cycle threshold value of polymerase chain reaction test, rate of detectable pneumonia on chest radiographs or chest computed tomography images, lymphocyte count, and the levels of C-reactive protein, interleukin-6, glucose, and glycated hemoglobin were significantly different between the two groups. Multivariate logistic regression analysis revealed that the coexistence of diabetes and the presence of detectable pneumonia on chest radiographs were independent factors predicting the progression to acute respiratory failure.

Conclusion: Acute respiratory failure after antibody therapy with casirivimab and imdevimab may develop in patients with diabetes or detectable pneumonia on chest radiographs at the first visit.

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Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Ct, cycle threshold; CT, computed tomography; HbA1c, glycated hemoglobin; IL-6, interleukin-6; OR, odds ratio; PCR, polymerase chain reaction.

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1. Introduction

Antibody therapy has recently emerged as a new treatment option for coronavirus disease 2019 (COVID-19). Casirivimab and imdevimab (REGEN-COV) is a combination therapy that uses two neutralizing monoclonal antibodies against the spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This treatment inhibits the binding of the S protein to angiotensin-converting enzyme 2 (ACE2) on the host cell surface and induces antibody-dependent cell-mediated cytotoxicity and cellular phagocytosis, thereby resulting in viral load reduction [1].

A previous clinical trial has reported that the efficacy of this treatment in reducing events such as hospitalization or death is approximately 70% in outpatients with COVID-19 who are at a risk of progressing to a severe disease state [2]. However, the results of the trial suggested that the administration of casirivimab and imdevimab cannot prevent disease progression and may lead to acute respiratory failure in some patients with COVID-19. Furthermore, in daily clinical practice, patients who are unresponsive to casirivimab and imdevimab and require further treatment with other drugs, such as remdesivir, corticosteroids, and baricitinib, are often encountered. To the best of our knowledge, only two observational studies have examined the risk factors for hospitalization after antibody therapies (bamlanivimab or casirivimab and imdevimab) [3,4]. These studies have reported that old age, male sex, chronic kidney disease, immunodeficiency, heart disease, and chronic lung disease are associated with hospitalization despite the above-mentioned monoclonal antibody therapies [3,4].

Some laboratory findings, such as lymphopenia, thrombocytopenia, and elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6), are known risk factors for progression to severe COVID-19 [5,6]. Moreover, chest imaging is a useful technique for assessing the underlying etiology of acute respiratory failure [7]. Thereby, it is possible that laboratory data and chest imaging findings at the first visit are closely associated with the change in the respiratory state after antibody therapy. However, previous studies did not investigate the influence of laboratory data and chest imaging findings before the initiation of antibody therapy. Therefore, we conducted this study to more precisely investigate the risk factors for progression to acute respiratory failure after the administration of casirivimab and imdevimab, including laboratory data and chest imaging findings.

2. Patients and methods

2.1. Study design and population

This retrospective study included 67 patients with COVID-19 who visited Hiroshima City Funairi Citizens Hospital and received casirivimab and imdevimab between August 6, 2021, and October 10, 2021. All patients were diagnosed with COVID-19 based on a positive polymerase chain reaction (PCR) test.

Casirivimab and imdevimab were administered if the patients met all of the following criteria: (i) presence of at least one risk factor for progression to a severe disease state, including age ≥ 50 years, body mass index ≥ 25 kg/m², and coexistence of diabetes, hypertension, chronic lung disease, or chronic kidney disease; (ii) percutaneous arterial oxygen saturation (SpO₂) $\geq 93\%$ at the first visit; and (iii) ≤ 7 days from onset to the first visit. As the use of casirivimab and imdevimab was approved in Japan only on July 19, 2021, all patients received this treatment under hospitalization for careful clinical observation, including the evaluation of adverse events.

2.2. Ethical approval

This study was approved by the institutional review board of Hiroshima City Funairi Citizens Hospital (approval no. 2021010; date of approval, December 14, 2021). The opt-out method was used to obtain informed consent from the study participants.

2.3. Data collection

We collected the following data from the hospital electronic medical records: medical history, comorbidities, smoking habit, height, weight, SpO₂ at rest, laboratory test results, and chest radiography and computed tomography (CT) findings at the first visit. For each patient, three pneumologists judged whether pneumonia could be detected on chest radiographs and CT images without obtaining the patients' clinical information. We used the cycle threshold (Ct) value from the PCR assay to evaluate the viral load.

2.4. Outcome measure

In this study, decreased SpO₂ ($<93\%$) on room air was defined as the criterion for progression to acute respiratory failure [8]. According to this criterion, we divided the patients into the following two groups: progressed and improved.

2.5. Statistical analysis

Data are presented as median (range) values, except for the percentages of indices, which are described using real counts. To compare the variables between the two groups, the t-test or Wilcoxon rank-sum test was used. Chi-square tests were performed for categorical variables. Furthermore, univariate and multivariate logistic regression analyses were performed to determine the independent factors for predicting the progression to acute respiratory failure after casirivimab and imdevimab administration. In logistic regression analyses, the cutoff values for lymphocyte count, serum CRP and IL-6 levels, Ct values of PCR performed for diagnosis, SpO₂ before casirivimab and imdevimab administration, and days from onset to administration were set to the median value for the whole data. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the statistical software JMP Pro (version 16.0.0; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Table 1 shows the background characteristics of all patients. The median age of the patients was 51 years (17–78 years). Of the 67 patients, 40 (59.7%) were men and 27 (40.3%) were women. The prevalence of comorbidities was as follows: diabetes, 17.9% (12 patients); hypertension, 25.4% (17 patients); chronic lung disease, 16.4% (11 patients); and chronic kidney disease, 0% (0 patient). Of the patients, 46 (68.7%) had not been vaccinated, 9 (13.4%) had received one dose of vaccination, and 12 (17.9%) had received two doses of vaccination. Pneumonia was detected on chest CT images obtained at the first visit in 41 patients (61.2%) and on chest radiographs obtained at the first visit in only 17 patients (25.4%).

The median number of days from the onset of disease to the administration of casirivimab and imdevimab was 3 days (1–6 days). Nine patients (13.4%) progressed to acute respiratory failure during the course of hospitalization. With respect to the timing of acute respiratory failure, five patients (55.6%) progressed on the day of administration, three patients (33.3%) after 1 day of administration, and one patient (11.1%) after 2 days of administration.

3.2. Comparison of the progressed and improved groups

Representative cases from the improved and progressed groups are shown in Fig. 1A and B and Fig. 1C and D, respectively. In the improved group, a 55-year-old woman with a high body mass index of 36.6 kg/m² and without comorbidities received casirivimab and imdevimab on the second day after onset. Localized ground-glass opacities were observed on the chest CT image (Fig. 1B) but not on the chest radiograph (Fig. 1A). The patient did not progress to acute respiratory failure during the course of hospitalization.

In contrast, in the progressed group, a 62-year-old man with hypertension received casirivimab and imdevimab on the fifth day after onset. The chest radiograph (Fig. 1C) and the CT image (Fig. 1D) revealed the presence of bilateral ground-glass opacities and infiltrates with peripheral distribution. The patient progressed to acute respiratory failure on the day of casirivimab and imdevimab administration and received additional treatment with remdesivir, corticosteroids, and baricitinib.

Patients in the progressed group were older and had higher coexistence rates of diabetes, more risk factors for severe COVID-19, lower Ct values of PCR performed for diagnosis, and lower SpO₂ levels before casirivimab and imdevimab administration than those in the improved group (Table 2). The proportion of patients whose pneumonia could be detected on chest radiographs and CT images was significantly higher in the progressed group than in the improved group. In addition, the lymphocyte count was lower and the CRP, IL-6, glucose, and glycated hemoglobin (HbA1c) levels were higher in the progressed group than in the improved group (Table 2). A subset analysis of the 12 patients with diabetes showed no significant difference in glucose and HbA1c levels between the

Table 1 – Background characteristics of the study patients (N = 67).

Characteristics	Data
Age, years, median (range)	51 (17–78)
≥ 50 years	40 (59.7%)
Sex	
Male	40 (59.7%)
Female	27 (40.3%)
BMI, kg/m ² , median (range)	27.3 (16.9–45.5)
≥ 25 kg/m ²	46 (68.7%)
Smoking habit	32 (47.8%)
Comorbidity	
Diabetes	12 (17.9%)
Hypertension	17 (25.4%)
Chronic lung disease	11 (16.4%)
Chronic kidney disease	0 (0%)
Vaccination	
None	46 (68.7%)
One dose	9 (13.4%)
Two doses	12 (17.9%)
SpO ₂ before casirivimab and imdevimab administration, %, median (range)	97 (93–99)
Detectable pneumonia on chest radiographs at the first visit	
Yes	17 (25.4%)
No	50 (74.6%)
Detectable pneumonia on chest CT images at the first visit	
Yes	41 (61.2%)
No	26 (38.8%)
Days from disease onset to casirivimab and imdevimab administration, median (range)	3 (1–6)
Ct value of PCR performed for diagnosis (n = 59 ^a), median (range)	25.0 (12.4–38.0)
Patients whose SpO ₂ decreased to < 93% after casirivimab and imdevimab administration	9 (13.4%)
On the day	5 (55.6%)
After 1 day	3 (33.3%)
After 2 days	1 (11.1%)
BMI, body mass index; Ct, cycle threshold; CT, computed tomography; PCR, polymerase chain reaction; SpO ₂ , percutaneous arterial oxygen saturation.	
^a All 67 patients underwent PCR testing; however, only 59 patients had available Ct values.	

progressed and improved groups (glucose, 223.0 vs. 186.5 mg/dL, P = 0.3367; HbA1c, 8.85% vs. 6.75%, P = 0.0802).

3.3. Risk factors for progression to acute respiratory failure

Table 3 presents the results of the univariate logistic regression analysis. Progression to acute respiratory failure was significantly associated with the coexistence of diabetes (odds ratio [OR], 5.000; 95% confidence interval [CI], 1.103–22.675; P = 0.0369), number of risk factors for severe disease ≥ 3 (OR, 4.327; 95% CI, 1.013–18.491; P = 0.0481), detectable pneumonia on chest radiographs (OR, 16.800; 95% CI, 3.030–93.147; P = 0.0012), CRP level ≥ 0.96 mg/dL (OR, 8.889; 95% CI, 1.043–75.769; P = 0.0457), and IL-6 level ≥ 14 pg/mL (OR, 9.920;

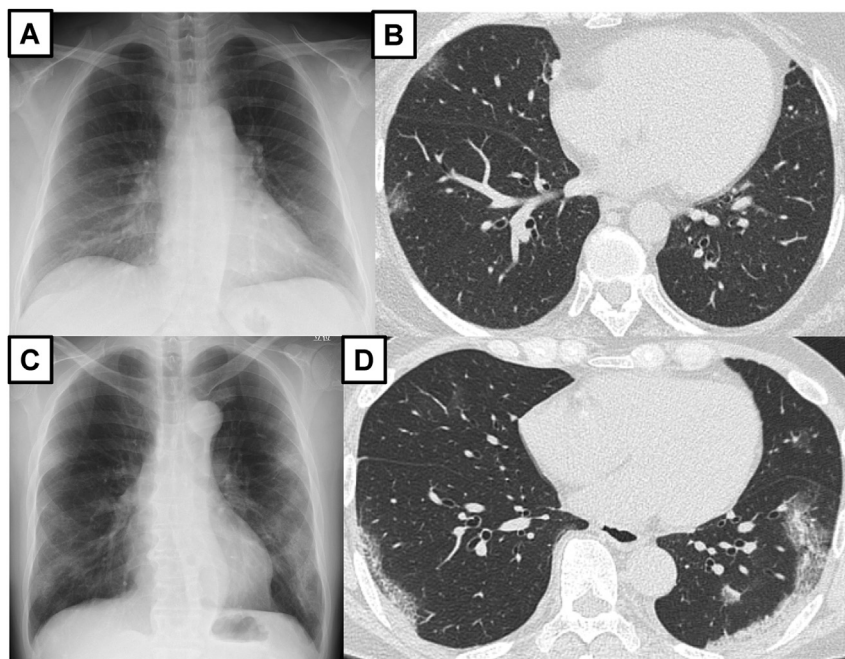


Fig. 1 – Chest radiographs (A, C) and computed tomography (CT) images (B, D) obtained at the first visit of representative patients from the improved and progressed groups. A 55-year-old woman with a body mass index of 36.6 kg/m² and with no comorbidities visited our hospital on the second day after disease onset and was administered casirivimab and imdevimab. She did not progress to acute respiratory failure. Her chest CT image showed ground-glass opacities confined to the outside of the right lung field (B); however, her chest radiograph findings were normal (A). A 62-year-old man with hypertension visited our hospital on the fifth day after disease onset. He was administered casirivimab and imdevimab but subsequently progressed to acute respiratory failure on the same day. The chest CT image showed bilateral ground-glass opacities and infiltrative shadows with peripheral distribution (D). The corresponding shadows can be detected on both sides of the lower lung field on the chest radiograph (C).

95% CI, 1.162–84.701; $P = 0.0360$). Multivariate logistic regression analysis was performed with the coexistence of diabetes, detectable pneumonia on chest radiographs, and CRP level ≥ 0.96 mg/dL as covariates because these three variables did not overlap with the other factors and are easily available in daily clinical practice. We found that the coexistence of diabetes (OR, 11.100; 95% CI, 1.057–116.520; $P = 0.0448$) and the presence of detectable pneumonia on chest radiographs (OR, 22.515; 95% CI, 2.210–229.341; $P = 0.0085$) were independent factors predicting the progression to acute respiratory failure after the administration of casirivimab and imdevimab (Table 4).

4. Discussion

To the best of our knowledge, this is the first study to focus on the risk factors for progression to acute respiratory failure after the administration of casirivimab and imdevimab in hospitalized patients with COVID-19. Diabetes as a comorbidity and detectable pneumonia on chest radiographs were significant predictors of hypoxemia with SpO₂ < 93% after this treatment.

Diabetes is a risk factor for the aggravation of COVID-19 severity. Although the underlying mechanism remains unclear, immune system imbalance, overactivated inflammatory

response, and increased ACE2 expression have been speculated to be involved [9]. ACE2 is essential for SARS-CoV-2 replication and for the onset of COVID-19 [10]. Diabetic mice have been demonstrated to have enhanced ACE2 expression in the lungs [11,12]. In addition, in a study that performed Mendelian randomized analysis, diabetes was found to be associated with increased ACE2 expression in the human lungs [13]. In another study, the ACE2 expression level in the lung tissue of surgical specimens was significantly higher in patients with diabetes than in those without diabetes [14]. These previous findings indicate that enhanced expression of ACE2 in lung tissues may be a mechanism for attenuating the effect of casirivimab and imdevimab in patients with COVID-19 and diabetes.

In the previous study, blood glucose levels were positively correlated with ACE2 expression, and patients with diabetes with HbA1c $\geq 8\%$ had higher ACE2 expression levels than those with HbA1c < 8% [14]. These results suggest that poor glycemic control is associated with increased ACE2 levels. Although our subset analysis of patients with diabetes showed that both blood glucose and HbA1c levels tended to be higher in the progressed group than in the improved group, these differences did not reach statistical significance. We attribute this to the small number of patients with diabetes included in our study. As a clinical question of great interest, it remains unclear whether improvement in diabetic control decreases ACE2 expression and ameliorates the effect of

Table 2 – Characteristics of patients stratified by progression to acute respiratory failure after casirivimab and imdevimab administration (N = 67).

Characteristics	Progressed group (n = 9)	Improved group (n = 58)	P
Age, years, median (range)	56 (48–76)	51 (17–78)	0.0081
Male sex	5 (55.6%)	35 (60.3%)	0.7852
BMI, kg/m ² , median (range)	29.4 (23.4–37.0)	27.3 (16.9–45.5)	0.6905
Smoking habit	3 (33.3%)	29 (50.0%)	0.3517
Vaccination	2 (22.2%)	19 (32.8%)	0.5261
Diabetes	4 (44.4%)	8 (13.8%)	0.0257
Hypertension	4 (44.4%)	13 (22.4%)	0.1576
Chronic lung disease	1 (11.1%)	10 (17.2%)	0.6441
Number of risk factors for severe disease, median (range)	3 (1–4)	2 (0–5)	0.0134
Days from disease onset to casirivimab and imdevimab administration, median (range)	4 (3–6)	3 (1–6)	0.1420
Number of patients with available Ct values	8	51	
Ct value, median (range)	19.9 (12.4–32.0)	25.8 (15.2–38.0)	0.0218
SpO ₂ before casirivimab and imdevimab administration, %, median (range)	95 (93–98)	97 (95–99)	0.0013
Detectable pneumonia on chest radiographs	7 (77.8%)	10 (17.2%)	0.0001
One side	2 (28.6%)	6 (60.0%)	0.2014
Both sides	5 (71.4%)	4 (40.0%)	
Detectable pneumonia on chest CT images	8 (88.9%)	33 (56.9%)	0.0478
One side	0 (0%)	8 (24.2%)	0.1206
Both sides	8 (100%)	25 (75.8%)	
Laboratory data, median (range)			
WBC, × 10 ³ μL ⁻¹	3.9 (3.5–7.8)	4.6 (1.8–11.1)	0.8975
Neu, × 10 ³ μL ⁻¹	3.0 (2.5–5.5)	2.8 (0.8–8.7)	0.1886
Lym, × 10 ³ μL ⁻¹	0.7 (0.6–1.6)	1.2 (0.4–3.0)	0.0460
Platelet, × 10 ⁴ μL ⁻¹	17.3 (10.2–25.8)	18.3 (10.2–46.3)	0.2467
AST, U/L	40 (16–66)	29 (13–128)	0.2465
ALT, U/L	34 (15–82)	32 (9–251)	0.7267
CRP, mg/dL	3.72 (0.35–9.74)	0.80 (0.04–13.50)	0.0090
Ferritin, ng/mL	281 (33–1356)	231 (5–965)	0.5625
IL-6, pg/mL	35 (13–177)	11 (3–97)	0.0006
Glucose, mg/dL	151 (94–405)	112 (83–395)	0.0300
HbA1c, %	6.4 (5.7–12.4)	5.7 (5.1–9.1)	0.0115

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; Ct, cycle threshold; CT, computed tomography; HbA1c, glycated hemoglobin; IL-6, interleukin-6; Lym, lymphocyte; Neu, neutrophil; SpO₂, percutaneous arterial oxygen saturation; WBC, white blood cell.

casirivimab and imdevimab. Thus, further studies are needed to clarify these issues.

In the current study, the presence of detectable pneumonia on chest radiographs was identified as another independent risk factor for progression to acute respiratory failure after the administration of casirivimab and imdevimab. Chest CT is superior to chest radiography in detecting early COVID-19 pneumonia with localized ground-glass opacities [15]. COVID-19 pneumonia can be observed on chest radiographs only when it becomes widespread or shows organizing change. As oxygenation gradually or suddenly worsens with the spread of COVID-19 pneumonia in both lung fields, patients with COVID-19 whose pneumonia can be detected on both chest CT images and radiographs are at a higher risk of acute respiratory failure than those whose pneumonia can be detected only on chest CT images. This result highlights the clinical significance of chest radiography at the first visit to prevent delay in the administration of casirivimab and imdevimab.

In contrast to the findings of two previous studies [3,4], this study did not identify old age, male sex, chronic kidney disease, immunodeficiency, heart disease, and chronic lung disease as risk factors predicting the progression to acute respiratory failure after the administration of casirivimab and imdevimab. This discrepancy in results can be attributed to the differences in the baseline characteristics of the included study participants (inpatient or outpatient) and in the clinical endpoint (acute respiratory failure or hospitalization).

This study had some limitations. First, it was conducted at a single facility. Second, the number of study participants was relatively small. Third, during the study period, most SARS-CoV-2 infections were caused by the delta variant; thus, it is unclear whether our findings can be applied to other variants. Fourth, because we focused on only one type of antibody therapy, there is no guarantee that the same results will be obtained when other antibody therapies are used. However, as most monoclonal antibodies bind to the SARS-CoV-2 S protein

Table 3 – Univariate logistic regression analysis for predicting the progression to acute respiratory failure after casirivimab and imdevimab administration.

Factors	Odds ratio	95% confidence interval	P
Age ≥ 50 years	6.500	0.763–55.373	0.0868
Male sex	0.821	0.199–3.385	0.7854
BMI ≥ 25 kg/m ²	1.705	0.323–9.007	0.5297
Smoking habit	0.500	0.114–2.193	0.3581
Vaccination	0.586	0.111–3.098	0.5297
Diabetes	5.000	1.103–22.675	0.0369
Hypertension	2.769	0.648–11.834	0.1693
Chronic lung disease	0.600	0.067–5.349	0.6472
Number of risk factors for severe disease ≥ 2	7.467	0.877–63.571	0.0658
Number of risk factors for severe disease ≥ 3	4.327	1.013–18.491	0.0481
Days from disease onset to casirivimab and imdevimab administration ≥ 4	1.902	0.462–7.839	0.3735
SpO ₂ before casirivimab and imdevimab administration $\leq 97\%$	6.500	0.763–55.373	0.0868
Detectable pneumonia on chest radiographs	16.800	3.030–93.147	0.0012
Detectable pneumonia on chest CT images	6.061	0.711–51.658	0.0993
Lym $\leq 1.1 \times 10^3$ μL^{-1}	2.143	0.489–9.399	0.3123
CRP ≥ 0.96 mg/dL	8.889	1.043–75.769	0.0457
IL-6 ≥ 14 pg/mL	9.920	1.162–84.701	0.0360
Ct value of PCR performed for diagnosis ≤ 25	8.522	0.9762–74.388	0.0526

BMI, body mass index; CRP, C-reactive protein; Ct, cycle threshold; CT, computed tomography; IL-6, interleukin-6; Lym, lymphocyte; PCR, polymerase chain reaction; SpO₂, percutaneous arterial oxygen saturation.

Table 4 – Multivariate logistic regression analysis for predicting the progression to acute respiratory failure after casirivimab and imdevimab administration.

Factors	Odds ratio	95% confidence interval	P
Diabetes	11.100	1.057–116.520	0.0448
Detectable pneumonia on chest radiographs	22.515	2.210–229.341	0.0085
CRP ≥ 0.96 mg/dL	3.019	0.288–31.601	0.3564

CRP, C-reactive protein.

[1], our findings may be helpful when administering other antibody therapies.

5. Conclusion

Patients with COVID-19 who have diabetes as a comorbidity or have detectable pneumonia on chest radiographs are likely to progress to acute respiratory failure even after the administration of casirivimab and imdevimab. Therefore, clinicians must pay careful attention to the change in the clinical course of these patients after the initiation of casirivimab and imdevimab in order to detect acute respiratory failure. Further studies are needed to confirm the findings of this study in a larger population of patients treated with other antibody therapies.

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Conflict of Interest

The authors declare no conflicts of interest.

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