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Changes in Clinical Features and Severity of COVID-19 with the Emergence of Omicron Variants: A Shift Towards a Common Disease

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Background: The emergence of the Omicron variant of severe acute respiratory syndrome coronavirus-2 has significantly altered the clinical features and severity of coronavirus disease 2019 (COVID-19).

Objective: This study aims to evaluate whether the clinical factors that previously predicted COVID-19 remain valid following the emergence of the Omicron variant.

Methods: This cross-sectional study was conducted at Showa University Fujigaoka Hospital from April 2022 to March 2023. A total of 576 patients with suspected COVID-19 were included, of which 258 (44.8%) were diagnosed with COVID-19 based on real-time reverse-transcription polymerase chain reaction tests. Clinical data were collected retrospectively, and multivariate logistic regression was used to analyze factors associated with a COVID-19 diagnosis.

Results: Of the 258 patients diagnosed with COVID-19, 60% had mild disease, and the overall severity was lower than in previous reports prior to the emergence of the Omicron variant. In the multivariate analysis, only C-reactive protein (CRP) levels were significantly associated with COVID-19 (odds ratio, 0.3164; 95% confidence interval, 0.2077–0.4819), while factors such as age, sex, body mass index, lactate dehydrogenase, and comorbidities were not significantly associated. Non-COVID-19 cases were primarily bacterial infections, accounting for 57.2% of the non-COVID-19 diagnoses. Mortality rates did not differ significantly between the COVID-19 and non-COVID-19 groups.

Conclusion: The clinical characteristics of COVID-19 have become less distinct since the emergence of the Omicron variant, with CRP being the primary marker associated with a COVID-19 diagnosis. As COVID-19 continues to transition towards a more common infectious disease, distinguishing it will become increasingly challenging.

Keywords: severe acute respiratory syndrome coronavirus-2, coronavirus disease 2019, Omicron variants, C-reactive protein

Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first emerged at the end of 2019, and Omicron variants have been reported worldwide since November 2021, raising concerns about their infectivity, transmissibility, and antigenicity.[1,2] Compared to previous lineages, Omicron variants exhibit increased infection rates and immune escape.[3,4] However, Omicron variants are associated with lower rates of severe disease and mortality compared to earlier lineages.[5,6] Even before the emergence of the Omicron variant, clinically suspected cases of coronavirus disease 2019 (COVID-19) were sometimes missed due to the lack of characteristic symptoms, resulting in large clusters in our hospital. To address this issue, we investigated the efficacy of combining real-time reverse transcription-polymerase chain reaction (rRT-PCR) testing with clinical features to predict COVID-19 in the context of nosocomial infection control. Among 1087 patients admitted to an

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isolation ward, several factors were identified as significant predictors of COVID-19. This previous study suggests that performing at least two rRT-PCR tests is necessary to reliably exclude COVID-19. These findings highlight the importance of utilizing both clinical factors and repeated rRT-PCR testing to effectively prevent nosocomial transmission of the virus.[7] In this study, we collected medical records after the emergence of Omicron variants in a similar manner. Although several studies have compared the clinical symptoms, imaging findings, and other characteristics of previous lineages and Omicron variants, no studies have compared established methodologies for the definitive diagnosis of COVID-19. Therefore, the aim of this study was to examine whether the clinical factors that predict COVID-19 remain valid following the emergence of Omicron variants.

Subjects and Methods

Population and Data Collection

In this cross-sectional study, the clinical factors used to diagnose COVID-19 during routine hospitalization at Showa University Fujigaoka Hospital from April 2022 to March 2023 were investigated. Patients with suspected COVID-19 were admitted to the isolation ward regardless of their SARS-CoV-2 vaccination status. The criteria for admission to the isolation ward had been previously reported and are as follows: body temperature ≥37°C, percutaneous oxygen saturation <96%, history of contact with patients diagnosed with COVID-19, or a ground-glass pattern on chest computed tomography images.[7] No exclusion criteria were established. All clinical data were collected from the patients' medical records on the day of admission. The study protocol was approved by the Institutional Ethics Committee of Showa University (approval no. 2023–133-A). The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study. All personal and medical information collected during this study will be handled in strict accordance with applicable data protection laws and regulations. Access to this information will be limited to authorized personnel, and any data shared will be anonymized to ensure that individual patients cannot be identified. The data will be used solely for the purpose of this study, and no unauthorized third parties will have access to it. Patient privacy is a priority, and we take all necessary measures to safeguard it. This study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Method for Diagnosing COVID-19 and Determining Severity

The diagnosis of COVID-19 was based on nucleic acid tests to detect SARS-CoV-2 RNA using nasopharyngeal samples.[8] Nasopharyngeal swabs were collected from patients with suspected COVID-19 and tested by rRT-PCR, as previously reported.[7] Severity was defined as follows: (i) mild (percutaneous oxygen saturation [SpO2] ≥96%), (ii) moderate I (93% < SpO2 <96%), (iii) moderate II (SpO2 ≤93%), or (iv) severe (patients receiving intensive care during the acute COVID-19 period).[9]

Statistical Analysis

All data were expressed as mean ± standard deviation for continuous variables or as percentages for categorical variables. Group mean values were compared using the Mann–Whitney rank-sum test. Pearson's chi-squared test or Fisher's exact test was used for the univariate analysis of the association between two categorical variables. The adjusted effects of multiple variables were evaluated using a logistic regression model, and the findings were presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was set at $P<0.05$. All statistical analyses were performed using JMP software version 17.0 (SAS Institute, Cary, NC).

Results

Patient Characteristics and COVID-19 Diagnosis

During the study period, 651 patients were admitted to the isolation ward (Figure 1). Of these, seven re-admitted patients and 68 patients with insufficient data were excluded, leaving 576 patients (258 [44.8%] with COVID-19 and 318 [55.2%] without COVID-19) for inclusion in the final statistical analysis. The characteristics of all patients, both with and without COVID-19, are shown in Table 1. Among all patients, 343 (59.5%) were male and 233 (40.4%) were female, with ages

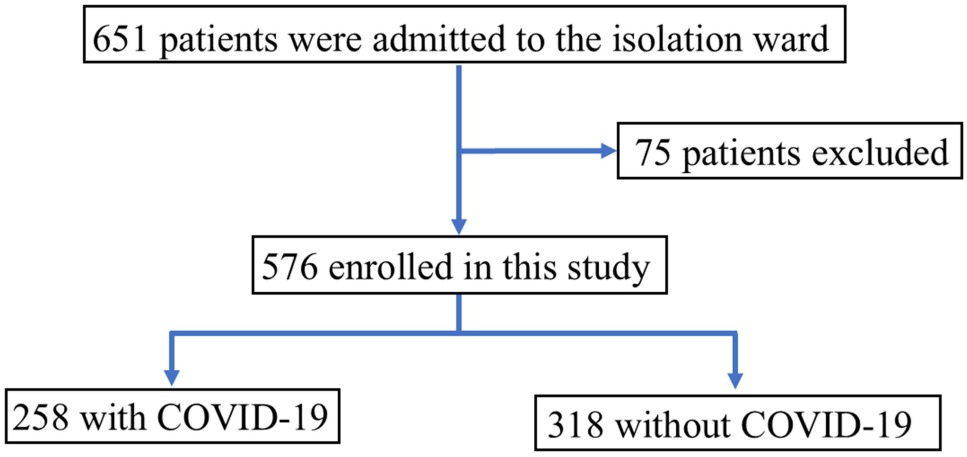

Figure 1 Flowchart of patient enrollment in the study. A total of 651 patients were admitted to the isolation ward. After excluding 75 patients based on study exclusion criteria, 576 patients were enrolled. Of these, 258 patients were confirmed with COVID-19, while 318 patients were admitted for non-COVID-19-related conditions. COVID-19, coronavirus disease 2019.

ranging from 6 to 104 years. The mean values of age, body mass index (BMI), serum albumin, lactate dehydrogenase (LDH), and C-reactive protein (CRP) were 73.4 ± 17.0 years, 20.6 ± 4.5 kg/m², 3.3 ± 0.7 g/dL, 272.2 ± 182.9 U/L, and 7.6 ± 8.4 mg/dL, respectively. Overall, 12 (2.0%) patients were receiving corticosteroids (at least 10 mg/day of

Table 1 Association of Each Variable with COVID-19

	All patients	Patients with COVID-19	Others	*P*-value
No. (%)	**576**	**258**	**318**	
Age (years)				
Mean ± SD	73.40±17.0	72.5±17.9	74.0±16.2	0.4084
Sex				
Male	343	159 (27.6)	184 (31.9)	0.3594
Female	233	99 (17.1)	134 (23.2)	
BMI (kg/m^2)				
Mean ± SD	20.56±4.53	20.73±4.48	20.42±4.57	0.3244
Albumin (g/dL)				
Mean ± SD	3.30±0.67	3.31±0.68	3.29±0.66	0.811
LDH (U/L)				
Mean ± SD	272.2±182.9	268.8±193.2	274.8±174.4	0.0526
C-reactive protein (mg/dL)				
Mean ± SD	7.6±8.4	5.4±6.24	9.48±9.47	<0.0001*
Receiving oral corticosteroids[a]				
Yes	12	7 (1.2)	5 (0.9)	0.3596
No	564	251 (43.5)	313 (54.3)	

(*Continued*)

Table 1 (Continued).

	All patients	Patients with COVID-19	Others	*P*-value
No. (%)	**576**	**258**	**318**	
Diabetes mellitus				
Yes	117	57 (9.9)	60 (10.4)	0.3395
No	459	201 (34.9)	258 (44.7)	
Malignancy				
Yes	126	57 (9.9)	69 (11.9)	0.9093
No	450	201 (34.3)	249 (43.2)	
CKD				
Yes	262	122 (21.1)	140 (24.3)	0.4344
No	314	136 (23.6)	178 (30.9)	
Autoimmune disease				
Yes	26	9 (1.5)	17 (2.9)	0.2806
No	550	249 (43.2)	301 (52.2)	

Notes: *$P<0.05$ was considered statistically significant. [a]More than 10 mg of prednisolone per day.
Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; LDH, lactate dehydrogenase; CKD, chronic kidney disease.

prednisolone) for various indications, and 117 (20.3%) had diabetes mellitus. Additionally, 126 (21.8%) patients had various malignancies (see details in Table S1), including 53 diagnosed within the past year and 43 receiving chemotherapies within the past three months. Furthermore, 262 (45.4%) patients had chronic kidney disease (CKD), and 26 (4.5%) had autoimmune diseases (see details in Table S2). Among the 258 patients diagnosed with COVID-19 based on rRT-PCR, 154 (60%) had mild disease at the time of admission, 21 (8%) had moderate I disease, 79 (31%) had moderate II disease, and 4 (1%) had severe disease, indicating that the severity of disease was lower than that observed before the emergence of Omicron variants (Figure 2).

Cases of Non-COVID-19

Table 2 provides details of the non-COVID-19 cases. The majority of these cases were bacterial infections, including respiratory, intra-abdominal, and urinary tract infections, which accounted for 57.2% (182 out of 318) of all non-COVID-19 cases. Among the non-infectious diseases, interstitial pneumonia, paraneoplastic fever, and cardiogenic pulmonary edema were frequently observed.

Statistical Analysis of COVID-19 and Clinical Features

In the univariate analyses, COVID-19 was found to be significantly associated with CRP levels (Table 1). However, no significant associations were found between COVID-19 and age, sex, BMI, serum albumin, LDH, oral corticosteroid use, diabetes mellitus, malignancy, CKD, or autoimmune disease. Multivariate analyses were employed to control for the potential confounding effects of these variables. Due to significant biases observed in the distributions, thresholds were established for age, LDH, and CRP (Figure S1). Table 3 presents the logistic regression models of factors associated with COVID-19. The frequency of COVID-19 decreased significantly in patients with CRP ≥10 mg/dL (OR, 0.3164; 95% CI, 0.2077–0.4819). Other factors were not significantly associated with COVID-19.

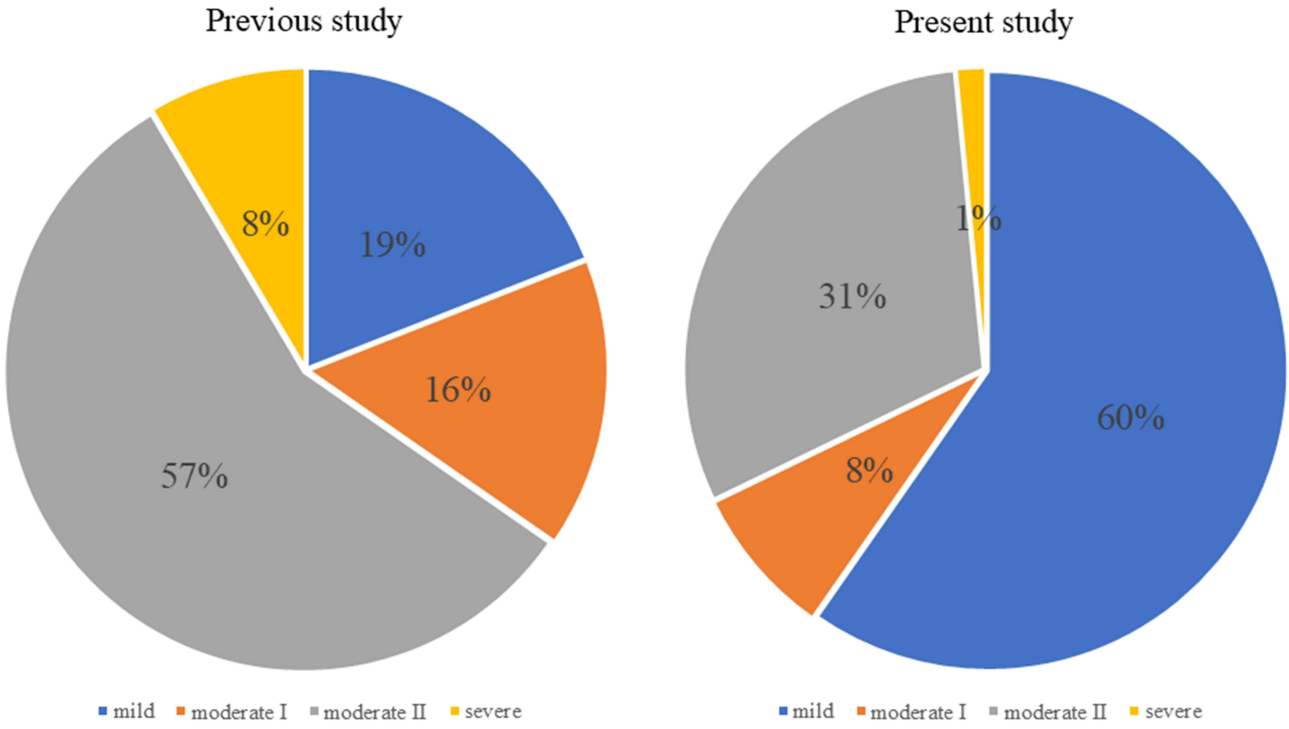

Figure 2 Comparison of COVID-19 severity distribution between the previous and present studies. The previous study categorized 67 patients as mild, 55 as moderate I, 200 as moderate II, and 30 as severe.[7] In the present study, 154 patients were categorized as mild, 21 as moderate I, 79 as moderate II, and 4 as severe. This distribution highlights the differences in patient severity between the two study periods. COVID-19, coronavirus disease 2019.

Outcome of Patients in the Isolation Ward

No significant difference in mortality was found between the COVID-19 group and the non-COVID-19 group in the isolation ward (Table 4). No patients were transferred to the intensive care unit (ICU) during the course of the study. The majority of deaths in the COVID-19 group were attributed to malignancy, followed by bacterial infection and COVID-19. In the non-COVID-19 group, the top three causes of death were bacterial infection, malignancy, and interstitial pneumonia.

Table 2 Cases of Non-COVID-19

	No. (%)
Lower respiratory tract infection	120 (37.7)
Interstitial lung disease	29 (9.1)
Intra-abdominal infection	28 (8.8)
Urinary tract infection	19 (5.9)
Paraneoplastic fever	18 (5.6)
Cardiac pulmonary edema	15 (4.7)
Pneumothorax	10 (3.1)
Upper respiratory tract infection	7 (2.2)
Hemoptysis	6 (1.8)
Cutaneous infection	6 (1.8)

(*Continued*)

Table 2 (Continued).

	No. (%)
Fever of undetermined origin	6 (1.8)
Drug-induced pneumonia	4 (1.2)
Malignant pleural effusion	3 (0.9)
Asthma attack	3 (0.9)
COPD exacerbation	3 (0.7)
Others*	41 (12.8)
Total	318 (100)

Notes: *Including two cases of meningitis. COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease.

Table 3 Logistic Regression Models of COVID-19

	Category	OR	95% CI	*P*-value
Age≥65 (years)	Yes/no	0.5125	0.1680–1.5625	0.2399
Sex	Female/male	1.215	0.8563–1.7240	0.2751
BMI (kg/m^2)		1.2421	0.3275–4.7106	0.7498
Albumin (g/dL)		0.4224	0.1481–1.2044	0.107
LDH≥300 (U/L)	Yes/no	0.7912	0.5184–1.2076	0.2777
C-reactive protein≥10 (mg/dL)	Yes/no	0.3164	0.2077–0.4819	<0.0001*
Receiving oral corticosteroids[a]	Yes/no	1.8349	0.5410–6.2225	0.33
Diabetes mellitus	Yes/no	1.149	0.7435–1.6507	0.5316
Malignancy	Yes/no	1.0756	0.7034–1.6448	0.7363
CKD	Yes/no	1.2423	0.8608–1.7929	0.2462
Autoimmune disease	Yes/no	0.5914	0.2440–1.4330	0.2448

Notes: [a]More than 10 mg of prednisolone per day. **P*<0.05 was considered statistically significant.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; LDH, lactate dehydrogenase.

Discussion

This study analyzed the correlation between COVID-19 and commonly measured clinical variables during the emergence of Omicron variants in patients with suspected COVID-19. Omicron variants first became a concern in November 2021.[10] In Japan, the BA.1 Omicron variant was dominant in January 2022, but by April 2022, BA.2 had gradually replaced BA.1.[11] Subsequently, BA.5, a sublineage of BA.2, became the dominant strain of SARS-CoV-2.[12] In this study, we did not perform genetic analysis of SARS-CoV-2 and, therefore, could not confirm the presence of the Omicron variant. However, as of April 2022, when the study began, the Omicron variant accounted for nearly all cases in Japan,[11] and this trend has persisted to the present day.

Multivariate analysis of the 258 patients diagnosed with COVID-19 in this study indicated that the likelihood of COVID-19 at the time of hospitalization was not significantly associated with age, sex, BMI, LDH, malignancy, albumin, corticosteroid use,

Table 4 Patient Outcome and Death Details

	All patients	Patients with COVID-19	Others	*P*-value
No. (%)	**576**	**258**	**318**	
Moving to the ICU	0	0	0	–
Death	31 (100)	15 (100)	16 (100)	0.679
Malignancy	10 (32.3)	5 (33.3)	5 (31.3)	
Bacterial pneumonia	9 (29)	2 (13.3)	7 (43.8)	
COVID-19[a]	3 (9.7)	3 (20.9)		
Interstitial pneumonia	3 (9.7)		3 (18.8)	
Myocardial infarction	1 (3.2)	1 (6.7)		
Urinary tract infection	1 (3.2)	1 (6.7)		
Cholangitis	1 (3.2)	1 (6.7)		
Sigmoid volvulus	1 (3.2)	1 (6.7)		
Femoral bone fracture	1 (3.2)	1 (6.7)		
Cardiac failure	1 (3.2)		1 (6.3)	

Notes: [a]Pneumonia caused by COVID-19.
Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

diabetes mellitus, CKD, or autoimmune diseases. Previously, we reported that several clinical factors, including CRP levels, were effective in distinguishing between patients with and without COVID-19 prior to the emergence of the Omicron variants.[7] In the present study, however, CRP levels were the sole indicator differentiating COVID-19 patients from non-COVID-19 patients. This suggests that clinical factors once effective in predicting COVID-19 prior to the emergence of the Omicron variant are no longer reliable in the post-Omicron era. Paradoxically, this finding implies that the distinctive features of COVID-19 have diminished, and the clinical presentation has become more generalized. In this study, bacterial infections accounted for more than half of the non-COVID-19 cases. CRP is typically elevated in bacterial infections but not in viral infections,[13] as this acute-phase protein binds specifically to phosphorylcholine on bacterial cell membranes, thereby activating the complement pathway of innate immunity.[14,15] As COVID-19 continues to transition into a more common disease state, distinguishing it will become increasingly challenging.

Omicron variants are estimated to be at least 10 times more infectious than the wild type.[16] This is partly due to mutations in the S gene, which encodes the spike protein, increasing its affinity for the angiotensin-converting enzyme 2 receptor.[3,12] Moreover, compared to previous lineages, Omicron variants have a shorter doubling time[17] and induce a higher viral load in upper airway cells,[18] further confirming their high infectivity. Along with increased infectivity, the severity of COVID-19 has changed since the emergence of these variants. It has been reported that Omicron variants secrete milder cytokines and chemokines compared to previous lineages.[19] In animal models of SARS-CoV-2 infection, Omicron variants have been shown to reduce the likelihood of severe disease,[20,21] a finding that has also been reported in clinical practice.[5,6,22–24] In the present study, the severity of COVID-19 was lower compared to our previous findings. Indeed, patients with COVID-19 caused by Omicron variants have a lower risk of hospitalization and ICU admission.[25,26]

This study found no significant differences in outcomes between the COVID-19 and non-COVID-19 groups. Furthermore, COVID-19 was no longer the leading cause of death in patients with COVID-19, which we attribute to the progress of the SARS-CoV-2 vaccination campaign, as well as the emergence of Omicron variants. At the start of this study, more than 80% of individuals in Japan had received their second SARS-CoV-2 vaccination.[11] In our previous study, conducted prior to the emergence of the Omicron variant, vaccinations were initiated in Japan during the study period. In that study, we compared the

severity and outcomes of COVID-19 before and after more than 80% of the Japanese population had been vaccinated, but no significant differences were observed (data not shown). Therefore, it is plausible that vaccination had a limited effect on mitigating the severity of COVID-19 or enhancing outcomes following the emergence of the Omicron variant, a conclusion supported by evidence from several studies.[6,23] In this study, antiviral, steroid, anticoagulant, and anti-IL-6 therapies were administered according to the severity of COVID-19. These treatments had been established before the emergence of the Omicron variant,[27] and they may have had minimal impact on COVID-19 outcomes, either before or after the appearance of the Omicron strain.

Our study has several limitations. First, it was conducted in a single facility, which may reduce the generalizability of the findings. Second, genetic analysis of the isolated viruses was not performed. However, as mentioned earlier, this study was conducted in Japan after the Omicron variant had become prevalent, based on epidemiological data. Third, this study lacked detailed information regarding the SARS-CoV-2 vaccination status of the patients.

Conclusion

This study identified the clinical findings of COVID-19 in routine practice since the emergence of the Omicron variants and compared the disease characteristics before and after their emergence. The results demonstrated a decrease in the severity of COVID-19, consistent with findings from previous studies. Concurrently, many of the distinct clinical features of COVID-19 have diminished since the emergence of the Omicron variants. As COVID-19 evolves toward becoming a more common and less distinct respiratory illness, developing updated diagnostic and preventive strategies will be essential to manage its spread effectively in healthcare settings.

Abbreviations

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; COVID-19, coronavirus disease 2019; rRT-PCR, real-time reverse-transcription polymerase chain reaction; SpO_2, percutaneous oxygen saturation, OR, odds ratio; CI, confidence interval; BMI, body mass index; LDH, lactate dehydrogenase; CRP, C-reactive protein; CKD, chronic kidney disease; ICU, intensive care unit.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for Publication

Not applicable.

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Disclosure

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