1 **SARS-CoV-2 Omicron BA.2.75 variant may be much more infective than**
2 **preexisting variants**
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28 **Running head:** Omicron BA.2.75 may be much more infective than preexisting
29 variants
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35 **Abbreviations:** spike protein gene, S gene; angiotensin-converting enzyme 2,

36 ACE2; receptor binding domain, RBD

ABSTRACT

Objectives: In our previous research, we developed a mathematical model via molecular simulation analysis to predict the infectivity of seven SARS-CoV-2 variants. In this report, we aimed to predict the relative risk of the recent new variants of SARS-CoV-2 as based on our previous research.

Methods: We subjected Omicron BA.4/5 and BA.2.75 variants of SARS-CoV-2 to the analysis to determine the evolutionary distance of the spike protein gene (S gene) of the variants from the Wuhan variant so as to appreciate the changes in the spike protein. We performed the molecular docking simulation analyses of the spike proteins with human angiotensin-converting enzyme 2 (ACE2) to understand the docking affinities of these variants. We then compared the evolutionary distances and the docking affinities of these variants with those of the seven variants that we had analyzed in our previous research.

Results: The evolutionary distances of the S gene in BA.4/5 and BA.2.75 from the Wuhan variant were longer than those of the other variants. BA.2.75 had the highest docking affinity of the spike protein with ACE2 (ratio per Wuhan variant).

Conclusion: The important results from this analysis are the following: BA.2.75 has both the highest docking affinity and the longest evolutionary distance of the S gene. These results suggest that BA.2.75 infection can spread farther than can infections of preexisting variants.

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58   **Keywords:** SARS-CoV-2; COVID-19; Infectivity; Spike protein; Docking affinity;

59   Mathematical model

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1. Introduction

In Japan, as of July 2022, infection with the Omicron BA.5 variant of SARS-CoV-2 has become an epidemic disease. In addition, Omicron BA.2.75 was discovered and is thought to present a particular risk inasmuch as it may cause a coming epidemic. We previously constructed a mathematical model to predict the infectivity of SARS-CoV-2 variants—Alpha, Beta, Gamma, Delta, Omicron BA.1and BA.2 as ratio per Wuhan variant (Takaoka et al., 2022). In this research here, we report the predicted risks for Omicron BA.4/5, and BA.2.75 which were recently recognized as being causes of epidemic diseases. For this purpose, we utilized the analyses of the evolutionary distance and of the docking simulation that we established in our previous research (Takaoka et al., 2022).

2. Materials and methods

2.1 Determination of the evolutionary distances between the Wuhan variant and variant spike protein genes (S genes), and docking affinities of the different spike proteins with ACE2

We analyzed the evolutionary distances of the S gene between the Wuhan variant and Omicron BA.4/5, or BA.2.75 according to our previously reported method (Takaoka et al., 2022). We obtained the sequences of the S gene by

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82   searching the EpiCoV database of GISAID for the complete sequence of the S

83   gene. Accession identifications were as follows: for Omicron BA.4/5,

84   EPI_ISL_13410397, and for BA.2.75, EPI_ISL_13438754 (Elbe et al., 2017;

85   Khare et al., 2021).

86   We used docking simulation and cluster analysis to investigate the docking

87   affinity of the receptor binding domain (RBD) of each variant spike protein with

88   ACE2 (Takaoka et al., 2022). We calculated the docking affinity by means of the

89   following expression:

90    $$\frac{A}{A_{Wuhan}}^{\left(\frac{B}{B_{Wuhan}}\right)}$$

91   where A is the average score of the most stable cluster and B is the score of the

92   most stable complex in the docking result.

93   We obtained the amino acid sequences of the spike proteins from the CoVariants

94   website, which classifies the variants according to Nextstrain clades: 22A

95   (Omicron, BA.4), 22B (Omicron, BA.5), and 22D (Omicron, BA.2.75) (Hadfield et

96   al., 2018; Hodcroft 2021). BA.4 and BA.5 have the identical spike proteins, and

97   thus we grouped the sequence of their S genes or their amino acid sequences

98   together in this research.

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101 **3. Results**

102 *3.1. Evolutionary distances for S gene variants and results of docking of the RBD*

103 *with ACE2 protein*

104 Table 1 shows the S gene evolutionary distances between the Wuhan variant and

105 each of the other variants, as well as the docking affinities of the RBD of the spike

106 protein with ACE2 (ratio per Wuhan variant), which we determined from the

107 docking simulation. The variants with longer evolutionary distances from the

108 Wuhan variant had a tendency toward causing more epidemics. The Omicron

109 BA.2.75 variant had the highest docking affinity of the spike protein with the ACE2

110 protein.

111 In comparison with BA.2, BA.4/5 had a longer S gene evolutionary distance but

112 showed a lower docking affinity. BA.2.75 had not only a longer evolutionary

113 distance but also a much higher docking affinity than did BA.2.

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116 **4. Discussion**

117 For this report, we analyzed the evolutionary distance of the S gene and the

118 docking affinity with ACE2 of the recent new Omicron variants, BA.4/5 and

119 BA.2.75. We focused on only the S gene sequence to calculate the evolutionary

120 distance and did not use the genome sequence, which are used for the phylogeny

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121   provided by Nextstrain (Hadfield et al., 2018).

122   Our analyses is based on the following two factors, which play important roles in

123   the infectivity of the virus variants: (1) the ability of the virus to enter human cells

124   and (2) the effect of a neutralizing antibody in humans or the effect of vaccines.

125   The first is demonstrated by the docking affinity of each RBD in the spike protein

126   with ACE2, that is, which docking affinity is greater. The second is shown by the

127   evolutionary distance of the S gene from the Wuhan variant: the longer the

128   distance is, the weaker the effect of vaccines. It is because the currently available

129   vaccines were developed on the basis of the Wuhan variant (Hassine 2022).

130   However, the risk for exacerbation of SARS-CoV-2 cannot be appreciated via the

131   methods for the two factors.

132   Omicron BA.2.75 showed the highest docking affinity of the spike protein with the

133   ACE2 protein compared with the other seven variants (ratio per Wuhan variant).

134   In addition, the S gene evolutionary distance of BA.2.75 from the Wuhan variant

135   was the longest of the variants. Therefore, BA.2.75 has a superior ability to enter

136   human cells, and also the current vaccines are much less effective against this

137   variant. These results suggest that the BA.2.75 infection can spread farther than

138   can infections of preexisting variants. In addition, our results indicate the need for

139   a great caution in managing BA.2.75 because the number of severely ill patients

140   or sufferers will be increased along with the increased number of infected

141   individuals even if this variant has low risk for exacerbation.

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5. Conclusion

145   We demonstrated here that the Omicron BA.2.75 variant of SARS-CoV-2 has the

146   longest results with regard to the evolutionary distance of the S gene from the

147   Wuhan variant and the highest results of the docking simulation for spike protein

148   with ACE2. Our results indicate that Omicron BA.2.75 poses a greater risk to

149   global health than other variants and that we must pay close attention to the

150   Omicron BA.2.75 infection trends.

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Data availability

154   Data that support the findings of this study are available from the corresponding

155   author upon reasonable request, except publicly available data source.

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Conflict of Interest Disclosures

158   Authors declare no conflict of interest.

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Author contributions

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175   Y.T. conceived and designed this research. Y.T. and A.S. preformed the analyses

176   and acquired the data. Y.T., A.S., and M.O. interpreted the data. Y.T. and A.S.

177   wrote the draft, and all authors reviewed and approved the manuscript.

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Ethical approval statement

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181   This research is not applicable because we performed computer analyses by

182   using sequence data obtained from public database.

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Table 1 The evolutionary distance of the S gene and the docking affinity of spike protein with ACE2 (ratio per Wuhan variant)

	Wuhan	Alpha	Beta	Gamma	Delta	Omicron BA.1	Omicron BA.2	Omicron BA.4/5	Omicron BA.2.75
Evolutionary Distance of S gene (from Wuhan) x 10^-3	-	4.2	4.5	10.8	12.1	14.3	25.6	41.2	46.8
Docking affinity (Ratio per Wuhan)	1	1.15	1.23	1.32	2.40	3.00	7.91	4.82	21.05

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