SARS-CoV-2 Omicron XBB.1.5 may be a cautionary variant by *in silico* study

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Running head: New Omicron variant XBB.1.5 may be most infective than preexisting variants

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Abbreviations: spike protein gene, S gene; angiotensin-converting enzyme 2, ACE2; receptor binding domain, RBD

ABSTRACT

In this research, we aimed to predict the relative risk of the recent new variants of SARS-CoV-2 as based on our previous research. First, we performed the molecular docking simulation analyses of the spike proteins with human angiotensin-converting enzyme 2 (ACE2) to understand the binding affinities to human cells of three new variants of SARS-CoV-2, Omicron BQ.1, XBB and XBB.1.5 Then, three variants were subjected to determine the evolutionary distance of the spike protein gene (S gene) from the Wuhan, Omicron BA.1 or Omicron BA.4/5 variants, to appreciate the changes in the S gene.
The result indicated that the XBB.1.5 had the highest binding affinity level of the spike protein with ACE2 and the longest evolutionary distance of the S gene. It suggested that the XBB.1.5 may be infected farther and faster than can infections of preexisting variants.

Keywords: SARS-CoV-2**;** COVID-19**;** Spike protein**;** Evolutionary distance; Binding affinity

1. Introduction

Currently the infection by the new Omicron variant of SARS-CoV-2 has an ongoing epidemic disease successively. In early 2023, Omicron BQ.1, XBB and XBB.1.5 were discovered in patients and is thought to present a particular risk in as much as it may induce a coming epidemic. Previously, we reported *in silico* infectivity of SARS-CoV-2 variants—Alpha, Beta, Gamma, Delta, Omicron BA.1, BA.2 and BA.2.75 as ratio per Wuhan variant and the absolute evolutionary distance of S gene between Wuhan and each variant [1]. In this research, we report the predicted risks for Omicron BQ.1, XBB and XBB.1.5 which were recently recognized as being causes of epidemic diseases. For this purpose, we utilized the analyses of the docking simulation and the evolutionary distance that we established in our previous research [1-3].

2. Materials and methods

2.1 Determination of the absolute evolutionary distances of variant S genes, and docking simulation for the affinities of the different spike proteins with ACE2

We analyzed the absolute evolutionary distances of the S gene from the Wuhan, Omicron BA.1or Omicron BA.4/5 variants for the variants —Alpha, Beta, Gamma, Delta, Omicron BA.1, BA.2, BA.4/5, BA.2.75, BQ.1, XBB and XBB.1.5 via the ClustalW program [4] and FastTree program [5]. We obtained the sequences of the S gene by searching NCBI (MN908947 for Wuhan, OW519813 for Alpha, OM791325 for BA.1) or the EpiCoV database of GISAID (https://gisaid.org) for the complete sequence of the S gene (EPI_ISL_5142896 for Beta, EPI_ISL_14534452 for Gamma, EPI_ISL_4572746 for Delta, EPI_ISL_13580480 for BA.2, EPI_ISL_13304903 for BA.4/5, and EPI_ISL_14572678 for BA.2.75, EPI_ISL_15638667 for BQ.1, EPI_ISL_16344389 for XBB, EPI_ISL_15802393 for XBB.1.5).

We obtained the information for the amino acid substitutions (see Table 1) of the spike proteins mostly from the CoVariants website (https://covariants.org). We then used the amino acid sequences for the analyses of the three-dimensional structures of each variant spike protein according to our previous research [1].

To clarify the ability to enter human cells of each variant, we used docking simulation to additionally analyze the binding affinity of the receptor binding domain (RBD) of spike protein with ACE2 for the three variants—BQ.1, XBB and XBB.1.5 with the same procedure in our previous research [3]. In this research, we defined the binding affinity as the most stable score in the docking results with the correct binding mode.

3. Results

3.1. Absolute evolutionary distances for S gene variants and results of docking of the RBD with ACE2 protein

Table 2 shows the binding affinities of the RBD of the spike protein with human ACE2 as ratio per Wuhan, in addition to the previous results [1], which we determined from the docking simulation.

The variants with longer evolutionary distances from the Wuhan, Omicron BA.1 or BA.4/5 suggest a tendency toward causing more epidemics based on our previous research [3]. The Omicron XBB.1.5 had highest level of binding affinity leading to the potential of high risk to enter human cells.

Table 2 also shows the absolute evolutionary distances of the S gene between the Wuhan variant and each of the other variants, as well as the evolutionary distances between the Omicron BA.1 or BA.4/5 variant. This data suggests that he Omicron XBB.1.5 had the potential of weak vaccine effect because it has the long absolute evolutionary distance from the three variants which are the basis to develop vaccine.

4. Discussion

In this research, two factors were chosen for an indicator of the virus infectivity based on our previous report [1] as follows: (1) binding affinities between the RBD of the spike protein and human ACE2, the ability of the virus to enter human cells; (2) evolutionary distance of S gene, the effect of vaccines by the neutralizing antibody in humans. So, we analyzed the binding affinity with ACE2 and the evolutionary distance of the S gene which were calculated from the Wuhan, Omicron BA.1 and Omicron BA.4/5, respectively.

The binding affinities of the RBD in the new variant spike proteins with ACE2 are greater than preexisting variants except Omicron XBB. The evolutionary distance of recent new Omicron variants, BQ.1, XBB and XBB.1.5 suggests the following possibilities: Omicron BQ.1. has a short evolutionary distance from the BA.4/5, which suggests that BA.4/5 based vaccine can be effective to this variant; Omicron XBB and XBB.1.5 have long evolutionary distance which suggests that currently available vaccines have low effect.

Thus, the Omicron XBB.1.5 showed the highest level of binding affinity of the spike protein with the human ACE2 protein compared with the other variants, and the S gene evolutionary distance from the three variants for the current vaccine ~~were~~ was the longest. This result suggests that the XBB.1.5 infection can spread farther than can infections of preexisting variants. Indeed, Yue et al. reported that the enhanced receptor-binding affinity were shown in XBB.1.5 under the Surface plasmon resonance analysis [6]. Tamura et al. reported that the XBB is the most greatly resistant variant to BA.2/5 infection sera ever and has strong ability of entering human cells than BA.2.75 [7]. In addition, Centers for Disease Control and Prevention (CDC) provided the forecast of XBB. 1.5 proportion in which it is estimated to account for 49.1%, as the largest, of the cases in the US in the week ended January 21st in 2023 (https://covid.cdc.gov/covid-data-tracker/#variant-proportions). These reports were consistent with our results *in silico*.

However in this research, the risk for exacerbation of SARS-CoV-2 cannot be appreciated via these two factors, that is, our results indicate the need for a great caution in managing XBB.1.5, because the number of severely ill patients or sufferers will be increased along with the increased number of infected individuals even if this variant has low risk for exacerbation.

5. Conclusion

We indicated here that the Omicron XBB.1.5 of SARS-CoV-2 has the longest evolutionary distance of the S gene from the Wuhan, Omicron BA.1 or Omicron BA.4/5 and the highest level of binding affinity by the docking simulation for spike protein with ACE2. These results suggested that Omicron XBB.1.5 poses a greater risk in the pandemic than other variants.

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Author contributions

Y.T. conceived and designed this research. Y.T., A.S., H.K, and M.O. preformed the analyses and acquired the data. Y.T., A.S., H.K., and M.O. interpreted the data. Y.T. and A.S. wrote the draft, and all authors reviewed and approved the manuscript.

Ethical approval statement

This research is not applicable because we performed computer analyses by using sequence data obtained from public database.

Declaration of Competing Interest

Authors declare no conflict of interest.

Data availability

Data that support the findings of this study are available from the corresponding author upon reasonable request, except publicly available data sources.

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Table 1. Amino acid substitutions of spike proteins of SARS-CoV-2 variants.

SARS-CoV-2 variants (Pango Lineage)	Mutations in spike protein
Alpha (B.1.1.7)	H69-V70del, Y144del, **N501Y**, A570D, D614G, P681H, T716I, S982A, D1118H
Beta (B.1.351)	D80A, D215G, L241-A243del, **K417N**, **E484K**, **N501Y**, D614G, A701V
Gamma (P.1)	L18F, T20N, P26S, D138Y, R190S, **K417T**, **E484K**, **N501Y**, D614G, H655Y, T1027I, V1176F
Delta (B.1.617.2)	T19R, G142D, E156-F157del, R158G, **L452R**, **T478K**, D614G, P681R, D950N
Omicron BA.1 (B.1.1.529/BA.1)	A67V, H69-V70del, T95I, G142-Y144del, Y145D, N211del, L212I, ins214EPE, **G339D**, **S371L**, **S373P**, **S375F**, **K417N**, **N440K**, **G446S**, **S477N**, **T478K**, **E484A**, **Q493R**, **G496S**, **Q498R**, **N501Y**, **Y505H**, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F
Omicron BA.2 (B.1.1.529/BA.2)	T19I, L24-P26del, A27S, G142D, V213G, **G339D**, **S371F**, **S373P**, **S375F**, **T376A**, **D405N**, **R408S**, **K417N**, **N440K**, **S477N**, **T478K**, **E484A**, **Q493R**, **Q498R**, **N501Y**, **Y505H**, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
Omicron BA.4/5 (B.1.1.529/BA.4/5)	T19I, L24-P26del, A27S, H69-V70del, G142D, V213G, **G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H**, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K,
Omicron BA.2.75 (B.1.1.529/BA.2.75)	T19I, L24-P26del, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, **G339H, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H**, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K

Omicron BQ.1 (B.1.1.529/BQ.1)	T19I, L24-P26del, A27S, H69-V70del, G142D, V213G, **G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N460K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H**, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
Omicron XBB (B.1.1.529/XBB)	T19I, L24-P26del, A27S, V83A, G142D, Y144del, H146Q, Q183E, V213E, **G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q498R, N501Y, Y505H**, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
Omicron XBB.1.5 (B.1.1.529/XBB.1.5)	T19I, L24-P26del, A27S, V83A, G142D, Y144del, H146Q, Q183E, V213E, G252V, **G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H**, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K

Amino acid substitutions from Wuhan variant. RBD substitutions are shown in bold-type. The substitution such as a reversion to Wuhan variant (R493Q) is excluded.

The information of amino acid substitutions are obtained from the following sources: Alpha, Beta and Gamma, https://covdb.stanford.edu/variants/; Delta, https://covariants.org/variants/21A.Delta (as of December 10, 2021); Omicron BA.1, https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html;
Omicron BA.2, https://covariants.org/variants/21L.Omicron; Omicron BA.4/5, https://covariants.org/variants/22A.Omicron (BA.4 and BA.5 have identical spike proteins.),
Omicron BA.2.75, https://covariants.org/variants/22D.Omicron,
Omicron BQ.1, https://covariants.org/variants/22E.Omicron,
Omicron XBB, https://covariants.org/variants/22F.Omicron,
Omicron XBB.1.5, Yue et al. (bioRxiv, DOI: https://doi.org/10.1101/2023.01.03.522427, 2023)

Table 2. The evolutionary distance of the S gene and the binding affinity of the spike protein with ACE2 (ratio per Wuhan variant).

Variants	Wuhan	Alpha	Beta	Gamma	Delta	Omicron BA.1	Omicron BA.2	Omicron BA.4/5	Omicron BA.2.75	Omicron BQ.1	Omicron XBB	Omicron XBB.1.5
Pango Lineage	B	B.1.1.7	B.1.351	P.1	B.1.617.2	B.1.1.529/ BA.1	B.1.1.529/ BA.2	B.1.1.529/ BA.4/5	B.1.1.529/ BA.2.75	B.1.1.529/ BQ.1	B.1.1.529/ XBB	B.1.1.529/ XBB.1.5
Binding affinity of S protein with ACE2 (ratio per Wuhan)	1	1.18	1.23	1.31	2.10	1.55	2.46	2.15	2.90	3.09	1.89	3.04
Absolute evolutionary distance of the S gene (from Wuhan) x 10^{-3}	-	2.06	2.06	3.54	3.24	10.68	8.29	9.17	10.95	10.06	12.44	13.03
Absolute evolutionary distance of the S gene (from BA.1) x 10^{-3}	-	-	-	-	-	-	5.60	6.48	8.24	7.36	9.71	10.29
Absolute evolutionary distance of the S gene (from BA.4/5) x 10^{-3}	-	-	-	-	-	-	-	-	2.97	1.02	4.44	5.02