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LETTER TO THE EDITOR

Expected Change of Limit of Detection Threshold of Rapid Diagnostic Tool Due to Omicron SARS CoV2 Subvariants

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LETTER TO THE EDITOR

Dear Editor, COVID-19 is a new disease caused by SARS CoV-2. After its first occurrence in China, it rapidly spread worldwide and finally resulted in a pandemic [1]. The recent introduction of a new COVID-19 vaccination brings the hope for success of pandemic control. The existing infectious disease diagnostic serology technique, which relies on sophisticated test workflows, laboratory-based equipment, and expensive materials for sample and reagent management, revealed its difficulties in the COVID-19 pandemic management. Longer wait periods for test results, the high cost of gold-standard PCR tests, and the limited sensitivity of rapid point-of-care tests all contributed to society's failure to rapidly identify COVID-19-positive people for quarantine, which has delayed the economy's recovery.

To solve the problem, development of new rapid diagnostic tools has been ongoing. A number of new fast diagnostic technologies are already on the market. The sensor should also be chosen based on the available data on the sensor's basic features as well as the diagnostic application's goal. Sensor performance metrics should be taken into account. Limit of detection (LOD), sensing range, reaction time, and sensing circumstances are all important pieces of information. The World Health Organization defines an acceptable LOD in culture media as 5.0×10^2 pfu/mL or 1.0×10^6 genome copies/mL [2].

There have already been new omicron subvariants discovered. Several Omicron lineages have been discover-

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Table 1. Molecular weight change due to omicron variant and subvariant and expected LOD change of rapid diagnostic tool.

Type	Change of molecular weight (times)	Expected LOD threshold after adjustment	
		pfu/mL	x 10^6 genome copies/mL
Wild type	**1**	**5**	**1**
Omicron variant			
BA.1 subvariant	**1.00106**	**5.0053**	**1.00106**
BA.1.1 subvariant	**1.00861**	**5.0043**	**1.00861**
BA.2 subvariant	**1.00052**	**5.0026**	**1.00052**
BA.3 subvariant	**0.998032**	**4.9902**	**0.99803**

ed after the first omicron variation was designated as a variant of concern (VOC) on November 26, 2021. WHO is tracking the Pango lineages BA.1/B.1.1.529.1, BA.2/B.1.1.529.2, and BA.3/B.1.1.529.3 under the 'Omicron' umbrella. BA.1, BA.2, and BA.3 are the three primary omicron subvariants moving around the world right now [3]. Clinical effects of the new omicron subvariants are not well clarified. In laboratory medicine, it is still a question whether the new subvariants can affect the diagnostic property of the currently available diagnostic tools or not.

Here, the authors use a clinical mathematical model technique to estimate the expected change of LOD threshold of rapid diagnostic tools due to omicron SARS CoV2 subvariants. Conceptually, the diagnostic test of SARS-Co-V2 infection is based on determining the biological reaction between pathogen and substrate of the diagnostic test kit. The basic biochemical principle can be used for explanation as the following equation "pathogen molecule + substrate molecule → resulting molecule to be detected by biosensor of the diagnostic tool". According to the mentioned equation, one to one pathogen molecule to substrate molecule is required to form the resulting molecule. When there is a molecular change due to the variant or subvariant of the SARS-Co-V2, it might affect the earlier mentioned normal intermolecular reaction. The change due to mutation in the variant and subvariant can result in a molecular weight change and this molecular change can further result in a change of the required enegery for a complete biochemical reaction with the substrate.

Here, the authors use the available data on the change of molecular weight in omicron subvariants as the primary parameter for clinical modelling. According to the previous study to assess the molecular weight [4], the wild type, Wuhan-Hu-1, has a molecular weight of 141,178.47 and the molecular weight of classical omicron variant is equal to 141,328.11. Regarding subvariants of omicron, BA.1, BA.1.1, BA.2, and BA.3 have a molecular weights of 141,328.11, 141,300.09, 141,185.78, and 140,900.6, respectively.

The change of molecular weight of each subvariant is calculated according to this formula "molecular weight of variant or subvariant/molecular weight of wild type". As mentioned earlier, one molecule of pathogen and one molecule of substrate are required for formation of one resulting molecule. In the model, the substrate is fixed but the pathogen molecule is variable and the resulting molecule therefore varies due to the pathogen molecule. Based on the present study, the changes in molecular weight due to omicron variants BA.1, BA. 1.1, BA.2, and BA.3 are presented in Table 1. Then the estimation of the change of LOD is done. Adjustment of the LOD according to the derived change is done using the equation "adjusted LOD of a variant/subvariant = standard LOD x change of molecular weight", where standard EOS is the value that is already mentioned in this article. The results for adjustment are presented in Table 1.

Based on this study, there is a change of molecular weight in the omicron variant and each subvariant, and it might further affect the LOD of the diagnostic tool. Most subvariants, except for BA.3 have an increased expected LOD. This might mean that there might be a chance of false negative of the currently available diagnostic test kit. Nevertheless, the magnitude of expected chance is low and it might not have clinical significance. Further study in a real-life situation in clinical laboratory can give more clinical evidence for a final conclusion.

Declaration of Interest:
None.

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