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Single-Nucleotide Polymorphisms in Host Pattern-Recognition Receptors Show Association with Antiviral Responses against SARS-CoV-2, *in-silico* Trial

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ABSTRACT

Introduction: Coronavirus infectious disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pathogen-associated molecular patterns (PAMPs) can be detected by host pattern-recognition receptors (PRRs) expressed in inherent immune cells. The polymorphisms in PRRs leads to different recognizing and immune responses against viral infections. **Methods:** Single-nucleotide polymorphisms of PRRs, minor allele frequency (MAF), and their geographical distribution were obtained from the Ensembl genome database. Interaction between the common polymorphic forms of PRRs (including TLR3, TLR7, RIG-1, and MDA-5) and SARS-CoV-2 virus genome (dsRNA) were predicted using the hybrid protein-RNA docking algorithm HDOCK server. Also, the global distribution of common SNPs and their MAFs were statistically analyzed using SPSS, ver.16. **Results:** The wild-type TLR3 and TLR3 SNP rs73873710 had the same docking energy score (-330.48 kcal/mol), and had lower docking energy scores compared to the other two SNPs, rs3775290 and rs3775291 (-301.42 and -295.81 kcal/mol, respectively). TLR7 SNP rs179008 had a higher docking energy score (-423.03 kcal/mol), comparing to the wild-type TLR7 (-445.46 kcal/mol). Also, there was a statistically significant direct relationship between MAF of TLR3 SNP rs3775290 and rs3775291 with SARS-CoV-2 prevalence ($P=0.021$ and $P=0.023$, respectively) and prevalence/population ratio of COVID-19 ($P=0.026$ and $P<0.001$, respectably). **Conclusion:** Wild-type TLR3 and TLR3 SNP rs73873710 can recognize the SARS-CoV-2 dsRNA genome through a better performance compared to TLR3 SNP rs3775290 and TLR3 SNP rs3775291. Therefore, our *in-silico* study established that PRRs SNPs are associated with antiviral responses against SARS-CoV-2.

INTRODUCTION

Coronavirus infectious disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a virus first discovered in Wuhan, China. Since the emergence of SARS-CoV-2 in December 2019, the virus pandemic has been expanding, with no signs of decrease. According to the World Health Organization (WHO), as of July 26, 2020, 216 countries were affected by COVID-19, and of 15,785,641 infected people, 640,016 died [1, 2].

Coronaviruses have a single-stranded positive-sense RNA genome and belong to the Coronaviridae family and Nidovirales order [3]. Innate immune antiviral responses are the first line of defense against viral infections and can suppress the proliferation and spread of the virus in the early stages of infection [4]. Inflammatory responses associated with coronaviruses are often generated by the innate immune system when viruses are detected [5]. Pathogen-associated molecular patterns (PAMPs) can be identified by host pattern-recognition receptors (PRRs) expressed in inherent immune cells, such as dendritic cells (DCs). By identifying PAMPs via PRRs, effective antiviral responses progress, *e.g.*, the production of different types of cytokines, the induction of inflammatory responses and signaling pathways, and the induction of acquired immunity [4]. Toll-like receptors (TLRs) and cytoplasmic retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are known to be the two main PRRs in recognizing the RNA viruses [6]. Various studies have shown that TLR3, TLR7, RIG-1, and melanoma differentiation-associated protein (MDA)-5 are important PRRs in coronaviruses and play an essential role as innate immune factors [7-10]. Respiratory viruses can be detected by TLR3 (recognizing the dsRNA in endosomes), TLR7

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(recognizing the ssRNA), RIG-1 (recognizing the dsRNA in the cytosol) and MDA-5 (recognizing the dsRNA in the cytosol) [9].

TLRs are most closely associated with adaptive immune responses among intrinsic immune receptors. They, therefore, play an essential role in antiviral immune responses [11]. Human TLR3 is a transmembrane receptor type I with a molecular weight of 125 kDa, which plays a crucial role in modulating inflammation and innate immunity. dsRNA molecules must be at least 40-50 base pairs long to be able to induce TLR3 signaling. Activation of signaling via TLR3 induces DC activation and cross-priming of T-cells, which is necessary to induce virus-specific T-cell responses [4].

The single-nucleotide polymorphisms play a critical role in the response of PRRs. Also, according to the importance of the innate immune response as the body's first line of defense against viral infections and the importance of identifying viral PAPMs by PRRs in response to intrinsic immunity as well as the significant impact of single-nucleotide polymorphisms (SNPs) in the response of PRRs, we decided to highlight the impact of SNPs in PAMP-interacting PRRs in SARS-CoV-2.

MATERIAL AND METHODS

Preparation of parameters for predicting interactions. Nucleotide sequences of PRRs, including TLR3, TLR7, RIG-1, and MDA-5, were received from the NCBI database. Also, SNPs of PRRs and their geographical distribution were obtained from the Ensembl database (the results were limited to missense mutations and minor allele frequencies (MAFs) between 0.05 and 0.95).

To select the appropriate area of the SARS-CoV-2 genome, we used the PRIdictor server [12] to predict the interaction between the virus genome (RNA) and TLR3, TLR7, RIG-1, and MDA-5 proteins. By predicting PRRs-binding sites in SARS-CoV-2 genome, we determined that the *ORF7b* in SARS-CoV-2 genome has the highest ratio of PRRs-binding capacity (TLR3, TLR7, RIG-1, and MDA-5 proteins account for 79, 100, 86, and 65% of the protein-binding ribonucleotide ratios in the *ORF7b* in SARS-CoV-2 genome, respectively). Therefore, we selected *ORF7b* for the subsequent analysis.

Protein-RNA Docking. Interaction between the wild-type TLR3 and its three main SNPs (rs3775290, rs3775291, and rs73873710), the wild-type TLR7 and its main SNPs (rs179008), the wild-type RIG-1 and its two main SNPs (rs10813831 and rs17217280), and the wild-type MDA-5 and its three SNPs (rs1990760, rs3747517, and rs10930046) with the *ORF7b* in SARS-CoV-2 virus genome were predicted using the hybrid protein-RNA docking algorithm HDOCK server. In the HDOCK server, the binding modes were ranked according to their binding energy scores, and the top-ten binding modes were provided to users. During the docking calculation, all the default parameters were used [13].

Statistics. All statistical analysis was performed using SPSS software, version 16. The significance level was considered as %95 (P-value<0.05). Also, statistics on COVID-19 prevalence and mortality were adopted from the official website of the World Health Organization (available on https://www.who.int/). Also, the correlation between MAF of PRRs (SNPs) and SARS-CoV-2 prevalence and mortality rate were applied via the Pearson and Spearman test.

RESULTS

The docking analysis was performed with the HDOCK server that uses a distance-dependent knowledge-based scoring function (ITScore-PP) to predict interactions [14]. The HDOCK server eventually gave us 100 three-dimensional interaction models along with their score as output for each of the docking [13]. In this study, the interaction of three-dimensional models of wild-type PRRs were compared to their common single-nucleotide polymorphic forms to their corresponding ligand.

Protein-RNA docking results of TLR3 and its common SNPs. The results of docking the wild-type TLR3 and its common SNPs with the *ORF7b* in SARS-CoV-2 genome showed that the wild-type TLR3 and TLR3 SNP rs73873710 had the same docking energy score (-330.48 kcal/mol) and lower docking energy scores compared to the other two SNPs, rs3775290 and rs3775291 (-301.42 and -295.81 kcal/mol, respectively). As a result, wild-type TLR3 and TLR3 SNP rs73873710 have more interaction with *ORF7b* in the SARS-CoV-2 genome, comparing to rs3775290 and rs3775291. Therefore, wild-type TLR3 and TLR3 SNP rs73873710 can recognize the SARS-CoV-2 dsRNA genome through better performance.

Protein-RNA docking results of TLR7 and its common SNPs. The results of docking the wild-type TLR7 and its common SNP with the *ORF7b* in the SARS-CoV-2 genome showed that TLR7 SNP rs179008 had a higher docking energy score (-423.03 kcal/mol), comparing to the wild-type TLR7 (-445.46 kcal/mol). As a result, the TLR7 SNP rs179008 has less interaction with *ORF7b* in the SARS-CoV-2 genome, comparing to the wild-type TLR7. Therefore, the TLR7 SNP rs179008 can recognize the SARS-CoV-2 ssRNA genome through a weaker performance.

Protein-RNA docking results of RIG-1 and its common SNPs. The results of docking the wild-type RIG-1 and its common SNPs with the *ORF7b* in the SARS-CoV-2 genome revealed that the wild-type RIG-1 and its two common SNPs (rs10813831 and rs17217280) had almost the same docking energy score (-287.02, -290.05 and -293.60 kcal/mol, respectively). As a result, the wild-type RIG-1 and its two common SNPs (rs10813831 and rs17217280) are not significantly different in their ability to recognize the SARS-CoV-2 dsRNA genome.

Protein-RNA docking results of MDA-5 and its common SNPs. The results of docking the wild-type MDA-5 and its common SNPs with the *ORF7b* in the SARS-CoV-2 genome showed that the wild-type MDA-5 and its three common SNPs (rs1990760, rs3747517, and rs10930046) had a completely equal docking energy score (-253.76 kcal/mol).

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As a result, wild-type MDA-5 and all common MDA-5 SNPs have precisely the same connection and interaction potential in identifying SARS-CoV-2 dsRNA.

Correlation of TLR3 polymorphism and SARS-CoV-2 prevalence and mortality rate. Our protein-RNA docking results established the direct correlation between the presence of SNP rs3775290 and rs3775291 variations in TLR3 and the less recognition of the SARS-CoV-2 genome, comparing to the wild-type and rs73873710. Therefore, we investigated the correlation between MAF of TLR3 SNPs and SARS-CoV-2 prevalence rate, mortality rate, and prevalence/population ratio via the Pearson and Spearman test.

Our results showed that there is a statistically significant direct relationship between MAF of TLR3 SNP rs3775290 and prevalence and prevalence/population ratio of COVID-19. (P=0.021, P=0.026, respectively). Also, the increase in MAF of rs3775291 is responsible for more prevalence and prevalence/population ratio of COVID-19. (P=0.023, P <0.001, respectively) Also, there was a significant reverse correlation between MAF of TLR3 SNP rs73873710 and the prevalence and prevalence/population ratio of COVID-19 (P=0.029, P=0.026, respectively). In other words, increasing in allele frequencies of TLR3 SNP rs3775290 and rs3775291 (which had less interaction with SARS-CoV-2) lead to the more prevalence and prevalence/population ratio of COVID-19. However, wild-type TLR3 and TLR3 SNP rs73873710 (which had more effective interaction with SARS-CoV-2, comparing to other SNPs) correspond for less prevalence and prevalence/population ratio of COVID-19 (Table 1 and Fig. 1).

There was no correlation between MAF of other PRRs SNPs and SARS-CoV-2 prevalence and mortality rate.

Table 1. Correlation of global distribution of the minor allele frequency of TLR3 SNPs with SARS-CoV-2 statistics

SNPs	Local minor allele frequencies														*P*-value and Co-efficiency			
	Barbados	Nigeria	Gambia	Kenya	Sierra Leone	Colombia	USA	Peru	Puerto Rico	Finland	Spain	Italy	Bangladesh	Pakistan	Mortality	Prevalence	Mortality/ prevalence Ratio	Prevalence/ population Ratio
TLR3 rs73873710	0.141	0.217	0.146	0.192	0.141	0.032	0.023	0.006	0.067	0.01	0.037	0.014	0	0	*p =0.081* *r =-0.482*	*p =0.029* *r =-0.581*	*p =0.964* *r =0.013*	*p =0.026* *r =-0.590*
TLR3 rs3775290	0.188	0.14	0.181	0.232	0.2	0.298	0.281	0.276	0.245	0.308	0.257	0.257	0.395	0.38	*p =0.070* *r =0.497*	*p =0.021* *r =0.607*	*p =0.469* *r =0.211*	*p =0.026* *r =0.590*
TLR3 rs3775291	0.042	0.007	0.018	0.035	0.012	0.356	0.32	0.353	0.212	0.333	0.285	0.308	0.273	0.24	*p =0.018* *r =0.622*	*p =0.023* *r =0.600*	*p =0.350* *r =0.270*	*p <0.001* *r =0.811*
TLR7 rs179008	0.159	0.131	0.088	0.091	0.133	0.248	0.177	0.178	0.227	0.312	0.169	0.211	0.077	0.049	*p =0.455* *r =0.218*	*p =0.876* *r =0.046*	*p =0.208* *r =0.358*	*p =0.064* *r =0.508*

DISCUSSION

Although vaccine production will provide ultimate protection against SARS-CoV-2, the production process is very time-consuming. Increasing knowledge about the innate immune response can be of great help in finding effective treatments for COVID-19. During a viral infection, host factors stimulate the immune response against the virus [5]. Identification of PAMPs by PRRs activates several signaling pathways and ultimately activates transcription factors, e.g., nuclear factor κB (NF-κB), activator protein 1 (AP-1), interferon response factor 3 (IRF3), and IRF7. NF-κB and AP-1 stimulate the expression of coding genes needed for inflammatory responses, including cytokines and inflammatory chemokines. IRF3 and IRF7 intensify the production of interferon type I (IFN-α and IFN-β), which are essential for intrinsic antiviral immune responses and can suppress the proliferation and spread of the virus in the early stages [15]. Previous studies have shown that the signaling of TLRs is essential for the identification of SARS-CoV by the inherent immune system [16]. One of these TLRs is TLR3, which has a protective effect against SARS-CoV. TLR3 is unique among TLRs because it can induce apoptosis through a pathway other than mitochondrial apoptosis as well as interaction with TRIF. The induction of apoptosis by TLR3 plays a vital role in the host's defense against the virus due to its limited spread of viral infection [9].

Unlike other TLRs, the TLR3 signaling pathway is MyD88-independent. dsRNA binds TLR3 with the resultant recruitment of the adaptor protein TRIF via a TIR–TIR domain interaction. TLR3 can also induce the pro-inflammatory NF-kB transcription factor with TRIF-dependent fashion via receptor-interacting protein 1 (RIP1) [17].

Considering three points, we can understand the critical role of TLR3 in controlling COVID-19 respiratory infection: (i) TLR3 is expressed in respiratory cells, e.g., nasal, alveolar, and bronchial epithelial cells [9]; (ii) TLR3 is expressed in viral respiratory infections such as influenza, rhinovirus, and RSV [18-20], *i.e.,* in infection with rhinoviruses for maximum inflammatory responses via IRF3-dependent pathway [21]; (iii) TLR3 signaling plays a central role in modulating innate immune responses in the airway [17].

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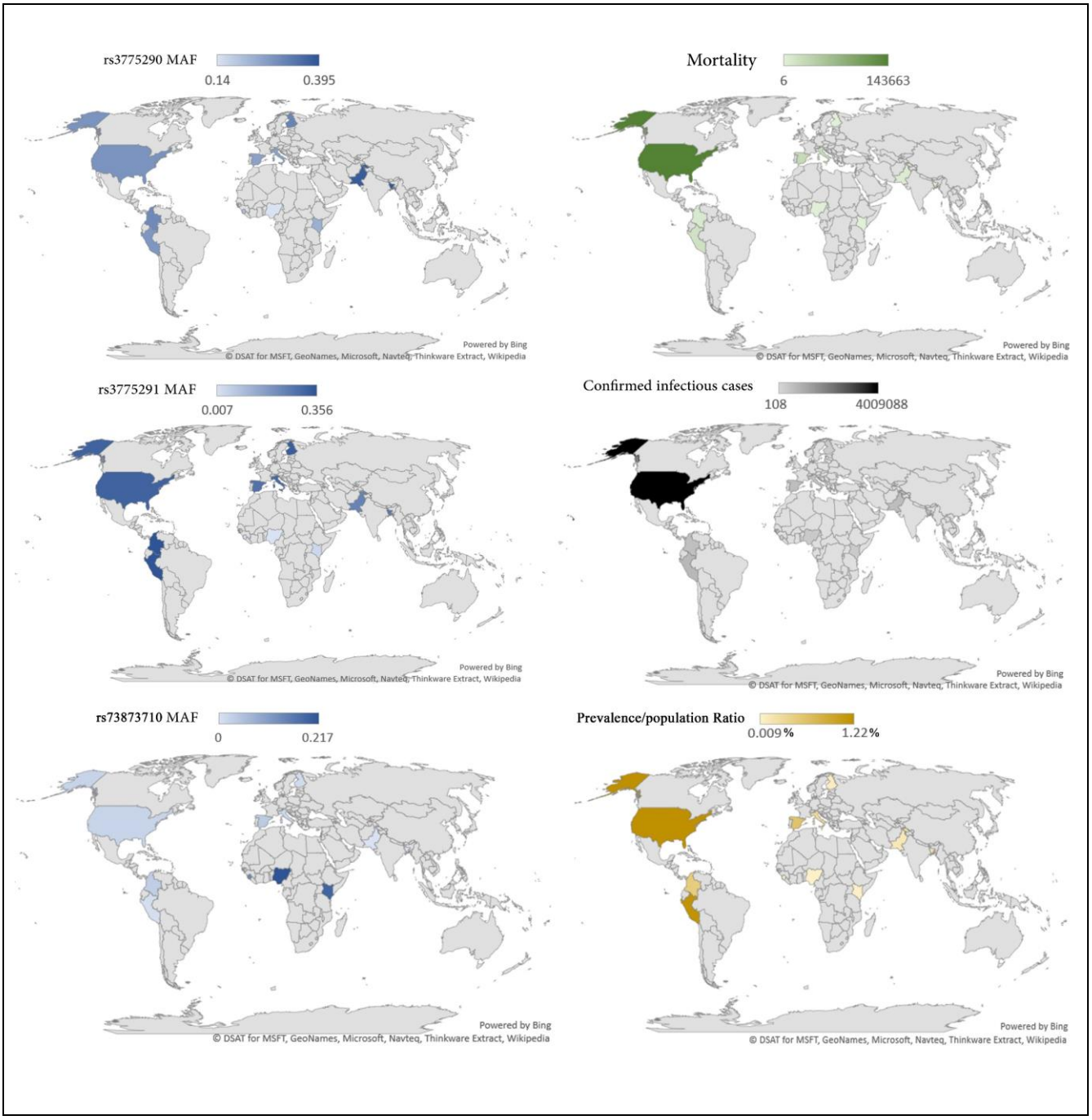

Fig. 1. Global distribution map of the minor allele frequency of TLR3 SNP rs73873710, rs3775290, rs3775291, mortality, prevalence, and prevalence/population ratio of COVID-19.

In our study, the results of the molecular docking showed that the wild-type TLR3 and TLR3 SNP rs73873710 were more closely interacted with dsRNA from the virus replication cycle and can better identify the SARS-CoV-2 dsRNA. TLR3 SNPs rs3775290 and rs3775291 are weaker in detecting SARS-CoV-2 dsRNA. Regarding the role of TLR3 in innate immune response and the milder performance of these two SNPs, people with TLR3 SNPs rs3775290 and rs3775291 probably have a lower protective function against SARS-CoV-2. Our study showed that there was a statistically significant relationship between the MAF of SNP rs3775290 in TLR3 and the number of COVID-19 infectious cases and prevalence/population ratio. Also, there was a statistically significant relationship between the prevalence of SNP rs3775291 in TLR3 with the number of COVID-19 infectious cases and prevalence/population ratio. As a result, the more prevalence of TLR3 SNP rs3775290 and TLR3 SNP rs3775291 leads to more prevalence, more prevalence/population ratio, and less immunity against SARS-CoV-2.

Previous studies have shown the role of TLR3 SNPs rs3775290 and rs3775291 in susceptibility to viral infections. A study by Sironi *et al.* (2012) showed the role of TLR3 SNP

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rs3775291 in the susceptibility of people to HIV-1 infection [22]. Also, a study by Rong *et al.* (2013) found that TLR3 SNP rs3775291 was associated with high susceptibility to chronic hepatitis B (CHB) in the Chinese population [23]. The study of Huang *et al.* (2015) established that TLR3 SNP rs3775290 was associated with a reduced risk of CHB as well as HBV-related liver cirrhosis (LC) and hepatocellular carcinoma (HCC) [24]. Barkhash *et al.* (2013) showed a link between the presence of allele G in TLR3 SNP rs3775291 with a predisposition to tick-borne encephalitis virus (TBEV) in the Russian population [25]. Also, Ishizaki *et al.* (2008) showed a direct association between TLR3 SNP rs3775291 and subacute sclerosing panencephalitis (SSPE) caused by measles virus [26]. Mukherjee *et al.* (2019) found that TLR3 SNP rs3775290 had a threefold more prevalence in the population of dengue fever (caused by the dengue virus) and was significantly associated with susceptibility to this disease [27]. The presence of TLR3 SNP rs3775290 exhibited a negative effect on HBV and HCV antiviral immunity [28]. Also, a study by Mosaad *et al.* (2019) confirmed the association between TLR3 SNP rs3775290 and HCV chronicity [29]. Due to the association of MAF of TLR3 polymorphisms with the susceptibility to viral infections, it can be concluded that TLR3 contains a high impact in pathogenicity and virulence of the virus. Considering that the severity of COVID-19 pathogenicity varies from person to person [30] and also due to the fact that differences in hosting factors can be a reason for different responses of individuals in the face of SARS-CoV-2, we addressed the impact of TLR3 SNPs as one of the effective hosting factors in response to intrinsic immunity.

As discussed, our results of molecular docking showed that the TLR3 SNP rs73873710, as well as wild-type TLR3, had a higher energy docking score than TLR3 SNP rs3775290 and TLR3 SNP rs3775291 and performed better in recognizing viral dsRNA. The results of our study show that the prevalence of TLR3 SNP rs73873710 is statistically significant and inversely related to the number of confirmed COVID-19 cases and prevalence/population ratio. Therefore, the higher frequency of TLR3 SNP rs73873710 leads to lower prevalence and prevalence/population ratio of COVID-19. The present study showed that TLR3 SNP rs3775290 and TLR3 SNP rs3775291 had a direct relationship, and TLR3 SNP rs73873710 had an inverse relationship, with the prevalence and prevalence/population ratio of COVID-19.

Despite various studies on SARS-CoV-2, there is limited knowledge about the host's immune response to SARS-CoV-2. Given the impact of TLR3 in viral infections, especially in SARS-CoV [8], it can be concluded that TLR3 is likely to be an essential factor in the innate immune response against SARS-CoV-2. Conducting *in-vitro* or *in-vivo* studies on the role of this PRR in SARS-CoV-2 infection can provide useful information for researchers to increase awareness about immune responses against SARS-CoV-2 and to find an effective treatment.

Limits of study. We had no access to the global disruption of SNP MAFs. Our data about MAF of SNPs, which provided by Ensembl database, was limited to 14 countries, including Barbados, Nigeria, Gambia, Kenya, Sierra Leone, Colombia, USA, Peru, Puerto Rico, Finland, Spain, Italy, Bangladesh, and Pakistan. Also, the statistics of SARS-CoV-2 were updated daily by WHO. Therefore, all statistical analyses, which included statistics related to SARS-CoV-2, were based on July 26, 2020 updates.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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