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The COVID-19 Deadly Risk Assessment upon the Updated Etiologic Computer Simulation by Quantum MicroRNA Language in SARS-CoV-2 Infection *in eo*

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ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19) is complexed infectious disease caused by severe respiratory syndrome human coronavirus 2 (SARS-CoV-2). We have previously shown that the microRNA (miRNA) entangling target sorter (METS) analysis with quantum miRNA/miRNA language plus artificial intelligence (AI) is available for the etiology investigation *in silico* of SARS-CoV-2 infection. Based on the up-to-dated COVID-19 *in silico* etiology data, the deadly risk assessment in SARS-CoV-2 infection was performed to further elucidate the difference of death rate among Asia and western country ethnics by using the USA model.

Materials and Methods: The information of coronavirus was extracted from database. Putative SARS-CoV-2 miRNAs and their targets were predicted by functionally analogy analysis. AI-machine learning was performed by Prediction One. The deadly risk calculation was performed by Excel.

Results: C1QA and C1QB complements, and MAVS/VISA were targeted by SARS-CoV-2 viral miRNAs. Genetical risk factors of the host, complement C1QA gene allele mutation (rs172378) and mitochondrial antiviral signaling protein (MAVS/VISA) gene allele C79F (rs11905552) were extracted from the data list of miRNA targets in the updated network data of COVID-19. The total deadly risk of SARS-CoV-2 infection was obtained as approximately 3.58%.

Conclusion: We found that MAVS/VISA and C1Q deficiency was the deadly risk factor of COVID-19. Higher ethnic risk (approximate 100 times) with haplotype C79F of MAVS/VISA was observed in Caucasian-American or African-American when compared with Asian-American in the USA model. The deadly risk of COVID -19 genome was the orf10.

Keywords: COVID-19, SARS-CoV-2, MicroRNA, Quantum MicroRNA Language, MAVS, C1Q

INTRODUCTION

We have found the third host defense neo-mechanism, 'the quantum miRNA immunity' against human hepatitis B virus (HBV), human hepatitis C virus (HCV), huma immunodeficiency virus type 1 (HIV-1) and severe respiratory syndrome human coronavirus 2 (SARS-CoV-2) [1,2]. The quantum miRNA immunity is programmed by the quantum miRNA language and it was identified from circulating miRNA biomarker panels or profiles; therefore, it is a new vital sign. One of the integrated bioinformatic technology, miRNA entangling target sorter (METS) analysis has elucidated the etiology of gastric cancer and gastric cancer with *Helicobacter pylori* infection, and that of coronavirus disease 2019 (COVID-19) by SARS-CoV-2 infection [2,3]. The artificial intelligence (AI) has been cooperated with the METS analysis with the big database (MIRAI). Consequently, COVID-19 pathogenicity was deeply associated with virus miRNAs (AUC: 0.840) and host miRNAs (AUC: 0.924) [2].

From MIRAI, we have documented that the clinical symptom of COVID-19 would be explained by host miRNAs and viral miRNAs [2].

1. While SARS-CoV-2 infection induces cytokine releasing syndrome (CRS) in the severe COVID-19 patients, such as high-level production of interleukin-6 (IL-6), interleukin-1β (IL-1β), induced protein 10 (IP10) and monocyte chemoattractant protein-1 (MCP-1) in patients' sera [4,5], high IL-6 production in CRS would be one of the quantum

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immunity by host miR-98-5p downregulation.

2. Systemic lupus erythematosus (SLE)-like symptom would be due to C1QA deficiency by viral Cov-miR-2 attack and blood clot producing would be associated with incomplete immunocomplex by the SLE-like hypocomplementemia.
3. Hypoxic pulmonary vascular hypertension including Kawasaki disease-like symptom would be induced by hypoxia inducible factor 1 subunit alpha (HIF1A) suppression by viral Cov-miR-5 charge and vascular endothelial cells under hypoxic condition would be apoptotic, which would also induce production of blood clots.
4. Incomplete immune memory establishment by C1QA deficiency would have an important role for the weak immune response of antibody production and/or quick reduction of antibody amounts after infection.

Subsequently, we have reported about the strategy of virally evading from the quantum miRNA immunity against SARS-CoV-2 infection [2]. The set of the quantum miRNA immunity vs SARS-CoV-2 infection was IL-6 production, anti-apoptotic BCL2 downregulation, cycling dependent kinase inhibitor 1A (CDN1A) augmentation and the mitochondrial antiviral signaling protein (MAVS/VISA) activation via HAUS augmin like complex subunit 8 (HAUS8) upregulation. IL-6 was described above. Antiviral activity of MAVS/VISA has been enhanced by HAUS8 complexes increasing [6]. MAVS/VISA on the outer membrane of the mitochondria is a key trigger in activation of innate immune response, such as type I interferon (IFN) production, following to variety of stress signals including RNA viral infection [7]. For instance, retinoic acid inducible gene-I (RIG-I)-like receptors (RLRs) recognizes dengue virus (DENV) RNA as a host defense signaling but DENV hijacks its RLR-mitochondrial defense system, RLR-MAVS/VISA signaling and finally blocks IFN-α and IFN-β production [8]. Like DENV, the 3' untranslated (3'UTR) regions of SARS-CoV-2 RNA has localized into the mitochondria [9] and SARS-CoV-2 has been speculated to hijacked host mitochondria [10]. SARS-CoV ORF-9b protein has suppressed host immunity through the MAVS/TNF receptor associated factor 3 (TRAF3)/TRAF6 signaling in the mitochondria of HEK293 cells [11] and genetical alteration of MAVS single nucleotide polymorphisms (SNPs) have been found to change anti-virus signaling [12]. We have not found any evading strategy by viral hijack of the quantum miRNA immunity; however, the C1QA deficiency by Cov-miR-2 would be absolutely increasing of viruses in infected individuals. The causes of COVID-19 deaths in aging, ethnic population and haplotypic bias by mitochondrial manipulation of SARS-CoV-2 RNA have not been cleared.
In this paper, the previous COVID-19 *in silico* etiological analysis data was updated and the deadly risk in SARS-CoV-2 infection was evaluated to further elucidate the difference of death rate between Asia and western country ethnics.

MATERIALS & METHODS

Database Usage

Google scholar (https://scholar.google.co.jp) was used for extraction of SARS-CoV-2 and target protein data. Total information content was 1,130 in the mitochondria and 3,172 in complement. The gene function of protein was searched by Gene Cards (www.genecards.org). Protein ontology was investigated by GO enrichment analysis in Geneontology (geneontology.org). Human disease-associated genes and gene variants search were performed by DisGeNET (disgenet.org).

Viral Mirna and Functionally Analogy Analysis

Data of viral miRNA and viral genome was extracted from Viral Genomes (ncbi.nim.nih.gov) and miRBase Ver. 22.1 (miRbase.org). The functional analogy analysis between viral miRNA and human miRNA was performed as previously described [13, 14].

METS Analysis and Deadly Risk Calculation

METS analysis updated was performed by the computer processing as described previously [14, 15]. Data of multi-targets to a miRNA was obtained from Target Scan Human 7.2 (targetscan.org) and miRTarBase Ver. 8.0 (mirtarbase.cuhk.edu.cn). Target protein/protein interaction and cluster analysis were performed by using STRING Ver. 11.0 (string-db.org). The deadly risk calculation was performed by Excel.

AI Analysis

Prediction One Ver. 04.08.20 (Sony Network communications Inc. Tokyo, Japan) was used for AI machine learning as previously described [1,2]. The area under the curve (AUC) in receiver operating characteristic (ROC), accuracy, precision, recall and F values were calculated by Prediction One.

MIRAI

Previous METS analysis data in hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus type 1 (HIV-1), SARS-CoV-2 infection was combined with the updated data through AI machine learning [1,2].

RESULTS AND DISCUSSION

Extraction of COVID-19 Death-Related Protein Target Data

METS analysis was performed and the data was updated by AI in SARS-CoV-2 infection. From the etiologic analysis of COVID-19 by METS-MIRAI simulation, disease death-related protein data in the genetics was extracted from the list **(Tables 1 and 2)**. In viral factors, since C1QB was newly targeted by hsa-miR-4291 in updated search of the

database, CoV-miR-2 targeted to the C1QB 3'UTR by the miRNA functional analogy analysis **(Table 1)**. C1QA, C1QB and HIF1A were selected. HIF1A is implicated in SARS-CoV-2 receptor ACE2 expression and pulmonary hypertension [2]. Since somatic mutations of the HIF1A gene are not frequently implicated in the pathogenesis of human diseases, such as a cancer [16], HIF1A genetic data was excluded. Subsequently, the genetical data of C1QA and C1QB were collected. Although patients of complete deficiency in C1Q gene, the allele of a variant (rs172378) of the C1QA gene has been found to decrease levels of C1Q in patients with subacute cutaneous lupus (SCLE) [17]. The allele of a variant (rs7549888) in the 3'UTR region of the C1QB locus is associated with 1/100 levels of C1Q production [18]. This rs7549888 is not significantly associated with systemic lupus erythematosus (SLE) but the luck of C1Q gene in humans causes development of systemic lupus erythematosus (SLE) and SLE-like hypocomplementemia [19]. Therefore, the relation between single nucleotide polymorphism (SNP) mutations and SLE has not yet been cleared. However, it is strongly suggested that functional mutations of C1QA and C1QB can reduce C1Q amounts in patients. The frequencies of the haplotype variant (rs172378) among Hispanic, African and Asian populations have been reported [20] but not in rs7549888 (data not shown). The stem loop 1 and 2 sequences in the 3' terminal non-coding region are conserved among SARS-CoVs [21], therefore, the targeting of Cov-miR-2 in stem loop1 to C1QA and C1QB would not be altered by SARS-CoV-2 RNA open-reading frame (ORF) mutations. Thus, C1Q deficiency by functional mutations and by virus miRNA attack would be the first deadly risk factor candidate of COVD-19 **(Figure 1)**.

Table 1. The list of updated SARS-CoV-2 virus miRNA and the protein Target.

Target protein	**Virus miRNA hub**	**miRNA branch**						
C1QA**	Cov-miR-2*	miR-6756-5p	miR-6870-5p	miR-6766-5p				
C1QB**	Cov-miR-2*	miR-6803-5p	miR-6751-5p					
MGST1**	Cov-miR-2*	miR-4505						
KRTAP9-9**	Cov-miR-2*	miR-4701-3p	miR-6736-5p					
MAVS/VISA**	Cov-miR-2*							
KRTAP21-2**	Cov-miR-4*	miR-432-5p						
MAVS/VISA**	Cov-miR-4*							
CAPN3**	Cov-miR-5*	let-7b-5p	miR-4458	let-7c-5p	let-7e-5p	let-7d-5p	let-7i-5p	let-7a-5p
FOXO1**	Cov-miR-5*	miR-196a-5p						
YWHAZ**	Cov-miR-5*	miR-375						
HIF1A**	Cov-miR-	miR-20a-	miR-18a-5p	miR-17-5p				

	5*	5p						
LDLR**	Cov-miR-5*	miR-17-5p						

**downregulation*
***upregulation.*
Thin: Key proteins
Data was based on [2]

Table 2. The list of updated host miRNA and the protein target in SARS-CoV-2 infected COVID-19.

Target protein	**Host miRNA hub**	**miRNA branch**						
PDCD1LG2**	miR-106a-5p*	miR-373-3p						
HAUS8**	miR-106a-5p*							
HMGA2**	miR-98-5p*	let-7b-5p	let-7e-5p	let-7c-5p	miR-4458	let-7a-5p	let-7i-5p	let-7d-5p
ARID3B**	miR-98-5p*	let-7b-5p	let-7e-5p	let-7c-5p	miR-4458	let-7a-5p	let-7i-5p	let-7d-5p
LIN28B**	miR-98-5p*	let-7b-5p	let-7e-5p	let-7c-5p	miR-4458	let-7a-5p	let-7i-5p	let-7d-5p
USP44**	miR-98-5p*	miR-7153-5p						
IGF2BP1**	miR-98-5p*	miR-383-5p						
YOD1**	miR-98-5p*	miR-196b-5p	miR-196a-5p					
S100A12*	miR-574-5p**	miR-1224-5p	miR-5589-5p	miR-5004-5p				
CDKN1A**	miR-106a-5p*	miR-93-5p	miR-298					
E2F1**	miR-106a-5p*	miR-149-3p	miR-34a-5p					
STAT3**	miR-106a-5p*	miR-4516						
HIF1A**	miR-106a-5p*	miR-20a-5p	miR-20b-5p	miR-18a-5p	miR-17-5p	miR-18b-5p		
ZBTB4**	miR-106a-5p*	miR-93-5p						

BCL2*	miR-497-5p**	miR-34a-5p						
CHEK1*	miR-497-5p**	miR-503-5p						
E2F2**	miR-98-5p*	let-7a-5p	miR-24-3p	miR-155-5p				
SOCS4**	miR-98-5p*							
IL6**	miR-98-5p*	let-7a-5p						

**downregulation*
***upregulation.*
Thin: Key proteins
Data was based on [2]

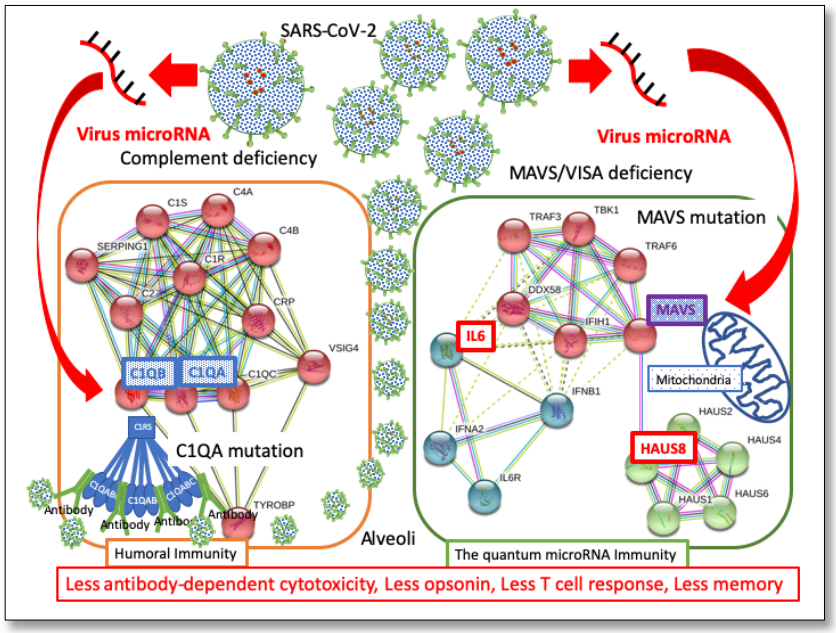

Figure 1. Deadly risk factors of COVID-19 in the complement and mitochondria. The complement deficiency was depicted as C1Q suppression causing by SARS-CoV-2 miRNA (the left panel). The MAVS/VISA deficient haplotype was also presented (the right panel). MAVS/VISA host defense system is one of the quantum miRNA immunity against SARS-CoV-2 infection.

About the evading from the quantum miRNA immunity by viral miRNA, host factors were selected from the list data in **Table 2**. HUSA8, CDKN1A, HIF1A, BCL2 and IL-6 data were collected form genetical database. IL-6 is related with CRS [5], and BCL2 and CDKN1A are implicated in apoptosis and the cell cycle, respectively [2]. Although BCL2 translocation mutation is related with follicular lymphoma progression [22], it was not suddenly lethal in human and is not associated with viral production. Somatic mutation of CDKN1A is associated with human neoplasia growth [23], however, it was not directly related with human death. BCL2 and CDNK1A were excluded from this time investigation. As the host defense mechanism, HIF1A was upregulated by host miR-106a-5p downregulation but viral Cov-miR-5 blocks it as described above. In viral evading factors, MAVS/VISA was newly targeted by hsa-miR-4291 and has-miR-576-3p in updated search of the database, therefore, Cov-miR-2 and Cov-miR-4 targeted to the MAVS/VISA 3'UTR by the miRNA functional analogy analysis **(Table 1)**. Then, MAVS/VISA allele data was extracted. Because, firstly, activation of MAVS/VISA is associated with enhancing of HUSA8 [4] and five functionally genetical alteration alleles have already found in the MAVS sequences from the National Center of Biotechnology Information Center (NCBI) database [10]. Secondary, human mitochondrial DNA haplogroups is

deeply distinctive among the ethnics [24,25]. At the third, although C1Q deficiency would induce SLE-like symptom in COVID-19, SLE bone marrow mesenchymal stem cells produce high levels of type I IFN via MAVS pathway on the mitochondria [26]. Therefore, SLE-related MAVS SNPs were searched by DisGeNET. The C79F allele (rs11905552) in MAVS is associated with low type 1 IFN production and absence of anti-RNA-binding protein autoantibodies [27]. Thus, MAVS C79F (rs11905552) was used for the calculation of COVID-19 death risk rate as the secondary deadly risk factor candidate **(Table 3)**. Since IL-6 was induced by MAVS activation via hypoxia [28], MAVS/VISA activation would be cooperated with hypoxia via HIF1A downregulation by virus miRNA. Therefore, excessed IL-6 production in CRS would be enhanced by double causes of host miR-98-5p downregulation and hypoxic pulmonary vascular hypertension by SARS-CoV-2 viral miRNA. Substantially, the C1QA/C1QB deficiency and the MAVS/VISA deficiency might have caused more severe COVID-19 condition in infected individuals **(Figure 1)**.

Calculation of COVID-19 Deadly Risk Rate

COVID-19 death risk rate was calculated in the USA model. Odds of C1QA synonymous and nonsynonymous mutations (GG→GA/AA) (rs172378) allele frequencies were statistically predicted as 0.025, 0.0101 and 0.018 in Caucasian-American plus Hispanic-American, African-American and Asian-American, respectively, according to Radanova's reports of healthy people [20]. Although statistically, the C1QA mutation allele of the Caucasian-American in SLE has not documented [20], mutation population of the Caucasian-American was tentatively placed to approximately same percentage of population in Hispanic-American because the C1QA allele SNP frequencies in healthy people were similarly found between the Caucasian-American and Hispanic-American **(Table 3)** [17]. The population percentage of Caucasian-American plus Hispanic-American, African-American and Asian-American in 2010 census were 63.4%, 13.1% and 8.8%, respectively (data.census.gov). Therefore, the ethnic group risk % of C1QA mutation was calculated as 1.58 of Caucasian-American plus Hispanic-American, 0.132 of African-American and 0.158 of Asian-American in **Table 3**. Deadly risk % by C1QA mutation in COVID-19 is the same as the ethnic group risk percentages. The different ethnic deadly risk by haplotype C1QA were observed as approximate 10 times in Caucasian-American to Asian-American in the USA model. The data of June, 30th, 2020 in USA shows approximate 77.6 times on an average of the deaths/100k population in China, Japan and South Korea when compared with the deaths/100k population in USA by Johns Hopkins University; therefore, the COVID-19 death among ethnics would not due to C1QA allele mutation. The total percentage of deadly risk by C1QA allele was 1.87%.

Table 3. Deadly risk of COVID-19 in complement and the mitochondria.

	Ethnic	Population % (a)	Mutation frequencies odds (b)	Population risk % of mutation allele (a)x(b)=(j)	Age	% of USA Population (e)	**Odds by mitochondria senescence (f)	Aged risk weighting by mitochondria senescence (e)x(f)=(k)	Deadly risk % in age (j)x(k)	Total %
C1QA mutation	+ Caucasian Hispanic-American	63.4	0.025	1.5	1-44	55.1				1.58
					45-64	25.4				
					>65	14.4				
	African-American	13.1	0.0101	0.132	1-44	55.1				0.132
					45-64	25.4				
					>65	14.4				
	Asian - A	8.8	0.018	0.158	1-44	55.1				0.158
					45-64	25.4				

					>65	14.4				
	Total % of MAVS deadly risk									**1.87**
MAVS C79F	Caucasian + Hispanic-American				1-44	55.1	0.1	0.0551	0.0595	0.7955
					45-64	25.4	1.23+0.08	0.321+0.02	0.347+0.02	
					>65	14.4	2.5+0.1	0.36+0.01	0.389+0.01	
	African-American				1-44	55.1	0.1	0.0551	0.0678	0.9048
					45-64	25.4	1.23+0.08	0.321+0.02	0.394+0.02	
					>65	14.4	2.5+0.1	0.36+0.01	0.443+0.01	
	Asian-American + Others				1-44	55.1	0.1	0.0551	5.51E-06	0.00681
					45-64	25.4	1.23+0.08	0.321+0.02	0.00321	
					>65	14.4	2.5+0.1	0.36+0.01	0.0036	
	Total % of MAVS deadly risk									**1.707**
	Total % of deadly risk									**3.58**

**(0) in a reference*
***Odds calculated from SOD2 activity in aging*

Odds of MAVS minor allele C79F frequencies were statistically predicted 0.017, 0.094 and 0.001 in Caucasian-American plus Hispanic-American, African American and Asian-American, respectively, according to Pothlichet's report [27]. Although statistically, the C79F alleles are not found in the Japanese population [12], 0% was tentatively replaced to 0.1% because Chinese population included into Asian-American population would have other functionally deficient alleles of MAVS **(Table 3)** [29]. The population pyramid by age in 2018 was searched as 55.1%, 25.4% and 14.4% in age: -44, 45-64 and 65-, respectively. Since age-related mitochondrial dysfunction in quality and quantity is associated with reduction activity of the mitochondrial superoxide dismutase (SOD2) [30], risk odds by mitochondria senescence was determined according to SOD2 activity in age -44, 45-64 and 65- **(Table 3)** [31,32]. Aged risk weighting by mitochondria senescence was 0.0551 in -44, 0.321±0.02 in 45-64 and 0.36±0.01 in 65-. Total deadly risk was calculated form the ethnic group % of MAVS mutation and aged risk weighting **(Table 3)**. The ethnic group risk % of MAVS mutation was calculated as 1.08 of Caucasian-American plus Hispanic-American, 1.23 of African-American and 0.01 of Asian-American in **Table 3**. Deadly risk % by MAVS mutation in COVID-19 was approximate 0.7995, 0.9048 and 0.00681 in Caucasian-American plus Hispanic-American, African-American and Asian-American, respectively. The computed ethnic deadly risk and the deadly risks by haplotype C79F were observed

as approximate 100 and 250 times in Caucasian-American plus African-American to Asian-American in the USA model, respectively. From computed deadly risk data in C79F, the ethnic deadly risk has a good match to the deaths/100k population ratio (100:77.6) but deadly risk including aged risk odds in computing was much higher (250:77.6) among ethnics. This lower deaths/100k population rate of Caucasian-American plus African-American would show the excellent medical treatment by medical staffs in USA. Further, there would be another possibility of high deadly risk ratio in Asian-American to be much frequencies of Asian MAVS C79F mutation more than 0.3. Under haplotype C79F frequency, age-dependent deadly risk was approximate 0.127% in -44, 0.744% in 45-64 and 0.836% in 65- **(Figure 2)**. Total deadly percentage by C79F was approximate 1.707%. COVID-19 in USA. is 3,355,646 cases and then the death is 137,403 on July, 12, 2020 (worldometers.info/coronavirus/country/us/); therefore, the death rate is 4.09%. Total deadly rate in C1QA mutation and C79F was calculated as approximately 3.58% **(Table 3 and Figure 2)**. Smoking and anamnesis of infected individuals would increase the deadly rate. The deadly rate of computing prediction would be close to the death rate in the wave data. Thus, it is suggested that MAVS in the mitochondria haplotype in host might be a factor causing the different death rate between western countries' and Asian populations **(Figures 1 and 2)**.

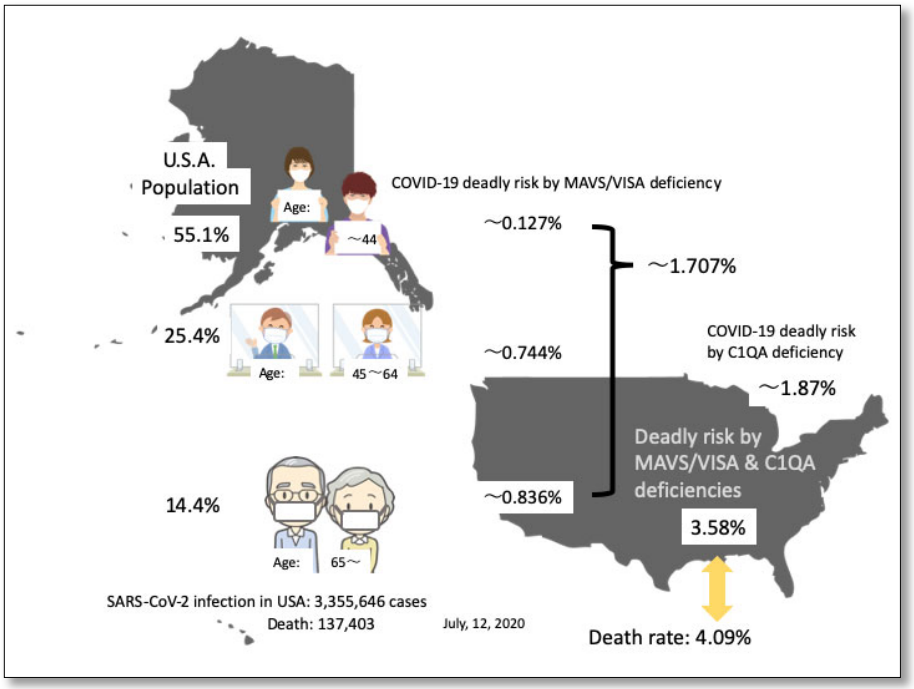

Figure 2. The deadly risk rate of COVID-19 in the USA model. The senescence risk rate and total risk rate of COVID-19 were calculated and shown as the USA model. Computed total risk % is compared with the percentage of deaths of COVID-19 in USA on July, 12, 2020 and asymptomatic carrier % was predicted.

The presence of asymptomatic carrier is known whereas in nursing facility in Washington, 57% was asymptomatic, and in Iceland, voluntary screening showed 50% asymptomatic carriers [33]. Therefore, it is suggested that there would be presence of asymptomatic carriers with normal MAVS/VISA haplotype patients bearing normal C1QA allele. Altogether, since an asymptomatic carrier reserves SARS-CoV-2 under the C1Q complement deficiency by viral miRNA charge and normal MAVS/VISA prevents much viral production in the balance, the aged- or stressed-mitochondria senescence factor would influence onset of COVID-19 to asymptomatic carriers. On the contrary, Type 1 INF decreasing through MAVS/VISA functional deficient allele and MAVS/VISA suppression by viral miRNAs would induce virus proliferation and unlimited. In mouse model, MAVS deleted mice die more rapidly after West Neil virus (WNV)-Texas infection but not against non-pathogenic WNV [34]. Thus, the MAVS/VISA deficiency is lethal to pathogenic SARS-CoV-2. Further, the conversion of the asymptomatic carrier to the symptomatic patient would be dependent on the ability of MAVS/VISA upon the mitochondria or the mitochondria senescence itself.

T-Cell Cross-Reactivity and a Weak Immune Response

Although the T cell cross-reactivity has been reported in recovered patients of COVID-19 [35], it is an innate immune phenomenon when patients would be recovered from mild severity dominant (70%). It is not severe individuals need a care of intensive care unit (ICU); therefore, it is not related with deadly condition. So, normal MAVS/VISA allele

patients' blood would be used for above Grifoni's *in vitro* experiment [35]. Furthermore, T cells used in their experiment includes NK-T cells as an innate immunity. NK-T recognizes antigen presenting molecule CD1d and prevents viral infections, such as human immunodeficiency virus type 1 (HIV-1), influenza and respiratory syncytial virus (RSV) [36]. But at least in HIV-1 and influenza virus infection, there is not so large different death rate between western and Asian people. In addition, the asymptomatic individuals have a longer duration of viral shedding than the symptomatic ones, and approximate 90% and 80% of asymptomatic patients reduces IgG and the neutralizing antibody levels during the early convalescent phase, respectively [37]. It is exactly that a weak immune response to SARS-CoV-2 in asymptomatic carriers would be due to the state of complement deficiency **(Figure 1)**.

Validation of the Updated Data by AI

The evaluation of statistical significance for COVID-19 pathology in the METS-MIRAI simulation updated was performed by the area under the curve (AUC) in receiver operating characteristic (ROC) using AI. The updated data including COVID-19 deadly factors was statistically higher AUC (0.9405 in host miRNAs; 0.9471 in virus miRNAs) than the previous data AUC (0.9236 in host miRNAs; 0.8406 in virus miRNAs) **(Table 4)**. Further, accuracy, precision and recall were over 0.95. It is strongly supported that C1Q and MAVS/VISA deficiencies are the deadly risk factor in the COVID-19 etiology. Although antibody-dependent type vaccines have been developed against SARS-CoV-2 coding proteins [38], the ability of virus miRNA to the host has completely been ignored. The effects of the quantum miRNA immunity were evaded by SARS-CoV-2 miRNAs. Therefore, type I IFN might recover the MAVS/VISA deficiency and C1Q complement agents would serve incomplete antibody-antigen reaction. Since the recombinant SARS-CoV vaccine has failed [39] and antibody-dependent enhancement of viral infection has been reported in SARS and MARS [40], and the weak immune response would be induced as described above, C1Q deficiency is a serious problem to develop the effective antibody-dependent vaccine. Thus, our updated results from METS-MIRAI may be all waring that antibody-dependent vaccines have no efficacy against the deadly risk of SARS-CoV-2 infection *in eo*. We should investigate that viral miRNA would be remained in a cell as the miRNA memory to be reserved into long noncoding RNA (lncRNA) [15, 41] and the viral miRNA memory would induce the sequelae for a long term. Further clinical/computer analysis is needed.

Table 4. AI analysis of the updated data.

Host miRNA	**Acute Inflammation**	
	Updated	**Previous Date***
AUC	0.9405	0.9236
Accuracy	0.9545	0.9000
Precision	0.9643	0.9804
Recall	0.9818	0.9091
F Value	0.9730	0.9434
Virus miRNA	**Virus Infection**	
	Updated	**Previous Date***
AUC	0.9405	0.8406
Accuracy	0.9545	0.7586
Precision	0.9643	0.9000
Recall	0.9818	0.7826
F Value	0.9730	0.8372

**Refer [2]*

CONCLUSION

METS-MIRAI analysis updated showed that C1QA, C1QB and MAVS/VISA are targeted by SARS-CoV-2 viral miRNAs. Therefore, we found that the C1Q deficiency and MAVS/VISA suppression would be the strategy of SRAS-CoV-2 to evade the host quantum miRNA immunity. We also found that MAVS/VISA deficient haplotype and the complement deficient haplotype in the host could be the deadly risk factor of COVID-19. On the contrary, normal host MAVS/VISA activation by HAUS8 aggregation would be a factor of increasing asymptomatic carriers under the C1Q deficiency by viral infection. Very high frequency (approximate 100 times) of haplotype C79F in Caucasian-American and African-American might cause the death rate difference among ethnic populations. Aged deadly risk in COVID-19 would be dependent on mitochondria senescence.

Although the stem loop 1 and 2 were located into the orf10 in the SARS-CoV-2 genome **(Figure 3)**, C1QA, C1QB and MAVS/VISA deficiencies were augmented by Cov-miR-2 and Cov-miR-4 in the stem loops of the orf10 **(Figures 1 and 4)**. Comparing with SARS coronavirus, the orf10 is a unique insert downstream of N orf **(Figure 3)**. Since loss of smell sense and taste would be the specific symptom of COVID-19, we investigated the neuro-pharmacologic targets. By Target Scan analysis at a ubiquitous network, we found that the 3'UTR of acetylcholine esterase (ACHE) was targeted by hsa-miR-663b, and the seed of miR-663b was partially homologous to that of Cov-miR-2. Therefore, the ACHE 3'UTR were tested to match the 8 seed of Cov-miR-2 **(Figure 4)**. Consequently, we found that the ACHE would be targeted by Cov-miR-2 **(Figure 5)**. Firstly, nerve transmission would be blocked by ACHE suppression; therefore, loss of smell sense and taste would be observed in infected individuals. Secondary, since acetylcholine was increased by suppression of ACHE, inflammation in the lung would be enhanced through the nicotinic acetylcholine receptor on the lung macrophages [42], suppression of heart rate would be induced and finally autonomic imbalance would be happened. In the deadly risk of COVID-19, smoking would cause the increase of the nicotinic acetylcholine receptor rather than the angiotensin-converting enzyme 2 (ACE-2) increasing [43], and then, the nicotinic acetylcholine receptor would enhance inflammation of the lung. If so, anti-choline agents, such as long acting muscarinic antagonist (LAMA) and long acting beta2-agonist (LAMA) would be available for treatment of COVID-19 with corticosteroid ones, which are used for chronic obstructive pulmonary disease (COPD) implicated in the nicotinic acetylcholine receptor gene haplotype [44]. After all, the deadly risk of COVID-19 RNA genome may be specifically explained as the effects of the inserted orf10 ribozyme-like structure **(Figure 5)** because hiv-miR-N367 in the HIV-1 nef/3'LTR region is implicated in HIV-1 clinical symptoms [1].

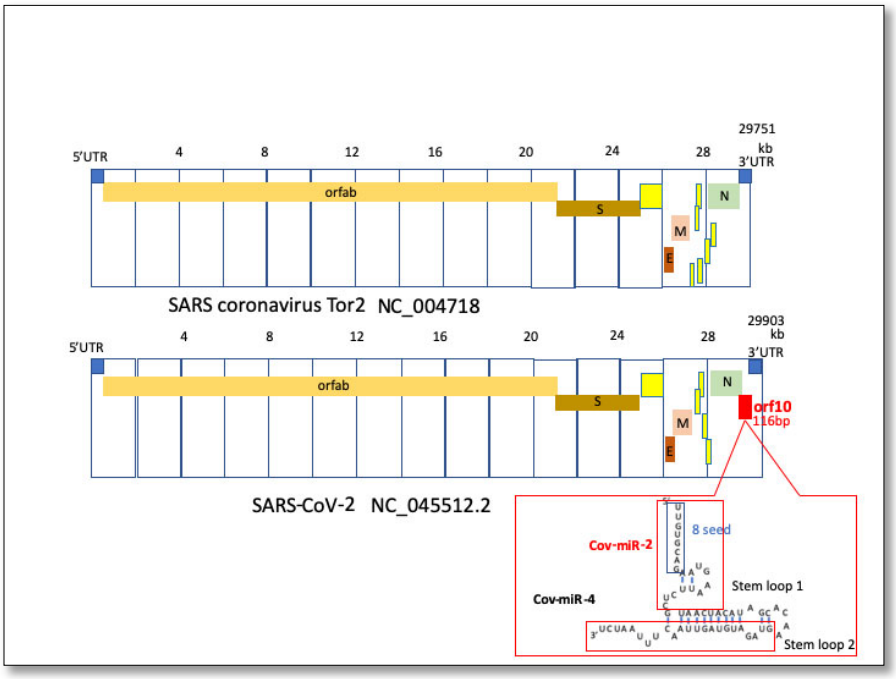

Figure 3. The genome structure of SARS coronaviruses. The RNA genomes of SARS coronavirus Tor2 (the upper panel) and SRAS-CoV-2 (the lower panel) were illustrated as open reading frame (orf). The stem loop 1 and 2 were contained in the orf10 of SARS-CoV-2 genome (red bar). Putative Cov-miR-2 and -4 were derived from stem loop 1 and 2, respectively.

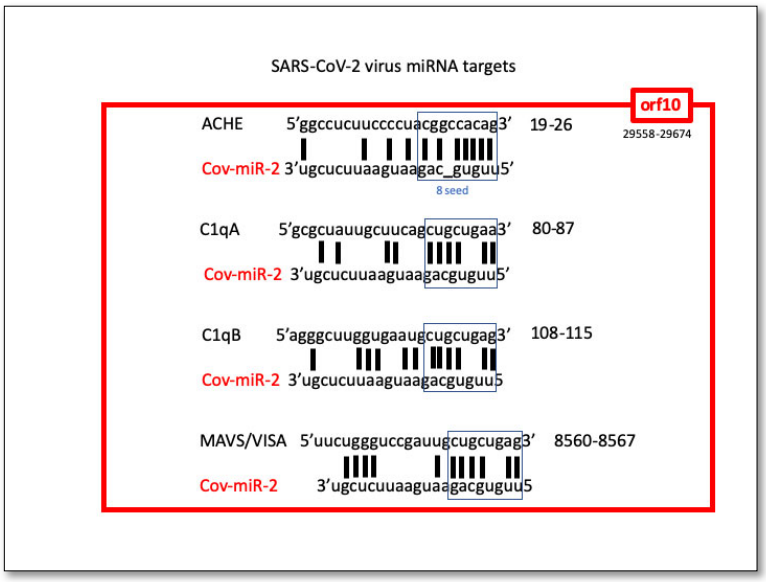

Figure 4. Cov-miR-2 target proteins. The 3'UTRs of ACHE, C1qA, C1qB and MAVS/VISA target site were depicted.

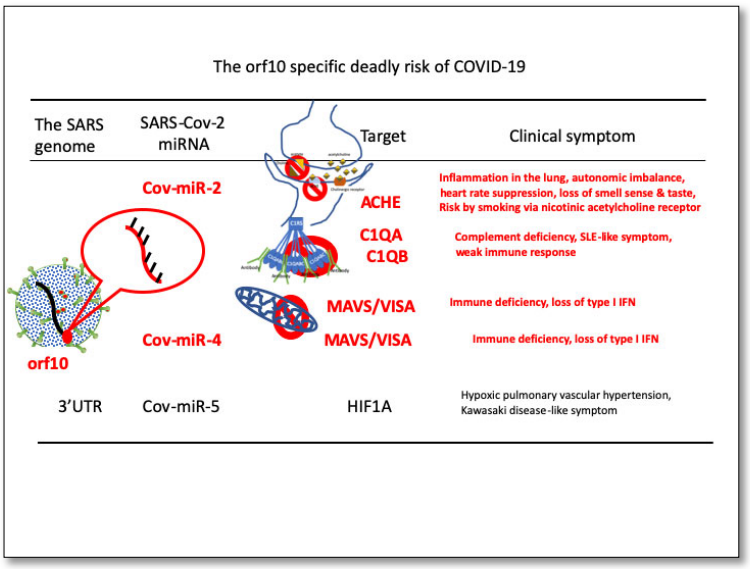

Figure 5. Orf10 specific deadly risk of COVID-19.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

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