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Genome analysis and prevalence of SARS-CoV-2 Indonesian variants and the correlation with the outbreak timeline

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Abstract

Since its first appearance in China, in the end of 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has mutated into several variants. The genome analysis of the spike of SARS-CoV-2 is necessary to identify the mutations in each variant. In this study, we obtained the whole genome sequences of SARS-CoV-2 Wild Type and variants from GenBank (National Center of Biotechnology Information, USA), and GISAID EpiCoV database (Germany). We analyzed the spike glycoprotein gene sequences using the Basic Local Alignment Search Tool (BLAST), and identified the changes in nucleotide and amino acid. Additionally, we also discuss the prevalence and correlation between the submission time of SARS-CoV-2 variants on the GISAID database with the outbreak timeline. The result of our analysis showed that there are 9 amino acid changes in SARS-CoV-2 alpha, beta and delta variants, and 3 amino acid changes in gamma variant. There were 8,861 submissions of Indonesian variants on the GISAID database per November 21, 2021. The correlation between submission time of SARS-CoV-2 variants and outbreak timeline showed that SARS-CoV-2 delta (B.1.617.2) variant potentially caused the sudden increase of COVID-19 confirmed cases from July to September 2021.

Keywords: COVID-19, Coronavirus, Mutation, Genome analysis

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1. Introduction

In the end of year 2019, China reported its first case of infectious disease in Wuhan, which is now known as the coronavirus disease (2019) or COVID-19. In Wuhan Jinyintan Hospital, three bronchoalveolar lavage samples were collected from a patient who had pneumonia with unknown etiology (or cause). Real time polymerase chain reaction (PCR) was performed on these three samples, and the assays showed positive results for pan-Betacoronavirus. The infectious disease is later known to be caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease quickly spread in other countries, causing a pandemic. [1] [2]

SARS-CoV-2 is the seventh of the coronaviruses that is known to infect humans, with the other six being MERS-CoV, SARS-CoV-1, HCoV-NL63, CoV-HKU1, HCoV-OC43, and HCoV-229E. SARS-CoV-2 is known to be closely related with the SARS-CoV-1 virus, a virus that originated from Guangdong, China in late 2002. [3, p. 6] As of November 2021, there are over 255 millions confirmed cases of COVID-19, with over 5 millions deaths worldwide. [4] While in Indonesia, there are over 4.25 million confirmed cases of COVID-19 with over 144 thousand deaths. [5]

SARS-CoV-2 is a single-stranded RNA virus [6]. Its entire genome has been characterized using RNA-based metagenomic next generation sequencing approach, resulting in 29,881 bp in length (GenBank no. MN908947), which encodes 9,860 amino acids [7]. The gene fragments express structural and non-structural proteins. Structural proteins are encoded by the S, E, M, and N genes. While non-structural proteins are encoded by the ORF region. [8]

The surface of SARS-CoV-2 is covered by a large number of glycosylated S proteins, which bind to the host cell receptor angiotensin-converting enzyme 2 (ACE2) and thus mediates viral cell entry. The binding of the S protein, widely known as spike protein, to the receptor promotes virus entry, allowing the viral RNA to be released and replicated in the host cell [9]. This explains how the spike protein of SARS-CoV-2 plays an important role in the infection process.

Mutations are changes or small errors in genetic sequence. Mutation is the cause of diversity among organisms [10]. Genetic mutation is also the reason why humans exist until today. Even though viruses are not living organisms, they are also known for their mutation ability as they infect their host's cells. The outcome of genetic mutation in viruses may cause them to infect a host more easily, or even evade the immune system defense [11]. It is known that RNA viruses are able to mutate at high rates [12]. There are several factors that determine viral mutation rates, which include: polymerase infidelity, template secondary structure, cellular microenvironment, replication mechanisms, proofreading, sequence context, and access to post-replicative repair [13]. SARS-CoV-2 virus typically accumulates two single-letter mutations in the genome each month [14].

According to WHO, there are several classifications of SARS-CoV-2 variants, including the: variants of concern (VOC), variants of interest (VOI), and variants under monitoring

(VUM). Variants of interest are the variants that have genetic mutations that can affect virus characteristics (such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape) and can cause significant community transmission or multiple COVID-19 clusters. Variants of concern are those that meet the criteria of variants of interest, and is associated in either increase in transmissibility or detrimental change in COVID-19 epidemiology; or increase in virulence or change in clinical disease presentation; or decrease in effectiveness of public health or available diagnostics, therapeutics or vaccines. While variants under monitoring are SARS-CoV-2 variants that have genetic mutations that are suspected to affect virus characteristics can pose a future risk, however the evidence of phenotypic or epidemiological impact is still unclear [15]

As of November 26 2021, the variants of concern according to WHO [15] are:

- Alpha variant, originated from United Kingdom, September 2020
- Beta variant, originated from South Africa, May 2020
- Gamma variant, originated from Brazil, November 2020
- Delta variant, originated from India, October 2020

The newly detected variant of concern is the omicron variant, which originated from South Africa and Botswana in November 2021 [15] [16].

In this study, we analyzed the change in nucleotide and amino acid in spike glycoprotein gene sequence of SARS-CoV-2 alpha, beta, delta and gamma mutations in Indonesia. Additionally, we also discuss the prevalence of SARS-CoV-2 variants in Indonesia; and the correlation between submission time of SARS-CoV-2 variants on the GISAID database with the outbreak timeline.

2. Results

Table 1. Submission of SARS-CoV-2 variants in Indonesia on GISAID database with time range

Time Range	Types of Variants	Total of submission
01 March 2020 - 01 May 2020	Alpha	0
Total submitted: 6	Beta	0
	Gamma	0
	Delta	0
	Wild Type	6
02 May 2020 - 01 July 2020	Alpha	0
Total submitted: 20	Beta	0
	Gamma	0
	Delta	0
	Wild Type	20

02 July 2020 - 01 September 2020	Alpha	0
Total submitted: 8	Beta	0
	Gamma	0
	Delta	0
	Wild Type	8
02 September 2020 - 01 November 2020	Alpha	0
Total submitted: 80	Beta	0
	Gamma	0
	Delta	0
	Wild Type	80
02 November 2020 - 01 January 2021	Alpha	0
Total submitted: 26	Beta	0
	Gamma	0
	Delta	0
	Wild Type	26
02 January 2021 - 01 March 2021	Alpha	0
Total submitted: 328	Beta	0
	Gamma	0
	Delta	0
	Wild Type	328
02 March 2021 - 01 May 2021	Alpha	13
Total submitted: 768	Beta	1
	Gamma	0
	Delta	2
	Wild Type	752
02 May 2021 - 01 July 2021	Alpha	34
Total submitted: 1,311	Beta	9
	Gamma	0
	Delta	382
	Wild Type	886
02 July 2021 - 01 September 2021	Alpha	18
Total submitted: 3,299	Beta	7

	Gamma	2
	Delta	1,889
	Wild Type	1,383
02 September 2021 - 21 November 2021	Alpha	12
Total submitted: 3,015	Beta	5
	Gamma	0
	Delta	2,707
	Wild Type	291

Submission of SARS-CoV-2 Indonesian Variants on GISAID with Time Range

Figure 1. Graph of submitted SARS-CoV-2 Indonesian variants on GISAID database with time range

Table 2. Cumulative confirmed COVID-19 cases and deaths in Indonesia

Date	Number of confirmed case	Number of confirmed death
02 March 2020	2	0
02 May 2020	10,843	831
02 July 2020	59,394	2,987
02 September 2020	180,646	7,616
02 November 2020	415,402	14,044
02 January 2021	758,473	22,555
02 March 2021	1.35 million	36,518
02 May 2021	1.68 million	45,796
02 July 2021	2.23 million	59,534
02 September 2021	4.10 million	133,676

02 November 2021	4.25 million	143,457
21 November 2021	4.25 million	143,739

Cumulative Confirmed COVID-19 Cases and Deaths in Indonesia

Figure 2. Graph of cumulative confirmed COVID-19 cases and deaths in Indonesia

Table 3. Total submission of SARS-CoV-2 variants in Indonesia on GISAID database until 21 November 2021

Types of Variants	Total of viruses	Percentages
VOC Delta GK/478K.V1 (B.1.617.2+AY.x) first detected in India	4,980	56,20%
Wuhan wildtype	3,780	42.66%
VOC Alpha 202012/01 GRY (B.1.1.7+Q.x) first detected in the UK	77	0.87%
VOC Beta GH/501Y.V2 (B.1.351+B1.351.2+B.1.351.2) first detected in South Africa	22	0.25%
VOC Gamma GR/501T.V3 (P.1+P.1.x) first detected in Brazil/Japan	2	0.02%

Total viruses: 8,861

Table 4. Spike glycoprotein gene sequence result of Wild Type vs Delta (B.1.617.2.55) variant

	Location from Wild type								
Accession ID	21618	21987	22028	22227	22917	22995	23073 23074	23403	23604
NC_045512.2 (Wuhan Wild type)	C (T)	G (G)	G (E)	C (A)	T (L)	C (T)	GT (G)	A (D)	C (P)
EPI_ISL_182 4604 (Delta)	G (R)	A (D)	A (K)	T (V)	G (R)	A (K)	NN (X)	G (G)	G (R)
	21594	21963	22004	22203	22893	22971	23049 23050	23379	23580
	Location from Delta Variant								

*Format: nucleotide(amino acid)

Table 5. Spike glycoprotein gene sequence result of Wild Type vs Alpha (B.1.1.7) variant

	Location from Wild type							
Accession ID	21765 21770	23063	23271	23403	23604	23709	24506	24914
NC_045512.2 (Wuhan Wild type)	TAC ATG (IHV)	A (N)	C (A)	A (D)	C (P)	C (T)	T (S)	G (D)
EPI_ISL_116 9047 (Alpha)	--T)	T (Y)	A (D)	G (G)	A (H)	T (I)	G (A)	C (H)
	-	23023	23231	23363	23564	23669	24466	24874
	Location from Alpha Variant							

*Format: nucleotide(amino acid)

Table 6. Spike glycoprotein gene sequence result of Wild type vs Beta (B.1.351) Variant

	Location from Wild type								
Accession ID	21801	22206	22280	22813	23012	23063	23149	23403	23664
NC_045512.2 (Wuhan Wild type)	A (D)	A(D)	A(T)	G(K)	G(E)	A(N)	G(K)	A(D)	C(A)
EPI_ISL_182 4605 (Beta)	C (A)	G(G)	A(P)	T(N)	A(K)	T(Y)	A(K)	G(G)	T(V)
	21777	22182	22258	22789	22988	23039	23125	23379	23640
	Location from Beta Variant								

*Format: nucleotide(amino acid)

Table 7. Spike glycoprotein gene sequence result of Wild type vs Gamma (B.1.470) Variant

	Location from Wild type		
Accession ID	21597	22286	23403
NC_045512.2 (Wuhan Wild type)	C(S)	C(L)	A(D)
EPI_ISL_2854770 (Gamma)	T(F)	T(F)	G(G)
	21550	22239	23356
	Location from Gamma Variant		

*Format: nucleotide(amino acid)

Table 8. Amino acid mutations in SARS-CoV-2 alpha, beta, delta and gamma variant

Amino acid mutations	SARS-CoV-2 variants			
	Alpha	Beta	Delta	Gamma
Δ68-69	✓			
A222V			✓	
A570D	✓			
A701V		✓		
D1118H	✓			
D215G		✓		
D614G	✓	✓	✓	✓
D80A		✓		
E156K			✓	
E484K		✓		
G142D			✓	
G504X			✓	
K417N		✓		
K529K		✓		
L242F				✓
L452R			✓	
N501Y	✓	✓		
P681H	✓			
P681R			✓	
S12F				✓
S982A	✓			
T19R			✓	
T240P		✓		
T478K			✓	
T716I	✓			
V70I	✓			
Total mutated amino acids	9	9	9	3

3. Discussion

3.1 Analysis of SARS-CoV-2 Indonesian variants spike protein sequence

In the alpha (B.1.1.7) variant, based on Table 5, the mutations in amino acids of the spike glycoprotein were: Δ 68-69, V70I, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H. The SARS-CoV-2 B.1.1.7 variant has the Δ 68-69 mutation, which is an amino-terminal domain deletion. The mutation N501Y in SARS-CoV-2 B.1.1.7 variant spike glycoprotein strengthens its binding to the receptor ACE2 [18]. Additionally, the mutation N501Y reduces neutralization by a small proportion of RBD (receptor binding domain) antibodies [19]. The mutation D614G in B.1.1.7 increases infectivity of the virus, which is correlated with S1 shedding and more incorporation of S protein into the pseudovirion [18][3].

According to Table 6, the mutations in amino acids of the spike glycoprotein of the beta (B.1.351) variant were: D80A, D215G, T240P, K417N, E484K, N501Y, K529K, D614G, and A701V. The existence of mutations K417N and E484K suggest that the SARS-CoV-2 B.1.351 variant may overcome polyclonal antibody response by reducing neutralization from class 1 and class 2 RBD-specific antibodies; with K417N playing an important role in viral escape [20]. Mutation N501Y of the spike glycoprotein in the SARS-CoV-2 B.1.351 variant allows the virus to strengthen its bond with the receptor ACE2 [18]. The infectivity of the SARS-CoV-2 beta variant is also increased by the mutation D614G [3, p. 6].

The mutations in amino acids of gamma (B.1.470) variant's spike glycoprotein as seen in Table 7 were: S12F, L242F, and D614G. Just like in SARS-CoV-2 alpha (B.1.1.7) and beta (B.1.351) variant spike glycoprotein sequence analysis, D614G mutation in SARS-CoV-2 B.1.470 variant also increases infectivity of the virus [3, p. 6]. The S12F mutation has a surface exposure, and might have an impact on cell interaction [21].

Meanwhile, from Table 3, the mutations in amino acids of delta (B.1.617.2.55 or AY.55) variant's spike glycoprotein were: T19R, G142D, E156K, A222V, L452R, T478K, G504X, D614G, and P681R. The delta variant mutations in T19R and G142D may cause disruption in binding some anti-NTD neutralizing antibodies obtained from the wild-type's spike [22]. The A222V mutation was present in the Delta Plus and Delta variants, at the prevalence of 58% and 9% respectively [23]. The L452R mutation caused structural change resulting in reduction of intramolecular and intermolecular contacts towards ACE2 binding [24]. In addition, another study reported that 14 out of 35 RBD-specific mAbs, including three clinical stage mAbs, had their neutralizing activity decreased or eliminated due to the L452R mutation [25]. Moreover, another report revealed that the L452R mutation allows viruses to evade HLA-24-restricted cellular immunity while also increasing viral infectivity, potentially encouraging viral reproduction [26]. The T478K mutation in the RBD is specific to the Delta B.1.617.2.55 variation and occurs in the epitope region, and is powerful in neutralizing 'Class 1' monoclonal antibodies [27]. The D614G mutation alters the spike protein to be more stable, allowing it to penetrate the host cell more efficiently [17]. The P681R mutation in the furin cleavage site

enhancing the basicity of the poly-basic stretch might aid in greater rate of membrane fusion, internalization and hence improved transmissibility [24].

3.2 Analysis of cumulative confirmed cases and deaths and submitted variants on GISAID database

Based on Table 2, the increase in the number of cumulative confirmed COVID-19 cases went steady from September 2020 to January 2021, in which the confirmed cases increased by around 300,000 every 3 months. However from January to March 2021, the number of confirmed cases increased by around 590,000 from 758,473 cases on January 2, 2021 to 1.35 million cases on March 2, 2021. The number of confirmed cases increased sharply from July to September 2021, which went from 2.23 million on July 2 2021 to 4.10 million on September 2 2021; with the number of deaths caused by COVID-19 also increased sharply from 59,534 to 133,676 deaths. By November 21 2021, the cumulative cases of COVID-19 reached the number of 4.25 million with 143,739 deaths caused by COVID-19. The increase in the number of confirmed COVID-19 cases and deaths in Indonesia can be seen in Figure 2.

Based on Table 1, from March-May 2021 to May-July 2021 there was a sudden increase in the number of submitted Indonesian delta variants which went from 2 submissions to 382 submissions on the GISAID EpiCoV database. The number increased to 1,889 submissions in July-September 2021, and kept increasing to 2,707 submissions in September-November 2021. The increasing number of Indonesian delta variant submissions as well as other submitted Indonesian variants on the GISAID EpiCoV database can be seen in Figure 1.

To analyze the correlation between the cumulative COVID-19 cases and deaths, with the cumulative submissions of SARS-CoV-2 Indonesian variants on the GISAID database, direct comparison of the data is performed. The direct comparison can be seen in Table 9 below.

Table 9. Cumulative submission of SARS-CoV-2 Indonesian variants, COVID-19 cases and deaths

Date	SARS-CoV-2 Indonesian variant					Case	Death
	Alpha	Beta	Gamma	Delta	WT		
01 May 2020	0	0	0	0	6	10,843	831
01 July 2020	0	0	0	0	26	59,394	2,987
01 September 2020	0	0	0	0	34	180,646	7,616
01 November 2020	0	0	0	0	114	415,402	14,044
01 January 2021	0	0	0	0	140	758,473	22,555
01 March 2021	0	0	0	0	468	1.35 million	36,518

01 May 2021	13	1	0	2	1,220	1.68 million	45,796
01 July 2021	47	10	0	384	2,106	2.23 million	59,534
01 September 2021	65	17	2	2,273	3,489	4.10 million	133,676
21 November 2021	77	22	2	4,980	3,780	4.25 million	143,739

In Table 9 above, the notable changes have been highlighted with pale yellow color. The notable change occurs from July 1 2021 to September 1 2021. On July 1 2021, the number of submissions of the SARS-CoV-2 delta variant in Indonesia on the GISAID database was 384, which then increased to 2,273 on September 1 2021. Meanwhile within the same time range, drastic increase of cumulative COVID-19 cases and deaths also occurred. On July 1 2021, the number of cumulative COVID-19 cases and deaths in Indonesia was respectively 2.23 million and 59,534, which then increased to 4.10 million cumulative cases and 133,676 deaths on September 1 2021. This analysis could show the correlation of the increasing number of delta variant of SARS-CoV-2 with the sudden increase of cumulative COVID-19 cases and deaths in Indonesia. This can be related with the clinical manifestations of the SARS-CoV-2 delta (B.1.617.2) variant, which are: (1) increased transmissibility, (2) potential vaccine effectiveness reduction against symptomatic COVID-19, and (3) potential reduction in monoclonal antibody therapies neutralization. Moreover, B.1.617.2 has a potential of increasing severity, judging from hospitalization rate [28]. However, the limitations to this analysis include: (1) lack of proof due to lack of data (especially about the precise number of COVID-19 cases caused by each variant of SARS-CoV-2), (2) lack of significant analysis that can lead to conclusive result, and (3) few mismatch of date between submissions and cases/deaths due to different sources.

4. Conclusion

As a conclusion, this research studied the genome analysis and prevalence of SARS-CoV-2 Indonesian variants, and the correlation between the submissions of SARS-CoV-2 Indonesian variants: alpha, beta, delta and gamma on the GISAID database with the outbreak timeline. From the genome analysis, the changes of amino acids in the SARS-CoV-2 variants' spike glycoprotein were obtained. The analysis of the submission time and outbreak timeline, supported by analysis of clinical manifestation caused by the mutations, showed that SARS-CoV-2 delta (B.1.617.2) variant might have caused the sudden increase of COVID-19 confirmed cases and deaths from July to September 2021.

5. Materials and Methods

5.1. Whole genome sequences of SARS-CoV-2

In this study, the SARS-CoV-2 whole genome sequences (WGS) were obtained from GISAID (the Global Initiative on Sharing All Influenza Data) EpiCoV database and GenBank (National

Center for Biotechnology Information). Registration to GISAID was required to access the database.

5.2. *SARS-CoV-2 submission timeline analysis*

The submission time of SARS-CoV-2 variants on the GISAID database was obtained by accessing the GISAID EpiCoV database. The time range used in this analysis was per 3 months (quarterly) starting from 01 March 2020 until 21 November 2021. The location was set to “Indonesia”, and the variant was set as one of the options below:

- VOC Delta GK/478K.V1 (B.1.617.2+AY.x) first detected in India
- VOC Alpha 202012/01 GRY (B.1.1.7+Q.x) first detected in the UK
- VOC Beta GH/501Y.V2 (B.1.351+B.1.351.2+B.1.351.3) first detected in South Africa
- VOC Gamma GR/501Y.V3 (P.1+P.1.x) first detected in Brazil/Japan
- Empty (to search all submissions within the time range)

5.3. *Analysis of cumulative confirmed COVID-19 cases and deaths in Indonesia*

The number of cumulative confirmed COVID-19 cases and deaths in Indonesia was obtained by accessing the ‘Our World in Data’ website via the link <https://ourworldindata.org/coronavirus-data?country=~IDN> . The country was set to ‘Indonesia’ and the data was recorded every 3 months.

5.4. *Genetic Composition Analysis*

The genetic composition of SARS-CoV-2 spike glycoprotein sequences were analyzed based on their nucleotide variants and amino acid mutations. In this study, the complete genome of SARS-CoV-2 isolate Wuhan-Hu 1 was used as a reference gene [17]. Afterwards, the results were compared to the previous studies and research journals.

5.5. *Similarity Analysis*

In order to analyze the similarity between the reference and the query sequences, a nucleotide Basic Local Alignment Search Tool (BLAST) provided by NCBI was used. A pairwise with dots for identities alignment view was utilized to locate the mutations in the nucleotides. In addition, the Coding Region Sequences (CDS) feature was used to analyze the isolates’ amino acids sequence.

Authors' Contribution

K.A.A. had overseen the project conceptualization process, acquired research funding for the study, designed the methodology for the study, and helped writing as well as reviewing the manuscript draft alongside M.P.I.M. and T.C.T. T.C.T. provided the whole genome sequence of SARS-CoV-2 Wild Type, while M.P.I.M. provided the whole genome sequences of the variants. M.P.I.M. provided the data of submission of SARS-CoV-2 variants in Indonesia on GISAID database and cumulative confirmed COVID-19 cases and deaths in Indonesia with time range, and the analysis of the correlation between the provided data. T.C.T. performed the genome sequence similarity analysis between Wild Type and each variant and provided the data of amino acid mutations in each variant. T.C.T. and M.P.I.M. provided analysis of each variant's mutation based on the data of amino acid mutations provided by T.C.T. All authors have read and approved the final version of the manuscript.

Competing Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Figures

Submission of SARS-CoV-2 Indonesian Variants on GISAID with Time Range

Figure 1

Graph of submitted SARS-CoV-2 Indonesian variants on GISAID database with time range

Cumulative Confirmed COVID-19 Cases and Deaths in Indonesia

Figure 2

Graph of cumulative confirmed COVID-19 cases and deaths in Indonesia