Acta Biochimica Indonesiana

https://doi.org/10.32889/actabioina.163

RESEARCH ARTICLE

Open Access

Genome analysis and prevalence of SARS-CoV-2 Indonesian variants and the correlation with the COVID-19 outbreak timeline

Maria Prevyolita Indra Muliawan, Timotius Christopher Tantokusumo, Amalda Siti Anisa, Kholis Abdurachim Audah*

Department of Biomedical Engineering, Swiss German University, Tangerang 15143, Indonesia

*Corresponding author: Kholis Abdurachim Audah. Department of Biomedical Engineering, Swiss German University, Tangerang 15143, Indonesia. Email: kholis.audah@sgu.ac.id

ABSTRACT

Background: Since its emergence in China at the end of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has undergone multiple mutations, leading to the development of various variants.

Objective: This study aims to identify the genetic mutations associated with the transmission and virulence of SARS-CoV-2 variants in Indonesia and to examine their correlation with the outbreak timeline.

Methods: We analyzed whole-genome sequences of SARS-CoV-2 wild type and variants isolated from Indonesian samples, sourced from GenBank (National Center for Biotechnology Information, USA) and the GISAID EpiCoV database (Germany). The spike glycoprotein gene sequences were examined using the Basic Local Alignment Search Tool (BLAST) to identify nucleotide and amino acid changes. Additionally, we investigated the prevalence of these variants and their submission timelines on the GISAID database, correlating them with the outbreak timeline.

Results: Our analysis identified nine amino acid changes in the Alpha, Beta, and Delta variants, and three in the Gamma variant, compared to the wild type (Wuhan strain). By November 21, 2021, 8,861 submissions of Indonesian variants were recorded in the GISAID database. A correlation between the submission timelines of SARS-CoV-2 variants and the outbreak timeline indicated that the Delta variant (B.1.617.2) likely contributed to the surge in COVID-19 cases from July to September 2021.

Conclusion: Mutations were detected in each variant, emerging at distinct times, and are likely to influence transmission rates and virulence. However, further research is needed to elucidate how structural changes in the spike protein impact these properties.

Keywords: coronavirus, COVID-19, genome analysis, Indonesian isolates, mutation

Introduction

In late 2019, China reported its first case of a novel infectious disease in Wuhan, later identified as coronavirus disease 2019 (COVID-19). Initial investigations at Wuhan Jinyintan Hospital involved collecting three bronchoalveolar lavage samples from a patient with unexplained pneumonia. Real-time polymerase chain reaction (PCR) tests on these samples yielded positive results for pan-Betacoronavirus. The causative agent was subsequently identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which rapidly spread to other countries, leading to a global pandemic [1,2].

SARS-CoV-2 is the seventh known coronavirus to infect humans, joining others such as MERS-CoV, SARS-CoV-1, HCoV-NL63, CoV-HKU1, HCoV-OC43, and HCoV-229E [3]. As of November 2021, over 255 million COVID-19 cases and more than 5 million deaths have been reported worldwide [4]. In Indonesia alone, the pandemic has resulted in over 4.25 million confirmed cases and more than 144,000 deaths [5].

SARS-CoV-2 is a single-stranded RNA virus with a genome characterized by an RNA-based metagenomic next-generation sequencing approach, spanning 29,881 base pairs and encoding 9,860

amino acids (GenBank no. MN908947) (6,7). The genome comprises structural and non-structural proteins, with the structural proteins encoded by the S, E, M, and N genes, and non-structural proteins encoded by the ORF region [8]. The virus's surface is adorned with glycosylated spike (S) proteins, which bind to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells, facilitating viral entry and subsequent RNA release and replication [9]. This highlights the critical role of the spike protein in the infection process.

Mutations are changes in the genetic sequence, which, though viruses are not living organisms, can enhance viral infectivity or enable immune evasion [10,11]. RNA viruses, including SARS-CoV-2, are known for their high mutation rates, accumulating approximately two single-letter mutations per month [12,13,14]. Factors influencing these rates include polymerase fidelity, template secondary structure, replication mechanisms, cellular environments,proofreading, sequence context, and access to post-replicative repair [13].

The World Health Organization (WHO) classifies SARS-CoV-2 variants into categories: variants of interest (VOI), variants under monitoring (VUM), and variants of concern (VOC). VOIs are variants with mutations that may affect viral characteristics, such as transmissibility or immune escape, while VUMs have mutations that could pose future risks, although their impact is not yet fully understood [14].

VOCs, such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2), are notable for their increased transmissibility, potential to cause severe disease, and reduced vaccine or treatment efficacy [15]. In Indonesia, these VOCs have significantly impacted the COVID-19 outbreak, with the Delta variant driving a surge in cases between July and September 2021. The Omicron variant, first identified in South Africa and Botswana in November 2021, represents the most recent addition to the VOC category [14,17].

The first reported case of SARS-CoV-2 in Indonesia occurred in early March 2020, prompting to a series of government interventions, including social restrictions and public health campaigns. Throughout 2020 and 2021, Indonesia experienced several waves of COVID-19 with varying degrees of severity, where many patients had mild to moderate symptoms. However, the number of severe cases and deaths was particularly high in 2021. The severity of the disease was influenced by factors such as age, pre-existing health conditions, and access to healthcare [18,19]. The COVID-19 pandemic has posed significant challenges to global health and economies, including in Indonesia, where managing healthcare systems and controlling the rapid spread of SARS-CoV-2 variants—such as Alpha, Beta, Gamma, and Delta—proved especially difficult, with a peak in cases during 2021 [20].

Understanding the genetic variations and mutations of SARS-CoV-2 is crucial for developing effective treatments, vaccines, and public health strategies. This study focuses on the genetic analysis of SARS-CoV-2 isolates in Indonesia, particularly mutations in the spike glycoprotein gene, which is essential for viral entry into host cells and serves as a primary target for vaccines and therapies. The study underscores the importance of understanding the mutations in the glycosylated spike proteins, as these mutations correlate with each variant's transmission rate and virulence. Variants exhibit unique molecular and structural characteristics depending on their geographic and temporal origins. Identifying and distinguishing these variants is vital for diagnostics and therapeutic purposes. Notably, some local variants in Indonesia, not found elsewhere, have been discovered [21].

This study analyzes the nucleotide and amino acid changes in the spike glycoprotein gene sequences of SARS-CoV-2 Alpha, Beta, Delta, and Gamma variants in Indonesia. It also examines the prevalence of these variants and their correlation with the outbreak timeline, as reflected by submission data in the GISAID database. The findings aim to provide valuable insights to inform local public health policies and support efforts to combat COVID-19.

Methods

SARS-CoV-2 submission timeline analysis

The submission timelines of SARS-CoV-2 variants in Indonesia were analyzed using data from the GISAID EpiCoV database. The analysis covered the period from March 1, 2020, to November 21, 2021, with data segmented quarterly. 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

The SARS-CoV-2 wild-type genome (Wuhan's original strain) was used as the reference gene.

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

Data on cumulative confirmed COVID-19 cases and deaths in Indonesia were obtained from the "Our World in Data" website (https://ourworldindata.org/coronavirus-data?country=~IDN). The country was set to 'Indonesia' and the data was recorded every three months.

Whole genome sequences of SARS-CoV-2

SARS-CoV-2 whole genome sequences (WGS) were obtained from the GISAID EpiCoV database (https://gisaid.org/) and GenBank (National Center for Biotechnology Information). Registration to GISAID was required to access the database.

Genetic composition analysis

The genetic composition of SARS-CoV-2 spike glycoprotein sequences was analyzed by examining nucleotide variants and amino acid mutations. The complete genome of the SARS-CoV-2 wild type (Wuhan's original strain) was used as the reference gene [22].

SARS-CoV-2 submission timeline analysis

To assess the similarity between the reference and the query sequences, the Basic Local Alignment Search Tool (BLAST) for nucleotides was employed. A pairwise alignment view with identity dots was used to identify nucleotide mutations. Additionally, the coding sequence (CDS) feature was utilized to analyze the amino acid sequences of the isolates.

Results

Analysis of confirmed cases, deaths, and variants SARS-CoV-2 on GISAID database

In this study, we analyzed the prevalence of SARS-CoV-2 variants in Indonesia and their correlation with the COVID-19 outbreak timeline, using data sourced from the GISAID EpiCoV database. The analysis covered the period from March 1, 2020, to November 21, 2021.

The distribution of SARS-CoV-2 variants in Indonesia shifted over time. From March 2020 to March 2021, the wild-type strain was predominantly circulating. The Alpha, Beta, and Delta variants first appeared on March 2, 2021, although their presence was initially minimal. However, from May to November 2021, the Delta variant became the dominant strain in Indonesia, surpassing the wild type in prevalence (Figure 1).

The spread of SARS-CoV-2 has significantly impacted Indonesia since the onset of the pandemic, with confirmed cases surging from just two on March 2, 2020, to 4.25 million by November 2021. Similarly, the number of deaths, initially nonexistent in March 2020, escalated to over 143,000 by November 2021. This dramatic increase highlights the rapid spread of the virus and its profound impact on the Indonesian population (Figure 2).

The increase in cumulative confirmed COVID-19 cases remained steady from September 2020 to January 2021, with approximately 300,000 new cases every three months. However, between January and March 2021, the number of confirmed cases surged by around 590,000, rising from 758,473 on January 2, 2021, to 1.35 million on March 2, 2021.

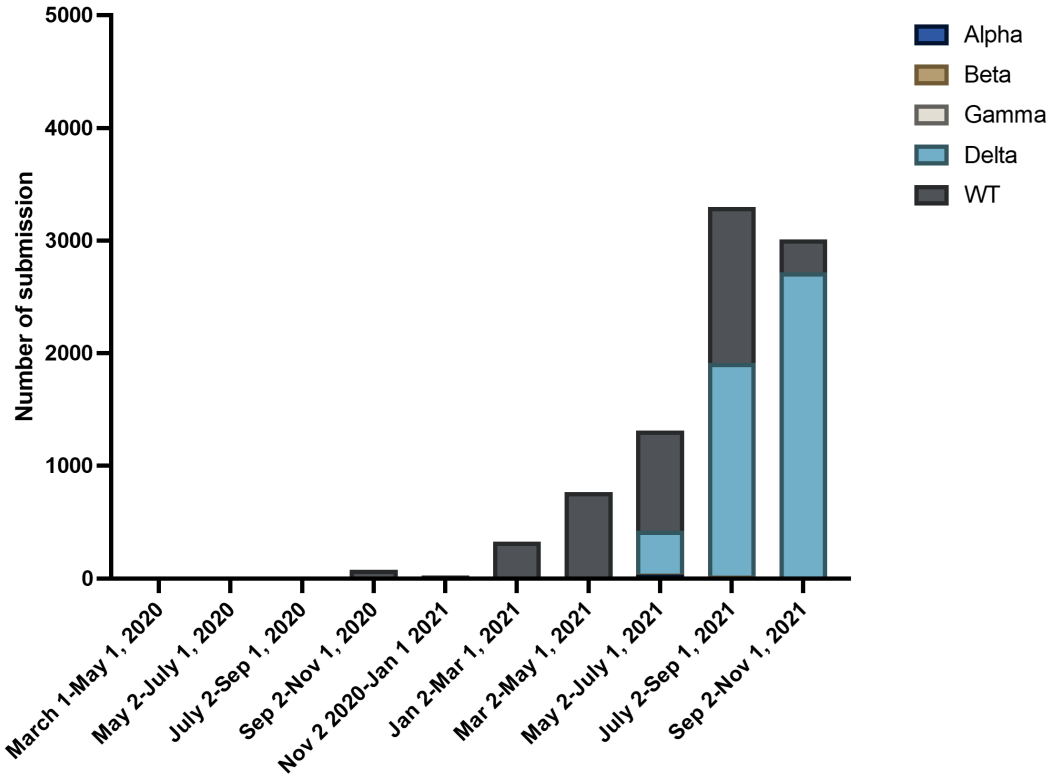

Figure 1. Graph of submitted SARS-CoV-2 Indonesian variants on GISAID database with time range

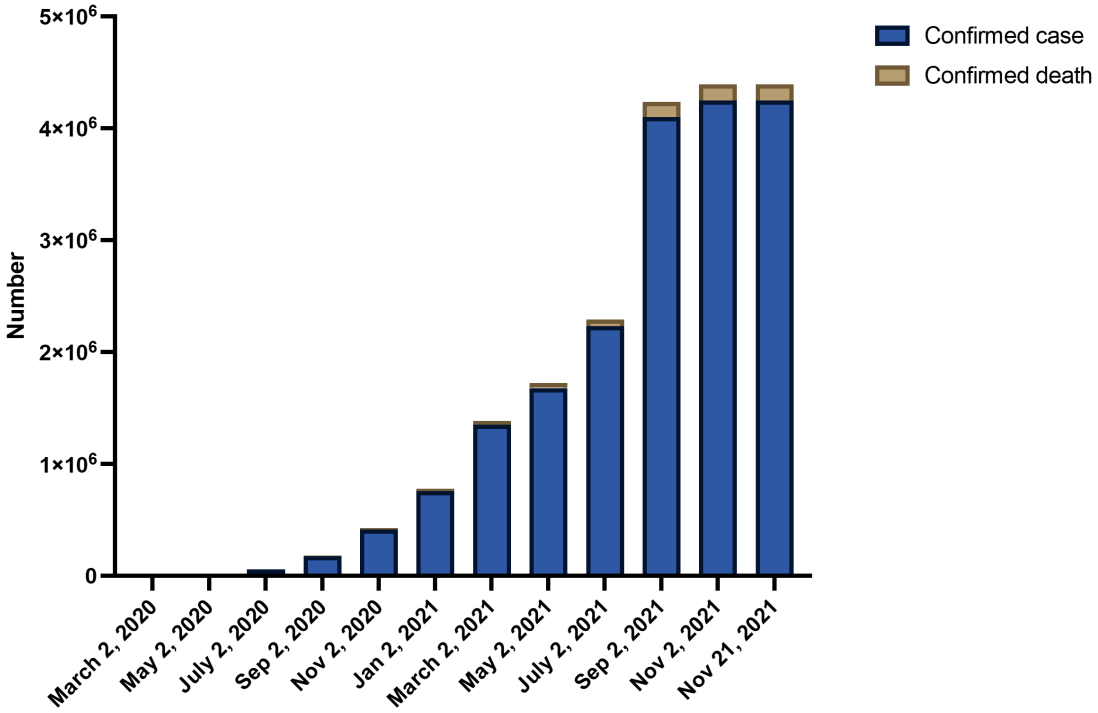

Figure 2. Graph of cumulative confirmed COVID-19 cases and deaths in Indonesia

The most profound increase occurred between July and September 2021, when confirmed cases nearly doubled from 2.23 million on July 2 to 4.10 million on September 2. During the same period, COVID-19-related deaths also surged dramatically, from 59,534 to 133,676. By November 21, 2021, the cumulative number of COVID-19 cases had reached 4.25 million, with 143,739 deaths.

Table 1. Total submission of SARS-CoV-2 variants in Indonesia on GISAID database until 21 November 2021

No.	Types of Variants	Total of viruses	Percentages (%)
1.	VOC Delta GK/478K.V1 (B.1.617.2+AY.x) first detected in India	4,980	56.20
2.	Wuhan wild type	3,780	42.66
3.	VOC Alpha 202012/01 GRY (B.1.1.7+Q.x) first detected in the UK	77	0.87
4	VOC Beta GH/501Y.V2 (B.1.351+B1.351.2+B.1.351.2) first detected in South Africa	22	0.25
5	VOC Gamma GR/501T.V3 (P.1+P.1.x) first detected in Brazil/Japan	2	0.02

Total viruses: 8,861

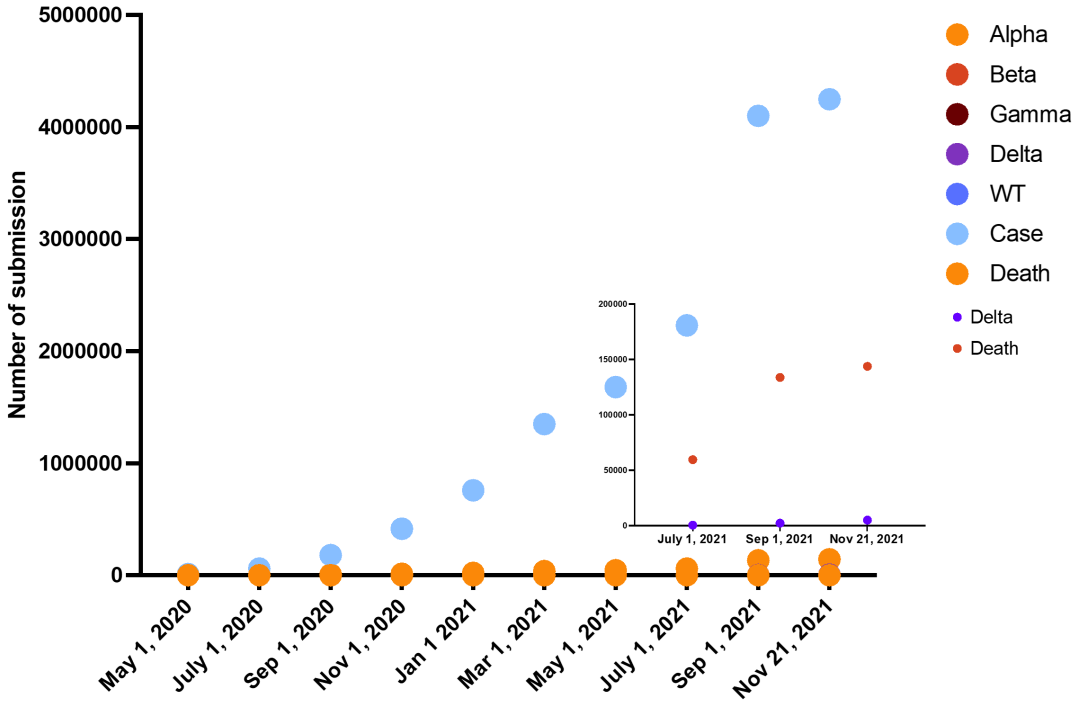

Figure 3. The cumulative submissions of SARS-CoV-2 Indonesian variants on the GISAID database. Imposed graphic shows number of Delta variants and death.

As shown in Table 1, the Delta variant dominated the SARS-CoV-2 population in Indonesia, comprising a significantly higher percentage of cases than other variants. While the Wuhan wild-type variant remained present, the Alpha, Beta, and Gamma variants were detected in much smaller numbers.

A significant surge was observed in the number of submitted Indonesian Delta variant sequences to the GISAID EpiCoV database, increasing from 2 submissions between March and May 2021 to 382 submissions between May and July 2021 (Figure 1). This number further rose to 1,889 submissions in July-September 2021 and 2,707 in September-November 2021. To analyze the correlation between cumulative COVID-19 cases and deaths and the cumulative submissions of SARS-CoV-2 Indonesian variants on the GISAID database, a direct comparison was performed.

As shown in Figure 3, a notable change occurred between July 1, 2021, and September 1, 2021. On July 1, 2021, the number of Delta variant submissions from Indonesia on the GISAID database was 384, which increased dramatically to 2,273 by September 1, 2021. During the same period, there was a corresponding sharp increase in cumulative COVID-19 cases and deaths in Indonesia. On July 1, 2021, the country recorded 2.23 million cumulative cases and 59,534 deaths,

Table 2. Spike glycoprotein gene sequence result of wild type vs Delta, Alpha, Beta, Gamma variant

	Location from wild type	NC_045512.2 (Wuhan wild type)	Mutation in variant	Location from variant
Delta Accesion ID: EPI_ISL_1824604	21618	C (T)	G (R)	21594
	21987	G (G)	A (D)	21963
	22028	G (E)	A (K)	22004
	22227	C (A)	T (V)	22203
	22917	T (L)	G (R)	22893
	22995	C (T)	A (K)	22971
	23073 23074	GT (G)	NN (X)	23049 23050
	23403	A (D)	G (G)	23379
	23604	C (P)	G (R)	23580
Alpha Accesion ID: EPI_ISL_1169047	21765 21770	TACATG (IHV)	-(--T)	-
	23063	A (N)	T (Y)	23023
	23271	C (A)	A (D)	23231
	23403	A (D)	G (G)	23363
	23604	C (P)	A (H)	23564
	23709	C (T)	T (I)	23564
	24506	T (S)	G (A)	24466
	24914	G (D)	C (H)	24874
Beta Accesion ID: EPI_ISL_1824605	21801	A (D)	C (A)	21777
	22206	A(D)	G(G)	22182
	22280	A(T)	A(P)	22258
	22813	G(K)	T(N)	22789
	23012	G(E)	A(K)	22988
	23063	A(N)	T(Y)	23039
	23149	G(K)	A(K)	23125
	23403	A(D)	G(G)	23379
	23664	C(A)	T(V)	23640
Gamma Accesion ID: EPI_ISL_2854770	21597	C(S)	T(F)	21550
	22286	C(L)	T(F)	22239
	23403	A(D)	G(G)	23356

Format: nucleotide (amino acid)

which surged to 4.10 million cases and 133,676 deaths by September 1, 2021. This analysis suggests a strong correlation between the rising number of Delta variant submissions and the sudden increase in cumulative COVID-19 cases and deaths in Indonesia.

SARS-CoV-2 Indonesian variants spike protein sequence

The Delta (B.1.617.2), Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1) variants were compared with the wild-type strain as the reference. Mutations across these variants have

Table 3. Amino acid mutations in SARS-CoV-2 Alpha, Beta, Delta, and Gamma variant

No.	Amino acid mutations	SARS-CoV-2 variants			
		Alpha	Beta	Delta	Gamma
1.	Δ68-69	√			
2.	A222V			√	
3.	A570D	√			
4.	A701V		√		
5.	D1118H	√			
6.	D215G		√		
7.	D614G	√	√	√	√
8.	D80A		√		
9.	E156K			√	
10.	E484K		√		
11.	G142D			√	
12.	G504X			√	
13.	K417N		√		
14.	K529K		√		
15.	L242F				√
16.	L452R			√	
17.	N501Y	√	√		
18.	P681H	√			
19.	P681R			√	
20.	S12F				√
21.	S982A	√			
22.	T19R			√	
23.	T240P		√		
24.	T478K			√	
25.	T716I	√			
26.	V70I	√			
Total mutated amino acids		9	9	9	3

occurred in several genes, potentially affecting the biological characteristics of SARS-CoV-2, which is crucial for developing effective disease control and prevention strategies (Table 2).

Discussion

There is a significant correlation between the rise in Delta variant (B.1.617.2) cases and the sharp increase in cumulative COVID-19 cases and deaths in Indonesia. This relationship can be attributed to the clinical characteristics of the Delta variant, including (1) increased transmissibility, (2) potential reduction in vaccine effectiveness against symptomatic COVID-19, and (3) potential reduction in the neutralization efficacy of monoclonal antibody therapies. Furthermore, the Delta variant has been associated with increased severity, as evidenced by higher hospitalization rates [23]. This observation is supported by the analysis of genomic/protein mutations (Table 1), which suggests that these mutations facilitate the variant's rapid development by enabling it to evade cellular immunity and enhance viral infectivity, potentially leading to increased viral replication [24].

This study utilized comprehensive data from reliable sources, including GISAID, GenBank, and the 'Our World in Data' website, ensuring that the analysis was grounded in extensive and diverse datasets. An in-depth examination of nucleotide and amino acid changes in the SARS-CoV-2 spike glycoprotein sequence provided valuable insights into the mutations occurring in SARS-CoV-2 variants in Indonesia. Additionally, the study demonstrated a correlation between the timing of SARS-CoV-2 variant submissions to the GISAID database and the COVID-19 outbreak timeline in Indonesia, offering insights into how specific variants may contribute to surges in cases.

However, this analysis has limitations, including (1) insufficient data to precisely quantify COVID-19 cases caused by each SARS-CoV-2 variant, (2) a lack of significant analysis leading to definitive conclusions, and (3) discrepancies between the dates of variant submissions and case/death data due to different sources.

Mutations are alterations in the sequence of DNA or RNA bases that can impact the structure and function of genes and the proteins they encode. In viruses, mutations can affect their ability to infect hosts, their resistance to treatments, and their response to vaccines. These changes can range from having no impact to significantly influencing viral behavior, potentially leading to increased transmissibility, severity, or immune evasion [25].

The Alpha (B.1.1.7) variant exhibits several spike glycoprotein mutations: Δ68-69, V70I, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H. The Δ68-69 mutation involves an amino-terminal domain deletion. The N501Y mutation enhances the spike protein's binding to the ACE2 receptor [26] and reduces neutralization by a subset of receptor-binding domain (RBD) antibodies [27]. The D614G mutation increases viral infectivity by promoting S1 subunit shedding and incorporating more spike proteins into the viral envelope [3,26].

The spike glycoprotein mutations in the Beta variant were D80A, D215G, T240P, K417N, E484K, N501Y, K529K, D614G, and A701V. The K417N and E484K mutations suggest the Beta variant may evade the polyclonal antibody response by reducing neutralization by class 1 and class 2 RBD-specific antibodies, with K417N playing a key role in immune escape [28]. The N501Y mutation, similar to the Alpha variant, strengthens the virus's binding to the ACE2 receptor, while D614G increases infectivity [26].

The Gamma variant has the following spike glycoprotein mutations: S12F, L242F, and D614G. The D614G mutation, also observed in the Alpha and Beta variants, enhances viral infectivity [3]. The S12F mutation, which is surface-exposed, may influence cell interaction [29].

The Delta (B.1.617.2.55 or AY.55) variant exhibits several mutations in the spike glycoprotein, including T19R, G142D, E156K, A222V, L452R, T478K, G504X, D614G, and P681R. The T19R and G142D mutations may disrupt the binding of certain anti-NTD (N-terminal domain) neutralizing antibodies derived from the wild-type spike protein [30]. The A222V mutation, found in both Delta and Delta Plus variants, appears with a prevalence of 58% and 9%, respectively [31].

The L452R mutation induces structural changes that reduce intramolecular and intermolecular contacts, weakening the binding affinity to the ACE2 receptor [32]. Additionally, this mutation has been shown to decrease or eliminate the neutralizing activity of 14 out of 35 RBD-specific monoclonal antibodies, including three in clinical stage [33]. Furthermore, the L452R mutation enables the virus to evade HLA-24-restricted cellular immunity while also enhancing viral infectivity, potentially leading to increased viral replication [23].

The T478K mutation, specific to the Delta B.1.617.2.55 variant, occurs within the RBD's epitope region and significantly impacts the neutralization of 'Class 1' monoclonal antibodies [34]. The D614G mutation stabilizes the spike protein, enhancing its ability to penetrate host cells more efficiently [21]. Lastly, the P681R mutation at the furin cleavage site increases the basicity of the polybasic stretch, which may facilitate a higher rate of membrane fusion and internalization, thereby improving transmissibility [32].

Conclusion

This research examined the genome analysis and prevalence of SARS-CoV-2 variants in Indonesia, focusing on the correlation between the submission timelines of the Alpha, Beta, Delta, and Gamma variants on the GISAID database and the COVID-19 outbreak timeline. The genome analysis identified amino acid changes in the spike glycoprotein of these variants. The analysis of submission timelines and outbreak data, combined with the clinical manifestations associated with these mutations, suggests that the SARS-CoV-2 Delta (B.1.617.2) variant likely contributed to the sharp increase in confirmed COVID-19 cases and deaths in Indonesia from July to September 2021.

Acknowledgment

We thank the Swiss German University for funding this research through the Faculty Research Fund granted to Kholis Abdurachim Audah.

Declaration of interest

Author declared have no conflict of interest.

Author contributions

Conceptualization, Funding acquisition, methodology: KAA; Data curation: MPIM, TCT, ASA; Writing – original draft: KAA, MPIM, TCT; Writing – review & editing: KAA, MPIM, TCT; Approval of final manuscript: All authors.

Received: January 19, 2024
Revised: July 21, 2024
Accepted: August 6, 2024
Published online: August 23, 2024

References

1. Mayo Clinic (2021) Coronavirus disease 2019 (COVID-19) - Symptoms and causes. https://www.mayoclinic.org/diseases-conditions/coronavirus/symptoms-causes/syc-20479963. Accessed date: December 2021.
2. WHO (2020) Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf#:~:text=People%20with%20COVID19,mild%20disease%20and%20recover. Accessed date: December 2021.
3. Zhang L, Jackson CB, Mou H et al. SARS-CoV-2 spike-protein D614G mutation increases virion spike density and infectivity. Nature Communications. 2020; 11 (1): 6013. https://doi.org/10.1038/s41467-020-19808-4
4. WHO. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int. Accessed date: December 2021.
5. Mathieu E, Ritchie H, Rodés-Guirao L et al. Coronavirus Pandemic (COVID-19). https://ourworldindata.org/coronavirus-data. 2020; Accessed date: December 2021.
6. Lu R, Zhao X, Li J et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The lancet 2020; 395 (10224): 565-574. https://doi.org/10.1016/S0140-6736(20)30251-8
7. Huang Y, Yang C, Xu X et al. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacologica Sinica. 2020; 41 (9): 1141-1149. https://doi.org/10.1038/s41401-020-0485-4
8. Chan JF-W, Kok K-H, Zhu Z et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerging microbes & infections. 2020; 9(1):221-236. https://doi.org/10.1080/22221751.2020.1719902
9. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses: methods and protocols. 2015; 1-23. https://doi.org/10.1007/978-1-4939-2438-7_1
10. Loewe L. Genetic mutation. Nature education. 2008;1(1):113.
11. Wei-Haas M. The coronavirus is mutating-but what determines how quickly? https://www.nationalgeographic.com/science/article/the-coronavirus-is-mutating-but-what-determines-how-quickly. 2021. Accessed date: December 2021.
12. Duffy S/ Why are RNA virus mutation rates so damn high? PLoS biology. 2018; 16(8): e3000003. https://doi.org/10.1371/journal.pbio.3000003
13. Sanjuán R, Domingo-Calap P. Mechanisms of viral mutation. Cellular and molecular life sciences. 2016; 73 4433-4448. https://doi.org/10.1007/s00018-016-2299-6
14. WHO. Tracking SARS-CoV-2 variants. https://www.who.int/emergencies/emergency-health-kits/trauma-emergency-surgery-kit-who-tesk-2019/tracking-SARS-CoV-2-variants. 2020. Accessed date: December 2021.
15. Centers for Disease Control and Prevention. SARS-CoV-2 Variant Classifications and Definitions. 2021; Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html.
16. Callaway E. The coronavirus is mutating - does it matter? Nature. 2020;585(7824):174-177. https://doi.org/10.1038/d41586-020-02544-6
17. ECDC. SARS-CoV-2 variants of concern as of 3 December

2021. https://www.ecdc.europa.eu/en/covid-19/variants-concern. 2021;Accessed date: December 2021.

18. World Health Organization. COVID-19 Weekly Epidemiological Update - 28 September 2021.2021. World Health Organization.
19. Ministry of Health Republic of Indonesia/ COVID-19 Situation Report - Indonesia. 2021; Ministry of Health Republic of Indonesia.
20. Indonesia Health Metrics and Evaluation/ Impact of COVID-19 on Indonesia: Trends and Insights. 2021; Indonesia Health Metrics and Evaluation.
21. Lie EL, Hermawan TD, Audah KA, Whole genome sequence analyses of Indonesian isolates SARS-CoV-2 variants and their clinical manifestations. Indonesian Journal of Biotechnology. 2023;28(1):1-13 https://dx.doi.org/10.22146/ijbiotech.73783
22. Wu F, Zhao S, Yu B et al. A novel coronavirus associated with human respiratory disease in China. Nature. 2020;579 (7798): 265-269. https://doi.org/10.1038/s41586-020-2008-3
23. UpToDate. SARS-CoV-2 Variants of Concern. https://www.uptodate.com/contents/image?imageKey=ID%2F131216. 2021; Accessed date: December 2021.
24. Motozono C, Toyoda M, Zahradnik J et al. An emerging SARS-CoV-2 mutant evading cellular immunity and increasing viral infectivity. BioRxiv.2021;2004-2021. https://doi.org/10.1101/2021.04.02.438288
25. Wood AR, Esko T, Yang J, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. Nat Genet. 2014;46(11):1173-86. https://doi.org/10.1038/ng.3097
26. Harvey WT, Carabelli AM, Jackson B et al. (2021) SARS-CoV-2 variants, spike mutations and immune escape. Nature Reviews Microbiology. 2021; 9(7):409-424. https://doi.org/10.1038/s41579-021-00573-0
27. Collier DA, De Marco A, Ferreira IATM et al. Sensitivity of SARS-CoV-2 B. 1.1. 7 to mRNA vaccine-elicited antibodies. Nature. 2021; 593(7857):136-141. https://doi.org/10.1038/s41586-021-03412-7
28. Wibmer CK, Ayres F, Hermanus T et al. SARS-CoV-2 501Y. V2 escapes neutralization by South African COVID-19 donor plasma. Nature medicine.2021;27(4):622-625. https://doi.org/10.1038/s41591-021-01285-x
29. Timmers LFSM, Peixoto JV, Ducati RG et al. SARS-CoV-2 mutations in Brazil: from genomics to putative clinical conditions. Scientific reports.2021; 11 (1): 11998. https://doi.org/10.1038/s41598-021-91585-6
30. Liu Y, Arase N, Kishikawa J et al. The SARS-CoV-2 Delta variant is poised to acquire complete resistance to wild-type spike vaccines. BioRxiv. 2021; 2008-2021. https://doi.org/10.1101/2021.08.22.457114
31. Kannan SR, Spratt AN, Cohen AR et al. Evolutionary analysis of the Delta and Delta Plus variants of the SARS-CoV-2 viruses. Journal of autoimmunity. 2021; 124 102715. https://doi.org/10.1016/j.jaut.2021.102715
32. Cherian S, Potdar V, Jadhav S et al. Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. bioRxiv 2021: 2021.04. 22.440932. https://doi.org/10.1101/2021.04.22.440932
33. McCallum M, Bassi J, De Marco A et al. SARS-CoV-2 immune evasion by the B. 1.427/B. 1.429 variant of concern. Science. 2021;373 (6555): 648-654. https://doi.org/10.1101/2021.03.31.437925
34. Planas D, Veyer D, Baidaliuk A et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021; 596(7871):276-280. https://doi.org/10.1038/s41586-021-03777-9