 doi:10.20944/preprints202210.0292.v1

Review

SARS-CoV-2 Omicron (B.1.1.529) Variant: A Challenge with Covid-19

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Abstract: Since the beginning of the coronavirus disease 2019 (Covid-19) pandemic, there have been multiple peaks of the SARS-CoV-2 (severe acute respiratory syndrome coronavirus virus 2) infection, mainly due to the emergence of new variants, each with a new set of mutations in the viral genome, which have led to changes in the pathogenicity, transmissibility, and morbidity. The Omicron variant is the most recent variant of concern (VOC) to emerge and was recognized by the World Health Organization (WHO) on November 26, 2021. The Omicron lineage is phylogenetically distinct from earlier variants, including the previously dominant Delta SARS-CoV-2 variant. Previous research has reported the most common clinical manifestations of the Omicron variant to be fever, runny nose, sore throat, severe headache, and fatigue. The reverse transcription-polymerase chain reaction (RT-PCR) test, rapid antigen assays, and chest computed tomography (CT) scans can help diagnose those with the Omicron variant. Furthermore, many agents are expected to have therapeutic benefits for those infected with the Omicron variant, including TriSb92, molnupiravir, nirmatrelvir, and their combination, corticosteroids, and interleukin-6 (IL-6) receptor blockers. Despite being milder than previous variants, the Omicron variant threatens many lives, particularly among the unvaccinated, due to its higher transmissibility, pathogenicity, and infectivity. This review summarizes the essential features of the Omicron variant, including its history, genome, transmissibility, clinical manifestations, diagnosis, management, and the effectiveness of existing vaccines against this VOC.

Keywords: Omicron; Covid-19; SARS-CoV-2; Variants of concern

1. Introduction

The SARS-CoV-2 virus, which has been prevalent worldwide for almost three years, has caused the death of more than 6 million people and infected more than 500 million people with Covid-19. It has a fragile possibility of elimination and is

 doi:10.20944/preprints202210.0292.v1

most expected to circulate endemically around the world [1, 2]. Despite such an expectation, the emergence of new variants that spread rapidly in countries and geographical regions threatens the predicted change to endemism for this virus [3]. since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the World Health Organization has declared 5 variants of concern, which are known as alpha, beta, gamma, delta, and finally omicron [4]. Changes in the viral genome can make these new variants more transmissible, lethal, and harder to treat. The most recent SARS-CoV-2 variant, omicron, has raised significant concern worldwide [5]. This review summarizes the essential features of the Omicron variant, including its history, genome, transmissibility, clinical manifestations, diagnosis, management, and the effectiveness of the existing vaccines against this VOC.

2. History

The Coronavirus disease 2019 (Covid-19) outbreak was identified in December 2019 [6]. Since this time, multiple peaks of the SARS-CoV-2 infection have emerged, mainly due to the emergence of new variants, including the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Epsilon (B.1.427 and B.1.429), Delta (B.1.617.2), Mu (B.1.621), and Lambda (C.37) variants, each with a new set of mutations in the viral genome, leading to different pathogenicity, transmissibility, and morbidity [7]. The Omicron (B.1.1.529) variant is the most recent VOC to emerge and was recognized by the World Health Organization (WHO) on November 26, 2021, from a sample collected on November 9, 2021 [8, 9]. This variant was first reported in Botswana and South Africa but quickly spread to other countries [10].

3. Genome

Letters and numbers are used to indicate mutations in different positions. For example, D614G shows that an amino acid D (aspartate) has changed to an amino acid G (glycine) at position number 614, for example, spike virus protein [11]. The Omicron lineage has been demonstrated to be phylogenetically distinct from the previous variants, including the previously dominant Delta SARS-CoV-2 variant [12]. The Omicron variant has experienced a total of 18,261 mutations in its genome, of which only 588 mutations were in the extragenic region, most of which occurred in the coding region. Among the mutations in the coding region, 2743 were synonymous single-nucleotide polymorphisms (SNPs) mutations, and 11995 were non-synonymous [13, 14].

The Omicron variant evolved due to 37 amino acid substitutions in the SARS-CoV-2 spike protein, several in the receptor-binding domain (RBD) [15] (Figure 1). According to a recent study, Omicron-BA.1 has undergone 50 mutations and has 34 changes in its spike protein gene, 15 of which occurred in the receptor-binding domain (RBD) [16, 17]. Thirty single-point substitutions (including A67V, T95I, G142D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F), three deletions (including Δ69-70, Δ143-145, and Δ211) and one insertion (ins214EPE) have been identified on the spike protein of the Omicron variant[18]. Several investigations in South Africa have revealed that D614G, N501Y, K417N, T478K (concerning the mutations), and some new mutations in this VOC are responsible for its relative resistance to the current vaccines and the enhancement of its reinfection rate [19]. ins214EPE is also a mutation with the insertion of three amino acids in Omicron-BA.1, which can be characteristic, but its role has not yet been determined [20]. D614G, E484K, K417N, T478K, and N501Y are substantial mutations in the RBD and have also been identified in previous variants of SARS-CoV-2, and based on previous studies, they can increase the overall risk of reinfection and relative resistance to existing vaccines [21]. E484K, a glutamic acid to lysine substitution at position 484, is a significant mutation that has also been detected in both the Beta and Gamma variants [22]. It has been

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 20 October 2022 doi:10.20944/preprints202210.0292.v1

hypothesized that this mutation led to the enhanced reinfection rate found in the Gamma variant [23].

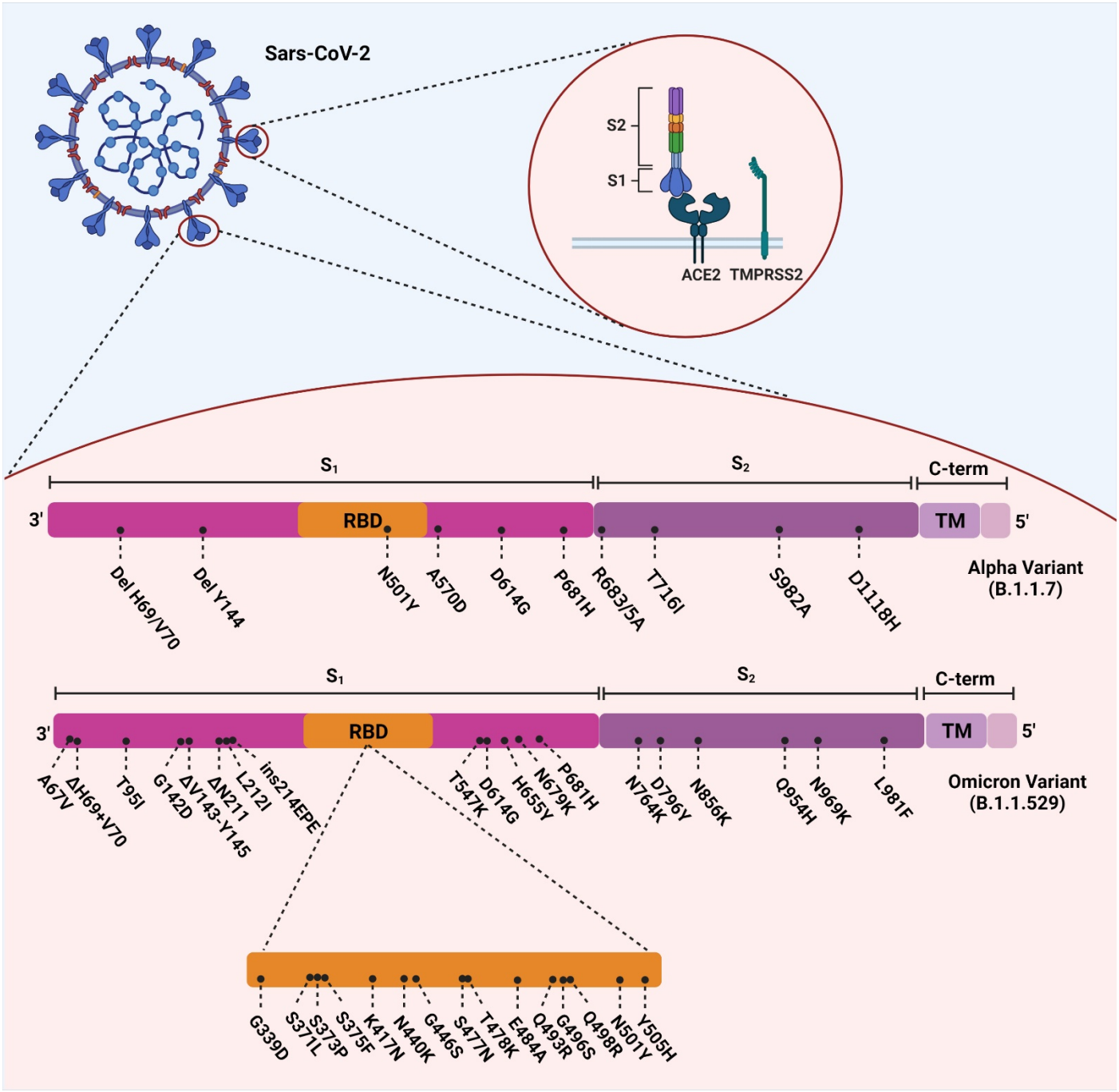

Figure 1. Overview of the mutations of SARS-CoV-2 alpha (B.1.1.7) and omicron (B.1.1.529) variants.

However, E484A, as the counterpart mutation, is a glutamic acid to alanine substitution at position 484, found in the Omicron variant. The mutation of glutamic acid (a hydrophilic amino acid) to alanine (a hydrophobic amino acid) might have the ability to change the interaction between the angiotensin-converting enzyme 2 (ACE2) and the RBD [22]. Interestingly, two of the three RBD mutations in the Omicron variant are shared with a previous VOC, the Delta variant. The first mutation is a lysine-to-asparagine exchange at position 417, which results in structural changes to the S protein, and is probably responsible for the variant's enhanced ability to escape the immune system. The second one, a threonine-to-lysine exchange at position 478, has probably ameliorated the residue's

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electrostatic potential and steric interference. Therefore, it has been linked to elevated RBD binding affinity and improved immunological evasion [24]. However, the mutation in the delta type by substituting leucine instead of arginine at position 452 strengthens the affinity of this variant to ACE2 receptors found in various human cells, including the lung, which is not present in the omicron variant [25]. The Omicron variant is split into two sublineages: BA.1 and BA.2 [26]. The Omicron variant has the most significant number of mutations of the known SARS-CoV-2 variants, which has made this variant more able to avoid the neutralizing antibodies induced by natural infection or vaccination [27].

4. Transmissibility and infectivity

Binding affinity with ACE2 complex and RBD in SARS-CoV-2 viruses plays a major role in determining their binding affinity, but furin cleavage sites also play an essential role in this field [28, 29]. According to this issue, it is evident that mutations in the viral genome can increase the affinity of the virus to the host cells and lead to higher transmissibility. This has been experienced previously, as the Alpha, Beta, and Delta variants have had 7-, 19-, and 11-times higher transmissibility than the original SARS-CoV-2 virus [30-32]. As some of the mutations of the Omicron variant are mapped on the receptor-binding motif (RBM), its spike protein affinity towards the angiotensin-converting enzyme 2 (ACE2) receptor is much higher than the previous variants [33]. Also, based on the studies conducted, omicron shows a significant change in its infectivity due to three mutations in the cutting site of furin and 15 mutations in RBD [28, 29, 34]. The ACE, coded on the RBD, is the main gate of viral entry into human cells. Therefore, 2- to 3-times increased transmissibility than the Delta variant would be expected [35, 36]. In a study that examined the infectivity of omicron, they observed that most of the RBD mutations, except for the G339D, S371L, S373P, and S375F mutations, were created close to the ACE2 and RBD binding interface, and as a result of these mutations, changes in binding free energy (BFE) is significantly increased, which makes omicron more infectious due to the increased binding affinity of the ACE2-RBD complex [34].

Furthermore, the shorter doubling time of the Omicron variant and the higher viral load induced in the nasopharyngeal and respiratory cells, compared with previous VOCs, also confirm its higher infectivity [37, 38]. It has been demonstrated that the infectivity of the Omicron variant is approximately 10-times higher than the wild-type strain [39]. It should be stated that, among all the possible factors, mutations have one of the most significant impacts on the high transmissibility of this VOC. The N501Y is one of the most critical mutations that can enhance the binding affinity with the ACE2 receptor, thus increasing transmission. In association with Q498R, the N501Y mutation can strengthen the binding affinity and make it easier for the Omicron variant to enter the host cells [19]. A recent study detected two subclades within the Omicron lineage, with K417N or K440N mutations and S446K. Subsequently, it has been mentioned that the K417N mutation, which has been found in the Beta variant, can also moderately enhance the surface expression of the RBD and increase resistance to the neutralizing monoclonal antibodies [40]. Furthermore, several studies have suggested that the furin cleavage site (FCS), located in the SARS-CoV-2 spike protein, boosts RBD exposure and its binding to the ACE2 receptor [41, 42]. Mutations like H655Y and N679K, located close to the FCS, can enhance spike cleavage and make the Omicron variant more transmissible [19]. According to recent studies, the H655Y mutation, detected in the Gamma and Omicron variants, was accompanied by antigenicity alterations, which enhanced monoclonal antibodies' evasion [43].

5. Clinical manifestations

It is believed that the incubation period of the Omicron variant is shorter than previous SARS-CoV-2 variants, with a median of three days, compared with at least four days for previous strains [44, 45]. The presentations of the Omicron variant were expected to

 doi:10.20944/preprints202210.0292.v1

be the same as with other variants. However, reviewing the available literature has revealed that fever, runny nose, sore throat, severe headache, and fatigue are the predominant clinical manifestations of this variant [46-48]. Among the two types of omicron, based on the available evidence, the severity of the disease in subtype BA2 is higher than its severity in B.1 [49]. Most reported Omicron cases have been mildly affected, especially those previously infected or vaccinated [50, 51]. Moreover, young and middle-aged individuals are more commonly infected with this variant than previous variants [52], as reflected in the rapid increase of pediatric admissions, due to SARS-CoV-2 infection, during the early days of the Omicron wave in South Africa [53]. Fortunately, most cases of omicron do not require hospitalization or intensive care unit (ICU) admission [54].

It is not yet understood whether the mild features of this variant are due to the attenuated nature of the virus or the existing immunity among those infected. However, some studies have concluded that the lower severity of the Omicron-induced infection could be due to its slower replication in the transmembrane serine protease 2 (TMPRSS2) than in previous variants [55]. The underlying reason might be that the TMPRSS2, a necessary component for activating the spike protein during membrane fusion, plays a less critical role in the Omicron variant [56]. Therefore, despite faster replication in the bronchus, it is believed that omicron replication is slower in the lung parenchyma compared with the previous strains, such as the Delta variant [57].

6. Disease severity

The available data in this area is incomplete. However, based on preliminary results in South Africa, this virus shows a lower hospitalization rate than previous infections caused by the delta variant. Also, according to the announcement of the insurance company Discovery Health, people with omicron have a 29% lower risk of hospitalization compared to the previous variant. Although this information can indicate that the severity of omicron infection is milder than in previous variants, it is still too early to conclude. Various factors can cause disturbances in these statistics, including the patient's previous exposure to the coronavirus and their age. It has also been confirmed that in South Africa, more than 70% of the population of Omicron-infected areas have already been exposed to SARS-CoV-2, and this point, along with the 40% statistics of injecting at least one dose of the Covid-19 vaccine in This population can affect the severity of the disease in them. These results are in contrast to the results of the Imperial College of London, which did not show any reduction in the hospitalization rate of Omicron patients compared to the Delta variant, and such a result was also seen in a study conducted in Denmark. However, both of these studies are not very reliable since they did not examine a large number of people. However, some studies have shown that, unlike the previous types, the severity of the disease was less for patients with the Omicron variant. This has been demonstrated in terms of a shorter hospitalization period, lower supplemental oxygen requirements, fewer ICU admissions, and lower mortality [58-63].

7. Diagnosis

Molecular tests, namely the reverse transcription-polymerase chain reaction (RT-PCR), have been the main laboratory-based diagnostic tests for detecting SARS-CoV-2 throughout the pandemic [64]. Nevertheless, as RT-PCR assays target the spike gene, and because the available RT-PCR assays cannot detect all target genes, it is possible that their failure rate in detecting the new variants, including omicron, will be higher than for previous strains [65]. The sensitivity of the RT-PCR tests for diagnosing the original SARS-CoV-2 has been estimated to be up to 60-70%, depending upon the stage and severity of the infection and the accuracy of the nucleic acid detection technique [66]. Nonetheless, it is reasonable to assume that new mutations in the viral spike protein and RBD can lead to

 doi:10.20944/preprints202210.0292.v1

decreased sensitivity of the molecular diagnostic methods. Moreover, serology assays may also have lower sensitivity based on the specific nucleotide polymorphisms (SNPs) of the early strain S protein [67]. However, despite the mutations mentioned above, using highly conserved domains of the SARS-CoV-2 genome as the RT-PCR targets, and performing variant-specific RT-PCR tests, can add to the sensitivity and reduce test failure [68, 69].

Furthermore, specific rapid antigen assays have been shown to detect omicron more accurately [70]. In addition, collecting saliva swab specimens instead of mid-turbinate swabs might further increase the sensitivity of these assays [71]. The abovementioned strategies could improve the timely diagnosis of patients and, as a result, the effective interruption of the transmission chain. Moreover, computed tomography (CT) chest scans are highly sensitive in detecting SARS-CoV-2 infection in previous variants [72], and it seems that the imaging findings of Omicron-induced pneumonia are no different. It is believed that the CT scan findings of those infected with omicron are consistent with minimal to mild pneumonia [73].

8. Management

The main route SARS-CoV-2 uses to enter the host cells is via spike glycoprotein attachment to the ACE2 receptors, so any variation in the virus's genome can reduce therapeutics' effectiveness, which aims to inhibit viral attachment. Therefore, the resistance of this variant to current therapeutics, including monoclonal antibodies (mABs), has been predicted [74]. In other words, as reported by a recent study, 7 out of 9 monoclonal antibodies (including bamlanvimab, etesevimab, casirivimab (REGN10933), imdevimab (REGN10987), sotrovimab (S309), DZIF-10c, P2B-2F6, C102, and Fab2-36) could not demonstrate efficient neutralizing activity against the Omicron variant. However, these effectively neutralized the Wu01 strain and the Alpha variant. Interestingly, the Delta and Beta variants showed partial resistance to these monoclonal antibodies, with 7 of 9 and 5 of 9 demonstrating sufficient neutralizing activity against the Delta and Beta variants, respectively[75]. However, many agents are predicted to have therapeutic benefits on the Omicron variant. For example, TriSb92, a trimeric human nephrocystin SH3 domain-derived antibody, is believed to inhibit the new variant if administered intranasally [76]. Furthermore, a group of recent studies has reported that some antivirals, including molnupiravir, nirmatrelvir, and their combination, could significantly prevent infection with omicron and previous VOCs [77-80]. According to an update on the Omicron variant by WHO, corticosteroids and IL6 receptor blockers can still manage severe Covid-19 cases [81]. Nevertheless, considering the novelty of the Omicron variant, more research is needed to understand the management options for this variant better.

9. Effectiveness of neutralizing antibodies and vaccines

Previous studies have shown that the Beta and Delta variants could evade convalescent serum and neutralizing antibodies, leading to a higher risk of reinfection than the wild-type and Alpha variants [82, 83]. Nonetheless, this issue is not well understood for the Omicron variant, with laboratory-based neutralization studies currently underway. However, clinical experiences confirm the immune evasion of this variant, as reinfections are being reported in individuals previously infected with other variants [5]. Moreover, due to the increased mutations in the RBD, and since the spike's RBD is the principal target for neutralizing antibodies, the Omicron variant is expected to be neutralized less effectively by antibodies and vaccination than the previous variants, including the delta variant [84]. Therefore, as some mABs are being used as therapeutics for those infected with SARS-CoV-2, it would seem likely that the Omicron variant will be resistant to some of the current treatment strategies, including most mABs [85]. Studies have demonstrated that a combination treatment of casirivimab/imdevimab (sold under the brand name REGEN-COV) cannot effectively neutralize the Omicron variant [86]. Nevertheless, despite

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their less beneficial effect, broadly neutralizing mABs with more conserved genome targets may be helpful against the Omicron strain [74].

Vaccination is considered the most effective means of preventing and controlling Covid-19, and four types of vaccines have been introduced for this disease, which includes viral vaccines, viral vector vaccines, DNA/RNA vaccines, and protein-based vaccines. Since the target of the current Covid-19 vaccines is the s protein of these viruses and due to the changes that have occurred in the spike protein of the Omicron variant, the ability of the variant to escape from the current vaccines may have significantly increased [87-89]. Similar to the Beta and Delta variants, the neutralization efficiency of the Covid-19 vaccines against the omicron variant is considerably lower than for the wild-type [90, 91]. The plasma of individuals who had received two mRNA vaccine doses had several times less potency against the Omicron variant than for the original strain [92]. It is predicted that the vaccine-escape ability of the Omicron variant is twice that of the Delta variant[93]. All these hypotheses have been confirmed because many of the Omicron variant-infected patients had already been fully vaccinated, proving the immune evasion of the Omicron variant [94]. Nonetheless, despite the reduced efficacy of current Covid-19 vaccines against the new variant, they have decreased severe disease, hospitalization, and mortality [59]. Previously vaccinated individuals are expected to develop less severe illnesses if infected with Omicron[95]. Moreover, it has been demonstrated that those with a history of SARS-CoV-2 infection and two vaccine doses or without a history of infection but who have received three vaccine doses have comparable immunity against these new variants and the wild-type virus [92, 96, 97].

A study has observed that even though omicron has reduced the effectiveness of the Pfizer-BioNTech vaccine, it can still reduce the risk of hospitalization. Also, Pfizer-BioNTech has stated that despite the mutations in the spike protein of this variant, two doses of these vaccines still protect the patient against severe disease because the T cells created after vaccination are not affected by these Omicron mutations [98, 99]. This reflects the synergistic effect of elevated antibody levels after being repeatedly exposed to the antigen, and the impact of affinity maturation [100, 101], further justifying the importance of the third vaccine dose. This is while the results of computer modeling show the ability of B.1.1.529 to prevent the development of immunity by T cells [102]. Also, in a study conducted by the most significant private health insurance company in South Africa, the effectiveness of the vaccine against omicron was reported to be 33%, while for the delta variant, the effectiveness of the vaccine was estimated to be 80% [98]. Also, based on another study conducted in South Africa, the serum levels of people who had injected the Pfizer-BioNTech vaccine showed 40 times less resistance to the Omicron variant than to the Delta variant [103].

10. Mortality and prognosis

Even though the previous VOCs, including Alpha, Beta, Gamma, and Delta variants, resulted in a high rate of mortality worldwide [104], this has not been true for the Omicron variant [105]. In the cohort comparison between the delta variant and omicron, it has been observed that the omicron variant has caused less mortality than the delta, and also the hospitalization rate and other factors related to the poor prognosis of the disease have also been seen less in the omicron variant [106]. However, it is essential to note the forthcoming triple respiratory virus threat, which consists of seasonal influenza and the Delta and Omicron variants, which might increase the mortality rate [107].

11. Prevention

As omicron is capable of transmitting more readily and rapidly, and since current therapeutics are expected to be less effective against this new variant, it is vital to take strict measures to prevent the spread of the virus, including wearing face masks, improving ventilation, keeping social distancing, frequent hand washing, restricting travel, and

 doi:10.20944/preprints202210.0292.v1

proper isolation and quarantine. Moreover, improving diagnostic methods to detect and treat infected individuals quickly can further diminish the transmission chain, all of which are the cornerstones of infection control [8, 37, 108]. In addition, considering the relatively long time since the start of the two-dose vaccination program in most countries, adding a booster dose can help to reduce the risk of spreading the new variant [109, 110]. Accordingly, some countries have planned more vigilant vaccination programs for their populations to prevent another outbreak. For example, the United States has mandated that all individuals aged 5 years and above receive at least two vaccine doses and that high-risk people should get a third vaccine dose [8]. Since the Omicron variant is expected to be the dominant SARS-CoV-2 strain worldwide, developing vaccines tailored explicitly to the Omicron variant, such as multivalent vaccine strategies, is mandated. Moreover, prioritizing vaccinating individuals at higher risk of severe disease and complications is highly recommended [111].

12. Conclusion

Despite being milder than previous types and having a shorter incubation period, omicron threatens many lives, especially among previously unvaccinated individuals, due to its higher transmissibility, pathogenicity, and infectivity. The clinical manifestations of this disease generally include fever, runny nose, sore throat, severe headache, and fatigue, and these manifestations are primarily mild in people who have been infected or vaccinated. The remarkable thing about this variant is that more young and middle-aged people are affected than the previous types. Although the incidence of this variant is higher, most cases do not require hospitalization or admission to the intensive care unit (ICU). However, specific strategies, such as using Omicron-targeted drugs and vaccines, are needed to prevent the spread of this type. In addition, implementing preventive measures other than vaccination should also be considered.

Acknowledgments

The authors would like to thank the clinical research development center of Imam Reza Hospital, Kermanshah University of Medical Sciences, for their kind support. All figures are created with BioRender.com. This research received no funding.

Data Availability Statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest disclosure

Terence T. Sio reports that he provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc. and also as a member of the Advisory Board to Galera Therapeutics, which are not in any way associated with the content or disease site as presented in this manuscript. All other authors have no relevant financial interests to be declared.

Author contributions

Zeinab Mohseni Afshar: Conceptualization, Writing - Original Draft; **Ali Tavakoli Pirzaman:** Investigation, Writing - Review & Editing; **Bardia Karim:** Investigation, Writing - Review & Editing; **Rezvan Hosseinzadeh:** Visualization, Writing - Review & Editing; **Arefeh Babazadeh:** Investigation, Writing - Original Draft; **Dariush Hosseinzadeh:** Investigation, Writing - Review & Editing; **Seyed Rouhollah Miri:** Investigation, Writing - Original Draft; **Terence T. Sio:** Writing - Review & Editing; **Mark J. M. Sullman:** Writing - Review & Editing; **Mohammad Barary:** Investigation, Writing - Original Draft, Writing - Review & Editing; **Soheil Ebrahimpour:** Conceptualization, Writing - Original Draft, Supervision.

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