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NARRATIVE REVIEW

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SARS-CoV-2 Omicron (BA.4, BA.5) variant: Lessons learned from a new variant during the COVID-19 pandemic

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Abstract

Background and Aim: In late 2021, the world faced the rapid spread of the SARS-CoV-2 Omicron variant, which quickly became the variant of concern. In April 2022, two new lineages of Omicron (BA.4/BA.5) emerged from Africa, where they caused the fifth wave of infection.

Method: We searched PubMed, Google Scholar, and Scopus online databases up to December 2023 for founding relevant studies.

Results: BA.4 and BA.5 subgroups, with changes in the spike protein, have a greater ability to escape from the immune system, which was possible with the help of L452R and F486V mutations. Epidemiologically, these evolving subtypes show similarities to seasonal influenza but with higher mortality rates. The symptoms of these subgroups are different from the previous types in the form of upper respiratory symptoms. Antiviral treatments, the use of antibodies such as bebtelovimab, and the development of vaccines are promising.

Conclusion: Consequently, we must continue to be vigilant in our joint surveillance efforts against COVID-19 in diagnosis and treatment.

KEYWORDS

BA.4, BA.5, COVID-19, Omicron, SARS-CoV-2, variants

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1 | INTRODUCTION

In November 2021, the SARS-CoV-2 Omicron variant was identified as a variant of concern (VOC) by the World Health Organization. In April 2022, two new Omicron lineages (BA.4 and BA.5) emerged from the Gauteng region of South Africa, initiating the fifth wave of infection there.[1]

Bayesian phylogenetic methods have demonstrated that BA.4 and BA.5 differ from Omicron's other lineages, while spike sequences of both variants are more similar to that of the BA.2 strain. Previous studies have shown that BA.4 and BA.5 RBD have a higher binding affinity for ACE2 compared with Omicron strains BA.1 and BA.2. Therefore, the two new variants have higher transmissibility, resulting in their quick spread to other parts of the world to effectively replace the previous variants.[2,3]

Although numerous mutations in Omicron's spike protein facilitate immune escape, the cellular immune response evoked by prior Omicron infection and vaccination offers protection against the new Omicron variant and probably reduces the chances of severe symptoms. Studies have shown that individuals with BA.4/BA.5 were no more likely to manifest severe symptoms or be hospitalized than those with BA.1. But the Delta variant caused more severe symptoms than BA.1.[4,5]

Consequently, we must be vigilant about the BA.4/BA.5 lineages as the Omicron SARS-CoV-2 lineage continues to evolve and successively produce subclades that are more transmissible and more elusive to antibodies.

2 | LITERATURE SEARCH

We searched online databases, including PubMed, Scopus, and Google Scholar, up to December 2023. The inclusion criteria included (1) Articles focused on BA.4 and BA.5 variants of SARS-CoV-2 Omicron, (2) Articles that provided information on virology, transmission, clinical signs and symptoms, and (3) how to deal with these subtypes. We only included English-language articles.

We excluded preprint articles, articles that addressed only other subtypes, articles with duplicate data, and articles in languages other than English.

3 | MAIN BODY

3.1 | Molecular profile

There are four amino acid differences between the BA.5 and BA.4 lineages in proteins, including Nucleocapsid (N), ORF7b, OFR1a, and ORF6, with one amino acid difference in each protein. In contrast, no amino acid differences exist in proteins, including Membrane (M), Envelope (E), ORF10, ORF1b, ORF8, and Spike. Also, the ORF6-D3N mutation is specific to BA.5, and N-P151S, ORF7b-D61L, while OFR1a-DEL141/143 mutations are specific to BA.4 lineage.[6,7]

Previous studies have shown differences in the spike protein among Omicron lineages BA.1, BA.2, and BA.3.[8] In contrast, BA.4 and BA.5 spike sequences are identical and more similar to BA.2 strain.[9] Compared with BA.2, BA.4/5 has the S mutations 69–70 deletion, F486V, and L452R amino acids substitutions in the RBD, as well as wild-type amino acid at position Q493.[9,10]

The L452R and F486V mutations in the RBD probably cause more antibody escape, whereas reversion to 493 may diminish escape from the responses to earlier viruses (Wuhan strain).[9]

L452 mutations in both variants show potential higher transmission than BA.2.12.1. The F486L mutation has been shown to directly increase virus entry into cells expressing mink/ferret ACE2.[11] In addition, mutation at F486 is a key site for immune evasion capability and reduces the neutralizing activity of antibodies.[12]

These mutations have given BA.4/5 tremendous antibody escape potential and increased transmissibility in the community (Figure 1). Although previous Omicron infection in triple-vaccinated individuals triggers a potent response to earlier pre-Omicron variants, unfortunately, it does not substantially protect against BA.4/5. Therefore, vaccine strategies that can quickly increase neutralization breadth to current lineages would be more practical in the future.

3.2 | Cell entry mechanisms

According to recent studies, the binding affinity of Omicron RBD for the ACE2 receptor is three times higher compared with Delta and Wuhan-Hu-1 RBDs.[13] To enter the host cells, Omicron uses a new pathway that does not involve the transmembrane serine protease 2 (TMPRSS2). Omicron uses either the plasma membrane pathway or the endocytic pathway for viral replication and entry rather than the TMPRS22 pathway, which could lead to differences in disease presentation after exposure to Omicron variants.[14] In addition, Omicron's fusion capacities and the syncytia generation potential are diminished compared to the Delta variant, making it more challenging to construct syncytia, resulting in milder clinical manifestation and tissue tropism.[15]

Because TMPRSS2 is plentifully expressed by supporting cells in the olfactory epithelium, these target cells may be less infected by the new Omicron variant.[16] Also, TMPRS22 is abundantly expressed in alveolar cells of the lung, which means lung involvement following exposure could be limited due to Omicron's lack of dependence on the TMPRS22 pathway.[17,18]

A study on the effect of Nafamostat (TMPRSS2 inhibitor) in genetically engineered ACE2/TMPRSS2 cell lines showed an 11-fold drop in Delta infectivity versus a threefold reduction for both BA.1 and BA.2. This confirms Delta's effective use of TMPRSS2 for viral entry as opposed to the poor use of TMPRSS2 by Omicron lineages BA.1/BA.2. Interestingly, the study observed a sevenfold drop in BA.5 infectivity in the presence of Nafamostat, which verifies that this cell line's increased infectivity-to-viral-particle ratio compared with other Omicron lineages is primarily due to more efficient use of TMPRSS2.[19] Therefore, the evidence suggests a shift in the tropism of BA.5 compared with ancestral strains. Figure 2 shows the preferred entry route of BA.4 and BA.5.

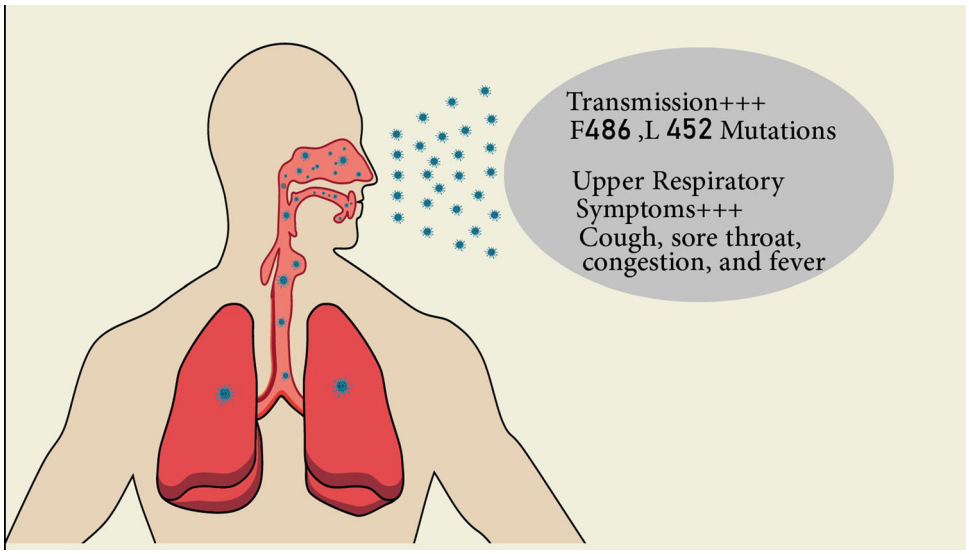

FIGURE 1 Omicron mainly affects the upper respiratory tract and mutations (F486, L452) in the Omicron spike protein lead to increased transmissibility.

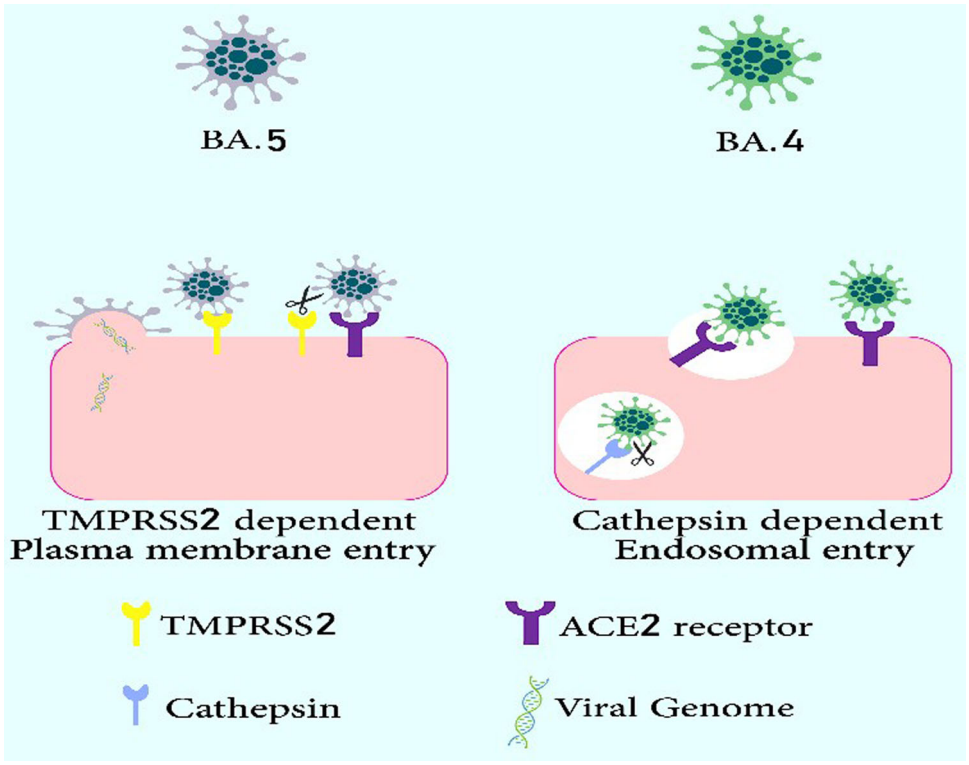

FIGURE 2 Preferred cell entry pathway of SARS-CoV-2 Omicron, BA.4 via cathepsin-dependent endosomal pathway (lack of S1/S2 cleavage site); BA.5 through a plasma membrane pathway that depends on transmembrane serine protease 2.

3.3 | Epidemiology

COVID-19 is still classified as a pandemic, and the Omicron strain is the dominant variant that comprises 99% of the global gene sequence. The evidence shows that many regions in different parts of the world are experiencing the seventh wave of infection. This new epidemic round is mainly due to the newer Omicron subvariants of BA.4 and BA.5. The epidemiological characteristics of these subvariants remain unclear, which could pose a challenge to preventing and monitoring the spread in different areas and countries.[20] It was possible that subvariants of Omicron with mutations similar to the Delta strain, such as BA.2.12.1, BA.4, and

BA.5 with L452R/Q, will rapidly spread and become the predominant variants. However, now the XBB 1.5 subgroup of omicron is expanding rapidly and is the dominant type.[21] It is worth noting that as Omicron evolves, its subtypes seem to acquire the characteristics of influenza antigenic drift. In terms of the epidemiological process, they become similar to seasonal influenza but with a higher mortality rate.[22]

3.4 | Diagnosis and symptoms

The Omicron variant is spreading globally and is divided into sub-lineages, two of which have been recently identified in South Africa, named BA.4 and BA.5, and are likely to cause a new wave of disease.[23] That is why there has been a sudden increase in laboratory reports of COVID-19 cases in the Gauteng province of South Africa, along with an increase in the number of samples with the S gene target failure (SGTF) in patients tested with TaqPath COVID-19 PCR test.[24] In general, COVID-19 is diagnosed by the SARS-CoV-2 RT-PCR test, in which samples are obtained from nasopharyngeal swabs.[25]

The severity of COVID-19 symptoms can generally vary from asymptomatic/mild in 80% of cases to severe in 5% of cases, potentially fatal. The exact percentage is determined by the type of infectious variant and the underlying immunity of the patients.[26] Clinical data have shown that COVID-19 is a multisystemic disease with possible nephrological, neurological, and thromboembolic symptoms.[27–29] According to studies, 54% of hospitalized and 34% of nonhospitalized patients continue to struggle with symptoms associated with COVID-19, including fatigue, muscle weakness, dyspnea, chest and joint pain, and neurocognitive disorders.[30,31] Several studies estimate the incidence of persistent post-COVID symptoms to be between 30% and 90% up to 6 months after the initial illness.[32]

The studies on the previous coronavirus strains indicate that in symptomatic patients, the lung is the most important organ affected by the virus, which in some cases leads to respiratory failure accompanied by progression to acute respiratory distress syndrome (ARDS). The patient will need respiratory ventilation.[33,34] Meanwhile, subvariants BA.4 and BA.5, unlike the previous variants, which were mostly associated with serious lower respiratory symptoms, are generally associated with upper respiratory symptoms due to the impaired cleavage of S1 and S2 and the inability to use TMPRSS2. However, these new subvariants have enhanced infectivity and immune evasion ability with less inflammation and milder symptoms.[22]

A study investigating the symptoms caused by different variants of the coronavirus across various waves of the pandemic has shown that in the Omicron period, cough (67.4%) and sore throat (43.4%) were more often listed among the symptoms of the disease compared with pre-Delta and Delta periods. Also, congestion during the Omicron period was more common (38.8%) than the pre-Delta period, while the loss of taste and smell (5.3%) and the occurrence of fever (30.4%) were less common. Notably, fever and myalgia were lower among those who received the booster dose than non-vaccinated individuals and those who received the primary series. Five days after the onset of symptoms, 31.1% of patients indicated that their symptoms did not change or worsen. Approximately 80.2% of symptomatic re-testers remained positive for 5 days and 60.5% 10 days after the onset of symptoms. The study also mentioned that during the Omicron period, the symptoms of cough, sore throat, and congestion, previously only common among symptomatic patients with a positive PCR test result, became common among symptomatic patients who tested negative. Compared to Delta and pre-Delta periods, Omicron subvariants have been associated with upper respiratory system symptoms, which can vary depending on the differences in individuals' vaccinations. During the Omicron period, the most common symptoms among those who tested positive for COVID-19 were as follows: cough (67.4%), sore throat (43.4%), congestion (38.8%), and headache (35.5%). Among the symptoms, loss of taste/smell (5.3%), nausea (5.0%), and diarrhea (4.8%) were the least prevalent. The study found that, interestingly, 47.7% of symptomatic children (under 12 years of age) who contracted COVID-19 reported only one symptom during the Omicron period. The fact that children, especially those under 5 years of age, may present only one sign of the disease is significant because it means parents and healthcare providers should consider a lower threshold level to detect any potential signs of COVID-19. Reporting a symptom for diagnosis is not common among adults (37.7%, $p < 0.001$) and adolescents (31.8%, $p < 0.001$). Also, among children, the most common symptoms were cough, fever, sore throat, and congestion. Loss of taste/smell (0.3%) among children seemed unusual compared to adolescents (5.8%, $p < 0.001$) and adults (5.8%, $p < 0.001$). The study also examined differences in symptoms depending on vaccination status and found that congestion was more common among those who took the booster dose. Also, fever occurred less often than those who were not vaccinated or vaccinated/non-boosted ($p < 0.05$). In addition, myalgia was less common among boosted individuals versus vaccinated/nonboosted people ($p = 0.01$). However, there is no difference in the prevalence of other symptoms based on vaccination status. Another issue investigated in this study was the trajectory of symptoms in people who tested positive for COVID-19. Five days from the onset of symptoms, 63.0% (95% confidence interval [CI]: 56.6–69.2) of patients were on the path to recovery, while 31.1% (95% CI: 25.3%–37.4%) had the same condition as before, and 5.9% (95% CI: 3.3%–9.7%) had worsened symptoms. However, in the subsequent examination 10 days after the onset of symptoms, the symptoms were improving in 82.2% (95% CI: 56.6%-69.2%) of the patients. In contrast, 17.8% (95% CI: 9.8%–28.5%) of the patients remained unchanged, and 0% (95% CI: 0%–4.9%) had worsened. Symptomatic individuals had a higher retest positivity than asymptomatic individuals on days 5 and 10.[35]

The increase in collective immunity during the Omicron surge and the characteristic features of the Omicron subvariants are likely responsible for the change in the symptomatology of subvariants

BA.4 and BA.5 compared with the Delta symptoms. In vitro investigations have shown that the virus is better replaced in the bronchial tissue compared to the deep sites of the lung.[36]

3.5 | Immunity effect

The two new Omicron subvariants have more similarities to BA.2 than to BA.1. However, BA.4/5 have particular mutations such as F486V, L452R, and R493Q in the spike protein of the virus that can increase their ability to bind to human host cells. These variants have the same protein as BA.2 except for 69–70 deletion.[37] Research indicates the presence of spike protein mutations in Omicron types such as BA.4 and BA.5. These mutations that occur in RBD are of different types, one of which is the R439Q mutation, and they increase the affinity to the ACE-2 receptor, thereby increasing their ability to transmit the virus to the cell.[2,38]

In a study by Cao et al.,[39] they engaged pseudo-virus neutralization assays and BA.4/5 variants against the plasma obtained from triple-vaccinated individuals. They found that these variants had increased immune evasion capability, showing that they can have an even stronger escape from antibodies. These variants significantly evade broad sarbecovirus-neutralizing antibodies that are enriched in vaccinated individuals. In conclusion, BA.4/5 have stronger humoral immune evasion than previous variants.

Another study compared neutralizations between vaccinated and unvaccinated individuals with prior BA.1 infection. Neutralization levels were higher in the vaccinated group, and the immune escape was gentler than compared with BA.1. However, the absolute neutralization was lower for BA.4/5, meaning it would not provide adequate protection against symptomatic infection.[40] Reductions in neutralization titers of BA.4/5 compared to BA.1/2 can decrease the efficacy of vaccines against infection. The neutralization of BA.4/5 against mABs was fully ceased in 10 mABs, and 4 of them had fold reduction.[23] It has been shown that patients with hybrid immunity caused by previous vaccination and infection make antibodies that cannot neutralize and incapacitate BA.4/5.[37] Advanced scanning suggests that the F486 is an important region for escaping vaccines and antibodies, even the ones that can neutralize previous Omicron variants.[41,42] Because of mutations, even vaccinated individuals can get infected with newer lineages of the Omicron variant.[43]

L452 mutation in BA.4/5 makes the escape from some antibodies much easier (from class 2 and 3 receptor-binding domains). In contrast, F486V mutation makes escape easier from certain class 1 and 2 antibodies but compromises the spike affinity for the viral receptor.[44]

3.6 | Suggested treatments

Paxlovid by Pfizer is used in combination with an HIV medicine called ritonavir. This protease inhibitor drug affects the NSP5 gene, which has no alterations in the Omicron variant. Consequently, there is no significant reduction in Paxlovid's efficacy against the new variant.

Molnupiravir lagevrio is another treatment choice. It acts like RNA structures and disrupts the viral replication process, resulting in a huge change in spike protein, although the Omicron variant might be so sensible against Molnupiravir. It is expected that Sotrovimab will overcome Omicron variant because several variants that consist of Omicron's mutations have been tested in labs. A recent study proposed favipiravir as an effective drug against coronavirus.[45] Another study concluded that neither convalescent plasma nor IVIG could cause neutralization against BA.4/5; on the other hand, hCoV-2IG 2022 convalescent plasma can resist these new variants and could be used in high-risk patients diagnosed with BA.4/5 infection.[46] Among several antibodies suggested for treatment, bebtelovimab is the only antibody with full potential against BA.4/5.[44]

In a study by Baerends et al., they evaluated Omicron-type specific antibody responses in individuals who received a bivalent BA.1 or BA.4/5 booster after receiving three prior doses of monovalent vaccine. They identified elevated antibody levels in subjects with prior SARS-CoV-2 infection before the fourth bivalent booster dose. Antibody levels to all Omicron variants were significantly increased by receiving either bivalent vaccine. However, the increase was greater for those without prior infection. The BA.1 vaccine was found to be dominant on serological imprinting for BA.1 and BA.3 antigens, while the BA.4/5 vaccine allowed extensive Omicron antigen imprinting.[47,48]

4 | CONCLUSION

In summary, the emergence of BA4 and BA5 omicron subgroups, unique molecular complex features, altered cell entry mechanisms, and epidemiologic patterns. These two subgroups have a greater ability to escape from the immune system, reducing current vaccines' effectiveness. These subgroups' clinical signs and symptoms are related to upper respiratory diseases and thus affect the diagnosis and complications of COVID-19. Useful treatments for these subgroups are antiviral drugs, specific antibodies, and the development of vaccines. However, more research is necessary to develop the necessary knowledge and treatments compatible with the new Omicron subtypes.

AUTHOR CONTRIBUTIONS

Gisou Erabi: Resources; writing—original draft. **Arezoo Faridzadeh**: Visualization; writing—original draft. **Ali Parvin**: Writing—original draft. **Niloofar Deravi**: Writing—review and editing. **Mohammad Rahmanian**: Writing—original draft. **Mobina Fathi**: Writing—original draft. **Elahe Aleebrahim-Dehkordi**: Writing—original draft. **Nima Rezaei**: Supervision; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request from the corresponding author.

TRANSPARENCY STATEMENT

The lead author Nima Rezaei affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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