

Characteristics of Covid-19 infection with the original SARS-Cov-2 virus and other variants: A comparative review

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ABSTRACT

The novel coronavirus infection (Covid-19) had enormous effects on global health. Since it first emerged (in China, three more clinically significant variants developed, which were differentiated from the original virus in terms of clinical course, hospitalization, mortality, and overall outcome. These variants are Alpha (British), Delta, and Omicron variants. Each variant was the prominent infectious variant of the Covid-19 virus for a specific time. While some variants were associated with higher mortality, others were associated with a higher spreading rate compared to the rest of the variants. The present review aimed to summarize the clinical characteristics, symptoms, need for hospitalization and intensive care, mortality, and overall outcomes of the original and other three significant variants of the Covid-19 infection. We also aimed to present a brief review of post covid syndrome.

Keywords: Covid-19, Alpha variant, Delta variant, Omicron variant, outcome.

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Received: 2022-11-05

Accepted: 2022-11-25, Published: 2022-12-28

Introduction

At the end of 2019, a new coronavirus disease, Covid-19 infection, has been emerged and caused the death of millions. The pneumonia cases of unknown etiology, which first appeared in Wuhan, China, prompted the World Health Organization [1] and the virus responsible for the infection named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The disease affected more than 200 countries and promoted the millennium pandemic by threatening public health since it caused severe infections and

death [3,4]. Today, the effect of the disease continues, albeit lessening.

Over time, SARS-CoV-2 developed genetic mutations [5-7], and numerous viral variants were characterized. While some have no phenotypic effects [8], some have been flagged as variants of concern because they have features such as increased transmissibility, infectivity, evasion of vaccination and immunization, and decreased susceptibility to monoclonal antibody treatments [9-11]. After the disease first appeared, the virus mutated over time, and variants emerged to lead to a clinical picture that showed some differences from the infection caused by the original form of the virus. Common symptoms of the disease include fever, myalgia, cough, runny nose, and nasal congestion, as well as atypical presentation findings.

The presenting symptoms of infections with Covid-19 variants differ from each other. Moreover, there are differences in disease duration, hospitalization rate, and duration, need for intensive care treatment, and mortality rates. After the first emergence of the Covid-19 virus, three clinically essential variants of the original virus have caused infections worldwide that affect the course of the pandemic. These variants of the actual virus are Alpha (British), Delta, and Omicron variants.

As mentioned before, the clinical presentation, disease course, prognosis, and mortality rates of the original virus that started the pandemic and its variants vary. Therefore, this review aims to present and compare the characteristics of the clinically important variants with the clinical picture caused by the infection with the original Covid-19 virus. For this purpose, first, the characteristics of the infection with the original virus that started the pandemic in late 2019 will be mentioned, and then the clinical features and prognosis of Covid-19 infections, which occur with Alpha, Delta, and Omicron variants will be discussed, respectively.

1. Characteristics of the infection with the virus that initiated the Millennium Pandemic

The SARS Cov-2 virus that emerged during the pandemic could be named as the original virus or the wild type. Whatever the name is, the infection with this virus caused massive destruction of the daily routine of billions. At the end of 2019, SARS-CoV-2 is seen in the city of Wuhan, China, and being highly transmissible, this novel coronavirus disease, also known as coronavirus disease 2019 (COVID-19), has spread fast all over the world [12,13].

Apart from China, the Ministry of Public Health, Thailand, witnessed and reported its first laboratory confirmed COVID-19 case on

January 13, 2020. The Ministry of Health, Labour and Welfare, Japan, and the National IHR Focal Point (NFP), Republic of Korea, reported their first COVID-19 case on the same day. Remarkably, both the identified cases in Thailand and Japan were imported cases from Wuhan, China [14,15].

Later, SARS-CoV-2 cases were also reported in the Macau Special Administrative Region, the United States of America, the Hong Kong Special Administrative Region, and Taipei Municipality, and wherein all these reported cases had a travel history to Wuhan. On January 20, 2020, the WHO released a situation report-1 for the COVID-19 pandemic indicating 282 laboratory-confirmed cases and six deaths globally, which has drastically increased to 21,294,845 laboratory-confirmed cases and 761,779 deaths as on August 16, 2020. WHO officially declared COVID-19 infection as a pandemic on March 11, 2020. The median incubation period for SARS-CoV-2 is estimated to be 5.1 days, and the majority of patients will develop symptoms within 11.5 days of infection [16].

Presentation of the subjects with the SARS Cov-2 virus infections

SARS-CoV-2 infections range from being asymptomatic to severely symptomatic. Respiratory droplets are the main source of transmission of SARS-CoV-2 from human to human. The median incubation period of SARS-CoV-2 varies from 4 to 6 days before developing symptoms [16-19].

The SARS Cov-2 primarily affects the respiratory system [1,14,17,20].

The presenting symptoms are a fever with dry cough and dyspnea accompanied by headaches, dizziness, muscle pain, joint pain, and fatigue with gastrointestinal symptoms, including vomiting and diarrhea [1,20].

Patients can also present with nonclassical symptoms, such as isolated gastrointestinal symptoms [21]. Olfactory and/or gustatory dysfunctions have been reported in 64% to 80% of patients [22-24].

Anosmia or ageusia may be the sole presenting symptom in approximately 3% of patients [24]. Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system. COVID-19 can lead to myocarditis, cardiomyopathy, ventricular arrhythmias, and hemodynamic instability [25,26]. Additional complications like acute respiratory distress syndrome, acute heart injury, and several secondary infections were found in individuals with advanced stages of infection in hospital intensive care units [1,27].

Hospitalization and mortality rates in the SARS Cov-2 virus infections

All ages are at risk for infection and severe disease. However, patients aged ≥ 60 years and patients with underlying medical comorbidities like obesity, cardiovascular disease, chronic kidney disease, diabetes, chronic lung disease, cancer, solid organ, or hematopoietic stem cell transplant patients are at an increased risk of developing severe COVID-19 infection. SARS-CoV2, the severity of the symptoms is strongly associated with the patients' age that may be explained by a weaker immune system [1,17,28].

In a clinical study with 452 COVID-19 patients, 286 were diagnosed as severely infected patients and were significantly older, with a median age of 61 when compared to the remaining 166 non-severe patients with a median age of 53. And that suggested that SARS-CoV-2 is highly dangerous to elderly patients who have a weak immune system [29]. More than 75% of patients hospitalized with COVID-19 require supplemental oxygen

therapy. For patients who are unresponsive to conventional oxygen therapy, heated high-flow nasal cannula oxygen may be administered [30].

Overall hospital mortality from COVID-19 is approximately 15% to 20%, but up to 40% among patients requiring ICU admission. However, mortality rates vary across cohorts, reflecting differences in the completeness of testing and case identification, variable thresholds for hospitalization, and differences in outcomes. Hospital mortality ranges from less than 5% among patients younger than 40 years to 35% for patients aged 70 to 79 years and greater than 60% for patients aged 80 to 89 years [31].

Outcome of the patients with the SARS Cov-2 virus infections

The subjects infected with the original variant of the SARS-Cov2 virus have various outcomes. Some have an asymptomatic disease course, and some require mechanical ventilation. Isolation and stay at home measures were effective in decreasing the spreading of the infection [32]. In addition, wearing a face mask was also considered a tool to reduce the spreading of the disease [33]. Yet, the original variant of the Covid-19 virus was a highly contagious form of the infection.

Comorbidities in Covid-19 patients, such as chronic pulmonary diseases, chronic kidney disease, cardiovascular conditions, diabetes mellitus, hypertension, obesity, and immunosuppression, are associated with poorer outcomes compared to those subjects without comorbidities [1,34]. Another worse outcome measure in subjects infected with the original Covid-19 variant was clinical hypoxia [35]. The rate of pulmonary involvement in radiological imaging studies [36], cardiac dysfunction [37], coagulation abnormalities [38], increased NLR

[39] and PLR [40], and elevated transaminases [41] were suggested as markers of poor prognosis in Covid-19 population. The presentation of these factors was considered a marker for unfavorable outcomes.

2. Characteristics of the infection with the Alpha (British) variant

The first clinically significant variant of Covid-19 is the Alpha (British) variant. The variant is called B.1.1.7, which was briefed first in the United Kingdom, followed by Denmark [42], and then in 135 countries [43], representing 95 percent of all cases [43]. This variant evolved the dominant SARS Cov-2 in time, representing 95 percent of all cases [43,44]. It was discussed that it should be even reemerged the new epidemic as Covid-20 [45]. However, this suggestion has not been supported widely in medical literature. The Covid-19 infections with the Alpha variant showed some differences from the infections with the previous SARS Cov-2 virus.

Presentation of the subjects with Alpha variant infections

The Alpha variant was reported to transmit 45-71% faster and reproduces 75-80% faster than the wild type [46]. Ong et al. apprised that it was more asymptomatic than Delta, whereas the most common clinical expression in symptomatic patients was fever [8]. It was declared to be weaker in showing symptoms than non-variant of concern cases [42]. The Alpha type was always more asymptomatic in all age ranges, and all vaccinated or unvaccinated patients compared to the Delta variant in a study conducted with approximately 12k patients in Italy [43]. In a study from Taiwan involving 141 patients, fever and cough were prominent clinical presentations, whereas other symptoms were

reported as shortness of breath, chest pain, runny nose, sore throat, diarrhea, muscle soreness, and impairment of smell or taste [47]. Also, this study revealed that fever was the prominent and more common manifestation in Alpha-infected patients than in original ones, which had more clinical presentation than Alpha ones [47]. Although the clinical presentation of patients infected with the original variant between February 1 and April 30, 2020, in this study, was more marked than those infected with Alpha, patients infected with Alpha had a higher incidence of fever [47]. Song et al. conducted research with thirty-three Alpha-infected patients, the prominent clinical expression was fever again, and in addition to the symptoms mentioned earlier in the patients, intolerance to cold, dry cough, expectoration, nasal congestion, dry throat, asthenia, dizziness, and chest tightness have also occurred [48]. In addition, Mark et al. [49] notified other relatively less common clinical manifestations such as abdominal pain, delirium, hoarseness, persistent cough, and anorexia.

The infections with the Alpha variant may present with atypical symptoms as well. Nakaya et al. examined three patients with red face symptoms and stated that it might be a specific sign of the Alpha variant and could accelerate the diagnosis, and they proved that this redness was not related to flushing due to the use of steroids prescribed to relieve the cytokine storm [50]. A case report of a 37-year-old pregnant woman who underwent a rapid cesarean section that was previously known to be infected with Alpha indicates that a severe and rapid-onset SARS-CoV-2 infection may cause placental insufficiency and result in fetal distress [51].

The literature has conflicting reports on the clinical features of Covid-19 variants. A study

about whether the Alpha strain is more dangerous than the wild one revealed no significant clinical difference in patients under 18, who were interpreted in terms of age, comorbidity, and ethnicity [52]. Thus, it is evident that Covid-19 has distinct symptoms from a wide angle of the spectrum.

Hospitalization and mortality rates in Alpha variant infections

Hospitalization, intensive care admission, and death rates generally increased when the Alpha type was evaluated against the original/wild type [53]. In a study conducted between November 2020 and January 2021, approximately 186k patients infected with the wild and the Alpha strain were followed up from the test positivity process, and the Alpha one was found to be risky at 62% in point of hospital stay and 73% in mortality [54]. Compared to the wild type, while raised mortality risk was not demonstrated in patients admitted to intensive care [44,55], it was observed in patients in the general population infected with Alpha. The reasons, such as the high mortality expected in the Alpha variant due to the increasing number of cases and the changes in the conditions of admission to the intensive care unit according to the clinician and the patient's life expectancy, these two results may not be conflict [54]

In another study with similar results, the number of hospitalizations in the first 14 days was 1.52 times higher than the wild type, and the number of deaths in the first 28 days was 1.59 times higher in patients infected with the Alpha variant [44]. Similarly, Funk et al. noted high rates of hospitalization at any age and more risky admission to intensive care for patients under 60 years infected with the Alpha variant of SARS Cov-2 [42]. In contrast, one study discovered that there was no difference

between the Alpha variant and the wild type in terms of hospital admission and mortality in the first 14 days after adjusting for potential risks, and the risk potentials were associated with being male, older age, Asian ethnicity, living in a care or nursing home [56]. Furthermore, an equivalent risk of ICU admission in Alpha and wild strain was noted by Frampton et al [55]. Consequently, several other reports suggested the results of Frampton et al.'s study [57]. Yet, Funk et al. [42] and Martinez Garcia et al. [58] reported low mortality rates in cases with Alpha variant, contrary to popular belief.

Daniela et al. encountered that Delta-infected patients in Southern Italy had more than three times the risk of symptomatic disease and more than two times the risk of hospitalization than Alpha-infected patients [43]. Additionally, these results were identical to the outcomes of the study conducted by Twohig et al. in the UK during the same period [49]. These data suggest that symptoms and course of Covid-19 infections vary by the variant which caused the infection.

Outcome of the patients with Alpha variant infection

While the Covid-19 variant is constantly altering and outstretching worldwide in many ways, people continue to become ill by showing different clinical manifestations, despite encountering the original variant [59]. The rapid spread of B.1.1.7 in Italy, England, and Brazil, despite measures such as significant quarantine restrictions and international border closures, revealed how high the Alpha variant's contagiousness is and the need for more comprehensive approaches [60]. In addition, the Alpha variant raised the burden on the healthcare system. However, the Alpha variant does not influence the effectiveness of vaccines. Effectiveness of the BNT162b2

(Pfizer-BioNTech), AstraZeneca, Moderna, and Novavax were reported as 93.7%, 74.5%, 100%, and 86%, respectively [61-63]

3. Characteristics of the infection with the Delta variant

The Delta variant of SARS-CoV-2 was originally found in India in December 2020, and over 26% of the Indian population was infected with the Delta variant in a three-month period [64,65]. It has spread quickly to over 206 countries. The WHO announced the third wave of the coronavirus pandemic in July 2021, and the leading factor was the Delta variant. The Delta variant is known as high infectivity, which is related to its high viral load and short incubation. It has proved transmissibility increases by the Delta variant (%97), Alpha variant (%29), and Beta variant (%38) compared to the original one, and the Delta variant has the highest number of effective reproductions [11].

Presentation of the subjects with Delta variant infections

Common symptoms of the respiratory system for the Delta variant are fever, shortness of breath, cough, and sore throat. On the other hand, the other symptoms include headache, myalgia, fatigue, and loss of taste and smell. The difference is the patients who have the Delta variant are becoming more rapidly ill and growing higher viral loads. Some reports attach the Delta variant to severe symptoms such as hearing impairment, blood clots, gangrene, and severe gastrointestinal issues [65].

The mutations (T19R, L452R, T478K, D614G, P681R) making infective the Delta variant more are mostly found in the spike protein. The L452R mutation substitutes an arginine for leucine at position 452, this mutation explicitly

promotes the interaction between the S protein and ACE2 receptor, so it increases spike stability, virus infectivity, and viral fusion. Some studies suggest this mutation can cause decreasing the vaccine-induced serum neutralizing antibody titer and can escape many authorized monoclonal antibodies [66-68]. T478K, which is located at the interface of Spike/ACE2 interactions, may be related to immune evasion [69]. Thus, it is evident that the symptoms of infection with the Delta variant have some differences from previous variants.

Hospitalization and mortality rates in Delta variant infections

The Delta variant has been shown to have a 108% increase in hospitalization risk, a 235% increase in ICU admission, and a 133% higher chance of death than the original variant. Studies from England [70] and Denmark [71] reported higher hospitalization rates of the cases infected with the Delta variant compared to the previous variants. Some studies have shown that fully vaccinated individuals who have the Delta variant presented with milder symptoms than those unvaccinated patients [72,73]. A study with 43338 Covid-19 positive patients from England has found that the Delta variant has higher hospital admission and emergency care attendance risk than the Alpha variant [70]. Moreover, Delta variant cases have more chance of experiencing long covid syndrome [74].

Patients infected with the Delta variant were more likely to be female, younger, and less likely to have comorbidities [75]. Moreover, the risk of hospitalization was still higher in subjects infected with the Delta variant compared to pre-Delta timeframes, even adjusting the risk for age, ethnicity, race, sex, body mass index, and the presence of

hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and kidney disease [75].

Two doses of BNT162b2 by Pfizer were found to be 93.7% effective against the Alpha vs. 88% effective against the Delta [76]. One study has reported that similar level of protection against hospitalization as that provided by two doses of the Oxford-AstraZeneca vaccine or one dose of the Pfizer or Moderna vaccines [77,78]. Effectiveness against hospitalizations from Delta or Alpha variants by the Pfizer vaccine is 94% after one dose and 96% after two doses, while for the AstraZeneca vaccine is 71% after one dose and 92% after two doses [78]

Outcome of the patients with Delta variant infection

Studies have shown that countries with high vaccination rates have lower rates of severe illness and mortality. Data from various countries worldwide have shown that most recent vaccination procedures cannot prevent Delta infection itself, but they effectively protect against severe disease and death [76]. Two doses of BNT162b2 by Pfizer were found to be 93.7% effective against the Alpha vs. 88% effective against the Delta [76]. A study has shown neutralizing antibody titer of the inactivated vaccine, Sinovac, decreased higher in the Delta variant (31.64 times) than Alpha (17.35 times) and beta (22.11 times) variants [76].

Overall, the effect of vaccination is decreased in the Delta variant since vaccination is associated with a lesser reduction in the spreading risk of the disease in the Delta surge compared to the Alpha era [79]. On the other hand, hospitalization rates were higher in Delta variant infections compared to the previous surges.

4. Characteristics of the infection with the Omicron variant

A strain was first discovered in Botswana, South Africa, on November 14 [80] as responsible for the fourth wave of Covid-19 [81] from a specimen collected from a patient on November 9, 2021 [82]. It was the most mutated variant of all SARS-CoV-2 strains, therefore classified as a variant of concern (VOC) and named "Omicron" by the WHO on November 26 [83]. Infections with the Omicron variant raised hope that this variant could end the devastating Covid-19 pandemic for the first time.

Presentation of the subjects with Delta Omicron infections

The World Health Organization declares no significant difference between the symptoms of Omicron and other variants [84]. The symptoms of patients infected with the Omicron variant can be listed as follows: a mild cough, fever, generalized muscle pain, weakness, scratchy but sore throat, body aches, moderate to severe headache [82], shortness of breath, a loss of taste or smell, and a runny nose and are indistinguishable from common cold [82,84-87]. Fever, cough, and loss of smell/taste are not seen as much as in previous variants. It has been reported by A. Maisa et al. that loss of taste and smell is rarer in Omicron cases compared to other variants, and observations made in South Africa and the UK support this report [88]. After a few days of illness, a rapid recovery process begins [80]. Min-Kyung Kim et al. reported Omicron's clinical features, hospitalization rates, and treatment requirements in findings obtained from 40 patients infected with SARS CoV-2, similar to other results [89].

Strains before Omicron mainly affected the lower respiratory tract and caused loss of taste

and smell in many patients. On the other hand, Omicron is a new variant that mostly affects the upper airways and causes symptoms such as acute laryngitis and epiglottitis [90,91].

In the literature review, several cases of acute epiglottitis accompanying Covid-19 were found before [92-97]. However, a new one was added to these clinical manifestations in Switzerland between 1st January and 23rd January 2022. There were consultations at the Ear, Nose, and Throat Emergency Department (ENT ED) with acute odynophagia, severe sore throat, and fever. A few patients diagnosed with covid 19-related acute viral laryngotracheitis and/or viral pharyngitis were hospitalized. Some had a secondary bacterial infection at admission, and no patient had acute epiglottitis [98].

Clinical symptoms of immunocompromised patients can be listed as rhinitis, cough, lethargy, fever, headache, sore throat, fatigue, muscle pain, and gastrointestinal complaints, and it can be seen that clinical manifestations are not different from other patients infected with Omicron [99].

Hospitalization and mortality rates in Omicron variant infections

Earlier Omicron cases in South Africa [100] and the 43 patients in the United States had experienced mild symptoms, and no death happened. Afterward, UKHSA informed that ten individuals known to be infected with Omicron needed to be hospitalized, and one death was reported [80]. It is clinically more moderate than other variants, and even patients require less oxygen support than those infected with different variants [86]. In Denmark, Laura et al. determined the hospitalization rate of patients infected with Omicron as 1.1%, and A. Maisa et al. showed it up as 2% [88,101]. The Omicron variant evaded the immune system more efficiently [85] and was considered more

contagious by Garcia-Beltran and his colleagues both because it can replicate 70 times faster than Delta in the human respiratory tract [102] and stay in tissue longer than Delta, even 48 hours after infection [103]. Thus, it seems that Omicron has replaced Delta [101]. However, hospitalization rates and the number of deaths were 65 percent lower, and ICU admissions or deaths were 83 percent lower than the Delta variant by Ana Cecilia et al [101]. Furthermore, in a study conducted by the University of Cambridge and UKHSA on November 22 and December 26, 2021, emergency care or hospitalization with Omicron was half the Delta, and hospitalization was only one-third of the Omicron. This finding suggests that both the number of seriously ill patients and the number of hospitalized patients decreased [104].

Omicron (VOC) is neither more to be worried about nor taken less seriously than other coronavirus subtypes). It was reported that 23 of 114 immunosuppressed for different reasons covid 19 Omicron-infected patients were hospitalized for an average of 11 days, and 1 of them died [99]. The rates and time of hospitalization of immunocompromised patients were high though the mortality rate was low [99].

The outcome of the patients with Omicron variant infection

It is known that this virus, which affects dozens of people in 57 countries, extends rapidly and can make itself more contagious with epidemiological and biological features. However, those who have had the disease show moderate symptoms such as headache, cough, fever, fatigue, and muscle pain, and high mortality rates are not observed [82]. Although the symptoms caused by Omicron variant infection appear to be less severe, one should be

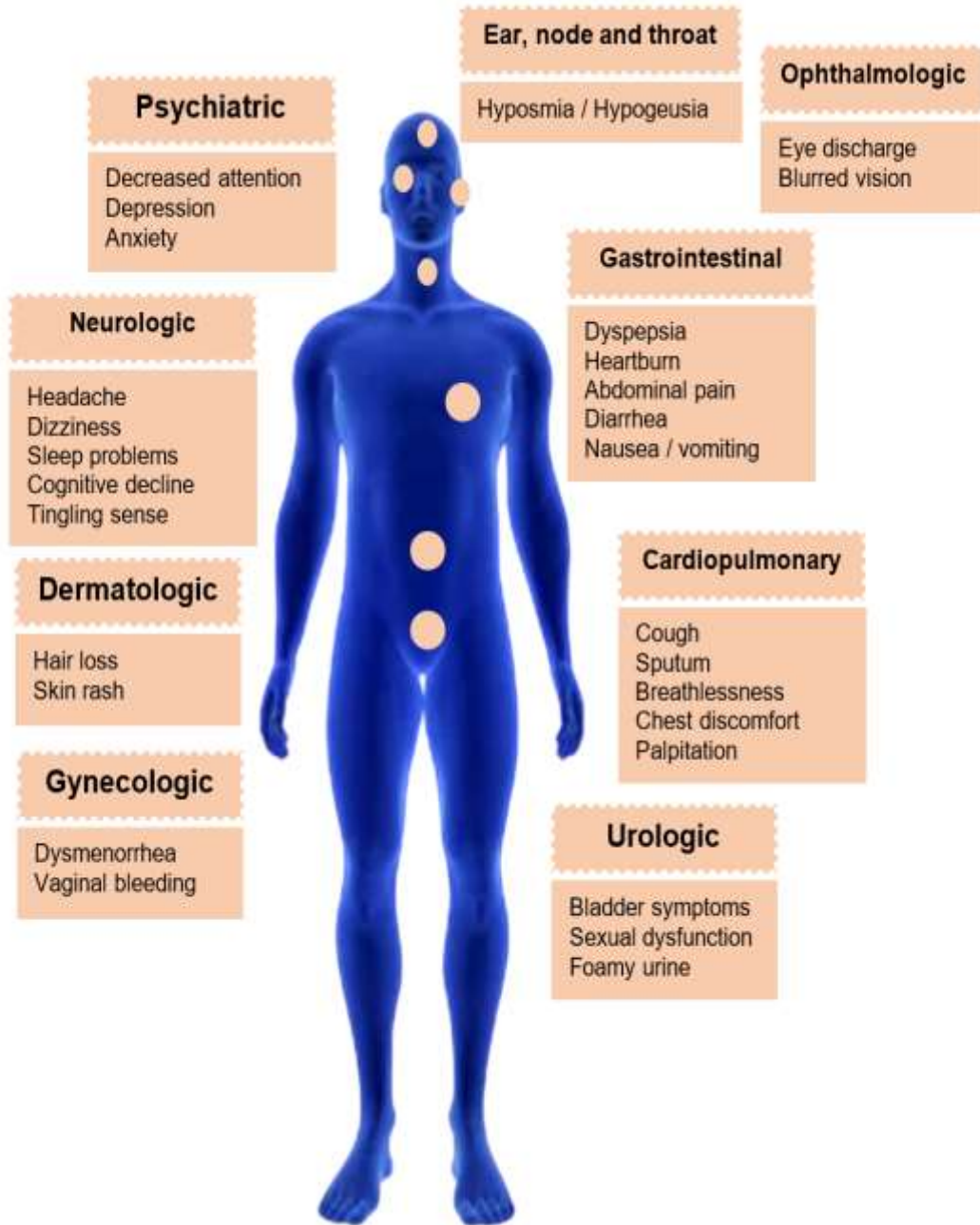


Figure 1. Lasting effects of post-acute coronavirus disease 2019.

prepared for serious delayed consequences. It would be better to avoid generalizing the results, as case symptoms may be relevant to individuals. Even if the symptoms of infection are not so severe for patients, spreading the disease too quickly can lead to a deadlock in the healthcare system [101].

The Omicron variant can be considered the most contagious form of the virus. It can infect subjects six times more than the Delta variant [105]. However, it is believed that the pandemic can end with a highly contagious but less infective variant, like Omicron.

Long Term Covid-19 Sequels

Covid 19 was known to leave persistent symptoms, and these long-term sequelae also have been reported [106-111]. There is disagreement as to what the long term means. WHO defines long-term as persistence for greater than two months; CDC defines it as after four weeks following acute disease, while ESCMID indicates after 12 weeks post-infection [106,107]. The lasting effects of COVID-19 infection have also been determined in the literature [112-114]. These findings suggest the first clues of post covid syndrome.

In the study of Young-hee Jung et al. on 1122 patients (675 were classified into the acute group and 447 were classified into the post-acute group), some symptoms were more common in those who had the disease acutely, while some were long-term effects in patients who had the disease before [115]. These symptoms were generally classified under ten categories, as seen in figure 1. The more common symptoms in the post-acute group are listed as fatigue, decreased attention or brain fog, depression, blurred vision, hair loss, and sexual dysfunction [115]. Whatever the cause, post covid syndrome was placed among conditions that patients encounter after acute infection.

Conclusion

Novel coronavirus infection has changed the lives of billions worldwide. Infection with different variants of the virus has common and also separate clinical features, disease courses, and outcomes. Although the original and Alpha variants caused more hospitalizations than the other variants, Delta and Omicron were associated with a more quickly spread of the disease. We think that outcome of the Covid-19 infection patients becomes more favorable with later variants, probably due to increased

accumulating knowledge about the disease and the milder course of the infection with the Omicron variant.

Funding: *The author(s) received no financial support for the research, authorship, and/or publication of this article.*

Conflict of Interest: *The authors declare that they have no conflict of interest.*

Ethical statement: *Since this research is a review study, no ethics committee decision was required.*

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