ORIGINAL RESEARCH

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Effect of SARS-CoV-2 Variants on the Progression of COVID-19 Disease: A Retrospective Analysis From a Pandemic Hospital

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Abstract

Objective: Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is an agent of the pandemic coronavirus disease-2019 (COVID-19). New variants that have emerged throughout these pandemic presented new challenges and made the disease control process even more difficult. In our study, we aimed to investigate the effect of variants on the progression of COVID-19 and add value to the medical literature by providing valuable information.

Materials and Methods: The current study was designed as a retrospective and single-center study. Three thousand and a hundred and ninety-three patients whose SARS-CoV-2 polymerase chain reaction tests came positive between June 1, 2020, and June 1, 2021, were included in the study. Demographic data and the medical history of patients were collected and recorded. The statistical significance level sought was $p<0.05$.

Results: Fifty percent of the cases were male and the mean age was 39.5 years. Among the variant types, the lowest median age was observed in the beta variant. Alpha is the most contagious SARS-CoV-2 variant, and the highest mortality was seen in the delta variant. Considering all SARS-CoV-2 variants, the most common patient complaints were dyspnea and fever. In fatal cases, blood pressure and saturation levels were low, whereas pulse rate and body temperature was higher. Additionally, compared to the non-fatal cases, the median age was higher in fatal cases, 39 years to 55 years. Most of the fatalities occurred in patients who required intensive care unit (ICU) admission. The mortality was low in people with double-dose vaccination, regardless of the variant types.

Conclusion: In this study, SARS-CoV-2 alpha variant was found to be more contagious, and the delta variant appeared more fatal. Patients with delta variant could be at a high risk of morbidity and mortality. Therefore, meticulous patient care should be delivered to patients with the delta variants, no history of the double-dose of vaccination, patients with unstable vital parameters, and patients who were admitted to the ICU.

Keywords: COVID-19, SARS-CoV-2, variants, pandemic, mutation

Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has had a devastating impact on the world since it emerged in Wuhan, China in 2019 and continues to do so. It has become the most catastrophic health event that emerged until today, after the Spanish flu pandemic of 1918 that resulted in 5.4 million deaths worldwide. Ever since the World Health Organization (WHO) declared the novel COVID-19 outbreak a pandemic in 2020, the virus has continued to be catastrophic. Several countries are still suffering from multiple waves of COVID-19 infections.

Adaptive mutations in the virus genome changes pathogenicity of the virus. Even a single amino acid change can lead the virus to gain the ability to evade the immune system [1]. While some evidence suggests that SARS-CoV-2 may adapt to the human host through recurrent mutations over time, as in other RNA viruses, it seems possible that these mutations may lead to the emergence of new variants by producing characteristics [2].

In the first half of the 2020, mutations in the genomic structure of SARS-CoV-2 were identified in some studies. Several new variants have emerged and been identified by genomic data analysis. Koyama et al. [3] examined 10,022 genomes in four

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different databases from 68 countries between February 1st and May 1st. In July 2020, they reported that several variants of the SARS-CoV-2 genome exist. Additionally, they noted that there were 5,775 distinct genomes, 2,969 of which contained missense mutations. Later, multiple researchers verified that the virus had acquired several mutations [3]. In late 2020s, some evidence revealed that the number of cases associated with some of these mutations had inclined, and these mutations were observed more frequently in the spike protein (S-protein) regions. With this altered spike protein, some variants become more contagious than others [4]. The WHO and the center for disease control reported the SARS-CoV-2 variants with high infectivity (such as the variant with D614G mutation) as the variants of concern (VOC) or variants of interest (VOI) [2,4,5].

Five major VOCs were recorded in three different parts of the world; the lineage B.1.1.7 in the UK (20I/501Y.V1-Alpha variant); the lineage B.1.351 (20H/501Y.V2-Beta variant) in South Africa; P.1 lineage in Brazil (20J/501Y.V3-Gamma variant); the lineage B.1.617.2 (Delta variant) in India and the lineage B.1.1.529 (Omicron variant) in South Africa. Additionally, WHO announced eight VOIs; the B.1.427/1.429 variants (Epsilon) detected in California/USA, the B.1.525 variant (Eta) and the B.1.526 variant (Iota) in New York/USA, the S.2 lineage (20J variant-Zeta variant) in Brazil, the P.3 lineage (Theta variant) in Japan and the Philippines, the B.1.617.1 (Kappa variant) in India, lineage C.37 (Lambda variant) in South Africa and the B.1.621 lineage (Mu variant) in Columbia [6,7].

Some evidence has suggested that some of these VOCs and VOIs causes an increase in the infectivity of virulence, decrease in neutralization that was elicited with natural or vaccinated antibodies, and change in the ability to evade detection and fatality.

In our study, we assessed the progression of COVID-19 based on variant types in patients with positive polymerase chain reaction (PCR) tests and provide some valuable information for future studies.

Materials and Methods

This single-center retrospective study was conducted on emergency department patients with suspected COVID-19 between June 1, 2020, and June 1, 2021. Three thousand one hundred and ninety three patients whose PCR test results were positive and met the inclusion criteria were included in the study.

The study hospital, University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, is an urban research and teaching hospital with a level I trauma center. It is the largest academic hospital in the western region of İstanbul with a bed capacity of 2,682. We accept most critically ill patients on the European side of İstanbul and nearby cities since our hospital involves the most critical units such as interventional radiology, cardiovascular intensive care unit (ICU), cardiac catheterization labs, etc. The average number of admissions per day to our emergency COVID-19 outpatient clinic was around 1,800 patients during the study period.

The hospital automation system, in other words hospital information management system (HIMS) was searched for the ICD10 code of "U07.3-COVID-19". According to the search results, 4,782 patients with positive SARS-CoV-2 PCR were identified. These patients were subjected to PCR test for having COVID-19 symptoms. Among these patients, patients under the age of 18, pregnant women, patients with chronic respiratory diseases, patients with multi-pathogen detected in respiratory tract tests, and subjects with missing data (unknown outcomes, unidentified variants, etc.) were excluded from the study (Figure 1). Overall, 3,193 patients were finally included in the study.

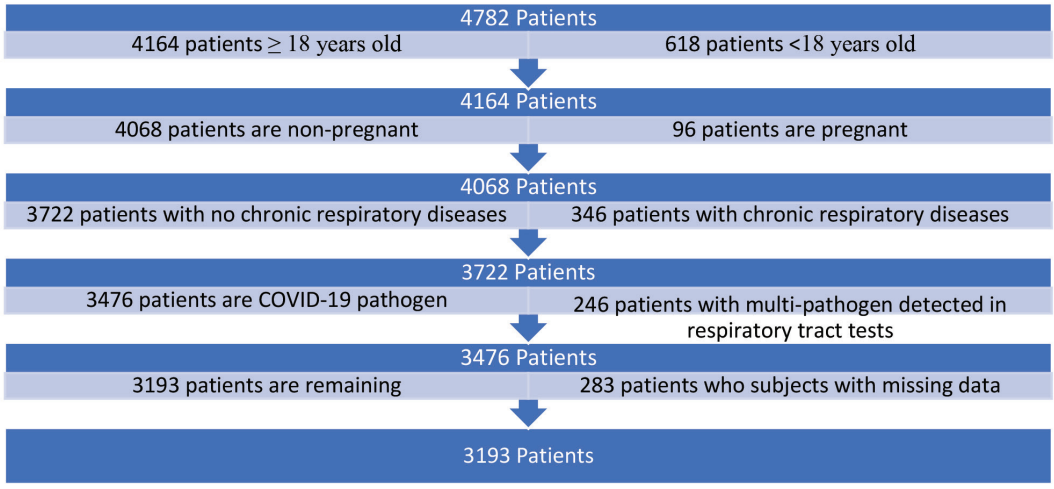

Figure 1. Flowchart of the cases included in the study

COVID-19: Coronovirus disease-2019

Patient demographics (age, sex, and vaccination history) and clinical characteristics (main complaints at admission, vital signs including systolic and diastolic blood pressure, pulse, fever, and saturation levels, the requirement for hospitalization, the clinical unit that patient was admitted to, clinical outcome, and re-admission rates) were assessed through HIMS, and study data were recorded in a study form. Epicrisis reports and consultation notes were also examined in the study. Patients with missing data were excluded from the study.

Ethics Committee Approval

The study protocol was approved by the Ethic Committee of University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (ethics committee meeting and decision dated 14.04.21 and ethics committee no: KAEK/2021.04.81) and followed the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Voluntary consent was obtained from all patients.

Statistical Analysis

Study data were analyzed using SPSS Statistics for Windows®, version 23.0 (IBM Inc. Chicago, IL, USA). Descriptive data were presented with number, percentage, mean, standard deviation, median, minimum, and maximum. Kolmogorov-Smirnov test was applied to determine whether study data were normally distributed. The Pearson chi-square test and Fisher's Exact test were used to compare categorical data. T-test was used to compare two independent numerical data and Kruskal-Wallis test was used to compare triple numerical data. In this study, $p<0.05$ was accepted as the level of significance.

Results

The study included 3,193 patients positive SARS-CoV-2 PCR test. When demographic data were examined; 50% (n=1,596) of the patients were female and 50% (n=1,597) of them were male. The median age was identified as 39.5 years in males and 39.0 years in females, with no statistically significant difference between the two groups. The most common complaints in both genders were noted as dyspnea and fever. In terms of patient complaints on admission, there was no statistically significant difference between the two groups. Vital parameters were used for emergency department admission are shown in Table 1. Our data analysis revealed no significant difference between the median values of vital parameters between the two genders. According to the oropharyngeal/nasopharyngeal swab results, the most identified SARS-CoV-2 variant was the alpha variant (UK variant) in both genders. The history of PCR positivity and history of COVID-19 vaccine in the patient's family are shown in Table 1. There was no significant difference in two genders of history of PCR positivity and history of COVID-19 vaccine in patients' families.

The clinical outcomes were assessed after each case was diagnosed, treated, and finalized. Follow-up records revealed that 3,126 patients were discharged from the hospital, and sixty-seven patients died. When vital parameters on admission were evaluated based on the clinical outcomes, it was found that systolic blood pressure, diastolic blood pressure and saturation levels were significantly lower in non-survivors. However, heart rate and body temperature were found to be significantly higher than survivors. Additionally, our data analysis demonstrated that there was no significant difference between survivors and non-survivors in terms of patient complaints on admission, SARS-CoV-2 variant types, and history of PCR test positivity in the family. However, the history of double-dose COVID-19 vaccine was found to be less in the non-survivor group and 61.2% (n=41) of these patients were hospitalized to the ICU (Table 2).

The median age based on the SARS-CoV-2 variants were 40.0 years (50-30 years) in the alpha variant; 26.0 years (30-22 years) in the beta variant; 42.0 years (55-36.5 years) in the gamma variant; 35.0 years (42-26 years) in the delta variant and 55.0 years (61.5-49.0) in the other variants. According to our statistical analysis, there was a statistically significant difference between the median age and the SARS-CoV-2 variants. The lowest the median age was observed in the beta variant group, other variant types had the highest median age ($p<0.001$), 26 years and 55 years, respectively.

There was no statistically significant difference between variant types and patient complaints on emergency department admission ($p>0.05$). Moreover, no statistically significant relationship was identified between variant types and current vaccination status.

Discussion

Since its emergence in Wuhan, China, in late 2019, SARS-CoV-2 has undergone several genomic mutations that resulted in different lineages and variants appearing in different parts of the world. Some of these mutations result in high transmission rates, complex clinical presentations, and increased severity of the disease [8,9]. It was observed that variants identified in patients with positive SARS-CoV-2 PCR test peaked in certain periods and increased the contagiousness and mortality in populations. With this study, we aimed to evaluate the contagiousness and mortality risk of variants detected in emergency patients and to provide valuable evidence to the literature and future studies.

With the rapid spread of SARS-CoV-2 variants across the globe, several COVID-19 waves have been observed in the last two years. Generally believed that transmission rates, mortality, and dominant clinical features vary during these waves. The literature reports valuable data regarding clinical presentations,

Table 1. Patient demographics and characteristics based on gender

Characteristics	Male n (%)/mean (IQR)	Female n (%)/mean (IQR)	p
Total	1596 (50)	1597 (50)	-
Age (years)	39.5 (49.5-30.0)	39.0 (50.0-29.0)	0.891*
Vital signs on admission			
Systolic blood pressure (mmHg)	120.0 (125.0-109.0)	118.0 (125.0-104.0)	0.627*
Diastolic blood pressure (mmHg)	65.0 (71.5-62.0)	63.0 (72.0-60.0)	0.527*
Saturation (%)	94.0 (96.0-92.0)	94.0 (96.0-92.0)	0.837*
Pulse (beats/min)	85.0 (94.0-77.0)	86.0 (94.0-76.0)	0.758*
Temperature (°C)	36.7 (37.2-36.2)	36.8 (37.3-36.2)	0.907*
Main presenting complaints			
Cough	184 (48.5)	195 (51.5)	0.644**
Shortness of breath	600 (49.6)	609 (50.4)	
Fever	374 (52.4)	340 (47.6)	
Diarrhea	142 (47.7)	156 (52.3)	
Nausea-vomiting	204 (48.8)	214 (51.2)	
Malaise/body aches	92 (52.6)	83 (47.4)	
SARS-CoV-2 variants			
Alfa (UK)	1189 (49.1)	1232 (50.9)	0.120**
Beta (South Africa)	56 (48.7)	59 (51.3)	
Gama (Brazil)	112 (48.3)	120 (51.7)	
Delta (India)	183 (56.1)	143 (43.9)	
Others	56 (56.6)	43 (43.4)	
Family history of positive SARS-CoV-2 PCR test			
Present	641 (49.2)	662 (50.8)	0.458**
None	955 (50.5)	935 (49.5)	
History COVID vaccine			
None	239 (47.7)	262 (52.3)	0.310**
One dose	683 (49.4)	699 (50.6)	
Two doses	674 (51.5)	636 (48.5)	

*Mann-Whitney U test is used, **Pearson χ^2 test is used, PCR: Polymerase chain reaction, IQR: Interquartile range, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID: Coronavirus disease

transmission rates and mortality of the SARS-CoV-2 pathogen when it first emerged in Wuhan, China. Based on these data, the effects of VOCs were evaluated. Mallavarpu Ambrose et al. [10] stated that the new variants identified in England, USA, India, and South Africa were more transmissible but less fatal compared to the SARS-CoV-2 detected in Wuhan. Davies et al. [11] reported that the UK variant (lineage B.1.1.7-Alpha variant) had higher transmission rates than existing variants in England. In our study, we demonstrated that the alpha variant (UK-B.1.1.7) was the most detected variant (75.8%) among our subjects. Additionally, the highest risk of mortality was in the delta variant (India- B.1.617.2) (4.0%). Regarding transmissibility, our results agreed with Davies et al. [11]. Among all SARS-CoV-2 variants, the most common complaints in our study were dyspnea and fever. Even though patient complaints on admission are not statistically significant among variants, patients with the delta variant should be meticulously evaluated since the mortality appears higher in this group.

The COVID-19 pandemic has led to the development of new treatment regimens and vaccines at an unprecedented pace. The emergence of new variants requires scientists to apply new studies and develop new generations of vaccines and treatments. In this rapidly evolving chaotic environment, the importance of vaccination and vaccine studies has shown itself once again. Literature has reported mixed results regarding the protection of neutralizing antibodies against SARS-CoV-2 variants. Although studies have indicated that the efficacy of current vaccines against emerging SARS-CoV-2 variants continues, some studies have emphasized the requirement of new vaccines [7,12,13].

Table 2. Clinical characteristics based on patient outcomes

Characteristics	Survivors n (%)/mean (IQR)	Non-survivors n (%)/mean (IQR)	p
Total	3126 (97.9)	67 (2.1)	-
Age (years)	39.0 (49.0-29.0)	55.0 (63.0-49.5)	**<0.001***
Vital signs on admission			
Systolic blood pressure (mmHg)	120.0 (125.0-110.0)	88.0 (125.0-78.0)	**<0.001***
Diastolic blood pressure (mmHg)	65.0 (72.0-62.0)	47.0 (66.0-42.5)	**<0.001***
Saturation (%)	94.0 (96.0-92.0)	86.0 (92.0-82.0)	**<0.001***
Pulse (beats/min)	85.0 (94.0-76.0)	104.0 (122.0-91.50)	**<0.001***
Temperature (°C)	36.7 (37.2-36.2)	36.8 (37.7-36.5)	**0.001***
Main presenting complaints			
Cough	376 (99.2)	3 (0.8)	0.232***
Shortness of breath	1178 (97.49)	31 (2.6)	
Fever	691 (96.8)	23 (3.2)	
Diarrhea	295 (99.09)	3 (1.0)	
Nausea-vomiting	411 (98.3)	7 (1.7)	
Malaise/body aches	175 (100.0)	0 (0.0)	
SARS-CoV-2 variants			
Alfa (UK)	2370 (97.9)	51 (2.1)	0.927***
Beta (South Africa)	114 (99.1)	1 (0.9)	
Gama (Brazil)	230 (99.1)	2 (0.9)	
Delta (India)	313 (96.0)	13 (4.0)	
Others	99 (100.0)	0 (0.0)	
Family history of positive SARS-CoV-2 PCR test			
Present	1274 (97.8)	29 (2.2)	0.677**
None	1852 (98.0)	38 (2.0)	
History COVID-19 vaccine			
None	482 (96.2)	19 (3.8)	**<0.001****
One dose	1341 (97.0)	41 (3.0)	
Two doses	1303 (99.5)	7 (0.5)	
Type of follow-ups			
Outpatient follow-up	2854 (99.99)	3 (0.01)	**<0.001****
Hospitalization	216 (89.6)	24 (10.4)	
ICU admission	56 (57.3)	40 (42.7)	

*Mann-Whitney U test is used, **Pearson χ^2 test is used, ***: Fisher's Exact test is used. PCR: Polymerase chain reaction, ICU: Intensive care unit, IQR: Interquartile range, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID-19: Coronavirus disease-2019

Our results demonstrated that 15.7% of the emergency patients with positive SARS-CoV-2 PCR were unvaccinated. 43.3% of these patients had a history of single-dose, and 41.0% had a double-dose of COVID-19 vaccine. There was no statistical difference between variant type and the history of vaccine in non-survivors. However, the mortality rate was 0.5% in patients with a history of the double-dose of the COVID-19 vaccine and it was higher in patients with a history of single-dose and unvaccinated patients, 3.0%, and 3.8%, respectively. Our results conclude that vaccine studies are significantly important in preventing mortality regardless of variant types.

Our study demonstrated that the median age was higher in non-survivors. Clinicians should be extremely careful in assessing the mortality risk in patients with unstable vital parameters on emergency department admission and patients requiring early ICU admission.

Study Limitations

There are some limitations to the present study. First, this was a retrospective study conducted through HIMS search. Even though we could access every single patient's medical record who was admitted to the emergency department with COVID-19 symptoms and offered a positive SARS-CoV-2 PCR, some of these files had missing study data that had us to exclude several patients from the study. Second, patient medical records involved the status of the COVID-19 vaccine, however type of vaccine or vaccine (Sinovac, Biontech, etc.) was not recorded. Lastly, our study did not include data on the omicron variant since the emergence of the variant comes across the time, we had completed the study.

Conclusion

The current study demonstrated that the alpha variant was the most contagious, and the mortality was seen as the highest in the delta variant. Additionally, we showed that a double-dose of COVID-19 vaccine can be protective against mortality regardless of SARS-CoV-2 variants. Our results emphasize that clinicians should provide meticulous care to COVID-19 patients with advanced age, unstable vital parameters on emergency admission and no history of double-dose of COVID-19 vaccines. We believe that future studies on this subject can provide valuable information for emergency doctors and clinicians who frequently encounter COVID-19 patients and guide them in improving pandemic patient management.

Acknowledgment

We would like to express our deepest gratitude to all healthcare workers and scientists who work devotedly, often putting themselves and their families in the back despite all challenges arising from the COVID-19 pandemic. Your efforts will not be forgotten.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethic Committee of University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (ethics committee meeting and decision dated 14.04.21 and ethics committee no: KAEK/2021.04.81) and followed the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Informed Consent: All patients were reached and voluntary consent was obtained. Consent was obtained from first-degree relatives in patients with a mortal course.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç., K.Ş., N.K., B.A., E.A., G.E., R.G., Concept: A.Ç., B.A., G.E., R.G., Design: A.Ç., K.Ş., E.A., R.G., Data Collection or Processing: A.Ç., K.Ş., N.K., E.A., G.E., Analysis or Interpretation: A.Ç., R.G., Literature Search: A.Ç., N.K., B.A., G.E., R.G., Writing: A.Ç., N.K., B.A.

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