











## RESEARCH ARTICLE

# Evaluation of childhood hospitalization rates and degree of severity of SARS-CoV-2 variants, including B.1.1.7 (Alpha), B.1.315/P.1 (Beta/Gamma), and B.1.617.2 (Delta)

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## Abstract

Severe acute respiratory syndrome coronavirus 2 is reappearing with an increasing number of variants every day; this study aimed to determine the effect of B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) variants on hospitalization rates. This single-center study was conducted at the University of Health Sciences Dr. Behçet Uz Children's Hospital from March 11 to August 27, 2021. Variant analyses of symptomatic patients admitted to the hospital who were found to be positive for COVID 19 PCR was performed. Out of 680 cases, 329 (48.4%) were B.1.1.7 variant, 17 (2.5%) were B.1.351/P.1 variant, and 165 (24.2%) were B.1.617.2 variant. One hundred and sixty-nine (24.9%) case variant analysis results were negative. The hospitalization rate of patients with the B.1.617.2 variant was 19.4%, the B.1.351/P.1 variant was 18%, the B.1.1.7 variant was 9.4%, and the negative variant was 10.1%. The B.1.617.2 (Delta) variant, which has become widespread all over the world recently, increases the rate of hospitalization in children.

## KEYWORDS

coronavirus, pandemics, SARS coronavirus

## 1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which entered our lives in December 2019 and still affects millions of people today, is going through a difficult process all over the world. SARS-CoV-2 are enveloped, positive-sense single-stranded RNA viruses of the *Betacoronavirus* genus of the *Coronaviridae* family.<sup>1</sup> The last two decades have seen three major outbreaks of pathogenic zoonotic diseases caused by *Betacoronaviruses* including SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and finally SARS-CoV-2 which causes the severe respiratory disease coronavirus disease 2019 (COVID-19).<sup>2</sup>

In SARS-CoV-2, which is an RNA virus, mutations occur naturally as the virus reproduces. So far, thousands of mutations have

emerged, but only a very small fraction are likely to matter and alter the virus in a significant way. The first mutation in the United Kingdom was detected in September 2020, and with the rapid increase of cases, in December 2020, it was named VUI-202012/01 (the first "Variant Under Study" in December 2020) and was identified with a set of 17 changes or mutations. One of the most important of these mutations has been identified as an N501Y mutation in the spike protein that the virus uses to bind to the human ACE2 receptor. Changes in this part of the spike protein are thought to increase the contagiousness of the virus.<sup>3</sup> This variant was named B.1.1.7 or Alpha variant.<sup>4</sup> Studies from the United Kingdom suggest an increase in the contagion of up to 71% over previous circulating strains of SARS-CoV-2.<sup>5</sup> At the same time, variant strains started to be seen in South Africa in a similar period, December 2020. The South African variant,

called the 501Y.V2 variant or Beta or B.1.351 lineage, is characterized by three mutations in the SARS-CoV-2 spike (S) protein: K417N, E484K, and N501Y. The N501Y mutation is also present in the United Kingdom VUI-202012/01 variant.<sup>6</sup> The third variant, the P.1 variant also known as Gamma variant or GR/501Y.V3, was identified in December 2020 in Brazil. The fourth variant, B.1.617.2 also referred to as the Delta variant, was initially identified in December 2020 in India.<sup>4</sup>

Among the variant viruses spreading all over the world, the B.1.1.7 variant was seen for the first time in January, the B.1.351 and P.1 variant was seen in February, and the B.1.617.2 variant was seen in April in Turkey.<sup>7-9</sup> The studies on the clinical importance of variant SARS-CoV-2 mainly focused on adults, while there was limited data about the effect of variants on the children's hospitalization rates. In this study, we aimed to investigate the effect of variant viruses on severity, hospitalization, and intensive care unit hospitalization rates.

## 2 | MATERIALS AND METHODS

This single-center study was conducted in Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, which is a referral center for pediatric patients in the Aegean Region of Turkey. The study included a total of 680 patients who were admitted to the emergency department and outpatient clinics of Behçet Uz Children's Hospital between March 11 and August 27, 2021. All patients were symptomatic patients and their nasopharyngeal swab samples were positive for COVID-19 real-time polymerase chain reaction (RT-PCR). Variant analysis was also performed in all patients who were found to be positive for COVID-19 RT-PCR.

Nasopharyngeal swabs from the suspected patients were delivered to the laboratory in viral transport medium (VTM) and samples from the VTM tubes were analyzed for SARS-CoV-2 genes by reverse transcription *real-time* PCR (RT-qPCR) assay. The target genes were different and associated with the procurement of the commercial kits developed according to the dynamics of the pandemic. At the earlier period, samples were analyzed for the qualitative detection of SARS-CoV-2-specific ORF1ab gene and nucleocapsid (N) gene targets by using a one-step reverse transcription real-time PCR assay (Bio-Speedy®- Double Gene RT-qPCR, Turkey).

With the rise of the B.1.1.7 variant (UK/Alpha variant) the kit has been altered to detect the Orf1ab and N gene regions found in all SARS-CoV-2 as well as an N gene region only found in VOC-202012/01 in a single multiplex reaction (Bio-Speedy® SARS-CoV-2 + VOC202012/01 RT-qPCR). Following the increasing reports of SARS-CoV-2 variants, targets for detection of the variants as the N D3L mutation for the B.1.1.7 detection and the E484K mutation were added to the routine analysis as well the *Orf1ab* and *N* gene regions found in all SARS-CoV-2 were analyzed within a single multiplex reaction by using a commercial RT-qPCR kit (Bio-Speedy® SARS-CoV-2 Variant Plus). Later, a newly developed kit which targets the *Orf1ab* and *N* gene regions found in all SARS-CoV-2 for the routine screening, as well as the N\_D3L mutation for the B.1.1.7 detection,

the E484K mutation for detection of the variants with a high possibility of escaping the antibody-mediated immunity and the L452R mutation for detection of the variants with higher transmissibility, were used (Bio-Speedy® SARS-CoV-2 Emerging Plus). PCR assays were performed through the Montana 4896 Real-Time PCR Instrument (Anatolia Gene works) and Rotor-Gene Q 2plex HRM Platform (Qiagen). The "Variant Oligo Mix" was targeted as SARS-CoV-2 reference genome region (ORF1ab + N) (FAM); nucleocapsid (N) D3L mutation for detection of Alpha variant (CY5); and spike (S) E484K mutation for detection of Beta, Gamma, Zeta, Eta, Teta, Lota variants (ROX).

Data such as age, gender, medical history, and variant types of the patients were collected through the electronic medical record system and patient files, and the effects of age, underlying disease, and variant types on hospitalization rates were evaluated.

Statistical analyses were performed using SPSS 20 software (IBM). First, numerical and categorical data were evaluated by descriptive statistical methods. Distributions of numerical variables were examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov). Characteristics of patients were described as count (percent) or mean value ( $\pm$ standard deviation) for qualitative and quantitative variables. Categorical variables were compared using Pearson  $\chi^2$  and Fisher's exact tests. A  $p \leq 0.05$  was considered statistically significant.

## 3 | ETHICAL CONSENT

This study was approved by the Local Ethical Committee of the University of Health Sciences Dr. Behçet Uz Children's Hospital.

## 4 | RESULTS

A total of 680 patients who underwent SARS-CoV-2 variant analysis were included in the study. Among the 680 patients, 334 (49.1%) were females and 346 (50.9%) were males. The median age was 9 years and 3 months (min 15 days, max 17 years). Regarding the age distribution, 78 (11.4%) of these patients were under the age of 1 year, 126 (18.6%) were between the ages of 1 and 5 years, 203 (29.9%) were between the ages of 5 and 12 years, and 273 (40.1%) were 12 years and older.

Further variant analysis of SARS-CoV-2 resulted in 329 (48.4%) B.1.1.7 variants, 17 (2.5%) B.1.351 and P.1 variants, and 165 (24.2%) B.1.617.2 variants. In 169 (24.9%) cases, the variant analysis results were negative.

While 83 (12.2%) of all patients required hospitalization and 597 (87.8%) of them were outpatients. Out of 83 hospitalized patients, 3 patients were hospitalized in the pediatric intensive care unit, 9 patients were hospitalized in the neonatal intensive care unit, and 71 patients were followed up in the pediatric infectious diseases service.

There was an additional underlying disease in 24 patients, and all of these patients were in the hospitalized group, and the ratio of

underlying disease was significantly higher in the hospitalized patients compared to outpatient groups ( $p < 0.001$ ). The underlying diseases were as follows: Down syndrome in 2 patients, neurological diseases such as epilepsy and cerebral palsy in 10 patients, haematological malignancies in 7 patients, immunodeficiency in two patients and laryngomalacia, nephrotic syndrome, prematurity with operated patent ductus arteriosus were detected in one patient each.

Considering the effect of age on hospitalization rate, the mean age of outpatients was 9 years and 8 months (minimum 1 month to maximum 17 years), and the mean age of hospitalized patients was 5 years and 10 months (minimum 15 days, maximum 17 years), and significantly higher in the outpatient group ( $p < 0.001$ ).

Considering hospitalization rates according to variant analysis, the hospitalization rate of patients with B.1.617.2 variant was found to be 19.4% (32/165), B.1.351/P.1 variant was found to be at 18% (3/17), at B.1.1.7 variant 9.4% (31/329), and variant negative 10.1% (17/169). The  $\chi^2$  independence test revealed an association between the type of variant and hospitalization rate ( $\chi^2 = 11.5$ ,  $p < 0.009$ ). The rate of hospitalization was significantly different between these groups, and the hospitalization rate was significantly higher in the patients with B.1.617.2 variant COVID-19 infections compared to non-variant infections and patients with B.1.1.7 variant ( $p = 0.016$  and  $p = 0.002$  consecutively). There was no significant difference between other variants regarding the hospitalization rates ( $p > 0.05$ , Table 1).

## 5 | DISCUSSION

In this study, following the literature, the variant type with the highest hospitalization rate was Delta. The second most frequent hospitalization after the Delta variant was in the Beta/Gamma variant.

The SARS-CoV-2 spike protein receptor-binding domain is the critical determinant of viral tropism and infectivity.<sup>10</sup> Studies show that SARS-CoV-2 can mutate spike proteins to evade antibodies and that these mutations are already present in some virus mutants.<sup>11</sup> SARS-CoV-2 was shown to be capable of mutations and studies

showed that it has undergone thousands of mutations since its emergence, and these resulting variants have been classified as a variant of interest (VOI), variant of concern (VOC), and variant under monitoring (VUM). Four variants, which were determined as VOC and started to spread from four different countries, gained importance and came to the fore due to the speed of spread. Of these mutations, Alpha (B.1.1.7) was first detected in England, Beta (B.1.351) in South Africa, Gamma (P.1) in Brazil, and Delta (B.1.617.2) in India, and spread all over the world.<sup>12</sup>

In a UK study, patients with the B.1.1.7 lineage were found to have a higher risk of 28-day mortality and intensive care unit admissions compared to SARS-CoV-2 patients without B.1.1.7.<sup>13</sup> In a study evaluating 49 930 pediatric and adult patients with positive Alpha and Delta variants, it was shown that patients with Delta variants had more than twice the risk of hospitalization compared to patients with Alpha variants.<sup>14</sup>

In the study of the European Center for Disease Prevention and Control (ECDC), which compared the severity of the disease between VOC cases and no variable cases reported in seven European countries; B.1.1.7 cases had 2.3–3 times higher hospitalization rates compared to non-VOC cases. B.1.351 cases had a 3.5–3.6 times higher hospitalization rate, and P.1 cases 3.0–13.1 times higher hospitalization rates compared to non-VOC cases.<sup>15</sup> In a retrospective study, the probability between infection with the B.1.617.2 variant and the possibility of developing pneumonia or severe COVID-19 was found to be higher than Alpha and Beta variants.<sup>16</sup> In a study conducted in Scotland, Delta VOC was found mainly in younger groups. Compared with Alpha VOC, the risk of COVID-19 hospitalization was approximately doubled in those with Delta VOC, particularly those with five or more related comorbidities, with an increased risk of admission.<sup>17</sup>

In our study, no significant difference was found in terms of hospitalization rates when the B.1.1.7 variant and those without variants were compared. However, as determined in other studies, when the hospitalization rate was evaluated in our study, the B.1.617.2 variant was found to be approximately two times higher than the other variant types, and it was found statistically significant. The second most frequent hospitalization rate was found in patients

	Delta variant (B.1.617.2)	Beta/Gamma variant (B.1.351/P.1)	Alpha variant(B.1.1.7)	No variant was detected	p value
Inpatient	32 (19.4%)	3 (17.6%)	31 (9.4%)	17 (10.1%)	<0.009
Outpatient	133 (80.6%)	14 (82.4%)	298 (90.6%)	152 (89.9%)	

**TABLE 1** The comparison of the hospitalization rates and present variants

Note: The  $\chi^2$  independence test revealed an association between the type of variant and hospitalization rate ( $\chi^2 = 11.5$ ,  $p < 0.009$ ).

Delta variant versus Beta/Gamma:  $p > 0.05$ .

Delta variant versus Alpha variant:  $p = 0.002$ .

Delta variant versus not detectable variant:  $p = 0.016$ .

Beta/Gamma variant versus Alpha variant:  $p > 0.05$ .

Beta/Gamma variant versus not detectable variant:  $p > 0.05$ .

Alpha variant versus not detectable variant:  $p > 0.05$ .

with the B.1.351/P.1 variant. B.1.351 and P.1 variants were studied together in the SARS-CoV-2 variant analysis in our hospital, a separate evaluation could not be made.

Considering the effect of age on hospitalization rate, we found that the age distribution of outpatients was higher than in hospitalized patients. It is known that the presence of an underlying comorbid disease increases the risk of COVID 19; in one study, it was found that 14% of those hospitalized had a comorbid disease, and in another study, it was observed that 74.3% of those admitted to the pediatric intensive care unit had a comorbid disease.<sup>18,19</sup> In our study, 24 patients had the comorbid disease and all patients with the underlying disease were hospitalized and followed up, so the presence of comorbid disease increases hospitalization rates.

The limitations of our study are that it is single-centered, and the Beta and Gamma variants cannot be evaluated separately because both variants are studied together. In addition, we did not include the first year of the pandemic because we did not have any variant analysis in that period, hence no routine analysis or recommendation for variant analysis. Second, we did not have any clinical information, including viral shedding, duration of fever, or fatigue severity scores to help further analysis for multivariate analysis for hospitalization. However, up to our knowledge, this is one of the limited studies focusing on the impact of SARS-COV-2 variants on the hospitalization of children.

In addition, we did not include the first year of the pandemic because we did not have any variant analysis at that time, and there were no recommendations for routine analysis or variant analysis, and therefore, the number of our patients was limited. In addition, since it was a retrospective study, it was not possible to evaluate the clinical severity.

In conclusion, the COVID 19 pandemic, which continues in waves today, comes across with new variants every day. The spread of COVID 19 in children is increasing with new variants; as it was determined in our study, the Delta variant, which is the variant that has recently increased all over the world, has significantly increased the hospitalization rates.

## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## ETHICS STATEMENT

Ethical approval for this study was obtained from Behçet Uz Children's Training and Research Hospital Institutional.

## AUTHOR CONTRIBUTIONS

Prof. Dr. İlker Devrim conceptualized and designed the study, carried out the initial analyses, and reviewed and revised the manuscript. Dr. Miray Yılmaz Çelebi collected data, carried out the initial analyses, and drafted the initial manuscript. Prof. Süleyman N. Bayram conceptualized and designed the study, coordinated, supervised data collection and reviewed and revised the manuscript. Dr. Elif Kıymet, Dr. Elif Böncüoğlu, Dr. Şahika Şahinkaya, Dr. Ela Cem, Dr. Mine Düzgöl, and Dr. Aybüke Akaslan

Kara designed the data collection instruments, collected data, and contributed essential intellectual content. Dr. Fahri Y. Ayhan designed the data collection instruments. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## DATA AVAILABILITY STATEMENT

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

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## REFERENCES

- Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 transmission and pathogenesis. *Trends Immunol.* 2020;41(12):1100-1115.
- Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell.* 2020;182(4):812-827. e19.
- Wise J. Covid-19: New coronavirus variant is identified in UK. *BMJ.* 2020;371:m4857. doi:10.1136/bmj.m4857
- Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di, Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). *StatPearls.* StatPearls Publishing; 2021.
- Tang JW, Tambyah PA, Hui DS. Emergence of a new SARS-CoV-2 variant in the UK. *J Infect.* 2021;82(4):e27-e28.
- Tang JW, Toovey OTR, Harvey KN, Hui DDS. Introduction of the South African SARS-CoV-2 variant 501Y.V2 into the UK. *J Infect.* 2021;82(4):e8-e10.
- DW AGENCY. Koca: mutasyonlu virüs tespit edilenlerin sayısı 128'e yükseldi. Accessed November 6, 2021. <https://www.dw.com/tr/koca-mutasyonlu-vir%C3%BCs-tespit-edilenlerin-say%C4%B1s%C4%B1-128e-y%C3%BCkseldi/a-56387919>
- Accessed November 6, 2021. [https://tr.wikipedia.org/wiki/T%C3%BCrkiye%27de\\_COVID-19\\_pandemisi](https://tr.wikipedia.org/wiki/T%C3%BCrkiye%27de_COVID-19_pandemisi)
- DW AGENCY. Delta varyantı: Türkiye'de ne kadar yaygın? Accessed November 6, 2021. <https://www.dw.com/tr/delta-varyant%C4%B1-t%C3%BCrkiyede-ne-kadar-yayg%C4%B1n/a-57984629>
- Ou J, Zhou Z, Dai R, et al. V367F Mutation in SARS-CoV-2 Spike RBD emerging during the early transmission phase enhances viral infectivity through increased human ACE2 receptor binding affinity. *J Virol.* 2021;95(16):e0061721. doi:10.1128/JVI.00617-21
- Weisblum Y, Schmidt F, Zhang F, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. *eLife.* 2020;9:e61312. doi:10.7554/eLife.61312
- Choi JY, Smith DM. SARS-CoV-2 variants of concern. *Yonsei Med J.* 2021;62(11):961-968. doi:10.3349/ymj.2021.62.11.961
- Patone M, Thomas K, Hatch R, et al. Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study. *Lancet Infect Dis.* 2021; 21(11):1518-1528.

14. Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis*. 2022;21(1):35-42. doi:10.1016/S1473-3099(21)00475-8
15. Funk T, Pharris A, Spiteri G, et al. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. *Euro Surveill*. 2021;26(16):2100348.
16. Ong SWX, Chiew CJ, Ang LW, et al. Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta) [published online ahead of print, 2021 Aug 23]. *Clin Infect Dis*. 2021: ciab721. doi:10.1093/cid/ciab721
17. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet*. 2021;397(10293):2461-2462. doi:10.1016/S0140-6736(21)01358-1
18. Shahbaznejad L, Rouhanizadeh H, Navaeifar MR, Hosseinzadeh F, Movahedi FS, Rezai MS. Clinical characteristics and outcomes of COVID-19 in children in Northern Iran. *Int J Pediatr*. 2021;2021:5558287. doi:10.1155/2021/5558287
19. Derespina KR, Kaushik S, Plichta A, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J Pediatr*. 2020;226:55-63.e2. doi:10.1016/j.jpeds.2020.07.039

**How to cite this article:** Yılmaz Çelebi M, Kıymet E, Böncüoğlu E, et al. Evaluation of childhood hospitalization rates and degree of severity of SARS-CoV-2 variants, including B.1.1.7 (Alpha), B.1.315/P.1 (Beta/Gamma), and B.1.617.2 (Delta). *J Med Virol*. 2022;94:2050-2054. doi:10.1002/jmv.27587