

# Comparison of clinical characteristics of wild-type SARS-CoV-2 and Omicron

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## SUMMARY

**OBJECTIVE:** This study aimed to investigate the effect of mutations by comparing wild-type SARS-CoV-2 and Omicron regarding clinical features in patients with COVID-19. It also aimed to assess whether SARS-CoV-2 cycle threshold value could predict COVID-19 severity.

**METHODS:** A total of 960 wild-type and 411 Omicron variant patients with positive results in SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction test from oropharyngeal and/or nasopharyngeal samples during their hospital admissions were included in this retrospective study. The reference symptoms of the patients were obtained from the hospital database. The correlation between chest computed tomography findings and the “cycle threshold” of patients with wild-type SARS-CoV-2 was assessed.

**RESULTS:** Cough, fever, shortness of breath, loss of taste and smell, and diarrhea were found to be statistically significantly higher ( $p=0.001$ ;  $0.001$ ;  $0.001$ ;  $0.001$ ; and  $0.006$ ; respectively) in the wild-type cohort, while in the Omicron cohort, sore throat and headache were found to be statistically significantly higher ( $p=0.001$  and  $0.003$ , respectively). An inverse relationship was found between chest computed tomography findings and viral load.

**CONCLUSION:** This study revealed that the Omicron variant tended to infect predominantly the upper respiratory tract and showed decreased lung infectivity, and the disease progressed with a milder clinical course. Therefore, the study showed that the tropism of the virus was changed and the viral phenotype was affected. It was also found that SARS-CoV-2 viral load did not predict COVID-19 severity in patients with wild-type SARS-CoV-2.

**KEYWORDS:** COVID-19. SARS-CoV-2 variants. Coronavirus. Viral load.

## INTRODUCTION

The massive spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enabled the rapid evolution of the virus, resulting in the emergence of numerous variants. The World Health Organization (WHO) classified these as “variant of concern” (VOC) that gained increased contagiousness, worsening of the clinical features, and affecting diagnosis and vaccine performance. Wild-type SARS-CoV-2, which started the pandemic, was replaced by variants, and five VOCs, Alpha, Beta, Gamma, Delta, and finally Omicron, have been identified so far<sup>1</sup>. Omicron is the most highly mutated one with 50 mutations accumulating in its genome. Studies comparing wild-type SARS-CoV-2 and other variants have shown that these mutations increase the contagiousness and infectivity of Omicron and facilitate its escape from immunity<sup>2</sup>.

Timely and accurate diagnosis of COVID-19 is critical to the successful management of the pandemic. Real-time

reverse transcriptase polymerase chain reaction (rRT-PCR) is the gold-standard test for diagnosing SARS-CoV-2. The rRT-PCR “cycle threshold” (Ct) – a semi-quantitative measure of viral load – is the number of cycles required for the fluorescent signal, resulting from amplification of the target gene, to cross the threshold. Because of the length of time and lack of sensitivity as well as false-negative results for rRT-PCR tests, chest computed tomography (CT) is recommended for the diagnosis of viral pneumonia<sup>3</sup>.

COVID-19 can progress with different clinical features, ranging from asymptomatic or mild clinical course to severe respiratory failure. Since variants of the virus have emerged, the virus-host relationship may also vary depending on these<sup>2</sup>.

This retrospective study aimed to investigate the effect of mutations by comparing wild-type SARS-CoV-2 and Omicron regarding clinical features in patients with COVID-19 who applied to Ankara City Hospital (Türkiye). The study also

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evaluated the relationship between SARS-CoV-2 Ct values detected by rRT-PCR and chest CT findings of the patients in the wild-type cohort to assess whether the SARS-CoV-2 Ct value could predict COVID-19 severity.

## METHODS

This retrospective study included 1371 patients with positive results in the SARS-CoV-2 rRT-PCR test from oropharyngeal and/or nasopharyngeal samples (OP/NP) during their hospital admissions, 960 with wild-type SARS-CoV-2 between April 1, 2020, and June 30, 2020, and 411 with Omicron between March 1, 2022, and March 31, 2022. The patients' demographic features and symptoms of admission to the emergency department were obtained from the hospital database.

At the beginning of the pandemic, a chest CT scan was performed for patients with suspected wild-type SARS-CoV-2 in our hospital. However, this approach was abandoned in patients infected with Omicron, and a chest CT scan was performed only in the elderly and in patients with low oxygen saturation and comorbidities. Patients aged  $\geq 18$  years diagnosed with COVID-19 by rRT-PCR and having a chest CT scan time interval of less than 72 h after obtaining OP/NP swab were included in this study. A correlation analysis was performed on the rRT-PCR Ct values and chest CT findings of a total of 960 patients with wild-type SARS-CoV-2 diagnosed by rRT-PCR and simultaneous chest CT.

### Detection of SARS-CoV-2

OP/NP samples from patients were placed in transfer tubes containing vNAT (Viral Nucleic Acid buffer/various manufacturers) and sent to the Molecular Microbiology Laboratory. Detection of SARS-CoV-2 in samples was performed by the rRT-PCR method with two commercial kits according to the manufacturer's instructions: the BioSpeedy COVID-19 RT-qPCR Detection Kit (Bioeksen, Türkiye) targeting the *RdRp* (RNA-dependent RNA polymerase) gene was used for the detection of the wild-type, and the SARS-CoV-2 Plus Omicron Variant Detection Kit (Gensutek, Türkiye) targeting SARS-CoV-2 specific "Orf1ab" and "N" genes as well as Omicron-specific genome regions was used for the detection of the Omicron variant. Both kits target the human RNaseP (Ribonuclease P) gene as an internal control to evaluate sample-based inhibition control and kit reagent control. The PCR reaction was performed on the Rotor-Gene Q (Qiagen, Germany) device. Ct values  $< 40$  in the detection of wild-type SARS-CoV-2 and  $\leq 38$  Ct values in the detection of Omicron were considered positive.

### Imaging technique and imaging interpretation

Thin-section, noncontrast, chest CT (Revolution, GE Medical System, Germany) examinations were performed. The tomography protocol was as follows: 100 kV, 110–400 mA, and a slice thickness of 2.5 mm in all cases. Images with a slice thickness of 0.625 mm were obtained by reconstruction. The sections were evaluated by two specialist radiologists.

According to the Radiological Society of North America (RSNA) Expert Consensus Statement, parenchymal pneumonic involvement was divided into four groups:

1. typical appearance,
2. indeterminate appearance,
3. atypical appearance, and
4. negative for pneumonia<sup>4</sup>.

In this study, disease severity is evaluated according to the RSNA classification.

### Statistical analysis

The statistical analysis was carried out using the SPSS software version 23.0 (IBM Corp.). The normality analysis of numerical data was evaluated by histogram and Kolmogorov-Smirnov tests. The difference between the groups was calculated by chi-square, Fisher's exact test, Student's t-test, and Mann-Whitney U test as appropriate. A p-value  $< 0.05$  was considered statistically significant.

## RESULTS

A total of 1371 SARS-CoV-2 patients were evaluated in this study, involving 960 wild-type and 411 Omicron variants. The percentage distributions of male and female patients in the wild-type and Omicron groups were 0.92 and 1.4, respectively ( $p=0.001$ ). The median age was 40 [interquartile range (IQR), 24] and 38 [IQR, 27] in the wild-type and Omicron groups, respectively. There was no statistically significant difference between the two groups regarding median age (Mann-Whitney U test,  $p=0.292$ ).

When admission symptoms were compared, cough (52.9%), fever (34.6%), shortness of breath (21.1%), loss of taste and smell (5.8%), and diarrhea (4.5%) were found to be statistically significantly higher in the wild-type group ( $p=0.001$ ; 0.001; 0.001; 0.001; and 0.006; respectively). In the Omicron group, symptoms of sore throat (17.5%) and headache (7.6%) were found to be statistically significantly higher ( $p=0.0001$  and 0.003, respectively). The clinical symptoms detected in the wild-type and Omicron groups are given in Table 1.

A chest CT was performed in all wild-type infected patients. The distributions of chest CT findings were found as follows: typical appearance 40.8%, negative for pneumonia 38.6%, indeterminate appearance 17.1%, and atypical appearance 3.4%. The comparison of chest CT findings classified according to RSNA and rRT-PCR Ct values of the wild-type infected patients is given in Table 2.

Chest CT was performed in only 3.9% (411/16) of Omicron-infected patients. The chest CT results were found as follows in the Omicron cohort: typical appearance 1.7%, atypical appearance 0.7%, negative for pneumonia 1%, and indeterminate appearance 0.5%.

When chest CT findings and Ct values were compared, the mean Ct value of the “negative for pneumonia” group was statistically significantly lower than the mean Ct value of those with “typical appearance” group ( $p=0.001$ ). The mean Ct value of those with “indeterminate appearance” was statistically significantly lower than the mean Ct value of those with “typical appearance” ( $p=0.043$ ).

## DISCUSSION

COVID-19 has a very broad clinical spectrum, ranging from mild to severe and critical course. In this study, the most common

symptoms found in the wild-type cohort were cough, fatigue/muscle-joint pain, fever, and shortness of breath as consistent with the literature<sup>5-8</sup>. The symptoms of sore throat, fatigue/muscle-joint pain, cough, and fever were detected in the Omicron cohort, as consistent with the literature<sup>9,10</sup>.

Omicron carries a large number (32) of mutation on the spike (S) protein, which is the main antigenic target of antibodies. The focus of mutations has been the receptor-binding domain (RBD) of the S protein due to its potential impact on infectivity and resistance to antibodies. This is because the RBD located on the S protein facilitates the binding between the S protein and the host angiotensin-converting enzyme 2 (ACE2). The S-ACE2 binding helps SARS-CoV-2 enter the host cell and initiate the infection process. Vaccine or natural infection-induced antibodies that bind strongly to RBD neutralize the virus directly. Therefore, this mutation in the RBD has led to new inquiries about the efficacy of current vaccines and the reinfection potential of the virus, thereby increasing the global panic<sup>11</sup>.

Results of early clinical studies show that the rapidly spreading Omicron variant is less dangerous than previous variants. A study with cell culture reported that compared to Delta, the Omicron variant may have lower replication capacity in the lungs<sup>12</sup>.

In a study, three-dimensional modeling of respiratory organs was used to demonstrate the entry of SARS-CoV-2<sup>13</sup>, and it was shown that Omicron exhibited less severe infection than Delta and Wuhan/D614G strain. Therefore, less access to the lower respiratory tract may mean milder symptoms when compared to other variants<sup>13,14</sup>.

Syrian golden hamsters suffering from weight loss and pneumonia following COVID-19 infection provide a robust model to study SARS-CoV-2 disease in humans. In a study, hamsters were infected with WA1/2020, Alpha, Beta, Delta, and Omicron variants, and weight loss occurred in variants other than Omicron<sup>15</sup>. In contrast to WA1/2020 infection, Omicron-infected hamsters had higher viral loads in the nose and lower viral loads in the lungs<sup>14</sup>.

**Table 1.** Distribution of clinical symptoms in wild-type and Omicron groups.

Symptoms	Wild-type (n=960)	Omicron (n=411)	p
Cough (%)	508 (52.9)	136 (33.1)	0.001
Fatigue/muscle-joint pain (%)	376 (39.2)	175 (42.6)	0.238
Fever (%)	332 (34.6)	84 (20.4)	0.001
Shortness of breath (%)	203 (21.1)	27 (6.6)	0.001
Sore throat (%)	168 (17.5)	186 (45.3)	0.001
Headache (%)	73 (7.6)	52 (12.7)	0.003
Loss of taste and smell (%)	56 (5.8)	4 (1)	0.001
Diarrhea (%)	43 (4.5)	6 (1.5)	0.006
Nausea-vomiting (%)	38 (4)	9 (2.2)	0.099

**Table 2.** Comparison of rRT-PCR cycle threshold values of chest computed tomography findings in wild-type infected patients.

Chest CT imaging findings	Typical appearance	Negative for pneumonia	Indeterminate appearance	Atypical appearance
rRT-PCR Ct value mean (SD)	26.5 (5.3)	23.9 (5.9)	25.4 (5.5)	28.3 (5.4)
Typical appearance	1	$p=0.001$	$p=0.043$	$p=0.060$
Negative for pneumonia		1	$p=0.004$	$p=0.001$
Indeterminate appearance			1	$p=0.008$
Atypical appearance				1

Ct: cycle threshold; CT: chest computed tomography.

When comparing admission symptoms, this study found that cough, fever, and shortness of breath, which indicate wild-type lower respiratory tract infection, were replaced by sore throat and headache, which indicate upper respiratory tract infection in the Omicron cohort. This result showed that Omicron tended to infect the upper respiratory tract, as discussed in previous studies<sup>13-15</sup>.

Suzuki et al., investigating the effect of mutations in the S protein on the viral phenotype, showed that Omicron in the hamster model caused lower infectivity and less pathogenicity in the lungs compared to Delta and wild-type SARS-CoV-2<sup>16</sup>. In our study, taste-smell loss and diarrhea were found to be statistically significantly lower in the Omicron cohort, suggesting that viremic activity is reduced in organs other than the respiratory system.

Due to the high contagiousness of the COVID-19, rapid diagnosis and isolation are critical for the struggle against the pandemic. It has been suggested that since rRT-PCR test results in several hours, it may be insufficient for rapid triage and that chest CT can be an alternative to the rRT-PCR test in the diagnosis of pneumonia<sup>4</sup>. In this study, “typical appearance” tomography findings supporting COVID-19 pneumonia radiologically were detected in 40.8% of wild-type and 1.7% of Omicron variant cases. These results support that the lung infectivity of Omicron is decreased and has a milder clinical course. In addition, the patients with SARS-CoV-2 positive on rRT-PCR and “negative for pneumonia” in chest CT were as high as 38.6% in the wild-type cohort. According to this result, only the chest CT scan for COVID-19 may cause misdiagnosis.

Liu et al. reported that viral load is crucial in determining disease severity<sup>17</sup>. Our study found an inverse relation – viral load being higher in the group “negative for pneumonia” – between chest CT findings and Ct values of wild-type infected patients, as consistent with previous studies<sup>3</sup>. The viral load of the group with pneumonia was low while the viral load of the group without pneumonia was found to be high, which may have been caused by the use of upper respiratory tract samples

in diagnosis. Therefore, we evaluated that it would be more appropriate to detect the viral load in lower respiratory tract samples in patients with pneumonia and to investigate the relationship between pneumonia severity and Ct values.

This study has some limitations. In previous studies, it has been reported that vaccinated individuals have a milder disease<sup>18</sup>. In our study, since data regarding vaccination status was not available, the milder clinical course may have been caused not only by mutations but also by immunity. The data provided by the Republic of Türkiye Ministry of Health show that the first dose of vaccination rate is as high as 93.20% and the second dose rate is as high as 85.51% (as of June 15, 2022)<sup>19</sup>. Although these rates are not directly applicable to this study’s patient population, they can still be generalized for our results too.

## CONCLUSIONS

This study compared the clinical features of wild-type SARS-CoV-2 and the Omicron variants to investigate the clinical effect of mutations and revealed that Omicron tended to infect predominantly the upper respiratory tract, showed decreased lung infectivity, and the disease progressed with a milder clinical course. As a result, this study showed that the tropism of the virus was changed and the viral phenotype was affected. It was also found that SARS-CoV-2 viral load did not predict COVID-19 severity in patients with wild-type SARS-CoV-2.

## AUTHORS’ CONTRIBUTIONS

**FK:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **SA:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **AG:** Formal Analysis. **AEK:** Data curation. **FAEÖ:** Formal Analysis. **YTT:** Data curation. **İOB:** Data curation. **PG:** Data curation. **RSÖ:** Formal Analysis. **BD:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

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