Characterizing the SARS-CoV-2 Omicron variant shedding and duration of RT-PCR and rapid antigen test positivity on vaccinated individuals.

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ABSTRACT

The SARS-CoV-2 Omicron variant has demonstrated increased transmissibility and ability to escape natural and vaccine-induced immunity. We aimed to characterize the duration of Omicron's shedding by comparing viral isolation to rapid antigen test (RAT) and real-time polymerase chain reaction (RT-PCR) positivity. Thus, we performed a cross-sectional study of 30 vaccinated individuals with mild COVID-19 to evaluate the ability to infect Vero cells at day 5, 7, 10 and 14 since symptoms onset. Viral growth was observed in 46% and 20% of respiratory samples at day 5 and 7, respectively, while all were negative from day 10. RAT showed 100% of sensitivity during the first 7 days of symptoms compared to viral isolation, being a better infectivity predictor than RT-PCR Ct values. In conclusion, immunocompetent vaccinated individuals with Omicron infection can still transmit the virus on the 7th day of symptoms. This data may impact decisions on end-isolation protocols for mild COVID-19.

Keywords: SARS-CoV-2, Omicron variant, RT-PCR, viral isolation, antigen rapid test.

INTRODUCTION

A new SARS-CoV-2 variant named *Omicron (B.1.1.529)* was reported in South Africa after an exponential rise in the number of cases of *Coronavirus disease 2019* (COVID-19) in November 2021[1]. The Omicron variant has been quickly designated as a variant of concern (VOC) due to potential high transmissibility and the capacity to escape natural and vaccine-induced immunity compared to Delta variant despite mass immunization programs[2,3,4]. According to preliminary data, Omicron may be over 10 times more transmissible than the ancestral virus and twice as contagious as the Delta variant[5]. In January 2022, Brazil experienced a 40-fold increase in daily cases, compared to December 2021 threatening the public health system[1,6,7].

Vaccine effectiveness, infectivity and transmissibility of the Omicron variant are not well established yet and shedding studies are lacking[3]. In this study, we aimed to characterize the Omicron variant shedding duration by comparing viral isolation, rapid antigen test (RAT) positivity and real-time polymerase chain reaction (RT-PCR) Ct values, in order to provide evidence on end-isolation precautions recommendations.

PATIENTS AND METHODS

Setting

Healthcare workers (HCW) from Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP) and Instituto de Medicina Tropical da Faculdade de Medicina da Universidade de São Paulo (IMT-FMUSP), Brazil, were invited to participate in this study in January 2022. The COVID-19 vaccination campaign with CoronaVac at HC-FMUSP started on January 18, 2021, and the third dose of COVID-19 vaccine started on October 4, 2021.

Study population

We included a convenience sample of 30 previously healthy individuals (28 HCW and two HCW partners) with symptomatic mild COVID-19 who had been immunized with at least two doses of any COVID-19 vaccine.

Study design

This is a cross-sectional study with four time points of respiratory sample collection, on day 5, 7, 10 and 14 since symptom onset. We considered the first day of symptoms as day 1. All participants were diagnosed with COVID-19 by RT-PCR or RAT during the first 5 days of symptoms. At each time point, a nasopharyngeal sample for RAT and combined nasopharyngeal and oropharyngeal samples for RT-PCR and viral isolation were collected in a biosafety level 3 laboratory or self-collected at home. We considered SARS CoV-2 Omicron variant infectivity based on viral isolation results. Viral RNA levels were inferred from the RT-PCR Ct values as inversely proportional results. Demographic and clinical data were obtained using an online questionnaire during the first time point. Participants were contacted by telephone for monitoring the evolution and duration of symptoms.

SARS-CoV-2 RT-PCR

To detect SARS-CoV-2 virus, an automated nucleic acid extraction using, EXTRACTA Kit FAST - DNA and RNA Viral (Loccus) and EXTRACTA 32 Loccus equipment was used according to the manufacturer's instructions. Real-time PCR assay developed by Altona Diagnostics (Hamburg, Germany, 2020) that amplifies the regions of the S gene (SARS-CoV-2 specific gene) and the E gene (gene common to the beta coronavirus strain B group), was performed as previously described[8].

SARS-CoV-2 Rapid Antigen test

The Hotgen Coronavirus (2019-nCoV), which is a rapid chromatographic immunoassay for the detection of SARS-CoV-2 nucleocapsid (N) antigen in respiratory specimens was employed. The test was performed according to the instructions provided by the manufacturer.

SARS-CoV-2 Viral Isolation

To isolate SARS-CoV-2, samples were always subjected to at least three passages in a blind manner in Vero E6 cells (ATCC® CCL-81™) and were inspected daily for cytopathic effect (CPE). SARS-CoV-2-induced CPE was confirmed by RT-PCR of culture supernatant from the third passage. Viral samples were considered isolated when the Ct value has dropped between passages one and three. We considered samples with Ct below 35 suitable for the next isolation passages. A non-isolated sample was considered in which the Ct value has not dropped [9, 10].

SARS CoV-2 Whole genome sequencing (WGS) for Omicron variant identification

The viral RNA extracted as described above, was also used for whole genome sequencing analysis at IMT-FMUSP. SARS-CoV-2 cDNA and multiplex PCR steps were performed and the amplicons were sequenced using

the MinION platform (Oxford Nanopore Technologies, ONT, UK)[11]. Variant calling and consensus sequences were performed using artic minion with Nanopolish version from ARTIC bioinformatics pipeline (https://github.com/artic-network/fieldbioinformatics). Genome regions with a depth of <20-fold were not included in final consensus sequences, and these positions are represented with N characters. Sequences with more than 50x genome coverage were used to lineage classification by the latest Pangolin version V3.1.5 (http://pangolin.cog-uk.io/)[12], Nextclade version 1.4.0 (https://clades.nextstrain.org) and confirmed by manual genotyping. All SARS-CoV-2 viral genomes were uploaded to the GISAID platform (Supplementary table S1).

Data Analysis

Demographic and clinical characteristics were presented as median (interquartile range (IQR)) for continuous parameters and frequency (percentage) for categorical variables. Graphics were generated using GraphPad Prism version 8.3.0. RAT sensitivity and specificity compared to viral isolation was calculated by SPSS software version 17.0. Serial Ct values of individuals were analyzed as a surrogate marker for the viral load. A mean of E gene and S gene Ct values was calculated for each patient at each time point of respiratory sample collection. The group median Ct values were considered for graphics and tables.

Ethical considerations

This study was approved by the Hospital's Ethics Committee (CAAE: 42708721.0.0000.0068). Informed consent was obtained from all study participants for respiratory samples and clinical data collection.

RESULTS

We included 30 participants with mild COVID-19 caused by the Omicron variant between January 11th to 24th, 2022. Half of them were male (53%), mostly of white ethnicity (74%), with a median age of 29,5 (25-36) years (Table 1). All participants had received at least two doses of a COVID-19 vaccine, predominantly CoronaVac (83%). Twenty-six HCW (87%) had received the third dose, mainly BNT162b2, with a median (25th-75thpercentile) interval between the third dose of the vaccine and symptoms onset of 92,5 (72-100) days (Table 1). Ten participants (33%) had previous COVID-19 with a median interval of reinfection of 579 (437 - 601) days. The most prevalent symptoms were coryza (90%), sore throat (83%) and cough (70%), with a median duration of symptoms of 6 (9 - 14,25) days (Table 1). Four participants remained symptomatic with dry cough for 20-32 days (Table 1). All SARS-CoV-2 isolates belong to the Omicron variant sublineage BA.1 or BA.1.1.

The RT-PCR analyses were positive for all samples at day 5 and 7 decreasing to 57% on day 14 (Figure 1; Table 2). RAT has shown positivity in 96%, 83% and 17% of the respiratory samples at day 5, 7 and 10, respectively. After 14 days, RAT results were all negative (Figure 1; Table 2). Viral isolation was positive for 46% and 20% of the samples at day 5 and 7, while negative at day 10 and 14 (Figure 1; Table 2).

Regarding the viral RNA load based on Ct values, our study showed that the highest levels were at day 5, with a median Ct value of 17 (18-22) and decreased progressively over time until day 14 (Figure 2). In addition, 16 patients were diagnosed by RT-PCR during the 2-4 days of symptoms at our laboratory, six of them presented lower Ct values at diagnosis varying from 12 to 16. In relation to the other 14 patients, seven were diagnosed by RAT, four by an external RT-PCR and five of them were diagnosed at day 5.

Seven participants (23%), four at day 7 and three at day 10, experienced a substantial decrease in the Ct values ≤21, however, only one of them had a positive viral isolation test at day 7 (Figure 3). Reinfection was ruled out by WGS confirming the same Omicron sublineage and with a subsequent increase in the Ct value and symptoms improvement at day 14. Curiously, one of these cases had a higher Ct value and a negative rapid antigen test at day 5 matching with a negative viral isolation, evolving with lower Ct value and positivity of the RAT and viral isolation on day 7. (Supplementary table 2).

At day 5, 83% of the respiratory samples had a Ct value <25 and only 46% were isolated. At day 7, 100% of the samples were positive with a Ct<30 and 80% of them had a Ct value <25 (Table 2). The median duration of viral shedding was 5 (5-7) days, taking in consideration only 17 samples from 14 participants isolated between day 5 and 7. The other 16 respiratory samples were not isolated along the study period. The SARS CoV-2 Omicron variant was isolated at day 5 with median Ct value of 17 (16-19) with 21 as the highest Ct value. Viral isolation at day 7 was positive with a median Ct value of 21 (20-22) with 24 as the highest Ct value (Figure 2).

The RAT analysis showed 100% of sensitivity and, a specificity of 20% for predicting the SARS-CoV-2 Omicron variant infectivity compared to viral isolation at day 7 of symptoms. All vaccinated individuals with a positive viral isolation also had a positive RAT. RAT positive samples had a median Ct value of 18 (17-24) and 22 (20-23) at day 5 and 7, respectively. In both cases, the highest Ct value was 25. At day 10, positive RAT samples presented a median Ct value of 24 (24-29) with the highest Ct value of 26.

On day 5, SARS-CoV-2 was isolated in 11 of 24 vaccinated persons, all having a positive RAT and RT-PCR with a median Ct value of 17 (17-20) and the highest Ct value of 21. At day 7, viral isolation and RAT positive samples had a median Ct value of 21 (20-22) with the highest Ct value of 24 (Figure 1 and 2).

Viral RNA remained detectable in 97% and 57% of the cases at days 10 and 14, respectively. At day 10, 28% of the vaccinated persons had a Ct value <25. However, no infectious SARS-CoV-2 virus was detected from the day 10 of symptoms (Table 2). RAT evidenced a better correlation with Omicron variant infectivity compared to RT-PCR results (Figure 1 and 2).

DISCUSSION

This is the first study that characterizes the Omicron variant shedding period on healthy vaccinated individuals with mild COVID-19, comparing viral isolation, rapid antigen test positivity and RT-PCR Ct values by days since

the symptom's onset. We observed that almost 50% of the vaccinated individuals' samples were isolated at day 5 with a Ct value ≤ 21 and 20% of the cases had a positive isolation test at day 7 with a Ct value ≤ 24. No infectious virus was detected from day 10 of symptoms, as showed in a preliminary report of 21 japanese Omicron cases[13]. Coincidently, they reported that 50% and almost 20% of patients samples, respectively, were isolated 3 to 6 days and 7 to 9 days since symptoms onset[13]. Our results evidenced that infectivity of patients with Ct > 24 with more than 7 days of symptoms may be low, agreeing with previously described data[14,15].

A review published in 2020 showed that RT-PCR positivity may persist for up to 63 days after symptom onset and appears to outlast symptom resolution. The median duration of detectable viral RNA in mild cases was from 10 to 20 days and up to 31 days for severe cases[16]. Other study of SARS-CoV-2 ancestral virus viability demonstrated that the virus can be cultured until the 7th day of symptoms onset in samples with more than 10^6 copies/mL[15]. A brazilian cohort study of unvaccinated individuals with COVID-19 showed that on the 14th, 21th and 30th day after symptoms onset, 71%, 44% and 16% of patients, respectively, were persistently RT-PCR positive[10]. In addition, the shedding duration was evaluated by viral culture in 51 patients, from whom SARS-CoV-2 was isolated in 27% at day 14 or later, even in cases with a Ct value >32[10].

In contrast, we found that most patients with Omicron infections attained high viral RNA levels at day 5 with a high proportion of them persisting with Ct values <25 at day 7, but this finding did not mean infectiousness. Nearly all RT-PCR positive patients reached Ct ≥ 30 or were RT-PCR negative by day 14, except two cases that exhibited Ct kinetics differences at day 7 or 10. Furthermore, the previous study conducted in Japan reported that almost 60% persisted with a positive RT-PCR up to 10-13 days after symptoms onset and 40% after 14 days[13]. However, persistent RT-PCR positivity and viral shedding differences between Omicron and ancestral virus infections in immunocompetent individuals could be due to the host immunization status with two to three doses of COVID-19 vaccines or to intrinsic characteristics from the Omicron variant.

In our study, seven participants experienced a decrease of Ct values at day 7 and 10 in comparison with day 5. WGS excluded a possible reinfection episode by confirming the same Omicron sublineage and suggesting a possible shedding increase. However, only one sample was isolated and a subsequent increase in the Ct value with symptoms improvement at day 14 was observed. Nevertheless, differences in collection techniques and sample conservation cannot be completely ruled out.

Furthermore, a previous study of 24 ambulatory vaccinated individuals compared Delta variant SARS-CoV-2 infection with non-Delta variant infections, showing that delta variant cases presented higher initial viral load and a longer duration of viral shedding detected by RT-PCR[17]. Additionally, Delta variant viruses could be cultured for up to 10 days of symptoms onset and culturable viruses were more common in delta variant infections (70% vs. 33%)[17]. An American retrospective study of COVID-19 cases studied the Omicron viral dynamics comparing Omicron and Delta variant infections. They observed that Omicron infections had a lower viral RNA peak based on Ct values (23.3 vs. 20.5) compared to Delta cases and the clearance phase was shorter than Delta (5.35 vs. 6.23)[18]. Nonetheless, our study showed higher RNA peaks at day 5 with median Ct values 17 (18-22) and lower

diagnostic Ct values during the first 3 days after symptoms onset varying from 12 to 16 in healthy individuals immunized with 3 doses of COVID-19 vaccine.

Our study shows that RT-PCR Ct values <25 between day 5 and 14 after symptoms onset were not accurate predictors of infectiousness compared with viral isolation positivity and RAT results. In addition, a prior study with ancestral SARS-CoV-2 infection compared the performance between RAT, RT-PCR and viral culture in unvaccinated patients with 0 to 7 days of symptoms. This study exhibited high correlation between RAT results and SARS-CoV-2 viral culture, representing a significant advancement in determining potential transmissibility[19]. Moreover, review studies about SARS-CoV-2 infectivity determinants described that RAT negative results predicted a no longer shedding of viable virus[20]. Thus, we demonstrated that virus isolation by cell culture showed positive correlation with RAT results, showing 100% of sensitivity for predicting Omicron variant shedding during the first 7 days of symptoms. Therefore, RAT seems to be a better infectivity predictor than RT-PCR Ct values and could be used to determine end-isolation timing, mainly in places facing their worst staffing shortage.

Our study has limitations; it is a cross-sectional study with a small sample size. In addition, based on the vaccination status and behavior characteristics of the HCW, this study might not be representative of the general population. Larger cohorts of Omicron cases of the general population are needed to help isolation timing recommendations.

In conclusion, immunocompetent vaccinated individuals infected with the SARS-CoV-2 Omicron variant can still transmit the virus on the 7th day of symptoms, hence are unlikely to shed infectious virus 10 days since the symptom onset. Rapid antigen tests could be used to estimate Omicron´s potential infectivity. This data may impact decisions on end-isolation protocols for mild COVID-19.

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AUTHOR CONTRIBUTIONS

SFC, ASL, ECS and MCMC contributed to project conceptualization and methodology. SFC contributed to the acquisition of the financial support for the project leading to this publication. ALM contributed to research activities execution. ALM, SVN, MFC, CL, JM, LG, JC, and PMT contributed to respiratory samples collection and rapid antigen test performance. AVP, LVB, AR and TRTM contributed with RT-PCR analyses and viral isolation. PAS contributed to the whole genome sequencing and analysis. ALM, SVN, MFC and NS contributed to data analysis and interpretation. ALM, SVN, AVP, MFC, JM, LG, JC, PMT, NS and VF wrote the first draft. All authors revised the final version of the manuscript.

DECLARATION OF COMPETING INTERESTS

The authors declare no competing interests.

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TABLES

Table 1. Demographic and clinical characteristics of the 30 participants with mild COVID-19 by Omicron variant.

Characteristic	N (%) or n (IQR)
Age (years)	29,5 (25-36)
Male	16 (53)
Ethnicity	
White	22 (74)
Mixed-race	6 (20)
Asian	1 (3)
Black	1 (3)
Type of COVID-19 vaccine of the first two doses	
CoronaVac	25 (83)
ChAdOx1	3 (10)
BNT162b2	1 (3)
Spikevax	1 (3)

Days between 2nd dose of COVID-19 vaccine and Omicron infection	326,5 (284 -333)
Had received three doses of COVID-19 vaccine	26 (87)
BNT162b2	23 (92)
ChAdOx1	1 (4)
CoronaVac	1 (4)
Days between 3rd dose of COVID-19 vaccine and Omicron infection.	92,5 (72-100)
Symptoms	
Coryza/Nasal congestion	27 (90)
Sore throat	25 (83)
Cough	21 (70)
Headache	17 (57)
Myalgia	16 (53)
Fatigue	15 (50)
Weakness	13 (43)
Fever	12 (40)

Smell and taste disorder	2 (7)
Symptoms duration (days)	9,5 (6 - 14,25)
Previous Covid-19	10 (33)
Days between previous Covid-19 and Omicron infection	579 (437 - 601)

Table 2. Omicron's variant shedding comparing SARS-CoV-2 Viral isolation to rapid antigen test (RAT) and real-time polymerase chain reaction (RT-PCR) positivity and Ct values.

Days of symptoms	Viral isolation positivity N (%)	RAT positivity N(%)	RT-PCR positivity N(%)	Number of positive RT-PCR isolates with Ct <30 N (%)	Number of positive RT-PCR isolates with Ct <25 N (%)
5	11/24 (46)[a]	23/24 (96)[a]	24/24 (100)[a]	24/24 (100)[a]	20/24 (83)[a]
7	6/30 (20)	25/30 (83)	30/30 (100)	30/30 (100)	24/30 (80)
10	0/30 (0)	5/30 (17)	29/30 (97)	23/29 (79)	8/29 (28)
14-15	0/30 (0)	0/30 (0)	17/30 (57)	2/17 (12)	1/17 (6)

[a] Six participants were included from day 7.

FIGURES

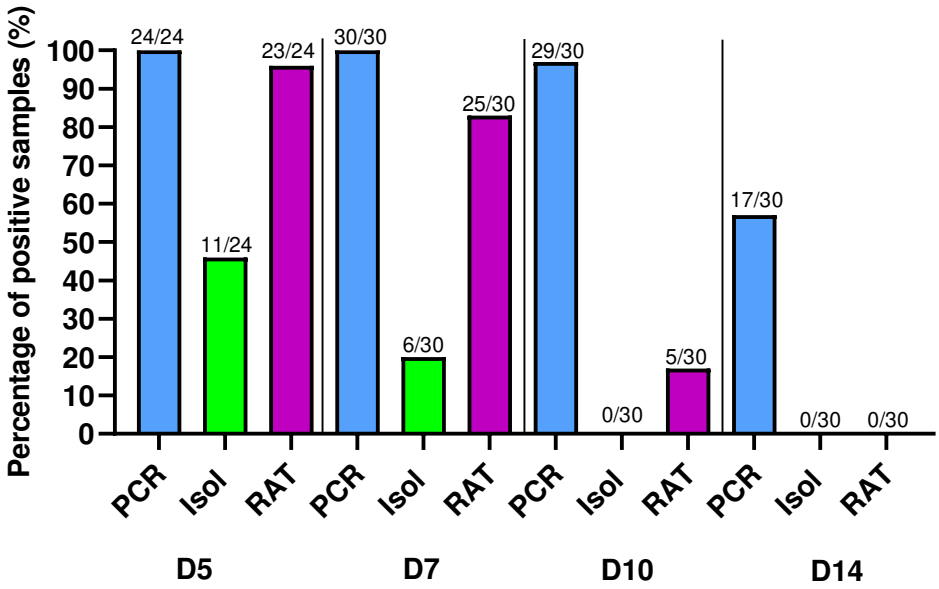

Figure 1. SARS-CoV-2 RT-PCR, rapid antigen test and virus isolation percentage of positive respiratory samples by days since symptoms onset. Six participants were included from day 7. The number of positive samples is represented at the top of the bars. (PCR: real-time polymerase chain reaction, RAT: rapid antigen test, Isol: Viral isolation)

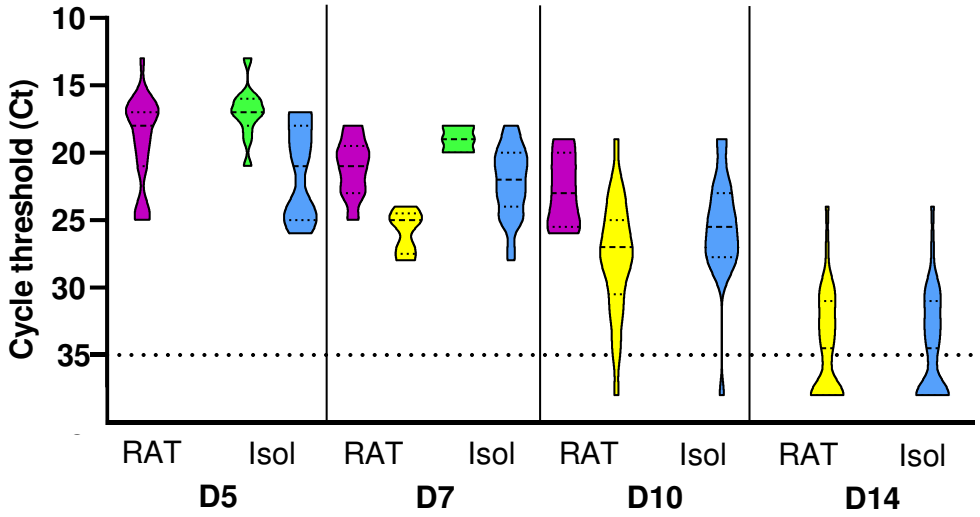

Figure 2. Kinetics of RNA levels in respiratory samples of Omicron cases comparing the rapid antigen test and viral isolation results by days since symptoms onset. A mean Ct value of the E and S genes was considered. RAT positive results are presented in purple and negative results in yellow. Viral isolation positive results are presented in green and negative results in blue. Dashed lines represent the RT-PCR detection limit. Results below the dashed lines were considered not detectable by RT-PCR. (RAT: rapid antigen test, Isol: Viral isolation).

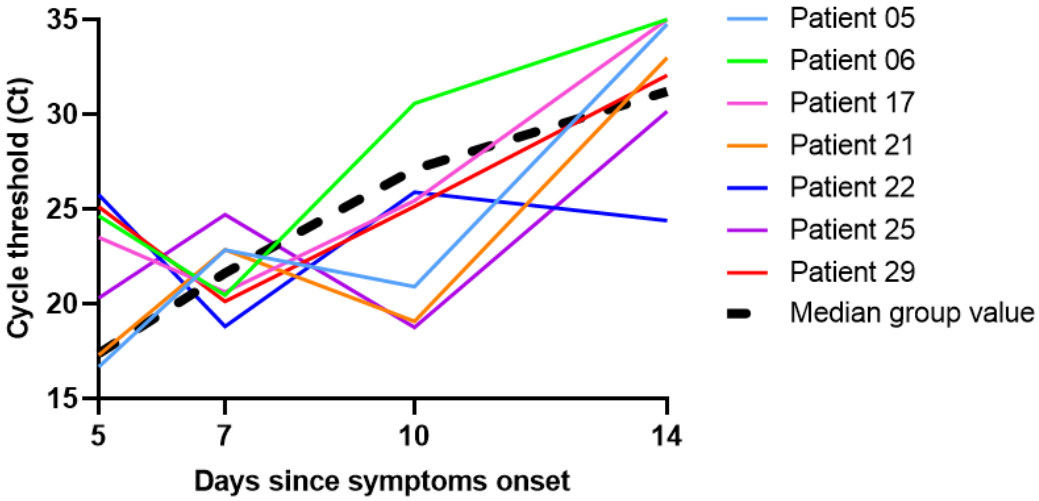

Figure 3. Kinetics of Viral RNA levels of seven participants. Variation of Ct values from seven participants (colored lines) presenting a decrease in the Ct at day 7 or 10 in comparison with the median values (dashed black) of the other 24 individuals.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytables.pdf