Duration of viral shedding in patients with COVID-19 and the redetectable positive cases with SARS-CoV-2: A hospital experience

A A. Al Qahtani¹, A M Bin Rasheed², A Al Abood³, Mohie E. Selim¹,³, A K Al Khalifah¹, A. Aurkmany², A Al-Odayani⁴, M C Te¹

¹Preventive Medicine Division, Prince Sultan Military Medical City, Riyadh, KSA (PSMMC), ²Family and Community Medicine Administration, PSMMC, ³Department of Public Health and Community Medicine, Faculty of Medicine, Assiut University, Assiut, ⁴Infection Prevention and Control Department, PSMMC, Egypt

ABSTRACT

Background: The study aimed to estimate the duration of viral shedding (DVS) in patients with confirmed coronavirus disease 2019 (COVID-19), investigated the factors affecting that duration, and identified the redetectable positive (RP) cases in the recovered COVID-19 patients in Prince Sultan Military Medical City (PSMMC). Methods: The study was a retrospective record base design in the PSMMC that included 171 confirmed COVID-19 patients from 15 March to 31 May 2020. Their clinical characteristics and laboratory findings were retrieved and reviewed based on the PSMMC COVID-19 database and the Ministry of Health (MOH) Health Electronic Surveillance Network. Data analysis used the SPSS software package to measure the DVS, explore its potential factors, and identify the RP cases. The data presented as frequency distribution tables, medians, and interquartile range (IQR). Mann–Whitney U and Kruskal–Wallis tests compared the medians to explore the significant variables that affect DVS. Results: The median DVS was 11 days, IQR was 7 to 15 days, and statistically significant longer the patient presented with fever (P = 0.025), among health care workers (HCWs) (P = 0.020), and the age group above 65 (P = 0.039). Overall, 13 patients (7.6%) were RP, statistically significantly higher among the contacts to confirmed COVID-19 cases. Conclusions: The DVS in PSMMC COVID-19 patients is comparable to the isolation period approved by MOH. Fever was a risk factor for a prolonged DVS, advised an extended follow-up period for these patients. RP cases were significantly higher among the contacts to COVID-19 cases than non-contacts. The study suggests future comprehensive research on the RP characteristics.

Keywords: COVID-19, duration of viral shedding, KSA, redetectable positive

Introduction

The COVID-19, a pandemic of the 21st century caused by novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated from China and shallowed world economy and human resources.[¹] It signifies a worldwide medical concern because of progressively increasing reported numbers globally, and all countries worldwide are affected. On the 2nd of March 2020, the Ministry of Health (MOH) in Saudi Arabia (KSA) confirmed the first case of COVID-19. Since then, the KSA has applied strict measures to contain the outbreak, such as establishing nationwide population movement restrictions, placing on inbound Umrah pilgrimage, and placing a ban on arriving travel from COVID-19-affected countries. [²]

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The duration of viral shedding (DVS) of SARS-CoV-2 mainly determines the disease transmission and the infectivity period, so it is used to define the appropriate period of patient isolation.\(^\text{[8]}\)

During a pandemic, primary care physicians provide care in the community to an increasing number of patients and immediately adopt infection prevention and control measures.\(^\text{[7,8]}\) Therefore, faced with this situation, proposed the duration of COVID-19 viral shedding and redetectable positive (RP) cases study.

The DVS is the time from the onset of the symptoms until the successive negative real time reverse transcription polymerase chain reaction (RT-PCR) test result.\(^\text{[9]}\) Thus, it is crucial to explore the DVS and its associated factors among confirmed COVID-19 patients.

During the follow-up of COVID patients, many studies reported that some patients RP after confirming their cure with negative swabs.\(^\text{[10,11]}\) Individuals with RP among recovered COVID-19 patients have been raised a public health concern. The causes of RP remain controversial under investigations by many studies,\(^\text{[12,13]}\) suggesting follow-up on RP patients to monitor their health status and exclude their infectivity.\(^\text{[14,15]}\) So, this study aims to estimate the DVS, describe the associated characteristics that affect that duration, and recognize the RP cases among recovered COVID-19 patients in prince sultan military medical city (PSMMC).

**Methods**

**Study design, study population, and setting**

This study was a retrospective, records-based study at PSMMC in Riyadh, including the 171 COVID-19 patients who attended the PSMMC from March 15 to May 31, 2020.

Since this time, that KSA became a part of the worldwide pandemic of COVID-19, PSMMC, a leading military medical city in KSA, JCI and SBAHI accredited, has activated a COVID-19 preparedness and response plan; coordinates communications, surveillance, resource allocation, and educational activities to prevent and control possible COVID-19 events. All confirmed COVID-19 positive based on the guidelines of specimen collection and shipment of SARS-CoV-2, handling of laboratory specimens of suspected COVID-19 patients, released by the MOH in KSA.\(^\text{[16]}\) The Central Research Ethics Committee of the PSMMC approved the study. The total study population was 1415 confirmed COVID-19 patients, including 125 health care workers (HCWs) and 1290 NHCWs attended the PSMMC from March 15 to May 31, 2020. The research team reviewed the PSMMC laboratory data of all the positive COVID-19 patients’ and compared it with the results of the MOH Reference Laboratory on Health Electronic Surveillance Network (HESN), then finally selected 171 patients according to the following inclusion criteria; First, had a confirmed positive nasopharyngeal swab by RT-PCR. Second, had at least one consecutive negative RT-PCR test result confirming the patient’s cure within 14 days after the first positive RT-PCR result; Third, patients aged more than 18 years old.

**Data collection**

The team retrieved the sociodemographic, clinical, and laboratory data of the selected 171 patients from the PSMMC COVID-19 database and the HESN program. The primary care physician did the series of RT-PCR as per MOH, KSA guidelines for follow-up, recovery, and resolution of viral shedding.\(^\text{[17]}\)

“Viral shedding” is a term used to describe a virus is released from an infected host. The DVS in this study was calculated based on the records as the number of days from the first confirmed positive RT-PCR to the date of the first confirmed negative RT-PCR. The RP referred to patients who had no respiratory symptoms, respiratory tract samples were reexamined after cure or discharge, and the RT-PCR test was positive again.\(^\text{[17]}\)

The research team collected the related DVS, the RP cases, and sociodemographic data in an excel data sheet, then imported it to SPSS 24 (Statistical Package for the Social Sciences).

**Statistical analysis**

Data analysis using SPSS software presented the results as frequency and percentages for qualitative variables; median and the interquartile range (IQR) for quantitative variables. Mann–Whitney U test was used to compare medians of the two qualitative variables; Kruskal–Wallis compared medians between more than two quantitative variables. Kaplan–Meier survival analysis to compare the survival distribution of DVS among the significant factors.

**Results**

Table 1 shows the test result for the DVS distribution that does not follow a normal distribution confirmed by Kolmogorov–Smirnova, and Shapiro–Wilks’s significant statistical results \((P = 0.000)\).

Table 2 presents the frequency distribution of the epidemiological and sociodemographic characteristics of the COVID-19 patients. The mean DVS was 11.96 days, and the median was 11 days; IQR was 7–15 days. The shortest observed period of viral shedding was 2 days, whereas the longest one was 46 days with a range of 44 days. The mean patients’ age was 37.7 years, the median age was 35, IQR was 26 to 48, and the age range was 75 (18 to 93) in years. Males were 58.5%, Saudi nationality was 80.7%, current

| Table 1: Normality tests of the distribution of viral shedding duration of 171 COVID-19 patients in PSMMC |
|---------------------------------|-------------|-----------|-----------------|-------------|
| Tests of Normality             | Kolmogorov–Smirnov | Shapiro–Wilks |
|--------------------------------|-------------------|-----------------|-----------------|-------------|
| Statistic                      | df                | Sig.            | Statistic        | df         | Sig.     |
|--------------------------------|-------------------|-----------------|-----------------|-------------|
| Duration viral shedding        | .138              | 171              | .000            | .887       | 171.000  |

*\(^\text{a}\)Effect size significance correction*
job HCWs were 43.3%, the clinical presentation with fever was 21.1%, contacts to a confirmed positive case were 57.3%, and the patients under home isolation was 97.1%. [Table 3] displays the Mann–Whitney U test results that compare the medians of DVS between the different sociodemographic characteristics. It finds a statistically significant longer median DVS among HCWs in comparison to non-HCWs (14 vs 10, \(P = 0.020\)), patients aged below 65 in contrast, to above 65 years (11 vs 7, \(P = 0.039\)), and patients presented with fever compared with afebrile patients (13 vs 10, \(P = 0.025\)). However, there was no statistically significant difference in the DVS between males and females, symptomatic cases with cough, shortness of breath, or other symptoms. [Table 4] presents the result of Kruskal–Wallis, which indicated a statistically significant difference in median DVS between different nationalities. The non-Saudi, Non-Filipino group had a longer median of viral shedding (\(P = 0.055\); meanwhile, the occupation category and a risk factor for COVID-19 had no significant difference. [Table 5] illustrates the frequency distribution of the RP cases; the total cases were 13 patients, representing a rate of 7.6% of RP cases among confirmed COVID-19 patients during the study period. The median DVS among RP cases was 8.9 days. The median period for redetection of RP cases (from the first negative RT-PCR to the second positive RT-PCR) was 9.7 days. The median duration between the first positive RT-PCR and the positive follow-up RT-PCR after the patient clearance as negative was 18.6 days. The rate of RP cases was statistically significantly higher among the contacts to confirmed COVID-19 cases than among not contact to confirmed cases (92.3% vs 7.7%, \(P = 0.013\)). There were no significant differences in RP rates based on gender, nationality, job, current occupation, or clinical presentations. Figure 1 demonstrates the Kaplan–Meier survival (time to event) test, which finds a statistically significantly longer DVS in patients presented with fever than those who were afebrile \(P = 0.047\).

### Discussion

Many studies defined the DVS as the time between the onset of COVID-19 symptoms up to the first negative RT-PCR. However, in this study, the DVS was measured starting from the first positive RT-PCR to the date of the first successive negative RT-PCR as most patients were outpatients, and 56.7% of patients were asymptomatic.

This study aimed to measure the DVS of 171 confirmed COVID-19 patients and investigate the factors that affect this period. The results revealed a skewed distribution of the DVS,
the median DVS was 11 days, IQR was 7 to 15 days. These findings were comparable with a retrospective cohort study results included 101 patients in Beijing with a median DVS of 11 days, IQR, 8 to 14.3 days.[21] Among other studies, patients with mild COVID-19, where the DVS was 8 days.[9]

Other studies’ findings were relatively more extended DVS than the current study result, like in Guangdong, China, where the median DVS in COVID-19 outpatients was 15 days.[22] Also, in Changsha, China, the median DVS was 17 days, IQR, 12 to 21 days.[9] In addition, in another study where the median DVS was 20.0 days, IQR, 17.0 to 24.0 days.[19]

Another study has shown that PCR test results remain positive for an extended period, up to 40 days or more in some cases.[23] The variations in DVS may be due to different operational definitions of DVS and the variabilities within clinical presentation between various studies. In this study, more than half of patients presented with mild clinical manifestations as contacted positive index patients in our study and 56.7% were non-symptomatic diagnosed by active surveillance, and 97.1% were outpatients under home isolation.

In univariate analysis, the current results showed that patients with fever had a significantly longer DVS. This finding was consistent with the findings that fever, corticosteroid therapy, and time from onset to hospitalization were associated with increased odds of prolonged DVS.[21] Current results did not find the age as a significant predictor for long DVS; this was in line with the conclusion that age on

| Characteristics | n  | Median | Inter quartile rang | Z     | Sig. (2-tailed) |
|-----------------|----|--------|---------------------|-------|----------------|
| Gender          |    |        |                     |       |                |
| Male            | 100| 10.50  | 7.00                | 14.00 | −.342          | .732  |
| Female          | 71 | 11.00  | 7.00                | 17.00 | −2.321         | .020  |
| Current Job     |    |        |                     |       |                |
| HCW             | 41 | 14.00  | 7.50                | 20.00 | −.573          | .567  |
| NHWCW           | 130| 10.00  | 6.75                | 14.00 | −.338          | .735  |
| Clinical Presentations | | | | | |
| Asymptomatic    | 97 | 10.00  | 7.00                | 14.00 | −2.067         | .039  |
| Symptomatic     | 74 | 11.00  | 7.00                | 16.25 |               |       |
| Age groups      |    |        |                     |       |                |
| <65 years       | 156| 11.00  | 7.25                | 15.00 | −2.247         | .025  |
| ≥65 years       | 15 | 7.00   | 6.00                | 13.00 |               |       |
| Sign and symptoms| | | | | |
| Fever           | 36 | 13.00  | 9.00                | 18.0  | −2.247         | .025  |
| No Fever        | 135| 10.00  | 7.00                | 14.00 | −.873          | .383  |
| Cough           | 41 | 12.00  | 7.00                | 18.00 | −.338          | .735  |
| No Cough        | 130| 10.00  | 7.00                | 14.00 |               |       |
| Shortness of Breath | 24 | 11.00  | 6.00                | 14.00 | −2.007         | .039  |
| No Shortness of Breath | 147| 10.00  | 7.00                | 15.00 |               |       |

Table 3: Comparison of the Median DVS by Mann-Whitney U test according the sociodemographic characteristics, sign and symptoms of 171 confirmed COVID-19 patients in PSMMC

| Characteristics | n  | Median | Inter quartile rang | Kruskal-Wallis H | df | Sig. |
|-----------------|----|--------|---------------------|------------------|----|------|
| Nationality     |    |        |                     |                  |    |      |
| Saudi           | 138| 10.00  | 7.00                | 14.00            | 10.523| 2   | .005 |
| Filipino        | 12 | 7.00   | 6.00                | 13.75            |     |      |
| Others          | 21 | 14.00  | 11.00               | 19.50            |     |      |
| Occupation Category |     | | | | |
| Medical Occupation | 46 | 13.50  | 7.00                | 19.25            | 5.266| 2   | .072 |
| Non-medical     | 106| 10.00  | 7.00                | 14.00            |     |      |
| No Job          | 19 | 10.00  | 5.00                | 13.00            |     |      |
| Risk Factors for COVID-19 | | | | | |
| Contact         | 98 | 10.00  | 7.00                | 14.25            | .194| 2   | .907 |
| No link         | 68 | 11.00  | 7.00                | 15.50            |     |      |
| Travel          | 5  | 10.00  | 4.50                | 20.00            |     |      |

Table 4: Comparison of the Median DVS by Kruskal-Wallis Test according the sociodemographic characteristics of 171 confirmed COVID-19 patients in PSMMC
Information about DVS and the associated factors had a significant clinical implication that allows public health officials to determine the appropriate period of isolation and help clinicians identify patients with expected prolonged viral shedding.

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**Table 5: Characteristics of RP cases out of 171 confirmed COVID-19 patients in PSMMC**

| Characteristics                        | Frequency of confirmed COVID-19 cases | RP Frequency (No.) | RP Percentage | Chi Square | P     |
|----------------------------------------|--------------------------------------|--------------------|---------------|------------|-------|
| Gender                                 |                                      |                    |               |            |       |
| Male                                   | 100                                  | 6                  | 46.2          | 0.385974   |       |
| Females                                | 71                                   | 7                  | 53.8          |            |       |
| Nationality                            |                                      |                    |               |            |       |
| Saudi                                  | 138                                  | 11                 | 84.6          | 0.728800   |       |
| Non-Saudi                              | 33                                   | 2                  | 15.4          |            |       |
| Current Job                            |                                      |                    |               |            |       |
| HCWs                                   | 41                                   | 3                  | 23.1          | 0.941557   |       |
| NHCWs                                  | 130                                  | 10                 | 76.9          |            |       |
| Occupation Category                    |                                      |                    |               |            |       |
| Medical                                | 46                                   | 3                  | 23.1          | 0.763665   |       |
| Non-medical, No Job                    | 125                                  | 10                 | 76.9          |            |       |
| Clinical Presentation                  |                                      |                    |               |            |       |
| Symptomatic                            | 74                                   | 6                  | 46.2          | 0.840024   |       |
| Asymptomatic                           | 97                                   | 7                  | 53.8          |            |       |
| Risk Factors for COVID-19              |                                      |                    |               |            |       |
| Contact to a confirmed positive case   | 98                                   | 12                 | 92.3          | 0.013106   |       |
| Not contact to a confirmed positive case| 73                                  | 1                  | 7.7           |            |       |
| Signs and Symptoms                     |                                      |                    |               |            |       |
| No Fever                               | 135                                  | 10                 | 76.9          |            |       |
| Yes Fever                              | 36                                   | 3                  | 23.1          | 0.863311   |       |
| No Cough                               | 41                                   | 2                  | 15.4          | 0.480366   |       |
| Yes Cough                              | 130                                  | 11                 | 84.6          |            |       |
| No Shortness of Breath                 | 24                                   | 2                  | 15.4          | 0.892879   |       |
| Yes Shortness of Breath                | 147                                  | 11                 | 84.6          |            |       |

The rate of RP among the COVID-19 confirmed patients = 13/171 = 7.6%

Median DVS among RP cases = 8.9 days
Median period for redetection of RP cases = 9.7 days
Median period between the first positive PCR and the positive follow-up PCR after the patient clearance = 18.6 days

The current findings showed that RP percentage among COVID-19 patients during the study period was 7.6%, close with a study in Wuhan, China reported 7.4% of patients were RP, 7.6% in a follow-up study by Wu New 20-21 and but higher than the 3% that said in other studies.

The rate of RP cases was statistically significantly higher among the contacts to COVID-19 cases than non-contacts. This finding may justify the need for follow-up among the patients who are contacts to the positive index cases; however, there are a limited proportion of recovered patients.
There are many possible causes of RP, as reinfection, sampling, insufficient use of antiviral drugs during hospitalization, the patient’s course and condition, and the patient’s immune system. Still, no one factor can fully explain this phenomenon.\textsuperscript{[17]}

In the same line, other studies pointed that PR can be attributed to false negatives RT-PCR tests because the lower limit of detection of commercial RT-PCR kits is relatively high.\textsuperscript{[7,13,24]} Also, the sampling quantity can affect detection results and the patient’s immune system.\textsuperscript{[14,25]} Meantime, CDC and the WHO do not recommend using any further testing as the virus culture to establish the infectivity, currently at this stage.\textsuperscript{[16]}

In summary, the median VDS among PSMMC COVID-19 patients was 11 days, agreeing with the recommended period of COVID-19 isolation implemented by the MOH authorities. Patients presented with fever may need a longer follow-up to ensure their viral clearance; the rate of RP cases was 7.6\% of the COVID-19 patients, close to many published studies and statistically significantly higher among the contacts to COVID-19 cases than non-contacts. The researchers recommended planning for future comprehensive research on the RP cases.

The take-home message from this manuscript
The important take-home message is that a prolonged DVS in patients with COVID-19 was associated with symptomatic infection.

The new knowledge emerging from this manuscript
The new knowledge may be the RP among recovered COVID-19 is significantly higher among contacts to confirmed cases than the non-contact.

Study Limitations
Many factors limited the study; First, the retrospective study design lacked data about the date of start symptoms before the laboratory COVID-19 confirmation. Second, the date of start symptoms was not applicable for non-symptomatic contact cases. Third, MOH, KSA guidelines for follow-up, recovery, and resolution of viral shedding had frequently updated the number and timing of the follow-up of negative swabs. At the beginning of the COVID-19 pandemic, retesting was required periodically, every 72 h after each positive swab or after a patient is clinically recovered. Patient recovery is considered after two negative samples 24 h apart. Afterward, MOH has modified to be non-periodic PCR nasopharyngeal swabs with only one negative swab.

Medical ethical approval
All patient samples and data used in this study were collected in the context of routine clinical patient care. The Institutional Review Board and the Central Research Ethics Committee of the PSMMC approved the study (Project No. 2020-011). All the identifying information was replaced with codes, and the data was accessible only to the research team.

Abbreviations
COVID-19, Novel Coronavirus Diseases Coronavirus Disease of 2019; DVS, Duration of Viral Shedding; HCWs, Health Care Workers; IQR, Interquartile range; SA, Kingdom of Saudi Arabia; PSMMC, Prince Sultan Military Medical City; RP, Redetectable positive; RT-PCR, Real-time reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

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Conflicts of interest
There are no conflicts of interest.

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