Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: a retrospective cohort study

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ABSTRACT

Objectives: To investigate factors associated with the duration of viral shedding in patients with COVID-19, outside of Wuhan.
Methods: In this retrospective cohort study, patients with laboratory-confirmed COVID-19 in Changsha, China were included. Clinical characteristics, laboratory findings, treatment, and outcome were retrieved. Univariate and multivariate analyses were performed to explore potential factors.
Results: Overall, 147 patients with COVID-19 were included. The median duration of viral shedding (the number of days from symptoms onset until the successive negative detection of SARS-CoV-2 RNA) was 17 days (interquartile range [IQR], 12–21). Multivariate Logistic regression analysis indicated that the highest temperature at admission (odds ratio [OR], 5.200; 95% confidence interval [CI]: 1.190–22.726; $p = 0.028$), time from symptom onset to admission (OR, 1.740; 95% CI: 1.296–2.337; $p < 0.001$) and hospital length of stay (OR, 1.604; 95% CI: 1.262–2.040; $p < 0.001$) were risk factors for prolonged duration of viral shedding.
Conclusions: This study, with a relatively large sample size, focused on the duration of viral shedding and related factors in patients with COVID-19, outside of Wuhan, China. Potential risk factors were identified and should be taken into consideration for the strategy of quarantining infected patients.

Introduction

The December 2019 outbreak of COVID-19 in Wuhan, China, has become a public health emergency of international concern (PHEIC) due to human-to-human transmission (Arshad Ali et al., 2020). As of May 11th, 2020, 84,450 cases have been diagnosed with COVID-19 in China, and 4644 deaths have been confirmed. New cases of COVID-19 in China have been declining due to strict and efficient measures launched by the government. At the same time, countries outside of China including Italy, United States, Iran, and South Korea, have been greatly affected by COVID-19 with an increasing number of confirmed cases (McBryde, 2020; Remuzzi and Remuzzi, 2020; Tanne, 2020).

Most patients with COVID-19 have mild clinical symptoms, while a small portion of them develop severe complications including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and multiple organ dysfunction syndrome (MODS), which usually lead to a worse prognosis (Chen et al., 2020; Xu et al., 2020b; Yang et al., 2020b; Zhou et al., 2020). It was reported that the mortality of adults with COVID-19 in Wuhan was associated with older age, high sequential organ failure assessment (SOFA) score, and d-dimer more than 1 μg/L (Zhou et al., 2020). Of interest, the mortality rate of COVID-19 outside Wuhan was much lower than that of patients in Wuhan (Tian et al., 2020; Yang et al., 2020a; Zhou et al., 2020).

Changsha is the capital of Hunan province, with a permanent population of 8.15 million. Hunan province is adjacent to Hubei province, and Changsha is only 300 km from Wuhan as the crow flies. The geographic proximity may allow easier transmission of COVID-19 with the cumulative confirmed cases of 242 in Changsha by March 14th, 2020. The majority of current published studies are concerned with Wuhan in Hubei province, China, while few shed light on patients with COVID-19 in neighboring cities (Chen et al., 2020; Ruan et al., 2020; Shi et al., 2020; Wang et al., 2020; Yang et al., 2020b; Zhang et al., 2020; Zhou et al., 2020).

The duration of viral shedding is a potential indicator concerning the infectivity and transmissibility of epidemic diseases (Ryoo et al., 2013); it is also one of the significant criteria for discharge (Zhou et al., 2020). However, the duration of viral shedding in adults with COVID-19 outside Wuhan hasn't been well explored. Therefore, utilizing the data of patients with COVID-19 from Changsha public health treatment center, the aims of this study were to describe the clinical characteristics of patients with COVID-19 in Changsha and analyze the factors associated with the duration of viral shedding.

Methods

Study design and population

This retrospective, single-center cohort study included patients with COVID-19 from Changsha's public health treatment center, the branch of the first hospital of Changsha that is the only appointed medical institution for the treatment of patients with COVID-19 in Changsha. Patients were diagnosed with COVID-19 based on the guidelines released by the National Health Commission of the People's Republic of China (Lin, 2020). This study was conducted following the Declaration of Helsinki. The study was approved by the institutional research ethics committee of the Second Xiangya Hospital (No.2020[017]). Due to this emergency public health event, written informed consents were waived and patients included in this study gave their oral consents.

From January 24th to March 8th, 2020, all patients diagnosed with COVID-19 in Changsha public health treatment center were screened. The specific inclusive criteria were as follows:

1) patients confirmed by positive detection of SARS-CoV-2 RNA from nasopharyngeal/throat swabs by real-time reverse transcription-polymerase chain reaction (RT-PCR);
2) patients aged more than 18 years old;
3) patients with a known date of performing different RT-PCR assays.

Data collection

Demographic and clinical characteristics, laboratory findings, radiography, treatment, and outcomes were retrieved from the electronic medical records. Exposure history was defined as having exposure to people diagnosed with COVID-19. The confirmation of COVID-19 was based on RT-PCR assays from different institutions, including Changsha public health treatment center and the Chinese center for disease control and prevention (CDC). During hospitalization, an RT-PCR assay was conducted every other day after the remission of clinical symptoms or radiography of patients, and the corresponding date was recorded. The duration of viral shedding was defined as the number of days from the onset of the symptoms until the successive negative detection of SARS-CoV-2 RNA, which was consistent with other studies of COVID-19 (Xu et al., 2020a; Zhou et al., 2020). Fever was defined as an axillary temperature ≥37.3°C. The clinical classification of COVID-19 was based on the guidelines

(Lin, 2020). The moderate type was defined as a patient with fever, respiratory tract symptoms, and imaging characteristics of confirmed pneumonia. The severe type was defined as patients with any of these conditions, including respiratory distress (respiratory rate ≥ 30 times/min), fingertip oxygen saturation ≤93% in the resting state, and partial pressure of oxygen /fraction of inspired oxygen ≤300 mmHg. The critical type was defined as patients with any of these conditions, including respiratory failure needing mechanical ventilation, shock, and any organ failure needing intensive care unit (ICU) admission. Laboratory examination and radiography of patients with COVID-19 on initial admission were extracted. The discharge criteria were: the absence of fever for over three days, significant remission of respiratory tract symptoms and radiography of lungs, and two continuous negative detections of SARS-CoV-2 RNA from nasopharyngeal/throat swabs by RT-PCR in a time interval of over 24 h.

All data extraction was conducted independently by two researchers; another researcher was invited to check if there was any discrepancy between the first two researchers. Patients in this study were followed until March 19th, 2020.

RT-PCR for SARS-CoV-2 detection

The primers and probes were designed to target ORF1ab and N genes based on the Chinese CDC guidelines. The cycle threshold (Ct) value is a quantitative indicator of viral load (Young et al., 2020). The Ct value of ORF1ab less than 40 was considered as the positive test results in this study.

Statistical analysis

Continuous variables were presented as the median and IQR. Categorical variables were described as frequency and percentage. Kaplan-Meier survival analysis was introduced to estimate the cumulative SARS-CoV-2 RNA-negativity rate. Patients were divided into two separate groups based on the median duration of viral shedding for all patients. The Mann-Whitney U test was introduced to compare the differences between two groups for quantitative variables. We also conducted Pearson's chi-square test and Fisher's exact test for categorical variables, to assess different characteristics of the two groups. Multivariate logistic regression was applied to determine potential factors associated with the duration of viral shedding. The Receiver Operating Characteristic (ROC) curve was introduced to evaluate the multivariate logistic regression model's potential. The corresponding area under the curve (AUC) was also calculated. All statistical analyses were conducted utilizing SPSS version 24 for Windows (IBM, Armonk, New York, USA). The figure illustrating the dynamics of the viral load in patients since the onset of symptoms was generated by GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). A two-sided P < 0.05 was defined as statistically significant.

Results

Demographic and clinical characteristics of patients

A total of 164 patients with laboratory-confirmed COVID-19 in the Changsha public health treatment center were screened. There was no data concerning the duration of viral shedding in 15 patients and two patients were under 18 years old. Finally, a total of 147 patients were included in the current study. The demographic and clinical characteristics of these 147 patients are presented in Table 1. The median age was 42 years old (IQR, 35–54), the percentage of females (54%, 80/147) was slightly higher than that of males (46%, 67/147), and the median body mass index (BMI) was 23.2 (IQR, 21.3–25.6). Seventy-three patients had been exposed to people diagnosed with COVID-19 before admission; patients

Table 1
Demographic and clinical characteristics of patients with COVID-19.

| Characteristics | All patients (n = 147) | Duration of viral shedding[a] | | p value |
		>17 days (n = 65)	≤17 days (n = 82)	
Age, years				
Median (IQR)	42.0 (35.0–54.0)	45.0 (37.5–59.5)	41.0 (32.5–50.0)	0.093
Range	19.0–81.0	19.0–78.0	21.0–81.0	
Sex				
Female	80 (54%)	40 (62%)	40 (49%)	0.123
Male	67 (46%)	25 (39%)	42 (51%)	
Comorbidity				
Hypertension	18 (12%)	9 (14%)	9 (11%)	0.573
Diabetes	6 (4%)	3 (5%)	3 (4%)	1.000
Signs and symptoms				
Fever	115 (78%)	55 (85%)	60 (73%)	0.095
Cough	122 (83%)	58 (89%)	64 (78%)	0.073
Expectoration	63 (43%)	34 (52%)	29 (35%)	0.039
Hemoptysis	5 (3%)	5 (8%)	0	0.015
Highest temperature (°C)[b]				
Median (IQR)	38.3 (37.9–38.5)	38.3 (38.0–38.8)	38.0 (37.8–38.5)	0.049
Range	37.0–39.7	37.4–39.7	37.0–39.3	
Finger oxygen saturation≤93%	3 (2%)	2 (3%)	1 (1%)	0.582
Time from symptom onset to admission, days				
Median (IQR)	6.0 (3.0–10.0)	8.0 (5.0–13.0)	5.0 (3.0–7.3)	<0.001
Range	1.0–41.0	1.0–30.0	1.0–41.0	
Clinical classification				
Moderate	127 (86%)	54 (83%)	73 (89%)	0.296
Severe	20 (14%)	11 (17%)	9 (11%)	

Abbreviation: COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
[a] The number of days from the symptoms onset till the successive negative detection of SARS-CoV-2 RNA.
[b] Data regarding highest temperature at admission were missing for 10 patients (7%).

associated with a familial cluster made up most of the study population (77%, 113/147). Nearly 20% of patients (30/147) had at least one comorbidity; the most common symptoms included fever (78%, 115/147) and cough (83%, 122/147), but fatigue was also relatively common in the included (42%, 62/147) patients. The median time interval from symptom onset to admission was six days (IQR, 3–10). According to clinical classification guidelines, 127 patients with COVID-19 were categorized into the moderate type, while 14% (20/147) were categorized into the severe type.

The median duration of viral shedding in the current study was 17 days (IQR, 12–21). The shortest and longest durations were six days and 47 days, respectively. The cumulative proportion of patients with detectable SARS-CoV-2 RNA is presented in Table S1 and Fig. S1. It was noted that the percentage declined to 50% about 17 days after symptoms onset. Based on the median as the cut-off point, the study population was further divided into two groups with a duration of viral shedding of more than 17 days (n = 65) and less than 17 days (n = 82). The prolonged period of viral shedding was defined as a duration of more than 17 days. There was no significant difference in the distribution of age and sex, BMI, exposure history, and comorbidities between the two duration groups in the univariate analysis (Table 1). The percentage of patients with hemoptysis was significantly higher in the group of prolonged duration of viral shedding (p = 0.015). There was also a significant difference in the highest temperature between the two groups (p = 0.049), with the median highest temperature of 38.3 °C in the prolonged duration group. Of note, patients with a prolonged duration of viral shedding had a significantly longer time from symptom onset to admission (p < 0.001).

Laboratory findings and radiography

All laboratory findings of patients on initial admission are presented in Table 2. Specific Ct values of only 61 in 147 patients were retrieved in this study. The initial Ct values in patients with prolonged duration of viral shedding (>17 days) were lower than those in patients with a duration of fewer than 17 days. The dynamics of the viral load in relation to the days since onset of symptoms in these 61 patients are presented in Figure 1. For patients with a duration of viral shedding less than 17 days, the SARS-CoV-2 RNA was undetectable for half of the patients (15/30) after 12 days from the onset of symptoms (Figure 1A). However, for patients with a prolonged duration of viral shedding of more than 17 days, the SARS-CoV-2 RNA was undetectable for about half of the patients (16/31) after 22 days from the onset of symptoms (Figure 1B).

On admission, almost 79% of patients with COVID-19 (115/147) showed abnormal results of blood gas analysis with a PH more than 7.45. The PaO$_2$ of five patients was below 60 mmHg, while the partial pressure of carbon dioxide (PaCO$_2$) of one patient was over 50 mmHg. The results of the blood gas analysis showed that the level of PaO$_2$ was lower in patients with prolonged duration of viral shedding (P = 0.034). About 37% of the patients (54/147) exhibited leucopenia (white blood cell count < 4.0 × 10^9/L), and 23% of the patients (34/147) developed lymphopenia (lymphocyte count < 0.8 × 10^9/L) at admission. The percentage of lymphopenia was higher in patients with prolonged duration of viral shedding (P = 0.050). The median platelet count of patients was 166 × 10^9/L (IQR, 138–226). The level of platelet count in ten patients was below 100 × 10^9/L. The median albumin of patients was 37.7 g/L (IQR, 35.3–40.5). The level of alanine aminotransferase (ALT) increased in 23 patients with COVID-19 (16%). Nearly 32% (46/147) and 50% (65/147) of the patients had an abnormal level of procalcitonin and serum ferritin, respectively. About 9% (13/147) of patients had a level of creatine kinase over 185 U/L. The level of serum ferritin was significantly elevated in the group of prolonged duration of viral shedding (P = 0.029).

All patients with COVID-19 received chest radiography at the initial admission. Abnormal radiographic chest signs were detected in all patients except for six. The chest radiography of most patients (85%, 124/147) suggested bilateral involvement of the lungs. No differences in chest radiography were noted between the two groups of shorter and prolonged duration.

Table 2
Laboratory findings and chest radiography of patients with COVID-19 at admission.

Variables	All patients (n = 147)	Duration of viral shedding[a]		p value
		>17 days (n = 65)	≤17 days (n = 82)	
Initial Ct value[b]				
Median (IQR)	33.5 (30.0–35.1)	32.4 (28.7–34.7)	34.1 (31.2–35.9)	0.072
Range	24.1–38.3	24.1–38.3	26.7–37.6	
PaO₂				
Median (IQR)	88.3 (75.4–107.9)	84.4 (71.4–99.8)	91.9 (76.2–124.7)	0.034
Range	54.9–182.1	56.4–170.2	54.9–182.1	
Lymphocyte count <0.8 × 10⁹/L	34 (23%)	20 (31%)	14 (17%)	0.050
Lactate dehydrogenase, U/L				
Median (IQR)	162.2 (138.1–211.9)	183.0 (143.0–230.4)	153.4 (132.0–192.1)	0.065
Range	77.9–373.3	77.9–343.1	93.2–373.3	
C-reactive protein (mg/L)				
Median (IQR)	12.9 (3.8–27.3)	14.4 (3.9–28.6)	12.5 (3.8–25.4)	0.574
Range	0.2–97.8	0.2–78.1	0.2–97.8	
Serum ferritin, μg/L[c]				
Median (IQR)	306.3 (150.4–593.6)	404.2 (204.3–682.1)	232.8 (123.3–517.7)	0.029
Range	9.5–1676.0	9.5–1676.0	21.3–1625.5	
>300	65 (50%)	37 (61%)	28 (41%)	0.027
Chest radiography				
Normal	6 (4%)	2 (3%)	4 (5%)	0.235
Abnormal				
Bilateral lung	124 (84%)	59 (90%)	65 (80%)	
Single lung—left	8 (6%)	3 (5%)	5 (6%)	
Single lung—right	8 (6%)	1 (2%)	7 (9%)	

Abbreviation: COVID-19, coronavirus disease 2019; PaO₂, partial pressure of oxygen.
[a] The number of days from the symptoms onset till the successive negative detection of SARS-CoV-2 RNA.
[b] Data regarding initial Ct value were missing for 86 patients (58%).
[c] Data regarding serum ferritin were missing for 18 patients (12%).
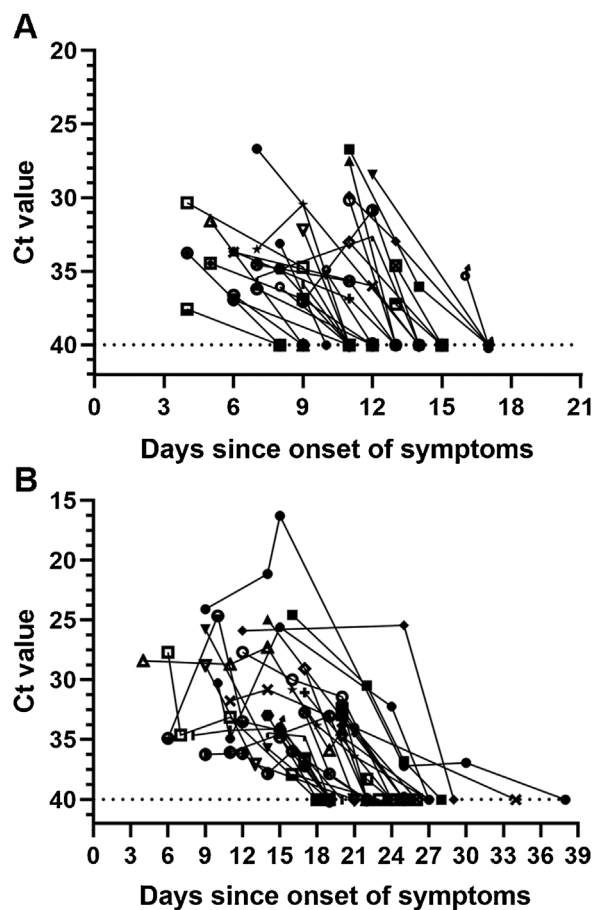
Figure 1. Dynamics of the viral load in patients with a duration of viral shedding less than 17 days (n = 30) (A) and patients with a duration of more than 17 days (n = 31) (B).

Treatment and prognosis

During hospitalization, all the patients with COVID-19 received antiviral treatment (Table 3). The protocol of antiviral treatment was based on the official guidelines with ribavirin and interferon most commonly used. Nearly 47% (64/147) of patients also received antibiotic treatment. Glucocorticoids and immunoglobulin were used in 39 and 37 patients, respectively. Among patients with the treatment that included antibiotics, glucocorticoids, and immuno-globulin, the percentage of the group with a prolonged duration was higher than that of the group with a duration of viral shedding less than 17 days. The majority of patients with COVID-19 (94%, 138/147) received respiratory support by nasal cannula. A high flow nasal cannula was only used in a small number of patients (3%, 5/147), and no significant difference was noted in the treatment of respiratory support between the two groups. There was only one patient treated with non-invasive ventilation in this study. In the current study, no patient with COVID-19 received advanced respiratory support, including mechanical ventilation and extra-corporeal membrane oxygenation (ECMO). There were very few patients exhibiting relatively serious complications, including ARDS, AKI, and MODS during admission. As of March 19th, 2020, all the patients in this study have been cured and discharged from the hospital. The follow-up survey of discharged patients was conducted mainly through periodic outpatient visits. Discharged patients were asked to visit the specialized outpatient clinic every week after discharge. In the specialized outpatient clinic, RT-PCR assays and radiography were performed; none of the patients were found changed from negative to positive by RT-PCR assays after hospital discharge.

Factors related to the duration of viral shedding

Factors that were statistically significant in the univariate analysis were further entered into the multivariate logistic regression analysis. As presented in Table 4, the multivariate

Table 3
Treatments and outcomes of patients with COVID-19.

| Treatments and outcomes | All patients (n = 147) | Duration of viral shedding[a] | | p value |
		>17 days (n = 65)	≤17 days (n = 82)	
Treatments				
Antiviral treatment	147 (100%)	65 (100%)	82 (100%)	NA
Antibiotics[b]	64 (47%)	34 (56%)	30 (40%)	0.058
Glucocorticoids	39 (28%)	24 (37%)	15 (20%)	0.020
Immunoglobulin	37 (26%)	23 (35%)	14 (18%)	0.022
Nasal cannula	138 (94%)	60 (92%)	78 (95%)	0.509
High flow nasal cannula	5 (3%)	3 (5%)	2 (3%)	0.655
Non-invasive ventilation	1 (1%)	1 (2%)	0	0.441
Invasive ventilation	0	0	0	
ECMO	0	0	0	
Outcomes				
ARDS	7 (5%)	4 (6%)	3 (4%)	0.700
AKI	1 (1%)	0	1 (1%)	1.000
MODS	1 (1%)	0	1 (1%)	1.000
Hospital length of stay, days				
Median (IQR)	13.0 (11.0–17.5)	16.0 (12.0–24.0)	12.0 (10.0–15.0)	<0.001
Range	5.0–37.0	5.0–37.0	5.0–24.0	

Abbreviation: COVID-19, coronavirus disease 2019; NA, not applicable; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; MODS, multiple organ dysfunction syndrome.
[a] The number of days from the symptoms onset till the successive negative detection of SARS-CoV-2 RNA.
[b] Data regarding antibiotics were missing for 10 patients (7%).

logistic regression analysis suggested that the highest temperature at admission (OR, 5.200; 95% CI: 1.190−22.726; $p = 0.028$), the time from symptom onset to admission (OR, 1.740; 95% CI: 1.296−2.337; $p < 0.001$) and the hospital length of stay (OR, 1.604; 95% CI: 1.262−2.040; $p < 0.001$) remained statistically significant in the final multivariate logistic regression analysis, and which were found to be risk factors for a prolonged duration of viral shedding of more than 17 days. The ROC curve was generated to further evaluate the potential of the final multivariate logistic regression model. As was illustrated in Figure 2, the ROC curve indicated optimal predictive capability (AUC = 0.935, 95%CI: 0.861−0.977).

Discussion

In the current study, we retrieved the data of 147 patients with laboratory-confirmed COVID-19. The clinical characteristics were described, and factors associated with the duration of viral shedding of COVID-19 were analyzed. Risk factors for the prolonged duration of viral shedding were identified, including the highest temperature at admission, time from symptom onset to admission, and hospital length of stay.

In influenza virus infections, it was reported that the duration of viral shedding was related to infectivity and transmissibility, serving as the significant factors of infection prevention and control (Ryoo et al., 2013). Therefore, it is of considerable significance to explore the duration of viral shedding and related factors in patients with COVID-19. The median duration of viral shedding in the current study was 17 days, which was close to that found in a recent study conducted in Wuhan (Zhou et al., 2020). There were 191 patients in Wuhan with a median duration of viral shedding of 20 days included in that study; 54 of them died during hospitalization. The minor difference in the duration of viral shedding between these two studies was probably based on the condition of patients, as the patients with the severe type of COVID-19 only made up a minor percentage in the current study. However, so far, there is no official definition of prolonged duration of viral shedding in COVID-19. In this study, the cut-off value was defined as the median of the duration of viral shedding. The same method of choosing the median of viral shedding as the cut-off value was found in one high-quality study concerning COVID-19, in which the cut-off value was close to that in our study (Xu et al., 2020a).

Middle-aged patients made up the majority of this study population. Although the patients with prolonged duration of viral shedding were slightly older, no significant difference was noted concerning the age between two groups with different durations of viral shedding. Advanced age was reported to be significantly associated with prolonged duration of viral RNA detection in patients with influenza A (H3N2) (Lee et al., 2009). Recent studies of patients with COVID-19 also suggested that older age might be a potentially significant predictor for severity and mortality (Zhang et al., 2020; Zhou et al., 2020). Older patients are more likely to exhibit severe comorbidities, which usually leads to worse prognosis compared to young patients. However, the percentage of patients with comorbidities and a severe type of COVID-19 was relatively lower in the current study; the effect of age on the duration of viral shedding in patients with COVID-19 still needs further investigation. Fever and cough were the most common symptoms of patients in the current study, which is consistent with previous studies with a large sample size (Guan et al., 2020). Of note, the highest temperature of patients was significantly associated with a prolonged duration of viral shedding in this study. Body temperature is one of the vital signs to assess a patient's condition. In influenza A viral infections, there was a positive correlation between the tympanic temperature and viral shedding (Lau et al., 2010).

One recent study also reported that the highest temperature at admission was a risk factor for the progression of COVID-19 (Liu et al., 2020). Therefore, patients with higher temperatures at admission are supposed to be closely monitored and quarantined for a longer time. The longest duration of viral shedding of patients in the current study was 47 days. A 40-year-old male who presented with symptoms on January 4th was diagnosed with COVID-19 based on RT-PCR assays on January 12th. He was admitted to the appointed medical institution on February 14th; the detection of SARS-CoV-2 RNA changed six days later. As we suggest in the current study, it may take a longer time for patients with prolonged duration of viral shedding to get admitted to a hospital after symptoms onset. The decreased time from symptoms onset to admission allowed prompt treatment, which was probably associated with the duration of viral shedding. Of note, in the early stage of clinical work in our center, respiratory tract specimens, including nasopharyngeal swab specimens, oropharyngeal swab specimens, and sputum specimens of patients were

Table 4
Factors associated with a duration of viral shedding of more than 17 days in patients with COVID-19.

Characteristics	Multivariable analysis		
	OR	95% CI	p value
Expectoration	1.745	0.448−6.793	0.422
Hemoptysis	NA	NA	0.999
Highest temperature (°C)	5.200	1.190−22.726	0.028
Time from symptom onset to admission	1.740	1.296−2.337	<0.001
PaO$_2$	0.990	0.969−1.011	0.349
Lymphocyte count <0.8 × 10^9/L	1.703	0.328−8.836	0.526
Serum ferritin >300 μg/L	0.969	0.219−4.291	0.967
Glucocorticoids	3.965	0.425−37.006	0.227
Immunoglobulin	0.098	0.009−1.102	0.060
Hospital length of stay, days	1.604	1.262−2.040	<0.001

Abbreviation: COVID-19, coronavirus disease 2019; NA, not applicable; OR, odds ratio; CI, confidence interval.
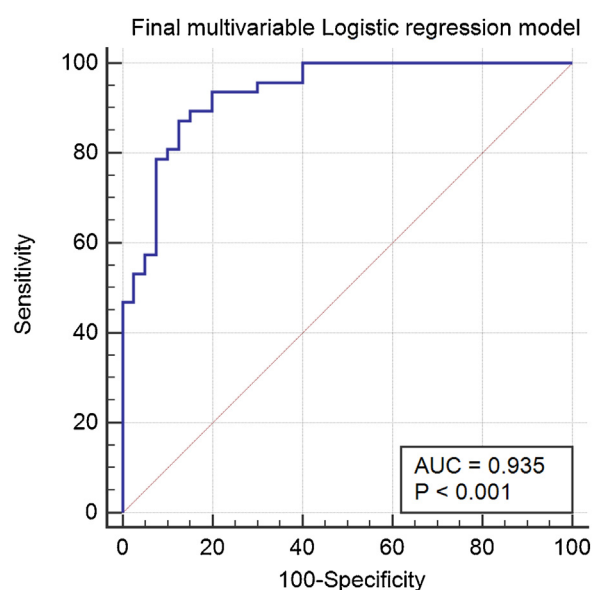
Figure 2. ROC curve of the final multivariate logistic regression model (AUC = 0.935, 95%CI: 0.861-0.977).

obtained. For nasopharyngeal swabs, the depth of collecting a sample is the critical factor, while this procedure seems more acceptable with relatively low exposure risk. However, in our center's practical clinical work, we found that collecting nasopharyngeal swabs might generate relatively high false-negative detection results. Besides, there is no firm evidence concerning the superiority of collecting nasopharyngeal swabs in COVID-19. Therefore, we mainly collected throat (oropharyngeal) swabs in subsequent clinical work.

Specific Ct values of 61 patients were retrieved in this study. Although the initial Ct values in patients with prolonged duration of viral shedding were lower, no statistically significant difference was noted between the two different duration groups. It was reported that viral shedding of most patients with COVID-19 was high in the early stage from the onset of symptoms (Wolfel et al., 2020). Besides, the severity of patients with COVID-19 was probably associated with lower Ct values (Zou et al., 2020). In the current study, it was noted that the patients' Ct values increased with the improvement of symptoms. For the results of blood gas analysis, the level of PaO$_2$ was significantly lower in the patients with a prolonged duration of viral shedding. The level of PaO$_2$ is the index reflecting arterial oxygenation while its role in the duration of viral shedding in COVID-19 still needs further study (Collins et al., 2015). The percentage of patients with

lymphopenia was much lower than that in a previous study, in which 75.4% of patients presented lymphopenia (Zhang et al., 2020). It was also noted that the patients with the severe type accounted for a relatively large part in that study. The level of inflammatory indicators, including c-reactive protein and procalcitonin, were similar in the two groups with different durations of viral shedding. More than half of patients had an abnormal range of serum ferritin, and serum ferritin was significantly elevated in the patients with a prolonged duration of viral shedding. For chest radiography, most patients with COVID-19 presented bilateral involvement of lungs, which was consistent with previous studies (Chen et al., 2020; Zhang et al., 2020; Zhou et al., 2020).

All the patients with COVID-19 in the Changsha public health treatment center received antiviral treatment. In recent studies concerning COVID-19 in Wuhan, the percentage of patients given antiviral treatment was much lower than that in the current study (Chen et al., 2020; Zhou et al., 2020). Before the COVID-19 outbreak, the Changsha public health treatment center was the appointed medical institution for patients infected with the human immunodeficiency virus (HIV). Therefore, antiviral treatment was more likely to be administered promptly as a routine treatment. However, it remains relatively unknown whether the antiviral treatment would shorten the duration of viral shedding, as all patients were treated with antiviral medication. Additionally, it was reported that lopinavir-ritonavir treatment didn't work effectively in patients with the severe type in a recent study (Cao et al., 2020). Patients with a prolonged duration of viral shedding tended to receive antibiotics, glucocorticoids, and immunoglobulin in the current study. These antibiotics may cover the typical spectrum of pathogens, but the use of glucocorticoids in viral pneumonia remains controversial (Russell et al., 2020; Wang et al., 2020; Yang et al., 2020b). Several mild complications were observed and treated promptly. The length of hospital stay in patients with the prolonged duration of viral shedding was much longer, where two continuous negative detections of SARS-CoV-2 RNA over 24 h were the significant criteria for discharge (Lin, 2020, Yang et al., 2020).

A recent study also focused on viral shedding in patients with COVID-19 in Qingdao, China (Hu et al., 2020). Of note, there were some differences between these two studies. The new definition called the communicable period was introduced in that study, which was defined as the duration from the first positive detection to the first successive negative detection of SARS-CoV-2 RNA. The median communicable period in that study was 14 days, which was close to the median duration of viral shedding in our study. The slight difference in duration may come from the different starting points in the definitions. In general, the onset of symptoms was earlier than the collection of specimens from patients. Besides, the definition of the duration of viral shedding

in this study was also consistent with that in one high-quality study of COVID-19 in Hangzhou, in which the median of the duration of viral shedding was also 17 days (IQR, 13–22 days) (Xu et al., 2020a). The study in Qingdao with 59 patients indicated that a prolonged communicable period was associated with older age and chest tightness, while the study in Hangzhou presented similar results compared to the current study. The heterogeneity was partly based on the relatively small sample size and different clinical classifications of patients. The above studies shed light on the viral shedding in patients with COVID-19, while relevant factors still need further investigation.

There are some limitations concerning the design and data in the present study. First, demographic and clinical characteristics, laboratory findings, and radiography were incomplete because of the retrospective study design. Second, the sample size in the single-center outside Wuhan remained relatively small, and most patients included in this study had mild clinical symptoms. Third, specimens from the respiratory tract, including sputum, nasopharyngeal swab, and oropharyngeal swab specimens, were collected in this study, most of which were throat (oropharyngeal) swab specimens. Another study reported that the continued presence of viral RNA could be found in fecal samples (Wu et al., 2020). The specific viral loads of 61 patients were obtained in this study, representing a relatively large sample size compared with another high-quality study of COVID-19 (Young et al., 2020). However, the viral load of the patient with the longest duration of 47 days wasn't included because of the lack of a corresponding Ct value. We were not able to further explore relevant factors due to the lack of specific data for some measures.

To the best of our knowledge, this is the first study with a relatively large sample size that focuses on the duration of viral shedding and related factors in patients with COVID-19, outside of Wuhan, China. We found that the highest temperature at admission, the time from symptom onset to admission, and the hospital length of stay were risk factors for a prolonged duration of viral shedding, which should be taken into consideration for a strategy of quarantining infected patients. A multi-center study with a large sample size is needed to further explore factors associated with the duration of viral shedding in adults with COVID-19.

Conflict of interest

The authors have no competing interest to declare.

Ethical approval

This study was conducted following the Declaration of Helsinki. The study was approved by the institutional research ethics committee of the Second Xiangya Hospital (No.2020[017]). Due to this emergency public health event, written informed consent was waived, patients included in this study gave their oral consent.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.05.045.

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