

The Correlation Between Clinical Features and Viral RNA Shedding in Outpatients With COVID-19

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Background. Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can shed virus, thereby causing human-to-human transmission, and the viral RNA shedding is commonly used as a proxy measure for infectivity.

Methods. We retrospectively reviewed confirmed cases of COVID-19 who attended the fever clinic of Wuhan Union Hospital from January 14 to February 24. In terms of the viral RNA shedding (median values) at first visit, patients were divided into a high-viral RNA shedding group and a low-viral RNA shedding group. Univariate and multivariate logistic regression analysis were performed to investigate the correlation between viral RNA shedding and clinical features.

Results. A total of 918 consecutive COVID-19 patients were enrolled, and severe patients made up 26.1%. After univariate and multivariate logistic regression, advanced age (odds ratio [OR], 1.02; 95% CI, 1.01–1.03; $P = .001$), having severe chronic diseases (OR, 1.44; 95% CI, 1.03–2.01; $P = .04$), and severe illness (OR, 1.60; 95% CI, 1.12–2.28; $P = .01$) were independent risk factors for high viral RNA shedding. Shorter time interval from symptom onset to viral detection was a protective factor for viral RNA shedding (OR, 0.97; 95% CI, 0.94–0.99; $P = .01$). Compared with mild patients, severe patients have higher virus shedding over a long period of time after symptom onset ($P = .01$).

Conclusions. Outpatients who were old, had severe illness, and had severe underlying diseases had high viral RNA shedding.

Keywords. clinical features; COVID-19; outpatients; SARS-CoV-2; viral RNA shedding.

As of April 24, 2020, coronavirus disease 2019 (COVID-19) has spread to 213 countries, infected more than 3 059 642 people, and caused 211 028 deaths [1]. The ongoing pandemic remains in the rapid progression period. Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) results in a wide range of clinical manifestations, ranging from asymptomatic or mild illness to respiratory failure [2]. Due to the differences in demographics and availability of medical resources, mortality rates vary substantially from region to region [3, 4].

The main model of SARS-CoV-2 transmission involved close contact with an infected person and spread of the virus via respiratory droplets or contact with fomites [5]. In asymptomatic patients and presymptomatic patients, the amount of SARS-CoV-2 RNA in specimens from the upper respiratory tract is

high [6], while the viral RNA shedding in subjects with severe acute respiratory syndrome coronavirus (SARS-CoV) is low in the initial few days of the illness [7]. These findings suggest that transmission of SARS-CoV-2 may occur earlier in the course of infection than that of SARS-CoV. In addition, polymerase chain reaction (PCR) found SARS-CoV-2 in the samples from air exhaust outlets of a hospital ward occupied by a COVID-19 patient, from a conventional surface swab sample from a toilet bowl and sink, and a sample from the surface of a shoe front [8]. Therefore, knowing how long the infectivity will persist in an individual is essential to the decision of how long a person sick with SARS-CoV-2 should be isolated to avoid further transmission. Identifying the relevant contributors to transmission is important to informed policy-making. Previous studies, based on influenza virus infections, have shown that viral RNA shedding is proportional to the infectivity around disease onset, a phenomenon that is subsequently used as a proxy for measuring infectivity [9, 10]. Characterizing the infectivity of SARS-CoV-2 is of great importance for the control and prevention of the condition. However, the relationship between clinical manifestations, host factors, and viral RNA shedding for COVID-19 is poorly understood.

In this study, we retrospectively reviewed all confirmed patients who consecutively attended the fever clinic of Wuhan Union Hospital during the entire course of the COVID-19 and compared subjects with high viral RNA shedding with their

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low-shedding counterparts. Specifically, we characterized patterns of SARS-CoV2 infection, based on demographic and epidemiological features, symptoms, laboratory test results, and size of pulmonary lesions, and found a correlation between the clinical features and infectivity in outpatients with COVID-19.

METHODS

Study Population

This retrospective observational study examined the patients who visited the clinic of Wuhan Union Hospital from January 14, 2020, to February 24, 2020. Wuhan Union Hospital was 1 of the designated hospitals that had a 24-hour fever clinic designed to preliminarily assess and identify suspected SARS-CoV-2-infected patients during the epidemic of COVID-19. According to the Diagnosis and Treatment Guideline for COVID-19 (7th edition, China) [11] from the National Health Commission of China, 1115 patients were confirmed in the fever clinic on the basis of nasopharyngeal swab samples positive for SARS-CoV-2 nucleic acid, as detected by real-time reverse transcription PCR (RT-PCR). One hundred ninety-seven patients were excluded due to absence of medical records. Nine hundred eighteen were finally enrolled in the study. In terms of illness severity, a patient was included in the severe COVID-19 group if he or she had (1) respiratory distress (respiratory rate ≥ 30 beats/min), (2) resting-state oxygen saturation $\leq 93\%$, and (3) arterial partial pressure of oxygen/oxygen concentration ≤ 300 mm Hg.

Data Collection

We reviewed electronic medical records, nursing records, laboratory results, and chest computed tomography (CT) scans for all confirmed patients. Data were collected on demographic and epidemiological features, symptoms, laboratory test results, and volume of pneumonia lesions measured on 3D CT images. The demographic and epidemiological data covered age, gender, underlying diseases, date of symptom onset, and exposure history. Severe chronic diseases included cancer, cardiovascular and cerebrovascular diseases, hypertension, diabetes, and chronic respiratory diseases. Symptoms and signs were recorded at clinic visits. Routine blood test, hypersensitive C-reactive protein (hsCRP), and serum biochemistry (including indices of renal and hepatic functions) were assessed at the first visit. Volume of pneumonia lesions of the whole lung was calculated using a computer-aided in-home detection system, which is detailed in the ensuing section.

Nucleic Acid Detection

Specimens were taken by throat swabbing. After RNA extraction, the SARS-CoV-2 was detected by RT-PCR using SARS-CoV-2-specific primers for 2 targets, ORF1ab gene and N gene, according to the standard protocols (BioGerm Inc., Shanghai, China). The RT-PCR was performed on a Roche Cobas z480 automated PCR Analyzer. Cycle threshold (Ct) value < 35 or a

Ct value > 35 and < 38 (twice) was defined as positive. The median value of the Ct value was used as a cutoff for the high- and low-viral RNA shedding groups.

CT Data Acquisition and Volume of Pneumonia Lesions of the Whole Lung as Measured on CT Images

The CT scans were performed in the Department of Radiology of Wuhan Union Hospital according to the standard departmental protocols [12]. All images were reconstructed by employing lung and soft tissue algorithms. Pneumonia lesions were automatically segmented by an in-home software package (FACT system). Then the volume of the lesions was calculated on 3-dimensional CT images. The lesion/whole lung ratio (V/V) was also calculated.

Statistical Analysis

All data were statistically analyzed using the SPSS software package (version 23.0; IBM Corp, Armonk, NY, USA). We used frequency rates and percentages to describe categorical data, and we analyzed them using the χ^2 test and Fisher exact test. Meanwhile, quantitative variables were presented as mean \pm SD and analyzed utilizing *t* tests. The multivariable logistic regression model was fit to estimate the effect of variables on outpatient viral RNA shedding. Data in Figure 1 from repeated measures were compared using the generalized linear mixed model. Groups and time points were fixed effects, and individuals were random effects. Statistical significance was set at $P < .05$.

RESULTS

Baseline Data at the First Visit

A total of 1115 consecutive patients underwent virology tests, to detect SARS-CoV-2, at the fever clinic of Wuhan Union Hospital from January 14, 2020, to February 24, 2020. Patients' baseline data are listed in Table 1. After exclusion, 918 were included in the study. We included 489 men and 429 women, with a mean age of 56 years. Based on clinical classification, 678 were diagnosed as having mild and 240 as having severe COVID-19. At the first visit, patients presented with various symptoms, including fever (73%), cough (47.7%), fatigue (20.3%), expectoration (14.7%), sore throat (4.8%), chest tightness (13.8%), diarrhea (9.4%), poor appetite (8.3%), shortness of breath (7.8%), myalgia (7.7%), difficulty breathing (6.9%), chill (5.3%), headache (3.2%), nausea and vomiting (3.2%), palpitation (2.0%), stuffy nose (1.5%), stomach ache (1.0%), chest pain (1.0%), abdominal distension (1.0%), dizziness (0.8%), and hemoptysis (0.3%). In terms of the first result of the SARS-CoV-2 nucleic acid detection, patients were divided into a high-viral RNA shedding group and a low-viral RNA shedding group. Specifically, the high-viral RNA shedding group comprised patients with a mean Ct value of 27.31, whereas those in the low-viral RNA shedding group had a mean Ct value of 35.16. At

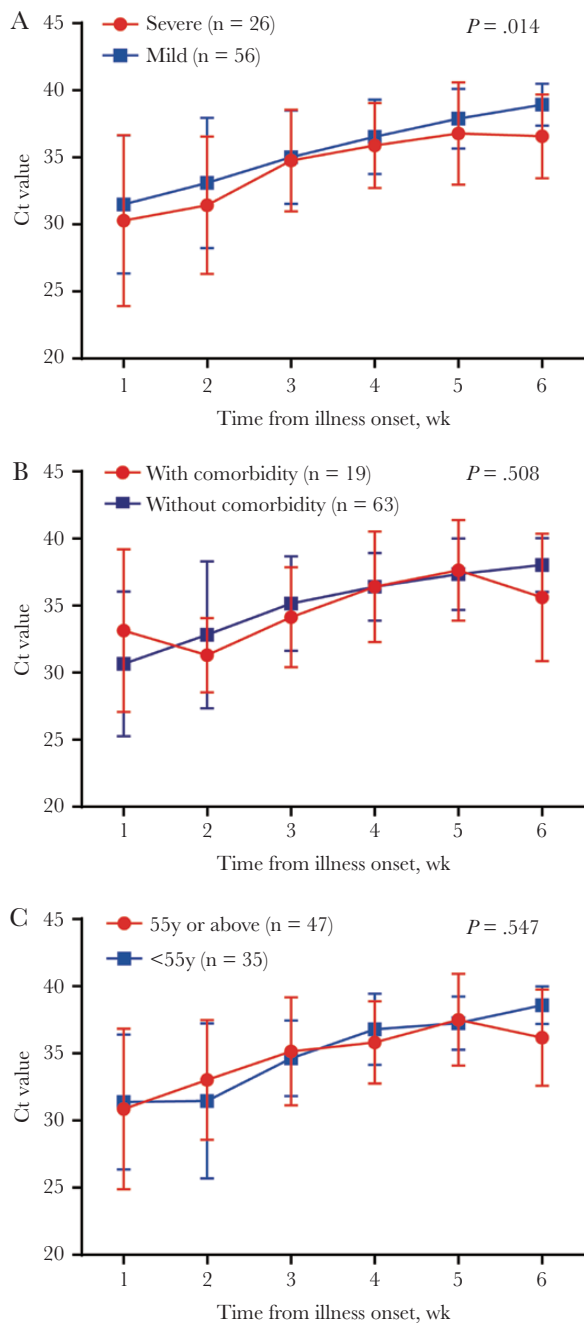


Figure 1. Dynamic change of viral RNA load in 82 patients. A, Patients with mild and in severe condition. B, Patients with and without comorbidities. C, Patients aged <55 years and patients aged ≥55 years. Linear mixed-effects model was used to analyze the difference between 2 groups.

the initial visit, patients in the high-viral RNA shedding group were significantly ($P < .001$) older than those in the low-viral RNA shedding group, with an average age of 57.9 and 53.7, respectively. Participants in the high-viral RNA shedding group were more likely to have a severe chronic illness than those in the low-shedding group (high- vs low-shedding groups: 32% vs 21%; $P < .001$) and to have severe COVID-19 disease (44% vs 29%; $P < .001$). In addition, the mean time from onset of illness

to positive SARS-CoV-2 nucleic acid detection was 8.7 days for the whole group. In the low-viral RNA shedding group, the mean time from illness onset to viral detection was 9.6 days, vs 7.9 days in the high-viral RNA shedding group ($P < .001$). No correlation was found between the viral RNA shedding at the first visit and symptoms, such as fever, cough, shortness of breath, fatigue, anorexia, and muscular soreness, except sore throat (Supplementary Table 1).

Laboratory Indices and CT Manifestations

Laboratory indices were collected at the first visit, including routine blood tests and blood biochemistry. Platelet count (high vs low: $185.37 \times 10^9/L$ vs $201.38 \times 10^9/L$; $P = .02$) and eosinophils count (high vs low: $0.02 \times 10^9/L$ vs $0.03 \times 10^9/L$; $P = .04$) were significantly lower in the high-viral RNA shedding group than in the low-viral RNA shedding group (Supplementary Table 2). CT images at initial diagnosis were collected, and pneumonia lesions were segmented and calculated using an in-home software package (FACT system). The results indicated significantly higher lesion volume in patients in the high-viral RNA shedding group than those in the low-viral RNA shedding group (high vs low: 417.50 mL vs 349.82 mL; $P = .03$). Moreover, a significantly higher lesion-to-lung ratio (0.12) was recorded in patients in the high- than those in the low-viral RNA shedding group (0.10; $P = .04$) (Table 2).

Multivariate Analyses of Associated Clinical Factors With Viral RNA Shedding

Univariate analysis revealed that age ($P < .001$), severe chronic diseases ($P < .001$), severity of illness ($P = .001$), days from symptom onset to viral detection ($P < .001$), platelet count ($P = .02$), eosinophils count ($P = .04$), and pneumonia lesion at the first visit ($P = .03$) were significantly related to viral RNA shedding. Platelet count, eosinophils count, and pneumonia lesion at the first visit were excluded because only half of the enrolled patients had complete data (50.4%). Then the other 4 factors were included in the binary logistic regression equation to analyze the independent risk factors associated with viral RNA shedding (76.3% cases were included) (Table 3). The results showed that advanced age (odds ratio [OR], 1.02; 95% CI, 1.01–1.03; $P = .001$), severe chronic diseases (OR, 1.44; 95% CI, 1.03–2.01; $P = .04$), and severe illness (OR, 1.60; 95% CI, 1.12–2.28; $P = .01$) were independent risk factors associated with high viral RNA shedding. Shorter interval time from symptom onset to viral detection was a protective factor to viral RNA shedding (OR, 0.97; 95% CI, 0.94–0.99; $P = .01$) (Table 3).

Dynamic Changes in Viral RNA Shedding

Among the 918 cases, we further analyzed 82 patients who underwent >1 nucleic acid test, then used the resulting average Ct values after every 7 days from symptom onset to reveal dynamic changes in viral RNA shedding (Figure 1). Summarily, viral

Table 1. Baseline Characteristics of High-Viral RNA Load and Low-Viral RNA Load Patients With COVID-19

Variables		Total (n = 918)	High Viral RNA Load (n = 459)	Low Viral RNA Load (n = 459)	P Value
Age, mean (SD), y		55.7 (14.52)	57.9 (14.6)	53.7 (14.1)	<.001
Cycle threshold, mean (SD)		31.2 (4.89)	27.31 (3.4)	35.16 (2.4)	<.001
Gender, No. (%)	Female	489 (53.3)	233 (50.8)	256 (55.8)	.13
	Male	429 (46.7)	226 (49.2)	203 (44.2)	
Severe chronic diseases, No. (%)	Without	448 (64)	181 (56.0)	267 (70.8)	<.001
	With	252 (36)	142 (44.0)	110 (29.2)	
Degree of illness, No. (%)	Mild	678 (73.9)	316 (68.8)	362 (78.9)	.001
	Severe	240 (26.1)	143 (31.2)	97 (21.1)	
Exposure history, No. (%)	Without	808 (88.1)	396 (86.3)	412 (90)	.09
	With	109 (11.9)	63 (13.7)	46 (10)	
Days from symptom onset to viral detection, mean (SD)		8.7 (6.21)	7.9 (5.4)	9.6 (6.8)	<.001

RNA shedding was highest within a week of symptom onset and could still be detected up to 6 weeks after the onset. In addition, patients with severe disease symptoms had significantly higher virus shedding over a long period of time after symptom onset than those with mild symptoms ($P = .01$). However, no significant differences were found between patients with and without comorbidity, as well as those age <55 and age ≥ 55 .

DISCUSSION

COVID-19 is caused by SARS-CoV-2 infection and can be transmitted via respiratory droplets and close contact. Although SARS-CoV-2 belongs to the same beta-coronavirus genus of the coronaviruses [13] culpable for the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), this novel virus has caused a large number of deaths due to its tremendous infectivity [14, 15]. As the ongoing COVID-19 pandemic shows no sign of subsiding, it is imperative to know the shedding pattern of the virus to effectively contain the spread of this disastrous infection.

In this study, we examined the relationship between viral RNA shedding, as measured by PCR detection of throat swab specimens, and the patients' features at the first visit in outpatients infected with SARS-CoV-2. This study, involving

only outpatients, showed that advanced age, concomitant severe underlying diseases, and severe condition were associated with high initial viral RNA shedding in the upper respiratory tract. Most of the previous studies on viral RNA load were conducted in inpatients. A recent observational study, including 23 COVID-19 patients, revealed that older age bore an association with higher viral RNA load, but the initial viral RNA load and peak viral RNA load did not differ between patients with chronic comorbidities and those without chronic comorbidities [16]. No significant differences were found in the median initial and peak viral RNA loads between severe cases and mild ones either. Nonetheless, other researches have demonstrated that hospitalized patients with severe COVID-19 tend to have a high viral RNA load and a long virus-shedding period [5, 17]. The discrepancy might be attributed to differences in the number of cases and analysis methods used. A recent study demonstrated that SARS-CoV-2 RNA load is positively correlated with interleukin-2 receptor (IL-2R), prothrombin time, lactate dehydrogenase, and hypersensitive troponin T [18]. In our study, changes in laboratory parameters, such as lower platelet and eosinophils counts and larger lung lesion size, were associated with higher initial viral RNA shedding. As viral RNA shedding is commonly used as an alternative measure for infectivity,

Table 2. CT Manifestations of High-Viral RNA Load and Low-Viral RNA Load Patients With COVID-19

CT Manifestations		All Patients	High Viral RNA Load (n = 459)	Low Viral RNA Load (n = 459)	P Value
Whole lung, lesion volume	Mean (SD)	381.54 (335.27)	417.50 (383.16)	349.82 (244.67)	.03
	No. (missing)	510 (408)	239 (220)	271 (188)	
Whole lung, lesion ratio	Mean (SD)	0.11 (0.10)	0.12 (0.11)	0.10 (0.087)	.04
	No. (missing)	510 (408)	239 (220)	271 (188)	
Whole lung, mean intensity	Mean (SD)	-491.5 (103.46)	-495.13 (102.51)	-488.34 (104.37)	.46
	No. (missing)	510 (408)	239 (220)	271 (188)	
Whole lung, nonsolid ratio	Mean (SD)	0.61 (0.16)	0.62 (0.15)	0.60 (0.16)	.34
	No. (missing)	510 (408)	239 (220)	271 (188)	

Abbreviation: CT, computed tomography.

Table 3. Binary Logistic Regression Analysis of Risk Factors for High Viral RNA Shedding

	PValue	OR	95% CI for OR	
			Lower	Upper
Advanced age	0.001	1.02	1.01	1.03
Days from symptom onset to viral detection	0.01	0.97	0.94	0.99
Severe chronic diseases	0.04	1.44	1.03	2.01
Severe illness	0.01	1.60	1.12	2.28

Abbreviation: OR, odds ratio.

this indicator should have important implications in policy-making. Our results suggest that patients who are older or whose condition is severe and those who have severe underlying diseases, lower platelets, a lower eosinophils count, or larger lung lesion volume at the first clinic visit should be immediately isolated. Added attention or protection should also be given to these patients in their treatment. Moreover, when an outpatient's internal time from symptom onset to nucleic acid detection exceeds 1 week and when a younger mild outpatient has no severe underlying diseases, detection should be repeated to avoid missed diagnosis, as viral RNA shedding in these people tends to be low.

In this study, we mainly focused on virus quantity, but viral RNA shedding duration is also an important factor. Both viral quantity and shedding duration are believed to be positively associated with viral transmission [19]. The previous study in hospitalized patients revealed that viral RNA load was higher at the time of symptoms onset and progressively decreased within days, following a different pattern than SARS, with which the highest shedding was found 10 days after the symptom onset [7, 20]. Our study yielded similar results. Compared with mild patients, we found that patients whose condition is severe have higher virus shedding over a long period of time after symptom onset [21].

Our study had several limitations. First, this project, despite its relatively large sample size, was a single-center retrospective study, which prevented us from acquiring more data on viral RNA shedding. Second, we only examined the relationship between viral RNA shedding and clinical characteristics of patients at their first outpatient visit. Due to lack of follow-up data, we were unable to study the association between viral RNA shedding and antiviral therapy and outcomes of the disease.

CONCLUSIONS

Overall, our results indicate that older outpatients, as well as those suffering from severe underlying diseases and severe conditions, have high viral RNA shedding at first visit. Moreover, patients with severe conditions have higher viral shedding over a long period of time after symptom onset relative to those with mild symptoms.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. Y.J. and T.L. designed the study. T.L., Z.Y., J.X., Z.L., S.W., L.D., and J.F. collected the demographic and clinical data and information on medical resources. T.L., Z.Y., and Z.L. summarized all data. Statistical analysis was conducted by T.L., Z.Y., and J.X. The manuscript was drafted by T.L., Z.Y., J.X., and Z.L. Y.J. and T.L. critically revised the manuscript.

Patient consent. This study was approved by the Ethics Commission of The Wuhan Union Hospital (No. 0036), Wuhan, China. Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious disease.

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