Factors Associated With Prolonged Viral RNA Shedding in Patients with Coronavirus Disease 2019 (COVID-19)

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**Background.** An outbreak of coronavirus disease 2019 (COVID-19) is becoming a public health emergency. Data are limited on the duration and host factors related to viral shedding.

**Methods.** In this retrospective study, risk factors associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA shedding were evaluated in a cohort of 113 symptomatic patients from 2 hospitals outside Wuhan.

**Results.** The median (interquartile range) duration of SARS-CoV-2 RNA detection was 17 (13–22) days as measured from illness onset. When comparing patients with early (<15 days) and late (≥15 days after illness onset) viral RNA clearance, prolonged SARS-CoV-2 RNA shedding was associated with male sex (P = .009), old age (P = .033), concomitant hypertension (P = .009), delayed admission to hospital after illness onset (P = .001), severe illness at admission (P = .049), invasive mechanical ventilation (P = .006), and corticosteroid treatment (P = .025). Patients with longer SARS-CoV-2 RNA shedding duration had slower recovery of body temperature (P < .001) and focal absorption on radiograph images (P < .001) than patients with early SARS-CoV-2 RNA clearance. Male sex (OR, 3.24; 95% CI, 1.31–8.02), delayed hospital admission (OR, 1.30; 95% CI, 1.10–1.54), and invasive mechanical ventilation (OR, 9.88; 95% CI, 1.11–88.02) were independent risk factors for prolonged SARS-CoV-2 RNA shedding.

**Conclusions.** Male sex, delayed admission to hospital after illness onset, and invasive mechanical ventilation were associated with prolonged SARS-CoV-2 RNA shedding. Hospital admission and general treatments should be started as soon as possible in symptomatic COVID-19 patients, especially male patients.

**Keywords.** coronavirus; viral shedding; risk factors; SARS-CoV-2; COVID-19.

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–induced pneumonia is becoming a public health emergency [1]. As of 20 March 2020, more than 260,000 confirmed infections have been reported worldwide, with over 11,000 deaths [2]. Several studies have summarized the clinical and epidemiological features of patients with coronavirus disease 2019 (COVID-19). Knowledge has been accumulating about the clinical course and outcomes of critically ill patients with COVID-19, while information about patients with mild severity is scarce. Compared with the severity of symptoms in patients in Wuhan, those patients outside Wuhan displayed more relatively mild symptoms [3]. According to the report with the largest sample size so far, 80.9% of the 44,672 patients displayed symptoms considered to be mild [4]. The data on the clinical course, particularly on viral RNA shedding of patients with mild COVID-19, are of paramount importance to optimize treatment options and prevent transmission of this disease.

One of the release criteria for hospitalized patients with mild symptoms is a negative sputum/oral swab test twice in a 24-hour interval [5]. The viral RNA excretion pattern in respiratory specimens during the process of SARS-CoV-2 infection has been analyzed in limited studies. Zou et al [6] studied the viral load in sequential nasal and throat swabs in patients with COVID-19. Higher viral loads were detected soon after symptom onset, while symptomatic and asymptomatic patients had similar viral loads [6]. It was suggested that the viral nucleic acid shedding pattern of patients with COVID-19 resembles that of patients with influenza and appears to be different from that seen in patients infected with SARS-CoV-1 [7, 8]. The pattern of SARS-CoV-2 RNA shedding during the course of treatment has not been well characterized. Zhang et al [9] found that, after 5 days of therapy, only 25% patients had negative oral swabs. However, in this research, little clinical information was involved and was not correlated with virological data.
Here, we conducted a retrospective study to elucidate trends in clinical illness and viral RNA shedding associated with COVID-19, and to identify risk factors influencing the persistence of SARS-CoV-2 RNA shedding. Our results suggest that male sex, delayed admission to hospital after illness onset, and invasive mechanical ventilation during hospitalization were associated with prolonged SARS-CoV-2 RNA shedding. These results reinforce guidance that hospital admission and general treatments should be started as soon as possible in symptomatic patients with COVID-19. Male patients need particular attention for their prolonged viral RNA shedding, which might be associated with poor treatment outcomes.

METHODS

Study Design and Participants
A total of 113 patients with confirmed SARS-CoV-2 infection admitted to the First Affiliated Hospital, School of Medicine, Zhejiang University and the Shenzhen Third People’s Hospital were enrolled (Figure 1). The earliest patient in Shenzhen Third People’s Hospital was admitted on 13 January 2020. And the first patient in The First Affiliated Hospital of Zhejiang University was admitted on 19 January 2020. As of 19 February, a total of 161 patients with confirmed COVID-19 were admitted to the 2 hospitals. Since COVID-19 is an emerging acute infectious disease, the primary purpose of this study was to evaluate the occurrence of viral RNA clearance in the first 21 days after illness onset. Patients were enrolled if they met 1 of the 3 inclusion criteria: (1) disease duration over 21 days without viral RNA clearance, (2) viral RNA clearance occurred within 21 days, or (3) death occurred within 21 days. According to the criteria, 47 patients were excluded if they were less than 21 days since illness onset and without viral RNA clearance. One patient was excluded because she was transferred to the local hospital without viral RNA clearance (Figure 1). In the cohort of 113 patients, 69 patients recovered and were released in 21 days, 13 patients remained hospitalized after 21 days but had viral RNA detectable after 21 days, and 2 patients died with viral RNA clearance within 21 days (Figure 1). Ethics approval was obtained from the Institutional Review Board of the First Affiliated Hospital, School of Medicine, Zhejiang University.

The diagnosis and severity of illness at admission were assessed based on the latest guidelines of SARS-CoV-2 infection enacted by the World Health Organization (WHO) on 13 March 2020 [10]. As described, patients could be categorized into 5 levels of severity: mild illness, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), and sepsis or septic shock. To simplify the analysis process, mild illness and pneumonia cases were combined as “mild cases” and severe pneumonia, ARDS, and sepsis or septic shock cases were combined as “severe cases” in this study. All the patients in this study were symptomatic patients. Most of the mild cases were patients with pneumonia, except for 2 cases who had no radiological manifestation. Critically severe illness was defined as occurrence of ARDS, sepsis, or septic shock.

Clinical characteristics, treatment, and outcome data were obtained from electronic medical records. The following results associated with treatment processes were recorded: (1) temperature recovery, indicated by a patient’s ear temperature decreasing to no higher than 37.5°C and not increasing thereafter; (2) radiological recovery was defined as improvement in initial pulmonary lesions without appearance of new radiological lesions at other sites; (3) duration of viral RNA shedding was considered the number of days from symptom onset to persistent negative detection of respiratory tract specimens (all subsequent samples from the same patient were then tested until 3 consecutive samples were negative, with the first negative sample defining the duration of shedding); (4) whether invasive mechanical ventilation was performed during hospitalization; and (5) duration of hospitalization.

Virological Investigations
SARS-CoV-2 infection was confirmed in all patients by testing respiratory specimens with a real-time reverse transcription-polymerase chain reaction assay (Shanghai Bio-germ Medical

![Figure 1](https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa351/5818308)
Technology Co Ltd). Respiratory tract specimens such as sputum, nasopharyngeal swab, or throat swab samples were collected daily. Since all of the patients in this study were hospitalized patients, lower respiratory tract specimens such as sputum, endotracheal aspirate, or bronchoalveolar lavage fluid were preferred over nasopharyngeal or throat swabs. The proportion of nasopharyngeal or throat swab samples taken was less than 10% of all samples. We performed the specimen collection process according to the manufacturer’s protocol. Diagnosis followed the criteria recommended by the National Institute for Viral Disease Control and Prevention (China) (http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html). A cycle threshold (Ct) value less than 37 was defined as a positive test result, while a Ct value of 40 or more was defined as a negative result. Specimens with a Ct value of 37 to 40 required confirmation by retesting.

**Statistical Analysis**

Continuous variables were expressed as medians with interquartile ranges (IQRs) and were compared by Kruskal-Wallis test. Categorical variables were expressed as number (%) and compared by chi-square ($\chi^2$) test or Fisher’s exact test (if $>20\%$ of the cells had an expected count of $<5$). Significant risk factors identified on univariate analyses were further analyzed by multiple logistic regressions to identify independent risk factors associated with the prolonged duration of SARS-CoV-2 shedding. We used Kaplan-Meier survival analysis to estimate the cumulative SARS-CoV-2 RNA–negativity rate and the stratified log-rank statistic to compare the difference of SARS-CoV-2 clearance between different groups. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Inc, Cary, NC). The significance level of the hypothesis tests was set at .05 (2-sided).

**RESULTS**

**Clinical Characteristics of Patients in This Study**

The study population included 113 symptomatic patients with confirmed SARS-CoV-2 infection. Clinical characteristics of these patients are summarized in Table 1. Among the 113 patients, the median age was 52 years and 58.4% were male. The epidemiological data showed that 62.8% had exposure history to Hubei province and 40.7% of patients had exposure history to patients with confirmed disease. The median time from illness onset to hospital admission was 5 days. Patients with severe disease at admission were 28.3%. The most common comorbidities were hypertension (23.0%) and diabetes (8.0%). The most common treatments were corticosteroid (56.6%) and umifenovir (48.7%). The duration of viral RNA shedding was 17 days. The duration from illness onset to radiologic recovery was 15 days. The duration from illness onset to temperature recovery was 11.5 days. Days of hospitalization were 18. The critical illness during hospitalization was 20.4%. Recovery in 21 days was 61.1%. In-hospital mortality in 21 days was 1.8%.

### Table 1. Comparison of Clinical Characteristics and Treatment Responses Between Groups With Different Shedding Durations

|                                | All Patients (N = 113) | Viral Shedding Duration After Illness Onset | P²  |
|--------------------------------|------------------------|--------------------------------------------|-----|
|                                | n          | Values                      | n <15 Days (n = 37) | n ≥15 Days (n = 76) |     |
| Age, years, median (IQR range) | 113        | 52 (43, 63)                 | 37 48 (34, 61)       | 76 54.5 (45, 63)   | .033 |
| Male sex, % (n)                 | 113        | 58.4 (66)                   | 37 40.5 (15)         | 76 67.1 (51)       | .009 |
| Exposure history in Hubei, % (n)| 113        | 62.8 (71)                   | 37 67.6 (25)         | 76 60.5 (46)       | .467 |
| Exposure history to confirmed patients, % (n) | 113        | 40.7 (46)                   | 37 51.4 (19)         | 76 35.5 (27)       | .108 |
| Duration from illness onset to hospital admission, median (IQR), days | 113        | 5 (3, 8)                    | 37 4 (2, 6)          | 76 6 (4, 9)        | .001 |
| Patients with severe disease at admission, % (n) | 113        | 28.3 (32)                   | 37 16.2 (6)          | 76 34.2 (26)       | .049 |
| Comorbidity, % (n)              | 113        |                             |                           |                   |     |
| Hypertension                   | 113        | 23.0 (26)                   | 37 8.1 (3)           | 76 30.3 (23)       | .009 |
| Diabetes                       | 113        | 8.0 (9)                     | 37 5.4 (2)           | 76 9.2 (7)         | .715 |
| Coronary heart disease         | 113        | 5.3 (6)                     | 37 5.4 (2)           | 76 5.3 (4)         | 1    |
| Current smoker                 | 113        | 7.1 (8)                     | 37 8.1 (3)           | 76 6.6 (5)         | .715 |
| Treatment, % (n)               | 113        |                             |                           |                   |     |
| Corticosteroid                 | 113        | 56.6 (64)                   | 37 40.5 (15)         | 76 64.5 (49)       | .025 |
| Umifenovir                     | 113        | 48.7 (55)                   | 37 43.2 (16)         | 76 51.3 (39)       | .420 |
| Ribavirin                      | 113        | 16.8 (19)                   | 37 8.1 (3)           | 76 21.1 (16)       | .084 |
| Invasive mechanical ventilation| 113        | 15.9 (18)                   | 37 2.7 (1)           | 76 22.4 (17)       | .006 |
| Outcome                        | 113        |                             |                           |                   |     |
| Duration of viral RNA shedding, median (IQR), a days | 113        | 17 (13, 22)                 | 37 11 (8, 13)        | 76 20 (16.5, 25.5) | <.001 |
| Duration from illness onset to radiologic recovery, median (IQR), a days | 106        | 15 (11, 15)                 | 37 12 (10, 15)       | 69 16 (13, 21)     | <.001 |
| Duration from illness onset to temperature recovery, median (IQR), a days | 91         | 11 (8, 14)                  | 29 7 (6, 11)         | 62 11 (10, 14)     | <.001 |
| Days of hospitalization, median (IQR), a days | 105        | 18 (14, 27)                 | 36 13.5 (11.5, 17)   | 69 22 (16, 30)     | <.001 |
| Critical illness during hospitalization, % (n) | 113        | 20.4 (23)                   | 37 5.4 (2)           | 76 27.6 (21)       | .006 |
| Recovery in 21 days, % (n)      | 113        | 61.1 (69)                   | 37 91.9 (34)         | 76 46.1 (35)       | .023 |
| In-hospital mortality in 21 days, % (n) | 113        | 1.8 (2)                     | 37 0.0 (0)           | 76 2.6 (2)         | 1    |

Data are shown as % (n) unless otherwise indicated. Values indicate number of positive results/total number of patients with available assay results. Abbreviation: IQR, interquartile range.

¹Chi-square ($\chi^2$) test or Fisher’s exact test was used, with $P<.05$ as significant.

²Hospitalization data as of 20 March 2020.
illness onset to hospital admission was 5 days (IQR, 3–8 days).
Common underlying concomitant diseases included hypertension (26 cases), diabetes (9 cases), and coronary heart disease (6 cases) (Supplementary Table 1). Among the patients, 8 patients were current smokers. Most of the patients had mild symptoms, and only 28.3% of the cohort were diagnosed as having severe illness at admission. Lopinavir-ritonavir and interferon-α were the most frequently used antiviral regimens (Supplementary Table 1). On the basis of lopinavir-ritonavir and interferon-α combination, 55 patients (48.7%) also received umifenovir, and another 19 patients (16.8%) were treated with ribavirin. Corticosteroids were used in 56.6% patients. The primary purpose of this study was to observe the clinical outcome of patients in the first 21 days after illness onset. There were 74.3% (84) patients who had viral RNA clearance within 21 days after illness onset (Figure 1). The median duration of viral shedding of these 84 patients was 15 days (IQR, 11.75–18 days). With the viral shedding duration of all of the 113 patients included, the median duration of SARS-CoV-2 RNA detection from illness onset was 17 days (IQR, 13–22 days). There were 69 (61.1%) patients of the cohort who recovered and were discharged after 3 weeks, with a median hospital stay of 15 days (IQR, 12–17 days). As of 20 March 2020, a total of 105 patients recovered and were discharged, with a median hospital stay of 18 days (IQR, 14–27 days). Twenty-three patients met the diagnostic criteria as having critically severe illness (ARDS, sepsis, or septic shock) during hospitalization, 18 patients underwent invasive mechanical ventilation, and 2 deaths occurred. Ninety-one patients had fever as an initial symptom of illness. The median time from illness onset to body temperature recovery to normal was 11 days (IQR, 8–14 days).

As of 22 March 2020, 106 patients had signs of recovery with radiological imaging, and the median duration from illness onset to radiological recovery was 15 days (IQR, 11–18 days).

### Risk Factors for Prolonged Duration of SARS-CoV-2 RNA Shedding

The primary purpose of this study was to observe the occurrence of viral RNA clearance within 21 days after illness onset. Among the 113 patients enrolled, there were 84 patients who had viral RNA clearance within 21 days. The median duration of viral RNA shedding for these 84 patients was 15 days. Patients were further divided into 2 groups; 1 group with patients who had persistent negative viral detection results less than 15 days after illness onset (n = 37) and another group of patients with prolonged viral RNA shedding 15 days or more after illness onset (n = 79). Epidemiological and clinical characteristics, treatment therapy, and outcomes were compared between the 2 groups (Table 1). Prolonged RNA shedding was associated with delayed recovery on radiological imaging (median days, 12 vs 16; P < .001), delayed recovery of body temperature (median days, 7 vs 11; P < .001), and prolonged hospital stay (median days, 13.5 vs 22; P < .001). More patients recovered and were released by 21 days after illness onset (91.9% vs 46.1%, P = .023) in the group with early viral RNA clearance than in the group with prolonged viral RNA shedding.

Variables that were statistically significant (P < .05) between early- and late-viral-RNA-clearance groups, including age, male sex, hypertension, use of corticosteroid, duration from illness onset to hospitalization, severe illness at admission, critically severe illness during hospitalization, and occurrence of mechanical ventilation, were tested in a multivariable model. Multivariate analysis indicated that the time from illness onset to hospital admission (odds ratio [OR], 1.30; 95% confidence interval [CI], 1.10–1.54; P = .002) and male sex (OR, 3.24; 95% CI, 1.31–8.02; P = .011) were independent factors associated with the duration of SARS-CoV-2 RNA shedding (Table 2). From the Kaplan-Meier curves, the cumulative probability of viral negative conversion was slightly higher in the female group than that in the male group (P = .043) (Figure 2A).

### Table 2. Multivariable Analyses of Factors Associated With Duration of SARS-CoV-2 Virus RNA Detection

| Variable | Multivariable Analysis | Stepwise Analysis |
|----------|------------------------|-------------------|
|          | OR     | 95% CI    | P      | OR     | 95% CI    | P      |
| Age      | 1.00   | .96–1.03  | .913   | ...    | ...       | ...    |
| Male sex | 2.89   | 1.10–7.58 | .031   | 3.24   | 1.31–8.02 | .011   |
| Hypertension | 3.94   | .96–18.15 | .079   | ...    | ...       | ...    |
| Corticosteroid | 1.38   | .52–3.65  | .519   | ...    | ...       | ...    |
| Time from illness onset to hospitalization, days | 1.31   | 1.08–1.58 | .005   | 1.30   | 1.10–1.54 | .002   |
| Patients with severe disease at admission | 1.10   | .32–3.81  | .882   | ...    | ...       | ...    |
| Critical illness during hospitalization | .42    | .03–5.22  | .497   | ...    | ...       | ...    |
| Invasive mechanical ventilation | 23.28  | .72–750.09 | .076   | 9.88   | 1.11–88.02 | .04    |

Abbreviations: CI, confidence interval; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
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curve analysis showed that patients admitted to the hospital 5 days after illness onset achieved a higher probability of faster viral RNA clearance ($P = .021$) (Figure 2B) than those patients admitted to the hospital more than 5 days after illness onset. SARS-CoV-2 RNA clearance was significantly delayed in patients who underwent invasive mechanical ventilation during hospitalization (OR, 9.88; 95% CI, 1.11–88.02; $P = .04$) compared with those who did not undergo invasive mechanical ventilation (Table 2) (Figure 2C).

Disease Progression Related to Sex and Hospital Admission Time

Among the 113 patients, 41.6% (47 patients) were female and 58.4% (66 patients) were male. Illness severity at admission and treatment outcomes were compared between male and female patients (Table 3). The median duration of SARS-CoV-2 RNA shedding was 15 days (IQR, 12–17 days) in the female group and 18.5 days (IQR, 15–25 days) in the male group ($P = .013$). The proportion of patients with severe disease at admission in the male group (37.9%) was significantly higher than that in the female group (14.9%, $P = .010$). The median length of hospital stay was longer in the male group than in the female group (median days, 15 vs 22; $P = .002$). Early ($\leq 5$ days) versus later (>5 days) hospital admission was significantly associated with viral RNA clearance speed ($P = .004$). Late hospital admission was associated with a higher proportion of patients with severe disease at admission (43.4% vs 15.0%, $P = .001$) and a higher frequency of critically severe illness during hospitalization (30.2% vs 11.7%, $P = .019$) than was early hospital admission (Table 3).

DISCUSSION

Studies on COVID-19 have generally been limited to the description of the initial clinical, hematological, and radiological findings. So far, there has been little investigation of the duration of SARS-CoV-2 RNA shedding. This study is the first to document the risk factors associated with prolonged SARS-CoV-2 shedding in the respiratory tract among a cohort of patients with COVID-19. We found that the median duration from onset of symptoms to RNA clearance was 17 days. Male sex, delayed hospital admission, and invasive mechanical ventilation were independent risk factors for prolonged SARS-CoV-2 RNA shedding.

Male patients usually had more severe symptoms at admission and longer duration of viral RNA shedding than female patients with COVID-19. This observation may indicate that males are more severely affected than females by the SARS-CoV-2 infection. Studies from the SARS and Middle East Respiratory syndrome (MERS) epidemics already indicated that there may be sex-related differences in disease outcomes [11, 12]. The findings here are consistent with a recent epidemiological report including 44 672 confirmed cases in China, which showed the case fatality rate was 2.8% for males and 1.7%
for females [4]. It was suggested that sex-related difference was confounded by other variables such as comorbidity conditions or smoking history. The smoking rates were comparable between the early-clearance group and the prolonged-shedding group in this study. There was a higher percentage of patients with hypertension in the prolonged-viral-RNA-shedding group than in the early-clearance group; however, hypertension was not a significant risk factor in the logistic regression model. Thus, it was suggested that sex itself is the influencing factor of disease progression.

The specific mechanism of sex-related difference in SARS-CoV-2 infection is unclear. Women as a population are thought to have stronger immune system response than males, as they exhibit lower infection and mortality rates with infectious diseases, and display higher responses to various types of vaccination than men [13]. The specific mechanism may be related to sex hormones, which could modulate immunocompetence [14]. Sex-specific immune responses have been found to contribute to enhanced susceptibility of male mice to SARS-CoV-1 infection [15]. We propose that another one of the potential mechanisms might be related to human angiotensin-converting enzyme 2 (ACE2) expression. ACE2 is a functional receptor for SARS-CoV-1 [16]. SARS-CoV-2 has been confirmed to use this same cell entry receptor as SARS-CoV-1 [17]. Results of animal studies demonstrated that tissue-specific regulation of ACE2 by sex hormones could contribute to sex-related differences in obesity-hypertension [18]. The modulation and angiotensin II level by ACE2 and ACE could partly explain the sex-specific susceptibility to diabetes and diabetic nephropathy [19]. Further in-depth mechanical studies are warranted to understand the sex-related dimorphism of COVID-19.

Our findings also suggest that symptomatic patients should be admitted to the hospital as early as possible if SARS-CoV-2 infection is confirmed. Delayed hospital admission was associated with more severe conditions at admission and worse treatment outcomes. There have been no specific antiviral drugs for SARS-CoV-2. In our study, lopinavir-ritonavir and interferon-α were the most frequently used antiviral regimens. It was hard to evaluate the efficacy of these 2-drug combination because of the lack of controls. However, the association between early admission to hospital and early viral RNA clearance might indicate a potential effect of these treatments [20, 21]. Recently, a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection showed no benefit of lopinavir-ritonavir treatment beyond standard care [22]. The efficacy of lopinavir-ritonavir and interferon-α in combination should be evaluated in clinical trials. General supportive treatment might also help to accelerate the process of recovery.

Several observational studies have reported that corticosteroid therapy was linked to persistent viral RNA shedding in patients with avian influenza A (H7N9), MERS, and SARS [23–25]. Corticosteroid usage was related to prolonged viral RNA shedding time in this report as well, as patients with early RNA clearance had lower proportion of patients using corticosteroid compared with patients with late RNA clearance (40.5% vs 64.5%, P = .025). However, this difference can be influenced by disease severity, as patients who were given corticosteroids usually had more severe disease than those who did not. Furthermore, corticosteroid use was not found to be an independent risk factor for prolonged viral RNA shedding in the multivariable model conducted in this report. Thus, a definitive conclusion that corticosteroid treatment is associated with prolonged viral RNA shedding duration in patients with COVID-19 cannot be drawn. The reason for the inconsistent results might be that the corticosteroid doses in this report were relatively low (0.5–1 mg methylprednisolone/kg body weight) for patients with COVID-19.

Table 3. Comparison of Treatment Outcomes Between Groups of Different Sex or Duration Time From Illness Onset to Hospital Admission

| Duration From Illness Onset to Hospital Admission | Sex | P     |
|---------------------------------------------------|-----|-------|
| ≤5 Days (n = 60) >5 Days (n = 53) | Female (n = 47) Male (n = 66) | P     |
| Patients with severe disease at admission, % (n)   | 15.0 (9) 43.4 (23) | 14.9 (7) 37.9 (25) | .010 |
| Duration of viral shedding, median (IQR), days     | 15 (10, 20) 19 (15, 25) | 15 (12, 17) 18.5 (15, 25) | .013 |
| Duration from illness onset to radiologic recovery, median (IQR), days | 15 (10, 13) 15 (13, 20) | 15 (12, 17) 16 (11, 20) | .567 |
| Recovery in 21 days, % (n)                          | 58.3 (35) 64.2 (34) | 72.3 (34) 53.0 (35) | .152 |
| In-hospital mortality, % (n)                        | 0.0 (0) 3.8 (2) | 0.0 (0) 3.0 (2) | .51 |

Data are shown as % (n) unless otherwise indicated. Values indicate number of positive results/total number of patients with available assay results. Abbreviation: IQR, interquartile range.

*Chi-square (χ²) test or Fisher’s exact test was used with P < .05 as significant.

Hospitalization data as of 20 March 2020.
Invasive mechanical ventilator support was found to be another important independent predictor of prolonged viral RNA shedding. There were several reasons for the delayed viral RNA clearance in patients who received invasive mechanical ventilator support. One was that the detection rate of coronavirus RNA differed among various types of respiratory tract specimens. Highly pathogenic avian influenza A(H5N1) virus RNA can be detected longer and at higher levels in lower respiratory tract specimens than in upper respiratory tract specimens [26]. For viruses that replicate primarily in lower respiratory tract tissue, endotracheal aspirate specimens from patients who receive invasive mechanical ventilation usually have higher and sustained viral RNA shedding than specimens in upper respiratory tract tissue [27–29]. Kinetic analysis of viral RNA shedding in patients with MERS showed that virus secretion in the lower respiratory tract was more sustained in patients who suffered from more severe pneumonia than those with mild disease [30]. Another potential reason for prolonged duration of viral RNA shedding is the emergence of drug resistance during antiviral treatment, since most of the patients who underwent invasive mechanical ventilation had a longer hospital stay.

This study had some limitations. First, although viral RNA was detected in most of the studies, viral RNA shedding is not exactly the same as viral shedding. So far, it is not known how shedding of viral RNA correlates with shedding of infectious virus. Second, the standard treatment included antiviral treatment with lopinavir–ritonavir, interferon-α, and general supportive treatment. Since nearly all the patients were given this standard treatment, we were not able to judge if these treatments had an effect on viral RNA shedding. Third, for patients who received invasive mechanical ventilation, lower respiratory tract specimens were collected. Bias might be introduced when comparing differences directly in viral RNA shedding between sputum versus endotracheal aspirate or bronchoalveolar lavage fluid.

In conclusion, prolonged SARS-CoV-2 RNA shedding in the respiratory tract was independently associated with delayed admission to hospital, male sex, and invasive mechanical ventilation. These results reinforce guidance that hospital admission and treatments should be started as soon as possible in patients with COVID-19. Male patients need particular attention to prolonged viral RNA shedding, which might be associated with poor treatment outcomes. Understanding the virological dynamics during the process of illness should be helpful in the clinical management of patients with COVID-19.

Supplementary Data
Supplementary materials are available at Clinical 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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