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Respiratory Medicine 178 (2021) 106328

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Factors associated with delayed viral shedding in COVID-19 infected patients: A retrospective small-scale study

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ARTICLE INFO

Keywords:
Viral shedding
COVID-19
Corticosteroid
Risk factor

ABSTRACT

Background: The outbreak of COVID-19 has caused ever-increasing attention and public panic all over the world. Until now, data are limited about the risk factors to virus shedding in COVID-19 infected patients.
Methods: In this retrospective study, data were collected from 87 patients hospitalized with COVID-19 infection in Suzhou. Using Cox proportional hazards regression and Kaplan-Meier survival analysis, the risk factors to COVID-19 RNA shedding was to be established according to demographic information, clinical characteristics, epidemiological history, antiviral medicine and corticosteroid administration.
Results: The median duration of COVID-19 RNA shedding from admission was 13.11 ± 0.76 days. There was no significant difference in viral shedding duration in terms of gender, age, history of Hubei province stay, characteristics of chest CT on admission, lymphocytopenia and clinical severity. By Cox proportional hazards model, excessive 200 mg cumulative corticosteroid (HR, 3.425 [95% CI, 1.339–7.143]), time from illness onset to hospitalization (<5 days) (HR, 2.503 [95% CI, 1.433–4.371]) and arbidol-included therapy (HR, 2.073 [95% CI, 1.185–3.626]) were the independent risk factors to delay COVID-19 RNA shedding. Besides of excessive 200 mg of cumulative corticosteroid (HR, 2.825 [95% CI, 1.201–6.649]), admission within 5 days from illness onset (HR, 2.493 [95% CI, 1.393–4.462]) and arbidol-included therapy (HR, 2.102 [95% CI, 1.073–4.120]), lymphocytopenia (HR, 2.153 [95% CI, 1.097–4.225]) was further identified as another unfavorable factor to 10-day viral shedding.
Conclusions: The potential risk factors could help clinicians to identify patients with delayed viral shedding, thereby providing the rational strategy of treatment and optimal anti-viral interventions.

1. Introduction

Since last December, the outbreak of COVID-19 has caused ever-increasing attention and public panic all over the world [1–3]. China's National Health Commission had released the seventh trial version of Diagnosis and Treatment Scheme for Pneumonitis with COVID-19 Infection, and provided a systematic treatment strategy for cases.

Unfortunately, there are still no specific antiviral medicines or vaccines recommended for COVID-19 infection. Without prior experience of therapy, the current treatment of COVID-19 infection is mainly empirical and symptomatic, and a limited number of therapeutics in ongoing clinical trial were adopted from previous research with Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome (MERS) [4–7]. Under the circumstances, studies of the association between duration of COVID-19 shedding and clinical factors may produce more interesting findings [8,9].

Here, we conducted a retrospective study of 87 hospitalized patients with laboratory-confirmed COVID-19 infection to assess the impact of treatment strategies and clinical features on the duration of COVID-19 shedding.

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https://doi.org/10.1016/j.rmed.2021.106328
Received 24 April 2020; Received in revised form 1 February 2021; Accepted 2 February 2021
Available online 6 February 2021

2. Patients and methods

2.1. Patients

All 87 patients were admitted to The Fifth People's Hospital of Suzhou and diagnosed with COVID-19 pneumonia from Jan 10 to Feb 16, 2020. Diagnosis of COVID-19 infection in patients was made by positive test for viral RNA of respiratory secretions obtained by bronchoalveolar lavage, sputum, nasopharyngeal swab, or oropharyngeal swab. Demographic information, clinical characteristics and chest CT scan results of each patient were obtained from the electronical medical record system of The Fifth People's Hospital of Suzhou. Severity of COVID-19 was defined according to the diagnostic and treatment guideline for COVID-19 pneumonia issued by Chinese National Health Committee (Version 1–7). The study was approved by the Ethics Committee of the Fifth People's Hospital of Suzhou (2020-005).

2.2. Virologic investigations

COVID-19 infection was confirmed in all patients by testing respiratory specimens with a real-time reverse transcription-polymerase chain reaction (RT-PCR) assay at the local laboratory of the Center for Disease Control and Prevention. During hospitalization, respiratory specimens (sputum, nasopharyngeal swab, or oropharyngeal swab) were collected every second day for detection of COVID-19 by real-time RT-PCR. We defined the interval from admission to the date of the first COVID-19 RNA-negative result before discharge as the COVID-19 RNA shedding duration.

2.3. Clinical investigations

Candidate clinical variables considered for analysis of prolonged duration of COVID-19 RNA shedding were sex, age, epidemiological history, clinical severity, lymphocytopenia, time from illness onset to hospitalization, specific antiviral medicine and corticosteroid administration. Corticosteroid treatment was defined as administration of a cumulative dose equivalent to ≥200 mg of methylprednisolone during hospitalization. Among the 87 patients, antiviral treatments included Arbidol monotherapy (18/87, 20.69%), Kaletra (Lopinavir/Ritonavir) monotherapy (37/87, 42.53%), Arbidol and Kaletra (25/87, 28.74%) and naive antiviral treatment (7/87, 8.05%). Limited by the number of cases, antiviral treatment was defined as Arbidol-included and Arbidol-excluded sub-groups.

2.4. Statistical analysis

Statistical analyses were performed using SPSS, version 24.0 for Windows. Mean values and standard deviations or median values with interquartile range were used to describe continuous variables, and absolute or relative frequencies were used to describe categorical variables. We used the Student *t*-test and the Mann-Whitney *U* test for analysis of continuous variables and the χ^2 test or Fisher exact test for analysis of discrete variables in bivariate analyses. Kaplan-Meier survival analysis was used to estimate the cumulative COVID-19 RNA-negativity rate. To identify risk factors associated with delayed duration of COVID-19 RNA shedding, we performed a time-dependent Cox proportional hazards model that adjusted for baseline covariates. For all analyses, probabilities were 2-tailed, and a 2-tailed *P* value of <0.05 was considered significant.

3. Results

3.1. Virologic outcomes

All patients had resolution of COVID-19 shedding and survived. Of the samples that yielded the COVID-19 RNA test results, all were from nasopharyngeal swab specimens before discharge. Only 21 patients (24.14%) had undetectable COVID-19 RNA within 7 days, 53 (60.92%) tested negative within 14 days, and 81 (93.10%) tested negative within 28 days of hospitalization (Fig. 1). COVID-19 RNA was undetectable among all patients within 37 days after hospitalization, but it turned positive in convalescence in a small subset of patients (data not shown) [10].

3.2. Duration of COVID-19 RNA shedding

The main characteristics of all patients are summarized in Table 1. The median duration of COVID-19 RNA shedding was 13.11 ± 0.76 days (3–37 days). In the analysis of subgroup, there was no significant difference in duration of viral RNA shedding in terms of gender, age, history of Hubei Province stay, characteristics of chest CT on admission, length of lymphopenia, and clinical severity.

Interestingly, high dosage of cumulative corticosteroid (≥200 mg) administration could delay the duration of viral RNA shedding compared with low dosage of cumulative corticosteroid ($P = 0.04$), patients with no usage and low dosage of cumulative corticosteroid (<200 mg) exhibited comparable duration of viral RNA shedding ($P = 0.73$). In terms of anti-viral treatment, patients who received arbidol-included therapy displayed longer duration of viral RNA shedding than those who received arbidol-excluded therapy ($P = 0.001$). Unexpectedly, patients who admitted within 5 days after illness onset experienced more days of viral RNA shedding than those who admitted over 5 days after illness onset ($P = 0.005$).

3.3. Risk factors for delayed viral shedding in a multivariable model

Then, we extended the data to time-dependent Cox proportional hazards model (Tables 2 and 3). Excessive 14 days were defined as delayed COVID-19 RNA shedding. Univariate analysis revealed that gender, age, history of Hubei province stay, characteristics of chest CT on admission, lymphocytopenia and clinical severity were not risk factors for delaying viral shedding. After multivariate logistic regression, only high dosage (≥200 mg) of cumulative corticosteroid administration (HR, 3.425 [95% CI, 1.339–7.143]), time from illness onset to hospitalization (<5 days) (HR, 2.503 [95% CI, 1.433–4.371]) and arbidol-included therapy (HR, 2.073 [95% CI, 1.185–3.626]) were the independent predictors of delaying COVID-19 viral shedding.

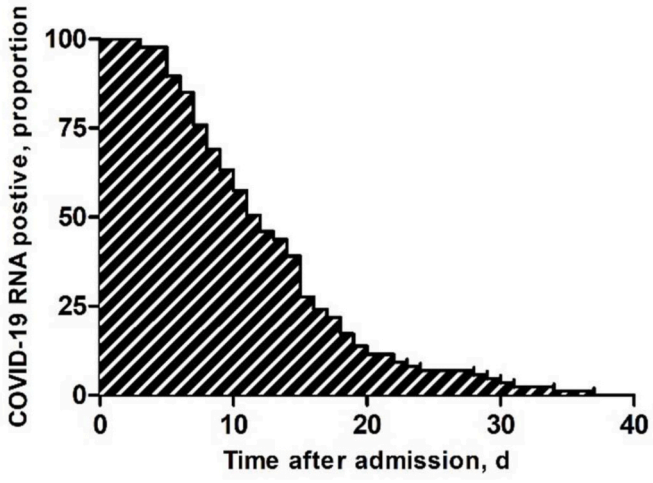

Fig. 1. Overview of duration of viral shedding in hospitalized COVID-19 infected patients.

Table 1
Duration of COVID-19 RNA shedding.

Variable	n	Duration of viral RNA shedding (days)	*P-value*
Age (yrs)			0.50
<50	53	12.70 ± 1.05	
≥50	34	13.76 ± 1.07	
Gender			0.33
Male	46	13.83 ± 1.13	
Female	41	12.32 ± 1.00	
History of Hubei Province stay			0.59
No	40	12.48 ± 1.06	
Yes	47	13.66 ± 1.09	
Characteristics of chest CT on admission			>0.05
No sign of pneumonia	7	12.14 ± 2.45	
GGOs	31	13.94 ± 1.42	
Crazy-paving pattern	24	12.79 ± 1.39	
Consolidative	25	12.68 ± 1.36	
Time from illness onset to hospitalization			0.005
<5 days	48	15.02 ± 1.06	
≥5 days	39	10.77 ± 0.98	
Cumulative corticosteroids dosage			
No	61	12.56 ± 0.97	*<0.05
<200 mg	11	11.73 ± 1.78	
≥200 mg	15	16.40 ± 1.33*	
Antiviral therapy			0.001
Arbidol-included	43	15.58 ± 1.18	
Arbidol-excluded	44	10.70 ± 0.83	
Length of lymphopenia			0.46
No	43	12.53 ± 1.20	
Yes	44	13.68 ± 0.95	
Clinical severity			0.30
Non-severe	66	12.67 ± 0.90	
Severe	21	14.52 ± 1.38	

3.4. Influencing factors on 10-day viral shedding

We chose 10-day COVID-19 RNA clearance as early virologic outcomes. Kaplan-Meier survival analysis was used to estimate the cumulative COVID-19 RNA-negativity rate (Fig. 2). In according to multivariable model, duration of viral shedding was significantly decreased in patients who received ≥200 mg of cumulative corticosteroid administration (HR, 2.825 [95% CI, 1.201–6.649]), arbidol-included therapy (HR, 2.102 [95% CI, 1.073–4.120]) or admitted within 5 days after illness onset (HR, 2.493 [95% CI, 1.393–4.462]). Interestingly, lymphocytopenia (HR, 2.153 [95% CI, 1.097–4.225]) was additionally identified as an unfavorable factor to 10-day viral shedding.

4. Discussion

To our knowledge, few previous studies have been done among patients with COVID-19 viral shedding [11]. Additionally, details of the clinical and virological course of illness have not yet been well described. Under the circumstances, the estimation of risk factors for viral shedding in cases series was very meaningful.

In the current study of 87 hospitalized COVID-19-infected patients, we identified independent risk factors for delayed viral shedding and examined the impact of clinical treatment regimens on COVID-19 RNA shedding. It should be noted that, as the incubation period for individual case increased uncertainty in the intervals of exposure and symptom onset [12,13], and almost half of all cases were admitted over 5 days after illness onset, we defined the interval from admission to the date of the first COVID-19 RNA negative result before discharge as the COVID-19 RNA shedding duration, which might also over-represent hospitalized impact on viral shedding.

Until now, there have been no effective antiviral treatments for the COVID-19 infection, although some medicines (Arbidol, Kaletra) have

Table 2
Clinical characteristics and duration of COVID-19 RNA shedding.

Variable	Viral shedding (≥14 days)	Viral shedding (<14 days)	*P-value*
Age (yrs)			
<50	19(55.9)	34(64.2)	0.441
≥50	15(44.1)	19(35.8)	
Gender			
Male	19(55.9)	27(50.9)	0.652
Female	15(44.1)	26(49.1)	
History of Hubei Province stay			0.246
No	13(38.2)	27(50.9)	
Yes	21(61.8)	26(49.1)	
Characteristics of chest CT on admission			0.724
No sign of pneumonia	2(5.9)	5(9.4)	
GGOs	13(38.2)	18(44.0)	
Crazy-paving pattern	11(32.4)	13(24.5)	
Consolidative	8(23.5)	17(32.1)	
Time from illness onset to hospitalization			0.006
<5 days	25(73.5)	23(43.4)	
≥5 days	9(26.5)	30(56.6)	
Cumulative corticosteroids dosage			0.056
No	21(61.8)	40(75.5)*	
<200 mg	3(8.8)	8(15.1)**	
≥200 mg	10(29.4)	5(9.4)***	
Antiviral therapy			0.006
Arbidol-included	23(67.6)	20(37.7)	
Arbidol-excluded	11(32.4)	33(62.3)	
Lymphopenia			0.428
No	15(44.1)	28(52.8)	
Yes	19(55.9)	25(47.2)	
Clinical severity			0.357
Non-severe	24(70.6)	42(79.2)	
Severe	10(29.4)	11(20.8)	

Note: *, $P = 0.908$, "No" with "<200 mg"; **, $P = 0.023$, "No" with "≥200 mg"; ***, $P = 0.047$, "<200 mg" with "≥200 mg".

Table 3
Multi-variate analysis of risk factor associated with prolonged viral shedding (≥14 days) in patients with COVID-19 infection.

Variable	Unadjusted HR (95% CI)	*P-value*	Adjusted HR (95% CI)	*P-value*
Age				
≥50 (yrs)	1.345 (0.767–2.359)	0.302		
Gender				
Male	1.216 (0.709–2.085)	0.477		
History of Hubei Province stay				
Yes	1.337 (0.779–2.293)	0.292		
Time from illness onset to hospitalization				
<5 days	2.235 (1.294–3.860)	0.004	2.503 (1.433–4.371)	0.001
Cumulative corticosteroids dosage				
<200 mg	0.894 (0.418–1.912)	0.771	0.852 (0.396–1.835)	0.683
≥200 mg	2.976 (1.172–7.576)	0.022	3.425 (1.339–7.143)	0.010
Antiviral therapy				
Arbidol-included	2.211 (1.266–3.862)	0.005	2.073 (1.185–3.626)	0.011
Lymphopenia				
Yes	1.488 (0.866–2.556)	0.150		
Clinical severity				
Severe	1.500 (0.771–2.918)	0.232		

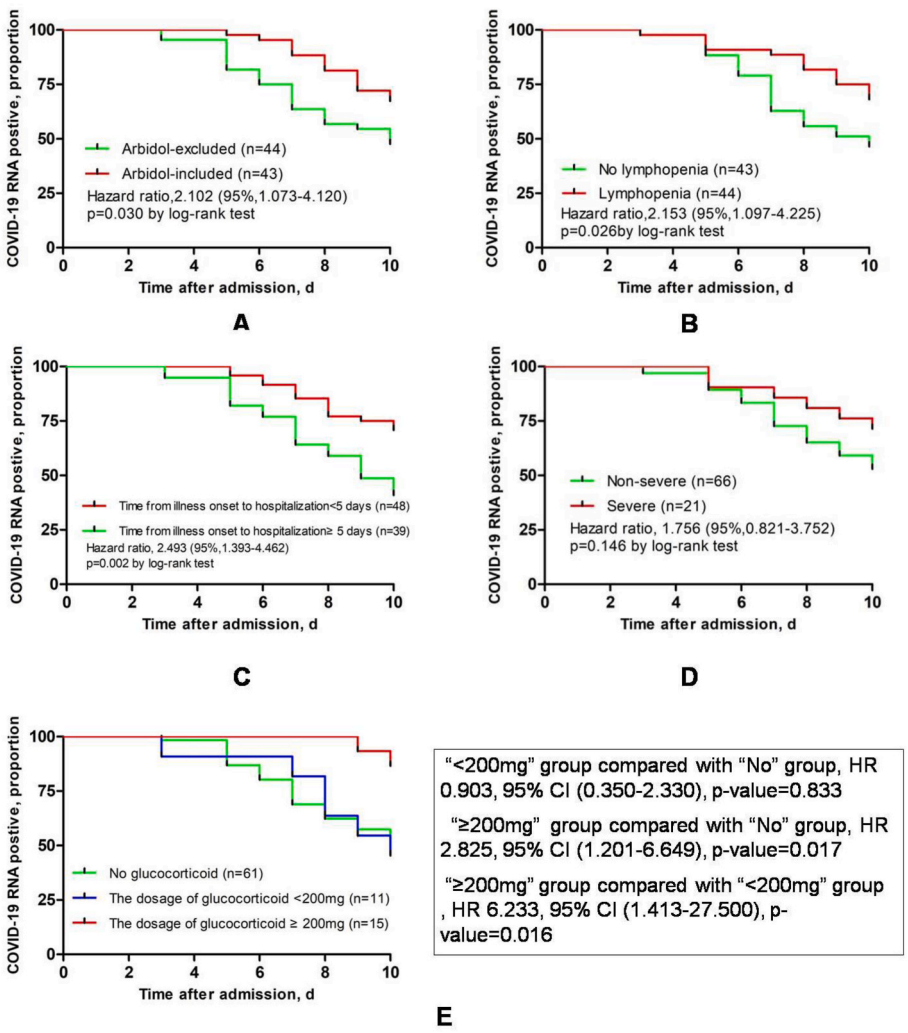

Fig. 2. Kaplan-Meier survival analysis was used to estimate the 10-day COVID-19 RNA clearance. A, Cumulative proportion of patients between who received arbidol-included therapy and those received arbidol-excluded therapy. B, Cumulative proportion of patients presented with or without lymphocytopenia. C, Cumulative proportion of patients admitted <5 days versus ≥5 days after illness onset. D, Cumulative proportion of non-severe and severe group. E, Cumulative proportion of patients treated with ≥200 mg, <200 mg of cumulative corticosteroid and no usage of corticosteroid.

been most commonly used, no controlled trials have demonstrated their benefits. Our study is earlier to assess the impact of different anti-viral regimens, including combination treatment on viral shedding. Due to the deficiency of sample size and an un-matched control group, we could not draw an accurate conclusion about the role of anti-viral regimens in patients with COVID-19. In spite of that, our finding strongly indicated that arbidol did not provide an additional virologic benefit as compared with baseline treatment.

Corticosteroids are widely used to prevent lung injury caused by severe community-acquired pneumonia (sCAP) [14]. More importantly, the severe H1N1-illness benefited from adjunctive treatment with low dose of corticosteroids [15]. However, most observational studies have reported that usage of corticosteroids was associated with persistent viral shedding in patients with seasonal influenza, MERS and SARS [7,16–18].

Nowadays, systematic corticosteroids treatment (methylprednisolone, <1–2 mg per kg body weight, for 3–5 days) was recommended to be an adjuvant therapy, which immediately raised concerns about whether COVID-19 infected patients could benefit from corticosteroids therapy. This present study indicated that over 200 mg of methylprednisolone-equivalent dose or an excessive cumulative dose was a risk factor associated with delayed viral clearance. In addition, a further study found that less 200 mg of methylprednisolone-equivalent dose or a cumulative dose was not considered as unfavorable factor to viral shedding compared with no usage of corticosteroids. Notably, we did not focus on the impact of duration of corticosteroids therapy on viral shedding, as almost all of cases received corticosteroids over 200 mg were corresponding to those received corticosteroids over 5 days. Hence, lower dose and short duration of corticosteroids treatment, along with adverse drug reaction monitoring, would be more beneficial in clinical management of critical patients with COVID-19 [19].

The presence of lymphocytopenia as a signature of severe COVID-19 was confirmed by Wang D et al., reported that ICU patients had a median lymphocyte count of 800 cells/mm^3 [3]. The presence of lymphocytopenia suggested the existence of immunological dysregulation serve as an accompanying event of the critical illness [20,21]. In this study, although cases presented with lymphocytopenia displayed the impaired viral shedding within the initial 10 days during hospitalization, lymphocytopenia was not considered to be able to generate delayed viral shedding across whole disease course.

All the patients confirmed to have COVID-19 infection have identifiable epidemiological connections. Of the index cases imported from Hubei province, they resulted in the occurrence of secondary infections in Suzhou. It was important to analyze and determinate the difference of viral shedding between index cases and their next-generation cases [13]. So far, of those with secondary infection, they displayed comparable duration of viral shedding with those who had the history of Hubei province stay.

As reported in H7N9 infection, it was reinforced guidance that NAI treatment should be started as soon as possible in patients [17]. Nevertheless, our data showed that time from illness onset to hospitalization (<5 days) was an independent predictor of delayed viral

shedding, which meant early hospitalization and therapy could not alter the virologic outcomes in patients with COVID-10 infection. It is suggested that pathophysiology and natural history of COVID-19 itself impact the virologic process [22,23].

Finally, limited by the deficiency of sample size and retrospective nature, we could not draw an accurate conclusion about the risk factors to the delayed viral shedding. Whatever, our clinical experiences and available descriptive data were prone to support clinicians to identify patients with delayed viral shedding, thereby providing the rational treatment and optimal anti-viral strategy [11].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We thank the patients, the nurses and clinical staff who are providing care for the patients, and staff at the local and state health departments.

Abbreviations

CAP	Community-acquired pneumonia
COVID-19	2019 Novel Coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
NAI	Neuraminidase inhibition
RT-PCR	Reverse transcription-polymerase chain reaction
SARS	Severe acute respiratory syndrome

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Fifth People's Hospital of Suzhou (2020-005).

Consent for publication

In this retrospective small-scale study, written informed consents from the patients were waived, which was approved by the Ethics Committee of The Fifth People's Hospital of Suzhou (2020-005).

Availability of data and material

All data generated during this study are included in this published article.

Funding

This work was supported by the Societal and Developmental Project of Suzhou City (SYS2020018, SYS2020008) and Postgraduate Research & Practice Innovation Program of Jiangsu Province SJCX20_1075. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

CC, HJA and SXH participated in the conception, the methodology, coordination of the study, original draft and review & editing. CHR and ZXY conceived of the study, and participated in its design, data analysis and data curation. ZL, ZH, GBB, TW and DJ participated in clinic care and data collection.

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