Prolonged viral RNA shedding is associated with improved prognosis in COVID-19 patients: a retrospective cohort study

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Abstract

Background: Whether there is also a correlation between viral shedding duration and the clinical course of illness in COVID-19 has not yet been determined. Methods: In this retrospective study, we included 239 adult inpatients (all [?]18 years old) with laboratory-confirmed COVID-19 from the Wuhan Tongji Hospital (Wuhan, China). Results: Of the subset of 239 patients included in this study, 33 patients died due to COVID-19 and 45 patients demonstrated clinical progression to critical illness. Patients with a long duration of viral RNA shedding as compared to short duration of viral RNA shedding also had significantly lower mortality rates ((9.5% vs. 18.6%, P= 0.04) and a lower rate of progression to critical illness (16.7% vs. 21.2%, P= 0.37). Viral RNA shedding is an independent risk factor for mortality within 28 days of observation (OR 0.94, 95% CI: 0.88-0.99, P= 0.025, by multivariable regression analyses) and increased duration of viral shedding is correlated with a significant survival advantage (P =0.047) and lower risk of progression to critical illness (P =0.029, by Kaplan-Meier analyses). Conclusions: Prolonged viral RNA shedding duration is associated with improved patient prognosis and reduces the risk of progression to critical illness in this subset of COVID-19 patients. Further clinical studies are necessary to determine if a longer duration of viral RNA shedding with COVID-19 is predictive of an overall better patient prognosis and outcome.

Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-Coronavirus-2 (SARS-CoV-2)), which causes coronavirus disease 2019 (COVID-19) has been the focus of global attention. This severe respiratory illness originated in Wuhan City in the Hubei province in China and is capable of rapid community transmission. Thus far, the most efficient effort at limiting disease spread has been by minimizing person-to-person contact and by isolating infected patients[1]. The clinical spectrum of COVID-19 includes asymptomatic infection, mild upper respiratory tract illness, severe viral pneumonia with respiratory failure, and death[2].

In previous studies of seasonal influenza, it has been shown that the longer duration of viral RNA shedding (among other factors such as the use of corticosteroids, the delay of antiviral treatment, and other comorbidities) is correlated with worse patient prognosis[3]). Furthermore, our previous studies have revealed that viral RNA clearance is associated with prognosis in patients infected with influenza A(H7N9)[4].

Although observational studies have shown that viral RNA concentration is independently associated with risk of complications and respiratory insufficiency in influenza [3-6], it has yet to be determined if a longer duration of viral RNA shedding in SARS-CoV-2 is also associated with worse patient prognosis and disease progression (including severe viral pneumonia with respiratory failure and/or death). Additionally, a previous study reported that the median duration of viral shedding in patients who recovered from COVID-19 was 20 days, although this study did not test if there was an association of viral shedding with patient recovery[2]. In

this retrospective study, we explore the correlation between the viral RNA shedding duration of SARS-CoV-2 and patient prognosis to determine if viral shedding duration time could be used to assess patient risk of transmission and to help guide clinical decisions for patients infected with COVID-19.

Methods

Study design and participants

In this retrospective study, we included 239 laboratory adult inpatients ([?] 18 years old) admitted at Wuhan Tongji Hospital (Wuhan, China) from February 9^{th}, 2020 to March 9^{th}, 2020 and who were diagnosed with COVID-19 according to to the Chinese management guideline for COVID-19 (version 7.0) and the World Health Organization interim guidance.

Severe and critically ill COVID-19 patients were identified by reviewing and analyzing admission logs and histories of all available electronic medical records and patient care resources independently by two physicians. The severe form of COVID-19 patients was defined as one or more of the following symptoms: 1. Shortness of breath, respiratory rate (RR) [?] 30 breaths/minute; 2. PaO_2/FiO_2 [?] 300mmHg; 3. SaO_2 or SpO_2 [?] 93% on room air. A patient was considered to have progressed to critical illness if they experienced at least one of the following criteria: 1. Respiratory failure requiring mechanical ventilation; 2. Shock; 3. Combined organ failure requiring monitoring and treatment in intensive care unit (ICU). This study was approved by the Institutional Review Board at Wuhan Tongji Hospital (Wuhan, China) and The First Affiliated Hospital of Soochow University (Suzhou, China). As COVID-19 is classified as an emerging infectious disease, written informed patient consent was exempt.

Data collection

Demographic characteristics (age and gender), clinical characteristics (comorbidities, laboratory findings, severity of illness scores, treatments, complications and outcomes) were recorded. Clinical data were reviewed independently by two physicians.

Patients were followed for up to 28 days after inpatient hospital admission until hospital discharge, or death, whichever came first. The primary outcome of our study was defined as mortality after admission (during the 28-day monitoring period). The secondary outcome of our study was defined as the patient's rate of progression to critical illness after admission (during the 28-day period of monitoring).

The SARS-CoV-2 RNA shedding duration was defined as the interval between illness onset and the date of the last pharyngeal swab with a positive finding. We excluded the patients whose pharyngeal swab test remain positive when died.

Corticosteroid treatment was defined as administration of a dose equivalent to [?]25 mg of methylprednisolone per day during hospitalization. The criteria for discharge were determined as: absence of fever for at least 3 days, substantial improvement in both lungs as determined by chest CT, clinical remission of respiratory symptoms, and two throat-swab samples with a SARS-CoV-2 RNA negative finding obtained at least 24 hours apart.

Statistical analysis

Continuous data with a normal distribution were presented as mean ± standard deviation. If continuous data showed a skewed distribution, they were presented as a median [interquartile range (IQR)]. Frequency data are expressed as proportions. Comparisons of continuous variables were made using Student's t test or the Mann-Whitney U test when appropriate, while differences in categorical variables were assessed using the X^2 test or Fisher's exact test, as appropriate.

Survival curves were plotted using the Kaplan-Meier method using a log-rank test. Multivariate logistic regression models were used to determine the independent risk factors for severe disease progression to critical illness during 28 days inpatient observation. Data were analyzed using SPSS 25.0. A two-tailed P value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 239 adult inpatients at Wuhan Tongji Hospital (Wuhan, China) who were diagnosed with COVID-19 according to to the Chinese management guideline for COVID-19 (version 7.0) and the World Health Organization interim guidance were included in this retrospective study. Five patients is excluded for death with positive pharyngeal swab test.(Figure1).In this patient population, the median age was 63.0 years old (IQR, 52.0, 72.0). Of the 239 patients, 50.2% (120/239) were male, 18.8% (45/239) of the patients progressed to critical illness (Table 1). Patients were considered progressing to critical illness if at least one of the following conditions were observed: 1. Respiratory failure requiring mechanical ventilation; 2. Shock; 3. Combined organ failure requiring monitoring and treatment in the intensive care unit (ICU).

Of the 239 patients, 13.8% (33/239) died during the first 28 days of hospitalization. The most common symptoms among the patients were fever 79.1% (189/239) and cough 79.9% (191/239). The most common reported comorbidity was hypertension 37.7% (90/239). For all patients in the retrospective study, the median viral RNA shedding duration time was 26 days (IQR, 20.0, 34.0). The median time from onset of symptoms to patient diagnosis with COVID-19 was 7 days (IQR,3.0, 13.0). The median time from onset of illness to inpatient admission at the hospital was 15 days (IQR,10.0, 21.0) and the median time from onset of illness to treatment with antiviral therapies was 5 days (IQR,1.0, 12.0).

Patients with prolonged viral RNA shedding duration ([?] 26 days) were younger (61.5 ys *vs.* 66.0 ys, P= 0.02), had a lower APACHE II score (5.0 *vs.* 6.0 , $P < 0.01$), a lower hs-CRP levels (3.6 mg/L *vs.* 8.9 mg/L, P= 0.03), and a higher lymphocyte count (1.4 x10^9 /L *vs.*1.2x10^9 /L, $P < 0.01$). Patients with a long viral RNA shedding duration had a viral RNA shedding duration 1.7 times greater than patients with a short viral RNA shedding duration (34 days *vs.* 20 days, $P < 0.01$). Patients with a long viral RNA shedding duration also had a longer time from illness onset to diagnosis with COVID-19 (10 days *vs.* 4 days, $P<$ 0.01), to hospital admission (7 days *vs.* 4 days,$P < 0.01$), and to antiviral treatment (19 days*vs.* 10 days, P < 0.01).

Viral RNA shedding duration and patient prognosis and progression to critical illness

The mortality of patients with a long viral RNA shedding duration ([?] 26 days) was significantly lower than patients with a short viral RNA shedding duration (<26 days). The overall mortality of patients with a long viral RNA shedding duration was 9.5%, nearly half that of the 18.6% overall mortality in patients with a short viral RNA shedding duration (P= 0.04). In patients with a long viral RNA shedding duration as compared to a short viral RNA shedding duration, the percentage of patients who progressed to critical illness was smaller, although this difference was not significant (16.7% *vs.*21.2%, P= 0.37).

By multivariate-adjusted logistic regression model analysis, the factors that were associated with increased mortality risk in patients during the 28 days of observation included increased patient age (OR 1.07, 95% CI: 1.02-1.10), decreased viral RNA shedding duration (OR 0.94, 95% CI: 0.88-0.99), increased SOFA score (OR 2.11, 95% CI: 1.56-2.85) and decreased lymphocyte count (OR 0.28, 95% CI: 0.09-0.91) (Table 2).

Kaplan-Meier analysis indicated that patients with long viral RNA shedding duration ([?] 26 days) as compared to patients with short RNA shedding duration (<26 days) had a significant survival advantage (Figure 2, log-rank P =0.047). Furthermore, the percentage of patients who progressed to critical illness was also significantly reduced in patients with short viral RNA shedding duration (Figure 3, log-rank P =0.029).

Discussion

This study is the first to investigate the relationship between viral shedding duration in COVID-19 and patient prognosis and disease progression to critical illness. In this study we determined that prolonged viral RNA shedding duration in COVID-19 is associated with improved patient prognosis. Furthermore, patients with long viral shedding duration as compared to short viral shedding duration had a lower rate of progression to critical illness. Finally, we determined the mortality of COVID-19 in patients with long

viral RNA shedding duration ([?]26 days) was nearly 50% less as compared to patients with short viral RNA shedding duration (<26 days). In this study, we have excluded 5 patients whose viral RNA shedding of SARS-CoV-2 was also detectable until death. So, the mortality is not a confounder of viral RNA shedding duration.

This finding is inconsistent with previous findings in different viruses including avian influenza A (H5N1) and respiratory syncytial virus, where longer viral shedding duration has been shown to be associated with increased risk of complications[2,4,5,7,8]. Furthermore, longer duration of viral shedding in H1N1 has been correlated with worse disease severity[9]. There are many differences in the pathology of SARS-CoV-2 that could potentially account for the different observations in the correlation between viral shedding duration and patient prognosis in COVID-19 as compared to other viruses (such as influenza). One possibility is that a destabilizing mutation in SARS-CoV-2 in the nsp3 protein (that is not observed in other viruses, such as SARS) could explain the unique correlation between decreased viral shedding duration and worse disease progression observed with COVID-19, although this remains to be tested[10].

Secondly, differences in virus subtypes of SARS-CoV-2 as compared to other viruses might explain the contrasting finding that increased viral shedding duration is associated with better patient prognosis in COVID-19. A recent study investigated the molecular divergence of SARS-CoV-2, in which it was determined the virus has two major types, L-type and S-type, each that has unique characteristics[11]. This study determined that L-type SARS-CoV-2, as compared to S-type, is detected in approximately 70% of all patients and is more prevalent and may be more transmissible than the L-type. It has been suggested that the diversity of COVID-19 mortality rates in different regions of China may be explained by the different virus subtypes, among other characteristics[12,13]. Currently, few studies have focused on defining the clinical features of these two sub-types of SARS-CoV-2. As we do not know the SARS-CoV-2 subtypes of the patients in our study, further analysis of the SARS-CoV-2 mRNA sequence of the virus type could help further stratify the findings in our study.

Previous studies have shown that correlations between viral load and immune system response are important determining factors in disease progression. It has also known that SARS-CoV-2 infection can activate innate and adaptive immune responses[14]. Therefore, it is possible an immune system response may influence the differences in viral load observed in the patients in our study. Consistent with prior studies that have shown lymphopenia is a common feature in severe COVID-19[14,15], we also frequently observed lymphocytopenia in the patients in our study. Patients with long viral RNA shedding duration as compared to short viral RNA shedding duration had a significantly higher absolute lymphocyte count, as well as higher levels of inflammatory markers (such as hs-CRP and IL-6). This suggests that patients with prolonged viral RNA shedding durations may also have increased innate and adaptive immune responses, although this remains to be tested.

Previous studies have observed that the median duration of viral shedding in COVID-19 survivors ranges from 17 days (IQR 13-22 days) to 20 days (IQR 17-24 days)[3,16]. The longest reported duration of viral shedding in COVID survivors was 37 days[3,16]. In our study, the median SARS-CoV-2 shedding duration was 26 days, and the longest duration was 62 days (reported in a 72-year-old male patient who survived COVID-19). Approximately 15% of in our study patients had a viral shedding duration of more than 6 weeks. This duration is significantly longer than has been previously reported[3,16]. This difference may be attributed to the fact that the patients enrolled in our study were from Wuhan, China where more severe cases of COVID-19 have been reported. Delayed hospital admission may also be associated with longer viral shedding duration as patients would not have received any medical care that could have minimized COVID-19 symptoms. This could also potentially contribute to the longer viral RNA shedding times detected in our studies.

There are limitations to this retrospective study. First of all, although we were able to detect viral RNA of SARS-CoV2, viral RNA shedding may not perfectly correlate with total viral load as quantified by virus isolation. However, viral RNA can be used as a surrogate for estimating the total viral load in a patient. Secondly, the viral RNA specimens were obtained from pharyngeal swabs and it is possible there may be

instances of false negative viral RNA detections. Respiratory tract specimens such as viral RNA detection from sputum, endotracheal aspirate, or bronchoalveolar lavage fluid would provide a more accurate level of detection for viral RNA, but obtaining these specimens from non-critical patients is not practical as it requires invasive mechanical ventilation. Finally, there were variations in the antiviral treatments patients received in this study. Lopinavir/ritonavir and interferon-α were used for many patients in our study, and because of the lack of standardized antiviral therapies for the patients in our study, we do not have statistical power to determine if these antiviral treatments had an effect on viral RNA shedding.

Conclusions

Our study demonstrates that prolonged SARS-CoV-2 viral RNA shedding time is associated with improved patient prognosis and a decreased rate progression to critical illness. Further studies are needed to determine if the duration of viral RNA shedding may be used as a prognostic factor in patients to determine which patients are at higher risk for adverse outcomes with COVID-19.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethics committee approval was obtained by the participating institutions according to local ethical regulations.

Consent for publication

Not applicable.

Conflicts of interest and Source of Funding

No reported conflicts of interest. Jiangsu Province's Key Provincial Talents Program (ZDRCA2016046); Key Health Talents in Gusu (GSWS2019009).

Declarations

The authors have disclosed that they do not have any potential conflicts of interest.

Author contributions: Data collection was performed by Fengyuan Li, Wei-yun Zhang and Bing Liang. Statistical analysis was conducted by Fengyuan Li, Da-xiong Zeng and Qiang Guo. Analysis, interpretation and drafting of the manuscript was conducted by Jia-lin Liu, Hong-yang Xu, Qingyuan Zhan, Shanshan Wang, Chang Gao, Jian-an Huang, Bo Shen, Alpaslan Tasdogan, Jessalyn M. Ubellacker. All authors approved the manuscript before submission.

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Tables :

Table 1. Comparison of characteristics of 239 hospitalized patients with COVID-19 infection in Wuhan with different durations of 2019-nCoV RNA shedding.

Characteristics	All patients (n=239)	Viral shedding duration¡26 days (n=113)	Viral shedding duration[?]26 days (n=126)	P
Age, y	63.0 (52.0, 72.0)	66.0 (54.0, 75.0)	61.5 (49.0, 69.0)	0.02
Male sex	120 (50.2%)	61 (54.0%)	59 (46.8%)	0.27
Symptoms				
Fever	189 (79.1%)	89 (78.8%)	100 (79.4%)	0.91
Cough	191 (79.9%)	87 (77.0%)	104 (82.5%)	0.29
Sputum	125 (52.3%)	52 (46.0%)	73 (57.9%)	0.07
Dyspnea	86 (36.0%)	44 (38.9%)	42 (33.3%)	0.37
Palpitation	29 (12.1%)	18 (15.9%)	11 (8.7%)	0.09
Fatigue	81 (33.9%)	37 (32.7%)	44 (34.9%)	0.72
Diarrhea	53 (22.2%)	30 (26.5%)	23 (18.3%)	0.12
Nausea and vomiting	16 (6.7%)	6 (5.3%)	10 (7.9%)	0.42
Comorbidity				
Hypertension	90 (37.7%)	42 (37.2%)	48 (38.1%)	0.88
Diabetes	30 (12.6%)	13 (11.5%)	17 (13.5%)	0.64

Characteristics	All patients (n=239)	Viral shedding duration¡26 days (n=113)	Viral shedding duration[?]26 days (n=126)	P
Cardiac disease [a]	30 (12.6%)	15 (13.3%)	15 (11.9%)	0.75
COPD	15 (6.3%)	7 (6.2%)	8 (6.3%)	0.96
Chronic renal insufficiency	3 (1.3%)	1 (0.9%)	2 (1.6%)	0.63
Immunosuppression [b]	6 (2.5%)	4 (3.5%)	2 (1.6%)	0.34
Severity score and laboratory finding upon admission	Severity score and laboratory finding upon admission	Severity score and laboratory finding upon admission	Severity score and laboratory finding upon admission	
APACHE II score	5.0 (3.0, 8.0)	6.0 (4.0, 8.0)	5.0 (2.0, 7.0)	<0.01
SOFA score	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	0.95
WBC count, $\times 10^9$ /L	5.9 (4.7, 7.7)	5.6 (4.6, 7.8)	5.9 (4.8, 7.5)	0.66
Lymphocyte count, $\times 10^9$ /L	1.3 (0.9, 1.7)	1.2 (0.8, 1.5)	1.4 (0.9, 1.8)	<0.01
Platelet count, $\times 10^9$ /L	229.0 (168.0, 304.0)	224.0 (164.0, 314.0)	229.0 (174.0, 304.0)	0.70
Creatinine level, μmol/L	69.0 (57.0, 82.0)	68.0 (57.0, 83.0)	70.0 (57.0, 80.0)	0.97
hs-CRP, mg/L	5.4 (1.2, 41.7)	8.9 (1.7, 49.5)	3.6 (0.9, 36.0)	0.03
AST level, U/L	25.0 (19.0, 37.0)	25.0 (19.0, 39.0)	26.0 (19.0, 34.0)	0.67
Creatine kinase level, U/L	56.0 (36.0, 96.0)	53.0 (35.0, 103.0)	56.5 (41.0, 90.0)	0.22
CK-MB, ng/mL	0.7 (0.4, 1.5)	0.8 (0.4, 1.7)	0.7 (0.4, 1.3)	0.69
IL-6, pg/mL	3.8 (1.7, 11.8)	4.1 (2.0, 21.4)	3.6 (1.5, 10.8)	0.08
Time to virological result, d	Time to virological result, d			
From illness onset to diagnosis	7.0 (3.0, 13.0)	4.0 (2.0, 8.0)	10.0 (6.0, 16.0)	<0.01
From illness onset to ART start	5.0 (1.0, 12.0)	4.0 (1.0, 9.0)	7.0 (1.0, 14.0)	<0.01
From illness onset to admission	15.0 (10.0, 21.0)	10.0 (7.0, 15.0)	19.0 (14.0, 31.0)	<0.01
Viral shedding duration [c]	26.0 (20.0, 34.0)	20.0 (15.0, 22.0)	34.0 (29.0, 43.0)	<0.01
Treatment or complication				
ICU admission	33 (13.8%)	19 (16.8%)	14 (11.1%)	0.20
Septic shock	25 (10.5%)	11 (9.7%)	14 (11.1%)	0.73
ECMO	1 (0.4%)	0 (0.0%)	1 (0.8%)	0.34
CRRT	16 (6.7%)	8 (7.1%)	8 (6.3%)	0.82
Invasive mechanical ventilation	36 (15.1%)	18 (15.9%)	18 (14.3%)	0.72
Corticosteroid therapy	55 (23.0%)	30 (26.5%)	25 (19.8%)	0.22
Outcome				

Characteristics	All patients (n=239)	Viral shedding duration¡26 days (n=113)	Viral shedding duration[?]26 days (n=126)	P
Progress to critical illness	45 (18.8%)	24 (21.2%)	21 (16.7%)	0.37
Day 28 mortality	33 (13.8%)	21 (18.6%)	12 (9.5%)	0.04

Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).

Abbreviations: WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; ART, antiviral treatment; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment; IL-6, interleukin-6.

[a] Includes congestive heart disease and coronary atherosclerotic heart disease.

[b] Defined as receipt of chemotherapy or radiotherapy within 1 month before the onset of illness or receipt of corticosteroid therapy (equivalent of 30 mg of prednisone per day) for 15 continuous days before the onset of illness.

[c] Data are based on real-time reverse transcription–polymerase chain reaction analysis.

Table 2. Multivariate logistic regression analysis of risk factors for death of 239 hospitalized patients with COVID-19 infection in Wuhan

Variables	Multivariate	Multivariate
	OR (95% CI)	P
Age, ys	1.07(1.02-1.1)	0.011
Viral shedding duration	0.94(0.88-0.99)	0.025
SOFA score	2.11(1.56-2.85)	0.000
Lymphocyte count, ×109 /L [a]	0.28(0.09-0.91)	0.034
IL-6, pg/mL [a]	1.01(1.01-0.99)	0.080

[a] Laboratory findings upon admission.

Abbreviations: SOFA score, sequential organ failure assessment; WBC, white blood cell; IL-6, interleukin-6; OR, odds ratio.

Figure Legends

Figure 1 Flow diagram of patients with confirmed COVID-19 included in this study .

Figure 2 Overall survival analysis of 239 patients with COVID-19 by a viral RNA shedding duration of [?]26 days or <26 days.

Figure 3 Overall rate of progression to critical illness among hospitalized patients by a viral RNA shedding duration of [?]26 days or <26 days.

Figure 1

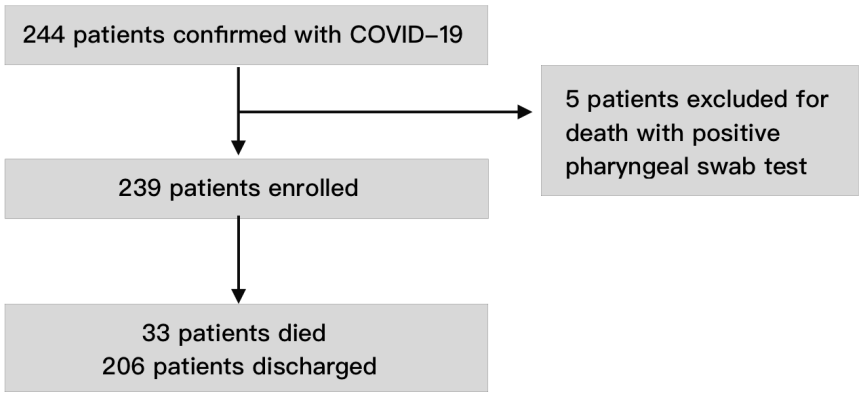
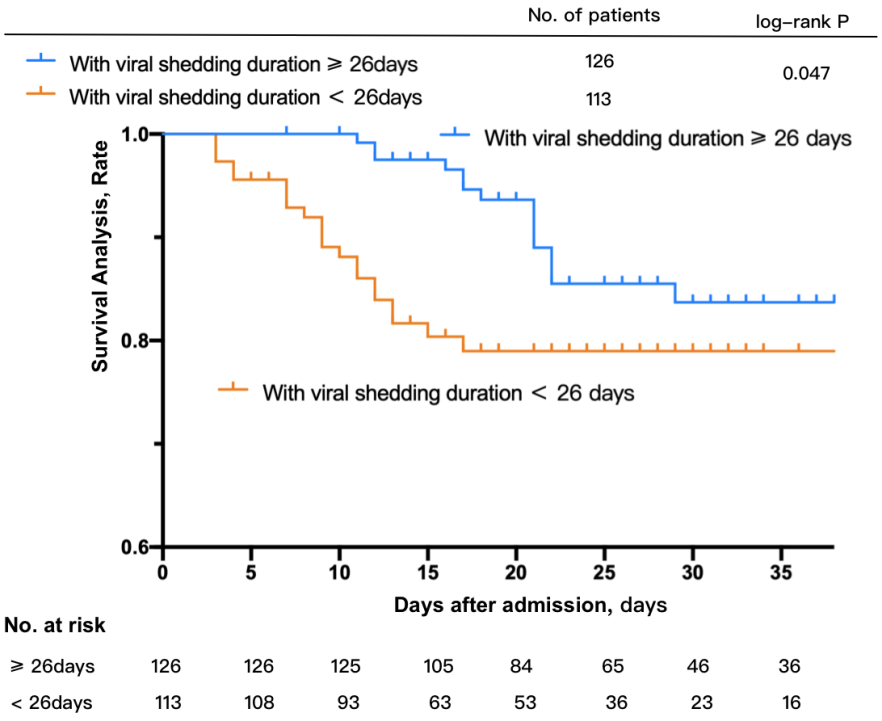


Figure 2



No. at risk

⩾ 26days	126	126	125	105	84	65	46	36
< 26days	113	108	93	63	53	36	23	16

Figure 3