Incidence rate, clinical course and risk factor for recurrent PCR positivity in discharged COVID-19 patients in Guangzhou, China: a prospective cohort study

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Abstract

Background: The phenomenon of COVID-19 patients tested positive for SARS-CoV-2 after discharge (redetectable as positive, RP) emerged globally. The data of incidence rate and risk factors for RP event and the clinical features of RP patients may provide recommendations for virus containment and discharge assessment for COVID-19.

Methods: The baseline included 285 adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 from Guangzhou Eighth People's Hospital. We started the Observation on Jan 20, 2020, and acquired all their definite clinical outcome (becoming RP or keeping normal during post-discharge surveillance) by Mar 10, 2020. The dynamic clinical data of patients during observation were prospectively collected and analyzed. Univariate and multivariate-adjusted logistic regression were used to explore the risk factors related to RP events in COVID-19 patients.

Results: By March 10, 27 (9.5%) discharged patients had tested positive for SARS-CoV-2 in their nasopharyngeal swab after a median duration of 7·0 days (IQR 5·0-8·0). Age, sex, epidemiological history, clinical symptoms and underlying diseases were similar between RP and non-RP patients (p>0.05). Compared to first admission, RP patients generally had milder clinical symptoms, lower viral load, shorter length of stay and improved pulmonary conditions at readmission (p<0.05). Elder RP patients (≥ 60 years old) were more likely to be symptomatic compared to younger patients (7/8, 87.5% vs. 3/19, 18.8%, p=0.001) at readmission. A prolonged duration of viral shedding (>10 days) during the first hospitalization [adjusted odds ratio [aOR]: 5.82, 95% confidence interval [CI]: 2.50-13.57 for N gene; aOR: 9.64, 95% CI: 3.91-23.73 for ORF gene] and higher Ct value (ORF) in the third week of the first hospitalization (aOR: 0.69; 95% CI: 0.50-0.95) were associated with RP events.

Conclusions: RP events occurred in nearly 10% of COVID-19 patients which deserves globally attention. During hospitalization, patients' low efficiency of viral clearance was a risk factor for RP event. Elderly RP patients were more likely to develop clinical symptoms. To reduce the possibility of reinfection and readmission during the management of COVID-19, more rigorously monitoring on patients' viral load should be carried out especially in elder patients and later stage of hospitalization.

Background

An outbreak caused by a novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in Wuhan in December 2019, [1] and has since spread within China and other countries. The WHO has declared the COVID-19 a pandemic on Mar 14, 2020.[2] As of May 4, 2020, more than three million confirmed cases and 238,730 deaths had been reported globally.[3]

So far, over tens of thousands of patients with COVID-19 have been clinically cured and discharged, but multiple COVID-19 cases showed SARS-CoV-2 positive again in discharged patients (redetectable as positive, RP),[4–9] which raises an attention for the discharged patients. Previously, Yao and colleagues conducted postmortem pathologic study in a ready-for-discharge COVID-19 patient who succumbed to sudden cardiovascular accident, and revealed negative SARS-CoV-2 results of nasopharynx swab may not reflect the virus in lung tissue.[10] However, Yao and colleagues' report was limited by sample size and urgent questions that need to be addressed promptly include what is the incidence of being redetectable as positive in discharged COVID-19 patients? What are the clinical characteristics of RP patients? What are the risk factors for RP event? The answers to these questions may lead to recommendations for clinical guideline for virus containment and discharge assessment.

To our knowledge, our study involved the largest cohort of patients receiving follow-up after recovering from COVID-19. Therefore, to facilitate efforts on above questions, we prospectively collected and analysed detailed clinical data from adult patients with laboratory-confirmed COVID-19 and a definite clinical outcome (becoming RP or haven't become RP during post-discharge surveillance) at Guangzhou Eighth People's Hospital, Guangzhou, China. In this study, we presented the clinical features of RP patients and explored the incident rate and risk factors for RP events.

Methods

Study design and participants

This prospective cohort study included a cohort of adult inpatients (≥ 18 years old) from Guangzhou Eighth People's Hospital (Guangzhou, Guangdong) with a diagnosis of COVID-19. The diagnosis of COVID-19 was based on the New Coronavirus Pneumonia Prevention and Control Program (7th edition) published by the National Health Commission of China.[11] Overall, 285 patients who were admitted between January 20 and February 18, 2020 were enrolled. March 10, all patients got a definite clinical outcome (becoming RP or haven't become RP during post-discharge surveillance). The final date of follow-up was March 14, 2020, the day all observed cases were discharged. This study

was approved by the institutional ethics board of Guangzhou Eighth People's Hospital and the requirement for informed consent was waived by the ethics board.

Data collection and processing

Both first and second hospitalization data including demographic information, epidemiological history, clinical signs and symptoms, underlying comorbidities, dynamic laboratory parameters, treatment measures and outcome data, were obtained from the electronic medical record system of Guangzhou Eighth People's Hospital by a trained team of experienced clinicians, epidemiologists and medical students using a standardized data collection form. During post-discharge surveillance (within 15 days after discharge), nasopharyngeal swab samples of patients were collected by staff of Guangzhou Center for Disease Control and Prevention (Guangzhou CDC) and submitted to Guangzhou Eighth People's Hospital for Reverse transcription polymerase chain reaction (RT-PCR) test. Two researchers (J.Z.Z. & R.Z.) independently reviewed and analysed the data and a third researcher (F.R.L.) adjudicated any difference in interpretation between the two primary reviewers.

Viral nucleic acid testing and analysis

Patients' nasopharyngeal swab specimens were collected for SARS-CoV-2 nucleic acid detection by RT-PCR at admission and once every two or three days during hospitalization and post-discharge surveillance. The detailed protocol of the RT-PCR is described elsewhere.[12] Threshold refers to the critical value of fluorescence signal in exponential growth period. Cycle threshold value (Ct value) refers to the number of cycles when the fluorescence signal reaches the threshold. A Ct-value less than 37 was defined as positive, a Ct-value ≥ 40 was defined as negative, and a medium load (Ct-value 37–40) was an indication for retesting.[13] Lower Ct value refers to higher viral load. Patients with positive nucleic acid tests in nasopharyngeal swab samples during post-discharge surveillance (within 15 days after discharge) were diagnosed as being RP.

Discharge criteria for COVID-19

Individuals meeting the following criteria could be discharged: absence of fever for at least three days, substantial improvement in both lungs in chest CT, clinical remission of respiratory symptoms, and two throat-swab samples negative for SARS-CoV-2 RNA obtained at least 24 h apart.[14]

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables are expressed as medians and interquartile ranges (IQRs). We compared the differences in epidemiological, clinical, and laboratory findings between patients who had a positive SARS-CoV-2 test after discharge and those who did not. Chi-square or Fisher's exact tests were used to compare categorical variables between different patient groups, as appropriate, and the Mann-Whitney test was used to compare the continuous variables. When comparing the characteristics of RP patients between the two hospitalizations, the Wilcoxon signed-rank test and McNemar's test were applied, as appropriate. To evaluate the dynamic changes in laboratory tests, including Ct values, the median value of the first three weeks were compared between the RP and NRP patients. To explore the risk factors associated with being RP, univariate and multivariate-adjusted logistic regression models were used. In the multivariate adjusted model, age, sex, hypertension, diabetes and liver disease were adjusted.

All statistical analyses were performed using Stata SE, version 15 (StataCorp) and graphs were generated and plotted using GraphPad Prism version 8.00 software (GraphPad Software Inc). A *P* value less than 0.05 (two-tailed) was considered statistically significant.

Results

Clinical data and laboratory findings during first hospitalization (RP vs. NRP patients)

From January 20 to March 4, 2020, 292 patients were admitted to Guangzhou Eighth People's Hospital. After excluding six patients who were minors (≤ 18 years) and one death case, we enrolled 285 adult patients with COVID-19 in our final analysis. By March 14, 2020, all patients were discharged. Of these discharged patients, 27 (9.5%) recovered from COVID-19 tested positive for SARS-CoV-2 during post-discharge surveillance. The basic information is shown in Table 1. The median age of the study population was 48.0 years old (IQR 35.0–62.0, range, from 18.0–90.0 years), and 128 patients (44.9%) were men. The median length of stay (LOS) for both RP patients and NRP patients was 18 days. Generally, Demographics, epidemiological history and clinical symptoms did not significantly differ between the two groups.

Table 1
Baseline characteristics of 27 RP patients and 258 non-RP patients

Characteristics	All patients (n = 285)	RP Patients (n = 27)	NRP patients (n = 258)	p value
Basic information				
Age, years	48.0 (35.0–62.0)	44.0 (32.0–62.0)	49.0 (35.0–62.0)	0.450
Men	128 (44.9)	12 (44.4)	116 (44.9)	0.959
Exposed to Wuhan or surrounding cities	179 (62.8)	19 (70.4)	160 (62.0)	0.393
Smoking history	31 (11.0)	1 (3.7)	30 (11.8)	0.332
Severity				0.703
Mild	22 (7.7)	3 (11.1)	19 (7.4)	
Moderate	257 (90.2)	24 (88.9)	233 (90.3)	
Severe	6 (2.1)	0 (0)	6 (2.3)	
Comorbidities				
Any Comorbidity	88 (31.4)	8 (29.6)	80 (31.0)	0.832
Hypertension	51 (17.9)	6 (22.2)	45 (17.4)	0.597
Diabetes	24 (8.4)	1 (3.7)	23 (8.9)	0.712
Liver disease	23 (8.1)	2 (7.4)	21 (8.1)	0.343
COPD	19 (6.7)	2 (7.4)	17 (6.6)	0.698
Cardiovascular disease	18 (6.3)	0 (0)	18 (6.9)	0.235
Kidney disease	8 (2.9)	0 (0)	8 (3.1)	..
Cancer	3 (1.1)	0 (0)	3 (1.2)	..
Clinical characteristic				
Symptoms				
Asymptomatic	34 (11.9)	5 (18.5)	29 (11.2)	0.343
Fever	193 (67.7)	18 (66.7)	175 (67.8)	0.902
Dry cough	159 (55.9)	14 (51.6)	145 (56.4)	0.649
Expectoration	59 (20.7)	6 (22.2)	53 (20.5)	0.838
Chills	58 (20.4)	2 (7.4)	56 (21.7)	0.079
Fatigue	37 (12.9)	4 (14.8)	33 (12.8)	0.764
Myalgia	34 (11.9)	1 (3.7)	33 (12.8)	0.222
Chest CT				
Bilateral involvement of chest CT scan	261 (95.6)	27 (100.0)	234 (95.1)	0.241
Small Pulmonary Nodules	13 (4.7)	3 (11.1)	10 (4.1)	0.125

Data are median (IQR) or n (%). p values comparing RP and NRP patients are from χ^2, Fisher's exact test, or Mann-Whitney U test. COPD = Chronic obstructive pulmonary disease. CT = computerized tomography scan. RP = re-detectable as positive. NRP = non-re-detectable as positive.

The medians of RP and NRP patients' parameters during whole hospitalization and each week after admission are shown in Table 2. Compared with NRP patients, RP patients had a significantly lower median LDH level during hospitalization (159.5 *vs.* 186.0, p = 0.034). RP patients showed lower LDH (159.0 *vs.* 192.0, p = 0.034) than NRP patients at first week after admission, whereas eosinophil count was higher (0.05 *vs.* 0.02, p = 0.018). Concerning Ct values of N and ORF gene, there were no significant differences between the two groups within two weeks after admission. Eventually, RP patients' median Ct values of ORF gene were significantly lower than NRP group (35.5 *vs.* 39.0, p =

0.031) at third week. Similar results also observed in Ct values of N gene (Fig. 1). The details of other markers between the two groups are described in **Supplementary Table S1**.

Table 2
Laboratory indicators of RP and NRP patients for the first three weeks of hospitalization

Parameter, week	Normal Range	All patients	RP Patients	NRP patients	p value
Positive Ct value (N)	≥ 40	37.0 (34.5–38.0)	35.5 (34.0–37.0)	37.0 (35.0–38.0)	0.044
1		36.0 (33.0–38.0)	35.0 (33.0–36.0)	36.0 (33.0–38.0)	0.197
2		37.0 (34.0-38.8)	35.8 (31.8–38.3)	37.0 (34.5–39.0)	0.275
3		38.0 (33.0–39.0)	36.0 (33.0–38.0)	38.0 (37.0–39.0)	0.045
Positive Ct value (ORF1ab)	≥ 40	38.0 (35.0–39.0)	37.0 (34.0–38.0)	38.0 (35.5–39.0)	0.061
1		37.0 (34.0–38.0)	35.0 (33.0-37.5)	37.0 (34.0–39.0)	0.088
2		38.0 (34.0–39.0)	36.3 (33.5–39.0)	38.0 (35.0–39.0)	0.224
3		38.0 (36.0–40.0)	35.5 (33.0–39.0)	39.0 (38.0–41.0)	0.031
White blood cell count, $\times 10^9$ /L	3.5–9.5	5.3 (4.4–6.3)	5.2 (4.2–5.6)	5.3 (4.4–6.4)	0.301
1		4.9 (3.9–6.3)	4.8 (4.2–5.5)	5.1 (3.9–6.3)	0.297
2		5.4 (4.5–6.8)	5.1 (4.6–5.7)	5.6 (4.5–6.8)	0.246
3		5.5 (4.6–6.5)	5.4 (4.4–6.3)	5.5 (4.6–6.5)	0.489
Eosinophil, $\times 10^9$ /L	0.02–0.52	0.08 (0.04–0.12)	0.08 (0.04–0.12)	0.08 (0.04–0.12)	0.767
1		0.03 (0.0-0.07)	0.05 (0.02–0.1)	0.02 (0.00-0.07)	0.018
2		0.09 (0.05–0.14)	0.08 (0.04–0.10)	0.1 (0.05–0.1)	0.208
3		0.12 (0.08–0.20)	0.11 (0.08–0.17)	0.12 (0.08–0.20)	0.729
Lactate dehydrogenase, U/L	125–243	185.0 (154.5–225.0)	159.5 (139.0-197.0)	186.0 (155.5–229.0)	0.034
1		188.0 (151.0-238.0)	159.0 (140.0-196.0)	192.0 (152.0-243.0)	0.022
2		183.0 (149.0-238.0)	159.5 (147.0-213.0)	184.0 (151.0-238.0)	0.493
3		179.0 (150.0-213.5)	166.0 (129.0-192.0)	180.0 (151.0-218.0)	0.069
C-reactive protein, mg/L	< 10	5.0 (5.0-12.7)	5.0 (5.0–5.0)	5.0 (5.0-13.4)	0.094
1		5.0 (5.0-23.5)	5.0 (5.0-10.2)	5.0 (5.0-26.2)	0.034
2		5.0 (5.0-11.5)	5.0 (5.0–5.0)	5.0 (5.0-12.3)	0.301
3		5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	0.537

Data are median (IQR) value of first three weeks after admission., the number of available test result of RP patients for the first, second and third weeks were 27, 27, 19, in contrast, 258, 249, 184 in NRP patients. P values comparing RP and NRP patients are from Mann-Whitney U test. RP = redetectable as positive. NRP = non-redetectable as positive.

As for clinical course, RP and NRP patients' length of hospital stay (LOS) were both 18 days. For RP patients, the median duration of viral shedding (N gene) after admission was 14.0 days (IQR 8.0–20.0 days) (Fig. 2), which was significantly longer than those in NRP patients (7.0 days [IQR 7.0–10.0]) ($p < 0.001$). 62.9% RP patients and 23.6% NRP patients presented positive RNA detection tests (N gene) for more than 10 days since hospital admission. The results were similar in ORF gene (Table 3).

Table 3
Clinical course and RNA test result of 27 RP patients and 258 non-RP patients

	RP (n = 27)	NRP (n = 258)	p value
First-hospitalization			
Time from illness onset to admission, days	3.0 (1.0–5.0)	3.0 (1.0–7.0)	0.923
Length of stay, days	18.0 (13.0–24.0)	18.0 (13.0–25.0)	0.822
Duration of viral shedding (N) after admission, days	14.0 (8.0–20.0)	7.0 (7.0–10.0)	< 0.001
Distribution, no (%)			
≤ 10 days	10 (37.0)	197 (76.4)	< 0.001*
> 10 days	17 (62.9)	61 (23.6)	
Duration of viral shedding (ORF) after admission, days	16.0 (8.0–21.0)	7.0 (7.0–10.0)	< 0.001
Distribution, no (%)			
≤ 10 days	8 (29.6)	203 (78.7)	< 0.001*
> 10 days	19 (70.4)	55 (21.3)	
Rehospitalization			
Quarantine site before rehospitalization			
Hospital	9 (33.3)	-	-
Home	18 (66.7)	-	-
Time from discharge to retest positive, days	7.0 (5.0–8.0)	-	-
Length of stay, days	7.0 (5.0–11.0)	-	-
Duration of viral shedding after being RP (N gene), days	3.0 (3.0–10.0)	-	-
Duration of viral shedding after being RP (ORF gene), days	7.0 (6.0–10.0)	-	-.
Lung inflammation compared with first hospitalization			
Normal	1 (3.7)	-	-
Improved	18 (66.7)	-	-
Stable	8 (29.6)	-	-
Aggravated	0	-	-

Data are median (IQR) or n (%). P values comparing RP and NRP patients are from χ^2, Fisher's exact test, or Mann-Whitney U test. ICU = intensive care unit. RP = redetectable as positive. NRP = non-redetectable as positive. *χ^2 test comparing all subcategories.

Clinical data and laboratory findings of RP patients (first vs. **second hospitalization)**

After discharged, RP patients readmitted to hospital after a median of 7.0 days (IQR 5.0–8.0 days) of surveillance. Compared with the first hospitalization, more asymptomatic persons (17 [62.9%] *vs.* 5 [18.5%], p = 0.013), shorter length of hospitalization (7.0 days [5.0–11.0] *vs.* 18.0 [13.0–24.0], p < 0.001) and higher Ct value of N gene (37.5 [36.0-38.5] *vs.* 35.0 [33.0–37.0], p = 0.042) were presented in RP patients' rehospitalization **(Supplementary Table S2)**. Elder RP patients (≥ 60 years old) were more likely to be symptomatic compared to younger RP patients (7/8, 87.5% vs. 3/19, 18.8%, p = 0.001) at readmission **(**Fig. 3**)**. Of those who underwent detection of the specific binding antibody to SARS-COV-2 in the plasma, twenty (100.0%) and sixteen (80.0%) showed positivity of IgG and IgM. During rehospitalization, duration of viral shedding from first positive tests (N gene) was 3.0 days (IQR 3.0–10.0 days) and 7.0 days (IQR 6.0–10.0 days) for ORF gene (Table 3). The monitoring results of RNA for 27 RP patients during rehospitalization were shown in Fig. 3.

Chest CT images during two hospitalizations of three RP patients and CT images taken at two different time during first hospitalization of one NRP patient were shown in Fig. 4. The typical findings of chest CT images of RP patients at readmission were the improved bilateral pulmonary inflammation.

Risk factors associated with RP events

In the univariate logistic regression model, decreased median Ct values of ORF gene at week three after admission (OR 0.76, 95% CI 0.60–0.97) and duration of viral shedding from admission greater than 10 days (OR 5.49, 95% CI 2.39–12.62 and OR 8.77, 95% CI 3.64–21.09, for N gene and ORF gene, respectively) were associated with increased risk of being RP. When adjusting for age, sex, hypertension, CVD and liver disease, our regression model showed similar results (Table 4).

Table 4
Risk factors associated with RP events

	Univariate OR	p value	Adjusted OR*	p value
Basic information				
Age, years	0.99 (0.97–1.02)	0.458	..	..
Male (*vs.* female)	0.98 (0.44–2.17)	0.959	..	..
Clinical severity				
Mild	1 (reference)		1 (reference)	
Moderate	0.65 (0.18–2.37)	0.522	0.72 (0.19–2.69)	0.632
Comorbidity				
Any comorbidity	0.91 (0.38–2.17)	0.832	0.89 (0.12–5.02)	0.711
Diabetes	0.39 (0.05–3.03)	0.370	..	..
Hypertension	1.35 (0.52–3.54)	0.539	..	..
Liver diseases	0.90 (0.20–4.08)	0.894	..	..
Laboratory findings				
Median Ct value (N gene)	0.96 (0.87–1.07)	0.496	0.96 (0.86–1.07)	0.487
Week1	0.96 (0.87–1.05)	0.367	0.96 (0.87–1.06)	0.385
Week2	0.95 (0.84–1.07)	0.380	0.94 (0.82–1.08)	0.368
Week3	0.85 (0.71–1.03)	0.103	0.88 (0.70–1.10)	0.256
Median Ct value (ORF gene)	0.91 (0.82–1.01)	0.071	0.89 (0.80–0.99)	0.042
Week1	0.93 (0.84–1.04)	0.193	0.93 (0.83–1.03)	0.167
Week2	0.90 (0.79–1.04)	0.144	0.87 (0.75–1.02)	0.078
Week3	0.76 (0.60–0.97)	0.030	0.69 (0.50–0.95)	0.022
Eosinophil,$\times 10^9$ /L	0.84 (0.63–1.11)	0.213	1.59 (0.24–10.75)	0.633
Week1	9.42 (0.07–54.09)	0.374	9.30 (0.06–49.06)	0.390
Lactate dehydrogenase, U/L	0.99 (0.99-1.00)	0.133	0.99 (0.99-1.00)	0.165
Week1	0.99 (0.99-1.00)	0.065	0.99 (0.99-1.00)	0.072
Week3	0.99 (0.98-1.00)	0.122	0.99 (0.98-1.00)	0.193
C-reactive protein, mg/L	0.98 (0.93–1.02)	0.303	0.98 (0.93–1.03)	0.392
Week1	0.97 (0.94–1.01)	0.102	0.97 (0.94–1.01)	0.108
Clinical course				
Duration of viral shedding from admission, days				
N gene				
≤10	1 (reference)		1 (reference)	
>10	5.49 (2.39–12.62)	< 0.001	5.82 (2.50-13.57)	< 0.001
ORF gene				
≤10	1 (reference)		1 (reference)	

OR = odds ratio. *Adjusted for age, sex, hypertension, diabetes and liver disease. OR value in continuous variables is the risk related to per 1 unit increase.

	Univariate OR	p value	Adjusted OR*	p value
>10	8.77 (3.64–21.09)	< 0.001	9.64 (3.91–23.73)	< 0.001

OR = odds ratio. *Adjusted for age, sex, hypertension, diabetes and liver disease. OR value in continuous variables is the risk related to per 1 unit increase.

Discussion

This study reported the incidence rate of and risk factors for RP events in adult patients with COVID-19 in Guangzhou. Additionally, the clinical and virological features of RP and NRP patients were compared. The viral load in both RP patients and NRP patients' nasopharyngeal swab samples were monitored with sustained viral detection by RT-PCR. As of March 14, 2020, the end of the follow-up, 27 (9.5%) patients had become RP during their post-discharge surveillance after a median duration of 7.0 days. We revealed that a longer duration of viral shedding and higher viral load in the later stage of hospitalization were risk factors for RP events in patients with COVID-19. Furthermore, our study found that elder RP patients (≥ 60 years old) were more likely to be symptomatic (7 of 8, 87.5%) at readmission compared to younger RP patients (3 of 19, 15.8%).

27 of 285 (9.5%) individuals had tested positive for SARS-CoV-2 after discharged which was higher than the rate reported by the study of Zhongnan Hospital, in which has detected two (3·23%) positive cases in recovered medical staff.[7] The heterogeneity is probably due to the disparities in the sample size and population characteristics. The incidence rate of our study is more representative due to the diverse characteristics of the study population. Since the outbreak of COVID-19 occurred earlier in China than in other countries, the outbreak is still increasing or plateauing in many other countries,[3] the high incidence rate (nearly 10%) in this study may provide a reference for the global disease management.

Previous studies found that age-dependent defects in T-cell and B-cell function and the excess production of type 2 cytokines could lead to more prolonged proinflammatory responses and constant clinical symptom,[15] potentially leading to poor outcome. This conclusion was confirmed by current study as clinical symptom were more commonly seen in elder RP patients. The persistent clinical symptoms of the elderly RP patients in this study indicate that they may not be completely cured and remain the possibility of transmission. Thus, enhanced follow up medical examination and treatment should be carried out in time for discharged elderly patients.

In multiple respiratory viruses, viral load could be a predictor of disease stage and progression.[15–18] In this study, Ct values of respiratory tract samples from both RP and NRP patients with COVID-19 peaked in the first week after admission which was similar to the results reported in Beijing,[19] but distinct from those observed in patients with SARS, which normally peaked at approximately ten days after onset.[20] Furthermore, we found that a higher level of viral load during the later stage of hospitalization and a longer duration of viral shedding were risk factors for RP events. Sustained viral shedding has been found to be associated with antiviral resistance in patients infected with the influenza H7N9 virus.[21, 22] On this basis, we speculate that the higher viral load and longer duration of positive test results in RP patients may be the consequence of their deficiency in control of viral replication and antiviral resistance. Since many RP patients showed the phenomenon of viral RNA shifting from the negative to positive again during their second hospitalization, as they performed at their first discharge, it might be reasonable to conclude that the lack of efficiency in virus clearance in RP patients may lead to their temporarily negative of RNA test and make them being RP subsequently. In previous study, benefit was observed with remdesivir treatment in curing patients with severe COVID-19 in recent clinical trials.[23] Considering that RP patients might still be virus carriers, it's plausible to conduct a longer duration of antiviral treatment on the patients with higher viral load in later stage of COVID-19 to reduce the virus load effectively, and thus limit the possibility of reinfection and transmission in patients after discharged.

Our study has some limitations. First, it's a single-centre study. However, by including adult patients with diverse characteristics, we believe our study population is representative. Second, the estimated duration of viral shedding is limited by the frequency of nasopharyngeal swab samples collection. Third, due to the limited duration of observation, the evaluation for further clinical progression in RP patients could not be carried out, which need a long-term follow-up.

Conclusions

In conclusion, a nearly 10% incidence rate of RP events in this study suggests a large number of RP patients may appear globally. We found that a prolonged duration of viral shedding during first hospitalization was a risk factor for RP events in adult patients with COVID-19. Additionally, clinical symptoms were more commonly shown in elder RP patients at readmission. RP patients' deficiency in control of viral replication and the remained clinical symptoms should not be ignored, indicating a portion of them might haven't been completely recovered and possess the possibility of transmission.

Abbreviations

RP=re-detectable as positive; NRP=non-re-detectable as positive. CI: Interval confidence; ICU: Intensive care unit; IQR: Interquartile range; OR: Odds ratio; RT-PCR: Reverse transcription polymerase chain reaction; Ct value: Cycle threshold value; CT: Computerized tomography scan; COPD: Chronic obstructive pulmonary disease

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests

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Availability of data and materials

All data generated or analysed during this study are included in this published article and supplementary information.

Ethics approval and consent to participate

This study was approved by the institutional ethics board of Guangzhou Eighth People's Hospital and the requirement for informed consent was waived by the ethics board.

Author's contributions

XW, CL, JZ designed the study. XW, CL had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CL, JZ, RZ, FC, KW, FL and GT had roles in the clinical management, patient recruitment, sample preparation and clinical data collection. FC, GT and JL had roles in the RNA and antibody detection experiments and data collection. JZ, RZ, ZY and YY had roles in statistical analysis. JZ, RZ, FC, FL and HL had roles in data interpretation. JZ, RZ and FC wrote the manuscript. JL, FL, HL CL and XW contributed to critical revision of the report. All authors reviewed and approved the final version of the manuscript.

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Figures

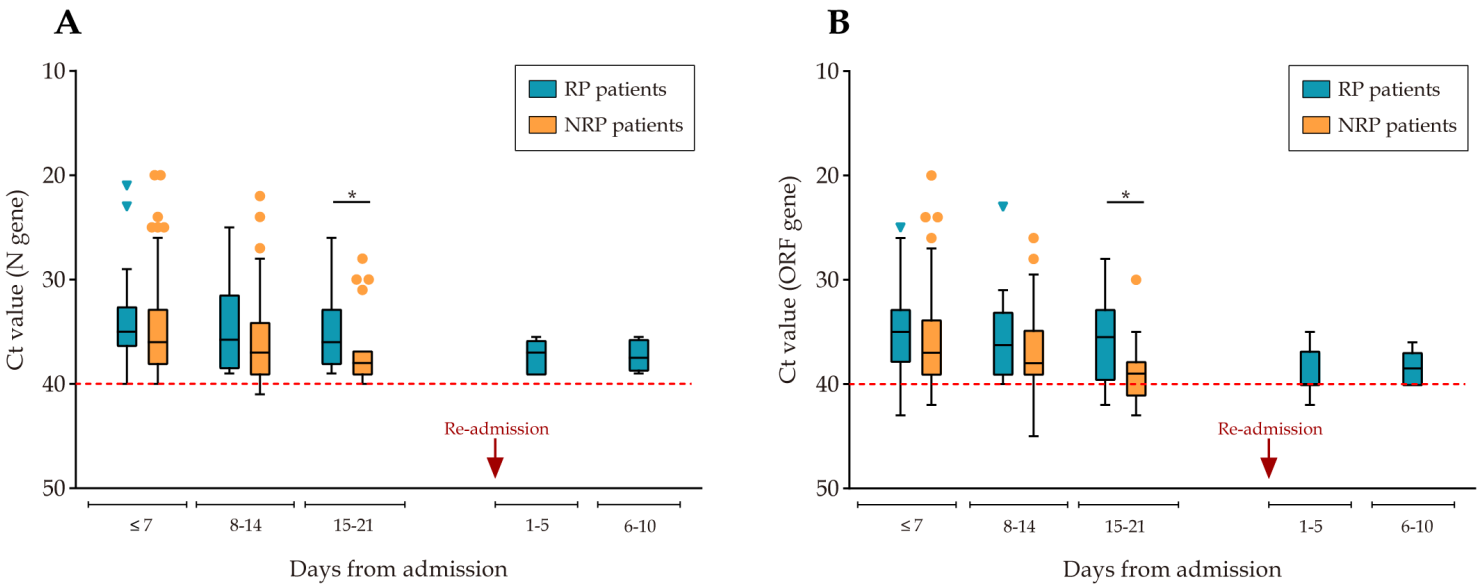

Figure 1

Comparison of Viral dynamics between RP and NRP patients. Figure shows temporal changes in median Ct value of N gene (A) and ORF gene (B) in different time period. Since we have only collected and analyzed the data during patients' hospitalization, Ct value at admission and readmission were unavailable. The dotted line in red shows the lower normal limit of Ct values. Ct=cycle threshold. RP=redetectable as positive. NRP=non-redetectable as positive.

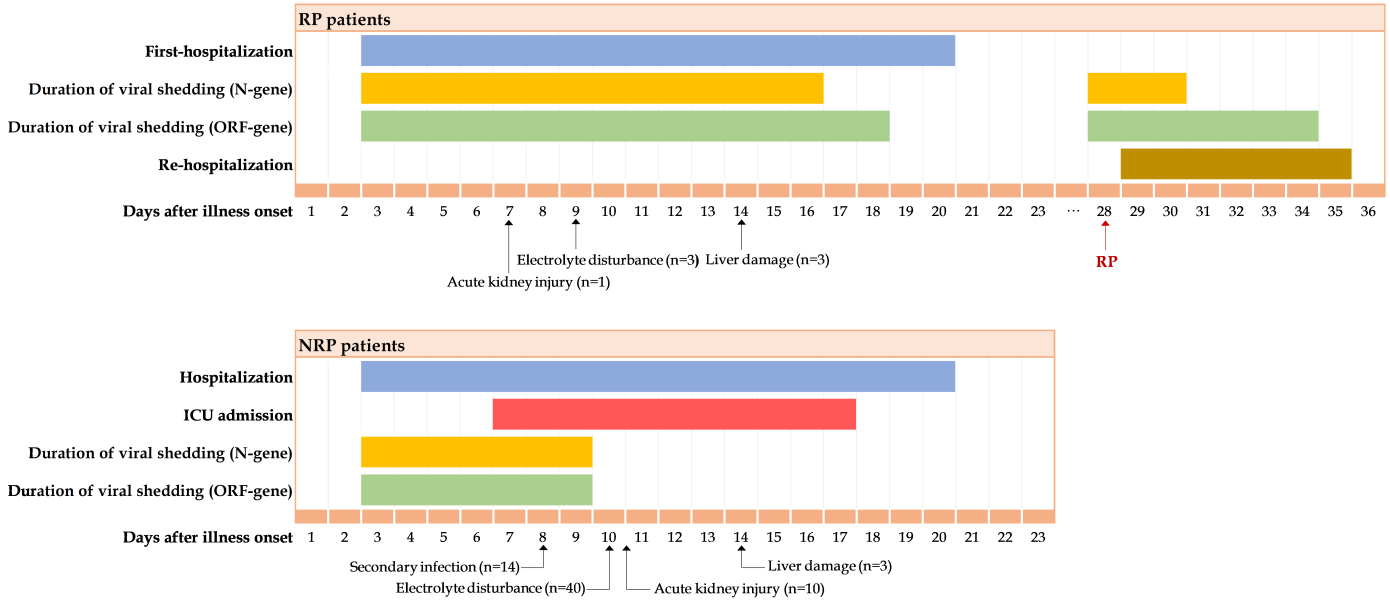

Figure 2

Clinical course, complications and duration of viral shedding from illness onset in patients hospitalized with COVID-19. Figure shows median duration of hospitalization and positive nucleic acid Ct value and onset of several complications. RP=redetectable as positive. NRP=non-redetectable as positive.

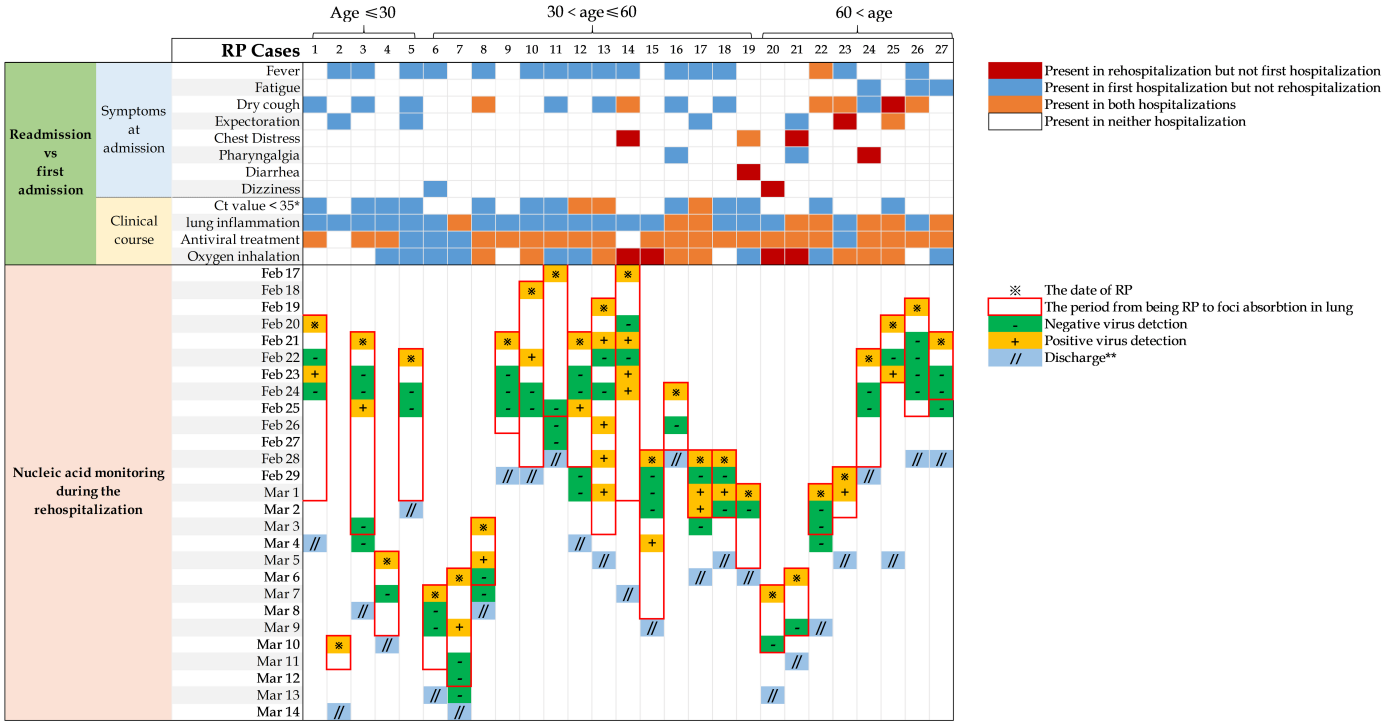

Figure 3

Comparison of the two hospitalization courses of 27 RP patients and result of series SARS-CoV-2 RNA test in nasopharyngeal swab specimens during the second hospitalization. Comparisons of clinical condition between first and second hospitalization are shown for each RP patient (upper panels). Timeline of series SARS-CoV-2 RNA test (lower panels) during rehospitalization are shown. *Ct value <35 refers to whether the lowest Ct value during hospitalization is lower than 35. **Discharge indicates two throat-swab samples negative for SARS-CoV-2 RNA obtained at least 24 h apart. This figure showed that elder RP patients (≥ 60 years old) were more likely to be symptomatic compared to younger RP patients (7/8, 87.5% vs. 3/19, 18.8%, p=0.001) at readmission. RP=redetectable as positive. NRP=non-redetectable as positive.

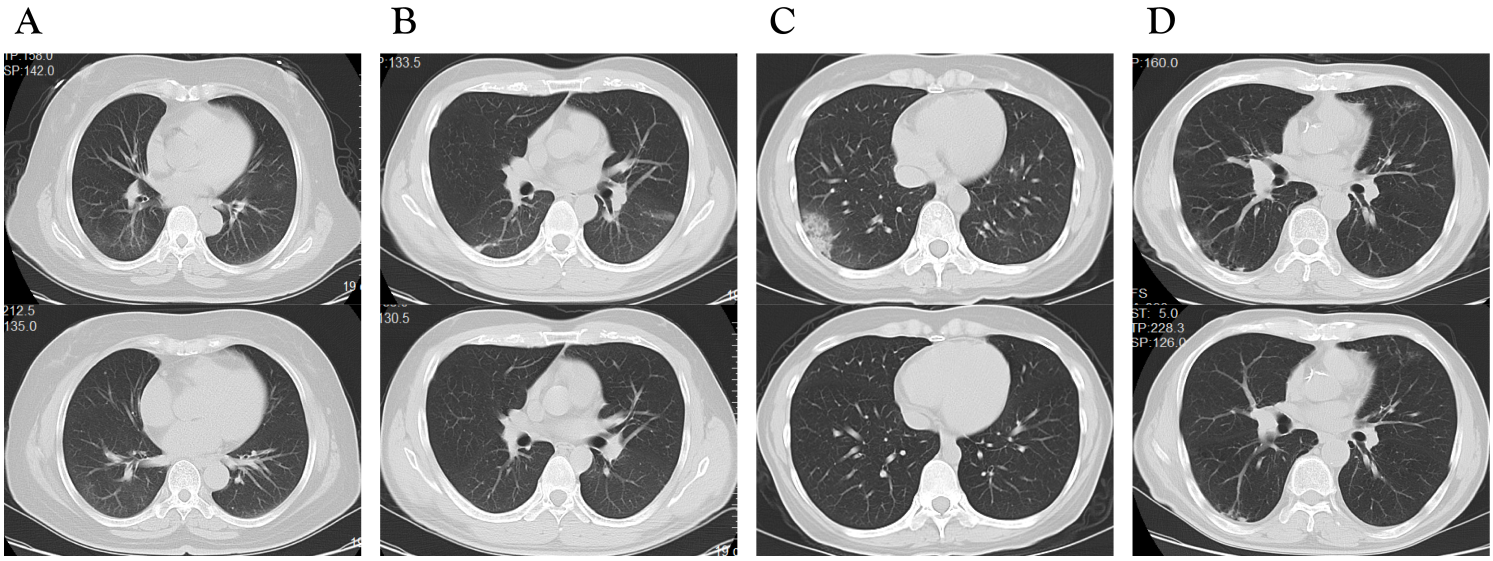

Figure 4

Chest CT images. (A) Transverse chest CT images from a 62-year-old woman who got RP 14 days after discharge, showing multiple inflammation in bilateral lungs at readmission (lower panel), which has partly absorbed compared to the condition at first discharged (upper panel). (B) Transverse chest CT images from a 30-year-old man who got RP 8 days after discharge, showing improved multiple inflammation and decreased shadows of fibrotic streaks at readmission (lower panel) compared to the condition at first discharged (upper panel). (C) Transverse chest CT images from a 32-year-old woman who got RP 6 days after discharge, showing inflammation on bilateral lower lobe at

readmission (lower panel), which has partly absorbed compared to the condition at first discharged (upper panel). (D) Transverse chest CT images from a 68-year-old male NRP patient, showing multiple inflammation in bilateral lungs 14 days after admission (lower panel), with no obvious change compared with the condition at admission (upper panel).

Supplementary Files

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- Supplementarytables.docx