Preplanned Studies

Dynamic Disease Manifestations Among Non-Severe COVID-19 Patients Without Unstable Medical Conditions: A Follow-Up Study — Shanghai Municipality, China, March 22–May 03, 2022

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Summary

What is already known about this topic?

High transmissibility of the Omicron variant has placed a huge burden on healthcare resources. The vast majority of Omicron infections are non-severe among the cases with less high risk factors.

What is added by this report?

In the Shanghai Omicron wave, the risk of developing severe illness was very low (0.065%, 22/33,816) in initially non-severe patients without unstable conditions. Older age, presence of comorbidities, initial symptoms, vaccination status, and several laboratory indicators were associated with prolonged viral shedding time, development of severe illness, and coronavirus disease 2019 (COVID-19) pneumonia.

What are the implications for public health practice?

This study provides evidence for refining COVID-19 public health strategies to minimize the risk of overwhelming of regional medical resources.

Since identification of Omicron in November 2021, Omicron variant infections have increased exponentially in multiple countries, and Omicron has become the main epidemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain in the world. Transmission of Omicron BA.2 is nearly 30% higher than Omicron BA.1 transmission and is significantly higher than transmission of the earlier non-Omicron variants.

Affected by the global spread of Omicron, Shanghai Municipality reported 626,863 Omicron infections between March 1 and June 4, 2022 (*1*). Preliminary data suggest that Omicron generally causes less severe symptoms than previous SARS-CoV-2 variants (*2*), but progression to severe cases occurs and is influenced by vaccination status, age, underlying medical conditions, and other factors (*3*). Given the high transmissibility of Omicron, the overall clinical profile and prognosis of the huge number of non-severe Omicron infections should strongly influence public health policies, including hospitalization and treatment strategies during the coronavirus disease 2019 (COVID-19) pandemic. For example, due to its high transmissibility and high force of infection, regions that previously admitted all SARS-CoV-2-infected individuals may not have sufficient hospital resources to admit non-severe Omicron patients (*4*). Therefore, reliable data on the spectrum of clinical features, risk factors for development of COVID-19 pneumonia, and viral shedding time (VST) of non-severe Omicron patients is critically important.

In this study, under the policy of "all those in need have been tested, and if positive, have been quarantined, hospitalized, or treated" in China, we conducted a large cohort study to describe the spectrum of clinical features, risk factors for progression, and dynamic changes in viral load among initially non-severe Omicron-infected patients in four Shanghai hospitals during the Omicron outbreak.

Our study was conducted between March 22, 2022 and May 03, 2022 at Huashan Hospital, Shanghai Sixth People's Hospital, Shanghai Ninth People's Hospital, and Shanghai Fourth People's Hospital. All admission, discharge, diagnostic, and therapeutic decisions were made based on the latest version of the national COVID-19 protocol (*5*). The study protocol was approved by the ethics committee of Huashan Hospital, receiving the ethics code number KY2000-596.

Patients were eligible for the study if they were diagnosed with non-severe COVID-19 upon hospital admission. Patients with unstable medical conditions were excluded. The definition of unstable medical conditions, complete exclusion criteria and research

details were in the Supplementary Material (available in https://weekly.chinacdc.cn/). Informed consents were gathered from eligible patients. Upon enrollment, physicians obtained baseline demographic and health information. Non-severe infections were defined as asymptomatic, mild, or moderate according to the latest version of the national COVID-19 protocol (*5*).

We used baseline information, VST, laboratory results, computer tomography (CT) scan results, and clinical prognosis for risk analyses. Measures of clinical prognosis included progression from infection to pneumonia and from infection to critical illness. Risk group were: patients ≥60 years old; patients who had stable underlying medical conditions (including cardiovascular disease, diabetes mellitus, lung disease, hepatic disease, cerebrovascular disease, and kidney disease) or who had an immunodeficiency [e.g., human immunodeficiency virus infection, chronic use of corticosteroids, or use of other immunosuppressive drugs] (*5*).

Statistical significance of comparisons of baseline clinical characteristics and demographics were tested with Mann-Whitney U, χ^2 test, or Fisher's exact test, as appropriate. Due to overlap of age and comorbidities with risk group, we developed two multivariable Cox regression models to estimate adjusted hazards ratios (aHR) for factors influencing VST. VST was defined as the difference in days between the first positive test and the first of two consecutively-negative tests. We adjusted for age, sex, comorbidities, vaccination status, final diagnose, and initial symptoms in model 1. We adjusted for risk group, sex, vaccination status, final diagnosis, and initial symptoms in model 2. We used logistic regression to estimate adjusted odds ratios (aOR) of risk factors for developing COVID-19 pneumonia. We adjusted for age, sex, comorbidities, vaccination status, and initial symptoms in the logistic model. All tests were two-sided; $P<0.05$ was considered statistically significant. Statistical analyses were performed with SPSS (version 20.0, IBM, Armonk, NY, USA), Stata (MP version 16.0, StataCrop, College Station, TX, USA), or GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA,USA).

We enrolled 33,816 SARS-CoV-2 positive participants (Supplementary Figure S1, available in https://weekly.chinacdc.cn/) 21,619 (63.9%) patients were male, the median age of patients was 44.5 years, 1,273 (3.7%) patients aged <18, 26,948 (76.7%) patients aged 18–59, and 5,595 (16.5%) patients aged ≥60. 9,260 (27.4%) patients had risk factors, and 6,333 (18.7%) of whom had comorbidities. Among patients with comorbidities, hypertension was the most common comorbidity (4,902/6,333, 77.4%), followed by diabetes mellitus (1,641/6,333, 25.9%) and lung disease (329/6,333, 5.2%) (Figure1A). Among all participants, most (32,688/33,816, 96.7%) had fewer than two comorbidities. Most of the participants had received full or booster vaccination: 73.1% in risk-group subjects and 80.6% in non-risk group subjects (Figure 1B); 76.2% and 78.6% of participants were ultimately diagnosed with asymptomatic infection in the risk group and the non-risk group, respectively (Figure 1C). Cough and sputum production were the most common symptoms (19.0%), followed by fatigue (5.2%) and fever (4.0%). VST was longer in the risk group [6 days, interquartile range (IQR): 4–9 days] than in the non-risk group (6 days, IQR: 3–8 days) ($P<0.001$) (Figure 1D). VST was shorter in vaccinated subjects (6 days, IQR: 3–8 days) than in non-vaccinated subjects (6 days, IQR: 3–8.25 days) ($P<0.001$). The median duration of symptom persistence was 7 days. Dynamic changes in viral load are shown in Supplementary Figure S2 (available in https://weekly.chinacdc.cn/).

Compared to patients under 40 years old, patients 40–59 years old [aHR: 0.90; 95% confidence interval (CI), 0.88–0.92], 60–79 years old (aHR: 0.85; 95% CI, 0.82–0.88) and ≥80 years old (aHR: 0.73; 95% CI, 0.65–0.84) had longer VSTs in the Cox proportional hazards model (Table 1). In model 1, presence of comorbidities (aHR: 0.96; 95% CI, 0.93–0.98) and being initially symptomatic (aHR: 0.95; 95% CI, 0.93–0.98) were also associated with increased VST; being fully vaccinated (aHR: 1.06; 95% CI, 1.03–1.10) and booster vaccinated (aHR: 1.07; 95% CI, 1.03–1.10) were associated with decreased VST. In model 2, VST was longer in the risk group than in the non-risk group (aHR: 0.89; 95% CI, 0.87–0.92) (Figure 1E).

In the entire study cohort, 22 patients developed severe/critical infection; all were in the risk group. Severity rates among all subjects and risk-group subjects were 0.065% and 0.238%, respectively. Hypertension (31.8%) was the most common comorbidity, followed by diabetes (13.6%) and lung disease (13.6%). Patients in the risk group who developed severe/critical infection were older (75.8±10.7 *vs.* 60.0±11.3, $P<0.001$) and were more likely to be unvaccinated (54.5% *vs.* 24.2%; $P=0.002$). (Table 2)

Seven hundred and eight patients suspected to have

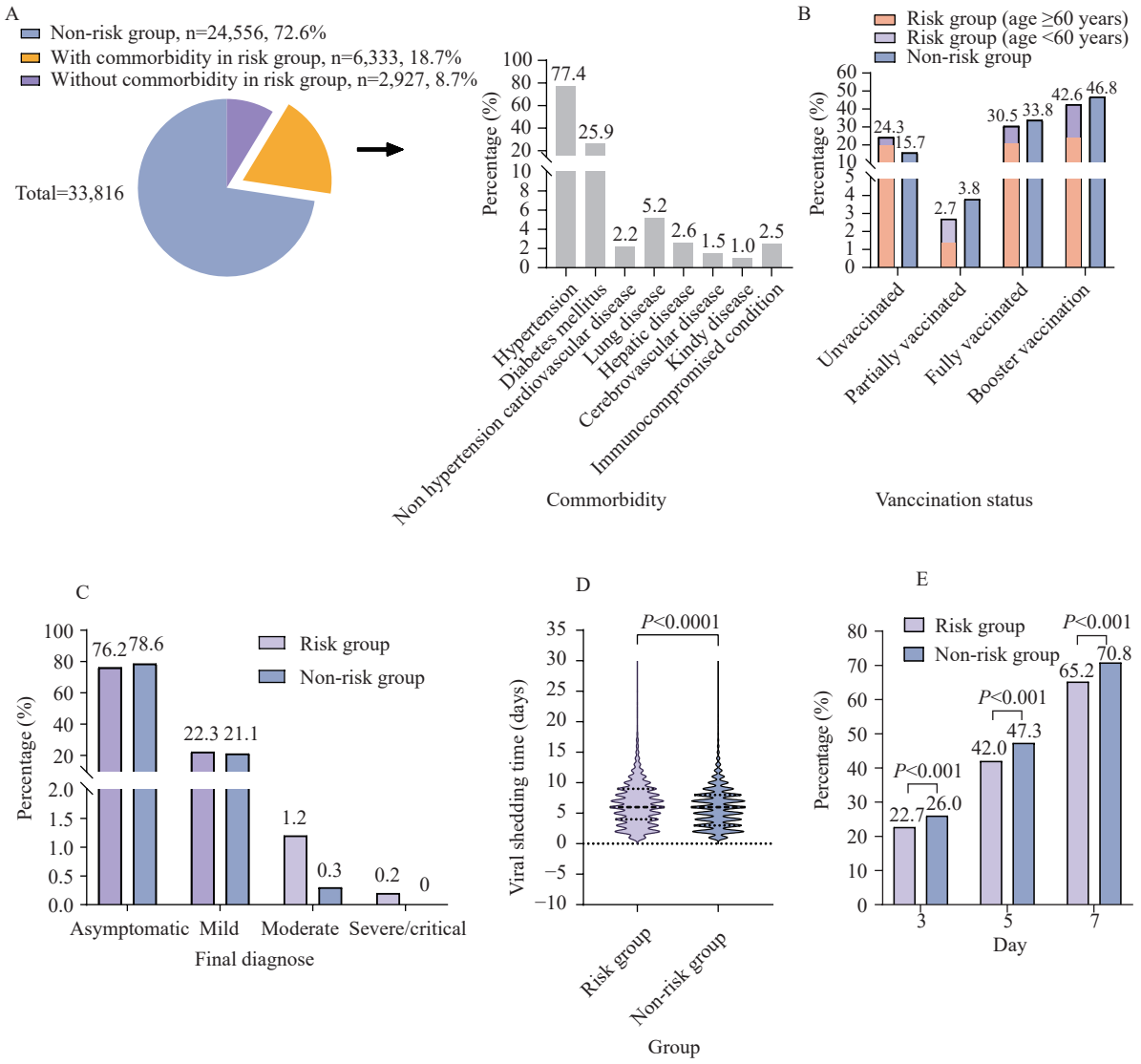

FIGURE 1. Commorbidities, vaccination status, viral shedding time, and final diagnose in risk group and non-risk group subjects. (A) Comorbidities in all patients; (B) Vaccination status and final diagnoses in risk group and non-risk group subjects; (C) Final diagnoses in risk group and non-risk group subjects; (D) Viral shedding times in risk group and non-risk group; (E) Nucleic acid test conversion in risk group and non-risk group.

COVID-19 pneumonia received chest CT scans; 14.0% (99/708) had manifestations of COVID-19 pneumonia on CT. The incidence of pneumonia in the risk group was 19.8% (72/363), which was higher than in the non-risk group (7.8%, 27/345, P<0.001). Multivariable logistic regression analysis (Table 3), showed that compared to patients under the age of 40, being 60–79 years old (aOR: 3.09; 95% CI, 1.41–6.80) or ≥80 years old (aOR: 3.68; 95% CI, 1.32–10.32) was associated with increased risk of COVID-19 pneumonia. Being male (aOR: 1.85; 95% CI, 1.16–2.94) was also associated with increased risk of pneumonia. Some patients (n=203) received laboratory examinations, and we found that lymphopenia (aOR: 6.56; 95% CI, 2.27–19.02), elevated C-reactive protein (CRP) (aOR: 4.64; 95% CI, 2.13–10.13), and prolonged prothrombin time (PT) (aOR: 24.30; 95% CI, 1.73–286.80) were associated with increased risk of COVID-19 pneumonia in multivariable logistic regression.

DISCUSSION

Analyzing dynamic changes of clinical characteristics and risk factors for illness progression among initially non-severe Omicron patients is essential to the construction of public health strategies that can minimize the risk of overwhelming regional medical

TABLE 1. Risk factors associated with prolonged viral shedding time calculated with a cox proportional-hazards model with baseline stratification factors as covariates.

Characteristic	Model 1*		Model 2†	
	aHR (95% CI)	*P* values	aHR (95% CI)	*P* values
Gender (male *vs.* female)	0.99 (0.97–1.01)	0.415	0.99 (0.98–1.01)	0.881
Age groups (years)				
<40	1.00		–	–
40–59	0.90 (0.88–0.92)	<0.001	–	–
60–79	0.85 (0.82–0.88)	<0.001	–	–
≥80	0.73 (0.65–0.84)	<0.001	–	–
Comorbidities (yes *vs.* no)	0.96 (0.93–0.98)	0.002	–	–
Risk group (yes *vs.* no)	–	–	0.89 (0.87–0.92)	<0.001
Vaccination status				
Unvaccinated	1.00		1.00	
Partially vaccinated	1.03 (0.97–1.10)	0.291	1.06 (1.00–1.13)	0.072
Fully vaccinated	1.06 (1.03–1.10)	0.001	1.08 (1.04–1.11)	<0.001
Booster vaccination	1.07 (1.03–1.10)	<0.001	1.06 (1.03–1.10)	<0.001
Final diagnoses				
Asymptomatic	1.00		1.00	
Mild	0.99 (0.96–1.02)	0.413	0.98 (0.95–1.01)	0.199
Moderate	0.84 (0.72–0.97)	0.017	0.82 (0.71–0.94)	0.006
Severe	0.65 (0.41–1.03)	0.064	0.61 (0.38–0.97)	0.035
Initial symptoms (yes *vs.* no)	0.95 (0.93–0.98)	<0.001	0.96 (0.94–0.99)	0.005

Abbreviations: CI=confidence interval; aHR=adjusted hazard ratio.
* Model 1: All basic characteristics of patients including age groups, comorbidities, vaccination status, final diagnose and initial symptoms were included in the model, and the analysis was performed for all patients (n=33,816).
† Model 2: Risk group and basic characteristics except age group and comorbidities were included in the model, and the analysis was performed in all patients (n=33,816).

TABLE 2. Comparison of severe/critical and non-severe Omicron infected patients in the risk group.

Characteristic	Severe/critical Omicron infected group (n=22)	Non-severe Omicron infected group (n=9,238)	*P*
Gender [male, n (%)]	15 (68.2)	5,572 (60.3)	0.451
Age (years, Mean ± SD)	75.8±10.7	60.0±11.3	<0.001
Comorbidities [n (%)]	13 (59.1)	6,279 (68.0)	0.373
Vaccination status [n (%)]			0.002
Unvaccinated	12 (54.5)	2,239 (24.2)	
Partially vaccinated	2 (9.1)	246 (2.7)	
Fully vaccinated	3 (13.6)	2,817 (30.5)	
Booster vaccination	5 (22.7)	3,936 (43.0)	
Initial symptoms [n (%)]	8 (36.4)	2,135 (23.1)	0.141

Abbreviations: SD=standard deviation.

resources. Our study was restricted to infected patients with non-severe illness upon hospital admission. No subjects had organ failure but upper respiratory symptoms were prevalent among the symptomatic patients in our study. Among those with symptoms in our study, the median duration of symptoms was 7 days, similar to the 5-day median duration of symptoms for Omicron infections in other studies (*6*). This suggests that despite the higher percentage of asymptomatic Omicron infections in Shanghai,

TABLE 3. Risk factors for Omicron pneumonia calculated with multivariate logistic regression analysis.

Characteristic	aOR (95% CI)	*P*
Gender (male *vs*. female)	1.85 (1.16–2.94)	0.010
Age group (years)		
<40	1.00	
40–59	1.55 (0.73–3.29)	0.251
60–79	3.09 (1.41–6.80)	0.005
≥80	3.68 (1.32–10.32)	0.013
Comorbidities (yes *vs*. no)	1.25 (0.75–2.10)	0.392
Vaccination status		
Unvaccinated	1.00	
Partially vaccinated	0.87 (0.24–3.19)	0.832
Fully vaccinated	0.86 (0.48–1.56)	0.621
Booster vaccination	0.71 (0.40–1.26)	0.239
Initial symptoms (yes *vs*. no)	1.22 (0.75–1.97)	0.427

Note: Case group (n=99): patients showed manifestations of COVID-19 pneumonia on CT scans; Control group (n=609): patients did not show manifestations of COVID-19 pneumonia on CT scans.
Abbreviations: CI=confidence interval; aOR=adjusted odds ratio; COVID-19=coronavirus disease 2019; CT=computed tomography.

specific symptoms persisted in some patients. Debilitating symptoms, such as fever, dizziness, and headaches were uncommon, which is also consistent with previous research (*6*).

VST is an important factor for assessing risk of transmission and for guiding decisions regarding non-pharmaceutical intervention application. According to previous research, the median VST was 6 days (interquartile range 4–8 days) in symptomatic Omicron infected outpatients (*7*). However, until now, no studies have reported VST among non-severe patients. In our study, the median VST in non-severe patients was 6 days (IQR 3–8 days). Other studies have shown that older age and hypertension are associated with longer VSTs (*8*), which is consistent with our research. We also found that the presence of other comorbidities and initial symptoms was also associated with increased VST, and that full vaccination and booster vaccination was associated with decreased VST. These findings have important implications for future COVID-19 public health strategic planning.

Twenty-two patients (0.065% of the total study cohort) developed severe or critical infections. These patients all had risk factors and were older on average and more likely to be unvaccinated — findings that are consistence with previous research (*9*–*10*). Compared to the initail wave of COVID-19 outbreak in Wuhan, 2020 (*11*), Omicron infected individuals in our study had a much lower rate of developing severe/critical infection (0.065%). There are several possible reasons for this large difference. First, previous studies showed Omicron infections were more likely to cause weaker attacks on the lungs, suggesting that Omicron may lead to a smaller percent of severe cases (*12*). Second, the enrolled patients in our study were all non-severe upon admission, and all without unstable conditions. Most of them had no more than two comorbidities. Our study therefore reflected the clinical manifestations and outcomes of relatively healthy Omicron-infected patients. However, considering the relatively high transmissibility of Omicron, the total number of severe infections can still rise rapidly during an epidemic.

Compared with Delta, Omicron's relative inability to colonize or damage the lungs may result in fewer cases of dangerous pneumonia and respiratory distress. However, we showed that some initially non-severe Omicron patients could still develop pneumonia. Our study found that patients with COVID-19 pneumonia were older and more likely to have comorbidities. However, young Omicron patients can also develop COVID-19 pneumonia. Recently, a case of COVID-19 pneumonia caused by the Omicron variant was reported in a 19-year-old woman who had no obvious risk factors (*13*). In our research, 11.1% of the COVID-19 pneumonia patients were younger than 40 years, and the youngest was 22 years old. Among young COVID-19 pneumonia patients above, 72.7% had no underlying medical conditions, and only 1 was unvaccinated. Although being younger, vaccinated, having no underlying diseases can serve as protective factors for progression to severe disease, these factors

do not provide 100% protection from pneumonia. We further analyzed laboratory indicators for pneumonia. Lymphopenia, elevated CRP, and prolonged PT were associated with development of pneumonia, as other studies have reported (*14*–*15*). Our finding can encourage clinicians to conduct CT screening among certain Omicron infected populations. Early identification and treatment of pneumonia may further reduce the risk of severe COVID-19 disease progression.

Our study had at least three limitations. First, we only enrolled non-severe, stabilized Omicron patients and therefore could not describe the overall clinical spectrum of Omicron infections, especially severe Omicron infections. Second, not all patients received CT scan and laboratory tests. Third, all symptoms were self-reported, potentially introducing bias.

Our study demonstrated the dynamic clinical manifestation, symptoms duration, and VST patterns among initially non-severe Omicron patients. Median symptom persistence was 7 days. Older age, having comorbidities, and being initially symptomatic were associated with longer VST, while vaccination was associated with shorter VST. The overall severity progression rate was very low in these initially non-severe patients without unstable conditions. Older age and lack of vaccination increased risk of progression to severe/critical illness. Male sex, older age, lymphopenia, elevated CRP, and prolonged PT were associated with higher risk of developing pneumonia.

Conflicts of interest: No conflicts of interest.

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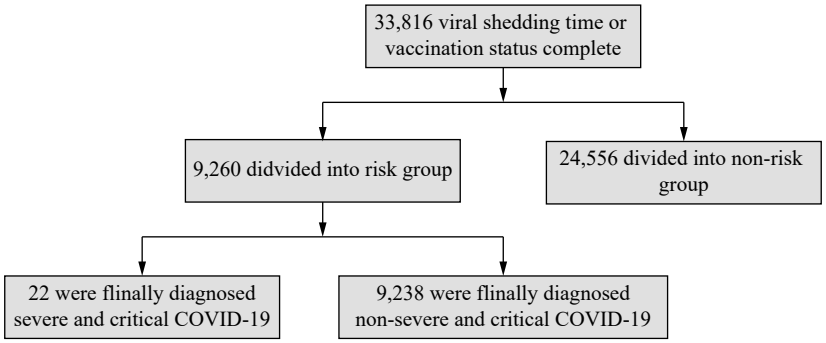
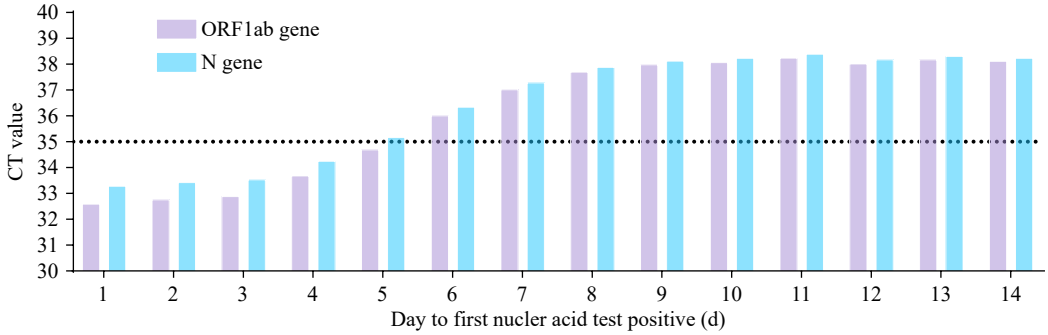
SUPPLEMENTARY MATERIAL

Participant exclusion criteria were: patients with severe or critical coronavirus disease 2019 (COVID-19); elder or disabled patients with no self-care ability or escort, young children unaccompanied by parents; patients with unstable medical conditions: 1.severe or rapidly progressive comorbidity, at episodes of mental illness or mania; 2.need for radiotherapy, chemotherapy, dialysis, mechanical ventilation, emergency surgery or surgical treatment, or having other emergencies (such as Acute Coronary Syndromes, acute pulmonary embolism); 3.history of CPR or major operation within one month, and patients with other potentially life-threatening clinical conditions or other special emergencies; 4.children with persistent high fever; 5.high-risk pregnant women or women in the third trimester of pregnancy.

Chest computer tomography and laboratory examination were performed if patients were suspected of having pneumonia or diseases progress. Participants received SARS-CoV-2 PCR test once a day, and the discharge standard was two consecutive negative results (both ORF1ab and N gene >35 cycle threshold). Symptom duration was calculated as first symptom onset date to disappearance date, and all symptoms collected from patients were self-reported.



SUPPLEMENTARY FIGURE S1. Flow chart of the study.



SUPPLEMENTARY FIGURE S2. Dynamic changes of ORF1ab gene and N gene in from the day first nuclear acid test positive.
Abbreviation: CT=cycle threshold.