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Coronavirus Pandemic

Consecutive positive nucleic acid tests in COVID-19 patients: a retrospective cohort study in Fangcang hospitals, Shanghai

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) spread rapidly in Shanghai in February 2022. Patients with asymptomatic and mild symptoms were admitted to Fangcang shelter hospitals for centralized quarantine.

Methodology: A total of 5,217 non-severe patients hospitalized in the Longyao Fangcang and Shilong Fangcang hospitals were included in the study. Demographic and clinical characteristics, comorbidity, exposure history, treatment and disease duration were analyzed. Univariate analysis and binomial logistic regression analysis were performed to identify the factors influencing nucleic acid change from positive to negative over 14 days.

Results: Consecutive positive nucleic acid test results (days) were significantly associated with advanced age (OR = 1.343, 95% CI 1.143 to 1.578, $p < 0.001$), smoking (OR = 0.510, 95% CI 0.327 to 0.796, $p = 0.003$) and vaccination (OR = 0.728, 95% CI 0.641 to 0.827, $p < 0.001$). However, there was no significant difference between asymptomatic and mild symptomatic patients ($p = 0.187$). In univariate analysis, comorbidities including diabetes, hypertension, cardiovascular system, malignant tumors, autoimmune diseases and cerebral apoplexy were associated with consecutive positive nucleic acid test results, but there was no significant difference in binomial logistics regression analysis.

Conclusions: Aging and comorbid conditions lead to the prolongation of positive nucleic acid test results for several days. Improving vaccination coverage is beneficial for prevention and control of the epidemic. The management and treatment methods of Shanghai Fangcang shelter hospitals had important referential significance, which can provide valuable guidance for the prevention and control of the COVID-19 epidemic in the future.

Key words: COVID-19; Fangcang; nucleic acid test; factors; vaccination.

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Introduction

A wave of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection broke out in Shanghai, China in late February 2022. According to the Shanghai Municipal Health Commission 626,811 cases had been identified, including 568,811 asymptomatic infections and 58,000 symptomatic cases, and 588 people had died of coronavirus disease 2019 (COVID-19) up to June 1, 2022 [1]. To cope with the rapid spread of COVID-19, Shanghai had set up shelter hospitals to receive asymptomatic and mildly symptomatic patients with positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) tests. A total of 27 national medical teams with 70,000 health professionals were dispatched across China, including the authors of this study.

Fangcang shelter hospitals were first implemented in Wuhan, China, to tackle the COVID-19 outbreak in 2019 [2]. They received non-severe individuals with positive SARS-CoV-2 tests, and provided medical care, disease monitoring, food, shelter, and social activities. They played an important role in the prevention and control of COVID-19 [3].

The dominant coronavirus strains causing the epidemic in Shanghai were Omicron BA.2 and BA.2.2, which had the characteristics of fast transmission and strong concealment [4,5]. Although Omicron BA.2 evolved towards less virulence, and the majority of patients presented with asymptomatic infection, a higher rate of severe outcomes and considerable mortality had been reported in unvaccinated people, especially the elderly [6].

Previous studies have shown that the main risk factors of severe COVID-19 included old age, male gender, hypertension, diabetes, obesity, chronic lung disease, heart disease, liver and kidney disease, tumor, pregnancy [7,8]. Unlike the COVID-19 incidence in Wuhan, most of the patients in the Shanghai shelter hospital were non-severe patients. In this study, we describe the clinical characteristics of 5,217 non-severe patients who were admitted to Longyao and Shilong Fangcang shelter hospitals in Shanghai. Moreover, we also investigated the factors influencing 181 patients whose nucleic acid test changed from positive to negative over 14 days. The study was approved by the Ethics Committee of Qilu Hospital of Shandong University, and the study was performed in accordance with the Declaration of Helsinki.

Methodology

Study setting

The Shanghai Longyao Road Fangcang shelter hospital (Longyao Fangcang hospital) had 1,175 beds available and started to receive patients on April 5, 2022. The shelter hospital was officially closed on May 10, 2022, and a total of 2,369 patients were treated, including 2,341 cured and 28 transferred out.

Shilong Road Fangcang shelter hospital (Shilong Fangcang hospital) had 1,548 beds available and started to receive patients on April 8, 2022. The shelter hospital was officially closed on May 16, 2022, and a total of 3,054 patients were treated, including 2,969 cured and 85 transferred out.

Study participants

The Fangcang shelter hospitals mainly treated mild and asymptomatic patients with positive SARS-CoV-2 RT-PCR tests. The admission criteria were as follows: (1) a positive result confirmed by standard SARS-CoV-2 RT-PCR test; (2) able to walk and live independently; (3) $SpO_2 > 93\%$, oxygenation index ≥ 300 mmHg, and breathing rate < 30 beats per min in resting state; and (4) no history of severe and unstable mental health conditions.

The patients meeting the following criteria were discharged: (1) temperature returned to normal for more than 3 days; (2) no obvious respiratory symptoms; and (3) CT value of nucleic acid of nasopharyngeal swab by RT-PCR greater than 35 for two consecutive times (with an interval of at least 24 hours).

If the patients' condition deteriorated, they were transferred to a higher-level hospital for further treatment. In this study, we included the 5,217 patients who recovered and were discharged from the Longyao and Shilong Fangcang Hospitals.

Data collection

Basic information (gender, age and comorbidity), symptoms (fever, runny nose, nasal congestion, sore throat, cough, expectoration, dyspnea, headache, hypogeusia, hyposmia, vomiting, diarrhea, abdominal pain, myalgia and fatigue), nucleic acid test results (RT-PCR was performed every 24 hours), vaccination status, smoking status (who smokes continuously or cumulatively for 6 months or more during their lifetime was defined as having a history of smoking) and epidemiological data were collected for each patient from electronic medical records.

Since the majority of the patients admitted in the shelter hospital were asymptomatic and mild patients, laboratory and radiological tests were not conducted in the Fangcang shelter hospital.

Statistical analysis

Categorical data were presented as counts and percentages, and continuous data were expressed as mean ± standard deviation (SD) or expressed as median with interquartile range (IQR) values if the data were not normally distributed. Student's t-test and Mann-Whitney U test were used to compare means and medians. Chi-square test was used to investigate the association between classification variables. Binomial logistic regression analysis was carried out on statistically significant variables to identify the influencing factors of patients whose nucleic acid persistently tested positive for over 14 days. A p value less than 0.05 was considered statistically significant for all the statistical tests. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Statistics version 26.0 software.

Results

General characteristics of patients with COVID-19 in Fangcang hospital

The general characteristics of the patients are presented in Table 1. The median age of the included patients was 45 years (IQR = 26), ranging from 2 to 91 years, and about 59.4% (n = 3100) were male. Patients with mild symptoms accounted for about 43.4% (n = 2266); the rest were asymptomatic patients.

Respiratory symptoms, including runny nose, nasal congestion, sore throat, cough, expectoration and dyspnea, were the most common clinical symptoms, accounting for 37.5% (n = 1957). Fatigue was recorded in 12.2% (n = 635) patients. Fever and muscle soreness

Table 1. General characteristics of patients in Longyao and Shilong Fangcang shelter hospitals in Shanghai.

Demographic characteristics	n (%)
Age	
Median (IQR)	45 (26)
Range (year)	2-91
Gender	
Male	3100 (59.4)
Female	2117 (40.6)
Clinical symptoms	
Asymptomatic	2951 (56.6)
Mild symptom	2266 (43.4)
Fever	515 (9.9)
Respiratory tract symptom (runny nose, nasal congestion, sore throat, cough, expectoration, dyspnea)	1957 (37.5)
Digestive tract symptom (anorexia, diarrhea, vomiting, abdominal pain)	11 (0.2)
Fatigue	635 (12.2)
Muscle soreness	493 (9.4)
History of chronic diseases	1256 (24.1)
Hypertension	850 (16.3)
Diabetes	257 (4.9)
Cardiovascular diseases	251 (4.8)
Respiratory diseases	203 (3.9)
Autoimmune diseases	52 (1.0)
Malignant tumor	54 (1.0)
Cerebral apoplexy	30 (0.6)
Chronic kidney disease	24 (0.5)
Vaccination (dose)	
0	668 (12.8)
1	174 (3.3)
2	1622 (31.1)
3	2753 (52.8)
Unvaccinated in different age groups	
<18	63 (1.2)
18-44	209 (4.0)
45-59	127 (2.4)
≥60	269 (5.2)
Medical treatment	
Traditional Chinese medicine (TCM)	5106 (97.9)
Antipyretic	515 (9.9)
Antitussive	953 (18.3)
Antibiotic	543 (10.4)
Length of hospital stay	
≤14	4369 (83.7)
>14	848 (16.3)
Interval between symptom onset to admission to Fangcang hospital (days)	
Median (IQR)	4 (5)

were observed in 9.9% (n = 515) and 9.4% (n = 493), respectively. Patients with digestive tract symptoms were few and observed in only 0.2% (n = 11).

In terms of comorbidity, 24.1% (n = 1256) of the patients had a history of chronic diseases. Hypertension was the most common, present in 16.3% (n = 850) patients. Diabetes and cardiovascular diseases (including coronary heart disease, arrhythmia and heart failure) were present in 4.9% (n = 257) and 4.8% (n = 251) respectively. Respiratory diseases including asthma, bronchiectasis, chronic bronchitis and chronic obstructive pulmonary disease were reported by 3.9% (n = 203) patients. Autoimmune diseases, malignant tumors, cerebral apoplexy and kidney diseases were reported by 1.0% (n = 52), 1.0% (n = 54), 0.6% (n = 30), and 0.5% (n = 24) patients, respectively.

Vaccination status of the patients is also presented in Table 1. In total, 52.8% (n = 2753), 31.1% (n = 1622) and 3.3% (n = 174) of all patients received 3, 2, and 1 shot of vaccine, respectively; 12.8% (n = 668) of patients were unvaccinated and nearly 50% of them were over 60 years old.

In terms of treatment, almost all the patients were treated with traditional Chinese Medicine. About 9.9%

Table 2. Factors associated with consecutive positive nucleic acid test results.

Characteristics	≤ 14 days (n = 5036)	> 14days (n = 181)	*p* value	Odds ratio (95% CI)
Age (categorical)			< 0.001	
< 18	263 (5.2)	3 (1.7)	< 0.001	
18-44	2236 (44.4)	54 (29.8)	0.211	2.109 (0.655-6.793)
45-59	1558 (30.9)	61 (33.7)	0.039	3.419 (1.065-10.978)
60-69	745 (14.8)	46 (25.4)	0.005	5.392 (1.663-17.485)
≥ 70	235 (4.7)	17 (9.4)	0.004	6.318 (1.828-21.830)
Gender				
Male	3006 (59.7)	95 (52.5)	0.053	1.340 (0.996-1.804)
Female	1030 (40.3)	86 (47.5)		
Clinical symptoms	2197 (43.6)	70 (38.7)	0.187	0.815 (0.601-1.105)
History of chronic diseases	1200 (23.8)	66 (36.5)	< 0.001	1.835 (1.346-2.500)
Diabetes	237 (4.7)	20 (11.0)	< 0.001	2.515 (1.552-4.076)
Hypertension	802 (15.9)	48 (26.5)	< 0.001	1.905 (1.358-2.673)
Cardiovascular diseases	235 (4.7)	16 (8.8)	0.010	1.981 (1.166-3.364)
Respiratory diseases	193 (3.8)	10 (5.5)	0.250	1.467 (0.763-2.821)
Autoimmune diseases	47 (0.9)	5 (2.8)	0.015	3.016 (1.185-7.675)
Malignant tumor	47 (0.9)	7 (3.9)	< 0.001	4.270 (1.903-9.583)
Cerebral apoplexy	25 (0.5)	5 (2.8)	< 0.001	5.694 (2.155-15.050)
Chronic kidney disease	23 (0.5)	1 (0.6)	0.852	1.211 (0.163-9.016)
Vaccination			< 0.001	
0	618 (12.3)	50 (23.2)	< 0.001	
1	166 (3.3)	8 (4.4)	< 0.001	0.466 (0.318-0.681)
2	1568 (31.1)	54 (29.8)	< 0.001	0.426 (0.287-0.632)
3	2684 (53.3)	69 (38.1)	< 0.001	0.318 (0.219-0.462)
Smoking				
Yes	1329 (26.4)	28 (15.5)	0.001	0.510 (0.340-0.767)
No	3707 (73.6)	153 (84.5)		

(n = 515) and 18.3% (n = 953) patients were treated with antipyretics and antitussives, respectively, and only 10.4% (n = 543) of patients received an antibiotic treatment.

The median time from symptoms onset to Fangcang hospitals admission was 4 days (IQR = 5). The length of hospital stay and the number of consecutive days with positive test results are presented in Table 1. Eight hundred forty-eight (16.3%) patients were hospitalized for more than 14 days, while 3.5% of the patients had nucleic acid test positive for more than 14 days. Among patients hospitalized for more than 14 days, the proportion of patients with positive RT-PCR for more than 14 days was about 21.3%.

Factors associated with recurrent positive RT-PCR results over several days

As shown in Table 2, the consecutive positive RT-PCR results (days) was significantly associated with age, common comorbidity, vaccination status and smoking status. Advanced age was significantly correlated with nucleic acid test continuous positive days ($p < 0.001$). Among the history of chronic diseases, diabetes, hypertension, cardiovascular diseases, autoimmune diseases, malignant tumor and cerebral apoplexy were significantly correlated with nucleic acid test continuous positive days ($p < 0.05$), and they were all risk factors. However, respiratory disease and chronic kidney disease were not significantly correlated in our study. Vaccination status and smoking were significantly correlated with nucleic acid test continuous positive days and they were protective factors for COVID-19 ($p < 0.001$). There was no significant difference between mild and asymptomatic patients ($p = 0.187$).

Results of logistic regression analysis

Binomial logistic regression analysis was conducted to analyze the factors influencing the nucleic acid test continuous positive days, and the results are shown in Table 3. Age was significantly associated with nucleic acid test continuous positive days, and advanced age was a risk factor (OR = 1.343, 95% CI 1.143 to 1.578, $p < 0.001$). The vaccination status was significantly associated with nucleic acid test continuous positive days, and the vaccine was a protective factor (OR = 0.728, 95% CI 0.641 to 0.827, $p < 0.001$). Intriguingly, smoking as a protective factor was significantly correlated with nucleic acid test continuous positive days (OR = 0.510, 95% CI 0.327 to 0.796, $p = 0.003$). In logistic regression analysis of common comorbidities, only cerebral apoplexy (OR =

Table 3. Logistic regression analysis on the factors associated with nucleic acid test continuous positive days.

Characteristics	*p* value	OR	95% CI
Age	< 0.001	1.343	1.143-1.578
Gender	0.988	1.003	0.724-1.389
History of chronic diseases	0.225	0.677	0.361-1.271
Diabetes	0.067	1.694	0.963-2.979
Hypertension	0.182	1.497	0.827-2.709
Cardiovascular diseases	0.528	1.215	0.664-2.222
Autoimmune diseases	0.117	2.262	0.815-6.280
Malignant tumor	0.046	2.467	1.015-5.995
Cerebral apoplexy	0.031	3.105	1.109-8.694
Vaccination	< 0.001	0.728	0.641 -0.827
Smoking	0.003	0.510	0.327-0.796

p values indicate differences between consecutive positive nucleic acid test results for more than 14 days and less or equal to 14 days. $p < 0.05$ denotes statistically significant difference. OR, odds ratio; CI, confidence interval.

3.105, 95% CI 1.109 to 8.694, $p = 0.031$) and malignant tumor (OR = 32.467, 95% CI 1.015 to 5.995, $p = 0.046$) had statistically significant differences.

Discussion

Our research found that advanced age and common comorbidities led to prolongation of the nucleic acid test continuous positive days and aging itself was a prominent risk factor for severe disease and death from COVID-19 [9]. Vaccination shortened the time of nucleic acid test continuous positive days, which was beneficial for the recovery of COVID-19 patients. In addition, Chinese medicine played an important role in the control of COVID-19 in Shanghai.

Hypertension, diabetes and cardiovascular diseases were common comorbidities among COVID-19 patients in our study. Among the common comorbidities in patients, univariate analysis showed that diabetes, hypertension, cardiovascular diseases, malignant tumors, autoimmune diseases and cerebral apoplexy were all related to the nucleic acid test continuous positive days, but binomial logistic regression analysis showed that only cerebral apoplexy and malignant tumor were related to the positive days, and other chronic comorbidities were not significantly related to the positive days. This may be related to the low pathogenicity of omicron BA.2 and BA.2.2 variants. Although it is still uncertain whether diabetes is a risk factor for severe COVID-19 [10,11], one study has shown that diabetes was related to longer hospital stay among non-severe COVID-19 patients [12]. Viral infection may cause blood glucose level fluctuations, aggravate the complications of diabetes and prolong the rehabilitation process [13]. In addition, the previous large-scale studies of COVID-19 patients in Wuhan showed that advanced age, diabetes, hypertension, history of other cardiovascular diseases, chronic kidney diseases and tumors were related to the adverse outcomes associated with COVID-19 [11,14,15]. Therefore, in the case of the elderly and patients with complications, early intervention should be taken to avoid disease aggravation.

Our results showed that vaccine was significantly correlated with the nucleic acid test continuous positive days and was a protective factor for COVID-19. At present, the total coverage rate of vaccination has exceeded 90% in Shanghai. However, vaccination coverage is still low among older adults. Among people aged 60 years and older, 62% have been vaccinated and, among them, only 38% have received a booster vaccination [16]. In order to maximize COVID-19 vaccination, health authorities should actively promote the effectiveness and importance of vaccination, while addressing concerns about vaccine safety among the public. In addition, authorities should develop strategies to raise awareness on the benefits of vaccination and ensure rapid and widespread media communication on local vaccine coverage [17,18].

Our results showed that smoking was a protective factor for COVID-19. At present, the influence of smoking on COVID-19 is controversial. A meta-analysis of smoking and pneumonia showed that smoking was a risk factor for progression of COVID-19, with smokers having 1.91 times the odds of progression to COVID-19 severity than non-smokers [19]. However, a study of 38 European countries found that smoking rates were negatively correlated with the incidence of COVID-19, but this association may not imply a true or causal relationship, and smoking was not advocated as a prevention or treatment of COVID-19 [20].

In terms of treatment, almost all patients were treated with traditional Chinese Medicine, including Lianhua Qingwen capsules/granule, Jinfang granule, and Qingfei Paidu decoction (the basic formula used was: Ma Huang 9 g, Zhi Gan Cao 6 g, Xing Ren 9 g, Sheng Shi Gao 15-30 g, Gui Zhi 9 g, Ze Xie 9 g, Zhu Ling 9 g, Bai Zhu 9 g, Fu Ling 15 g, Chai Hu 16 g,

Huang Qin 6 g, Jiang Ban Xia 9 g, Sheng Jiang 9 g, Zi Wan 9 g, Kuan Dong Hua 9 g, She Gan 9 g, Xi Xin 6 g, Shan Yao 12 g, Zhi Shi 6 g, Chen Pi 6 g, and Huo Xiang 9 g) [21]. Dozens of Chinese herbal medicines and hundreds of natural Chinese herbal ingredients have been reported to possess antiviral activities and can be used to prevent and treat viral infections [22]. Previous studies have shown that Lianhua Qingwen capsules could shorten the recovery time of COVID-19 and ameliorate symptoms of fever, cough and weakness [23]. Compared with western medicine alone, Qingfei Paidu decoction along with western medicine had significantly better anti-inflammatory effect in patients with mild and moderate COVID-19, and could also mitigate the extent of multi-organ impairment [24].

Strengths and limitations

Our study was a two-center study with a very large sample size. It was aimed at the omicron BA.2 pandemic in Shanghai and added clinical data for the study of the omicron strain. In this study, almost every patient was treated with traditional Chinese medicine, which effectively alleviated their symptoms and helped them recover better. Finally, the Shanghai Fangcang hospital management method was proven to be very effective in this outbreak.

Our study also has some limitations. Fangcang shelter hospitals are not regular hospitals. Routine tests such as blood routine examination, C-reactive protein and chest computed tomography (CT) could not be carried out in Fangcang shelter hospitals. Moreover, the discharged patients may need to be followed up in the long term, and the coronavirus antibody levels and sequelae of COVID-19 were not followed.

Conclusions

Aging and comorbid conditions led to the prolongation of nucleic acid test continuous positive days and improving vaccination coverage was beneficial for epidemic prevention and control. Smoking was a protective factor of COVID-19, but this association may not imply a true or causal relationship, and smoking was not advocated as a prevention or treatment of COVID-19. In addition, the treatment and management methods at Shanghai Fangcang shelter hospitals can constitute significant reference protocols for the prevention and control of COVID-19 in the future.

Availability of data and materials

The dataset used and analyzed in the study is available from the corresponding author on reasonable request.

Author contributions

Xiaoyan Xiao, Hui Dong and Jiaojiao Yang designed the study; Xiaoqing Ren, Jinxiang Wu and Lianhai Hu collected the epidemiological and clinical data; Jiaojiao Yang and Zhang Qi analyzed the data; Jiaojiao Yang drafted the manuscript. Xiaoyan Xiao revised the final manuscripts.

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