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Original article

Clinical characteristics of COVID-19 patients in three consecutive generations of spread in Zhejiang, China

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ABSTRACT

Objectives: The aim was to determine the clinical characteristics of COVID-19 patients because the SARS-CoV-2 virus continues to circulate in the population.
Methods: This is a retrospective, multicentre, cohort study. Adult COVID-19 cases from four hospitals in Zhejiang were enrolled and clustered into three groups based on epidemiological history. First-generation patients had a travel history to Hubei within 14 days before disease onset; second-generation patients had a contact history with first-generation patients; third-generation patients had a contact history with second-generation patients. Demographic, clinical characteristics, clinical outcomes and duration of viral shedding were analysed.
Results: A total of 171 patients were enrolled, with 83, 44 and 44 patients in the first-, second-, and third-generation, respectively. Compared with the first and second generations, third-generation patients were older (61.3 vs. 48.3 and 44.0 years, $p < 0.001$) and had more coexisting conditions (56.8% vs. 36.1% and 27.3%, p 0.013). At 7 ± 1 days from illness onset, third-generation patients had lower lymphocyte (0.6 vs. 0.8 and 0.8 × 109/L, p 0.007), higher C-reactive protein (29.7 vs. 17.1 and 13.8 mg/L, p 0.018) and D-dimer (1066 vs. 412.5 and 549 μg/L, p 0.002) and more lesions involving the pulmonary lobes (lobes ≥5, 81.8% vs. 53.0% and 34.1%, $p < 0.001$). The proportions of third-generation patients developing severe illness (72.7% vs. 32.5% and 27.3%, $p < 0.001$), critical illness (38.6% vs. 10.8% and 6.8%, $p < 0.001$) and receiving endotracheal intubation (20.5% vs. 3.6% and 2.3%, p 0.002) were higher than in the other two groups.
Discussion: Third-generation patients were older, had more underlying comorbidities and had a higher proportion of severe or critical illness than first- and second-generation patients. **Y. Yao, Clin Microbiol Infect 2020;26:1380**

Introduction

Patients with Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were first reported in Wuhan, Hubei province, China in December 2019 [1–3]. Several clinical studies have comprehensively demonstrated the basic characteristics of the COVID-19 disease [1,4–8]. SARS-CoV-2 spreads mainly through respiratory droplets or close contact [9]. The incubation period of COVID-19 was 1–14 days, with the majority being 3–7 days [9]. Early symptoms of COVID-19 include fever, dry cough and fatigue [5]. Most patients had mild clinical symptoms and a good prognosis. A proportion of patients progressed to symptoms of shortness of breath and hypoxaemia, usually around the second week of the illness [8,10]. About 10–20%

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of patients developed acute respiratory distress syndrome (ARDS) around 8–14 days of illness [5,8,11]. Risk factors for developing severe or critical symptoms included advanced age and underlying comorbidities [8,10,12]. According to WHO data, until 15 June 2020, the global average mortality was about 5.5% [13], and mortality fluctuated between 0.7% and 24.3% among different populations in different reports [5,14–16]. Risk factors for mortality included advanced age, higher Sequential Organ Failure Assessment (SOFA) scores and D-dimer greater than 1 μg/mL [7].

Zhejiang province, located in eastern China, confirmed its first COVID-19 case on 16 January. Wuhan was under lockdown from 23 January. On the same day, Zhejiang province launched a level 1 response to the emergency public health situation and investigated all persons from Hubei province who entered Zhejiang province. Home quarantine was quickly implemented. Soon afterwards, all COVID-19 patients were admitted to the hospital for isolation, observation and treatment. Strict epidemiological investigations were conducted to identify the source of infection and the contact population. The outbreak was soon brought under control and no patients were diagnosed on 22 February in Zhejiang province. The epidemiological background of most COVID 19 patients in Zhejiang province was evident and clinical data were relatively complete. This provided an excellent sample for us to analyse the clinical characteristics of COVID 19 populations with different epidemiological backgrounds.

Methods

Study design and participants

This study was a retrospective, multicentre cohort study and included four hospitals in Zhejiang province: the First Affiliated Hospital, School of Medicine, Zhejiang University, the First Hospital of Jiaxing, Taizhou Hospital of Zhejiang Province and the First people's Hospital of Yuhang District of Hangzhou City. The four hospitals were all designated hospitals for COVID-19 in Zhejiang province. All adult COVID-19 patients admitted to these four hospitals by 10 March 2020 were enrolled in this study. COVID-19 cases were confirmed based on the WHO interim guidelines; in short, patients who had fever and/or respiratory symptoms and had a positive result of SARS-CoV-2 nucleic acid testing. Only patients with a laboratory-confirmed infection were enrolled. Patients with ambiguous infections as determined by epidemiological surveys and patients with incomplete clinical data were excluded from this study.

Based on epidemiological history, patients were divided into three groups. First-generation patients had a clear travel history to Hubei province within 14 days before disease onset. Second-generation patients had a clear contact history with first-generation patients and third-generation patients had a clear contact history with second-generation patients (please see supplementary material).

Ethics

The study was approved by the Research Ethics Commission of The First Affiliated Hospital, School of Medicine, Zhejiang University (IIT20200129A), and was supported by the Research Ethics Commissions of the other three hospitals. Owing to the urgency to collect data on this emerging pathogen, the requirement for informed consent was waived by the Ethics Commission.

Data collection

Demographic, epidemiological history, clinical, laboratory examination, viral nucleic acid detection, pulmonary imaging, clinical prognosis and other data were obtained through patient medical records. Medical staff treating patients with COVID-19 were responsible for collecting and reviewing the data. We used a standardized case report form to collect clinical data. Epidemiological data were collected through patient interviews and focused on exposure history with individuals from Hubei province or patients with confirmed or suspected SARS-CoV-2 infection during the 2 weeks before disease onset. Data were verified by two physicians and a third researcher (H.Z.) resolved any differences in interpretation between the two primary reviewers. Concerning ambiguous data, study investigators in Hangzhou contacted the doctor responsible for treating the patient for clarification. The deadline for data collection was 10 March 2020.

Nucleic acid detection

Sputum or nasopharyngeal swab samples obtained from patients at admission were tested using real-time reverse transcription polymerase chain reaction for SARS-CoV-2 RNA within 8 hr [17]. Nasopharyngeal, sputum or bronchoalveolar lavage fluids were obtained every 1–3 days to determine the presence of SARS-CoV-2 nucleic acids during the disease period.

Laboratory tests and lung computed tomography scan

Laboratory tests included a complete blood count, coagulation profile, interleukin-6 (IL-6). In addition, chest computed tomography (CT) scans were performed on all inpatients. Frequency and type of test were determined by the treating physician based on clinical symptoms.

Definitions

The illness severity of COVID-19 was defined based on the Chinese management guideline for COVID-19 with modifications in this study [9]. Patients were defined as severe when one of the following were met: arterial oxygen pressure (PaO_2)/fraction of inspired oxygen (FiO_2) $\leq$300 mmHg (1 mmHg = 0.133 kPa), oxygen saturation $\leq$93% at resting state or respiratory rate $\geq$30/min. Patients who meet any of the following criteria were defined as critically ill: respiratory failure and requirement for mechanical ventilation, shock, in combination with other organ failure requiring ICU care [9]. CURB-65 scores were calculated based on the referenced publication [18]. Briefly, the highest CURB-65 score was 5 points, with 1 point assigned for each of the following criteria: mental confusion, respiratory rate $\geq$30/min, diastolic blood pressure $\leq$60 mmHg, blood urea >7 mmol/L and age $\geq$65 years [18].

Statistical analysis

Mean and standard deviation was calculated for continuous variables that were normally distributed. Median and interquartile range (IQR) were calculated for non-normally distributed data. Student's t-test, Mann–Whitney test and Kruskal–Wallis test were used to compare continuous variables, and the chi-square test or Fisher's exact test was used for independent binomial variables based on the number of observations. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Science (IBM SPSS (V.19), Chicago, IL, USA). Figures were generated using the GraphPad Prism 5.0 software.

Table 1
Basic information of COVID-19 patients at the time of diagnosis

	First generation ($n = 83$)	Second generation ($n = 44$)	Third generation ($n = 44$)	Total ($n = 171$)	p
Gender					0.232
Male	49 (59.0)	19 (43.2)	24 (54.5)	92 (53.8)	
Female	34 (41.0)	25 (56.8)	20 (45.5)	79 (46.2)	
Age[a,b]	48.3 ± 13.1	44.0 ± 14.3	61.3 ± 14.4	50.5 ± 15.2	**<0.001**
Coexisting conditions[a,b]					
No	53 (63.9)	32 (72.7)	19 (43.2)	104 (60.8)	**0.013**
Any	30 (36.1)	12 (27.3)	25 (56.8)	67 (39.2)	
Hypertension[a]	19 (22.9)	5 (11.4)	17 (38.6)	41 (24.0)	**0.011**
Diabetes	9 (10.8)	7 (15.9)	5 (11.4)	21 (12.3)	0.694
Chronic obstructive pulmonary disease	0 (0.0)	1 (2.3)	2 (4.5)	3 (1.8)	0.134
Cerebrovascular disease	2 (2.4)	1 (2.3)	3 (6.8)	6 (3.5)	0.431
Renal diseases	1 (1.2)	0 (0)	1 (2.3)	2 (1.2)	1.000
Tumour	2 (2.4)	0 (0.0)	1 (2.3)	3 (1.8)	0.804
Others	6 (7.2)	4 (9.1)	4 (9.1)	14 (8.2)	0.906
Smoking					0.181
Persistent	6 (7.2)	1 (2.3)	7 (15.9)	14 (8.2)	
Quit status	3 (3.6)	3 (6.8)	2 (4.5)	8 (4.7)	
Non-smokers	74 (89.2)	40 (90.9)	35 (79.5)	149 (87.1)	
Time from illness onset to first hospital admission (days)	2 (1, 5)	2.5 (1, 5)	1 (0, 4)	2 (1, 5)	0.259
Blood urea nitrogen (mmol/L)[a,b]	4.1 (3.4, 5.2)	3.7 (3.0, 5.0)	4.6 (3.7, 6.9)	4.1 (3.4, 5.4)	**0.004**
CURB-65[b]					**<0.001**
0–1	83 (100.0)	42 (95.5)	36 (81.8)	161 (94.2)	
2	0 (0)	1 (2.3)	7 (15.9)	8 (4.7)	
3	0 (0)	1 (2.3)	1 (2.3)	2 (1.2)	

Values are *n* (%) unless stated otherwise.
[a]p-Value between group 2 and 3 < 0.05.
[b]p-Value between group 1 and 3 < 0.05.
These bold values represent P < 0.05.

Results

During the study period, a total of 194 COVID-19 patients were diagnosed and admitted to the four hospitals listed previously. Twenty-three cases were excluded, of which 22 had an unclear epidemiological history and one was a child. Finally, a total of 171 patients were enrolled in this retrospective study. Based on epidemiological history, 171 patients were divided into three groups. This included 83/171 (48.5%) first-generation patients, 44/171 (25.7%) second-generation patients and 44/171 (25.7%) third-generation patients. Among the 171 patients, the earliest diagnosis was on 20 January 2020, and the final diagnosis was on 18

Table 2
Laboratory and chest radiography findings of COVID-19 patients on day 7 ± 1 since symptom onset

	First generation (n = 83)	Second generation (n = 44)	Third generation (n = 44)	Total (n = 171)	p
White blood cell count (4–10 × 109/L)	5.3 (4.0, 6.7)	4.4 (3.1, 6.5)	5.6 (4.4, 6.5)	5.1 (3.8, 6.6)	0.339
White blood cell count (×109/L)					0.257
<4	20 (25.0)	16 (37.2)	9 (20.5)	45 (26.9)	
4–10	55 (68.8)	22 (51.2)	32 (72.7)	109 (65.3)	
>10	5 (6.3)	5 (11.6)	3 (6.8)	13 (7.8)	
Lymphocyte count (0.8–4.0×109/L)[a,b]	0.8 (0.4, 1.3)	0.8 (0.6, 1.2)	0.6 (0.2, 1.1)	0.7 (0.4, 1.3)	**0.007**
Lymphocyte count (×109/L)[a,b]					**0.021**
<0.8	36 (45.0)	18 (41.9)	30 (68.2)	84 (50.3)	
≥0.8	44 (55.0)	25 (58.1)	14 (31.8)	83 (49.7)	
Platelet count (100–300×109/L)[b]	198.5 ± 66.1	201.4 ± 87.4	168.4 ± 84.4	191.3 ± 77.7	0.073
Platelet count (×109/L)[b]					**0.014**
<100	4 (5.0)	5 (11.6)	10 (22.7)	19 (11.4)	
≥100	76 (95.0)	38 (88.4)	34 (77.3)	148 (88.6)	
C-reactive protein (0.0–8.0 mg/L)[a,b]	17.1 (4.9, 41.0)	13.8 (3.3, 38.0)	29.7 (11.0, 89.0)	19.5 (5.5, 45.4)	**0.018**
Interleukin-6 (0.1–2.9 pg/mL)	16.4 (4.9, 34.4)	23.7 (9.5, 51.2)	22.6 (8.8, 81.3)	20.6 (7.9, 59.5)	0.150
D-dimer (0–700 μg/L)[a,b]	412.5 (240, 964)	549 (280, 892)	1066 (390, 2731)	576 (280.3, 1125.3)	**0.002**
D-dimer (0–700 μg/L)[a,b]					**<0.001**
≤500	41 (56.9)	17 (45.9)	13 (29.5)	71 (46.4)	
>500, ≤1000	15 (20.8)	14 (37.8)	7 (15.9)	36 (23.5)	
>1000	16 (22.2)	6 (16.2)	24 (54.5)	46 (30.1)	
Involvement of lung lobes on chest computed tomography[a,b]					**<0.001**
0	3 (3.6)	1 (2.3)	0 (0.0)	4 (2.3)	
1–3	26 (31.3)	22 (50.0)	6 (13.6)	54 (31.6)	
4	10 (12.0)	6 (13.6)	2 (4.5)	18 (10.5)	
5	44 (53.0)	15 (34.1)	36 (81.8)	95 (55.6)	

Values are *n* (%) unless stated otherwise. Data loss: white blood cell, lymphocyte and platelet counts in four cases (three in the first generation and one in the second generation, D-dimer in 18 cases (11 cases in the first generation and seven cases in the second generation).
[a]p Value between group 2 and 3 < 0.05.
[b]p Value between group 1 and 3 < 0.05.
These bold values represent P<0.05.

Table 3
Clinical outcome and duration of viral shedding from illness onset for the 3 patient groups with COVID-19

	First generation (n = 83)	Second generation (n = 44)	Third generation (n = 44)	Total (n = 171)	p
Severe illness[a,b]	27 (32.5)	12 (27.3)	32 (72.7)	71 (41.5)	**<0.001**
Time from illness onset to severe illness (days)	8.0 (6.0, 10.0)	8.0 (6.0, 11.0)	7.5 (6.0, 9.25)	8.0 (6.0, 10.0)	0.501
Critical illness)[a,b]	9 (10.8)	3 (6.8)	17 (38.6)	29 (17.0)	**<0.001**
Time from illness onset to critical illness (days)	10.1 ± 2.1	9.0 ± 4.6	8.6 ± 3.7	9.1 ± 3.4	0.561
Intubation[a,b]	3 (3.6)	1 (2.3)	9 (20.5)	13 (7.6)	**0.002**
Time from illness onset to intubation (days)	9.5 ± 2.1	10.0	8.6 ± 2.9	8.8 ± 2.6	0.836
Extracorporeal membrane oxygenation (ECMO)	3 (3.6)	1 (2.3)	5 (11.4)	9 (5.3)	0.135
Time from illness onset to ECMO (days)	18.0 ± 9.9	29.0	19.2 ± 6.1	20.1 ± 7.0	0.453
Duration of viral shedding from illness onset (days)	17.0 (11.0, 24.0)	16.5 (12.3, 20.8)	18.0 (13, 26.5)	17.0 (12.0, 24.0)	0.706

Data are presented as n (%) unless stated otherwise. ECMO, extracorporeal membrane oxygenation.
[a]p Value between groups 2 and 3 0 < .05.
[b]p Value between groups 1 and 3 < 0.05.
These bold values represent P<0.05.

February 2020. The final data collection deadline was on 10 March 2020. By the deadline, 157/171 (91.8%) patients were discharged and nasopharyngeal swabs were negative for SARS-CoV-2 virus RNA for 168/171 (98.2%) cases. Of the 14/171 (8.2%) patients that were not discharged, 2/14 (14.3%) patients had severe disease, 12/14 (85.7%) patients were critically ill and 10/14 (71.4%) patients were on endotracheal intubation and extracorporeal membrane oxygenation (ECMO) (see Fig. 1).

Basic demographic information of the 171 COVID-19 patients is shown in Table 1. There was no significant differences between the three groups in terms of gender, smoking history and time from illness onset to diagnosis. Patients in the third generation were older, had more coexisting conditions and had a higher proportion of hypertension than the other two groups (p < 0.001, p 0.013 and p 0.011, respectively). On admission, patients in the third generation group had higher levels of urea nitrogen (p 0.004), and significantly higher CURB-65 scores (p < 0.001) than the other two groups (Table 1).

Almost all the patients underwent comprehensive laboratory tests and lung CT examinations on 7 ± 1 days after illness onset; these data are shown in Table 2. The proportion of patients in the third generation with decreased lymphocyte and platelet counts was significantly higher than in the other two groups (p 0.021 and p 0.014, respectively). Patients in the third-generation group had higher C-reactive protein and D-dimer levels and more pulmonary lobe lesions than the other two groups (p 0.018, p 0.002 and p < 0.001, respectively) (Table 2).

Data about clinical development and outcome of the three groups are shown in Table 3. There were no patient deaths during the study period. There were no differences in the proportions of patients who developed severe, critical illness, endotracheal intubation and ECMO between the first and second generations. The proportion of patients who developed severe illness in the third generation (72.7%, 32/44) was significantly higher than the first group (32.5%, 27/83) and second group (27.3%, 12/44) (p < 0.001). The proportion of patients who developed critical illness in the third-generation group (38.6%, 17/44) was also higher than in the first (10.8%, 9/83) and second groups (6.8%, 3/44) (p < 0.001). The percentage of patients who received endotracheal intubation in the third-generation group was 20.5% (9/44), which was much higher than in the first group (3.6%, 3/83) and second group (2.3%, 1/44) (p 0.002). There were no significant differences between the three groups with regards to time from onset to severe, critical illness, endotracheal intubation and ECMO (Table 3).

The mean duration of SARS-CoV-2 viral shedding from illness onset is shown in Table 3 and Fig. 2, with no significant differences observed between the three groups.

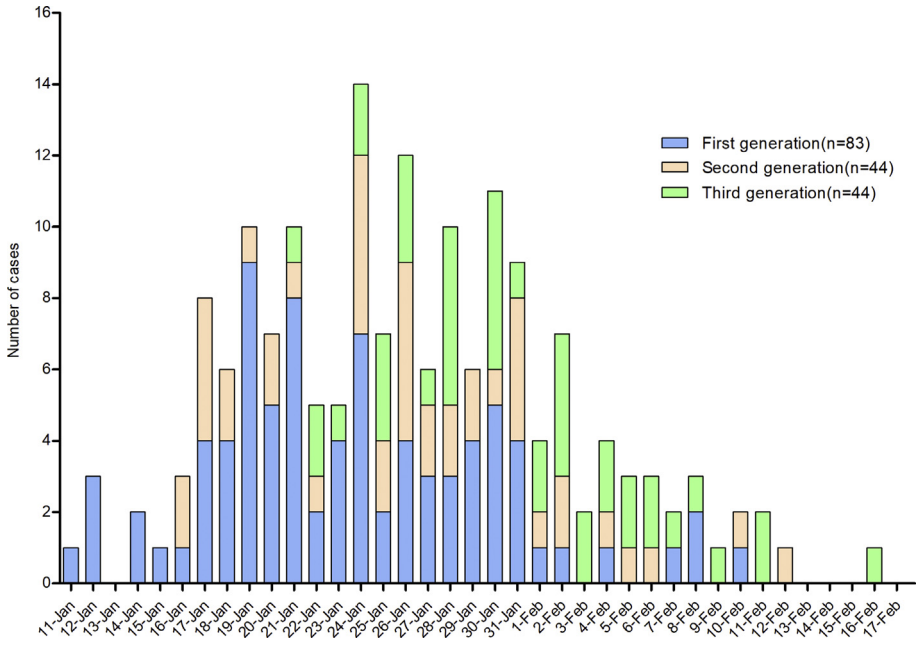

Fig. 1. The total number of new patients from the day of illness onset until the end of the study period. No cases were diagnosed from February 18 to March 10, 2020.

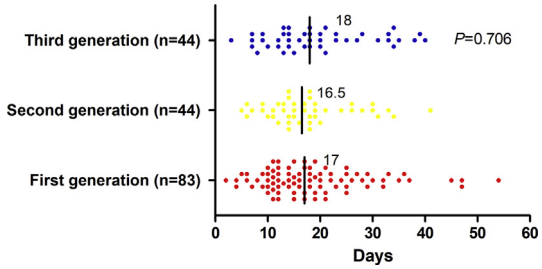

Fig. 2. Duration of SARS-CoV-2 viral shedding in the different groups (mean days labelled days). The duration of viral shedding was calculated from the date of disease onset to the date when PCR was negative for viral RNA from nasopharyngeal swabs. The mean duration of viral shedding for the first, second and third generation of patients was 17 (11.0, 24.0) days, 16.5 (12.3, 20.8) days and 18 (13.0, 26.5) days respectively. There were no significant differences between the three groups (p 0.706).

Discussion

The first generation of cases were individuals who returned to Zhejiang province from Hubei province. Most of them worked or went to school in Hubei, with the majority being young and middle-aged people. The second generation of cases was more likely to get sick after being exposed to the first generation of individuals during early social gatherings during the epidemic. Hence, the second generation of cases was also mainly young and middle-aged individuals with an active social life. From 23 January 2020 a strict home quarantine policy for all people was implemented in Zhejiang Province, almost all social activities were suspended. After the implementation of strict home-based isolation measures, individuals who were infected were mainly family members [6], some of which were elderly people. Patients in the third generation were older and had more comorbidities.

Patients in the third generation had higher CURB-65 scores, lower lymphocyte counts and higher D-dimer levels at the early stage of disease, in addition to higher rates of subsequent severe and critical illness and endotracheal intubation. This may be related to age and the presence of underlying disease in patients in the third generation group.

Owing to the short epidemic time in Zhejiang province, only three generations of cases were enrolled and analysed in this study. Furthermore, the basic conditions in the third-generation group were significantly different from patients in the first and second generations. Thus, we could not confirm whether there was any variation of virulence after SARS-CoV-2 virus passage in the population.

There are some limitations to this research. First of all, this study was a retrospective observational study and was not a large-scale study. Secondly, the first-generation patients enrolled in this study may be infected by the virus that had circulated different generations in Hubei province, it is hard to confirm the “first-generation” to be the same generation. Thirdly, the three groups of patients in this study are not homogeneous. Patients in the third-generation group were older, had more underlying comorbidities and had a higher proportion of severe or critical illness than other groups, which might be due to the susceptibility of older people to the virus. And, there were only three generations of patients and the epidemic lasted only about a month. Limited data did not produce perfect results. Thus, prospective, extensive and well-designed clinical studies are needed to confirm the characteristics of COVID-19 patients in different epidemiology waves during SARS-CoV-2 passing through a population.

Transparency declaration

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Contributors

H.Z. and J.Z. conceived and designed the study. Y.Y., W.C., X.W., L.S, L.S. and M.Y. collected clinical data. H.Z., Y.Y. and L.S. contributed to data analysis. H.Z. and Y.Y. wrote the manuscript and generated tables and figures. Y.F. and Q.Y. contributed to the literature search. H.Z., Y.Y., L.S., Y.F. and Q.Y. contributed to data interpretation. All authors critically reviewed and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.06.018.

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