Epidemiological and Clinical Features of Imported and Local Patients with Coronavirus Disease 2019 (COVID-19) in Hainan, China

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Abstract

Background: Hainan Island, a popular tourist destination, had received many imported cases of Coronavirus disease 2019 (COVID-19), but successfully contained the epidemics in one month. We described epidemiological and clinical characteristics of COVID-19 in Hainan and compared these features between imported and local cases to provide information for other international epidemic areas.

Methods: We included 91 patients (56 imported and 35 local cases) from two designed hospitals for COVID-19 in Haikou, China, from January 20 to February 19, 2020. Data on demographic, epidemiological, clinical and laboratory characteristics were extracted from medical records. Patients were followed up until April 21, 2020, the levels of antibodies in the follow-up were also analyzed.

Results: Of the 91 patients, 78 (85.7%) patients were diagnosed within the first three weeks after the first case identified (Day 1: Jan 22, 2020), while the number of local cases started to increase from the third week. No new cases occurred after Day 29. Fever and cough were two main clinical manifestations. 15 (16.5%) were severe, 14 (15.4%) had complicated infections, nine (9.9%) were admitted to ICU, and three died. Median duration of viral shedding in feces was longer than that in nasopharyngeal swabs (19 days vs 16 days, P=0.007). Compared with local cases, imported cases were older, have higher incidence of fever and concurrent infections. There was no difference in outcomes between the two groups. IgG was positive in 92.8% patients (77/83) in the follow-up of week 2 after discharge, 88.4% patients (38/43) had a reduction in IgG levels in the follow-up of week 4 after discharge, and the median level was lower than that in the follow-up of week 2 (10.95 S/CO vs 15.02 S/CO, $P<0.001$)

Conclusion: Imported cases were more severe than local cases, but could have similar prognosis. The level of IgG antibodies declined from week 6 to week 8 after onset. The short epidemic period in Hainan suggests that the epidemics could be quickly brought under control if proper timely measures were taken.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and characterized by lung damage, was first reported in Wuhan, China in December 2019 [1, 2]. By June 28, 2020, it has spread to 213 countries worldwide, causing 10,082,618 cases and 501,309 deaths, with crude mortality of 5.0% [3]. Although the COVID-19 is likely a zoonotic disease, it could be transmitted from person to person [4, 5], with a reproductive number of 1.5-4 [6, 7]. COVID-19 was mainly transmitted by contact and droplet. Recently, it was reported that SARS-CoV-2 was detected and isolated in feces, tears and urine [8, 9], suggesting that the disease may be transmitted through the digestive tract and conjunctiva. At present, the numbers of COVID-19 cases in USA, Brazil and other countries are increasing rapidly, many of which were local incident cases [3]. As known to all, the containment of epidemic at early age is most critical, effective and efficient before the outbreak go out of control. Most of countries have just started local transmission by receiving imported cases that could still be possibly contained. However, whether there is a difference between local cases and imported cases in clinical and epidemiological characteristics is unclear.

Hainan province, is a popular domestic and international tourist destination with 9.34 million permanent residents. During the spring festival holiday, many people, including those from Wuhan and its surrounding areas, chose to spend their vacations on Hainan island. According to the statistics, from December 30, 2019 to January 22, the day before Wuhan was locked-down, about 74,600 tourists had travelled from Wuhan to Hainan by plane [10]. In Hainan Province, the first reported case of COVID-19 was reported on January 22, 2020 (Day 1), and the last confirmed patient on February 19, 2020 (Day 29) (Fig. 1) [11], the relative short epidemics period implies that the measures Hainan adopted to contain the epidemics were timely and successful. Thus, Hainan's experience may have important implication for other international epidemics areas.

This study describes epidemiological and clinical characteristics of COVID-19 in Hainan and compares these features between imported and local cases, which may be an instructive example for countries and regions that are vulnerable for upcoming epidemics.

Methods

Study design and participants

We retrospectively included all the patients with COVID-19 in Hainan General hospital and The Second Affiliated Hospital of Hainan Medical University from January 22 to February 19, 2020. These two hospitals were designated hospitals for treating adult patients in Haikou, the capital city of Hainan province. Patients were followed-up until April 21, 2020, when the last discharged patient was followed up for four weeks. This study was approved by the Ethics Committee of Hainan General Hospital and The Second Affiliated Hospital of Hainan Medical University (HN-2020-31), and oral consents were obtained from all patients. All patients with COVID-19 enrolled in this study were diagnosed according to the WHO interim guidance [12], and were divided into imported cases group and local cases group according to epidemiological data.

Definitions

Imported case was defined as the patients who came from the COVID-19 epidemic area (Hubei province) within 14 days or came from the COVID-19 epidemic area and could not trace the source of infection. The local case was defined as the patients stayed in the locality more than 14 days before onset and had not gone to the epidemic area. If two or more confirmed cases were found concurrently and there is the possibility of human-to-human transmission due to close contact or infection due to co-exposure, then it is determined as a clustered case [13,14]. Fever was defined as axillary temperature of at least 37.3°C. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition [15]. We defined the degree of severity of COVID-19 (severe vs. mild) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia [16].

Data collection

The epidemiological characteristics (including residence, whether from the epidemic area, recent exposure history and so on), clinical symptoms and signs, laboratory data, chest computed tomography (CT) findings, SARS-CoV-2 RNA, IgM antibody and IgG antibody against SARS-CoV-2 were extracted from electronic medical records.

Laboratory confirmation of SARS-CoV-2 infection

SARS-Cov-2 RNA test was performed by the hospital's laboratory and the key laboratory of Hainan Centre for Disease Control and Prevention (CDC), China, by real-time RT-PCR according to the Chinese national CDC recommended protocol. The nasopharyngeal swab and feces were collected every 2-7 days during hospitalization and every 7 days for two times during follow-up for discharged cases. Then the RNA samples from the nasal swab and feces specimens were extracted and subjected to the real-time RT-PCR test using SARS-CoV-2 specific primers and probes. Specifically, the primers for the open reading frame 1ab (ORF1ab) are 5'-CCCTGTGGGTTTTACACTTAA-3'(Forward) and 5'-ACGATTGTGCATCAGCTGA-3'(Reverse); the corresponding probe is 5'-CY3-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3'. Primers for nucleocapsid protein (N) are 5'-GGGGAACTTCTCCTGCTAGAAT-3' (Forward) and 5'-CAGACATTTTGCTCTCAAGCTG-3' (Reverse); the corresponding probe is 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'. The duration of SARS-CoV-2 shedding was defined as the time from symptom onset to the first SARS-CoV-2 RNA turned to be negative after the last SARS-CoV-2 RNA positive during the follow-up.

Antibody measurement

IgM and IgG antibodies against SARS-CoV-2 in plasma samples were tested using Diagnostic Kit for Novel Coronavirus (2019-nCOV) IgM/IgG Antibody (Magnetic particle CLIA) supplied by Bioscience (ChongQing) Diagnostic Technology Co. according to the manufacturer's instructions.

Statistical Analysis

Continuous variables were expressed as mean (SD) or median (IQR) and compared by the t-test or Mann-Whitney U test; categorical variables were expressed as frequency (%) and compared by χ^2 test or Fisher's exact test between the imported cases and local cases. For laboratory indicators, we categorized the results into normal or abnormal (increased or decreased). IgG levels in the follow-up were compared using Wilcoxon matched-pairs signed ranks test. We used SPSS (IBM, version 26.0) for all analyses.

Results

Demographics and epidemiological characteristics

All the 91 patients with confirmed COVID-19 in Hainan General Hospital (n = 69) and The Second Affiliated Hospital of Hainan Medical university (n = 22) were enrolled. 56 of the 91 patients were imported and 35 were local patients. The mean age was 50 years (range, 21–83 years), and 57.1% were men. This outbreak lasted one month from the first patient admitted on Jan 20, 2020, to the last patient on Feb 19, 2020 (Fig. 1). Of these patients, 78 were admitted within the first three weeks after the first case identified, 88.6% (31/35) local patients were admitted from day 14, these were similar to the whole patients in Hainan Province, of all the 168 patients, 142 new cases were confirmed before day 21, and 52 local patients were diagnosed after day 14 (Fig. 1). Among 56 imported patients in two hospitals, 53 (94.6%) came from the epidemic centre, Wuhan city and its surrounding area. The median interval from leaving the epidemic centre to symptom onset in 53 patients was five days (IQR 2–12, range 1–34). 42 (46.2%) had the history of contacting with the confirmed COVID-19 patients, with a median interval before onset of eight days (IQR 4–13, range 1–22). Compared to imported patients, the local patients were significantly younger (mean age, 46 years vs 52 years; $P = 0.03$), more likely to occur in cluster outbreak (77.1% vs 46.4%, $P = 0.004$), and had close contacting with COVID-19 patients (68.6% vs 32.1%, $P = 0.001$) (Table 1).

Table 1
Demographics and epidemiological characteristics of patients with COVID-19

	All patients (N = 91)	Local cases (N = 35)	Imported cases (N = 56)	*P* values
Characteristics				

Data are n (%) unless specified otherwise. N is the total number of patients with available data. ARDS = acute respiratory distress syndrome. COVID-19 = coronavirus disease-19. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.
*Epidemic area refers to Wuhan and other epidemic areas in Hubei Province.
NA, not available.

	All patients (N = 91)	Local cases (N = 35)	Imported cases (N = 56)	*P* values
Age, years, Mean (SD)	50 (14)	46 (12)	52 (15)	0.030
Range	21–83	21–73	27–83	0.410
≤29	6 (6.6%)	2 (5.7%)	4 (7.1%)	0.670
30–39	20 (22.0%)	10 (28.6%)	10 (17.9%)	0.074
40–49	15 (16.5%)	8 (22.9%)	7 (12.5%)	0.120
50–59	25 (27.5%)	9 (25.7%)	16 (28.6%)	0.645
60–69	19 (20.9%)	5 (14.3%)	14 (25.0%)	0.152
≥70	6 (6.6%)	1 (2.9%)	5 (8.9%)	0.243
Sex	39 (42.9%)	16 (47.2%)	23 (41.1%)	0.521
Female	52 (57.1%)	19 (52.8%)	33 (58.9%)	0.645
Male	31 (34.1%)	8 (22.9%)	23 (41.1%)	1.000
Chronic medical illness	12 (13.2%)	2 (5.7%)	10 (17.9%)	1.000
Hypertension	5 (5.5%)	1 (2.9%)	4 (7.1%)	0.385
Cardiovascular disease	5 (5.5%)	0 (0.0%)	5 (8.9%)	0.400
Diabetes	7 (7.7%)	1 (2.9%)	6 (10.7%)	
Respiratory system disease	2 (2.2%)	0 (0.0%)	2 (3.6%)	
Thyroid disease	5 (5.5%)	1 (2.9%)	4 (7.1%)	
Chronic liver disease	3 (3.3%)	1 (2.9%)	2 (3.6%)	
Chronic kidney disease	2 (2.2%)	1 (2.9%)	1 (1.8%)	
Digestive system disease	1 (1.1%)	1 (2.9%)	0 (0.0%)	
Malignant tumor	6 (6.6%)	1 (2.9%)	5 (8.9%)	
Other				
Epidemiological survey				

Data are n (%) unless specified otherwise. N is the total number of patients with available data. ARDS = acute respiratory distress syndrome. COVID-19 = coronavirus disease-19. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.

*Epidemic area refers to Wuhan and other epidemic areas in Hubei Province.

NA, not available.

	All patients (N = 91)	Local cases (N = 35)	Imported cases (N = 56)	*P* values
Live or travel history in epidemic area*	53 (58.2%)	0 (0.00%)	53 (94.6%)	< 0.001
Time of out of epidemic area to onset, days, n = 53, Median (IQR), [range]	5 (2–10) [1–34]	NA	5 (2–10) [1–34]	NA
Close contacts with COVID-19 patient	42 (46.2%)	24 (68.6%)	18 (32.1%)	0.001
Time of contacted COVID-19 patient to onset, days, n = 26, Median (IQR) [range]	26/42; 8(4–13) [1–22]	17/24; 6 (4–15) [1–22]	9/18; 8 (5–16) [2–20]	0.570
Cluster outbreak	53 (58.2%)	27 (77.1%)	26 (46.4%)	0.004

Data are n (%) unless specified otherwise. N is the total number of patients with available data. ARDS = acute respiratory distress syndrome. COVID-19 = coronavirus disease-19. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.

*Epidemic area refers to Wuhan and other epidemic areas in Hubei Province.

NA, not available.

Clinical Characteristics And Complications

The most common symptoms at onset of illness were fever (79.1%), dry cough (79.1%), expectoration (39.6%), fatigue (38.5%), and shortness of breath (29.7%), diarrhea (14.3%), nausea and vomiting (7.7%) were not rare. 87 (95.6%) patients had more than one sign or symptom, 23 patients had combined fever, cough, and shortness of breath. Only four (4.4%) cases had no symptom. The median of highest temperature was 38.0℃, and the median duration of fever was eight days. Nine (9.9%) patients were admitted and transferred to the ICU because of the ARDS and organ dysfunction. The median durations from first symptoms to hospital admission, and ARDS were 5 days (IQR, 3–9) and 8 days (IQR, 6–10), respectively.

Clinically, the patients were diagnosed as mild (76 cases, 83.5%) and severe (15 cases, 16.5%) cases. Fifteen severe patients including 3 local and 12 imported cases. Among these severe patients, 14 had complicated bacterial infection, 9 septic shock, 13 ARDS, 6 multiple organ dysfunction syndrome (MODS), and 3 patients died. Compared with local patients, the imported patients had higher prevalence of fever ($P = 0.001$), higher peak temperature ($P = 0.028$), more complicated infection ($P = 0.043$), and tend to be more severe (21.4% vs 8.6%) (Table 2).

Table 2
Clinical characteristics of patients with COVID-19

	All patients (N = 91)	**Local cases (N = 35)**	**Imported cases (N = 56)**	***P* values**
Illness station				
First symptom to, Median (IQR), days	5.0 (3.0–9.0)	6.0 (2.0–10.0)	5.0 (3.0-7.8)	0.670
	8.0 (5.5–9.5)	N = 2, Range 4–6	N = 7, 9.0 (6.0–10.0)	0.184
Hospital admission				
	9 (9.9%)		7 (12.5%)	0.291
ARDS		2 (5.7%)		
	76 (83.5%)		44 (78.6%)	0.149
Admission to intensive care unit		32 (91.4%)		
	15 (16.5%)		12 (21.4%)	
Clinical classification		3 (8.6%)		
Mild				
Severe				
Signs and symptoms				
Fever	72 (79.1%)	21 (60.0%)	51 (91.1%)	0.001
Peak temperature, °C, Median (IQR)	38.0 (37.5–38.7)	37.8 (36.9–38.6)	38.0 (37.7–38.7)	0.028
			8.0 (4.8–10.0)	0.506
Days of fever, Median (IQR)	8.0 (4.0–10.0)	6.0 (3.0-10.5)		
			42 (75.0%)	0.221
Dry cough		30 (85.7%)		
	72 (79.1%)		20 (35.7%)	0.343
Expectoration		16 (45.7%)		
	36 (39.6%)		24 (42.9%)	0.276
Fatigue		11 (31.4%)		
	35 (38.5%)		18 (32.1%)	0.639
Shortness of breath		9 (25.7%)		
	27 (29.7%)		8 (14.3%)	0.521
Myalgia		3 (8.6%)		
	11 (12.1%)		10 (17.9%)	0.218
Diarrhea		3 (8.6%)		
	13 (14.3%)		8 (14.3%)	0.306
Sore throat		2 (5.7%)		
	10 (11.0%)		5 (8.9%)	0.703
Nausea and vomiting		2 (5.7%)		
	7 (7.7%)		54 (96.4%)	0.637
More than one sign or symptom		33 (94.3%)		
	87 (95.6%)		16 (28.6%)	0.360
Fever, cough, and shortness of breath		7 (20.0%)		
	23 (25.3%)			

Data are n (%) unless specified otherwise. N is the total number of patients with available data.

COVID-19 = coronavirus disease-19. ARDS = acute respiratory distress syndrome. MODS = multiple organ dysfunction syndrome. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.

	All patients (N = 91)	Local cases (N = 35)	Imported cases (N = 56)	*P* values
Complication				
Any	14(15.4%)	2 (5.7%)	12 (21.4%)	0.043
Infection	14 (15.4%)	2 (5.7%)	12 (21.4%)	0.043
ARDS	9 (9.9%)	2 (5.7%)	7 (19.6%)	0.474
Septic shock	9 (9.9%)	2 (5.7%)	7 (12.5%)	0.474
Cardiac insufficiency	8 (8.8%)	2 (2.9%)	6 (10.7%)	0.706
Metabolic acidosis	8 (8.8%)	1 (2.9%)	7 (12.5%)	0.146
Acute renal injury	5 (5.5%)	1 (2.9%)	4 (7.1%)	0.645
MODS	6 (6.6%)	1 (2.9%)	5 (8.9%)	0.400
Data are n (%) unless specified otherwise. N is the total number of patients with available data.				
COVID-19 = coronavirus disease-19. ARDS = acute respiratory distress syndrome. MODS = multiple organ dysfunction syndrome. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.				

Laboratory Examination And Imaging Findings Of Patients With Covid-19

Of the 91 patients, 21(23.1%) had a white cell count of less than 4.0×10^9/L, 39 (42.9%) had lymphocyte count of less than 1.1×10^9/L. The blood lymphocyte count, platelet count and serum albumin of the imported cases were significantly lower, while the levels of blood creatine kinase and CRP were significantly higher than those in local patients (all $P < 0.05$). All the patients had abnormality in chest CT scan, 79 (86.8%) patients' lesions located at lung periphery, and 75 (82.4%) showed bilateral involvement. The main manifestations were ground-glass opacity (87.9%), and multiple infiltration (83.5%), and 70 (76.9%) combined with bilateral lung periphery ground-glass opacity. Less common imaging findings were nodule, consolidation and pleural effusion (Fig. 2). No different imaging features were shown between imported and local patients (Table 3).

Table 3

Laboratory data and imaging finding of patients with COVID-19

	All patients (N = 91)	Local cases (N = 35)	Imported cases (N = 56)	*P* values
Blood routine				
White cell count (× 10^9/L), Mean (SD)	5.45 (2.42)	5.57 (1.70)	5.38 (2.79)	0.502
>10.0	5 (5.5%)	1 (2.9%)	4 (7.1%)	0.645
<4.0	21 (23.1%)	5 (14.3%)	16 (28.6%)	0.116
Lymphocytes (× 10^9/L), Mean (SD)	1.26 (0.62)	1.45 (0.59)	1.14 (0.61)	0.022
< 1.1	39 (42.9%)	8 (22.9%)	31 (55.4%)	0.002
Platelets (× 10^9/L), Mean (SD)	205.8 (69.9)	239.7 (68.3)	184.6 (62.6)	0.001
<150	23 (25.3%)	3 (8.3%)	20 (35.7%)	0.005
Hemoglobin (g/L), Mean (SD)	133.0 (18.1)	131.7 (17.7)	133.8 (18.5)	0.412
Blood biochemistry				

Data are n (%) and mean (SD). N is the total number of patients with available data. COVID-19 = coronavirus disease-2019. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.

	All patients (N = 91)	Local cases (N = 35)	Imported cases (N = 56)	*P* values
Alanine aminotransferase (U/L, normal range 3–35), Median (IQR)	21.3 (14.7–34.8)	22.0 (15.0–31.0)	20.7 (13.8–35.4)	0.427
Increased (n, %)	20 (22.0%)	6 (17.1%)	14 (25.0%)	0.379
Aspartate aminotransferase (U/L, normal range 3–40), Median (IQR)	22.0 (17.0-30.1)	24.0 (20.0–32.0)	20.0 (15.3–28.0)	0.170
Increased (n, %)	12 (13.2%)	4 (11.4%)	8 (14.3%)	0.761
Total bilirubin (μmol/L, normal range 4.0-17.1), Median (IQR)	9.0 (6.5–13.4)	9.8 (5.9–13.9)	8.4 (6.5–11.8)	0.410
Increased (n, %)	13 (14.3%)	3 (8.6%)	10 (17.9%)	0.218
Albumin (g/L, normal range 35.0–55.0), Median (IQR)	42.3 (36.2–47.1)	46.7 (41.4–49.6)	39.3 (34.7–44.4)	0.001
Decreased (n, %)	18 (19.8%)	4 (11.4%)	14 (25.0%)	0.114
PT (sec), Median (IQR)	11.3 (10.8–11.8)	11.3 (10.3–12.4)	11.4 (10.8–12.5)	0.407
Serum creatinine (μmol/L), Median (IQR)	65.8 (48.0-76.9)	68.0 (50.9–77.0)	59.0 (47.0-76.8)	0.835
Creatine kinase (U/L), Median (IQR)	63.0 (46.0-93.6)	70.0 (46.0-127.0)	62.0 (45.0–84.0)	0.013
C-reaction protein (mg/L), Median (IQR)	12.3 (2.2–45.1)	5.3 (1.2–30.5)	17.0 (3.0-51.3)	0.022
Procalcitonin (ng/mL), Median (IQR)	0.04 (0.02–0.06)	0.04 (0.02–0.09)	0.03 (0.01–0.06)	0.778
Chest CT finding				

Data are n (%) and mean (SD). N is the total number of patients with available data. COVID-19 = coronavirus disease-2019. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.

	All patients (N = 91)	Local cases (N = 35)	Imported cases (N = 56)	*P* values
Unilateral pneumonia	16 (17.6%)	8 (22.9%)	8 (14.3%)	0.296
Bilateral pneumonia	75 (82.4%)	27 (77.1%)	48 (85.7%)	0.296
Lung periphery	79 (86.8%)	29 (82.9%)	50 (89.3%)	0.526
Ground-glass opacity	80 (87.9%)	30 (85.7%)	50 (89.3%)	0.743
Multiple Infiltration	76 (83.5%)	26 (74.3%)	50 (89.3%)	0.061
Bilateral lung periphery ground-glass opacity	70 (76.9%)	25 (71.4%)	45 (80.4%)	0.325
Nodule	11 (12.1%)	2 (5.7%)	9 (16.1%)	0.193
Lung consolidation	8 (8.8%)	3 (8.6%)	5 (8.9%)	1.000
Pleural effusion	2 (2.2%)	0 (0.0%)	2 (3.6%)	0.521

Data are n (%) and mean (SD). N is the total number of patients with available data. COVID-19 = coronavirus disease-2019. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.

Treatment And Prognosis Of Patients With Covid-19

The median time for patients stayed in hospital was 14 days (IQR 11–18). All the patients took Chinese traditional medicine treatment, and 89 (97.8%) patients were treated with antiviral therapy, including Lopinavir and Ritonavir (Kaletra), arbidol and atomized inhalation of interferon α. 22 patients were treated with immunoglobulin and 20 with thymosin α-1. 13 patients received short-term corticosteroids treatment, with 40–80 mg/d methylprednisolone for 3–5 days. Only one patient needed extracorporeal membrane oxygenation (ECMO), but died. By Mar 24, 2020, 88 of 91 patients had been discharged, 3 patients died. There was no significant difference in treatment, length of hospitalization and the clinical outcome between the imported and local patients (Table 4). All the patients had been followed up for more than 14 days after discharge, no nucleic acid detection for SARS-CoV-2 RNA turned positive. IgM and IgG antibodies against SARS-CoV-2 in plasma samples were tested in 83 patients in the follow-up of week 2 after discharge. IgM was positive in 33 patients (39.8%) and IgG was positive in 77 patients (92.8%). As some of the patients had left Hainan, only 43 patients had a second detection of antibodies in the follow-up of week 4 after discharge (median, 48 days from onset; IQR, 44–53 days). Among these patients, 88.4% (38/43) had a reduction in IgG levels. The IgG levels (median S/CO, 10.95; IQR, 3.74–20.95) at week 4 after discharge were significantly lower than the levels (median S/CO, 15.02; IQR, 4.24–36.23) at week 2 ($P < 0.001$, Fig. 3).

Table 4

Treatment, virus changes and outcome of patients with COVID-19

	All patients (N = 91)	**Local cases (N = 35)**	**Imported cases (N = 56)**	***P* value**
Treatment				
Chinese traditional medicine	91 (100.0%)	35 (100.0%)	56 (100.0%)	1.000
Antiviral therapy	89 (97.8%)	33 (94.3%)	56 (100.0%)	0.112
Oxygen therapy	46 (50.5%)	14 (40.0%)	32 (57.1%)	0.306
Intravenous immunoglobulin therapy	22 (24.2%)	5 (14.3%)	17 (30.4%)	0.081
Thymosin alpha1	20 (22.0%)	9 (25.7%)	11 (19.6%)	0.496
Glucocorticoids	13 (14.3%)	3 (8.6%)	10 (17.9%)	0.218
Intravenous antibiotic	12 (13.2%)	2 (5.7%)	10 (17.9%)	0.120
Mechanical ventilation	10 (11.0%)	2 (5.7%)	8 (14.3%)	0.385
Non-invasive (ie, face mask)	1 (1.1%)	1 (2.9%)	0 (0.0%)	0.145
Invasive	9 (9.9%)	1 (2.9%)	8 (14.3%)	0.385
ECMO	1 (1.1%)	1 (2.9%)	0 (0.0%)	0.145
Hospital stay, days, Median (IQR)	14 (11–18)	14 (11–17)	15 (11–14)	0.403
Duration of SARS-CoV-2 RNA positive from onset				
Nasopharyngeal swabs, days	11 (6–16)	8 (5–16)	12 (8–16)	0.084
Median (IQR), [range]	[1–39]	[1–37]	[4–39]	0.216
Faeces, days	79/91, 13 (10–19)	29/35, 13 (6–18)	50/56, 13 (10–20)	
Median (IQR), [range]	[1–40]	[1–37]	[4–40]	
Duration of SARS-CoV-2 shedding from onset				

Data are n (%) and mean (SD). N is the total number of patients with available data. COVID-19 = coronavirus disease-2019. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. ECMO = extracorporeal membrance oxygenation. NA, not available. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.

	All patients (N = 91)	Local cases (N = 35)	Imported cases (N = 56)	*P* value
Nasopharyngeal swabs, days	16 (13–23)	15 (10–22)	17 (14–23)	0.148
Median (IQR), [range]	[6–43]	[8–37]	[6–43]	0.242
Faeces (days)	79/91, 19 (14–26)	29/35, 18 (11–24)	50/56, 19 (15–27)	
Median (IQR), [range]	[6–43]	[6–37]	[8–43]	
Clinical outcome				
Discharged	88 (96.7%)	34 (97.1%)	54 (96.4%)	1.000
Died	3 (3.3%)	1 (1.1%)	2 (3.6%)	1.000
Data are n (%) and mean (SD). N is the total number of patients with available data. COVID-19 = coronavirus disease-2019. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. ECMO = extracorporeal membrance oxygenation. NA, not available. *P* values for comparing two groups were derived using Fisher's exact test for categorized variables and t-test for continuous variables.				

Sars-cov-2 Rna In Nasopharyngeal Swabs And Feces

We tested SARS-CoV-2 RNA in nasopharyngeal swabs and feces of all the patients at an interval of 2 to 7 days dynamically. All 91 patients had detectable SARS-CoV-2 RNA in nasopharyngeal, and 79 in feces. SARS-CoV-2 RNA could be detected in nasopharyngeal swabs and feces at a median of 11 days (IQR 6–16, range 1–39) and 13 days (IQR 10–19, range 1–40), respectively. The viral shedding duration in these two types of samples were 16 days (IQR 13–23, range 6–43 days) and 19 days (IQR 14–26, range 6–43) from onset, respectively. The duration of SARS-CoV-2 RNA being positive and viral shedding in feces were longer than that in nasopharyngeal swabs ($P = 0.02$ and $P = 0.007$, respectively). In samples (including nasopharyngeal swabs and feses) from three dead patients, the SARS-CoV-2 RNA remained positive on the day of death (37 days, 20 days and 17 days from symptom onset, respectively). There was no significant difference in duration of SARS-CoV-2 RNA positivity and duration of viral shedding in nasopharyngeal swabs and feces between the imported and local patients (Table 4).

Discussion

According to the data released by Hainan Health Commission [11], by Mar 24, 2020, 162 of 168 patients had been discharged, 6 patients died, with the mortality rate of 3.6%. No new cases occurred from Feb 19, 2020 [14]. The 91 cases in study accounted for 54.2% of all the confirmed cases in Hainan, with similar trend in epidemic course (see Fig. 1). Of the 91 patients, three patients died. The mortality was 3.3%, which also similar to that of the whole Hainan province.

Our study shows that during the 29-day epidemic period, most of the patients were diagnosed within the first three weeks after the first identified imported case. In the early period, imported cases were predominant in the epidemics. In the later period, local cases were more common and 77.1% of the patients appeared clustering, mainly in families. Cluster outbreak was also found in Guangzhou patients in Lin's study [17]. These finding suggest increasing transmissibility of the virus during the spreads [18] and hence a great challenge to the entire prevention and control. However, the local cases did not lead to continuous community transmission, reflected by the short epidemic period (29 days). This may be attributed to the effective implementation of prevention and control policies and self-protection awareness of the public in Hainan (Fig. 1). The measures include establishing fever clinic for screening suspicious patients, designating hospitals focusing on treating patients with COVID-19 [19], raising the level of emergency response to COVID-19 prevention and control to first level promptly at Day 4. At the same time, other measures also work well for blocking the routes of transmission and reducing the chance of infection. For examples, encouraging the public to wear face masks, wash hands more frequently, and stay at home unless necessary, activating joint prevention and control mechanism, cross-sectors control for traffic control at community level. Moreover, delaying the resumption of work and school, implementing work-from-home for employee and online teaching for students were adopted to reduce the probability of cluster [20]. The reported estimate incubation time of the SARS-CoV-2 was based on limited data. Zhong reported the median incubation period was 4 days in 291 cases in China [21]. Jiang Xu et al. find there is no observable difference between the incubation time for SARS-CoV-2, severe acute respiratory syndrome coronavirus (SARS-CoV), and middle east respiratory syndrome coronavirus (MERS-CoV), with a mean of 4.9 days for SARS-CoV-2, 4.7 days for SARS, and 5.8 days for MERS [22]. To avoid the risk of virus spread, all potentially exposed subjects are required to be isolated for 14 days, which is the longest predicted incubation time. Our epidemiological investigation for 53 patients from Wuhan found that the median time of symptom onset was 5 days, with a range of 1 day to 34 days. The patient with the longest incubation period, a male in their 70's, flew from Wuhan to Hainan on January 2, 2020 and had no contact with confirmed or suspected COVID-19 patients. He occasionally went to the farmers' market near his residence to buy vegetables, but there were no confirmed COVID-19 patients associated with the market. He developed symptoms on February 5 and was diagnosed on February 7, 2020 [11]. This particular case indicates that the longest incubation time may be more than 34 days.

This study showed the main symptoms of the patients in Hainan Province were fever, cough, and 30% of the patients had shortness of breath. Compared with early COVID-19 cases in Wuhan, diarrhea (14.3%) was relatively more common in Hainan patients [23]. The main complications include infections and ARDS. Six severe cases developed to MODS. In general, the proportion of severe patients and mortality are lower than that of Wuhan and similar to the national data [24, 25].

In the imported cases, the proportion of patients with fever, the peak temperature, the level of blood CRP, the proportion of severe cases, and the incidence of complications, especially infections, were higher than those in the local cases. Meanwhile, the lymphocyte and platelets counts were significantly lower in imported cases than that of local ones. Data showed imported cases were older and coexisting illness was more common than the local ones, which might demonstrate why the imported ones are severer. Another possible explanation is that the time of infecting SARA-CoV-2 in imported cases is earlier, with a more virulent virus subtype. However, this requires further study of genomic and pathogenicity of SARA-CoV-2 at different stages of transmission. Tang's research indicates that the SARS-CoV-2 had formed two subtypes of S and L during the transmission process, and changes in viral genes will cause changes in its pathogenicity and transmission [18]. The similar study had been corroborated in the study of the MERS virus, which had shown that the virus becomes weaker during transmission [26]. It remains to be further studied whether there is virus mutation in the process of virus transmission from imported cases to local cases, which may lead to the weakening of its pathogenicity.

All 91 patients, including four asymptomatic patients, had CT changes in the lungs, which mainly manifested as ground-glass opacity in lung periphery at early stage. However, as the disease progressed, some patients had pulmonary consolidation and pleural effusion. Therefore, pulmonary CT examination is a sensitive indicator for the screening of COVID-19 and is recommended for all suspected patients [27].

Even so, SARS-CoV-2 RNA is the direct evidence for confirming COVID-19. Among all our patients, SARS-COV-2 RNA were detected in nasopharyngeal swab, but RNA was not detected in 12 patients' feces. Due to the positive detecting of SARS-CoV-2 RNA in feces, the problem of gastrointestinal transmission and even aerosol transmission has attracted broad attention. Since then, multiple research teams have isolated viruses in the feces, further illustrating the risk of gastrointestinal transmission. However, for a new viral infectious disease, there is no exact data on how long virus would be shed through respiratory and digestive tract. Our study found that the median duration of fecal SARS-CoV-2 shedding was longer than that in nasopharyngeal swabs, which was 19 and 16 days, respectively. And the longest time of SARS-CoV-2 RNA persistent positive and viral shedding were 40 days and 43 days, respectively. The relative long virus shedding duration could impose great challenge for health system as the patient pool flows slow and taking up substantial health facility. While it is impossible to host all positive cases in hospitals throughout the virus shedding period, it is possible to shift less acute cases to other temporary facilities like Wuhan. It is worth noting that the nasopharyngeal swabs and feces collected on the day of death of the three critically ill patients were still positive. This suggests that the persistence of the virus may have an impact on disease prognosis, and it is urgent to screen and develop effective antiviral drugs.

Unfortunately, until now, there are no effective antiviral drugs. Drugs such as remdesivir, kaletra, arbidol, chloroquine phosphate and some Chinese traditional medicine have shown certain effects, but still lack of rigorous and proven evidence [28–31]. Clinical trials of these drugs are currently ongoing. Treatment of all our patients was basically based on the interferon alpha nebulization, plus the antiviral regimen of arbidol or kaletra. However, without controlled study, it is difficult to determine whether it is the natural fluctuation of the virus replication or the effect of the drug.

Since there was no available testing kits at the early stage of COVID-19 epidemic, data on antibodies against SARS-CoV-2 were only collected in the follow-up after discharge. We observed a high positive rate of IgG, and a reduction in the IgG level at a median of 48 days (IQR 44 to 53 days) from symptom onset, which was within 6 to 8 weeks from onset. As reported by Long, that IgG levels start to decrease within 2–3 months after infection [32]. These findings may challenge the attempts to control COVID-19 through universal immunization, as patients with reduced antibody levels may re-infect. Of course, the subsequent changes in antibody levels require further observation.

There are some limitations in this study: Due to the barriers to data collection, clinical data of all 168 patients in the entire Hainan Province have not been collected.

Conclusion

Our study revealed the epidemiological and clinical characteristics, and outcomes of imported and local cases outside Hubei Province, suggesting that the imported cases were more severe than local cases, but the prognosis could be similarly good. The short epidemic period in Hainan suggests that the epidemics could be quickly brought under control if proper timely measures were taken. This study also suggests that the longest incubation period for COVID-19 may be over 34 days, and the maximum duration of SARS-CoV-2 shedding is at least 43 days. The positive rate of SARS-CoV-2 IgG antibody was high during the convalescence, however, the level of IgG declined from week 6 to week 8 after onset..

Abbreviations

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARDS, acute respiratory distress syndrome; CT, computed tomography; CRP, C-reactive protein; PCT, procalcitonin; CDC, Centre for Disease Control and Prevention; MODS, multiple organ dysfunction syndrome; ECMO, extracorporeal membrane oxygenation.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hainan General Hospital and The Second Affiliated Hospital of Hainan Medical University (HN-2020-31), oral consents were obtained from all patients.

Consent for publication

Written informed consent for publication of the clinical details was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

With the permission of the corresponding authors, we can provide participant data without names and identifiers, but not the study protocol, statistical analysis plan, or informed consent form. Data can be provided after the Article is published. Once the data can be made public, the research team will provide an email address for communication. The corresponding authors have the right to decide whether to share the data or not based on the research objectives and plan provided.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

B Wu, ZY Lei, KL Wu, JR He, J Fu, F Chen, Y Chen, B Chen, XL Zhou, T Wu, YG D, SX Chen, FR Xiao, J He, F Lin and BL Lin collected the epidemiological and clinical data and processed statistical data. ZY Lei, HJ Cao and BL Lin drafted the manuscript. BL Lin, F Lin and J He revised the final manuscript. BL Lin and F Lin are responsible for summarizing all data related to the virus and clinical data. B Wu and KL Wu are responsible for summarizing all epidemiological data. F Lin, B Wu and BL Lin provided administrative, technical, or material support. All authors read and approved the final manuscript.

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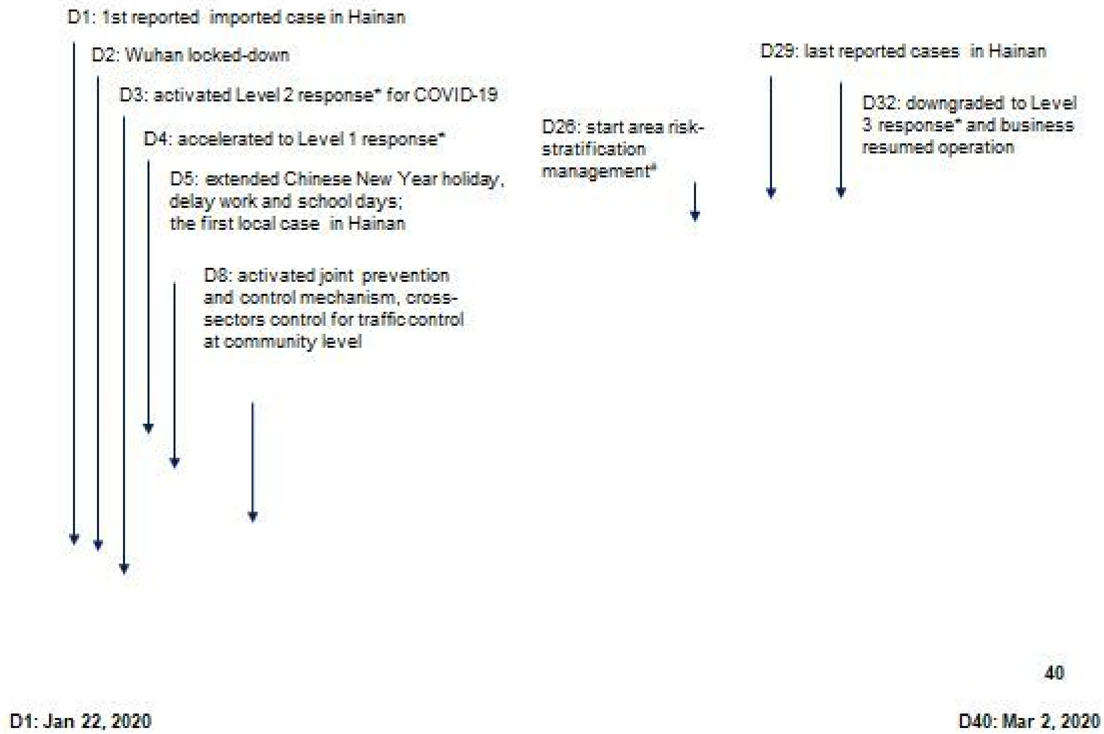
Figures



*, the response levels for Hainan Province Public Health Emergency range from Level 3 (low) to Level 1 (highest, but not including lock-down of the whole province).
#, risk-stratification management was based on COVID-19 risks (low, moderate, high) and adopts different measures to minimize effects on societal operation.
Data source: http://wst.hainan.gov.cn/yqfk/(accessed June 28, 2020)

Figure 1

Epidemic tendency of COVID-19 and the measures adopted for epidemic control in Hainan Province. The first patient with coronavirus disease 2019 (COVID-19) was identified on Jan 22, 2020 (Day1), and the last one on Feb 19, 2020 (Day 29) in Hainan Province. Most of the new imported cases confirmed within first three weeks, and the number of local cases raised from Day 14. Since the first imported case was identified, Hainan provincial government has taken a series of measures to prevention and control the coronavirus disease 2019 (COVID-19), and the epidemic was controlled in a short period.

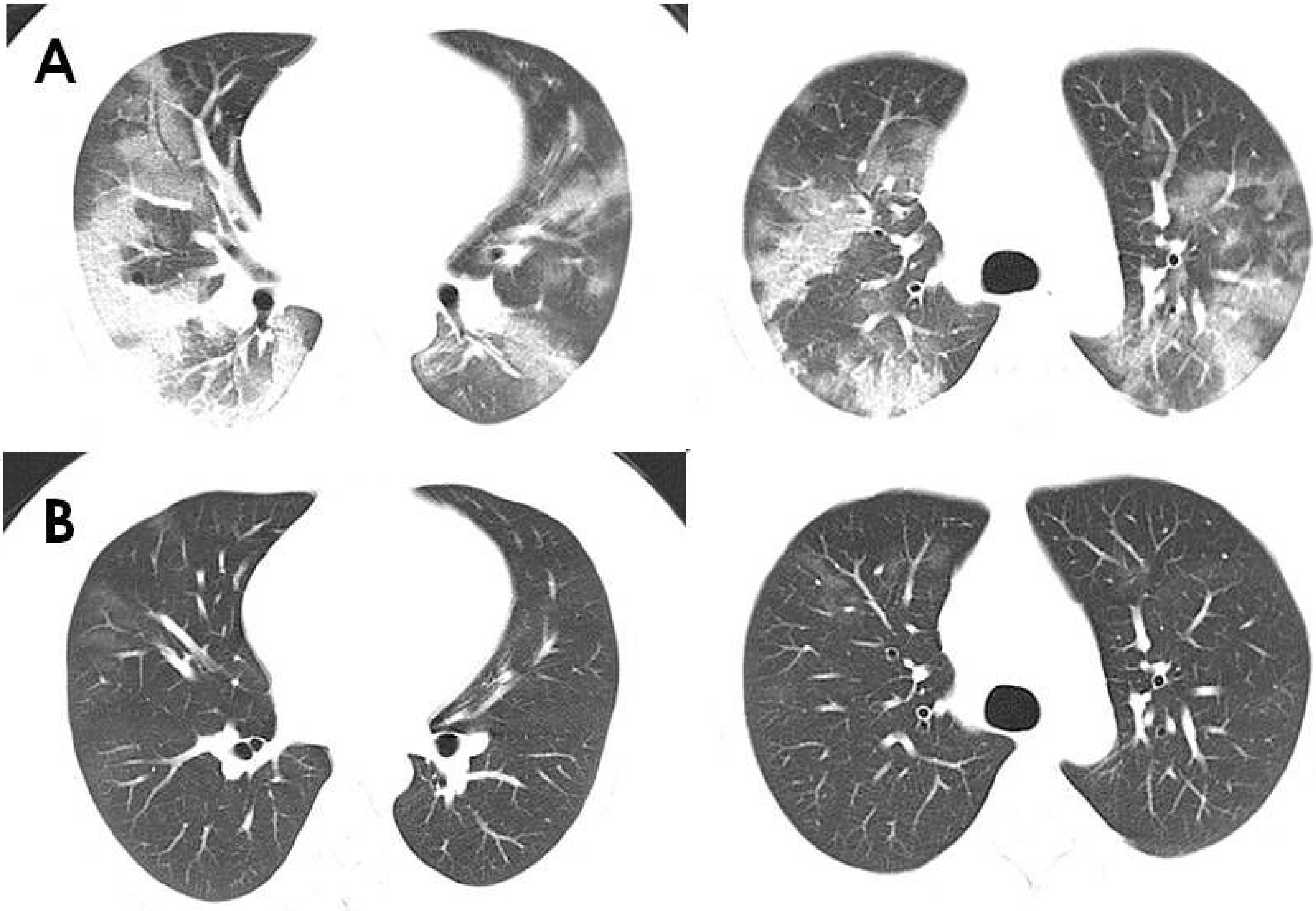


Figure 2

Chest computed tomographic images of a 28-year-old Patient with 2019 coronavirus disease (COVID-19). A, Chest computed tomographic images obtained on Feb 4, 2020, show ground glass opacity in both lungs on day 5 after symptom onset. B, Images taken on Mar 4, 2020, show the absorption of bilateral ground glass opacity after the treatment.

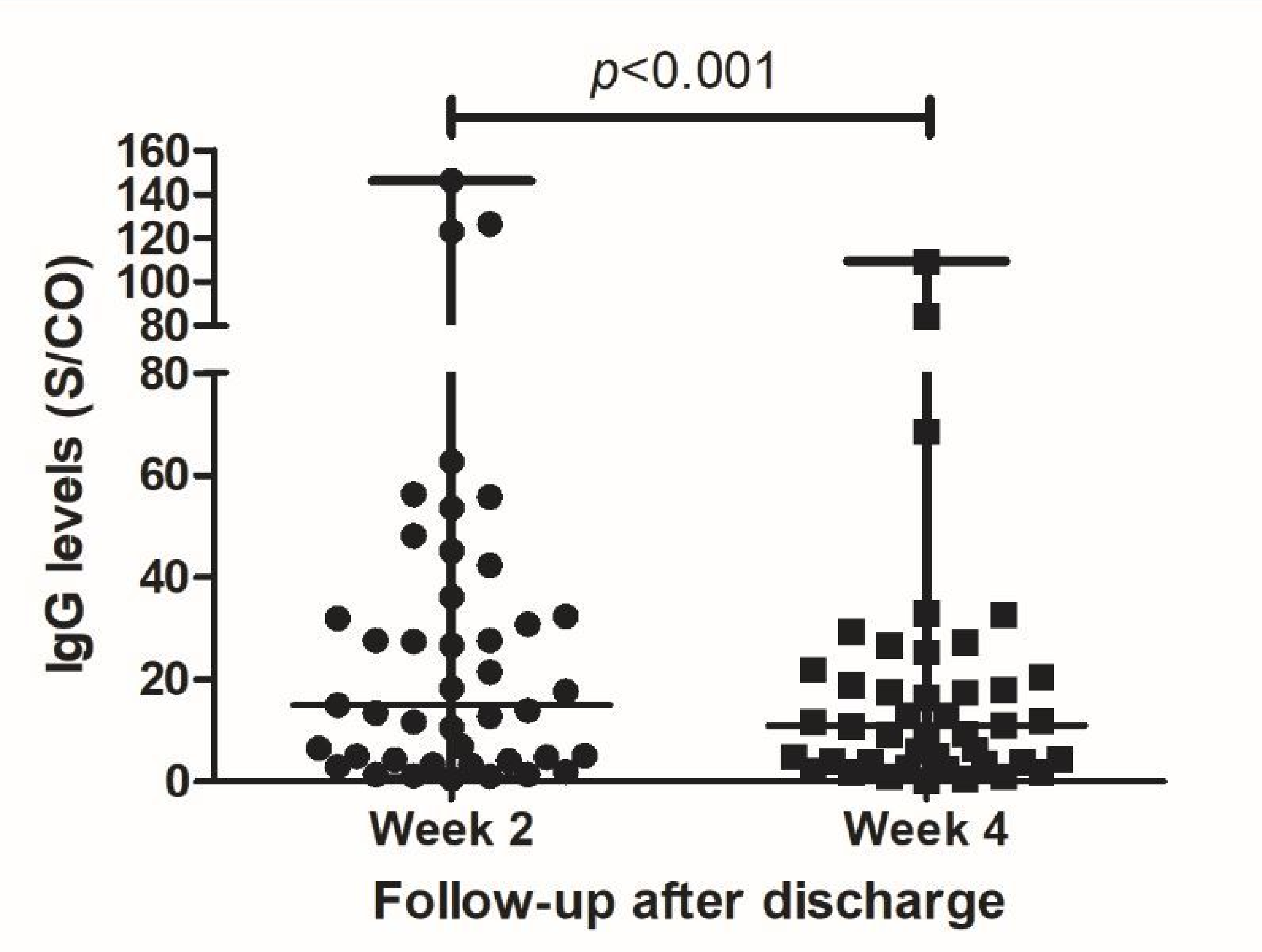


Figure 3

Comparison of IgG antibodies levels of 43 COVID-19 patients between the follow-up of week 2 and week 4 after discharge. The cutoff values for IgG was S/CO=1, results are shown as median and range. The time of week 4 after discharge was equal to a median of 48 days (IQR, 44-53 days; range, 38-77 days) from symptoms onset.