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Clinical features and viral RNA shedding of imported and local cases with COVID-19 in Wenzhou, China

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Abstract

Wenzhou had the highest number of confirmed novel coronavirus 2019 (COVID-19) cases outside the Hubei province. The aim of this study was to identify the difference in clinical features and viral RNA shedding between the imported and local COVID-19 cases in Wenzhou.

All patients with confirmed COVID-19 admitted to Wenzhou Sixth People's Hospital, Wenzhou Central Hospital Medical Group, from January 17 to February 11, 2020, were enrolled in this study. Data was analyzed and compared for the imported and local cases with regard to epidemiological, demographic, clinical, radiological features, and laboratory findings. Outcomes for the enrolled participants were followed up until May 7, 2020.

Of the 136 cases, 50 were imported from Wuhan. The median age was 45 years and 73 (53.7%) were men. The most common symptoms at onset were fever (104 [76.5%]) and cough (85[62.5%]). Pleural effusion was more common among imported cases compared to local cases. The white blood cell count, neutrophil count, lymphocyte count and platelet count of the imported cases were significantly lower than those of the local cases, while the prothrombin time was significantly longer than that of the local cases. Severe and critically ill patients accounted for 15.4% and 2.9%, respectively. The median duration of SARS-CoV-2 RNA shedding from symptom onset was 26 days (IQR 17–32.3 days) and there were no significant differences in duration of viral RNA shedding between the two groups.

The study findings suggest that imported cases from Wuhan were more likely to be severe compared to the local cases in Wenzhou. However, there was no difference between imported and local cases on the viral shedding among the COVID patients.

Abbreviations: ACTH = adrenocorticotropic hormone, ADE = antibody dependent enhancement, ARDS = Acute respiratory distress syndrome, BMI = Body Mass Index, COVID-19 = coronavirus disease 2019, CT = chest computed tomography, FiO_2 = oxygen concentration, ICU = intensive care unit, IQR = Inter Quartile Range, NA = Not Applicable, PaO_2 = arterial partial pressure of oxygen, RNA = Ribonucleic Acid, RR = respiratory rate, RT-PCR = Reverse Transcription-Polymerase Chain Reaction, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, WHO = World Health Organization.

Keywords: COVID-19, imported case, SARS-CoV-2, viral shedding

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1. Introduction

COVID-19 is a newly emerged infectious disease that began as an outbreak in Wuhan, China in December 2019. The cases are climbing steeply across the world, and as of June 2020, the global number of confirmed COVID-19 cases has reached 6,140,934. These confirmed cases spanned 216 countries, areas or territories and resulted in 373,548 deaths.[1]

Global COVID-19 case fatality rates have varied from 0.06% in Qatar to 16.25% in Belgium.[2] In China, the case fatality rate of COVID-19 in Wuhan was 4.9%, which is much higher than that of other provinces and territories in China (0.16%).[3] This difference could be partly explained by the limited available medical resources in Wuhan. Until now, most studies focused on the clinical features of cases from Wuhan.[4–6] Interestingly, patients outside Wuhan have shown different clinical symptoms at the time of onset, e.g 8% diarrhea, 34% headache, both of which are higher than those of Wuhan.[4,7]

The comparison of COVID-19 cases from Wuhan and outside Wuhan could contribute to a better understanding of the evolution of symptoms during the outbreak. Wenzhou, with a population of 8 million, has approximately 100 thousand people who routinely travel to Wuhan on business, and who also traveled home for the Chinese Lunar New Year before January 23, 2020. The distances between Wenzhou and Wuhan is about 900 km, and Wenzhou was the most affected city outside Hubei province with 504 confirmed cases. In the present study, we linked the clinical records with epidemiology data from hospitalized, confirmed cases of COVID-19 from Wenzhou to examine this relationship.

2. Methods

2.1. Study design and participants

For this retrospective, single-center cohort study, all patients with confirmed COVID-19 admitted to Wenzhou Sixth People's Hospital, Wenzhou Central Hospital Medical Group from January 17 to February 11, 2020, were enrolled and followed until March 7, 2020. Wenzhou Sixth People's Hospital, Wenzhou Central Hospital Medical Group is a designated hospital specializing in infectious diseases and is responsible for the treatment of COVID-19 patients. All patients enrolled in this study were diagnosed based on WHO interim guidance for COVID-19.[8]

2.2. Data collection

We reviewed medical records, laboratory findings, and chest computed tomography (CT) for all patients with laboratory confirmed SARS-CoV-2 infection who were reported by the Center for Disease Control. Available RNA virologic data was used to estimate the duration of viral shedding. Clinical data was obtained from the hospital electronic medical record and directly communicated with patients or their families to verify these data and histories. Two researchers independently reviewed all data collection forms to double check the data collected.

2.3. Definitions

In the present study, imported cases are defined as a patient who travelled to Wuhan in the two weeks before the onset of symptoms. Local cases are defined as patients with no travel history in the two weeks prior to symptom onset. Clinical classification of disease severity and discharge criteria were defined in accordance with Tentative Sixth Edition of Diagnosis and Treatment Plan Coronavirus Disease 2019 issued by the national health commission.[9] Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition.[10] Duration of viral shedding was defined as the interval from the date of symptom onset to the date when SARS-CoV-2 RNA was undetectable by RT-PCR of two consecutive nasopharyngeal swabs, or oropharyngeal swabs or sputum specimens (at least 24 h apart), without converting positive thereafter.

Definition of clinical classification of disease severity and discharge criteria are as follows:

Clinical classification

1. Mild cases: The clinical symptoms are mild and no pneumonia manifestation can be found in imaging.
2. Moderate cases: Patients have symptoms like fever and respiratory tract symptoms, etc. and pneumonia manifestation can be seen in imaging.
3. Severe cases: Meeting any of the following:
   a) Respiratory distress, respiratory rate (RR) $\geq$30 breaths/min;
   b) The oxygen saturation is less than 93% at a rest state;
   c) Arterial partial pressure of oxygen (PaO_2) / oxygen concentration (FiO_2) $\leq$300 mmHg (1 mmHg = 0.133 kPa).

For high altitude areas (above 1 km), PaO_2/FiO_2 values should be adjusted based on equation of $PaO_2/FiO_2 \times$ [Atmospheric Pressure (mmHg)/760]. Patients with >50% lesions progression within 24 to 48 h in pulmonary imaging should be treated as severe cases.

Critically ill Cases: Meeting any of the following:

1. Respiratory failure occurs, and mechanical ventilation is required;
2. Shock occurs;
3. Complicated with other organ failure that requires monitoring and treatment in intensive care unit (ICU).

Discharge criteria:

1. Body temperature returns to normal for more than 3 days;
2. Respiratory symptoms improved significantly;
3. Pulmonary imaging showed significant improvement of acute exudative lesions.
4. Negative nucleic acid test for two consecutive respiratory tract samples (sampling interval at least one day).

2.4. Statistical analysis

Continuous variables were described as median and interquartile range (IQR) and compared with the Mann – Whitney *U* test. Categorical variables were described as number (%) and compared using χ^2 test or Fisher's exact test between imported and local cases. Ranked data was used to compare between both groups with the non-parametric rank sum test. Statistical analyses were done using the SPSS software version 19.0 (IBM Corp, Armonk, NY), unless otherwise indicated. The curve of SARS-CoV-2 RNA conversion between imported and local cases was illustrated by GraphPad Prism 5.0 and tested by log-rank. A two-sided α of less than.05 was considered statistically significant.

3. Results

3.1. Epidemiological, sociodemographic and clinical manifestations

Between January 17 and February 11, 2020, 136 patients with confirmed COVID-19 were admitted to Wenzhou Sixth People's Hospital, Wenzhou Central Hospital Medical Group in Wenzhou, Zhejiang Province. Of the 136 cases, 50 cases were imported cases (3 cases were related with Wuhan Seafood Wholesale Market). Another 86 cases were local cases, in which 37 cases were linked to a cluster outbreak in a local shopping mall. While another 42 cases occurred in other public places, communities or families. Only 7 cases had an unknown history of exposure.

The median age of the patients was 45 years (IQR 35–52; Table 1). Three were children (all from local cases) aged 2 to 11 years. There was no significant difference in the age distribution or gender distribution between imported and local cases.

More than a third of patients had underlying diseases (54 [39.7%]), including hypertension (33 [24.3%]), chronic liver disease (17 [12.5%]), and diabetes (11 [8.1%]). However, there were no significant differences between the two groups with respect to underlying diseases or smoking history (Table 1). The most common initial symptoms at onset were respiratory in nature, which accounted for 86% of cases, and 5.9% of patients were asymptomatic (Table 2). The most common symptoms at presentation were fever (104 [76.5%]), cough (85[62.5%]), and fatigue (34[25.0%]). However, a considerable proportion of patients presented initially with asymptomatic or atypical symptoms, such as diarrhea and nausea, vomiting, abdominal pain, hemoptysis, or anorexia. There were no significant differences in initial symptoms between groups, and there were no significant differences in vital signs (including heart rate, respiratory rate, systolic pressure, finger oxygen saturation) on admission between the two groups (Table 2).

3.2. Laboratory parameters and imaging findings

Significant differences were noted in laboratory findings between the two groups (Table 3), including lower mean white blood cell, neutrophil counts, lymphocyte and platelet counts, as well as longer prothrombin time among the imported cases. However, no significant differences were found in other laboratory parameters. Chest CT scans demonstrated bilateral involvement, ground glass opacity and consolidation in 85.3%, 91.9% and 61.0% of patients, respectively (Table 3; Fig. 1 refer to the CT image). Additionally, pleural effusions were noted in five (3.7%) patients of imported cases, but in none of the local cases. There was no difference in CT imaging between two groups, except for pleural effusion ($P = .006$).

3.3. Severity of illness, complications and treatment

Most cases were relatively mild, with mild type and moderate type accounting for 84.5% of the total cases. The severe type and critically ill type accounted for 15.4% and 2.9% respectively, with imported cases being more severe than local cases (Table 4). In fact, the imported cases were more likely to have severe or critical disease (26.0%), compared to the local cases (14.0%, $P = .034$)

Common complications among the 136 patients included secondary infection (33 [24.3%]) and ARDS (4 [2.9%]). No significant differences in complications were observed among the two groups (Table 4). Supplemental oxygen was required by 45.6% of patients and there was no difference in oxygen use

Table 1

Baseline characteristics of patients with SARS-CoV-2 infection.

	No. (%)			
	Total (n = 136)	Imported cases (n = 50)	Non-imported cases (n = 86)	*P*
Age, median (IQR), years	45 (35–52)	44 (37–53)	48 (31–56)	.448
Age groups				.988
0–14	3 (2.2)	0	3 (3.5)	
15–44	57 (41.9)	22 (44.0)	35 (40.7)	
45–64	65 (47.8)	25 (50)	40 (46.5)	
≥65	11 (8.1)	3 (6.0)	8 (9.3)	
Sex				.076
Female	63 (46.3)	18 (36.0)	45 (52.3)	
Male	73 (53.7)	32 (64.0)	41 (47.7)	
BMI, median (IQR)	24.3 (22.7–26.9)	24.2 (21.3–25.9)	24.5 (21.1–26.3)	.900
Smoking history				.630
Never smokers	99 (72.8)	35 (70.0)	64 (74.4)	
Ex-smokers	28 (20.6)	12 (24.0)	16 (18.6)	
Current smokers	9 (6.6)	3 (6.0)	6 (7.0)	
Comorbidities	54 (39.7)	25 (50)	29 (33.7)	.071
Hypertension	33 (24.3)	17 (34.0)	16 (18.6)	.061
Diabetes	11 (8.1)	3 (6.0)	8 (9.3)	.746
Malignancy	2 (1.5)	2 (4.0)	0	.133
Chronic liver disease	17 (12.5)	9 (18.0)	8 (9.3)	.180
Chronic kidney disease	1 (0.7)	0	1 (1.2)	1.000
Cardiovascular disease	1 (0.7)	0	1 (1.2)	1.000
Previous history of tuberculosis	3 (2.2)	2 (4.0)	1 (1.2)	.554
Onset of symptom to admission, days	5.0 (3.0–7.8)	5.0 (3.0–7.3)	5.0 (2.0–8.3)	.642

BMI = Body mass index, IQR = Inter quartile range.

Table 2

Baseline symptoms on presentation of patients with SARS-CoV-2 infection.

	No. (%)			
	Total (n = 136)	Imported cases (n = 50)	Non-imported cases (n = 86)	*P*
Initial symptoms*				
Asymptomatic	8 (5.9)	1 (2.0)	7 (8.1)	.257
Respiratory symptoms	117 (86.0)	45 (90.0)	72 (83.7)	.443
Digestive symptoms	6 (4.4)	3 (6.0)	3 (3.5)	.669
Other symptoms	5 (3.7)	1 (2.0)	4 (4.7)	.652
Signs and symptoms				
Fever	104 (76.5)	42 (84.0)	62 (72.1)	.144
Highest temperature during course of disease (°C)				.154
<37.3	25 (18.4)	7 (14.0)	18 (20.9)	
37.4–38	46 (33.8)	17 (34.0)	29 (33.7)	
38.1–39	53 (38.9)	18 (36.0)	35 (40.7)	
>39.0	12 (8.8)	8 (16.0)	4 (4.7)	
Cough	85 (62.5)	33 (66.0)	52 (60.5)	.584
Expectoration	50 (36.8)	21 (42.0)	29 (33.7)	.361
Myalgia	12 (8.8)	4 (8.0)	8 (9.3)	1.00
Fatigue	34 (25.0)	13 (26.0)	21 (24.4)	.838
Pharyngalgia	18 (13.2)	9 (18.0)	9 (10.5)	.294
Diarrhea	15 (11.0)	6 (12.0)	9 (10.5)	1.00
Dyspnea	15 (11.0)	7 (14.0)	8 (9.3)	.572
Dizziness	8 (5.9)	5 (10.0)	3 (3.5)	.143
Headache	11 (8.1)	3 (6.0)	8 (9.3)	.746
Nausea	5 (3.7)	3 (6.0)	2 (2.3)	.357
Vomiting	1 (0.07)	1 (2.0)	0	.368
Abdominal pain	2 (1.5)	1 (2.0)	1 (1.2)	1.00
Hemoptysis	5 (3.7)	2 (4.0)	3 (3.5)	1.00
Anorexia	16 (11.8)	7 (14.0)	9 (10.5)	.586
Rhinobyon	6 (4.4)	1 (2.0)	5 (5.8)	.414
Rhinorrhoea	6 (4.4)	1 (2.0)	5 (5.8)	.414
Chest pain	7 (5.1)	2 (4.0)	5 (5.8)	1.00
Vital Signs on admission				
Systolic pressure, median (IQR), mmHg	128 (119–140)	129 (120–142)	128 (115–140)	.313
Respiratory rate, median (IQR), bpm	20 (20–20)	20 (19–20)	20 (20–20)	.084
Heart rate, median (IQR), bpm	89 (82–99)	92 (81–100)	89 (82–98)	.785
Finger oxygen saturation, median (IQR), %	97 (96–98)	92 (81–100)	89 (82–99)	.240

IQR = Inter quartile range.

between the two groups. Non-invasive ventilation was required for 2.9% of the patients. Only one patient in each group was transferred to an ICU of another hospital for invasive mechanical ventilation. Regarding treatment, 99.3% of patients received antiviral therapy including lopinavir/ritonavir (95.6%), interferon alpha-2b (97.8%), and arbidol (79.4%). Nearly a third of the patients received antibacterial therapy, and 12.5% received glucocorticoid therapy. One (0.7%) patient received kidney replacement therapy for uremia. There were no significant differences in treatments between imported cases and local cases (Table 4).

3.4. SARS-CoV-2 RNA conversion and duration of viral shedding

Thirty patients without available complete virological dynamic data were excluded from the analysis. The RT-PCR RNA conversion of the remaining 106 cases (42 imported vs 64 local) was determined. The curve showed there was no significant difference in the proportion of RT-PCR RNA conversion over time between the imported and local cases (P = -.9016) (Fig. 2).

The median duration of SARS-CoV-2 RNA shedding was 26 days (IQR 17–32.3 days) from symptom onset, 20 days (IQR 11–25.3 days) from first RT-PCR RNA positive onset, and 20 days (IQR11.8–25 days) from treatment onset, respectively. However, the median duration of SARS-CoV-2 shedding did not differ significantly between the imported and local cases (Table 4).

3.5. Outcomes

As of March 7, 2020, 134 (98.5%) of 136 patients had met discharge criteria, and two patients were transferred to ICU of another hospital for further treatment due to progressing to critically illness, but eventually recovered and were discharged. Among these 134 discharged patients, the median hospital stay was 23 days (IQR, 18–28.3). There were 9 patients (6.7%) with recurrence of positive RNA during follow-up visit after discharge and there was no significant difference on recurrence rate of positive RNA between imported cases and local cases (6.1% vs 7.1%) (Table 4).

4. Discussion

Our findings suggest that the prevalence of the severe cases was significantly higher among the imported cases than that of local cases, but there was no significant difference in conversion of

Table 3

Baseline laboratory findings, and imaging characteristics of patients with SARS-CoV-2 infection.

		Median (IQR)			
	Normal Range	Total (n = 136)	Imported cases (n = 50)	Non-imported cases (n = 86)	*P*
Blood routine					
White blood cell count, $\times 10^9$/L	3.5–9.5	4.6 (3.7–6.1)	4.3 (3.1–5.8)	4.8 (3.8–6.3)	.016
Neutrophil count, $\times 10^9$/L	1.8–6.3	2.9 (2.3–3.7)	2.7 (2.1–3.2)	3.1 (2.5–4.1)	.038
Lymphocyte count, $\times 10^9$/L	1.1–3.2	1.1 (0.8–1.7)	1.0 (0.8–1.4)	1.2 (0.9–1.7)	.024
Haemoglobin, g/L	130–175	145 (134–153)	135 (126–145)	136 (126–147)	.874
Platelet count, $\times 10^9$/L	125–350	179 (146–226)	161 (129–204)	188 (154–237)	.008
Coagulation function					
Prothrombin time, s	9.4–12.5	12.7 (12.0–13.3)	12.9 (11.2–13.7)	12.6 (11.9–13.1)	.027
Fibrinogen*, g/L	2.0–4.0	3.6 (3.1–4.1)	3.6 (3.0–4.2)	3.5 (3.1–4.1)	.907
D-dimer*, μg/L	<300	135 (89–201)	144 (91–186)	134 (88–205)	.831
Blood biochemistry					
Alanine aminotransferase, U/L	9–50	26 (19–44)	22 (13–27)	22 (13–28)	.053
Aspartate aminotransferase, U/L	15-40	27 (22–36)	23 (20–32)	27 (19–36)	.219
Total bilirubin, mmol/L	<26	12.1 (9.6–15.9)	12.3 (8.8–15.6)	11.3 (8.9–15.6)	.627
Albumin g/L	40–55	42.7 (39.8–45.2)	42.7 (39.8–44.8)	42.1 (38.9–45.0)	.840
Blood urea nitrogen, mmol/L	3.1–8.0	3.9 (3.4–4.5)	3.1 (3.7–4.1)	3.6 (3.0–4.3)	.719
Creatinine, μmol/L	53–108	78 (68–89)	69 (55–80)	65 (57–79)	.840
Lactate dehydrogenase, U/L	120–250	203 (169–255)	189 (154–253)	206 (173–256)	.433
Creatine kinase, U/L	50–310	73 (49–113)	78 (49–120)	72 (49–106)	.592
Creatine Kinase Isoenzyme, U/L	<25	12 (10–16)	12 (10–16)	12 (9–16)	.967
Serum potassium, mmol/L	3.5–5.3	3.6 (3.4–3.70	3.5 (3.3–3.7)	3.6 (3.4–3.9)	.066
Serum sodium, mmol/L	137–147	137 (134–139)	138 (134–140)	137 (135–139)	.848
Lactic acid**, mmol/L	0.5–1.6	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.9–1.5)	.705
Infection-related biomarkers					
Erythrocyte sedimentation rate**, mm/h	<22	22 (13–35)	21 (15–30)	24 (13–39)	.376
C-reactive protein, mg/L	<8	10.0 (2.9–29.3)	9.1 (2.9–29.4)	12.0 (2.2–30.4)	.821
Procalcitonin***, μg/mL	<0.5	0.04 (0.02–0.06)	0.04 (0.01–0.06)	0.04 (0.02–0.06)	.970
Chest CT findings					
Bilateral involvement, No. (%)	NA****	116 (85.3)	44 (88.0)	72 (83.7)	.619
Ground-glass opacity, No. (%)	NA	125 (91.9)	47 (94.0)	78 (90.7)	.746
Consolidation, No. (%)	NA	83 (61.0)	34 (68.0)	49 (56.9)	.274
Pleural effusion, No. (%)	NA	5 (3.7)	5 (10)	0 (0)	.006

CT = Chest computed tomography, NA = Not Applicable.
* n = 76, imported cases vs non-imported cases = 17 *vs* 59. ** n = 116, imported cases vs non-imported cases = 45 vs 71. *** n = 90, imported cases vs non-imported cases = 35 vs. 55.

RT-PCR RNA and duration of viral shedding between the two groups. Local cases had significantly higher white blood cell counts as well as neutrophil and lymphocyte count and platelet counts, but the imported cases had significantly higher prothrombin times. Lymphopenia has been previously noted as a clinical feature of severe COVID-19 disease.[11,12] These features could help to explain the difference in severity of COVID-19 between local and imported cases. However, the pathology COVID-19 in humans is still not fully understood. Neutrophil counts noted during the 2003 epidemic of SARS-CoV were significantly higher among severe patients compared to non-severe patients.[13] Similar results were observed with COVID-19 caused by SARS-CoV-2.[14] These differences may be related to secondary infections. However, the neutrophils count of the imported cases in this study were significantly lower than that of the local cases. The leukopenia observed by our group may be related to the suppression of bone marrow by the virus itself. Of note, our study is focused on clinical features of the imported and local cases, but not on severe and non-severe cases. Most important, there is no solid evidence to support that the neutrophil levels are the predicator or causal risk factor of the severe cases in those diseases.

Among SARS patients, hematological change was associated with severity of the disease. Lymphopenia frequently resolves when the patient improves.[15] Glucocorticoids may be driving circulating T lymphocyte out from the intravascular compartment resulting in lymphopenia.[16] Hence, activation of the hypothalamic–pituitary–adrenal axis during critical disease, could increase adrenocorticotropic hormone (ACTH) and cortisol resulting in T lymphocytes moving out of the peripheral circulation.[16,17] Also, similar hematological changes (e.g thrombocytopenia) in COVID-19 have been reported in SARS.[18] One proposed biological mechanism of SARS-associated thrombocytopenia is viral infection bone marrow cells.[19,20]

Usually, it is difficult to trace the original source of a pandemic outbreak, and one possible hypothesis is Wuhan Huanan Seafood Wholesale Market was not the original source.[5] Of note, it was the first one reported because it close to the Wuhan hospital where lot of healthcare workers have been infected. There might be other earlier cases which were asymptomatic or had mild clinical symptoms and could have resolved without treatment and may not have been not hospitalization. In the presented study,

Tseveral local cases could not be epidemiologically linked. Further, since viral sequencing was not performed in the present study, a genetic comparison of imported and local cases could not be performed.

One possible hypothesis is that most local cases were in the early stage of the disease with only slight symptoms. Typically,

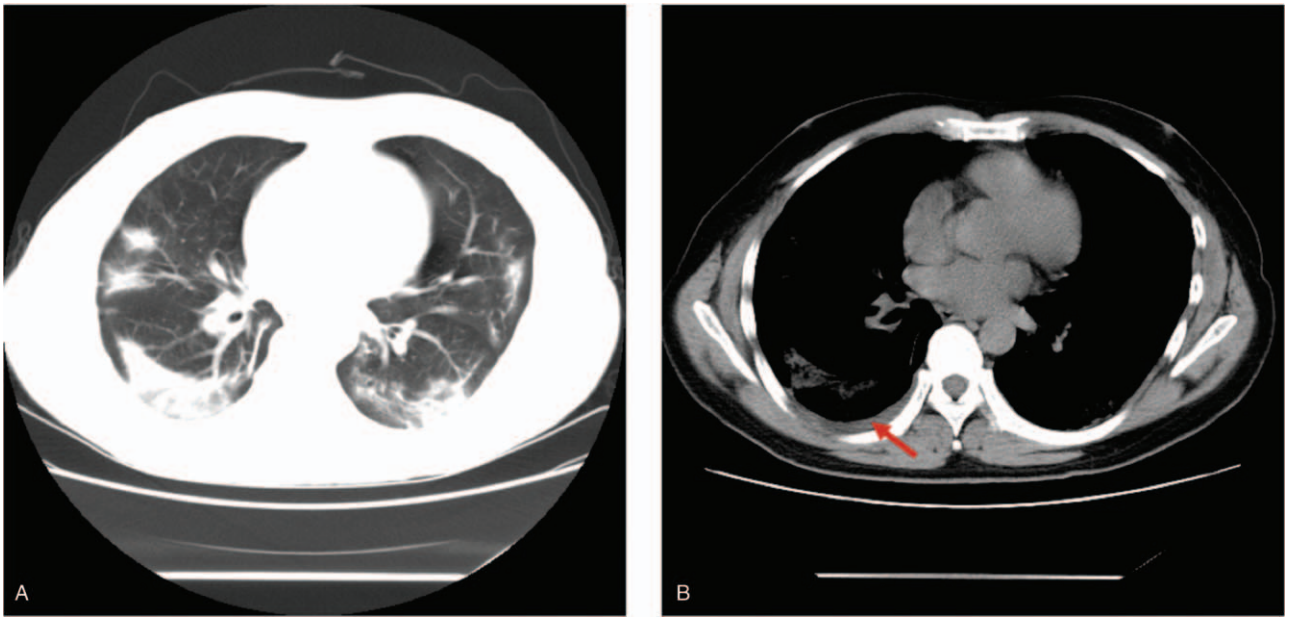

Figure 1. Chest CT from a 45 year-old man, showing consolidation of bilateral lungs near the pleura (A) and pleural effusion (B, arrow mark) on day 16 from symptom onset.

Table 4.

Severity, complications, treatment and outcomes of patients with SARS-CoV-2 infection.

	No. (%)			
	Total (n = 136)	**Imported cases (n = 50)**	**Non-imported cases (n = 86)**	***P***
Severity of illness				.034
Mild type	7 (5.1)	1 (2.0)	6 (6.9)	
Moderate type	108 (79.4)	37 (74.0)	71 (82.6)	
Severe type	21 (15.4)	10 (20.0)	11 (12.8)	
Critically ill type	4 (2.9)	3 (6.0)	1 (1.2)	
Complications				
Secondary infection	33 (24.3)	14 (28)	19 (22.1)	.534
ARDS	4 (2.9)	3 (6.0)	1 (1.2)	.141
Treatment				
Oxygen inhalation	62 (45.6)	26 (52.0)	36 (41.9)	.287
Non-invasive mechanical ventilation	4 (2.9)	3 (6.0)	1 (1.2)	.141
Invasive mechanical ventilation	2 (1.5)	1 (2.0)	1 (1.2)	1.000
Antiviral therapy	135 (99.3)	49 (98.0)	86 (100)	.368
Antibiotic therapy	44 (32.4)	21 (42.0)	23 (26.7)	.087
Use of corticosteroid	17 (12.5)	8 (16.0)	9 (10.5)	.422
Use of intravenous immunoglobin	17 (12.5)	8 (16.0)	9 (10.5)	.422
Continuous renal replacement therapy	1 (0.7)	0	1 (1.2)	1.000
Outcomes				
Viral shedding				
Days from symptom onset to RT-PCR RNA negative*, days, Median (IQR)	26 (17–32.3)	25 (15.8–33)	26 (20–29)	.677
Days from first RT-PCR RNA positive onset to negative*, days, Median (IQR)	20 (11–25.3)	18.5 (8–28)	20.5 (14.3–24.8)	.574
Days from treatment onset to RT-PCR RNA negative*, days, Median (IQR)	20 (11.8–25)	18 (7.8–27)	20 (14.3–24)	.653
Recurrence of positive viral RNA during follow-up after discharge †	9 (6.7)	3 (6.1)	6 (7.1)	1.000
Length of stay †, days, Median (IQR)	23 (18–28.3)	23 (17.5–31)	23 (18–27)	.616
Discharge				1.000
Meeting discharge standards	134 (98.5)	49 (98.0)	85 (98.8)	
Transfer to the ICU of another hospital	2 (1.5)	1 (2.0)	1 (1.2)	

ARDS = Acute respiratory distress syndrome, ICU = Intensive care unit, IQR = Inter quartile range, RNA = Ribonucleic acid, RT-PCR = Reverse transcription-polymerase chain reaction.

* n = 106, imported cases vs non-imported cases = 42 vs 64.

† n = 134, imported cases vs non-imported cases = 49 vs 85.

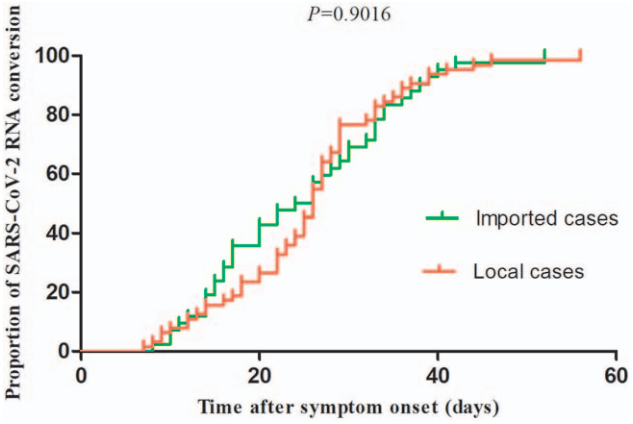

Figure 2. Cumulative proportion of patients with undetectable SARS-CoV-2 by day after symptom onset between imported and local cases.

the imported cases are likely to be the index in a cluster of infections, while the local cases are more likely to be found through screening of the close contacts. Also, there is a small proportion of asymptotic cases in the general population who are more likely to be identified through screening. Those cases are more likely to resolve quickly if therapy was administered. Thus, the hematological change (e.g lymphocyte count) and clinical features, such as pleural effusion, may reflect the stage of COVID-19 disease. The difference in severity between imported and local COVID-19 cases could be partly due to the differences in time from symptom onset to diagnosis. This difference might contribute to the presentation of symptoms and disease characteristics. However, there was no significant difference in time from symptom onset to admission and in the number of hospital days between the imported and local COVID-19 cases in our cohort. Additionally, there is no standard treatment protocol for the COVID-19 until now. However, patient reporting of time from onset to presentation may be biased and inaccurate.

Etro suggested that antibody dependent enhancement (ADE) of SARS-CoV-2 due to prior exposure to other coronaviruses.[21] This immune response could be explained by the severity found between imported and local COVID-19 cases. Because ADE modulates the immune response and can elicit sustained inflammation, lymphopenia, and/or cytokine storm, one or all of which have been documented in severe cases and deaths.[21] However, there is no evidence that imported cases were previously infected by other coronaviruses. Also, most imported cases are residents who had traveled to Wuhan. Theoretically, there should not be a difference between the two group in other characteristics. An alternative explanation is that the virulence of the SARS-CoV-2 virus decreases during the chain of transmission. Future studies on the virulence of the virus, supported by epidemiological data on transmission is warranted.

To date, comparative data on the duration of SARS-CoV-2 RNA shedding between imported and local cases have been limited. Our study found the median duration of viral RNA shedding from symptom on set was up to 26 days, which was significantly longer than those previously reported (less than 20 days).[22–24] It has been reported that the duration of Middle East Respiratory Syndrome Coronavirus shedding in severe cases was significantly longer than that in non-severe cases.[25] Although our study found that the number of severe or critically ill cases in imported cases was significantly higher than that in local cases, there was no difference in the duration of viral shedding between the two groups.

Recent studies showed that the prolonged viral shedding was not associated with the severity of illness, but with the time of admission to hospital[24] and antiviral treatment.[26] The prolonged SARS-CoV-2 RNA shedding is relevant not only for the control of nosocomial infection, but also for discharge management.

In the initial stages of COVID 19 outbreak in China, the severe rate or mortality of COVID-19 cases in Wuhan was higher than those of cases outside Wuhan. But in Wenzhou, the severe rate of COVID-19 among imported cases from Wuhan was higher than that of the local cases. This could be due to the adequate medical resources and high capacity of therapy available in Wenzhou, which guaranteed zero death case in COVID-19 cases. Hence, there is no significant difference between the two groups being more likely due to the treatment.

This study systematically compares the clinical features and viral RNA shedding between imported and local cases. However, our study has serval limitations. First, some epidemiological details are missing in the imported cases such as whether they are secondary infectious cases. Second, the RT-PCR testing was not conducted at fixed timepoints during hospitalization. Although we excluded those patients without no available complete virological dynamic data, there might have still been some selection bias in the remaining data. Third, the physical examine results from admission at the hospital could be affected by the timepoints of prognosis because people's admission into the hospital was varied. Also, we did not identify the sub-clinical type for the most non-severe cases. Some potential indices of virus performance (e.g CD4 or CD8 counts or ratio) were not collected in the present study. Forth, as we know COVID-19 is dangerously pathogenic and the currently study was completed in February 2020. Since the outbreak of COVID-19, the state has strictly prohibited the preservation or outward detection of all highly pathogenic samples. Therefore, in the early stages of this study, there was no outward sample gene sequencing to compare the differences between the two groups. In future similar studies, we will compare the differences between the two groups of genetic genes from the perspective of origin. Despite some defects, it is still of good clinical reference significance for COVID-19. Final, other respiratory virus were not tested among the cases.`

5. Conclusion

Our results suggest that the severity of illness, laboratory test results, and CT scan images of local cases of COVID-19 are less severe than imported cases of COVID-19 from Wenzhou. However, there was no difference between imported and local cases on the viral shedding among the COVID patients. These results could help physicians and other healthcare providers to better understand the pathogenesis and virological dynamics during the process of illness, which should be helpful in the clinical management of patients with COVID-19.

Author contributions

Dr He and Dr Wu conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript.
Dr Huang reviewed and revised the manuscript.

Prof Schieffelin conceptualized and designed the study, and reviewed and revised the manuscript.
Dr Dai collected data, reviewed and revised the manuscript.
Prof Gamber carried out the analyses, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript.
Dr Hu was responsible for the laboratory analysis.
Dr Chen and Dr Si were responsible for the imaging analysis.
Prof Sun and Dr Cai carried out the analyses and reviewed and revised the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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Writing – review & editing: Jing Wu, Jianping Huang, John S Schieffelin, Michelle Gamber, Wenjie Sun, Jing Cai.

References

[1] Coronavirus disease (COVID-19) pandemic. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
[2] Oke J, Heneghan C. Global Covid-19 Case Fatality Rate. Available at: https://www.cebm.net/global-covid-19-case-fatality-rates/ [access date May 26th, 2020 , English version].
[3] Coronavirus (COVID-19) Mortality Rate. Available at: https://www.worldometers.info/coronavirus/coronavirus-death-rate/.
[4] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
[5] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[6] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020.
[7] Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606.
[8] World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. Published January 28, 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novelcoronavirus-(ncov)-infection-is-suspected [access date February 11 2020].
[9] National Health Commission of the People's Republic of China. Diagnosis and treatment protocols of the novel coronavirus pneumonia (trial version 6). Beijing: National Health Commission of the People's Republic of China; 19 Feb 2020.Chinese.Available at: http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/b218cfeb1bc54639af227f922bf6b817.pdf.
[10] Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526–33.
[11] Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395:514–23.
[12] Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020.
[13] Wang YH, Lin AS, Chao TY, et al. A cluster of patients with severe acute respiratory syndrome in a chest ward in southern Taiwan. Intensive Care Med 2004;30:1228–31.
[14] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020.
[15] Hon KL, Leung CW, Cheng WT, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet 2003;361:1701–3.
[16] Panesar NS. Lymphopenia in SARS. Lancet 2003;361:1985.
[17] Thompson BT. Glucocorticoids and acute lung injury. Crit Care Med 2003;31(4 Suppl):S253–257.
[18] Yang M, Ng MH, Li CK. Thrombocytopenia in patients with severe acute respiratory syndrome (review). Hematology 2005;10:101–5.
[19] Jolicoeur P, Lamontagne L. Impaired T and B cell subpopulations involved in a chronic disease induced by mouse hepatitis virus type 3. J Immunol 1994;153:1318–7.
[20] Jolicoeur P, Lamontagne L. Impairment of bone marrow pre-B and B cells in MHV3 chronically-infected mice. Adv Exp Med Biol 1995;380:193–5.
[21] Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect 2020;22:72–3.
[22] Wang L, Gao YH, Lou LL, et al. The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China. Eur Respir J 2020;55(4.):
[23] Zuo Y, Liu Y, Zhong Q, et al. Lopinavir/ritonavir and interferon combination therapy may help shorten the duration of viral shedding in patients with COVID-19: a retrospective study in two designated hospitals in Anhui, China. J Med Virol 2020.
[24] Xu K, Chen Y, Yuan J, et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19. Clin Infect Dis 2020.
[25] Killerby ME, Biggs HM, Midgley CM, et al. Middle East respiratory syndrome coronavirus transmission. Emerg Infect Dis 2020;26:191–8.
[26] Yan D, Liu XY, Zhu YN, et al. Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir treatment in hospitalised non-critically ill patients with SARS-CoV-2 infection. Eur Respir J 2020.