Letter to the Editor

Clinical features of 64 patients (outside Hubei) with COVID-19 in Wenzhou, China

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Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Given its rapid spread worldwide, the epidemiological and clinical features of COVID-19 mandate further clarification. According to previous Wuhan-based studies, which respectively included 41 (2), 99 (3) and 52 (4) laboratory-confirmed COVID-19 patients, SARS-CoV-2 mimicked severe acute respiratory syndrome coronavirus in terms of severity and high mortality, however, a subsequent study conducted on 13-cases in Beijing demonstrated that all patients were mildly infected (5). Results of these studies varied greatly and were contradictory, therefore, we collected the data from 64 patients admitted to Oujiangkou Branch, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, aiming to describe the epidemiological and clinical characteristics of COVID-19 patients in Wenzhou city which, although far away from Hubei Province, is the most-affected area in China outside Hubei.

For this retrospective study, 64 laboratory-confirmed COVID-19 patients, admitted from Feb 6, to Feb 11, 2020 in above mentioned hospital were recruited. Confirmation of SARS-CoV-2 was done by real-time RT-PCR assay of sputum, throat-swab specimen. Patients were categorized into 3 groups, uncomplicated illness, mild-pneumonia and sever-pneumonia respectively, according to the severity defined by World Health Organization interim guidance (6). Epidemiological, demographic, clinical, laboratory and radiological data were extracted from medical records of patients. CT score was obtained by synthesizing the grading of range and density of the exudative lesion, following protocol from a previous study (7). Present study was approved by the Ethics Committee of above-mentioned Hospitals of Wenzhou Medical University (L-2020-13), along with a waiver of informed consent.

Of all the 64 cases, 38 (59.4%) were male. Median age was 48.5 years (range, 10–77). Fever (71.9%) and cough (64.1%) were the most common symptoms, whereas nausea/vomiting (3.1%), abdominal pain/diarrhea (10.9%), and conjunctival congestion (1.6%) were rare (*Table 1*). A 5th-generation case was found in the study (*Figure 1A*). Patient 1 (Generation 2), who had never contacted with wildlife or Huanan Seafood Market, transmitted the SARS-CoV-2 to Patient 2 (Generation 3) during his visit. The latter transmitted the virus to his family members (Patient 3 & 4, Generation 4). Finally, the virus reached to hairstylist (Patient 5, Generation 5) when he repeatedly contacted with one of the family members and got laboratory-confirmed

Table 1 Clinical features of patients with COVID-19

Clinical features	All patients (n=64)	Uncomp. (n=3)	Mild (n=57)	Severe (n=4)	P value (mild *vs*. uncomp.)	P value (severe *vs*. uncomp.)	P value (severe *vs*. mild
Age (years), median [range]	48.5 [10–77]	19 [10–32]	49 [20–77]	44 [41–49]	–	–	0.11
Male, (%)	38/64 (59.4)	0/3 (0.0)	34/57 (59.6)	4/4 (100.0)	0.076	0.029	0.29
Family onset, (%)	25/64 (39.1)	-	-	-	–	–	–
Symptoms, (%)							
None	6/64 (9.4)	1/3 (33.3)	5/57 (8.8)	0/4 (0.0)	0.28	0.43	–
Fever	46/64 (71.9)	1/3 (33.3)	41/57 (71.9)	4/4 (100.0)	0.21	0.14	0.57
Cough	41/64 (64.1)	0/3 (0.0)	39/57 (68.4)	2/4 (50.0)	0.039	0.43	0.59
Sputum production	23/64 (35.9)	0/3 (0.0)	21/57 (36.8)	2/4 (50.0)	0.55	0.43	0.63
Myalgia	15/64 (23.4)	1/3 (33.3)	12/57 (21.1)	2/4 (50.0)	0.53	–	0.22
Nausea/vomiting	2/64 (3.1)	0/3 (0.0)	2/57 (3.5)	0/4 (0.0)	–	–	–
Abdominal pain/diarrhea	7/64 (10.9)	0/3 (0.0)	7/57 (12.3)	0/4 (0.0)	–	–	–
Conjunctival congestion	1/64 (1.6)	0/3 (0.0)	1/57 (1.8)	0/4 (0.0)	–	–	–
Laboratory findings							
White blood cell ($\times10^9$/L)							
Mean (SD)	4.77 (1.23)	5.70 (2.21)	4.67 (0.21)	5.49 (0.60)	0.16	0.86	0.18
<4, (%)	16/64 (25.0)	1/3 (33.3)	15/57 (26.3)	0/4 (0.0)	–	0.43	0.56
Lymphocyte ($\times10^9$/L)							
Mean (SD)	1.36 (0.44)	1.86 (0.76)	1,35 (0.41)	1.09 (0.39)	0.51	0.14	0.22
<1.1, (%)	17/64 (26.6)	0/3 (0.0)	15/57 (26.3)	2/4(50.0)	0.57	0.43	0.31
Eosinophil ($\times10^9$/L)							
Mean (SD)	0.055 (0.062)	0.063 (0.051)	0.057 (0.064)	0.028 (0.045)	0.87	0.38	0.37
<0.02, (%)	23/64 (35.9)	0/3 (0.0)	20/57 (35.1)	3/4 (75.0)	0.54	0.14	0.15
CRP (mg/L)							
Mean (SD)	23.89 (32.71)	2.32 (3.39)	22.48 (30.13)	60.22 (57.09)	0.051	0.057	0.068
>8, (%)	36/64 (56.3)	0/3 (0.0)	32/57 (56.1)	4/4 (100.0)	0.096	0.029	0.14
D-Dimer (μg/mL)	23/61 (37.7)	0/2 (0.0)	20/55 (36.4)	3/4 (75.0)	0.54	0.40	0.32
CT findings							
Left lung involvement only, (%)	4/64 (6.3)	0/3 (0.0)	4/57 (7.0)	0/4 (0.0)	–	–	–
Right lung involvement only, (%)	7/64 (10.9)	0/3 (0.0)	7/57 (12.3)	0/4 (0.0)	–	–	–
Bilateral involvement, (%)	50/64 (78.1)	0/3 (0.0)	46/57 (80.7)	4/4 (100.0)	0.011	0.029	–
CT score, mean (SD)	24.9 (22.2)	0 (0.0)	22.2 (16.24)	47.8 (2.90)	–	–	0.0028
Medical therapies, (%)							
Interferon	49/64 (76.6)	3/3 (100.0)	45/57 (78.9)	1/4 (25.0)	–	0.14	0.043
Antiviral agents	58/64 (90.6)	2/3 (66.7)	53/57 (93.0)	3/4 (75.0)	0.23	–	0.30
Corticosteroid	4/64 (6.3)	0/3 (0.0)	1/57 (1.8)	3/4 (75.0)	–	0.14	–
Antibiotics	11/64 (17.2)	0/3 (0.0)	9/57 (15.8)	2/4 (50.0)	–	0.43	0.15
Oxygen therapy, (%)	62/64 (96.9)	3/3 (100.0)	55/57 (96.5)	4/4 (100.0)	–	–	–
Outcomes cure, (%)	64/64 (100.0)	3/3 (100.0)	57/57 (100.0)	4/4 (100.0)	–	–	–

Data are presented as median (range), mean (standard deviation) or n/N (%), where N is the total number of patients. P values comparing uncomp., mild, and severe respectively are from χ^2, Fisher's exact test, independent-samples *t*-test, or one-way ANOVA. Uncomp., uncomplicated illness; mild, mild pneumonia; severe, severe pneumonia.

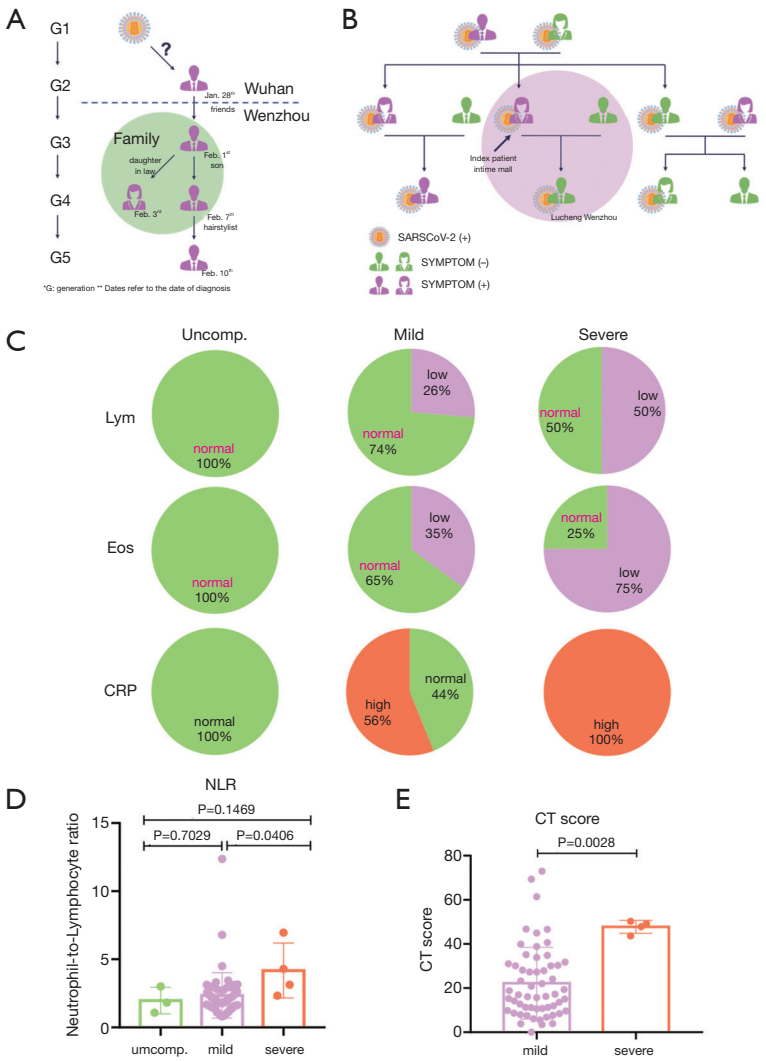

Figure 1 Demographic and clinical features of patients with COVID-19. (A) A 5th-generation case. P1 (G2), who had never contacted with wildlife or Huanan Seafood Market, came back from Wuhan and visited his friend (P2, G3) on Jan 19, the next day after which P1 (G2) developed fever and diagnosed COVID-19 On Jan 28, 2020. On Jan 31, 2020, 12 days after the visit, P2 was also diagnosed positive for COVID-19 on Feb 1 after having fever for 1-day. Later, P2's daughter-in-law (P3, G4) and son (P4, G4) also developed symptoms and were confirmed on Feb 3 and Feb 7, 2020, respectively. During this period, Patient 4 contacted his hairstylist (P5, G5) on Jan 29, and Jan 31, who developed fever on Feb 9 and then finally was laboratory-confirmed for COVID-19 on Feb 10, 2020. (B) 9-member cluster from a 12-member family, originated from a local epidemic area (Intime Mall). Index patient in this family cluster worked at Intime Mall and lived with her husband and son in Lucheng District. The couple and their son traveled to their hometown in Wencheng District on Jan 23, 2020, and repeatedly visited all of their relatives after that. 8 days later, the index patient's father developed fever and diagnosed COVID-19 on Feb 2, 2020. One of her sister-in-law developed fever on Feb 3, 2020, and got diagnosed with COVID-19 the following day. The index patient felt no symptoms until she finally developed fever on Feb 5, 2020 and then laboratory-confirmed COVID-19, on the same day. Afterwards, all of the remaining 9 members of the family underwent SARS-CoV-2 RNA detection and 6 were confirmed positive, among whom 4 were asymptomatic. Although 2 patients of this family cluster were admitted in another hospital, we obtained their information by the detailed description of their relatives in our hospital. *, G: generation; **, dates refer to the date of diagnosis. Patients were grouped into three categories as per WHO interim guidance. Uncomp., uncomplicated illness; mild, mild pneumonia; severe, severe pneumonia. (C) Patients with abnormal lymphocyte count, eosinophil count and CRP of different groups were analyzed. (D) Neutrophil-to-lymphocyte ratio was compared among three groups. (E) Comparison of CT score was made among two groups with pneumonia.

for COVID-19 on the following day.

Twenty-five (39.1%) cases were involved in SARS-CoV-2 infected family clusters (*Table 1*), among them was a 9-member cluster from a 12-member family, which originated from a local epidemic area (Intime-Mall). Index patient worked at a local epidemic Mall. She spread the virus to 8 other members of the family when she traveled to her hometown in another District with her husband and son (*Figure 1B*). Presence of a considerable number of family clusters strengthened.

Lymphopenia was observed in 15 (26.3%) patients with mild-pneumonia and 2 (50.0%) patients with severe-pneumonia. Eosinophils reduction was also documented in 20 (35.1%) patients of the mild-pneumonia group and 3 (75.0%) of severe-pneumonia group. CRP rose in 32 (56.1%) patients of mild-pneumonia group and 4 (100%) of severe-pneumonia group, but in none of the uncomplicated-illness group (*Table 1*, *Figure 1C*). Neutrophil to lymphocytes ratio (NLR) of severe-pneumonia group was significantly higher than that of mild-pneumonia group (P=0.0406) (*Figure 1D*). Level of D-Dimer rose in 20 (36.4%) of 55 patients of mild-pneumonia group and 3 (75%) of 4 patients of severe-pneumonia group while normal levels of alanine aminotransferase, PCT, bilirubin, serum creatinine were documented only in a small number of patients (data not shown). CT findings showed that 50 (78.1%) patients manifested bilateral involvement. Average CT score was 24.9±22.2. Compared to that of mild-pneumonia group (22.2±16.24), CT score of the severe-pneumonia group (47.8±2.9) was markedly higher (P=0.0028) (*Table 1*, *Figure 1E*). All 64 patients in our study were cured and discharged till March 10, 2020, although 3 of them were transferred to Intensive Care Unit once during treatment. In this study, the cure rate was 100% and the mortality was 0 (*Table 1*).

For treatment, oxygen therapy, antiviral therapy, interferon inhalation, intravenous antibiotics and glucocorticoid therapy were selectively initiated in different patients (*Table 1*).

Before the official announcement of Wuhan lockdown, around 20,000 Wenzhou businessmen traveled back to Wenzhou for the spring festival, thus making it the most seriously hit city outside Hubei, where then strictest quarantine strategy was implemented. Interestingly, we found that the severity and mortality in Wenzhou-cases were much milder than those in Hubei-cases. A significantly lower fatality rate was found in Wenzhou (outside Hubei), compared to previous Wuhan-based studies where it was 15% (2) and 4.3% (8). Moreover, we discovered that rate of severity and complications related to COVID-19 was very low in Wenzhou, as compared to those in Wuhan. The low mortality in Zhejiang Province (9) suggests the prominent role of quarantine policies and emphasizes their strict implementation as the global epidemic continues to worsen (10).

Family clusters accounted for 39.1% of all cases in our study, strengthening the idea of efficient human-to-human transmission. Consistently, strong longitudinal infectivity was further proved by our discovery of a 5th-generation COVID-19 case. Our study also revealed the presence of asymptomatic cases (9.4%), which might be a potential source of infection. Aiming to extend the diagnostic parameters, we looked for new markers to predict the severity of COVID-19 and discovered that NLR and CT score were significantly elevated in severe-pneumonia group.

Presence of a considerable number of asymptomatic patients in our study cohort draws attention towards more strict screening and contact tracing of infected individuals, because of the likelihood that presence of asymptomatic patients might lead to misdiagnosis of the potential infected source and contribute to the rapid spread of the virus. Specifically involving Wenzhou-patients, the study is limited by the small sample size of severe-pneumonia group. Finally, considering the recruitment of Wenzhou-based patients only, our study depicts a true picture of the clinical condition and characteristics of patients outside Hubei.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work (including full data access, integrity of the data and the accuracy of the data analysis) 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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