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Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19

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A R T I C L E   I N F O

A B S T R A C T

Objectives: To compare the clinical characteristics and the dynamics of viral load between imported and non-imported patients with COVID-19.
Design and methods: Data from 51 laboratory-confirmed patients were retrospectively analyzed.
Results: The incubation period in the tertiary group was longer than that in the imported and secondary groups (both $p < 0.05$). Fever was the most common symptom at the onset of illness (73.33%, 58.82%, and 68.42%, respectively), and half of the patients had a low-grade temperature (<38.0 °C) with a short duration of fever (<7 days). CT scans showed that most patients in the three groups had bilateral pneumonia (80.00%, 76.47%, and 73.68%, respectively). Ct values detected in the tertiary patients were similar to those for the imported and secondary groups at the time of admission (both $p > 0.05$). For the tertiary group, the viral load was undetectable in half of the patients (52.63%) on day 7, and in all patients on day 14. For one third of the patients in the imported and secondary groups, the viral load remained positive on day 14 after the admission.
Conclusions: COVID-19 can present as pneumonia with a low onset of symptoms, and the infectivity of SARS-CoV2 may gradually decrease in tertiary patients.

Introduction

The 2019 novel coronavirus (nCoV-2019, now known as SARS-CoV-2) infection, which can cause respiratory failure, poses a global threat to public health (Chan et al., 2020a; Chen et al., 2020a). The coming weeks are crucial in monitoring the status of community transmission (Heymann and Shindo, 2020; Hui et al., 2020).

The imported patients with COVID-19 in this study were those who had visited or originated from Wuhan city, and were detected at the end of January 2020; subsequently, secondary and tertiary transmissions occurred nationwide (Lipsitch et al., 2020). Person-to-person transmission of SARS-CoV-2 in hospital and family settings was confirmed in other geographical regions (Chan et al.,

2020b). Although the speed of transmission declined in China, concerns about the outbreak of pneumonia in other countries are constantly rising (Hui et al., 2020; Boldog et al., 2020; Mahase, 2020). To date, the differences between cases of imported, secondary, and tertiary transmission remain largely unknown.

For this study we analyzed the characteristics of COVID-19 in Changzhou city, Jiangsu province. The clinical, laboratory, and radiological characteristics, as well as the dynamics of viral load, were compared between the imported, secondary, and tertiary patients.

Methods

Patients

A cohort of 51 patients in Changzhou was confirmed with COVID-19, according to Chinese guidelines for the diagnosis and treatment of COVID-19 (Anon., 2020), and admitted to the Third Hospital of Changzhou, a designated hospital, between January 23

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and February 18, 2020. The outcomes were followed up until February 27, 2020. Epidemiological history and symptom data were confirmed by two doctors in a negative-pressure ward. Viral RNA was detected in throat swabs obtained from the patients, and a computed tomography (CT) scan was acquired immediately after symptom onset.

The 51 patients were divided into three groups — imported (15 cases), secondary (17 cases), and tertiary (19 cases) — according to their epidemiological history. The imported patients with COVID-19 were those who had visited or originated from Wuhan city, Hubei province. Secondary patients were defined as those who had not visited or come from Wuhan, but who had been in close contacted with the imported patients. The tertiary cases were those had not visited Wuhan or come into contact with the imported patients, but had acquired infection through contact with the secondary cases (Huang et al., 2019; Lim et al., 2020; Park et al., 2016).

All data for the included individuals were reported to the Chinese Center for Disease Control and Prevention (CDC).

Reverse transcriptase-polymerase chain reaction (RT-PCR) assay

COVID-19 was confirmed according to the cycle threshold (Ct) values for *Orf1ab* and *N* genes ascertained by RT-PCR assay. The assay was performed by Changzhou CDC and the Clinical Laboratory of The Third People's Hospital of Changzhou using a commercial kit (Biogerm Medical Biotechnology Co., Shanghai, China). Ct values were inversely related to viral RNA copy numbers (Zou et al., 2020), with a Ct value <40 being considered positive.

Statistical analysis

Continuous variables were expressed as median (IQR) or mean ± standard deviation and compared using the Kruskal–Wallis test or one-way ANOVA, followed by post-hoc tests to compare the differences between the three groups. Categorical values were expressed as frequencies, and the differences were analyzed using Fisher's exact test. All analyses were performed using SPSS 23.0 software (Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

Results

Demographics and clinical characteristics of patients with COVID-19

The demographic and clinical characteristics of the patients are shown in Table 1. Twelve family clusters were found in this study. Six patients without any symptoms were diagnosed according to the chest CT scans and the Ct values detected in throat swabs. 10/15 (66.67%) patients in the imported group were males, while almost half of the patients in the secondary and tertiary groups were females. The patients in the tertiary group were significantly older than those in the secondary group ($p = 0.03$) and had more comorbidities than those in the imported group ($\chi^2 = 8.259$, $p < 0.01$).

Since none of the patients developed severe pneumonia or ARDS, all patients survived, and no mechanical ventilation was given in this study. Interestingly, the incubation period for the tertiary group was longer than that for the imported and secondary groups ($p < 0.01$ and $p = 0.03$, respectively).

Fever was the most common symptom at the onset of illness (73.33%, 58.82%, and 68.42%, respectively), with about half of the patients (45.45%, 50.00%, and 61.54%, respectively) having a low-grade temperature ($<38.0\ °C$) with a short duration of fever (<7 days). However, no significant differences were detected in the development of fever and other symptoms, including cough, sputum production, pharyngalgia, fatigue, myalgia, dyspnea, and diarrhea, between the three groups (all $p > 0.05$).

Laboratory and radiology findings for patients with COVID-19

Four patients in the tertiary group showed an elevated level (<85 U/L) of alanine transaminase (ALT) and aspartate aminotransferase (AST) at admission. The levels of D-dimer, troponina, and creatine kinase were normal in all patients.

Table 1
Demographic and clinical characteristics of patients with COVID-19.

Variables	Imported ($n = 15$)	Secondary ($n = 17$)	Tertiary ($n = 19$)	Z or χ^2	p-value
Age, years	35.0 (29.0–51.0)	37.0 (24.0–47.5)	53.0 (35.0–65.0)[*]	5.614	0.06
Male, n (%)	10 (66.7)	7 (41.2)	8 (42.1)	2.601	0.28
Comorbidity, n (%)	0 (0)	4 (23.5)	8 (42.1)[**]	8.766	0.01
Pulmonary disease	0 (0)	0 (0)	1 (5.3)	1.648	0.99
Cardiovascular disease	0 (0)	2 (11.8)	3 (15.8)	2.383	0.36
Diabetes	0 (0)	1 (5.9)	3 (15.8)	2.463	0.37
Chronic liver disease	0 (0)	0 (0)	1 (5.3)	1.648	0.99
Chronic kidney disease	0 (0)	1 (5.9)	0 (0)	1.871	0.63
Incubation period, days	8.0 (4.0–10.0)	8.0 (4.0–11.0)	12.0 (9.0–14.0)[*,**]	10.943	< 0.01
Fever, N (%)	11 (73.3)	10 (58.8)	13 (68.4)	0.820	0.75
Highest temperature < 38°C, n (n/N, %)	5 (45.5)	5 (50.0)	8 (61.5)	0.742	0.76
Duration, days	2.0 (0–3.0)	2.0 (0–4.0)	2.0 (0–5.0)	0.573	0.75
Duration < 7 days, n (n/N, %)	11 (100.0)	8 (80.0)	11 (84.6)	2.278	0.43
Cough, n (%)	5 (33.3)	9 (52.9)	9 (47.4)	1.309	0.53
Sputum production, n (%)	3 (20.0)	6 (35.3)	4 (21.1)	1.258	0.56
Pharyngalgia, n (%)	1 (6.7)	0 (0)	2 (10.5)	1.746	0.50
Fatigue, n (%)	1 (6.7)	1 (5.9)	0 (0)	1.547	0.52
Myalgia, n (%)	4 (26.7)	2 (11.8)	2 (10.5)	1.814	0.44
Dyspnea, n (%)	2 (13.3)	1 (5.9)	1 (5.3)	0.982	0.67
Diarrhea, n (%)	2 (13.3)	1 (5.9)	2 (10.5)	0.623	0.86

Data are expressed as median (IQR) and n (%). Comparisons were conducted using the Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical values.

[*] Tertiary vs secondary, $p < 0.05$.
[**] Tertiary vs imported, $p < 0.05$.

Table 2
Laboratory and radiology findings of patients with COVID-19.

Variables	Imported (n = 15)	Secondary (n = 17)	Tertiary (n = 19)	Z or χ^2	p-value
Laboratory findings					
ALT, U/L	22.9 (16.6–31.0)	13.5 (11.6–21.1)	25.2 (11.7–36.2)[*]	7.785	0.02
AST, U/L	19.0 (17.0–31.0)	17.0 (12.5–19.5)	22.0 (17.0–34.0)[*]	9.382	< 0.01
C-reactive protein, mg/L	4.4 (1.3–11.2)	2.2 (1.0–16.2)	7.0 (0.8–20.0)	0.930	0.63
WBC, E + 09/L	5.2 (4.6–6.3)	4.8 (3.4–6.2)	3.9 (3.1–5.7)[**]	5.747	0.06
WBC < 4 E + 09/L, n (%)	1 (6.67)	6 (35.29)	10 (52.63)[**]	8.295	0.01
Lymphocytes, E + 09/L	1.5 (0.9–2.1)	1.1 (1.0–1.9)	1.3 (0.9–1.6)	1.077	0.58
CD3+ T lymphocyte, %	69.9 (62.9–78.2)	65.9 (60.0–72.9)	72.2 (65.8–76.1)	2.297	0.32
CD4+ T lymphocyte, %	39.9 (38.2–45.7)	37.5 (32.2–43.9)	37.4 (32.6–40.4)	3.266	0.20
CD8+ T lymphocyte, %	28.7 (22.7–33.9)	26.7 (20.8–31.9)	30.3 (26.0–34.0)	1.592	0.45
B lymphocyte, %	13.9 (9.8–18.1)	11.4 (8.4–16.1)	9.1 (7.5–10.9)[**]	7.425	0.02
CT findings					
Unilateral pneumonia	2 (13.3)	3 (17.7)	3 (15.8)	0.256	0.99
Bilateral pneumonia	12 (80.0)	13 (76.5)	14 (73.7)	0.269	0.99
Multiple mottling and ground-glass opacity	1 (6.7)	1 (5.9)	2 (10.5)	0.517	0.99
Ct value on admission					
ORF1ab gene	28.0 (26.0–30.0)	30.0 (28.0–31.5)	30.0 (22.0–34.0)	1.301	0.52
N gene	30.0 (26.0–32.0)	30.0 (27.5–32.0)	32.0 (26.0–34.0)	0.778	0.68
Ct < 40 on day 7, n (%)					
ORF1ab gene	9 (60.0)	15 (88.2)	9 (47.4)[*]	6.767	0.03
N gene	7 (46.7)	14 (82.4)[***]	7 (36.8)[*]	8.088	0.02
Ct < 40 on day 14, n (%)					
ORF1ab gene	5 (33.3)	6 (35.3)	0 (0)[*,**]	8.345	0.02
N gene	4 (26.7)	5 (29.4)	0(0)[*,**]	6.530	0.04

Data are expressed as median (IQR) and n (%). Comparisons were conducted using the Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical values.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell counts; CT, computed tomography; Ct, cycle threshold.
[*] Tertiary vs secondary, p < 0.05.
[**] Tertiary vs imported, p < 0.05.
[***] Imported vs secondary, p < 0.05.

Leucopenia (white blood cell count <4 × 10^9/L) was more common in the tertiary group than in the imported patients (χ^2 = 8.295, p = 0.01) (Table 2). Moreover, B lymphocyte counts were lower in the tertiary patients compared with those in the imported group (p < 0.01).

CT scans showed that most patients in the three groups had bilateral pneumonia (80.00%, 76.47%, and 73.68%, respectively).

Dynamic changes of Ct value in patients with COVID-19

Of the 51 patients, 49 (96.08%) showed positive RNA tests in the throat swabs, while one patient had a positive RNA test in the bronchoalveolar lavage fluid, and another tested positive in the anal swab. As shown in Figure 1, the viral load in throat swabs with respect to days was analyzed after admission.

Ct values detected in the tertiary patients were similar to those for the imported and secondary groups on admission (both p > 0.05). For the tertiary group, the viral load was undetectable in half of the patients (52.63%) on day 7 and in all patients on day 14, but remained positive in one-third of the patients in the imported and secondary groups on day 14 after admission.

Discussion

For this study we analyzed the clinical, laboratory, and radiological characteristics, as well as the dynamics of viral load, in patients with COVID-19. Half of the patients had low-grade (<38.0 ℃) fever of short duration (<7 days). The incubation period in the tertiary group was longer than that in the imported and secondary groups, with the viral load undetectable in the early stages.

Compared with SARS-CoV infection, COVID-19 shows less onset of symptoms (Sun et al., 2020; Wu and McGoogan, 2020). Gao et al. (Huang et al., 2020) reported that the majority of the patients in Wuhan presented a moderate or high temperature (>38.0 ℃),

while low-grade fever with or without mild respiratory symptoms was common in our study because no patients with severe pneumonia were included. Moreover, SARS-CoV-2 causes lower respiratory tract lesions even in patients without any clinical symptoms (Chen et al., 2020b; Wang et al., 2020). Interestingly, six patients in our study had radiological evidence of pneumonia, but with no fever or cough during infection. These findings were in agreement with those of previous studies (Chen et al., 2020b; Huang et al., 2020). Thus, chest CT scans need to be monitored routinely in clinical practice.

Although none of the patients developed a severe infection in this study, comorbidities were common in the tertiary patients, demanding a focus on elderly patients. Moreover, low B lymphocyte counts in the tertiary patients may be related to these comorbidities, thereby necessitating additional studies to elucidate the immunological mechanisms during COVID-19 infection (Li et al., 2020).

To date, the epidemiological characteristics of COVID-19 are unclear. Notably, the long incubation period suggests a potential transmission route in tertiary, even asymptomatic, patients. Although lopinavir/ritonavir and arbidol have been administered in clinical practice, their effectiveness in inhibiting SARS-CoV-2 replication is not yet confirmed (Anon., 2020). Interestingly, the viral load could not be detected early in tertiary patients; thus, it could be speculated that the infectivity of SARS-CoV-2 may gradually decrease.

This study has several limitations. First, the incubation period may have been short for several of the patients who lived in Wuhan because they were infected several days before coming to Changzhou. Second, the number of patients was limited, and therefore a multicenter study with a large sample size would be essential to further substantiate our findings.

In conclusion, COVID-19 can present as pneumonia with the onset of few symptoms, and the infectivity of SARS-CoV-2 may gradually decrease in tertiary patients.
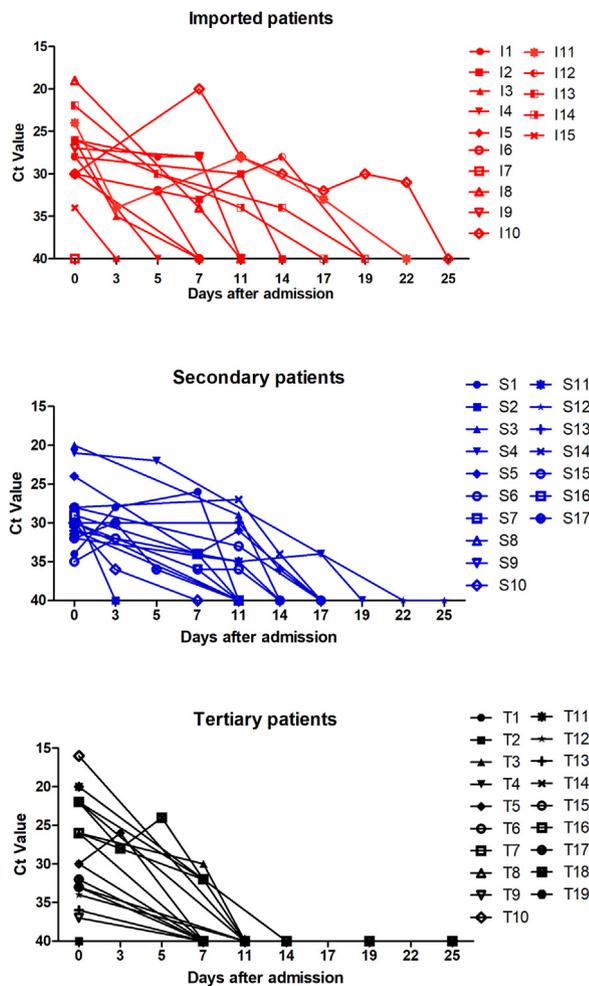
Figure 1. Dynamic changes in cycle threshold (Ct) values in patients with imported, secondary, and tertiary COVID-19.

Authors' contributions

Study design: Yuan Xue and Hong Dai. Data collection: Zhen Zhu, Manman Cui, Chunhua Chen, Cong Chen, and Yuan Xue. Data analysis: Yuan Xue, Tianmin Xu, and Cong Chen. Writing: Yuan Xue, Tianmin Xu, and Cong Chen. All authors read and approved the final manuscript. Tianmin Xu and Cong Chen contributed equally to this work.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval

The study was anonymous, and the protocol was approved by the Ethics Committee of The Third People's Hospital of Changzhou, according to the Declaration of Helsinki, 2013. Written informed consent was obtained from all participants.

Acknowledgment

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.03.022.

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