Differential diagnosis of coronavirus disease 2019 from pneumonias caused by other etiologies in a fever clinic in Beijing

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Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ Fever clinics in general hospitals were requested to reinforce surveillance of this highly contagious disease. Patients with body temperatures ≥37.3°C were asked to firstly visit fever clinics, where a triage strategy was implemented, and probable or possible cases were identified by experts or expert panels, and samples were sent for quick viral detection. During this period, pneumonias caused by other etiologies such as influenza were also prevalent in Beijing, as in other regions of the country; it was a challenge for physicians to identify suspected COVID-19 from patients with fever, particularly from pneumonias of varied etiologies. Therefore, information was needed to help differentiate COVID-19 from pneumonias caused by other etiologies in this critical situation.

We conducted a retrospective, single-centered study and recruited patients visiting the fever clinic at Peking University Third Hospital from January 21 to February 15, 2020. Based on epidemiological history, clinical and radiological manifestations, cases with possible or probable COVID-19 were sent for panel discussion and then for SARS-CoV-2 detection by reverse transcription-polymerase chain reaction (RT-PCR). Pediatric patients were not included in our study. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Peking University Third Hospital (No. IRB00006761-M2020189), and the data were analyzed anonymously.

The diagnosis and severity assessment of COVID-19 were according to Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infection by the National Health Commission.² Laboratory testing of SARS-CoV-2 in throat swabs was performed by both Beijing Center for Disease Control and Prevention (CDC) and Haidian District CDC of Beijing.

Demographic and epidemiological data were collected. Epidemiological data included: if the patient came from Wuhan City or other cities of Hubei Province in 2 weeks, if the patient ever had close contact with individuals from Wuhan or other cities of Hubei province, or with individuals who had confirmed COVID-19 in 2 weeks, and if the onset of pneumonia occurred in family members in a short period. Clinical indices and symptoms on admission were also recorded. Data from laboratory examinations including blood routines, and computed tomography (CT) findings were collected. CT features were reviewed by experts of Pulmonary and Critical Care Medicine and Radiology.

Continuous variables were expressed as the mean ± standard deviation or median (interquartile range). Categorical variables were expressed as numbers (%). Student’s t test or Mann-Whitney U test was used to compare differences between groups for continuous variables and Chi-square test or Fisher’s exact test was used to analyze categorical variables, respectively. Results were considered statistically significant at P < 0.05. Statistical analyses were performed using SPSS software, version 22.0 (IBM, Armonk, NY, USA).

From January 21 to February 15, 2020, physicians at the Fever Clinic referred 156 cases to panel discussion by
multi-discipline experts. After discussion, 110 were considered to be possible or probable cases of COVID-19, and received SARS-CoV-2 RT-PCR testing, which was positive in 19 cases (COVID-19 group). For the remaining 91 cases with negative viral detection, 2 cases were not included in the final analysis because they had epidemiological evidence with interstitial pneumonia in CT findings and COVID-19 could not be completely excluded, 22 were excluded from the analysis because of lack of CT scan or no signs of pneumonia on CT scan, and finally 67 patients were included as the non-COVID-19 group [Supplementary Figure 1, http://links.lww.com/CM9/A337].

The demographics and baseline characteristics of the 19 patients with COVID-19 were shown in Supplementary Table 1, http://links.lww.com/CM9/A337. The median age was 44.0 (33.0 – 69.0) years. Men and women were equally affected. Seventeen patients (17/19, 89.5%) had a clear epidemiological history of COVID-19. Six patients had close contact with their family members who were infected by SARS-CoV-2. In the two patients with unclear epidemiological link, one was a social worker contacting a confirmed COVID-19 case, and the other one had no epidemiological history on presentation, but another patient, who had had dinner with him, was also diagnosed to have COVID-19 later. An incubation period was elicited from 11 patients, ranging from 2 to 10 days with a median of 6.0 days. Most of the patients (17/19, 89.5%) were mild-moderate in disease severity. Two patients were classified as severe cases with pulse oxygen saturation (SpO2) < 93% on presentation, while no critical cases were identified in our series.

On admission, most patients (17/19, 89.5%) had fever with a mean body temperature of 37.8°C. Cough (7/19, 36.8%), expectoration (6/19, 31.6%), fatigue (10/19, 52.6%), and headache or dizziness (7/19, 36.8%) were common symptoms. Other symptoms included shortness of breath, myalgia or arthralgia, sore throat, nasal symptoms and diarrhea. Compared with non-COVID-19 patients, a higher proportion of COVID-19 patients had an identified epidemiological history (89.5% vs. 32.8%, P < 0.001). Clinical symptoms were similar between cases of COVID-19 and non-COVID-19, except for cough [Table 1].

Blood routine showed decreased lymphocyte count in 42.1% (8/19) of the COVID-19 patients. More than 80% of COVID-19 patients had normal white blood cell (WBC) and neutrophil counts. Compared with admission, but another patient, who had had dinner with him, was also diagnosed to have COVID-19 later. An incubation period was elicited from 11 patients, ranging from 2 to 10 days with a median of 6.0 days. Most of the patients (17/19, 89.5%) were mild-moderate in disease severity. Two patients were classified as severe cases with pulse oxygen saturation (SpO2) < 93% on presentation, while no critical cases were identified in our series.

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![Image](http://links.lww.com/CM9/A337)

Table 1: Epidemiological history, symptoms and blood routine test on admission between patients with COVID-19 and non-COVID-19.

| Parameters                      | COVID-19 (n = 19) | Non-COVID-19 (n = 67) | Statistics | P     |
|--------------------------------|------------------|----------------------|------------|-------|
| Epidemiological history        |                  |                      |            |       |
| Clear                          | 17 (89.5)        | 22 (32.8)            | --         | <0.001† |
| Unclear                        | 1 (5.3)          | 5 (7.5)              |            |       |
| None                           | 1 (5.3)          | 40 (59.7)            |            |       |
| Fever                          | 17 (89.5)        | 56 (83.6)            | --         | 0.724‡ |
| Cough                          | 7 (36.8)         | 53 (79.1)            | 12.535     | <0.001‡ |
| Expectoration                  | 6 (31.6)         | 30 (44.8)            | 1.059      | 0.303‡ |
| Dyspnea or shortness of breath | 1 (5.3)          | 11 (16.4)            |            | 0.286‡ |
| Fatigue                        | 10 (52.6)        | 27 (40.3)            | 0.918      | 0.338‡ |
| Myalgia or arthralgia          | 4 (21.1)         | 17 (25.4)            | 1.000      |       |
| Sore throat                    | 2 (10.5)         | 15 (22.4)            | 0.340      |       |
| Nasal symptoms                 | 0 (0.0)          | 10 (14.9)            |            | 0.108‡ |
| Headache or dizziness          | 7 (36.8)         | 15 (22.4)            |            | 0.238‡ |
| Diarrhea                       | 2 (10.5)         | 5 (7.5)              | 0.647      |       |
| Leucocyte count (×10^9/L)      | 5.30 ± 1.48      | 7.21 ± 2.94          | −3.861     | <0.001‡ |
| Leucocytes                     |                  |                      | 0.047      |       |
| Decreased                      | 2 (10.5)         | 4 (6.0)              |            |       |
| Normal                         | 17 (89.5)        | 49 (73.1)            |            |       |
| Increased                      | 0 (0.0)          | 14 (20.9)            |            |       |
| Hemoglobin (g/L)               | 144.4 ± 13.9     | 134.4 ± 23.4         | 1.765      | 0.081‡ |
| Platelets (×10^3/L)            | 168.8 ± 58.3     | 189.8 ± 67.8         | −1.226     | 0.224‡ |
| Lymphocyte count (×10^9/L)     | 1.22 ± 0.66      | 1.19 ± 0.62          | 0.189      | 0.850‡ |
| Lymphocytes                    |                  |                      | 0.190      | 0.663‡ |
| Decreased                      | 8 (42.1)         | 32 (47.8)            |            |       |
| Normal                         | 11 (57.9)        | 35 (52.2)            |            |       |
| Neutrophil count (×10^9/L)     | 3.10 (2.28, 4.51)| 4.45 (3.24, 7.11)    | −2.758     | 0.006§ |
| Neutrophils                    |                  |                      | 0.049      |       |
| Decreased                      | 2 (10.5)         | 4 (6.0)              |            |       |
| Normal                         | 16 (84.2)        | 42 (62.7)            |            |       |
| Increased                      | 1 (5.3)          | 21 (31.3)            |            |       |

Values are presented as n (%), mean ± standard deviation or median (Q1, Q3). † Fisher exact test. ‡ Chi-square test. § Independent-samples t test. § Mann-Whitney U test. COVID-19: Coronavirus disease 2019.
COVID-19 patients, non-COVID-19 patients had higher total WBC (7.21 ± 2.94) × 10^9/L vs. (5.30 ± 1.48) × 10^9/L, t = −3.861, P < 0.001) and neutrophil counts (4.45 [3.24, 7.11] × 10^9/L vs. 3.10 [2.28, 4.51] × 10^9/L, Z = −2.758, P = 0.006). Additionally, more non-COVID-19 patients had increased WBC (20.9% vs. 0.0%, P = 0.047) and neutrophil counts (31.3% vs. 5.3%, P = 0.049). However, lymphocyte counts and the proportions of patients with decreased lymphocytes were not statistically different between the two groups [Table 1].

In non-COVID-19 patients, infiltrates on the CT scan mainly involved 1–2 lung lobes, while in COVID-19 patients, lesions involving 4–5 lobes were more common (COVID-19 vs. non-COVID-19: 50.0% vs. 16.4%, P = 0.009). In COVID-19 patients, lung lesions were mostly peripheral or subpleural in distribution (14/18, 77.8%), and in severe cases were diffusely distributed (4/18, 22.2%) [Supplementary Figure 2, http://links.lww.com/CM9/A337]. In non-COVID-19 patients, 34.3% (23/67) showed airway-dominant lesions, while diffuse distribution was found in only 4.5% (3/67) of the patients. The patterns of the lesions (ground-glass opacity [GGO], consolidation or mixed GGO and consolidation) showed no significant difference between the two groups (P = 0.165). However, centrilobular nodules were observed in non-COVID-19 patients but not in COVID-19 patients [Supplementary Table 2, http://links.lww.com/CM9/A337].

In this study, we found that epidemiological history was extremely important for identification of suspected cases of COVID-19 and for differential diagnosis. Over 90% of the COVID-19 patients had clearly identified epidemiological evidence, while in non-COVID-19 patients, epidemiological links could only be found in about 30%. In the early phase of our study, most cases were imported from the city of Wuhan or other cities in Hubei Province, including traveling to or living in Wuhan or other cities in Hubei province, and a few had a history of close contact with individuals from the above mentioned areas. In the later phase, contact with family members with confirmed COVID-19 was an epidemiological feature and five family clusters were found.

Our study showed that the total WBC count and the neutrophil count were different between COVID-19 and non-COVID-19 patients. Leukocytosis and neutrophilia were more common in patients with non-COVID-19 pneumonia. In contrast, although decrease of lymphocytes was also common in our study, the difference between COVID-19 and non-COVID-19 cases was not significant, probably due to the fact that pneumonias enrolled for this analysis were mostly viral (for example, influenza) or atypical, as classical bacterial pneumonia had been excluded by first screening/triage. Leukocytosis and neutrophilia may be helpful to exclude COVID-19, especially in those without clear epidemiological history. Persistent lymphopenia is a predictor of severe cases of COVID-19.[3] A recent study demonstrated that serum albumin and C-reactive protein were also the risk factors for disease progression.[4]

Unlike pneumonia caused by other pathogens, COVID-19 has some unique characteristics on the CT scan. Firstly, multi-lobe involvement was more common in COVID-19 as compared with non-COVID-19 pneumonia. The lesions, including ground-glass opacity (GGO), mixed GGO and patchy consolidation, were mainly distributed in peripheral and sub-pleural areas in mild to moderate cases, while in severe cases diffuse ground glass lesions were present. These features were consistent with a previous study.[5]

In conclusion, epidemiological evidence was important for prompt COVID-19 case finding, and lower blood WBC and neutrophil counts may be useful for differentiating it from pneumonia of other etiologies. Our findings also added to the knowledge of COVID-19 for clinical practice in fever clinics facing newly emerging respiratory infections. However, as a single-center study in the early period of the epidemic, our findings were limited by the small number of cases and the fact that the pathogens in non-COVID-19 pneumonias were not identified, which needed to be clarified in larger studies.

Conflicts of interest
None.

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