

## Letter to the Editor

**Coronavirus Disease 2019 versus Influenza A in Children: An Observational Control Study in China**

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This study aimed to understand the differences in clinical, epidemiological, and laboratory features between the new coronavirus disease 2019 (COVID-2019) and influenza A in children. Data of 23 hospitalized children with COVID-19 (9 boys, 5.7 ± 3.8 years old) were compared with age- and sex-matched 69 hospitalized and 69 outpatient children with influenza A from a hospital in China. The participants' epidemiological history, family cluster, clinical manifestations, and blood test results were assessed. Compared with either inpatients or outpatients with influenza A, children with COVID-19 showed significantly more frequent family infections and higher ratio of low fever (< 37.3 °C), but shorter cough and fever duration, lower body temperature, and lower rates of cough, fever, high fever (> 39 °C), nasal congestion, rhinorrhea, sore throat, vomiting, myalgia or arthralgia, and febrile seizures. They also showed higher counts of lymphocytes, T lymphocyte CD8, and platelets and levels of cholinesterase, aspartate aminotransferase, lactate dehydrogenase, and lactic acid, but lower serum amyloid, C-reactive protein, and fibrinogen levels and erythrocyte sedimentation rate, and shorter prothrombin time. The level of alanine aminotransferase in children with COVID-19 is lower than that in inpatients but higher than that in outpatients with influenza A. Pediatric COVID-19 is associated with more frequent family infection, milder symptoms, and milder immune responses relative to pediatric influenza A.

The coronavirus disease 2019 (COVID-19) is a severe acute respiratory disease caused by the new coronavirus SARS-CoV-2<sup>[1]</sup>. COVID-19 was first discovered in China at the end of 2019 and has been detected in almost every country. It has caused more than three hundred thousand deaths worldwide.

Pediatric COVID-19 is usually associated with mild symptoms<sup>[2]</sup>; however, knowledge on the differences between pediatric COVID-19 and other pediatric diseases is rare.

Influenza A is a common and fatal respiratory viral infectious disease in children of all ages. School institutions are prone to cause large-scale infections among children. During the influenza season, > 40% of pre-school children and 30% of school-age children may be infected with influenza A<sup>[3]</sup>. Although most children will recover within a week, some high-risk children may develop serious complications which can result in death. Young children are especially vulnerable with about one-third of these deaths occurring in children under 5 years old who do not exhibit underlying comorbidities. Death can occur within 3–7 d of symptom onset.

Nucleic acid detection is essential for the diagnoses of COVID-19 and influenza A viruses, given that COVID-19 does not have typical early detection symptoms. However, only a few hospitals and agencies are qualified to perform nucleic acid tests for COVID-19. Therefore, a comprehensive comparison of the clinical and non-clinical features of influenza A and COVID-19 will help in the early diagnosis and treatment of these two diseases.

This study compared the clinical characteristics, epidemiology, and routine laboratory test results between 23 inpatients (5.7 ± 3.8 years; 9 boys, 39% of total) with pediatric COVID-19 (recruited from January 1 to March 28, 2020) and age- and sex-matched 69 inpatients and 69 outpatients with pediatric influenza A (from January 1 to December 31, 2019) who received treatment in the Beijing Ditan Hospital in Beijing, China, which has been

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designated as treatment facility of infectious diseases including COVID-19.

The study followed the Helsinki Declaration and was approved by the Ethics Committee of Beijing Ditan Hospital Affiliated to Capital Medical University. Written informed consents of both pediatric patients (if possible) and their guardians were obtained.

To avoid biases induced by illness severity (inpatients are often related to more severe symptoms than outpatients), both inpatients and outpatients with pediatric influenza A were recruited. A group of outpatients with pediatric COVID-19 were not included because all children diagnosed with COVID-19 should be hospitalized in China. The diagnostic criteria for children with COVID-19 were based on the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)* issued by the China National Health Commission & State Administration of Traditional Chinese Medicine<sup>[4]</sup>. The inclusion criteria for the (1) COVID-19 group were inpatients aged < 16 years and diagnosed by SARS-CoV-2 nucleic acid test and for the (2) influenza A groups were inpatients and outpatients aged < 16 years old and diagnosed by influenza A antigen. Children were excluded if they showed positive results in any of the following tests and diagnoses: respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, sputum culture, throat swab, blood culture, mycoplasma condensation test, chlamydia antibody, rotavirus, norovirus, immunodeficiency disease, and other underlying diseases.

Qualified professionals in Beijing Ditan Hospital collected oropharyngeal or nasal swabs or sputum from children suspected to have COVID-19 and nasal swabs or sputum from children suspected to have influenza A. SARS-CoV-2 nucleic acid positive detection was performed by real-time fluorescence reverse transcription polymerase chain reaction (RT-PCR kit: 2019-nCoV ORF 1ab/N PCR fluorescence probe method). Influenza A antigen was determined with immunofluorescence by an immunology laboratory. Nasal swabs or sputum respiratory pathogens (chlamydia, influenza A and B, adenovirus, respiratory syncytial virus, rhinovirus, and coxsackie virus) were detected by immunofluorescence. Patients with diarrhea were tested with RT-PCR to detect rotavirus, *Shigella* utilized agglutination assay, and mycoplasma with condensation agglutination test. Bacterial infection was detected by sputum culture or with blood culture methods. The values of white blood cell

classification vary with age in children. There are different characteristics of lymphocyte distribution in normal children throughout development. The proportions of lymphocytes and neutrophils are the same in children between 4 and 6 years old. Lymphocyte counts are greater before age 4, but after age 6, the neutrophil count is higher. These counts are divided into three age groups: < 4 years old, 4–6 years old, and > 6 years old.

MATLAB (v2020a; MathWorks, Inc., Natick, MA, USA) software was utilized for statistical analyses. Continuous variables were analyzed with either two-sample *t*-tests or Mann–Whitney *U* tests, depending on whether the assumptions of normal distribution and variance homogeneity were met. Categorical variables were analyzed using Chi-squared tests. Two-tailed *P* value < 0.05 was considered statistically significant.

We found that patients with COVID-19 was associated with a higher ratio of in-home infection than influenza A inpatients (95.6% vs. 21.7%, *P* < 0.001, Table 1), consistent with previous reports<sup>[2]</sup>. We observed that most children with COVID-19 were infected primarily by family members, while children with influenza A were infected by family members, classmates, and other patients in the hospital. The incidence of COVID-19 infection not due to family cluster is rare because Chinese children have been quarantined at home since the outbreak of COVID-19. However, the potential outbreak of COVID-19 in schools is high in countries considering lifting the quarantine to reopen schools. The association between COVID-19 and the fatal Multisystem Inflammatory Syndrome in Children (MIS-C) warned by United States Centers for Disease Control and Prevention<sup>[5]</sup> creates further concern for a serious outbreak among children.

As shown in Table 1, compared with both inpatients and outpatients with influenza A, patients with COVID-19 showed significantly shorter cough duration [(2.0 ± 5.2) vs. (2.4 ± 3.2) vs. (3.8 ± 2.3) d for COVID-19, influenza A inpatients and outpatients, respectively; both *P*-values < 0.05], lower body temperature [(37.4 ± 1.2) vs. (38.2 ± 1.5) vs. (39.2 ± 0.9) °C; both *P*-values < 0.05], shorter fever duration [(1.0 ± 1.4) vs. (2.4 ± 3.0) vs. (4.0 ± 1.5) d; both *P*-values < 0.05], as well as lower rates of high fever (i.e., > 39.0 °C; 8.7% vs. 37.7% vs. 60.9%; both *P*-values < 0.05), nasal congestion (4.3% vs. 31.9% vs. 30.4%; both *P*-values < 0.05), rhinorrhea (4.3% vs. 29.0% vs. 27.5%; both *P*-values < 0.05), sore throat (0.0% vs. 37.8% vs. 23.2%; both *P*-values < 0.05), and vomiting (0.0% vs. 27.5% vs. 24.6%; both *P*-values <

0.05). Compared with influenza A inpatients only, patients with COVID-19 also showed lower rates of myalgia or arthralgia (0.0% vs. 30.4% for COVID-19 and influenza A inpatients, respectively;  $P = 0.006$ ) and febrile seizures (0.0% vs. 33.3%,  $P = 0.001$ ). Compared with influenza A outpatients only, patients with COVID-19 also showed lower rates of cough (17.4% vs. 72.5% for COVID-19 and influenza A outpatients, respectively;  $P < 0.001$ ) and fever (43.5% vs. 91.3%, as higher rate of low fever (i.e.,  $< 37.3$  °C: 56.5% vs. 1.4%,  $P < 0.001$ ).

The mortality rate of COVID-19 is higher in adults (e.g.,  $> 4\%$  in Wuhan City, Hubei, China) than in children<sup>[6]</sup>. SARS-CoV-2 invades the human body through angiotensin-converting enzyme 2 (ACE 2) which infects human respiratory epithelial cells<sup>[7]</sup>. The intracellular response induced by ACE 2 in alveolar epithelial cells is lower in children than in adults<sup>[1]</sup>, which may explain the milder COVID-19 symptoms experienced by children than by adults.

The symptoms of fever, cough, and diarrhea

**Table 1.** Demographic and clinical information

Measure	COVID-19	Influ-in	oInflu-out	P1	P2
Age (years)	5.7 ± 3.8	5.7 ± 3.8	5.7 ± 3.8	0.996	1.000
Male	9 (39.1)	27 (39.1)	27 (39.1)	0.805	0.805
Family infection	22 (95.6)	15 (21.7)	– <sup>a</sup>	$< 0.001$	–
Cough	4 (17.4)	23 (33.3)	50 (72.5)	0.234	$< 0.001$
Cough duration (d)	2.0 ± 5.2	2.4 ± 3.2	3.8 ± 2.3	0.024	$< 0.001$
Fever	10 (43.5)	39 (56.5)	63 (91.3)	0.278	$< 0.001$
Temperature (°C)	37.4 ± 1.2	38.2 ± 1.5	39.2 ± 0.9	0.033	$< 0.001$
< 37.3	13 (56.5)	28 (40.6)	1 (1.4)	0.183	$< 0.001$
37.3–38.0	2 (8.7)	0 (0.0)	6 (8.7)	0.099	0.669
38.1–39.0	6 (26.1)	15 (21.7)	19 (27.5)	0.886	0.892
> 39.0	2 (8.7)	26 (37.7)	42 (60.9)	0.019	$< 0.001$
Fever duration (d)	1.0 ± 1.4	2.4 ± 3.0	4.0 ± 1.5	0.037	$< 0.001$
Wheezing	0 (0.0)	13 (18.8)	4 (5.8)	0.057	0.555
Diarrhea	3 (13.0)	3 (4.4)	2 (2.9)	0.163	0.184
Headache	1 (4.3)	12 (17.4)	10 (14.5)	0.226	0.354
Nasal congestion	1 (4.3)	22 (31.9)	21 (30.4)	0.018	0.024
Rhinorrhea	1 (4.3)	20 (29.0)	19 (27.5)	0.031	0.041
Sneezing	1 (4.5)	10 (14.5)	14 (20.3)	0.384	0.161
Sore throat	0 (0.0)	26 (37.8)	16 (23.2)	0.001	0.026
Nausea	1 (4.3)	12 (17.4)	6 (8.7)	0.226	0.820
Vomit	0 (0.0)	19 (27.5)	17 (24.6)	0.012	0.020
Myalgia or arthralgia	0 (0.0)	21 (30.4)	9 (13.0)	0.006	0.156
Fatigue	1 (4.3)	16 (23.9)	9 (13.0)	0.079	0.439
Febrile seizures	0 (0.0)	23 (33.3)	6 (8.7)	0.001	0.331
Viral encephalitis	0 (0.0)	1 (1.4)	– <sup>a</sup>	0.499	–
Abnormal chest CT	7 (30.4)	28 (40.6)	– <sup>a</sup>	0.535	–
Death	0 (0.0)	1 (1.4)	– <sup>a</sup>	0.499	–

**Note.** P1, P-values of COVID-19 vs. influenza A inpatients. P2, P-values of COVID-19 vs. influenza A outpatients. <sup>a</sup>No case in this group; thus, there were no statistical outputs. Mean ± SD for continuous variables and number of positive cases (proportion of positive cases) for categorical variables are shown. COVID-19, COVID-19 group; Influ-in, influenza A inpatient group; Influ-out, influenza A outpatient group.

were found in both patients with COVID-19 and influenza A. Therefore, the diagnosis of either disease should rely on other clinical indices. High fever temperature, stuffy nose, runny nose, sore throat, vomiting, and muscle pain in the limbs were less frequently detected in children with COVID-19 than in those with influenza A. Cases of viral meningitis, high fever convulsions, and death were not found in pediatric COVID-19 but in pediatric influenza A. However, milder symptoms in pediatric COVID-19 do not imply that fewer efforts are necessary for diagnosis, early monitoring, and treatment of COVID-19. In the early epidemic studies in China, including this study, pediatric COVID-19 cases are scarce, and children with COVID-19 have been found to exhibit milder symptoms than both adults with COVID-19 and children with influenza A. However, more pediatric cases worldwide have been reported since the pandemic of COVID-19 started. Studies in the United Kingdom and Italy report that children with COVID-19 experience systemic rash, heart inflammation, and arterial swelling symptoms, which are similar to Kawasaki disease<sup>[8]</sup>, but these have not yet been reported in children in China. It is possible that the SARS-CoV-2 has mutated during the pandemic and has induced new symptoms. Moreover, some of the symptoms may have been overlooked at the beginning of the pandemic due to the limited cases of pediatric COVID-19. New manifestations of pediatric COVID-19 and the development of novel diagnoses and treatments targeting these new symptoms require continuous attention.

As shown in Table 2, compared with both inpatients and outpatients with influenza A, children with COVID-19 exhibited higher levels of aspartate aminotransferase [(37.5 ± 56.1) vs. (35.5 ± 72.8) vs. (28.6 ± 11.1) U/L for COVID-19, influenza A inpatients, and outpatients, respectively; both *P*-values < 0.001] and cholinesterase [(9476.2 ± 2414.1) vs. (6512.7 ± 2085.9) vs. (7391.4 ± 1193.5) U/L; both *P*-values < 0.001], as well as lower C-reactive protein level [(2.2 ± 4.4) vs. (48.0 ± 74.8) vs. (7.9 ± 9.0) mg/L; both *P*-values < 0.001] and erythrocyte sedimentation rate [(9.6 ± 9.8) vs. (21.2 ± 18.5) vs. (22.2 ± 7.0); both *P*-values = 0.019].

Compared with influenza A inpatients only, children with COVID-19 also showed higher counts of lymphocytes (COVID-19 vs. influenza A inpatients: (56.3 ± 21.7) vs. (37.2 ± 19.8) for < 4 years, *P* = 0.035; (47.5 ± 10.8) vs. (20.8 ± 10.1) for 4–6 years, *P* < 0.001; (44.6 ± 14.3) vs. (26.6 ± 12.8), *P* = 0.005],

platelets [(287.7 ± 68.5) vs. (236.4 ± 126.3) 10<sup>9</sup>/L, *P* = 0.004], and TCD8 [(820.4 ± 378.0) vs. (510.6 ± 392.0) cells/μL, *P* = 0.006] and lactic acid level [(2.5 ± 1.2) vs. (1.7 ± 0.9) mmol/L, *P* = 0.011], as well as lower serum amyloid level [(25.2 ± 80.7) vs. (128.8 ± 120.7) mg/L, *P* < 0.001], alanine aminotransferase (ALT) level [(36.3 ± 37.1) vs. (46.0 ± 83.7) U/L, *P* < 0.001], prothrombin time [(11.6 ± 0.7) vs. (13.3 ± 2.4) s, *P* = 0.001], and fibrinogen level [(244.3 ± 108.8) vs. (312.4 ± 83.9) mg/dL, *P* = 0.002]. Compared with influenza A outpatients only, children with COVID-19 also showed higher level of ALT [(36.3 ± 37.1) vs. (24.8 ± 9.4) U/L for COVID-19 and influenza A outpatients, respectively; *P* < 0.001] and lower level of lactate dehydrogenase [(250.9 ± 81.0) vs. (307.4 ± 89.9) U/L, *P* = 0.032].

These laboratory findings suggest milder immune responses and therefore fewer immune damages in pediatric COVID-19 than in influenza A. This is consistent with the clinical manifestations of children with COVID-19. We also found higher cholinesterase level in children with COVID-19 than those with influenza A. During the immune response, an acetylcholine transmitter is released from peripheral nerve endings and activates α7nAChR on the surface of the macrophage membrane. This response links the anti-inflammatory effects of the nervous system to the immune system and mediates a more direct and quicker inflammation response<sup>[9]</sup>. Studies on the cholinergic anti-inflammatory pathway in COVID-19 may help in understanding the pathogenesis of COVID-19, which could contribute to more precise interventions or prevention strategies.

Abnormal blood coagulation is an important comorbidity of patients with severe COVID-19<sup>[10]</sup>. Autoimmune disorders are closely related to COVID-19 in adults with abnormal coagulation and thrombotic event. Children with COVID-19 did not exhibit abnormal changes in coagulation function and even showed shorter prothrombin time and lower fibrinogen quantitative than children with influenza A. These findings suggest the differences in the pathogenesis between pediatric and adult COVID-19 and between pediatric COVID-19 and pediatric influenza A.

This study has several limitations. First, the sample size of the pediatric COVID-19 group was small due to the control of the outbreak in China and the relatively low incidence of COVID-19 in children. Second, the samples are only from China and do not reflect specific effects of race, culture, and socioeconomic status on global pediatric

COVID-19. Third, the differences and associations between COVID-19 and infectious diseases other than influenza A are still unknown. International collaborations are urgently needed to investigate the pathogenesis and clinical responses of pediatric COVID-19 and to develop widely applicable diagnoses and intervention approaches.

In conclusion, pediatric COVID-19 is associated with higher incidence of family cluster, milder symptoms, and milder immune responses than

pediatric influenza A.

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**Table 2.** Laboratory test results

Measure	COVID-19	Influ-in	Influ-out	P1	P2
WBC (10 <sup>9</sup> /L)	6.4 ± 2.2	7.1 ± 3.8	7.8 ± 3.2	0.465	0.067
Lymphocyte (years)					
< 4	56.3 ± 21.7	37.2 ± 19.8	44.1 ± 22.6	0.035	0.191
4–6	47.5 ± 10.8	20.8 ± 10.1	47.3 ± 20.5	< 0.001	0.993
> 6	44.6 ± 14.3	26.6 ± 12.8	26.4 ± 14.7	0.005	0.400
Platelet (10 <sup>9</sup> /L)	287.7 ± 68.5	236.4 ± 126.3	292.1 ± 119.5	0.004	0.396
SAA (mg/L)	25.2 ± 80.7	128.8 ± 120.7	36.5 ± 40.3 <sup>a</sup>	< 0.001	–
CRP (mg/L)	2.2 ± 4.4	48.0 ± 74.8	7.9 ± 9.0	< 0.001	< 0.001
AST (U/L)	37.5 ± 56.1	35.5 ± 72.8	28.6 ± 11.1	< 0.001	< 0.001
ALT (U/L)	36.3 ± 37.1	46.0 ± 83.7	24.8 ± 9.4	< 0.001	< 0.001
Cholinesterase (U/L)	9476.2 ± 2414.1	6512.7 ± 2085.9	7391.4 ± 1193.5	< 0.001	< 0.001
TCD_4 (cells/μL)	1027.0 ± 495.6	842.9 ± 665.8	312.0 ± 0.0 <sup>b</sup>	0.103	–
TCD_8 (cells/μL)	820.4 ± 378.0	510.6 ± 392.0	190.0 ± 0.0 <sup>b</sup>	0.006	–
NK (cells/μL)	466.1 ± 401.8	320.1 ± 235.9	163.0 ± 0.0 <sup>b</sup>	0.565	–
B (cells/μL)	460.2 ± 284.7	602.1 ± 554.4	306.0 ± 0.0 <sup>b</sup>	0.806	–
LDH (U/L)	250.9 ± 81.0	289.7 ± 137.6	307.4 ± 89.9	0.245	0.032
CK-MB (U/L)	27.3 ± 13.3	27.6 ± 12.7	28.2 ± 25.7	0.988	0.170
HBDH (U/L)	229.4 ± 57.1	269.7 ± 81.3	261.8 ± 70.5	0.063	0.071
PT (s)	11.6 ± 0.7	13.3 ± 2.4	– <sup>c</sup>	0.001	–
APTT (s)	34.6 ± 4.7	31.2 ± 8.6	– <sup>c</sup>	0.104	–
Fibrinogen (mg/dL)	244.3 ± 108.8	312.4 ± 83.9	– <sup>c</sup>	0.002	–
Lactic acid (mmol/L)	2.5 ± 1.2	1.7 ± 0.9	– <sup>c</sup>	0.011	–
ESR (mm/h)	9.6 ± 9.8	21.2 ± 18.5	22.2 ± 7.0	0.019	0.019

**Note.** P1, P-values of COVID-19 vs. influenza A inpatients. P2, P-values of COVID-19 vs. influenza A outpatients. <sup>a</sup>Only two cases in this group. <sup>b</sup>Only one case in this group. <sup>c</sup>No case in this group. <sup>a, b, c</sup>Not enough data for statistical analyses. Mean ± SD for continuous variables and number of positive cases (proportion of positive cases) for categorical variables are shown. COVID-19, COVID-19 group; Influenza A inpatient group; Influenza A outpatient group. ALB, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; B, B lymphocyte; CK-MB, creatine kinase isoenzyme; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBDH, hydroxybutyrate dehydrogenase; LDH, lactate dehydrogenase; NK, natural killer cell; PT, prothrombin time; SAA, serum amyloid; U/L, units per liter; WBC, white blood cell.

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