

# Differences on Pyrexia Related Immune Responses Between COVID-19 and Influenza A Children

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## Research article

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# Abstract

**Background:** Coronavirus disease-2019 has brought rapid challenge to the current health care system raising millions of infected patients globally. The clinical manifestations of asymptomatic patients especially children and young people will contribute to the management of current pandemic.

**Methods:** To provide precise and comprehensive information on the less symptomatic COVID-19 children, total 62 hospitalized children aged 1-14 years with confirmation infection of either SARS-CoV-2 or influenza A were enrolled for past half of year from September 2019 to February 2020. The epidemiological, demographic, clinical, radiologic and laboratory findings were extracted from the electronic medical records of the patients.

**Results:** We reported less fever (43.33% vs 100%,  $p < 0.001$ ) with lower body temperature ( $p < 0.001$ ) and hypoinflammatory responses occurred in COVID-19 children in comparison with influenza infection. We further showed the significant correlations between initial body temperature and multiple immune parameters to imply the role of thermoregulation on asymptomatic COVID-19 children.

**Conclusions:** COVID-19 children were more likely to have mild symptoms and relatively slow progression. Furthermore, correlations between initial body temperature and immunological functional parameters suggested that non-susceptibility of children to SARS-CoV-2 virus may lie in the low sensitivity on thermal regulation of immune activation.

## Introduction

The escalating epidemic of Coronavirus Disease 2019 (COVID-19) has spanned over the world resulting in millions of confirmed cases and hundreds of thousands of death globally. According to the published data, predominance of child and younger teen COVID-19 patients represented mild symptom<sup>1</sup> with less than 1% of confirmed cases<sup>2</sup>. Several studies had given the glance at the epidemiological characteristics of COVID-19 confirmed children<sup>3</sup>. Here we provide precise and comprehensive comparisons on SARS-CoV-2 infected children and influenza A virus patients to elucidate the relationship between thermal activation and immune responses in the asymptomatic COVID-19 infection.

## Methods

In this retrospective cohort study, medical records of admitted children aged from 1 to 14 years with laboratory confirmation of either SARS-CoV-2 or influenza A infection were collected from September 2019 to February 2020. Total 30 SARS-CoV-2 and 32 influenza A confirmed cases were enrolled in this past half of year. Confirmed SARS-CoV-2 or influenza A infection was defined as detection of virus RNA by the real-time fluorescent polymerase chain reaction (PCR) in pharyngeal swabs. Fever was defined as an axillary temperature of 37.5°C or higher. Comparisons were conducted by using the Mann-Whitney non-parametric test. Mean  $\pm$  standard deviation (SD) and 95% confidence interval were reported for normally distributed, continuous variables. Categorical variables were reported as counts and

percentages. While for data not normally distributed, median with interquartile range (IQR) was used. Pearson correlation coefficients were used to assess the relation of inflammatory parameters and body temperatures. All statistical analysis was done on SPSS version 25.

## Results

The median age of 30 COVID-19 confirmed children was 5.29 years (IQR: 3.04-7.61), while that of 32 influenza A infected children was 7.09 years (4.08-11.05) (shown in Table 1). Overall, 63.33% of COVID-19 children were girls and the influenza A group showed the opposite portion with 59.38% of boys. Comparison on onset symptoms showed that instead of 100% exhibition of both fever and cough in influenza A infected children, only 43.33% ( $p < 0.001$ ) and 26.67% ( $p < 0.001$ ) patients represented fever and cough respectively in COVID-19 infected cases.

On admission day, lymphocyte count and serum lactate dehydrogenase (LDH) were elevated dramatically beyond the normal ranges in both two groups. On the other hand, compared with extremely higher levels of serum C-reactive protein (CRP), procalcitonin (PCT) as well as erythrocyte sedimentation rate (ESR) in influenza A infected children, those of COVID-19 patients were considered within the normal ranges. Particularly, COVID-19 children had significantly less severe neutrophilia with an average count of  $29.6 \times 10^9/L$  (95%CI:  $20.06-38.72 \times 10^9/L$ ), while that of influenza A patients was as high as  $58.07 \times 10^9/L$  ( $46.04-73.08 \times 10^9/L$ ).

Once they were admitted to hospital, total (100%) influenza A patients represented fever with the average body temperature of  $39.5^\circ C$  ( $39.3-39.7^\circ C$ ). While only 13 (43.3%) COVID-19 children exhibited with fever on the significantly lower ( $p < 0.001$ ) average body temperature of  $38.3^\circ C$  ( $37.8-38.8^\circ C$ ). After 3 days of hospital stay, there remained 23 influenza A patients with continuous fever on average of  $38.8^\circ C$  ( $38.5-39.1^\circ C$ ). In contrast, only 5 COVID-19 children's body temperature were hotter than  $37.5^\circ C$  (shown as Figure 1A & B). Simultaneously, with 3 days of hospital care, the influenza A infected children represented with significantly decreased WBC, neutrophil and lymphocyte counts (shown as Figure 1C-E). On the contrary, there is nearly no change on those of COVID-19 patients. Remarkably, both patients showed obviously elevated platelet levels (shown as Figure 1F). Besides, radiographical imaging indicated that typical pneumonia patterns of initial 23 (71.88%) influenza A patients predominately had obvious improvements in 3-5 days. In contrast, 9 (30%) COVID-19 children showed few changes in extent of the ground-glass opacities and another 2 children represented increased parenchymal density. Subsequently, all influenza A patients recovered after an average of 5.31 days (4.58-6.04) of hospitalization. 7 COVID-19 children were still in hospital with 15 to 21 days of current stays and the average length of hospital stay was 15.53 days (13.91-17.16).

Further Pearson correlation analysis indicated that there were substantially significant positive correlations between the degree of body temperature and these immunological parameters on admission day for COVID-19 patients (shown in Table 2, WBC:  $r = 0.414$ ,  $p = 0.028$ ; HB:  $r = -0.387$ ,  $p = 0.042$ ; CRP:  $r = 0.509$ ,

$p=0.011$ ; PCT:  $r=0.51$ ,  $p=0.013$ ). Dissimilarly, only admission PCT level was significantly correlated with the body temperature of influenza A children.

## Discussion

COVID-19 disease in adults was typically identified with severe interstitial pneumonia and subsequent acute respiratory distress syndrome by hyperactivation of the inflammatory cascade<sup>1,4</sup>. As for COVID-19 children patients, most of them were more likely to have mild symptoms<sup>5</sup> with different epidemiological characteristics<sup>6</sup>, clinical manifestations<sup>7</sup>, as well as transmission patterns<sup>8</sup> from adult patients, probably due to the weaker immune response<sup>9</sup>. We described the COVID-19 children with lower body temperature and significantly lower neutrophil count, as well as attenuated CRP and PCT levels in comparison with influenza A children. We further elucidated the significant correlations between initial body temperature and multiple immune functional parameters in COVID-19 children instead of influenza kids. These findings offer some clue to differing pathogenesis of COVID-19 for further study. In addition, corresponded with recent COVID-19 children cases of the development of high fever and cytokine storm in Kawasaki disease<sup>10</sup>, our results clarify the less activated immune status in asymptomatic COVID-19 children and suggested that non-susceptibility of children to SARS-CoV-2 virus may lie in the low activity of immune response. Further explorations will contribute to the management and development of therapeutics for COVID-19 patients.

Some limitations should be considered. First, influenza A data was collected from almost 5-month span, while that of COVID-19 cases were derived from recent two months affected by the outbreak of COVID-19 pandemic, which probably resulted in unavoidable bias. Second, in this retrospective study, COVID-19 confirmed cases were originated from several hospitals in Shenzhen, China, subsequently transferred to Shenzhen Third People's Hospital for quarantine and medical treatment. Whereas influenza A data came from an independent single center. Data collection of the similar cohort would be better to avoid statistical disequilibrium.

## Conclusion

By comprehensive comparison on clinical characteristics of COVID-19 children and influenza A infected children, our study revealed that COVID-19 children were more likely represented as asymptomatic and mild cases with subclinical manifestations and relatively slow progression. Furthermore, correlations between initial body temperature and immunological functional parameters suggested that non-susceptibility of children to SARS-CoV-2 virus may lie in the low sensitivity on immune activation.

## Abbreviations

novel coronavirus disease

COVID-19

white blood cell

WBC

hemoglobin

HB

albumin

ALB

alanine aminotransferase

ALT

aminotransferase

AST

lactate dehydrogenase

LDH

creatine kinase

CK

blood urea nitrogen

BUN

erythrocyte sedimentation rate

ESR

creatinine

Cr

procalcitonin

C-reactive protein

PCT

CRP

# Declarations

## Ethical approval:

This study was approved by Shenzhen Third People's Hospital Ethics Committee and informed consent in influenza cohort was obtained from parents or guardians. For COVID-19 patients, written informed consent was waived by the Ethics Commission. Any data we collected and analyzed was derived from clinical raw record without any intervention and influence on clinical treatment. And no additional collection of human sample or genetic resource materials was performed in our study.

**Consent for publication:** Not applicable

## Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Conflict of interest:

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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## Authors' contributions:

Shanglong Kou and Senlin Zhan contribute equally to this work. Jing Yuan and Yanchao Pan are co-corresponding authors. Shanglong Kou, Yanchao Pan conceptualized and designed the study, carried out the initial analyses, and drafted the initial manuscript. Senlin Zhan and Guofang Deng designed the data collection instruments, collected data and revised the manuscript. Xiaohe Li, Mingxia Zhang and Jing Yuan supervised data collection, and critically reviewed the manuscript for important intellectual content.

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## Tables

Table 1. Baseline characteristics of COVID-19 and influenza A infected children.

	COVID-19 Group, N=30		Influenza A Group, N=32		<i>p</i> value
Age (median, IQR)	5.29	(3.04-7.61)	7.09	(4.08-11.05)	0.155
Sex (Number, Percentage)					
Male	11	36.67%	19	59.38%	0.076
Female	19	63.33%	13	40.62%	
Onset of signs and symptoms (Number, Percentage)					
Fever	13	43.33%	32	100.00%	<b>&lt;0.001</b>
Dry cough	8	26.67%	32	100.00%	<b>&lt;0.001</b>
Pharyngalgia	2	6.67%	5	15.63%	0.268
Fatigue	2	6.67%	2	6.25%	0.948
Diarrhea	1	3.33%	0	0.00%	0.326
Interval of onset to admission (days), (median, IQR)	1	1-1.25	3	2-5.75	0.417
laboratory parameters once admission (mean±SD, 95%CI)					
WBC (10 <sup>9</sup> /L)	6.27±2.87	(5.05-7.86)	8.52±4.61	(4.69-10.83)	<b>0.029</b>
Neutrophil (10 <sup>9</sup> /L)	29.60±20.83)	(20.06-38.72)	58.07±17.69	(46.04-73.08)	<b>&lt;0.001</b>
Lymphocyte (10 <sup>9</sup> /L)	35.34±24.00	(22.65-43.72)	32.11±16.43	(17.71-43.77)	0.541
Platelet (10 <sup>9</sup> /L)	247.64±62.35	(219.00-275.27)	255.12±72.81	(195.06-309.54)	0.673
HB (g/L)	132.57±10.71	(128.97-139.13)	120.34±14.97	(110.41-133.39)	<b>0.001</b>
ALB (g/L)	45.19±2.69	(43.92-46.31)	43.39±3.34	(40.19-44.03)	0.280
ALT (U/L)	17.47±10.88	(13.61-23.90)	16.73±13.27	(5.01-34.60)	0.815
AST (U/L)	33.10±12.95	(26.47-38.48)	42.37±16.60	(22.52-49.56)	<b>0.020</b>
LDH (U/L)	322.50±193.43	(236.74-408.26)	369.70±165.79	(251.10-488.30)	0.285

CK (U/L)	70.36±40.92	(34.17-103.84)	132.19±88.06	(77.50-147.41)	<b>0.035</b>
BUN (mmol/L)	4.55±2.27	2.87-8.29	3.19±0.92	2.85-3.70	<b>0.006</b>
ESR (mm/h)	11.11±6.61	(6.57-14.60)	21.65±12.80	(14.54-29.21)	<b>0.003</b>
Cr (umol/L)	36.70±15.66	(25.22-42.38)	36.42±13.82	(28.66-37.27)	0.942
PCT (ng/ml)	0.07±0.08	(0.02-0.10)	0.32±0.36	(0.15-0.38)	<b>0.001</b>
CRP (mg/L)	5.34±10.34	(0.98-9.71)	17.22±17.61	(10.87-23.57)	<b>0.003</b>
Oxygenation Index	448.52±239.08	(345.13-551.91)	441.63±55.55	(395.19-488.07)	0.899
Length of hospital stay (day), (mean±SD; (95%CI))	15.53±4.35	(13.91-17.16)	5.31±2.02	(4.58-6.04)	<b>&lt;0.001</b>
Hospital cost (RMB), (mean±SD; (95%CI))	12015.87±4449.26	(10179.31-13852.43)	4168.61±1524.21	(3619.07-4718.15)	<b>&lt;0.001</b>

Data of continuous variables are given as mean±SD with 95% CI. While for data not normally distributed, median with interquartile range (IQR) is used. Categorical variables are given as counts and percentages. Abbreviations: WBC, white blood cell; HB, hemoglobin; ALB, Albumin; ALT, alanine aminotransferase; AST, aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; Cr, creatinine; PCT, procalcitonin; CRP, C-reactive protein. P values in bold are considered to be significant.

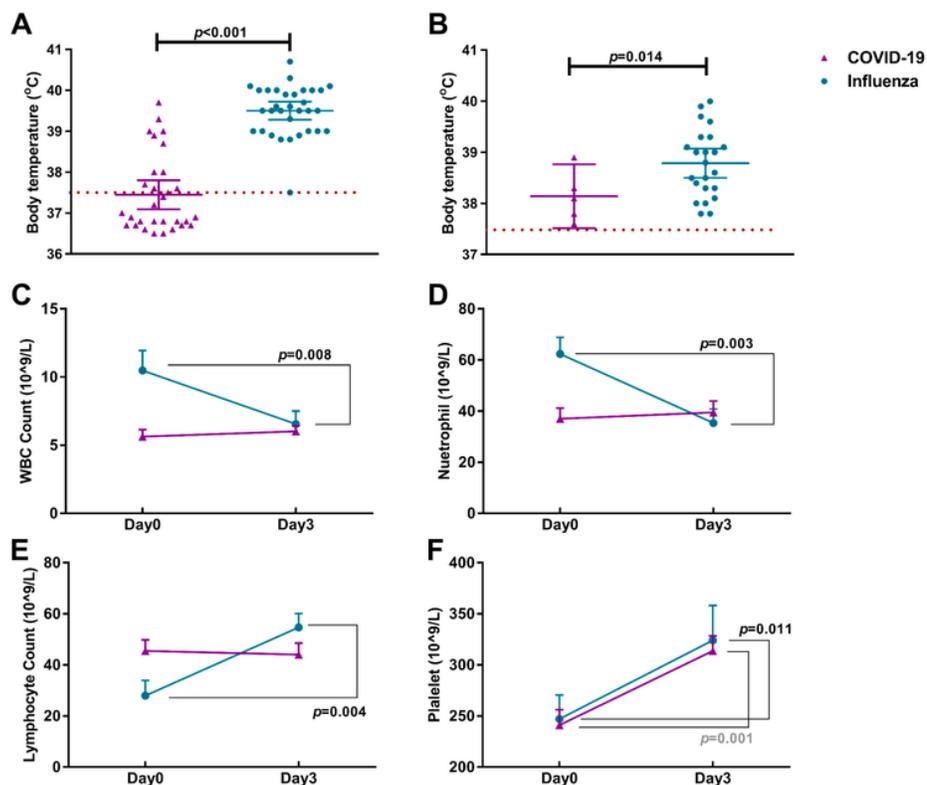
Table 2. Correlation analysis between body temperature and hematological parameters.

	WBC		HB		CRP		PCT	
	coefficient	P-value	coefficient	P-value	coefficient	P-value	coefficient	P-value
COVID-19 group	0.414	<b>0.028</b>	-0.387	<b>0.042</b>	0.509	<b>0.011</b>	0.51	<b>0.013</b>
Influenza A group	-0.081	0.658	-0.161	0.379	0.105	0.568	0.477	<b>0.01</b>

Pearson's correlation coefficients between body temperature on admission day and immune function

parameters. P values in bold are considered to be significant. Abbreviations: WBC, white blood cell; HB, hemoglobin; CRP, C-reactive protein; PCT, procalcitonin.

## Figures



**Figure 1**

Changes of body temperature and laboratory parameters in the peri-hospitalization period. Box plot with the mean line and 95% CI of the body temperature observations showing comparisons between COVID-19 and influenza A infected children before hospital admission (A) and after 3-day of hospital stay (B). Only 5 children's body temperature exceeded 37.5°C while 23 patients remained continuous fever after 3 days of hospital stay. Comparisons on counts of white blood cell (WBC) (C), neutrophil (D), lymphocyte (E), as well as platelet (F) showed significant increase in influenza A infected children represented with blue triangles. While those of COVID-19 children were represented with purple dot. Error bars: Mean ± SEM.