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A comparative-descriptive analysis of clinical characteristics in 2019-Coronavirus-infected children and adults

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Running title: Differences in 2019-Coronavirus-infected children and adults

Abstract

Acute respiratory disease (ARD) caused by 2019 novel coronavirus (2019-nCoV) has rapidly spread throughout China. Children and adults show a different clinical course. The purpose of the current study is to comparatively analyze the clinical characteristics of 2019-nCoV infection in children and adults and to explore the possible causes for the discrepancies present. The medical records of 25 adults and 7 children confirmed cases of 2019-nCoV ARD were reviewed retrospectively. All children were family clusters. The total adult patients were differentiated into: the local residents of Wuhan, a history of travel to Wuhan and direct contact with people from Wuhan. The numbers were 14 (56%), 10 (40%) & 1 (4%), respectively. The median incubation period of children and adults was 5 days (range 3-12 days) and 4 days (range 2-12 days), respectively. Diarrhoea and/or vomiting (57.1%) were more common in children, whereas for adults it was myalgia or fatigue (52%). On admission, the percentage of children having pneumonia (5, 71.4%) was roughly the same as adults (20, 80%). 20% of adults had leucopenia, but leukocytosis was more frequently in children (28.6%,

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P=0.014). A higher number of children had elevated creatine kinase isoenzyme (57.1% vs. 4%, P=0.004). Antiviral therapy was given to all adult patients but to none of the children. In summary, knowledge of these differences between children and adults will not only be helpful for the clinical diagnosis of 2019 novel coronavirus disease (COVID-19), but also for a future discussion on age-specific coronavirus infection.

Key words: 2019 novel coronavirus; clinical manifestations; laboratory parameters; comparative analysis; differences between children and adults

Introduction

In December 2019, pneumonia associated with the 2019 novel coronavirus (2019-nCoV) emerged in Wuhan, China, and has spread rapidly around the world ^{1,2}.

Previous studies indicated that at the whole-genome level, the 2019-nCoV is 96% identical to a bat coronavirus, which resembled Severe Acute Respiratory

Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) Coronavirus

^{3,4}. People of all ages are susceptible to 2019-nCoV infection, which is declared as

a pandemic by World Health Organization (WHO) ⁵. As of 28th February 2020, a

total of 79,251 cases have been reported in China, which includes more than 400

children ^{6,7,8}. Among the confirmed children, the reported minimum age is 30

hours and the maximum age is 17 years old. It includes critical cases with early

neonatal infection⁹. Even though the pediatric patients account for a lower proportion (0.35%, below 10 years old)¹⁰, we should give importance to early diagnosis and treatment.

To our knowledge, many studies have been conducted to describe the clinical manifestations in children and adults. Nevertheless, no study is available that compares the clinical features of children with confirmed 2019-nCoV infection to those of infected adults. In this regard, the purpose of our retrospective study is to analyze the clinical manifestations of confirmed n-CoV infection in children and adults. Furthermore, we compared all the parameters between these two groups, which will assist the practitioners to explore the possible causes of the discrepant aspects and lead to an accurate diagnosis and efficient treatment.

Methods

Patients

We retrospectively reviewed records of 32 cases confirmed with 2019-nCoV ARD, who were managed at Xian eighth hospital (Shaanxi, China) from 31st January to 16th February 2020. Cases were confirmed by clinical and epidemiological evidence, and approximately 93.8% (30/32) of them were also laboratory-confirmed. Diagnosis and the severity of 2019-nCoV ARD was defined according to National Recommendations for Diagnosis and Treatment of

pneumonia caused by 2019-nCoV (5th edition)¹¹. Patients <18 years were grouped as children/pediatric patients, while those ≥ 18 years as adults. Written informed consent was obtained from all participants enrolled in the study, including children under 18 years-old, whose consent was provided by their parents or guardians.

Data collection

Clinical data including epidemiological, demographical, clinical symptoms, laboratory measurements, imaging findings, management and outcome were recorded. Incubation period is the duration from the exposure of the pathogen to the onset of symptoms. All patients underwent imaging examination on admission. Discharge criteria includes body temperature returning to normal for a minimum of 3 days, significant improvement in respiratory symptoms and completion of 2 consecutive negative tests of respiratory pathogenic nucleic acid (sampling interval of at least 1 day)¹².

Throat swab specimens from the upper respiratory tract were collected from all patients at admission and stored in a viral transport medium. The presence of 2019-nCoV virus nucleic acid was detected using rRT-PCR through the Shaanxi Center for Disease Control and Prevention (CDC).

Statistical analysis

All statistical data were processed using IBM SPSS 19.0 statistical software. Continuous variables were expressed as the means and standard deviations or medians and range (min to max) as appropriate. T-test or Wilcoxon rank-sum tests were applied to continuous variables, while chi-square tests or Fisher's exact tests were used to compare categorical variable as appropriate. $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 32 cases with 2019-nCoV infection were reported in this study, including 7 children and 25 adults. The children group (below 18 years old) comprised 3 girls and 4 boys, with the mean age of 1.3 years (range 2 months to 13 years). The adult group included 12 men and 13 women, with the mean age of 44 years (range 22 to 70 years).

As shown in Table 1, there was no significant difference in gender distribution between the two groups. All children were family clusters or had a clear history of close contact with 2019-nCoV-confirmed patients. In adult patients, 14 (56%) patients were local residents of Wuhan, 10 (40%) patients recently travelled to Wuhan, and only 1 (4%) patient had a close contact with individuals from Wuhan.

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None of the patients had a history of contact with wildlife. The median incubation period of children and adult was 5 days (range 3-12 days) and 4 days (range 2-12 days), respectively; which indicated no statistical significance ($P=0.408$).

Altogether 10 adult patients had an underlying comorbidity; especially diabetes (9, 36%) & hypertension (7, 28%), which was absent in pediatric population.

Clinical Manifestation

The main symptoms found in our study group were fever (≥ 37.3 °C) and cough, followed by shortness of breath and myalgia or fatigue. Diarrhoea, vomiting and pharyngalgia were also recorded (Table1). Furthermore, it is worth mentioning that children suffered more frequently from diarrhoea and/or vomiting with a statistically significant difference (57.1% vs. 8%, $p=0.012$), whereas in adults myalgia or fatigue were observed more frequently with no significant difference (52% vs 0, $P=0.25$). There was no difference in upper limit of body temperature between the two groups ($38.24\pm 1.10^{\circ}\text{C}$ vs 38.18 ± 0.62 , $P=0.958$). The median duration of fever was 1 day (range 0-3days) in the pediatric group, and 4 days (range 1-10 days) in the adult group ($P = 0.011$).

Radiological and laboratory findings

71.4% of children and 80% of adults showed positive findings suggestive of pneumonia, on chest X-ray and computed tomography (Table 2). The two groups

shared a multitude of common imaging findings including ground-glass opacity and segmental consolidation in bilateral lung fields, especially in the peripheral zones. Figure1 demonstrates the radiological findings in pediatric and adult patients with 2019-nCoV ARD. It showed no prominent differences in severity of radiologic abnormalities. However, 28.6% of the affected children and 20% of adult cases did not have any significant radiological findings ($p=0.632$).

Diagnostic confirmation in such cases was done on the basis of clinical findings and positive RT-PCR results.

The analysis of laboratory parameters revealed leucopenia (leucocyte count $<3500/ml$) as a common finding among adults (20%) while leukocytosis being more frequent in children (28.6%) ($p=0.014$) (Table2). Laboratory reports showed thrombocytopenia in 8% (2 adults) of the adult patients and thrombocytosis in another 8% adults. In children, the corresponding values were 0 and 14.3% respectively. Hypoalbuminemia was observed in 18 patients and different degrees of renal function damage was revealed in 20 cases, all of whom were from the adult group, ($p=0.001$ and 0.025 , respectively). Moreover, 4 children and 6 adult patients had differing degrees of liver function abnormality, with increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST). Most of the children had elevated creatine kinase isoenzyme compared to adults ($P=0.004$). All other myocardial damage indexes such as lactate dehydrogenase, myoglobin

and brain natriuretic peptide (BNP) showed no distinct difference in two groups. More adults suffered from coagulation disorder (child/adult: 71.4% vs 88%, $P=0.296$), especially increased activated partial thromboplastin time (APTT, $p=0.003$) and fibrinogen ($P=0.049$). Regarding the infection-related biomarkers, erythrocyte sedimentation rate (ESR, child/adult: 42.9% vs 84%, $P=0.047$) and procalcitonin (PCT, child/adult: 42.9% vs 0, $P=0.007$) were elevated prominently in adult and children, respectively.

All patients were tested for common respiratory pathogens, including the nucleic acid of influenza viruses A and B, but all of them were negative.

Clinical classification, treatment and outcome

All children were diagnosed with mild infection, without any severe symptoms or complication. They recovered within 1 to 2 weeks with prompt symptomatic treatment. Two children developed shortness of breath and received oxygen therapy; an infant had bilateral pneumonia for which low-dose glucocorticoids were injected intravenously in order to prevent the progression. In adult group, four patients suffered from severe pneumonia; while in others mild severity was noticed. Similarly, 12 of the adult patients required oxygen inhalation. Antiviral therapy was given to all adult patients but to none of the children. In the adult group, empirical antibiotic treatment was initiated in 8 cases at the same time. No

death was reported in either group, and the rate of discharge from the hospital was 100%.

Discussion

Since the beginning of 2019-nCoV pandemic, the infection rate of children is relatively lower. The previous published data reports the age group of 30-69 years old accounting for 77.8% of the entire case load; our study further confirms the fact that n-CoV affects primarily the adults⁸. Similar characteristics have been reported in the infection of SARS-CoV and MERS-CoV. A previous study concludes that lower risk of exposure, incomplete diagnosis, presence of mild symptoms or asymptomatic disease in the unaffected age group, may be a reason for one particular age group appearing to be more susceptible. The presence of resistance to infection by the unaffected age group is out of question¹³. Our study shows that the presentation of symptoms in all of the seven children started after a confirmed diagnosis in family member, whereas in adults the routes of infection were diverse. Another reason for children appearing to be protected is the presence of comorbidities like diabetes, hypertension, coronary artery disease etc., in more than 50% of the adults affected with n-CoV, which makes adult population more susceptible to the n-Coronavirus infection^{14,15}.

Consistent with recent publications^{1,10,13-17}, fever and cough were the dominant symptoms in both children and adults. It was noted that adult patients rarely developed intestinal signs and symptoms (e.g. diarrhea and/or vomiting), whereas about 57.1% of children patients had diarrhea. Another study, at prestigious Wuhan hospital, focusing on the gastrointestinal symptoms of n-CoV pneumonia, demonstrated that 49.5% of patients had diarrhea¹⁸. A longer observation period in following hospitalization may increase the ratio of gastrointestinal symptoms and demonstrate a different result, whereas in our study those were observed at an early time point. Zhou et al found that 2019 n-CoV uses the same cell entry receptor, Angiotensin convertase enzyme (ACE2), as SARS-CoV³. ACE2 is not only expressed in respiratory organs, but also in the digestive system¹⁹. Some scholars speculate that 2019-nCoV may interact with ACE2 receptor in gastrointestinal tract, impair the intestinal mucous membrane barrier and increase the inflammatory cytokines production²⁰. Therefore, whether a higher rate of gastrointestinal symptoms in children group is related to higher expression of ACE2 in gastrointestinal tract or different functions of ACE2 remains to be confirmed by further research. Similarly, duration of fever in adult was longer than children. This was due, at least in part, to differences in immune responses, especially specific immune response. Adults seemed more susceptible to a harmful immune response.

In laboratory tests, we found that children had different laboratory parameters than adults. It was observed that White blood count (WBC) was frequently elevated among children contrary to adults, majority of which showed leucopenia. The recent report on the absolute value of lymphocytes showed either normal or reduced numbers in majority of the adults^{14,16}. It may be due to dissimilar immune response of different individuals to n-CoV. We also observed that abnormal coagulation function, hypoalbuminemia and hypouricemia were more common in adult patients which might be associated with presence of underlying disease in the adults. Myocardial zymography revealed, elevated levels of Creatine kinase (CK) isoenzyme, higher in children than in adults. This may be explained by intense chills associated with high fever or by the higher incidence of myocardial damage in children.

As 2019-nCoV is an emerging virus, there are currently no effective vaccines or anti-viral drugs. Experts consensus (the fourth edition) listed IFN- α nebulization as a treatment of choice for 2019-nCoV pneumonia²¹. The combination of Lopinavir and Ritonavir is another recommended antiviral regimen¹¹. Lopinavir and Ritonavir are Anti-HIV (human immunodeficiency virus) protease inhibitor, which are also used to treat HIV-1 in adults and children above 14 days of age²². That fewer adverse clinical outcomes were reported among SARS-CoV patients revealed that lopinavir/ritonavir benefited the patients in clinical practice

substantially²³. None of the 32 patients required intensive care or mechanical ventilation or had any severe complications. Because of the limited number of subjects in this study, it is difficult to compare the clinical outcomes related to treatment between the two groups. More effort should be made to elaborate on this issue in future research.

The limitation of this research is its small sample size. In addition, the sampling site to detect viral nucleic acid sequences was limited, which could lead to false positive or false negative into the study. Research recommends strict medical quarantine and observation for all patients with suspected disease until the results of nucleic acid amplification tests from throat swabs, sputum, and even lung lavage are obtained^{24,25}. In our study, diagnosis relies on the integration of epidemiology, clinical manifestations, laboratory and radiographic examinations, and viral nucleic acid detection, as such, we believe that the physician reported diagnosis is credible. Finally, the 2019-nCoV evaluation was qualitative so that quantitative virus titer was not obtained to provide more information to compared the difference between the children and adults in details.

In conclusion, our multi-dimensional study demonstrates that children with 2019-nCoV infection present a clinical picture which is often distinct from that of adults. Knowledge of these differences will be helpful for the clinical diagnosis of

2019 novel coronavirus disease (COVID-19) and for a future discussion on age-specific coronavirus infection.

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Conflict of interest

The authors declare that they have no conflict of interest

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Authors' contributions

WY and FY designed this study; they conducted the study in a reputed hospital after required permission and collected the relevant clinical information along with XYM and RXX. HYN and FZW drafted the initial manuscript, which was later submitted after subsequent revisions and approval by all the authors.

Statistical analysis of the data was done by SLN and WH.

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Availability of data and materials

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

Ethics approval and consent to participate

The study was reviewed and approved by the ethics committee of The Affiliated Children's Hospital of Xi'an Jiaotong University (No. 20200003). Written informed consents were obtained from all the participants enrolled in the study. An assent was taken from children under 18 years of age while informed consent was provided by their parents or guardians.

Consent for publication

Not applicable.

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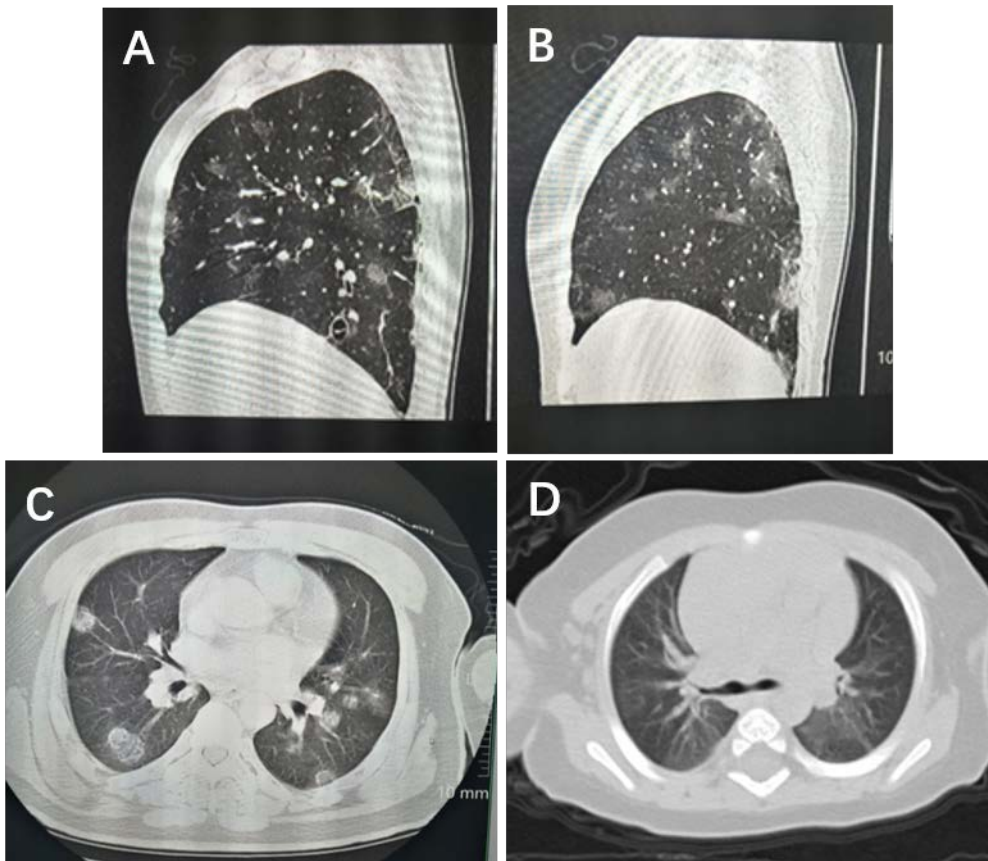
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Figure

Figure1 Representative images of the thoracic X-ray and CT scans showing multifocal patchy ground-glass opacities in the lung.(A-C) from a 64 years old female, who was diagnosed with severe pneumonia with the main symptoms of fever, cough and shortness of breath. (D)shows mild pneumoniaof a 1 year and 4 months old girl, who had fever,cough and diarrhoea on admission and was diagnosed as mild type.



Table**Table 1: Baseline characteristics and clinical manifestation of patients
infected with 2019-nCoV**

	Children (n=7)	Adults(n=25)	p value
Characteristics			
Age, years	1.3(0.2-13)	44(22-70)	
Sex(n,%)			
Men	4(57.1%)	12(48%)	
Female	3(42.9%)	13(52%)	
Exposure history (n,%)			
Local residents of Wuhan	0	14(56%)	
Recently been to Wuhan	0	10(40%)	
Contacted with people from Wuhan	7(100%)	1(4%)	
Incubation period(days)	5(3-12)	4(2-12)	0.408
Comorbidity(n,%)			
Diabetes	0	9(36%)	

Hypertension	0	7(28%)	
other	0	0	
Symptoms			
Fever(n,%)	5(71.4%)	24(96%)	0.113
Cough(n,%)	5(71.4%)	19(76%)	1
Myalgia or fatigue(n,%)	0	13(52%)	0.25
Diarrhea and/or Vomiting(n,%)	4(57.1%)	2(8%)	0.012
Shortness of breath(n,%)	3(42.9%)	10(40%)	1
Pharyngalgia(n,%)	1(14.3%)	6(24%)	1
Highest body temperature (°C)	38.24±1.10	38.18±0.62	0.958
Duration of fever(days)	1(0-3)	4(1-10)	0.011

Data are presented as medians (ranges,Min to Mix) or Mean \pm SD and n/N (%).

p values comparing the children(<18 years) and the adults(\geq 18 years) group from χ^2 test, Fisher's exact test, T test.

Table 2: Radiographic and laboratory findings of patients infected with 2019-nCoV on admission to hospital

	Children (n=7)	Adults (n=25)	p value	Normal Range
Chest x-ray and CT findings				
No signs of pneumonia	2(28.6%)	5(20%)	0.632	
pneumonia	5(71.4%)	20(80%)		
Blood routine				
Leucocytes ($\times 10^9$ per L)				
Increased	2(28.6%)	0	0.014	Child/Adult:3.5-9.5
Decreased	0	5(20%)		
Neutrophils ($\times 10^9$ per L)				
Increased	1(14.3%)	2(8%)	0.536	Child:2-7 Adult:1.8-6.3
Lymphocytes ($\times 10^9$ per L)				
Decreased	0	9(36%)	0.149	Child:0.8-4 Adult:1.1-3.2
Platelets ($\times 10^9$ per L)				

	Children (n=7)	Adults (n=25)	p value	Normal Range
Increased	1(14.3%)	2(8%)	0.673	Child:100-350 Adult:125-350
Decreased	0	2(8%)		
Blood biochemistry				
Albumin (g/L)				
Decreased	0	18(72%)	0.001	Child:37-51 Adult:40-55
Alanine aminotransferase (U/L)				
Increased	1(14.3%)	4(16%)	1	Child:0-37 Adult:9-50
Aspartate aminotransferase(U/L)				
Increased	3(42.9%)	5(20%)	0.327	Child:10-50 Adult:15-40
Total bilirubin (µmol/L)				
Increased	1(14.3%)	7(28%)	0.646	Child:17.1-34.2 Adult:3.4-17.1
Blood urea nitrogen (mmol/L)				
Increased	0	0	0.025	Child:1.8-6

	Children (n=7)	Adults (n=25)	p value	Normal Range
Decreased	0	13(52%)		Adult:3.6-9.5
Serum creatinine (μmol/L)				
Increased	0	0	0.066	Child:18-52
Decreased	0	11(44%)		Adult:57-111
Creatine kinase isoenzyme (U/L)				
Increased	4(57.1%)	1(4%)	0.004	Child:0-30 Adult:0-24
Lactate dehydrogenase (U/L)				
Increased	2(28.6%)	1(4%)	0.113	Child:155-395 Adult:120-250
Myoglobin (ng/mL)				
Increased	2(28.6%)	1(4%)	0.113	Child:10-45 Adult:0-146.9
Brain natriuretic peptide(pg/ml)				
Increased	5(71.4%)	10(40%)	0.209	Child/Adult:0-125
Coagulation function				

	Children (n=7)	Adults (n=25)	p value	Normal Range
Activated partial thromboplastin time (s)				
Increased	3(42.9%)	0	0.003	Child:24-38 Adult:28-43.5
Decreased	3(42.9%)	18(72%)		
Fibrinogen (s)				
Increased	0	8(32%)	0.049	Child/Adult:2.0-4.0
Decreased	1(14.3%)	0		
D-dimer (µg/L)				
Increased	2(28.6%)	7(28%)	1	Child/Adult: 0-1.0
Infection-related biomarkers				
Erythrocyte sedimentation rate (mm/h)				
Increased	3(42.9%)	21(84%)	0.047	Child/Adult: 0-15.0
C-reactive protein (mg/L)				
Increased	2(28.6%)	11(44%)	0.671	Child/Adult: 0-10.0
Procalcitonin (ng/L)				

	Children (n=7)	Adults (n=25)	p value	Normal Range
Increased	3(42.9%)	0	0.007	Child/Adult: 0-0.5

P values denoted the comparison between children cases and adult cases.

Table 3. Clinical classifications, treatment and outcomes of patients with 2019-nCoV ARD

	Children(n=7)	Adults(n=25)
Clinical classifications		
Mild type*	7(100%)	21(84%)
Severe pneumonia	0	4(16%)
Critical cases	0	0
Treatment		
Oxygen therapy	2(28.6%)	12(48%)
Antibiotic treatment	0	8(32%)
Antiviral treatment	0	25(100%)
Glucocorticoids	1(14.3%)	0

Clinical outcome

Discharge from hospital	7(100%)	25(100%)
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*This type of patient includes those with asymptomatic infection, upper respiratory infection (URI) and mild pneumonia.