Comparative Analysis of Clinical Characteristics in Children and Adults with 2019 Novel Coronavirus Infection: A Descriptive Study

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Abstract

Background: Since December 2019, acute respiratory disease (ARD) caused by 2019 novel coronavirus (2019-nCoV) rapidly spread throughout China. Children and adults seemed to differ in the clinical course of the disease. The purpose of the current study is to comparatively analyze the clinical characteristics of children and adult patients with 2019-nCoV infection and to explore the possible causes for the discrepant aspects.

Methods: In this retrospective study, the medical records of 32 cases confirmed with 2019-nCoV ARD from Xi'an eighth hospital (Shaanxi, China) from January 31 to February 16, 2020 were reviewed.

Results: In all 32 patients contained 7 children and 25 adults. All children were family cluster. For adult patients, local residents of Wuhan, recently travelled to Wuhan, patient contacted with people from Wuhan were 14 (56%), 10 (40%), 1 (4%), respectively. The median incubation period of children and adult was 5 days (range, 3 to 12) and 4 days (range, 2 to 12), respectively. Altogether 10 (40%) adult patients had underlying conditions significantly, but no children had. Fever (Children 71.4% vs. Adult 96%) and cough (Children 71.4% vs. Adult 76%) were the most common symptoms in both groups. The third symptom observed in children was diarrhea and/or vomiting (57.1%), for adult it was myalgia or fatigue (52%). On admission, 5 (71.4%) children patients showed pneumonia roughly the same as adult patients (20, 80%), and that the two group shared a multitude of common imaging characteristics. 20% of adult with leucopenia, but leukocytosis was significantly more frequently in children (28.6%, $P=0.014$). More children had elevated creatine kinase isoenzyme (57.1% vs. 4%, $P=0.004$). All patients were discharged after symptomatic treatment, including oxygen therapy, antiviral treatment, antibiotic treatment. Only one infant was intravenously injected low-dose glucocorticoids.

Conclusions: Our results multi-dimensionally demonstrate 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 diseases (COVID-19) and for a future discussion on age specific infection case definitions.

Background

In December 2019, a 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 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus, which resembled severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus ^[3-4]. People of all ages are susceptible to 2019-nCoV infection, which was declared as a public health emergency of international concern by World Health Organization (WHO) ^[5]. As of February 28, 2020, a total of 79,251 cases had been reported in China, with more than 400 children ^[6-8]. Among the confirmed children patients, the reported minimum age was 30h and the maximum age was 17 years old, including critical cases and early neonatal infection ^[9]. Even though the pediatric patients account for a lower proportion

(0.35%, below 10 years old) ^[10], we should attach importance to diagnosis and treatment in children and further researches are still required.

To our knowledge, many studies were conducted to describe the clinical manifestations either of children or of 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 was to analyze the clinical manifestations (patient's characteristic, symptoms, medical laboratory parameters, treatment response, etc.) of children and adults with confirmed 2019-nCoV infection. Furthermore, we compared all these parameters between the two groups in order to enable practitioners to explore the possible causes for the discrepant aspects and make a more accurate clinical decision of 2019-nCoV infection in these two different age groups.

Methods

We retrospectively reviewed records of 32 cases confirmed with 2019-nCoV ARD who were managed at Xi'an eighth hospital (Shaanxi, China) from January 31 to February 16, 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 (the 5th edition) ^[11]. Patients <18 years were divided as children patients, while those ≥ 18 years were divided 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.

Clinical data including epidemiological, demographic, clinical symptoms, laboratory measurements, imaging findings, management, and outcome were recorded. A definition of incubation period was the duration from the contact of the transmission source to the onset of symptoms. All patients underwent imaging examination on admission. Discharge criteria: with body temperature back to normal for at least 3 days, significant improvement in respiratory symptoms, and completion of two 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 viral transport medium. The presence of 2019-nCoV virus nucleic acid was detected using rRT-PCR through the Shaanxi CDC.

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 2019nCoV 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 cluster or with a clear history of close contact with 2019-nCoV-confirmed patients. For adult patients, 14 (56%) patients were local residents of Wuhan, 10 (40%) patients recently travelled to Wuhan, and only 1 (4%) patient contacted with people from Wuhan. None of the patients had a history of contact with wildlife. The median incubation period of children and adult was 5 days (range, 3 to 12) and 4 days (range, 2 to 12), respectively, which indicated no statistical significance ($P=0.408$). Altogether 10 (40%) adult patients had underlying conditions with one or more comorbidities significantly, especially in the group of diabetes (9, 36%) and hypertension (7, 28%), while no children patient had any underlying disorder.

Clinical Manifestation

The main symptoms found in our study group were fever ($\geq 37.3^{\circ}\text{C}$) and cough, followed by shortness of breath and myalgia or fatigue, diarrhea, vomiting and cyanosis was also recorded (Table 1). Furthermore, it is worth mentioning that children suffered more frequently from diarrhea 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 highest 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 to 3 days) in the children group, and 4 days (range, 1 to 10 days) in the adult group ($P = 0.011$).

Radiologic and laboratory findings

According to chest x-ray and computed tomography, 5 (71.4%) children patients showed pneumonia roughly the same as adult patients (20, 80%) (Table 2). The two group shared a multitude of common imaging characteristics, including ground-glass opacity and segmental consolidation in bilateral lungs, especially in the lung periphery. Figure demonstrates the representative radiologic pictures of children and adult patients with 2019-nCoV ARD, which showed no prominent differences in severity of radiologic abnormalities. In addition, 2 out of 7 (28.6%) in children cases compared with 5 out of 25 adult cases (20%) who had no abnormal radiological findings, but were confirmed by symptoms plus RT-PCR positive findings ($P=0.632$).

The analyses of the clinical laboratory parameters (Table 2) revealed that more adults (20%) with leucopenia (leucocytes count $<3500/\text{ml}$), but leukocytosis ($>9,500$ leucocytes/ ml) was more frequently in children (28.6%, $P=0.014$). Platelets were below the normal range in 2 (8%) patients and also above the

normal range in 2 (8%) patients in adult while in children group the corresponding values were 0 and 1 case (14.3%), respectively. Albumin decreased 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 with 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 in activated partial thromboplastin time (APTT, $p=0.003$) and fibrinogen ($P=0.049$). Regarding the infection-related biomarkers (child 42.9% vs adult 84%, $P=0.047$), erythrocyte sedimentation rate (ESR, child 42.9% vs adult 0, $P=0.007$) and procalcitonin were elevated prominently in adult and children, respectively. All patients were tested for common respiratory pathogens, also the nucleic acid of influenza viruses A and B, but all of them were negative.

Clinical classifications, treatment and clinical outcome

All children patients were diagnosed with mild type without severe and critical case. Therefore, they had good prognosis by symptomatic treatment and recovered within 1–2 weeks after disease onset. Only two children received oxygen therapy because of shortness of breath and one infant who had bilateral pneumonia was intravenously injected low-dose glucocorticoids at the initiation of treatment to prevent the development and progression of disease. In adult group, 4 patients suffered from severe pneumonia; the others were mild type. Similarly, 12 of adult patients adopted oxygen therapy. Moreover, 100% adult patient were administered with antiviral treatment but none in the children group. Among the adult group, empirical antibiotic treatment was prescribed in 8 cases at the same time. 2019nCoV infection associated radiographically confirmed pneumonia (Table2) as one of the most common complications occurred in only 5 out of 7 children versus 20 out of 25 adult patients. No death was reported in either group, and the rate of discharge was 100%.

Discussion

Since the beginning of 2019nCoV pandemic, the infection rate of children is relatively lower, and it seems that this virus affects primarily adult people, which is in accordance to these previous published data as the 30-69 age group accounted for 77.8% of all patients^[8]. Similar characteristics have been reported in the infection of SARSCoV and MERSCoV. One previous study considers that it may be due to a lower risk of exposure or incomplete identification due to mild or asymptomatic disease, rather than resistance to infection^[13]. In our study, all 7 children's symptom onset occurred after at least 1 confirmed family member infection, while adult had a more diverse set of infected routes. Additionally, approximate half of adult patients infected by 2019nCoV had chronic underlying diseases, mainly cardiovascular and diabetes, resembling that in a previous study^[14-15]. This is another reason for which child seemed to be more protected.

Consistent with recent publications^[1,10,13-16], fever and cough were the dominant symptoms in both children and adults. It is 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 in our study. Another single-center, descriptive study, which focused on the gastrointestinal symptoms caused by 2019-nCoV infection, demonstrated that manifestation of digestive system of hospitalized novel coronavirus pneumonia (NCP) patients in Wuhan was significant, and the ratio of patients with diarrhea was up to 49.5%^[17]. 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 (on admission). Additionally, Zhou et al found that this novel CoV uses the same cell entry receptor, ACE2, as SARS-CoV^[18]. ACE2 is not only expressed in respiratory organs, but also in the digestive system^[19]. Some scholars speculated that 2019-nCoV may interact with ACE2 receptor in gastrointestinal tract, then further impaired the intestinal mucous membrane barrier and increase the inflammatory cytokines production^[20]. Therefore, 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 terms of laboratory tests, we found that children had a different spectrum of pathological routine laboratory parameters than adults. Lymphocyte count is commonly examined as a component of a complete blood cell count with differential. The significantly more frequently observed elevated white blood cell (WBC) count in children are inconsistent with the observation that more adults had decreased WBC count. Math with recent reports^[14,16], the absolute value of lymphocytes in most patients was normal or reduced, especially in adult group. The differences may be related to the different immune response to 2019-nCoV infection. Moreover, we observed that abnormal coagulation function, reduction in the level of albumin and the content of blood urea nitrogen (BUN) were more common in adult patients than that in children group, which might be associated with presence of underlying disease in adults.

As far as the elevation of myocardial zymogram is concerned, more children had elevated Creatine kinase (CK) isoenzyme levels when compared to adults which may be explained either by the intensive chills associated with higher fever or by the presence of myocardial damage. This finding possibly indicates that myocardial damage may be a quite frequent but 2019-nCoV associated complication in children.

As 2019-nCoV is an emerging virus, there are currently no effective vaccines or anti-viral drugs. Experts' consensus (the fourth edition) statement listed IFN- α nebulization as a choice of treatment for 2019-nCoV pneumonia^[21]. The combination of lopinavir and ritonavir is currently another recommended antiviral regimen^[11]. Lopinavir/ritonavir is a human immunodeficiency virus (HIV) medicine which was used in combination with other medicines to treat adults and children over 14 days of age infected with HIV-1^[22]. That fewer adverse clinical outcomes was reported among SARS-CoV patients revealed that lopinavir/ritonavir benefited the patients in clinical practice substantially^[23]. 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 some treatment between the two group. More effort should be made to elaborate on this issue in future research.

Obviously, small sample size is a limitation in this research, as described above, which also may cause some interference to the results of the study. Moreover, the sampling site to detect viral nucleic acid sequences was limited, which could lead to false positive or false negative into the study. 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.

Conclusions

In conclusion, our study multi-dimensionally 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 diseases (COVID-19) and for a future discussion on age specific infection case definitions.

Abbreviations

COVID-19: 2019 novel coronavirus diseases; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; WHO: World Health Organization; CT: Computed tomography; rRT-PCR: real-time reverse-transcriptase polymerase chain reaction; CDC: Center of Disease Control and Prevention; WBC: White blood cell; CK: Creatine kinase; BUN: Blood urea nitrogen; ARD: Acute respiratory disease; NCP: Novel coronavirus pneumonia; URI: Upper respiratory infection

Declarations

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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.

Authors' contributions

WY and FY designed this study; WY and FZW was assigned to a designated hospital for support, and provided clinical information, and critically reviewed the manuscript; HYN and FZW drafted the initial manuscript, and led in manuscript revision and submission; SLN and WH statistically analyzed the data. XYM and RXX collected clinical data, provided important interpretations of the data; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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 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.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Tables

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

	Children≤18 years (n=7)	Adults≥18 years (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,%)	0	10(40%)	
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±SD and n/N (%).

p values comparing the children and the adult 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≤18 years (n=7)	Adults≥18 years (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 (× 10 ⁹ per L)			0.014	Child/Adult:3.5-9.5
Increased	2(28.6%)	0		
Decreased	0	5(20%)		
Neutrophils (× 10 ⁹ per L)			0.536	Child:2-7 Adult:1.8-6.3
Increased	1(14.3%)	2(8%)		
Lymphocytes (× 10 ⁹ per L)			0.149	Child:0.8-4 Adult:1.1-3.2
Decreased	0	9(36%)		
Platelets (× 10 ⁹ per L)			0.673	Child:100-350 Adult:125-350
Increased	1(14.3%)	2(8%)		
Decreased	0	2(8%)		
Blood biochemistry				
Albumin (g/L)			0.001	Child:37-51 Adult:40-55
Decreased	0	18(72%)		
Alanine aminotransferase (U/L)			1	Child:0-37 Adult:9-50
Increased	1(14.3%)	4(16%)		
Aspartate aminotransferase(U/L)			0.327	Child:10-50 Adult:15-40
Increased	3(42.9%)	5(20%)		
Total bilirubin (μmol/L)			0.646	Child:17.1-34.2 Adult:3.4-17.1
Increased	1(14.3%)	7(28%)		
Blood urea nitrogen (mmol/L)			0.025	Child:1.8-6 Adult:3.6-9.5
Increased	0	0		
Decreased	0	13(52%)		
Serum creatinine (μmol/L)			0.066	Child:18-52 Adult:57-111
Increased	0	0		
Decreased	0	11(44%)		
Creatine kinase isoenzyme (U/L)			0.004	Child:0-30 Adult:0-24
Increased	4(57.1%)	1(4%)		
Lactate dehydrogenase (U/L)			0.113	Child:155-395 Adult:120-250
Increased	2(28.6%)	1(4%)		
Myoglobin (ng/mL)			0.113	Child:10-45 Adult:0-146.9
Increased	2(28.6%)	1(4%)		
Brain natriuretic peptide(pg/ml)			0.209	Child/Adult:0-125
Increased	5(71.4%)	10(40%)		
Coagulation function				
Activated partial thromboplastin time (s)			0.003	Child:24-38 Adult:28-43.5
Increased	3(42.9%)	0		
Decreased	3(42.9%)	18(72%)		
Fibrinogen (s)			0.049	Child/Adult: 2.0-4.0
Increased	0	8(32%)		
Decreased	1(14.3%)	0		
D-dimer (μg/L)			1	Child/Adult: 0-1.0
Increased	2(28.6%)	7(28%)		
Infection-related biomarkers				

Erythrocyte sedimentation rate (mm/h)				Child/Adult: 0-15.0
Increased	3(42.9%)	21(84%)	0.47	
C-reactive protein (mg/L)				Child/Adult: 0-10.0
Increased	2(28.6%)	11(44%)	0.671	
Procalcitonin (ng/L)				Child/Adult: 0-0.5
Increased	3(42.9%)	0	0.007	

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 $\leq$ 18 years (n=7)	Adults $\geq$ 18 years (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%)

*This type of patient includes those with asymptomatic infection, upper respiratory infection (URI) and mild pneumonia.

Figures

Figure 1

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 short of breath. D) showed mild pneumonia infection of a 1 year and 4 months old girl, who had fever, cough and diarrhea on admission and was diagnosed as mild type.