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Original Article

Comparing Chinese children and adults with RT-PCR positive COVID-19: A systematic review

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ABSTRACT

Background: The various clinical manifestations of COVID-19 with RT-PCR positive patients have been reported. However, the differences in the clinical presentation between children and adults were unclear. Thus, we aimed to investigate the differences in the clinical manifestations and imaging characteristics between Chinese children and adults with COVID-19 by systematically analyzing the data derived from some latest literatures.
Methods: An extensive search of COVID-19 papers was conducted in PubMed and Chinese medical journal network, and relevant articles were selected based on some standard requirements. The included papers were analyzed for differences in clinical manifestation between children and adults with COVID-19 after the quality evaluation with the QUADAS-2 tool. The differences in the clinical features and CT findings were analyzed using a Pearson χ^2 test or Fisher's exact test. Patients who underwent CT examination were divided into the initial examination (0–4days) and follow-up examination groups (5–14 days).
Results: A total of 345patients (70 children and 275 adults) with RT- PCR (+) were included in our study (5 papers for children and 5 papers for adult groups). Significant differences between children and adults were found in exposure history ($p < 0.001$, $\chi^2 = 166.890$), fever ($p = 0.016$, $\chi^2 = 5.757$), white cell count ($p < 0.001$, $\chi^2 = 14.043$), and CT features in the initial ($p < 0.001$, $\chi^2 = 60.653$) and follow-up stages ($p < 0.001$, $\chi^2 = 52.924$); and the involved lung in the follow-up stage ($p < 0.001$, $\chi^2 = 16.776$).
Conclusions: Some differences have been presented between children and adults with RT-PCR positive COVID-19, which are helpful in the management and protection of children with COVID-19.

Introduction

It is unfortunate for the Chinese that their cheerful spring festival has been ruined by the sudden 2019 novel coronavirus attack, which started from the city of Wuhan, Hubei province, China, and then spread rapidly to other cities and countries such as Vietnam, South Korea, and the USA [1,2]. Coronavirus disease (COVID-19), as is currently referred to by the World Health Organization (WHO), is posing a significant threat to international health. By 18:00 on March 11, 2020, WHO has reported 80,981 confirmed cases in China, and 46,725 confirmed cases in other countries. Unfortunately, about 900 children were included in the disaster [3].

Currently, some characteristics regarding the clinical presentation, computed tomography (CT) images and epidemiology that are very vital to the development of a treatment guideline for COVID-19 have been reported [4–6]. However, to our knowledge, the differences between children and adults in the clinical manifestation of COVID-19 is unclear. Therefore, the purpose of our study is to investigate the key differences in COVID-19 presentation between Chinese children and adults by systematically analyzing the data obtained from some latest literatures. Our findings will be useful in the development of a management plan and choosing an

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individualized therapy method for the protection of children with COVID-19.

Methods

Literature search

We searched MEDLINE (PubMed, https://www.ncbi.nlm.nih.gov/pubmed/) and the Chinese medical journal network (http://medjournals.cn/index.do) for potential studies published before March 3, 2020, using the following terms: (COVID-19), (SARS-COV-2), (2019-nCOV), (novel coronavirus disease) or (novel coronavirus pneumonia). Then, a manual search of the reference lists of all retrieved articles was performed to obtain additional studies.

Study selection

COVID-19 Studies were screened by Yigang Pei and Wenguang Liu based on the following criteria: (1) the paper was primary research or a case report that focused on the clinical and CT features of children and adults with an RT-PCR positive COVID-19 and published within the last 40 days. (2) the study's demographics were exclusively Chinese to avoid distortions caused by racial differences, (3) the paper must come from different institutions in China to avoid data overlap. For papers from the same institution, the article that best meets our criteria was included. Finally, EndNote Reference Manager software was used to remove all duplicates, and relevant papers were divided into the children and adult groups according to the titles and article abstracts (children: 0–18 old years, Adults: >18 old years) (Fig. 1).

Data extraction

We (Yigang Pei and Wenguang Liu) extracted article related data such as the first author, the date of publication, the corresponding author's institution, and region. We collected participant related data that constituted of gender and age, the exposure history (1. living in Wuhan, 2. recent travel to Wuhan within two weeks, 3. cluster or exposure to infected patient(s), 4. unknown exposure), clinical symptoms (1. asymptomatic, 2. fever, 3. cough, 4. myalgia or fatigue, 5. sputum production or expectoration, 6. dyspnea, 7. digestive symptoms, 8. headache, 9. other), any comorbidity (1. cardiovascular and cerebrovascular diseases, 2. endocrine disorders (e.g. diabetes), 3. malignant tumor, 4. nervous system disease, 5. others), laboratory results (white blood cell count), the status of RT- PCR (+), the CT images' characteristics (1. normal, 2. ground-glass opacity (GGO), 3. consolidation, 4. crazy-paving), the number of affected lungs (unilateral and bilateral pneumonia) on CT images caused by COVID-19, and the follow-up results. The data were used to assess the key differences between adults and children.

Risk of bias assessment

Quality assessment was conducted on this particular review with the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [7]. The QUADAS-2 format includes four key domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing (http://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/). For these domains, the risk of bias and concerns about applicability (the fourth domain not applying for the applicability) were analyzed and rated as a low, high or unclear risk. The results of the quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to investigate potential sources of heterogeneity. Two authors (Yigang Pei and Wenguang Liu) independently evaluated the methodological quality, using a standard form with quality assessment criteria and a flow diagram. The disagreements were resolved by discussion between them to reach a consensus (Table 1) [4,8–16]. Risk of bias and applicability concerns graphs were drawn using RevMan (RevMan 5.3, Cochrane Collaboration, Oxford, UK) (Fig. 2).

The methodology of quality criteria was based on: the description of the inclusion and exclusion criteria for the patient selection domain, a description about the clinical presentations, CT features, and RT-PCR (+) of children and adults that were performed and interpreted for the index test domain, a description of the reference standard used, and a description of the time elapsed from the index test assessment to the reference standard result.

Statistical analysis

The statistical heterogeneity of studied paper was evaluated by Yigang Pei and Wenguang Liu. All data were statistically analyzed using SPSS (SPSS for Windows, version 18.0; SPSS, Chicago, IL) in our study. The comparison of discrete variables between groups was performed using the Pearson $\chi 2$ test or Fisher's exact test. $P < 0.05$ was regarded as statistically significant.

Results

Search results

A total of 345 patients with RT-PCR(+) were included to assess the differences between children and adults with COVID-19, including 70 children and 275 adults obtained from 10 articles that met the requirements of our study (Children: 5 papers, Adults: 5 papers).

Exposure history

There was a significant difference in exposure history between children and adults ($p < 0.001$, $\chi^2 = 166.890$). The first exposure element was the cluster for children [53/70 patients (75.7%)] and recent travel to Wuhan for adults [130/275 patients (47.3%)]. In addition, habitation in Wuhan was an additional vital exposure factor for adults with COVID-19 [102/275 patients (37.1%)] (Table 2).

Clinical symptom

Children were significantly different from adults in fever ($p = 0.016$, $\chi^2 = 5.757$), there were 30 patients (42.9%) in children and 77 patients (28.0%) in adults without fever. Furthermore, 14 children (20.0%) and 15 adults (5.5%) without any clinical symptom were found. Also, adults in contrast to children usually had other clinical symptoms and comorbidities such as myalgia, fatigue, cardiovascular and cerebrovascular diseases (Table 2).

Laboratory results

There was a significant difference in white cell count between children and adults except for 2 children (reference 11, 13) and 121 adults (reference 4) who had no details on white blood cell count information ($p < 0.001$, $\chi^2 = 14.043$) (Table 2).

The CT findings

Ground-glass opacity (GGO), consolidation and crazy-paving were the main characteristic features on CT images (Fig. 3). The significant differences between children and adults were found in the first examination ($p < 0.001$, $\chi^2 = 60.553$) and follow-up stages ($p < 0.001$, $\chi^2 = 52.924$). In the first examination, 69 children and 159 adults had a CT scan within 0–4 days from the disease onset.

Table 1
The included literatures in our study and the risk of bias and applicability evaluated by QUADAS-2 tool.

No.	Study ID	The name of the journal	Number of subjects and region in China	Risk of bias				Applicability concerns		
				Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
1	Feng Pan [8], 20200213	Radiology	N = 21, Wuhan (Union hospital)	Low(U/Y/Y)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Low	Low	Low
2	Heshui Shi [9], 20200224	Lancet Infectious Diseases	N = 81, Wuhan (Jinyintan hospital)	Low(U/Y/Y)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Low	Low	Low
3	Fengxiang Song [10], 20200206	Radiology	N = 51, Shanghai (Shanghai public health clinical center)	Unclear(U/Y/N)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Low	Low	Low
4	Adam Bernheim [4], 20200220	Radiology	N = 121, Nanchang (The first affiliated hospital of Nanchang University), Zhuhai (The fifth affiliated hospital), Chengdu (west china hospital), Guilin (Nanxishan hospital)	Low(Y/Y/Y)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Low	Low	Low
5	Jiangping Wei [11], 20200226	Korean Journal Radiology	N = 1, Nanchang (Jiangxi provincial people's hospital)	High(N/U/N)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Unclear	Low	Low
6	Kai Feng [12], 20200216	Chinese Journal of Pediatrics	N = 15, Shenzhen (the third people's hospital of Shenzhen)	Low(U/Y/Y)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Low	Low	Low
7	Jiehao Cai [13], 20200204	Chinese Journal of Pediatrics	N = 1, Shanghai (children' s hospital of Fudan University)	High(N/U/N)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Unclear	Low	Low
8	Yuehua Zhang [14], 20200211	Chinese Journal of Pediatrics	N = 1, Haikou (Haikou people's hospital)	High(N/U/N)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Unclear	Low	Low
9	Huijing Ma [15], 20200210	Chinese Journal of Radiology	N = 22, Wuhan (Wuhan children's hospital)	Low(U/Y/Y)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Low	Low	Low
10	Duan Wang [16], 20200302	Chinese Journal of Pediatrics	N = 31, Six provinces (Shanxi, Gansu, Ningxia, Hebei, Henan and Shandong)	Low(U/Y/Y)	Low(Y/U)	Low(Y/U)	Low(U/Y/Y/Y)	Low	Low	Low

Note: The evaluation of QUADAS-2 with Y(Yes)/N(No)/U(Unclear) in the risk of bias and Low/High/Unclear in the risk of bias and applicability.
Union hospital = union hospital, Tongji medical college, Huazhong university of science and technology.
Nanxishan hospital = Nanxishan hospital, Guangxi zhuang Autonomous Region.
The fifth affiliated hospital = The fifth affiliated hospital, Sun Yat-sen University, new Xiangzhou, Zhuhai, Guangdong province.

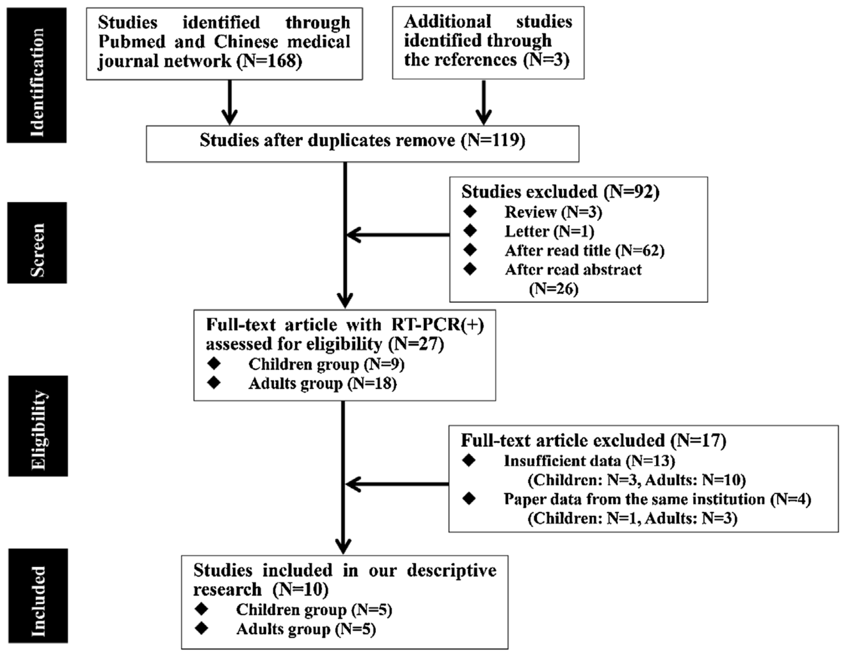

Fig. 1. Flowchart of the study selection process.

Table 2
Summary of clinical features and laboratory results of pediatric and adult groups.

Clinical features Subjects	Children [n(%)] n = 70	Adults [n(%)] n = 275	P-value
Gender			
Male	18 (46.2%)	134 (48.7%)	0.763, χ^2 = 0.091
Female	21 (53.8%)	141 (51.3%)	
Unclear	31[a]	0	
Exposure history			
Wuhan area	9 (12.9%)	102 (37.1%)	<0.001, χ^2 = 166.890
Recent travel to Wuhan	3 (4.3%)	130 (47.3%)	
Cluster(Exposure to Infected Patient)	53 (75.7%)	18 (6.5%)	
Unknown exposure	5 (7.1%)	25 (9.1%)	
Clinical symptom			
Asymptomatic	14 (20.0%)	15 (5.5%)	N/A
Fever			
Yes	40 (57.1%)	198 (72.0%)	0.016, χ^2 = 5.757
No	30 (42.9%)	77 (28.0%)	
Cough	23 (32.9%)	142 (51.6%)	
Myalgia or fatigue	3(4.3%)	40 (14.5%)	
Sputum production (expectoration)	6(8.6%)	51 (18.5%)	0.003, χ^2 = 16.370
Dyspnoea	0	41 (14.9%)	
Digestive Symptoms (diarrhea, emesis et al.)	5(7.1%)	8 (2.9%)	
Headache	3(4.3%)	13 (4.7%)	
Other	0	38[b] (13.8%)	N/A
Laboratory results			
White blood cell count ($\times 10^9$cells per L)			
Normal or decreased	65 (95.6%)	114 (74.0%)	<0.001, χ^2 = 14.043
Increased	3(4.4%)	40 (26.0%)	
Unclear	2[c]	121[d]	N/A
RT- PCR(+)	70 (100%)	275 (100%)	N/A

Note:
[a] Unclear gender for 31 children in Ref. [16].
[b] Some accompanying symptoms in 38 adults, from references 8–10, such as throat pain (dysphagia), loss of appetite, chills, and chest pain.
[c] With no detailed white blood cell count result for 2 patients in Refs. [[11] and 13].
[d] No white blood cell count results for 121 adults in Ref. [4].

CT examination showed GGO in 34 children (49.3%) and 119 adults (74.8%), and a normal finding in 25 children (36.2%) and 4 adults (2.5%). In the follow-up stage, 17 children and 116 adults underwent a CT within 5–14 days from the disease onset. The main feature was GGO (70.6%) for children and GGO (72.4%) and consolidation (63.8%) for adults. For lung involvement during follow-up, the number of bilateral pneumonia was higher in adults than in children; however, the reverse was observed with unilateral pneumonia ($p < 0.001$, $\chi^2 = 16.776$) (Table 3). Additionally, three children primarily underwent X-ray in some of the studies.

Clinical outcomes

84 adults and 36 children were discharged from the hospital. However, in Ref. [10] (paper 3) and Ref. [4] (paper 4), discharge

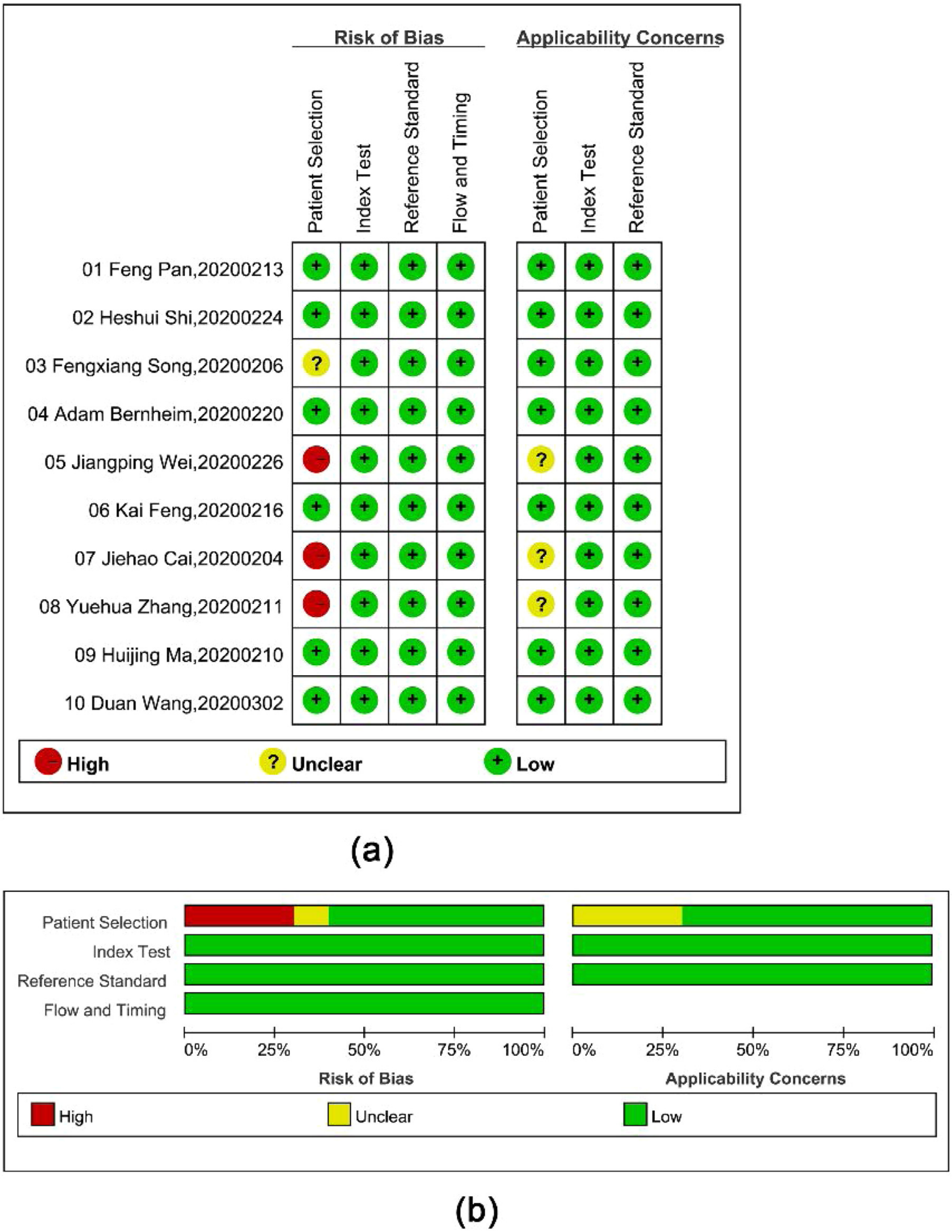

Fig. 2. Risk of bias and applicability concerns. (a) Risk of bias and applicability concerns summary. (b) Risk of bias and applicability concerns graph.

status was unclear (Fig. 4). In addition, A total of 3 adults died (no mortality in the children group) from the references – except for references 10 and 14 who had no mortality record.

Discussion

The novel coronavirus disease (COVID-19) outbreak has a potentially far-reaching public health ramification that needs all the people in the world to work hard to prevent and control the disease – one world, one health– because of the increasing number of patients confirmed with the disease; especially with the steep rise in the number of cases in South Korea, Japan, and Italy. Differences have been discovered in the manifestations of RT-PCR positive COVID-19 in children and adults patients with respect to epidemiology, clinical symptoms, laboratory tests, and CT imaging characteristics. These variations are crucial in wiping out the novel coronavirus disease and protection of the people's health, especially for children.

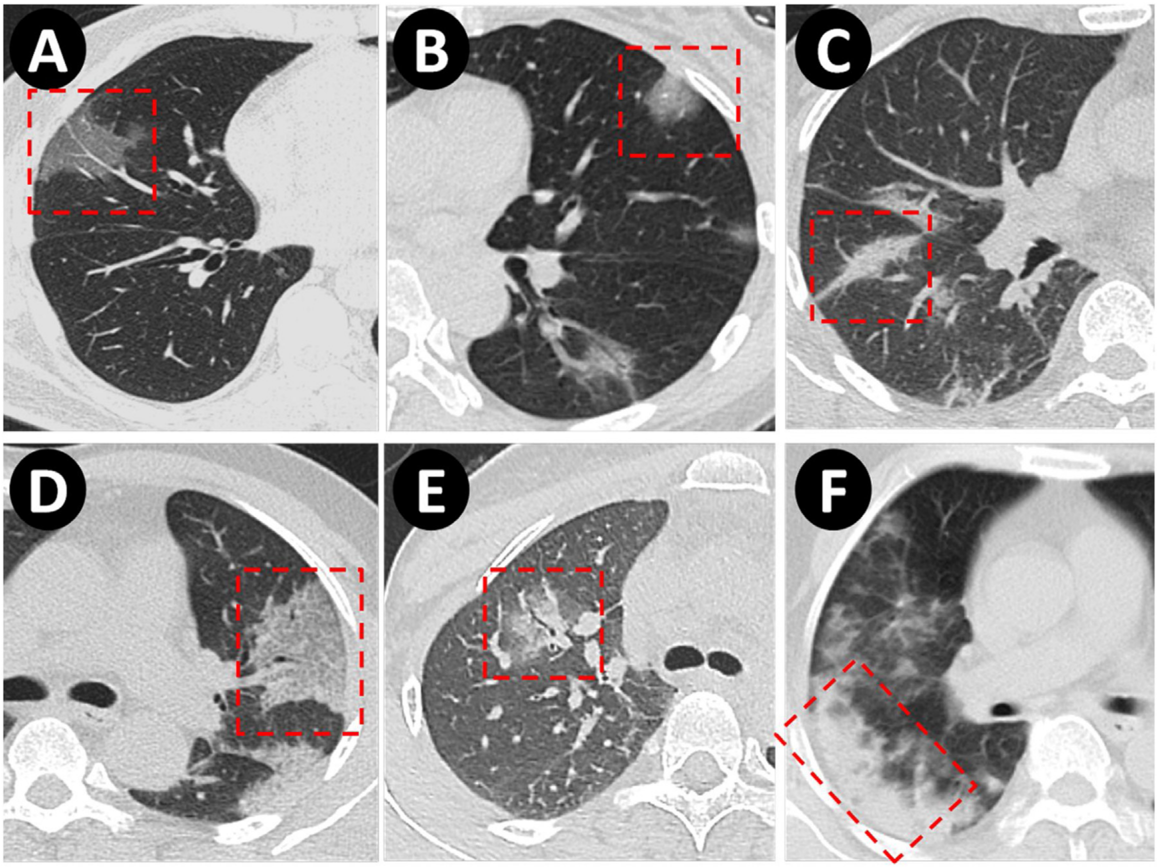

Fig. 3. Diagram of the CT features. The red boxes indicated the abnormalities. (A, B and C) different shapes of ground-glass opacity (GGO), (D) GGO with crazy-paving pattern, (E) GGO with consolidation, (F) consolidation.

Table 3
Summary of imaging features and Lung Changes On Chest CT.

The findings of CT images	The initial stage (rang 0–4 days)			Follow -up stage (5–14days)		
	Children	Adults	P value	Children	Adults	P value
The images' characteristic	N = 69	N = 159		N = 17	N = 116	
Normal	25 (36.2%)	4 (2.5%)		5 (29.4%)	1 (0.9%)	
Ground-glass opacity (GGO)[a]	34 (49.3%)	119 (74.8%)	<0.001, χ^2 = 60.653	12 (70.6%)	84 (72.4%)	<0.001, χ^2 = 52.924
Consolidation	4 (5.8%)	42 (26.4%)		0	74 (63.8%)	
Crazy-paving	2 (2.9%)	7 (4.4%)		0	20 (17.2%)	
Involvement	N = 39	N = 155		N = 12	N = 115	
Unilateral pneumonia	12 (30.8%)	62 (40.0%)	0.289, χ^2 = 1.125	7 (58.3%)	14 (12.2%)	<0.001, χ^2 = 16.776
Bilateral pneumonia	27 (69.2%)	93 (60.0%)		5 (41.7%)	101 (87.8%)	

Note: The initial stage was 0–4 days and the follow-up stage was 5–14 days from disease onset.
[a] GGO included pure GGO (patchy/ punctate GGO, rounded morphology GGO, Linear GGO) and GGO with consolidation.

Based on our data analysis, we found that the main exposure history for adults is living in or recent travel to Wuhan. In contrast, the most common exposure history for children is family clustering. This hinted the need to observe the child and carry out a nucleic acid testing, even if asymptomatic, whenever a family member is diagnosed with COVID-19. Thus, asymptomatic children need to start personalized therapy as soon as possible before worsening of the disease condition. Jasper Fuk-Woo et al. reported a child without any symptom to have accepted treatment when he tested positive for the RT- PCR [17]. In our collected data, 14 children (20.0%) and 15 (5.5%) adults were asymptomatic with positive nucleic acid tests.

Consistent with other literature reports, fever is the most common clinical symptom in both children and adults with COVID-19 [18–20]. In our study, the incidence rate of fever was over 50% at the time of presentation (Children: 40 (57.1%), Adults: 198 (72.0%)). A recent study found that fever was only 43.8% for patients on admission in 1099 subjects confirmed with COVID-19 [20]. Interestingly, the proportion of children with no fever (30/70, 42.9%) is significantly higher than that of adults (77/275, 28.0%) in our data. We speculate that the possible reason is that children's immunity is weaker than that of adults, and the protective physical symptoms such as fever do not occur easily. Furthermore, children have fewer other clinical symptoms than adults, such as cough, myalgia, fatigue, cardiovascular, and cerebrovascular diseases suggesting that children have a better prognosis compared to adult patients.

In this study, there was a significant difference in white cell count between children and adults. White blood cell counts were normal or low in all children but high in some adults. The reason was that there were more severe cases in adults than in children from several studies reviewed [9,21]. The adults had some comorbidities such as diabetes and cerebrovascular diseases that can decrease immunity and lead to an increase in the white blood cells.

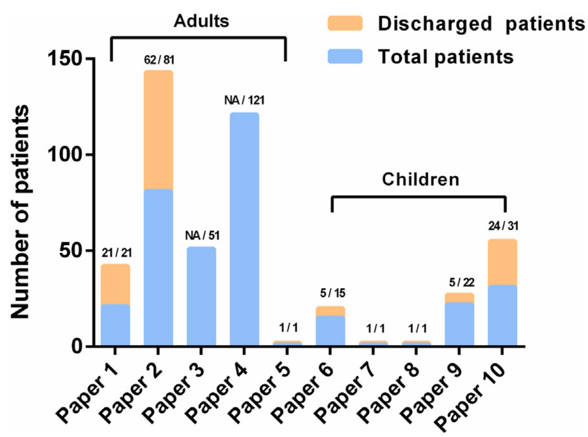

Fig. 4. Number of discharged patients. NA = no information about discharged patients in the paper.

High-resolution chest CT is recommended as the key component for the diagnostic work-up of COVID-19 patients because it can clearly display the lesions in the involved lung [22]. Characteristic CT features differ in various stages and consist of varying proportions of ground-glass opacity (GGO), consolidation and(or) crazy-paving in the peripheral lung [8,23]. Imaging features of COVID-19 are similar to SARS and MERS because the virus family shares similar pathogenesis [22]. In adults, the dominating CT characteristic was GGO in the initial stage (0–4 days) and consolidation in the follow-up stage (5–14 days). This finding implies that the follow-up stage can cause obvious inflammatory reactions leading to the accumulation of a large number of inflammatory exudates in the alveoli [24]. Also, COVID-19 was complicated by bilateral pneumonia in 69.2% of pediatric and 60.0% of adult cases within 0–4 days, and in 41.7% of pediatric and 87.8% of adult cases in the follow-up stage (5–14 days). We speculate that adult subjects having some background diseases can further develop bilateral multiple ground-glass opacities, infiltrating shadows, and pulmonary consolidation, with infrequent pleural effusion. Thus, there are more severe cases in adults than in children, which commonly presents as bilateral pneumonia in the follow-up stage [9]. During follow-up, there were more pediatric cases with a gradual recovery of lesions and a relatively better prognosis. Furthermore, three children primarily underwent Chest X-ray in our data, which showed multiple small patchy shadows and interstitial changes [25]. It is the first choice of imaging for children due to the low radiation level. Sometimes, it may be negative in the early stage of pneumonia cases, and a low dose of CT should thus be considered for children.

For the management of COVID-19 patients, First, patients with COVID-19 should be treated in designated hospitals with effective isolation and protection conditions. Second, they should rest in bed and be closely monitored for: vital signs (heart rate, respiratory rate, blood pressure, pulse oxygen saturation) and supervised for routine blood tests, C-reactive protein, procalcitonin, organic function tests (liver enzymes, bilirubin, myocardial enzyme, creatinine, urea nitrogen, urine volume, etc.), coagulation function, arterial blood gas analysis and chest imaging. In our data, all cases performed high-resolution chest CT. Third, patients should receive a supportive treatment to ensure sufficient energy intake, hydration, electrolytes and acid-base levels. Fourth, critical cases must be admitted into the intensive care unit as soon as possible and should receive effective oxygen therapy with a nasal catheter, an oxygen mask, a high-flow nasal oxygen therapy, non-invasive ventilation or invasive mechanical ventilation. Furthermore, Extracorporeal Membrane Oxygenation (ECMO) should be considered for patients with refractory hypoxia that is difficult to correct with protective lung ventilation [26].

There are some limitations to this study. First, the number of children included is relatively small because about 900 children have already been confirmed with the disease [3] and only a few papers were found. Second, all pediatric cases were obtained from Chinese journals with a low impact factor. However, the data is trustworthy because all cases were hospitalized in the best pediatric and famous general hospitals in the corresponding provinces of China. Finally, the total sample is not large enough, but significant in patients with COVID-19, especially in a pediatric case.

Conclusion

In general, the child should be carefully cared for even if asymptomatic when a family member is diagnosed with COVID-19 because children with COVID-19 have some differences compared to adults in their exposure history, clinical symptoms, laboratory findings, and CT image characteristics. This finding will help establish a management plan and choose an individualized therapy for the prevention of COVID-19 and the protection of children.

Funding

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Competing interests

None declared.

Ethical approval

Not required.

Authors' contributions

S Hu and WZ Li had the idea for and designed the study and participated in the entire process of the research. YG Pei and WG Liu collected the data, evaluated the risk of bias, and contributed to the writing of the paper with IB Masokano and Fang Li. S Hu, WZ Li and XY Long contributed to critical revision of the paper. WH Liao, SM Xie and GF Zhou contributed to the statistical analysis. All authors contributed to data screening, data analysis, or data interpretation, and reviewed and approved the final version.

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