Research Article

Clinical and immunological features of convalescent pediatric patients infected with the SARS-CoV-2 Omicron variant in Tianjin, China

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ABSTRACT

COVID-19 has spread surprisingly fast worldwide, and new variants continue to emerge. Recently, the World Health Organization acknowledged a new mutant strain "Omicron", with children were accounting for a growing share of COVID-19 cases compared with other mutant strains. However, the clinical and immunological characteristics of convalescent pediatric patients after Omicron infection were lacking. In this study, we comparatively analyzed the clinical data from pediatric patients with adult patients or healthy children and the effects of SARS-CoV-2 vaccine on the clinical and immune characteristics in convalescent pediatric patients. Our results indicated that convalescent pediatric patients had unique clinical and immune characteristics different from those of adult patients or healthy children, and SARS-CoV-2 vaccination significantly affected on the clinical and immune characteristics and the prevention of nucleic acid re-detectable positive (RP) in convalescent patients. Our study further deepens the understanding of the impact of Omicron on the long-term health of pediatric patients and provides a valuable reference for the prevention and treatment of children infected with Omicron.

1. Introduction

There is a current outbreak of COVID-19 in many countries, with a global spread on a large scale that is causing severe damage to global healthcare systems and human health worldwide (Lu et al., 2020; Zhou et al., 2020). As of April 1, 2022, 486,761,597 confirmed cases of COVID-19 were reported to World Health Organization (WHO), including 6,142,735 deaths (https://covid19.who.int/). Although most patients present with mild diseases and recover from the infection, life-threatening disease can occur resulting in hospitalization or even death. SARS-CoV-2, similar to other RNA viruses, has a higher mutation rate than DNA viruses. Up to now, several SARS-CoV-2 variants have appeared and become the prominent epidemic strains in the world, including four variants of concern as defined by WHO, i.e., Alpha, Beta, Gamma, and Delta. Recently, the new SARS-CoV-2 variant (B.1.1.529) was first identified and acknowledged by WHO as the fifth variant of concern, also known as Omicron (WHO, 2021). As the highest mutated SARS-CoV-2 variant, the Omicron variant spreads faster, has higher infectivity, and escapes more from immunity compared with the wild-type strain and the other four variants (CDC COVID-19 Response

Team, 2021; Kannan et al., 2021; Schmidt et al., 2021; Zhang et al., 2021). The Omicron variant is also characterized by rapid transmission, high viral load, and strong transmission ability (Tian et al., 2022). As Omicron variant strain has spread in more and more countries and regions around the world, it was becoming the dominant epidemic strain in many countries worldwide, not only bringing new challenges to the prevention and control of COVID-19, but also posing a huge threat to global human health.

Due to the weak awareness of seeking medical care, weaker immunity and the lower rate of COVID-19 vaccinations, children are more likely to be affected by SARS-CoV-2 Omicron variant infection and to become the infector and spreader. Consequently, the number of children infected with the SARS-CoV-2 Omicron variant has been rapidly increasing worldwide. Existing studies suggested that more than 3.87 million children (0–16 years old) have tested positive since the COVID-19 outbreak began, accounting for approximately 11.6% of all cases in the United States (https://covid.cdc.gov/covid-data-tracker/, accessed on November 29, 2021). Although much of the mortality has occurred in older adults, substantial morbidity and mortality are also found in children. Besides, another research indicated that pediatric SARS-CoV-2

infections and hospitalizations are rising in many countries after the emergence of the Omicron variant (Cloete et al., 2021). Generally, COVID-19 seems to be a less severe disease for children than adults (Nikolopoulou and Maltezou, 2022). Approximately 90% of pediatric patients are diagnosed as asymptomatic, mild, or moderate disease (Dong et al., 2020; Qiu et al., 2020). Nevertheless, most current research findings are regarding adult cases, which are not always transferrable to children. Therefore, clinical studies on children infected with the Omicron variant are particularly important to understand and control the development of the epidemic in children populations.

SARS-CoV-2 Omicron variant first emerged on the Chinese mainland in Tianjin in January 2022, triggering a large wave of infections, among which 25.6% were children. However, the clinical and laboratory data of Omicron compared to Delta are still lacking in children ≤ 16 years old. In addition, although several reports about children with COVID-19 have been published, there is still insufficient knowledge on the long-term effects of Omicron variant on the clinical and immunologic characteristics of the pediatric patients. In this study, we recruited 438 convalescent COVID-19 patients, including 110 pediatric patients and 328 adult patients, between 21 January and March 15, 2022. In order to facilitate the efforts to prevent and control COVID-19 in children, we performed a comprehensive exploration of the characteristics of the convalescent pediatric patients on admission to the hospital and compared the clinical and immune features of pediatric cases with adult cases during convalescence or with healthy children. In addition, we also further analyzed the effect of SARS-CoV-2 vaccination on clinical and immune-associated data in convalescent pediatric patients. These findings not only deepen our understanding of the long-term health effects of children infected with Omicron, but also provide a reference for prevention and treatment of COVID-19 in children.

2. Materials and methods

2.1. Study design and participants

A total of 438 patients were diagnosed with SARS-CoV-2 infection by real time-polymerase chain reaction (RT-PCR) assays in Tianjin Haihe Hospital between January 2022 and February 2022. RT-PCR was performed following the WHO protocol to detect two target genes, the open reading frame of 1 ab (ORF1ab) and the nucleocapsid protein (N) in a Light-Cycler 480 real-time PCR system (WHO, 2020). Diagnosis, clinical classifications, and complication definitions for COVID-19 were based on the New Coronavirus Pneumonia Prevention and Control Program (8th edition), published by the National Health Commission of China (http://www.gov.cn/zhengce/zhengceku/2021-04/15/content_5599795.htm). Severity of COVID-19 infection was categorized as (1) mild, if there was no radiographic evidence of pneumonia; (2) moderate, if pneumonia was present along with fever and respiratory tract symptoms; (3) severe, if respiratory rate $\geq$ 30/min, oxygen saturation $\leq$ 93% when breathing ambient air, or $PaO_2/FiO_2 \leq$ 300 mm Hg (1 mm Hg = 0.133 kPa); or (4) critical, if there was respiratory failure requiring mechanical ventilation, shock, or organ failure requiring intensive care.

All those patients met the following criteria for hospital discharge from Tianjin Haihe Hospital: the normal temperature for longer than three days; obvious improvement in respiratory symptoms and acute exudative lesions on chest computed tomography images; twice successive negative results of SARS-CoV-2 RNA test (separated by at least 24 h). After being discharged from Tianjin Haihe Hospital, the patients were transferred to Tianjin First Central Hospital for a period of 14 days of isolation, rehabilitation and medical observation. Daily follow-up in person and SARS-CoV-2 RNA detection were also performed simultaneously. Inclusion criteria were: (1) negative results of the SARS-CoV-2 RNA test in two consecutive samples taken 48 h apart. Exclusion criteria were: (1) positive RT-PCR results for COVID-19; (2) patients who could not sign informed consent or missing important case information; and (3) patients with major underlying medical conditions.

The present study included 110 pediatric patients, 320 adult patients and 45 age-matched healthy children recruited from Tianjin Children's Hospital as controls. Tianjin Children's Hospital provided clinical and laboratory data on healthy children. A re-detectable positive SARS-CoV-2 RNA diagnosis in patients during rehabilitation or post-discharge was defined as RP, otherwise, it was defined as non-RP (NRP).

2.2. Collection of clinical and laboratory data

A retrospective analysis was performed on the clinical and laboratory test results of the convalescent patients with Omicron variant in Tianjin First Central Hospital on the seventh day after admission. Demographic, clinical, laboratory and outcome data were reviewed from patients' electronic medical records. Prior to discharge from Tianjin first central Hospital, clinical and laboratory test data of each patient were collected and compiled. The demographic, and clinical characteristics of enrolled patients, such as age, sex, symptoms, clinical classification, white blood cell count, and lymphocyte counts, were taken from the medical records. Two researchers independently reviewed the data collection forms to verify data accuracy.

2.3. Novel coronavirus Serologic assays

Novel coronavirus-specific IgG and IgM were detected in serum samples using chemiluminescence microparticle immuno assay (CMIA) developed by Bioscience (Tianjin, China). Patient serum was sent to the laboratory for routine testing. The assay uses a recombinant antigen corresponding to the nucleocapsid protein (N) of the SARS-CoV-2 wild-type genome.

2.4. Statistical analysis

Continuous variables are presented as median [interquartile range (IQR)] or mean (SD) and categorical variables as number and percentage [N (%)]. Significant differences for continuous variables are compared using unpaired *t*-tests when the data were normally distributed; otherwise, the Mann-Whitney *U* test was used. Proportions for categorical variables were compared using the $\chi 2$ test or the Fisher exact test. All statistical analyses were performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA) or GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA, USA) without filling in the missing data. *P*-value < 0.05 (two-sided) was considered as statistically significant.

3. Results

3.1. Demographic characteristics and baseline clinical features of convalescent patients infected with SARS-cov-2 omicron variant

The study flowchart showing the strategy of case inclusion or exclusion is illustrated in Fig. 1A total of 438 patients with novel coronavirus Omicron infection were diagnosed in Tianjin Haihe Hospital. The recovered patients with SARS-CoV-2 nucleic acid negative transitions were transferred to Tianjin First Central Hospital. Patients who could not sign informed consent, or with missing important case information, or with major underlying medical conditions were excluded from further analysis. Out of 438 recovered patients with COVID-19, 430 (98.2%) were enrolled in the final analysis, including 110 (25.6%) pediatric patients (≤ 16 years) and 320 (74.4%) adult patients. Eight patients (1.8%) were excluded because of major underlying medical conditions.

Table 1 showed the comparative analysis of demographic data and baseline clinical features between pediatric patients and adult patients on admission. Among the 320 adult patients, the median (IQR) age was 46 (34–58) years and 182 (56.9%) of the adult patients were women. The pediatric patients had a median (IQR) age of 10 (8–11) years, and 54 (49.1%) were male and 56 (50.9%) were female. Compared with adult patients, 6 (5.5%) pediatric patients were asymptomatic, 91 (82.7%)
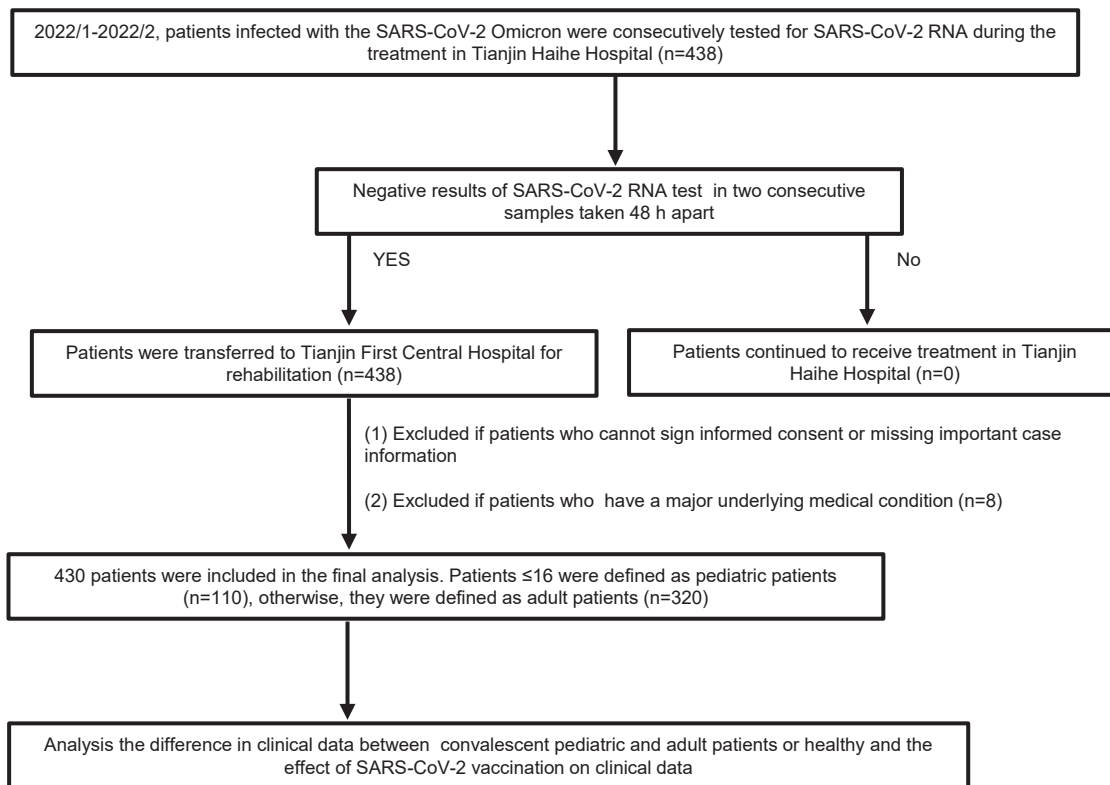
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│  2022/1-2022/2, patients infected with the SARS-CoV-2 Omicron were            │
│  consecutively tested for SARS-CoV-2 RNA during the treatment in              │
│  Tianjin Haihe Hospital (n=438)                                               │
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              ┌──────────────────────────────────────────────┐
              │  Negative results of SARS-CoV-2 RNA test in   │
              │  two consecutive samples taken 48 h apart     │
              └──────────────────────────────────────────────┘
         YES                                              No
          │                                                │
          ▼                                                ▼
┌────────────────────────────────┐        ┌────────────────────────────────┐
│ Patients were transferred to   │        │ Patients continued to receive  │
│ Tianjin First Central Hospital │        │ treatment in Tianjin Haihe     │
│ for rehabilitation (n=438)     │        │ Hospital (n=0)                 │
└────────────────────────────────┘        └────────────────────────────────┘
          │
          │  (1) Excluded if patients who cannot sign informed consent or
          │      missing important case information
          │
          │  (2) Excluded if patients who have a major underlying medical
          │      condition (n=8)
          ▼
┌────────────────────────────────────────────────────────────────────┐
│ 430 patients were included in the final analysis. Patients ≤16 were │
│ defined as pediatric patients (n=110), otherwise, they were defined │
│ as adult patients (n=320)                                           │
└────────────────────────────────────────────────────────────────────┘
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┌────────────────────────────────────────────────────────────────────┐
│ Analysis the difference in clinical data between convalescent       │
│ pediatric and adult patients or healthy and the effect of           │
│ SARS-CoV-2 vaccination on clinical data                             │
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Fig. 1. The flow chart of the critical of cases inclusion or exclusion.

Table 1

Baseline characteristics of 430 convalescent patients infected with the SARS-CoV-2 Omicron variant.

Characteristic	No. (%)			P value[a]
	Total (N = 430)	Adult patients (n = 320)	Pediatric patients (n = 110)	
Age, median (IQR), yr	36 (14–55)	46 (34–58)	10 (8–11)	NA
Gender				0.28
Male	192 (44.7)	138 (43.1)	54 (49.1)	NA
Female	238 (55.3)	182 (56.9)	56 (50.9)	
Clinical classification [b]				
Asymptomatic	7 (1.6)	1 (0.3)	6 (5.5)	<0.001
Mild	205 (47.7)	114 (35.6)	91 (82.7)	<0.001
Moderate	216 (50.2)	203 (63.4)	13 (11.8)	<0.001
Severe	2 (0.5)	2 (0.6)	0	1.00
Signs and symptoms				
Fever	130 (30.2)	92 (28.8)	38 (34.5)	0.25
Cough	157 (36.5)	126 (39.4)	31 (28.2)	0.04
Runny nose	53 (12.3)	41 (12.8)	12 (10.9)	0.60
Congestion	48 (11.2)	38 (11.9)	10 (9.1)	0.42
Pharyngodynia	82 (19.1)	65 (20.3)	17 (15.5)	0.26
Fatigue	53 (12.3)	46 (14.4)	7 (6.4)	0.03
Diarrhea	4 (0.9)	4 (1.3)	0	0.58
Dysosmia	4 (0.9)	4 (1.3)	0	0.58
Dysgeusia	5 (1.2)	5 (1.6)	0	0.13
Conjunctivitis	20 (4.7)	16 (5.0)	4 (3.6)	0.56
Low blood pressure	20 (4.7)	17 (5.3)	3 (2.7)	0.27
Clinical outcome				
NRP	345 (80.2)	247 (77.2)	98 (89.1)	0.007
RP	85 (19.8)	73 (22.8)	12 (10.9)	0.007
Died	0	0	0	1.00
Vaccination status				0.375
Vaccinated	392 (91.2)	294 (91.9)	98 (89.1)	NA
Non-vaccinated	38 (8.8)	26 (8.1)	12 (10.9)	

Note: data are presented as median (IQR) or No. (%). No. is the number of patients with available data. Percentages may not total 100 because of rounding.

Abbreviations: IQR, interquartile range; NA, not applicable; RP, nucleic acid re-detectable positive in patients during rehabilitation or post-discharge, otherwise, it was defined as non-RP (NRP).

[a] P values when comparing adult and pediatric cases using the $\chi 2$ test, Fisher exact test, or Mann-Whitney U test. $P < 0.05$ indicates statistical significance.

[b] Clinical classification: the clinical classification of patients with confirmed COVID-19 was based on the New Coronavirus Pneumonia Prevention and Control Program (8th edition), published by the National Health Commission of China.

were with mild conditions and 13 (11.8%) were with moderate conditions, which is consistent with previous studies (Tezer and Bedir Demirdağ, 2020), suggesting that pediatric patients were more likely to develop mildly infected conditions than adult patients. In addition, the incidence of cough and fatigue was notably lower in pediatric patients than in adult patients during recovery ($P < 0.05$). Unlike adult patients, convalescent pediatric patients had a higher NRP rate (89.1%) and lower RP rate (10.9%), suggesting that adult patients had more risk factors for developing RP during recovery or after hospital discharge than pediatric patients. Additionally, no other clinical characteristics varied significantly between pediatric patients and adult patients. These results were consistent with several existing studies about other SARS-CoV-2 variant (Chang et al., 2020; Tezer and Bedir Demirdağ, 2020; Li et al., 2021), suggesting that pediatric patients had fewer clinical symptoms, lower RP rates and better prognosis compared with adults patients during recovery.

3.2. Characteristics of infection and organ function-associated biomarkers of pediatric patients during the recovery period

So far, most studies about the SARS-CoV-2 Omicron variant have focused on adult patients, while studies on children in China are lacking. Although COVID-19 primarily affects the respiratory system, more and more emerging evidence highlights the impact of this viral infection on other organ systems (Guan et al., 2020; Huang et al., 2020; Xu et al., 2020; Zhang et al., 2020; Skok et al., 2021). To understand the long-term health consequences of the pediatric patients infected with SARS-CoV-2 Omicron, we collected and comparative analyzed the clinical data between convalescent pediatric patients and adult cases or healthy children. Table 2 and Supplementary Table S1 presented the findings of laboratory examinations related to infection, liver, and renal damage. Compared with adult patients [median (IQR), 0.97 (0.41–1.95)] or healthy children [median (IQR), 3.22 (2.13–4.94)], pediatric patients have obviously lower levels of C-reactive protein (CRP) [median (IQR), 0.26 (0.20–0.56); $P < 0.05$)], although CRP levels were within the normal range in the majority of convalescent patients. Furthermore, pediatric patients had lower alanine aminotransferase (ALT) levels [median (IQR), 13.48 (11.50–16.88)] than adult patients [median (IQR), 33.44 (20.62–66.51); $P < 0.001$] and the proportion of abnormally increased ALT was lower in pediatric patients than in adult patients (Table 2). Similarly, we observed the same phenomenon in aspartate

aminotransferase (AST), another liver function indicator, between pediatric patients and adult patients. However, pediatric patients had higher AST levels compared with healthy children, although AST levels were within the normal range in most pediatric patients (Supplementary Table S1). Interestingly, only a fraction of adult patients [57 (17.8%)] and healthy children [2 (2.2%)] had reduced creatinine levels, while 98 (89.1%) pediatric patients had abnormally reduced creatinine levels ($P < 0.001$) (Table 2 and Supplementary Table S1).These results suggested that liver function indicator was less affected but creatinine levels were abnormally reduced in pediatric patients compared with adult patients during the recovery period.

3.3. Immunologic features of pediatric patients during the recovery period

The immune system played an important role in antiviral infection and rehabilitation. In order to further study the immune characteristic of convalescent pediatric patients, we reviewed and analyzed laboratory data of immune-related indicators. As shown in Table 3 and Supplementary Table S2, virus-specific IgG levels were lower in pediatric patients [(median (IQR), 185.46 (141.89–209.68)] than in adult patients [median (IQR), 207.24 (179.34–236.74), $P < 0.001$] but significantly higher than in healthy children [(median (IQR), 4.32 (1.28–18.78), $P < 0.001$]. However, the levels of virus-specific IgM revealed no difference between the different groups. Although the levels of white blood cells (WBCs), neutrophils, monocytes and eosinophils were within the normal range in most convalescent patients, there were significantly different between pediatric and adult patients (Table 3). Nevertheless, the levels of these cells mentioned above were no difference between convalescent pediatric patients and healthy children (Supplementary Table S2).

It was worth noting that the proportion of adult patients [33 (10.33%)] with increased monocytes was higher than pediatric patients [1 (0.9%), $P = 0.002$]. As for the T lymphocyte subset, the levels of CD3$^+$ T cells were lower in pediatric patients compared with adult patients (Table 3 and Fig. 2A). Further analysis of helper T cell subsets (CD4$^+$ T cells) and cytotoxic T cell subsets (CD8$^+$ T cells) showed that there was a lower level of CD4$^+$ T cells in pediatric patients than in adult patients ($P < 0.001$), but there was no discernible difference in the levels of CD8$^+$ T cells between the two groups (Table 3 and Fig. 2B and C). However, the proportion of pediatric patients [2 (1.8%)] with abnormally increased CD8$^+$ T proportion was lower in pediatric patients than in adult patients [29 (9.1%), $P < 0.05$]. Further analysis showed that pediatric patients

Table 2
Differences in laboratory findings between pediatric patients and adult patients during rehabilitation.

| Biomarker	Median (IQR)			P value[a]
	Total (N = 430)	Adult patients (n = 320)	Pediatric patients (n = 110)	
Infection				
CRP (NR: 0–10 mg/L)				
Level, mg/L	0.75 (0.28–1.77)	0.97 (0.41–1.95)	0.26 (0.20–0.56)	<0.001
Increased, No. (%)	15 (3.5)	13 (4.1)	2 (1.8)	0.374
Liver function				
ALT (NR: M, 0–50 U/L; W, 0–35 U/L)				
Level, U/L	26.48 (15.29–57.61)	33.44 (20.62–66.51)	13.48 (11.50–16.88)	<0.001
Increased, No. (%)	149 (34.7)	142 (44.4)	7 (6.4)	<0.001
AST (NR: 17–59 U/L)				
Level, U/L	28.04 (23.27–36.29)	28.92 (23.17–38.77)	26.91 (23.82–30.89)	0.024
Increased, No. (%)	42 (9.8)	41 (12.8)	1 (0.9)	<0.001
Renal function				
Creatinine (NR: M, 58–110 μmol/L; W, 46–92 μmol/L)				
Level, μmol/L	52.68 (43.03–66.99)	59.63 (49.47–70.40)	37.93 (36.63–43.51)	<0.001
Reduced, No. (%)	155 (36.0)	57 (17.8)	98 (89.1)	<0.001
BUN (NR: 2.5–7.1 mmol/L)				
Level, mmol/L	3.99 (3.29–4.85)	4 (3.34–4.89)	3.83 (3.15–4.64)	0.188
Increased, No. (%)	8 (1.9)	7 (2.2)	1 (0.9)	0.275

Note: data are presented as median (IQR) or No. (%). No. is the number of patients with available data. Percentages may not total 100 because of rounding.
Abbreviations: IQR, interquartile range; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; NR, normal range; M, man; W, woman.
[a] P values when comparing adult and pediatric cases using the $\chi 2$ test, Fisher exact test, or Mann-Whitney U test. $P < 0.05$ indicates statistical significance.

Table 3
Differences in immune features between pediatric patients and adult patients during the recovery phases.

Biomarker	Median (IQR)			P value
	Total (N = 430)	Adult patients (n = 320)	Pediatric patients (n = 110)	
IgG, AU/mL	200.38 (168.85–230.03)	207.24 (179.34–236.74)	185.46 (141.89–209.68)	<0.001
IgM, AU/mL	0.46 (0.25–0.83)	0.48 (0.26–0.87)	0.43 (0.24–0.79)	0.256
WBCs, 10^9/L (NR, A 3.5–9.5, C 4.4–11.9)	6.33 (5.32–7.55)	6.20 (5.24–7.38)	6.64 (5.66–8.17)	0.006
Increased, No. (%)	25 (5.8)	16 (5.0)	9 (8.2)	0.219
Neutrophils, 10^9/L (NR, A 1.8–6.3, C 1.2–7.0)	3.42 (2.69–4.26)	3.57 (2.85–4.35)	2.99 (2.28–3.86)	<0.001
Increased, No. (%)	14 (3.3)	11 (3.4)	3 (2.7)	1.00
Lymphocytes, 10^9/L (NR, A 1.1–6.3, C 1.8–6.3)	2.20 (1.77–2.73)	2.05 (1.61–2.43)	2.95 (2.53–3.56)	0.905
Increased, No. (%)	3 (0.6)	0 (0.0)	3 (2.7)	0.016
Monocytes, 10^9/L (NR, A 0.1–0.6, C 0.12–0.93)	0.42 (0.34–0.52)	0.42 (0.35–0.51)	0.43 (0.34–0.53)	<0.001
Increased, No. (%)	34 (7.9)	33 (10.33)	1 (0.9)	0.002
Eosinophils, 10^9/L (NR, A 0.02–0.523, C 0–0.68)	0.14 (0.09–0.21)	0.13 (0.09–0.19)	0.18 (0.13–0.32)	<0.001
Increased, No. (%)	8 (1.9)	4 (1.3)	4 (3.6)	0.120
Basophils, 10^9/L (NR, A 0–0.06, C 0–0.07)	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.2886
Increased, No. (%)	9 (2.1)	9 (2.8)	0 (0.0)	0.119
CD3$^+$ T cells (NR, 56%–86%)	72.51 (67.34–76.87)	74.0 (67.39–77.79)	71.38 (67.51–74.53)	0.023
Increased, No. (%)	9 (2.1)	8 (2.5)	1 (0.9)	0.458
CD4$^+$ T cells (NR, 33%–58%)	38.95 (34.23–45.53)	40.8 (34.78–47.11)	36.47 (32.56–40.01)	<0.001
Increased, No. (%)	4 (0.9)	4 (1.3)	0	0.576
CD8$^+$ T cells (NR, 13%–39%)	25.18 (20.38–30.34)	25.02 (19.57–30.57)	25.67 (21.93–30.06)	0.369
Increased, No. (%)	31 (7.2)	29 (9.1)	2 (1.8)	0.011
CD4$^+$/CD8$^+$ (NR, 1.4–2.0)	1.61 (1.17–2.08)	1.67 (1.19–2.15)	1.42 (1.15–1.75)	<0.001
Increased, No. (%)	115 (26.7)	98 (30.6)	17 (15.5)	0.002
Reduced, No. (%)	157 (36.5)	105 (32.8)	53 (48.2)	<0.001

Note: Data are presented as median (IQR) or No. (%). No. is the number of patients with available data. Percentages may not total 100 because of rounding.
Abbreviations: IQR, interquartile range; WBCs, white blood cells; NR, normal range; A, adult; C, child.
a P values when comparing pediatric patients and adult patients using the χ2 test, Fisher exact test, or Mann-Whitney U test. P < 0.05 indicates statistical significance.
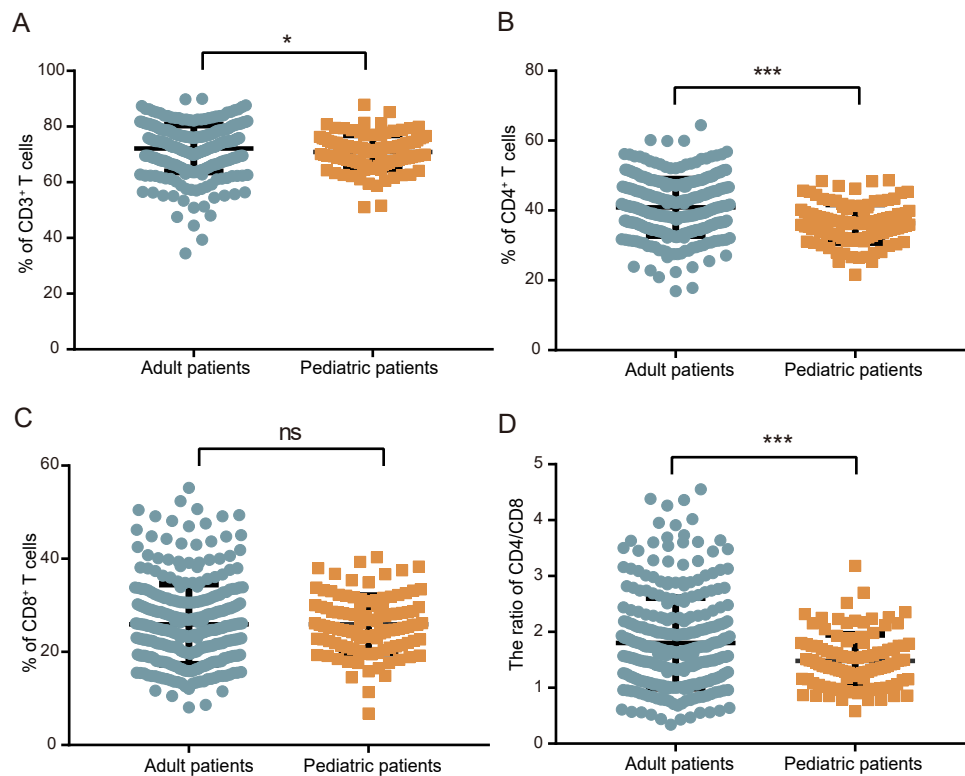
Fig. 2. T lymphocyte subsets were detected in convalescent pediatric and adult patients infected with Omicron. **A–C** Comparisons of the percentage of CD3$^+$ T (**A**), helper T cell subsets (**B**), and cytotoxic T cell subsets (**C**) between different groups. **D** The ratio of the CD4$^+$/CD8$^+$ T cell between different groups. Each dot represents one donor. Data were analyzed using Mann-Whitney U test (ns, P > 0.05, *P < 0.05, **P < 0.01, and ***P < 0.001). Error bars represent the mean and SD.

had a lower ratio of CD4$^+$/CD8$^+$ T cells than adult patients (Table 3 and Fig. 2D). Interestingly, we found less pediatric patients with abnormally increased CD4$^+$/CD8$^+$ ratio but more of them with abnormally reduced CD4$^+$/CD8$^+$ T ratio compared with adult patients.

In addition, compared with the healthy children, we observed that pediatric patients had lower CD4$^+$ T cells and CD8$^+$ T cells levels, and there was a lower proportion of pediatric patients with abnormally increased CD4$^+$ and CD8$^+$ T cells but a higher proportion of pediatric

patients with abnormally reduced CD4$^+$ T cells (Supplementary Table S2 and Fig. S1). These results showed that convalescent pediatric patients had unique immunological characteristics different from convalescent adult patients or healthy children, which meant that although the SARS-CoV-2 RNA test was negative, the effect of SARS-CoV-2 on the immune system of children was long-lasting.

3.4. The effects of SARS-CoV-2 vaccine on characteristics of infection and organ function-associated biomarkers in convalescent pediatric patients

Vaccination was considered the most promising strategy to combat and control the COVID-19 pandemic. Ninety-eight (89.1%) pediatric patients and 294 (91.9%) adult patients have been vaccinated with SARS-CoV-2 vaccines in this study (Table 1). However, whether the SARS-CoV-2 vaccine had an effect on clinical testing indicators in convalescent pediatric patients was unclear. Obviously, as shown in Table 4, we observed that vaccinated pediatric patients had higher levels of CRP and creatinine but lower levels of AST and blood urea nitrogen (BUN) compared with unvaccinated pediatric patients ($P < 0.05$), although these indicators other than creatinine were within the normal range in most convalescent pediatric patients (Table 4). Unlike pediatric patients, as shown in Supplementary Table S3, vaccinated adult patients had lower levels of CRP compared with unvaccinated adult patients and the proportion of vaccinated adult patients with abnormally increased CRP were significantly less than unvaccinated adult patients. In addition, vaccinated adult patients had higher levels of ALT than unvaccinated adult patients, while there was no difference in AST levels between the two groups. Furthermore, there was a lower proportion of vaccinated adult patients with abnormally reduced creatinine than unvaccinated adult patients. These results suggested that SARS-CoV-2 vaccine had a significant effect on infection and organ function-associated indicators in both convalescent pediatric and adult patients.

3.5. The effects of SARS-CoV-2 vaccine on immunological features in convalescent pediatric patients

We further investigated the effects of SARS-CoV-2 vaccine on immune-related indicators in pediatric patients. As shown in Table 5 and Fig. 3A, similar to adult patients (Supplementary Table S4 and Fig. S2A), there was a significant increased virus-specific IgG levels in vaccinated

pediatric patients compared with unvaccinated pediatric patients, while vaccination did not affect virus-specific IgM levels in pediatric patients (Table 5 and Fig. 3B), which was completely different from adult patients (Supplementary Table S4 and Fig. S2B). Furthermore, we found that vaccinated pediatric patients had lower WBCs levels compared with unvaccinated pediatric patients, and the same phenomenon was observed in adult patients (Table 5 and Supplementary Table S4). Interestingly, we further found that vaccinated pediatric patients had lower lymphocytes and monocytes levels but higher CD3$^+$ T and CD8$^+$ T cells levels compared with unvaccinated pediatric patients (Table 5 and Fig. 3C–E). There was no doubt that a significant increase in CD8$^+$ T cells resulted in a decrease ratio of CD4$^+$/CD8$^+$ T cells in vaccinated pediatric patients compared with unvaccinated pediatric patients (Fig. 3F). Unexpectedly, there was no significant difference in other immune indicators between vaccinated and unvaccinated adult patients (Supplementary Table S4 and Figs. S2C–F). These results showed that SARS-CoV-2 vaccine had more notable effects on the immune systems in pediatric patients than in adult patients. In short, not only SARS-CoV-2 vaccination increased virus-specific IgG levels and reduce WBCs levels in convalescent patients, but also it specifically affected the cell-mediated immunity profile of convalescent pediatric patients, particularly CD3$^+$ T and CD8$^+$ T cells.

3.6. The correlation between SARS-CoV-2 vaccination and RP in convalescent pediatric patients

Increasing research have revealed that RP results of the SARS-CoV-2 RNA test could be observed in some recovered patients (An et al., 2020; Li et al., 2021). A total of 85 (19.8%) RP patients, including 12 pediatric patients, were detected in this study (Table 1). To explore the protective effect of the SARS-CoV-2 vaccine on the prevention of RP in convalescent patients, we further analyzed the correlation between vaccination and RP. As shown in Table 6, pediatric patients with vaccination had lower rate of RP (9.4%) than who without vaccination (21.4%), but there was no significance ($P = 0.177$). One possible explanation was that the sample size of pediatric patients was small. However, vaccinated adult patients had significantly lower rate of RP (20.6%) than unvaccinated cases (50.0%, $P = 0.001$). In summary, these results showed that SARS-CoV-2 vaccination had a significant protective effect on the prevention RP in convalescent patients, especially in adult patients.

Table 4
Differences in laboratory findings between vaccinated and unvaccinated pediatric patients during the recovery phases.

Biomarker	Median (IQR)			P value
	Total (N=110)	Unvaccinated pediatric Patients (n=14)	Vaccinated pediatric Patients (n=96)	
Infection				
CRP				
Level, mg/L	0.26 (0.20–0.56)	0.20 (0.20–0.20)	0.29 (0.2–0.64)	0.006
Increased, No. (%)	2 (1.8)	1 (7.1)	1 (1.0)	0.225
Liver function				
ALT				
Level, U/L	13.48 (11.50–16.88)	13.85 (13.07–15.87)	13.41 (11.24–17.34)	0.705
Increased, No. (%)	7 (6.4)	0 (0)	7 (7.3)	0.596
AST				
Level, U/L	26.91 (23.82–30.89)	35.33 (31.72–39.11)	26.19 (23.20–29.43)	<0.001
Increased, No. (%)	1 (0.9)	0 (0)	1 (1.0)	1.00
Renal function				
Creatinine				
Level, μmol/L	37.93 (36.63–43.51)	30.27 (27.95–32.30)	39.21 (34.24–44.187)	< 0.001
Reduced, No. (%)	98 (89.1)	13 (92.9)	85 (88.5)	0.354
BUN				
Level, mmol/L	3.83 (3.15–4.64)	4.28 (3.49–5.83)	3.82 (3.10–4.60)	0.048
Increased, No. (%)	1 (0.9)	1 (7.1)	0 (0)	0.119

Note: data are presented as median (IQR) or No. (%). No. is the number of patients with available data. Percentages may not total 100 because of rounding.
Abbreviations: IQR, interquartile range; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen.
a P values when comparing vaccinated and unvaccinated pediatric cases using the $\chi2$ test, Fisher exact test, or Mann-Whitney U test. $P < 0.05$ indicates statistical significance.

Table 5
Differences in immune features between vaccinated and unvaccinated pediatric patients during the recovery phases.

Biomarker	Median (IQR)			P value
	Total (N=110)	Unvaccinated Pediatric Patients (n=14)	Vaccinated Pediatric Patients (n=96)	
IgG, AU/mL	185.46 (141.89–209.68)	7.91 (1.77–15.59)	190.24 (156.49–211.95)	<0.001
IgM, AU/mL	0.43 (0.24–0.79)	0.32 (0.22–0.93)	0.45 (0.24–0.78)	0.953
WBCs, 10^9/L	6.64 (5.66–8.17)	9.72 (7.56–10.24)	6.47 (5.49–7.66)	0.001
Increased, No. (%)	9 (8.2)	1 (7.1)	8 (8.3)	1.00
Neutrophils, 10^9/L	2.99 (2.28–3.86)	2.99 (2.11–4.38)	2.99 (2.31–3.74)	0.740
Increased, No. (%)	3 (2.7)	1 (7.1)	2 (2.1)	0.338
Lymphocytes, 10^9/L	2.95 (2.53–3.56)	4.70 (4.09–4.87)	2.90 (2.37–3.25)	<0.001
Increased, No. (%)	3 (2.7)	2 (14.3)	1 (1.0)	0.0422
Monocytes, 10^9/L	0.43 (0.34–0.53)	0.61 (0.45–0.64)	0.41 (0.34–0.51)	0.003
Increased, No. (%)	1 (0.9)	1 (7.1)	0 (0.0)	0.127
Eosinophils, 10^9/L	0.18 (0.13–0.32)	0.18 (0.10–0.22)	0.19 (0.14–0.32)	0.410
Increased, No. (%)	4 (3.6)	1 (7.1)	3 (3.1)	0.425
Basophils,10^9/L	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.624
Increased, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
CD3$^+$ T cells	71.38 (67.51–74.53)	65.04 (61.07–66.87)	72.33 (68.40–74.74)	0.002
Increased, No. (%)	1 (0.9)	0 (0.0)	1 (1.0)	1.00
CD4$^+$ T cells	36.59 (32.56–40.01)	36.29 (33.61–40.23)	36.40 (32.14–39.67)	0.855
Increased, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
CD8$^+$ T cells	25.67 (21.93–30.06)	18.30 (15.83–22.93)	26.16 (22.88–30.60)	<0.001
Increased, No. (%)	2 (1.8)	1 (7.1)	1 (1.0)	0.239
CD4/CD8	1.42 (1.15–1.75)	1.98 (1.55–2.24)	1.37 (1.07–1.67)	0.001
Increased, No. (%)	17 (15.5)	6 (42.9)	11 (11.5)	0.008
Reduced, No. (%)	53 (48.2)	2 (14.3)	51 (53.1)	0.007

Note: data are presented as median (IQR) or No. (%). No. is the number of patients with available data. Percentages may not total 100 because of rounding.
Abbreviations: IQR, interquartile range; WBCs, white blood cells.
a P values when comparing vaccinated and unvaccinated pediatric cases using the $\chi2$ test, Fisher exact test, or Mann-Whitney U test. $P < 0.05$ indicates statistical significance.

4. Discussion

As of Mar 15, 2022, the cumulative number of confirmed cases infected with SARS-CoV-2 Omicron variant in Tianjin city has reached 438, 110 (25.1%) of whom were pediatric patients. The severity of clinical symptoms and prognosis of children with COVID-19 has always been the focus of research on SARS-CoV-2 infection and immunization

(García, 2020). Several studies suggested that the clinical features of pediatric patients with COVID-19 are much milder than those of adults (Chang et al., 2020; Chen et al., 2020b; Wu et al., 2020). Consistent with previous studies, we found that the proportion of pediatric patients with asymptomatic or mild symptoms was higher than adult patients, and pediatric patients had a lower proportion of moderate symptoms than adult patients. As a special group, children with COVID-19 have their
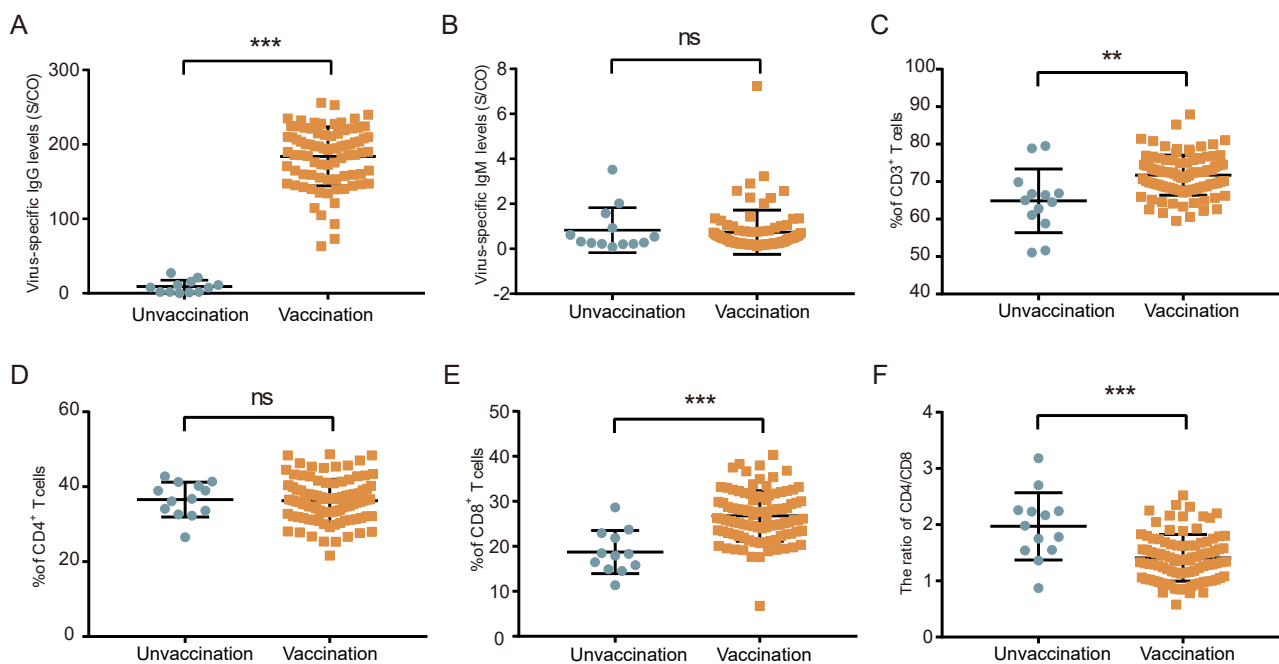
Fig. 3. Differences in immunological characteristics of pediatric patients with or without SARS-CoV-2 vaccination. **A, B** The levels of virus-specific IgG (**A**) and virus-specific IgM (**B**) between different groups. **C–E** Comparisons of the percentage of CD3$^+$ T cell subsets (**C**), CD4$^+$ T cell subsets (**D**) and CD8$^+$ T cell subsets between different groups (**E**). **F** The ratio of the CD4$^+$/CD8$^+$ T cells between different groups. Each dot represents one donor. Data were analyzed using Mann-Whitney U test (ns, $P > 0.05$, *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$). Error bars represent the mean and SD.

Table 6
Correlation between SARS-CoV-2 vaccination and nucleic acid re-detectable positive.

	Pediatric Patients (n = 110)		P value	Adult Patients (n = 320)		P value	Total (n = 430)		P value
	Unvaccinated (n = 14)	Vaccinated (n = 96)		Unvaccinated (n = 24)	Vaccinated (n = 296)		Unvaccinated (n = 38)	Vaccinated (n = 392)	
NRP, No. (%)	11 (78.6)	87 (90.6)	0.177	12 (50.0)	235 (79.4)	0.001	23 (60.5)	322 (82.1)	0.001
RP, No. (%)	3 (21.4)	9 (9.4)		12 (50.0)	61 (20.6)		15 (39.5)	70 (17.9)	

Note: data are presented as No. (%). No. is the number of patients with available data. Percentages may not total 100 because of rounding. RP, nucleic acid re-detectable positive in patients during rehabilitation or post-discharge, otherwise, it was defined as non-RP (NRP).
a P values when comparing vaccinated and vaccinated cases using the $\chi 2$ test. $P < 0.05$ indicate statistical significance.

unique characteristics. However, there is insufficient knowledge on the characteristics of the clinical laboratory data of convalescent pediatric patients infected with SARS-CoV-2 Omicron.

In this study, we compared and analyzed the clinical features and laboratory data between convalescent pediatric and adult patients or healthy children. Our result showed that pediatric patients had less clinical symptoms and fewer rates of RP compared with adult patients during the recovery period. Abnormal liver function indicators were rarely observed in convalescent pediatric patients compared with adult patients. There was an obviously lower proportion of pediatric patients with abnormally increased ALT and AST levels compared with adult patients, which indicated that children infected with Omicron had less risk of liver injury. Cai et al. reported that 21.5% of COVID-19 patients with elevated levels of ALT and AST had a liver injury during hospitalization and patients with abnormal liver tests were at increased risk of progressing to severe disease (Cai et al., 2020). Nardo et al. reported that the reasons of liver injury in COVID-19 may range from direct infection by SARS-CoV-2, indirect involvement by systemic inflammation, iatrogenic causes such as drugs and ventilation to exacerbation of underlying liver disease (Nardo et al., 2021). In addition, compared with the reference range, we found that the proportion of pediatric patients with abnormally reduced creatinine levels was visibly higher than adult patients and healthy children. It was unclear what caused this phenomenon. One of the possible explanation might be that pediatric patients lack exercise and eat an unbalanced diet during recovery phases.

We further compared the immune profiles between pediatric and adult patients or healthy children and found that the level of WBCs, lymphocytes, monocytes and eosinophils in pediatric patients was higher than in adult patients but similar to healthy children, although those biomarkers in most convalescent patients were within the normal range. However, the SARS-CoV-2-specific IgG levels were lower in pediatric patients than in adult patients but significantly higher than in healthy children. Research in adult patients has identified the importance of CD4$^+$ T cells in controlling and fine-tuning the pathogenesis and outcomes of SARS-CoV and Middle East respiratory syndrome CoV infection (Chen et al., 2020a). Interestingly, we found that the CD4$^+$ T cell levels were obviously lower in pediatric patients than in adult patients or healthy children, and the proportion of abnormally reduced CD4$^+$ T in pediatric patients was higher than in healthy children. Wu et al. showed that the counts of CD4$^+$ T cells were positively associated with liver and myocardial injury biomarkers in pediatric patients (Wu et al., 2020). Qin et al. suggested that a decrease of CD4$^+$ T cells was common in adult patients with severe and moderate COVID-19, however, this was rarely seen in pediatric patients [3 (1.9%)]. In fact, they were even increased in 14 moderate cases (15.9%) (Qin et al., 2020). In this study, pediatric patients had lower levels of liver injury indicators (AST and ALT) and CD4$^+$ T cells levels than adult patients who were more prone to liver injury. Therefore, the role of CD4$^+$ T cells in COVID-19 warrants further investigation. In addition, we observed that the proportion of adult patients with abnormally increased monocytes

was higher than pediatric patients, while it was not clear what caused this phenomenon.

In the context of the global COVID-19 pandemic, vaccination is the most effective measure to prevent and combat the spread of COVID-19 (Štefan et al., 2021). Over the past two years, mass vaccination programs have been carried out globally. The clinical presentation of infections with SARS-CoV-2 is very heterogeneous and the risk of a severe course clearly increases with age. Therefore, older adults have always been an important target group for vaccinations. However, children's awareness of the virus is relatively weak, and it is difficult for them to maintain safe social distancing. At present, various countries are also vigorously carrying out the work of childhood vaccination. In this study, we found that vaccinated pediatric patients had higher CRP and creatinine levels but lower AST and BUN levels than unvaccinated pediatric patients, which was completely different from adult patients. In addition, compared with unvaccinated pediatric patients, vaccinated pediatric patients had notably higher IgG, CD3$^+$ T cells and CD8$^+$ T cells levels during the recovery. Interestingly, SARS-CoV-2 vaccines had a completely different effect on immune characteristics in adult patients. The explanation for this phenomenon is still unclear and needs further research.

Some previous studies have reported on RP diagnoses of SARS-CoV-2 RNA test in some recovered patients (An et al., 2020; Lan et al., 2020; Ling et al., 2020; Qu et al., 2020; Li et al., 2021). An et al. reported that young patients, with a mild diagnosis of COVID-19 were more likely to display RP status after discharge (An et al., 2020). In this study, all of the 430 enrolled patients infected with the SARS-CoV-2 Omicron variant were confirmed as RNA-negative by a commercial kit before being discharged from Tianjin Haihe Hospital, however 12 (10.9%) pediatric patients and 73 (22.8%) adult patients received RP diagnoses during the recovery phases in Tianjin First Central Hospital or after discharging from Tianjin First Central Hospital. In contrast with An et al., our result suggested that convalescent pediatric patients had lower RP rates than adult patients (Table 1). However, whether the SARS-CoV-2 vaccine has had an effect on preventing RP in recovered patients remains unclear. In this study, the results showed that SARS-CoV-2 vaccine had a significant protective effect on the prevention RP in convalescent patients, especially in adult patients. Vaccination is regarded as a means of ending the global COVID-19 pandemic, but some individuals still get infected with SARS-CoV-2 after immunization, which is known as breakthrough infection. In fact, breakthrough infections are being reported globally. In this study, 392 (91.2%) patients, including 96 pediatric patients and 296 adult patients, had been vaccinated with SARS-CoV-2 vaccines but had breakthrough infection after vaccination. Although the mechanism of SARS-CoV-2 Omicron breakthrough infection was explored in several studies currently (Jamal et al., 2022; Lee et al., 2022; Zhang et al., 2022), due to its ability to rapidly evolve, the SARS-CoV-2 virus may never be eradicated. Therefore, there are many important new topics to work on if we need to live with SARS-CoV-2 for a long time.

Several important limitations in our study that might create bias. First of all, this was a retrospective and single-center study of convalescent patients admitted to the hospital, standardized data of a larger cohort might more suitable to evaluate the change of immune response in convalescent pediatric patients after SARS-CoV-2 Omicron variant infection. Therefore, further studies with large multi-center samples are needed. Secondly, since all the clinical data were collected retrospectively, the information, particularly laboratory-related information, was incomplete for some individuals.

5. Conclusions

To our knowledge, this is the first study to comparatively analyze the differences in clinical and immunological features between pediatric and adult patients or healthy children during the recovery phases. This study showed that convalescent pediatric patients had significantly different clinical and immune characteristics from convalescent adult patients or healthy children. Moreover, SARS-CoV-2 vaccines not only had a notably impact on the clinical data of convalescent patients, but also played an active role in preventing nucleic acid re-detectable positive in convalescent patients. Our findings provide new insights into realizing the effects of Omicron on the long-term health of pediatric patients and provide a reference for prevention and treatment measures for children infected with Omicron.

Data availability

All the data generated during the current study are included in the manuscript. Further information and requests for resources and reagents should be directed to H.M.

Ethics statement

This study was reviewed and approved by the Tianjin Municipal Health Commission and the Medical Ethics Committee of Tianjin First Central Hospital (Ethics committee archiving No. 2022N052KY, Approval Date: January 24, 2022) and conducted in accordance with the Declaration of Helsinki 1975 (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/), which was revised in 2013. All enrolled patients and participants gave written consent (provided by at least a parent or guardian) to the passive use of their medical records and clinical information for research purposes and the data generated from the published study.

Author contributions

Jing-Yu Wang: methodology, investigation, data curation, formal analysis, visualization, validation, writing-original draft. Tian-Ning Li: software, data curation. Chun-Lei Zhou: formal analysis, investigation. Jie Zhao: data curation, formal analysis, software. Meng Wang: investigation, visualization. Yuan Wang: investigation. Yan Jiang: investigation. He-Nan Dong: software. Qian-Ru Qi: data curation. Mu Hong: project administration, conceptualization, supervision, writing-review & editing.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.virs.2022.10.009.

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