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Clinical features of Chinese children with COVID-19 and other viral respiratory infections

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Abstract

Objective: Few studies have explored the clinical features in children infected with SARS-CoV-2 and other common respiratory viruses, including respiratory syncytial virus (RSV), Influenza virus (IV), and adenovirus (ADV). Herein, we reported the clinical characteristics and cytokine profiling in children with COVID-19 or other acute respiratory tract infections (ARTI).

Methods: We enrolled 20 hospitalized children confirmed as COVID-19 positive, 58 patients with ARTI, and 20 age and sex-matched healthy children. The clinical information and blood test results were collected. A total of 27 cytokines and chemokines were measured and analyzed.

Results: The median age in the COVID-19 positive group was 14.5 years, which was higher than that of the ARTI groups. Around one-third of patients in the COVID-19 group experienced moderate fever, with a peak temperature of 38.27°C. None of the patients displayed wheezing or dyspnea. In addition, patients in the COVID-19 group had lower white blood cells, platelet counts as well as a neutrophil-lymphocyte ratio. Lower serum concentrations of 14 out of 27 cytokines were observed in the COVID-19 group than in healthy individuals. Seven cytokines (IL-1Ra, IL-1β, IL-9, IL-10, TNF-α, MIP-1α, and VEGF) changed serum concentration in COVID-19 compared with other ARTI groups.

Conclusion: Patients with COVID-19 were older and showed milder symptoms and a favorable prognosis than ARTI caused by RSV, IV, and ADV. There was a low grade or constrained innate immune reaction in children with mild COVID-19.

KEYWORDS

ARTI, COVID-19, cytokines, pediatrics

Zhen-Zhen Zhang, Da-Peng Chen, and Quan-Bo Liu contributed equally to this study.

1 | INTRODUCTION

The coronavirus disease-2019 (COVID-19) infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) caused a global pandemic.[1] The clinical spectrum of COVID-19 varies from asymptomatic carriers to severe pneumonia characterized by acute respiratory distress syndrome (ARDS) and multiorgan failure with mortality.[2–4] Emerging evidence suggests that older age, male, obesity, and comorbidities such as diabetes, and cardiovascular diseases, are major risk factors among patients with COVID-19.[5,6] Although both adults and children are vulnerable to SARS-CoV2, children are relatively spared from this disease, with significantly reduced prevalence, severity, and mortality. The potential mechanisms of this disparity remain to be clarified. The entry of SARS-CoV-2 into host cells relies upon the binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor and the priming of the S protein by host proteases, such as TMPRSS2.[7] Therefore, one hypothesis is that reduced viral entry and replication in the lung resulted in mild symptoms in children. However, several studies have discovered similar viral load in children and adult.[8–10] Furthermore, recently another study compared the mRNA level of ACE2 and TMPRSS2 in nasal mucosa between children and adults, which showed that the expression of ACE2 and TMPRSS2 was not correlated with age and viral infection.[11] The role of the SARS-CoV-2 receptor in pediatric COVID-19 needs further study. Another plausible theory is that children might have a distinct response to SARS-CoV-2 compared to adults, attributed to the differences in the composition and functional responsiveness of the immune system.[12,13]

Recently, Suratannon et al. have put forward that trained immunity acquired from various respiratory viral infections, routine vaccinations, such as Bacillus Calmette–Guérin (BCG) vaccination, shapes and enhances the innate immune response to SARS-CoV-2 in children.[14]

Although children are less affected by SARS-CoV-2 infection, other respiratory viruses such as a respiratory syncytial virus (RSV) or Influenza virus have marked predilections for children, resulting in significant morbidity and mortality.[15,16] To date, no study has investigated the immune status between COVID-19 and other common respiratory virus infections in the pediatric population. Herein, we compared the clinical features and cytokine expression among COVID-19 children patients with acute respiratory tract infection (ARTI) caused by RSV, Influenza virus (IV), adenovirus (ADV). This study tries to delineate the immune profiling caused by SARS-CoV2 in children, which adds to our understanding of the immunopathologic mechanisms of SARS-CoV-2 infection in children.

2 | PATIENTS AND METHODS

2.1 | Patients

Twenty hospitalized children confirmed as COVID-19 positive were enrolled in this study from the designated treatment hospitals of COVID-19 in Chongqing from January 2020 to March 2020. The patients were diagnosed according to the "Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance" released by the National Health Commission of China[17,18] and confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) or next-generation sequencing. Fifty-eight patients infected with ARTI (RSV = 19, IV = 19, ADV = 20) and 20 healthy controls from Children's Hospital of Chongqing Medical University were included. Clinical information and laboratory results were collected posthospitalization. The disease severity was defined as asymptomatic, mild, mild to moderate, moderate to severe, and severe based on Florin's research.[19] This study was approved by the Research Ethics Commission of Chongqing Medical University (KY-2020-01.01).

2.2 | Cytokines measurement

The serum of patients diagnosed with COVID-19 was collected at the earliest after hospitalization. The serum of 20 age and sex-matched healthy subjects were collected later. The serum samples of ARTI were taken from the BioBank of Children's Hospital of Chongqing Medical University. Following manufacturer instructions, the cytokine and chemokine concentrations were measured by the Bio-Plex Human Cytokine Screening Panel (27-Plex #12007283; Bio-Rad). The cytokines included were interleukins (IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, and IL-17), colony-stimulating factors (GM-CSF, G-CSF), interferons (IFN-γ), tumor necrosis factor (TNF-α), growth factors (basic fibroblast growth factor [FGF], platelet-derived growth factor [PDGF-BB], vascular endothelial growth factor [VEGF]), and chemokine family (Eotaxin, inducible protein-10 [IP-10], monocyte chemoattractant protein-1 [MCP-1], macrophage-inflammatory protein [MIP-1α], MIP-1β, regulated upon activation normal T-cell expressed and secreted [RANTES]).

2.3 | Statistical analysis

All continuous variables were described as mean with standard deviation (*SD*), while categorical characteristics were described as counts and percentage (%). Mann–Whitney *U* test was applied for comparison between two groups, and analysis of variance (ANOVA) was used to compare COVID-19 and ARTI groups, respectively. $p < 0.05$ was considered statistically significant, and $p < 0.001$ was considered highly statistically significant. Statistical analysis was performed using the R software, version 3.6.0.

3 | RESULTS

3.1 | Demographic and clinical characteristics COVID-19 and other ARTI patients

There was a significant difference between COVID-19 and other ARTI in demographic features and clinical manifestations (Table 1). In general, patients with COVID-19 were older and showed milder symptoms and disease severity than the other three groups. The median age

TABLE 1 Demographic and clinical characteristics of pediatrics with COVID-19 and ARTI

	COVID-19 (*N* = 20)	RSV (*N* = 19)	FLU (*N* = 19)	ADV (*N* = 20)	*p*
Gender(male) (*n*,%)	12 (60.0)	9 (47.4)	9 (47.4)	18 (90.0)	0.015
Age (median, range)	14.50 (0.64-17.00)	0.48 (0.08-11.66)	2.00 (0.25-7.25)	1.25 (0.33-14.75)	<0.0001
Fever (*n*,%)	7 (35.0)	8 (42.1)	17 (89.4)	18 (90.0)	<0.0001
Duration of fever (median, range)	6 (1-13)	4 (1-7)	6 (1-8)	6.5 (2-14)	0.0152
Peak temp (℃)	38.27	39.37	39.32	40.12	
Cough (*n*, %)	15 (75.0)	19 (100.0)	18 (94.7)	17 (85.0)	0.072
Dyspnea (*n*, %)	0 (0.00)	8 (42.1)	4 (26.7)	7 (35.0)	0.012
Wheezing (*n*, %)	0 (0.00)	9 (47.4)	5 (26.3)	9 (45.0)	0.003
Diarrhea	0 (0.0)	2 (10.5)	4 (21.1)	7 (35.0)	0.022
Disease severity (*n*, %)					0.0002
Asymptomatic	6 (30.0)	0 (0.00)	0 (0.00)	0 (0.00)	
Mild	14 (70.00)	11 (57.89)	5 (26.32)	3 (15.00)	
Mild to moderate	0 (0.00)	6 (31.58)	10 (52.63)	8 (40.00)	
Moderate to severe	0 (0.00)	2 (10.53)	4 (21.05)	5 (25.00)	
Severe	0 (0.00)	0 (0.00)	0 (0.00)	4 (20.00)	
WBC (*10^9, Ref 4–12)	5.33 ± 1.33	11.09 ± 5.95	7.55 ± 5.54	13.99 ± 9.83	<0.0001
RBC (*10^12, Ref:3.8-5.5)	4.6 ± 0.41	4.27 ± 0.45	4.52 ± 0.59	4.59 ± 0.38	0.162
PLT (*10^9, Ref:100–380)	222.8 ± 52.14	364.5 ± 135.5	265.7 ± 165.1	309.4 ± 155.7	0.035
NLR(mean, range)	1.70 (0.68-4.57)	1.36 (0.33-4.05)	2.23 (0.3-6.18)	3.29 (0.35-12.86)	0.035
CRP > 8 mg/L (*n*, %)	1 (8.3)	4 (21.1)	5 (26.3)	8 (40.0)	0.177
PCT > 0.25 ng/L (*n*, %)	4 (20.0)	8 (42.1)	7 (36.8)	11 (55.0)	0.195

Abbreviations: CRP, C-reaction protein; WBC, white blood cell; NLR, Neutrophil-lymphocyte ratio; PCT, procalcitonin; PLT, platelet; RBC, red blood cell.

of the COVID-19 group was 14.5 years (0.64–17.0 years). All patients in the COVID-19 positive group were either asymptomatic or showed mild infection. In contrast, two (10.53%) cases in the RSV group, four (21.03%) cases in the FLU group, and five (25%) cases in the ADV group showed moderate to severe symptoms respectively, and four (20%) patients in the ADV group showed severe disease after infection. As to clinical symptoms, cough and fever were the most frequent symptoms of all four groups. Except for the COVID-19 group, patients in the other three groups had high fever with peak body temperature exceeded 39°C. In addition, dyspnea, wheezing, and diarrhea were absent in the COVID-19-infected group but common in the remaining three groups.

Next, we compared the peripheral blood abnormalities among the four groups. There were significant differences between the COVID-19-infected and other groups in white blood cells (WBC), platelet (PLT) counts as well as neutrophil-lymphocyte ratio (NLR). Albeit there was no statistical significance of the C-reaction protein (CRP) and procalcitonin (PCT) level, the ARTI resulting from RSV, IVA/B, and ADV showed a higher rate of CRP(>8 mg/L) and PCT (>0.25 ng/L) level. These results suggested that the inflammation response was stronger in ARTI caused by RSV, IVA/B, and ADV.

Finally, we compared the radiology characteristics of different pathogens. For most patients with COVID-19, there were few positive lesions observed through radiology exam, and ground-glass opacity (GGO) was the main finding (Figure 1A,B). By contrast, patients with other ARTI showed extensive injuries, including consolidation, tree-in-bud sign, extensive interlobular septa thickness mosaic signs (Figure 1C–H). Taken together, SARS-CoV-2 is prone to affect the school-age and adolescents, with milder symptoms and lower inflammation response compared to other respiratory pathogens.

3.1.1 | Cytokines expression profile in COVID-19 patients and healthy children

Since children with COVID-19 showed mild disease with normal laboratory tests, we speculate the inflammatory reaction might be mild or absent in patients with these mild cases. We first compared the circulating cytokines levels in COVID-19 patients with age and gender-matched healthy subjects. Of all 27 cytokines detected, more than half (15/27) showed changed serum levels after SARS-CoV-2

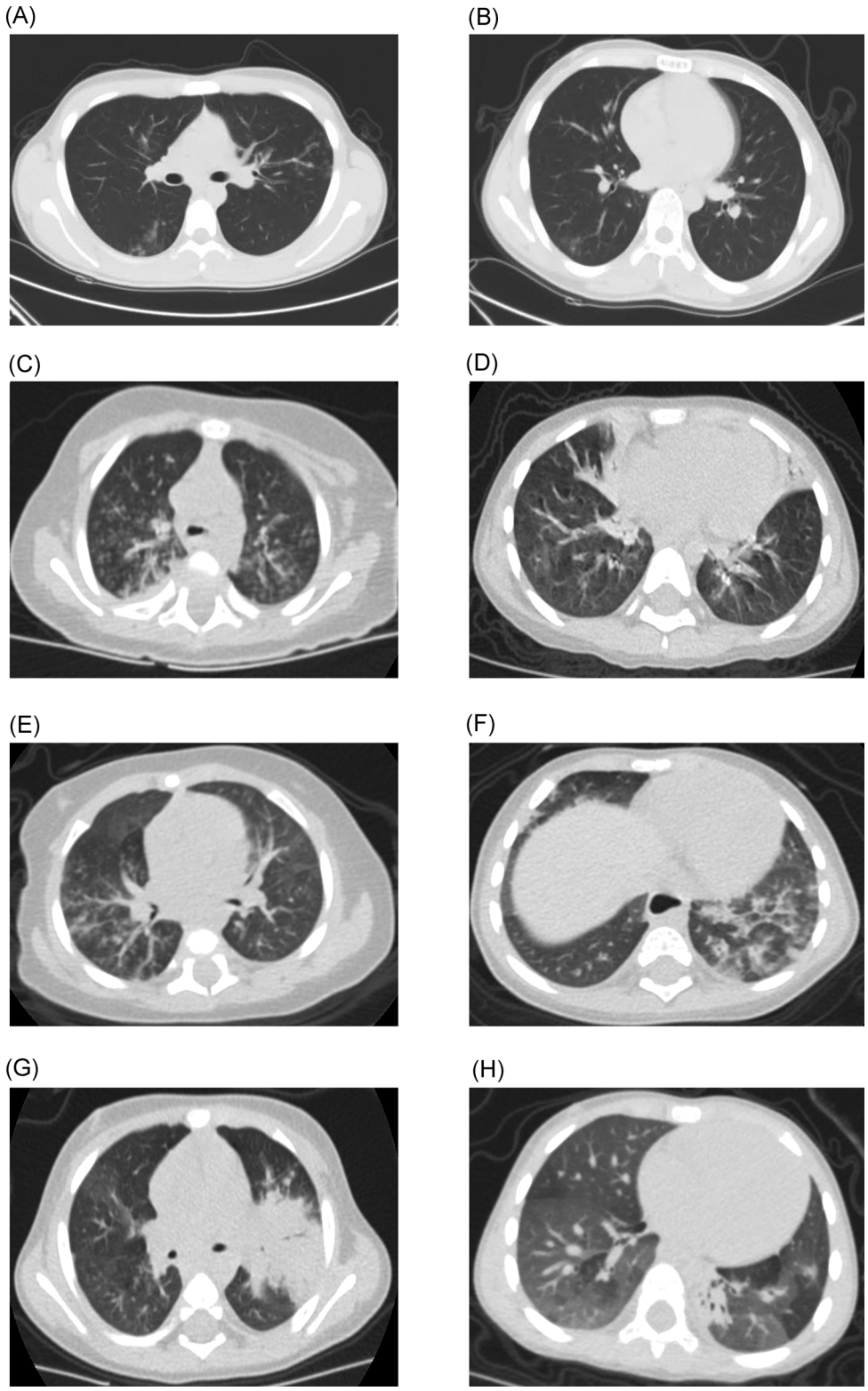

FIGURE 1 (See caption on next page)

infection, with the majority (14, 93.7%) showing decreased serum concentrations (Figure 2). Proinflammation cytokines including IL-1β, IL-1RA, IL-4, IL-8, IL-9, IL-17, TNF-α, INF-γ, G-CSF, and chemokines such as Eotaxtin, MIP-1β, MIP-1α, RANTES were decreased while VEGF significantly increased in serum concentration in the COVID-19-infected group ($p < 0.05$). No statistical differences were observed between two groups in IL-2, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, MCP-1, PDGF-BB, GM-CSF, and IP-10. These results suggested that the inflammation response was inhibited in mild COVID-19 patients in children.

3.1.2 | Serum cytokines levels in COVID-19 and ARTI pediatric patients

Next, we investigated the serum cytokines in the COVID-19 group against RSV, IVA/B, and ADV groups, respectively. Seven cytokines (TNF-α, IL1-RA, IL-1β, IL-9, IL-10, MIP-1α, VEGF) simultaneously altered all RSV, FLU, and ADV subgroup, and VEGF was present the only cytokine increased in COVID-19 group (Figure 3A–G). As expected, cytokines expression exhibited different profiling when the ARTI subgroup was compared to the COVID-19 group, respectively. The FLU and ADV subgroup share similar profiles as IL-6, IL-17, IP-10, Eotaxin, FGF, MIP-1β, and RANTES significantly changed compared to the COVID-19 group. INF-γ and IL-1β expression were increased only in the FLU and ADV groups, respectively. Interestingly, only IL-15 and INF-γ changed in the RSV group comparing to the COVID-19 group (Figure 3H; Table S1). These results suggested a stronger inflammation with more cytokines perturbed in the ARTI groups, especially in the FLU and ADV subgroup.

4 | DISCUSSION

This study described the clinical features and cytokines profile in pediatric patients infected with SARS-CoV-2, RSV, IVA/B, and ADV. Children in the COVID-19 groups were older compared to the other groups, and 30% of cases were asymptomatic. This is consistent with the view that severe conditions such as acute respiratory distress syndrome and multisystem inflammatory syndrome rarely happen in COVID-19-children.[20–22] In our observation, patients in the COVID-19 group showed mild to moderate fever and cough. Unlike infection with other ARTI viruses, dyspnea, wheezing, and gastrointestinal symptoms were absent in the mild COVID-19 group. As to the laboratory examination, patients infected with SARS-CoV-2 had lower inflammatory indexes, including CRP and PCT. Comparing to ARTI caused by RSV, FLU, or ADV, COVID-19 children showed limited GGO in the chest radiology, which indicated mild injury of the lungs.

Similar to adult COVID-19, the immune status closely associated with disease severity and prognosis in children. Xiong et al. described the hematological and immunological results of 244 children patients with COVID-19.[23] There were higher absolute lymphocyte counts, IgG and IgA levels, and IL-6, IL-10, TNF-α, INF-γ levels in symptomatic patients in contrast to the asymptomatic cases. In another retrospective study enrolled 127 COVID-19 children patients, the author reported that decreased IgA, CD4 + CD25 + T lymphocyte percentage, and increased CRP, PCT, and IL-10 were associated with COVI-19 pneumonia.[24] Wu et al. discovered IL-10 markedly increased in moderate cases of pediatric patients with COVID-19.[25] Recently, interferons have been proposed as effective antivirus for COVID-19 patients with different severity in adults.[26,27] In the current study, we included more cytokines and various disease conditions. Cytokines related to inflammation and chemokines presented different profiling in COVID-19, with a majority decreased in both healthy children and other ARTI patients. Moreover, the cytokines profiling of IVA/B and ADV resembled each other. Given more severe cases in the FLU and ADV group in our observation, it is possible that the change of cytokines correlated with disease severity but not the pathogen infected with.

Interestingly, in our observation, VEGF significantly increased in patients after SARS-CoV-2 infection. Chi et al. discovered that the serum VEGF was positively correlated with viral titers. The underlying mechanism might be related to the SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 virus bind to ACE2 and then activated the renin-angiotensin system (RAS), which induced the inflammatory response and VEGF synthesis.[25] However, the role of VEGF in the development of pediatric COVID-19 needs extensive studies to disclosure the underlying mechanism.

This study had several limitations. First, all pediatric patients with COVID-19 were mild cases. We, therefore, could not analyze pediatric COVID-19 with different severity. The cytokines profiling underwent remarkable differences among asymptomatic, mild, severe, and critically ill patients through other observations. In our study, we did not observe PIMS-TS patients after more than 2 months of follow-up. In addition, patients with COVID-19 were older than the other group, including the ARTI group, which might affect the immune status and partially ascribed to the difference among groups. Finally, all COVID-19 children were enrolled in the study, and all the serum samples of patients were taken at the early stage of hospitalization. We could not investigate the kinetics of cytokines.

In conclusion, pediatric patients with COVID-19 showed mild symptoms and favorable prognoses compared with ARTI caused by RSV, IV, and ADV. The change of cytokine expression demonstrated a low grade or constrained innate immune reaction in children with mild COVID-19. To the best of our knowledge, the current study was the first one that compared the clinical feature and the cytokines profiling of COVID-19 and other ARTI in the pediatric population, which help pediatricians better understand these diseases.

FIGURE 1 Radiology exam of patients with COVID-19 (A,B), RSV (C,D), FLU (E,F), and ADV (G,H). (A) A 16-year-old patient presented with fever and fatigue for 3 days. The CT scan showed ground-glass opacity (GGO) on both lobes. (B) A 14-year-old patient admitted to the hospital with a cough and fever. The CT scan showed GGO on the lower right lobe. (C) A 1-year-old patient with RSV infection, CT scan indicated extensive lesions in both two lobes. There was a tree in bud sign in the two lungs. (D) A 2-year-old patient with RSV infection, CT showed consolidation change of both lungs. (E) A 2-year-old patient infected with Influenza virus B. There was a tree in bud sign in the upper right lobe. (F) An 84-day patient with IVA infection. Radiology indicated the extensive thickening of the interlobular septa in the low left lobe. (G) 1-year-old patients infected with ADV, CT showed extensive consolidation lesion in the upper left lobe. (H) A 2-year-old patient with adenovirus pneumonia, a mosaic sign in both lungs indicated extensive airway injury postinfection. In addition, the image also presented a consolidation lesion in the lower left lobe

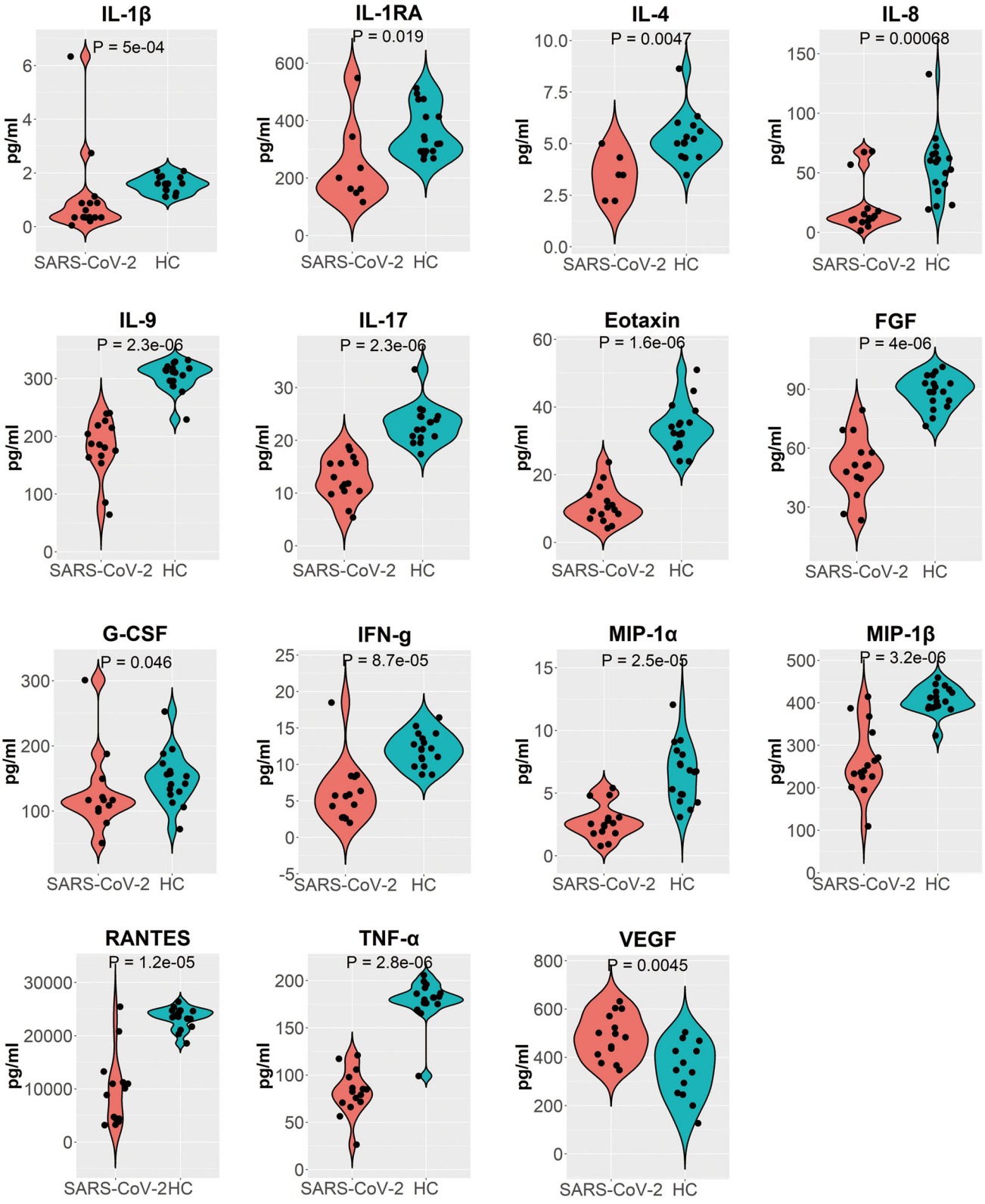

FIGURE 2 Cytokines dysregulated children infected with SARS-CoV-2. Blood samples were collected from pediatric patients with COVID-19 and healthy children match with age and sex [Color figure can be viewed at wileyonlinelibrary.com]

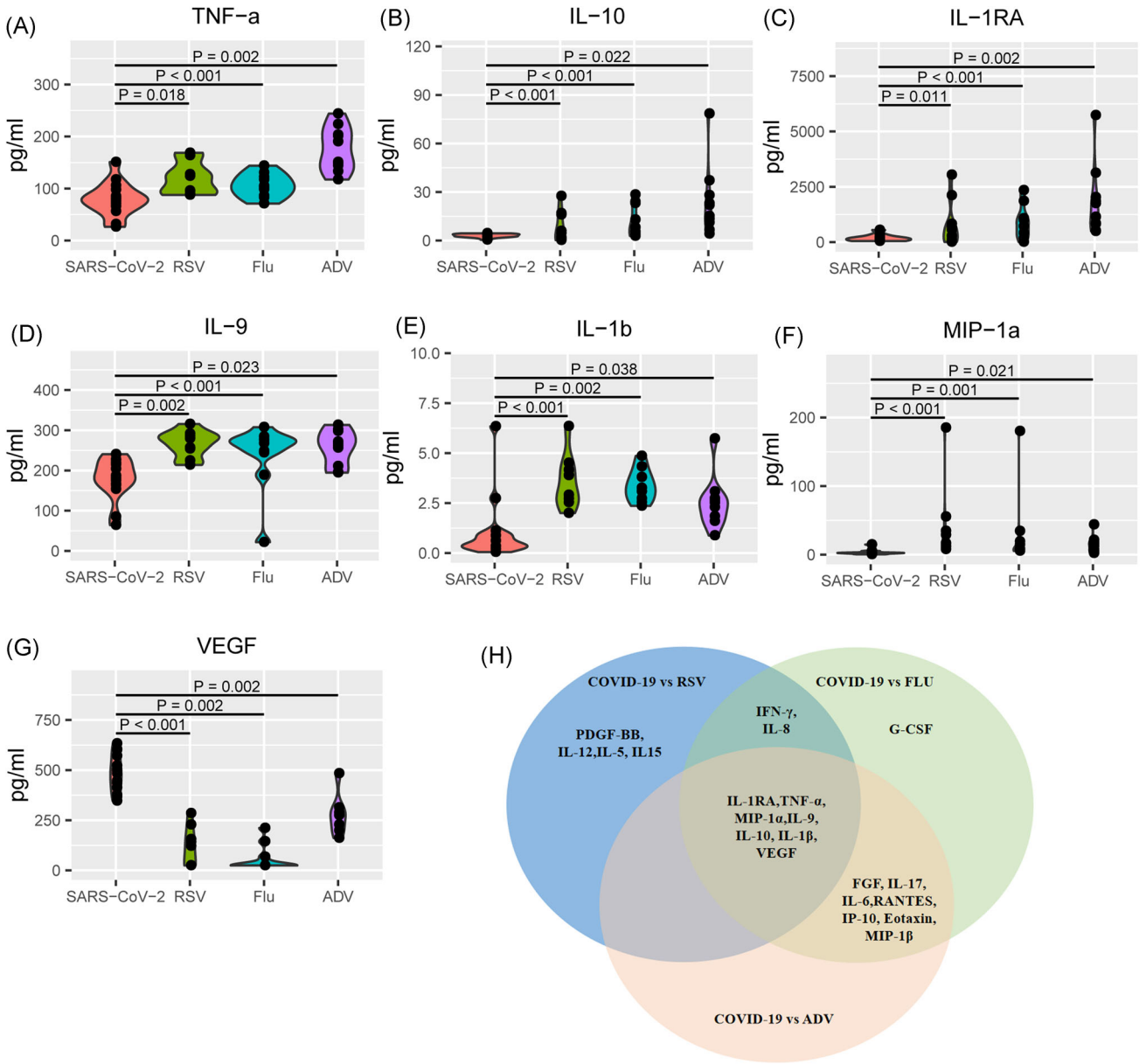

FIGURE 3 Cytokines vary in COVID-19 and ARTI caused by RSV, IVA/B, and ADV. (A–G) Serum cytokines concentration changed in all RSV, ADV, and Influenza groups comparing to the COVID-19 group. Black lines indicate statistical analysis and *p* values across indicated populations. (H) cytokines altered in COVID-19 against RSV, FLU, and ADV, respectively [Color figure can be viewed at wileyonlinelibrary.com]

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

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