

## Multi-organ Presentation of Children with COVID-19 Infection in the North of Iran: A Retrospective Study

Masood Kiani<sup>1</sup>, Ali Mohammadpour-Mir<sup>2</sup>, Hadi Sorkhi<sup>3</sup>, Mohammadreza Esmaeili Dooki<sup>3</sup>, Maryam Nikpour<sup>4</sup>, Kazem Babazadeh<sup>1</sup>, Mohamadreza Tabatabaie<sup>2</sup>, Sanaz Meherabani<sup>1</sup>, Morteza Alijanpou<sup>5</sup>, Sareh Hosseinpour<sup>1</sup>, Hassan Mahmoodi-Nesheli<sup>5</sup>, Sahar Sadr Moharerpour<sup>1</sup>, Ahmad Tamaddoni<sup>3</sup>, Mohammadreza Salehiomran<sup>5</sup>, Paiam Payandeh<sup>1</sup>, Iraj Mohammadzadeh<sup>5</sup>, \*Mohsen Mohammadi<sup>1</sup>

<sup>1</sup>Assistant Professor, Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran. <sup>2</sup>MD, Clinical Research Development Center, Amircola Children's Hospital, Babol University of Medical Sciences, Babol, I.R.Iran. <sup>3</sup>Professor, Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran. <sup>4</sup>PhD of Health Sciences, Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran. <sup>5</sup>Associate Professor, Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran.

### Abstract

**Background:** COVID-19 can cause various symptoms in children. The aim of the study was evaluation of multi-organ presentation of children with COVID-19 infection in Amirkola Children's Hospital in Babol, Iran.

**Materials and Methods:** This study was conducted retrospectively and data were extracted from medical records. All children with suspected COVID-19 infection who were referred to Amirkola Children's Hospital in Babol (north of Iran) from March 4, 2020 to May 30, 2020 were enrolled. Clinical features of the respiratory and digestive system and Multisystem Inflammatory Syndrome in Children (MIS-c) were assessed. In all children WBC, RBC, Hb, MCV, Lymphocyte, CRP, ESR, ALT, AST, PT, PTT and platelets were also evaluated. Data analysis was conducted with SPSS software version 16.0.

**Results:** Totally 37 children were recruited to the study. The most common clinical symptoms in children were fever (86.5%), weakness (75.7%) anorexia (73%) abdominal pain (48.6.9%), diarrhea (45.9%) nausea and vomiting (37.8%), cough (32.4%). About 60% and 8% of children had Hb and MCV less than normal levels respectively, So that 80% and 60% of children had abnormal elevations in CRP and ESR, respectively. Also, 32% and 35% of them had an increase in ALT and AST levels respectively and about 40% of them had hypoalbuminemia. Additionally, 7 of 37 (18.9%) children had MIS-c. The result of the study demonstrated that 10/37 (32.4%) of children had pulmonary involvement.

**Conclusion:** In this study gastrointestinal symptoms were more common than respiratory symptoms in children with COVID-19 infection. Also, about one- fifth of children with COVID-19 had MIS-c. Attention to manifestations of organs other than respiratory system in children with COVID-19 infection is necessary.

**Key Words:** Children, COVID-19, Gastrointestinal symptoms, Respiratory symptoms.

\*Please cite this article as: Kiani M, Mohammadpour-Mir A, Sorkhi H, Esmaeili Dooki M, Nikpour M, Babazadeh K, et al. Multiorgan Presentation of Children with COVID-19 Infection in the North of Iran: A Retrospective Study. Int J Pediatr 2021; 9(4): 13411-419. DOI: **10.22038/IJP.2020.51187.4065**

### \*Corresponding Author:

Mohsen Mohammadi, MD, Assistant Professor of Pediatric Infectious Disease, Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R. Iran.

Email: dr.mohamadi61@yahoo.com

Received date: Aug.23, 2020; Accepted date: Jan. 22, 2021

## 1- INTRODUCTION

At the end of 2019, a new virus was detected in Wuhan, China, which caused widespread pneumonia in humans, World Health Organization (WHO) reported the pandemic of novel coronavirus worldwide in October 2020 (1). Up to 23 August 2020, about 23 million and 356 thousand people in the world and in Iran have been infected with COVID-19 infection, respectively (2). COVID-19 infection affects all age groups (3), but severe disease in children is less common than adults (4). CDC reported 146,790 patients with COVID-19, 1.7 percent were under 18 years old (5). The main involvement of COVID-19 infection is the respiratory tract, it can damage to vital organs such as lung, liver, heart, kidney, and gastrointestinal (GI) tract (4, 6). Fever and cough are the most common symptoms. Other symptoms include diarrhea, abdominal pain, sore throat, nasal congestion, and vomiting.(7).

Also, new studies from the UK (8, 9), Europe, Canada, the US (10, 11) and other countries (12, 13), reported that children with COVID-19 show Multisystem Inflammatory Syndrome in Children (MIS-C) with COVID-19 infection. Most of the children with MIS-C have incomplete or complete criteria of Kawasaki disease. However, these patients were different from Kawasaki disease epidemiologically and most of the cases MIS-C were detected in older children and adolescents (14). Laboratory findings in children with COVID-19 also change. Researchers reported changes in white blood cell (WBC), c-reactive protein (CRP), lymphocyte, high lactate dehydrogenase (LDH), and inflammatory markers (procalcitonin, ferritin) associated with COVID-19 infection(15). Additionally, abnormal levels of liver function tests like alanine aminotransferase (ALT), aspartate aminotransferase (AST), were also reported (16). Chest radiography can be

unremarkable or indicate findings in favor of pneumonia (17). These findings include glass ground opacity, unilateral or diffuse shadows, and involvement (17). Although studies were performed on the clinical symptoms, laboratory and radiography features of children with COVID-19, various aspects of this infection in children especially in Iran have not yet been agreed upon. The aim of the study was an evaluation of multiorgan presentation of children with COVID-19 infection in Amirkola Children's Hospital in Babol city, Iran.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population.

This study was conducted by retrospective method and data were extracted from medical records. All children with suspected COVID-19 infection who were referred to Amirkola Children's Hospital in Babol (north of Iran) from March 4, 2020 to May 30, 2020 were enrolled. Children in the study were defined with a suspected or confirmed COVID-19 infection (18, 19).

If children had the appendix symptoms, they would be considered as suspected:

- A child with a history of sore throat, chills or dry cough with dyspnea and with or without fever which could not be attributed to another etiological factor.
- A child with fever and respiratory symptoms and a history of having contact with COVID- 19 patient,
- A child with pneumonia who despite adequate treatment did not have a good clinical response.

If they had the appendix symptoms, they would be considered as confirmed one:

- with positive oropharyngeal and nasopharyngeal swab specimens for SARS-CoV-nucleic acid using real-time reverse-transcriptase

polymerase-chain-reaction (RT-PCR) assay;

- or with a radiological presentation that strongly suggests a COVID-19 infection according to the pediatric radiologist and infectious disease specialist's opinion (18, 19).

## 2.2. Data collection

Data were collected by two specialists (one was specialized in pediatric infection sciences and another in health sciences). The information extracted include demographic epidemiologic variables, clinical symptoms, laboratory results, radiographic finding and pharmacological treatments.

### 2-2-1. Evaluation of clinical manifestations and management

Clinical manifestations of children with COVID-19 infection include fever, shortness of breath, cough, weakness, anorexia, diarrhea, and nausea-vomiting, rash, and abdominal pain. All treatment measures including drug and supportive therapies were also evaluated.

### 2-2-2. Evaluation of Multisystem inflammatory syndrome (MIS-c)

According to the definition of World Health Organization, MIS-c was diagnosed (20). For all children with MIS-c symptoms, echocardiography was performed by a pediatric cardiologist.

### 2-2-3. Evaluation of laboratory results and radiographic finding

After admission, Oropharyngeal and nasopharyngeal swab specimens were taken from all children and the real time polymerase chain reaction (RT-PCR) test for SARS-Cov-2 RNA was done. All tests were evaluated at Caspian Core Research Laboratory. In all children, complete blood count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured (the information was taken from

hospital records). Normal cut-off levels were considered for CRP <10 mg/dL and ESR <25 mm/hr (6). White blood cells (WBC), Red blood cells (RBC), hemoglobin (Hb), Mean Cell Volume (MCV) were also conducted. Normal cut-off levels were considered for WBC ( $5-11 \times 10^3$  cell/l), RBC ( $4-11 \times 10^6$  cell/l), Hb (> 11 mg) and MCV (70-96). Liver enzymes like ALT, AST and albumin were evaluated. Normal cut-off levels were considered for ALT, AST less than 35 and 40 IU/l for girls and boys, respectively and albumin between 3-5.5gr/dl (21).

Additionally, some of the coagulation factors such as Prothrombin Time (PT), Partial Thromboplastin Time (PTT) and Platelets (Plt) ( $150-450 \times 10^3$  cell/l) were assessed. All tests were performed in the laboratory of Amirkola Children's Hospital. A Chest X-ray or computed tomography (CT) was taken from all children to assess pulmonary lesion. In imaging evaluation, some features such as the number of lobe involvement, the location of the involvement (unilateral or bilateral), predominant distribution (central or peripheral) were examined. All imaging features were evaluated by an infectious diseases specialist, pediatric pulmonologist and one experienced pediatric radiologist.

### 2-2-4. Demographic and epidemiological information

Demographic, epidemiological and medical characteristics such as age, gender, place of residence, history of having contact with infected individuals, living at the epidemic site of the disease and recent travel were recorded. In addition, the consequences of the disease in the child including the length of hospital stay, hospitalization in the intensive care unit and mortality were assessed.

## 2-3. Ethical considerations

This study was approved by the Health Research Institute of Babol University of Medical Sciences (ID:

IR.MUBABOL.REC. 1399.184). This study was performed retrospectively from the medical records, and children their parents were allowed to publish information in this article.

#### 2-4. Inclusion and exclusion criteria

Inclusion criteria were children between two months and 18 years old, and having no history of chronic liver, kidney disease, neuromuscular and congenital heart disease and also immune system deficiency. The exclusion criterion was infectious diseases other than COVID-19.

#### 2-5. Data Analyses

Statistical analysis was performed using SPSS software version 16.0 through descriptive and analytical indicators.  $P < 0.05$  was considered as significant level in the study.

### 3- RESULTS

Totally 37 children were recruited to the study. These children with a suspected

diagnosis of COVID-19 were admitted to Amirkola Children's Hospital of Babol University of Medical Sciences from March 5, 2020 to May 30, 2020. Of these 37 children, 21 (56.8 %) children were identified as confirmed cases with COVID-19 infection, and 16 (43.2%) were suspected or probable cases.

#### 3-1. General and epidemiological information

The median age of children was 6.00 (IQR 3.50, 10.00) years. The majority of them were male (75%) and live in the city (61%). Twelve percent of children had a history of diseases such as asthma or hypothyroidism. All children lived in epidemic region with COVID-19 infection. Thirty-six children were admitted to the hospital and 1 child was managed at home. The median of hospital stay and interval of the onset of symptoms at admission (day) in affected children was 8.00 (IQR 6.50, 10.50) (day), and 4.00 (IQR 2.00, 6.00) (day), respectively (**Table.1**).

**Table-1:** Demographics, clinical findings and imaging result of 37 patients with COVID-19.

Variables	Value
Age in years, median (IQR)	6.00 (3.50-10.00)
Weight in kg, median (IQR)	20.00 (16.00-3
Gender: Male, no. (%)	20 (54.10)
Place of residence: Urban, no. (%)	25 (67.6)
The length of stay in the hospital, median (IQR)	8.00 (6.50- 10.50)
Time from beginning of symptoms to hospitalization	4.00 (2.00-6.00)
<b>Clinical findings</b>	
Fever, no. (%)	32 (86.5)
Anorexia (%)	27 (73.0)
Weakness (%)	28 (75.7)
Dry-cough, no. (%)	12 (32.4)
Sort throat	11 (29.7)
Rash, no. (%)	6 (16.2)
DispenH (%)	10 (27.0)
Nausea/vomiting, no. (%)	14 (37.8)
Abdominal pain, no. (%)	18 (48.6)
Myalgia, no. (%)	13 (35.10)

Tiredness, no. (%)	11 (24)
Diarrhea, no. (%)	16 (36)
Sore throat, no. (%)	7 (16)
<b>Imaging results</b>	
Pulmonary involvement, no. (%)	10 (32.4)
Bilateral lung, no. (%)	6 (60)
Multilobar lung involvement, no. (%)	7 (70)
Predominant central distribution, no. (%)	7 (70)
GGO with consolidation no. (%)	7 (70)
Consolidation no. (%)	3 (30)
Pleural Effusion no (%)	2 (20)

IQR: Interquartile range.

### 3-2. Clinical symptoms and treatment

The most common clinical symptoms in children were fever (86.5%), weakness (75.7%), and anorexia (73%). Also, these children experience symptoms such as abdominal pain (48.6.9%), diarrhea (45.9%), nausea and vomiting (37.8%), cough (32.4%), sore throat (29.7%), and dyspnea (27%). Additionally, 6 (16.2%) of them had a rash. All cases with COVID-19 infection and lung involvement received antibiotics such as ceftriaxone, clindamycin and antiviral such as Kaletra. Also, if needed, the patient was put on bronchodilators like Duolin or Ventolin with a nebulizer and supplemental oxygen with nasal cannula. All children were discharged with the good general condition.

### 3-3. Multisystem inflammatory syndrome

The findings of the study indicated that, 7 of 37 (18.9%) children had MIS-c. All children with MIS-c syndrome experienced rash, erythema in different parts of the body, also 2 of them experienced conjunctivitis. Also, most of them (70%) had gastrointestinal symptoms such as anorexia, diarrhea and abdominal pain. Two of them had sore-throat and one child was admitted to the intensive care unit. Additionally, echocardiographic

findings showed 4 of 7 with MIS-c syndrome had heart involvement like pericardial effusion (PE), myocarditis, and inflammation in the coronary arteries. Corticosteroids were used to treat all of them.

### 3-4. Laboratory and Radiographic findings

Findings of the study showed that 38.5% of children were positive for SARS-CoV-2 RT-PCR and 13.5 % were positive for SARS-CoV-2 antibody testing. The result of study illustrated the median WBC and RBC counts were 8900 (IQR 7 100, 11650) cells/l and 4120 (3790-4570) cells/l respectively. The median of Hb was 10.50 (IQR 10.1, 11.60) mg/d, and the median of MCV was 78.00 (IQR 74.10, 80.35) FL.

About 60% and 8% of children had Hb and MCV less than the normal level. Also, 14/37 (37.8%) of children had lymphopenia. Markers of inflammation were assessed with median ESR 35.00 (IQR 16.50, 76.50) mm/hr and CRP 35.00 (IQR 16.50, 76.50) mg/L. So that 80% and 60% of children had elevated CRP and ESR, respectively. Additionally, the median of liver enzymes such as ALT and AST and albumin were 30.50 (IQR 24.75, 51.50) U/L, 29.00 (IQR 14.75, 54.50) U/L and 3.45 (IQR 2.95, 4.20) g/dl, respectively. Also, 32% and 35% of them had an increase in ALT and AST levels

respectively and about 40% of them had blood albumin less than normal level. The median of coagulation factors such as PT, PTT and platelets are shown in **Table.2**.

The result of the study demonstrated that 10/37 (32.4%) of children experienced pulmonary involvement (**Table.1**).

**Table-2:** Laboratory findings of 37 patients with COVID-19.

Parameter	Value
Immunoglobulin M no. (%)	13 (21.3)
Immunoglobulin G no. (%)	13 (21.3)
Immunoglobulin M and Immunoglobulin G, no. (%)	7 (11.5)
Immunoglobulin M in cells/uL, median (IQR)	8900 (7100-11650)
Red blood cells in cells/uL, median (IQR)	4120 (3790-4570)
Hemoglobin in g/dL, median (IQR)	10.50 (10.1- 11.60)
Mean Cell Volume in femtoliter median (IQR)	78.00 (74.10-80.35)
Platelets in thousands/uL, median (IQR)	263000 (19000- 423000)
Absolute lymphocyte count in thousands/uL, median (IQR)	2130 (1012-3111)
Erythrocyte sedimentation rate in mm/hr, median (IQR)	35.00 (16.50- 76.50)
C-reactive protein in mg/L, median (IQR)	43.00 (21.50- 65.00)
Aspartate Aminotransferase in U/L, median (IQR)	30.50 (24.75- 51.50)
Alanine aminotransferase in U/L, median (IQR)	29.00 (14.75- 54.50)
Albumin in g/dl, median (IQR)	3.45 (2.95- 4.20)
PT in ng/mL, median (IQR)	13.10 (12.50-14.10)
PTT in pg/mL, median (IQR)	33.50 (30.00- 38.50)

IQR: Interquartile range.

#### 4- DISCUSSION

Aim of this study was evaluation of multiorgan presentation of 37 children with COVID-19 infection. The results demonstrated that the most common clinical presentations of COVID-19 in children were fever, weakness, anorexia, abdominal pain, diarrhea, nausea, respectively. The most important abnormal laboratory results were an increase in CRP, ESR, low hemoglobin and elevated liver enzymes, respectively. Also, 18% and 32% of them had MIS-C and the lung lesion, respectively. In the study, fever, weakness and anorexia, were the most common symptoms and then gastrointestinal symptoms such as abdominal pain and diarrhea. Based on various studies, the most common symptoms in children with COVID-19 were cough and fever (7, 22). Whereas only one-third of children in our

study had cough. One justification for this discrepancy can be that clinical presentations of COVID-19 infection are different in the world (3). In our region, it mostly presents in the form of gastrointestinal symptoms. Also, another justification may be due to a change in the behavior of the virus over time. The result of the study illustrated that 18% of children had MIS-C. Children with MIS-C experience problems such as gastrointestinal symptoms, rash, red eyes and heart involvement. Children with MIS-C, in studies of the United States (23), and UK (9), Italy (24), and France (25) also had the same symptoms. SARS-CoV-2 can act as a direct stimulant of autoimmune or auto inflammatory conditions, with unknown mechanisms(26). Also, SARS-CoV-2 can block types I and III interferon responses

following causing cytokine storm (27). The finding of the study indicated that about 78.4% of children had abnormal inflammatory indexes. Compared to the past studies, it has been higher (85). This difference in results may be due to measurement methods and laboratory kits used. Sixty percent of children had hemoglobin less than 11 mg/dl which has not been reported in previous studies. It is unknown whether COVID-19 is a cause of anemia. In patients with COVID-19 infection inflammatory cytokines such as interleukin-6, -10 and  $1\beta$  were elevated. Interleukin -6 regulates hepcidin and increases hepcidin level in both chronic and acute inflammation (28).

Hepcidin is secreted from hepatocytes and it can inhibit iron secretion from macrophages and reduce iron absorption from the intestinal lumen (28). Of course, hereditary anemia (minor thalassemia) or iron deficiency and malnutrition may have influenced our results. About 30% of children had elevated ALT and AST association with decreased albumin. The result was in line with Cai et al.'s study (29), and Qiu et al.'s study (6). Elevated liver enzymes reported in different studies were between 6% and 70% (6, 29).

Possible mechanism may be related to the presented angiotensin-converting enzyme 2 (ACE2) in intestines (16, 30). In previous studies, lymphopenia was not common in children, and most indexes in CDC were normal (6, 10); while in the study, lymphopenia in about 37.8 % of children was a significant laboratory finding. Of course, more sample sizes, as well as genetic factors, can be the reason for the difference in results. About a third of children had respiratory symptoms. But chest x-rays were reported in most patients with no specific findings. These findings are similar to past studies, and results showed a simple chest x-ray has low specificity compared to lung CT scan (31). The most common finding on lung CT

scan was bilateral GGO. These results have been matched by the findings of chest CT scans in adults and children with COVID-19. Hoang et al. in a systematic review study of 7748 children with COVID-19 reported that 32% of them had pulmonary involvement and ground glass opacities were the most frequent CT abnormality (3).

#### 4-1. Study Limitations

This study had some limitations. First, we did not measure procalcitonin, ferritin, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), D-dimer and CPK. Second, the study was retrospective.

#### 5- CONCLUSION

In the study, gastrointestinal symptoms were more common than respiratory symptoms in children with COVID-19 infection. Also, about one-fifth of children with COVID-19 had MIS-C. Attention to manifestations of organs other than the respiratory system in children with COVID-19 infection is necessary.

#### 6- AUTHORS' CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by MN and MM. The first draft of the manuscript was written by MN and MM. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**7- CONFLICT OF INTEREST:** None.

#### 8- REFERENCES

1. Jun Yasuhara, Kae Watanabe, Hisato Takagi, Naokata Sumitomo, Toshiki Kuno, COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis, *Pediatric Pulmonology*. 2021;56:252–263
2. World Health Organization. WHO Coronavirus (COVID-19) Dashboard.

Available at: <https://covid19.who.int/27Aguest2020>.

3. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. *EClinicalMedicine*. [serial online] 100433 [cited 2020, June 9] Available from: ScienceDirect.
4. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *The Pediatric infectious disease journal*. 2020;39(5):355.
5. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children - United States F-A, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69:422.
6. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *The Lancet Infectious Diseases*. 2020. 20(6):689-696
7. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in pediatric emergency departments in Italy. *New England Journal of Medicine*. 2020. 9;383(2):187-190.
8. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *The Lancet*. 2020;395(10237):1607-8.
9. Whittaker E, Bamford A, Kenny J, Kafrou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA*. 2020. 324(3):259-269.
10. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatrica*. 2020;109(6):1088-95.
11. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York city. *JAMA* 2020;324:294-6,
12. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem Inflammatory Syndrome in Children during the COVID-19 pandemic: a case series. *Journal of the Pediatric Infectious Diseases Society*. 2020. [Serial online] 101232 [cited 2020, May 23] Available from: ScienceDirect.
13. Dolinger MT, Person H, Smith R, Jarchin L, Pittman N, Dubinsky MC, et al. Pediatric Crohn's Disease and Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 Treated with Infliximab. *Journal of Pediatric Gastroenterology and Nutrition*. 2020. 71(2):153-55.
14. Hennon TR, Penque MD, Abdul-Aziz R, Alibrahim OS, McGreevy MB, Prout AJ, et al. COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; a Western New York approach. *Progress in Pediatric Cardiology*. 2020. 23:101232.
15. Jiang M, Guo Y, Luo Q, Huang Z, Zhao R, Liu S, et al. T cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of COVID-19. *The Journal of Infectious Diseases*. 2020. 29; 222(2):198-202.
16. Musa S. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? *Arab Journal of Gastroenterology*. 2020. 21(1):3-8.
17. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. *JAMA*. 2020. 323(21):2195-98.
18. Guildline diagnosis and tretment for children and infant with COVID-19 infection. six flowchart. 2021. Available at: <https://www.irimc.org/Portals/0/Images/News/>
19. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology*. 2020: 296 (2): E32-E40.
20. WHO. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Scientific brief. 2020 [cited 2020

May 15] Available at: [WHO /2019 n CoV / Sci Brief/ Multisystem Syndrome Children /2020.1](#)

21. Kleinman RE, Goulet O-J, Mieli-Vergani G, Sanderson IR, Sherman PM, Shneider BL. Walker's pediatric gastrointestinal disease: physiology, diagnosis, management: 6nd ed PMPH USA, Ltd; 2018.

22. Schwierzeck V, König JC, Kühn J, Mellmann A, Correa-Martínez CL, Omran H, et al. First reported nosocomial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a pediatric dialysis unit. *Clinical Infectious Diseases*. 2020. 27;72(2):265-70.

23. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis K. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: a single center experience of 44 cases. *Gastroenterology*. 2020. 159(4):1571-1574.

24. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet*. 2020; 395: 1771–78.

25. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al.

Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020; 3;369: m2094.

26. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. *Nature Reviews Rheumatology*. 2020;16:413-14.

27. Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell*. 2020. 28;181(5):1036-45.

28. Camaschella C, Nai A, Silvestri L. Iron metabolism and iron disorders revisited in the hepcidin era. *haematologica*. 2020;105(2):260-72.

29. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: abnormal liver function tests. *Journal of hepatology*. 2020. 73(3):566-74.

30. Pirola CJ, Sookoian SC. COVID-19 and ACE2 in the liver and gastrointestinal tract: Putative biological explanations of sexual dimorphism. 2020. 159(4):1620-21

31. Silverstein WK, Stroud L, Cleghorn GE, Leis JA. First imported case of 2019 novel coronavirus in Canada, presenting as mild pneumonia. *The Lancet*. 2020; 395(10225): 734.