**Liječ Vjesn** 2022;144;suplement 1:153–157
https://doi.org/10.26800/LV-144-supl1-24

**Izvorni rad | Original article**

# Evaluation of coronary artery and immunologic status in post-COVID-19 children in Sarajevo

## Evaluacija koronarnih arterija i imunološkog statusa kod post-COVID-19 djece u Sarajevu

Senka Mesihović-Dinarević[1,2]✉, Jasminka Prguda-Mujić[3], Timur Šečić[2]

[1] Academy of Arts and Sciences of Bosnia and Herzegovina
[2] Eurofarm Center Polyclinic, Department of Pediatrics, Sarajevo, Bosnia and Herzegovina
[3] Eurofarm Center Polyclinic, Clinical Laboratory Department, Sarajevo, Bosnia and Herzegovina

**Key words**
POST-COVID-19,
SEROPOSITIVITY,
CORONARY ARTERY

**SUMMARY.** *Introduction:* Although evidence has demonstrated that SARS-COV-2 primarily affects the upper respiratory tract, other systems are also involved such as gastrointestinal and cardiovascular system. At present, there is insufficient data on cardiovascular and immunologic involvement in COVID-19 paediatric patients. *Patients and Methods:* This study evaluated 70 children previously healthy or with no pre-existing heart disease from Sarajevo with positive post-COVID history. Detailed cardiovascular examination was performed, with parameters of body weight, height, oxygen saturation, pulse, blood pressure, electrocardiogram (ECG), 24hrs Holter ECG, echocardiography. Laboratory tests included values of polymerase chain reaction (PCR) and SARS-COV-2 immunoglobulin G /IgG/ and immunoglobulin M /IgM/, CBC /complete blood count/, creatinine phosphokinase myofibrilae /CPKMB/, creatinine phosphokinase/CPK/, lactate dehydrogenase /LDH/, liver enzymes, D dimer, C reactive protein/CRP/ and urine. *Results:* Majority of children (64.3%) were asymptomatic. ECG was normal in relation to patients' age, except in eight patients (intermittent palpitations on exertion): short PR interval, so in 24hrs ECG Holter there was no significant arrhythmias except incomplete right branch block / IRBB/ in 12%, monofocal ventricular ectopicextrasystole /VES/ in 15%. Echocardiogram was normal in all patients with normal ejection fraction of the left ventricle, no pericardial effusion, vegetations or thrombus was detected. Mean diameter of coronary arteries right /RCA/ and left /LCA/ ranged from 1.98 mm to LCA 2.09 mm except in one symptomatic patient a diameter of left coronary artery /LCA/ was enlarged up to 3.8 mm. The concentration levels of COVID-19 IgG showed a statistical significance when compared between younger and older age groups in examined children ($p < 0.05$; $p = 0.043$). *Conclusion:* Cardiovascular evaluation should always be an option in post-COVID patients. Immunological assessment is necessary in post-COVID patients in order to gain a further understanding of patient's status.

**Ključne riječi**
POSTCOVID-19,
SEROPOZITIVNOST,
KORONARNE ARTERIJE

**SAŽETAK.** *Uvod:* Iako su rezultati studija pokazali da SARS-COV-2 prvenstveno utiče na gornje respiratorne puteve, uključeni su i gastrointestinalni i kardio vaskularni sistem. Trenutno,nema dovoljno podataka o kardiovaskularnoj i imunološkoj zahvaćenosti kod COVID19 pedijatrijskih pacijenata. *Pacijenti i metode:* U studiji je učestvovalo 70 djece iz Sarajeva, koja su prethodno bila zdrava ili nisu imala srčane bolesti, s pozitivnom anamnezom nakon COVID-a. Urađen je detaljan kardiovaskularni pregled, uz parametre tjelesne težine, visine, mjerenja saturacije kiseonika, pulsa, krvnog pritiska, elektrokardiogram (EKG), 24 satni Holter EKG, ehokardiografija i laboratorijski testovi koji su uključivali vrijednosti lančane reakcije polimeraze (PCR) i SARS-COV-2 imunoglobulina G /IgG/ i imunoglobulin M /IgM/, KKS /kompletna krvna slika/, kreatinin fosfo kinaza miofibrila /CPKMB/, kreatinin fosfokinaza /CPK/, laktat dehidrogenaza /LDH/, enzimi jetre, D-dimer, C reaktivni protein /CRP/ i urin. *Rezultati:* Većina djece (64.3%) bila je asimptomatska. EKG je bio uredan u odnosu na dob pacijenata osim kod osam pacijenata /intermitentne palpitacije na napor/sa skraćenim PR intervalom, a u 24h Holter EKG nije bilo signifikantne aritmije osim u 12% inkompletan blok desne grane i kod 15% monofokalne ventrikularne ektopične ekstrasistole. Ehokardiogram je bio uredan kod svih pacijenata sa normalnom ejekcionom frakcijom lijeve komore, bez perikardne efuzije, vegetacije ili tromba. Prosječan dijametar koronarnih arterija desne i lijeve je iznosio od 1.98 mm do 2.09 mm osim kod jednog simptomatskog pacijenta: uvećan dijametar lijeve koronarne arterije / LKA/ do 3.8 mm. Nivoi koncentracije COVID-19 IgG pokazali su statističku značajnost u poređenju između mlađe i starije starosne grupe kod ispitivane djece ($p<0,05;p=0,043$). *Zaključak:* Kardiovaskularna evaluacija bi uvijek trebala biti opcija kod pacijenata nakon COVID-a. Imunološka procjena je neophodna kod pacijenata nakon COVID-a kako bi se steklo dalje razumijevanje statusa pacijenta.

✉ **Adresa za dopisivanje:**
Prof. dr. Senka Mesihović-Dinarević, https://orcid.org/0000-0002-0862-0103
Academy of Arts and Sciences of Bosnia and Herzegovina, e-pošta: dinarevicsenka@gmail.com

The SARS-COV-2 (COVID19) has become a major concern due to its high death rate and its unknown nature[1]. SARS-COV-2 continues to spread rapidly across the globe causing serious concerns. Although evidence has demonstrated that SARS-COV-2 primarily affects the upper respiratory tract followed by lower respiratory tract damage leading to severe pneumonia, other systems are also involved such as gastrointestinal and cardiovascular as well[2,3]. Studies have shown that patients with cardiovascular diseases may be subject to an increased risk of death[4]. The clinical manifestation varied among the population and the main symptoms of the infection are fever, dry cough, headache, and dyspnoea, with the progress to pneumonia[5]. The manifestation and the behaviour of the virus infection in children are poorly defined[6]. Severe manifestation of SARS-COV-2 in children is rear and the hospitalisation rate is significantly lower compared to adults[7]. Similar to adults, the respiratory tract is affected most commonly. In the largest study up to date, 2143 paediatric patients, 94.1% of the children were either asymptomatic or had mild to moderate disease. The study also showed that, 5.2% of children had respiratory distress or hypoxia and 0.6% who progressed to acute respiratory distress syndrome or multiple organ dysfunctions[8]. Most of the studies have shown that SARS-COV-2 infection is involved in cardiovascular system, however, mostly in adults[9]. Earlier studies showed a milder clinical course for infants; few of them needed the intensive-care treatment. At present, there is insufficient data on cardiovascular and myocardial involvement in COVID-19 paediatric patients.

**The aim of this study** is to evaluate the cardiovascular status and immunological in post-COVID-19 children in Sarajevo.

## Patients and methods

The total of 70 paediatric patients previously healthy or with no pre-existing heart disease from Sarajevo region with positive post-COVID history were evaluated. They were examined in the Eurofarm Polyclinic in Sarajevo, from October 2020 until April 2021. Patients were referred from local paediatrician or by parents concerned due to child's symptoms. The children have been previously SAR-COV-2 positive or had a previous contact with a positive person. Epidemiological data were collected, establishing the 1$^{th}$ day of the symptoms or the contact with SARS-COV-2 positive person, a detailed examination was performed, including parameters such as oxygen saturation, pulse, blood pressure (BP), body weight and height. Echocardiography was performed by a paediatric cardiologist. The examination included left ventricle ejection fraction (LVEF), left ventricle end-diastolic diameter (LVEDD), left ventricle end-systolic diameter (LVESD), S (septum), LVPW (left ventricle posterior wall), diameter of RCA (right coronary artery) and LCA (left coronary artery). In addition, blood examination was performed including complete blood count (CBC), C-reactive protein (CRP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), creatinine phosphokinase myofibrilae (CPKMB), creatinine phosphokinase (CPK), lactate dehydrogenase (LDH) and tests for immunological status: values of polymerase chain reaction (PCR) or serological test on corona: immunoglobulin G /IgG/ and immunoglobulin M /IgM.

### Statistical Analysis

All data were analysed using the SPSS version (Version 26.0.0.0.2019) in this study.

### Ethical considerations

The informed consent form was obtained from all parents following the explanation the aim of the study.

## Results

In the group of 70 children (40 boys and 30 girls) there were: infants <1 (n =10), 1–5 years (n= 20); 6–10 years (n=12); 11–15 years (n=21) and 16–18 years (n= 7) (Table 1.). All children were in relation to percentile scale within the average height and weight range from 25p-97p. The mean body temperature at the time of examination was: 36.6°C (34.3–37.6°C), mean oxygen saturation was 97.6% (94–99%). Pulse rate was within a normal range for age as was BP for age, height, and sex. Before referral to paediatric cardiologists, 24 patients were seen by local paediatrician. The period from contact with COVID-19 through a family member or at school, until referral to paediatrician was 7.5 days (1–21 days). Symptoms differed depending on age group; younger children had no or mild symptoms in comparison to the older group of children (Table 1). Majority of children (64.3%) were asymptomatic, except two 14-year-old boys, with palpitation on exertion, shortness of breath, including ECG changes: denivelation of ST segment in lead II, V5 and V6, lower oxygen saturation 91% and 94%, elevated CPKMB (38 and 45), with mildly enlarged in one patient a diameter of left coronary artery (LCA) up to 3.8 mm, no aneurysm, no skin changes, and with normal EF of LV. They were on short period (10–15 days) nonsteroids treatment, including low doses of Aspirin and vitamins (C and D), rest and no physical activity. Following the treatment and non-activity regime, they were fully recovered, free of symptoms, with normal oxygen saturation and normal values of CPKMB and CBC, diameter of LCA was within the normal range according to patients' age and body

Table 1. Clinical characteristic

| Clinical presentation | Children, No./total No. (%) |
|---|---|
| **Sex (n =70)** | |
| Boys | 40 (57.1%) |
| Girls | 30 (42.9%) |
| **Age groups** | |
| <1 year | 10 (14.2%) |
| 1–5 y | 20 (28.5%) |
| 6–10y | 12 (17.1%) |
| 11–15y | 21 (30.1%) |
| 16–18y | 7 (10.1%) |
| **Symptoms** | |
| Asymptomatic | 45(64.2%) |
| Cough | 15(21.4%) |
| Tiredness | 2(2.8%) |
| Sweats | 5(7.14%) |
| Palpitation on exertion | 8(11.4%) |
| Abdominal pain | 4(5.71%) |
| Fever | 21(30.1%) |
| Diarrhoea | 4(5.71%) |
| Exanthema | 3(4.28) |
| Shortness of breath | 2(2.85) |

Table 2. Laboratory parameters

| Laboratory parameters | Mean (±SD) |
|---|---|
| Complete blood count | |
| Lymphocytes ($10^9$/L) | 7.01 (±3.28) |
| RBC ($10^{12}$/L) | 4.70 (±1.7) |
| Hb (g/L) | 115 (±30.4) |
| Plt ($10^9$/L) | 311 (±118) |
| AST (U/L) | 16.0 (±6.3) |
| ALT (U/L) | 17.0 (±6.5) |
| CPK | 1.22 (±1.18) |
| CK-MB | 26.1 (±12.1) |
| D-DIMER (mg/L) | 0.2 (±0.4) |
| SARS-COV-2 IgG | 42.7 (±22.3) |
| SARS-COV-2 IgM | 0.25 (±0.35) |

weight. CBC, including platelets and white blood count, were within normal range, as well as urine, D-dimer, CRP, LDH, liver enzymes, CPK, CPKMB except as mentioned earlier (Table 2). ECG was normal, corresponding to patients' age, except in eight patients (intermittent palpitations on exertion) who had short PR interval 0.120–0.140 ms, with no delta wave, so 24 h ECG Holter was performed without any significant arrhythmias, except incomplete right branch block / IRBB/ that has been documented in 12%, and monofocal ventricular ectopic extrasystole in 15% (Table 2). The concentration of SARS-COV-2 IgG showed a statistical significance when compared between age groups ($p < 0.05$; $p = 0.043$). Echocardiogram was normal in all patients with normal ejection fraction of left ventricle (Table 3). No pericardial effusion, vegetation's or thrombus was detected. Mean diameter of coronary arteries right (RCA) and left (LCA) ranged 1.98 mm to LCA 2.09 mm. Z score calculation for coronary arteries including: body weight, height and gender of every patient, was within normal values for RCA and LCA (21,22). No anomalies were detected in their flow and diameter, with no aneurisms, except stated earlier in the text.

Table 3. Echocardiography parameters

| Echocardiography parameters | Mean (SD ±) | p values |
|---|---|---|
| LVEF (%) | 69.7 (±3.27) | 0.38 |
| LVEDD (mm) | 29.7 (± 3.7) | 0.42 |
| LVESD (mm) | 32.1 (±1.8) | 0.56 |
| RCA (mm) | 1.98 (±0.38) | 0.41 |
| LCA (mm) | 2.09 (± 0.29) | 0.38 |

## Discussion

The present study was conducted to evaluate the cardiovascular and immunological status in post-COVID-19 children in Sarajevo. Cardiovascular system complications such as heart failure, myocardial infarction, and arrhythmia, are not uncommon among adult patients infected with COVID-19[10]. However, the proportion of severe and critical cases in children was 10.6% under 1 year of age, and 3.0% among the 1–5, 6–10, 11–15, and >15 years' subsets, suggesting that infants may be at higher risk of severe respiratory failure than firstly thought[8]. Most commonly, the COVID-19 infection is manifested as mild disease in children according to the literature and data in our study.

Analysing the symptoms in children, fever is present in 40–60% of children, cough occurs in 40–50% of children, and headache, myalgia, and sore throat are more common than shortness of breath. After 7–10 days[19], children usually recover, whereas more severe forms are characterized by dyspnoea, hypoxia, cyanosis, dehydration with signs of respiratory distress syndrome, shock, myocardial lesions, or multiorgan failure[19].

A study conducted in the past among children showed that symptoms such as fever is present in 40–60% of children, cough occurs in 40–50% of children, whereas headache, myalgia, and sore throat are more common than shortness of breath. After 7–10 days, children usually recover, and more severe forms are characterised by dyspnoea, hypoxia, cyanosis, dehydration with signs of respiratory distress syndrome, shock, myocardial lesions, or multiorgan failure (27–29). In our study group, fever was present in 15 (70), cough 21 (70), shortness of breath 8 (70) patients, and majority were asymptomatic, which is the case with most of reported paediatric patients in post-COVID period. Identical changes have been reported by An-

dina et al.[30] in Madrid in 22 children, aged 6–17 years with moderate symptoms of COVID-19 disease. These atypical manifestations of COVID-19 disease did not require treatment and had a good outcome prognosis.

A study conducted in the past has revealed that children have a qualitatively different response to SARS-CoV-2, which may be related to the characteristics of their immune system to better control and localise COVID-19 infection to the upper respiratory tract resulting in milder infections[12,13]. Study conducted by Wang *et.al* has reviled during the examination that 7.2% of 138 COVID-19 adult patients had myocarditis[10]. While in another study performed by Zeng *et al.* 419 patients have been examined and increased LVED diameter, decreased LVEF and interventricular septum thickening was found in 11 patients[13]. Unlike during the previous study, we did not find any significant difference in terms of echocardiography examination, such as LVEF and LVED diameter, among examined children except for two 14-year-old boys with ECG changes: denivelation of ST segment in lead II, V5 and V6, lower oxygen saturation 91% and 94% respectively, elevated CPKMB with mildly enlarged diameter of left coronary artery (LCA) up to 3.8 mm in one patient, with no aneurysm, no skin changes, and with normal EF of LV. They were on short period (10–15 days) on nonsteroids treatment, including low doses of Aspirin and vitamins (C and D), with recommended rest and no physical activity. After the treatment and non-activity regime, they were fully recovered, free of symptoms, with normal oxygen saturation and normal values of CPKMB and FBC, diameter of LCA was within the normal range according to patients' age and body weight.

In the previous studies, few children have developed multisystem inflammatory response to SARS-COV-2 in common with Kawasaki disease, staphylococcal and streptococcal toxic shock syndrome, bacterial sepsis, and macrophage activation syndrome[14]. The main manifestation in Kawasaki disease in children <5 years is characterized by fever, skin rash, lymphadenopathy, and conjunctivitis. Inflammation of the coronary arteries occurs in severe cases of Kawasaki disease that spreads, causing a coronary artery aneurysm with the possibility of myocardial infarction in children, which is verified by ultrasound colour Doppler examination of the heart[15,16]. In our study group of children, there were no cases of multisystem inflammatory response to SARS-COV-2. Study conducted by Licciardi *et al* showed a Kawasaki-like hyper inflammatory syndrome in two children (7 and 2-year-old boys) as a delayed response to SARS-COV-2 infection, which caused mucocutaneous changes, elevated markers of inflammation, lymphopenia, thrombocytopenia[17]. Multisystem inflammatory response to SARS-COV-2 could be associated with altered cardiac parameters[18], however, in the series of patients evaluated in the current study, none of them fulfilled the MISC, typical or atypical Kawasaki disease criteria. All the patients were evaluated for coronary artery involvement, which was negative for all of them except as stated earlier.

Studies have shown that adults are more susceptible to severe infections and even severe forms of COVID-19 due to the large release of cytokines (cytokine storm) from macrophages, monocytes, and lymphocytes, leading to lung tissue damage and multiorgan failure[11,12]. In our study, the values of immunoglobulin G were significantly higher in the older group of children which indicates that with age the immune system is getting more responsive to the virus.

## Conclusion

Cardiovascular evaluation should always be an option in post-COVID patients. Immunological assessment is necessary in post-COVID patients in order to gain a further understanding of patient's status.

### *Conflict of interest*

The authors declare no conflict of interest.

*The paper has been revised and proofread by Samra Mušija, certified translator/interpreter for English with an extensive experience in translation, revision and proofreading of medical-related papers and documents.*

## REFERENCE


1. *Lai C-C, Ko W-C, Lee P-I, Jean S-S, Hsueh P-R.* Extra-respiratory manifestations of COVID-19. Int J Antimicrob Agents. (2020) 2020:106024. doi: 10.1016/j.ijantimicag.2020.106024.
2. *Bertoncelli D, Guidarini M, Della Greca A, Ratti C, Falcinella F, Iovane B, et al.* COVID19: potential cardiovascular issues in pediatric patients. Acta Bio Med AteneiParmensis. 2020;91: 177. doi: 10.23750/bm.v91i2.9655.
3. *Dhakal BP, Sweitzer NK, Indik JH, Acharya D, William P.* SARS-CoV-2 infection and cardiovascular disease: COVID-19 heart. Heart Lung Circ. 2020; 29:973–87. doi: 10.1016/j.hlc.2020.05.101.
4. *Zheng YY, Ma YT, Zhang JY, Xie X.* COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17(5):259–60.
5. *Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):1–4. doi: 10.1038/s41586-020-2012-7.
6. *Sinha IP, Harwood R, Semple MG, Hawcutt DB, Thursfield R, Narayan O, et al.* COVID-19 infection in children. Lancet Respir Med. 2020;8:446–7. doi: 10.1016/S2213-2600(20)30152-1.
7. *Leeb RT, Price S, Sliwa S, Kimball A, Szucs L, Caruso E, et al.* COVID-19 trends among school-aged children United States, March 1-September 19, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1410–5.

8. *Dong Y, Mo X, Hu Y, Qi X,Jiang F, Jiang Z.* Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020.
9. *Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A.* Myocardial injury and COVID-19: possible mechanisms. Life Sci. (2020) 2020:117723. doi: 10.1016/j.lfs.2020.117723.
10. *Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9. doi: 10.1001/jama.2020.1585.
11. *Dhochak N, Singhal T, Kabra SK, Lodha R.* Pathophysiology of COVID-19: Why children fare better than adults? Indian J Pediatr 2020;87(7):537–46.
12. *Brodin P.* Why is COVID-19 so mild in children? Acta Paediatr 2020;109(6):1082 ps://doi.org/10.1111/apa.15271.
13. *Zeng J-H, Liu Y, Yuan J, Wang F, Wu W-B, Li J-X, et al.* Clinical characteristics and cardiac injury description of 419 cases of COVID-19 in Shenzhen, China. (2020). doi: 10.2139/ssrn.3556659.
14. *Royal College of Pediatrics and Child Health.* Guidance-Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19; 2020. Available from: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19. [Last accessed on 2020 May 17].
15. *Viner RM, Whittaker E.* Kawasaki-like disease: Emerging complication during the COVID-19 pandemic. Lancet 2020; 395(10239):1741–3.
16. *Dinarević S, Henein MY, Zaghal AA, Shinebourne EA, Gibson DG.* Exercise stress echocardiography in children with Kawasaki disease-left ventricular axis selectively impaired. The second world congress of paedatric cardiology and cardiac surgery. Am J Cardiol 1998;81(11):1356–9.
17. *Rodriguez-Gonzalez M, Rodríguez-Campoy P, Sánchez-Códez M, Gutiérrez-Rosa I, Castellano-Martinez A, Rodríguez-Benítez A.* New onset severe right ventricular failure associated with COVID-19 in a young infant without previous heart disease. Cardiol Young 2020;30(9):1346–9.
18. *Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al.* Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am CollCardiol. 2020;76: 1947–61. doi: 10.1016/j.jacc.2020.08.056.
19. *CDC COVID-19 Response Team.* Coronavirus disease 2019 in children-United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69(14):422–6.
20. *Andina D, Noguera-Morel L, Bascuas-Arribas M, Gaitero-Tristán J, Alonso-Cadenas JA, Escalada-Pellitero S, et al.* Chilblains in children in the setting of COVID-19 pandemic. PediatrDermatol 2020;37(3):406–11.
21. *Kobayashi T, Fuse S, Sakamoto N, Mikami M, Ogawa S, Hamaoka K, et al.* New Z score curve of the coronary arterial internal diameter using the lambda-mu-sigma method in a pediatric population. J Am SocEchocardiogr 2016;29(8): 794–801.e29.
22. *Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, et al.* Relationship of echocardiographic Z scores adjusted for body surface area to age, sex, race, and ethnicity: The pediatric heart network normal echocardiogram database. CircCardiovasc Imaging 2017;10(11):e006979