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Presentation and Outcome of Congenital Heart Disease During Covid-19 Pandemic: A Review

Azam Soleimani[a,b,*], and Zahra Soleimani[c,d]

From the [a] Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran, [b] Chamran Cardiovascular Medical and Research Center, Echocardiography department, Isfahan University of Medical Sciences, Isfahan, Iran, [c] Perinatologist, Nephrology and Urology research center, Baqiyatallah University of Medical Sciences, Tehran, Iran and [d] Fetal Health Research center, Hope Generation Foundation, Tehran, Iran.

Abstract: Severe Acute Respiratory Syndrome Corona Virus 2 ($SARS\text{-}COV_2$) infection is a rapid evolving pandemic with multiple peaks of outbreak and substantial mortality worldwide. It has been proposed that infants are more vulnerable to SARS-COV-2 infection. On the other hand, children with COVID-19 have generally milder disease compared to infected adults and more often presented with gastrointestinal symptoms compared to respiratory ones. Multisystem inflammatory syndrome in children (MIS-c) is an ominous demonstration of COVID-19 with cardiac involvement and mortality rate <2%. From cardiovascular point of view, wide spectrum of manifestations including subclinical myocardial injury, myocarditis, stress cardiomyopathies, cardiac arrhythmias, pulmonary thromboembolism and thrombus formation in cardiac chambers and vascular bed has been reported in COVID-19 disease. Congenital heart disease (CHD), assumed as the most prevalent form of congenital disease. Advances in medical and surgical treatments for CHD have led to more alive patients with underlying heart disease secondary to congenital defects. These group of pediatric patients are prone to heart failure, arrhythmia and embolic events. In this

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narrative review, we intended to evaluate the cardiovascular and pediatric presentations of COVID-19 as well as the manifestation and outcomes of SARS-CoV-2 infection on pediatric patients with CHD. (Curr Probl Cardiol 2022;47:100905.)

Introduction

COVID-19 disease caused by infection with "Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-COV_2)" started at Wuhan, China at 2019 and converted to a pandemic soon after.[1] SARS-COV_2 infection, most often manifested with mild symptoms, have led to significant mortality worldwide in patients with moderate to severe disease. This viral infection has been reported to be associated with wide spectrum of cardiovascular symptoms and expressions from subclinical myocardial injury, myocarditis, stress cardiomyopathies and cardiac arrhythmias to cardiac and pulmonary thromboembolism.[2] Acute heart failure due to multi system inflammatory syndrome in children is a known manifestation of SARS-CoV-2 infection in pediatric patients.[3] It is suggested that underlying cardiovascular disease leads to raised morbidity and mortality in patients with COVID-19 disease.[4,5]

Congenital heart diseases (CHD) are the most common form of congenital disease and has a wide spectrum from asymptomatic mild forms of valvular lesion and trivial shunts to severe complex defects that contradicts with continuation of life.[6] Here in we have argued the impact of COVID-19 disease on pediatric and adolescents with congenital heart disease as a common underlying cardiac disease in this population.

Materials and Methods

For the evaluation of cardiovascular and pediatric presentation of COVID-19 with focus on outcomes of this viral infection in patients with CHD, we searched the major electronic database including Web of Science, Cochrane, PubMed, Embase and Scopus. The main key words for searching were combination of each of these words: ["congenital heart disease", "pediatrics", "cardiac arrhythmia", "cardiomyopathies", "myocarditis"] AND ["SARS-CoV-2" OR "COVID-19" OR "2019-nCoV"]. At the first step, 67 articles were found by primary search. The abstract and full document of all papers were evaluated by an expert echo cardiologist, trained in congenital heart disease with experience on COVID-19 management and one perinatologist, expert in high risk

pregnancies. The included articles were cohorts, national and multicenter studies, local and national registries, retrospective analysis, review articles and COVID- case series with more than four patients. No randomized trials were included in this topic. Excluding the articles that were irrelevant, finally, 37 articles were selected and were analyzed.

The analysis results are presented in four section:(1) CHD description and classification (5 articles), (2) Cardiac involvement during COVID-19 disease (14 articles), (3) COVID-19 disease in childhood (13 articles), (4) Congenital heart disease during COVID-19 disease (6 articles).

The Classification of Congenital Heart Disease

Normal heart anatomy consists of a sequential blood flow in the cardiac chambers and great vessels with no mixing, that leads the unsaturated systemic venous blood to go to the lungs via pulmonary artery and the saturated blood to go to the vital organs along the aorta. Any derangement in this anatomy or ventricular or valvular function in the fetus, can lead to CHD in newborns.

Beside classifications based on the heart anatomy and location of the defect, a more practical definition has been proposed from pathophysiological aspects and clinical consequence to classify CHD to five groups: (1) CHD associated with high pulmonary flow as left-to right shunts without barrier in pulmonary circulation, (2) CHD with low pulmonary flow as septal defects with right to left shunt due to obstruction in pulmonary flow pathway, (3) CHD without shunt but with obstruction in blood flow, (4) CHD that are incompatible with newborn blood circulation, (5) CHD that are asymptomatic till adulthood.[7]

In adolescence and adult patient, the American college of cardiology (ACC) recommends the anatomic and physiological classification (AP classification) for adult CHD (ACHD). In this classification, anatomic (A) categorization proposed three categories for I: simple, II: moderate and III: great complexity and physiologic (P) classification applies to stage A to D base on New York Heart association (NYHA) function class I-IV, hemodynamic and systemic sequels.[8] A similar categorization has been proposed by European society of cardiology (ESC) thereafter.[9] These categorizations are applied for managements of older pediatric patients.

The age adjusted mortality rate of CHD have been decreased significantly during the last 3 decades in spite of the constant incidence.[10] Improvements in medical and surgical therapies for CHD have led to more alive patients with underlying heart disease secondary to congenital defects. the most complications that are observed in patients with CHD are ventricular dysfunction or heart failure, arrhythmias and embolic events.

Cardiac involvement during COVID-19 disease

It has been confirmed that COVID-19 disease has various types of cardiovascular involvement in previously healthy infected subjects.[11] The similarity between Corona virus spike protein (S protein) and angiotensin-converting enzyme 2 (ACE-2) receptor that is located in cardiomyocytes, intestines, kidneys and the lung epithelial tissue may explain some cardiac manifestations of SARS-COV_2 infection.[4]

Cytokine storm including increased level of IL-6 and tumor necrosis factor-α (TNF- α) and the systemic inflammatory response as well as direct myocardial injury is responsible for myocarditis and subsequent ventricular dysfunction as a well-known complication in COVID-19 disease.[12,13] Hypercoagulation state due to systemic inflammation, immobility secondary to moderate to severe illness, lung endothelial damage as well as hypoxemia are proposed as the main mechanisms for pulmonary thromboembolism and thrombus formation in cardiac chambers.[14,15]

Ischemic coronary injury secondary to thrombus formation in coronary arterial bed in hypoxemic patient is responsible for myocardial infarction and unstable coronary syndromes in COVID era that can lead to ventricular dysfunction and cardiac arrhythmia.[16,17] Cardiac arrhythmias including sinus bradycardia, different degrees of atrioventricular (AV) block, inappropriate sinus tachycardia as well as long QT syndrome and ventricular arrhythmia have been observed in patients infected with SARS-CoV-2.[18] Myocardial ischemia, side effects of drugs, underlying myocarditis and electrolytes abnormalities have been proposed for the underlying mechanism for cardiac arrhythmias.[18]

COVID-19 Disease in Childhood

At the initial time of COVID-19 outbreak, observational cohorts have proposed that no vertical transmission from infected mothers to neonates occurs.[19-21] Definite trans placental transmission of SARS-COV_2 infection with neurological manifestation of COVID-19 disease in a new born neonate has changed the hypothesis, so this disease can involve all age spectrum from neonate to adulthood.[22]

A cohort of 2135 pediatric patients suspected for COVID-19 disease in China, of whom 34.1% had proven SARS-CoV-2 viral infection demonstrated equal prevalence in both genders and median age of them was 7 years. It has been proposed that children with COVID-19 generally have milder disease than adult patients with 94.1% of all children had non severe disease. Severe disease was more common in younger pediatrics specially in infants.[23]

In a report from Italy at the peak time of outbreak with the first mortality ranking in the world, 1% of infected population were children under the 18 years old, with 11% hospitalization rate and no death.[24] In a cohort of 100 children in this country, 21% were asymptomatic, with prevalence of mild, moderate and severe disease as 58%, 19% and 1% respectively.[25] It is supposed that children were less prone to severe infection due to the lower maturation and activity of ACE2 receptor compared to adults.[26]

In a cohort of 37 pediatrics in north region of Iran, fever, weakness and anorexia (prevalence of 86.5%, 75.7% and 73% respectively) were the main presentive symptoms. More common gastrointestinal presentation compared with respiratory symptoms and no mortality was observed. Multisystem inflammatory syndrome in children (MIS-c) was the main manifestation in 18.9% of children. The study demonstrated pulmonary involvement in 32.4% of children.[27]

Multisystem inflammatory syndrome in children with COVID-19 disease, also named MIS-c is a confirmed serious potentially lethal clinical presentation of COVID-19 disease with various definitions[28]. Centers for Disease Control (CDC) defines MIS-c in patients with COVID-19 disease and all four criteria: (1) Age under 21 years; (2) Confirmed SARS-CoV-2 infection or exposure during last 4 weeks; (3) Clinical presentation with fever $>38^{\circ}C$ for more than 24 hours, evidence of significant inflammation in laboratory data [increased C-reactive protein (CRP), d-dimer, erythrocyte sedimentation rate (ESR), interleukin 6, fibrinogen, procalcitonin, lactic acid dehydrogenase (LDH) and ferritin] and severe multiorgan disease ($\geq$2 of neurologic system, heart, lung, hematologic, skin, gastrointestinal or kidneys) needs to be hospitalized; (4) Other diagnosis should be ruled out.[29] Cardiac manifestations of this syndrome are systolic dysfunction (in all patients), aneurysm formation in coronary arteries and elevated cardiac biomarkers such as N terminal-pro brain natriuretic peptide (NT-pro BNP) and cardiac troponin I (cTnI).[29]

A multicenter registry of 35 children (median age:10 years) hospitalized with MIS-c due to COVID-19 in Europe, reported gastrointestinal complaints as the dominant feature. Cardiogenic shock and collapse were observed in 80% of cases. Near third presented with left ventricular ejection fraction (LVEF) <30%, the remaining had LVEF of 30% -50%. The main treatments were intra venous inotropic support, intravenous immunoglobulin (IVIG) and steroid therapy, with favorable outcome and normal LVEF at 7th day of admission for all patients without mortality.[30]

In a systematic analysis, 662 pediatrics with MIS-c were evaluated. 71% of patients were admitted in intensive care unit (ICU) with 1.7% mortality (11 patients). Fever (100%), diarrhea or abdominal pain

(73.7%) and vomit (68.3%) were the first ranking of clinical expressions. More than half of them had left ventricular systolic dysfunction.[31]

Congenital Heart Disease During COVID-19 Disease

Patients with underlying cardiovascular disease are vulnerable to more severe COVID-19 involvement and have higher mortality.[4]

It has been proposed that the milder presentation of pediatric patients with COVID-19 doesn't apply to the cases with CHD. In a case series of nine pediatric patients with COVID-19 disease and CHD, two patients died, both with severe forms of CHD and severe COVID-19 presentation. One was a 14 years old girl with significant aortic stenosis (AS) and the other was a complex form of CHD, hypoplastic left heart syndrome (HLHS) and patent ductus arteriosus (PDA), in a 10-month-old male. Laboratory measures of C-reactive protein (CRP) and partial thromboplastin time (PTT) were higher in these patients.[32]

A national multicenter Italian study of 76 patients with SARS-CoV-2 infection and CHD, showed benign clinical outcome. Heart failure (9%) was the most common complication followed by arrhythmias, stroke and pulmonary hypertension (3% for each one). In this cohort, only 4 of the CHD were children (from 2 months to 2 years old).[33]

In another multicenter survey of 7 children with CHD and COVID-19, all experienced acute decompensation with one case of mortality in an 18-year-old patient with hypertrophic cardiomyopathy (HCMP). Five were at first year of life (3 had atrioventricular septal defect). History of Fontan surgery for double inlet left ventricle was reported in one of them.[34]

In a study of 53 patients with CHD infected with SARS-CoV-2, 10 patients (19%) were under 18 years age. Moderate to severe COVID-19 disease was observed in 9 (7 adult, 2 children: both common atrioventricular canal) with no mortality in children but 3 death in adult group. In this cohort, genetic syndrome, ACHD physiologic stage C and pulmonary hypertension were the strongest predictors for moderate to severe COVID-19 in all patients with CHD (Odds ratios: 35.82, 19.38 and 15.25 respectively).[35]

A multicenter case series of 7 patients with CHD and symptomatic COVID-19 disease from Iran presented the age range of 2 months to 14 years, four infants and two adolescents, two Eisenmenger syndrome (one HLHS that finally deceased, another Down syndrome with common atrioventricular canal) and one case of severe pulmonary hypertension. In this series of complex CHD with confirmed COVID-19, the main presentation was pulmonary symptoms in all, with two case of mortality, one in infant male with HLHS and the other an adolescent girl (14 years) with severe AS.[36]

In these mentioned studies, Down syndrome with common atrioventricular canal is the most common underlying heart disease. Mortality is rare and was reported in patients with severe AS, HCMP and HLHS.

In the recent ESC guideline for COVID-19 disease in adult CHD, patients with systolic dysfunction, unrepaired complex defects, Fontan patients with single ventricle physiology, severe pulmonary hypertension, Down syndrome and patients with significant hypoxemia are considered at increased risk of complications.[37] Based on the mentioned studies, these groups seem to be at increased risk in pediatric CHD too.

Conclusion

According to the available data, pediatric patients with CHD may be more prone to more severe COVID-19 illness with increased mortality. Down syndrome with common atrioventricular canal is the most common underlying CHD in COVID studies. The more severe complexity and worse NYHA functional class, the more associated risk of adverse outcomes with COVID-19 disease.

Careful monitoring, while continuing the essential drugs for underlying heart disease and antithrombotic prophylaxis based on available guidelines is recommended.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel Coronavirus in Wuhan, China. *The Lancet* 2020;395:497–506.
2. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and Cardiovascular disease. *Circulation* 2020;141:1648–55.
3. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Ciriculation* 2020;142:429–36.
4. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol* 2020;17:543–58.
5. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with covid-19 in Wuhan, China. *JAMA Cardiology* 2020;5:802–10.
6. Soleimani A, Dehghan H, Soleimani M. Giant right atrium: case report of a rare congenital disease in adulthood. *J Echocardiogr* 2019;19:125–7.
7. Thiene G, Frescura C. Anatomical and pathophysiological classification of congenital heart disease. *Cardiovas Pathol* 2010;19:259–74.
8. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. AHA/ACC guideline for the management of adults with congenital heart disease: a

report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139(14):e698–800.
9. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller G-P, et al. 2020 ESC Guidelines for the management of adult congenital heart disease: The Task Force for the management of adult congenital heart disease of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Adult Congenital Heart Disease (ISACHD). *Eur Heart J* 2020;42:563–645.
10. Wu W, He J, Shao X. Incidence and mortality trend of congenital heart disease at the global, regional, and national level, 1990-2017. *Medicine* 2020;99:e20593.
11. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med* 2020;38(7):1504–7.
12. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. *Eur Heart J* 2020;42:206.
13. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020;20:363–74.
14. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res* 2020;194:101–15.
15. Dehghan H, Soleimani A. Pulmonary thromboembolism with multiple right heart mural thrombus in a patient with COVID-19. *J Echocardiogr* 2020:1–2.
16. Mansueto G, Niola M, Napoli C. Can COVID 2019 induce a specific cardiovascular damage or it exacerbates pre-existing cardiovascular diseases? *Pathol Res Pract* 2020;216:153086.
17. Schiavone M, Gobbi C, Biondi-Zoccai G, D'Ascenzo F, Palazzuoli A, Gasperetti A, et al. Acute coronary syndromes and covid-19: exploring the uncertainties. *Journal of Clinical Medicine* 2020;9(6):1683.
18. Bhatla A, Mayer MM, Adusumalli S, Hyman MC, Oh E, Tierney A, et al. COVID-19 and cardiac arrhythmias. *Heart Rhythm* 2020;17:1439–44.
19. Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, et al. Clinical characteristics of pregnant women with covid-19 in Wuhan, China. *N Engl J Med* 2020;382:e100.
20. Soleimani Z, Soleimani A. ADRS due to COVID-19 in midterm pregnancy: successful management with plasma transfusion and corticosteroids. *J Matern Fetal Neonatal Med* 2020:1–4.
21. Kazemi Aski S, Norooznezhad AH, Shamshirsaz AA, Mostafaei S, Aleyasin A, Nabavian SM, et al. Clinical features and risk factors associated with acute respiratory distress syndrome in pregnant women diagnosed with COVID-19: a multi-center case-control study. *J Matern Fetal Neonatal Med* 2021:1–5.
22. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. *Nat Commun* 2020;11(1):3572.
23. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics* 2020;145:e20200702.
24. Lazzerini M, Putoto G. COVID-19 in Italy: momentous decisions and many uncertainties. *Lancet Glob Health* 2020;8:e641–e2.

25. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in pediatric emergency departments in Italy. *N Engl J Med* 2020;383:187–90.
26. Fang F, Luo XP. Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives. *Zhonghua Er Ke Za Zhi* 2020;58:81–5.
27. Kiani M, Mohammadpour-Mir A, Sorkhi H, Esmaeili-dooki M, Nikpour M, Babazadeh K, et al. Multi-organ presentation of children with COVID-19 infection in the North of Iran: a retrospective study. *J Int J Pediatr* 2021;9:13411–9.
28. Kwak JH, Lee S-Y, Choi J-W. Clinical features, diagnosis, and outcomes of multisystem inflammatory syndrome in children associated with coronavirus disease 2019. *Clin Exp Pediatr* 2021;64:68–75.
29. Smith SW, Strobel AM, Saenger AK, Apple FS. Laboratory findings in a child with SARS-CoV-2 (COVID-19) multisystem inflammatory syndrome. *J Clin Chem Labor Med* 2021;59(6):e259–61.
30. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation* 2020;142:429–36.
31. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine* 2020;26:100527.
32. Haji Esmaeil Memar E, Pourakbari B, Gorgi M, Sharifzadeh Ekbatani M, Navaeian A, Khodabandeh M, et al. COVID-19 and congenital heart disease: a case series of nine children. *World J Pediatr* 2021;17:71–8.
33. Sabatino J, Ferrero P, Chessa M, Bianco F, Ciliberti P, Secinaro A, et al. COVID-19 and congenital heart disease: results from a nationwide survey. *J Clin Med* 2020;9:1774–82.
34. Simpson M, Collins C, Nash DB, Panesar LE, Oster ME. Coronavirus disease 2019 infection in children with pre-existing heart disease. *J Pediatr* 2020;227. 302-7.e2.
35. Lewis MJ, Anderson BR, Fremed M, Argenio M, Krishnan U, Weller R, et al. Impact of coronavirus disease 2019 (COVID−19) on patients with congenital heart disease across the lifespan: the experience of an academic congenital heart disease center in New York City. *Journal of the American Heart Association* 2020;9:e017580.
36. Esmaeeli H, Ghaderian M, Zanjani KS, Ghalibafan SF, Mahdizadeh M, Aelami MH. COVID-19 in children with congenital heart diseases: a multicenter case series from Iran. *Case Rep Pediatr* 2021;2021:6690695.
37. Diller G-P, Gatzoulis MA, Broberg CS, Aboulhosn J, Brida M, Schwerzmann M, et al. Coronavirus disease 2019 in adults with congenital heart disease: a position paper from the ESC working group of adult congenital heart disease, and the International Society for Adult Congenital Heart Disease. *Eur Heart J* 2020;42(19):1858–65.