ARYA Atherosclerosis J

Original Article Open Access

Vascular function and arterial stiffness in multisystem inflammatory syndrome in children with Covid-19

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Received: 2024.11.19
Accepted: 2025.02.15

How to cite this article:
Ahmadi A, Sabri MR, Ghaderian M, Dehghan B, Mahdavi C, Ramezaninezhad D, et al. **Vascular function and arterial stiffness in multisystem inflammatory syndrome in children with Covid-19.** ARYA Atheroscler. 2025; 21(1): 54-62.

DOI:
https://doi.org/10.48305/arya.2025.43214.3008

Abstract

BACKGROUND: Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but severe condition that can develop in children who have had COVID-19. It can lead to cardiovascular complications, potentially caused by endothelial dysfunction and arterial stiffness.

METHODS: This study aimed to investigate the cardiovascular health of children with MIS-C compared to healthy controls. Fifty-nine children with MIS-C and fifty-nine healthy individuals were included in this cohort study. Non-invasive techniques were employed to measure the brachial artery's flow-mediated dilation (FMD), aortic distensibility (AD), and aortic strain (AS).

RESULTS: The MIS-C group demonstrated significantly higher systolic blood pressure ($P = 0.012$), with a mean of 100.2 (10.1) mmHg compared to 95.3 (9.6) mmHg in the healthy group. The relative risk (RR) for elevated pulse pressure in the MIS-C group was borderline higher than in the healthy group (RR 95% CI: 1.06 [1.01–1.14]; $P = 0.046$). However, FMD, AS, and AD values were lower in the MIS-C group, with means of 13.6 (8.9), 10.4 (4.1), and 15.5 (2.7), respectively, although no significant differences were observed ($P > 0.05$).

CONCLUSION: Children with MIS-C exhibited higher pulse pressure, indicating potential arterial stiffness. They also showed lower FMD, suggesting endothelial dysfunction. FMD appears to be a more reliable indicator of endothelial dysfunction in MIS-C patients compared to aortic strain. These findings underscore the importance of early assessment and monitoring of cardiovascular complications in MIS-C patients. Endothelial dysfunction and arterial stiffness are well-established risk factors for future cardiovascular events.

Keywords: MISC Associated with COVID-19; Arterial Stiffness; Cardiovascular System; Blood Pressure; Mucocutaneous Lymph Node Syndrome

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has profoundly impacted global health. While primarily affecting the respiratory system, COVID-19 can also lead to various extrapulmonary complications involving multiple organ systems, including cardiovascular, neurological, and gastrointestinal manifestations[1-3]. One such complication is multisystem inflammatory syndrome in children (MIS-C), a rare but severe condition that affects children and adolescents. MIS-C often requires intensive care and may result in long-term health issues[4].

MIS-C is considered a post-infectious complication of COVID-19, typically occurring weeks after the initial SARS-CoV-2 infection or exposure. While the exact pathophysiology remains unclear, it is thought to involve an abnormal immune response triggered by the virus, resulting in systemic inflammation and potential organ damage. Among the affected organ systems, cardiovascular complications have emerged as a significant concern in MIS-C patients[4].

The cardiovascular manifestations of MIS-C can range from mild myocarditis to severe heart failure, arrhythmias, and coronary artery abnormalities. These complications underscore the importance of understanding the underlying mechanisms and identifying reliable biomarkers to enable the early detection and monitoring of cardiovascular involvement in MIS-C patients[5].

One potential mechanism contributing to cardiovascular complications in MIS-C is endothelial dysfunction, which refers to the impaired functioning of the endothelium. Endothelial dysfunction can lead to altered vascular reactivity, increased inflammation, and thrombosis, ultimately contributing to the development of cardiovascular diseases[6].

The noninvasive assessment of systemic endothelial function has become an essential tool in evaluating cardiovascular function and predicting future cardiovascular events in patients with existing cardiovascular disease[7]. In this study, endothelial dysfunction was assessed using flow-mediated dilation (FMD), and the brachial artery diameter was measured with a high-resolution linear probe. Arterial stiffness, a general term describing distensibility, compliance, and the elastic properties of the arterial vascular system, is similarly predictive of future cardiovascular events in such patients. To evaluate arterial stiffness, measurements of aortic strain and aortic distensibility were performed. These parameters offer valuable insights into the mechanical properties of the arterial system and overall cardiovascular function. Likewise, FMD measures the dilation of an artery in response to increased blood flow, serving as a reliable indicator of endothelial function[8,9].

Currently, there is insufficient and conclusive information about systemic arterial dysfunction in inflammatory cardiovascular diseases, such as Kawasaki disease and MIS-C. This issue remains underexplored, with growing concern regarding subclinical systemic arterial abnormalities in patients with cardiovascular involvement or even in those with normal cardiovascular findings. This concern prompted an evaluation of preclinical vascular dysfunction in systemic arteries in MIS-C syndrome, where generalized inflammation may affect the vascular endothelium[6,10,11].

In this context, the assessment of endothelial dysfunction and arterial stiffness using noninvasive techniques, such as Systolic Aortic Distensibility (SAD), Diastolic Aortic Distensibility (DAD), Aortic Distensibility (AD), Aortic Strain (AS), and FMD, holds significant promise[12]. These approaches may offer critical insights into the cardiovascular complications associated with COVID-19 and MIS-C. Understanding the underlying mechanisms and identifying potential biomarkers or risk factors could pave the way for enhanced risk stratification, timely intervention, and targeted therapeutic strategies, providing hope in addressing this complex condition.

Methods

Ethics approval

This prospective study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1401.147). The research was conducted in accordance with the principles of the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients and their parents before their participation in the study.

Study Protocol and Patient Characteristics

The study included non-obese Asian patients aged 1–16 years and was conducted at the pediatric cardiology clinic of Imam Hossein Hospital between May 2022 and July 2023. All participants had negative blood, urine, and stool cultures, as well as normal growth and development. Most patients in both groups reported mild respiratory symptoms in the preceding 1–2 months. MIS-C was diagnosed based on CDC/WHO criteria, which include the presence of fever, evidence of inflammation, multisystem involvement, and a confirmed connection to COVID-19.

Inclusion Criteria:

- Age 1-16 years
- No cardiac history or impaired function
- The control group was matched for age and sex and cleared of heart conditions.

Exclusion Criteria:

- Obesity, smoking, hypertension, diabetes, kidney impairment
- Kawasaki disease, Toxic Shock Syndrome, pneumonia, viral/bacterial gastroenteritis
- Technically insufficient echocardiographic images

Sample size calculation

The confidence interval was set at 95%, with a statistical power of 80%. The standard deviation (S) was 3.8, and the mean difference in FMD between the two groups was 2 [6]. Based on these parameters, a sample size of 57 was calculated as necessary for each group.

Clinical Assessment

Data collection included sex, age, height, weight, and BMI. Blood pressure was measured using a sphygmomanometer (ALP K2) after 5 minutes of rest. Pre-treatment assessments included echocardiography, aortic distensibility, and flow-mediated dilation (FMD) of the brachial artery.

Echocardiographic Examination

A Pediatric Cardiologist conducted an echocardiographic examination meticulously, utilizing advanced techniques such as Two-dimensional imaging, M-mode, pulsed Doppler, and color flow Doppler (Samsung MEDISON EKO 7, 3-MHz transducer). Continuous electrocardiogram monitoring was performed during the examination.

The M-mode echocardiography in the parasternal long-axis view was used to evaluate left ventricular systolic function over three consecutive cardiac cycles, with the mean values calculated. Atrioventricular and semilunar valve regurgitation was assessed using color Doppler and categorized as mild, moderate, or severe insufficiency. The assessment also included identifying pericardial and pleural effusions, as well as any coronary abnormalities[13].

Evaluation of arterial stiffness using aortic distensibility

Arterial elasticity was evaluated with meticulous precision. Patients were positioned in the left lateral decubitus position with continuous electrocardiographic monitoring. Using the parasternal long-axis view, the ascending aorta was measured 3 to 5 cm above the aortic valve using a Samsung MEDISON EKO 7 with a 3-MHz transducer. The systolic aortic diameter (AoS) was recorded at the point of maximum aortic valve opening, while the diastolic aortic diameter (AoD) was measured at the peak of the QRS complex on the electrocardiogram (Fig. 1). The mean of three consecutive measurements for both systolic and diastolic values was calculated. The following formulae were used to assess arterial elasticity:

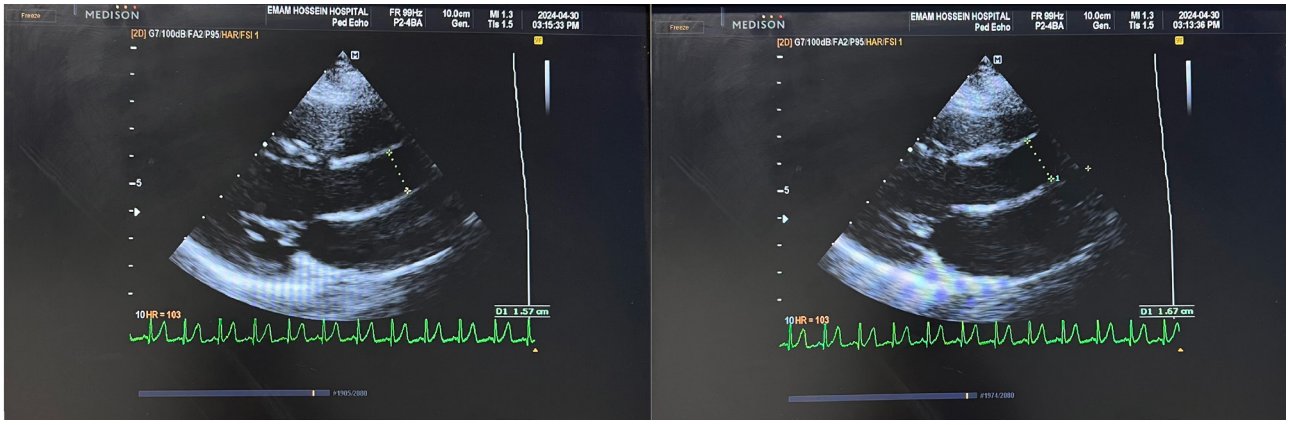

Fig. 1. Evaluation of arterial stiffness using aortic distensibility

- PP = Systolic Blood Pressure − Diastolic Blood Pressure
- AS (%) = [(AoS − AoD) ÷ AoD] × 100
- AD = 2 × [(AoS − AoD) ÷ AoD] / PP [14].

FMD

Ensuring patient comfort and safety was a priority during the flow-mediated dilation (FMD) measurement. The patient was positioned supine, with their hand placed in a comfortable position, maintained for at least one minute. The brachial artery diameter was measured above the antecubital fossa, prior to branching, using a Doppler ultrasound system equipped with a high-resolution transducer (Samsung MEDISON EKO 7, 10 MHz linear transducer). The diameter of the brachial artery was initially measured at rest three times, and the mean values were recorded as the baseline diameter. Measurements were taken at the end of diastole with continuous electrocardiogram monitoring.

The cuff of the blood pressure device was placed in the upper part of the right antecubital fossa to create current impulses in the brachial artery. After determining the base diameter, ischemia was induced by inflating the cuff to increase pressure to 50 mmHg higher than the systolic blood pressure (SBP), and the cuff was released after 5 min. After deflating the cuff, two-dimensional longitudinal images of the brachial artery were obtained, and the maximum diameter of the brachial artery was measured within sixty seconds. The FMD values were calculated using the baseline and maximum diameters of the brachial artery. FMD was calculated as FMD = 100 × (the maximum diameter after hyperemia − baseline diameter ÷ baseline diameter) [6].

Statistical analysis

Our statistical analyses, conducted using SPSS version 16, adhered to a stringent threshold for statistical significance. Categorical data were presented as frequencies and percentages, while quantitative data were described as the mean with standard deviation or the median with interquartile range, depending on the results of normality tests. For simple group comparisons, Chi-square tests, independent t-tests, and Mann-Whitney U tests were utilized. To compare two groups in multiple tests (adjusted for sex, age, weight, height, and blood pressure), we employed generalized linear models (gamma distribution with log link) and ANCOVA. Specifically, an independent t-test and ANCOVA (adjusted for sex, age, weight, height, and blood pressure) were used for normally distributed variables (AS and DAD), while the Mann-Whitney test and generalized linear models (gamma distribution with log link, adjusted for the same variables) were used for non-normally distributed variables (PP, AD, SAD, and FMD) to compare the two groups. Effect size was expressed as relative risk (RR), and statistical significance was

defined as a two-tailed p-value of less than 0.05, emphasizing the relevance of our findings.

Results

Data from a total of 118 participants was analyzed for the study. The median age was 6.0 years, with an interquartile range of 4.0-8.0, and 57.6% of the participants were male. The two groups were compared based on demographic and clinical variables, and the results are presented in Table 1.

Table 1. Demographic and Clinical Variables of participants in Healthy and MIS-C groups

Variable		Healthy group (n=59)	MIS-C (n=59)	P-value
Sex	Male	33 (56.9)	35 (60.3)	0.709[1]
	Female	26 (33.1)	24 (39.7)	
Weight (Kg)		18.0 [14.0-28.0]	18.0 [13.0-27.0]	0.785[2]
Age (Year)		7.0 [5.0-8.5]	6.0 [4.0-8.0]	0.302[3]
Height (cm)		114.0 (22.1)	113.8 (24.6)	0.966[3]
SBP (mmHg)		95.3 (9.6)	100.2 (10.1)	**0.012**[3]
DBP (mmHg)		62.8 (8.1)	65.5 (10.2)	0.128[3]
PE (Yes)		0 ()	4 (6.8)	0.119[1]
Coronary Aneurysms (Yes)		0 ()	2 (3.4)	0.496[1]
MR (Yes)		2 (3.4)	8 (13.6)	0.094[1]
TR (Yes)		4 (6.8)	13 (22.0)	**0.034**[1]
AI (Yes)		0 ()	6 (10.2)	**0.027**[1]
PI (Yes)		3 (5.1)	8 (13.6)	0.204[1]
LVIDs (mm)		20.0 [19.0-23.0]	20.0 [18.0-22.0]	0.703[2]
LVIDd (mm)		33.0 [30.0-37.0]	32.0 [30.0-37.0]	0.895[2]
SF (%)		40.0 [38.0-42.0]	38.0 [35.0-41.0]	**0.003**[2]
EF (%)		71.0 [69.0-74.0]	69.0 [67.0-73.0]	**0.009**[2]

[1] Chi-square, No (%)

[2] Mann Whitney, median [interquartile range]

[3] Independent t-test, mean (standard deviation)

MIS-C: Multisystem Inflammatory Syndrome in Children, *PE*: Pericardial Effusion, *MR*: Mitral Regurgitation, *TR*: Tricuspid Regurgitation, *AI*: Aortic Insufficiency, *PI*: Pulmonary Insufficiency, *LVIDs*: Left Ventricular Internal Dimension Systolic, *LVIDd*: Left Ventricular Internal Dimension Diastolic, *SF*: Shortening Fraction, *EF*: Ejection Fraction, *SBP*: Systolic Blood Pressure, *DBP*: Diastolic Blood Pressure

Table 2. Evaluation of endothelial function and arterial stiffness between Healthy and MIS-C group

Variable	Healthy group (n=59)	MIS-C (n=59)	Unadjusted model	Adjusted model	
			P-value*	P-value**	RR (Confidence Interval 95%)†
PP(mmHg)	30.0 [30.0-35.0]	30 [25.0-35.0]	0.696	**0.046**	1.06 (1.01-1.14)
SAD (10^{-3}mmHg^{-1})	1.6 [1.4-1.7]	1.6 [1.4-1.9]	0.692	0.535	0.99 (0.94-1.03)
DAD (10^{-3}mmHg^{-1})	1.4 (0.2)	1.5 (0.3)	0.531	0.533	0.98 (0.92-1.04)
AD (10^{-3}mmHg^{-1})	1.6 [1.4-1.7]	1.6 [1.4-1.8]	0.706	0.527	0.99 (0.94-1.03)
AS (%)	10.4 (4.1)	10.0 (5.2)	0.647	0.961	0.96 (0.16-5.6)
FMD (%)	12.5 [6.5-18.2]	7.0 [3.5-12.8]	**0.006**	0.129	0.77 (0.55-1.09)

Data was showed mean (SD) or median[IQR]

MIS-C: Multisystem Inflammatory Syndrome in Children, *PP*: Pulse Pressure, *SAD*: Systolic Aortic Distensibility, *DAD*: Diastolic Aortic Distensibility, *AD*: Aortic Distensibility, *AS*: Aortic Strain, *FMD*: Flow-mediated dilation, *SD*: Standard Deviation, *RR*: Relative Risk

*: Mann Whitney or Independent t-test (Unadjusted model)

**: Generalized linear model (gamma distribution with log link adjusted with adjusted for sex, age, weight, and height) or ANCOVA (adjusted for sex, age, weight, height, and blood pressure)

†: Reference for RR: Healthy group

The analysis showed no significant difference between the two groups regarding sex, age, weight, height, DBP, LVIDs, LVIDd, PE, and coronary aneurysms. However, the MIS-C group had significantly higher SBP (P=0.012), AI (P=0.027), TR (P=0.034), and lower SF (P=0.003) and EF (P=0.009) (Table 1).

Further analysis was conducted using independent t-tests and ANCOVA (adjusted for sex, age, weight, height, and blood pressure), as well as Mann-Whitney U tests and generalized linear models (gamma distribution with log link, adjusted for the same variables), to compare the two groups (Table 2).

Based on the results presented in Table 2, the FMD was significantly higher in the healthy group compared to the MIS-C group (P=0.006). There were no significant differences in other variables (PP, SAD, DAD, AD, and AS) (P>0.05).

The multiple ANCOVA test indicated that PP was approximately 6% higher in the MIS-C group than in the healthy group, with statistical significance (P=0.046). The multiple test results for other variables showed that SAD was about 1% lower, DAD was about 2% lower, AD was about 1% lower, AS was about 4% lower, and FMD was about 23% lower in the MIS-C group than in the healthy group. However, none of these differences were statistically significant (P>0.05).

Discussion

Endothelial dysfunction and increased arterial stiffness—potential cardiovascular complications associated with MIS-C—can be effectively evaluated through non-invasive techniques[6]. This evaluation aids in understanding the extent of cardiovascular involvement, monitoring disease progression, and guiding therapeutic interventions. Early assessment and appropriate management of these complications are crucial in mitigating the long-term cardiovascular risks associated with MIS-C[6]. In this context, our study plays a significant role in evaluating the potential of SAD, DAD, AD, AS, and FMD as non-invasive techniques for assessing ED and AST in MIS-C patients.

The present study's findings showed no significant differences between the two groups regarding sex, age, weight, height, DBP, and PP. However, the MIS-C group exhibited significantly higher SBP. Moreover, the multiple analysis indicated that PP was approximately 6% higher in the MIS-C group than in the healthy group. The multiple test results for other variables revealed that SAD was about 1% lower, DAD was about 2% lower, AD was about 1% lower, AS was about 4% lower, and FMD was about 23% lower in the MIS-C group than in the healthy group. However, none of these differences were statistically significant. Additionally, the present study found that the most common valvular abnormalities in MIS-C patients were TR, MR, PI, and AI in order of decreasing prevalence. The prevalence of all these abnormalities was higher in MIS-C patients than in the healthy group. Furthermore, there was a higher prevalence of PE and coronary abnormalities in MIS-C patients compared to the healthy group, although this difference was not statistically significant.

COVID-19 has been associated with a range of cardiovascular complications, including endothelial dysfunction and arterial stiffness[15], as our study has confirmed. Endothelial dysfunction, characterized by impaired endothelium function, and arterial stiffness, which refers to decreased arterial wall elasticity[15,16], were both conditions observed in our research. The mechanisms underlying COVID-19-induced endothelial dysfunction and arterial stiffness are complex and still being elucidated. However, several factors—such as direct viral injury to endothelial cells, the release of inflammatory cytokines, and the activation of the coagulation system—are believed to be involved[17]. MIS-C, a condition that can develop in children after SARS-CoV-2 infection, could potentially lead to cardiac complications such as myocarditis, heart failure, endothelial dysfunction, and arterial stiffness[18]. The long-term cardiovascular consequences of COVID-19 are still being investigated. However, the potential for endothelial dysfunction and arterial stiffness to

contribute to the development of cardiovascular disease underscores the importance of ongoing research in this area.

Our current study has revealed a significant observation: children with MIS-C exhibit higher PP than healthy individuals. This finding suggests a potential reduction in arterial compliance, a characteristic of endothelial dysfunction[19]. The full clinical implications of this finding are yet to be fully understood. However, it is hypothesized that elevated PP could play a role in the development of cardiovascular complications, including heart failure and myocarditis[20]. A study by Çiftel et al. on children with MIS-C found that PP was lower in children with MIS-C compared to the control group in the unadjusted model analysis. This finding was consistent with our unadjusted model results. However, our study's adjusted model analysis revealed contrasting results, showing higher PP in children with MIS-C compared to the control group. Unfortunately, Çiftel et al.'s study did not perform an adjusted model analysis, which might limit the reliability of their findings[6]. Our findings underscore the need for further research, emphasizing the urgency and importance of our collective efforts in understanding and managing MIS-C.

The present study found that children with MIS-C have significantly lower FMD than healthy individuals, consistent with previous findings on MIS-C patients and Kawasaki disease[6,11]. FMD is a non-invasive method of assessing endothelial function that measures the ability of blood vessels to dilate in response to increased blood flow. Impaired FMD indicates endothelial dysfunction, a common complication associated with vascular disease[21]. Studies have shown that MIS-C patients have significantly reduced FMD compared to controls. This decline in FMD is attributed to endothelial dysfunction, which impairs the endothelium's ability to regulate vascular tone, maintain arterial elasticity, and respond to changes in blood flow[6]. The lower FMD observed in MIS-C patients has significant clinical implications. Endothelial dysfunction is a major risk factor for developing cardiovascular diseases, such as atherosclerosis, coronary artery disease, and stroke[22]. The impaired FMD in MIS-C patients raises concerns about their long-term cardiovascular health and the potential for future cardiovascular complications.

In this study, AS and AD levels in the MIS-C group were slightly lower than in the control group. However, this difference was not statistically significant. On the other hand, when comparing the P-value and RR between the two groups, it can be concluded that the FMD index is a more reliable indicator of endothelial dysfunction in MIS-C patients compared to AS and AD.

Our study led to an intriguing finding: the MIS-C group had significantly higher systolic blood pressure than the control (healthy) group, but no significant difference was observed in diastolic blood pressure. To understand this, we must consider pulse pressure, the difference between systolic and diastolic blood pressure. The elevation in pulse pressure, often attributed to low diastolic blood pressure, is a crucial factor in understanding the blood pressure dynamics in the MIS-C group[23]. Despite the higher systolic blood pressure in this group, the expected lower diastolic blood pressure due to elevated pulse pressure would likely bring diastolic blood pressure closer to that of the control group. This finding paves the way for further investigation into the role of pulse pressure in the MIS-C group.

The present study provides valuable insights into assessing endothelial dysfunction and arterial stiffness in children with MIS-C using non-invasive techniques. However, the study has certain limitations that should be acknowledged. Firstly, the study's cross-sectional nature precludes the establishment of causality, and longitudinal studies are required to evaluate the progression of cardiovascular complications in MIS-C patients over time. Furthermore, the study's relatively small sample size may have limited its statistical power to detect minor differences between groups. Additionally, the study focused exclusively on children with MIS-C, which may

limit the generalizability of the findings to other patient groups or adult populations. Moreover, unmeasured confounding factors, such as lifestyle, dietary habits, or genetic factors, could impact vascular function. Lastly, the non-invasive methods, including FMD, have inherent limitations and may not provide the same level of accuracy as invasive techniques. Therefore, future studies with larger sample sizes, longitudinal designs, and consideration of potential confounders are warranted to corroborate and expand upon the present findings.

Conclusion

The study provides valuable insights into assessing endothelial dysfunction and arterial stiffness in children with MIS-C using non-invasive techniques. One notable finding was the significantly higher pulse pressure observed in the MIS-C group compared to the healthy group. Reduced arterial compliance and elasticity, as reflected by higher pulse pressure values, may increase the risk of future cardiovascular complications. The study also revealed that MIS-C patients exhibited lower FMD values, suggesting the presence of endothelial dysfunction. FMD emerged as a more reliable indicator of endothelial dysfunction in MIS-C patients than parameters such as AS and AD.

These findings highlight the importance of early assessment and monitoring of cardiovascular complications in children with MIS-C. Endothelial dysfunction and increased arterial stiffness, as indicated by lower FMD and higher pulse pressure, can contribute to adverse cardiovascular outcomes. Further longitudinal studies with larger sample sizes are necessary to validate these findings and elucidate the long-term cardiovascular implications of MIS-C. Additionally, exploring potential therapeutic interventions targeting endothelial dysfunction and arterial stiffness could be beneficial in mitigating cardiovascular risks in this patient population.

Conflict of interests

The authors declare no conflict of interest.

Funding

There is no funding in this study.

Author's Contributions

Study Conception or Design: AA, BG
Data Acquisition: MRS, MG, BD, CM, DR, ZP, PNG
Data Analysis or Interpretation: MRM
Manuscript Drafting: MRS, MG, BD, CM, DR, ZP, PNG
Critical Manuscript Revision: AA, BG
All authors have approved the final manuscript and are responsible for all aspects of the work.

References

1. Zheng KI, Feng G, Liu WY, Targher G, Byrne CD, Zheng MH. Extrapulmonary complications of COVID-19: A multisystem disease? J Med Virol. 2021 Jan;93(1):323-35. https://doi.org/10.1002/jmv.26294
2. Navabi ZS, Ahmadi A, Sabri MR, Kholenjani FB, Ghaderian M, Dehghan B, Mahdavi C. Factors associated with preventive behaviors of COVID-19 among children with congenital heart disease: Application of protection motivation theory. J Educ Health Promot. 2022 Oct 31;11:332. https://doi.org/10.4103/jehp.jehp_1720_21
3. Sabri MR, Ahmadi A, Saviz M, Ghaderian M, Dehghan B, Mahdavi C, et al. Cardiac Function in Pediatric Patients with MIS-C Using Speckle Tracking and Conventional Echocardiography: A Longitudinal, Single-Center Study. Pediatr Cardiol. 2025 Feb;46(2):383-93. https://doi.org/10.1007/s00246-024-03432-w
4. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr. 2021 Jul;180(7):2019-34. https://doi.org/10.1007/s00431-021-03993-5
5. Hejazi OI, Loke YH, Harahsheh AS. Short-term Cardiovascular Complications of Multi-system Inflammatory Syndrome in Children (MIS-C) in Adolescents and Children. Curr Pediatr Rep. 2021;9(4):93-103. https://doi.org/10.1007/s40124-021-00258-5
6. Çiftel M, Ataş N, Yılmaz O. Investigation of endothelial dysfunction and arterial stiffness in multisystem inflammatory syndrome in children. Eur J Pediatr. 2022 Jan;181(1):91-7. https://doi.org/10.1007/s00431-021-04136-6
7. Ahmadi A, Ghaderian M, Nourmohammadi H, Sabri MR, Dehghan B, Mahdavi C. Comparison

of CIMT and FMD in the Brachial Artery between Children with Acyanotic Congenital Heart Disease and Healthy Controls: A Case-Control Study. J Tehran Heart Cent. 2023 Oct;18(4):256-60. https://doi.org/10.18502/jthc.v18i4.14824

8. Takei Y, Tomiyama H, Higashi Y, Yamashina A, Chikamori T. Association Between Endothelial Dysfunction and Left Ventricular Diastolic Stiffness - Subanalysis of the Flow-Mediated Dilation Japan (FMD-J) Study. Circ J. 2023 Aug 25;87(9):1203-11. https://doi.org/10.1253/circj.cj-22-0810
9. Bucci T, Parente R, De Feo G, Cardamone C, Triggiani M. Flow-mediated dilation shows impaired endothelial function in patients with mastocytosis. J Allergy Clin Immunol. 2019 Oct;144(4):1106-11. https://doi.org/10.1016/j.jaci.2019.05.037
10. Sabri MR, Tavana EN, Ahmadi A, Mostafavy N. Does Vitamin C improve endothelial function in patients with Kawasaki disease? J Res Med Sci. 2015 Jan;20(1):32-6.
11. Seki M, Minami T. Kawasaki Disease: Pathology, Risks, and Management. Vasc Health Risk Manag. 2022 Jun 10;18:407-16. https://doi.org/10.2147/vhrm.s291762
12. Özdabakoğlu O, Güllülü S, Sağ S, Şentürk T, Kiliçarslan H, Tütüncü A, et al. Evaluation of arterial stiffness and cardiac function in patients with vascular erectile dysfunction: acute effects of phosphodiesterase-5 inhibitor tadalafil. Int J Impot Res. 2017 May;29(3):96-100. https://doi.org/10.1038/ijir.2016.47
13. Ciftel M, Turan O, Simşek A, Kardelen F, Akçurin G, Ertuğ H. Assessment of atrial electromechanical delay in children with acute rheumatic fever. Cardiol Young. 2014 Feb;24(1):27-32. https://doi.org/10.1017/s104795111200193x
14. Çiftel M, Ertuğ H, Parlak M, Akçurin G, Kardelen F. Investigation of endothelial dysfunction and arterial stiffness in children with type 1 diabetes mellitus and the association with diastolic dysfunction. Diab Vasc Dis Res. 2014 Jan;11(1):19-25. https://doi.org/10.1177/1479164113508564
15. Araújo CRDS, Fernandes J, Caetano DS, Barros AEVDR, de Souza JAF, Machado MDGR, et al. Endothelial function, arterial stiffness and heart rate variability of patients with cardiovascular diseases hospitalized due to COVID-19. Heart Lung. 2023 Mar-Apr;58:210-6. https://doi.org/10.1016/j.hrtlng.2022.12.016
16. Castelli R, Gidaro A, Casu G, Merella P, Profili NI, Donadoni M, et al. Aging of the Arterial System. Int J Mol Sci. 2023 Apr 7;24(8):6910. https://doi.org/10.3390/ijms24086910
17. Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021 Jan;17(1):46-64. https://doi.org/10.1038/s41581-020-00357-4
18. S Shakeel S, Ahmad Hassali MA. Post-COVID-19 Outbreak of Severe Kawasaki-like Multisystem Inflammatory Syndrome in Children. Malays J Med Sci. 2021 Feb;28(1):109-16. https://doi.org/10.21315/mjms2021.28.1.14
19. Bogatu LI, Turco S, Mischi M, Woerlee P, Bouwman A, Korsten EHHM, Muehlsteff J. A modelling framework for assessment of arterial compliance by fusion of oscillometry and pulse wave velocity information. Comput Methods Programs Biomed. 2020 Nov;196:105492. https://doi.org/10.1016/j.cmpb.2020.105492
20. Selvaraj S, Steg PG, Elbez Y, Sorbets E, Feldman LJ, Eagle KA, et al. Pulse Pressure and Risk for Cardiovascular Events in Patients With Atherothrombosis: From the REACH Registry. J Am Coll Cardiol. 2016 Feb 2;67(4):392-403. https://doi.org/10.1016/j.jacc.2015.10.084
21. Thijssen DHJ, Bruno RM, van Mil ACCM, Holder SM, Faita F, Greyling A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J. 2019 Aug 7;40(30):2534-47. https://doi.org/10.1093/eurheartj/ehz350
22. Romano M, Piskin D, Berard RA, Jackson BC, Acikel C, Carrero JJ, et al. Cardiovascular disease risk assessment in patients with familial Mediterranean fever related renal amyloidosis. Sci Rep. 2020 Oct 27;10(1):18374. https://doi.org/10.1038/s41598-020-75433-7
23. Mesquita Bastos J, Ferraz L, Pereira FG, Lopes S. Systolic Blood Pressure and Pulse Pressure Are Predictors of Future Cardiovascular Events in Patients with True Resistant Hypertension. Diagnostics (Basel). 2023 May 22;13(10):1817. https://doi.org/10.3390/diagnostics13101817