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Longitudinal Echocardiographic Follow-Up of a Pediatric Multisystem Inflammatory Syndrome Cohort

Pediatrik Multisistem İnflamatuvar Sendrom Kohortunun Uzun Dönemli Ekokardiyografik İzlemi

ABSTRACT

Objective: Significant involvement of the cardiovascular system is known in multisystem inflammatory syndrome in children (MIS-C). This study aimed to examine the recovery of affected cardiovascular parameters over a medium-term follow-up.

Methods: A cohort of 69 children was studied prospectively. Assessments of left ventricular (LV) function and coronary artery abnormalities (CAA) were conducted at admission, 1.5 months, and 3 months. Coronavirus Disease 2019 (COVID-19) antibody titers were assessed at these three time points. Echocardiographic and antibody parameters (rising/decreasing) were analyzed for correlation. Outcomes were assessed using logistic regression.

Results: At admission, among the 78.2% of patients who were tested, 88.9% tested positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). A quarter of the patients had pericardial effusion, and half had valvulitis. Decreased ejection fraction, global circumferential strain (GCS), and global longitudinal strain (GLS) were seen in 54.4%, 68.6%, and 35.8% of patients, respectively. CAAs were observed in 27.78% of patients. Systolic dysfunction was significantly associated with older age. During follow-up, severe LV dysfunction normalized within 6-7 weeks, while mild to moderate dysfunction reached normalcy by two weeks. Both GCS and GLS reached normalcy within a median of two weeks. Diastolic parameters recovered by six weeks. Most small and moderate coronary aneurysms resolved, but a giant aneurysm in an infant remained large even after 15 months. Trends in antibodies and ejection fraction (EF) at three months were significantly correlated. Admission EF, GLS (at 6 weeks) and deceleration time (at 3 months) were significantly associated with intensive care unit (ICU) admission. The median segmental strain of the cohort remained low in certain segments at three months.

Conclusion: Smaller CAAs resolve, whereas giant CAAs persist. EF and GLS are important predictors of Pediatric Intensive Care Unit (PICU) stay. The residual impairment of median segmental strain and persistent diastolic dysfunction at three months indicate the need for long-term follow-up.

Keywords: Strain imaging, coronary artery abnormality, COVID-19, ventricular systolic function, diastolic function, MIS-C

ÖZET

Amaç: Çocuklarda multisistem inflamatuar sendromda kardiyovasküler sistemin önemli bir yer aldığı bilinmektedir. Bu çalışma, orta vadede etkilenen kardiyovasküler parametrelerin iyileşmesini incelemeyi amaçlamıştır.

Yöntem: Bu çalışmada 69 çocuk hastadan oluşan bir kohort prospektif olarak incelendi. Sol ventrikül (LV) fonksiyonu ve koroner arter anormallikleri (KAA) değerlendirmeleri başvuru, 1,5 ay ve 3 ayda yapıldı. Korona virüs hastalığı 2019 (COVID-19) antikor titreleri bu üç zaman noktasında değerlendirilmiştir. Ekokardiyografik ve antikor parametreleri (artan/azalan) korelasyon açısından analiz edilmiştir. Sonuçlar lojistik regresyon kullanılarak değerlendirilmiştir.

Bulgular: Başvuru sırasında hastaların %78,2'si test edildi ve %88,9'unda Şiddetli Akut Solunum Sendromu Korona virüs 2 (SARS-CoV-2) pozitif çıkmıştır. Hastaların dörtte birinde perikardiyal efüzyon ve yarısında valvülit vardı. Hastaların sırasıyla %54,4'ünde, %68,6'sında ve %35,8'inde ejeksiyon fraksiyonunda, global çevresel strainde (GCS) ve global uzunlamasına strainde (GLS) azalma görülmüştür. Hastaların %27,78'inde KAA gözlenmiştir. Sistolik disfonksiyon ileri yaş ile anlamlı derecede ilişkiliydi. Takip sırasında, ciddi LV disfonksiyonu 6-7 hafta içinde normale dönerken, hafif ila orta dereceli disfonksiyon iki hafta içinde normale ulaştı. Hem GKS hem de GLS medyan iki hafta içinde normale ulaştı. Diyastolik parametreler altı hafta içinde düzelmiştir. Küçük ve orta dereceli koroner anevrizmaların çoğu düzelmiştir, ancak bir bebekte görülen dev anevrizma 15 ay sonra bile büyük kalmıştır. Antikorlardaki eğilim ile üç aylık ejeksiyon fraksiyonu

ORIGINAL ARTICLE
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(EF) arasında anlamlı bir korelasyon vardı. Başvuru EF'si, GLS (6. haftada) ve yavaşlama süresi (3. ayda) yoğun bakım ünitesine yatış ile anlamlı derecede ilişkiliydi. Kohortun medyan segmental gerilimi üç ayda belirli segmentlerde düşük kalmıştır.

Sonuç: Küçük KAA'lar düzelirken, dev KAA'lar devam etmektedir. EF ve GLS, pediatrik yoğun bakım ünitesinde kalış süresinin önemli belirleyicileridir. Üç ayda medyan segmental strainde rezidüel bozulma ve kalıcı diyastolik disfonksiyon uzun süreli takip ihtiyacını göstermektedir.

Anahtar Kelimeler: Strain görüntüleme, koroner arter anormalliği, COVID-19, ventriküler sistolik fonksiyon, diyastolik fonksiyon, MIS-C

Whether pediatric Multisystem Inflammatory Syndrome in Children (MIS-C) leads to long-term cardiovascular consequences is unknown. Following the initial report of MIS-C from the United Kingdom (UK),[1] larger series from other countries[2,3] described in-hospital outcomes in children. Most children with severe MIS-C eventually recovered uneventfully despite initial turbulent courses. Although mortality was uncommon, concerns about residual cardiovascular impairment persisted. Studies evaluating short-term echocardiographic outcomes[4,5] and longitudinal clinical outcomes[6] have been reassuring. The Coronavirus Disease 2019 (COVID-19) outbreak in India began a few months later than in China and the West. The first cases of MIS-C in India were reported in May 2020.[7,8] Our objective was to follow up on echocardiographic parameters over a medium-term period to assess for cardiovascular sequelae.

Materials and Methods

Study Design and Study Population

This prospective cohort study was conducted from September 2020 to November 2021 after obtaining approval from the Institutional Ethics Committee for Observational Studies of Jawaharlal Institute of Postgraduate Medical Training and Research (Approval number: JIP/IEC/2020/209, Date: 07.09.2020) at a tertiary care government teaching hospital in Southern India. Sixty-nine hospitalized children, aged one month to fifteen years and fulfilling the World Health Organization (WHO) case definition criteria for MIS-C, were consecutively enrolled. Those presenting with coronary artery abnormalities (CAA) or severe left ventricular (LV) dysfunction during admission underwent more frequent follow-up examinations. We analyzed the admission, 6-week, and 3-month follow-up echocardiograms in our cohort.

Case records were analyzed for demographic and clinical profiles and investigation reports. For Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) testing, swabs were collected, transported, and analyzed as per the Indian Council of Medical Research guidelines. Serological antibody assays for SARS-CoV-2 were performed using the Cobas e 601 ECLIA analyzer (Roche Diagnostics). Results were reported as a cut-off index (COI; signal sample/cut-off). A COI of < 1.0 and ≥ 1.0 were considered negative and positive for anti-SARS-CoV-2 antibodies, respectively. Management of children who tested positive on Reverse Transcription Polymerase Chain Reaction (RT-PCR) was conducted as per our Institute's guidelines.

Since the study began when the association between COVID-19 antibodies and MIS-C had not been established, we planned to send COVID-19 antibody titers at three time points. Therefore, in most children, apart from the sample drawn during admission (S1), second (S2) (2 months) and third samples (S3) (at 4 months from the onset of illness) were also drawn for sero-analysis of antibodies to the SARS-CoV-2 virus. Antibody titer trends were plotted and classified as "rising" or "declining," if they were found to rise or fall, respectively, in comparison to the baseline, at any of the following two time points.

Echocardiographic Evaluation

For sick children admitted to the Pediatric Intensive Care Unit (PICU), an initial bedside echocardiogram assessing left ventricular (LV) ejection fraction (EF) by the Biplane Simpson's method (Biplane EF) was performed using the Vivid S5 (General Electric Medical Systems, Horten, Norway). Strain analysis was conducted later once they were deemed fit to be shifted to the echocardiography room. For children who were fit for shifting, biplane EF, LV global longitudinal and circumferential strain (GLS and GCS) by speckle tracking, coronary assessment, and LV diastolic function were assessed at admission using the Philips EPIQ 7G (Philips Healthcare, Andover, MA).

Ejection Fraction

Children were classified as having normal or reduced systolic function based on their biplane ejection fraction (EF). A cut-off of 55% was used, following adult guidelines.[9,10] LV dysfunction was sub-classified as mild (45-54%), moderate (30-44%), and severe (< 30%).[11]

Strain Analysis

Strain analysis was performed using the QLAB application version 10.5 (Philips Healthcare, Andover, MA). A 17-segment polar plot (Bull's eye) provided a quantitative representation of left ventricular (LV) myocardial strain. Segment nomenclature followed the European Association of Cardiovascular Imaging/American Society of Echocardiography (EACVI/ASE) consensus document.[12] At baseline (admission), children were categorized into one of three groups based on their GLS values (≥ -20.2, ≥

ABBREVIATIONS

CAA	Coronary artery abnormalities
COVID-19	Coronavirus Disease 2019
DT	Deceleration time
EF	Ejection fraction
ESR	Erythrocyte Sedimentation Rate
GCS	Global circumferential strain
GLS	Global longitudinal strain
ICU	Intensive care unit
LV	Left ventricular
MIS-C	Multisystem Inflammatory Syndrome in Children
PICU	Pediatric Intensive Care Unit
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

-14 and < -20.2, and < -14) and their GCS values (> -22.3, ≥ -14 and < -22.3, and < -14). Although age-specific normal ranges for children are available,[13] we chose to follow a single cut-off regardless of age, in line with previous studies on MIS-C.[5,6] This cut-off, derived from Levy et al.,[13] was used as the upper limit in classifying children into one of the three tertiles based on GLS and GCS values at admission, similar to the approach of Sanil et al.[5] For GCS and GLS, values of < -22.3% and < -20.2% were considered abnormal,[13] respectively.

Left Ventricular Diastolic Dysfunction

Spectral Doppler assessed early (E) and late (A) mitral inflow peak velocities, deceleration time (DT), and tissue Doppler assessed early (E') and late (A') diastolic velocities as well as systolic velocity (s') at the mitral (lateral) and septal (medial) annulus of the left ventricle. E/e' values were calculated for the medial and lateral annuli. Since normal values for E/A, septal, and lateral E/e' are available,[14] z-scores were calculated for these using the regression equations provided in Eidem et al.,[14] as done by Doyon et al.[15] For DT, we used the z-score charts of Dallaire et al.[16] as a reference. Z-scores > +2.5 or < -2.5 were considered abnormal for E/A and E/e', while Z-scores > +2 or < -2 were considered abnormal for DT.

Coronary Artery Abnormalities

Quantification of CAA z-scores was performed. Coronary arteries were optimally visualized using an S8-3 MHz probe (Philips Medical System, Andover, MA) with appropriate depth, sector width, gain, and persistence settings.[17,18] Once an appropriate definition of the vessel's inner edge was attained, measurements were made on the zoomed image. We used the Risk Assessment Instrument for Screening and Evaluation (RAISE) study nomogram to calculate z-scores.[19] We then subclassified the results into categories: no involvement of coronaries, dilatation only, small, moderate, and giant aneurysms. These categories were defined as follows: no involvement (z < +2), dilatation only (≥ 2 to < +2.5), small aneurysm (≥ 2.5 to < 5), moderate aneurysm (≥ 5 to < 10), and giant aneurysm (≥ 10). In absolute dimensions in millimeters, > 8 mm and < 8 mm were taken as giant and moderate aneurysms, respectively.[20]

Correlation with Antibody Trends

For children who had at least two serology titers, including the admission value, an attempt was made to correlate the antibody trends with the echocardiographic parameters.

Statistical Analysis

Categorical data were represented as proportions (percent) and continuous variables as medians (interquartile range). The normalcy of data was evaluated using the Kolmogorov-Smirnov test. The association between clinical and echocardiographic parameters was assessed using the Chi-square test for categorical variables and the Mann-Whitney U test or Student's T-test for continuous variables, depending on the normalcy of the data. A p-value of < 0.05 was considered significant. Variables emerging as significant in univariate analysis were subjected to multivariate logistic regression analysis. The statistical analysis was conducted using IBM's Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp).

Results

At Admission: The baseline characteristics and investigations of the study cohort are summarized in Table 1. SARS CoV-2 test results were available in 78.2% of the participants, with a positivity rate of 88.9%. Eighteen participants had mild pericardial effusion at presentation. Valvulitis in the form of mitral regurgitation was observed in 35 patients (trivial - 20; mild - 10; moderate - 5), tricuspid regurgitation in 30 (trivial -12; mild -18), and pulmonary regurgitation in 5 (trivial - 2; mild - 3).

Coronary Artery Abnormalities: Children who developed CAA were considerably younger, though not to a statistically significant extent. The median weight (P = 0.03) and height (P = 0.03) were significantly lower in those with CAA, while D-Dimer levels (P = 0.08) were higher, approaching statistical significance (Table 2).

Table 1. Baseline Characteristics

Characteristic	No. of Children Available for Analysis (n)	Results
Age (months)	69	56 (18-103)
Sex (male: female)	69	40:29
Rash (%)	69	37 (53.62%)
Duration of Fever (days)	69	5 (3-7)
Weight (kg)	69	18.1 (10.9-27.1)
Underweight (%)	69	15 (21.7%)
Overweight and Obesity (%)	69	12 (17.4%)
Height (cm)	69	119 (81-126)
Stunting (%)	69	12 (17.4%)
Platelet Count (×10^3/µl)	69	160 (114-255)
ESR (mm/hr)	62	71 (51-99)
CRP (mg/dl)	43	6.9 (2.4-15)
Serum Ferritin (ng/ml)	56	309 (146-614)
Serum Triglyceride (mg/dl)	25	267 ± 114
Serum Fibrinogen (mg/dl)	37	335 ± 124
d-Dimer (µg/ml)		1.3 (0.6-3.65)
COVID-19 Positivity (%)	54	48 (88.9%)

Data are expressed as ratio, number (percentage), median (interquartile range), or mean ± standard deviation.
CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate.

Table 2. Association Between Echocardiographic Parameters and Clinical Parameters (n=69)

Clinical Parameter	With Cardiac Abnormality	Without Cardiac Abnormality	*P*	Odds Ratio (95% CI)
Coronary Artery Abnormality (n=15)				
Categorical Variables				
Sex (M:F)	11:4	29:25	0.293	2.13 (0.42, 6.5)
Rash (%)	10 (66.6)	28 (51.8)	1.0	1.01 (0.31, 3.3)
Hypotension (%)	5 (33.3)	21 (38.8)	0.42	0.54 (0.15, 1.83)
COVID Positivity (%)	11 (73.3)	37 (68.5)	0.51	0.69 (0.17, 2.8)
Continuous Variables				
Median Age (months)	39	84	0.2	
Duration of Fever (days)	6	5	0.63	
Weight (kg)	11.2	20.9	**0.03**	
Height (cm)	92.6	122	**0.03**	
Platelet Count (×10^3/µl)	2.6	1.64	0.37	
ESR (mm/hr)	72	79	0.92	
CRP (mg/dl)	5.9	7.58	0.51	
Serum Ferritin (ng/ml)	209	302	0.29	
Serum Triglyceride (mg/dl)	178	226	0.86	
Serum Fibrinogen (mg/dl)	365	374	0.58	
d-Dimer (µg/ml)	2.613	0.912	0.08	
Systolic Dysfunction (n=29)				
Categorical Variables				
Sex (M:F)	17:12	23:17	1.0	1.18 (0.38, 3.29)
Rash (%)	20 (68.3)	15 (37.5)	0.28	1.87 (0.62, 5.6)
COVID Positivity (%)	18 (62.08)	18 (45)	1.0	1.1 (0.34, 3.6)
Continuous Variables				
Age (months)	87	36	**0.031**	
Duration of Fever (days)	5	8	0.34	
Weight (kg)	21	11.5	**0.008**	
Height (cm)	121	95	**0.029**	
Platelet Count (×10^3/µl)	1.2	2.1	**0.002**	
ESR (mm/hr)	74	70	0.836	
CRP (mg/dl)	7.8	3.4	0.572	
Serum Ferritin (ng/ml)	398	223	0.092	
Serum Triglyceride (mg/dl)	226	208	0.78	
Serum Fibrinogen (mg/dl)	375	348	0.62	
d-Dimer (µg/ml)	1.98	0.823	0.091	
GCS < -22.3 (n=46)				
Categorical Variables				
Sex (M:F)	27:19	12:9	**0.041**	0.332 (0.11, 0.95)
Rash (%)	17 (36.9)	11 (52.3)	0.596	1.7 (0.49, 4.1)
Hypotension (%)	17 (36.9)	9 (42.8)	0.79	1.15 (0.41, 3.21)
COVID Positivity (%)	31 (67.1)	16 (76.1)	1.0	1.21 (0.31, 3.3)
Continuous Variables				
Age (months)	62	58	0.89	
Duration of Fever (days)	5	5	0.26	
Weight (kg)	20	19	0.97	
Height (cm)	118	110	0.774	
Platelet Count (×10^3/µl)	1.4	1.55	0.82	
ESR (mm/hr)	84	60	**0.02**	
CRP (mg/dl)	8.3	6.9	0.53	
Serum Ferritin (ng/ml)	331	251.4	0.35	
Serum Triglyceride (mg/dl)	146	233	0.059	
Serum Fibrinogen (mg/dl)	374	301	0.29	
d-Dimer (µg/ml)	2.156	0.92	0.079	

Table 2. Association Between Echocardiographic Parameters and Clinical Parameters (n=69) *(continued)*

Clinical Parameter	With Cardiac Abnormality	Without Cardiac Abnormality	*P*	Odds Ratio (95% CI)
GLS < -20.2 (n=24)				
Categorical Variables				
Sex (M:F)	14:10	25:18	0.144	0.29 (0.06, 1.308)
Rash (%)	7 (29.1)	33	0.47	2.23 (0.42, 11.67)
Hypotension (%)	6 (25)	20 (46.5)	0.144	3.4 (0.76, 15.11)
COVID Positivity (%)	14 (58.33)	32 (74.6)	0.42	3.1 (0.35, 26.74)
Continuous Variables				
Age (months)	144	60	**0.004**	
Duration of Fever (days)	3	5	0.227	
Weight (kg)	32	19	**0.001**	
Height (cm)	140	115	**0.001**	
Platelet Count ($\times 10^3/\mu l$)	1.02	1.9	**0.023**	
ESR (mm/hr)	78	70	0.59	
CRP (mg/dl)	10.2	5.8	**0.012**	
Serum Ferritin (ng/ml)	516	252	0.055	
Serum Triglyceride (mg/dl)	237	208	0.239	
Serum Fibrinogen (mg/dl)	401	348	0.41	
d-Dimer (µg/ml)	2.194	0.98	0.35	

CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; F, Female; GCS, Global Circumferential Strain; GLS, Global Longitudinal Strain; M, male.

Table 3. Echocardiography Parameters

Characteristic	No. of Children Available for Analysis (n)	Results
Coronary Artery Abnormalities (%)	69	15 (21.78%)
Giant Aneurysm		1 (1.4%)
Moderate Aneurysm		1 (1.4%)
Small Aneurysm		13 (19.03%)
Hypotension for Age (%)	69	26 (37.68%)
Systolic Dysfunction (%)	68	37 (54.4%)
Strain		
Mean GCS	67	-21.2 ± 3.8
No. of Children with GCS < -14 (%)		4 (5.9%)
No. of Children with GCS – 14 to -22.3 (%)		42 (62.6%)
No. of Children with GCS > -22.3 (%)		21 (31.3%)
Mean GLS	67	-22.45 ± 3.4
No. of Children with GLS < -14(%)		1 (1.5%)
No. of Children with GLS (-14 to -20.2) (%)		23 (34.21%)
No. of Children with GLS > -20.2 (%)		43 (64.1%)

GCS, Global Circumferential Strain; GLS, Global Longitudinal Strain.

Systolic Dysfunction: Children with LV systolic dysfunction at admission were significantly older (*P* = 0.031), weighed more (*P* = 0.008), and were taller (*P* = 0.029) than those without. Thrombocytopenia was statistically more common (*P* = 0.002) in this group. D-Dimer levels were considerably higher (*P* = 0.091), but this did not reach statistical significance (Table 2).

Global Circumferential Strain: Erythrocyte Sedimentation Rate (ESR) levels were significantly higher (*P* = 0.02) in children with reduced GCS. D-Dimer levels (*P* = 0.079) were considerably higher but did not reach statistical significance (Table 2).

Global Longitudinal Strain: Similar to the GCS findings, females were more prevalent in the affected group, while males were more common in the unaffected group. This difference was not statistically significant. Those with reduced GLS were significantly older (*P* = 0.004), weighed more (*P* = 0.001), and were taller (*P* = 0.001) than those unaffected. Reduced GLS was significantly associated with thrombocytopenia (*P* = 0.023) and elevated C-Reactive Protein (CRP) levels (*P* = 0.012). Serum ferritin levels were also considerably higher, although not statistically significant (Table 2).

In the multivariate regression analysis, height emerged as an important predictor of CAA (P value=0.014), where children with CAA were shorter than those without CAA. A low platelet count was significantly associated with systolic dysfunction (*P* value=0.043), and lower GLS showed a trend towards significance (*P* value=0.078). There was a significant association between ESR values and GCS (*P* value=0.041), with higher ESR values observed in children with poorer GCS scores (worse than -22.3).

Not all parameters were available for every child. The number of children analyzed in each category and the results are presented in Table 3. When the cohort was divided into tertiles based on

Table 4. Proportion of Children with Abnormal Diastolic Function at Different Time Points

Echo Parameter	Data	Admission	6 Weeks	3 Months	*P*
E/A	Number Available for Analysis	61	56	58	0.79
	Abnormal (> +2.5 Z score)	2	1	3	
	Normal	59	55	55	
Lateral E/e'	Number Available for Analysis	56	51	54	0.89
	Abnormal (> +2.5 Z score)	2	2	2	
	Normal	54	49	52	
Septal E/e'	Number Available for Analysis	49	49	51	0.71
	Abnormal (> +2.5 Z score)	7	5	4	
	Normal	42	44	47	

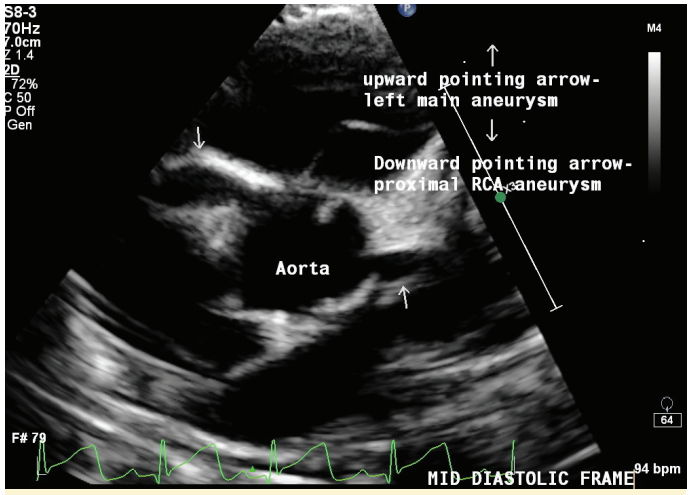

Figure 1. Fusiform aneurysms of the proximal right coronary artery (RCA) and left main coronary artery.

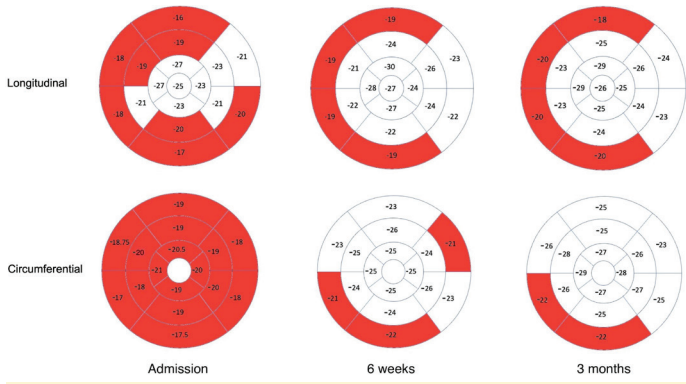

Figure 2. Median LV regional strain of the cohort at admission, 6 weeks' follow-up, and 3 months' follow-up.

GCS and GLS values at admission, four children had GCS < -14%. One was a young infant with a giant CAA of the Left Main (LM) coronary artery. A 10-year-old girl with a low admission GCS of < -14% also had a GLS < -14%. Twenty-one children had normal GCS values, and 43 children had normal GLS values at admission (Table 4).

Diastolic Dysfunction

Deceleration Time: DT was assessed and followed up in 61 children. DT was abnormally low in four children and elevated in six children. In the rest, all values at admission and follow-up were in the normal range.

E/A: One child had an abnormal E/A ratio, amounting to a z-score of +3.69 at admission.

Septal E/e'and Lateral E/e': Seven children had abnormal septal E/e' values (> z-score +2.5) at admission. Two of these also had abnormal lateral E/e' values.

Coronary Artery Abnormalities: The first child in this series developed a moderate fusiform aneurysm of proximal Right Coronary Artery (RCA) (z-score +8.62) and a moderate aneurysm of the LM (z-score +7.2) (Figure 1). A 3-month-old infant, with 20 days of unrelenting fever and admitted in March 2021, had a giant aneurysm of the LM (z-score + 11.1) and a moderate aneurysm of the RCA (z-score +5.9). Both of these children were treated with intravenous immunoglobulin, initiated on anticoagulation, and their coronary dimensions were followed up with serial echocardiograms. Although the RAISE study nomogram categorized the first child's RCA aneurysm as moderate, it was categorized as giant when two other nomograms were employed.[21] Due to this discrepancy and to avoid the risk of coronary thrombosis, he too received anticoagulation for six months until a decrease in z -score could be documented.

On Follow-Up

Ejection Fraction: Two children with severe LV dysfunction at admission reached an EF > 55% in 6-7 weeks. Among those with moderate dysfunction, five reached an EF ≥ 52% within a week, and four within two weeks. While two needed more than two months, two reached normalcy within a month.

Global Circumferential Strain: Of the 46 with reduced GCS, four were not analyzed as their strain values on admission were unavailable. Of the four whose admission GCS was < -14%, a 10-year-old (with severe LV dysfunction at admission) reached normalcy in a month, and the infant with the giant CAA in three months. The third, a 1.5-year-old child, had a GCS that remained just short of the normal value at the three month-review.

Global Longitudinal Strain: Of the 24 with reduced GLS, six were not analyzed due to inadequate follow-ups. The median

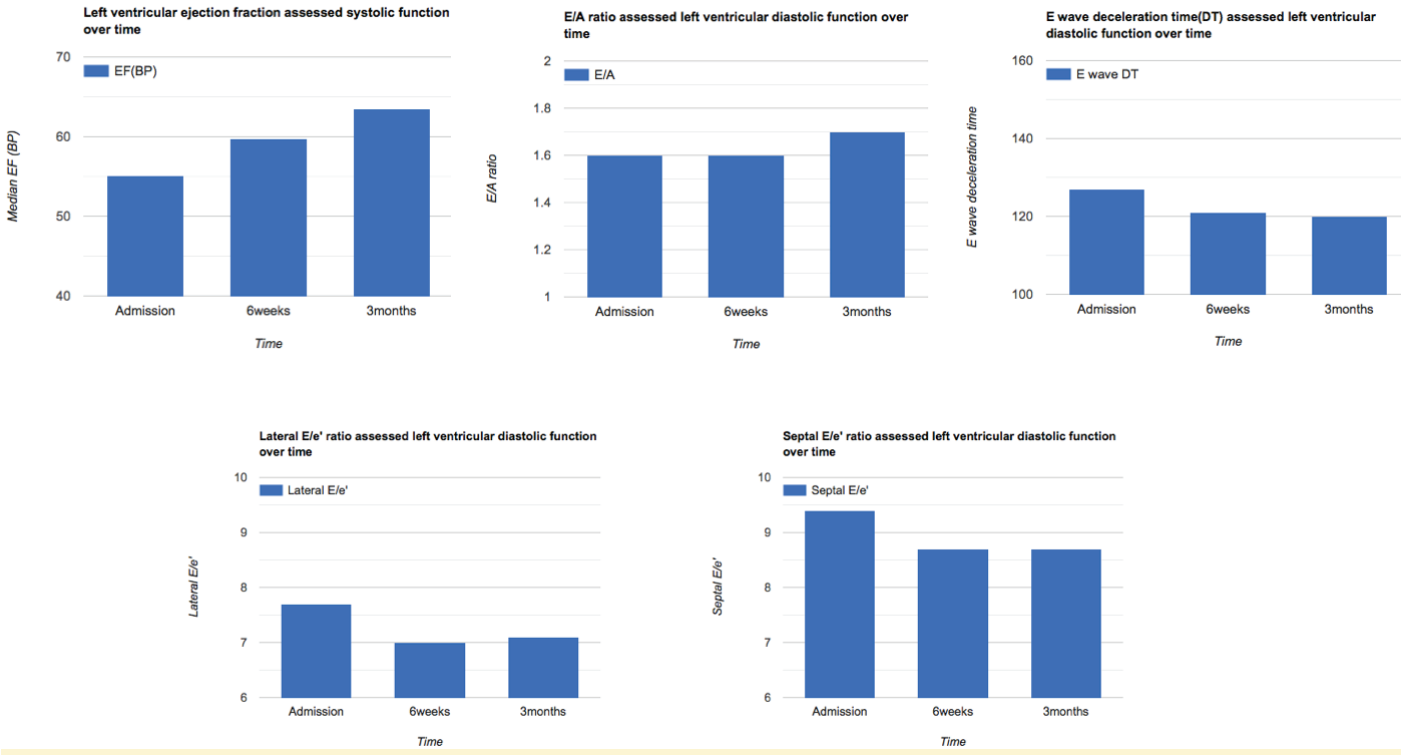

Figure 3. Trends of 2-dimensional EF (by Biplane Simpson's method) and diastolic function parameters over time.

time to reach normalcy was two weeks (Interquartile Range [IQR]: 1 week - 4 weeks). The 10-year-old child, whose GLS fell in the lowest tertile at admission, had reached a normal GLS value at the 1-month follow-up.

Segmental Strain: Median longitudinal strain (LS) and circumferential strain (CS) values of individual segments of the entire cohort were plotted, and their evolution over the follow-up was analyzed (Figure 2). For LS, segments with values < -20.2 and for CS, values < -22.3 are highlighted in red. All basal segments, other than the basal anterolateral, as well as all mid segments, excluding the mid inferoseptal, mid anterolateral, and mid inferolateral, exhibited reduced segmental LS at admission. The apical segments were uninvolved. All segments showed involvement when CS was assessed at admission.

Diastolic Function: The trends of diastolic function parameters in the cohort are illustrated in Figure 3.

Coronary Artery Aneurysm

The infant with a giant aneurysm of the LM coronary artery continued to have z-scores > 10 (latest review in June 2022; age one year and three months) and remains on anticoagulation therapy. He was transitioned from injectable to oral anticoagulation in June 2022. The child with a moderate RCA aneurysm experienced a reduction in size, and anticoagulation was withdrawn.

Most children with small aneurysms showed resolution, while one infant continued to have the aneurysm of the same dimensions as observed at admission during the 7-month follow-up.

Correlation of Antibody Trends with Echocardiographic Parameters: There was a significant association between EF measured by biplane method at three months and antibody trends (*P* value=0.041). A significant association was also found between admission to the intensive care unit and DT at three months (*P* value=0.042).

The correlation between acute phase reactants and echocardiographic parameters at admission is presented in Table 5.

It was observed that lower platelet counts and ESR values were associated with longer LV systolic function recovery times.

Discussion

In our cohort, male children were more prevalent, constituting 57.9%, compared to an equal representation of male and female children in Matsubara et al.[4] (50%) and a lower percentage (46%) in Sanil et al.[5] Less than one-fifth of our cohort fell into the overweight/obese category, in contrast to half of the subjects in Matsubara et al.[4] The median LVEF in our cohort was 55.1% (range 46.5-55.6), compared to 57% (range 48-61) in Matsubara et al. A higher percentage of children in our study had LV systolic dysfunction (EF < 55%) at admission (52.9%), than in Matsubara et al.[4] (42.8%) or in Sanil et al.[5] (42%). In our cohort, GCS and GLS were deranged on admission in 68.6% and 35.8% of cases, respectively. Sanil et al.[5] reported that 66.6% of their cohort had an Apical 4-Chamber Longitudinal Strain (A4C LS) < -19% at admission.

Time to Reach Normalcy

Global Longitudinal Strain: The median time to reach normalcy in our cohort was two weeks. Sanil et al.[5] reported that an initial Left Ventricular Apical 4-Chamber Longitudinal Strain (LVA4LS) of ≤ -16.2% (sensitivity - 100%; specificity - 66%) and Left Ventricular Global Longitudinal Strain (LVGLS) of < -15.2%

Table 5. Correlation Between Acute Phase Reactants at Admission and Echocardiogram Findings at Admission

Echo Parameter	*P* and Correlation Coefficient	Platelet Count	ESR	CRP	Ferritin	Triglyceride	Fibrinogen	d-Dimer
GLS at Admission	Correlation Coefficient	0.167	-0.12	-0.34	-0.084	0.073	0.1	-0.043
	P	0.312	0.146	0.61	0.683	0.821	0.398	0.407
GCS at Admission	Correlation Coefficient	0.047	-0.035	-0.246	-0.149	0.254	-0.25	-0.165
	P	0.135	0.119	0.391	0.519	0.372	0.365	0.382
EF (BP)	Correlation Coefficient	0.0352	-0.116	-0.236	-0.288	-0.156	-0.006	-0.129
	P	0.441	0.337	0.141	0.401	0.283	0.284	0.471
E/A	Correlation Coefficient	-0.079	0.076	-0.055	-0.011	-0.297	0.037	0.11
	P	0.134	0.187	0.617	0.671	0.399	0.386	0.464
DT	Correlation Coefficient	-0.011	-0.057	-0.098	-0.108	0.17	-0.079	-0.188
	P	0.229	0.319	0.154	0.817	0.624	0.591	0.361
Lateral E/e'	Correlation Coefficient	0.16	-0.033	-0.295	-0.195	-0.091	-0.264	-0.143
	P	0.138	0.281	0.572	0.541	0.719	0.584	0.663
Septal E/e'	Correlation Coefficient	0.045	0.261	0.202	0.38	-0.092	0.16	0.066
	P	0.139	0.181	0.436	0.611	0.418	0.794	0.763

Platelet Count	ESR	CRP	Ferritin	Triglyceride	Fibrinogen	d-Dimer
1.6 (1.03-2.53)	73.5 (50-93.75)	7.5 (1.8-14)	294.55 (136.9-564)	226 (158-292)	357 (254-478)	1.4 (0.58-2.97)

BP, Biplane; CRP, C-Reactive Protein; DT, Deceleration Time; EF, Ejection Fraction; ESR, Erythrocyte Sedimentation Rate; GCS, Global Circumferential Strain; GLS, Global Longitudinal Strain.

(sensitivity - 100%; specificity - 74%) predicted persistent abnormal LVA4LS and abnormal GLS, respectively, at 10 weeks. Since some of the sickest children in our cohort did not undergo strain assessment in the initial days of their admission, only one child in our cohort had a GLS < -14%. She recovered her EF, GLS, and GCS much earlier than predicted by Sanil et al.[5]

Global Circumferential Strain: The median time to reach normalcy in our cohort was two weeks. Four children had a GCS < -14% at admission. The use of GCS at admission as a predictor of time to return to normalcy has not been reported previously.

CAAs were present in 27.78% of patients in our study. In contrast, 4% of patients in Matsubara et al.[4] and 11% in Sanil et al.[5] had small aneurysms. Nine percent of patients in Rakha et al.[22] had CAA, while Harahsheh et al.[23] reported a 45% and 21% incidence of CAA, respectively. Another study from India,[24] reported a prevalence of CAA of 68%. The high incidence of CAA in our study, as well as in the studies by Elilarasi et al.[24] and Rakha et al.,[22] might be attributed to late referrals resulting in delayed initiation of appropriate management.

Platelet count and ESR are markers of the degree of inflammatory activity. Both were significantly associated with echocardiographic abnormalities: systolic function and GLS with platelet count, and GCS with ESR. The degree of inflammatory activity is likely to affect cardiomyocyte function, manifesting as systolic dysfunction and abnormal strain patterns. Although levels of inflammatory cytokines were not measured, we observed that these markers acted as negative inflammatory markers. Higher inflammatory activity is likely to consume fibrinogen, reduce ESR escalation, and suppress the marrow, thereby reducing platelet counts. Those with lower values exhibited slower recovery of echocardiographic abnormalities, suggestive of severe cardiac dysfunction in children with severely uncontrolled inflammatory activity.

Although we strictly adhered to the WHO case definition for diagnosing MIS-C in our series, there might have been some overlap with Kawasaki Disease (KD), which is inevitable given the clinical nature of the diagnostic criteria. Dufort et al.'s [25] series from New York indicated that 36% had received a diagnosis of KD. In that series, 48% of children under five years of age, 43% of children in the 6-12 age group, and seven out of the nine with CAA had either typical or atypical KD features. Although subtle differences exist between the two conditions, making a clear distinction based on clinical and laboratory parameters becomes difficult, especially in very young children who have

also had exposure to a confirmed case of COVID-19, if RT-PCR or antibody testing is negative.[26-29] Despite our best efforts, 15 members of our cohort did not have laboratory evidence of COVID-19 positivity. Among those tested, 88.9% were positive for SARS-CoV-2.

The study by Theocharis et al.[30] on Cardiac Magnetic Resonance (CMR) imaging in MIS-C reported myocardial edema in 50% of cases and subendocardial infarcts in 5% early in the disease course. Benvenuto et al.'s[31] study found that one-fourth of their cohort showed persistence of late gadolinium enhancement (LGE) at a three-month follow-up. Sirico et al.[32] and Chakraborty et al.[33] reported persistent LGE on CMR in one-third and one-sixth of their study patients at a six-month follow-up, respectively. Sirico et al.[32] also noted persistent impairment of LV GLS in 13% of their study cohort at a six-month follow-up. A follow-up assessment by Karagozlu et al. [34] on children with abnormal findings on CMR at a median of 2.3 months revealed no abnormalities at a one-year follow-up.

He et al.[6] analyzed the regional strain values (median values) of their entire cohort. They found reduced LS values in the mid and basal anterolateral, as well as mid and basal inferoseptal segments. Impaired strain values in the basal anterolateral segment persisted even in subacute and chronic follow-up phases. CS was impaired in mid inferior/infero-septal and infero-lateral segments in the acute phase but recovered upon follow-up. In our cohort, when conducting a similar analysis, we found similar results. Whether this will translate into long-standing residual impairment in the affected territories needs to be assessed.

Limitations

Many of the sick children did not receive a strain evaluation immediately upon hospitalization. As a result, a complete assessment of disease severity might have gone unrecorded. Serial antibody titers were not available for everyone, as lockdown restrictions at various times hindered timely follow-ups. Right ventricular systolic function, LV diastolic and systolic strain rates, and left atrial strain were not assessed.

Conclusion

Younger children were more prone to developing CAA, while older children were more likely to develop systolic dysfunction. Most children with mild to moderate LV dysfunction returned to normalcy in less than 4 weeks, whereas those with severe LV dysfunction required 6-7 weeks for recovery. The median time for GCS and GLS to normalize was two weeks. Diastolic dysfunction, though rare, persisted in a minority of cases at three months. The median segmental LS and segmental CS in our cohort remained impaired in certain segments, particularly in the inferior and infero-septal regions. These findings indicate the need for a longer follow-up period for this cohort.

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