Role of laboratory investigations and imaging in Kawasaki disease

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Background

- **Role of various laboratory investigations in the diagnosis of KD**
- **Role of 2-D echocardiography in diagnosis of KD**
- **Limitations of 2-D echocardiography**
- **Role of coronary CT angiography and magnetic resonance imaging**

Facts about Kawasaki disease

- **Diagnosis of KD is clinical**
- **Laboratory investigations only support a diagnosis of KD**
- **2-D echocardiography should NEVER be used to diagnose KD but only to assess the coronary artery abnormalities**

Laboratory findings commonly seen in KD

Often non-specific

1. Neutrophilic leukocytosis
2. Elevated ESR and CRP
3. Anemia
4. Thrombocytosis (thrombocytopenia may be seen in the acute phase)
5. Sterile pyuria (may be confused with UTI)
6. Elevated transaminases
7. CSF pleocytosis (may be confused with meningitis)
8. Elevated N-terminal pro-BNP (useful marker)

Reddy M, Singh S, Rawat A, et al. Pro-brain natriuretic peptide (ProBNP) levels in North Indian children with Kawasaki disease. Rheumatol Int. 2016 Apr;36(4):551-9

Iwashima S, Ishikawa T. B-type natriuretic peptide and N-terminal pro-BNP in the acute phase of Kawasaki disease. World J Pediatr. 2013 Aug;9(3):239-44.

Evaluation of suspected incomplete KD

Fever $\geq$ 5 days with 2 or 3 principal clinical criteria or infant with fever $\geq$ 7 days without any other explanation

↓

C-reactive protein and erythrocyte sedimentation rate

↓

CRP > 30 mg/l and ESR $\geq$ 40 mm in 1^{st} hour

↓

<u>3 or more laboratory findings:</u>

- Anemia for age
- Platelet counts > 450×10^9/l after day 7 of fever
- Albumin $\leq$3 gm/dl
- Elevated ALT levels
- White cell counts >15×10^9/l
- Urine >10 WBCs/HPF

OR

- Positive echocardiography

Yes → Treat

No → Serial clinical and laboratory re-evaluation if fever persist; 2-D Echocardiography**

CRP < 30 mg/l and ESR < 40 mm in 1^{st} hour

↓

Serial clinical and laboratory re-evaluation if fever persist

2-D Echocardiography**

Diagnosis of incomplete KD is usually clinical and should not be delayed

Age appropriate upper limit for ProBNP

Patient age	NT-proBNP, Cut-off value (pg/mL)	Median (pg/mL)
1–11 months	1000	140
1 year	900	130
2 years	800	110
3 years	700	90
4 and 5 years	600	80
6 and 7 years	500	60
8 and 9 years	400	50
10–15 years	300	30

Hirai S, Nakamura T, Misawa M. Predictive potential of age- group cut- off values of N- terminal pro- brain natriuretic peptide in Kawasaki disease. Pediatr Int. 2022;64:e15371

Imaging modalities in Kawasaki disease

- 2 D echocardiography: remains the standard imaging modality for assessment of coronary artery abnormalities

- Other imaging modalities include
  - CT coronary angiography
  - Magnetic resonance coronary angiography
  - Catheter angiography

2-D echocardiography

- Echocardiography remains the standard imaging modality for patients with KD in the acute phase
- The initial echocardiogram should be performed as soon as the diagnosis is suspected, but initiation of treatment should not be delayed by the timing of the study
- An initial echocardiogram in the first week of illness is typically normal and does not rule out the diagnosis

2-D echocardiography

- Aneurysms are classified as saccular if axial and lateral diameters are nearly equal or as fusiform if symmetrical dilation with gradual proximal and distal tapering is seen
- Sometimes aneurysms occur in series with interposing narrow segments
- When a coronary artery is dilated without a segmental aneurysm, the vessel is considered ectatic

Views in 2-D echocardiography

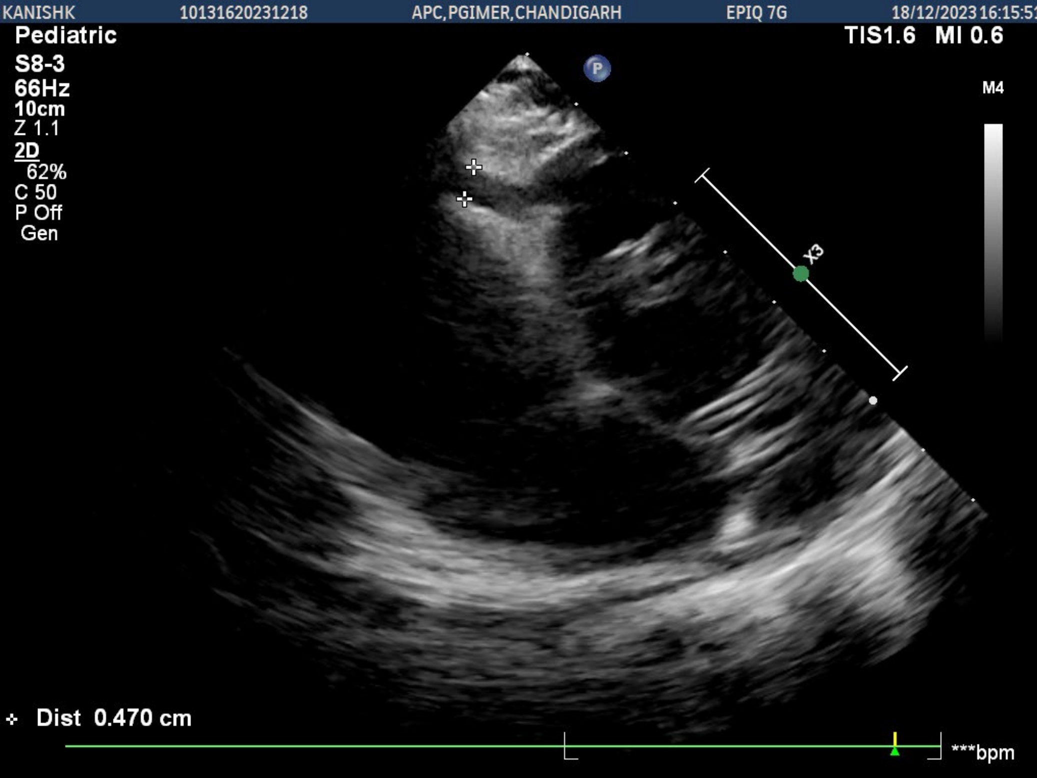
- **Parasternal short axis view**
- **Parasternal long axis view**
- **Apical 5 chamber view**

Definition of aneurysms

- The Japanese guidelines classify coronary arteries by absolute or relative internal lumen diameter
- **Dilation or small aneurysms:** Localized dilation of the internal lumen diameter but <4 mm, or if the child is ≥5 years of age, dilation but with an internal diameter of a segment measuring ≤1.5 times that of an adjacent segment
- **Medium aneurysms:** Internal lumen diameter >4 mm but ≤8 mm, or if the child is ≥5 years of age, an internal diameter of a segment measuring 1.5 to 4 times that of an adjacent segment
- **Large or giant aneurysms:** Internal lumen diameter >8 mm, or if the child is >5 years of age, an internal diameter of a segment measuring >4 times that of an adjacent segment.

Z-Score Classification of aneurysms

- **No involvement:** Always <2
- **Dilation only:** 2 to <2.5; or if initially <2, a decrease in Z score during follow-up ≥1
- **Small aneurysm:** ≥2.5 to <5
- **Medium aneurysm:** ≥5 to <10, and absolute dimension <8 mm
- **Large or giant aneurysm:** ≥10, or absolute dimension ≥8 mm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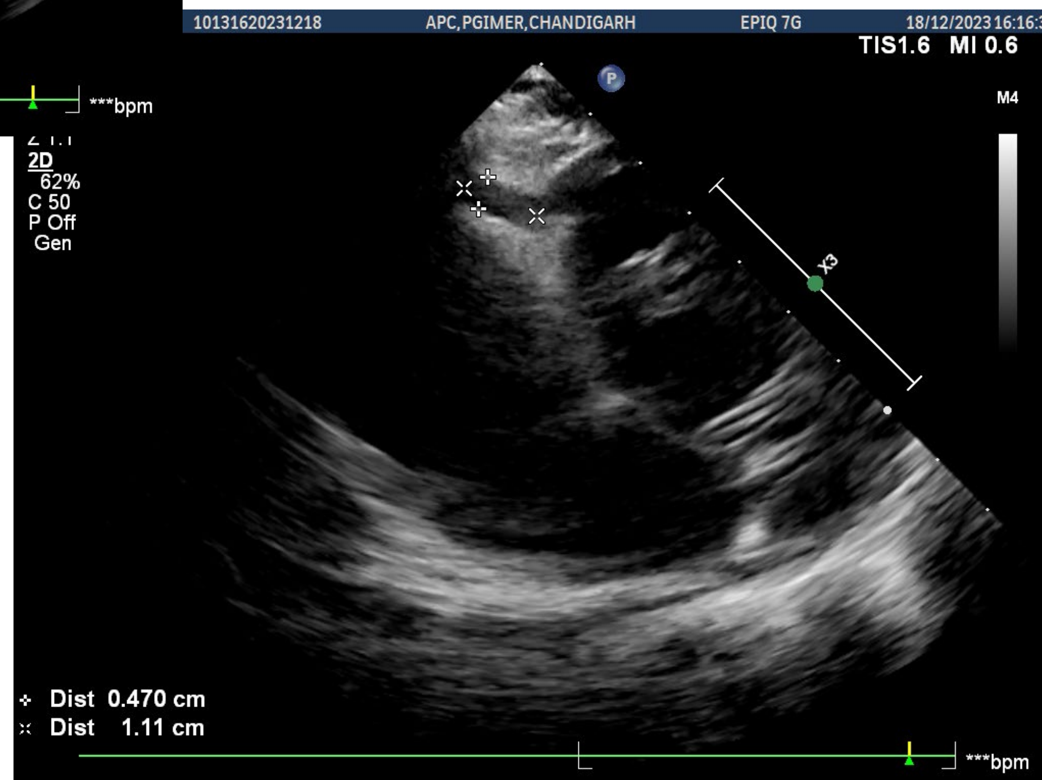
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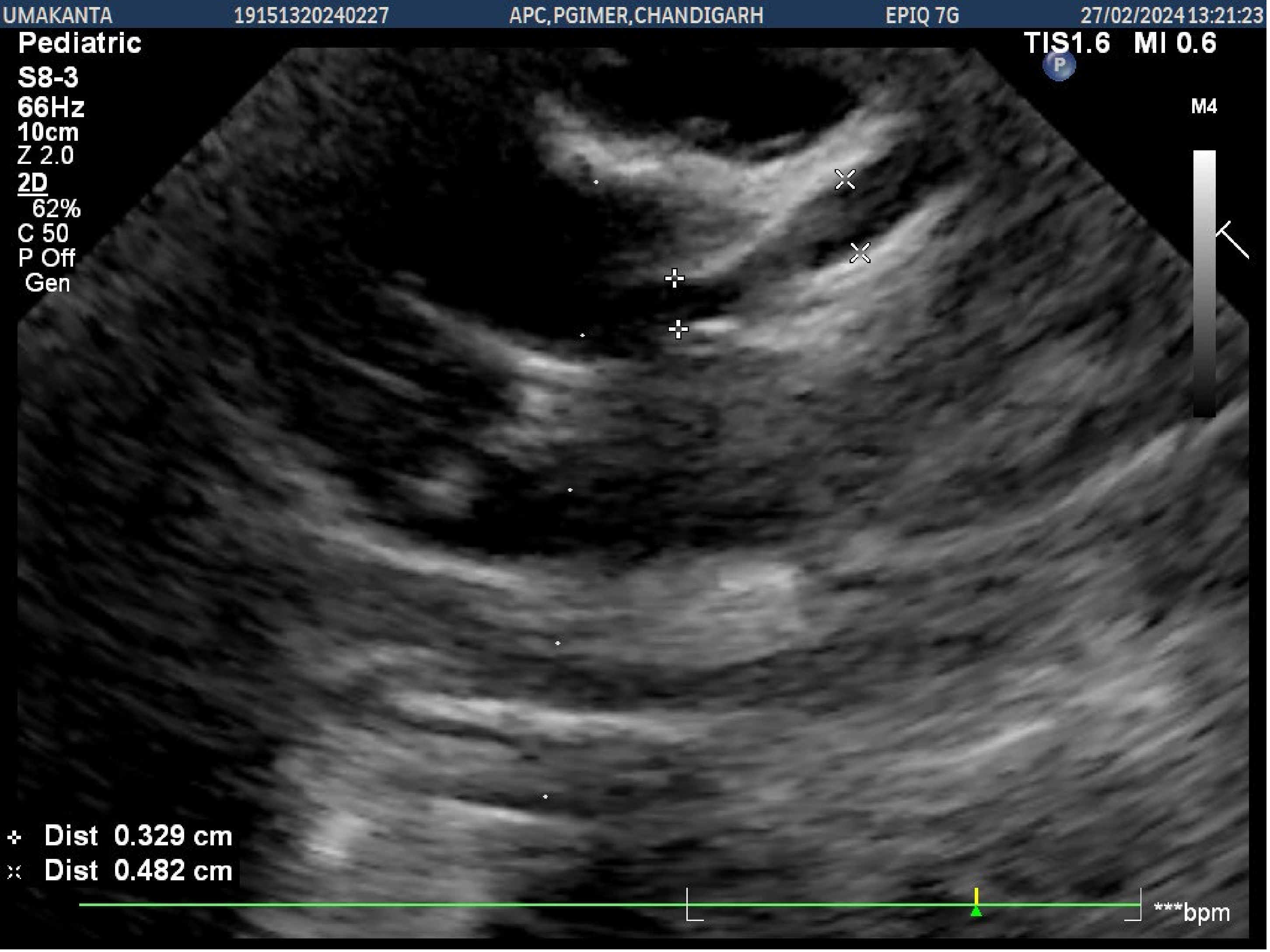
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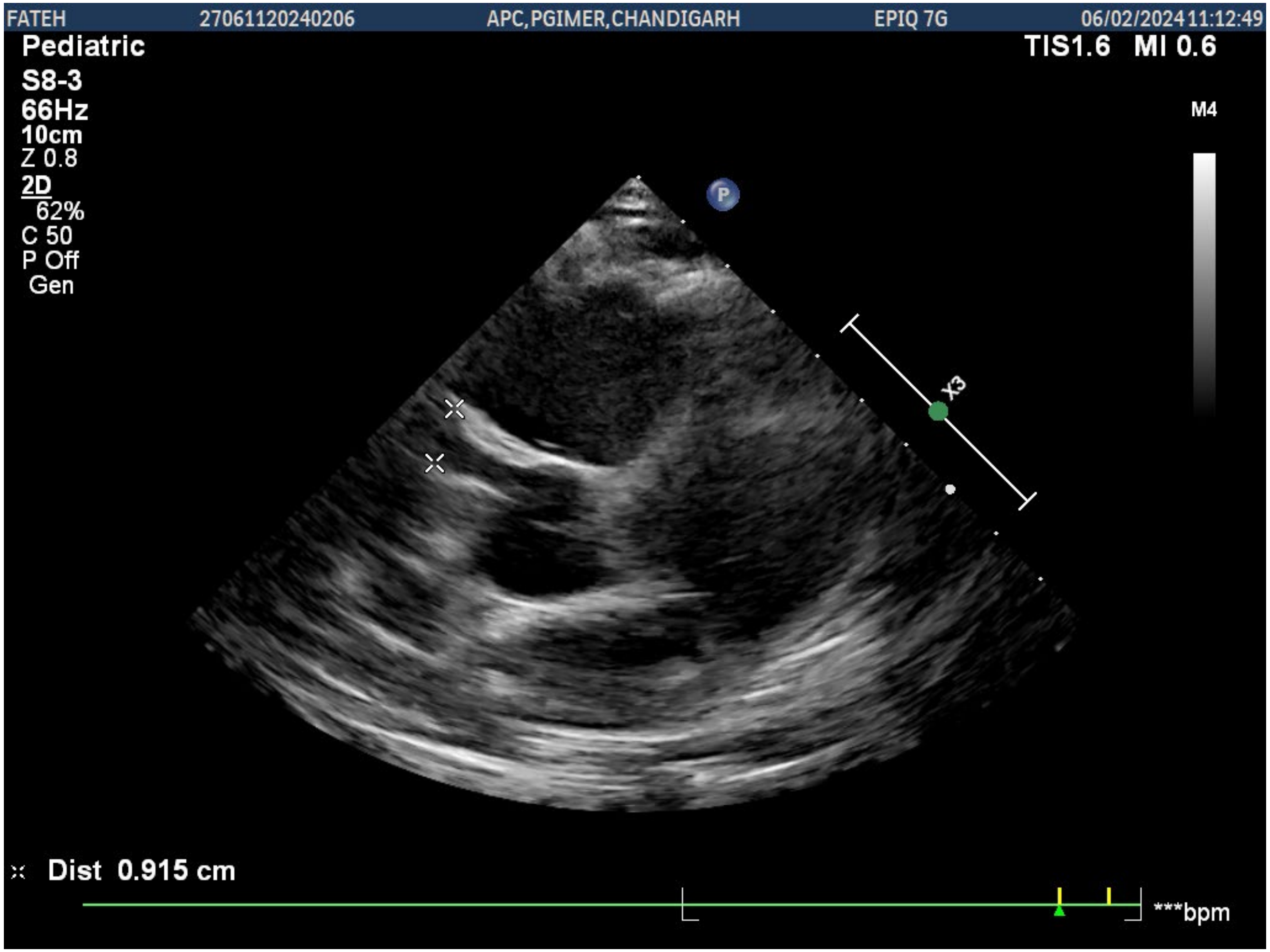
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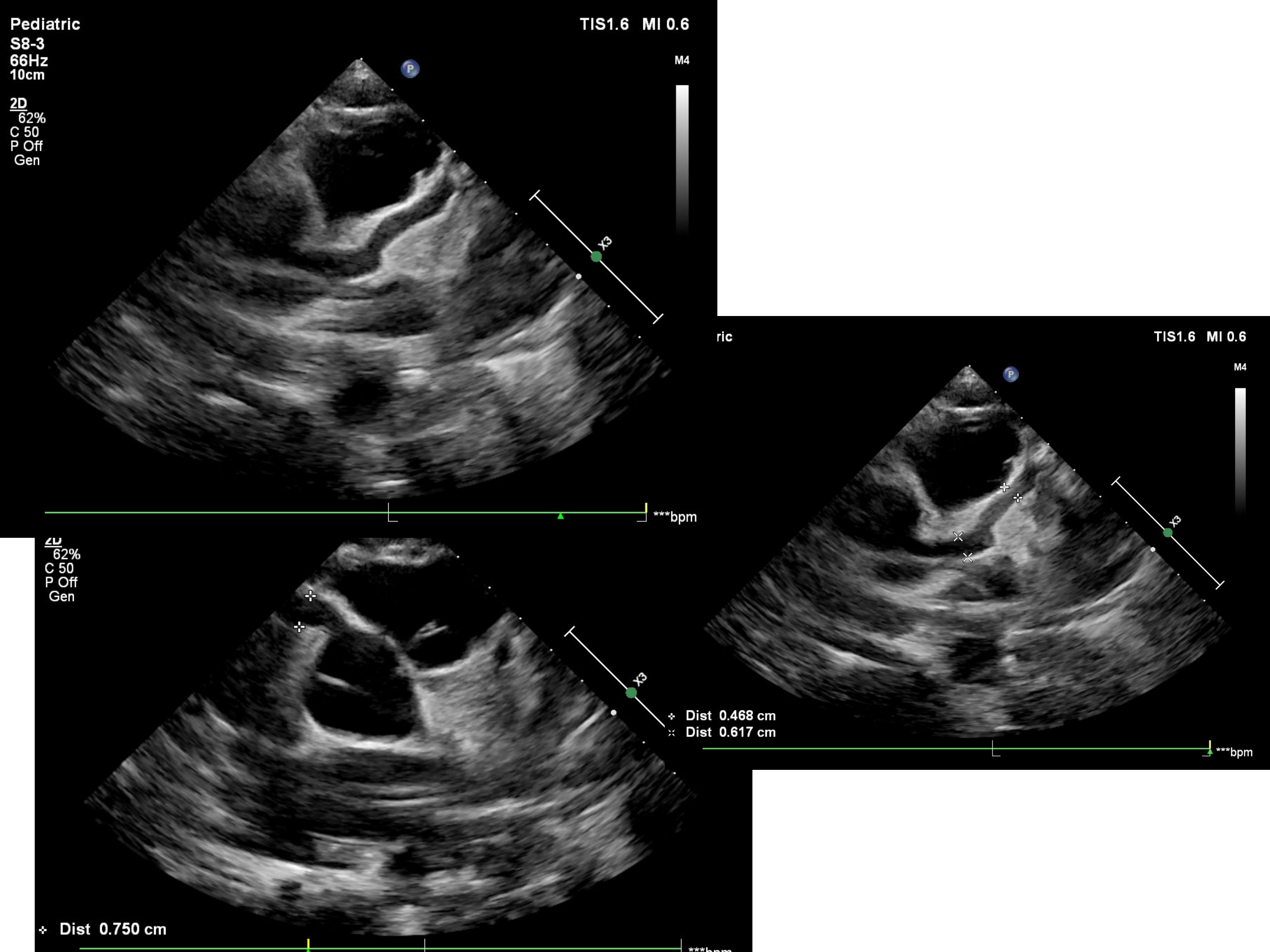
Pediatric
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2D
62%
C 50
P Off
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M4
X3
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TIS1.6 MI 0.6
M4
X3
Dist 0.468 cm
Dist 0.617 cm
***bpm
2D
62%
C 50
P Off
Gen
X3
Dist 0.750 cm

Limitations of 2-D echocardiography for assessment of coronary artery abnormalities in KD

- **Difficulty to visualize left circumflex coronary artery and distal segments of coronary arteries**
- **Observer dependent**
- **Difficult to interpret in older children because of thick chest wall**
- **Problems with 'Z' score calculations**

Jrad M, Ben Salem F, Barhoumi C,et al. The Role of Computed Tomography Coronary Angiography in Kawasaki Disease: Comparison with Transthoracic Echocardiography in a 25-Case Retrospective Study. Pediatr Cardiol. 2019 Feb;40(2):265-275.
Chu WC, Mok GC, Lam WW, Yam MC, Sung RY. Assessment of coronary artery aneurysms in paediatric patients with Kawasaki disease by multidetector row CT angiography: feasibility and comparison with 2D echocardiography. Pediatr Radiol. 2006 Nov;36(11):1148-53.
Singhal M, Singh S, Gupta P, Sharma A, Khandelwal N, Burns JC. Computed Tomography Coronary Angiography for Evaluation of Children With Kawasaki Disease. Curr Probl Diagn Radiol. 2018 Jul-Aug;47(4):238-244.

A. Should Z scores be used for assessment of CAAs in patients with KD?

- **Yes, definitely**

B. Which Z scores to be used?

	De Zorzi et al[138]	Kurotobi et al[142]	Tan et al[143]*	McCrindle et al[139]	Olivieri et al[144]	Kobayashi et al[145]	Dallaire et al[146]
Year of publication	1998	2002	2003	2007	2009	2009	2011
Number of subjects	89	71	390	221	432	5344	1036
Country	USA	Japan	Singapore	USA	USA	Japan	Canada
Regression method for model fitting of BSA	Linear	Linear	Linear	Exponential	Logarithmic	LMS	Square root
BSA calculation method	NS	NS	NS	Haycock	Dubois	Haycock	Haycock
Values for left circumflex	No	No	No	No	No	Yes	Yes

Review › Circulation. 2017 Apr 25;135(17):e927-e999. doi: 10.1161/CIR.0000000000000484.
Epub 2017 Mar 29.

Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association

Brian W McCrindle, Anne H Rowley, Jane W Newburger, Jane C Burns, Anne F Bolger, Michael Gewitz, Annette L Baker, Mary Anne Jackson, Masato Takahashi, Pinak B Shah, Tohru Kobayashi, Mei-Hwan Wu, Tsutomu T Saji, Elfriede Pahl;
American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention

parameter by Rady Children's Hospital

Go to Rady Children's Hospital

120 cm Height | 25 kg Weight

6 years Age | Female Sex, Birth Assigned

17.36 BMI | 0.91 BSA Haycock

Echocardiography

Coronary Artery Z Scores (Dallaire & Dahdah, JASE 2011)

New equations and a critical appraisal of coronary artery Z scores in healthy children.

Dallaire F, Dahdah N.

J Am Soc Echocardiogr. 2011 Jan;24(1):60-74.; 2011

AGE 0.16 - 18 years old | **BSA** 0.08 - 2.72 m2

Find a specific area of interest

Left Main Coronary Artery	3.6 mm	2.34 (1.77 - 3.46)
Left Anterior Descending Coronary Artery	2.5 mm	1.24 (1.24 - 2.80)
Circumflex Coronary Artery	2.4 mm	0.97 (1.09 - 2.85)
Proximal Right Coronary Artery	2.6 mm	0.62 (1.45 - 3.20)
Mid Right Coronary Artery	2.2 mm	0.46 (1.11 - 2.88)
Distal Right Coronary Artery	2.5 mm	1.42 (1.08 - 2.74)

120 cm Height | 25 kg Weight

6 years Age | Female Sex, Birth Assigned

17.36 BMI | 0.91 BSA Haycock

Echocardiography

Coronary Artery Z-Scores using LMS Method (Kobayashi et al., JASE 2016)

Find a specific area of interest

Left Main Coronary Artery	3.6 mm	2.73 (1.78 - 3.27)
Left Anterior Descending Coronary Artery	2.5 mm	1.28 (1.43 - 2.80)
Circumflex Coronary Artery	2.4 mm	1.48 (1.18 - 2.63)
Proximal Right Coronary Artery	2.6 mm	1.19 (1.47 - 2.92)

Summary

120 cm
Height

25 kg
Weight

6 years
Age

Female
Sex, Birth Assigned

17.36
BMI

0.91
BSA
Haycock

Echocardiography

PHN Echocardiographic Z Scores (Lopez et al., Circ CV Img 2017)

Relationship of Echocardiographic Z Scores Adjusted for Body Surface Area to Age, Sex, Race, and Ethnicity: The Pediatric Heart Network Normal Echocardiogram Database.
Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, Pearson G, Camarda J, Cnota J, Cohen M, Dragulescu A, Frommelt M, Garuba O, Johnson T, Lai W, Mahgerefteh J, Pignatelli R, Prakash A, Sachdeva R, Soriano B, Soslow J, Spurney C, Srivastava S, Taylor C, Thankavel P, van der Velde M, Minich L
Circ Cardiovasc Imaging. 2017 Nov;10(11).; 2017

AGE

Find a specific area of interest

Aortic Isthmus	0 mm	
Left Main Coronary Artery	3.6 mm	1.40 1.74 - 3.93
Left Anterior Descending Coronary Artery	2.5 mm	2.07 1.17 - 2.48
Proximal Right Coronary Artery	2.6 mm	0.70 1.17 - 3.28
Pulmonary Valve Annulus	0 mm	
Pulmonary Valve Annulus, PLAX	0 mm	
Main Pulmonary Artery	0 mm	

C. Are there specific Z scores for Indian population?

- **No published data**
- **Small cohort data from Chandigarh, India (reliability and reproducibility??)**

- ***Urgent need to develop Body surface area appropriate, gender appropriate and race appropriate CAA 'Z' scores for Indian children***

- ***Till then, we may use the 'Z' score criteria proposed by Dallaire et al***

A few important tips

- *It is important to use the same 'Z' score criteria every time*

- *A small error in measurement of the CA dimension can translate into a significant difference in Z scores, changing the CA classification, particularly in young patients*

- *Accurate weight and height measurements (at each visit) are necessary for accurate body surface area calculation to avoid errors in measurements that may lead to over- or underestimation of CA Z scores*

Role of coronary CT angiography and magnetic resonance imaging

- ***Availability and expertise needed to analyze the imaging is a limitation***
- ***CT coronary angiography is a better imaging modality for left circumflex coronary artery and to assess distal coronary arteries. It can also assess the calcification, thrombosis and stenosis.***
- ***Role of cardiac magnetic resonance imaging is under investigation***

Distal Coronary Artery Abnormalities in Kawasaki disease: experience on CT Coronary Angiography in 176 children. Singhal M, Pilania R, Jindal AK et al. Rheumatology, 2022.

- **176 patients underwent CTCA** (128-Slice Dual Source scanner)
- **CTCA identified 60 aneurysms:** 37 proximal (36 fusiform; 1 saccular) and **23 distal (17 fusiform; 6 saccular)**
- **9 patients showed non-contiguous aneurysms in both proximal and distal segments**

- **Four patients showed distal segment aneurysms in absence of proximal involvement of same coronary artery**
- **On 2-D echocardiography, only 40 aneurysms could be identified**
- **CTCA also identified complications (thrombosis, mural calcification and stenosis) that were missed on 2-D echocardiography**