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Cardiac Biomarkers in Differentiating Kawasaki Disease and Multisystem Inflammatory Syndrome in Children Associated with COVID-19

Mollie Walton
Children's Mercy Hospital

Geetha Raghuveer
Children's Mercy Hospital

K Kamakoti

N Dahdah

L Garrido

See next page for additional authors

Authors

Mollie Walton, Geetha Raghuveer, K Kamakoti, N Dahdah, L Garrido, S Tierney, T Harris, M Khoury, M Hicar, E Braunlin, D Thacker, M Khare, F Dallaire, R Lowndes, I Glassmeyer, J Ballweg, G Goldenberg, S Merves, C Manlhiot, P Farid, and BW McCrindle

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for the **International Kawasaki Disease Registry**

Introduction

- Kawasaki disease (KD) and Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 are both inflammatory disease processes with significant clinical overlap, making differentiation challenging.
- KD is an acute systemic vasculitis often with coronary artery involvement. MIS-C is a late manifestation of COVID-19 often with myocardial involvement.
- Both are clinical diagnoses, and there is no definitive diagnostic test specific for either disease process.

Objectives

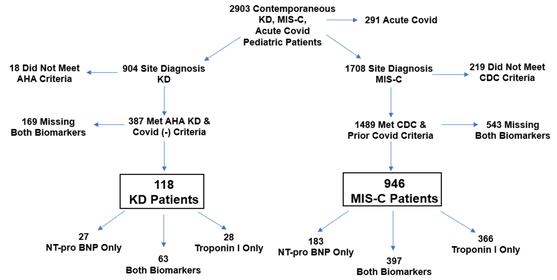
- To determine how cardiac biomarkers might differentiate MIS-C from KD.
- To determine the association of cardiac biomarkers with clinical features and outcomes for MIS-C and KD.

Methods

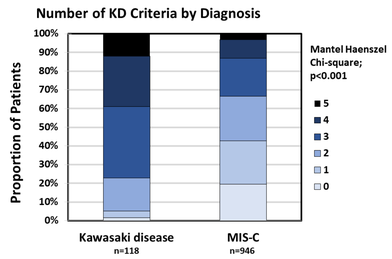
- Study period: January 2020 to July 2022.
- Population: Contemporaneous KD and MIS-C patients from 42 sites in 8 countries.
- MIS-C defined by site and confirmed by CDC criteria with documented evidence of prior COVID-19 infection.
- KD defined by site and confirmed by AHA guideline criteria with documented evidence of no prior COVID-19 infection.
- Included patients had at least one measurement of NT-pro BNP or troponin I and echocardiogram.
- Normalizing logarithmic transformation was applied to biomarker levels.
- Multiple imputation of missing values of factors was performed for multivariable analyses.
- Multivariable general linear regression models for associated factors with cardiac biomarkers were adjusted for diagnosis, age, and creatinine at presentation.
- ROC curves were used to determine biomarker cut points differentiating MIS-C vs KD.

Results

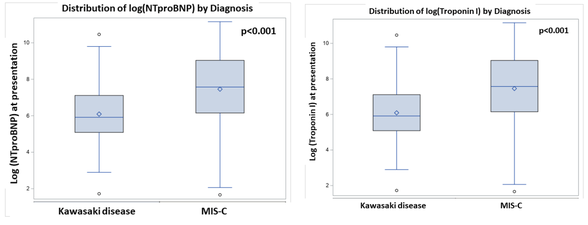
Patient Inclusion Flowchart



Phenotypic Overlap



Distribution of Cardiac Biomarkers by Diagnosis



Biomarkers and Outcomes

Adjusted for diagnosis, age and creatinine

- Higher log(NT-pro BNP) and log(Troponin I) associated with shock at presentation (p<0.001, p<0.001).
- Higher log(NT-pro BNP) and log(Troponin I) associated with ICU admission (p=0.003, p<0.001).
- Higher log(NT-pro BNP), but not log(Troponin I), was associated with longer LOS (p<0.001, p=0.23).

Myocardial Involvement

- Left ventricular ejection fraction (LVEF) was lower for MIS-C vs KD (median 56% vs 63%; p <0.001).
- Higher baseline log(NT-pro BNP) was associated with lower LVEF (p<0.001) and LVEF<55% (p<0.001).
- Higher baseline log(Troponin I) was associated with lower LVEF (p=0.03) and LVEF<55% (p=0.03).

Coronary Artery Involvement

- Maximum coronary artery Z-score was greater for KD vs MIS-C (median 1.36 vs 1.23; p<0.05).
- Higher baseline log(NT-pro BNP) was not associated with maximum coronary artery Z score (p=0.36) but with maximum coronary artery Z-score ≥2 (p=0.02).
- Baseline log(Troponin I) was not associated with higher maximum coronary artery Z-score (p=0.23) or maximum Z-score ≥2 (p=0.72).

Independent Factors Associated with Cardiac Biomarkers

Higher log(NTproBNP)*

Variable		Parameter Estimate	Standard Error	P value
Intercept		15.98678	2.38126	
Diagnosis of MIS-C (vs KD)		1.00363	0.21845	<0.0001
Younger age at presentation	(per year)	-0.05295	0.01670	0.002
Labs at presentation				
Higher creatinine	(per umol/L)	0.00457	0.00137	0.0009
Higher white cell count	(per x10^9/L)	0.06655	0.01243	<0.0001
Higher lymphocytes	(per x10^9/L)	0.08561	0.03760	0.03
Lower platelets	(per x10^9/L)	-0.00343	0.00055189	<0.0001
Lower albumin	(per g/L)	-0.07643	0.01061	<0.0001
Lower sodium	(per mmol/L)	-0.08531	0.02247	0.0002
Higher chloride	(per mmol/L)	0.03902	0.01613	0.02
Higher fibrinogen	(per g/L)	0.08560	0.03631	0.02

*Adjusted model R^2 0.29

Higher log(Troponin I)*

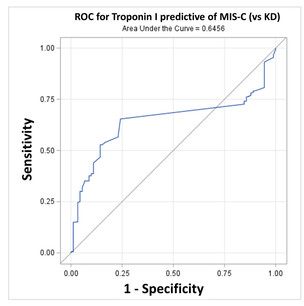
Variable		Parameter Estimate	Standard Error	P Value
Intercept		-1.05499	1.09819	
Diagnosis of MIS-C (vs KD)		-0.23802	0.42997	0.59
Age at presentation	(per year)	-0.02459	0.03338	0.47
Labs at presentation				
Creatinine	(per umol/L)	-0.00046709	0.00280	0.87
Higher alanine aminotransferase	(per U/L)	0.00668	0.00223	0.003
Higher international normalized ratio (INR)	(per unit)	2.29535	0.77139	0.004
Higher ferritin	(per ug/L)	0.00021640	0.00008937	0.02
Higher fibrinogen	(per g/L)	0.21893	0.07710	0.005
Higher lactate dehydrogenase	(per U/L)	-0.00156	0.00046405	0.0008

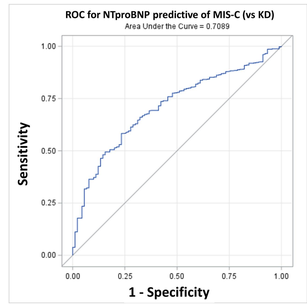
*Adjusted model R^2 0.07

Distribution map, International Kawasaki Disease Registry

Prediction of MIS-C vs. KD

- Baseline troponin I >10 ug/L (c-statistic 0.65) predicted MIS-C vs KD with a sensitivity of 58% and specificity of 77%.
  - Troponin I >20 ug/L predicted MIS-C vs KD with a sensitivity of 44% and specificity of 89%.
- Baseline NT-pro BNP >500 ng/L (c-statistic 0.71) predicted MIS-C vs KD with a sensitivity of 74% and specificity of 54%.
  - NT-pro BNP >1000 ng/L: 61%, 72%, respectively.
  - NT-pro BNP >1500 ng/L: 56%, 77%, respectively.
- C-statistic: 0.74 with both biomarkers together.
- C-statistic: 0.78 with both biomarkers at peak.





Questions? Contact mmwalton@cmh.edu

Conclusions

- **Higher baseline levels of troponin I and NT-pro BNP are predictive of MIS-C versus KD with reasonable sensitivity and specificity.**
- **Higher baseline cardiac biomarker levels are associated with an increased likelihood of shock and ICU admission. Higher NT-pro BNP was associated with increased hospital length of stay.**
- **Both biomarkers were independently associated with markers of inflammation, with troponin I also associated with greater hepatic involvement.**
- **Lower LVEF, more pronounced for MIS-C, is associated with higher NT-pro BNP and troponin I levels.**
- **Increased likelihood and higher magnitude of coronary artery involvement, greater for KD, are not associated with levels of either cardiac biomarker.**
- **These findings indicate that cardiac biomarkers may be helpful in differentiating MIS-C vs KD, and may be prognostic of clinical severity.**

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