Diagnostic Yield of Cardiac Biomarker Testing in Predicting Cardiac Disease and Multisystem Inflammatory Syndrome in Children in the Pandemic Era

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Objectives: This study aimed to assess whether elevations in cardiac biomarkers are associated with pediatric cardiac diagnoses in the era of COVID-19 and multisystem inflammatory syndrome in children (MIS-C).

Study Design: This single-center retrospective study analyzed children with a troponin drawn in the emergency department or inpatient unit between April 21 and December 31, 2020. The primary outcome was the presence of a cardiac diagnosis or MIS-C. Relationships among demographics, complaint, cardiac diagnostics, and cardiac biomarkers were analyzed.

Results: Four hundred eighty-six patients (mean ± SD; age 13.1 ± 7.8 years; 46.7% women) met inclusion criteria, for whom a cardiac diagnosis (excluding MIS-C) was made in 27 (5.6%) patients, with MIS-C diagnosed in 14 (2.9%) patients. The sensitivity and specificity of an elevated initial high-sensitivity troponin T (hsTropT) value (>14 ng/L) in predicting the composite outcome of a cardiac diagnosis or MIS-C were 54% and 89%, respectively. Four percent of patients with negative initial troponin values were found to have a cardiac diagnosis or MIS-C. Multivariable regression analysis demonstrated that elevated hsTropT (>14 ng/L; odds ratio [OR] [95% confidence interval]: 4.9 [1.70–14.0]) and elevated N-terminal pro B-type natriuretic peptide values (>500 pg/mL; 6.4 [2.01–20.1]) were associated with increased odds of a cardiac diagnosis or MIS-C.

Conclusions: Children with elevated cardiac biomarkers have increased odds of a cardiac diagnosis or MIS-C and warrant workup regardless of indication for testing. Although a negative hsTropT may reassure providers, further investigation is critical in developing algorithms to reliably exclude cardiac disease.

Key Words: cardiology, cardiovascular disorders, COVID-19, MIS-C, troponin, cardiac biomarker

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The emergence of acute coronavirus disease 2019 (COVID-19), the related multisystem inflammatory syndrome in children (MIS-C), and the concern for vaccine-induced myocarditis in the pediatric population has led to a significantly increased use of cardiac biomarkers as a critical part of diagnostic evaluation.[1–3] The scenarios for obtaining cardiac biomarkers in children have expanded greatly, bringing with that an increased amount of data requiring rapid interpretation for clinical assessment in the emergency department.

The cardiac biomarkers troponin and B-type natriuretic peptide (BNP) have been studied to varying extents in the pediatric population. Troponin detects myocyte damage, with assays evolving through time, becoming more sensitive and specific through *generations* because the fourth-generation and fifth-generation troponin assays are currently most widely in use. The fifth-generation troponin can detect levels of cardiac troponin (either I or T) five- to one hundred-fold lower than the preceding fourth-generation assay.[4,5] The cardiac biomarker BNP is used in the diagnosis of heart failure and released from cardiac myocytes in response to mechanical stretch.

Because of the low incidence of cardiac pathology in pediatrics and the ambiguity regarding interpretation of *elevated* values, cardiac biomarker screening in children with potential heart disease varies widely without established pediatric reference ranges for interpretation. The Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) published reference intervals and 99th-percentile cutoffs range for fifth-generation high-sensitivity-troponin T (hsTropT) and N-terminal pro B-type natriuretic peptide (NT-proBNP) in children, although this has not been validated.[6,7] In one large study by Brown et al,[8,9] a possible benefit of fourth-generation troponin testing was suggested, supported by a more recent study of patients with and without cardiac disease where elevation in fourth-generation troponin-T assay in patients younger than 21 years with a cardiac presentation had a positive predictive value of 85% and a negative predictive value of 96% for the presence of cardiac disease. However, to add to the challenges of interpreting pediatric values, another study analyzing pediatric patients screened for chest pain with a troponin-I test found minimal benefits and associated increased resource usage.[10]

Despite advances in sensitivity, interpretation of cardiac biomarkers remains challenging and understudied, and little data exist on investigating interpretation of hsTropT in the pediatric population and in the MIS-C era. Although elevation may aid in the diagnosis of MIS-C with paralleled severity of cardiac involvement on echocardiogram,[1,2,11] the interpretation of elevated biomarkers is often less clear when the diagnosis is not MIS-C. Furthermore, studies examining the usefulness of biomarkers in diagnosing MIS-C routinely exclude patients with cardiac disease, making unclear the ability of biomarkers to discern between MIS-C and other cardiac diagnoses such as Kawasaki disease (KD) or myocarditis. It also remains unclear what degree of troponin elevation may be expected as part of the natural course of illness for common pediatric inflammatory conditions such as an upper respiratory infection or pneumonia.

The existing challenges with biomarker interpretation have now been compounded by increased use of hsTropT and NT-proBNP in testing for COVID-19 acute infection and MIS-C, creating a dilemma for diagnostic and triage decisions. This study examined the sensitivity and specificity of cardiac biomarkers, hsTropT and NT-proBNP, for an ultimate outcome of cardiac

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diagnoses or MIS-C in pediatric patients in the current era of COVID-19.

METHODS

We performed a retrospective study at a single institution between April 21, 2020, and December 31, 2020. Inclusion criteria were 1) at least 1 hsTropT at an emergency department visit or inpatient stay and 2) aged younger than 21 years at the time of the encounter. Children with a history of cardiac disease (defined as previous diagnosed congenital or acquired cardiac disease with potential for ongoing hemodynamic sequela) were excluded. April 21, 2020, was selected because the first case of identified MIS-C at our institution was detected on this date, correlating with initial reports from the United Kingdom describing this syndrome.[12,13]

The primary outcome was a composite outcome of a final diagnosis of a cardiac diagnosis or MIS-C. A power calculation was performed with the knowledge that, during the prespecified time span, 605 patients met the inclusion criteria. Assuming 10% dropout rate because of missing data or meeting exclusion criteria, a ratio of 10:1 of those with noncardiac to composite diagnoses, α of 0.05, and a β of 0.80, the study would be powered such that the area under the curve (AUC) of greater that 0.62 would be statistically significant. The study was approved by the institutional research review board.

All patients meeting inclusion criteria were identified using our institutional research patient data registry (RPDR) from the electronic health record. Four study authors (initials redacted for anonymity) were trained in the use of the standardized data abstraction tool (Research Electronic Data Capture [REDCap]), which was used to collect patient demographics, chief complaint, final diagnoses, hsTropT values, NT-proBNP values, electrocardiograms (ECGs), and echocardiograms. Data abstractors were not blinded to study hypothesis. Final diagnoses were reviewed by authors (initials redacted for anonymity) to verify cardiac and MIS-C diagnoses.

An hsTropT (Elecsys® Troponin T Gen 5 Short Turn Around Time; Roche Diagnostics GmbH, Mannheim, Germany) value higher than 14 ng/L and an NT-proBNP (Cobas® NT-proBNP; Roche Diagnostics GmbH, Mannheim, Germany) value higher than 500 pg/mL were considered abnormal, consistent with the reference ranges at our institution. The following were considered cardiac diagnoses: symptomatic arrhythmia (supraventricular tachycardia [SVT], ventricular tachycardia [VT], ventricular fibrillation [VF], atrial fibrillation [afib]), pericarditis, myocarditis (non-MIS-C), KD (non-MIS-C), and myocardial infarction. The following findings on ECG were defined as abnormal: ST-segment changes, afib, atrioventricular block (2nd degree Mobitz II or 3rd degree), SVT, or ventricular arrhythmia (VT or VF). Abnormal echocardiogram finding was defined as the presence of any of the following findings: reduced left ventricular ejection fraction (<55%), right ventricular dysfunction, ventricular dilation, ventricular hypertrophy, pericardial effusion (mild or larger), valvular stenosis, or valvular regurgitation (mild or greater). All ECGs and echocardiograms were reviewed by a pediatric cardiologist (initials redacted for anonymity). Complaints were categorized as either cardiac, respiratory, gastrointestinal, febrile, or other (which were further subcategorized). In the case of multiple chief complaints (eg, fever and chest pain), both categories were selected.

Categorical variables were described using frequencies and percentages; continuous variables were described using mean, median, SD, and interquartile range (IQR). Categorical data were analyzed by χ^2 or Fisher exact tests, accordingly. Parametric data were analyzed by *t* tests. Unless otherwise specified, all cardiac biomarkers represent the initial value for the patient (initial hsTropT and initial NT-proBNP). Continuous variables including hsTropT and NT-proBNP were assessed through receiver operating characteristic (ROC) curves, and optimal cutoffs were chosen based on the Youden index.[14–16] As a sensitivity analysis, ROC curves were also analyzed for the outcomes of MIS-C and cardiac diagnosis separately. In addition, because there is some indication

TABLE 1. Demographics, Chief Complaint, and Cardiac Studies Based on Final Diagnosis

Demographics	Cardiac Diagnosis or MIS-C	Noncardiac Diagnosis	*P*
n (%)	41 (8.4)	445 (92)	
Age, mean (SD)	10.8 (7.8)	13.3 (7.7)	0.051
Sex, n (%)			
Female	10 (24)	217 (49)	0.010
Male	31 (76)	227 (51)	
Other	0 (0)	1 (0.2)	
Chief complaint, n (%)			
Cardiac	20 (49)	98 (22)	<0.001
Respiratory	2 (4.9)	103 (23)	0.010
Gastrointestinal	11 (27)	63 (14)	0.053
Fever	24 (59)	185 (42)	0.053
Other	3 (7)	137 (31)	0.003
ECG abnormal†, n (%)	13 (33)	79 (22)	0.217
Echocardiogram abnormal‡, n (%)	14 (38)	16 (16)	0.009
hsTropT§ (ng/L)			<0.001
Median (IQR)	17 (6–129)	<6 (<6 – <6)	
Abnormal, n (%)	21 (51)	42 (9.4)	
NT-proBNP§ (pg/mL)			<0.001
Median (IQR)	39 (99–2235)	85 (23–194)	
Abnormal, n (%)	16 (43)	19 (6.4)	
Myopericarditis	7 (26)	6 (14.6)	
Arrhythmia	6 (22)	6 (14.6)	
Kawasaki	4 (15)	4 (10.5)	
Other (cardiac)	10 (37)	10 (24.4)	
MIS-C	14 (100)	14 (100)	
Viral illness (not SARS-CoV-2)	0 (19.1)	93 (21)	
SARS-CoV-2 (not MIS-C)	51 (10.4)	51 (11)	
Noncardiac chest pain	33 (6.8)	33 (7.0)	
Trauma	28 (5.7)	28 (6.3)	
Urinary tract infection	16 (3.2)	16 (3.6)	
Overdose/toxidrome	14 (2.8)	14 (3.1)	
Musculoskeletal	12 (2.7)	12 (2.7)	
Asthma	11 (2.5)	11 (2.5)	
Other (noncardiac)	87 (42)	187 (42)	

*Abnormal ECG finding defined as ST-segment changes, atrial fibrillation, atrioventricular block (2nd degree Mobitz II or 3rd degree), SVT, or ventricular arrhythmia (VT or VF); n missing = 93.

†Abnormal echocardiogram finding defined as the presence of any of the following findings: reduced left ventricular ejection fraction (<55%), right ventricular dysfunction, ventricular dilation, ventricular hypertrophy, pericardial effusion (mild or larger), valvular stenosis, or valvular regurgitation (mild or greater); n missing = 346.

‡Abnormal troponin value defined as 5th-generation hsTropT > 14 ng/L.

§Abnormal NT-proBNP value defined as >500 pg/mL; n missing = 150.

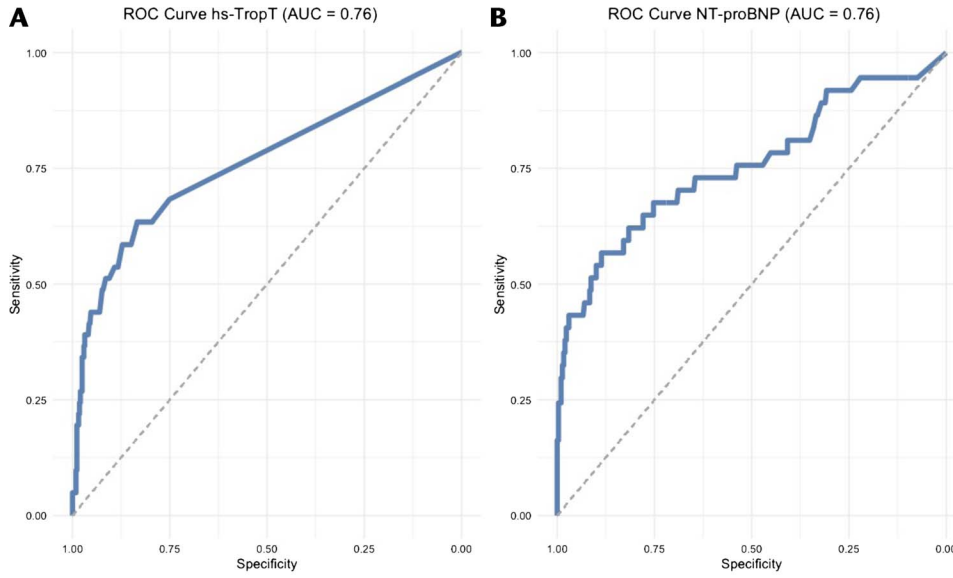

FIGURE 1. Receiver operating characteristics curves for hsTropT and NT-proBNP. The ROC curves are displayed for hsTropT (A) and NT-proBNP (B), predicting the composite outcome of cardiac disease or MIS-C. The AUC for hsTropT was 0.76 and for NT-proBNP was 0.76. Based on the Youden index, ideal cutoffs for hsTropT and NT-proBNP were >9 ng/L and >344 pg/mL, respectively.

that a different threshold for cardiac biomarkers may be needed for children aged younger than 1 year, a separate sensitivity analysis was performed including only children aged older than 1 year.[7] Univariate and multivariable logistic regression were performed to evaluate the association with the composite outcome. Variables with more than 50% missing data were excluded from regression models. For the multivariable analysis, variables with a *P* value less than 0.20 on univariate analysis were included. Data were analyzed with R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance for variables was defined as *P* value of less than 0.05.

RESULTS

A total of 486 patients (mean ± SD; age 13.1 ± 7.8 years; 46.7% women) were identified (Table 1). Fever was the most prevalent chief complaint (n = 209, 43%) with a cardiac chief complaint noted in 118 (24%) patients. The aggregate outcome cardiac diagnosis or MIS-C were observed in 41 (8.4%) patients. A cardiac diagnosis was made in 27 (5.6%) patients, and MIS-C was diagnosed in 14 (2.9%) patients. The most common cardiac diagnoses were myopericarditis (7/27, 26%), arrhythmia (6, 22%), and KD (4, 15%). The most common noncardiac diagnosis was non-SARS-CoV-2 viral illness (93/486, 19.1%) (Table 1). The value of HsTropT was elevated in 63 (13.0%) patients, and of these, 21 (33.3%) were found to have a cardiac diagnosis or MIS-C. In patients without an elevated hsTropT, 20 (4.7%) had a cardiac diagnosis or MIS-C ($P < 0.0001$). In patients where the initial hsTropT was negative, repeat hsTropT was obtained in 183 (38%) patients, with 12 (6.5%) having an elevated value on subsequent testing. Of these 12 patients, 5 (2.7% of the total 183) were found to have a cardiac diagnosis or MIS-C. Additional cardiac biomarker testing and diagnostics (ECG, echocardiogram, NT-proBNP) are summarized in Table 1.

The positive predictive value of an elevated initial hsTropT for a cardiac diagnosis or MIS-C was 31%, whereas the negative predictive value was 95%. The ROC curves were analyzed for the hsTropT and NT-proBNP to predict the outcome of cardiac diagnosis or MIS-C (Fig. 1). The AUC for the aggregate outcome was 0.76 (95% CI: 0.68–0.85) for hsTropT and 0.76 (95% CI: 0.66–0.86) for NT-proBNP (Table 2). Using the laboratory-assigned reference range as cutoffs (hsTropT > 14 ng/L; NT-proBNP > 500 pg/mL), the specificity and sensitivity for hsTropT were 0.89 and 0.54, respectively, whereas for NT-proBNP they were 0.94 and 0.43. Based on the Youden index, ideal cutoffs for hsTropT and NT-proBNP were greater than 9 ng/L and greater than 344 pg/mL, respectively. Minimal change in the specificity and a modest increase in the sensitivity were seen using the ideal cutoff compared with the reference range cutoffs (Table 2). Area under the curve, sensitivity, and specificity were similar when hsTropT and NT-proBNP were used to predict the outcomes of MIS-C and cardiac diagnoses independently or when children aged younger than 1 year were excluded (Supplemental Table 2 http://links.lww.com/PEC/B7).

Univariate regression analysis demonstrated that cardiac biomarker elevation (both hsTropT and NT-proBNP), male sex, and cardiac chief complaint were most strongly associated with increased odds of the outcome. These factors remained statistically

TABLE 2. Sensitivity and Specificity Based on Current Laboratory Cutoffs and Optimal Cutoffs Based on Youden Index

		Cutoff	Sensitivity	Specificity
Laboratory reference range	hsTropT	>14 ng/L	0.54	0.89
	NT-proBNP	>500 pg/mL	0.43	0.94
Youden index	hsTropT	>9 ng/L	0.63	0.83
	NT-proBNP	>344 pg/mL	0.57	0.89

TABLE 3. Univariate and Multivariable Regression Analysis Predicting MIS-C or Cardiac Disease

	Univariate			Multivariable		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age, mean (SD) (per 1-y increase)	0.96	0.92–1.00	0.054	0.97	0.91–1.05	0.48
Sex						
Female	1			1		
Male	2.96	1.42–6.19	<0.01	4.13	1.54–11.10	<0.01
Other	0.00	−882–882	0.99	0.00	−1455–1455	0.99
Chief complaint:						
Cardiac	3.37	1.76–6.47	<0.001	6.38	1.50–27.1	0.01
Resp	0.17	0.04–0.72	0.02	0.23	0.05–1.11	0.07
Gastrointestinal	2.22	1.06–4.66	0.03	3.62	1.22–10.8	0.02
Fever	1.98	1.04–3.80	0.04	2.97	0.73–12.1	0.13
Other	0.18	0.05–0.58	<0.01	0.47	0.08–2.88	0.41
ECG abnormal*	1.67	0.82–3.39	0.16	1.31	0.40–4.34	0.65
Troponin abnormal†	10.1	5.05–20.1	<0.001	4.88	1.70–14.0	<0.01
NT-proBNP abnormal‡	11.2	5.05–25.0	<0.001	6.36	2.01–20.1	<0.01

*Abnormal ECG finding defined as ST-segment changes, atrial fibrillation, atrioventricular block (2nd degree Mobitz II or 3rd degree), SVT, or ventricular arrhythmia (VT or VF); n missing = 82.

†Abnormal troponin value defined as 5th-generation hsTropT > 14 ng/L.

‡Abnormal NT-proBNP value defined as >500 pg/mL; n missing = 144.

significant predictors after multivariable analysis (Table 3). Abnormal ECG finding was not associated with a statistically significant increased odds in univariate or adjusted analysis. Adjusted analysis demonstrated that an elevated hsTropT value was associated with a 4.9-fold (95% CI: 1.70–14.0; $P < 0.01$) increased odds of the composite outcome, and that an elevated NT-proBNP value was associated with a 6.4-fold increased odds (95% CI: 2.01–20.1; $P < 0.01$; Fig. 2). Excluding all children aged younger than 1 year, cardiac biomarkers remained strongly and significantly associated with increased odds of the composite outcome (Supplemental Table 3 http://links.lww.com/PEC/B8).

DISCUSSION

The pediatric approach to the spectrum of illness presentations has changed dramatically since the unrelenting worldwide disease burden of the SARS-CoV-2 pandemic. Cardiac biomarker evaluation is now routinely included in the emergency department

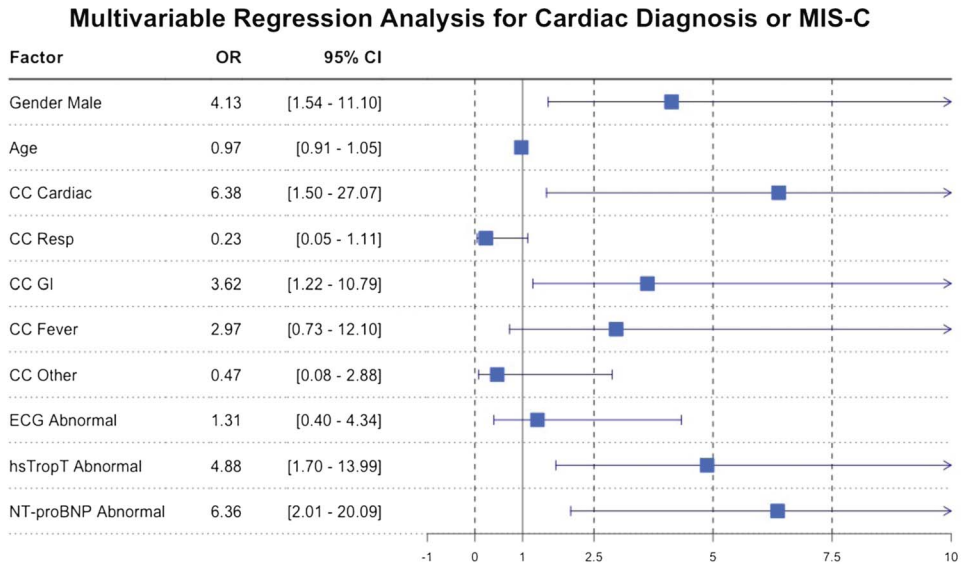

FIGURE 2. Multivariable regression analysis for cardiac diagnosis. Multivariable logistic regression analysis was performed in predicting cardiac diagnosis or MIS-C using all factors with $P < 0.20$ on univariate logistic regression. The OR for cardiac diagnosis or MIS-C and 95% confidence interval for ORs are displayed. For age, analysis used per 1-year increase as the interval. Chief complaints (CC) were categorized as cardiac, respiratory (resp), gastrointestinal (GI), febrile (fever), or other. Cardiac biomarkers and electrocardiography (ECG) were categorized as normal, abnormal, or not performed. Abnormal hsTropT and NT-proBNP were defined as >14 ng/L and >500 pg/mL, respectively.

laboratory evaluation of common pediatric complaints, causing great difficulty in interpretation of specific clinical scenarios given the lack of standardized pediatric reference ranges. Emergency medicine physicians are tasked with triaging care and management of unexpected abnormal values with recommendations on appropriate clinical follow-up for patients who, pre-COVID, would not have had such testing included in their evaluation. To our knowledge, this is the first study evaluating the diagnostic usefulness of cardiac biomarkers in identifying pediatric cardiac diagnoses during this era of acute SARS-CoV-2 and MIS-C. Our results demonstrate the significant finding that an abnormal initial fifth-generation hsTropT value (>14 ng/L) had a specificity of 89% and a sensitivity of 54% for an underlying cardiac diagnosis or MIS-C. The NT-proBNP value (>500 pg/mL) performed similarly, with a specificity of 94% and a sensitivity of 43%.

Despite the expansion in indications for cardiac biomarker testing as a result of the pandemic and the change to hsTropT, these findings in fact demonstrate similar performance of the test compared with previous work studying older versions of the troponin assay.[8] An abnormal NT-proBNP value was strongly associated with increased odds of a cardiac diagnosis or MIS-C, similar to that of hsTropT. These associations remained strong after multivariable analysis, with an elevated hsTropT (>14 ng/L) and elevated NT-proBNP (>500 pg/mL) correlating with 4.9- and 6.4-times increased odds of cardiac diagnosis, respectively.

Although it was not previously known if the expanded use of cardiac biomarkers would decrease their usefulness, these findings suggest that pediatric patients with abnormal hsTropT or NT-proBNP values should receive further diagnostic evaluation for possible cardiac diagnoses. The test characteristics (using either laboratory reference or Youden cutoff) did not vary significantly whether biomarkers were used to test for cardiac diagnosis, MIS-C, or the composite outcome, indicating that biomarkers can help diagnose both cardiac diagnoses and MIS-C but likely do not aid greatly in distinguishing between these 2 groups. A negative cardiac biomarker may also be clinically useful because hsTropT seems to contribute toward ruling out cardiac diagnoses given its robust specificity. However, notably, half of the patients with a cardiac diagnosis, representing approximately 4% of the overall study population, had a negative hsTropT.

Elements of the history also proved just as helpful as biomarkers in changing odds of cardiac diagnosis. A cardiac chief complaint correlated with a higher odds of a cardiac diagnosis, similar to what was seen in previous studies.[8] Yet, whereas previous work found that an abnormal ECG finding was associated with an increased odds of cardiac diagnosis, our study did not demonstrate that an abnormal ECG finding increased the odds of cardiac diagnosis.[8] One possible explanation for this variation may be attributed to the subjective nature of ECG interpretation, and the difference observed may be the result of such.

This retrospective study has limitations that are worth noting. All diagnoses were made using manual chart review, and the indication for troponin testing was not assessed. Selection bias remains possible because there was variability in diagnostic testing (ECG, echocardiography, and NT-proBNP). The use of the composite outcome of cardiac diagnosis or MIS-C limits the ability to interpret our results for those diagnoses individually. Although all possible cardiac and noncardiac diagnoses were reviewed with pediatric cardiologists (initials redacted for anonymity), there were no predefined definitions of cardiac disease. We attempted to normalize variability in ECG reads by having 1 investigator verify all findings. although we acknowledge potential variability in the interpretations. Our chart review included self-identified patient sex but did not include sex. This study analyzed a population during the COVID-19 pandemic while local guidelines and clinical reasoning regarding whom to send troponins to was an evolving process. Finally, our analysis was performed before reports of post-vaccination myocarditis in pediatric patients were reported, thus limiting the usefulness of this work in that setting.[17]

In conclusion, fifth-generation hsTropT may identify cardiac diagnoses in children, particularly in the current pandemic era of increasing biomarker evaluation, as part of the MIS-C and COVID-19 workup. Although false positives exist given the low incidence of cardiac disease in the population, an elevated hsTropT should raise concern for a cardiac diagnosis or MIS-C and serve as a trigger for further evaluation. Future investigation is critical, involving multimodal approaches and algorithms to better understand and identify the diagnostic yield of cardiac biomarker evaluation in this current era of significantly increased pediatric testing.

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