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RESEARCH LETTER

Laboratory trends in severe MIS-C

Multisystem inflammatory syndrome in children (MIS-C) has been recognized as a rare illness associated with a recent coronavirus disease 2019 (COVID-19) infection and consists of a fever, laboratory evidence of inflammation, and multisystem (≥2) involvement.[1,2] A spectrum of illness has been appreciated, and those with severe MIS-C may exhibit significant cardiac disease, shock, and death.[3]

Given the wide clinical spectrum, identifying children at risk for severe disease is critical to optimizing care. Those at risk for severe MIS-C have been shown to more likely be non-Hispanic black, obese, male, 13–18 years of age, and have higher peak laboratory markers (troponin, brain natriuretic peptide [BNP], ferritin, C-reactive protein [CRP], interleukin 6 [IL-6]).[4] While studies have attempted to identify laboratory predictors of severe MIS-C, they have not accounted for the patients' day of illness (DOI).[5] It is unclear when each of the laboratory markers rise. The objective of this study is to describe the temporal relationship between serial laboratory markers and symptom onset for severe and non-severe MIS-C. Our overall hypothesis was that that DOI biomarker trajectories would differ between groups, with greater overall concentrations in severe versus non-severe cases.

We performed a retrospective chart review of all patients with MIS-C treated at a single institution from April 1, 2020, to February 15, 2021. Patients met published Centers for Disease Control (CDC) criteria for MIS-C, and severe MIS-C was defined as cardiovascular shock (need for vasopressors), cardiac arrhythmia requiring intervention, or respiratory failure (need for positive pressure ventilation). DOI was defined as the onset of any symptom related to MIS-C, with the first day defined as day 1. Symptom onset was identified using the emergency department (ED) note and was identified on all patients. If symptom onset was not explicitly mentioned in the ED note, the hospital admission note was used. Patients who met criteria for severe MIS-C at any point during the hospital course were included in analysis. Descriptive data for the overall cohort are presented as medians with inter-quartile range (IQR) or proportions. Laboratory values on the day of ED presentation were compared using the Wilcoxon rank-sum test. Linear mixed-effects models were used to examine the relationship between repeated measures of laboratory values (outcome) in those with moderate versus severe MIS-C. Based on model diagnostics and visual inspection of residual plots, all lab values, except albumin, were log transformed. Model outputs for transformed variables are interpreted as the percentage difference in marginal mean lab value in severe versus moderate MIS-C (calculated as one-parameter estimate × 100). Covariates were selected based on review of prior studies as well as biologic and/or clinical plausibility and included DOI, age, race, and DOI-MIS-C category interaction (DOI × MIS-C); a random intercept was included in all models. Biologic sex was considered as a covariate but was non-significant for all models and worsened model fit so was excluded. Model fit was assessed using Bayesian Information Criteria and covariance structure was selected using the null model likelihood ratio test. A two-tailed significance level was set at 0.05. Data analysis was performed using SAS version 9.4 (SAS Institute). This study was approved by the Institutional Review Board of Central Michigan University.

During the study period, we identified 32 patients with severe and 29 patients with non-severe MIS-C with single ED visits. Those with severe disease were older (7.6 vs. 4.9 years) and more often black (59.4% vs. 42.9%), with roughly half (54%) of patients in both cohorts being female. There was no difference in median days of symptoms at ED presentation (4.0 [IQR 3.0–5.0 days] in severe vs. 5.0 [IQR 2.5–7.0 days] for non-severe, $p = 0.46$). Criteria for severe MIS-C were met in the ED for 10 patients, with 15 meeting criteria on hospital day 1, 3 on hospital day 2, and 3 on hospital day 3, and 1 on hospital day 6. Median DOI for meeting severe criteria was 6 (IQR 4–6). In the severe group, 31 patients were treated with intravenous gamma globulin (IVIG) and 22 with steroid administration. In non-severe patients, 20 were treated with IVIG and 2 with steroids. The median DOI was similar for IVIG administration in severe (5.0, IQR 4.0–6.0 days) versus moderate (6.0, 3.0–8.0 days) groups, $p = 0.29$. A total of 24 patients received at least one dose of steroids, with 22 in the severe and 2 in the moderate group. Median DOI for first steroid dose was 6.0 (IQR 3.0–8.0 days) for severe versus 8.0 days for moderate.

While not all subjects had biomarkers checked on each hospital day, any patient with at least one measured value of the biomarker of interest was included in the model for that outcome. Description of missing biomarker data is provided in the supplement; there were no missing values for any covariates. On day of ED presentation, patients who developed severe MIS-C had greater median troponin (29 ng/ml, IQR 11–183 vs. 11 ng/ml, IQR 4–45.5, $p = 0.027$); ferritin (311.8 μg/L, IQR 188.3–452.7 vs. 137.9 μg/L, IQR 116.2–246.2, $p = 0.03$); and d-dimer (2.44 ng/ml, IQR 1.38–32.9 vs. 1.38 ng/ml, IQR 0.74–2.32, $p = 0.034$).

For the mixed-effects model analysis, only mean BNP and CRP varied significantly by DOI (DOI × MIS-C) between non-severe and severe MIS-C. For CRP, severe MIS-C patients had greater initial CRP that declined faster than non-severe MIS-C. For BNP, initial levels were greater and subsequently declined in severe MIS-C, whereas

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non-severe patients had a slow increase (Figure 1). For other laboratory parameters, trends by DOI were similar for all patients, but the severe MIS-C group had greater mean troponin (185%, 95% confidence interval [CI] 46–456, $p = 0.002$), ferritin (46%, 95% CI −1.1 to 117, $p = 0.05$), and d-dimer (116%, 95% CI 46–218, $p = 0.0002$), whereas albumin was 0.6 g/dl lower (95% CI −0.8 to −0.4, $p < 0.001$).

Patients with severe MIS-C have been shown to have higher peak laboratory markers compared to non-severe MIS-C and severe COVID-19.[4] Our data demonstrate this same trend upon ED presentation with a higher median troponin, d-dimer, and ferritin. However, when the laboratory trends of each patient were compared by DOI, only the BNP and CRP showed a significant difference. The severe cohort had an earlier increase in both the BNP and CRP, and then a steady decline over the course of the illness. Patients with non-severe disease presented with a lower BNP early in illness, which slowly rose over time. BNP is secreted by cardiac myocytes in the ventricles in response to wall stretch or mechanical load, and levels typically rise reliably with cardiac dysfunction.[6] Thus, the etiology of the decline in BNP levels in patients with severe cardiac disease is unclear. This could represent the natural history of the disease, recognition of cardiac dysfunction with appropriate treatment (fluid restriction or diuresis), or residual confounding. The influence of treatments, including IVIG and steroids, on biomarker concentrations and trajectories remains unclear as we did not adjust for these given our small sample size and the complexities of modeling multiple time-varying treatments and their interaction. Presentation

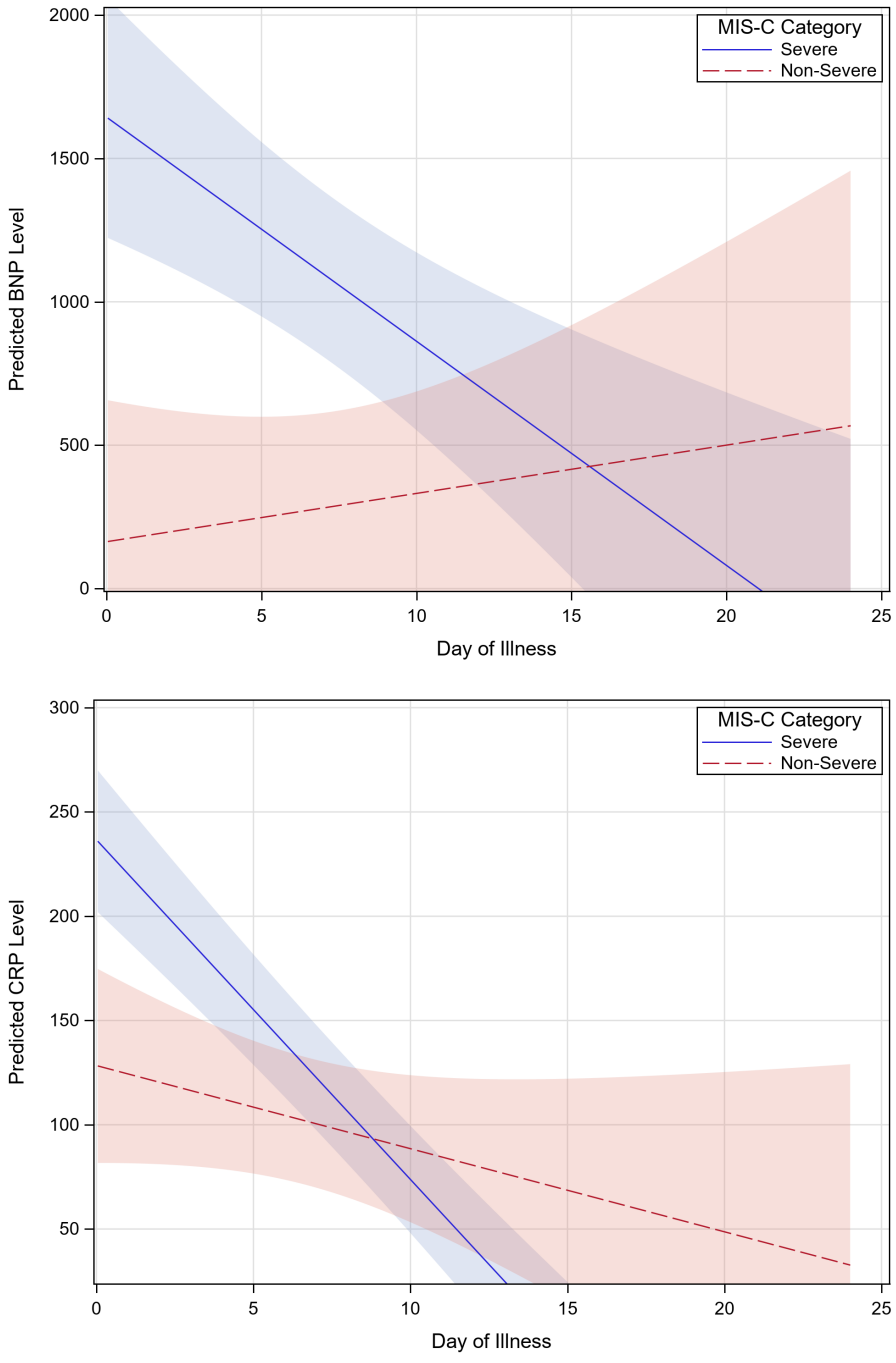

FIGURE 1 Interaction plot of DOI with MIS-C category showing that the trajectory of BNP and CRP over the course of illness is different for those with severe versus non-severe MIS-C. Fit was computed at mean age (7 years) and for black race.

DOI and initiation of treatments were similar, and while one would expect severe patients to have greater concentrations of inflammatory markers, and treatment-associated declines in all patients, the BNP trajectory in moderate patients is less intuitive. Determination of whether this represents natural disease course, confounding due to treatments administered, or other patient-level factors requires further study.

Our study is limited by sample size and risks inherent to a retrospective study from a single site. We did not adjust for multiple comparisons (of investigated biomarkers) as our goal was to minimize false negatives and crude adjustment methods (e.g., Bonferroni) drastically reduce power.[7] While this can increase the false positive rate, we felt the overall benefit outweighed the potential harms given that these biomarkers are routinely obtained but there remains a paucity of data on temporal laboratory trends in MIS-C. Follow-up studies from larger data sets are needed to confirm our findings.

In conclusion, we found that patients with severe MIS-C had higher levels of laboratory markers when compared to non-severe MIS-C, with similar trends across DOIs in both groups for most biomarkers. However, the CRP and BNP levels were significantly greater among patients with severe MIS-C earlier in the disease course. Further investigation may reveal that these two markers may help identify patients at risk for severe MIS-C prior to clinical deterioration.

AUTHOR CONTRIBUTIONS

Study concept and design (Curt Stankovic, Amy DeLaroche, Rajan Arora, Priya Spencer), acquisition of data (Priya Spencer), data analysis and interpretation (Curt Stankovic, Robert R. Ehrman, Amy DeLaroche, Robert R. Ehrman), drafting of the manuscript (Curt Stankovic, Robert R. Ehrman, Rajan Arora, Amy DeLaroche, Priya Spencer), statistical expertise (Robert R. Ehrman), funding acquisition (Curt Stankovic).

CONFLICT OF INTEREST

We have no conflict of interest.

PRESENTATION

This manuscript will be presented at the Pediatric Academic Society meeting on April 22, 2022.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.