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Measuring the inflammatory response in viral infections with an eye towards MIS-C

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Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) caused by a recent SARS CoV2 infection in a child, led to broad screening of acutely ill children for widespread inflammation and systemic disease due to need for early diagnosis and therapeutic intervention. This broad laboratory screening to rule-out MIS-C also inadvertently captured the patients who were found to have seasonal viral upper respiratory infections. Thus, this screening provided a unique opportunity to study the inflammatory response to some of the common viral infections. We performed a retrospective chart review for all patients under 18 who presented to the ER or were admitted to the hospital with a positive test for either 1) Viral URI, 2) Acute COVID-19, or 3) positive SARS CoV2 IgG, suggesting previous COVID-19 infection; between March 2020-October 2022. We reviewed 6628 patient encounters with 5312 encounters meeting inclusion criteria. Here we report that patients who had COVID IgG without other infection identified, most frequently showed widespread inflammation, as indicated by 56.7% of patients with 4 or more positive MIS-C criteria suggesting a diagnosis of MIS-C. One patient had a peak of 15 positive MIS-C criteria. Several seasonal viruses showed multisystem inflammatory responses in limited patients with the most frequent occurring in adenovirus (7.6% ≥4 criteria), and peaks of 9 or 10 criteria in sporadic patients for three seasonal viruses (adenovirus, rhinovirus/enterovirus, and parainfluenza viruses). Acute SARS CoV2 demonstrated elevated inflammatory states similar to seasonal cold viruses with a limited number of patients (4.3%) with ≥4 positive criteria markers of MIS-C, and a peak of 9 criteria. The most significant and largest differences between groups were observed in COVID IgG positive patients in comparison to each of the other viral groups followed by adenovirus compared to 5 out of 6 remaining viral pathogens.

Keywords: URI, MIS-C, Inflammation, COVID-19

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1. Introduction

The common cold, or viral upper respiratory infections (URIs), represents a significant burden of illnesses in children [1]. A non-exhaustive list of viral symptoms can include cough, congestion, rhinorrhea, fevers, upset stomach, nausea, vomiting, diarrhea, muscle aches, and/or weakness. Prior to 2020, broad laboratory workups were rare for these common infections for children older than one year of age, and children typically recovered with supportive care alone [1].

After the emergence of SARS CoV2, there was a small subset of pediatric patients who developed a post-acute infectious condition 3 to 6 weeks after initial infection called Multisystem Inflammatory Syndrome in Children (MIS-C) [2]. Initial observations noted that this syndrome resembled Kawasaki Disease (KD), with several hallmarks of widespread inflammation including: fevers for more than 3 days, rash, bilateral non-purulent conjunctivitis, muco-cutaneous lesions, and elevated laboratory markers of inflammation [3]. However, MIS-C is different from KD in several aspects of typical presentations. MIS-C patients were generally older than typical KD patients [4]. Hematologic labs showed leucopenia (MIS-C) vs leukocytosis (KD) and thrombocytopenia (MIS-C) vs thrombocytosis (KD)[4, 5]. GI symptoms were more likely to be seen in MIS-C vs KD [5].

Additional specific organ dysfunction including hepatic dysfunction (elevated liver enzymes and coagulopathy), renal (increased Cr, BUN), respiratory (tachypnea, hypoxemia, respiratory failure), dermatologic (rash, chilblains), cardiac (cardiomyopathy with increased BNP, troponins), and neurologic changes (headaches, photophobia, increased intracranial pressure) were all seen in patients with MIS-C [3]. The specific pathogenesis of MIS-C is still being elucidated but is presumed to be related to a process of post-infectious immune dysregulation [6].

Due to the severity of illness that MIS-C can cause, broad screening criteria were introduced in 2020 to ensure that cases were not missed and early treatment initiated for better outcomes. The Centers for Disease Control and Prevention (CDC) initially defined broad criteria for MIS-C as, “An individual <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement” [7]. Two other criteria required were lack of alternate diagnosis and current or recent SARS CoV2 infection as determined by positive RT-PCR, COVID IgG, COVID antigen test; or history of exposure to COVID-19 within the past 4 weeks (Figure 1) [7].

In 2021, the American College of Rheumatology published guidelines for evaluation of MIS-C congruent with the CDC definition with refined criteria and lab evaluation with thresholds indicating significant changes in labs consistent with MIS-C [8]. These labs and the cut-off values indicating elevated inflammation for MIS-C are included in Table 1. These values provide a reference threshold for each of these labs to indicate an elevated inflammatory state or organ damage.

The vast screening criteria for MIS-C led to extensive laboratory evaluation on many patients that ultimately detected non-COVID viruses as part of the respiratory pathogen panels used to rule-out likely alternative diagnoses. This provided a unique opportunity to study the inflammatory response to some of the common viral infections. The goal of this study was to understand whether widespread inflammatory responses were unique to post-acute COVID-19 infections (MIS-C), or if similar responses could also be found in acute COVID-19 infections and previously known seasonal viral infections.

2. Methods

We performed a retrospective chart review by EMR query of all pediatric patient encounters with the following criteria: 1) Patients less than 18 years of age, and 2) with positive polymerase chain reaction (PCR) respiratory pathogen tests (BioFire respiratory panel, COVID-19/influenza/respiratory syncytial virus (RSV) combined test), COVID-19-

Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

[i]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
[ii]Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Figure 1. CDC case definition of MIS-C.

Materials developed by CDC. Guidance for case definition as provided on May 14th, 2020. This material is available free of charge on the CDC website under CDCHAN-00432.

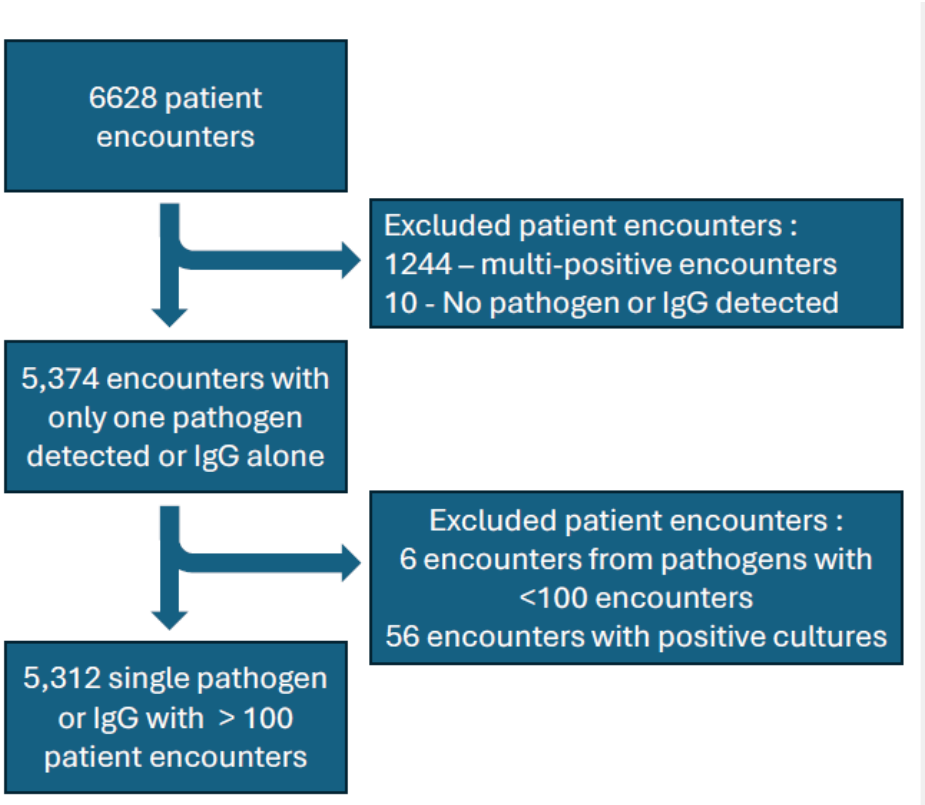

Figure 2. Patient Selection and Inclusion.

All patients (n=6,628) <18 years old with a positive pathogen test or positive COVID IgG result, and additional lab screening between March 2020 and October 2022 were queried from EMR records. Patient encounters were excluded for multiple simultaneous pathogens identified (n=1244), positive urine or blood culture results (n=56), pathogens with <100 samples for adequate sampling for statistical analysis (n=6). Chlamydophila pneumophilia, Influenza A, Bordetella pertussis, and Mycoplasma pneumoniae were the pathogens identified and excluded for low sampling.

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only PCR or positive COVID-19 IgG test, and 3) excluded patients with concurrent positive blood or urine cultures. The patient encounters were from patients seen in the emergency room (ER) or admitted from March 2020-October 2022 at a single hospital location. Laboratory criteria for case definitions for MIS-C consistent with American College of Rheumatology guidance included the following markers: total white blood cell (WBC), hemoglobin, platelet count, absolute lymphocyte count, absolute neutrophil count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum values of sodium, creatine (Cr), alanine aminotransferase (ALT), albumin, troponin, brain natriuretic peptide (BNP), D-dimer, ferritin, fibrinogen, international normalized ratio (INR), and activated partial thromboplastin time (aPTT) (Table 1). We obtained initial laboratory results and maximum temperature obtained in the ER/hospital encounter.

The hospital's COVID-19 IgG test detected IgG against the nucleocapsid protein, indicating exposure or infection with COVID-19 and not vaccination with the spike protein. (confirmed by personal communication with director of the Microbiology lab)

We included patients with only a single virus identified in the analysis and counted positive COVID-19 IgG as separate from acute COVID-19. We pooled the parainfluenza viruses (1-4) as a single entity and similarly pooled previously identified coronaviruses on the panel (229E, HKU1, NL63, OC43). Analysis was performed on pathogens that were positive in 100 patient encounters or more which included the following: acute COVID-19 (C19), Human Metapneumovirus (HMV), Adenovirus (ADN), Rhinovirus/Enterovirus (REV), Parainfluenza Virus (PFV), Respiratory syncytial virus (RSV), Other Coronavirus (COV), and COVID-19 IgG (IgG) without other infection.
Our positive MIS-C criteria marker counts consisted of summing each MIS-C criteria in Table 1 for each patient encounter, given a binary value of 1 for each value above threshold and a value of 0 for each value below threshold. If a criterion lab was not obtained, it was considered negative (value = 0).

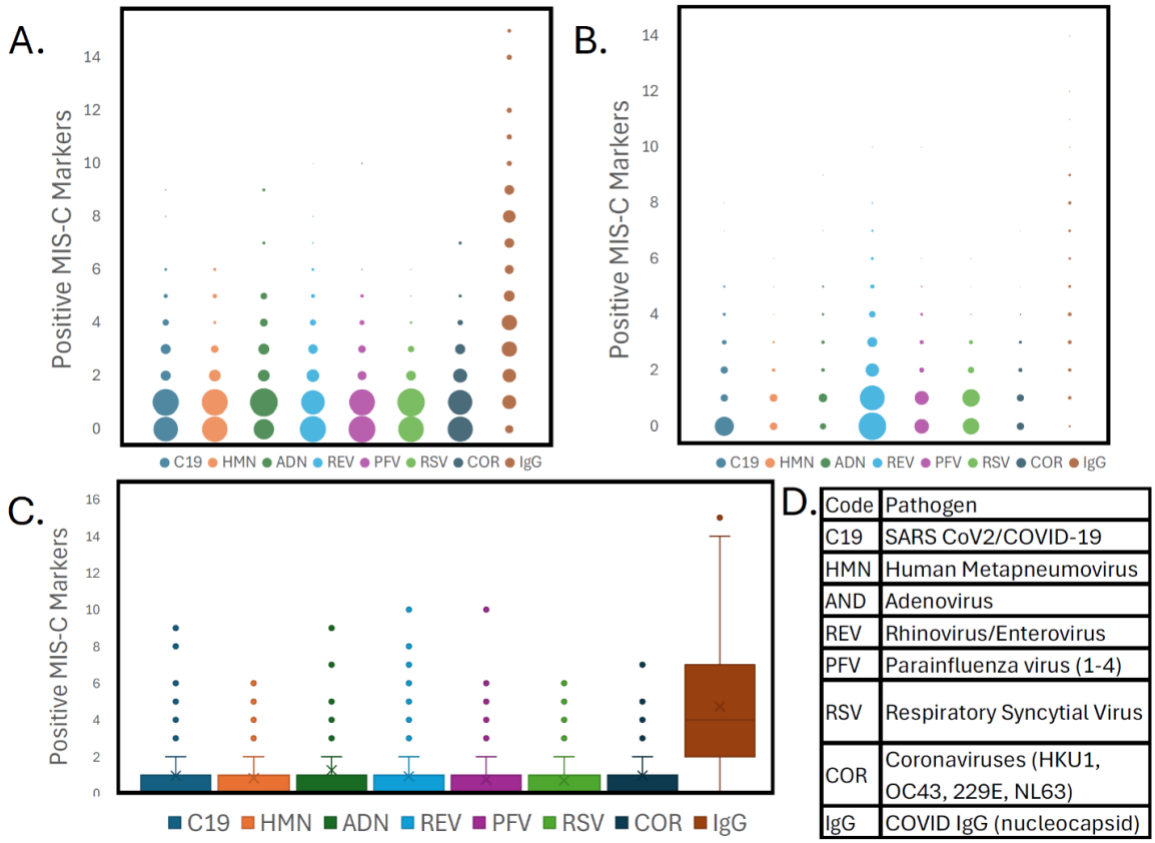
Data were imported into Microsoft Excel (Microsoft® Excel® for Microsoft 365 MSO (Version 2412 Build 16.0.18324.20092) 64-bit), and R (R studio 2023.06.1 Build 524, with stats package version 4.2.2) for processing and figure formation. A One-way ANOVA was performed with Tukey HSD post-hoc analysis to identify differences between the sample groups using R studio.
This study was approved by the Institutional Review Boards of the University of Toledo (IRB #: 301491) and ProMedica (IRB 22-208).

3. Results

Our data produced 6,628 viral PCR or IgG positive patient encounters, with 5,374 patient encounters with only one pathogen detected or IgG alone. Our final analysis included 5,312 instances with a single pathogen or COVID IgG alone identified with more than 100 patient encounters per pathogen without positive bacterial culture results (Figure 2).

Our sample was slightly male predominant (55.9%) and had the most patients in the 0-2 year age bracket (46.5%) (Table 2).

Most patients had limited workup beyond identifying the virus that brought the child to seek treatment. Basic workup, consisting of CBC and BMP, was obtained for 27% of the encounters. Troponin was only obtained for 5% of the encounters (Table 1).



Code	Pathogen
C19	SARS CoV2/COVID-19
HMN	Human Metapneumovirus
AND	Adenovirus
REV	Rhinovirus/Enterovirus
PFV	Parainfluenza virus (1-4)
RSV	Respiratory Syncytial Virus
COR	Coronaviruses (HKU1, OC43, 229E, NL63)
IgG	COVID IgG (nucleocapsid)

Figure 3. Elevated Inflammatory Markers by Pathogen

Distribution of number of elevated inflammatory MIS-C markers per patient is shown by pathogen with A. circles scaled to the proportion of positive samples for each count relative to the total samples of each detected pathogen, B. circles scaled to the total samples at each total marker count for each pathogen, and C. a box and whisker plot to represent distribution of samples by positive marker count. D. Pathogens included in the analysis with 3-letter codes for simplification. Analysis for between group differences with significant findings is shown in Table 5.

COVID IgG-only samples had higher positive MIS-C criteria counts on average compared to all the other viral sources (Figure 3, Table 3). ANOVA with post hoc pairwise analysis showed that IgG had significantly more markers across the threshold than each of the 7 comparison viral groups (Table 4, Table 5). COVID IgG also showed the highest peak value (15) of markers over threshold. COVID IgG group showed the most significant elevations in MIS-C markers relative to the other viral groups.

Acute SARS CoV2 infection did not appear to be any more or less likely to be pro-inflammatory than the other seasonal viruses (Table 5). Of seasonal viruses, adenovirus had significantly higher positive MIS-C criteria counts on average than other groups, except COVID IgG and original coronavirus infections (Table 5). Adenovirus also showed higher proportion of total adenovirus-positive patients with greater than or equal to 2 and 4 elevated MIS-C inflammatory markers than other pathogens, including SARS CoV2, but was markedly lower than COVID IgG.

Several seasonal viruses also had individual samples with a max value of 10 positive MIS-C inflammatory markers, including parainfluenza group and rhinovirus/enterovirus group, even though, on average, these patients exhibited <1 elevated MIS-C marker per sample for those viruses (Table 3). Of note, kurtosis was more leptokurtic for parainfluenza than other pathogens indicating wider tails of the sample distribution. This is likely due to the large gap in samples from 6 to 10 positive markers for the parainfluenza group.

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MIS-C Criteria Measure	*Cutoff*	% obtained during encounter
Temperature (°C)	*≥ 38.0*	99%
Total WBC (x1,000 per µL)	*≥ 15.0*	27%
Hemoglobin (g/dL)	*< 10.0*	27%
Platelet count (x1,000 per µL)	*< 150*	26%
Absolute Lymphocyte (x1,000 per µL)	*< 1.0*	27%
Absolute Neutrophil (x1,000 per µL)	*≥ 7.7*	27%
CRP (mg/dL)	*≥ 5*	11%
ESR (mm/h)	*≥ 40*	4%
Sodium (mmol/L)	*< 135*	27%
Creatine (mg/dL)	*≥ 0.5*	27%
ALT (U/L)	*≥ 41*	18%
Albumin (g/dL)	*< 3.0*	18%
Troponin (ng/mL)	*≥ 0.1*	5%
BNP (pg/mL)	*≥ 400*	4%
D-Dimer (ng/mL)	*≥ 2000*	5%
Ferritin (ng/mL)	*≥ 500*	4%
Fibrinogen (mg/dL)	*≥ 500*	4%
INR	*≥ 1.3*	5%
aPTT (sec)	*≥ 35*	4%

Table 1. MIS-C Criteria Measures With Threshold Value and % Obtained
Threshold value indicating an elevated inflammatory state or organ damage. % obtained indicates percentage of patients with each measure obtained during the encounter.

Age	Male (%)	Female (%)	Total (%)
0-2 yrs	1450 (27.3)	1021 (19.2)	2471 (46.5)
2-5 yrs	772 (14.5)	609 (11.5)	1381 (26.0)
5-10 yrs	414 (7.8)	361 (6.8)	775 (14.6)
10 +	333 (6.3)	352 (6.6)	685 (12.9)
Total (%)	2969 (55.9)	2343 (44.1)	5312

Table 2. Demographic Characteristics

The patient population is presented by developmental age grouping and sex. Nearly half of all patient encounters were children 0-2 years and there was a slight male predominance in patients 0-10 years, but sex distribution was nearly even in patients over 10 years old.

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	C19	*HMN*	*ADN*	*REV*	*PFV*	*RSV*	*COR*	*IgG*
Mean	**0.955**	**0.832**	**1.272**	**0.929**	**0.756**	**0.706**	**0.964**	**4.725**
Standard Error	**0.035**	0.076	**0.102**	0.025	0.042	0.027	0.087	**0.303**
Median	**1**	1	**1**	1	1	1	1	**4**
Mode	**1**	1	**1**	0	0	1	0	**3**
Standard Deviation	**1.151**	1.000	**1.384**	1.190	1.014	0.763	1.126	**3.315**
Sample Variance	**1.325**	1.001	**1.915**	1.416	1.028	0.582	1.268	**10.991**
Kurtosis	**6.082**	6.637	**6.584**	6.274	15.016	5.298	5.124	**0.320**
Skewness	**2.047**	2.105	**2.141**	2.060	2.840	1.592	1.802	**0.848**
Range	**9**	6	**9**	10	10	6	7	**15**
Min	**0**	0	**0**	0	0	0	0	**0**
Max	**9**	6	**9**	10	10	6	7	**15**
Sum	**1008**	144	**234**	2060	444	570	162	**567**
% ≥ 2	**16.9%**	14.5%	**23.9%**	19.9%	11.2%	9.0%	22.0%	**83.3%**
% ≥ 4	**4.3%**	2.3%	**7.6%**	4.1%	2.6%	0.6%	3.0%	**56.7%**
Count	**1056**	173	**184**	2217	587	807	168	**120**

Table 3. Descriptive Statistics of MIS-C Markers by Pathogen:
Statistical distribution characteristics are presented for inflammatory marker elevation counts per sample, by pathogen. Samples with ≥ 2 ($n_{2+\ positive}$) and ≥ 4 ($n_{4+\ positive}$) elevated markers are reported as a proportion (%) of total detected pathogen samples ($n_{pathogen}$), by pathogen. Bolded row of mean # of MIS-C markers and columns for acute Covid-19 (C19), Adenovirus (AND), and COVID IgG (IgG) for emphasis.

Anova: Single Factor						
SUMMARY						
Groups	*Count*	*Sum*	*Average*	*Variance*		
C19	1056	1008	0.954545	1.324946		
HMN	173	144	0.83237	1.000807		
ADN	184	234	1.271739	1.914825		
REV	2217	2060	0.929184	1.416012		
PFV	587	444	0.756388	1.027583		
RSV	807	570	0.70632	0.582379		
COR	168	162	0.964286	1.268178		
IgG	120	567	4.725	10.99097		
ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	1798.628	7	256.9469	178.1609	1E-237	2.01131
Within Groups	7649.524	5304	1.442218			

Table 4. ANOVA Analysis of MIS-C Markers by Pathogen:
Single Factor ANOVA was performed to evaluate differences between pathogens for significance. P-value was highly significant for differences between the pathogen groups.

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4. Discussion

Prior analyses of laboratory profiles and inflammatory response of common cold viruses in the general population are very sparse, likely due to the typically benign response most people show to viruses. Limited studies have been undertaken in flu, which was a leading seasonal viral cause of mortality and morbidity prior to the presentation of the COVID pandemic [9]. In this study, we were not able to provide an adequate comparison to flu due to low flu positivity during the study period. Although many clinical courses are benign, some patients will develop a more severe inflammatory response to viruses leading to prolonged hospital stay with risk for morbidity and mortality [10, 11]. Identifying patients and pathogens with more severe inflammatory responses may allow for better management of patient care and potentially reduce hospital admissions and length of stay, particularly in pediatrics. This study helps lay the groundwork for understanding the inflammatory response during acute "common cold" infections and may guide understanding of risks and severity of seasonal virus infections. Here, we have shown viruses present prior to the SARS CoV2 pandemic can sometimes cause a broadly elevated inflammatory response in children.

It is clear that the post-infectious inflammatory response in COVID IgG positive patients that most likely represent the population of MIS-C patients during this period, presents a much greater inflammatory state than a typical viral infection. However, several viruses (SARS CoV2, adenovirus, parainfluenza viruses and picornaviruses: rhinovirus, enterovirus) show potential to reach similarly broad inflammatory responses at 9 and 10 indicators of inflammation over MIS-C thresholds in some patients. We have examined thresholds at both ≥2 and ≥4 MIS-C markers to compare limited and extended multi-system involvement. COVID IgG-only samples had 89% of samples ≥2 and 59% of samples ≥4 markers, with adenovirus the only other pathogen with more than 5% of samples above the cutoff at ≥4, and the highest at 23.9% at ≥2 markers (Table 3).

Although there is a notable difference between likely MIS-C cases and common viruses, there are a high number of total cases showing broad inflammation from long-present seasonal viruses that present risk for severe courses of disease.

Limitations of this study include the study's retrospective nature and that labs were only obtained on patients who were sick enough to present to the ER or get admitted to the pediatric floor at a single site. We assumed that if there was not enough clinical suspicion to obtain the specific lab, it would be less likely to show elevation above the cutoff, so we did not count it towards the positive MIS-C criteria marker. This is most certainly an underestimation of the biochemical markers of MIS-C cutoffs present in this sample population, but is likely underrepresented equally across all viral groups.

We see that acute COVID-19 infections have a wide variety of clinical inflammation and significance, like the rest of the circulating respiratory viruses in the population. It is the post-acute infection where we see the global increase in inflammatory markers very frequently rising above cutoff with concern for MIS-C, as seen in the COVID IgG-only dataset.

Further exploration is needed as to the mechanism for an immune-mediated etiology for MIS-C, however a few hypotheses have been presented primarily within two categories of mechanisms 1) Dysregulated immune cell activation and 2) Cytokine storm-like presentations [6, 12]. Although these two concepts can be inter-related, the multisystem inflammatory markers elevated in the laboratory and clinical findings in this study suggest that cytokine signaling is most likely a proliferating driver of increased inflammatory response in viral cases with higher inflammation. Viral response, particularly in younger children, can have higher activation of interferon gamma (IFNγ)-mediated pathways. IFNγ plays a major role in cellular immunity, particularly in response to viral pathogens, and has been found to be significantly elevated in MIS-C patients and can lead to leukocytosis [13]. It has also been noted to be low in patients with poor immune response to acute viral infection with SARS CoV2 leading to poor disease outcomes [13]. IFNγ-mediated cytokines have also been shown to separate MIS-C from Kawasaki Disease, demonstrating distinct patterns of inflammation between these conditions that present similarly and are suspected of being peri-infectious [14]. Interferon signatures have also been implicated in hyperinflammatory states (autoinflammatory disease, macrophage activation syndrome) that demonstrate the multi-systemic, highly inflammatory nature of dysregulated interferon signaling [15]. This may be a significant driver of the high inflammatory response to some viruses and particularly in younger patients, although we were not able to examine this directly in our current study. This is an area for focus in future

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studies, particularly where biological samples may be available for reanalysis after viral diagnosis.

Post-Hoc Tukey HSD			
Pair comparison	Difference	95 % CI	P-value
IgG-HMN	**3.89263006**	**[3.460038143, 4.32522197]**	**0.0000000**
IgG-C19	**3.77045455**	**[3.419670897, 4.12123819]**	**0.0000000**
IgG-COR	**3.76071429**	**[3.325493887, 4.19593468]**	**0.0000000**
IgG-ADN	**3.45326087**	**[3.025997639, 3.88052410]**	**0.0000000**
REV-IgG	**-3.79581642**	**[-4.137099021, -3.45453382]**	**0.0000000**
PFV-IgG	**-3.96861158**	**[-4.333414496, -3.60380867]**	**0.0000000**
RSV-IgG	**-4.01868030**	**[-4.374943313, -3.66241728]**	**0.0000000**
RSV-ADN	**-0.56541943**	**[-0.862893700, -0.26794516]**	**0.0000002**
PFV-ADN	**-0.51535071**	**[-0.823001119, -0.20770031]**	**0.0000108**
RSV-REV	**-0.22286388**	**[-0.372566547, -0.07316121]**	**0.0001752**
RSV-C19	**-0.24822575**	**[-0.418479219, -0.07797229]**	**0.0002686**
REV-ADN	**-0.34255555**	**[-0.621914496, -0.06319660]**	**0.0049990**
HMN-ADN	**-0.43936919**	**[-0.824989949, -0.05374843]**	**0.0129508**
C19-ADN	**-0.31719368**	**[-0.608083303, -0.02630405]**	**0.0213520**
PFV-C19	**-0.19815704**	**[-0.385624559, -0.01068952]**	**0.0295666**
REV-PFV	**0.17279517**	**[0.003772335, 0.34181800]**	**0.0408943**
RSV-COR	-0.25796601	[-0.566760231, 0.05082821]	0.1817222
COR-ADN	-0.30745342	[-0.696020530, 0.08111370]	0.2417886
PFV-COR	-0.20789730	[-0.526506304, 0.11071171]	0.4966101
RSV-HMN	-0.12605024	[-0.431128655, 0.17902818]	0.9157984
HMN-C19	-0.12217551	[-0.420836979, 0.17648595]	0.9198593
REV-HMN	0.09681364	[-0.190629082, 0.38425636]	0.9713727
HMN-COR	-0.13191577	[-0.526334710, 0.26250317]	0.9724736
RSV-PFV	-0.05006871	[-0.247599062, 0.14746164]	0.9946505
PFV-HMN	-0.07598153	[-0.390990523, 0.23902747]	0.9960688
REV-C19	-0.02536187	[-0.161511501, 0.11078776]	0.9992492
REV-COR	-0.03510213	[-0.326485640, 0.25628137]	0.9999594
COR-C19	0.00974026	[-0.292715857, 0.31219638]	1.0000000

Table 5. Post-Hoc Tukey HSD Analysis of MIS-C Markers by Pathogen, sorted by P-value. Interactions are sorted by P-value and show highly significant differences between COVID IgG and all pathogens. Lower and upper bounds determined by 95% confidence interval. Bolded samples highlight pairs that have p value <0.05. All pair comparison differences are expressed as difference from first factor relative to second factor.

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Maria Roufaeil contributed to the conception and design, and critically reviewed and revised the manuscript.

Drs. Brian N. Fink and Sharon T. Thomas contributed to the analysis and interpretation of the data, and critically reviewed and revised the manuscript.

Dr. Deepa Mukundan contributed to the conception and design, analysis and interpretation of data, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This study was approved by the Institutional Review Boards of the University of Toledo (IRB #: 301491) and ProMedica (IRB 22-208)

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