Title Case-Controlled Study of Multisystem Inflammatory Syndrome in Children (MIS-C)

Frances Fonacier , Robin Demmrich , Donna Mendez *

Posted Date: 14 August 2024

doi: 10.20944/preprints202408.0975.v1

Keywords: COVID;children;MIS-C;PICU;Emergency Department

Article

Title Case-Controlled Study of Multisystem Inflammatory Syndrome in Children (MIS-C)

Frances Sparks Fonacier [1], Robin Daemmrich [2] and Donna Mendez [3,*]

[1] Maria Farari Children's Hospital; fonacierr@gmail.com
[2] Baylor College of Medicine; rddaemmrich@bcm.edu
[3] The University of Texas Medical Branch at Galveston
* Correspondence: drmendez@utmb.edu; Tel.: +713-301-301-4136

Abstract: BACKGROUND Studies concerning multisystem inflammatory syndrome in children (MIS-C) and how those patients present to the Emergency Department (ED) are scarce. Our study sought to investigate whether abnormal laboratory values were associated with worse outcomes. METHODS This was a retrospective case-control study from March 2020 to June 2020. Patients with MIS-C were compared to a control group. Laboratory values were compared whether admitted to PICU or not. The Pearson's Chi-square test and Fisher's exact test were conducted for associations. RESULTS A total of 80 patients were included in the study (41MISC, 39 control). There were significant associations between patients admitted to the PICU and neutrophilia ($p = 0.03$) and elevated troponin ($p = 0.01$). There were no significant associations between having a non-good outcome and obesity, neutrophilia, lymphopenia, or elevated troponin. When MIS-C patients were compared to the control group MISC-C patients had more obesity and elevated troponin. CONCLUSIONS Patients admitted to the PICU had more neutrophilia and elevated troponin yet had a fairly good outcome. When compared to control patients, there was a significant association with obesity and elevated troponin in the MIS-C group.

Keywords: COVID; children; MIS-C; PICU; emergency department

1. Introduction

In April 2020, what is now known as Multi-system Inflammatory Syndrome in Children (MIS-C) was first recognized in the United Kingdom [1]. Patients presented similarly to those with incomplete Kawasaki Disease (KD) or Toxic Shock Syndrome after having COVID-19 [2–4]. Due to the novelty of the disease, existing studies have been mostly descriptive of the clinical characteristics associated with MIS-C. Studies concerning MIS-C and how those patients present to the Emergency Department (ED) are scarce. There are studies describing the progression of the disease during hospitalization and outcomes and comparing those who have severe versus nonsevere MIS-C. It remains unclear how frequently children progress from mild to more severe manifestations, and what the risk factors are for such progression.

Prior studies have shown an association with MIS-C and abnormal laboratory values including lymphopenia, neutrophilia, elevated troponins, elevated C-reactive protein (CRP), elevated ferritin, and elevated D-dimer [5–7]. Our study sought to confirm prior findings as well as investigate if these abnormal laboratory values were associated with worse outcomes based on hospital placement (not requiring admission, admission to the pediatric floor, admission to pediatric intensive care unit [PICU), as well outcomes at the time of disposition. The findings of this study may help physicians at the frontlines help identify those who will develop more severe symptoms of MIS-C that may develop with the evolving COVID-19 variants and have worse outcomes on their initial clinical and laboratory findings on presentation to the ED.

 doi:10.20944/preprints202408.0975.v1

2. Materials and Methods

This retrospective case-control study took place at a tertiary care pediatric children's hospital in a metropolitan area. Medical records of patients diagnosed with COVID-19 or MIS-C per the World Health Organization (WHO) criteria from March 2020 to June 2020 were reviewed.

Patients were included in the study if they met the following criteria: 1) age 0-21 years old, 2) MIS-C per WHO criteria [6] 3) hospitalized at Children's Memorial Hermann Hospital, 4) suspected COVID-19 infection. Patients were excluded if: 1) age >21 years, 2) the patient was not hospitalized, 3) patient did not meet criteria for MIS-C per WHO guidelines. Children presented to the ED and MIS-C were diagnosed once hospitalized and found to have laboratory findings consistent with MIS-C.

Demographic data obtained were age, sex, and race. Other metrics studied included obesity (defined as body mass index [BMI] of 30 or greater), leukopenia (defined as <1,000/ml), neutrophilia (defined as >7,700/ml), lymphopenia (defined as <1,000/ml), elevated troponin (defined as >0.4ng/ml), elevated CRP (defined as >3.0mg/L), elevated ferritin (defined as >275ng/mL), and elevated d-dimer (defined as <0.50mcg/mL). Outcomes were given numerical scores based on the Pediatric Overall Performance Category scale as seen in Table 3 (1 = Good performance, 2 = Mild overall disability, 3 = Moderate overall disability, 4 = Severe overall disability, 5 = Coma/Vegetative state, 6 = Brain death) [8]. We considered a scale of 2-6 as a good outcome and a scale of 1 as a good outcome.

Table 3. Association of Non-Good Outcome ≥ 2 with Obesity, Neutrophilia, Lymphopenia, and Elevated Troponin.

	Good Outcome = 1 N = 22	**Non-Good Outcome ≥ 1 N = 9**	**P-Value** [a]
Obesity, n (%)	9 (40.9)	4 (44.4)	1.00
Neutrophilia, n (%)	5 (22.7)	4 (44.4)	0.57
Lymphopenia, n (%)	5 (22.7)	4 (44.4)	0.57
Elevated Troponin, n (%)	2 (9.1)	2 (22.2)	0.21

a: All covariates are tested with Fisher's exact test.

Our study compared patients who met MIS-C criteria who tested positive for COVID on polymerase chain reaction (PCR) at least twice and those who met MIS-C criteria but tested negative on PCR. Control cases were defined as patients who met the criteria for diagnosis of MIS-C but were found to be negative on COVID-19 PCR testing. These control cases were compared to those patients diagnosed with MIS-C who also had a positive COVID result on PCR.

All patients diagnosed with MIS-C were also divided into subgroups based on their disposition from the ED. Patients admitted to the PICU were compared to patients who were not admitted to the PICU (either discharged home from the ED or admitted to the pediatric floor).

Statistics Analysis

Our first aim was to compare patients with MIS-C who were admitted to the PICU to those who were either discharged home or admitted to the pediatric floor. The two subgroups were compared regarding obesity, neutrophilia, lymphopenia, and the presence of an elevated troponin. To assess the association between the groups and obesity, Pearson's Chi-square test was conducted. To assess the association between the groups regarding neutrophilia, lymphopenia, and elevated troponin, Fisher's exact test was conducted.

Our second aim was to compare patients based on outcomes. We assessed the association of outcomes with the diagnoses of obesity, neutrophilia, lymphopenia, and elevated troponin. Outcomes were based on the Pediatric Overall Performance Category scale and an outcome ≥ 1 was considered poor. We conducted Fisher's exact test on performance outcome with diagnoses of obesity, neutrophilia, lymphopenia, and elevated troponin.

Our final aim was to determine the association between the control group versus the MIS-C group concerning obesity, neutrophilia, lymphopenia, and elevated troponin. We conducted

 doi:10.20944/preprints202408.0975.v1

Pearson's Chi-square test on control versus MIS-C grouping with diagnoses of obesity, neutrophilia, and lymphopenia. We conducted Fisher's exact test on control versus MIS-C grouping with a diagnosis of elevated troponin.

3. Results

A total of 80 patients were included in the study. Of the total, 41 were diagnosed with COVID-19 with confirmatory PCR that was performed twice and met the MIS-C criteria and 39 met all MIS-C criteria but had a negative PCR for COVID-19 and were considered the control group. The MIS-C patients included five patients seen in the ED and discharged home, 12 admitted to the pediatric floor, nineteen admitted to the PICU initially, and one who was only in the PICU for all of the hospital stays.

Only six patients had an abnormal echocardiogram (19%). All of those patients were admitted to the PICU. Five patients had cardiac dysfunction and one had no cardiac dysfunction and only tricuspid valve regurgitation. For those with abnormal echocardiograms, two had a good outcome, two had a mild overall disability and two had a moderate overall disability.

In reference to treatment, all of those with cardiac dysfunction had treatment with IVIG and steroids. All but one patient with an abnormal echocardiogram received IVIG and steroids. The one patient who did not receive IVIG and steroids had only mild tricuspid valve regurgitation on an echocardiogram. For the whole group with MIS-C, only one patient required high flow nasal cannula (HFNC), five non-HFNC, and none were intubated. The one patient who was on HFNC had no echocardiogram abnormalities but was hypoxic and had pneumonia on chest x-ray.

Only one patient required pressor support and did have cardiac dysfunction. No patients in the MIS-C or control group required ventilation or extracorporeal membrane oxygenation (ECMO).

Patients with MIS-C admitted to the PICU were compared to those discharged from the ED or admitted to the pediatric floor. Table 1a shows the comparison between the two regarding obesity, neutrophilia, lymphopenia, and elevated troponin. There were significant associations between patients admitted to the PICU and neutrophilia ($p = 0.03$) and between patients admitted to the PICU and elevated troponin ($p = 0.01$).

Table 1. Characteristics between Control/MISC Group.

	All Group N = 64	**Control N = 33**	**MISC N = 31**	**P-Value** [a]
Age, median (IQR [b])	10 (3.5 – 16)	10 (3 – 14)	14 (4 – 16)	0.32
Gender, n (%)				0.24
Male	34 (53.1)	20 (60.6)	14 (45.2)	
Female	29 (45.3)	12 (36.4)	17 (54.8)	
Race, n (%)				0.25
White	14 (21.9)	9 (27.3)	5 (16.1)	
Black	9 (14.1)	6 (18.2)	3 (9.7)	
Hispanic	29 (45.3)	14 (42.4)	15 (48.4)	
Other	11 (17.2)	3 (9.1)	8 (25.8)	

a: Continuous variables (age) is tested with Wilcoxon rank sum test. Categorical variables (gender and race) are tested with Pearson's Chi-square test; b: IQR stands for inter-quartile range.

Table 1b demonstrates the association of outcomes of those with MIS-C with obesity, neutrophilia, lymphopenia, and elevated troponin. There were no significant associations between having a non-good outcome and obesity, neutrophilia, lymphopenia, or elevated troponin. No patients died nor had moderate to severe disability, coma/vegetative, or brain death. Of those MIS-C

 doi:10.20944/preprints202408.0975.v1

patients in our group, 18 (58%) had a good performance, 6 (19%) had a mild overall disability and 3 (1%) had moderate overall disability.

The vital signs as reported upon presentation to the ED were compared for those admitted to the PICU to those who were discharged from the ED or admitted to the pediatric floor. There were no significant differences among the group for temperature elevation, hypoxia, hypotension, or tachycardia. Patients who were admitted to the PICU had significantly more tachypnea than those who were not admitted to the PICU.

General demographics between patients with MIS-C with diagnosed COVID-19 were compared to the control group and are displayed in Table 2a. No significant difference or association was found between those with MIS-C and controls about age, gender, or race. The median age for the MIS-C group was 14 years. The MIS-C group was 55% female, 45% male, 48% Hispanic, 25% other race, 16% white, and 10% Black.

Table 2. Association of MISC with Obesity, Neutrophilia, Lymphopenia, and Elevated Troponin .

	PICU N = 17	ED/Floor N = 14	P-Value [a]
Obesity, n (%)	7 (41.2)	6 (42.9)	0.93
Neutrophilia, n (%)	8 (47.1)	1 (7.1)	0.03
Lymphopenia, n (%)	7 (41.2)	2 (14.3)	0.17
Elevated Troponin, n (%)	4 (23.5)	0 (0.0)	0.01

a: Diseases with expected cell frequencies greater than 5 (obesity) were tested with Pearson's Chi-square test. All others with expected cell frequencies less than 5 were tested with Fisher's exact test.

MIS-C patients were compared to the control group in terms of elevated troponin, CRP, and neutrophilia as seen in Table 2b. There were significant associations between patients with MIS-C and obesity, as well as between patients with MIS-C and elevated troponin.

4. Discussion

As more literature becomes available regarding the novel MIS-C syndrome, this study adds critical information regarding the initial presentation in the ED, and progression of the disease during hospitalization, and compares outcomes of pediatric patients based on severity. No study has been published examining the presenting clinical and laboratory findings of those with MIS-C upon presentation to the ED and how they may differ in their presentation if they required admission to the PICU. Our findings found: 1) there was a significant association between MIS-C patients admitted to the PICU and neutrophilia and elevated troponin, 2) there was no association between having a non-good outcome and obesity, neutrophilia, lymphopenia, or elevated troponin in MIS-C patients, 3) demographics between MIS-C patients and controls were not significantly different, and 4) when MIS-C and controls were compared, elevated troponin and obesity were significantly associated with MIS-C patients.

There was a significant association between those admitted to the PICU and neutrophilia and elevated troponin, but not for obesity or lymphopenia. Elevated troponin has been reported as the most abnormal MIS-C marker [9]. Prior studies have shown an association between MIS-C and obesity, neutrophilia, lymphopenia, and elevated troponin levels [7,8,10,11]. An association between PICU admission and elevated troponins is to be expected, as the presence of elevated troponins alone would warrant ICU admission due to cardiac involvement [12]. Neutrophilia, however, which can be seen across all severities of sepsis as well as other diseases with a systemic inflammatory response syndrome (SIRS), is characterized by a marked increase (up to ten-fold) and is significantly associated with PICU admission [13]. Neutrophilia has also been seen in severe viral infections such as RSV [14].

These same four variables (obesity, neutrophilia, lymphopenia, and elevated troponin levels) were assessed to see if there was any association with the outcome at the time of hospital discharge. None of these variables were associated with outcomes at discharge. Thus, it could be inferred that while neutrophilia and elevated troponin may initially be associated with the need for a higher level

 doi:10.20944/preprints202408.0975.v1

of care, there was no relationship with the outcome at discharge. Elevated troponin levels in individuals with COVID-19 are independent prognostic markers of poor outcomes [15]. However, it is unknown if troponin levels correlate or can prognosticate specific abnormalities in a patient with MIS-C. Our study showed no association of troponin or other laboratory or clinical abnormalities such as obesity, neutrophilia, and lymphopenia related to MISC outcome.

Our study's outcomes were similar to other studies finding that death is rare, with reports of death as low as 1.7% in the U.S. and 1.4% in Europe [7,8,13]. We did not have any reported deaths, those requiring ventilation, or those requiring ECMO, which are markers of severity. This could possibly be explained by our patients receiving glucocorticoids and intravenous immunoglobulin (IVIG) quickly upon admission. Of those patients who received IVIG and glucocorticoids, all received treatments within 48 hours of presentation to the ED. Unlike our study, Feldstein and colleagues found their MIS-C patients received IVIG and glucocorticoids on days five to eight [11]. The severity of MIS-C has been associated with cardiac dysfunction, intubation, pressor support, and ECMO [10,11]. We had only 19% of patients with cardiac involvement per echocardiogram, with previous studies reporting 50-80% [16]. Previous reports of required intubation were up to 18%, whereas our study did not have any patients intubated. Also, pressor support has been reported to be 47% whereas it was only required in one of our patients. A study by Ahmed did report 1% requiring pressor support which is comparable to our study [17]. In previous studies, ECMO was necessary for 4% of patients [17].

Our study showed no difference in the incidence of MIS-C among racial groups. This is unlike prior studies which have shown a higher incidence of MIS-C amongst Black, Hispanic, and South Asian people (8, 10, 13). In our study, the highest incidence of patients with MIS-C was Hispanic, followed by other races, White, then Black. Surprisingly, there were not as many Black patients affected as in previous literature. Houston is the most diverse city in the nation; thus, it is unlikely that our sample was affected by racial bias.

There was a significant association between MIS-C patients and obesity as well as elevated troponin. This association of obesity and MIS-C is interesting since we have a high percentage of obesity in our city. Nationally, Houston is number seven in overweight and obese residents in the U.S. Obesity has been noted to be a risk factor for COVID and MIS-C. Proposed mechanisms explaining why obesity may be a risk factor include the accumulation of inflammatory cells in adipose tissue, fat tissue-associated cytokines being proinflammatory, impaired respiratory function, and adipose cells having more SARS-CoV-2 binding receptors [18–22].

Most patients with MIS-C recover with intensive care and medications such as IVIG, glucocorticoids, anti-tumor necrosis factor (TNF), interleukin-1 (IL-1) or 6 inhibitors (IL-6). Of the patients in our study who were in the PICU, eleven received IVIG, ten received steroids, one received pressors, one received IL-6 inhibitor, none received IL-8 inhibitor, and none received anti-TNF. None of the patients who were admitted to the floor received IVIG, glucocorticoids, anti-TNF, IL6, or IL-8 inhibitor. All of our patients with cardiac dysfunction received IVIG and glucocorticoids. Of those without cardiac dysfunction, three patients received IVIG only one patient received glucocorticoids only, and one received both IVIG and glucocorticoids. Full recovery in MIS-C patients at discharge has been reported) with the majority of the patients with cardiac involvement having full recovery [23,24]. A recent study by Son and colleagues showed a lower risk of cardiovascular dysfunction after the administration of IVIG and glucocorticoids (17% vs 31%) [17]. This was similar to our study results, with the six patients with abnormal echocardiograms who received IVIG and glucocorticoids having good recovery by the Pediatric Overall Performance Category Scale by the time they were discharged from the hospital even though they had cardiac dysfunction while in the PICU. Unlike other studies, five of our MIS-C patients were discharged home from the ED without any treatment. This can be explained by the period in which we did our study. Our study started when MIS-C was minimally apparent. These patients looked well and did not return to our ED from our chart review. Hospital follow-up communication with families also did not inform us of the patients presenting to an outside hospital with severe illness.

 doi:10.20944/preprints202408.0975.v1

In reference to those who were not well appearing and were instead admitted, any patient initially admitted to the PICU was eventually transferred to the pediatric floor before discharge home. This indicates the progression of illness was from severe to less severe. Markers of inflammation were consistent with this, with CRP being elevated upon presentation to the ED. We can assume these patients were studied at the peak of illness since none of the patients with MIS-C were upgraded from the floor to the PICU. In addition, their CRP was elevated when they presented to the ED. This indicates that we saw them in their acute versus recovery phase, which may have changed their treatment and outcome.

Our findings of comparable vital signs upon presentation of those admitted to the PICU versus those discharged home from the ED or admitted to the pediatric floor are very interesting. Fever, tachycardia, tachypnea, and hypotension have been strongly associated with shock [25]. All of the vital signs were similar among those admitted to the PICU versus those not requiring PICU, except for tachypnea. One would think the vital signs would be abnormal among those who were admitted to the PICU. We could not explain why tachypnea was the only vital sign abnormal when the groups were compared. It is possible that since it became our hospital's practice to admit children with MIS-C with elevated troponin, their vital signs may not have been significantly different. In our study, those with an initially elevated troponin had normal vital signs upon presentation but then became abnormal during their hospital stay.

Limitations to the study include its retrospective nature where all the variables may have not been collected. Additionally, MIS-C is a rare disease, limiting our data. The incidence of long-term follow-up was not always available, including echocardiograms. Also, mild cases due to lack of recognition or lack of COVID testing were not included. Therefore, the numbers in the study may have underestimated the true number of cases of MIS-C.

In conclusion, this study was done to help distinguish patients diagnosed with MIS-C who required PICU admission and those who did not and to look at the outcomes of each group. This study adds useful information about how those with MIS-C versus those with MIS-C-like symptoms but with negative COVID testing present to the ED and progress during hospitalization.

Author Contributions: Dr. Frances Sparks Fonacier- She contributed to the conceptualization, investigation, formal analysis, and writing-original draft preparation. This author has read and agreed to the published version of the manuscript. Dr. Robin Daemmrich ‑He contributed to the formal analysis, investigation, writing-review and editing. This author has read and agreed to the published version of the manuscript. Dr. Donna Mendez- She contributed to investigation, writing-review and editing, supervision and project administration. This author has read and agreed to the published version of the manuscript.

Funding: This research did not receive any funding.

Institutional Review Board Statement: We did get approval from our Institutional Review Board at protocol The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of The University of Texas Health Science Center/McGovern Medical School, protocol HSC-MS-**20-0657**).” OR “Not applicable” for studies not involving humans or animals.

Informed Consent Statement: Patient consent was waived due to retrospective nature of study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A. MIS-C per WHO Criteria

All 6 criteria must be met:
1. Age 0 to 19 years
2. Fever for ≥3 days

 doi:10.20944/preprints202408.0975.v1

3. Clinical signs of multisystem involvement (**at least 2** of the following):
▪ Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
▪ Hypotension or shock
▪ Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP)
▪ Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
▪ Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
6. Evidence of SARS-CoV-2 infection
▪ **Any** of the following: • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • Contact with an individual with COVID-19

Appendix B. Pediatric Overall Performance Category Scale

Score	Category	Description
1	Good overall performance	Healthy, alert, and capable of normal activities of daily life
2	Mild overall disability	Possibility of minor physical problem that is still compatible with normal life; conscious and able to function independently
3	Moderate overall disability	Possibility of moderate disability from non-cerebral systems dysfunction alone or with cerebral system dysfunction; conscious and performs independent activities of daily life but is disabled for competitive performance in school
4	Severe overall disability	Possibility of severe disability from non-cerebral systems dysfunction alone or with cerebral system dysfunction; conscious but dependent on others for activities of daily living support
5	Coma or vegetative state	
6	Brain death	

 doi:10.20944/preprints202408.0975.v1

References

1. Riphagen, Shelley et al. "Hyperinflammatory Shock in Children During COVID-19 Pandemic." *The Lancet (British edition)* 395.10237 (2020): 1607–1608. Web.
2. Kaushik, Ashlesha et al. "A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection." *The Pediatric infectious disease journal* 39.11 (2020): e340–e346. Web.
3. Abrams, Joseph Y et al. "Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2: A Systematic Review." *The Journal of pediatrics* 226 (2020): 45–54.e1. Web.
4. Center for Disease Control and Prevention, Center for Preparedness and Response: Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19), Clinician Outreach and Communication (COCA) Webinar. Available at: https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp?deliveryName=USCDC_1052-DM28623 (Accessed on May 19, 2020).
5. Riollano-Cruz, Mariawy et al. "Multisystem Inflammatory Syndrome in Children Related to COVID-19: A New York City Experience." *Journal of medical virology* 93.1 (2021): 424–433. Web.
6. Kaushik, Shubhi et al. "Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection (MIS-C): A Multi-Institutional Study from New York City." *The Journal of pediatrics* 224 (2020): 24–29. Web.
7. Chiotos, Kathleen et al. "Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series." *Journal of the Pediatric Infectious Diseases Society* 9.3 (2020): 393–398. Web.
8. Pollack, Murray et al. "Relationship Between the Functional Status Scale and the Pediatric Overall Performance Category and Pediatric Cerebral Perforce Category Scales." JAMA pediatrics 168.7(2014):671-676.Web.
9. Xu H, Aheng L, Dent J, et al. High expression of ACE2 receptor of 2019-COVID on the epithelial cells of oral mucosa, Int J Oral Sc 2020;12:8)
10. Whittaker, Elizabeth et al. "Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2." *JAMA : the journal of the American Medical Association* 324.3 (2020): 259–269. Web.
11. Feldstein, Leora R et al. "Multisystem Inflammatory Syndrome in U.S. Children and Adolescents." The New England journal of medicine 383.4 (2020): 334–346. Web.
12. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, et al., Multisystem Inflammatory Syndrome in Children in New York State N Engl J Med. 2020;383(4):347.).
13. Drifte G, Dunn-Siegrist I, Tissières P, Pugin J. Innate immune functions of immature neutrophils in patients with sepsis and severe systemic inflammatory response syndrome. Crit Care Med.2013;41(3):820-832).
14. O'Donnell DR, Carrington D. Peripheral blood lymphopenia and neutrophilia in children with severe respiratory syncytial virus disease. Pediatr Pulmonol. 2002 Aug;34(2):128-30)
15. Zhao B, Liu W, Lei S, et al. Prevalence and prognostic value of elevated troponins in patients hospitalised for coronavirus disease 2019: a systematic review and meta-analysis. J of Intensive Care . 2020;: 88.
16. Ahmed M, Advani S, Moreira A. et al. Multisystem inflammatory syndrome in children: A systematic reviewEClinicalMedicine . 2020 Sep;26:100527.
17. Son MBF, Murray N, Friedman K, Young CC, Newhams MM,et al. Multisystem Inflammatory Syndrome in Children - Initial Therapy and Outcomes. N Engl J Med . 2021 Jul 1;385(1):23-34.

 doi:10.20944/preprints202408.0975.v1

18. Petrakis, Demetrios et al. “Obesity-a Risk Factor for Increased COVID-19 Prevalence, Severity and Lethality.” Molecular medicine reports 22.1 (2020): 9–19. Web.
19. Stefan, Norbert et al. “Obesity and Impaired Metabolic Health in Patients with COVID-19.” Nature reviews. Endocrinology 16.7 (2020): 341–342. Web.
20. Iannelli, Antonio et al. “Obesity and COVID-19: ACE 2, the Missing Tile.” Obesity surgery 30.11 (2020): 4615–4617. Web.
21. Anderson, Michaela R et al. “Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection A Retrospective Cohort Study.” Annals of internal medicine 173.10 (2020): 782–790. Web.
22. Petrakis, Demetrios et al. “Obesity-a Risk Factor for Increased COVID-19 Prevalence, Severity and Lethality.” Molecular medicine reports 22.1 (2020): 9–19. Web.
23. Capone CA, Subramony A, Sweberg T, et al. Northwell Health COVID-19 Research Consortium. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr. 2020;224:141–145.
24. Greene AG, Saleh M, Roseman E, et al. Toxic shock-like syndrome and COVID-19: a case report of multisystem inflammatory syndrome in children (MIS-C). [published online ahead of print, 2020 Jun 6]. Am J Emerg Med. 2020;S0735-6757(20)30492-7. doi: 10.1016/j.ajem.2020.05.117.
25. Recognition of shock. In: Pediatric Advanced Life Support Provider Manual. Chameides L. Samson RA, Schexnayder SM. Hazinski MF (Eds), American Heart Association, 2011: p.68) 12. Capone, Christine A et al. “Characteristics, Cardiac Involvement, and Outcomes of Multisystem