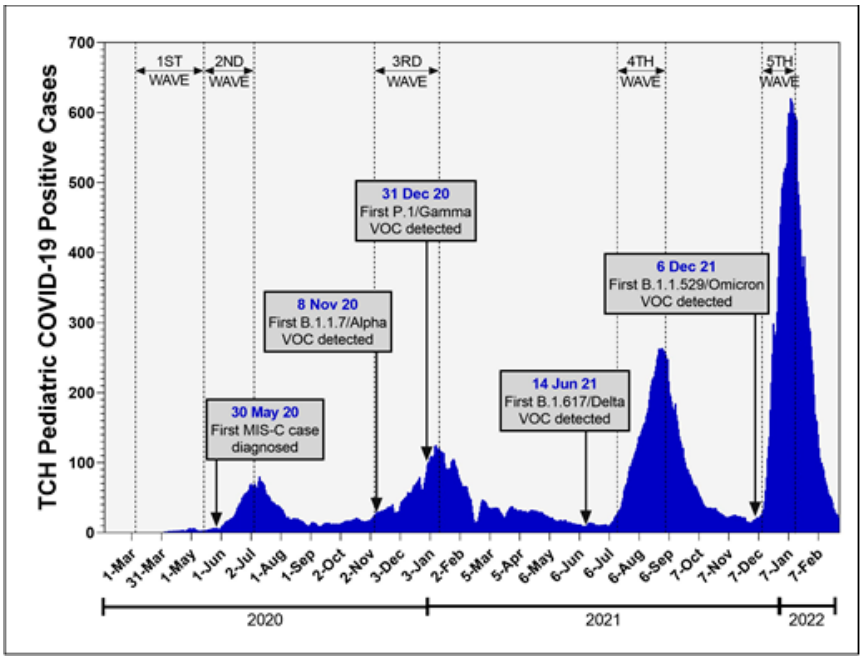
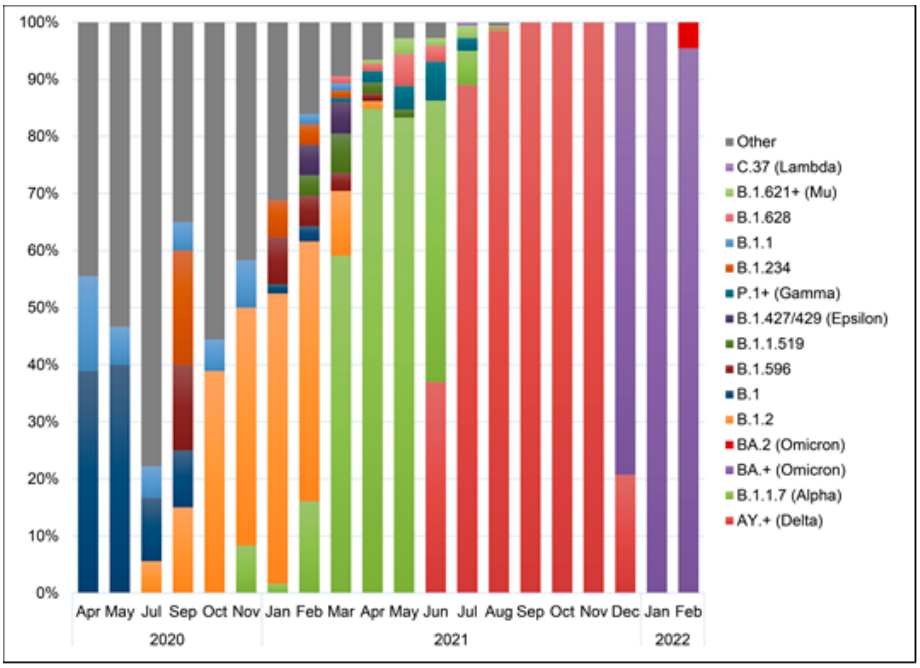
Supplementary Material

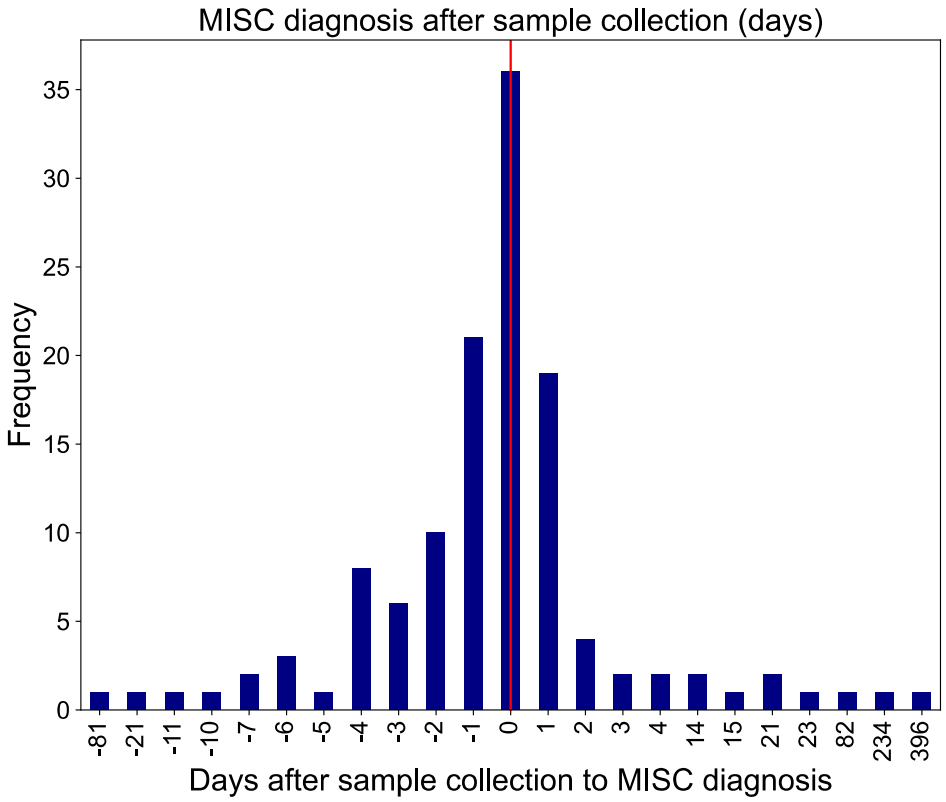
Supplementary Figure S1a: SARS-CoV-2 positive case trends at TCH during the COVID-19 pandemic. These data represent the 7-day average of SARS-CoV-2 positive cases over time from March 2020 – February 2022. Specimens from positive cases have been stored at TCH-CB for future studies.



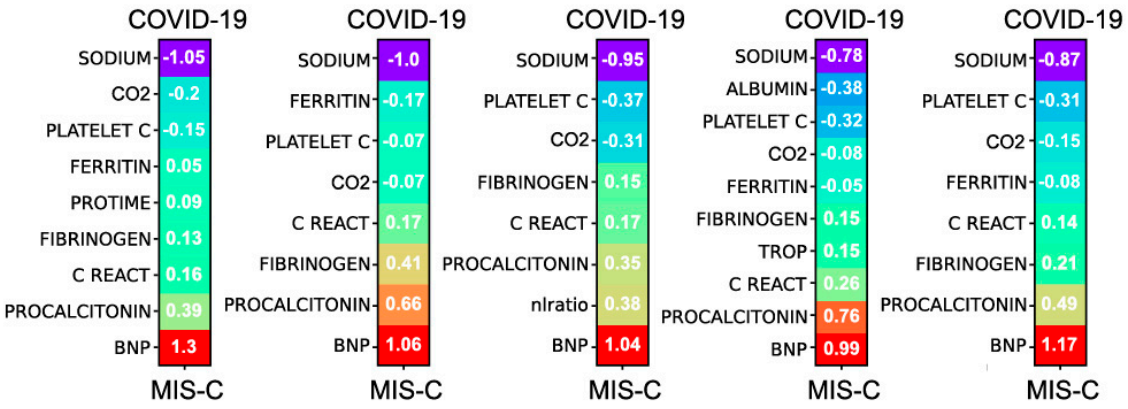
Supplementary Figure S1b: Temporal changes in circulating SARS-CoV-2 variants in pediatric patients. Significant changes have been observed in SARS-CoV-2 variants identified at TCH over the past 22 months. Predominance of lineages have shifted from B.1 in 2020 and B.1.2 in January 2021 to a rapidly shifting variant profile with the emergence of VOCs B.1.1.7 (Alpha), B.1.617/AY.+ (Delta), and BA.+ (Omicron).



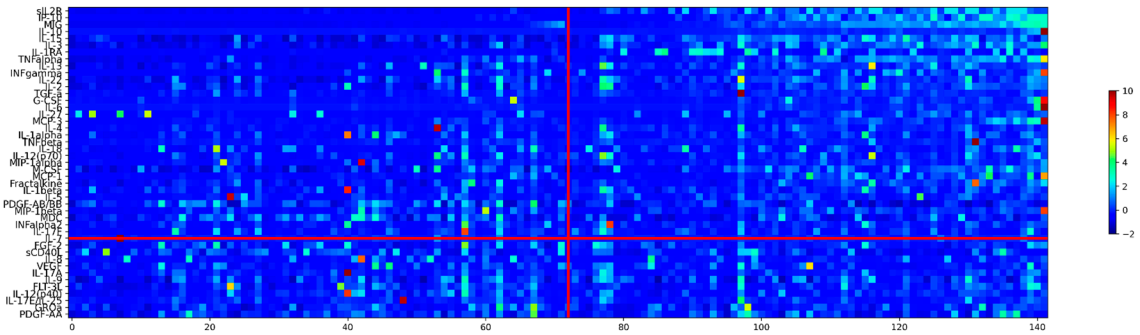
Supplementary Figure S2: Distribution of the number of days after sample collection that a diagnosis of MIS-C was made in the MIS-C cohort in the training set, and validation sets 1 and 2. Negative numbers on the x-axis indicates the sample collection was made after the diagnosis of MIS-C was called. More than half of the MIS-C group had their samples collected prior to diagnosis.



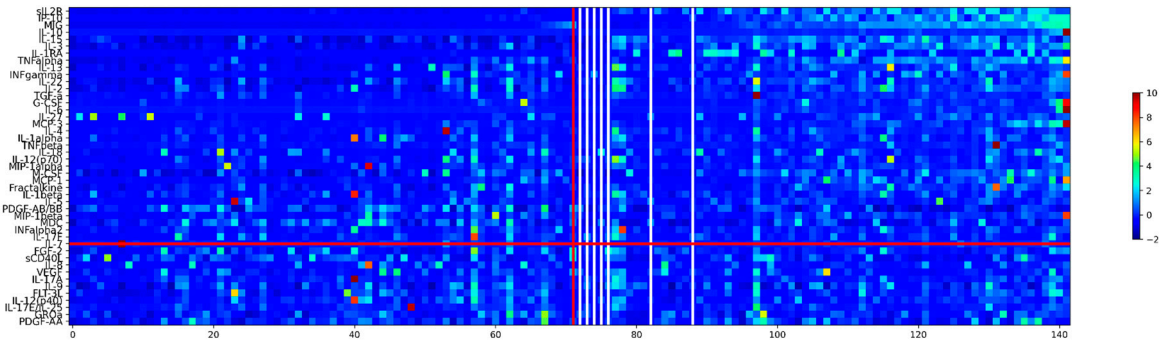
Supplementary Figure S3: 5-fold cross-validated L1 regularized model logistic trained by cross-validation using lab biomarker data only. The model uses a total of 12 lab biomarkers, note that the model does not select Troponin I.



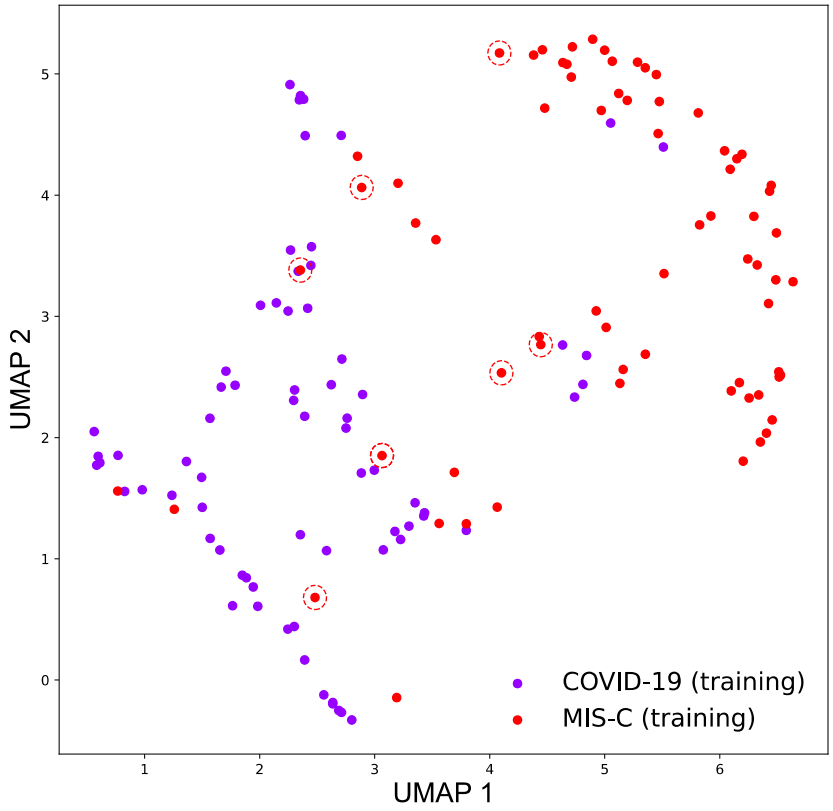
Supplementary Figure S4a: Sorted heat map of 45 measured cytokines/chemokines for the MIS-C and COVID-19 patients in the training set. Each column represents the chemokine/cytokine profile for a patient. The color gradient represents the standardized values of each of the cytokines/chemokines. Patients to the left of the red vertical line are COVID-19 patients, while those to the right are MIS-C. The MIS-C cohort has elevated levels of cytokines/chemokines on average, although the COVID-19 cohort also has patients with elevated levels at the right end. The cytokines/chemokines on the y-axis are sorted in ascending order based on the p-value of the Wilcoxon-rank-sum test to differentiate COVID-19 samples from MIS-C. The horizontal red line demarcates those cytokines/chemokines whose p-value falls above 0.05.



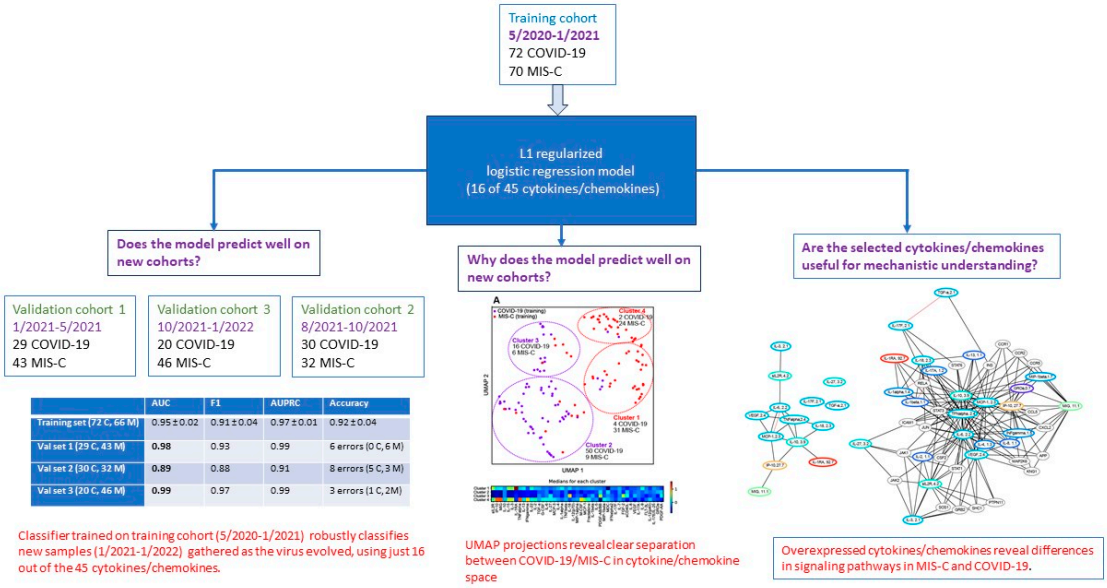
Supplementary Figure S4b: Top: Sorted heat map of 45 measured cytokines/chemokines for the MIS-C and COVID-19 patients in the training set, with classification errors made by the model on the training set itself. Each column represents the chemokine/cytokine profile for a patient. The color gradient represents the standardized values of each of the cytokines/chemokines. Patients to the left of the red vertical line are COVID-19 patients, while those to the right are MIS-C. Note that all seven errors are MIS-C patients with low inflammation levels. **Bottom:** The classification errors in the training set projected into the UMAP space. Note that all seven errors are MIS-C patients, and that six of them map into the COVID-19 clusters, indicating lower than expected inflammation levels, resembling COVID-19 rather than MIS-C.



Supplementary Figure S5: ROC curves and confusion matrix for the training cohort, as well as the three validation cohorts.



Supplementary Figure S6: Flow chart summary.



	AUC	F1	AUPRC	Accuracy
Training set (72 C, 66 M)	0.95 ± 0.02	0.91 ± 0.04	0.97 ± 0.01	0.92 ± 0.04
Val set 1 (29 C, 43 M)	0.98	0.93	0.99	6 errors (0 C, 6 M)
Val set 2 (30 C, 32 M)	0.89	0.88	0.91	8 errors (5 C, 3 M)
Val set 3 (20 C, 46 M)	0.99	0.97	0.99	3 errors (1 C, 2M)

Inclusion criteria: age 18 and under, treated at the TCH system for COVID-19, who consented to providing serum samples.
Exclusion criteria: pregnant, having other inflammatory conditions (such as HLH, Kawasaki, sepsis) not related to SARS-Cov-2.

Supplementary Table S1: Performance of logistic regression model trained on laboratory biomarkers of the initial cohort and tested on three *denovo* validation sets.

	AUC	F1	AUPRC	Accuracy
Training set (72 C, 66 M)	0.86 ± 0.05	0.78 ± 0.07	0.88 ± 0.06	0.81 ± 0.06
Val set 1 (29 C, 43 M)	0.85	0.81	0.89	15 errors (5 C,10 M)
Val set 2 (30 C, 32 M)	0.84	0.75	0.84	14 errors (3 C,11 M)
Val set 3 (20 C, 46M)	0.83	0.71	0.86	16 errors (4 C, 12 M)

Supplementary Table S2: Characterizing cytokine/chemokine derived UMAP clusters by lab and hospital data. Medians and interquartile ranges are shown for the lab markers. Cluster 2 and Cluster 3 contain predominantly COVID-19 patients, while Cluster 1 and Cluster 4 are primarily MIS-C.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
CRP	7.3 (2.6,18.1)	3.2 (0.9,7.4)	6.3 (0.8,16.9)	16.4 (4.3,22.2)
Procalcitonin				
D-Dimer	2.1 (1.3,3.5)	1.3 (0.6,2.6)	1.7 (0.5,3.9)	3.9 (2.1,5.8)
BNP	109.4 (50.0,342.9)	63.8 (17.9,68.3)	66.8 (29.6,138.7)	300.1 (65.0, 706.2)
Sodium	134 (132,139)	138 (135,140)	136.5 (133.3,138)	134.5 (131.3, 137)
Platelet counts	207 (119.5,277.5)	243 (161.5,396)	181 (149.8,313.5)	166 (144.3,241)
Albumin	3.3 (2.9,3.8)	4.0 (3.4,4.6)	3.5 (3.2,4.2)	3.4 (3.1,3.6)
Fibrinogen	458 (383.8, 558)	406.3 (325,535.5)	449 (389.5,596)	485 (385.9,583.8)
Protime	15.3 (14.2,16.5)	14.8 (14,15.2)	14.9 (14.7,16.1)	15.3 (14.5,16.2)
NL ratio	9.1 (3.5,14.7)	2.4 (1.3,5.4)	5.3 (2.7,11.0)	6.1 (1.9,14.6)
CO_2	24 (21,28)	26 (23,27)	26 (24,27.8)	23 (20,26)
Ferritin	327.2 (159,485.5)	254.0 (117.5,379.7)	324.4 (147,507.2)	242 (124.3,649.0)
Troponin I	0.04 (0.01, 0.11)	0.02 (0.01, 0.07)	0.02 (0.01,0.07)	0.02 (0.01,0.07)
Length of stay (days) med	7.9	6.7	5.2	7.82
ICU LOS (days) median	3.7	0	2.4	4.47
ECMO (%)	0.0	2.1	0.0	10.7
CPAP (%)	11.1	17.0	25.0	32.1
Ventilator (%)	8.3	23.4	33.3	35.7

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
AKI (%)	11.1	12.8	45.8	35.7
IVIg/steroids 7dys (%)	38.9	34.0	50.0	39.3