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Supplemental information

Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children

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SUPPLEMENTAL INFORMATION

Characteristic	All MIS-C (n=23)	Severe (n=14)	Moderate (n=9)
Age (years)	10.2 (2-18)	11.3 (3-18)	8.4 (2-17)
Sex: Male: Female	10:13	6:8	4:5
Race: Black	4 (17%)	2 (14%)	2 (22%)
Hispanic/ Latino	16 (70%)	10 (71%)	6 (67%)
White	1 (4%)	0 (0%)	1 (11%)
Mixed	2 (9%)	2 (14)	0 (0%)
Body Mass Index (kg/m2)	22.7 (13.8-33.8)	23.2 (17.9-33.8)	21.9 (13.8-30.3)
Past Medical History*	8 (35%)	3 (21%)	5 (56%)
Known COVID+ contact	12 (52%)	6 (43%)	6 (67%)
SARS-CoV-2 PCR+	10 (43%)	8 (57%)	2 (22%)
Anti-SARS-CoV-2 IgG+	23 (100%)	13 (100%)**	9 (100%)
Other infection* **	1 (4%)	1 (7%)	0 (0%)
Clinical features			
Fever	22 (96%)	13 (93%)	9 (100%)
GI:			
Abdominal pain	16 (70%)	10 (71%)	6 (67%)
Emesis	20 (87%)	12 (86%)	8 (89%)
Diarrhea	17 (74%)	12 (86%)	5 (56%)
Cardiovascular:			
Chest pain	3 (13%)	2 (14%)	1 (11%)
Cardiogenic Shock	11 (48%)	11 (79%)	0 (0%)
Distributive Shock	14 (61%)	13 (93%)	1 (11%)
Neurologic:			
Headache	10 (43%)	7 (50%)	3 (33%)
Confusion	3 (13%)	0 (0%)	3 (33%)
Rash	15 (65%)	10 (71%)	5 (56%)
Conjunctivitis	15 (65%)	10 (71%)	5 (56%)
Sore throat	8 (35%)	6 (43%)	2 (11%)
Muscle aches	5 (22%)	4 (29%)	1 (11%)
Lymphadenopathy	2 (9%)	2 (14%)	0 (0%)
Diagnostics			
ECHO:			
Depressed Left Ventricular function	11 (48%)	10 (71%)	1 (11%)
Coronary aneurism (z score>2)	4 (17%)	4 (29%)	0 (0%)
Therapy			
Respiratory Support:			
Intubation	2 (9%)	2 (14%)	0 (0%)
Non-invasive PPV	1 (4%)	1 (7%)	0 (0%)
Oxygen support			
Regular NC	3 (13%)	2 (14%)	1 (11%)
HFNC	3 (13%)	3 (21%)	0 (0%)
Corticosteroids	23 (100%)	14 (100%)	9 (100%)

Intravenous Immunoglobulin	21 (91%)	14 (100%)	7 (78%)
Anakinra	9 (39%)	6 (43%)	3 (33%)
Tocilizumab	1 (4%)	1 (7%)	0 (0%)
Remdesivir	1 (4%)	1 (7%)	0 (0%)
Heparin	8 (35%)	6 (43%)	2 (22%)
Aspirin	23 (100%)	14 (100%)	9 (100%)
Antibiotics	16 (70%)	11 (79%)	5 (56%)
Convalescent plasma	1 (4%)	1 (7%)	0 (0%)
Vasoactive medication	13 (57%)	13 (93%)	0 (0%)
Outcomes			
Length of Stay, days	6.5 (2-15)[+] n=22	7.4 (4-15)[+] n=13	5.2 (2-9)
Death	0	0	0

Table S1, related to Figure 1. **Patient characteristics**.

* asthma, seizures, developmental delay, sickle cell trait, substance abuse/mental illness, 1 critical patient with chronic kidney disease (CKD) and chronic heart failure (CHF) diagnosed at the time of MIS-C work up.

** 1 patient IgG not checked

*** 1 patient with group A strep found on throat culture

[+] Length of Stay for one patient excluded as still admitted

Characteristic	All MIS-C (n=23)	Severe (n=14)	Moderate (n=9)
Laboratory Tests:			
Ferritin, ng/mL	1,829 (100-12,823)	2,607 (138-12,823)	599 (100-2,615)
BNP, pg/mL	13,144 (2,065->70,000) n=22	17,373 (2,653->70,000) n=13	4,070 (28.4-9,313)
Troponin, ng/mL	0.10 (<0.01-0.40) n=22	0.14 (0.01-0.40)	0.02 (0.01-0.06) n=8
Creatinine, mg/dL	1.55 (0.3-11.17)	1.78 (0.40-11.17)	1 (0.3-4.70)
AST, U/L **ALT, U/L**	207.6 (17-2,799) 126.2 (14-1,343)	250.6 (23-2,799) 154.1 (16-1,343)	140.7 (17-552) 90.2 (14-280)
Albumin, g/dL	2.5 (1.8-3.9)	2.2 (1.8-2.8)	3.0 (2-3.9)
Lactate, mmol/L	4.3 (0.9-14.0) n=19	5.2 (1.1-14.0)	1.8 (0.9-3.8) n=5
D-dimer, mg/L	4.8 (1.5-21.0)	6 (2.4-21.0)	2.8 (1.5-6.6)
CRP, mg/L	195.3 (70-302)	187.5 (6-302)	185.7 (93-300)
Absolute Lymphocyte Count, x1000/μL	0.95 (0.0-5) n=22	0.74 (0.0-1.8) n=13	1.2 (0.3-5)
Procalcitonin, ng/mL	12.1 (0.7-73.6) n=22	14.5 (0.1-73.6) n=13	10.3 (1.5-36.6)
CD25, pg/mL	15,723 (1,565-48,300) n=4	20,442 (2,598-48,300) n=3*	1,565 n=1
IL-6, pg/mL	69.2 (1.8-295) n=12	86.3 (5-295) n=8	35.2 (1.8-78.6) n=4
IL-10, pg/mL	126.5 (7.4-259.0) n=5	137.9 (7.4-259.0) n=4	80.9 n=1
IFNγ, pg/mL	6.3 (<4.2-13.0) n=5	6.8 (4-13.0) n=4	4.2 n=1

Table S2, related to Figure 1. Clinical laboratory tests. BNP- B-type natriuretic peptide; AST- aspartate aminotransferase; ALT- alanine aminotransferase; CRP- c-reactive protein.
* 1 patient CD25 likely too high to measure

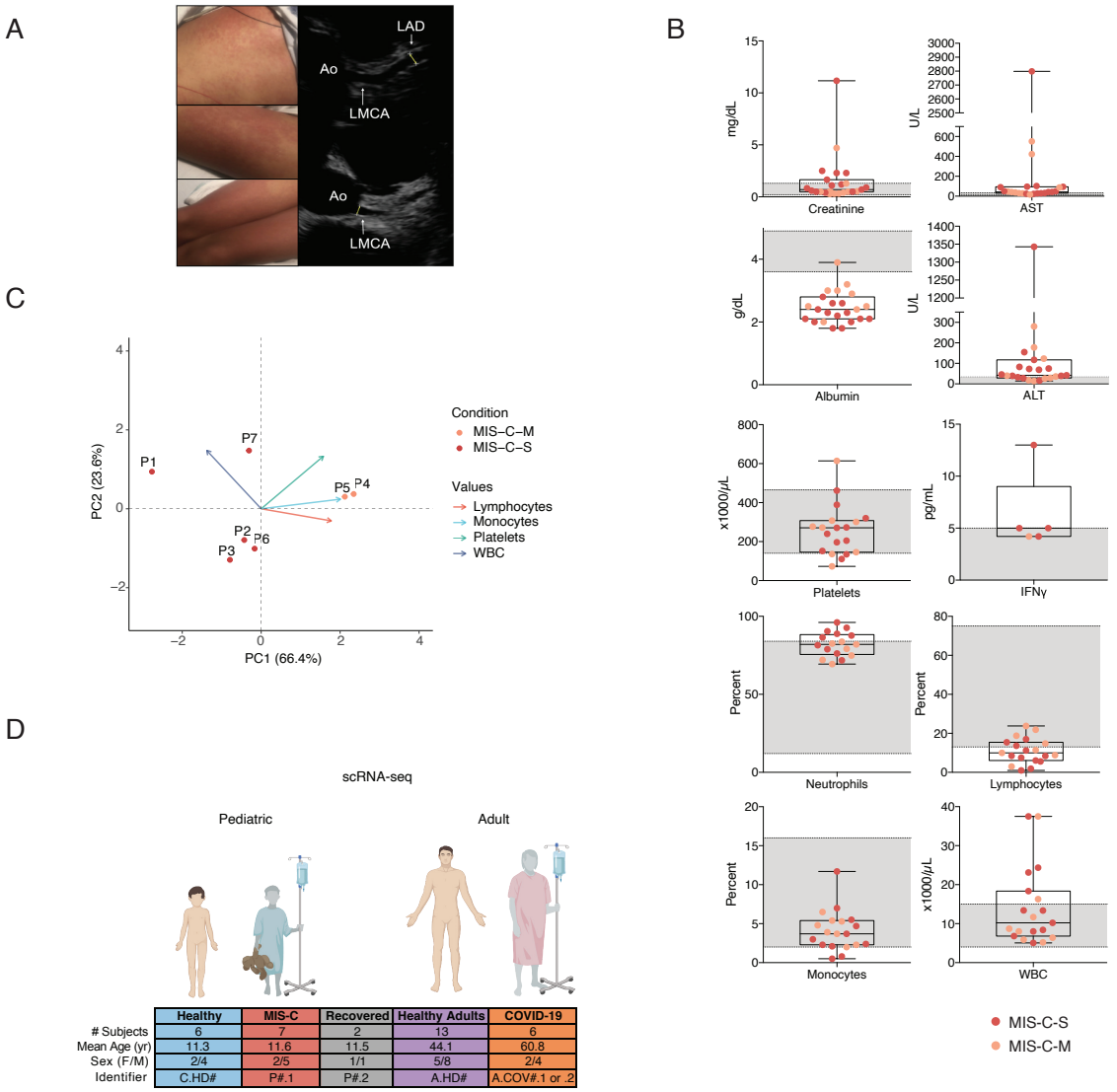
ID	Sex, Race	BMI (kg/ m2)	Medical History	Other Infection	Symptoms	Immune modulation prior to blood sample
P1	M Hisp	19.4	None	Throat: Group A Strep	Fever, rash, conjunctivitis, abdominal pain, vomiting, diarrhea, myalgia, sore throat	Methylpred, IVIG, anakinra
P2	M Hisp	22	Smoker	None	Fever, rash, conjunctivitis, vomiting, diarrhea, shortness of breath	Methylpred, IVIG, aspirin, convalescent plasma, anakinra
P3	M Black	24.6	None	None	Fever, rash, conjunctivitis, abdominal pain, vomiting, diarrhea, chest pain	Remdesivir, anakinra
P4	F Hisp	21.4	None	None	Fever, rash, abdominal pain, vomiting, diarrhea	Methylpred, aspirin
P5	F Latino	17.2	Seizures	None	Fever, abdominal pain, vomiting, diarrhea	Methylpred, aspirin
P6	M Hisp	29.8	DD, CKD, CHF	None	Chills, shortness of breath, cough, abdominal pain, vomiting, diarrhea, anorexia, myalgia sore throat, headache	Methylpred, anakinra
P7	M Hisp	32.3	None	None	Fever, rash, fatigue, vomiting, diarrhea, headache and altered mental status	Methylpred, IVIG, aspirin, anakinra,

Table S3, related to Figure 1. **Characteristics of patients included in single-cell RNA sequencing**. M- male; F- female; DD-developmental delay; CKD- chronic kidney disease; CHF- chronic heart failure; Hisp- Hispanic; Methylpred- methylprednisolone; IVIG- intravenous immunoglobulin.

Sample ID	Condition	Subject ID	Time point	# days between hosp. and draw	Sex	Processing Lab	Storage	Blood shipped o/n (y/n)	# hours between draw and ficoll	Age group	Donor/Patient	ICU status	Severity
P1.1	MIS-C	P1	A	4	M	Lucas1	fresh	N	less than 3	Ped	Pt	Y	MIS-C-S
P2.1	MIS-C	P2	A	4	M	Lucas1	fresh	N	less than 3	Ped	Pt	Y	MIS-C-S
A.HD1	A.HD	A.HD1	NA	NA	M	Lucas1	fresh	N	less than 3	Adult	HD	NA	NA
A.HD2	A.HD	A.HD2	NA	NA	F	Lucas1	fresh	N	less than 3	Adult	HD	NA	NA
A.HD3	A.HD	A.HD3	NA	NA	M	Lucas1	fresh	N	less than 3	Adult	HD	NA	NA
A.COV1.1	COVID19-A	A.COV1	A	2	M	Kaminski	cryopreserved	N	NA	Adult	Pt	N	NA
A.COV1.2	COVID19-B	A.COV1	B	6	M	Kaminski	cryopreserved	N	NA	Adult	Pt	N	NA
A.COV2.1	COVID19-A	A.COV2	A	3	F	Kaminski	cryopreserved	N	NA	Adult	Pt	N	NA
A.COV2.2	COVID19-B	A.COV2	B	6	F	Kaminski	cryopreserved	N	NA	Adult	Pt	N	NA
A.COV3.1	COVID19-A	A.COV3	A	3	M	Kaminski	cryopreserved	N	NA	Adult	Pt	N	NA
A.COV3.2	COVID19-B	A.COV3	B	15	M	Kaminski	cryopreserved	N	NA	Adult	Pt	N	NA
A.COV4.1	COVID19-A	A.COV4	A	2	F	Kaminski	cryopreserved	N	NA	Adult	Pt	N	NA
A.COV4.2	COVID19-B	A.COV4	B	6	F	Kaminski	cryopreserved	N	NA	Adult	Pt	N	NA
A.COV5.2	COVID19-B	A.COV5	B	12	M	Kaminski	cryopreserved	N	NA	Adult	Pt	Y	NA
A.COV6.2	COVID19-B	A.COV6	B	8	M	Kaminski	cryopreserved	N	NA	Adult	Pt	Y	NA
A.HD4	A.HD	A.HD4	NA	NA	M	Kaminski	cryopreserved	N	NA	Adult	HD	NA	NA
A.HD5	A.HD	A.HD5	NA	NA	M	Kaminski	cryopreserved	N	NA	Adult	HD	NA	NA
A.HD6	A.HD	A.HD6	NA	NA	M	Kaminski	cryopreserved	N	NA	Adult	HD	NA	NA
A.HD7	A.HD	A.HD7	NA	NA	M	Kaminski	cryopreserved	N	NA	Adult	HD	NA	NA
A.HD8	A.HD	A.HD8	NA	NA	F	Hafler	fresh	N	NA	Adult	HD	NA	NA
A.HD9	A.HD	A.HD9	NA	NA	F	Hafler	fresh	N	NA	Adult	HD	NA	NA
A.HD10	A.HD	A.HD10	NA	NA	F	Hafler	fresh	N	NA	Adult	HD	NA	NA
A.HD11	A.HD	A.HD11	NA	NA	M	Hafler	fresh	N	NA	Adult	HD	NA	NA
A.HD12	A.HD	A.HD12	NA	NA	F	Hafler	fresh	N	NA	Adult	HD	NA	NA
A.HD13	A.HD	A.HD13	NA	NA	M	Hafler	fresh	N	NA	Adult	HD	NA	NA
P3.1	MIS-C	P3	A	2	M	Lucas2	cryopreserved	N	less than 6	Ped	Pt	Y	MIS-C-S
P4.1	MIS-C	P4	A	2	F	Lucas2	cryopreserved	N	less than 6	Ped	Pt	N	MIS-C-M
P5.1	MIS-C	P5	A	2	F	Lucas2	cryopreserved	N	less than 6	Ped	Pt	N	MIS-C-M
P6.1	MIS-C	P6	A	3	M	Lucas2	cryopreserved	N	less than 6	Ped	Pt	Y	NA
P7.1	MIS-C	P7	A	1	M	Lucas2	cryopreserved	Y	about 24	Ped	Pt	Y	MIS-C-S
P3.2	MIS-C-R	P3	B	73	M	Lucas2	cryopreserved	N	less than 6	Ped	Pt	NA	NA
P4.2	MIS-C-R	P4	B	45	F	Lucas2	cryopreserved	N	less than 6	Ped	Pt	NA	NA
C.HD1	C.HD	C.HD1	NA	NA	F	Lucas2	cryopreserved	N	less than 6	Ped	HD	NA	NA
C.HD2	C.HD	C.HD2	NA	NA	M	Lucas2	cryopreserved	Y	about 24	Ped	HD	NA	NA
C.HD3	C.HD	C.HD3	NA	NA	F	Lucas2	cryopreserved	N	less than 6	Ped	HD	NA	NA
C.HD4	C.HD	C.HD4	NA	NA	M	Lucas2	cryopreserved	Y	about 24	Ped	HD	NA	NA
C.HD5	C.HD	C.HD5	NA	NA	M	Lucas2	cryopreserved	Y	about 24	Ped	HD	NA	NA
C.HD6	C.HD	C.HD6	NA	NA	M	Lucas2	cryopreserved	Y	about 24	Ped	HD	NA	NA

Table S4, related to Figure 2. Meta-data for sequencing samples.
Indicated are unique sample IDs, subject IDs, patient characteristics (age, sex, condition, icu status etc.), and processing conditions. Also indicated are the lab from which the samples originated (where Lucas1 and Lucas2 batches were processed on different days),

the number of days between hospitalization and blood draw (no_days_bt_hosp_blood_draw), and the number of hours between blood draw and processing by Ficoll (no_hrs_bt_draw_and_ficoll).



	Healthy	MIS-C	Recovered	Healthy Adults	COVID-19
# Subjects	6	7	2	13	6
Mean Age (yr)	11.3	11.6	11.5	44.1	60.8
Sex (F/M)	2/4	2/5	1/1	5/8	2/4
Identifier	C.HD#	P#.1	P#.2	A.HD#	A.COV#.1 or .2

Figure S1, related to Figure 1. Supplemental clinical features. (**A**) MIS-C rash on patient P1 and coronary aneurism in left anterior descending coronary artery, Z score of 3.51, in patient P3. Ao-aorta; LMCA- left main coronary artery; LAD- left anterior descending coronary artery. (**B**) Acute phase laboratory values (creatinine, ALT/AST, albumin, IFNγ) and laboratory values on the day of blood sampling/protocol consent (WBC n=19, neutrophils n=17, lymphocytes n=19, platelets n=19, monocytes n=19). Severe MIS-C (MIS-C-S) is highlighted in red dots and moderate MIS-C (MIS-C-M) in light red dots. Normal range represented by gray shading. AST- aspartate aminotransferase; ALT- alanine aminotransferase; WBC- white blood cells. Refer to Table S2 for number of patients represented for each value. (**C**) PCA plot of scRNA-seq cohort separates severe and moderate patients by complete blood count values at time of blood sampling. (**D**) Overview of single-cell RNA sequencing cohorts.

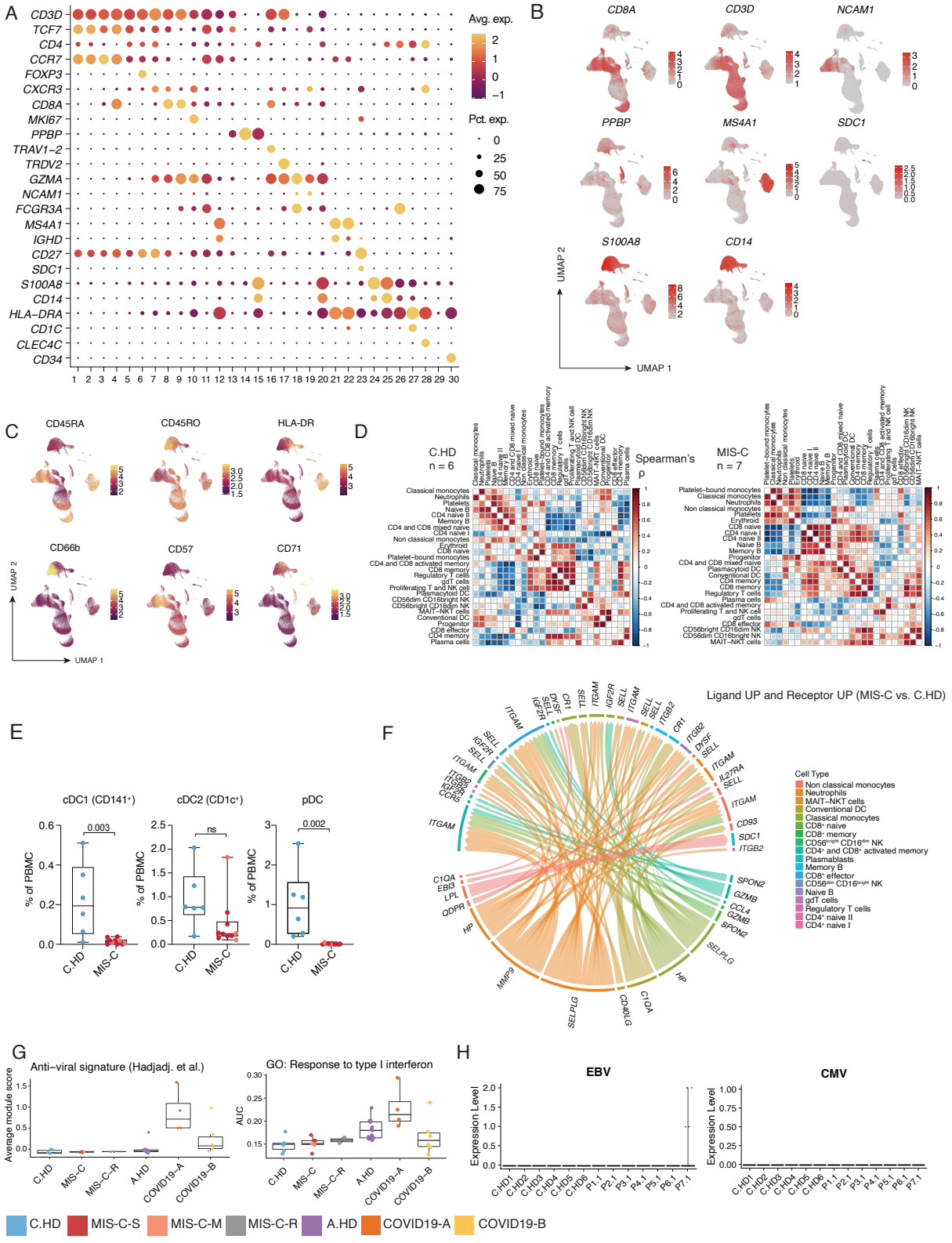

A
CD3D
TCF7
CD4
CCR7
FOXP3
CXCR3
CD8A
MKI67
PPBP
TRAV1–2
TRDV2
GZMA
NCAM1
FCGR3A
MS4A1
IGHD
CD27
SDC1
S100A8
CD14
HLA–DRA
CD1C
CLEC4C
CD34
Avg. exp.
Pct. exp.
B
CD8A
CD3D
NCAM1
PPBP
MS4A1
SDC1
S100A8
CD14
UMAP 1
UMAP 2
C
CD45RA
CD45RO
HLA-DR
CD66b
CD57
CD71
D
C.HD
n = 6
MIS-C
n = 7
Spearman's ρ
E
cDC1 (CD141⁺)
cDC2 (CD1c⁺)
pDC
% of PBMC
0.003
ns
0.002
C.HD
MIS-C
F
Ligand UP and Receptor UP (MIS-C vs. C.HD)
Cell Type
Non classical monocytes
Neutrophils
MAIT−NKT cells
Conventional DC
Classical monocytes
CD8⁺ naive
CD8⁺ memory
CD56bright CD16dim NK
CD4⁺ and CD8⁺ activated memory
Plasmablasts
Memory B
CD8⁺ effector
CD56dim CD16bright NK
Naive B
gdT cells
Regulatory T cells
CD4⁺ naive II
CD4⁺ naive I
G
Anti–viral signature (Hadjadj. et al.)
GO: Response to type I interferon
Average module score
AUC
C.HD
MIS–C
MIS–C–R
A.HD
COVID19–A
COVID19–B
H
EBV
CMV
Expression Level
C.HD1
C.HD2
C.HD3
C.HD4
C.HD5
C.HD6
P1.1
P2.1
P3.1
P4.1
P5.1
P6.1
P7.1
C.HD
MIS-C-S
MIS-C-M
MIS-C-R
A.HD
COVID19-A
COVID19-B

Figure S2, related to Figure 2. Comprehensive analysis of PBMC clusters, receptor-ligand pairs, and viral gene modules. (**A**) Dot plot depicting extensive PBMC cell lineage markers, as in Figure 2b. (**B**) UMAP overlay of markers delineating major cell types including T cells, NK cells, plasma cells, B cells, monocytes, and neutrophils. Scale represents normalized GEX feature counts. (**C**) PBMC UMAPs with overlay of CITE-seq data. Scale represents normalized CITE-seq feature counts. (**D**) Correlation matrix of cell frequencies within C.HD (left) and within MIS-C cohorts (right). Scale represents Spearman's rho. P-values, where depicted, were calculated using Wilcoxon rank sum test, and adjusted for multiple comparisons using the Benjamini Hochberg procedure (Benjamini and Hochberg, 1995). *** indicates $p < 0.001$. (**E**) Quantification of DC populations in PBMC of C.HD (n=6) and MIS-C (n=10) by flow cytometry. Statistical significance was calculated using a two-sided unpaired t-test. (**F**) Predicted ligand-receptor interactions from genes that are significantly up-regulated in MIS-C vs. C.HD. (**G**) (Left) Anti-viral module score based on type I interferon signature reported in a recent study of COVID-19 patients. (Hadjadj et al., 2020) (Right) AUCell signature enrichment of 82 genes in GO: 0034340 Response to type I interferon. (**H**) Counts mapping to EBV and CMV reference transcriptomes.

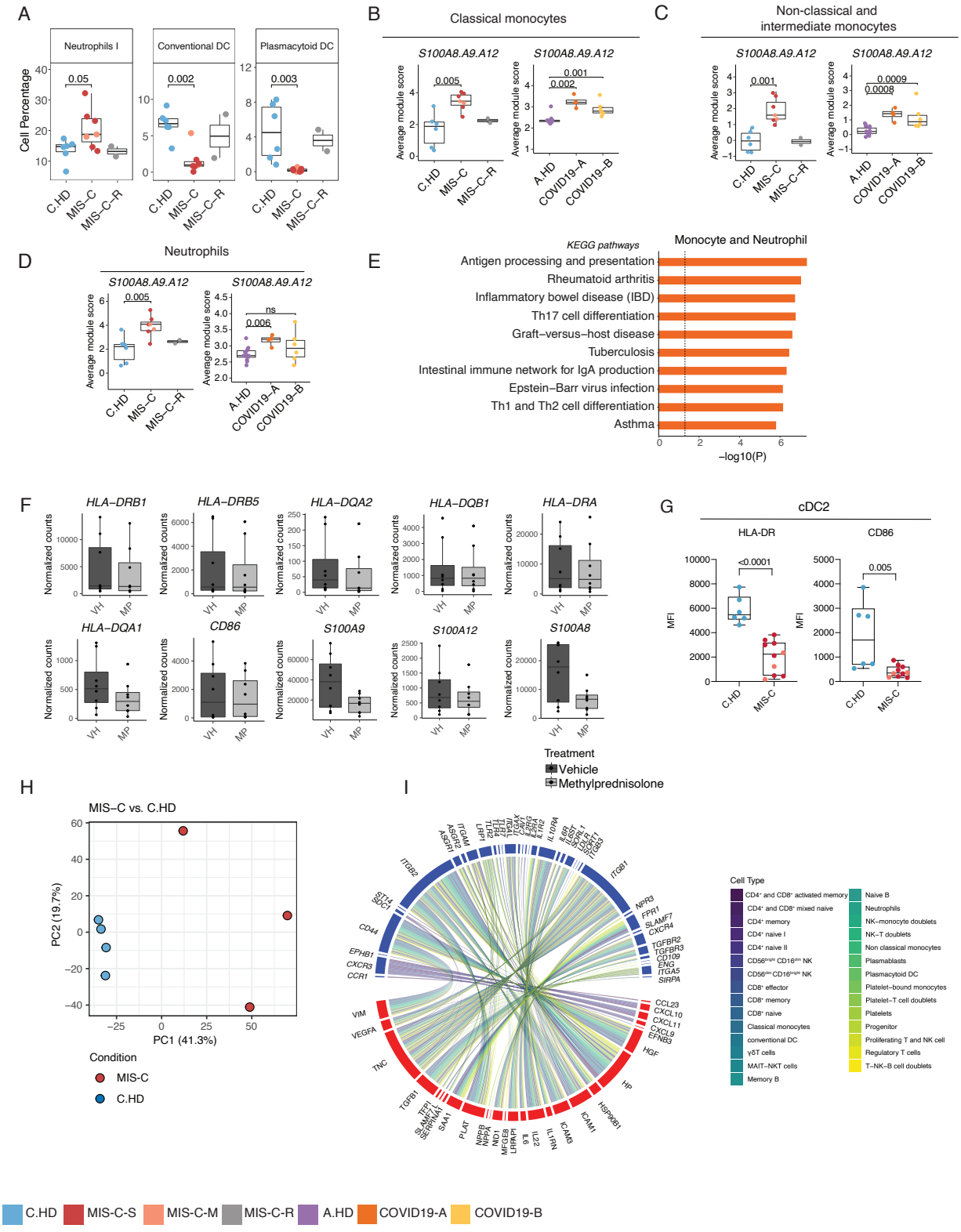


Figure S3, related to Figure 3. Supplemental myeloid cell and DC findings and serum ligand-PBMC receptor connectome. (**A**) Cell type percentages across donors by scRNA-seq

among myeloid cells and DCs. Statistical significance is calculated using a two-sided Wilcoxon rank sum test. *S100A8*, *A9*, and *A12* score in (**B**) classical monocytes, (**C**) non-classical and intermediate monocytes, and (**D**) neutrophils across pediatric and adult donors. Statistical significance calculated as in (**A**). (**E**) Pathways enriched in down-regulated differentially expressed genes shared by monocytes and neutrophils between MIS-C vs. C.HD. (**F**) *S100*-, *CD86*, and *HLA* gene expression changes are quantified based on a publicly available RNA-sequencing data of *in vitro* steroid treatment of myeloid cells for 6 hours with methylprednisolone or DMSO (Franco et al., 2019). (**G**) Flow cytometric evaluation of CD86 and HLA-DR expression on cDC2 in C.HD (n=6) and MIS-C (n=10). Statistical significance computed with a two-tailed unpaired t-test. (**H**) PCA of individuals based on serum proteomic data. Conditions healthy pediatric donors (n = 4) and MIS-C patients (n = 3). (**I**) Connectivity network representing top 40 differentially expressed serum ligands (red) and receptor pairs (blue), where receptors are expressed in at least one PBMC cluster (minimum percentage cutoff = 0.25). Ribbon colors represent receptor-associated cell type.

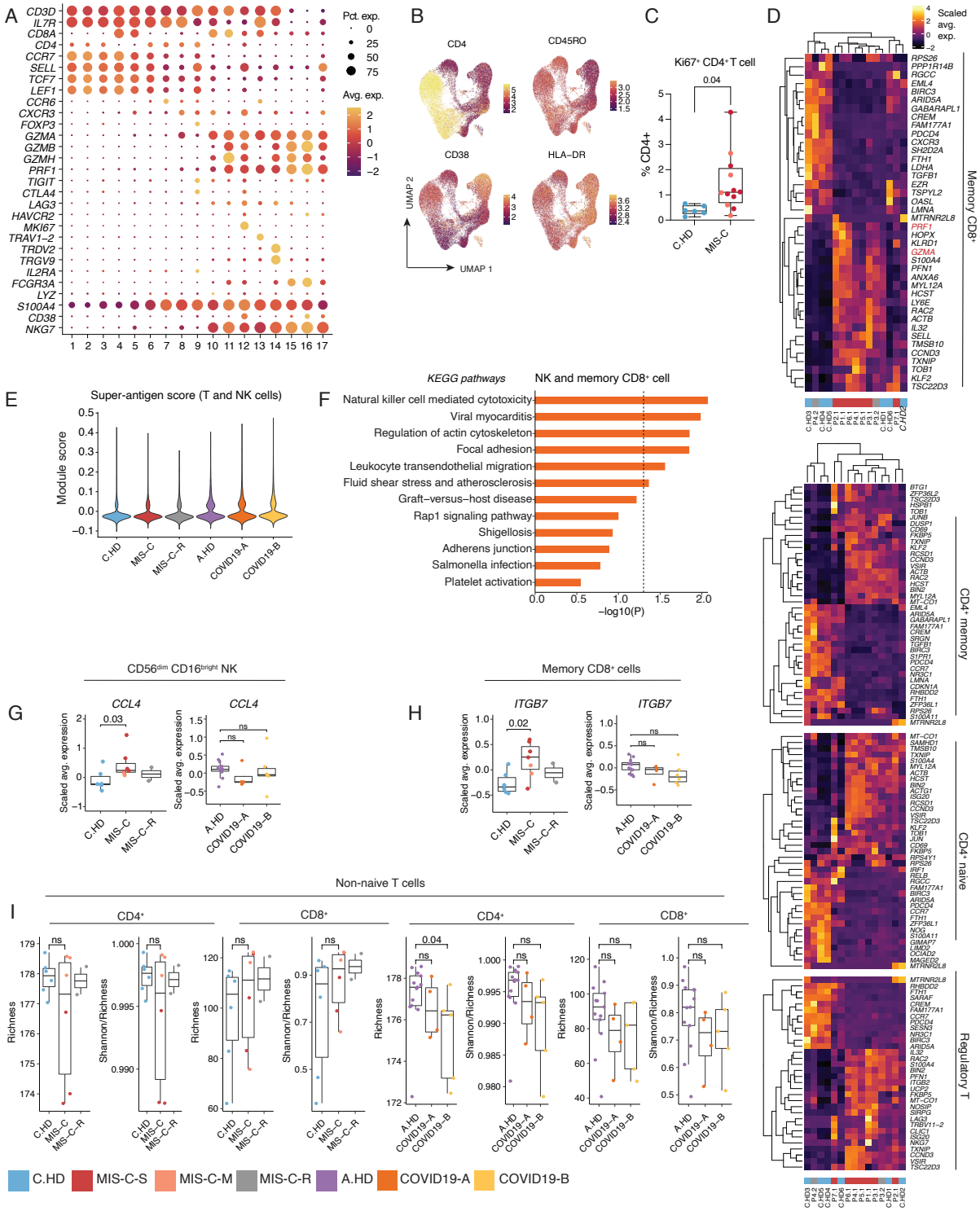


Figure S4, related to Figure 4. Supplemental NK and T cell findings. (**A**) Dot plot depicting extensive T cell sub-clustering lineage markers. (**B**) T cell UMAPs with overlay of CITE-seq data.

(**C**) Flow cytometric evaluation of Ki67 in $CD4^+$ T cells across C.HD (n=6) and MIS-C (n=12). Statistical significance calculated using a two-sided unpaired t-test. (**D**) Heatmap representing top differential expressed genes between MIS-C vs. C.HD in memory $CD8^+$ T cells (top) and $CD4^+$ T cell subsets (bottom). (**E**) Super-antigen module score depicted across T and NK cells. (**F**) Analysis of pathways using Enrichr for shared up-regulated genes in NK and memory $CD8^+$ T cells. (**G**) *CCL4* expression in $CD56^{dim}$ NK cells. Statistical significance calculated using a two-sided Wilcoxon rank sum test. (**H**) *ITGB7* expression in $CD8^+$ memory cells across pediatric and adult donors. Statistical significance calculated as in (**G**). (**I**) Rarefied diversity indices (richness and evenness) of non-naive T cells in TCR data analysis. Statistical significance calculated as in (**G**).

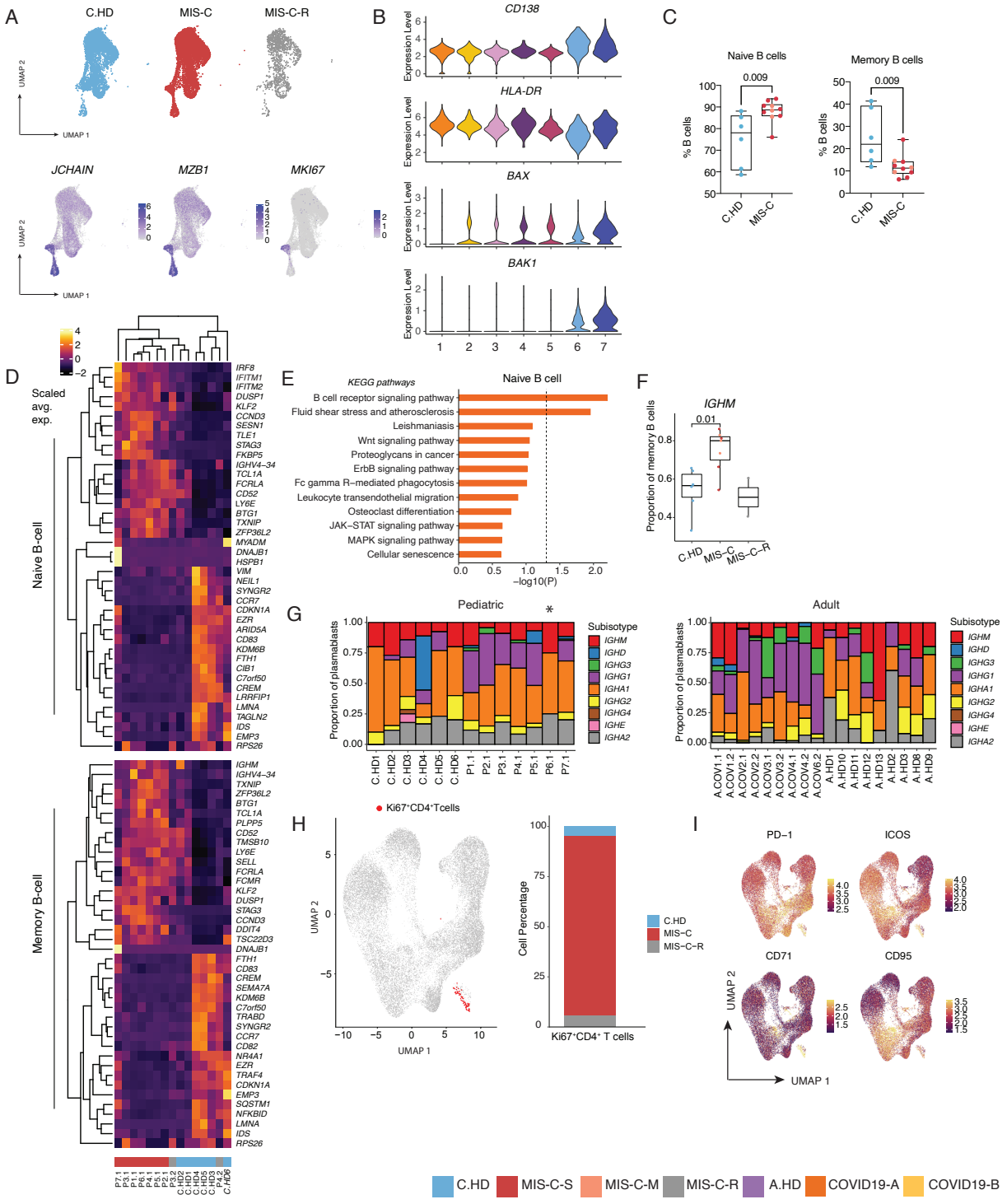


Figure S5, related to Figure 5. Supplemental B cell findings. (**A**) B cell UMAP split across pediatric conditions (C.HD, MIS-C, and MIS-C-R) (top). Marker genes delineating dividing

plasmablasts are overlayed onto fully integrated UMAP (bottom). (**B**) Markers used to define short-lived plasmablasts among B cell clusters. (**C**) Flow cytometric quantification of naïve and memory B cells of total B cells ($CD19^+CD20^+$), across C.HD (n=6) and MIS-C (n=10). Statistical significance calculated using a two-sided unpaired t-test. (**D**) Heatmap depicting differential expressed genes in naïve B cells and memory B cells. (**E**) Pathway analysis of up-regulated differentially expressed genes in naïve B cells. (**F**) Proportion of *IGHM*$^+$ memory B cells by analysis of constant regions. Statistical significance calculated using a two-sided Wilcoxon rank sum test. (**G**) Isotype compositions of pediatric and adult cohorts. *P6.1 also had chronic kidney and heart disease. (**H**) $Ki67^+$ $CD4^+$ T cells are labeled on T cell UMAP (left). Proportion of $Ki67^+$ $CD4^+$ T cells across pediatric cohorts (right). (**I**) CITE-seq overlay on T cell UMAP depicting expression of B helper surface markers in the $Ki67^+$ $CD4^+$ T cells.

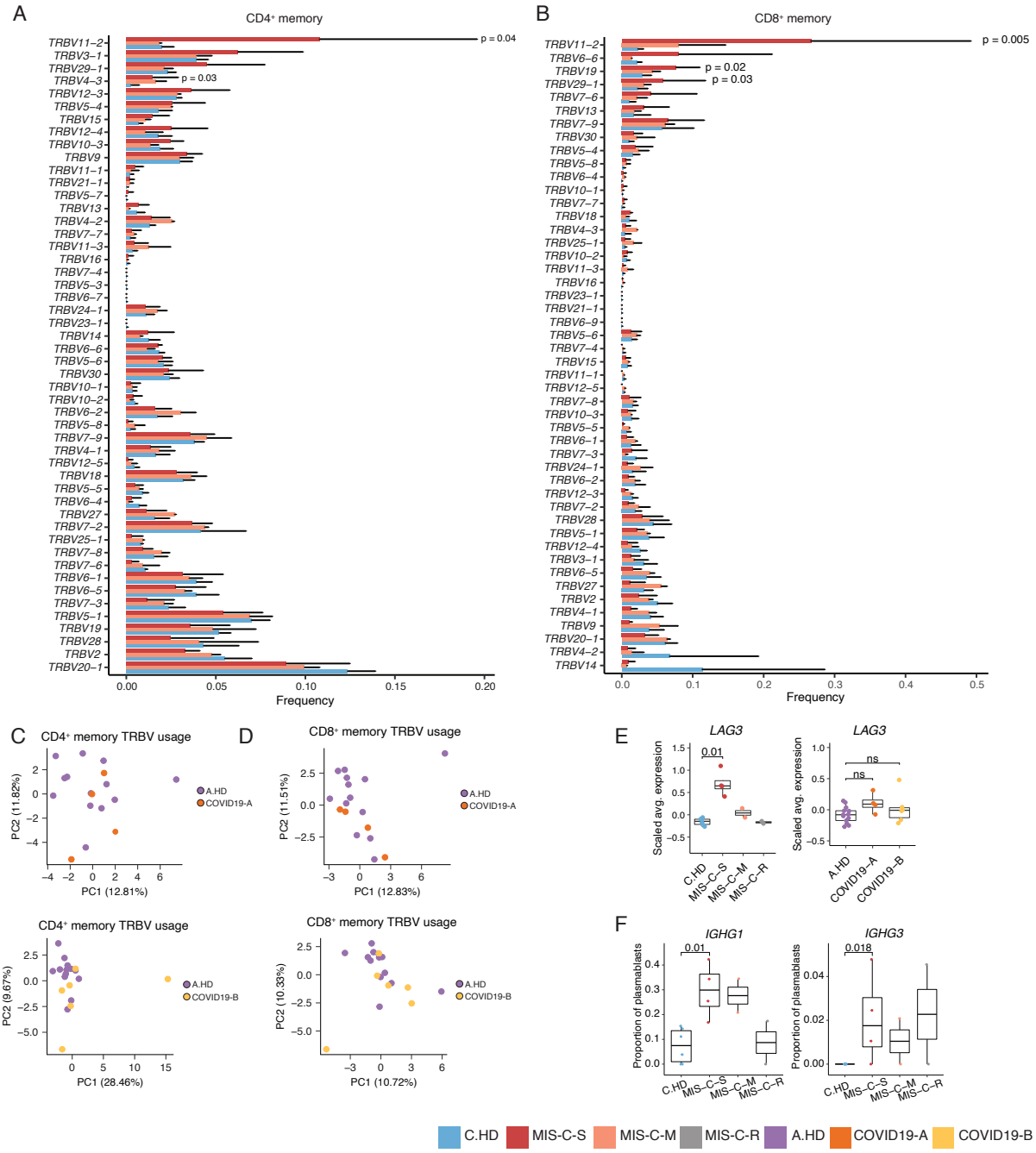

A
CD4⁺ memory
p = 0.04
p = 0.03
Frequency
B
CD8⁺ memory
p = 0.005
p = 0.02
p = 0.03
Frequency
C
CD4⁺ memory TRBV usage
A.HD
COVID19-A
PC1 (12.81%)
PC2 (11.82%)
CD4⁺ memory TRBV usage
A.HD
COVID19-B
PC1 (28.46%)
PC2 (9.67%)
D
CD8⁺ memory TRBV usage
A.HD
COVID19-A
PC1 (12.83%)
PC2 (11.51%)
CD8⁺ memory TRBV usage
A.HD
COVID19-B
PC1 (10.72%)
PC2 (10.33%)
E
LAG3
0.01
Scaled avg. expression
C.HD
MIS-C-S
MIS-C-M
MIS-C-R
LAG3
ns
ns
Scaled avg. expression
A.HD
COVID19-A
COVID19-B
F
IGHG1
0.01
Proportion of plasmablasts
IGHG3
0.018
Proportion of plasmablasts
C.HD
MIS-C-S
MIS-C-M
MIS-C-R
A.HD
COVID19-A
COVID19-B

Figure S6, related to Figure 6. Supplemental findings in severe MIS-C patients. (**A**) Distribution of *TRBV* gene usage in $CD4^+$ memory (see **Figure 6A**) with statistical significance computed between MIS-C-S and C.HD using a one-sided Wilcoxon rank sum test. (**B**) As in (**A**), for $CD8^+$ memory. (**C**) PCA of *TRBV* usage in $CD4^+$ memory cells for A.HD and COVID19-A (top) and A.HD and COVID19-B (bottom). (**D**) As in (c), for $CD8^+$ memory. (**E**) *LAG3* expression across pediatric and adult donors. Statistical significance computed using a two-sided Wilcoxon rank sum test. (**F**) Proportion of *IGHG1* and *IGHG3* plasmablasts compared between C.HD and MIS-C-S. Statistical significance computed using a two-sided Wilcoxon rank sum test.