SUPPLEMENTARY INFORMATION

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Supplementary Table 2: Clinical, demographic and laboratory features of children included in the Transcriptomic Cohort.

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Supplementary Figure 1. Duration of prior fever, admission to wards and paediatric intensive care units (PICU) and convalescence relative to sampling at T1, T2 and T3 for individual patients grouped by their severe febrile illness (all patients recruited to the study).

Supplementary Figure 2. Upset plot visualizing counts of patients/controls across different assays.

Supplementary Figure 3. Mass cytometry methods

Supplementary Figure 4. Immune cell populations and expression of markers by mass cytometry. a, Heatmaps displaying hierarchical clustering of immune cell populations from manually gated mass cytometry data in children with acute (time point 1, T1) multisystem inflammatory syndrome in children (MIS-C, n=35), severe bacterial infection (SBI, n=17), severe viral infection (SVI, n=10), Kawasaki disease (KD, n=4) and healthy paediatric controls (HPC, n=10). **b,** Heatmaps displaying hierarchical clustering of immune cell populations from manually gated mass cytometry data in children with MIS-C at time point 1 (T1, acute febrile within 48 hours of admission, n=35), time point 2 (T2, defervescence with CRP concentration <100 mg/l, n=16) and timepoint 3 (T3, convalescence at follow-up clinic, n=26) and healthy paediatric controls (n=10). **c,** Heatmaps displaying hierarchical clustering of immune cell populations from manually gated mass cytometry data in children with severe bacterial infection (SBI) at time point 1 (T1, acute febrile within 48 hours of admission, n=17), time point 2 (T2, defervescence with CRP concentration <100 mg/l, n=8) and timepoint 3 (T3, convalescence at follow-up clinic, n=6) and healthy paediatric controls (n=10).

Supplementary Figure 5. Hierarchical clustering for children with no immunomodulation at T1 sampling.

Supplementary Figure 6. MOFA of immune features from immunophenotyping shows differences between disease groups and key factors of protein expression and cell proportion features in acute (T1) disease and over the trajectory of illness.

Supplementary Figure 7. Factors 1-3 by disease groups and timepoints.

Supplementary Figure 8. Markers of immune cell activation and return to baseline in innate immune cells (mature neutrophils, immature neutrophils, monocytes, myeloid DCs, plasmacytoid DCs, CD4 memory T cells, CD8 memory T cells, memory regulatory T cells). For all figures, patients with MIS-C are represented in shades of purple for T1–T3 and patients with SBI are represented with shades of orange for T1–T3. P values for pairwise-comparisons across time are using Wilcoxon rank sum testing.

Supplementary Figure 9. a, Markers of T cell activation, exhaustion and apoptosis in memory CD4 T cells. **b,** Markers of T cell activation, exhaustion and apoptosis in memory CD8 T cells. **c,** Markers of T cell activation, exhaustion and apoptosis in memory regulatory T cells.

Supplementary Figure 10. Co-expression of CD279 PD1 with markers of activation, exhaustion and apoptosis in CD4 memory T cells. Representative examples of CD279 PD-1 expression (x axis, all plots) versus **a,** HLA-DR; **b,** CD38; **c,** CD152 CTLA4; **d,** CD134 OX40, **e,** CD278 ICOS, **f,** CD95 Fas, **g,** intracellular IFNγ in memory CD4 T cells and naïve/effector CD4 T cells.

Supplementary Figure 11. K-means clustering analysis: effects of immunomodulatory treatment on supernatant cytokines.

Supplementary Figure 12. Supernatant cytokine analysis 1**:** interferons.

Supplementary Figure 13. Supernatant cytokine analysis 2**:** remaining cytokines.

Supplementary Figure 14. Supernatant cytokine sub-analysis of MIS-C T1 by clusters identified on mass cytometry.

Supplementary Figure 15. Heatmap summarising mass cytometry results of stimulated samples.

Supplementary Figure 16. Gene set enrichment analysis (GSEA) results. **a,** children with MIS-C (TP1) versus pediatric healthy controls; **b,** children with definite bacterial infection (TP1) versus pediatric healthy controls; **c,** children with definite viral infection (TP1) versus pediatric healthy controls; **d,** children with MIS-C versus children with definite bacterial infection. GSEA was undertaken in the R statistical environment, using pathways annotated by the Gene Ontology (GO) database.

DIAMONDS Consortium Membership

Supplementary Table 1: Demographic features and COVID-19 vaccination details of healthy adult controls

Participant ID	Sex	Age (years)	Self-reported ethnicity	Date of sample	COVID-19 vaccine received	Date of vaccination	Dose of last vaccine prior to sampling
Healthy adult control 1	Male	> 21	North/Mid/East European	06/07/2021	mRNA Vaccine BNT162b2	10/03/2021	Second
Healthy adult control 2	Female	> 21	North/Mid/East European	06/07/2021	mRNA Vaccine BNT162b3	21/04/2021	Second
Healthy adult control 3	Female	> 21	North/Mid/East European	06/07/2021	mRNA Vaccine BNT162b4	04/03/2021	Second
Healthy adult control 4	Female	> 21	South Asian	06/07/2021	mRNA Vaccine BNT162b5	07/04/2021	Second
Healthy adult control 5	Female	> 21	North/Mid/East European	13/07/2021	mRNA Vaccine BNT162b6	13/04/2021	Second
Healthy adult control 6	Male	> 21	North/Mid/East European	13/07/2021	mRNA Vaccine BNT162b7	16/03/2021	Second
Healthy adult control 7	Male	> 21	North/Mid/East European	13/07/2021	Non-replicating viral vector vaccine AZD1222 (ChAdOx1)	20/05/2021	Second
Healthy adult control 8	Male	> 21	African - other	13/07/2021	mRNA Vaccine BNT162b4	31/03/2021	Second
Healthy adult control 9	Female	> 21	North/Mid/East European	13/07/2021	mRNA Vaccine BNT162b4	01/07/2021	Second
Healthy adult control 10	Female	> 21	North/Mid/East European	14/07/2021	mRNA Vaccine BNT162b4	20/03/2021	Second
Healthy adult control 11	Male	> 21	South American - other	14/07/2021	mRNA Vaccine BNT162b4	12/05/2021	Second
Healthy adult control 12	Male	> 21	North/Mid/East European	15/07/2021	mRNA Vaccine BNT162b4		
Healthy adult control 13	Male	> 21	North/Mid/East European	22/07/2021	mRNA Vaccine BNT162b4	10/03/2021	Second
Healthy adult control 14	Male	> 21	North/Mid/East European	22/07/2021	Non-replicating viral vector vaccine AZD1222 (ChAdOx1)	24/06/2021	Second
Healthy adult control 15	Female	> 21	North/Mid/East European	03/02/2021	mRNA Vaccine BNT162b4	04/01/2021	First
Healthy adult control 16	Female	> 21	North/Mid/East European	05/02/2021	mRNA Vaccine BNT162b4	01/01/2021	First
Healthy adult control 17	Female	> 21	East Asian	06/10/2021	mRNA Vaccine BNT162b4	19/03/2021	Second
Healthy adult control 18	Female	> 21	North/Mid/East European	06/10/2021	mRNA Vaccine BNT162b4	22/03/2021	Second
Healthy adult control 19	Male	> 21	South American - other	06/10/2021	mRNA Vaccine BNT162b4	26/08/2021	Second
Healthy adult control 20	Female	> 21	North/Mid/East European	06/10/2021	mRNA Vaccine BNT162b4	10/04/2021	Second
Healthy adult control 21	Female	> 21	North/Mid/East European	26/11/2021	mRNA Vaccine BNT162b4	07/10/2021	Booster
Healthy adult control 22	Male	> 21	North/Mid/East European	26/11/2021	mRNA Vaccine BNT162b4	02/10/2021	Booster
Healthy adult control 23	Male	> 21	South Asian	26/11/2021	mRNA Vaccine BNT162b4	04/05/2021	Second
Healthy adult control 24	Female	> 21	East Asian	01/12/2021	mRNA Vaccine BNT162b4	17/11/2021	Booster
Healthy adult control 25	Male	> 21	North/Mid/East European	01/12/2021	mRNA Vaccine BNT162b4	03/04/2021	First
Healthy adult control 26	Male	> 21	Middle Eastern - Arab	01/12/2021	mRNA Vaccine BNT162b4	11/07/2021	Second
Healthy adult control 27	Male	> 21	North/Mid/East European	01/12/2021	mRNA Vaccine BNT162b4	> 14 days prior to sampling	Second

Supplementary Table 2: Clinical, demographic and laboratory features of children included in the Transcriptomic Cohort. Healthy controls were used for normalisation of the data but not for differential expression analysis or feature selection.

	MIS-C (n=38)	***KD (n=136)***	***Viral (n=138)***	***Bacterial (n=188)***	***Healthy controls (n=134)***
Age in months	126 (65-151)	30 (16-52)	7 (2-20)	38 (11-96)	92 (29 – 154)
Sex at birth (female, %)	13 (39%)	59 (43%)	45 (33%)	85 (45%)	63 (47%)
Days since symptom onset	6 (5-7)	6 (5-8)	5 (2-6)	2 (1-4)	-
Required inotropic support (n, %)	20 (52.6%)	2 (1.4%)	3 (2%)	50 (26.6%)	-
Required non-invasive ventilation (n, %)	5 (13.2%)	2 (1.4%)	6 (4.3%)	46 (24%)	-
Required invasive ventilation (n, %)	4 (10.5%)	0	7 (5.1%)	16 (8.5%)	-
Admitted to PICU (n, %)	23 (60.6%)	1 (0.7%)	25 (18%)	84 (44.7%)	-
White blood cells (10^9/L)	9.7 (8.1-11.5)	13.2 (10.4-18)	9.9 (6-14)	13.2 (8.1-20.6)	-
Neutrophils (10^9/L)	8.1 (4.5-11.0)	9.2 (6.3-11.5)	3.6 (1.8-6.5)	14.1 (6-47)	-
Lymphocytes (10^9/L)	1.2 (0.8-1.8)	2.8 (1.7-4.9)	4.7 (2.8-6.7)	2.8 (1.5-8.6)	-
Monocytes (10^9/L)	0.3 (0.2-0.4)	0.7 (0.5-1.1)	0.8 (0.5-1.4)	1.6 (0.7-4.8)	-
Platelets (10^9/L)	209 (144-300.5)	343 (257-426)	365 (245-509)	243 (157-329)	-
CRP (mg/L)	173 (99-250)	73 (43-162)	13.2 (4.1-38)	116.8 (40.3-212)	-

Supplementary Table 3: Clinical characteristics of patients included in the mass cytometry experiment.

Characteristics	MIS-C	SBI	SVI	KD	HPC
n	35	17	10	4	10
Age (years) (median, IQR)	8.0 (2.6–13.3)	6.4 (2.6–13.9)	2.6 (1.4–10.1)	0.8 (0.6–2.1)	6.6 (5.1–10)
Female (n, %)	14 (40%)	5 (31%)	7 (70%)	1 (25%)	4 (40%)
Self-reported ethnicity					
Asian (n, %)	5 (15%)	1 (5.9%)	1 (10%)	1 (25%)	0
Black (n, %)	8 (24%)	1 (5.9%)	2 (20%)	0	2 (20%)
Other (n, %)	9 (26%)	1 (5.9%)	0	1 (25%)	1 (10%)
White (n, %)	12 (35%)	14 (82%)	7 (70%)	2 (50%)	7 (70%)
Comorbidity[1]	4 (11%)	7 (41%)	1 (10%)	1 (25%)	0
Presenting clinical features					
Gastrointestinal symptoms	27 (77%)	12 (71%)	3 (30%)	3 (75%)	–
Oral mucositis	4 (11%)	0	0	2 (50%)	–
Rash	23 (66%)	5 (29%)	2 (20%)	4 (100%)	–
Respiratory symptoms	8 (23%)	12 (71%)	7 (70%)	0	–
Additional findings during admission					
Maximum CRP concn (mg/l) (median, IQR)	200 (143–270)	197 (168–299)	129 (67–150)	111 (89–147)	–
Maximum neutrophil count ($x10^9$/l) (median, IQR)	13 (9.8–18)	15 (9.0–20)	8.8 (7.2–13)	14 (11–16)	–
Minimum lymphocyte count ($x10^9$/l) (median, IQR)	0.6 (0.4–1.2)	1.3 (0.6–2.9)	1.0 (0.7–2.0)	2.4 (1.7–3.2)	–
Coronary artery aneurysm (n, %)	5 (14%)	0	0	1 (25%)	–
Treatments during admission					
Mechanical ventilation (n, %)	3 (8.8%)	8 (47%)	8 (80%)	0	–
Vasoactive infusion (n, %)	32 (94%)	9 (56%)	3 (3.3%)	0	–
Intravenous immunoglobulin	12 (34%)	2 (12%)	0	4 (100%)	–
High dose corticosteroids	33 (94%)	1 (5.8%)	0	3 (75%)	–
Monoclonal antibody therapy[2]	8 (23%)	0	0	0	–
Outcome					
PICU admission (n, %)	34 (97%)	16 (94%)	9 (90%)	0	–
Hospital length of stay (days) (median, IQR)	6.7 (5.5–8.2)	8.7 (7.8–17)	14 (7.4–28)	6.7 (4.9–8.6)	–
In-hospital mortality (n, %)	1 (2.9%)	1 (5.9%)	1 (10%)	0	–
Infections identified					
SARS-CoV-2 PCR/antigen positive (n, %)	1 (2.9%)	0	3 (30%)	0	–
SARS-CoV-2 IgG antibody positive (n, %)	33 (94%)	0	3 (30%)	0	–

[1]MIS-C: Minor neurological co-morbidities 2, respiratory 1, endocrinological 1; SBI: respiratory 2, cardiac 1, endocrinological 1, minor neurological 2, other genetic syndrome 1; SVI: other genetic syndrome 1; KD: renal 1 child. [2]MIS-C: tocilizumab in 8 children.

Supplementary Table 4. Clinical characteristics of children within Cluster 1 and Cluster 2 as defined by immunophenotyping using mass cytometry data. Statistical comparisons between Cluster 1 and Cluster 2 were made using the two-sided Fisher exact test of proportions or two-sided Wilcoxon test with no adjustments for multiple comparisons.

	Cluster 1	**Cluster 2**	**p**
n	29 (44%)	37 (56%)	
Disease group			
MIS-C	22 (76%)	13 (35%)	0.001
SBI	4 (14%)	13 (35%)	0.087
SVI	3 (10%)	7 (19%)	0.493
KD	0	4 (11%)	0.125
Age (years) (median, IQR)	9.3 (4.9–14)	5.4 (1.6–8.9)	<0.001
Female (n, %)	12 (41%)	15 (41%)	1
Self-reported ethnicity			
Asian (n, %)	1 (3%)	2 (5%)	1
Black (n, %)	5 (17%)	5 (14%)	0.738
Other (n, %)	10 (34%)	9 (24%)	0.419
White (n, %)	13 (45%)	21 (57%)	0.457
Additional findings during admission			
Maximum CRP concentration (mg/l) (median, IQR)	209 (134–288)	179 (124–220)	0.392
Treatments during admission			
Mechanical ventilation (n, %)	7 (24%)	9 (24%)	1
Vasoactive infusion (n, %)	19 (66%)	15 (41%)	0.051
Intravenous immunoglobulin (pre-T1 sampling)	5 (17%)	5 (14%)	0.738
High dose corticosteroids (pre-T1 sampling)	12 (41%)	8 (22%)	0.108
Monoclonal antibody therapy[2] (pre-T1 sampling)	0	1 (3%)	1
Outcome			
PICU admission (n, %)	23 (79%)	25 (68%)	0.405
Hospital length of stay (days) (median, IQR)	6.8 (6.2–7.9)	8.1 (5.5–10)	0.413

Supplementary Table 5. Summary of supernatant cytokine analysis following cell stimulation experiments. Median values by cohort and timepoint for baseline results and percentage change from baseline following stimulation with SARS-CoV-2 antigen and mitogen (phytohemagglutinin) are shown. Patients with Multisystem Inflammatory Syndrome in Children (MIS-C), Severe bacterial illness (SBI), Kawasaki disease (KD), Severe viral illness (SVI) and other inflammatory conditions at acute (TP1) and convalescence (TP3), as well as healthy paediatric controls and healthy COVID-19 vaccinated adults were included. The number of samples are indicated in the table for each result. Units are pg/ml for all cytokines are derived from a standard curve for each assay. Abbreviations: IL, interleukin; TNF, tumour necrosis factor; IP, interferonγ induced protein, GMCSF, granulocyte-macrophage colony stimulating factor; IFN, interferon.

	Highest value
	50th Percentile
	Lowest value

	BASELINE - median results for each cohort/timepoint										
Disease group and timepoint	MIS-C - TP1	MIS-C - TP3	SBI - TP1	SBI - TP3	KD - TP1	KD - TP3	SVI - TP1	SVI - TP3	Inflammatory - TP1	HPC	HAC
IL1b	42	70	86	134	NA	158	65	8	69	54	64
IL6	103	55	164	179	NA	187	83	149	389	86	319
TNFα	24	54	35	208	NA	118	41	1	44	33	44
IP10	948	101	256	78	27	143	757	1071	190	79	167
IFNλ1	82	170	123	97	1000000	240	229	10	264	119	80
IL8	541	2384	3314	3365	7386	3359	1494	210	5469	1769	4512
IL12p70	2	8	4	4	4	4	2	0	3	3	2
IFNα2	9	16	14	14	23	34	11	4	14	11	3
IFNλ2/3	232	175	292	130	215	385	252	60	226	213	210
GMCSF	6	35	20	24	18	9	12	0	10	8	0
IFNβ	14	0	27	10	0	43	7	3	14	0	0
IL20	32	11	23	7	28	6	31	157	14	11	5
IFNγ	169	307	156	89	88	413	215	114	110	122	29
Number of samples	41	15	13	3	1	3	7	1	9	15	25
SARS-CoV-2 AG STIMULATION - median percentage change from baseline for each cohort/timepoint											
Disease group and timepoint	MIS-C - TP1	MIS-C - TP3	SBI - TP1	SBI - TP3	KD - TP1	KD - TP3	SVI - TP1	SVI - TP3	Inflammatory - TP1	HPC	HAC
IL1b	8%	22%	8%	-22%	NA	-9%	-22%	15%	-2%	2%	28%
IL6	-4%	35%	3%	-43%	NA	79%	5%	-25%	0%	-2%	45%
TNFα	-16%	19%	25%	-18%	NA	125%	49%	-42%	-12%	-26%	66%
IP10	0%	60%	1%	5%	107%	19%	-7%	9%	3%	26%	427%
IFNλ1	1%	-6%	5%	633305%	-100%	29%	-51%	-100%	-22%	6%	7%
IL8	51%	36%	40%	68%	97%	37%	67%	89%	21%	67%	78%
IL12p70	6%	3%	14%	6%	14%	-1%	-10%	-24%	-14%	-2%	9%
IFNα2	7%	4%	6%	-7%	14%	12%	-1%	-50%	-24%	9%	15%
IFNλ2/3	-2%	15%	6%	-25%	24%	26%	-40%	-33%	-32%	18%	10%
GMCSF	-10%	6%	14%	-31%	22%	44%	-7%	-100%	-32%	2%	32%
IFNβ	-10%	12%	-12%	28%	3771%	89%	-87%	-100%	-61%	-41%	141%
IL20	-2%	27%	7%	-23%	3%	24%	12%	-22%	-7%	-11%	56%
IFNγ	8%	47%	26%	4%	20%	36%	2%	-68%	-13%	25%	246%
Number of samples	35	15	13	3	1	3	6	1	9	14	22
MITOGEN STIMULATION - median percentage change from baseline for each cohort/timepoint											
Disease group and timepoint	MIS-C - TP1	MIS-C - TP3	SBI - TP1	SBI - TP3	KD - TP1	KD - TP3	SVI - TP1	SVI - TP3	Inflammatory - TP1	HPC	HAC
IL1b	85%	346%	17%	649%	NA	573%	210%	96%	15%	402%	692%
IL6	114%	6492%	64%	1772%	NA	7063%	911%	554%	-1%	8673%	3102%
TNFα	107%	268%	87%	959%	NA	920%	349%	85%	46%	3266%	2924%
IP10	18%	1331%	38%	2116%	568%	2172%	99%	1510%	20%	2178%	1125%
IFNλ1	7%	18%	7%	52%	-100%	220%	14%	15%	70%	83%	24%
IL8	495%	419%	142%	450%	249%	144%	620%	230%	17%	757%	355%
IL12p70	15%	27%	8%	32%	65%	145%	32%	54%	-35%	51%	211%
IFNα2	3%	36%	10%	-19%	54%	31%	20%	61%	-15%	43%	47%
IFNλ2/3	-7%	29%	1%	-10%	57%	44%	11%	9%	22%	20%	36%
GMCSF	32%	183%	24%	1561%	98%	566%	98%	122%	33%	1591%	16706%
IFNβ	13%	59%	7%	130%	9047%	1626%	360%	187%	-31%	101%	289%
IL20	24%	1342%	41%	5137%	24%	3122%	242%	104%	2%	2464%	10328%
IFNγ	139%	2025%	265%	23720%	306%	5776%	803%	1168%	36%	6683%	91444%
Number of samples	35	15	13	3	1	3	6	1	9	14	22

Supplementary Table 6. Clinical characteristics of patients and controls included in the cell stimulation mass cytometry experiment. Abbreviations: HPC, healthy pediatric controls.

	MIS-C (N = 12)	**HPCs (N = 3)**
Age (years), median [IQR]	6.0 [4.0 - 11]	9.5 [6.0-12]
Male sex, n (%)	8 (66.7%)	2(66.7%)
Ethnicity		
Black	6 (50.0%)	0 (0%)
Asian	2 (16.7%)	0 (0%)
White	3 (25.0%)	3 (100%)
Other/Not known	1 (8.3%)	0 (0%)
Maximum CRP (mg/L), median [IQR]	220 [160 - 300]	-
Maximum Neutrophil count ($x10^9$/L), median [IQR]	14 [11 - 18]	-
Maximum Lymphocyte count ($x10^9$/L), median [IQR]	7.5 [5.0 - 12]	-
IVIG pre-mass cytometry sample, n(%)	5 (41.7%)	-
Steroids pre-mass cytometry sample, n(%)	10 (83.3%)	-
Monoclonal antibodies pre-mass cytometry sample, n(%)	3 (25.0%)	-
ITU, n (%)	10 (83.3%)	-
Shock, n (%)	9 (75.0%)	-
Inotropes, n (%)	9 (75.0%)	-
Invasive ventilation, n (%)	1 (8.3%)	-
Death, n (%)	0 (0%)	-
Length of hospital admission (days), median [IQR]	6.5 [5.0 - 8.0]	-
SARS-CoV-2 PCR positive, n (%)	0 (0%)	-
SARS-CoV-2 Serology positive, n (%)	10 (83%)	-

Supplementary Table 7. Strobe Checklist

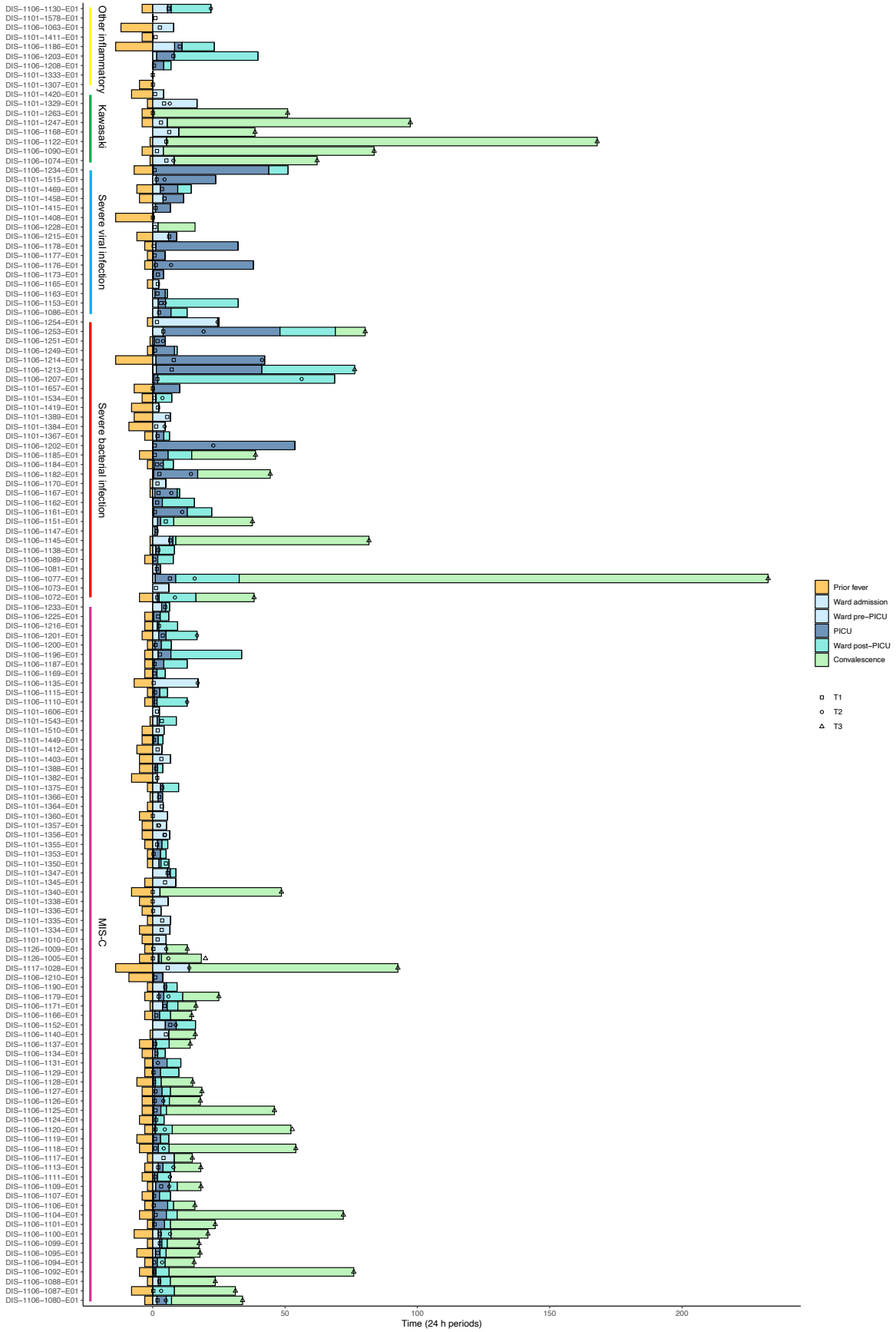
STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5–6	
Objectives	3	State specific objectives, including any prespecified hypotheses	5–6	
Methods				
Study design	4	Present key elements of study design early in the paper	5–6	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	17–18	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	17–18	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	17–18 and Suppl. Figure 1	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Table 1 and Figures	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	18–26 and Suppl. Figures 2–4.	

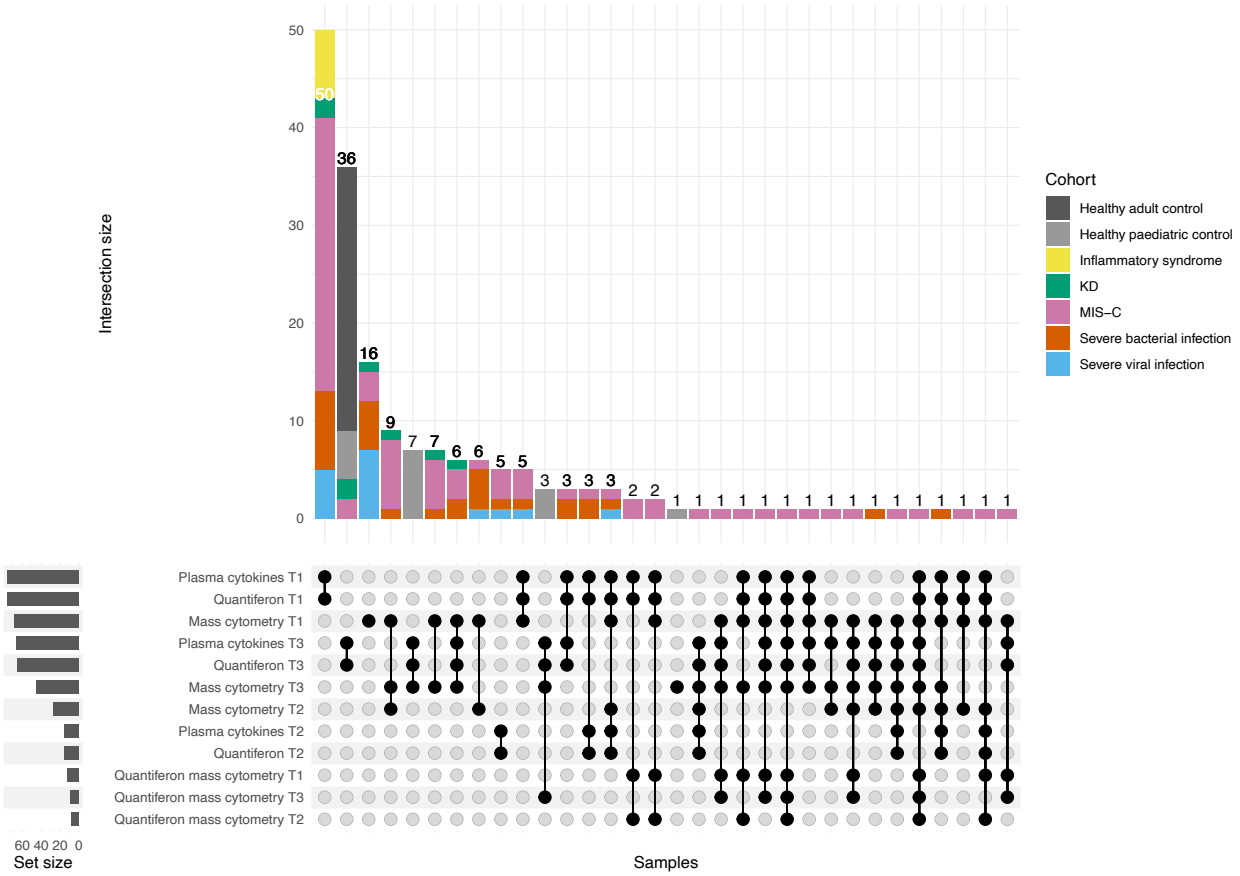
Bias	9	Describe any efforts to address potential sources of bias	5–6, 18–26
Study size	10	Explain how the study size was arrived at	5–6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	18–26
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	18–26
		(*b*) Describe any methods used to examine subgroups and interactions	18–26
		(*c*) Explain how missing data were addressed	18–26
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Suppl. Figure 1
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Suppl. Figures 1 and 2, Table 1
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Suppl. Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Suppl. Figure 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1

		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figures 1–5
		(*b*) Report category boundaries when continuous variables were categorized	Figures 1–5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figures 1–5
Discussion			
Key results	18	Summarise key results with reference to study objectives	14–16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14–16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14–16
Generalisability	21	Discuss the generalisability (external validity) of the study results	14–16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	37

Supplementary Figure 1. Duration of prior fever, admission to wards and paediatric intensive care units (PICU) and convalescence relative to sampling at T1, T2 and T3 for individual patients grouped by their severe febrile illness (all patients recruited to the study).



Supplementary Figure 2. Upset plot visualizing counts of patients/controls across different assays. The number of patients and controls analyzed by various combination of assays is shown by vertical bars on the top of the diagrams. The total number of patients analyzed with each assay is indicated by horizontal bars on the right of each panel. Acute (T1), defervescence (T2) and convalescence (T3) are shown. Abbreviations: KD, Kawasaki disease.



Supplementary Figure 3. Mass cytometry methods. **a–d,** Antibodies used for the mass cytometry methods. Antibodies were from Fluidigm (CA, USA) unless specified. Biolegend (CA, USA) antibodies were custom conjugated to metal tags at the at Guy's and St Thomas' NHS Foundation Trust. Antibodies used for analysis of cell proportions are denoted with an asterisk (also see gating strategy that details this analysis). Note CD8a and CD64 were chelated to the same metal tag but manually gated separately using CD3 as a marker for T cells. **e,** Manual gating strategy, and **f,** implementation of this strategy on a single representative patient (drawn from FlowJo, Beckmann-Coulter based directly on gating in Cytobank, Beckmann-Coulter). **g,** Expression of markers on cell populations from patients with acute MIS-C (other time points and severe febrile illnesses were examined in the same manner).

a, *Barcoding mastermixes*

Sample 1	CD45-**106Cd** CD45-**110Cd**
Sample 2	CD45-**106Cd** CD45-**198Pt**
Sample 3	CD45-**106Cd** CD45-**89Y**
Sample 4	CD45-**110Cd** **CD45-198Pt**
Sample 5	CD45-**110Cd** CD45-**89Y**
Sample 6	CD45-**198Pt** CD45-**89Y**

b, *Cell surface mastermix*

Cell surface stain	Metal Tag
CD3 UCHT1 (Biolegend)*	111Cd
CD4 RPA-T4 (Biolegend)*	113Cd
CD25 (2A3)*	169Tm
CD127/IL-7Ra (A019D5)*	176Yb
CD45RO (UCHL1)*	149Sm
HLA-DR (G46- 6)*	151Eu
CD197/CCR7 (G043H7)*	167Er
CD45RA (HI100)*	155Gd
CD38 HB-7 HIT2 (Biolegend)*	161Dy
CD8a RPA-T8 (Biolegend)*	116Cd
TCRgd (11F2)*	152Sm
CD19 HIB19 (Biolegend)*	112Cd
CD14 RMO52 M5E2 (Biolegend)*	114Cd
CD15 W6D3 (Biolegend)*	142Nd
CD16 (3G8)*	209Bi
CD20 (2H7)*	171Yb
CD11c (Bu15)*	159Tb
CD27 (L128)*	162Dy
CD5 UCHT2 (Biolegend)	141Pr
CD64 10.1 (Biolegend)	116Cd
CD278/ICOS (C398.4A)	143Nd
CD11b/Mac-1 (ICRF44)	144Nd
CD223/LAG- 3 (11C3C65)	150Nd
CD10 HI10a	156Gd
CD134/OX40 (ACT35)	158Gd
CD95/Fas DX2 (Biolegend)	163Dy
CD161 (HP- 3G10)	164Dy
CD206/MMR (15-2)	168Er
CD279/PD-1 (EH12.2H7)	174Yb
CD28 (CD28.2)	160Gd

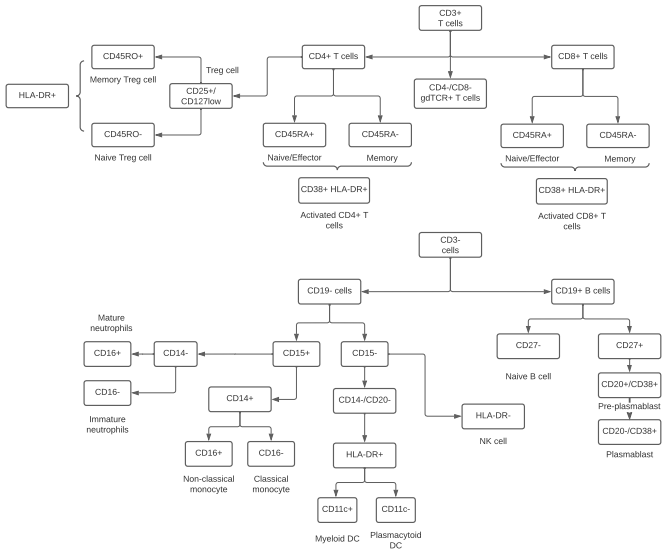
c, *Intracellular cytokine mastermix*

Intracellular cytokines	Metal Tag
IL-6 (MQ2- 13A5)	154Sm
IL-17A (BL168)	148Nd
IFNg (B27)	165Ho
TNFa (MAb11)	146Nd
IL-2 MQ1-17H12 (Biolegend)	145Nd
CD152/CTLA-4 (14D3)	170Er

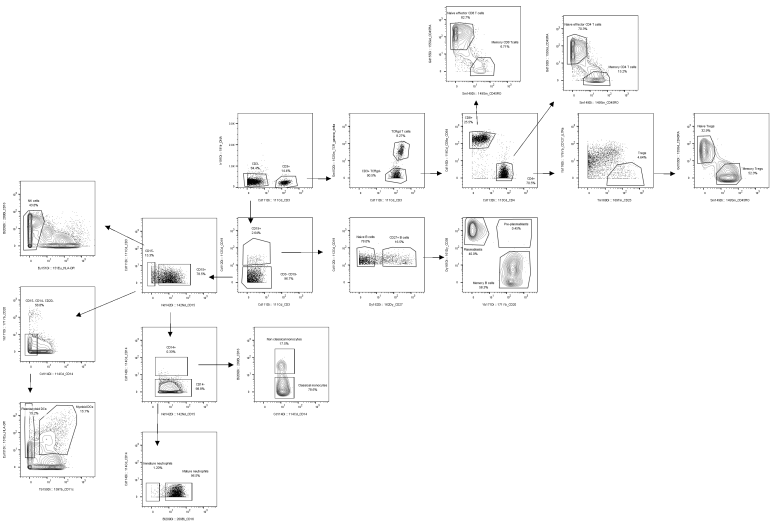
d, *Phosphorylated marker mastermix*

Phosphorylated targets	Metal Tag
pStat5 [Y694] (47)	147Sm
pStat1 [Y701] (4a)	153Eu
pS6 [S235/S236] (N7- 548)	175Lu
pNFkBp65 [S529] (K10x)	166Er

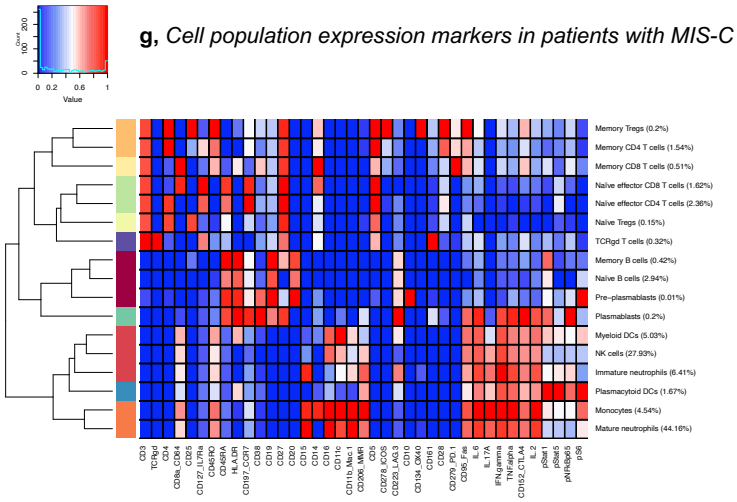
e, *Manual gating of cell populations*



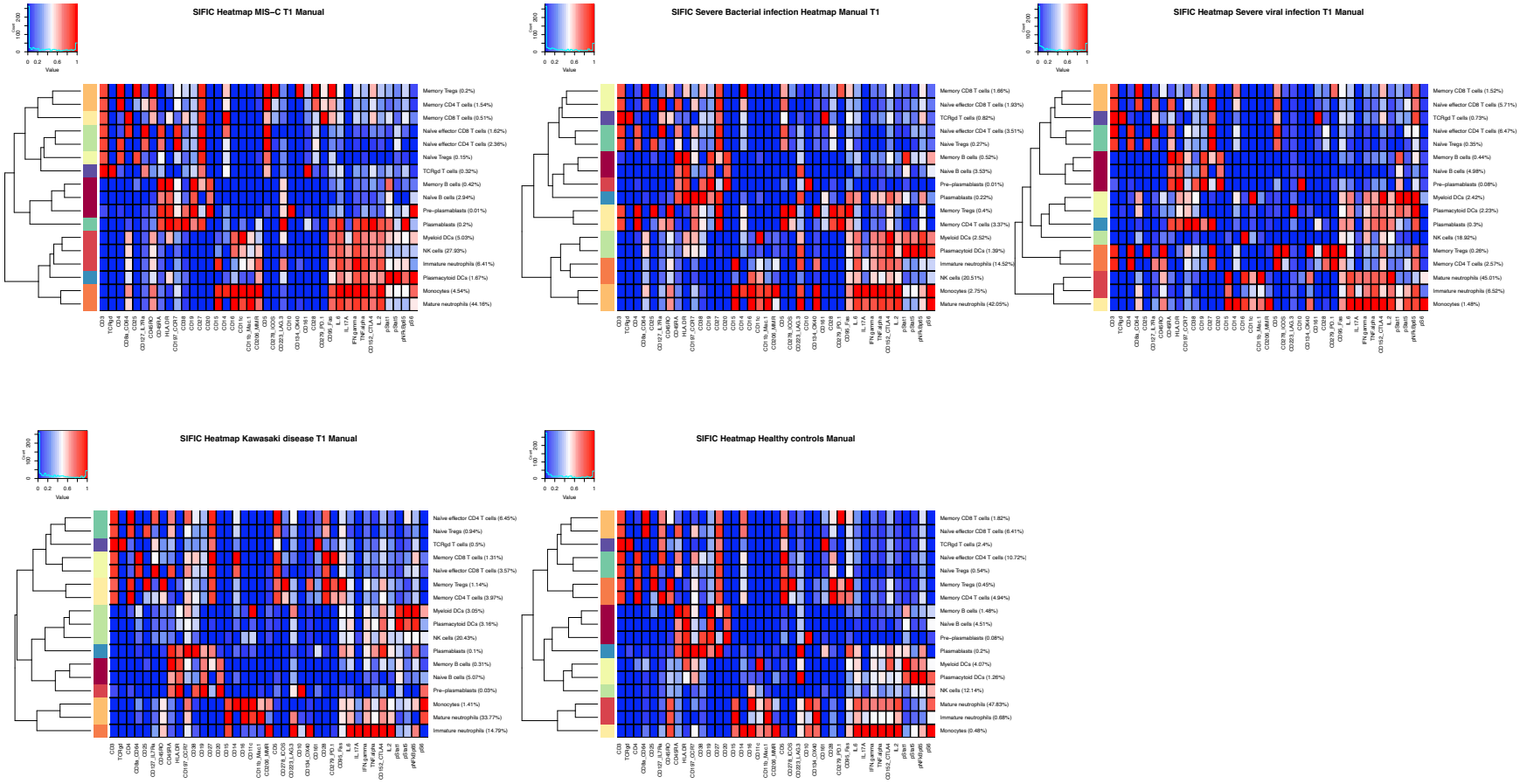
f, *Implementation of manual gating on a single patient with acute MIS-C*



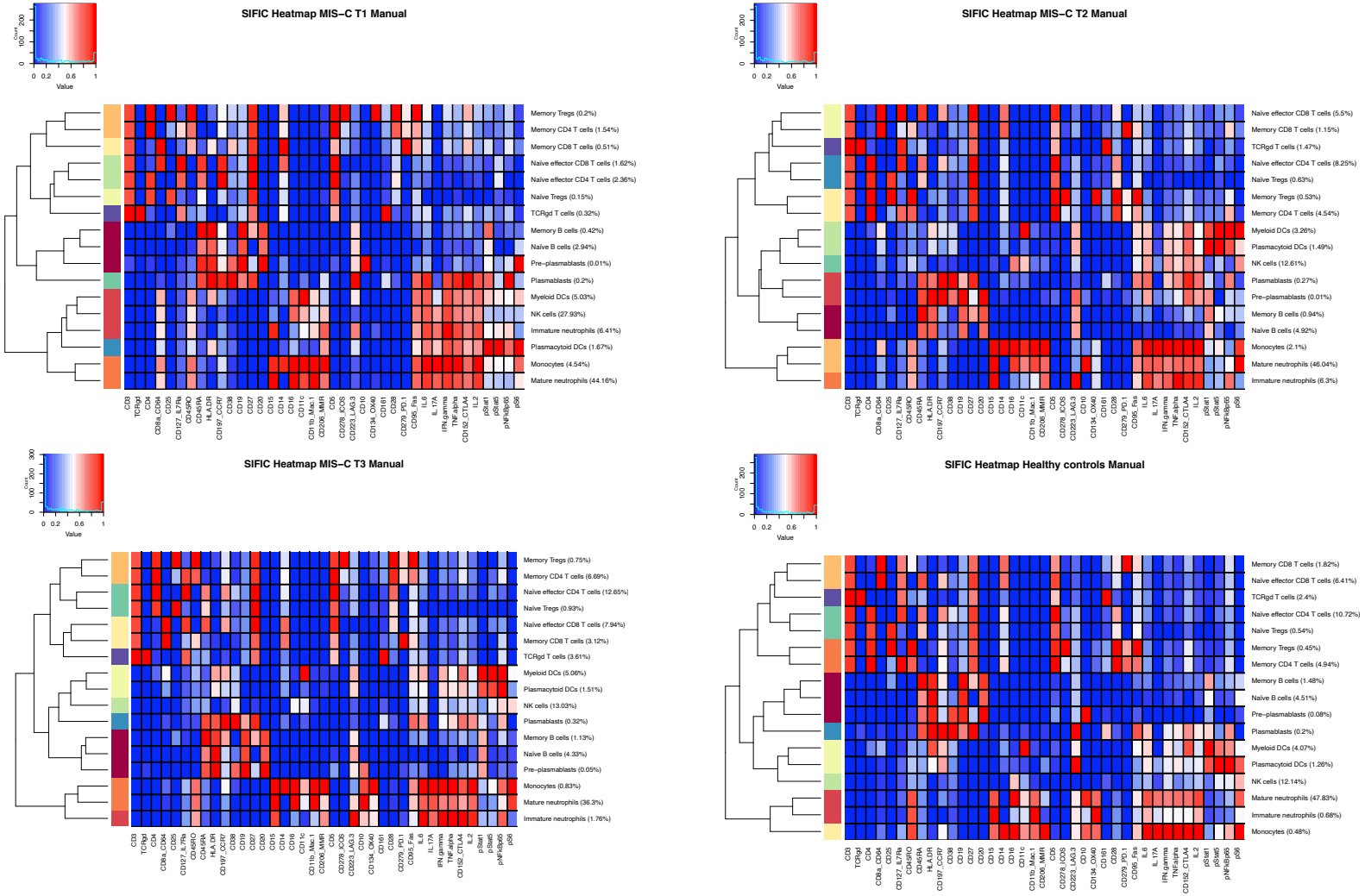
g, *Cell population expression markers in patients with MIS-C*



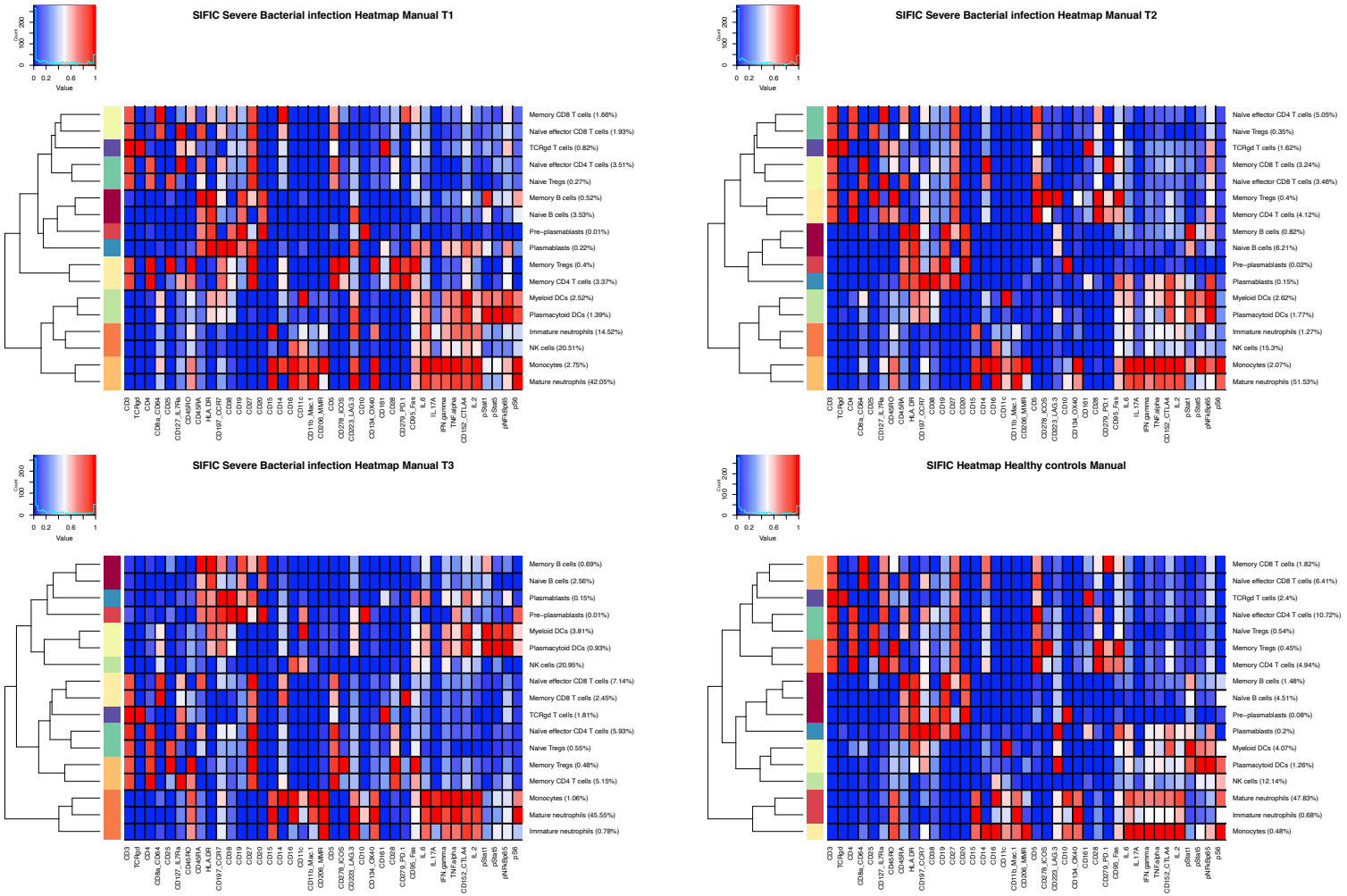
Supplementary Figure 4. Immune cell populations and expression of markers by mass cytometry. a, Heatmaps displaying hierarchical clustering of immune cell populations from manually gated mass cytometry data in children with acute (time point 1, T1) multisystem inflammatory syndrome in children (MIS-C, n=35), severe bacterial infection (SBI, n=17), severe viral infection (SVI, n=10), Kawasaki disease (KD, n=4) and healthy paediatric controls (HPC, n=10), used in the main manuscript. Cells are coloured by the expression of cell markers in an immune cell population, normalised to the expression of that marker across all immune cells analysed. Each heatmap describes a different severe febrile illness at timepoint 1.



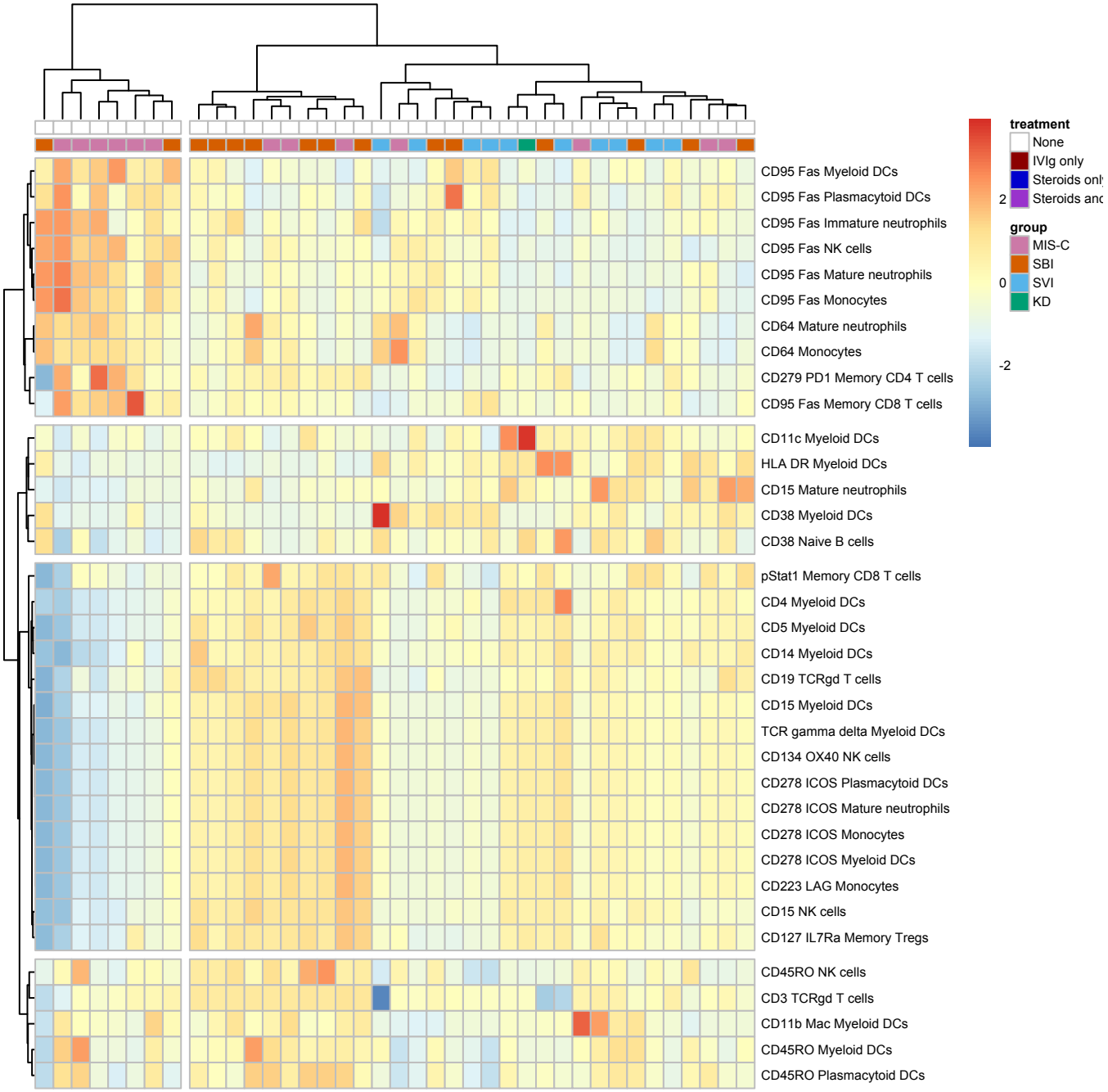
b, Heatmaps displaying hierarchical clustering of immune cell populations from manually gated mass cytometry data in children with MIS-C at time point 1 (T1, acute febrile within 48 hours of admission, n=35), time point 2 (T2, defervescence with CRP concentration <100 mg/l, n=16) and timepoint 3 (T3, convalescence at follow-up clinic, n=26) and healthy paediatric controls (n=10). Cells are coloured by expression as for **a** (above).



c, Heatmaps displaying hierarchical clustering of immune cell populations from manually gated mass cytometry data in children with severe bacterial infection (SBI) at time point 1 (T1, acute febrile within 48 hours of admission, n=17), time point 2 (T2, defervescence with CRP concentration <100 mg/l, n=8) and timepoint 3 (T3, convalescence at follow-up clinic, n=6) and healthy paediatric controls (n=10). Cells are coloured by expression as for **a** and **b** (above).



Supplementary Figure 5. Hierarchical clustering for children with no immunomodulation at T1 sampling. Heatmap displaying protein expression and cell proportion data that associated with disease group (**b**) with disease groups clustered as columns (Ward's hierarchical clustering).

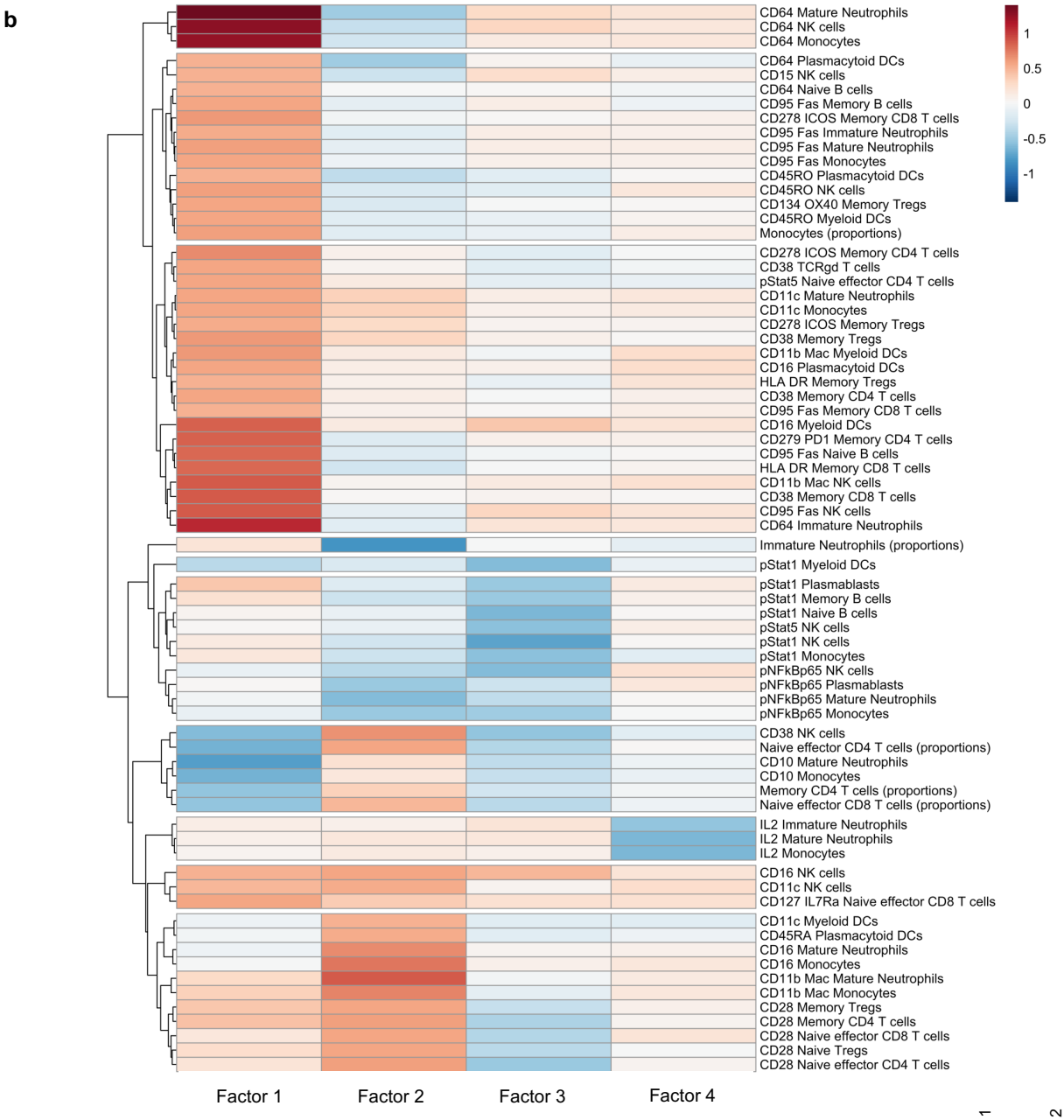


Supplementary Figure 6. MOFA of immune features from immunophenotyping shows differences between disease groups and key factors of protein expression and cell proportion features in acute (T1) disease and over the trajectory of illness. **a,** Variance in data by MOFA Factor, and contribution to the variance by the immune cell proportion data and the cell population expression data. **b,** Relative contribution of features to the top four factors derived from MOFA. **c,** Correlation of Factors to disease group and time point. **d,** Correlation of Factors to Cluster 1 and 2 (from Figure 2c) *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Data shown are normalized to the median value for HPCs.

a

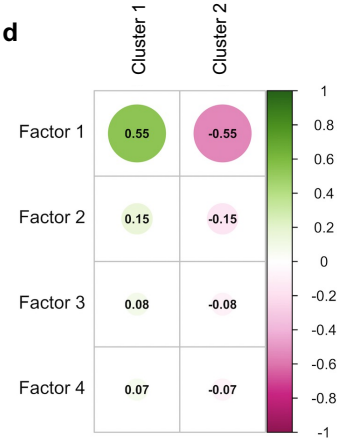
	Variance explained		
	Expression	**Proportions**	**Total by Factor**
Factor 1	17.8%	18.2%	36.0%
Factor 2	8.72%	15.7%	24.4%
Factor 3	6.34%	6.17%	3.84%
Factor 4	4.82%	1.51%	12.5%
Factor 5	2.18%	2.60%	4.78%
Total	5.00%	10.3%	81.5%

b

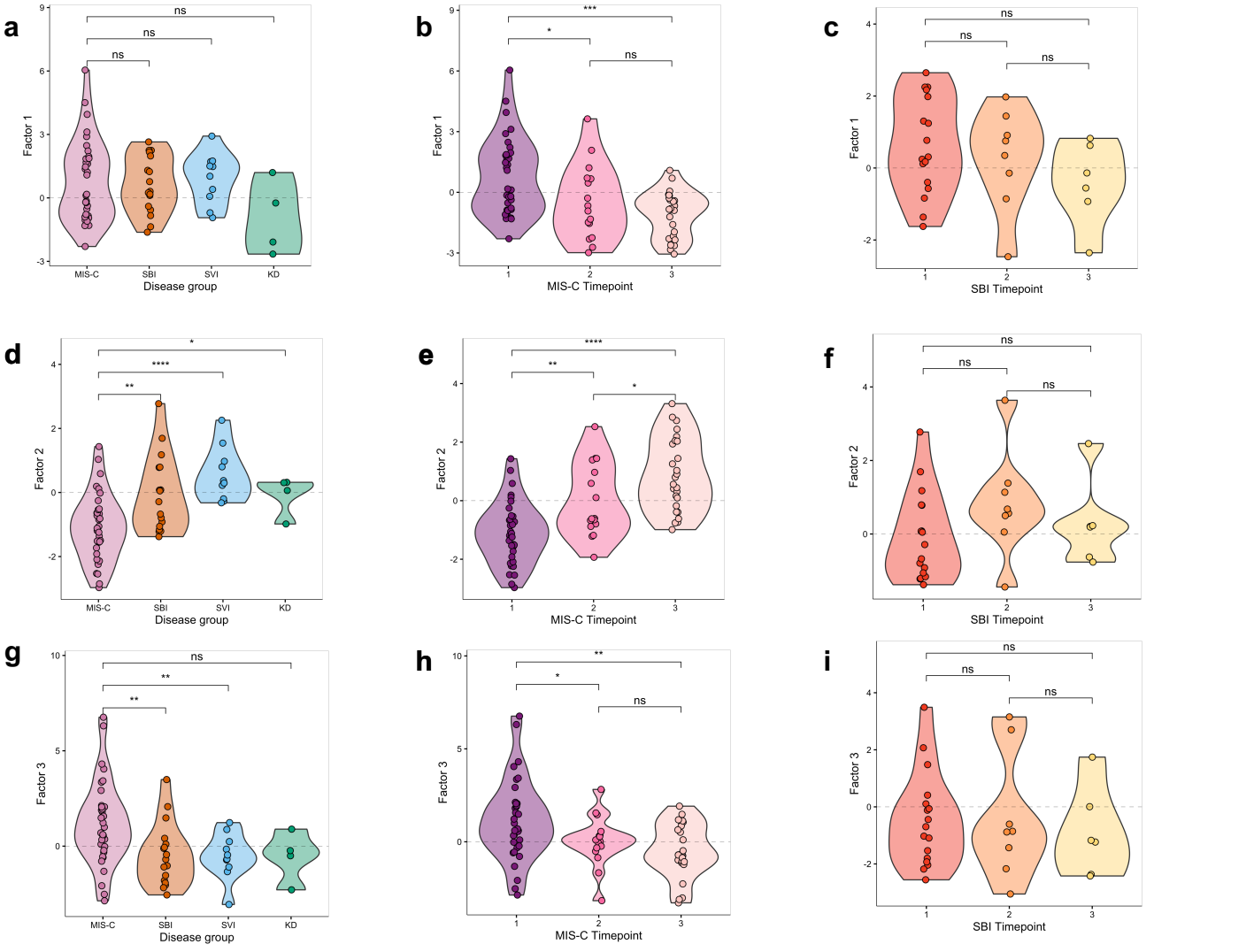


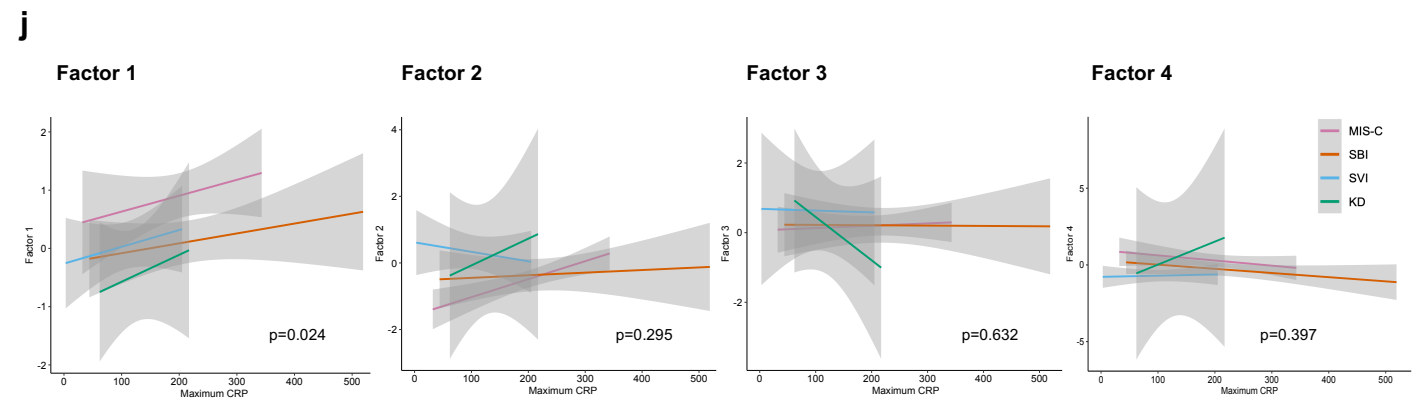
c

d



Supplementary Figure 7. Factors 1-3 by disease groups and timepoints. **a,** Factor 1 by illness group; **b,** Factor 1 for MIS-C patients over trajectory of illness; **c,** Factor 1 for SBI over trajectory of illness. **d,** Factor 2 by disease group; **e,** Factor 2 for MIS-C patients over trajectory of illness; **f,** Factor 2 for SBI over trajectory of illness. **g,** Factor 3 by disease group; **h,** Factor 3 for MIS-C patients over trajectory of illness; **i,** Factor 3 for SBI over trajectory of illness. **j,** GLM for association of inflammation severity (C-reactive protein concentration) with Factors 1–4 by illness group.

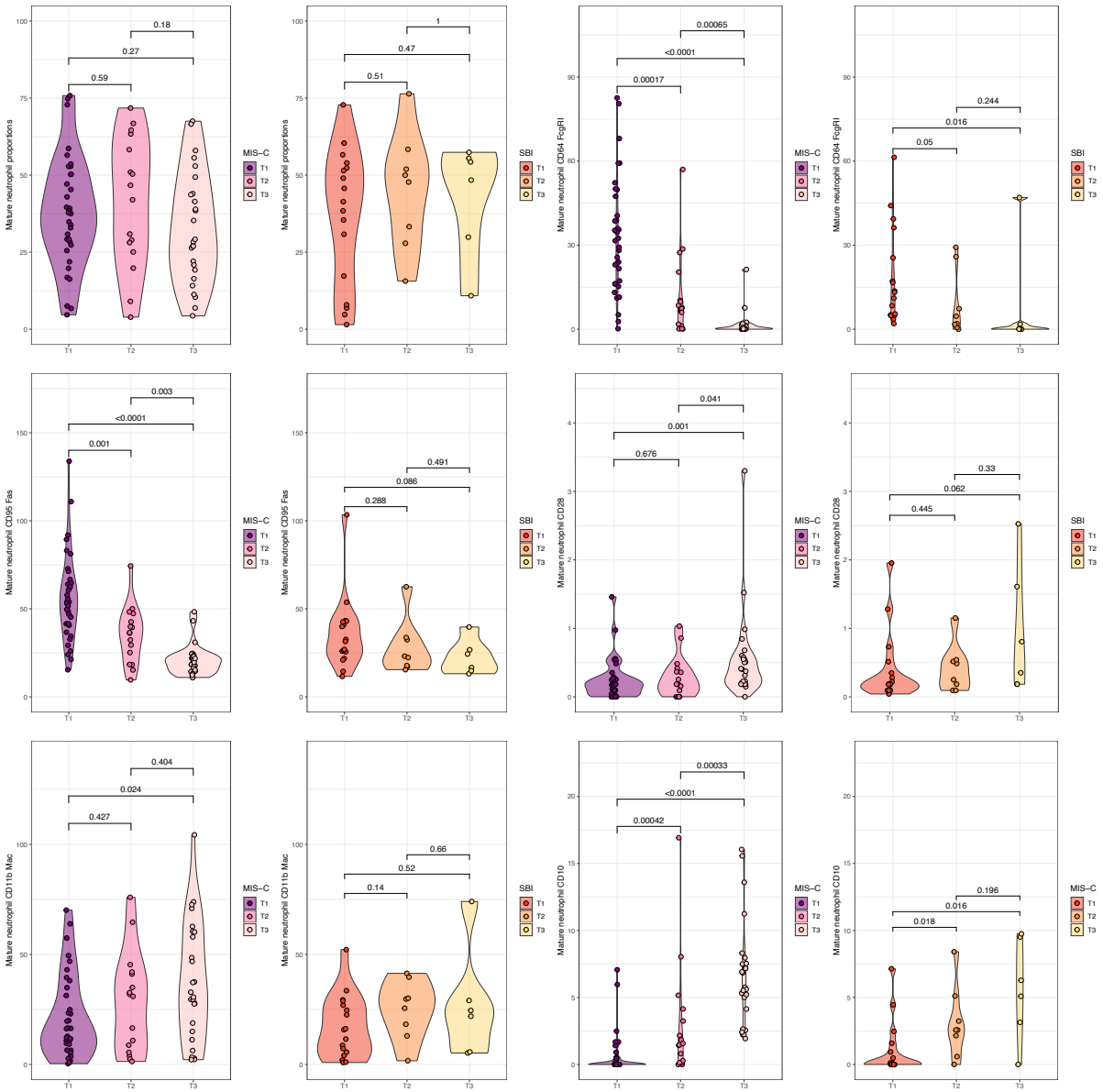




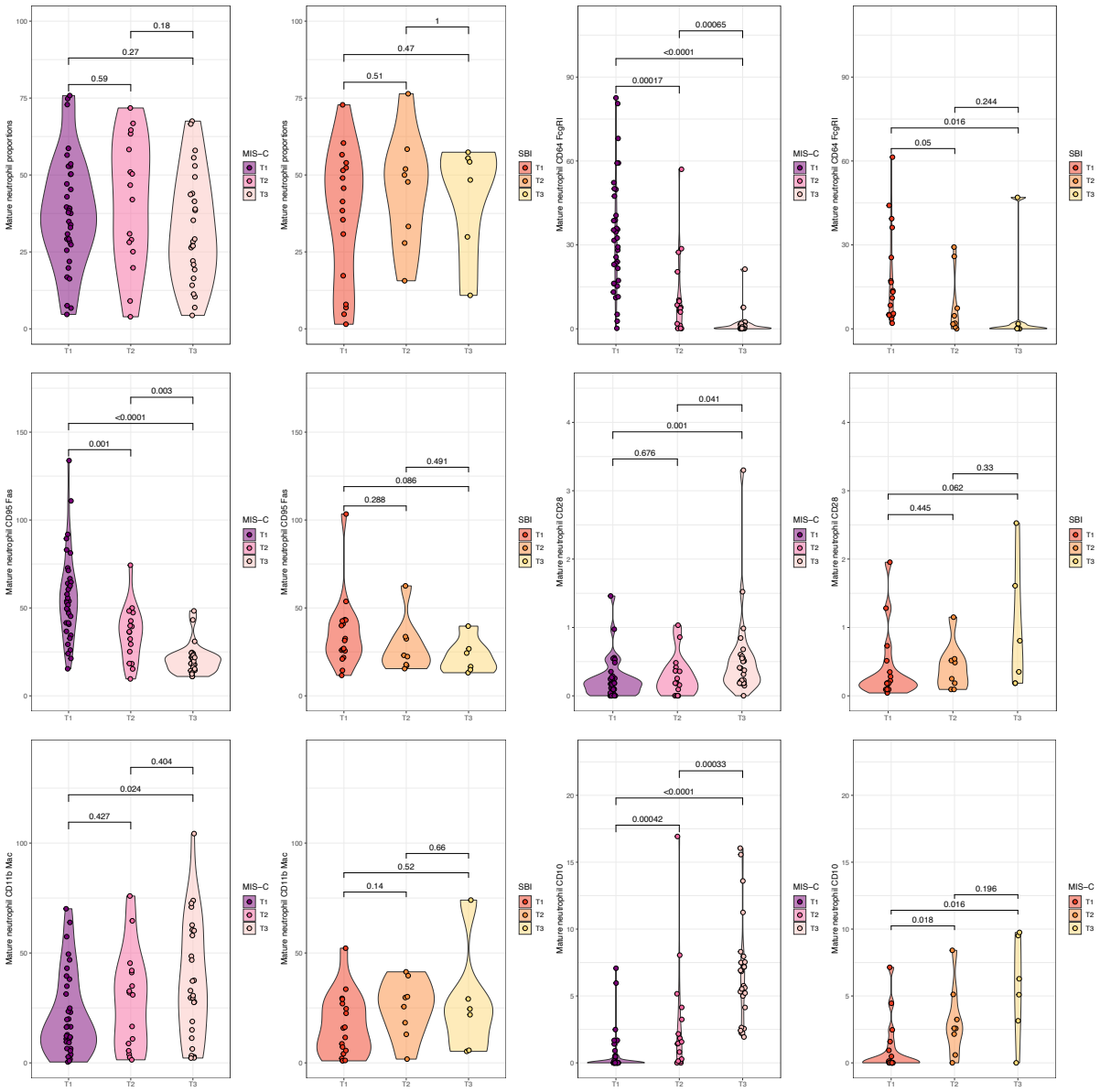
Supplementary Figure 8. Markers of immune cell activation and return to baseline in innate immune cells (mature neutrophils, immature neutrophils, monocytes, myeloid DCs, plasmacytoid DCs, CD4 memory T cells, CD8 memory T cells, memory regulatory T cells). Timepoints included are T1 (acute), T2 (defervescence) and T3 (convalescence). For all figures, patients with MIS-C are represented in shades of purple for T1–T3 and patients with SBI are represented with shades of orange for T1–T3. P values for pairwise-comparisons across time are using Wilcoxon rank sum testing.

Innate immune cells

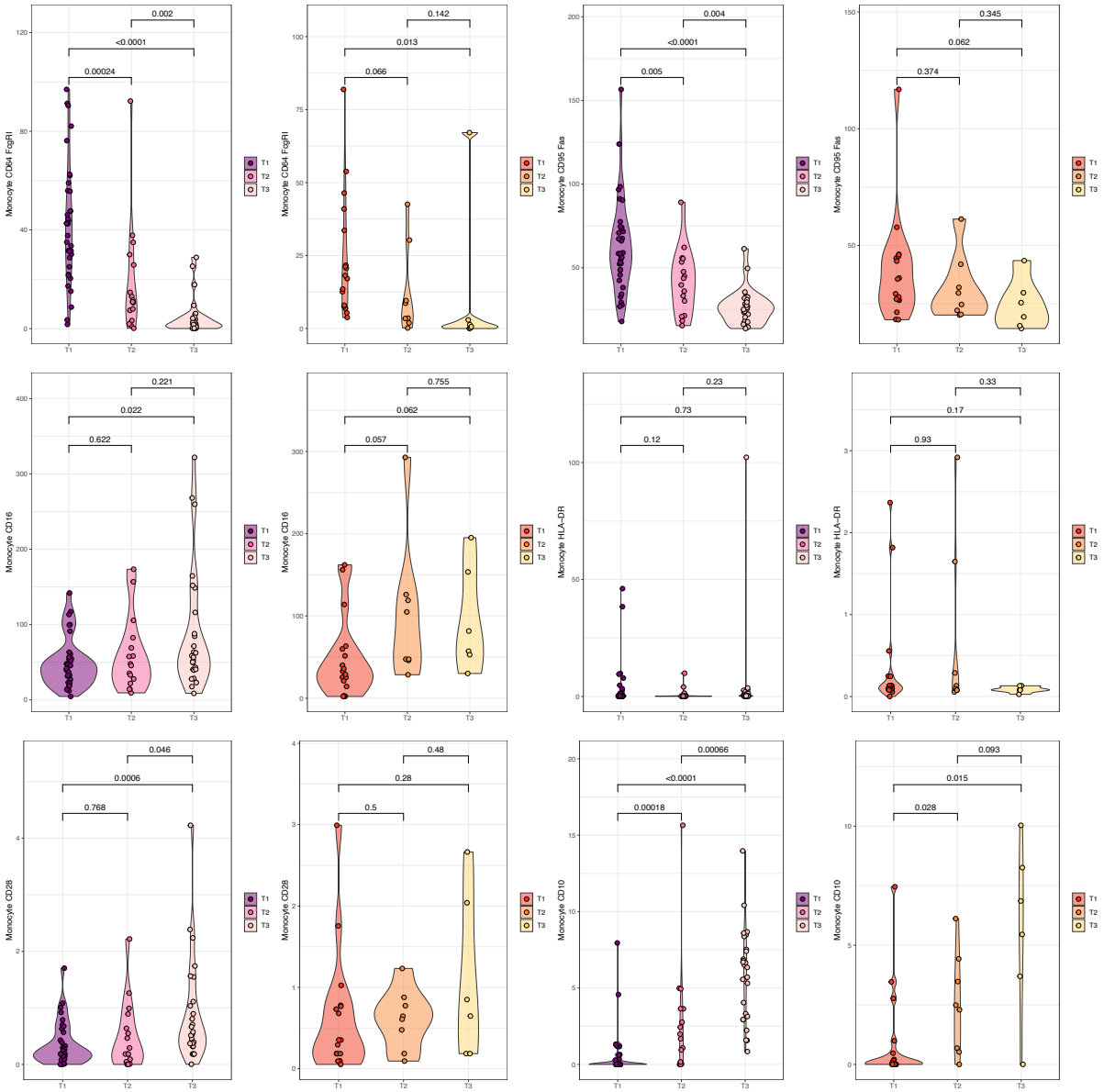
a, Mature neutrophils. Mature neutrophil proportions, CD64 FcγRI, CD95 Fas, CD28, CD11b Mac, CD10.



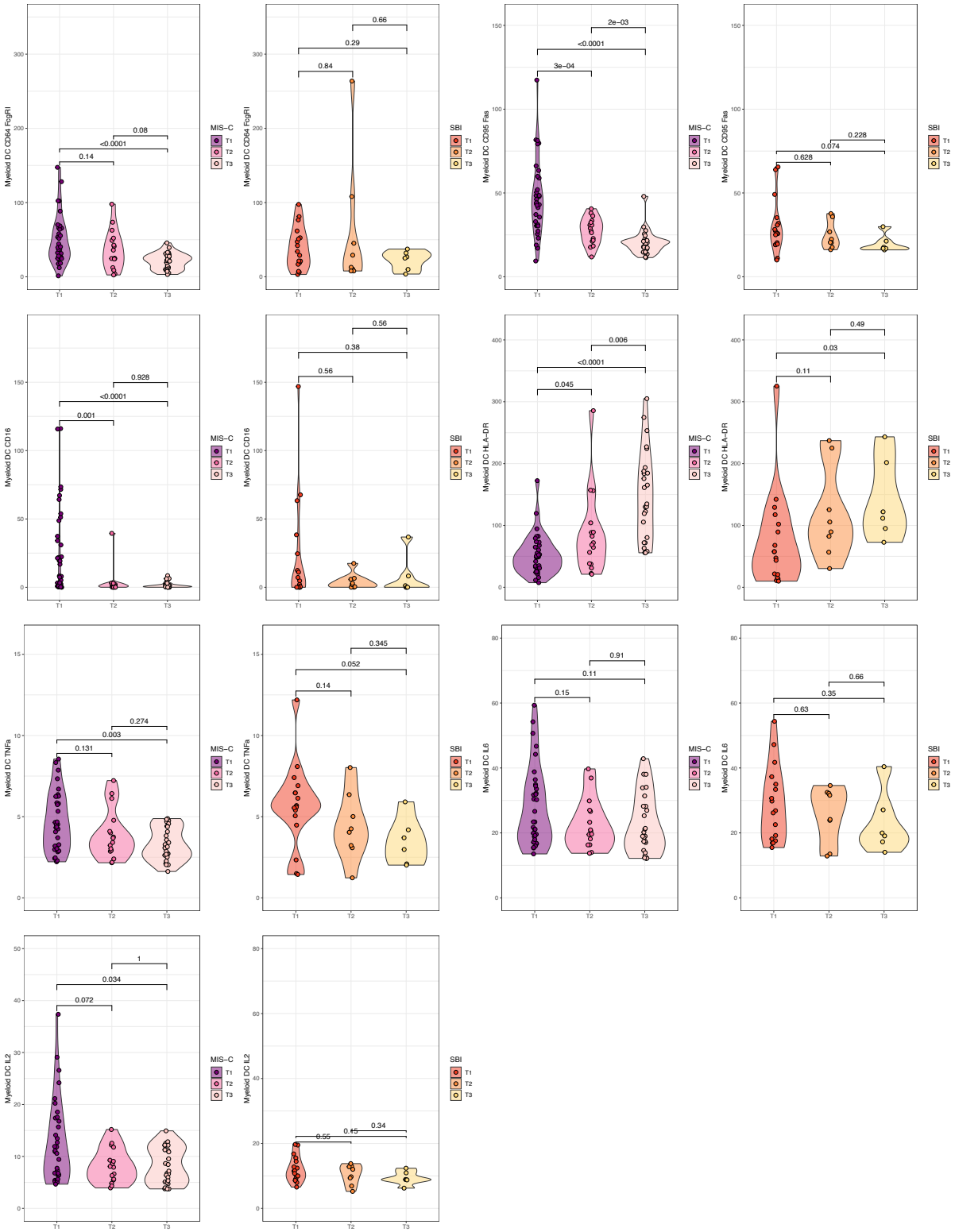
b, Immature neutrophils. Immature neutrophil proportions, CD64 FcγRI, CD95 Fas, CD28, CD11b Mac, CD10.



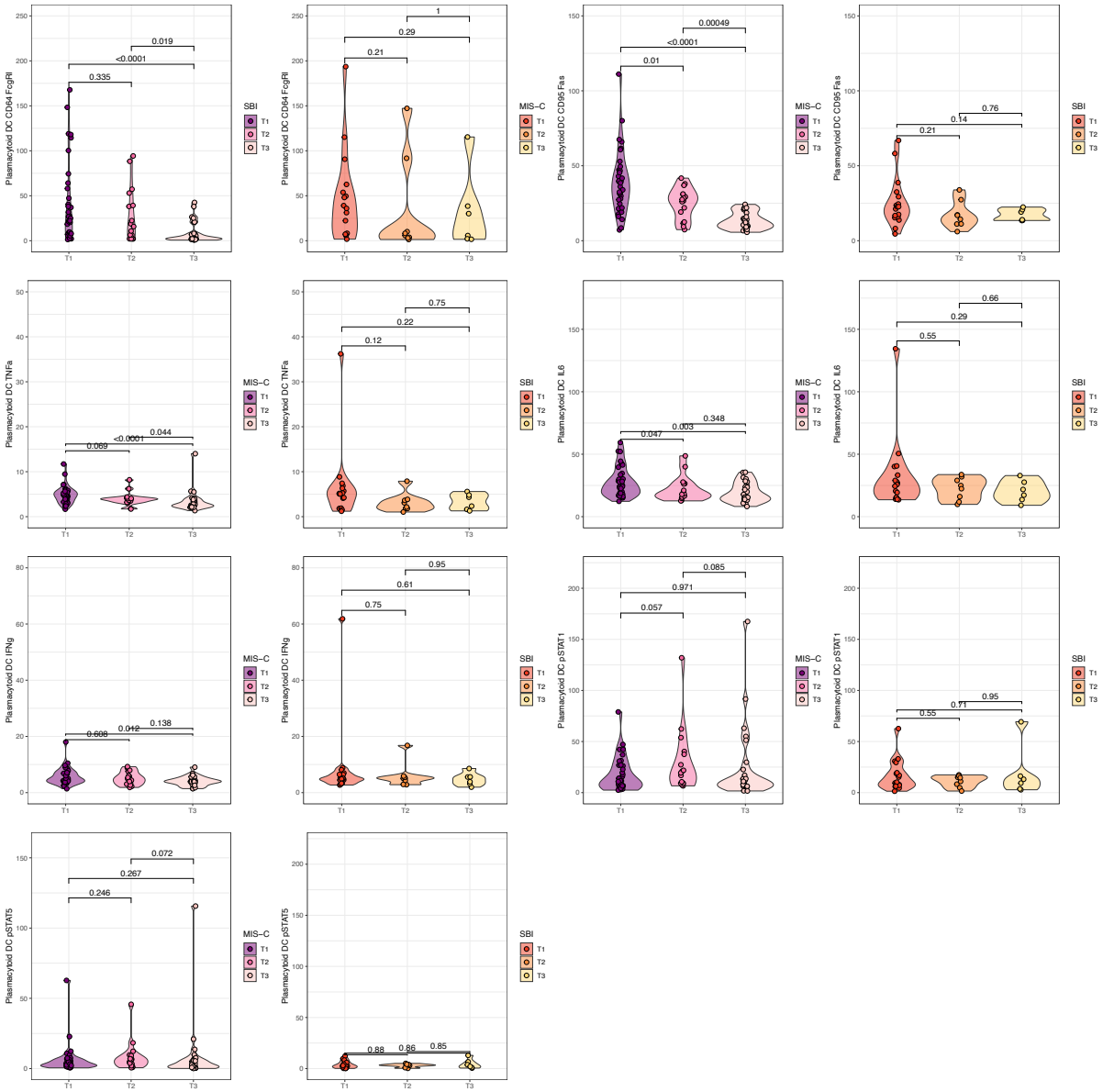
c, Monocytes. CD64 FcγRI, CD95 Fas, CD16, HLA-DR, CD28, CD10.



d, Myeloid DCs. CD64 FcγRI, CD95 Fas, CD16, HLA-DR, TNFα, IL6, IL2.

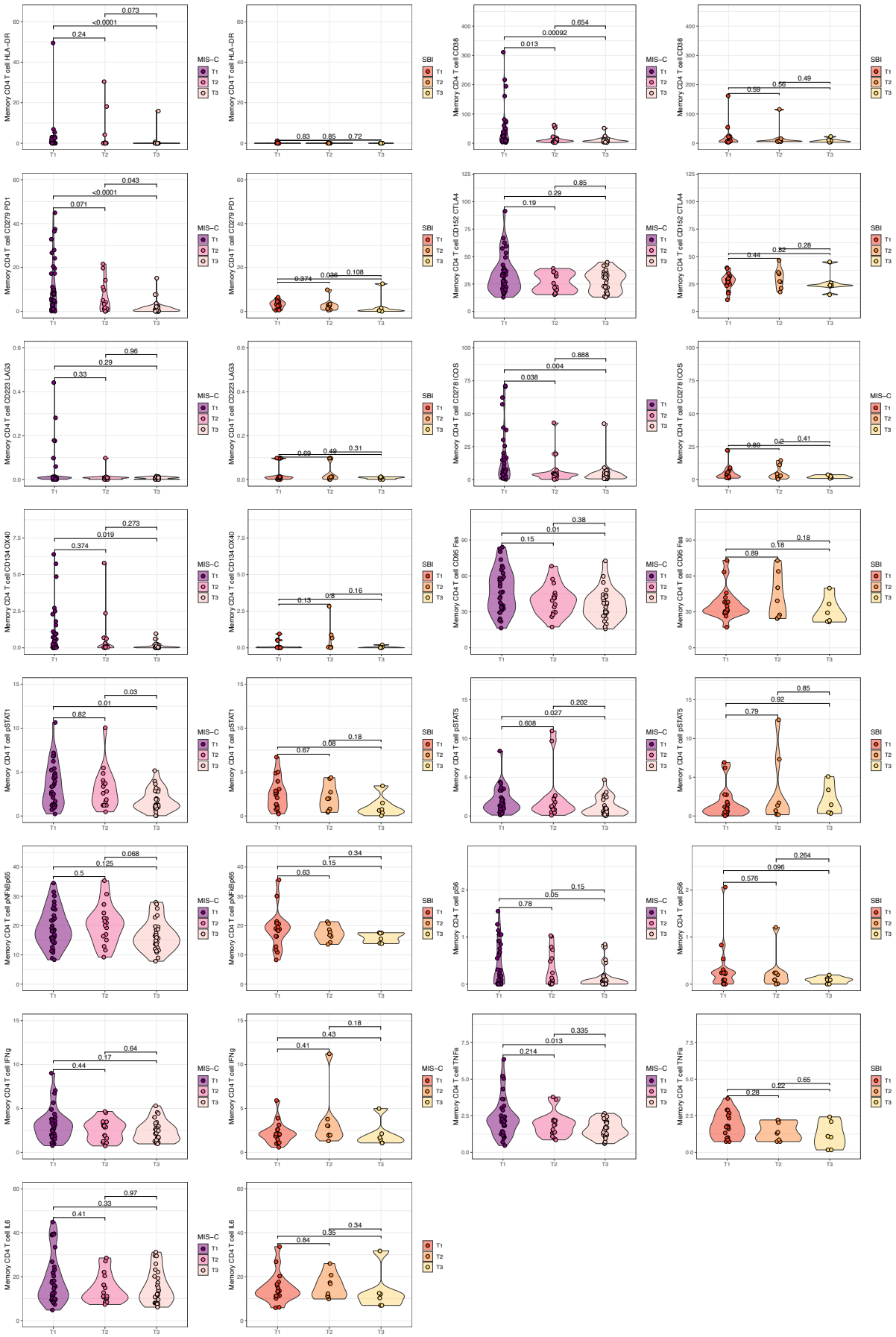


e, Plasmacytoid DCs. CD64 FcγRI, CD95 Fas, TNFα, IL6, IFNγ, pSTAT1, pSTAT5.

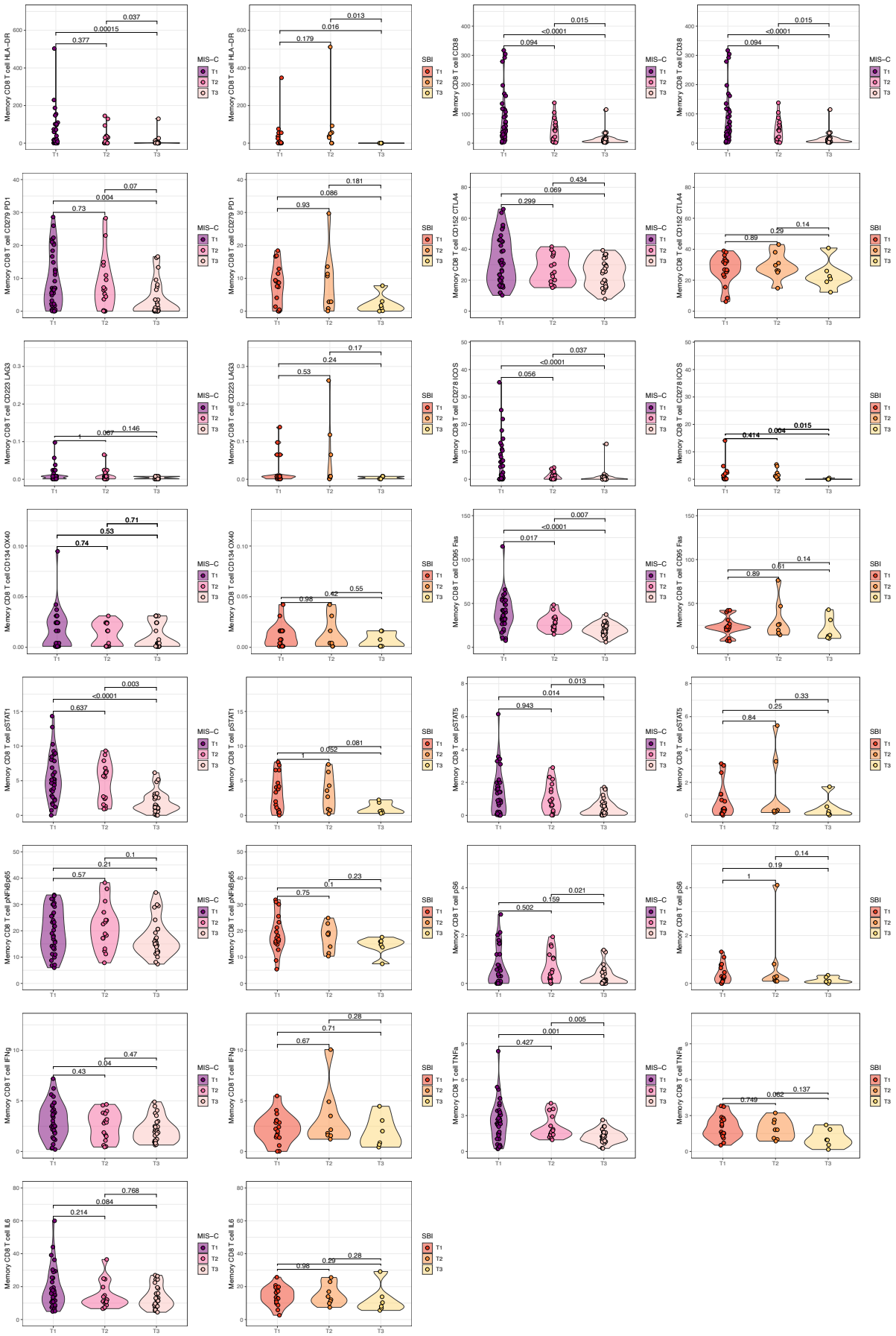


Adaptive immune cells

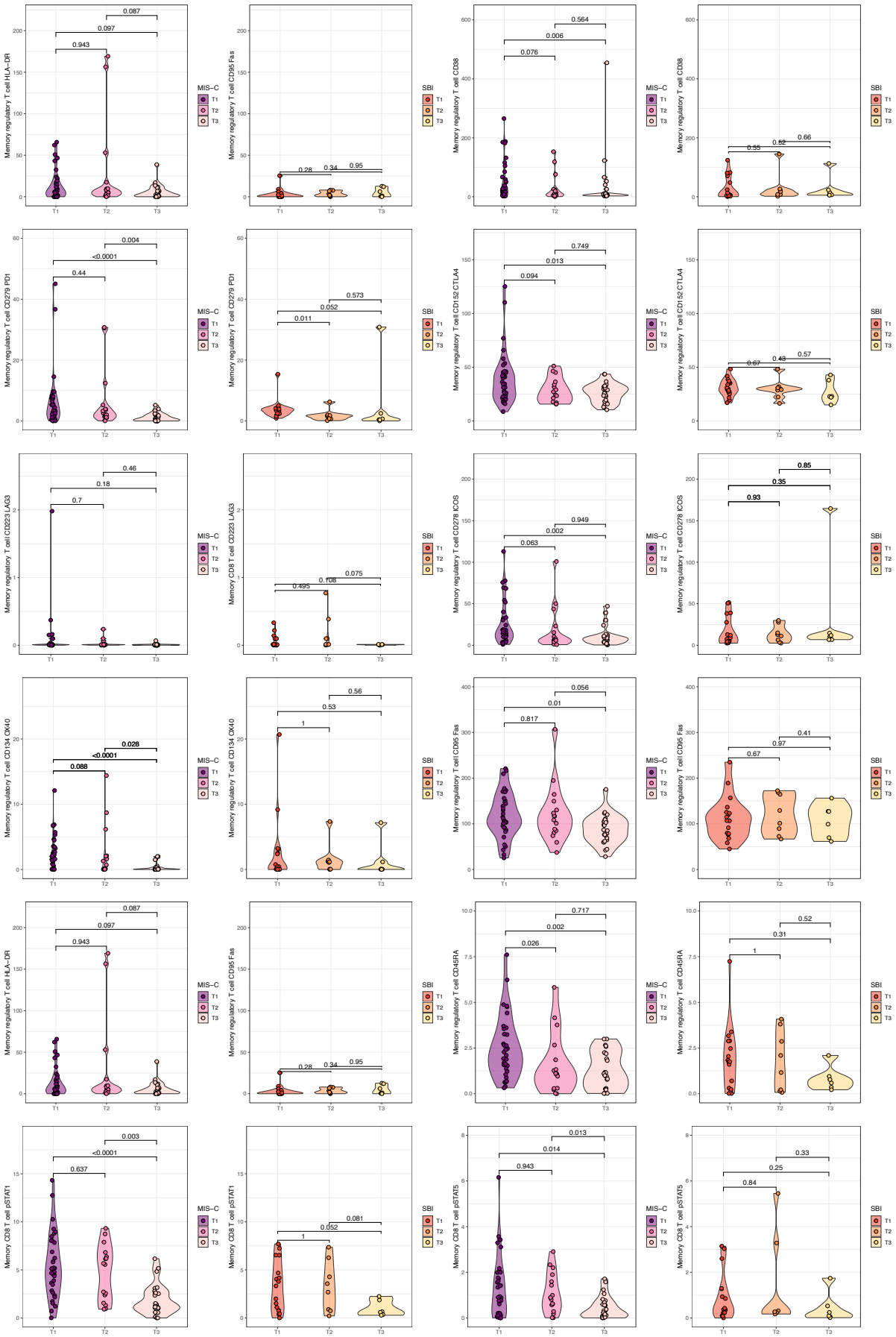
f, Memory CD4 T cells. HLA-DR, CD38, CD279 PD1, CD152 CTLA4, CD223 LAG3, CD278 ICOS, CD134 OX40, CD95 Fas, pSTAT1, pSTAT5, pNFκBp65, PS6, IFNγ, TNFα, IL6


Memory CD4 T cell HLA−DR
0.073
<0.0001
0.24
0.83
0.85
0.72
Memory CD4 T cell CD38
0.654
0.00092
0.013
0.59
0.56
0.49
Memory CD4 T cell CD279 PD1
0.043
<0.0001
0.071
0.374
0.036
0.108
Memory CD4 T cell CD152 CTLA4
0.85
0.29
0.19
0.44
0.82
0.28
Memory CD4 T cell CD223 LAG3
0.96
0.29
0.33
0.69
0.49
0.31
Memory CD4 T cell CD278 ICOS
0.888
0.004
0.038
0.89
0.2
0.41
Memory CD4 T cell CD134 OX40
0.273
0.019
0.374
0.13
0.8
0.16
Memory CD4 T cell CD95 Fas
0.38
0.01
0.15
0.89
0.18
0.18
Memory CD4 T cell pSTAT1
0.03
0.01
0.82
0.67
0.08
0.18
Memory CD4 T cell pSTAT5
0.202
0.027
0.608
0.85
0.92
0.79
Memory CD4 T cell pNFkBp65
0.068
0.125
0.5
0.63
0.15
0.34
Memory CD4 T cell pS6
0.15
0.05
0.78
0.264
0.096
0.576
Memory CD4 T cell IFNg
0.64
0.17
0.44
0.41
0.43
0.18
Memory CD4 T cell TNFa
0.335
0.013
0.214
0.65
0.22
0.28
Memory CD4 T cell IL6
0.97
0.33
0.41
0.34
0.55
0.84
MIS−C
SBI
T1
T2
T3

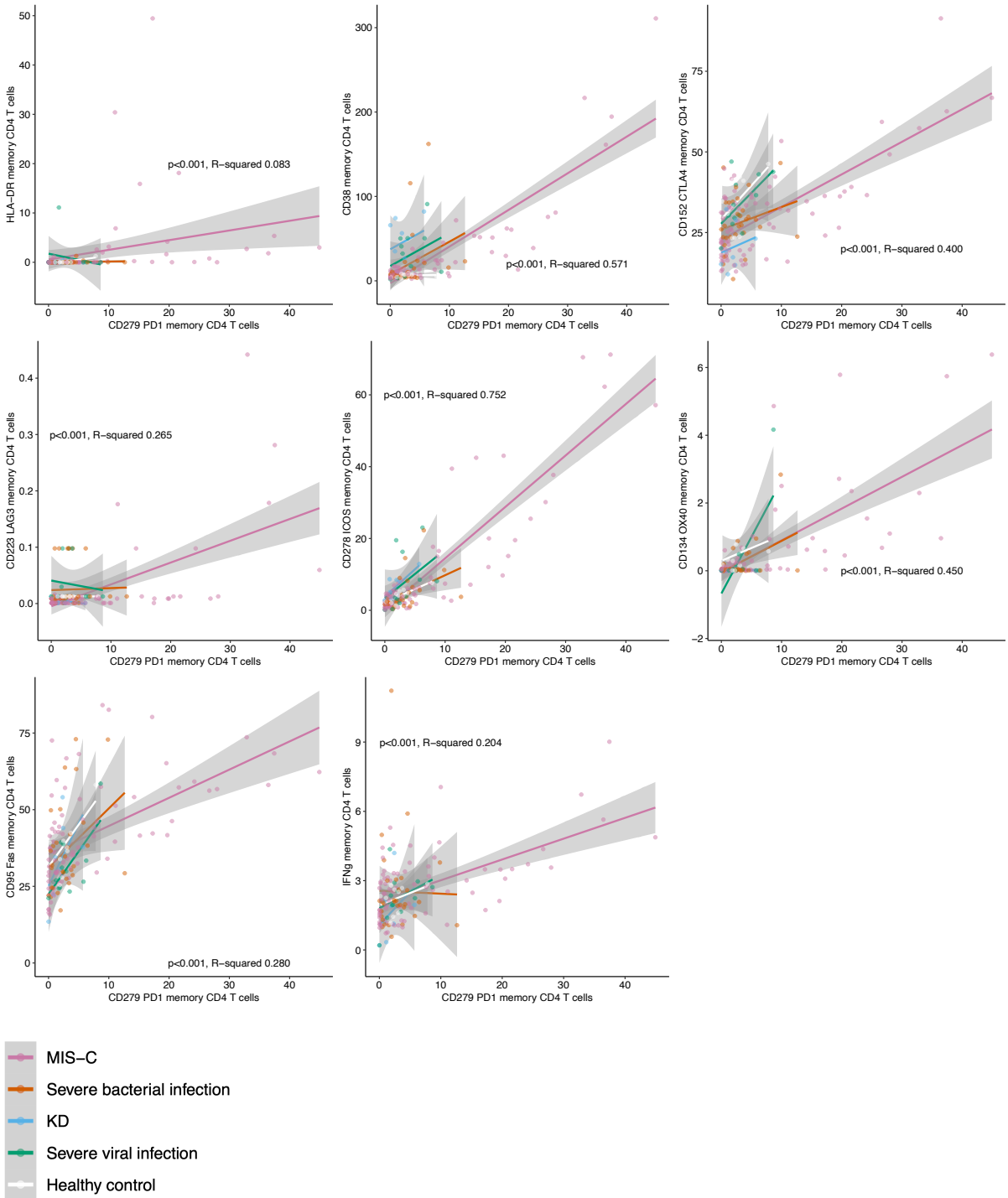
g, Memory CD8 T cells. HLA-DR, CD38, CD279 PD1, CD152 CTLA4, CD223 LAG3, CD278 ICOS, CD134 OX40, CD95 Fas, pSTAT1, pSTAT5, pNFκBp65, PS6, IFNγ, TNFα, IL6.


Memory CD8 T cell HLA−DR
Memory CD8 T cell CD279 PD1
Memory CD8 T cell CD223 LAG3
Memory CD8 T cell CD134 OX40
Memory CD8 T cell pSTAT1
Memory CD8 T cell pNFkBp65
Memory CD8 T cell IFNg
Memory CD8 T cell IL6
Memory CD8 T cell CD38
Memory CD8 T cell CD152 CTLA4
Memory CD8 T cell CD278 ICOS
Memory CD8 T cell CD95 Fas
Memory CD8 T cell pSTAT5
Memory CD8 T cell pS6
Memory CD8 T cell TNFa
MIS−C
SBI
T1
T2
T3

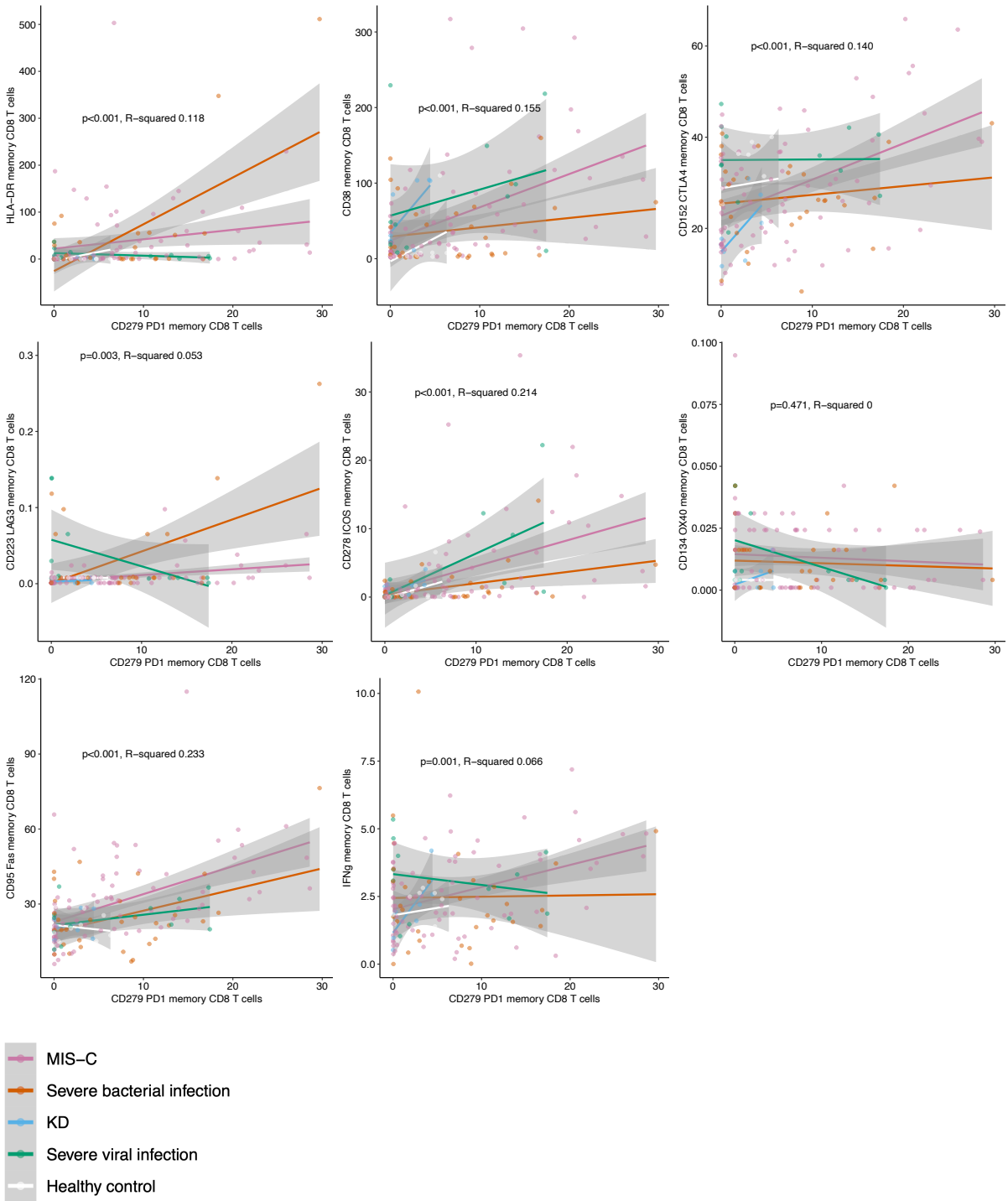
h, Memory regulatory T cells. HLA-DR, CD38, CD279 PD1, CD152 CTLA4, CD223 LAG3, CD278 ICOS, CD134 OX40, CD95 Fas, HLA-DR, CD45RApSTAT1, pSTAT5.


Memory regulatory T cell HLA−DR
Memory regulatory T cell CD95 Fas
Memory regulatory T cell CD38
Memory regulatory T cell CD279 PD1
Memory regulatory T cell CD152 CTLA4
Memory regulatory T cell CD223 LAG3
Memory CD8 T cell CD223 LAG3
Memory regulatory T cell CD278 ICOS
Memory regulatory T cell CD134 OX40
Memory regulatory T cell CD45RA
Memory CD8 T cell pSTAT1
Memory CD8 T cell pSTAT5
MIS−C
SBI
T1
T2
T3

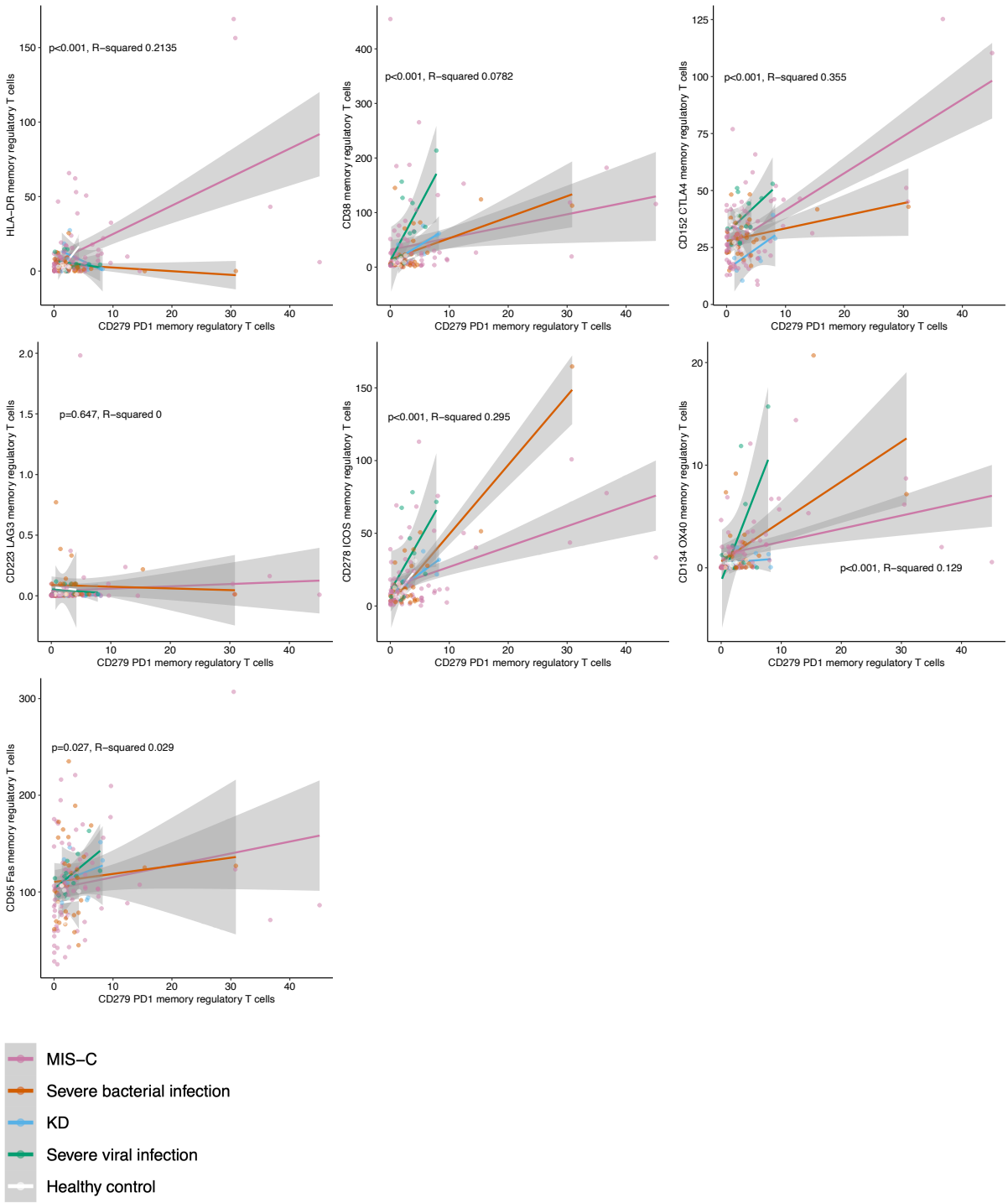
Supplementary Figure 9. a, Markers of T cell activation, exhaustion and apoptosis in memory CD4 T cells. Co-expression of HLA-DR, CD38, CD279 (PD-1) with CD152 (CTLA4), CD223 (LAG3), CD278 (ICOS), CD134 (OX40), CD95 (Fas), and intracellular IFNγ expression in memory CD4 T cells in all children with at T1, T2 and T3 (colored by illness group). P-values and adjusted R-squared values are for all observations (regardless of illness group).



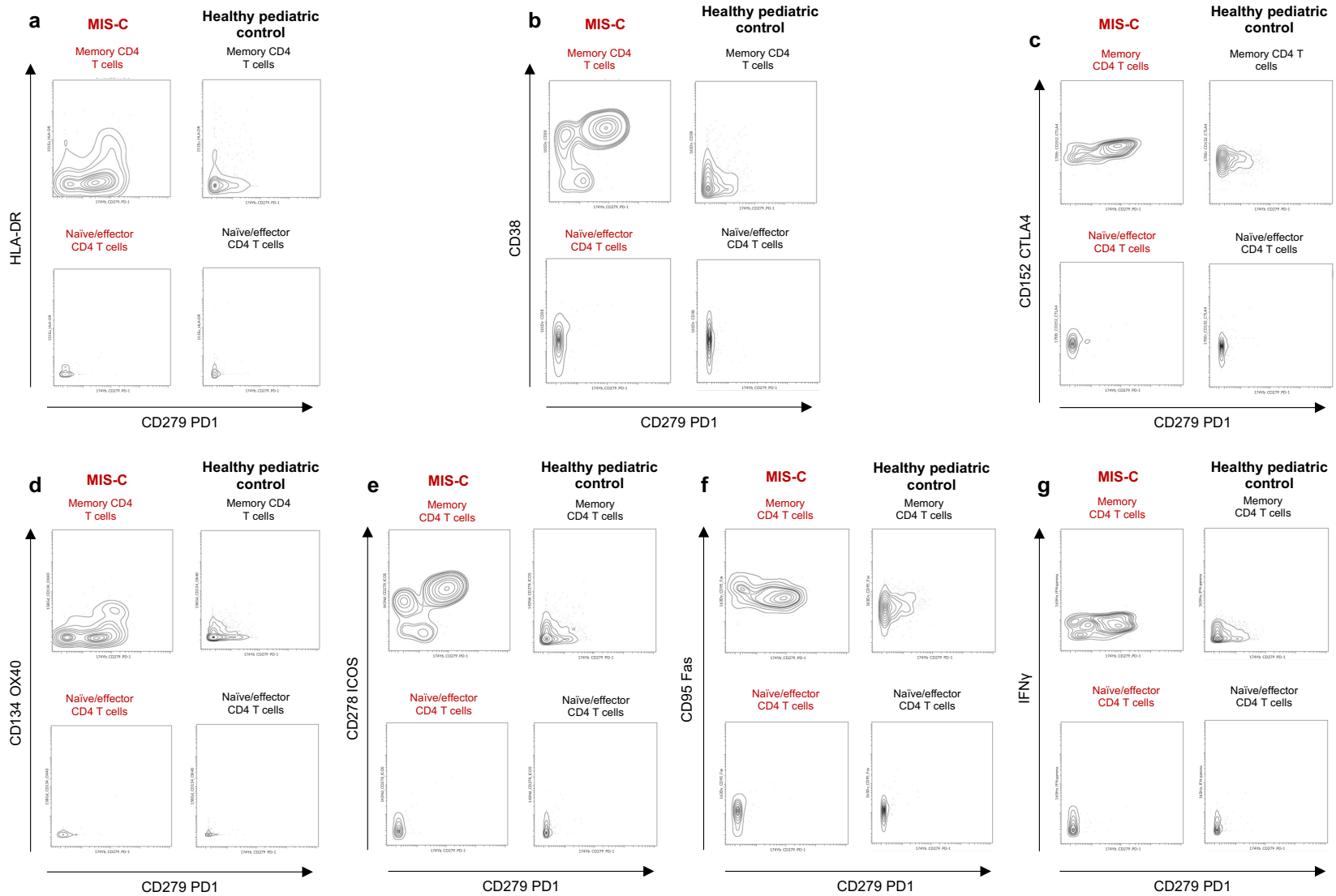
b, Markers of T cell activation, exhaustion and apoptosis in memory CD8 T cells. Co-expression of CD279 (PD-1) with CD152 (CTLA4), CD223 (LAG3), CD278 (ICOS), CD134 (OX40), CD95 (Fas), and the intracellular IFNγ in memory CD8 T cells in all children with at T1, T2 and T3 (colored by illness group). P-values and adjusted R-squared values are for all observations (regardless of illness group).



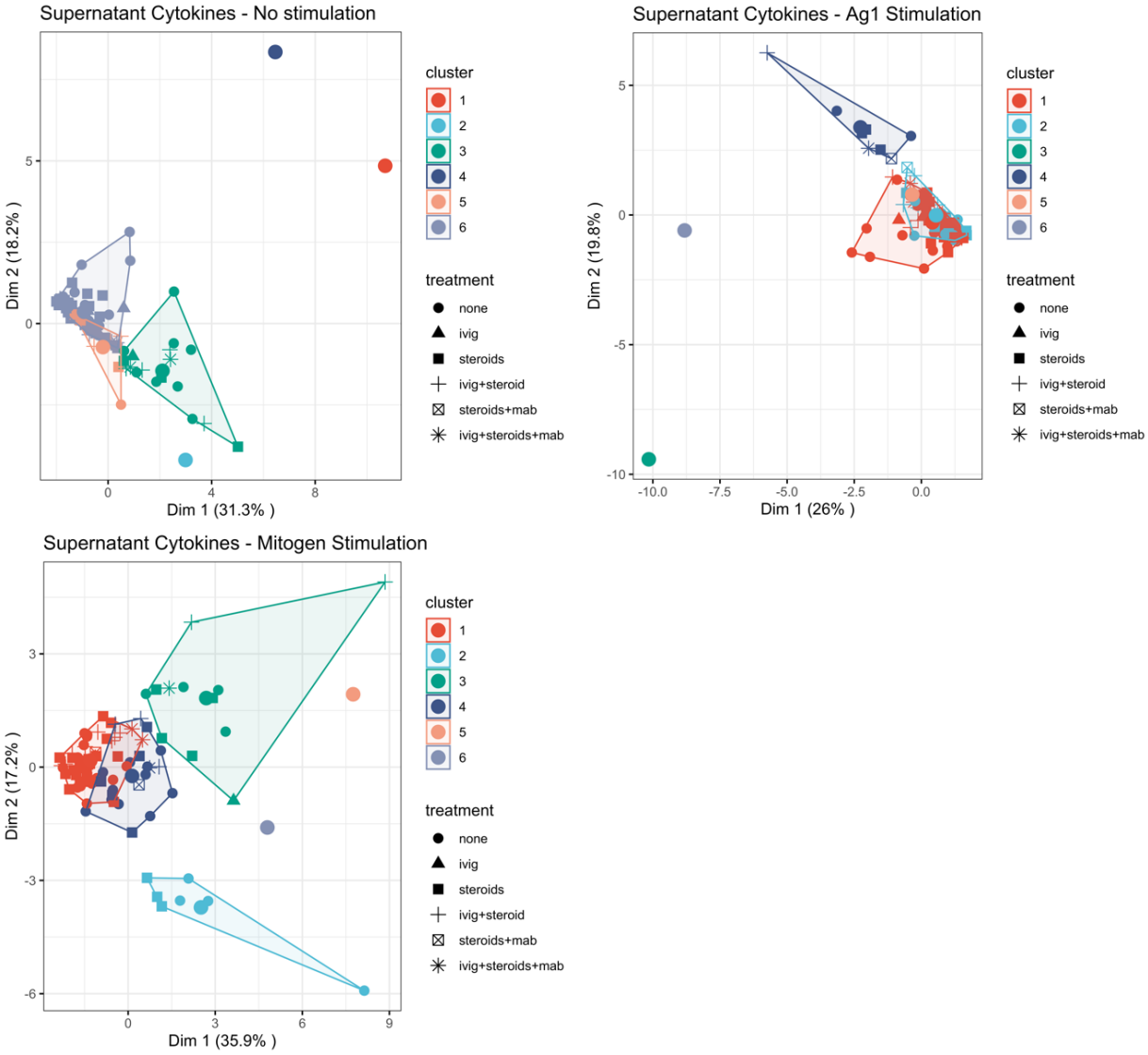
c, Markers of T cell activation, exhaustion and apoptosis in memory regulatory T cells. Co-expression of CD279 (PD-1) with CD152 (CTLA4), CD223 (LAG3), CD278 (ICOS), CD134 (OX40), CD95 (Fas) memory regulatory T cells in all children with at T1, T2 and T3 (colored by illness group). P-values and adjusted R-squared values are for all observations (regardless of illness group).



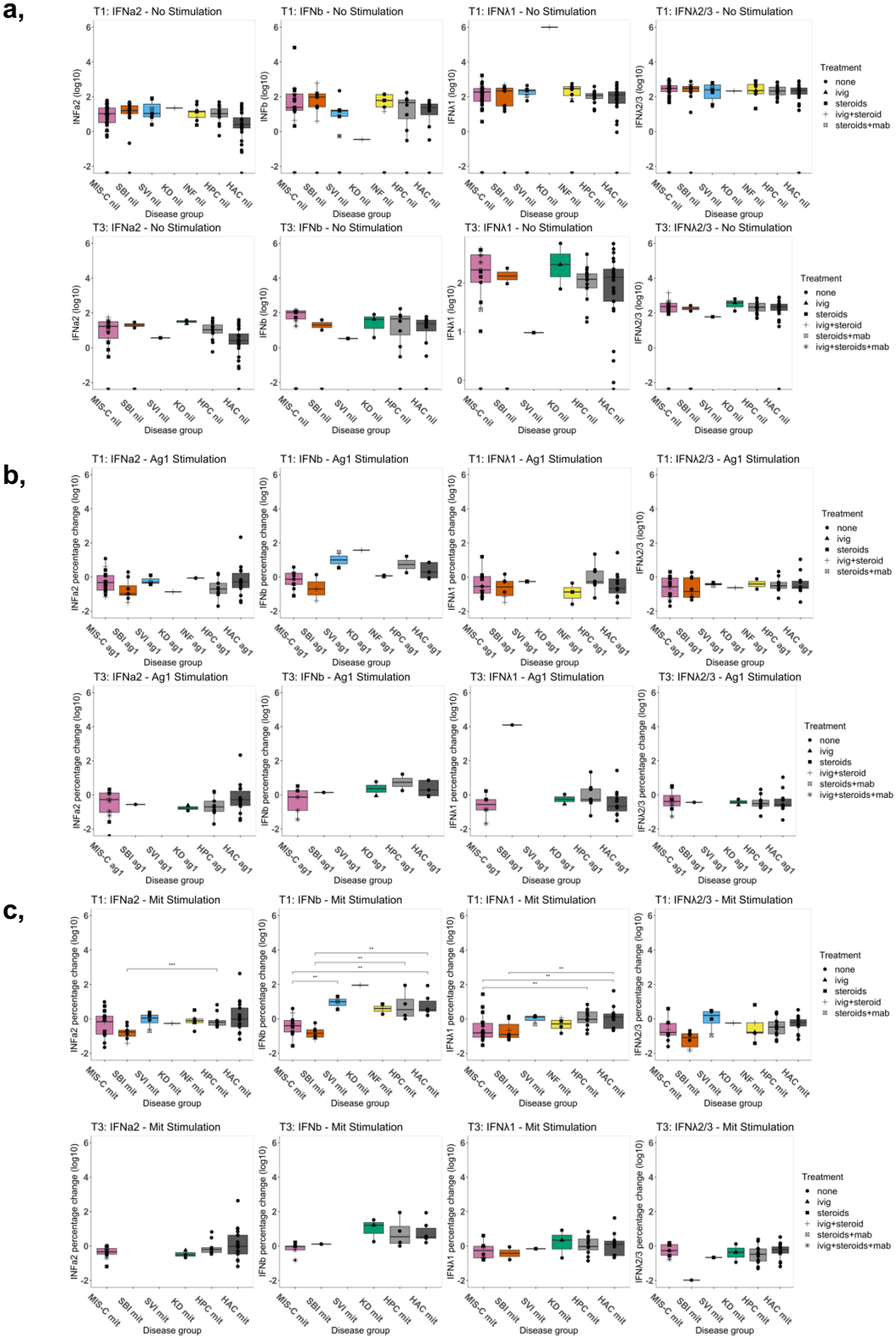
Supplementary Figure 10. Co-expression of CD279 PD1 with markers of activation, exhaustion and apoptosis in CD4 memory T cells. Representative examples of CD279 PD-1 expression (x axis, all plots) versus **a,** HLA-DR; **b,** CD38; **c,** CD152 CTLA4; **d,** CD134 OX40, **e,** CD278 ICOS, **f,** CD95 Fas, **g,** intracellular IFNγ in memory CD4 T cells and naïve/effector CD4 T cells. Plots show data from T1 from a sample from a child with MIS-C with high expression of CD279 PD1; and a healthy paediatric control sample.


a
MIS-C
Healthy pediatric control
Memory CD4 T cells
Memory CD4 T cells
Naïve/effector CD4 T cells
Naïve/effector CD4 T cells
HLA-DR
CD279 PD1
b
MIS-C
Healthy pediatric control
Memory CD4 T cells
Memory CD4 T cells
Naïve/effector CD4 T cells
Naïve/effector CD4 T cells
CD38
CD279 PD1
c
MIS-C
Healthy pediatric control
Memory CD4 T cells
Memory CD4 T cells
Naïve/effector CD4 T cells
Naïve/effector CD4 T cells
CD152 CTLA4
CD279 PD1
d
MIS-C
Healthy pediatric control
Memory CD4 T cells
Memory CD4 T cells
Naïve/effector CD4 T cells
Naïve/effector CD4 T cells
CD134 OX40
CD279 PD1
e
MIS-C
Healthy pediatric control
Memory CD4 T cells
Memory CD4 T cells
Naïve/effector CD4 T cells
Naïve/effector CD4 T cells
CD278 ICOS
CD279 PD1
f
MIS-C
Healthy pediatric control
Memory CD4 T cells
Memory CD4 T cells
Naïve/effector CD4 T cells
Naïve/effector CD4 T cells
CD95 Fas
CD279 PD1
g
MIS-C
Healthy pediatric control
Memory CD4 T cells
Memory CD4 T cells
Naïve/effector CD4 T cells
Naïve/effector CD4 T cells
IFNγ
CD279 PD1

Supplementary Figure 11. K-means clustering analysis: effects of immunomodulatory treatment on supernatant cytokines. K-means clustering plots for supernatant cytokines samples with no stimulation (**a**), stimulation with SARS-CoV-2 antigen (ag1) (**b**) and stimulation with mitogen (phytohemagglutinin) (**c**). The clusters and their respective centre points are represented by different colours. The shape of each point represents the treatment received prior to research blood sampling.



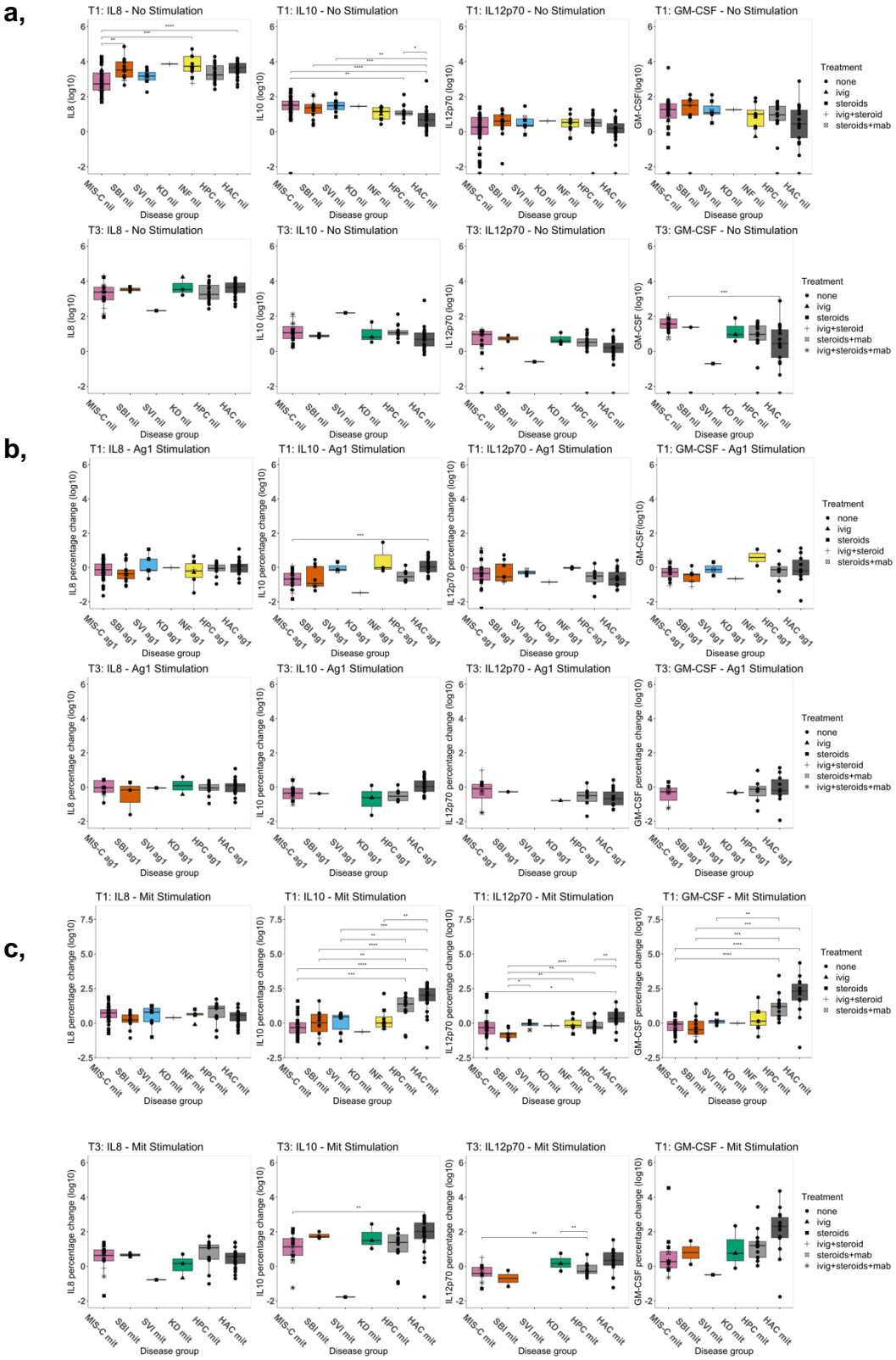
Supplementary Figure 12. Supernatant cytokine analysis 1**:** interferons



Box plots showing concentration of cell stimulation assay supernatant cytokines levels: interferon (IFN)α2, IFNβ, IFNλ1, IFNλ2/3; Log_{10} values are shown. Each point representations a participant for the following groups: Multisystem inflammatory syndrome in children (MIS-C), severe bacterial illness (SBI), severe viral illness (SVI), Kawasaki disease (KD), other inflammatory disease. Absolute cytokine levels from acute (T1) and convalescent (T3) samples at baseline – unstimulated (**a**) percentage increase from baseline following stimulation with mitogen (mit) (**b**), and absolute

increase from baseline following stimulation with SARS-CoV-2 antigen (ag1) (**c**) are shown. The shape of each point indicates the treatment received prior to sampling.

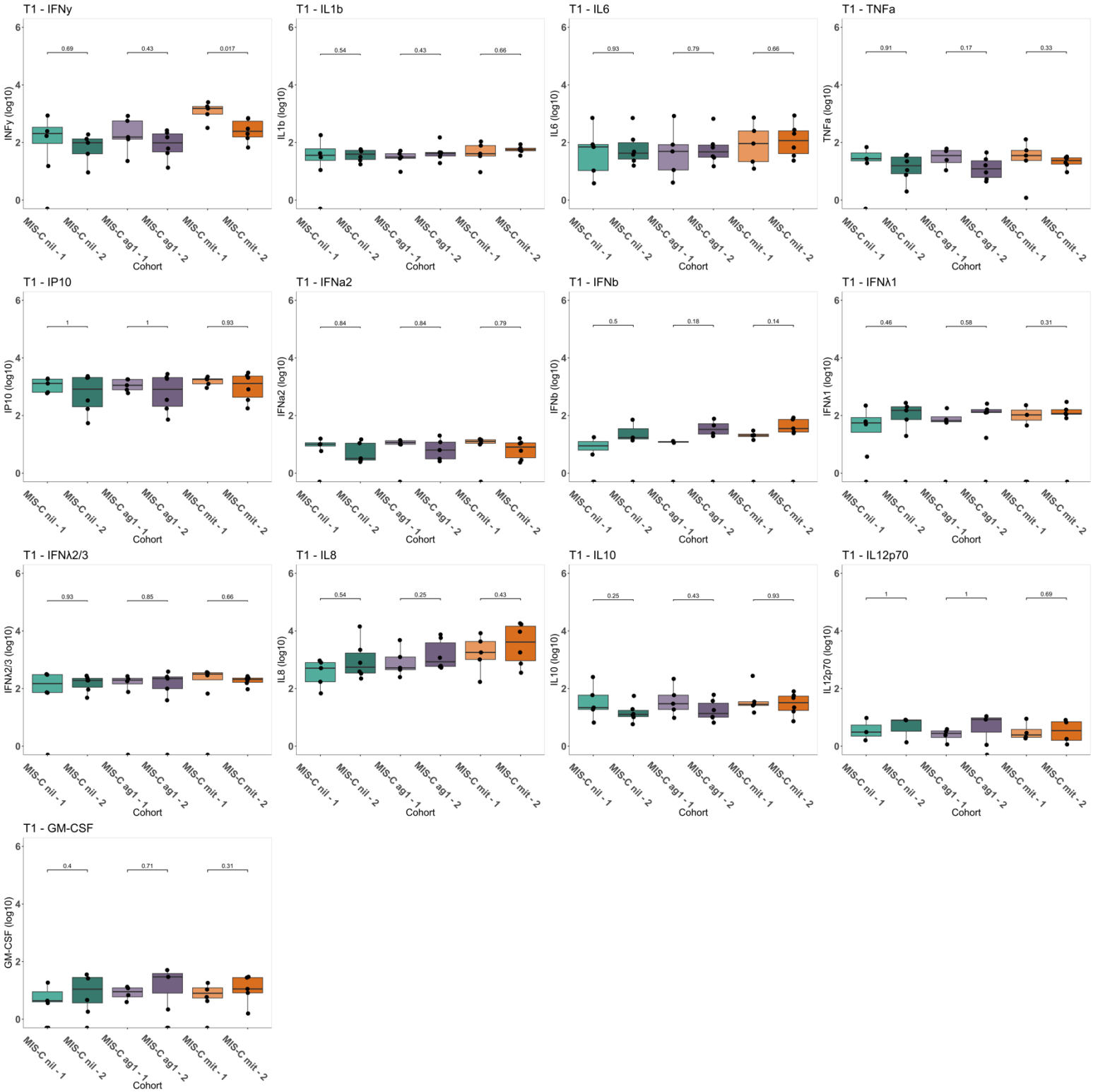
Supplementary Figure 13. Supernatant cytokine analysis 2: remaining cytokines



Box plots showing concentration of cell stimulation assay supernatant cytokines levels: interleukin (IL)8, IL10, IL12p70, granulocyte-macrophage colony-stimulating factor (GM-CSF). Log_{10} values are shown. Each point representations a participant for the following groups: Multisystem inflammatory syndrome in children (MIS-C), severe

bacterial illness (SBI), severe viral illness (SVI), Kawasaki disease (KD), other inflammatory disease. Absolute cytokine levels from acute (T1) and convalescent (T3) samples at baseline – unstimulated (**a**) percentage increase from baseline following stimulation with mitogen (mit) (**b**), and absolute increase from baseline following stimulation with SARS-CoV-2 antigen (ag1) (**c**) are shown. The shape of each point indicates the treatment received prior to sampling.

Supplementary Figure 14. Supernatant cytokine sub-analysis of MIS-C T1 by clusters identified on mass cytometry.

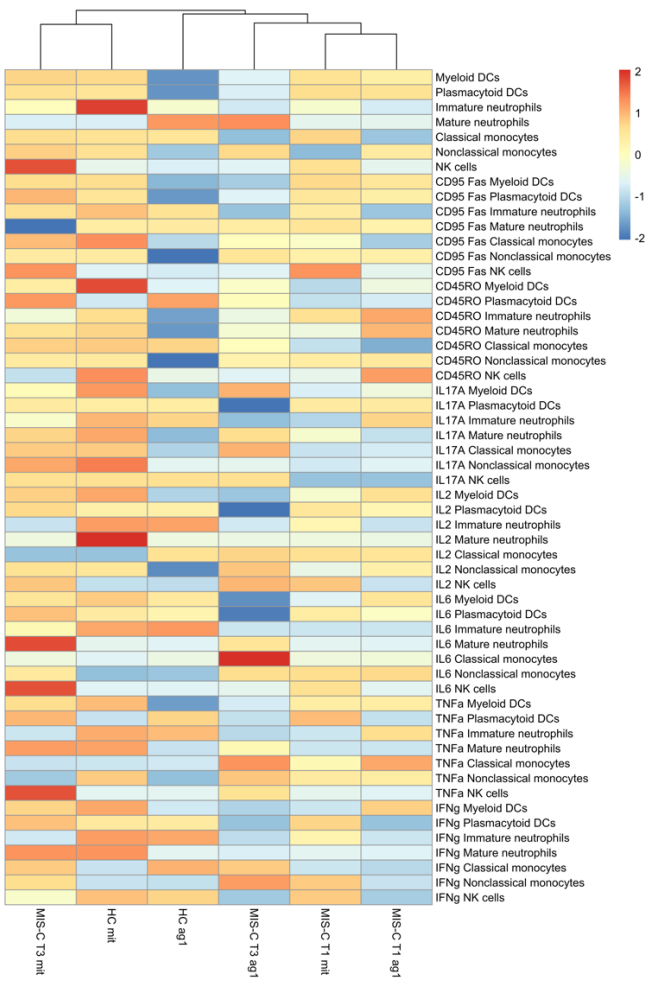


Box plots showing concentration of cell stimulation assay supernatant cytokines levels in acute (T1) MIS-C by clusters 1 and 2 identified on mass cytometry: IFNγ, IL1β, IL6, TNFα, IP10, IFNα2, IFNβ, IFNγ, IFNλ1, IFNλ2/3, IL8, IL10, IL12p70 and GM-CSF.

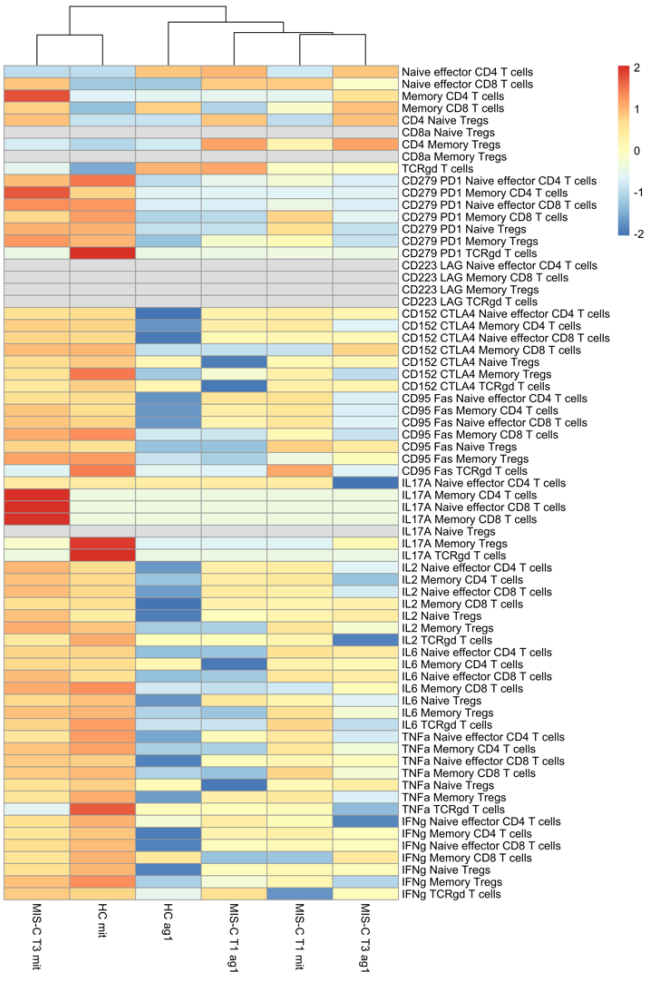
Log_{10} transformed raw data at baseline and following stimulation with SARS-CoV-2 antigen (ag1) and mitogen (mit) are shown. Each point represents a patient sample. P values from Wilcoxon pairwise comparisons are displayed.

Supplementary Figure 15. Heatmap summarising mass cytometry results of stimulated samples: foldchange from baseline following stimulation with SARS-CoV-2 antigen and mitogen for variables related to the a) innate immune response and b) T cell immune response.

a

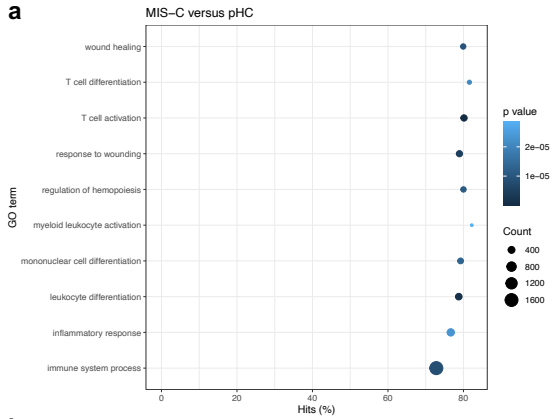


b



Supplementary Figure 16. Gene set enrichment analysis (GSEA) results. **a,** children with MIS-C (TP1) versus pediatric healthy controls; **b,** children with definite bacterial infection (TP1) versus pediatric healthy controls; **c,** children with definite viral infection (TP1) versus pediatric healthy controls; **d,** children with MIS-C versus children with definite bacterial infection. GSEA was undertaken in the R statistical environment, using pathways annotated by the Gene Ontology (GO) database.

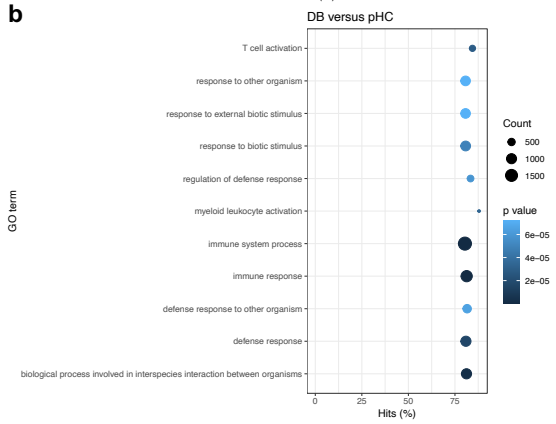
a



MIS-C versus pediatric healthy controls

Term	DE genes	Genes in category	Percent DE genes (hits)
Myeloid leukocyte activation	157	191	82.2
T cell differentiation	186	228	81.6
T cell activation	339	423	80.1
Regulation of haemopoiesis	256	320	80.0
Wound healing	255	319	79.9
Mononuclear cell differentiation	290	366	79.2
Response to wounding	326	413	78.9
Leukocyte differentiation	367	466	78.8
Inflammatory response	456	595	76.6
Immune system process	1649	2265	72.8

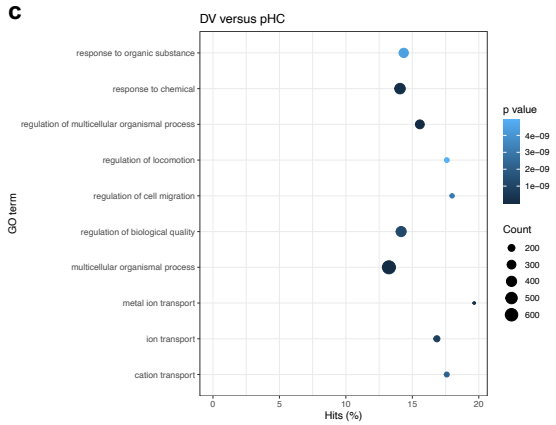
b



Definite bacterial infection (DB) versus pediatric healthy controls

Term	DE genes	Genes in category	Percent DE genes (hits)
Myeloid leukocyte activation	168	191	88.0
T cell activation	357	423	84.4
Regulation of defense response	416	499	83.4
Defense response to other organism	680	834	81.5
Immune response	1290	1587	81.3
Biological process involved in interspecies interaction between organisms	1023	1260	81.2
Defense response	1024	1266	80.9
Response to biotic stimulus	939	1163	80.7
Response to external biotic stimulus	911	1129	80.7
Immune system process	1820	2265	80.4

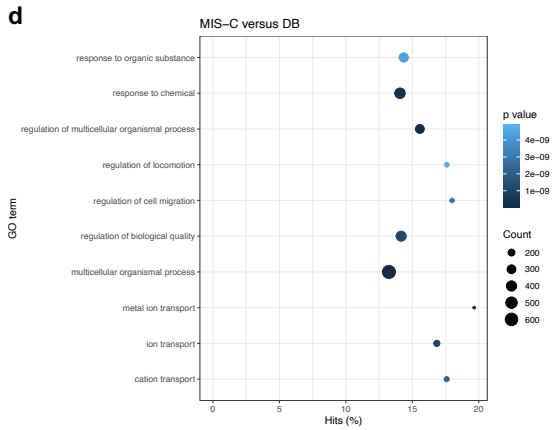
c



Definite viral infection (DV) versus pediatric healthy controls

Term	DE genes	Genes in category	Percent DE genes (hits)
Innate immune response	451	682	66.1
Response to cytokine	472	743	63.5
Defense response to other organism	529	834	63.4
Defense response	785	1266	62.0
Biological process involved in interspecies interaction between organisms	779	1260	61.8
Response to external biotic stimulus	697	1129	61.7
Response to other organism	697	1129	61.7
Response to external stimulus	1238	2049	60.4
Response to organic substance	1370	2306	59.4
Response to stress	1793	3045	58.9

d



MIS-C versus definite bacterial infection (DB)

Term	DE genes	Genes in category	Percent DE genes (hits)
Metal ion transport	114	580	19.7
Regular of cell migration	129	717	18.0
Cation transport	140	796	17.6
Regulation of locomotion	136	773	17.6
Ion transport	173	1027	16.8
Regulation of multicellular organismal process	306	1966	15.6
Response to organic substance	331	2306	14.4
Regulation of biological quality	393	2776	14.2
Response to chemical	423	3006	14.1
Multicellular organismal process	660	4986	13.2

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