

SARS-CoV2 pneumonia recovery is linked to expansion of Innate Lymphoid Cells type 2
expressing CCR10.

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Supplementary Tables and Figures

Supplementary Table 1. Clinical Parameters at Admission and Recovery

Parameter	Admission	Recovery	P value	Controls
Lymphocytes / μ l	910 (818 - 1481)	1845 (1340 - 2415)	0.0085	2046 (1606 - 2793)
Neutrophils / μ l	5599 (3545 - 8379)	4484 (3473 - 11281)	0.5416	3228 (2699 - 6525)
Lymphocyte/Neutrophil ratio	0.18 (0.11 - 0.48)	0.39 (0.16 - 0.63)	0.2813	0.51 (0.41 - 0.69)
Eosinophils / μ l	12 (6 - 33)	46 (26 - 118)	0.0245	188 (80 - 364)
Basophils/ μ l	24 (15 - 37)	26 (15 - 49)	0.5416	38 (24 - 70)
Monocytes / μ l	435 (277 - 714)	517 (389 - 770)	0.1937	423 (351 - 749)
T cells (CD3 ⁺) / μ l	375 (285 - 751)	802 (737 - 1408)	0.0009	1285 (879 - 1663)
B cells (CD19 ⁺) / μ l	82 (45 - 132)	214 (134 - 369)	0.0009	187 (134 - 286)
CD4 ⁺ T cells / μ l	223 (122 - 321)	524 (382 - 865)	0.0031	768 (544 - 998)
CD8 ⁺ T cells / μ l	155 (78 - 261)	301 (162 - 467)	0.0052	414 (158 - 577)
NK cells / μ l	92 (60 - 185)	92 (53 - 153)	0.8552	249 (146 - 286)
$\gamma\delta$ T cells / μ l	18 (11 - 42)	32 (18 - 75)	0.0353	29 (16 - 55)
P/F	185.4 (116.1 - 279.2)	336.9 (277.6 - 448.8)	0.0001	ND
C-reactive protein (mg/dl)	11.64 (5.24 - 26.85)	0.90 (0.39 - 4.65)	0.0195	ND
Procalcitonin (ng/ml)	0.20 (0.13 - 1.04)	0.10 (0.05 - 0.15)	0.0078	ND
Ferritin (mg/dL)	1164 (521 - 1906)	993 (372 - 1290)	0.2500	ND
D- dimers (g/ml)	0.55 (0.25 - 0.83)	0.43 (0.24 - 0.75)	0.2188	ND
LDH (U/L)	380 (251 - 479)	293 (278 - 362)	0.0391	ND
AST (U/L)	33 (25 - 51)	34 (18 - 67)	0.8438	ND
ALT (U/L)	44 (30 - 60)	54 (37 - 157)	0.1484	ND
Creatinin (mg/dl)	0.8 (0.70 - 1.02)	0.74 (0.51 - 0.98)	0.0391	ND
SARS-CoV2 specific IgM titer	800 (300 - 2400)	3200 (1200 - 9600)	0.0205	ND
SARS-CoV2 specific IgG titer	400 (0 - 4800)	12800 (6400 - 25600)	0.0002	ND
SARS-CoV2 specific IgA titer	1600 (800 - 4800)	12800 (2400 - 25600)	0.0161	ND
SARS-CoV2 plasma viral load (cps/ml of plasma)	36 (11 - 150)	Undetectable	NA	ND

Data are presented as Median (Interquartile Range). Comparison of 14 patients at admission and recovery time-points using a Wilcoxon matched-pairs signed rank test. *P* values <0.05 were considered significant and are highlighted in bold. Data from the 9 studied controls are shown. P/F – arterial oxygen partial pressure/fractional inspired oxygen. ND – not done. NA – not applicable.

Supplementary Table 2. Parameters from COVID-19 Patients and Healthy Controls

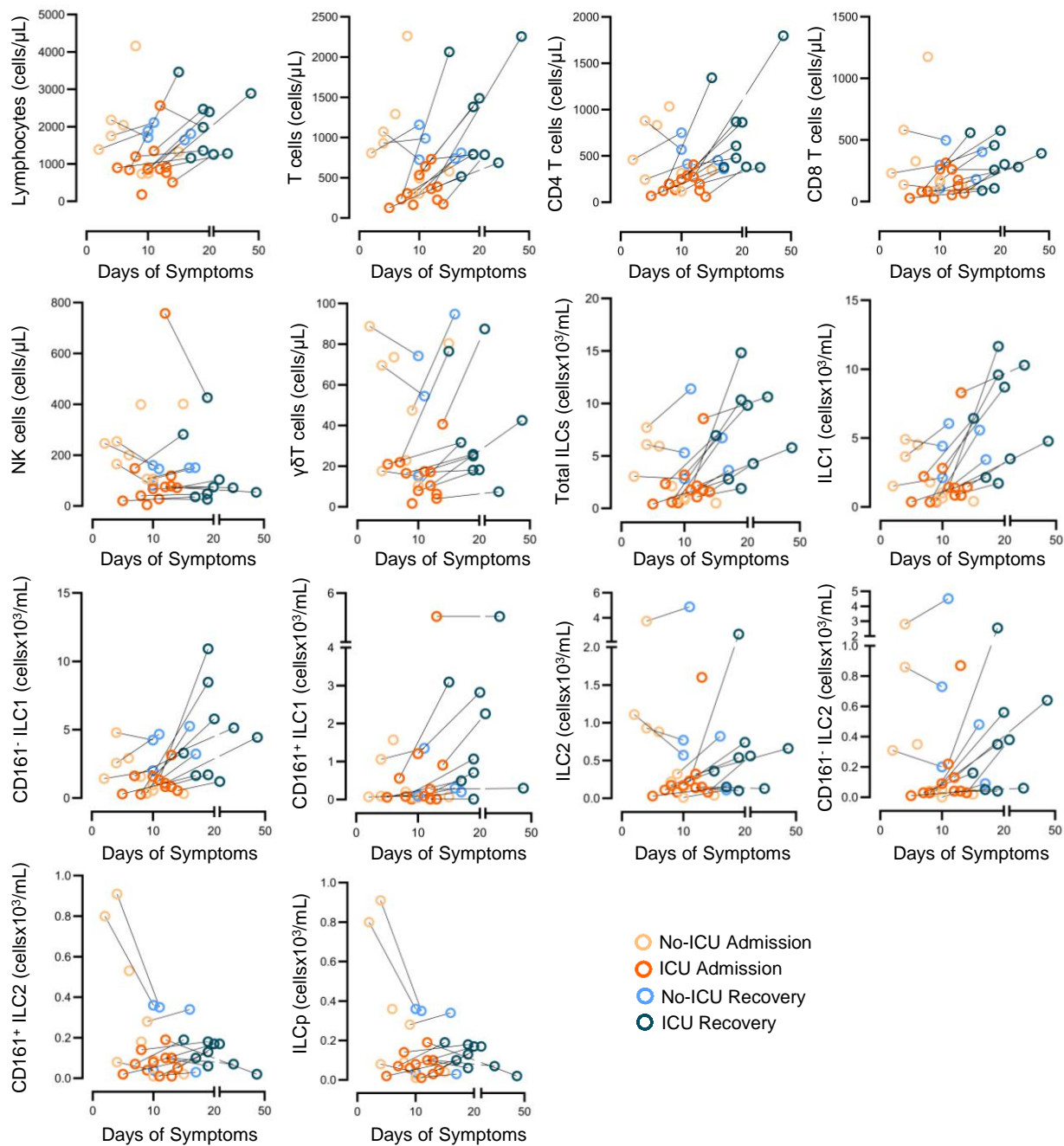
Parameter	COVID-19 patients		P value	Controls
	Admission	Recovery		
ILC1/ul	1 (1 - 3)	6 (3 - 9)	0.0005	7 (4 - 14)
CD161-ILC1/ul	1 (0.46 - 2.10)	4 (2 - 6)	0.0005	5 (3 - 12)
%CD161- in ILC1	80 (63 - 94)	88 (59 - 94)	0.3105	88 (79 - 94)
%CD161+ in ILC1	17.85 (4.93 - 32.55)	8.7 (5.15 - 36.30)	0.3575	11.50 (5.47 - 20.10)
CD161+ ILC1/ul	0.09 (0.06 - 0.99)	0.71 (0.25 - 2.54)	0.0010	0.70 (0.49 - 1.29)
%CD69 in ILC1	3 (2 - 11)	2 (1 - 3)	0.0142	1.63 (0.95 - 1.93)
%CD69+ in CD161+ ILC1	20 (6 - 37)	5 (3 - 30)	0.0266	6 (4 - 8)
%CD69+ in CD161- ILC1	2 (1 - 4)	1 (1 - 2)	0.0681	0.66 (0.60 - 1.06)
%CD56 in ILC1	6 (2 - 12)	4 (2 - 8)	0.1294	4 (2 - 6)
%CD56+ in CD161+ ILC1	18 (7 - 33)	15 (4 - 25)	0.4973	10 (9 - 25)
%CD56+ in CD161- ILC1	3 (2 - 10)	2 (1 - 3)	0.0017	1 (1 - 4)
MFI CD56 in CD56+ ILC1	2132 (1873 - 3129)	2969 (2427 - 3967)	0.0171	2485 (2193 - 3758)
MFI CD56 in CD161+ CD56+ ILC1	2271 (1876 - 3606)	2723 (1988 - 3167)	0.4973	2411 (2213 - 3171)
MFI CD56 in CD161- CD56+ ILC1	2565 (1575 - 3386)	3388 (2864 - 4141)	0.0105	2899 (2599 - 4020)
CCR10+ ILC1/ul	0.07 (0.04 - 0.17)	0.54 (0.19 - 0.91)	0.0005	0.46 (0.34 - 1.06)
%CCR10 in ILC1	9 (3 - 11)	7 (5 - 15)	0.4548	8 (4 - 15)
%CCR10+ in CD161+ ILC1	1.69 (0.42 - 7.06)	2.88 (0.48 - 13.05)	0.2974	4 (1 - 6)
%CCR10+ in CD161- ILC1	8 (4 - 13)	8 (5 - 10)	0.8394	7 (3 - 12)
CCR10 MFI in CCR10+ ILC1	2969 (2564 - 4227)	3649 (3123 - 4491)	0.6355	2339 (2074 - 2549)
CCR10 MFI in CCR10+ CD161- ILC1	2619 (2240 - 3690)	3413 (2652 - 4391)	0.2654	2236 (1888 - 2506)
CCR10 MFI in CCR10+ CD161+ ILC1	2103 (1567 - 2841)	2236 (1701 - 2737) ^a	0.4263	1424 (1264 - 1900)
%CCR6+ in ILC1	13.05 (5.09 - 27.83)	9.75 (5.97 - 30.53)	0.6698	10.40 (4.76 - 24.30)
%CCR6+ in CD161+ ILC1	86.75 (74.80 - 94.18)	87.25 (80.88 - 92.85)	0.9460	88.60 (75.70 - 96.60)
%CCR6+ in CD161- ILC1	3.85 (2.30 - 7.58)	3.91 (1.04 - 6.22)	0.4631	3.04 (1.58 - 5.67)
ILC2/ul	0.17 (0.10 - 0.32)	0.56 (0.14 - 0.80)	0.0061	0.61 (0.44 - 1.00)
CD161- ILC2/ul	0.04 (0.03 - 0.18)	0.38 (0.08 - 0.69)	0.0039	0.38 (0.32 - 0.56)
%CD161- in ILC2	41 (28 - 63)	68 (45 - 93)	0.0012	54 (50 - 80)
%CD161+ in ILC2	60.15 (42.53 - 71.20) ^b	32.70 (6.59 - 55.43)	0.0006	45 (19.55 - 49.90)
CD161+ILC2/ul	0.08 (0.02 - 0.12)	0.17 (0.07 - 0.19)	0.1260	0.29 (0.14 - 0.39)
%CD69 in ILC2	1 (0 - 1)	17 (9 - 25)	0.0266	0.41 (0.25 - 1.47)
%CD69+ in CD161+ ILC2	2 (0 - 6)	0.7 (0 - 3.2)	0.1294	0.57 (0.45 - 1.97)
%CD69+ in CD161- ILC2	3.03 (0.25 - 5.32)	0.84 (0.37 - 1.43)	0.1099	0.19 (0 - 0.36)
%c-kit in ILC2	58 (26 - 70)	19 (8 - 43)	0.0007	50 (11 - 54)
%c-Kit+ CD161+ in ILC2	54.65 (21.20 - 69.38)	17.35 (4.58 - 30.8)	0.0017	41.90 (10.15 - 47.60)
CCR10+ ILC2/ul	0.03 (0.01 - 0.06)	0.20 (0.06 - 0.32)	0.0002	0.17 (0.10 - 0.23)
%CCR10 in ILC2	14 (9 - 32)	27 (18 - 46)	0.0105	26 (18 - 309)
%CCR10+ in CD161+ ILC2	3 (0 - 7)	5 (2 - 14)	0.3013	5 (3 - 6)
%CCR10+ in CD161- ILC2	33 (16 - 40)	39 (20 - 58)	0.2163	24 (19 - 36)
CCR10 MFI in CCR10+ ILC2	3004 (1408 - 4410)	3777 (3151 - 5052)	0.0398	2279 (1861 - 2754)
CCR10 MFI in CCR10+ CD161- ILC2	2181 (1718 - 3790)	3708 (3139 - 5134)	0.0134	2549 (2084 - 2976)
CCR10 MFI in CCR10+ CD161+ ILC2	1173 (0 - 3059)	1842 (1200 - 3175)	0.2439	2253 (1576 - 2543)
%CCR6+ in ILC2	5.77 (1.45 - 29.93)	6.66 (1.29 - 17.58)	0.7354	6.75 (3.29 - 22.30)
%CCR6+ in CD161+ ILC2	14.50 (7.48 - 41.30)	19.55 (7.55-52.15)	0.1909	44.80 (29.20 - 57.00)
%CCR6+ in CD161- ILC2	0.57 (0 - 4.79)	1.61 (0.02 - 5.09)	0.9492	1.35 (0.45 - 1.86)
ILCp/ul	0.06 (0.02 - 0.15)	0.12 (0.05 - 0.21)	0.3848	0.31 (0.21 - 0.47)
%CD69 in ILCp	17 (9 - 25)	4 (3 - 6)	0.0002	2 (1 - 4)
%CCR6+ in ILCp	18.30 (6.87 - 34.70)	19.05 (10.25 - 35.48)	0.9032	13.90 (12.30 - 23.35)
Serum Levels (pg/ml)				
CCL28 ^c	501(483 - 522) ^b	515 (484 - 557) ^b	0.0906	420 (382 - 458)
IL-22BP ^c	27942 (18658 - 46010)	41824 (26525 - 60111) ^b	0.2412	22070 (16851-24511)
SPD ^c	2490 (464 - 10627)	3060 (596 - 7404) ^b	0.9999	768 (6 - 1830)
RAGE ^c	455 (348 - 735) ^d	76 (38 - 201)	0.0004	146 (91 - 208)
CCL21	315 (118 - 448) ^b	318 (134 - 404) ^b	0.7354	78 (56 - 160)
CXCL13	90 (75 - 147) ^e	38 (21 - 67) ^b	0.0002	19 (5 - 28)
CTACK	590 (401 - 852)	614 (406 - 823)	0.8394	711 (419 - 775)
EGF	73.3 (132.5 - 279.5)	139 (102.9 - 389.4)	0.3396	127 (35 - 192)
ENA-78	603.9 (331 - 1072)	1227 (816.3 - 1480)	0.1937	1704 (832 - 1939)
Eotaxin-2	341 (162 - 711)	838 (717 - 1610)	0.0002	745 (236 - 1306)
FGF-2	114 (50 - 137) ^b	72 (35 - 137)	0.4143	43 (30 - 75)
FLT-3L	13.99 (11.09 - 21.92)	9.54 (7.13 - 16.14)	0.0034	9 (5 - 17)

Fractalkine	78.99 (48.63 – 218.9)	112.4 (43.97 – 194.1)	0.7869	70 (34 – 267)
G-CSF	27 (21 – 47)	9 (2 – 10)	0.0002	5 (0.2 – 39.7)
GM-CSF	64 (24 – 118)	27 (22 – 76)	0.0215	19 (15 – 226)
GROalpha	43 (33 – 57) ^b	35 (34 – 49) ^b	0.0942	19 (9 – 25)
I-309	0.78 (0.64 – 2.47)	0.70 (0.39 – 0.99)	0.0681	0.76 (0.42 – 1.10)
IFN-alpha2	56 (14 – 70) ^b	23 (10 – 147)	0.9697	10 (8 – 46)
IFN-gamma	2 (2 – 9)	1 (0.61 – 4.27)	0.1294	1.8 (0.3 – 7.6)
IL-1alpha	25 (13 – 37)	25 (6 – 34)	0.5417	9 (5 – 19)
IL-1beta	33 (13 – 48)	27 (5 – 48)	0.6355	14 (3 – 32)
IL-1RA	14 (10 – 60) ^e	11 (8 – 22) ^e	0.2163	2 (2 – 4)
IL-2	2 (0.58 – 3.46)	1 (0.45 – 3.22)	0.3396	1 (0.29 – 6.38)
IL-3	0.2 (0.15 – 0.29)	0.2 (0.18 – 0.29)	0.7695	0.19 (0.12–0.22)
IL-4	2 (1 – 3)	2 (1 – 2)	0.1272	0.75 (0.24 – 4.47)
IL-5	2 (0.66 – 3.88)	3 (0.88 – 4.71)	0.3757	3 (2 – 14)
IL-6	21 (5 – 44) ^d	4 (1 – 15) ^b	0.0017	0.5 (0.2 – 1.2)
IL-7	16 (8 – 22) ^b	5 (4 – 11)	0.0081	4 (2 – 8)
IL-8	18 (18 – 23) ^b	18 (15 – 38) ^b	0.4548	10 (6 – 18)
IL-9	4 (2 – 6)	5 (2 – 11)	0.4973	4 (2 – 4)
IL-10	17 (6 – 50) ^d	4 (0.49 – 8.38) ^b	0.0012	0.3 (0.1 – 0.6)
IL-12p40	62 (29 – 167)	39 (14 – 79)	0.0034	42 (21 – 71)
IL-12p70	1 (0.63 – 3.58)	0.72 (0.45 – 7.92)	0.3120	2.53 (0.28 – 14.69)
IL-13	56 (34 – 174)	52 (35 – 173)	0.7354	87 (8 – 197)
IL-15	27 (21 – 32) ^d	19 (13 – 21) ^b	0.0017	7 (5 – 8)
IL-17A	9 (4 – 16) ^b	9 (2 – 20)	0.6848	3 (2 – 4)
IL-25	219 (194 – 264) ^b	219 (90 – 342)	0.8926	105 (39 – 171)
IL-17F	13 (7 – 20) ^d	11 (6 – 19) ^b	0.3054	5 (5 – 6)
IL-18	95 (49 – 145) ^b	26 (19 – 69) ^b	0.0002	15 (5 – 25)
IL-20	5 (3 – 18)	5 (4 – 126)	0.0081	3 (2 – 5)
IL-21	3 (2 – 4) ^b	3 (2.47 – 3.59) ^b	0.5771	2 (2 – 3)
IL-22	69 (15 – 115)	47 (22 – 102)	0.9999	55 (8 – 90)
IL-27	3894 (2345 – 5001) ^b	2346 (855 – 3184)	0.0002	1584 (602–2249)
IL-33	28 (2 – 58) ^b	16 (2 – 92) ^b	0.6377	2 (1 – 7)
IP-10	1495 (740 – 13957) ^d	69 (26 – 185)	0.0002	35 (25 – 50)
LIF	5 (4 – 10)	6 (4 – 8)	0.8394	6 (4 – 11)
MCP-1	374 (304 – 585)	281 (167 – 528)	0.2734	458 (253 – 530)
MCP-2	86 (81 – 99) ^d	23 (21 – 34)	0.0005	20 (19 – 24)
MCP-3	18 (11 – 39)	11 (10 – 23)	0.1514	10 (5 – 37)
MCP-4	9 (4 – 11) ^b	14 (5 – 39) ^b	0.0574	5 (3 – 16)
M-CSF	255 (124 – 354) ^b	171 (77 – 219) ^e	0.0081	52 (18 – 82)
MDC	362 (262 – 707)	408 (238 – 521)	0.1909	899 (744 – 1344)
MIG_CXCL9	1662 (1026 – 4134)	1573 (1111 – 2531)	0.2163	1044 (974 – 1369)
MIP-1alpha	25 (20 – 31)	23 (18 – 27)	0.6724	20 (18 – 41)
MIP-1beta	32 (20 – 43)	53 (36 – 61) ^b	0.0002	21 (16 – 34)
MIP-1delta	2176 (1223 – 3388) ^e	2676 (1378 – 3683) ^d	0.1677	821 (475 – 918)
PDGF-AA	3807 (3172 – 4140) ^d	3642 (2342 – 5306) ^b	0.8394	2255 (1490 – 2441)
PDGF-AB_BB	19922 (16423 – 23458)	22545 (19112 – 27973)	0.2734	21517 (15029 – 26297)
RANTES	2442 (921 – 2869)	1980 (1251 – 2799)	0.8926	2388 (2013 – 3509)
sCD40L	6797 (4907 – 13568) ^b	7363 (4004 – 17234)	0.4143	4353 (2470 – 6572)
SCF	0.33 (0.09 – 6.75)	0.72 (0.32 – 1.61)	0.4143	0.24 (0.04 – 0.75)
SDF-1alpha+beta	1589 (668 – 2154)	1815 (540 – 3597)	0.0398	2497 (1649 – 4000)
TARC	16 (7–21) ^b	28 (12 – 30)	0.0327	25 (17 – 52)
TGFalpha	34 (15 – 39) ^b	15 (10 – 26) ^b	0.0327	9 (8 – 10)
TNFalpha	170 (83 – 203)	62 (43 – 172)	0.0134	44 (19 – 203)
TNFBeta	21 (14 – 43)	19 (12 – 31)	0.2036	12 (7 – 29)
TPO	795 (379 – 1426) ^b	862 (345 – 2069) ^b	0.5879	249 (236 – 442)
TRAIL	27 (19 – 46) ^b	55 (44 – 73)	0.0295	61 (49 – 77)
TSLP	2 (1 – 10)	5 (1 – 15) ^b	0.8525	1 (1 – 2)
VEGF-A	382 (283 – 727)	467 (269 – 558)	0.5417	180 (97 – 387)

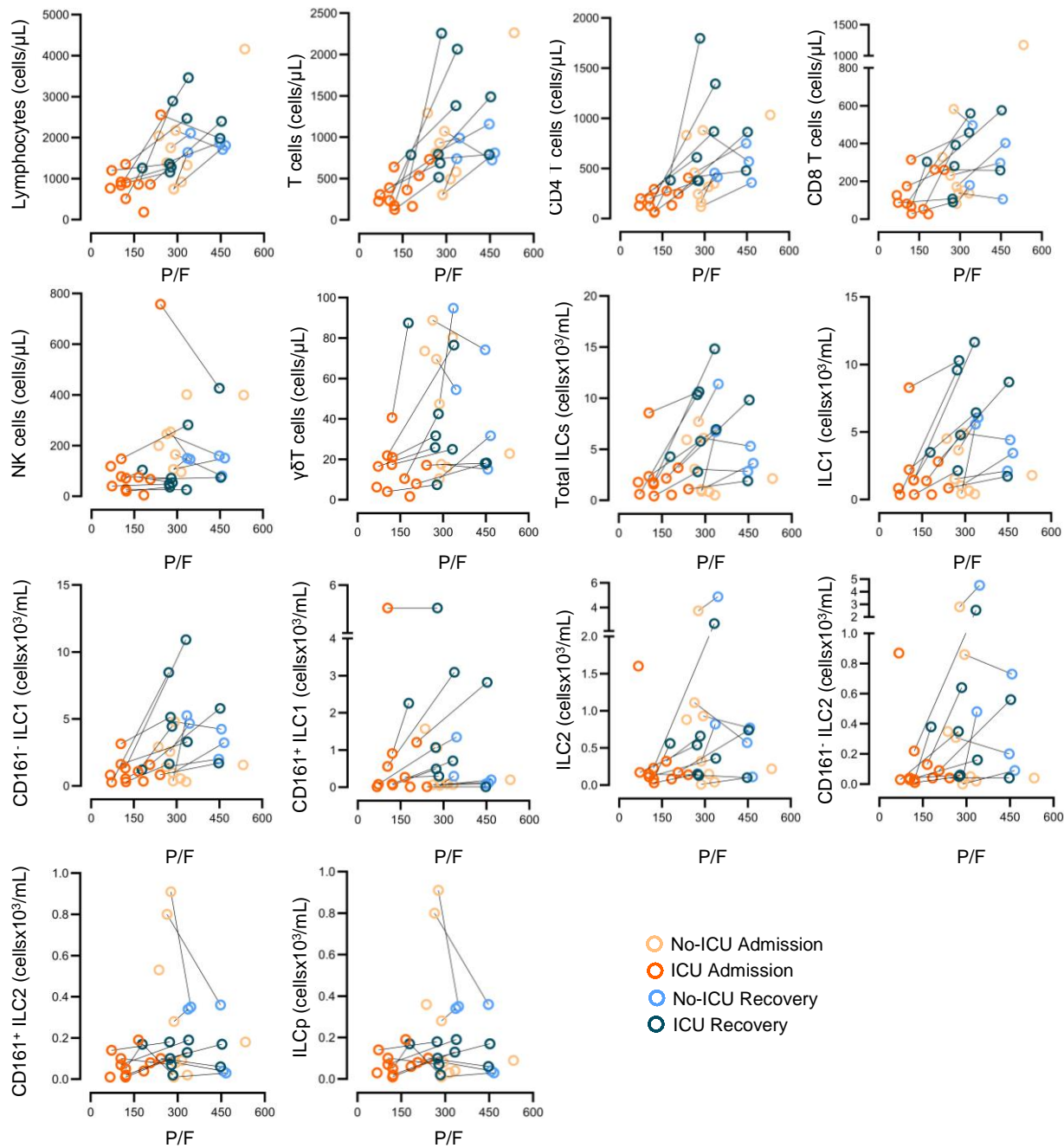
Data are shown as Median (Interquartile Range). Comparison of 13 patients with admission and recovery time-points using Wilcoxon matched-pairs signed rank test. P values <0.05 were considered significant and are highlighted in bold. Serum levels were only performed in 6 out of the 9 healthy subjects studied (4 male/6, median age 59 (57–61) years). Mann-Whitney U-test was performed to compare admission and recovery with the controls. ^a P values <0.01 as compared to controls; ^b P values <0.05 as compared to controls; ^c Quantified using an ELISA kit, all the rest were quantified using Multiplexing LASER Bead. Assay; ^d P values <0.0001 as compared to controls; ^e P values <0.001 as compared to controls.

Supplementary Table 3. Monoclonal Antibodies used in Flow Cytometry Staining

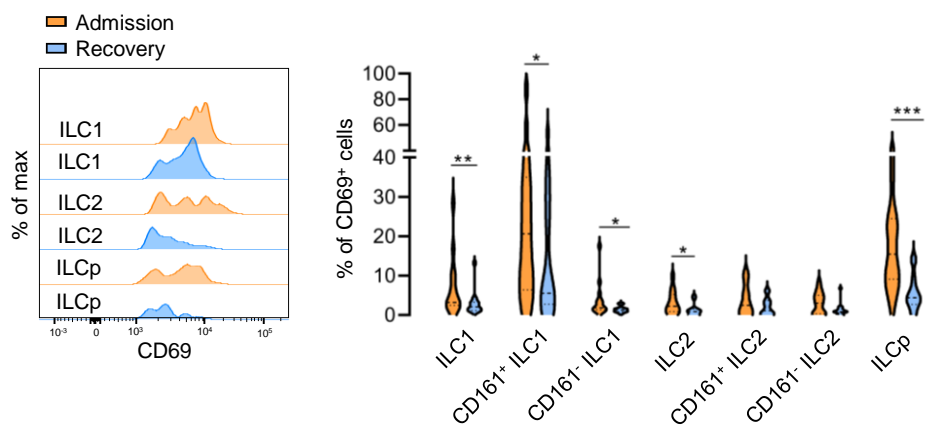
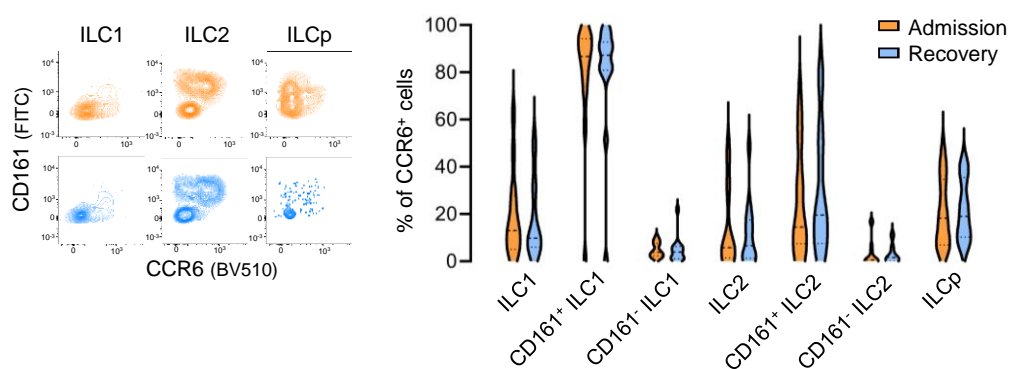
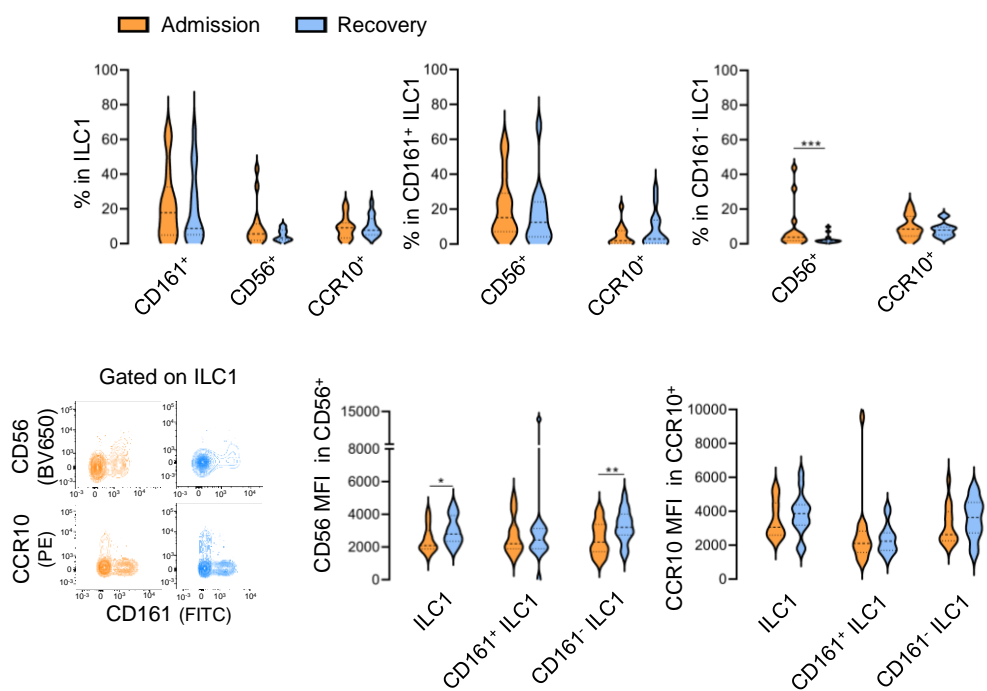
Antibody	Fluorochrome	Clone	Source
CD123	BV421	6H6	Biolegend
CD11c	BV421	3.9	Biolegend
CD14	EF450	61D3	eBioscience
CD19	EF450	H1B19	eBioscience
CCR6	BV510	11A9	BD Horizon
CD45	BV605	HI30	BD Horizon
CD56	BV650	HCD56	Biolegend
CD4	BV711	RPA-T4	Biolegend
CD69	BV785	FN50	Biolegend
CD161	FITC	DX12	BD Biosciences
c-Kit	PerCPef710	104D2	eBioscience
CCR10	PE	1B5	BD Pharmingen
CD3	PEdazzle594	UCHT1	Biolegend
CD25	PE-Cy5	BC96	Biolegend
CD94	PE-Cy7	DX22	Biolegend
CRTH2	Alexa647	BM16	BD Pharmingen
CD16	AF700	3G8	Biolegend
CD127	APCef780	eBioRDR5	Invitrogen
CD27	BV421	M-T271	BD Horizon
IgM	BV510	MHM-88	Biolegend
CD4	V500	RPA-T4	BD Horizon
IgD	BV605	IA6-2	Biolegend
CD8 α	BV605	RPA-T8	Biolegend
HLA-DR	BV650	L243	Biolegend
CD21	BV711	B-ly4	BD Horizon
CD45RO	BV785	UCHL1	Biolegend
CCR7	FITC	150503	R&D Systems
CD3	PerCP Cy5.5	OKT3	eBioscience
CD56	PE	C5.9	Cytognos
CXCR5	PE Dazzle594	J252D4	Biolegend
CD38	PE-Cy5	HIT2	Biolegend
TCR- $\gamma\delta$	PE-Cy7	11F2	BD Biosciences
CD19	PE-Cy7	J3-119	Beckman Coulter
CD25	APC	2A3	BD Biosciences



Supplementary Figure 1. *Peripheral blood counts of the main ILC populations and other lymphocyte subsets in relation to time since the beginning of symptoms. Data from 20 COVID-19 patients, with 14 patients contributing with two time-points (admission and recovery). Each dot represents one individual / time-point.*

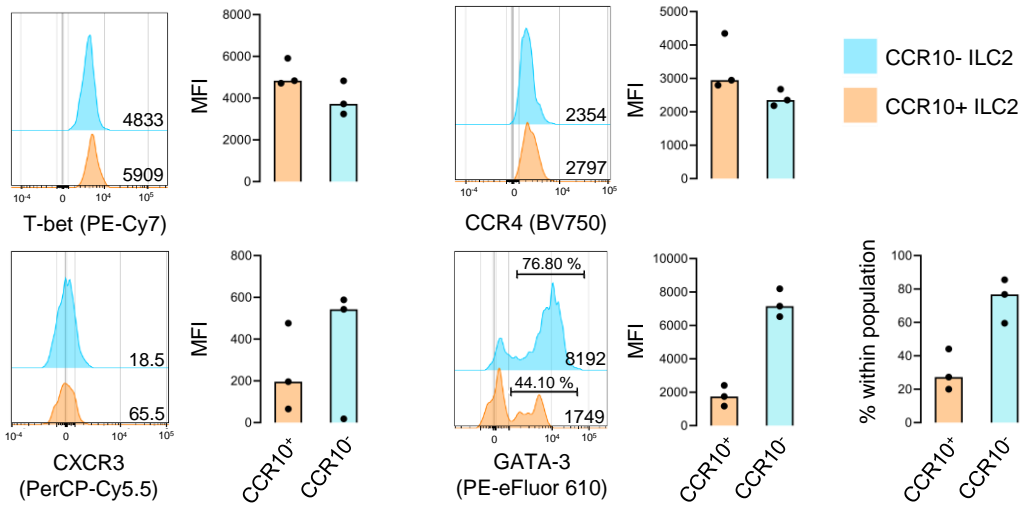


Supplementary Figure 2. Peripheral blood counts of the main ILC populations and other lymphocyte subsets in relation to P/F. Data from 20 COVID-19 patients, with 14 patients contributing with two time-points (admission and recovery). Each dot represents one individual / time-point.

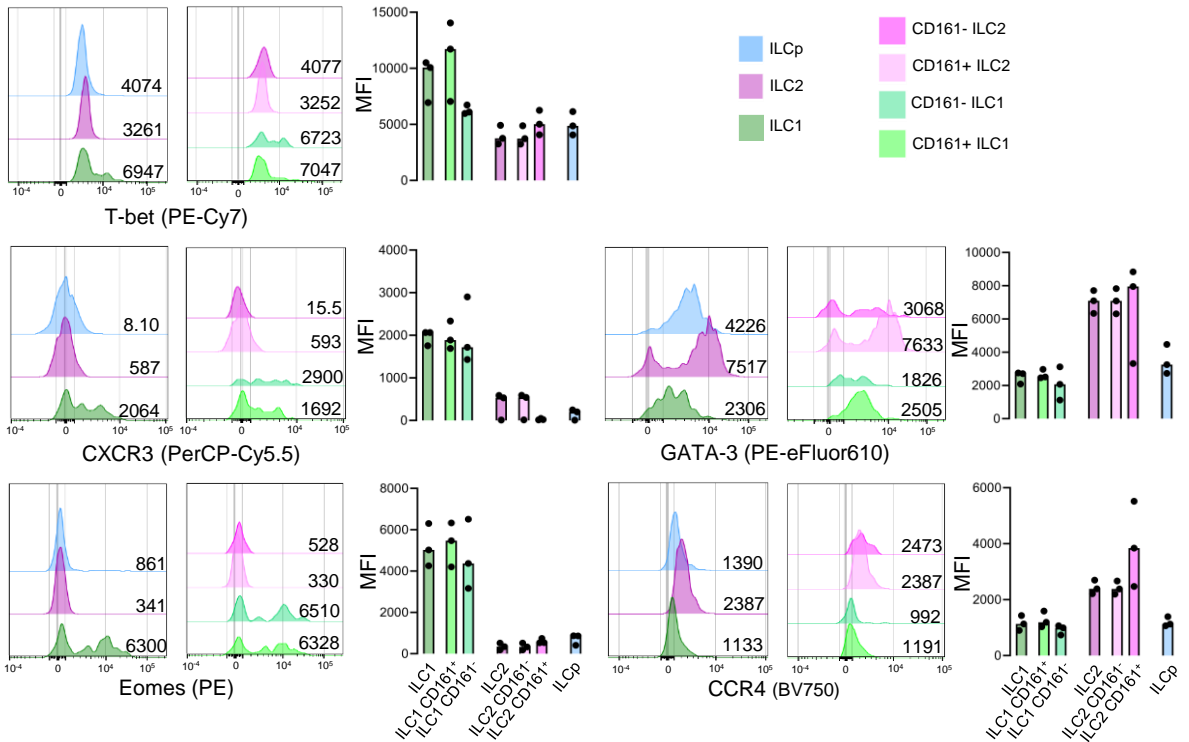
A**B****C**

Supplementary Figure 4. *ILC phenotype in COVID-19 patients at admission and recovery.* (A) Histogram overlay representing the expression of CD69 within ILC1, ILC2 and ILCp at the admission and recovery time points; the violin plots show the comparison of the frequency of CD69-expressing cells within the main ILC populations at admission and recovery. (B) Contour plots of CCR6 vs CD161 within ILC1, ILC2 and ILCp from a representative patient at admission and recovery; the violin plots show the comparison of the frequency of CCR6-expressing cells within the main ILC populations at admission and recovery. (C) Contour plots of CD56 and CCR10 vs CD161 of a representative patient at admission and recovery; the violin plots show the comparison of the frequency of CD161+, CD56+ and CCR10+ cells within ILC1, the frequency of CD56+ and CCR10+ cells within CD161+ and CD161- ILC1, and the MFI of CD56 and CCR10 within ILC1, CD161+ ILC1 and CD161- ILC1 at admission and recovery. Data from 14 patients were compared using Wilcoxon matched-pairs signed ranked test; *** $p < 0,001$; ** $p < 0,01$; * $p < 0,05$. The healthy control values for all parameters are listed in Supplementary Table 2.

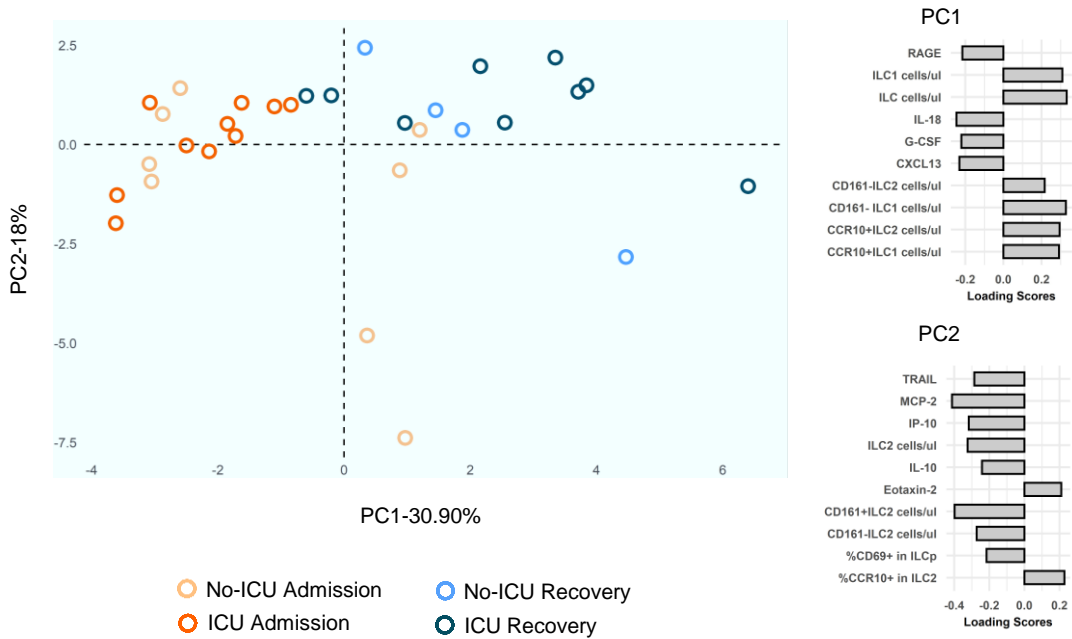
A



B



Supplementary Figure 5. Markers of ILC differentiation. Expression of GATA-3 (TWAJ, Invitrogen, PE-eFluor610), CCR4 (1G1, BD Biosciences, BV750), Tbet (eBio4B10, eBioscience, PE-Cy7), CXCR3 (1C6, BD Biosciences, PerCPCy5.5), and Eomes (WD1928, eBioscience, PE), in circulating ILC2 subsets according to CCR10 (A) and ILCp, ILC2, and ILC1 in subsets defined by CD161 (B) in healthy donors (n=3). Samples were acquired in Aurora flow cytometer (Cytek Biosciences, Fremont, CA), histogram refers to one illustrative individual and numbers refer to Mean Fluorescence Intensity (MFI). Bars refer to the median of the MFI or frequency of the population and each dot represents one individual.



Supplementary Figure 6. *Identification of major contributors to disease recovery.* PCA analysis of the 22 analytes and cell populations with a significant fold change $> |2|$ within the 2 patient groups, No-ICU and ICU, at admission and recovery. The top 10 loading scores in absolute value of PC1 and PC2 are represented. Each dot represents one patient.