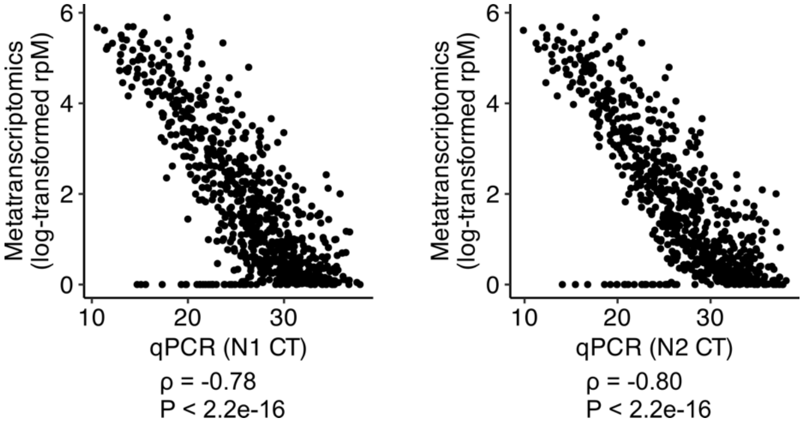
Supplementary Materials

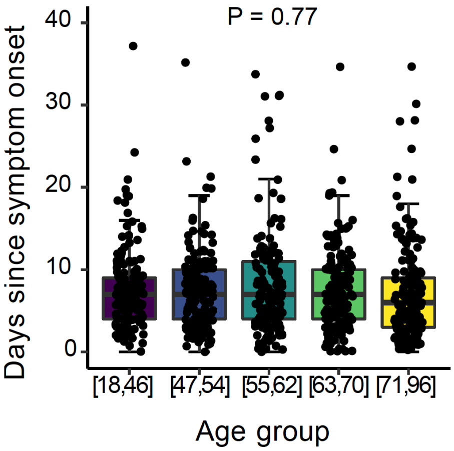
Supplementary Table 1. Clinical and demographic characteristics of the cohort at baseline (Visit 1). P values were calculated using Chi-square test for categorical variables, and Kruskal-Wallis test for continuous variables. Percentages might not sum to 100% due to rounding. The number of patients who died within 28 days is the same as the number of patients in trajectory group 5 (TG5).

Demographics		Overall population n = 1031	Age group [18,46] n = 206	Age group [47,54] n = 187	Age group [55,62] n = 216	Age group [63,70] n = 199	Age group [71,96] n = 223	P-value
Age at enrollment (years), median (IQR) (n=1031)		59.0 (20.0)	37.0 (11.0)	51.0 (4.0)	59.0 (4.0)	67.0 (5.0)	77.0 (8.0)	<0.001
Sex, No. (%)	Male	639 (62%)	128 (62%)	108 (58%)	135 (63%)	123 (62%)	145 (65%)	0.68
	Female	392 (38%)	78 (38%)	79 (42%)	81 (38%)	76 (38%)	78 (35%)	
Race, No. (%)	White	517 (50%)	79 (38%)	85 (45%)	95 (44%)	118 (59%)	140 (63%)	0.002
	Black/ African American	228 (22%)	49 (24%)	47 (25%)	53 (25%)	35 (18%)	44 (20%)	
	Asian	40 (4%)	12 (6%)	6 (3%)	6 (3%)	9 (5%)	7 (3%)	
	Other/Declined/ Unknown	246 (24%)	66 (32%)	49 (26%)	62 (29%)	37 (19%)	32 (14.3%)	
Ethnicity, No. (%)	Non-Hispanic	670 (65%)	114 (55%)	120 (64%)	119 (55%)	137 (69%)	180 (81%)	<0.001
	Hispanic	319 (31%)	82 (40%)	63 (34%)	83 (38%)	57 (29%)	34 (15%)	
	Unknown	42 (4%)	10 (5%)	4 (2%)	14 (6%)	5 (3%)	9 (4%)	
Comorbidities, No. (%)	None	65 (6%)	23 (11%)	13 (7%)	11 (5%)	10 (5%)	8 (4%)	
	Hypertension	592 (57%)	57 (28%)	96 (51%)	134 (62%)	141 (71%)	164 (74%)	<0.001
	Diabetes	384 (37%)	45 (22%)	67 (36%)	90 (42%)	95 (48%)	87 (39%)	<0.001
	Chronic lung disease	208 (20%)	14 (7%)	22 (12%)	43 (20%)	54 (27%)	75 (34%)	<0.001
	Asthma	149 (14%)	34 (17%)	30 (16%)	28 (13%)	36 (18%)	21 (9%)	0.085
	Chronic cardiac disease	282 (27%)	18 (9%)	38 (20%)	55 (25%)	70 (35%)	101 (45%)	<0.001
	Chronic kidney disease	155 (15%)	17 (8%)	22 (12%)	41 (19%)	31 (16%)	44 (20%)	0.004
	Chronic liver disease	51 (5%)	4 (2%)	9 (5%)	14 (6%)	14 (7%)	10 (4%)	0.14
	Chronic neurological disorder	123 (12%)	11 (5%)	13 (7%)	22 (10%)	21 (11%)	56 (25%)	<0.001
	Organ Transplantation	47 (5%)	7 (3%)	10 (5%)	16 (7%)	13 (7%)	1 (0%)	0.004
	HIV/AIDS	13 (1%)	3 (1%)	3 (2%)	6 (3%)	1 (1%)	0 (0%)	0.092
	Malignancy	101 (10%)	9 (4%)	6 (3%)	17 (8%)	25 (13%)	44 (20%)	<0.001
BMI Category in Kg/m2, No. (%)	Underweight	12 (1%)	3 (1%)	1 (1%)	1 (0%)	4 (2%)	3 (1%)	<0.001
	Normal weight	145 (14%)	19 (9%)	17 (9%)	19 (9%)	27 (14%)	63 (28%)	
	Overweight (25.1-29.9)	265 (26%)	41 (20%)	43 (23%)	58 (27%)	52 (26%)	71 (32%)	
	Class 1-2 Obesity (30-39.9)	424 (41%)	82 (40%)	84 (45%)	100 (46%)	85 (43%)	73 (33%)	

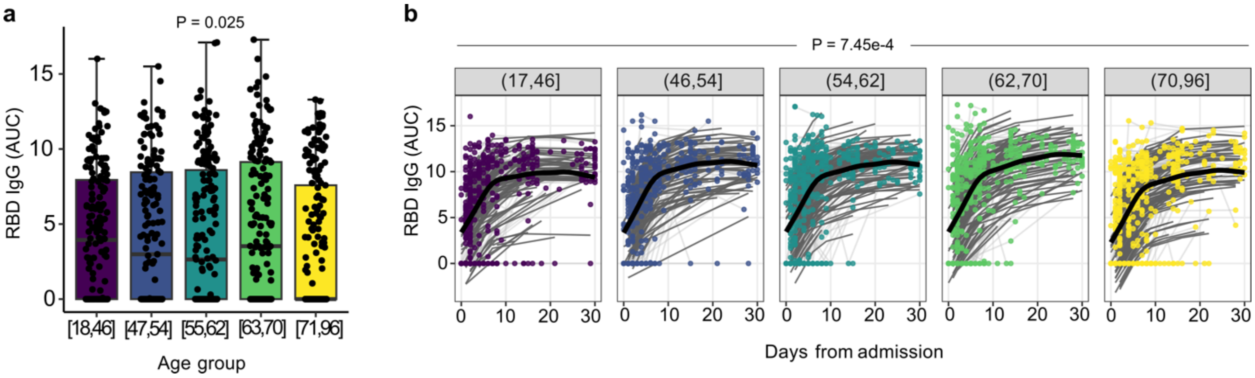
	Class 3 Obesity (40+)	147 (14%)	44 (21%)	38 (20%)	31 (14%)	23 (12%)	11 (5%)	
	Missing	38 (4%)	17 (8%)	4 (2%)	7 (3%)	8 (4%)	2 (1%)	
Length of hospital stay (days), median (IQR) (n=890)		6.0 (8.0)	5.0 (5.0)	5.5 (6.5)	6.0 (7.0)	7.0 (8.0)	8.0 (11.0)	<0.001
At baseline visit (V1)								
7-point respiratory Ordinal Score (OS), No. (%)	Mechanically ventilated or ECMO (OS=6)	126 (12%)	19 (9%)	27 (14%)	31 (14%)	25 (13%)	24 (11%)	0.002
	Non-invasive ventilation or high flow O2 (OS=5)	235 (23%)	32 (16%)	30 (16%)	52 (24%)	63 (32%)	58 (26%)	
	Supplemental oxygen (not high flow) (OS=4)	443 (43%)	92 (45%)	82 (44%)	91 (42%)	78 (39%)	100 (45%)	
	None (OS=3)	225 (22%)	63 (31%)	47 (25%)	41 (19%)	33 (17%)	41 (18%)	
	Missing	2 (0%)	0 (0%)	1 (1%)	1 (0%)	0 (0%)	0 (0%)	
SpO2/FiO2 ratio category, No. (%)	235 or lower	246 (24%)	29 (14%)	45 (24%)	49 (23%)	64 (32%)	59 (26%)	0.002
	236-315	170 (16%)	32 (16%)	26 (14%)	43 (20%)	36 (18%)	33 (15%)	
	315 or higher	566 (55%)	137 (67%)	108 (58%)	113 (52%)	93 (47%)	115 (52%)	
	Missing	49 (5%)	8 (4%)	8 (4%)	11 (5%)	6 (3%)	16 (7%)	
Lymphopenia, No. (%)	<500/microliter	132 (13%)	13 (6%)	19 (10%)	32 (15%)	28 (14%)	40 (18%)	0.004
Thrombocytopenia, No. (%)	<100,000/microliter	53 (5%)	3 (1%)	8 (4%)	13 (6%)	15 (8%)	14 (6%)	0.054
D-dimer, No. (%)	>0.5 mg/L	542 (53%)	91 (44%)	83 (44%)	126 (58%)	108 (54%)	134 (60%)	<0.001
Creatinine, No. (%)	>=1.5 mg/dL	169 (16%)	18 (9%)	25 (13%)	43 (20%)	31 (16%)	52 (23%)	<0.001
CRP, No. (%)	>=10 mg/L	446 (43%)	71 (34%)	88 (47%)	99 (46%)	95 (48%)	93 (42%)	0.04
Across all visits (V1-V6)								
IMPACC trajectory group, No. (%)	TG1	217 (21%)	60 (29%)	44 (24%)	41 (19%)	38 (19%)	34 (15%)	<0.001
	TG2	270 (26%)	71 (34%)	57 (30%)	53 (25%)	45 (23%)	44 (20%)	
	TG3	251 (24%)	52 (25%)	44 (24%)	56 (26%)	43 (22%)	56 (25%)	
	TG4	191 (19%)	20 (10%)	33 (18%)	44 (20%)	51 (26%)	43 (19%)	
	TG5	102 (10%)	3 (1%)	9 (5%)	22 (10%)	22 (11%)	46 (21%)	
28-day mortality, No. (%)	Yes	102 (10%)	3 (1%)	9 (5%)	22 (10%)	22 (11%)	46 (21%)	<0.001
	No	929 (90%)	203 (99%)	178 (95%)	194 (90%)	177 (89%)	177 (79%)	
Treatment with steroids, No. (%)	Yes	711 (69%)	124 (60%)	137 (73%)	150 (69%)	155 (78%)	145 (65%)	0.001
	No	320 (31%)	82 (40%)	50 (27%)	66 (31%)	44 (22%)	78 (35%)	
Treatment with remdesivir, No. (%)	Yes	645 (63%)	122 (59%)	114 (61%)	133 (62%)	137 (69%)	139 (62%)	0.33
	No	386 (37%)	84 (41%)	73 (39%)	83 (38%)	62 (31%)	84 (38%)	



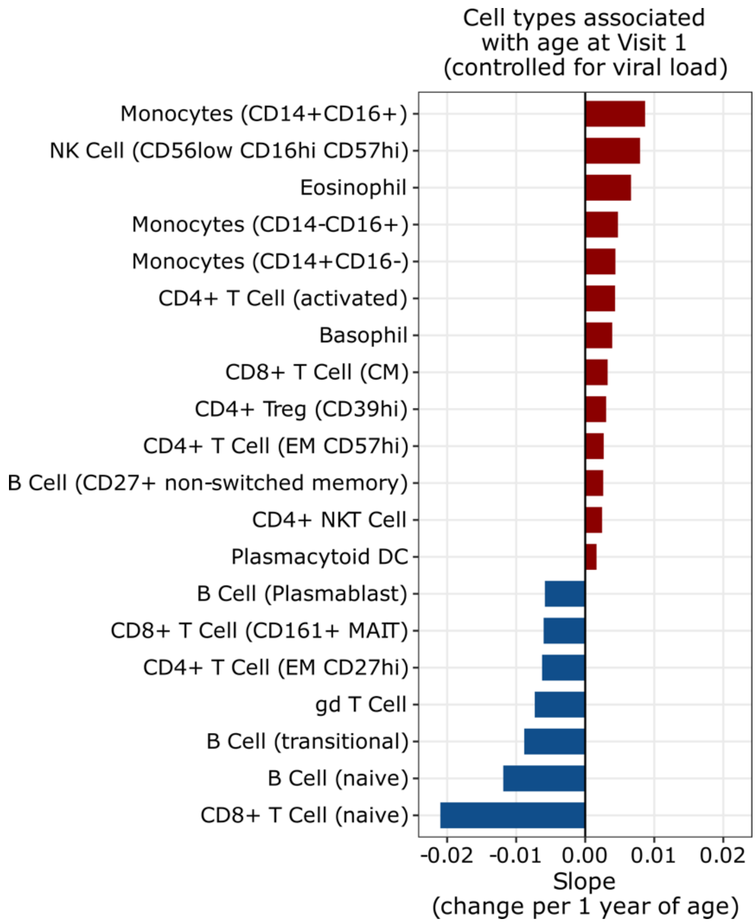
Supplementary Figure 1. Comparison of viral load as measured by nasal swab qPCR and nasal swab RNA-seq (metatranscriptomics). The Pearson's correlation coefficient and its P value are shown below each panel.



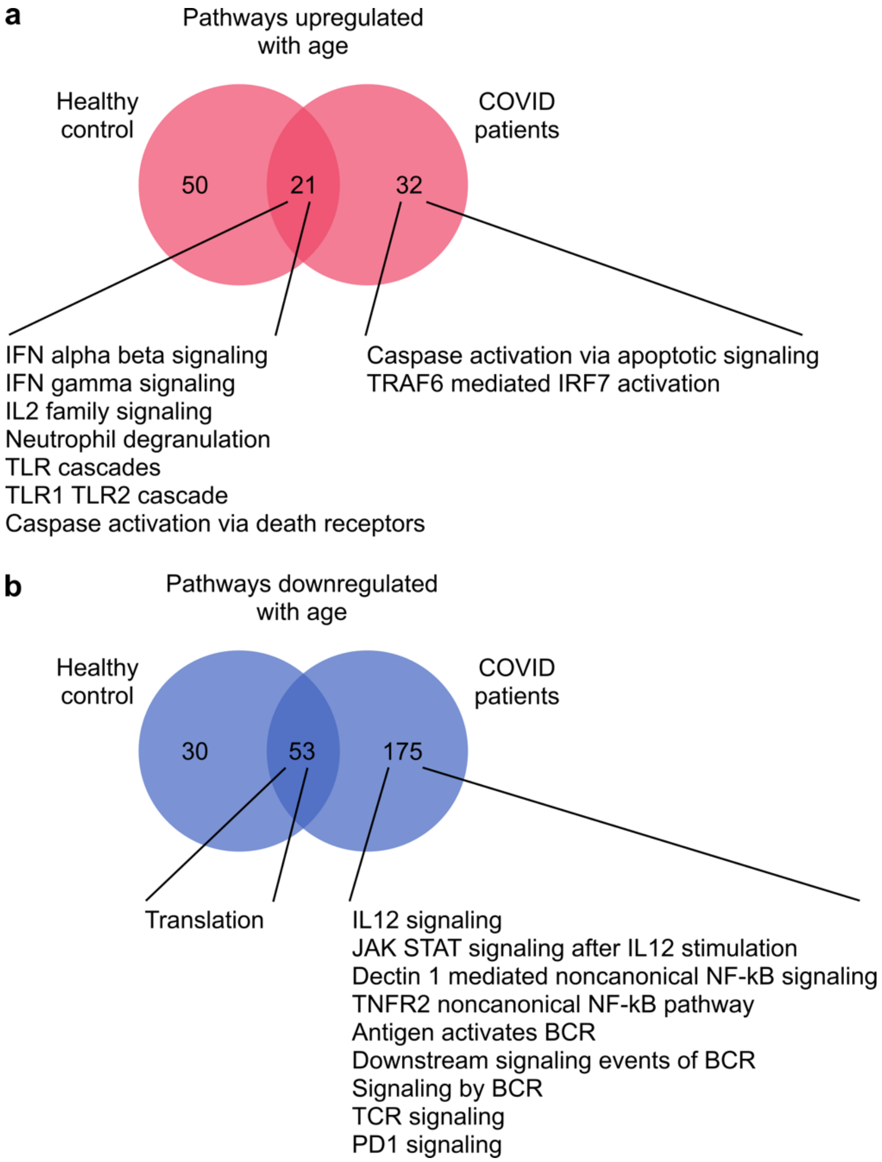
Supplementary Figure 2. Time since symptom onset across age groups at Visit 1. Data is available for a subset of patients (n=796 of 963 Visit 1 samples). Two outliers with >40 days since symptom onset are excluded from the plot. P value is calculated by one-way ANOVA test.



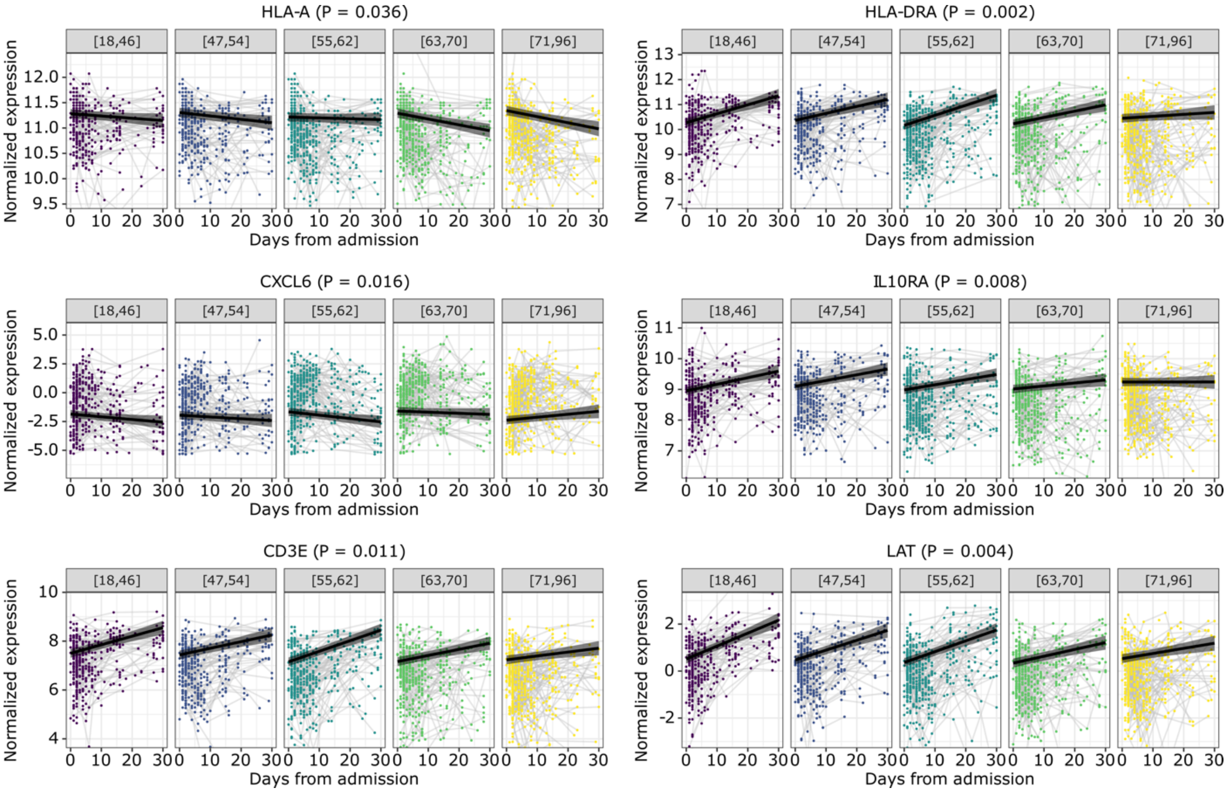
Supplementary Figure 3. Visit 1 analysis and longitudinal analysis of IgG levels. (a) RBD IgG at visit 1 in each age group. P-value determined by likelihood ratio test. (b) RBD IgG levels, as measured by area under the curve (AUC, see methods), over time in each age group. P-value determined by a generalized additive mixed model. Values plotted represent the area under the curve of the optical density (OD).



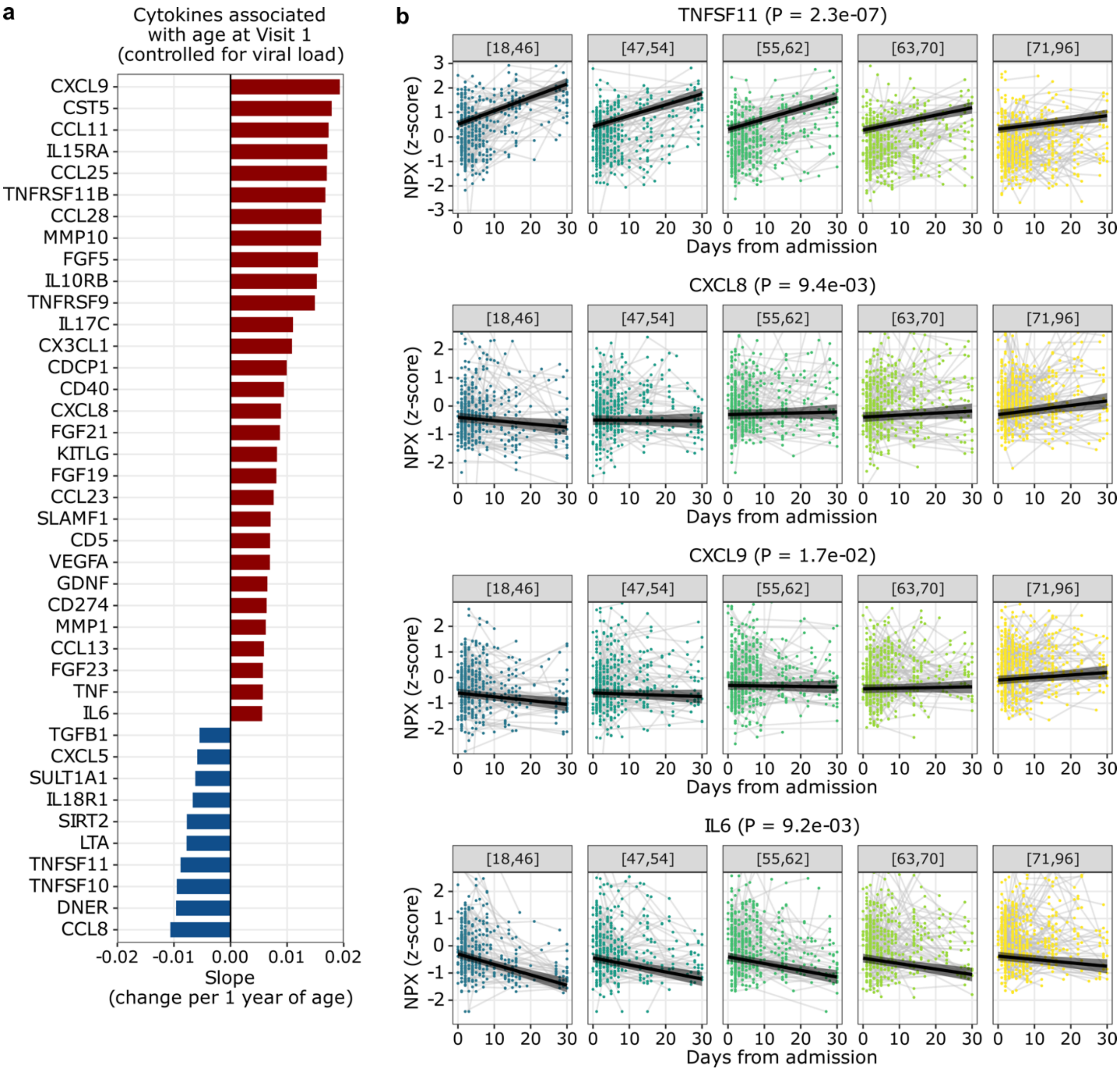
Supplementary Figure 4. Visit 1 analysis of CyTOF data while controlling for viral load. Bar plot highlighting cell types that are significantly associated with age ($P < 0.05$, calculated with linear regression and Benjamini-Hochberg correction). Analogous to the analyses in Figure 3b, but controlled for viral load.



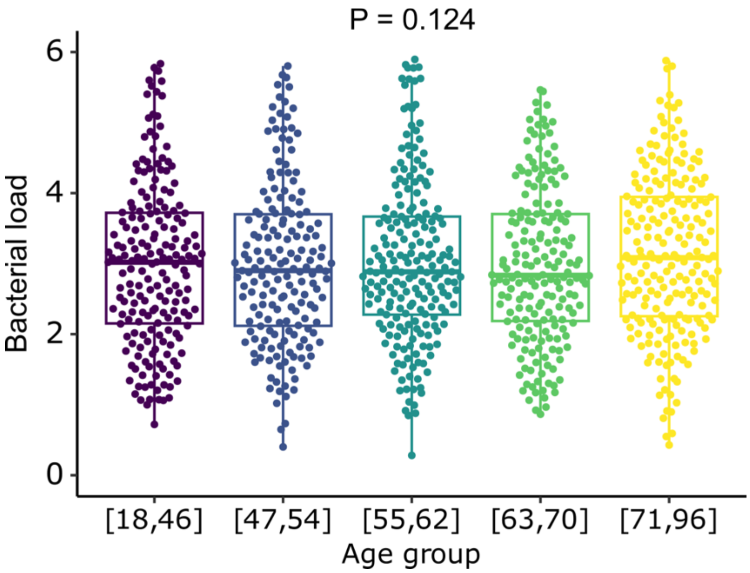
Supplementary Figure 5. Comparison of PBMC RNA-seq data from this study to healthy control datasets[5], with differential gene expression analyses performed using age as a continuous variable. (a, b) Venn diagrams of the Reactome pathways that are (a) upregulated and (b) downregulated with age. The numbers in the left circles indicate the number of pathways that are up- or down-regulated with age in the healthy control data only. The numbers in the right circles indicate the number of pathways that are up- or down-regulated with age in COVID-19 patients (our data) only. The numbers in the overlapping regions indicate the number of pathways that are up- or down-regulated with age in both healthy control and COVID-19 patients. Some examples of overlapping pathways, and of pathways that are associated with age in COVID-19 patients only are included under each Venn diagram.



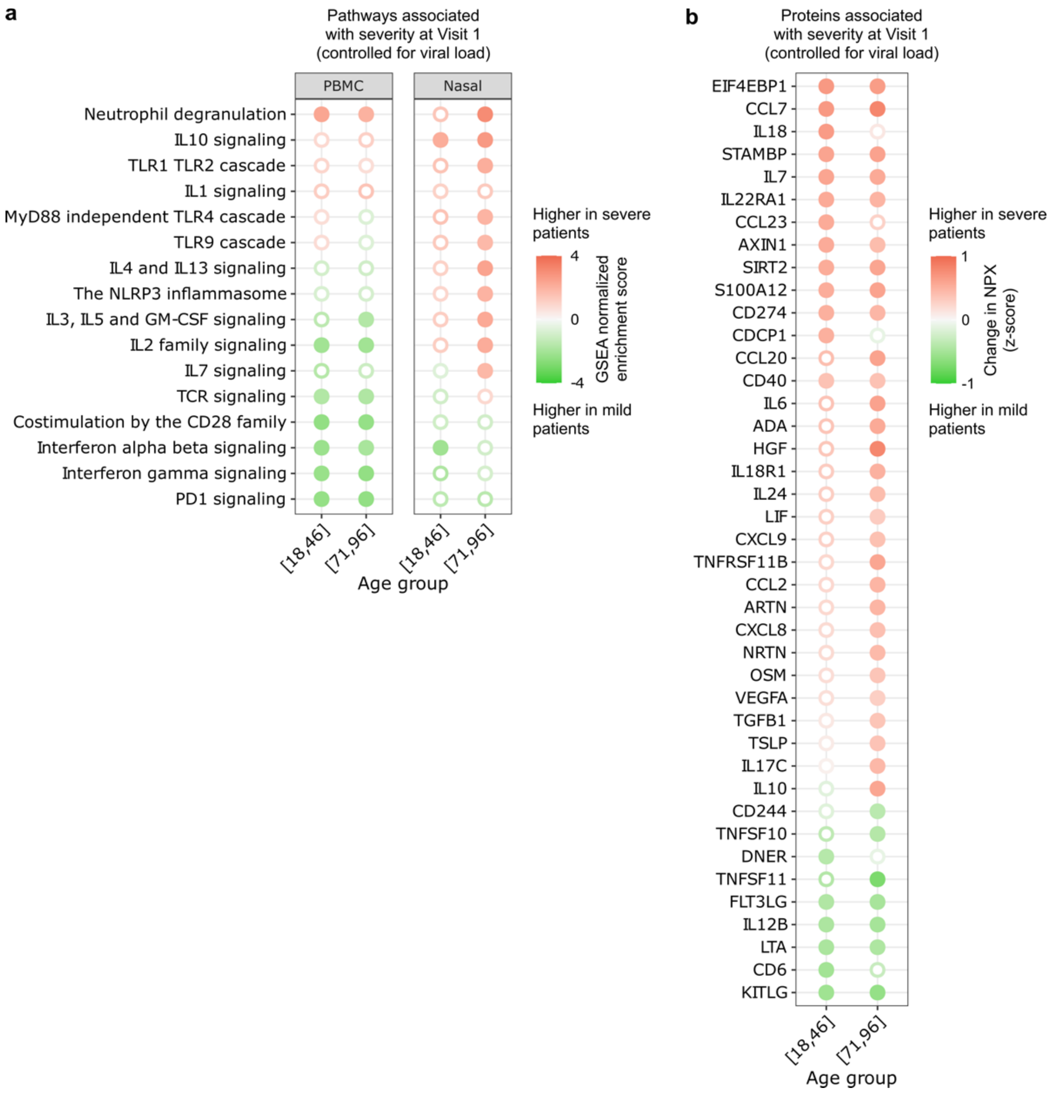
Supplementary Figure 6. Plots of the dynamics of 6 example genes in PBMC samples. Black lines indicate the regression lines for the fixed effects of the linear mixed-effects model. The grey ribbons indicate the 95% confidence intervals of the regression lines. The y-axes were truncated at 1.5× the interquartile range below the first quartile and above the third quartile. P values are calculated using the likelihood ratio test and Benjamini-Hochberg correction.



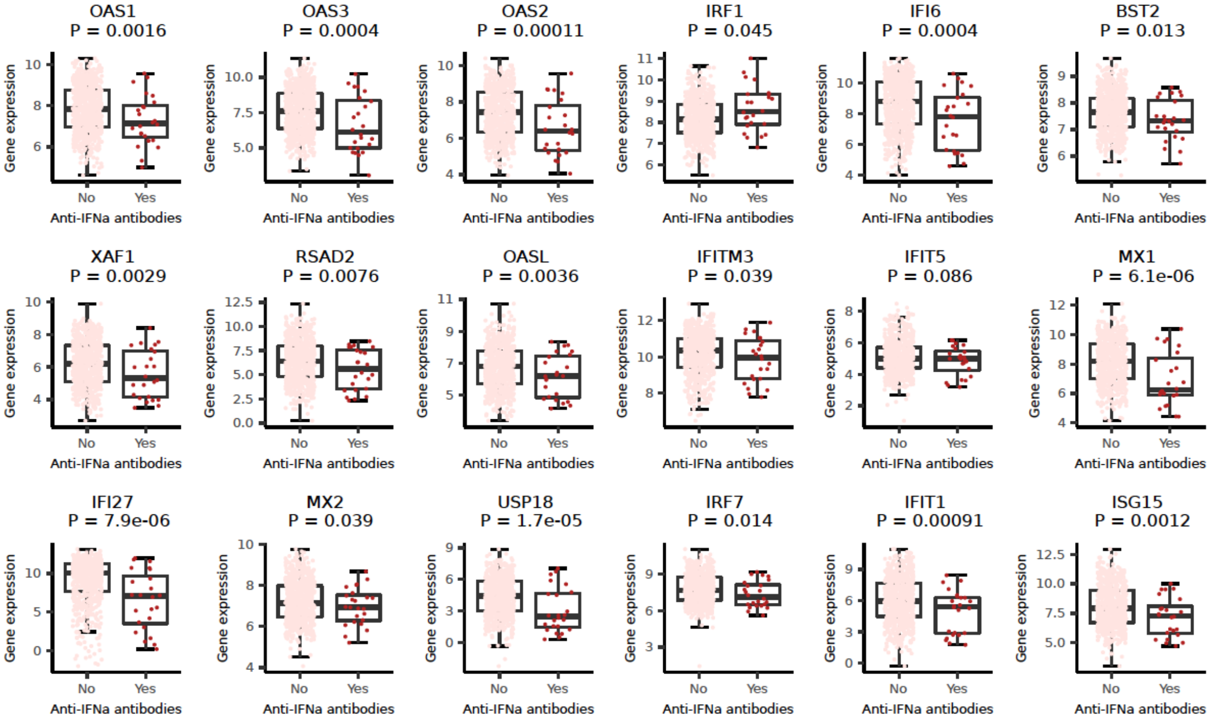
Supplementary Figure 7. Effect of SARS-CoV-2 viral load on age-cytokine relationship at Visit 1, and the dynamics of 4 example cytokines. (a) Bar plot depicting cytokines associated with age (P < 0.05, calculated with linear regression and Benjamini-Hochberg correction), while controlling for SARS-CoV-2 viral load. Supplementary Figure 6a differs from Figure 4a in that the former controlled for viral load, while the latter did not. (b) Plots demonstrating the dynamics of four cytokines TNFSF11, CXCL8, CXCL9, and IL6. Black lines indicate the regression lines for the fixed effects of the linear mixed-effects model. The grey ribbons indicate the 95% confidence intervals of the regression lines. The y-axes were truncated at 1.5× the interquartile range below the first quartile and above the third quartile. P values were calculated using the likelihood ratio test and Benjamini-Hochberg correction.



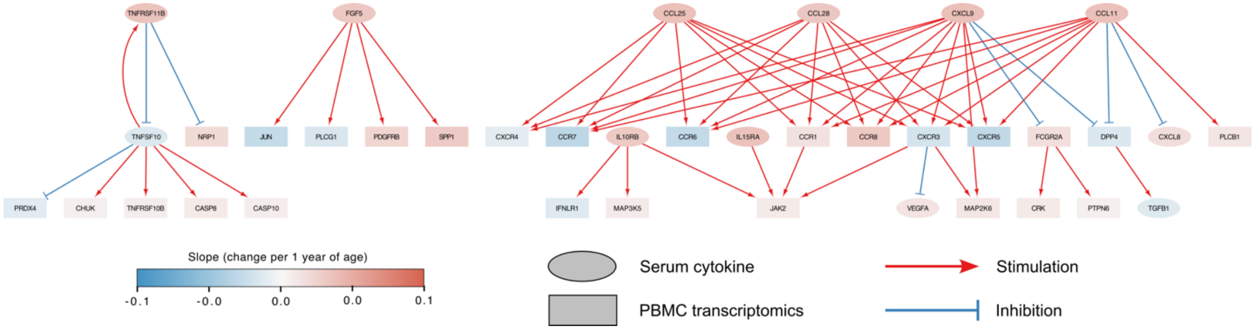
Supplementary Figure 8. Bacterial load (reads per million, rpM) versus age quintiles. Total bacterial abundance (log-transformed rpM, as measured by nasal metatranscriptomics) in each of the age quintiles. P value was calculated with one-way ANOVA test.



Supplementary Figure 9. Aging and COVID-19 severity, analyses controlled for viral load. (a, b) Dot plots depicting a) select Reactome pathways in PBMC or nasal RNA-seq data, and b) serum cytokines (olink) that were upregulated in severe patients (NIAID ordinal scales 5-6) compared to mild/moderate (NIAID ordinal scales 3-4) patients at Visit 1, stratified by age group (youngest or oldest). Analogous analyses to Fig. 7, but controlled for viral load.



Supplementary Figure 10. Expression of interferon-related genes in patients with or without anti-IFN-α antibodies at Visit 1. Normalized gene expression is plotted for the subset of samples with both PMBC RNA-seq and anti-IFNα antibody data available (n=732 visit 1 samples). All genes from the Reactome interferon alpha/beta signaling pathway with an adjusted P-value < 0.05 are included (n=18).



Supplementary Figure 11. Network analysis of the top 10 significant serum proteins and their receptors and downstream signaling. PBMC RNA-seq and serum cytokine data was integrated using Cytoscape.

Supplementary Table 2. Prevalence of viral cases by age quintile over time in the nasal virome. Adjusted P values (P adj, Benjamini-Hochberg method) are determined by ANOVA with respect to change in prevalence of virus over time within each age quintile. HHV = human herpes virus, CMV = cytomegalovirus, EBV = Epstein Barr virus, HSV = herpes simplex virus.

Virus	Age Quantile	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	P adj
CMV (HHV-5)	[18,46]	0.52% (1/191)	1.01% (1/99)	0% (0/53)	1.61% (1/62)	0% (0/4)	0% (0/39)	1.0
	[47,54]	0% (0/175)	0.95% (1/105)	1.61% (1/62)	1.79% (1/56)	0% (0/17)	0% (0/36)	0.61
	[55,62]	0.49% (1/205)	0% (0/128)	0% (0/79)	0% (0/70)	0% (0/20)	0% (0/42)	1.0
	[63,70]	0% (0/190)	1.79% (2/112)	1.24% (1/81)	1.49% (1/67)	4.17% (1/24)	3.03% (1/33)	0.24
	[71,96]	0.47% (1/212)	0% (0/133)	0% (0/94)	1.27% (1/79)	11.54% (3/26)	6.90% (2/29)	1.70E-03
EBV (HHV-4)	[18,46]	0% (0/191)	0% (0/99)	0% (0/53)	0% (0/62)	0% (0/4)	0% (0/39)	1.0
	[47,54]	1.14% (2/175)	3.8% (4/105)	1.61% (1/62)	0% (0/56)	0% (0/17)	0% (0/36)	0.71
	[55,62]	0.49% (1/205)	2.34% (3/128)	2.53% (2/79)	4.29% (3/70)	5.0% (1/20)	4.76% (2/42)	0.24
	[63,70]	1.58% (3/190)	0.89% (1/112)	4.94% (4/81)	2.99% (2/67)	8.33% (2/24)	0% (0/33)	0.24
	[71,96]	0% (0/212)	1.50% (2/133)	4.26% (4/94)	1.27% (1/79)	7.70% (2/26)	3.45% (1/29)	0.039
Pegivirus	[18,46]	0% (0/191)	0% (0/99)	0% (0/53)	1.61% (1/62)	0% (0/4)	2.56% (1/39)	0.24
	[47,54]	0.57% (1/175)	1.9% (2/105)	1.6% (1/62)	5.36% (3/56)	0% (0/17)	5.56% (2/36)	0.24
	[55,62]	0.98% (2/205)	0.78% (1/128)	0% (0/79)	1.43% (1/70)	0% (0/20)	0% (0/42)	1.0
	[63,70]	0% (0/190)	0% (0/112)	0% (0/81)	0% (0/67)	0% (0/24)	0% (0/33)	1.0
	[71,96]	0% (0/212)	0% (0/133)	0% (0/94)	1.27% (1/79)	0% (0/26)	0% (0/29)	0.43
HSV (HHV-1/2)	[18,46]	4.71% (9/191)	8.08% (8/99)	9.43% (5/53)	3.23% (2/62)	0% (0/4)	2.56% (1/39)	0.71
	[47,54]	3.43% (6/175)	5.71% (6/105)	6.45% (4/62)	7.14% (4/56)	11.77% (2/17)	5.56% (2/36)	0.71
	[55,62]	2.44% (5/205)	6.25% (8/128)	8.86% (7/79)	11.43% (8/70)	5.0% (1/20)	9.52% (4/42)	0.13
	[63,70]	3.16% (6/190)	5.36% (6/112)	12.35% (10/81)	13.43% (9/67)	12.50% (3/24)	6.06% (2/33)	0.056
	[71,96]	2.36% (5/212)	5.26% (7/133)	4.26% (4/94)	16.46% (13/79)	30.77% (8/26)	17.24% (5/29)	4.50E-06