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Supplementary Materials

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Supplementary Methods

T cell proliferation staining panels

For PBMCs stained with carboxyfluorescein succinimidyl ester (CFSE; Life Technologies), cells were then washed and stained with anti-CD3 PE-Cy7 (clone SK7; BioLegend), anti-CD8 APC (clone SK1; BioLegend), anti-CD4 BV711 (clone RPA-T4; BioLegend), and LIVE/DEAD violet viability dye (Life Technologies).

For PBMCs stained with Cell Trace Far Red Proliferation Dye (CTFR, Invitrogen), cells were then washed and stained with anti-CD3 APC-Cy7 (clone UCHT1; BioLegend), anti-CD8 BV605 (clone SK1; BioLegend), anti-CD4 PE-Cy7 (clone OKT4; BioLegend), and LIVE/DEAD violet viability dye (Life Technologies).

Generalized estimating equation (GEE)

GEE was performed using “geepack” package (version 1.3.9) in R[1]. In the GEE model, family was set as “gaussian”, and the correlation structure (“corstr”) was set as “independence”. Quasi Information Criterion (QIC) was used to compare models using “independence”, “exchangeable” and “ar1” and the one with “independence” had the lowest QIC. Monoclonal antibody (Mab) use, weeks since symptom onset or first positive PCR, numbers of vaccinations before enrollment, sex, and age were adjusted for in these models. Logarithm base 10 of the neutralizing antibody levels were treated as dependent variables and other variables as independent. Coefficients for all the independent variables were then transformed to the power of 10 and was shown in this figure as fold-change compared to reference group.

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Supplementary Tables

Supplementary Table 1. Categorization for immunocompromising conditions.

Non-Severe (NS)		• Autoimmune disease, receiving immunosuppressants that are not B cell/plasma cell targeted therapy within 12 months of study entry • Solid malignant tumor on treatment (excluding those who underwent resection and were considered in remission after resection) • Corticosteroid use equivalent to Prednisone >20mg daily for at least 14 consecutive days within 30 days prior to study entry • HIV infection with CD4 cell count >200 cells/mm^3
Severe	Severe- Hematological malignancy/Transplant (S-HT)	• Solid organ transplant (SOT) • Hematopoietic stem cell transplant (HSCT) • Lymphoma, leukemia • Immune-Related Adverse Event (irAE) on multiple immunosuppressants targeting different pathways
	Severe- Autoimmune and other B cell deficiency (S-A)	• Autoimmune disease receiving B cell targeted therapy within 12 months of study entry • Congenital or late onset B cell deficiency (e.g. Common Variable Immunodeficiency)

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Supplementary Table 2. Diagnoses for immunocompromised participants and categorization.

ID	Diagnosis	Immunosuppressants/Treatment	Group
100	Antiphospholipid syndrome	Prednisone, eculizumab, rituximab, cyclophosphamide	S-A
101	Heart and kidney transplant	Everolimus, Prednisone 5mg daily, Tacrolimus	S-HT
107	Rheumatoid arthritis	Tocilizumab	NS
113	Minimal change disease	Rituximab within 12 months of COVID-19	S-A
126	RA	Abatacept+ Prednisone 5mg daily	NS
217	RA	Methotrexate+ Prednisone 5mg daily	NS
240	Chronic myelogenous leukemia	Dasatinib	S-HT
245	Diffuse large B-cell lymphoma	Rituximab+Polatuzumab+Prednisone, CAR-T, Chemotherapy, Tocilizumab	S-HT
388	Adenocarcinoma of pancreas	Chemotherapy and radiation	NS
449	Granulomatosis with polyangiitis	Rituximab within 12 months of COVID-19	S-A
459	Immune Related Adverse Events, Metastatic Merkel cell carcinoma	Pembrolizumab, Tacrolimus, Prednisone, Mycophenolate	S-HT
470	Multiple sclerosis	Ocrelizumab within 12 months of COVID-19	S-A
471	Marginal zone lymphoma (CR)	Obinutuzumab+CHOP	S-HT
475	Multiple sclerosis	Rituximab within 12 months of COVID-19	S-A
497	Diffuse large B-cell lymphoma (CR), Hypogammaglobulinemia	Rituximab-CHOP	S-HT
531	Sarcoidosis	Infliximab	NS
532	Granulomatosis with polyangiitis	Mycophenolate	NS
533	Diffuse large B cell lymphoma, Hypogammaglobulinemia after CAR-T	CAR-T, Tocilizumab, Pembrolizumab, Rituximab, Corticosteroid	S-HT
534	RA, Sjogren's syndrome, Hypogammaglobulinemia; cryoglobulinemia	IVIG	S-A
547	RA	Tocilizumab+Methotrexate	NS
548	RA	Rituximab within 12 months of COVID-19+ Leflunomide	S-A
549	Bechet’s disease	Azathioprine	NS
550	RA	Methotrexate+ Hydroxychloroquine	NS
551	Psoriatic arthritis	Infliximab	NS
552	Seronegative spondyloarthropathy	Adalimumab+ Methotrexate	NS
557	RA, SLE	Methotrexate	NS
558	SLE	Belimumab	S-A
563	RA	Adalimumab	NS
564	Multiple myeloma	Daratumumab+ Dexamethasone	S-HT
569	SLE	Hydroxychloroquine+ Methylprednisolone daily 6mg	NS
573	Inflammatory arthritis	Adalimumab+ Hydroxychloroquine	NS

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597	Giant cell arteritis, polymyalgia rheumatica	Tocilizumab+ Prednisone orally 5mg daily	NS
604	CVID	IVIG every 4 weeks	S-A
610	Ulcerative colitis	Infliximab	NS
658	RA	Tocilizumab	NS
678	RA	Tofacitinib	NS
687	SLE, RA	Hydroxychloroquine, methotrexate	NS
688	Mantle cell lymphoma	Zanubrutinib+Venetoclax; Last dose of Obinutuzumab within 12 months	S-HT
691	RA	Rituximab	S-A
708	Minimal change disease	Rituximab	S-A
716	RA	Methotrexate	NS
723	Multiple sclerosis, acquired hypogammaglobulinemia	IVIG every 4 weeks; Ocrelizumab within 12 months	S-A
725	RA	Infliximab, methotrexate, hydroxychloroquine	NS
735	Psoriatic arthritis	Adalimumab	NS
768	Ankylosing spondylitis	Secukinumab	NS
793	RA	Adalimumab, methotrexate	NS
805	Ulcerative colitis, inflammatory arthritis	Golimumab, methotrexate	NS
870	Mantle cell lymphoma	Bendamustine and rituximab within 12 months	S-HT
892	HIV infection	N/A, on antiretroviral therapy, CD4 cell count>200	NS
936	RA	Etanercept, hydroxychloroquine	NS
945	IgG4 related disease	Rituximab	S-A
946	Diffuse large B-cell lymphoma	R-CHOP	S-HT
952	Inflammatory arthritis	Adalimumab	NS
953	RA	Infliximab, methotrexate, prednisone 3mg	NS
965	Breast cancer	Trastuzumab deruxtecan within 12 months, then Olaparib	NS
982	Follicular lymphoma	Bendamustine, Obinutuzumab within 12 months	S-HT

S-HT, severe hematological oncology/Transplant; S-A, severe autoimmune disease/B-cell deficient; NS, non-severe immunocompromise; CAR-T, chimeric antigen receptor T-cell therapy; CR, complete remission; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, Rituximab in combination with CHOP; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; CVID, common variable immunodeficiency

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Supplementary Table 3. Monoclonal antibody use.

	S-HT (N=12)	S-A (N=13)	NS (N=31)	None (N=184)	Overall (N=240)
Bamlanivimab-Etesevimab	1	0	0	4	5
Casirivimab-Imdevimab	0	2[b]	2	5	9
Sotrovimab	4[a]	1	1	0	6
Bebtelovimab	3	2	2	1	8
Tixagevimab-Cilgavimab	5[c]	4	0	0	9

a, three participants received Sotrovimab after blood draws.

b, one participant received Casirivimab-Imdevimab after blood draws.

c, two participants received both Tixagevimab-Cilgavimab and Sotrovimab and one participant received both Tixagevimab-Cilgavimab and Bebtelovimab

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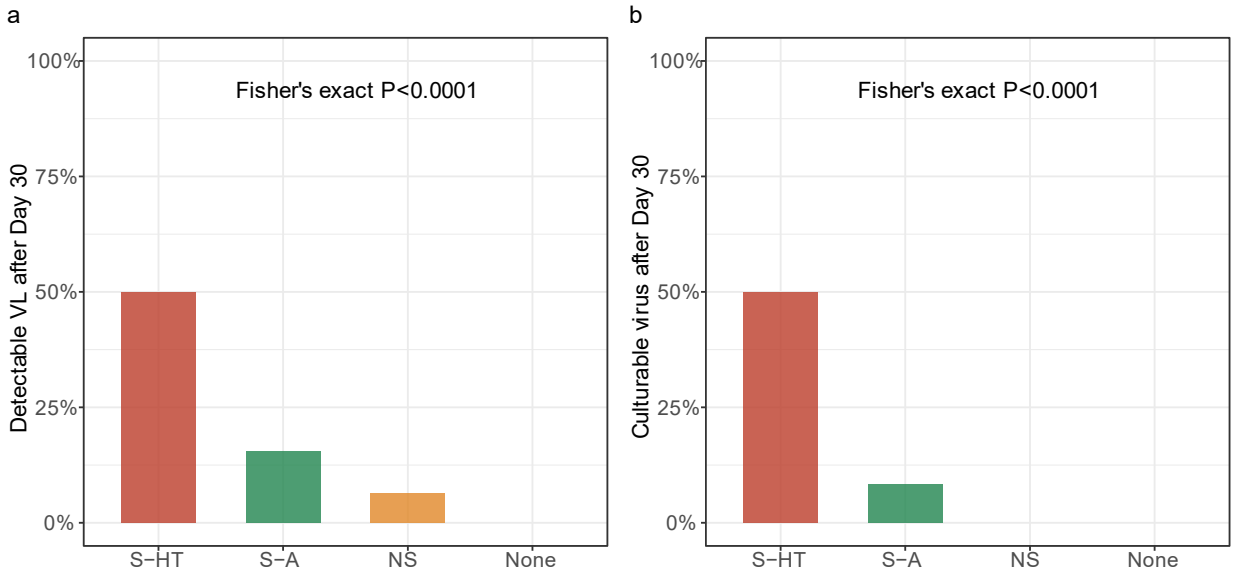
Supplementary Figures



Supplementary Figure 1. Detectable SARS-CoV-2 viral RNA (a) and culturable SARS-CoV-2 virus (b) beyond 30 days after symptom onset or first positive PCR/antigen tests, supplemental to Fig. 1.

Fisher's exact test was used to calculate the P values.

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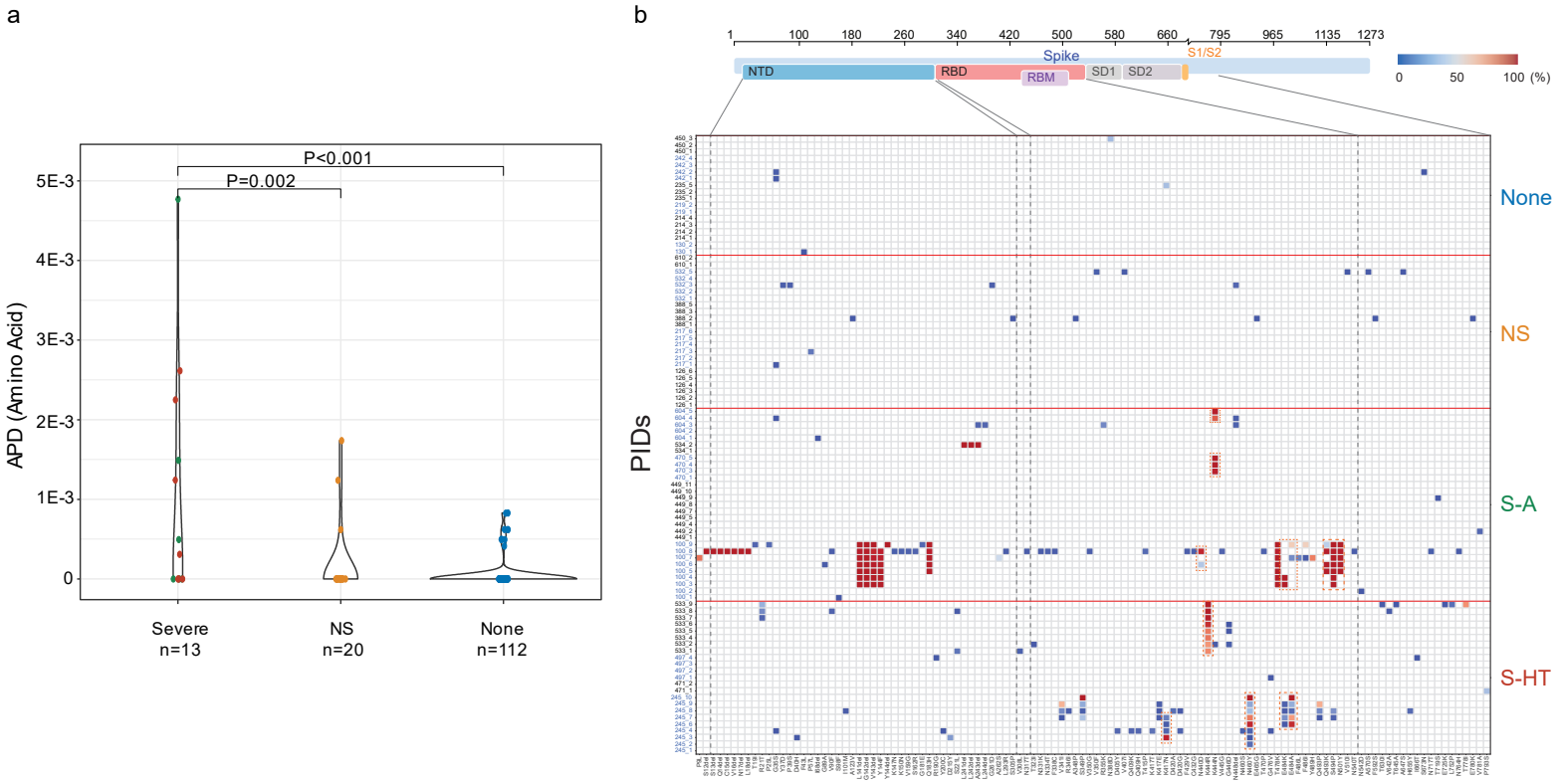

Supplementary Figure 2. SARS-CoV-2 mutations among different immunocompromised groups, supplementary to Fig. 2.

(a), SARS-CoV-2 intrahost mutations at the amino acid level among different immunocompromise groups. (b), Heat map showing distribution of Spike polymorphisms from participants receiving mAb treatment longitudinally. In the heatmap, y axis indicates participants' ID (PID) followed by sequential numbers of sample collection, while x axis shows amino acid positions in the Spike gene. Different domains of Spike are shown at the top. Colors indicate frequency of polymorphisms, with blue indicating the lowest value and red indicating the highest value in the scale. Participants in different study groups are separated by a red horizontal line. mAb resistance mutations are shown by red dotted box.

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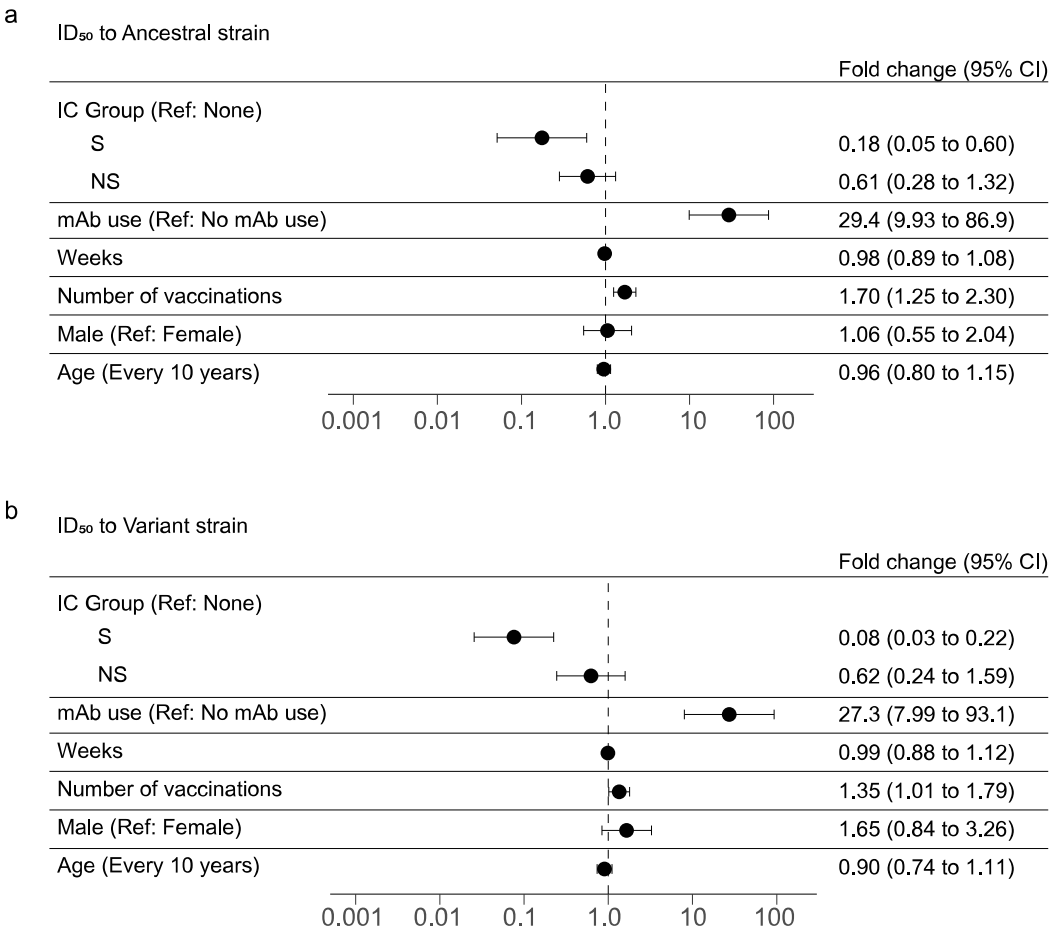

Supplementary Figure 3. Severe immunocompromise is associated with lower neutralizing antibody levels, supplemental to Fig. 3.

Generalized estimation equation to account for longitudinal repeated measurements was used to estimate the association between immunocompromise groups and neutralizing antibody levels against ancestral SARS-CoV-2 Spike protein (a) and variant-specific Spike protein (b). Monoclonal antibody (mAb) use, weeks since symptom onset or first positive PCR/antigen, numbers of vaccinations before enrollment, sex, and age were adjusted for in these models.

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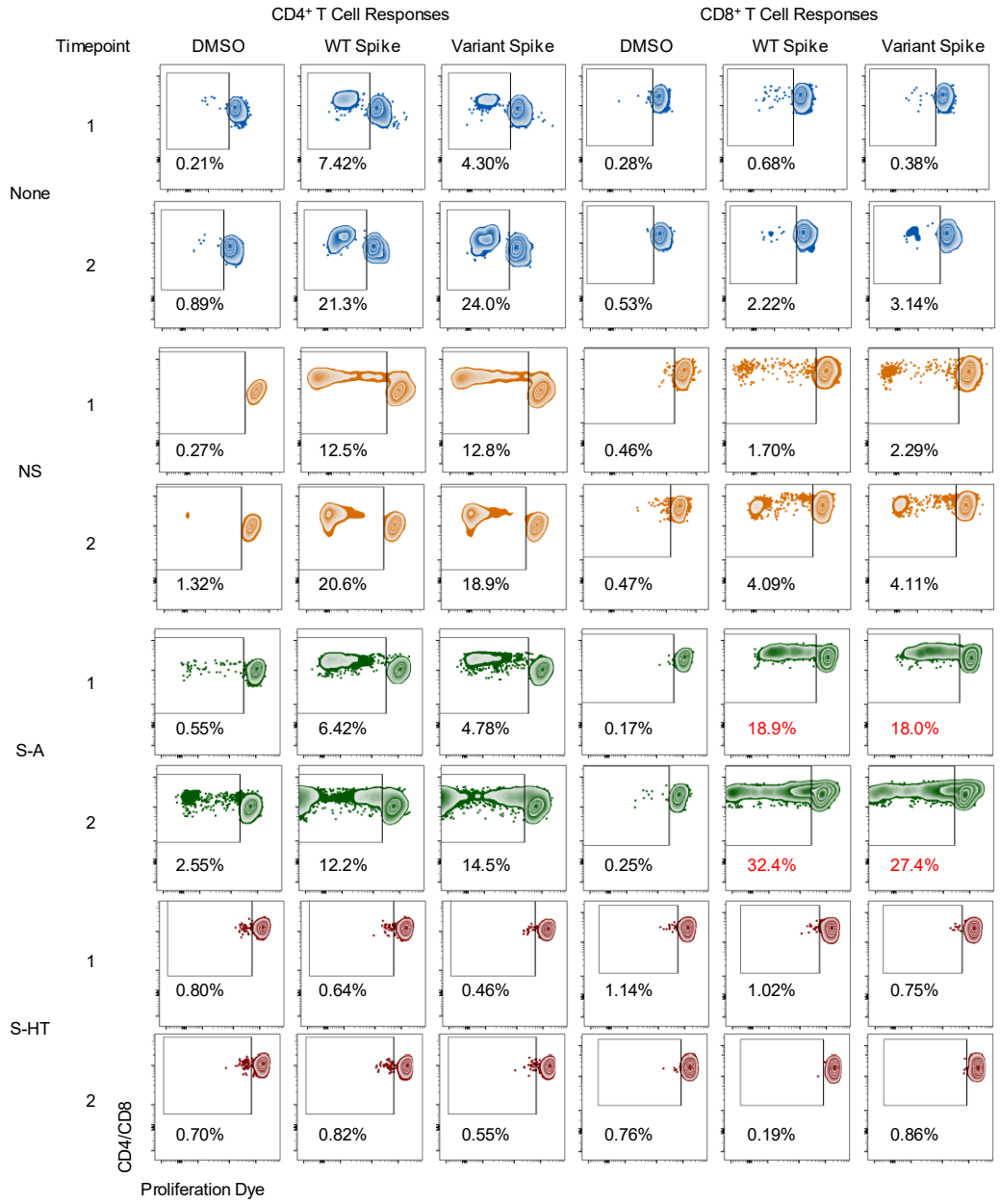

Supplementary Figure 4. Representative T cell proliferation assay gating scheme, supplementary to Fig. 4.

CD4+ and CD8+ T cell proliferation results from representative participants in each immunocompromise group are shown. Non-immunocompromised group, ID=261 (Omicron, BA.1); Non-severe group (NS), ID= 768 (Omicron, BF.5); Severe-autoimmune/B-cell deficient (S-A), ID=534 (Omicron, BA.2); Severe- hematological malignancy/transplant (S-HT), ID= 245 (Delta, B.1.617.2).

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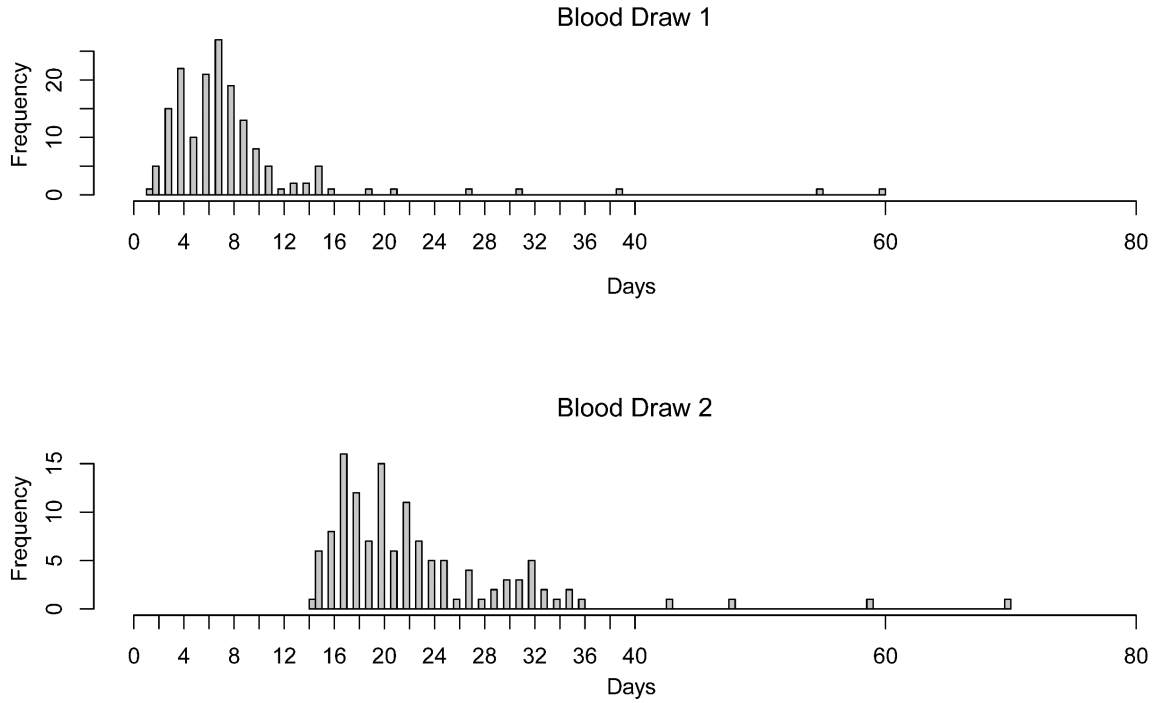

Supplementary Figure 5. Distribution of duration between symptom onset or first positive PCR and blood draws.

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