Immune responses and clinical outcomes after COVID-19 vaccination in patients with liver disease and in liver transplant recipients

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Supplementary methods

Ethical and regulatory approvals

All centres involved in the EASL supported COVID-Hep vaccine registry recruited participants through local ethics approvals as follows: University Medical Center Hamburg-Eppendorf (approved by local ethics committee, Hamburg, Germany) ref No. PV7103 and PV7298; Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico: part of PoIImmuneCOVID study (No. 286_2021) approved by INMI "Lazzaro Spallanzani" Ethics Committee (Roma, Italy); University of Padova: URC code COVID16; University of Barcelona: Reg. No. HCB/2021/0632 approved by Comité de ética e investigación médica (CEIM). The UK OCTAVE study was approved by the UK Medicines and Healthcare Products Regulatory Agency and London and Chelsea Research Ethics Committee (REC reference: 21/HRA/0489). The PITCH study is a sub-study of the SIREN study, which was approved by the Berkshire Research Ethics Committee, Health Research 250 Authority (REC reference: 20/SC/0230). All PBMCs collected at participating sites that were centralised to the University of Oxford were transferred and stored in accordance with the UK Human Tissue Act.

Anti-SARS-CoV-2 VoC IgG binding and ACE2 inhibition

In order to assess antibody responses to VoC, IgG titres to the spike protein of wild-type SARS-CoV-2 and nine of the most prevalent Omicron subvariants (as of February 2023: B.1.1.529/BA.1/BA.1.15, BA.2.75, BA.2.75.2, BA.4.6, BA.5, BF.7, BQ.1, BQ.1.1, and XBB.1) were assessed using a multiplexed MSD® immunoassay (K15668U). In brief, antigens were spotted at 200−400 µg/mL in 96-well plates which were blocked with MSD® Blocker A for 30 minutes. Following washing plasma/serum samples were diluted 1:10,000 and 1:30,000 in diluent buffer and incubated for 2 hours. Samples were then washed and detected using a MESO® SECTOR S 600 Reader. Concentrations were expressed in Units/ml (U/mL).

To assess functional antibody responses, a V-PLEX SARS-CoV-2 Panel 33 (ACE2) Kit (K15679U) was used to measure the ability of serum/plasma samples to inhibit angiotensin-converting enzyme 2 (ACE2) binding to the RBD of wild-type and the same Omicron subvariants listed above. Assays were performed as per manufacturer's instructions with 1:10 and 1:100 dilutions of serum/plasma. Percentage ACE2 inhibition was determined by comparison of chemiluminescence of sample spots compared to negative controls (blanks) on each plate.

IFNγ T-cell ELISpot assay

200,000 thawed PBMCs were rested for 3 hours and added to Multiscreen-IP filter plates (Millipore) coated with capture antibody (clone 1-D1K). Overlapping peptide pools (18-mers with 10 amino acid overlap, Mimotopes) representing wild-type S1 and S2 regions, membrane, and N proteins were added at a final concentration of 2ug/ml for 16–18hrs at 37°C. Selected samples also included pools covering

the entire Omicron (B.1.1.529, BA.1) S1 and S2 regions, and pools including only peptides which contained mutations in BA.1 spike, or the analogous peptides from wild-type (minipools). CEF and concanavalin A were used as positive controls, DMSO in Rab10 was used as a negative control. Plates were developed and then read using a CTL immunocapture (Cellular Technology Limited) plate reader, using Smartcount® settings. Mean spots from DMSO negatives are removed from stimulation to give antigen-specific responses. A positive IFNγ response was defined as mean DMSO + 2 standard deviations.

Breakthrough SARS-CoV-2 infection after COVID-19 vaccination

Rates of breakthrough infection were plotted over time for each of the 4 recruiting countries alongside the corresponding proportions of circulating viral variants. Country-specific proportions of SARS-CoV-2 variants were calculated based on data shared via GISAID [1] EpiCoV database, downloaded 23 March 2023. The date on which Omicron became the dominant variant (defined as representing >90% of circulating variants) was 1st January 2022 in the UK, 16th January 2022 in Italy and Spain, and 23rd January 2022 in Germany.

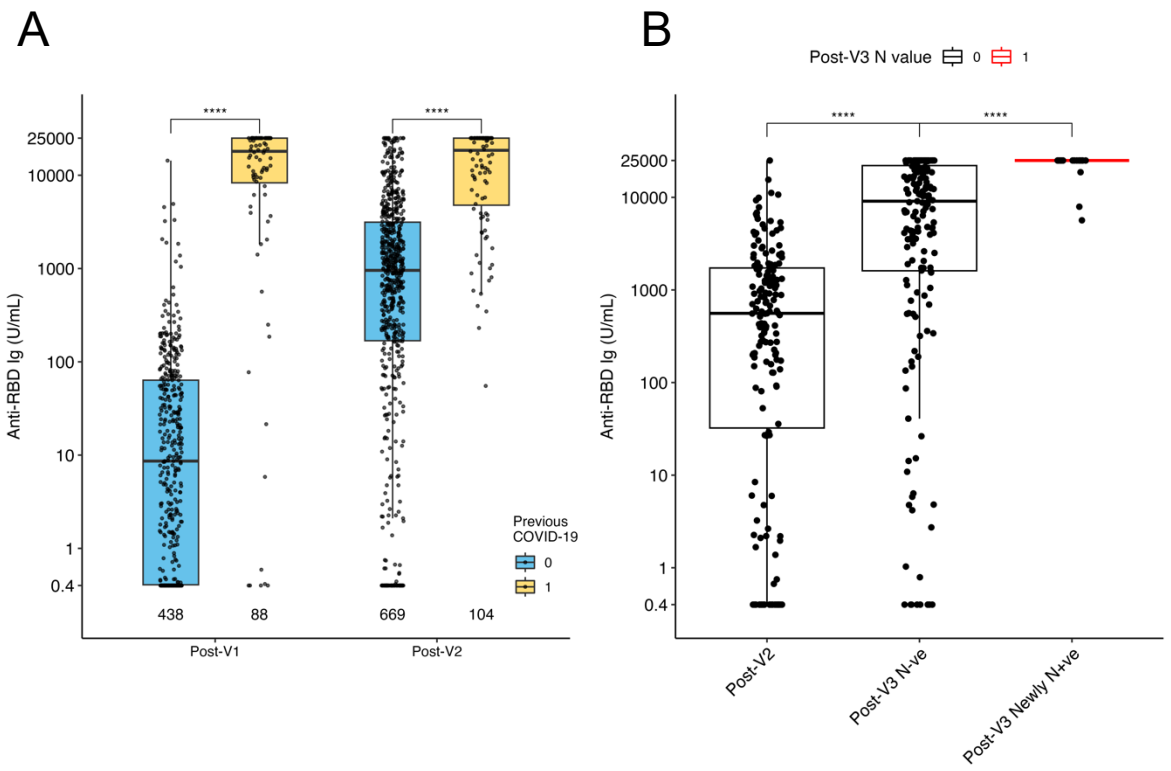

Fig. S1. A) Magnitude of anti SARS-CoV-2 RBD Ig in infection naïve and previously SARS-CoV-2 infected individuals at post-V1 and post-V2 timepoints. B) Magnitude of anti SARS-CoV-2 RBD Ig in Naïve individuals at post-V2 and post-V3 timepoints and in individuals who became nucleocapsid positive between second and third vaccines (Post-V3 Newly N+ve). Boxes represent median and IQR, whiskers represent +/- 1.5x IQR. Mann Whitney U test used, adjusted P value presented.

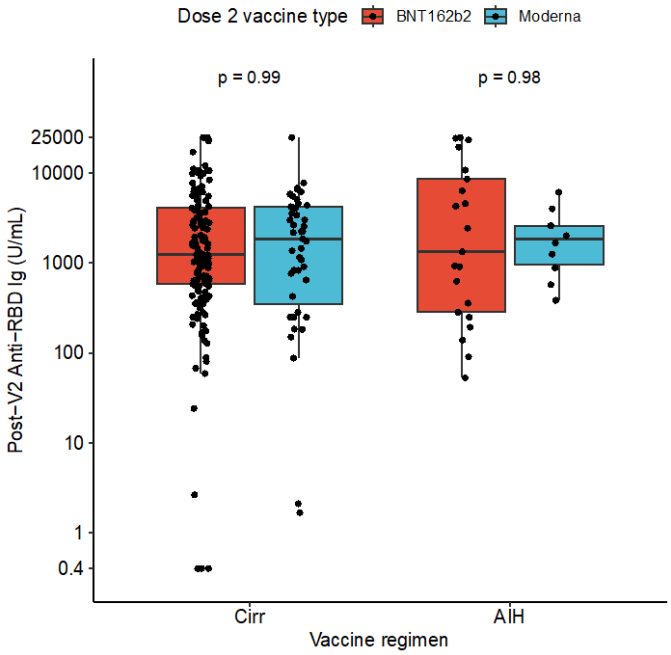

Fig. S2. Magnitude of anti-SARS-CoV-2 RBD Ig in BNT162b2 and mRNA=1273 (Moderna) vaccinated SARS-CoV-2 infection naive individuals from the cirrhosis and autoimmune hepatitis (AIH) disease groups at the post-V2 timepoint. Boxes represent median and IQR, whiskers represent +/- 1.5x IQR. Mann-Whitney U test used, adjusted P value presented.

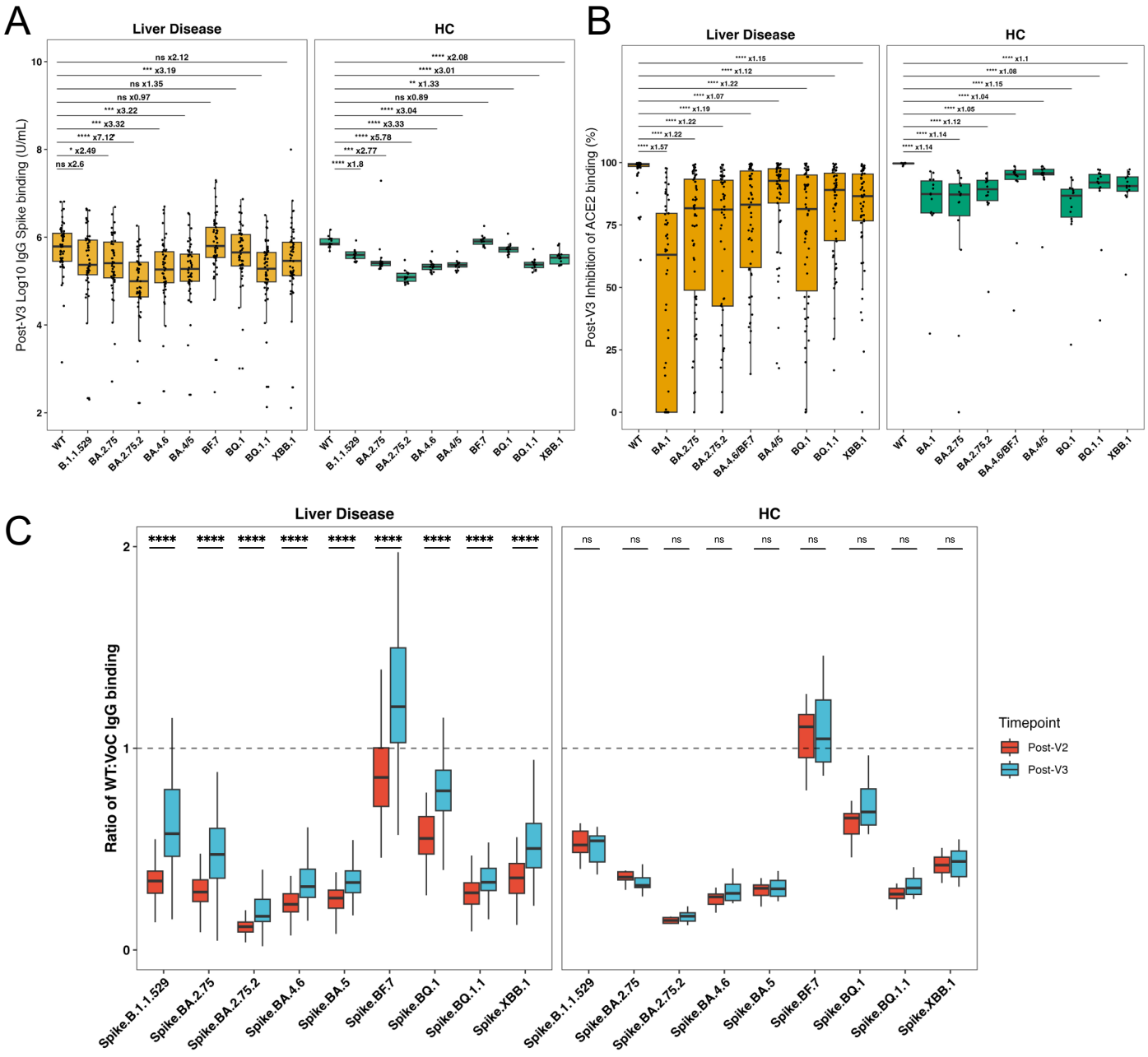

Fig. S3. Post-v3 IgG (A) and ACE2 inhibition (B) to SARS-CoV-2 VoC, separated by liver disease versus healthy controls. C) Ratio of IgG binding to WT and each respective VoC at post-v2 and post-v3 timepoints in liver disease and HC. Two-sided Mann-Whitney U test adjusted with Holm-Bonferroni. Fold-change of median depicted. Boxes represent median and IQR, whiskers represent +/- 1.5x IQR. HC = healthy controls; ACE2 = angiotensin-converting enzyme 2, WT = wild-type. * = P<0.05, ** = P<0.01, *** = P<0.001, **** = P < 0.0001.

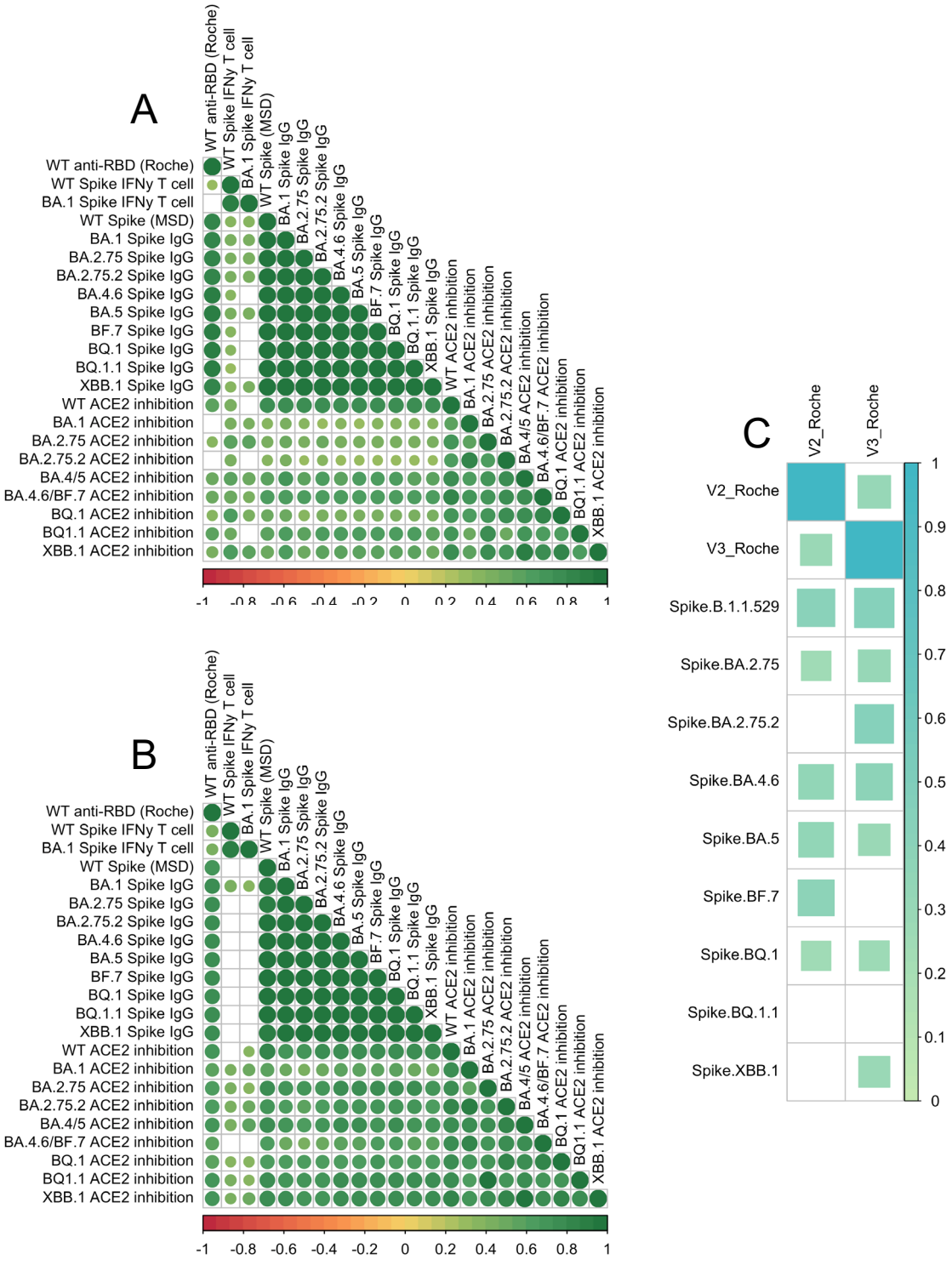

Fig. S4. Correlation of immune assays at A) post-v2 and B) post-v3 timepoints. C) correlation of WT anti-RBD Ig with ratios of WT:VoC binding at post-V2 and post-V3 timepoint. Only significant correlations (P<0.05) are shown. Spearman's correlation. Size and shade of spots/squares represent r value**.** V2_Roche = post-V2 anti-RBD Ig; V3_Roche = post-V3 anti-RBD Ig

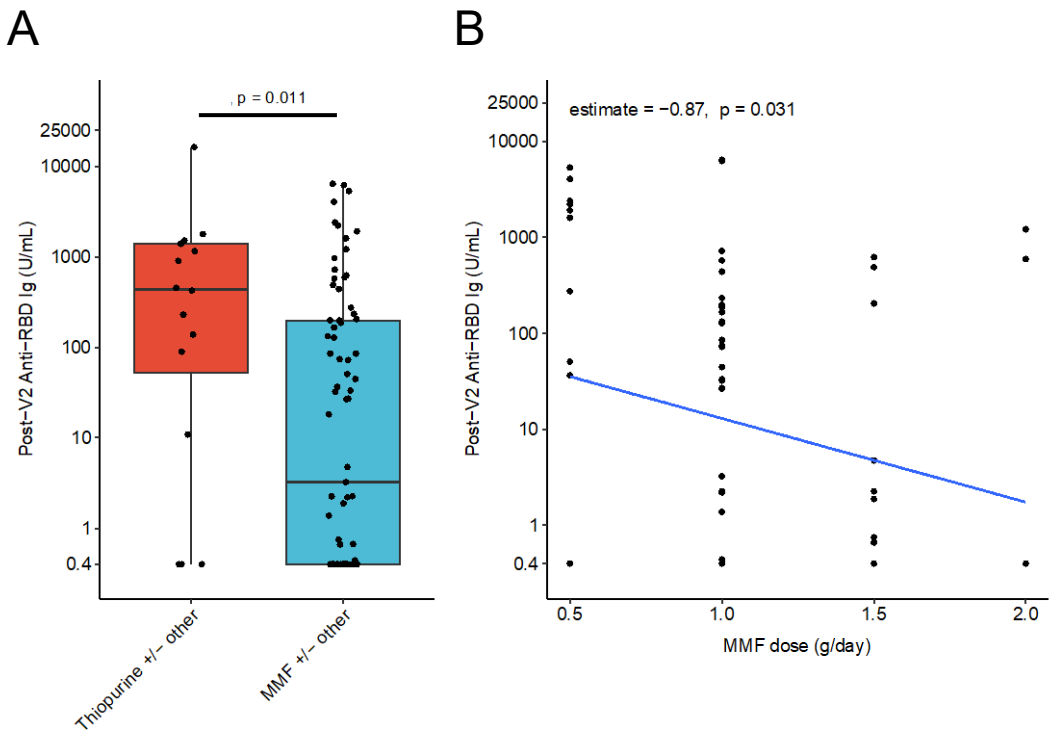

Fig. S5. A.) Anti-RBD Ig responses at the post-V2 timepoint in SARS-CoV-2 infection naive LT recipients who received either thiopurine (Azathioprine or 6-mercaptopurine) or Mycophenolate mofetil (MMF) as an immunosuppressive therapeutic. Participants may have received other immunosuppressive therapeutics in addition. B) MMF dose breakdown (gram/day) in SARS-CoV-2 infection naïve LT recipients at post-V2 timepoint. Linear model of log10 transformed Anti-RBD Ig compared with daily MMF dose. Line represents linear fit, shading represents 95% confidence interval. Boxes represent median and IQR, whiskers represent +/- 1.5x IQR. A) Statistical comparison with Mann-Whitney U test.

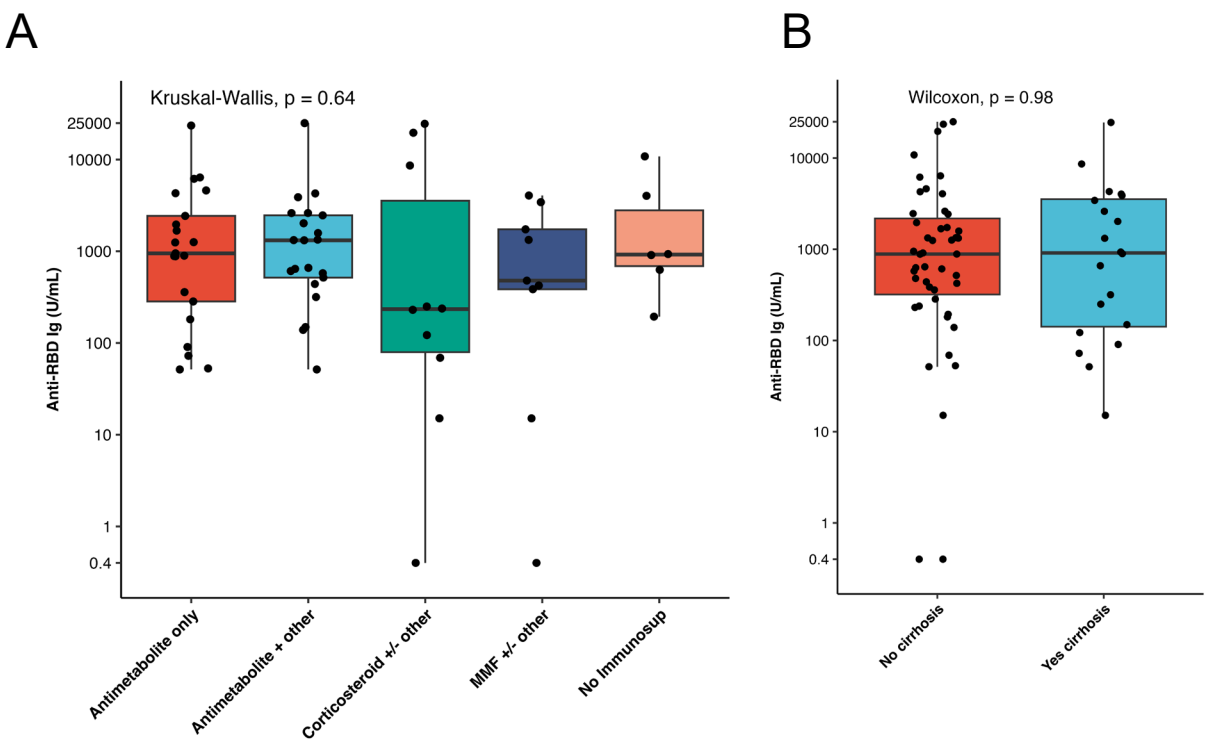

Fig. S6. SARS-CoV-2 infection naïve patients with autoimmune hepatitis at post-v2 timepoint, comparing A) immunosuppressive therapies and B) presence of cirrhosis. Boxes represent median and IQR, whiskers represent +/- 1.5x IQR. Kruskal Wallis (A) or Two-sided Mann-Whitney U test (B). Antimetabolites include 6-mercaptopurine and azathioprine. MMF = Mycophenolate mofetil.

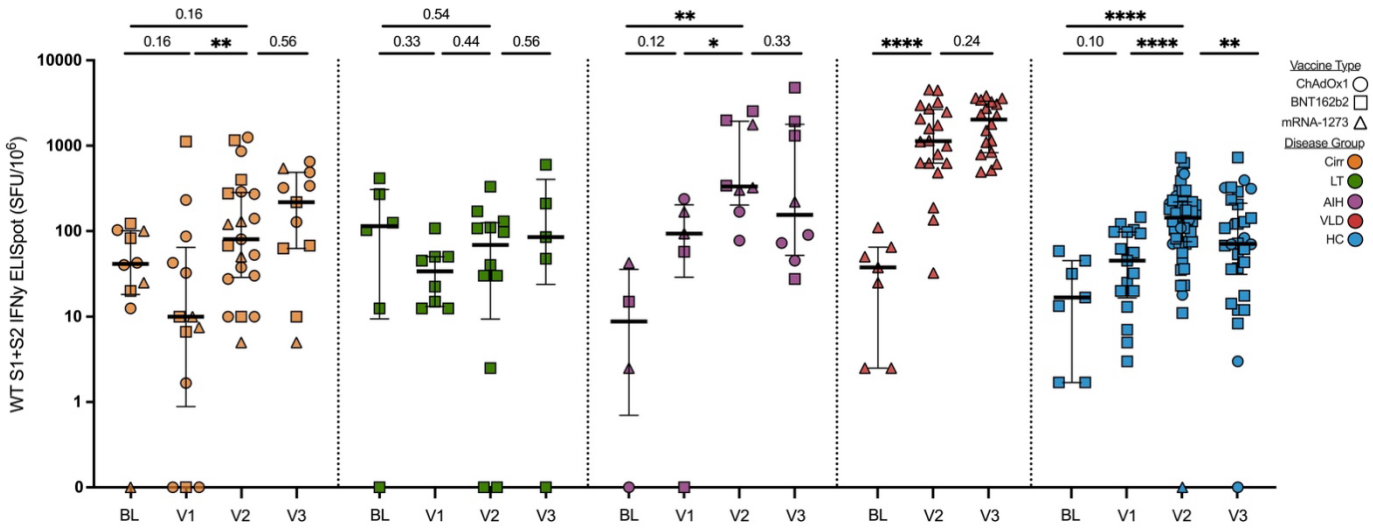

Fig. S7. As in Figure 5A, magnitude of IFN-γ T cell response to wild-type SARS-CoV-2 spike peptides across time in a subgroup of SARS-CoV-2 naïve people with cirrhosis (Cirr, n = 24), liver transplant recipients (LT, n = 12), autoimmune hepatitis (AIH, n=12), vascular liver disease (VLD, n = 22) and healthy controls (HC, n = 28). Baseline data are from same individuals later timepoints. Vaccine type indicated by point of shape. Mann-Whitney U test.

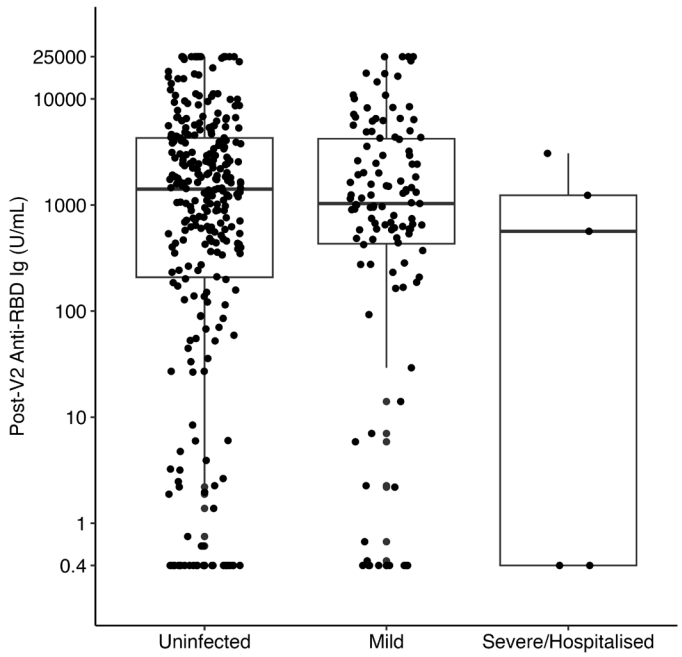

Fig. S8. Anti-RBD Ig at post-v2 timepoint in individuals who did not get breakthrough SARS-CoV-2 infection, had mild-moderate breakthrough SARS-CoV-2 infection or had severe SARS-CoV-2 breakthrough infection after vaccination.

		Baseline		Post-V1			Post-V2			Pre-V3			Post-V3			
Vaccine Type	**Disease group**	**N**	**Median (IQR)**	**N**	**Median (IQR)**	**P val[1]**	**N**	**Median (IQR)**	**Pval[2]**	**N**	**Median (IQR)**	**P val[3]**	**N**	**Median (IQR)**	**P val[4]**	**P val[5]**
ChAdOx1	Cirr	15	0.4 (0.4-0.4)	34	19.6 (3.3-37.1)	1	85	1106 (395-1838)	$7.2x10^{-11}$	4	637 (281-6956)	1	6	15368 (11784-22791)	1	0.3
	AIH	6	0.4 (0.4-0.4)	20	15.1 (1.6-41.9)	1	34	498 (129-1323)	$4.3x10^{-4}$	2	312 (237-387)	1	3	15401 (11133-20201)	1	1
	LT	6	0.4 (0.4-0.4)	27	0.4 (0.4-19.0)	1	52	63 (0.4-608)	0.1	2	151 (133-170)	1	2	3133 (1572-4694)	1	1
	HC	-	-	10	187.5 (87.0-392)	N/A	20	1198 (855-1546)	0.02	-	-	N/A	-	-	N/A	N/A
mRNA	Cirr	156	0.4 (0.4-0.4)	153	13.3 (2.5-55.6)	$9.2x10^{-11}$	204	1413.5 (578-4140)	$6.6x10^{-23}$	52	476 (214-958)	0.35	102	18015 (5927-25000)	$1.5x10^{-8}$	$2.2x10^{-6}$
	AIH	19	0.4 (0.4-0.4)	19	16.6 (1.8-71.6)	0.87	33	1341 (577-4605)	0.002	11	815 (316-2035)	1	10	18280.5 (13784-25000)	0.73	1
	LT	117	0.4 (0.4-0.4)	119	0.4 (0.4-1.6)	0.09	179	114 (0.4-1113)	$2.9x10^{-13}$	105	92 (7-390)	1	95	1861 (34-13534)	0.003	$9.4x10^{-5}$
	VLD	30	0.4 (0.4-0.4)	29	147 (116-203)	0.10	27	4880 (3203-7663)	$4.7x10^{-4}$	25	1943 (1441-2907)	1	24	25000 (25000-25000)	0.002	0.1
	HC	-	-	27	98.7 (57.2-148)	N/A	35	15634 (10829-21445)	$3.2x10^{-11}$	22	2171 (1584-3416)	0.007	23	25000 (18359-25000)	$2.1x10^{-5}$	1

Table S1: In SARS-CoV-2 infection naïve individuals, Roche anti-RBD antibody response to one, two and three doses of COVID-19 vaccine, separated by vaccine type and disease group. [1] comparison of Baseline and Pre-V2, [2] comparison of Pre-V2 and Post-V2, [3] comparison of Post-V2 and Pre-V3, [4] comparison of Pre-V3 and Post-V3, [4] comparison of Post-V2 and Post-V3. Kruskal Wallis with Dunn's post-hoc test, adjusted for multiple comparisons using Bonferroni correction. Cir = Cirrhosis, AIH = Autoimmune hepatitis, LT = Liver transplant, Az = AstraZeneca vaccine.

	Univariable		Multivariable	
Variable	**Estimate (95% CI)**	**P value**	**Estimate (95% CI)**	**P value**
Age 45-64	-0.6 (-0.8 - -0.3)	4.81E-06	-0.3 (-0.6 - -0.1)	0.0034
Age 65-74	-0.9 (-1.2 - -0.7)	5.22E-11	-0.5 (-0.8 - -0.3)	8.91E-05
Age 75+	-1 (-1.4 - -0.7)	1.38E-07	-0.6 (-0.9 - -0.2)	0.001
Male sex	-0.3 (-0.5 - -0.1)	0.0030	-0.1 (-0.3 - 0)	0.12
Obesity	0.2 (-0.1 - 0.4)	0.17	-	NA
Hypertension yes	-0.3 (-0.5 - -0.1)	0.013	0 (-0.2 - 0.1)	0.75
Current smoker	0.2 (-0.1 - 0.5)	0.21	-0.1 (-0.4 - 0.1)	0.33
Previous smoker	0.2 (-0.1 - 0.4)	0.16	0.1 (-0.1 - 0.3)	0.29
AIH	-1 (-1.3 - -0.6)	6.81E-08	-0.3 (-0.7 - 0)	0.084
Cirr	-0.7 (-1 - -0.5)	5.01E-08	-0.1 (-0.4 - 0.2)	0.50
LT	-2.1 (-2.4 - -1.8)	1.11E-46	-1.4 (-1.7 - -1.1)	6.18E-18
VLD	-0.2 (-0.7 - 0.2)	0.33	0.2 (-0.3 - 0.6)	0.50
mRNA vaccine	0.3 (0.1 - 0.5)	0.011	0.4 (0.2 - 0.6)	3.39E-06
Heterologous vaccine	1 (0.3 - 1.7)	0.0074	1.3 (0.8 - 1.9)	6.18E-06
Previous COVID-19	1.4 (1.1 - 1.6)	3.43E-23	1 (0.8 - 1.2)	1.47E-16

Table S2: Linear regression model of post-v2 log10 transformed anti-RBD Ig across entire cohort. Age variable is compared to 18-44year old age group. * indicates significant values (P<0.05)

	Comparison groups		Timepoints	
	Group 1	Group 2	Post-V2 (p val)	Post-V3 (p val)
AstraZeneca	Cirr	AIH	0.06	-
	Cirr	LT	2.00E-08*	-
	Cirr	HC	0.57	-
	AIH	LT	0.01*	-
	AIH	HC	0.06	-
	LT	HC	0.000017*	-
mRNA	Cirr	AIH	0.69	0.50999
	Cirr	LT	2.00E-15*	1.98E-08*
	Cirr	VLD	0.0039*	0.00031*
	Cirr	HC	1.30E-10*	0.06007
	AIH	LT	3.40E-06*	0.00219*
	AIH	VLD	0.05	0.12800
	AIH	HC	5.96E-06*	0.57498
	LT	VLD	5.90E-12*	9.10E-13*
	LT	HC	1.28E-27*	1.6641E-07*
	VLD	HC	0.03*	0.23352

Table S3: In infection naïve individuals, comparison of Roche anti-RBD antibody response across disease groups at post-V2 and post-V3. Comparisons at post-v3 in AstraZeneca vaccinated individuals not made due to low n numbers. Kruskal Wallis with Dunn's post-hoc test, adjusted for multiple comparisons using Benjamini Hochberg. Cir = Cirrhosis, AIH = Autoimmune hepatitis, LT = Liver transplant, Az = AstraZeneca vaccine. * indicates statistical significance (P<0.05)

Disease group	Vaccine platform	Timepoint	Seronegative (%)	Seropositive (%)
Cir	ChAdOx1	Post-V1	4 (12%)	30 (88%)
		Post-V2	-	85 (100%)
		Post-V3	-	6 (100%)
	mRNA	Post-V1	20 (13%)	133 (87%)
		Post-V2	4 (2%)	200 (98%)
		Post-V3	2 (2%)	100 (98%)
LT	ChAdOx1	Post-V1	14 (52%)	13 (48%)
		Post-V2	18 (35%)	34 (65%)
		Post-V3	-	2 (100%)
	mRNA	Post-V1	80 (67%)	39 (33%)
		Post-V2	52 (29%)	127 (71%)
		Post-V3	9 (9%)	86 (91%)
AIH	ChAdOx1	Post-V1	4 (20%)	16 (80%)
		Post-V2	2 (6%)	32 (94%)
		Post-V3	-	3 (100%)
	mRNA	Post-V1	4 (21%)	15 (79%)
		Post-V2	-	33 (100%)
		Post-V3	-	10 (100%)
VLD	mRNA	Post-V1	1 (3%)	28 (97%)
		Post-V2	-	27 (100%)
		Post-V3	-	24 (100%)
HC	ChAdOx1	Post-V1	-	10 (100%)
		Post-V2	-	20 (100%)
		Post-V3	-	-
	mRNA	Post-V1	-	27 (100%)
		Post-V2	-	35 (100%)
		Post-V3	-	23 (100%)

Table S4: In infection naïve individuals, comparison of Roche anti-RBD antibody response rate across disease groups at post-V2 and post-V3. Seropositive defined as >0.8AU/mL by anti-RBD Ig assay. Cir = Cirrhosis, AIH = Autoimmune hepatitis, LT = Liver transplant, VLD = Vascular liver disease; HC = healthy control

	Univariable		Multivariable	
Variable	**Odds Ratio (95% CI)**	**P value**	**Odds Ratio (95% CI)**	**P value**
Age 45-64	0.61 (0.3 - 1.2)	0.17	0.36 (0.078 - 1.2)	0.14
Age 65-74	0.33 (0.16 - 0.69)	0.0035	0.19 (0.038 - 0.67)	0.017
Age 75+	0.49 (0.2 - 1.2)	0.11	0.38 (0.067 - 1.8)	0.23
Male sex	0.69 (0.44 - 1.1)	0.12	0.96 (0.48 - 1.9)	0.9
ALF	0.98 (0.4 - 2.4)	0.96	-	-
HCC	0.99 (0.54 - 1.8)	0.97	-	-
Decompensation	0.77 (0.49 - 1.2)	0.25	-	-
<2yrs post-transplant	0.52 (0.28 - 0.96)	0.038	0.43 (0.18 - 1)	0.054
mTORi only	0.83 (0.32 - 2.2)	0.7	0.49 (0.12 - 2.2)	0.32
CNI + Other	0.66 (0.38 - 1.2)	0.14	0.56 (0.23 - 1.3)	0.2
CNI + MMF	0.37 (0.22 - 0.63)	0.00029	0.42 (0.19 - 0.93)	0.036
mRNA vaccine	1.3 (0.76 - 2.2)	0.34	1.6 (0.74 - 3.3)	0.23

Table S5: Logistic regression models of anti-RBD seropositivity (>0.8U/mL) in liver transplant recipients following two doses of COVID-19 vaccine. Age is a continuous variable, all other variables are discrete. Age is compared to 18-44 age group. Previous COVID-19 was removed as a variable as 100% of patients with previous COVID-19 had responses >0.8U/mL.

	Univariable		Multivariable	
Variable	**Odds Ratio (95% CI)**	**P value**	**Odds Ratio (95% CI)**	**P value**
Age 45-64	-0.49 (-1.1 - 0.14)	0.13	-0.31 (-0.9 - 0.28)	0.31
Age 65-74	-0.62 (-1.3 - 0.08)	0.081	-0.55 (-1.2 - 0.12)	0.11
Age 75+	-0.5 (-1.5 - 0.51)	0.32	-0.81 (-1.8 - 0.14)	0.1
Antimetab. +/- other	0.16 (-0.4 - 0.72)	0.56	-0.0093 (-0.55 - 0.53)	0.97
Cirrhosis yes	0.1 (-0.39 - 0.59)	0.68	0.092 (-0.36 - 0.54)	0.69
Corticosteroid +/- other	-0.49 (-1.2 - 0.22)	0.17	-0.46 (-1.2 - 0.23)	0.2
Male sex	0.4 (-0.22 - 1)	0.2	0.36 (-0.24 - 0.97)	0.24
MMF +/- other	-0.45 (-1.2 - 0.27)	0.22	-0.34 (-1 - 0.35)	0.34
mRNA vaccine	0.83 (0.42 - 1.2)	0.00013	0.76 (0.31 - 1.2)	0.0016
No immunosupp.	0.45 (-0.32 - 1.2)	0.25	-0.47 (-1.3 - 0.33)	0.26
Previous COVID-19	1.1 (0.26 - 2)	0.011	1.1 (0.28 - 2)	0.012

Table S6: Linear regression models of log10 anti-RBD in autoimmune hepatitis patients following two COVID-19 vaccine. Age is compared to 18-44year old category. Drugs compared to antimetabolite alone group.

	Univariable		Multivariable	
Variable	**Estimate (95% CI)**	**P value**	**Estimate (95% CI)**	**P value**
Age 45-64	-0.27 (-0.64 - 0.11)	0.16	-0.37 (-0.8 - 0.069)	0.098
Age 65-74	-0.32 (-0.7 - 0.069)	0.11	-0.39 (-0.83 - 0.055)	0.086
Age 75+	-0.55 (-1 - -0.088)	0.02	-0.52 (-1 - -0.029)	0.038
Male sex	-0.032 (-0.22 - 0.16)	0.74	0.0087 (-0.19 - 0.2)	0.93
MELD	-0.064 (-0.11 - -0.02)	0.0043	-0.085 (-0.13 - -0.039)	0.00032
CP-B/C	0.042 (-0.15 - 0.23)	0.67	0.071 (-0.16 - 0.3)	0.54
ALD	0.04 (-0.14 - 0.22)	0.67	0.0091 (-0.2 - 0.22)	0.93
HBV	0.1 (-0.25 - 0.45)	0.56	0.0061 (-0.36 - 0.37)	0.97
HCV	-0.1 (-0.32 - 0.11)	0.34	-0.13 (-0.39 - 0.13)	0.33
NAFLD	0.034 (-0.17 - 0.23)	0.74	0.075 (-0.15 - 0.3)	0.5
mRNA Vaccine	0.17 (-0.026 - 0.36)	0.09	0.26 (0.05 - 0.47)	0.015
Previous COVID-19	0.88 (0.63 - 1.1)	1.90E-11	0.9 (0.65 - 1.2)	1.40E-11

Table S7: Linear regression models of log10 transformed anti-RBD antibody (>0.8U/mL) in cirrhosis patients at the Post-V2 timepoint. MELD is a continuous variable, all other variables are discrete. Age is compared to 18-44 year old group. CP = Child's Pugh class, INR = International normalized ratio, CI = Confidence interval.

Supplementary reference

[1] Elbe S, Buckland-Merrett G. Data, disease and diplomacy: GISAID's innovative contribution to global health. Global Challenges 2017;1:33-46.