

# Histological and serological features of acute liver injury after SARS-CoV-2 vaccination

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**Table S1: Co-mediations**

<b>Co-mediations (n=59)</b>	<b>n</b>
<b>Yes</b>	36 (61%)
<b>No</b>	23 (39%)
Anti-hypertensive drugs	21
Anti-hyperlipidemic drugs	10
Anti-diabetic drugs	9
Vitamins	8
Aminosalicylates	8
Proton pump inhibitors	7
Diuretics	7
L-thyroxine	5
Non-steroidal anti-inflammatory drugs	4
Anti-epileptic drugs	4
Monoclonal antibodies*	3
Herbal remedies	3
Selective serotonin re-uptake inhibitors	2
Anxiolitics/hypnotics	2
Anti-tumor drugs**	2
Azathioprine	1
Others	8

\* Denosumab (RANKL-inhibitor); Ocrelizumab (anti-CD20); Risankizumab (anti-IL23)

\*\* Letrozole, Ribociclib

**Table S2: Autoimmune extrahepatic co-morbidities**

<b>Autoimmune co-morbidities (n=59)</b>	<b>n</b>
<b>Yes</b>	18 (31%)
<b>No</b>	41 (69%)
Autoimmune thyroid disease	6
Psoriasis	2
Celiac disease	3
Sarcoidosis	1
Multiple sclerosis	2
Autoimmune hemolytic anemia	1
Ulcerative colitis	1
Crohn's disease	1
Rheumatoid arthritis	1
Cushing syndrome	1

**Table S3: Comparison of clinical features between cases with predominantly lobular and predominantly portal hepatitis**

	Lobular hepatitis N=45	Portal hepatitis N=10	p value	test
Female sex	28 (62%)	5 (50%)	0.49	Fisher's exact
Median age (years)	54	59	0.23	Mann-Whitney U
Last vaccine before hepatitis: mRNA	34 (75%)	6 (60%)	0.43	Fisher's exact
Heterologous vaccination	6 (13%)	1 (10%)	1.00	Fisher's exact
Hepatitis after first dose	19 (42%)	2 (20%)	0.30	Fisher's exact
Hepatitis after second dose	25 (55%)	7 (70%)	0.49	Fisher's exact
Hepatitis after third dose	1 (2%)	1 (10%)	0.33	Fisher's exact
Time from last vaccine to hepatitis diagnosis, median (days)	24	10	0.06	Mann-Whitney U
ALT at diagnosis, x ULN (median, U/l)	26 (1002)	15 (656)	0.27	Mann-Whitney U
AST at diagnosis, x ULN (median, U/l)	28 (968)	14 (469)	0.02	Mann-Whitney U
Alkaline phosphatase at diagnosis, x ULN (median, U/l)	171	121 (n=9)	0.09	Mann-Whitney U
Total bilirubin at diagnosis, x ULN (median, $\mu\text{mol/l}$ )	138	29 (n=9)	0.03	Mann-Whitney U
Hepatocellular liver injury pattern	43	9 (n=9)	1.00	Fisher's exact
Mixed liver injury pattern	2	0	n.a.	Fisher's exact
Hy's criteria met	25	4 (n=9)	1.00	Fisher's exact
New Hy's law met	24	4 (n=9)	1.00	Fisher's exact
No concomitant medication	19	4	1.00	Fisher's exact
No medications for vaccine side effects	16 (n=26)	7 (n=7)	0.07	Fisher's exact
ANA positive	35 (n=44)	7 (n=9)	1.00	Fisher's exact
SMA positive	18	4 (n=7)	0.43	Fisher's exact
Anti-LKM positive	4 (n=38)	0 (n=8)	1.00	Fisher's exact
AMA positive (1 borderline)	6 (n=40)	0 (n=7)	0.57	Fisher's exact
IgG, g/l, (median)	16.9	18.8	0.78	Mann-Whitney U
IgM, g/l (median)	1.21(n=37)	1.61 (n=8)	0.40	Mann-Whitney U
Treatment	41	9	1.00	Fisher's exact
Normal ALT at 3 months	18 (n=42)	3 (n=7)	1.00	Fisher's exact

Normal ALT at 6 months	22 (n=29)	4 (n=7)	0.37	Fisher's exact
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ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG/M Immunoglobulin, G/M; ULN, upper limit of normal; SMA, anti-smooth muscle antibody; ANA, anti-nuclear antibody; LKM, liver kidney microsomal; AMA, anti-mitochondrial antibody; n.a. not applicable.

Numbers shown in paranthesis as "n= " represent the number of patients for whom the piece of data is available.

Table S4: Comparison of clinical features between cases with and without advanced liver fibrosis

n=59		Ishak F0/1/2 (n=52)			Ishak F ≥3 (n=7)			p-value	test
		n	%	median (min; max)	n	%	median (min; max)		
<b>Sex</b>	male	21	40		3	43		.901	Chi <sup>2</sup>
<b>Age (years)</b>				54 (19;78)			60 (37;92)	.327	Mann-Whitney U
<b>COVID-19 before liver injury</b>	yes	4	8		1	14		.557	Chi <sup>2</sup>
<b>Vaccination</b>									
<b>Heterologous vaccination</b>	yes	7	14		1	20		.732	Chi <sup>2</sup>
<b>Last vaccine before hepatitis</b>	RNA	35	67		7	100		.200	Chi <sup>2</sup>
	vector	16	31		0	0			
	inactivated	1	2		0	0			
<b>Vaccine before hepatitis</b>	mRNA-1273 (Moderna)	10	19		2	29		.523	Chi <sup>2</sup>
	BNT162b2 (Pfizer)	25	48		5	71			
	AZD1222 (Astra)	11	21		0	0			
	Ad26.COV2.S (Johnson&Johnson)	0	0		0	0			
	Gam-COVID-Vac (Sputnik V)	5	10		0	0			
	BBIBP-CorV (Sinopharm)	1	2		0	0			

<b>Vaccine to hepatitis (days)</b>				24 (1;74)			19 (1; 48)	.573	Mann-Whitney U
<b>Hepatitis post vacc 1 vs 2/3</b>	post 1st vaccination	18	35			2	29	.751	Chi <sup>2</sup>
	post 2nd/3rd vaccination	34	65			7	71		
<b>Vaccination after hepatitis</b>	no	37	71			7	100	.100	Chi <sup>2</sup>
	yes	15	29			0	0		
<b>Vaccine post hepatitis</b>	mRNA	8	53			0	0		
	vector	6	40			0	0		
	protein-based	1	78			0	0		
<b>Medications for vaccine side effects</b>	no	26	50			6	86	.094	Chi <sup>2</sup>
	yes	4	8			1	14		
	unknown	22	42			0	0		
<b>Autoimmune comorbidities</b>	no	30	58			6	86	.341	Chi <sup>2</sup>
	yes	17	33			1	14		
	unknown	5	10			0	0		
<b>AIH simplified diagnostic score</b>				6 (3; 8)			7 (3;9)	.497	Mann-Whitney U
<b>Biopsy scan</b>									
<b>Interface</b>				1 (0; 4)			3 (1; 4)	.017	Mann-Whitney U
<b>Confluent</b>				2 (0; 6)			1 (0; 5)	.441	Mann-Whitney U

<b>Lobular</b>				3 (0; 4)			2 (2; 3)	.483	Mann-Whitney U
<b>Portal</b>				2 (0; 3)			2 (2; 3)	.049	Mann-Whitney U
<b>Ishak</b>				9 (0; 14)			10 (6; 11)	.757	Mann-Whitney U
<b>Simplified AIH</b>	typical	9	17		5	71		.006	Chi <sup>2</sup>
	compatible	32	62		2	29			
	atypical	11	21		0	0			
<b>New histological criteria</b>	likely	34	65		7	100		.175	Chi <sup>2</sup>
	possible	13	25		0	0			
	unlikely	5	10		0	0			
<b>Predominant histology</b>	lobular	42	81		3	43		.010	Chi <sup>2</sup>
	portal	6	12		4	57			
	others	4	8		0	0			
<b>Predominant histology - subtype</b>	confluent necrosis	30	58		3	43		.180	Chi <sup>2</sup>
	panlobular	7	13		0	0			
	>mild interface hepatitis	4	8		3	43			
	bland cholestasis	2	4		0	0			
	mild interface hepatitis	2	4		1	14			
	central perivenulitis	5	10		0	0			
	minor change	1	2		0	0			
	steatohepatitis	1	2		0	0			
<b>Centralized autoantibody testing</b>									



<b>centralized autoantibody testing</b>	yes	28	54		3	43		.585	Chi <sup>2</sup>
<b>ANA</b>	present	21/28	75		2/3	67		.754	Chi <sup>2</sup>
<b>ANA titer</b>	80	4	19		0	0		.182	Chi <sup>2</sup>
	160	10	48		0	0			
	>160	7	33		2	100			
<b>AMA</b>	positivity	4/28	14		0/3	0		.483	Chi <sup>2</sup>
<b>AMA titer</b>	160	3	75		0	0			
	>160	1	25		0	0			
<b>SMA</b>	positivity	19/28	68		1/3	33		.235	Chi <sup>2</sup>
<b>SMA titer</b>	80	9	47		0	0		.009	Chi <sup>2</sup>
	160	9	47		0	0			
	>160	1	5		1	100			
<b>SMA pattern</b>	V	11	58		0	0		.000	Chi <sup>2</sup>
	VGT	7	37		0	0			
	G	1	5		0	0			
	GT	0	0		1	100			
<b>LKM</b>	positivity	4/28	14		0/3	0		.483	Chi <sup>2</sup>
<b>LKM titer</b>	80	1	25		0	0			
	160	3	75		0	0			
<b>Western blot</b>	negative for LKM1, LKM2, LKM3	4	80		0	0			
	borderline for PDH-E2 and BCKD-E2	1	20		0	0			
<b>Others</b>	positivity	9/27	33		0/0	0			
<b>Other type</b>	PCA	7	78		0	0			
	ARA	1	11		0	0			
	PCAl like	1	11		0	0			

Other titer	80	2	22		0	0			
	160	6	67		0	0			
	>160	1	11		0	0			
Hep2 ANA	positivity	25/28	89		2/3	66		.232	Chi <sup>2</sup>
Hep2 ANA titer	40	0	0		0	0		.023	Chi <sup>2</sup>
	80	6	24		0	0			
	160	15	60		0	0			
	>160	4	16		2	100			
Hep2 ANA pattern*	homogen	5	20		1	33		.860	Chi <sup>2</sup>
	fine speckled	17	68		2	67			
	nucleolar	5	20		0	0			
	centromere	1	4		0	0			
Hep2 SMA, AMA	SMA	13	76		1	100		.839	Chi <sup>2</sup>
	AMA	2	12		0	0			
	AMA-like	2	12		0	0			
Hep2 SMA, AMA (titer)	80	6	43		0	0			
	160	6	43		0	0			
	>160	2	14		0	0			
Liver LIA	positivity	5/28	18		0/2	0		.513	Chi <sup>2</sup>
Liver LIA	LKM1	1	20		0	0			
	AMA M2	4	80		0	0			
Gastro LIA	PCA borderline	1	25		0	0			
	PCA	3	75		0	0			
pIgG (normalized arbitrary units)				1.2 (0.4; 2.7)			1.2 (0.4; 1.4)	.391	Mann-Whitney U
pIgG (cut-off 1,27)	negative	13	52		2	67		.630	Chi <sup>2</sup>
	positive	12	48		1	33			
<b>Treatment</b>									

<b>Treatment</b>	no	6	12		1	14		.833	Chi <sup>2</sup>
	yes	46	88		6	86			
<b>Steroids for initial therapy</b>	no	0	0		0	0		1	Chi <sup>2</sup>
	yes	46	100		6	100			
<b>Doses Steroids for initial therapy, prednisolone (mg/day)</b>				50 (10; 625)			45 (30; 50)	.277	Mann-Whitney U
<b>Azathioprine therapy</b>	no	40	87		6	100		.347	Chi <sup>2</sup>
	yes	6	13		0	0			
<b>Azathioprine dose (mg/d)</b>				50 (25; 150)					
<b>Liver values</b>									
<b>diagnosis</b>	<b>n=52</b>			<b>n=7</b>					
<b>ALT/ULN</b>	24.5 (3.9; 111.3)			19.7 (11.6; 52.5)			.845	Mann-Whitney U	
<b>AST/ULN</b>	22.1 (3.0; 169.1)			18.6 (9.7; 42.3)			.829	Mann-Whitney U	
<b>ALP/ULN</b>	1.4 (0.5; 8.2)			1.0 (0.8; 2.9)			.657	Mann-Whitney U	
<b>GGT/ULN</b>	4.3 (0.4; 38.0)			3.7 (1.1; 9.4)			.683	Mann-Whitney U	
<b>Total bilirubin/ULN</b>	5.7 (0.4; 34.4)			2.7 (0.8; 24.7)			.680	Mann-Whitney U	

<b>INR</b>				1.2 (0.7; 3.2)			1.2 (1.0; 2.2)	.543	Mann-Whitney U
<b>IgG (g/l)</b>				16.8 (6.6; 34.7)			21.7 (8.7; 39.9)	.036	Mann-Whitney U
<b>IgM (g/l)</b>				1.2 (0.2; 5.3)			1.2 (0.9; 9.8)	.616	Mann-Whitney U
<b>original Hy's law</b>	yes	29	59		3	43		.414	Chi <sup>2</sup>
	no	20	41		4	57			
<b>new Hy's law</b>	yes	26	53		4	57		.839	Chi <sup>2</sup>
	no	23	47		3	43			
<b>R</b>				16.8 (2.3; 92.0)			16.5 (8.8; 28.2)	.981	Mann-Whitney U
<b>Liver injury pattern</b>	hepatocellular (R≥5)	48	94		7	100		.510	Chi <sup>2</sup>
	mixed (R 2-5)	3	6		0	0			
<b>Outcome</b>									
<b>Outcome</b>	spontaneous remission	4	8		1	14		.158	Chi <sup>2</sup>
	remission under immunosuppression (IS) & successful IS withdrawal	8	15		1	14			
	remission under IS & IS withdrawal is still ongoing	23	44		1	14			

remission & IS withdrawal failure	2	4	2	29		
improvement no remission despite treatment	11	21	1	14		
transplantation or liver related death	1	2	0	0		
death, non liver related	1	2	1	14		
relapse treated with steroids after spontaneous remission	2	4	0	0		

\* multiple answers possible, \*\* AST is missing for some patients

Abbreviations: SARS-CoV-2 Severe Acute Respiratory Coronavirus 2, COVID-19 Coronavirus disease 2019, AIH Autoimmune Hepatitis, IgG/M Immunoglobuline G/M, ULN Upper limit of normal, ALT Alanine aminotransferase, INR International Normalized Ratio, AST Aspartate aminotransferase, SMA Anti-smooth cell antibody, ALP Alkaline phosphatase, ANA Anti-nuclear antibody, LKM Liver kidney microsomal, AMA Anti-mitochondrial antibody, SLA Soluble liver antigen, PIgG Polyreactive immunoglobulin G, PCA Parietal cell antibody, IS Immunosuppression. R value: ALT/ULN divided by ALP/ULN.