



PROGRAMMA WEBINAR MINNAJA

Martedì 15 Marzo 2022



Vaccinazione anti-Covid 19 nei pazienti epatopatici e sottoposti a trapianto di fegato: efficacia e nuove evidenze

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Outline

- Impact of Sars-Cov 2 infection and Hepatology
- Sars-Cov 2 Vaccination

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Sars-Cov-2

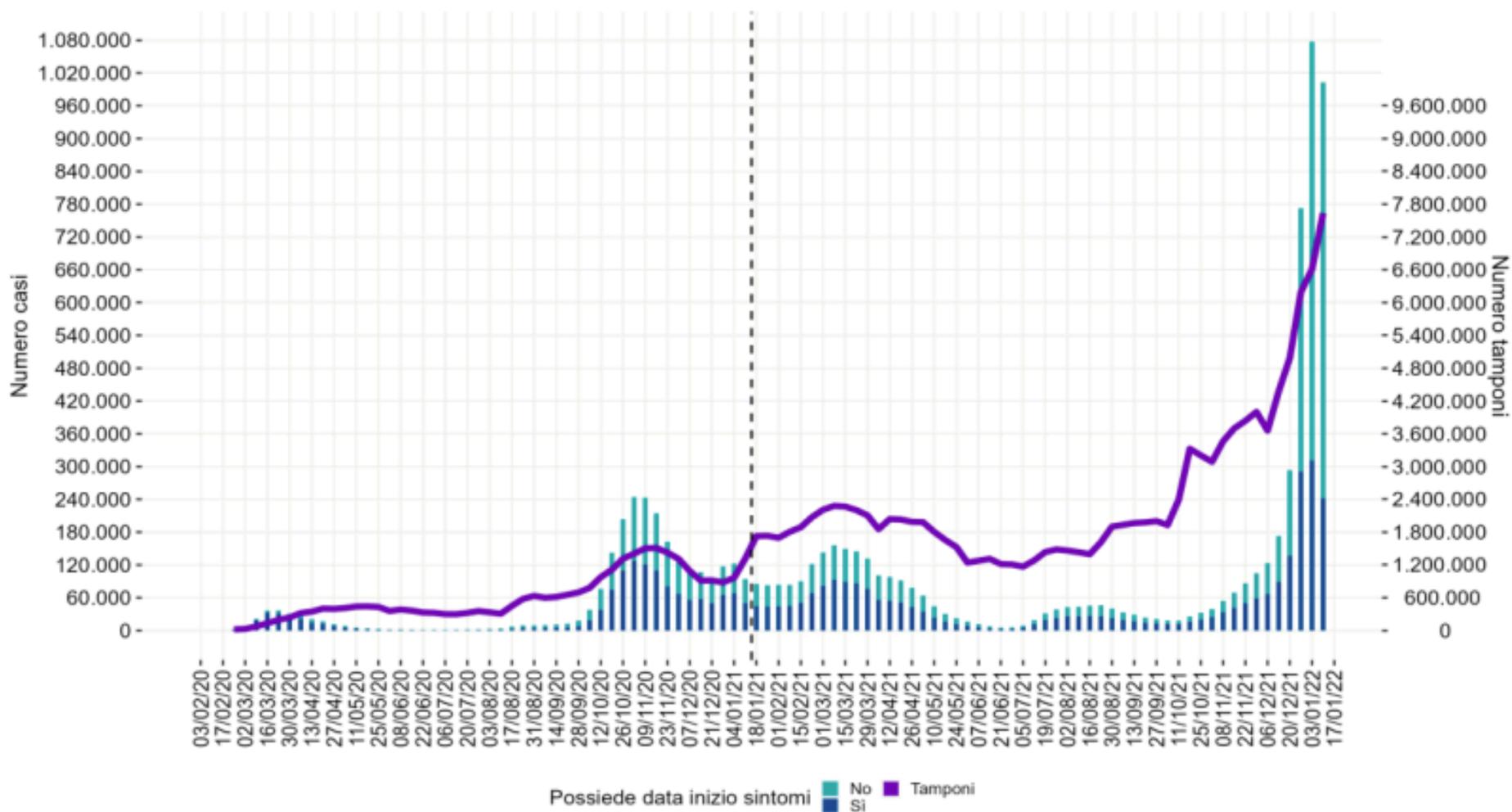
1.231.987 new cases in last
24hrs

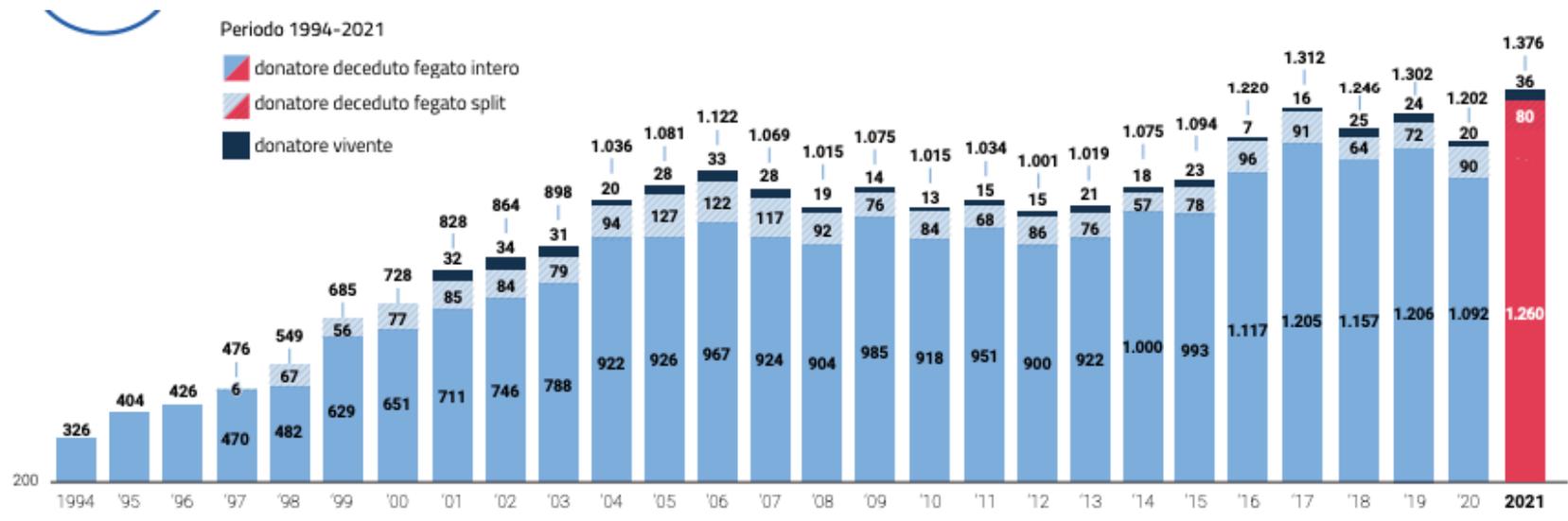
456.797.217 cumulative cases

6.043.094 cumulative deaths

Dall'inizio della pandemia, in Italia:

- Circa 8.800.000 casi
- Circa 140.000 decessi







CORONAVIRUS: IMPATTO SULL'ATTIVITÀ

Andamento settimanale delle donazioni e dei trapianti

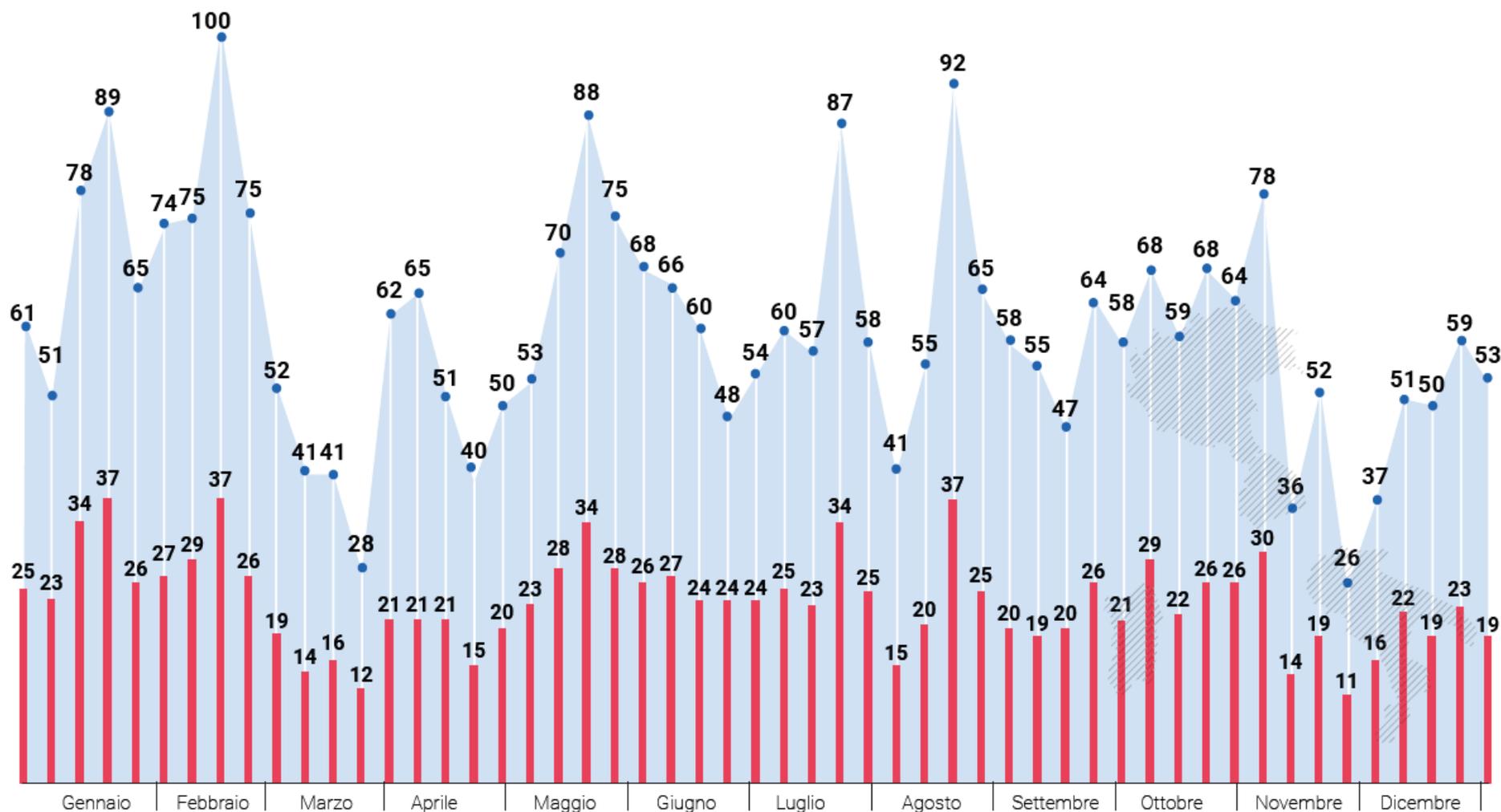
2020



Trapianti



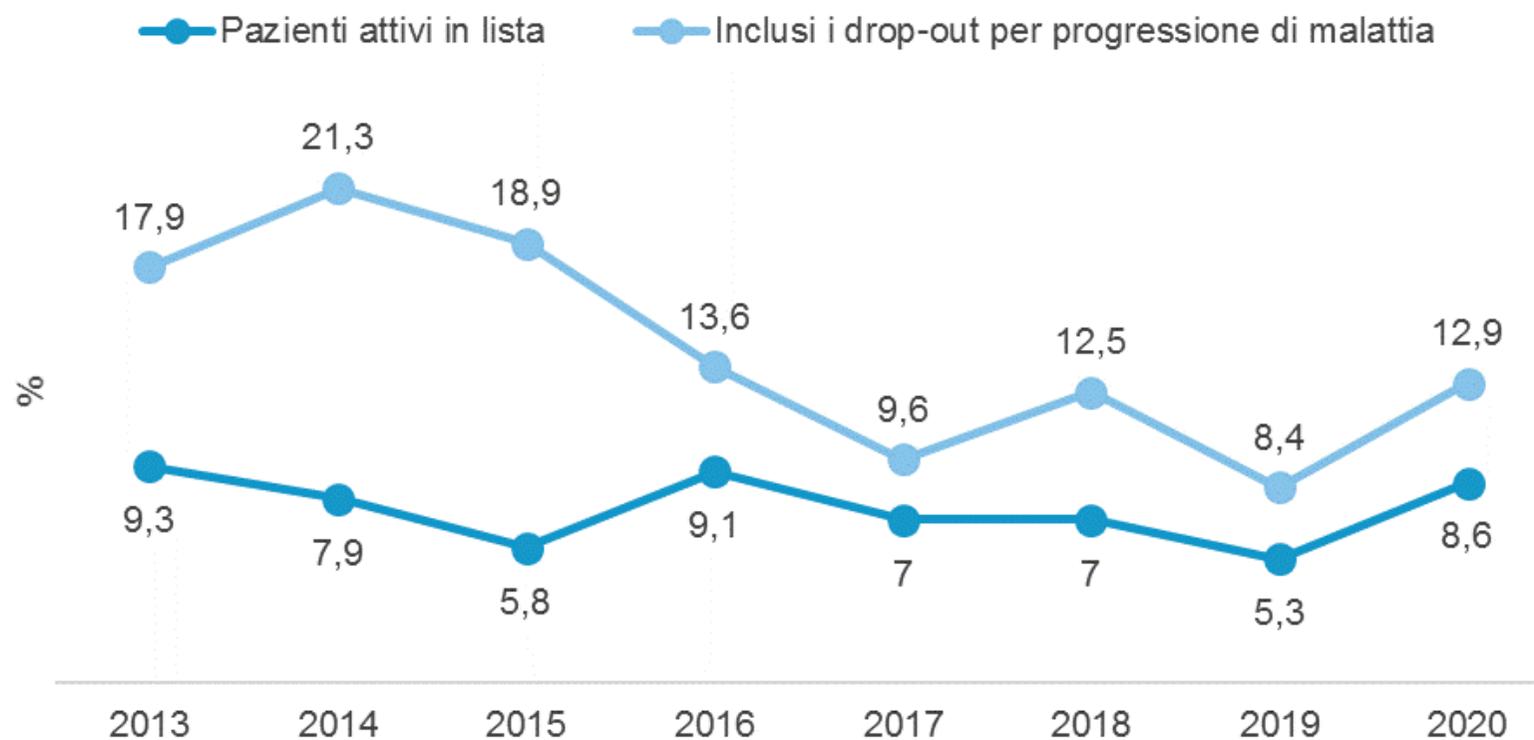
Donatori utilizzati



FONTE: 2020, DATI PRELIMINARI CNT OPERATIVO

Centro Trapianti di Fegato di Padova

Impatto del COVID19 sulla mortalità in lista d'attesa per trapianto di fegato a Padova



Deceased Donation Activity

- Hold on DDLT program

Up to 1 month:

The Americas 46%

Europe 50%

Africa/Australia/Asia 29%

>1 month:

The Americas 54%

Europe 50%

Africa/Australia/Asia 71%

% of Centers with Higher DCD Activity: 2019

	2019	2020	P-value
The Americas	40%	25%	NS
Europe	50%	24%	0.013
Africa/Australia/Asia	--	--	

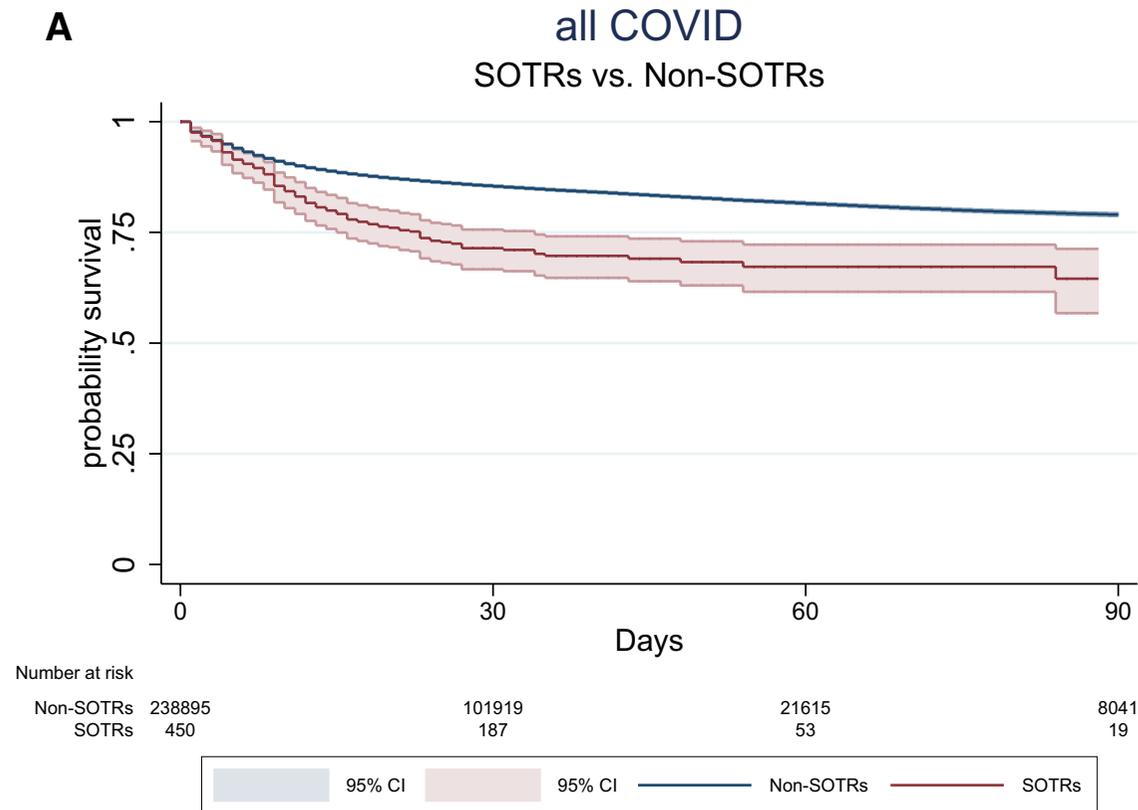
ALF remained exemption to the hold

The Americas 53%

Europe 55%

Africa/Australia/Asia 31%

Incidence and outcome of SARS-CoV-2 infection on solid organ transplantation recipients: A nationwide population-based study



Outline

- Impact of Sars-Cov 2 infection in Hepatology
- **Sars-Cov 2 Vaccination**

Groups to be prioritised for COVID-19 Vaccination

- Advanced liver disease
- Liver transplant
- Hepatobiliary cancer
- Immunosuppressed chronic liver disease

Russo FP et al 2021 DLD
Cornberg M et al 2021 J Hepatology

Groups to be prioritised for COVID-19 Vaccination

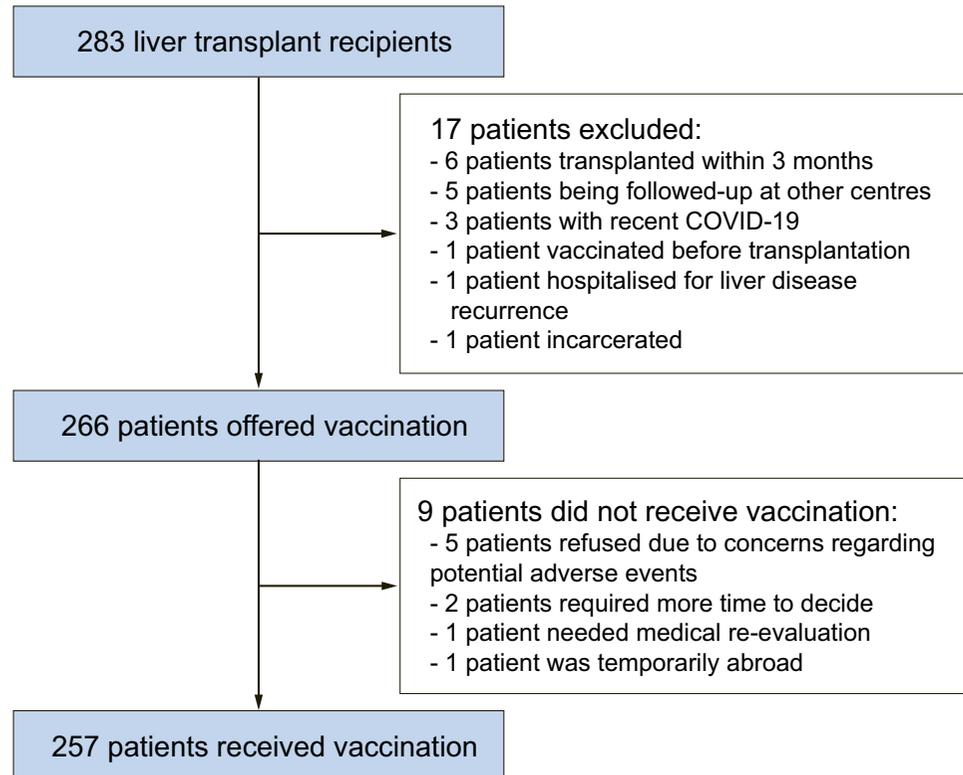
- Partners
- Caregivers
- Relatives residing with the patients

should be encouraged due to the following concerns:

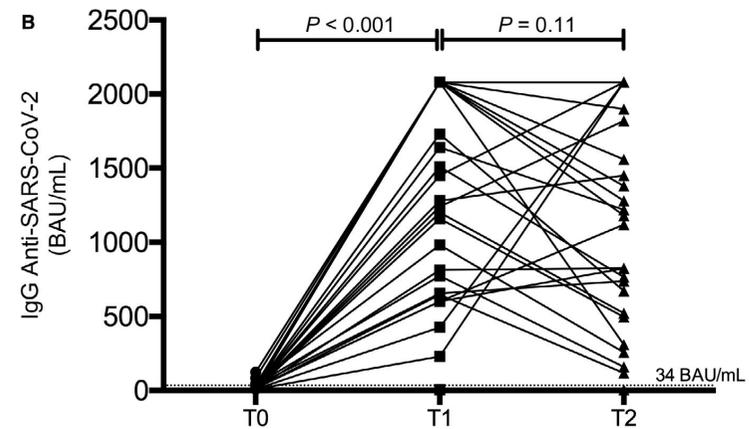
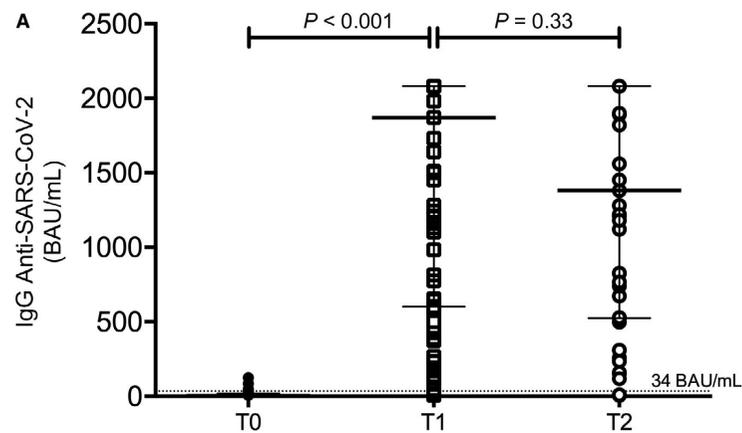
- (i) the response to other vaccinations is reported to be weaker in the patients who have undergone transplantation
- (ii) reduced transmission from vaccinated patients is expected, even if not demonstrated as yet.

Russo FP et al 2021 DLD
Cornberg M et al 2021 J Hepatology

High acceptance rate of COVID-19 vaccination in liver transplant recipients



Seroconversion After Coronavirus Disease 2019 Vaccination in Patients Awaiting Liver Transplantation: Fact or Fancy?

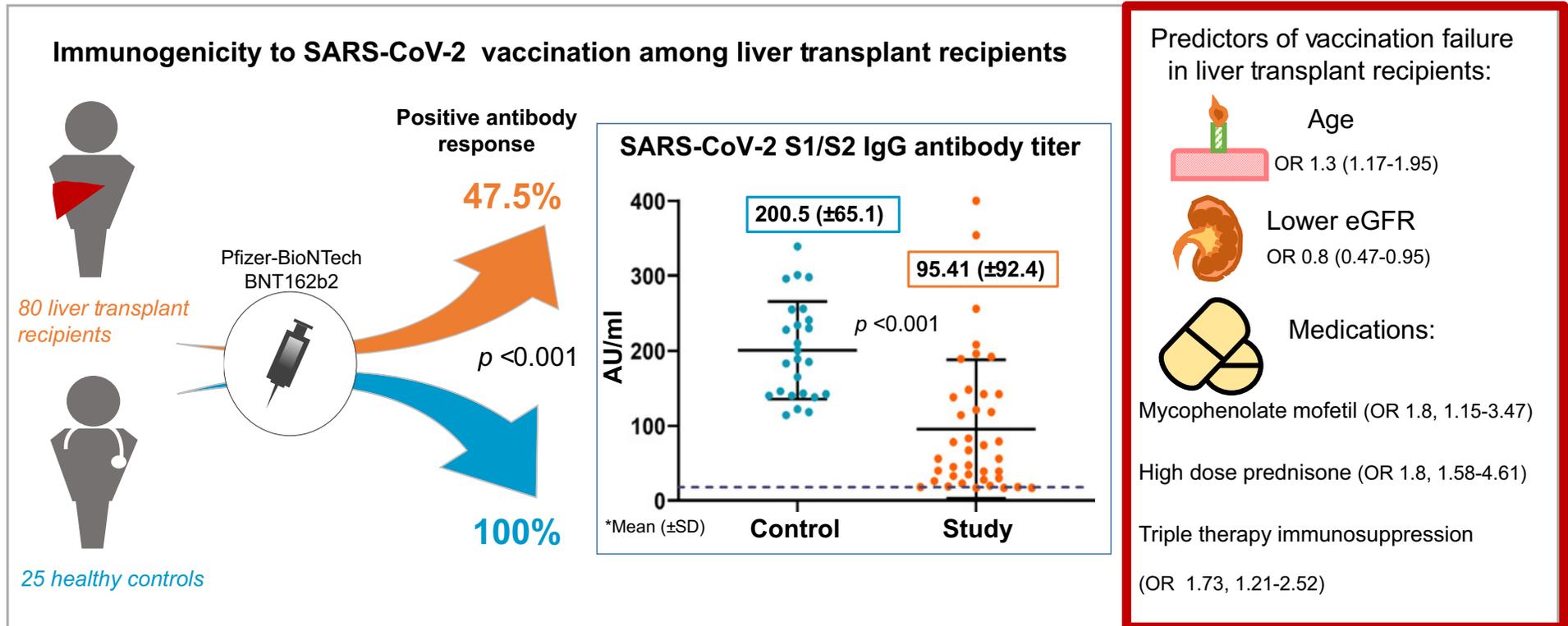


Calleri et al 2021 Liv Transpl

Paper	Number of patients	LT	Type of SARS-CoV-2 vaccine	Positive serological response rate	Antibody titer compared to control group	Factors related to reduced response rate
Guarino et al	365		Pfizer- BioNTech BNT162b2	74.8%	214.79±143 vs. 314.32±94.1 AU/ml (p<0.0001)	Age >65yrs, higher BMI, shorter time from LT, immunos. regimens with multiple drugs, antimetabolite T
Rabinowich et al	80		Pfizer- BioNTech BNT162b2	47.5%	95.41±92.4 vs. 200.5±65.1) AU/ml (p<0.001)	Age, lower eGFR, high dose predn. in the past 12, triple therapy immunos., MMF
Strauss et al	161		Pfizer- BioNTech BNT162b2 Moderna mRNA-1273	81%	81.9-250 U/ml, no control	antimetabolite ther., type of vaccine
Rashidi-Alavjeh et al	43		Pfizer- BioNTech BNT162b2	79%	552.7 vs. >2080 BAU/ml (p=0.0001)	MMF
Boyarsky et al	129 (cohort of 658 SOT)		Pfizer- BioNTech BNT162b2 Moderna mRNA-1273	79.8%		SOT:age, type of organ, years since TR, antimetabolite therapy, type of vaccine
Marion et al	58 (cohort of 367 SOT)		Pfizer- BioNTech BNT162b2 Moderna mRNA-1273	50%		No clinical data
Mazzola et al	58 (cohort of 143 SOT)		Pfizer- BioNTech BNT162b2	37.5%		SOT: age>60, type of organ, treated with corticoids, triple- therapy immunosu., T <2 years, diabetic patients
Ruether et al	141 (cohort of 194 pts, 53 cirr)		Pfizer- BioNTech BNT162b2 Moderna mRNA-1273 Astra Zeneca	anti-S RBD 73.9% or the anti-S Trimer 63.0%	163 (12-1060) 154 (1-1723)	age >65y and arterial hypertension , vaccination failure was less likely with CNi monotherapy
Fernandez Ruiz et al	14 (cohort of 44 patients, 28 kidney transplant, and 2 double organ)		Moderna mRNA-1273	anti-S 57.1% N-Ab activity 47.5%		MMF, Time from transplant >6 years, age>55 years
D'Offizi et al	61		BNT162b2 or mRNA-1273	anti-S 77 % N-Ab activity 57.5%		

Burra and Russo Liv Int in press

Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients



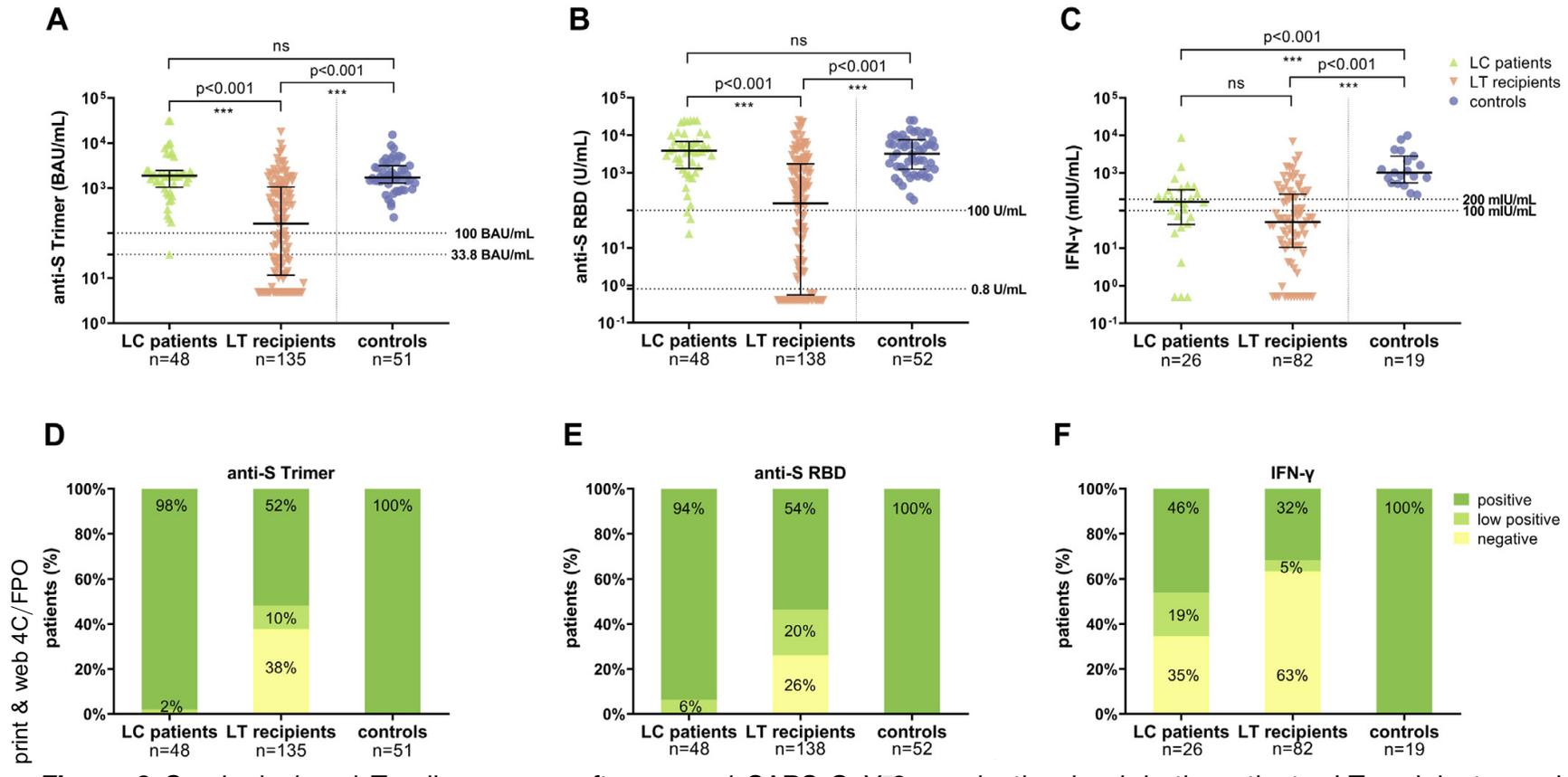
Rabinowich et al J Hepatology 2021

Characteristics of LT recipients stratified according to the serologic response after 2 doses of the BioNTech BNT162b2 SARS-CoV-2 vaccine

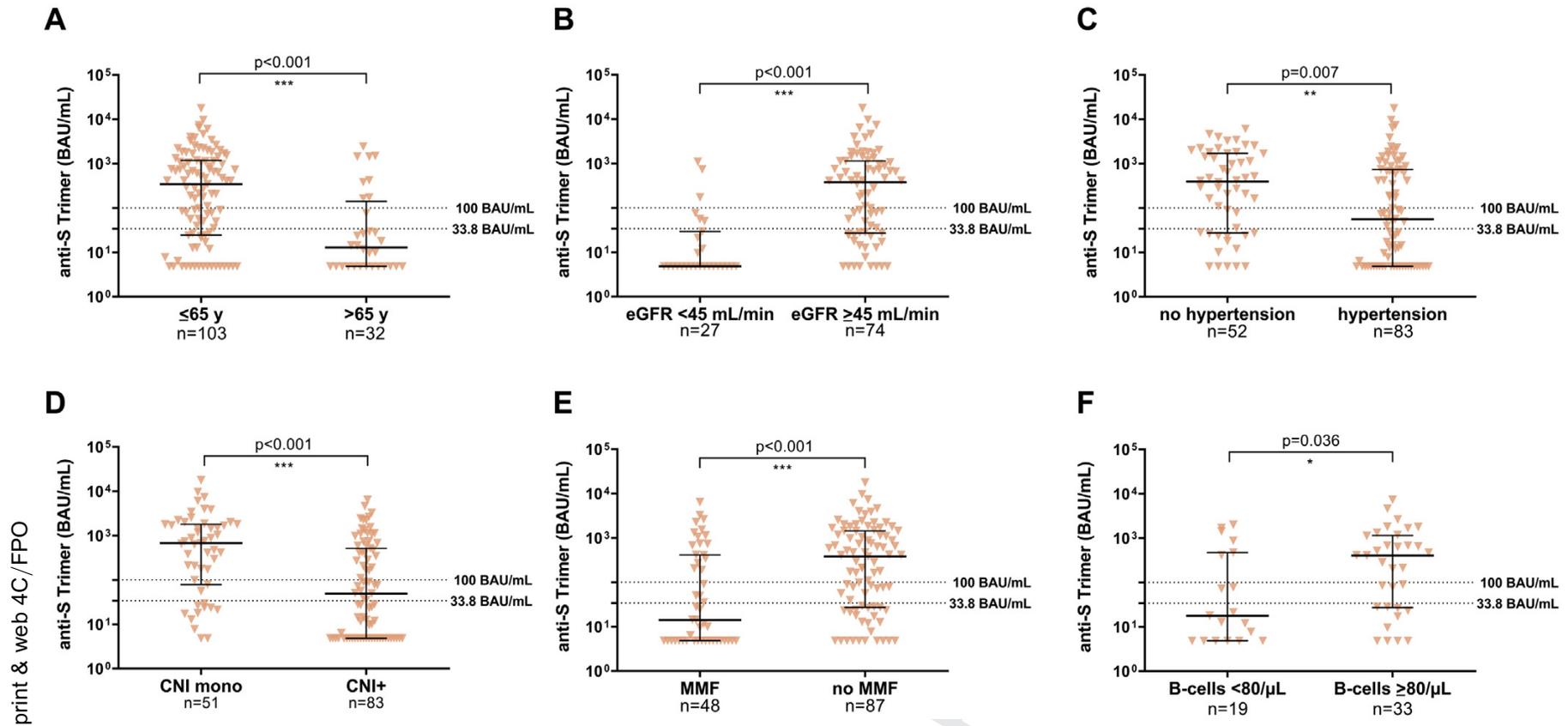
Characteristics	Overall (n = 365)	SARS-CoV-2 seronegative (n = 92)	SARS-CoV-2 seropositive (n = 273)	p value
Age, years (mean ± SD)	62.52 ± 12.97	65.01 ± 9.32	61.68 ± 13.9	<0.0001*
<40 years, n (%)	28 (7.6%)	1 (1.08%)	27 (9.8%)	<0.0001**
40-65 years, n (%)	150 (41.1%)	43 (46.7%)	107 (39.2%)	0.071**
>65 years, n (%)	187 (51.23%)	48 (52.17%)	139 (50.9%)	0.036**
Male, sex, n (%)	279 (76.4%)	73 (79.3%)	206 (75.4%)	0.06**
BMI, kg/m ² (mean ± SD)	26.56 ± 4.52	27.7 ± 7.09	26.77 ± 4.59	0.031*
Time from transplantation, years (mean ± SD)	14.08 ± 8.84	11.94 ± 8.72	14.79 ± 8.77	<0.001*
<1 year, n (%)	7 (1.91%)	5 (5.4%)	2 (0.7%)	<0.0001**
1-5 years, n (%)	69 (18.9%)	22 (23.9%)	47 (17.21)	0.0025**
5-10 years, n (%)	58 (15.89%)	15 (16.3%)	43 (15.75%)	0.058**
>10 years, n (%)	231 (63.21%)	50 (54.3%)	181 (66.3%)	<0.0001**
Immunosuppressive therapy, n (%)				
Calcineurin inhibitor	299 (81.9%)	72 (78.3%)	227 (83.1%)	0.19**
Antimetabolite	132 (36.2%)	49 (53.3%)	83 (30.4%)	<0.0001**
mTOR inhibitor	85 (23.3%)	30 (32.6%)	55 (20.1%)	0.021**
Single immunosuppressive agent, n (%)	218 (59.7%)	34 (36.9%)	184 (67.3%)	<0.0001**
Two or more immunosuppressive agents, n (%)	147 (40.3%)	58 (63.1%)	89 (32.7%)	<0.0001**
Steroids, n (%)	28 (7.6%)	9 (9.8%)	19 (6.9%)	0.07**

Guarino et al J Hepatology 2021

Serological and T-cell response after second SARS-CoV-2 vaccination in cirrhotic patients, LT recipients, and healthy controls



Serological and T-cell response after second SARS-CoV-2 vaccination in cirrhotic patients, LT recipients, and healthy controls



print & web 4C/FPO

Higher Proinflammatory Cytokines Are Associated With Increased Antibody Titer After a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients

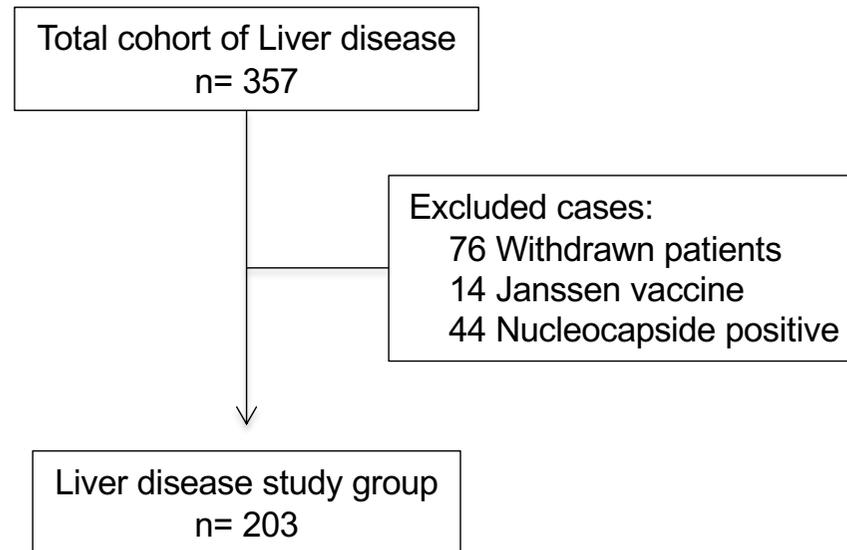
	SOTR dose 2 (N = 58), n (%)	SOTR dose 3 (N = 35), n (%)	<i>P</i> ^a	HC (N = 16), n (%)
Postvaccine SARS-CoV-2 IgG				
Negative	24 (41)	13 (37)	0.827	0 (0)
Positive	34 (59)	22 (63) ^d		16 (100)
Low titer	32 (55)	19 (54)	1.000	0 (0)
High titer	26 (45)	16 (46)		16 (100)

Karaba et al 2022 Transplantation in press

HEPCOVIVAC REGISTRY

Immunological response in patients with liver disease vaccinated against COVID-19

Case selection flowchart



Demographic and clinical features of the study cohort

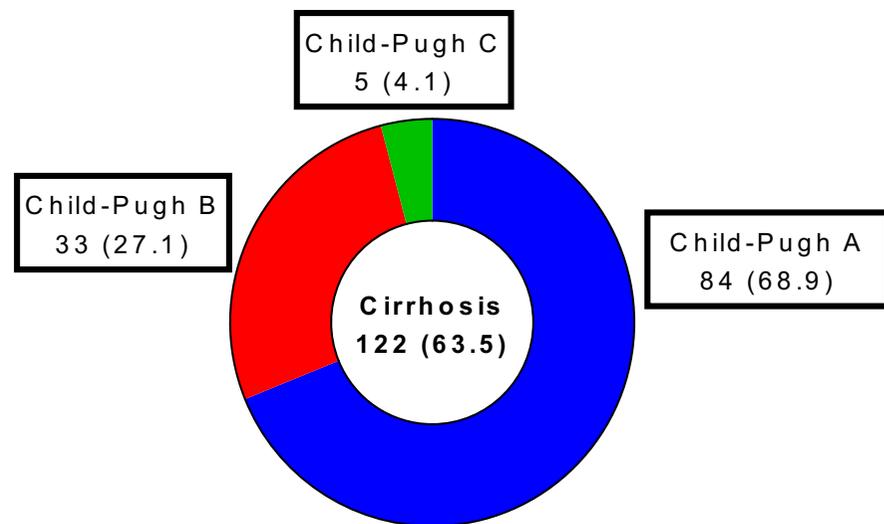
Variables	Liver disease group [n= 203]	Healthy volunteers [n= 132]	p-value
Age , median (IQR)	58.0 (53.0 – 65.0)	45.0 (37.0 – 57.0)	<0.0001
Gender , n (%)			
Male	115 (56.7)	37 (28.0)	<0.0001
Female	88 (43.3)	95 (72.0)	
BMI (kg/m ²), median (95%CI)	26.5 (23.3 – 30.5)	25.8 (23.6 – 27.6)	<i>ns</i>
Race , n (%)			
Caucasian	193 (95.1)		
Asian	3 (1.5)	Missing	
Black	3 (1.5)		
Other	4 (2.0)		

Demographic and clinical features – LIVER DISEASE GROUP

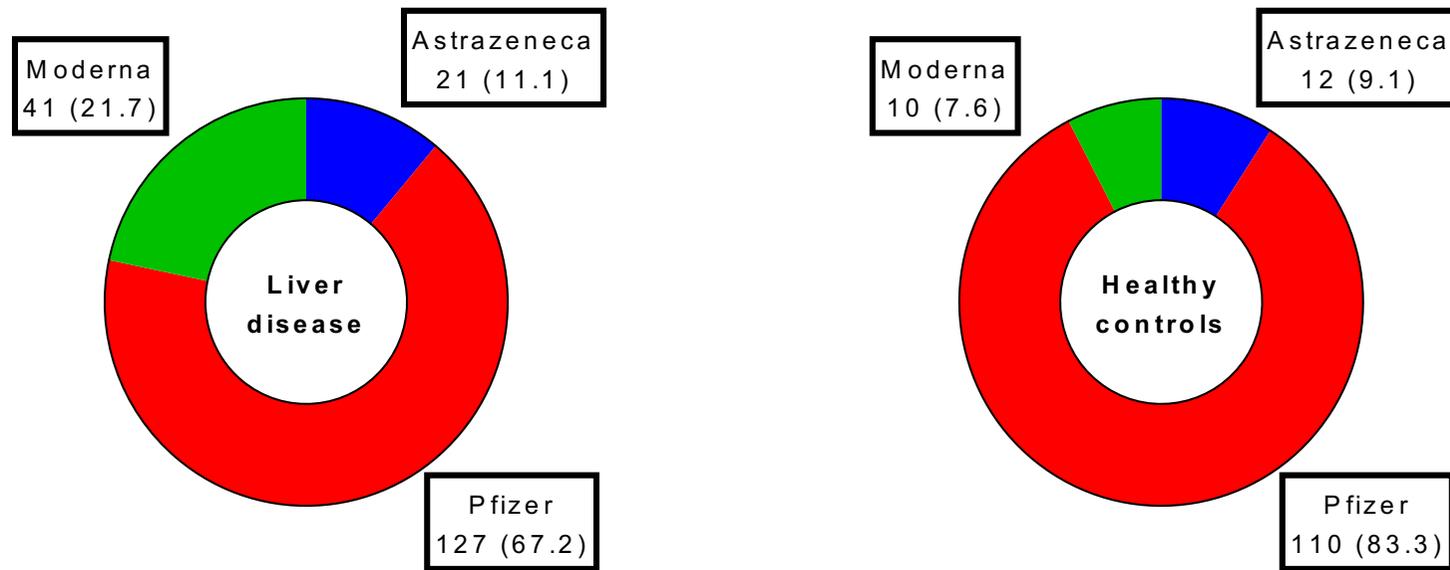
Comorbidities, n (%)	
Diabetes Mellitus	53 (26.1)
Arterial hypertension	63 (31.0)
Obesity	39 (19.2)
Hypertriglyceridemia	13 (6.4)
Hypercholesterolemia	29 (14.3)
Renal insufficiency	8 (3.9)
Asthma	7 (3.4)
Chronic obstructive pulmonary disease (COPD)	1 (0.5)
Heart/cardiovascular disease	23 (11.3)
Tobacco	27 (13.3)

Liver disease etiology

Liver disease etiology, n (%)	
HCV	59 (29.1)
Alcohol	57 (28.1)
NAFLD	42 (20.7)
HBV	34 (16.7)
AIH	13 (6.4)
PBC	13 (6.4)
HDV	4 (2.0)
PSC	3 (1.5)
Wilson	1 (0.5)
Haemocromatosis	1 (0.5)
Other	11 (5.4)

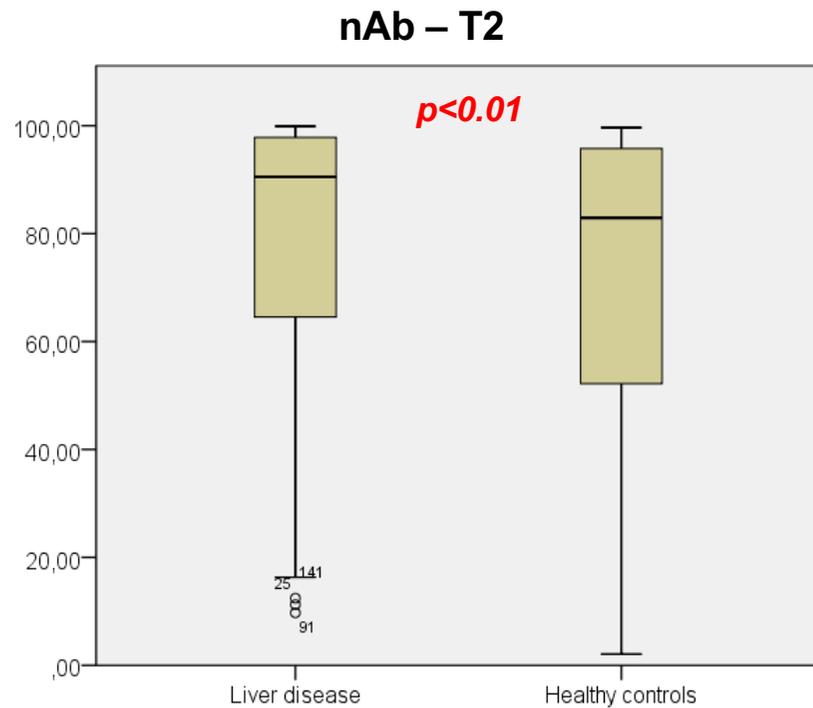


COVID-19 vaccines



Pearsons' Chi-square test $p < 0.01$

Neutralizing antibodies - 2 wks after 2nd dose (1st for Astrazeneca)

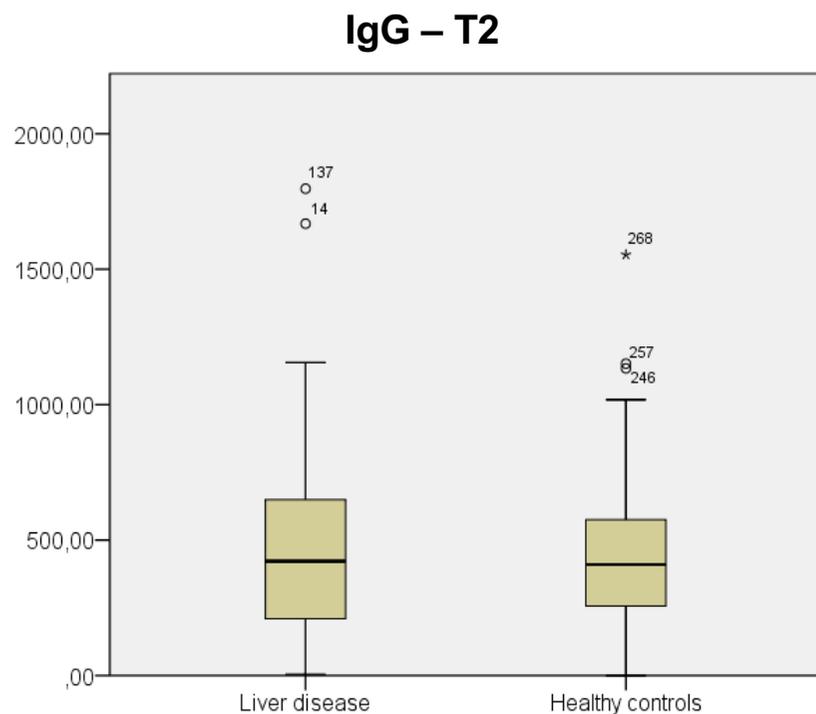


		Frecuencia	Porcentaje	Porcentaje válido
Válido	LOW	121	38,4	46,0
	HIGH	142	45,1	54,0
	Total	263	83,5	100,0
Perdidos	Sistema	52	16,5	
Total		315	100,0	

MULTIVARIATE *			
COVARIABLES	OR	95% CI	p value
Age, (continuous)	0.98	0.97 – 1.00	<i>ns</i>
Sex, female (vs male)	0.99	0.60 – 1.65	<i>ns</i>
Type of vaccine, (vs Astrazeneca)			
Moderna	13.75	4.20 – 45.0	<0.0001
Pfizer-BioNTech	4.63	1.69 – 12.72	<0.01
Condition, liver disease (vs healthy controls)	1.88	1.09 – 3.22	<0.05

*Low nAb levels as reference value

IgG (wt) - 2 wks after 2nd dose (1st for Astrazeneca)



		Frecuencia	Porcentaje	Porcentaje válido
Válido	LOW	128	40,6	47,9
	HIGH	139	44,1	52,1
	Total	267	84,8	100,0
Perdidos	Sistema	48	15,2	
Total		315	100,0	

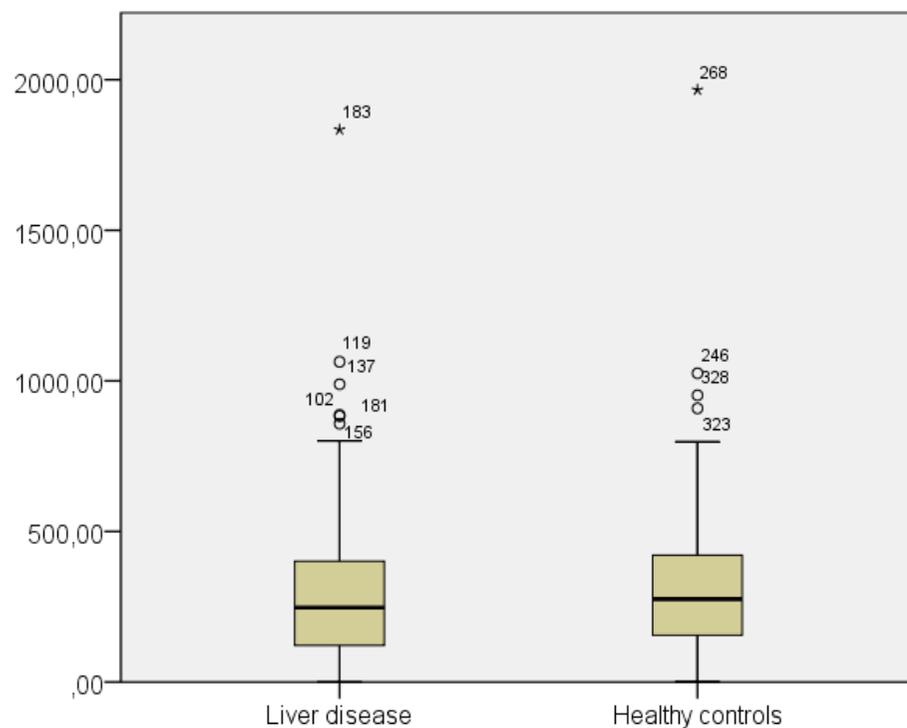
MULTIVARIATE *

COVARIABLES	OR	95% CI	p value
Age, (continuous)	0.97	0.96 – 0.99	<0.05
Sex, female (vs male)	1.65	0.99 - 2.74	ns
Type of vaccine, (vs AstraZeneca)			
Moderna	22.61	6.36 – 80.32	<0.0001
Pfizer-BioNTech	5.53	1.85 – 16.51	<0.01
Condition, liver disease (vs healthy controls)	1.28	0.74 – 2.22	ns

*Low IgG levels as reference value

IgG (delta) - 2 wks after 2nd dose (1st for Astrazeneca)

IgG (delta) – T2



		Frecuencia	Porcentaje	Porcentaje válido
Válido	LOW	126	40,0	47,5
	HIGH	139	44,1	52,5
	Total	265	84,1	100,0
Perdidos	Sistema	50	15,9	
Total		315	100,0	

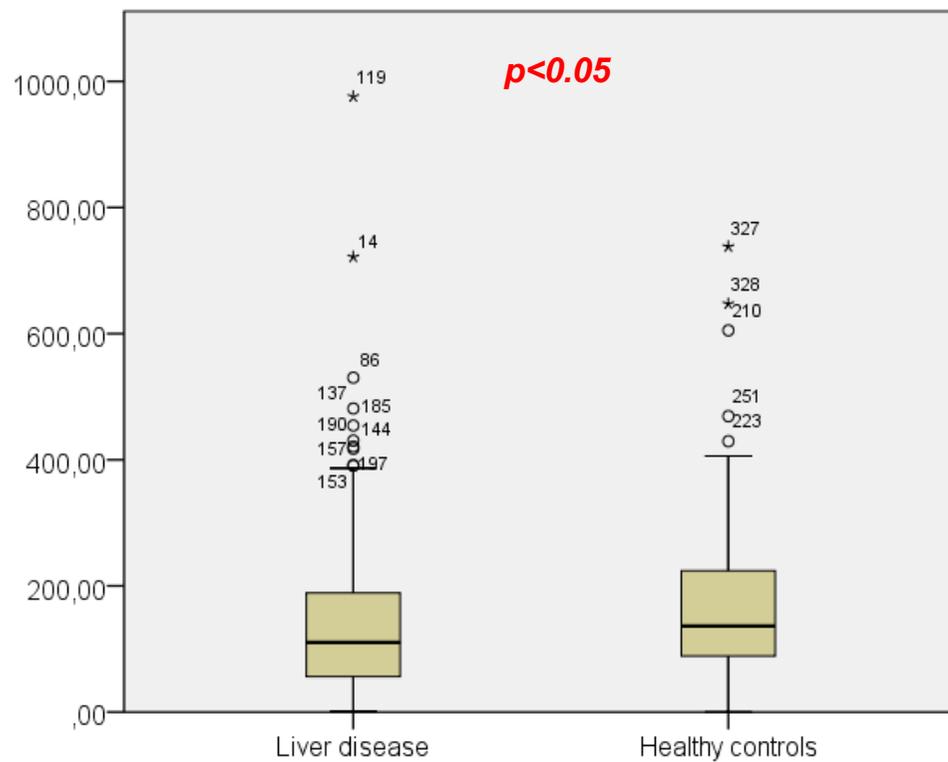
MULTIVARIATE *

COVARIABLES	OR	95% CI	p value
Age, (continuous)	0.99	0.97 – 1.01	ns
Sex, female (vs male)	1.45	0.89 - 2.36	ns
Type of vaccine, (vs Astrazeneca)			
Moderna	7.83	2.62 – 23.43	<0.0001
Pfizer-BioNTech	3.43	1.33 – 8.84	<0.01
Condition, liver disease (vs healthy controls)	0.79	0.47 – 1.33	ns

*Low IgG (delta) levels as reference value

IgG (delta) - 2 wks after 2nd dose (1st for Astrazeneca)

IgG (omicron) – T2



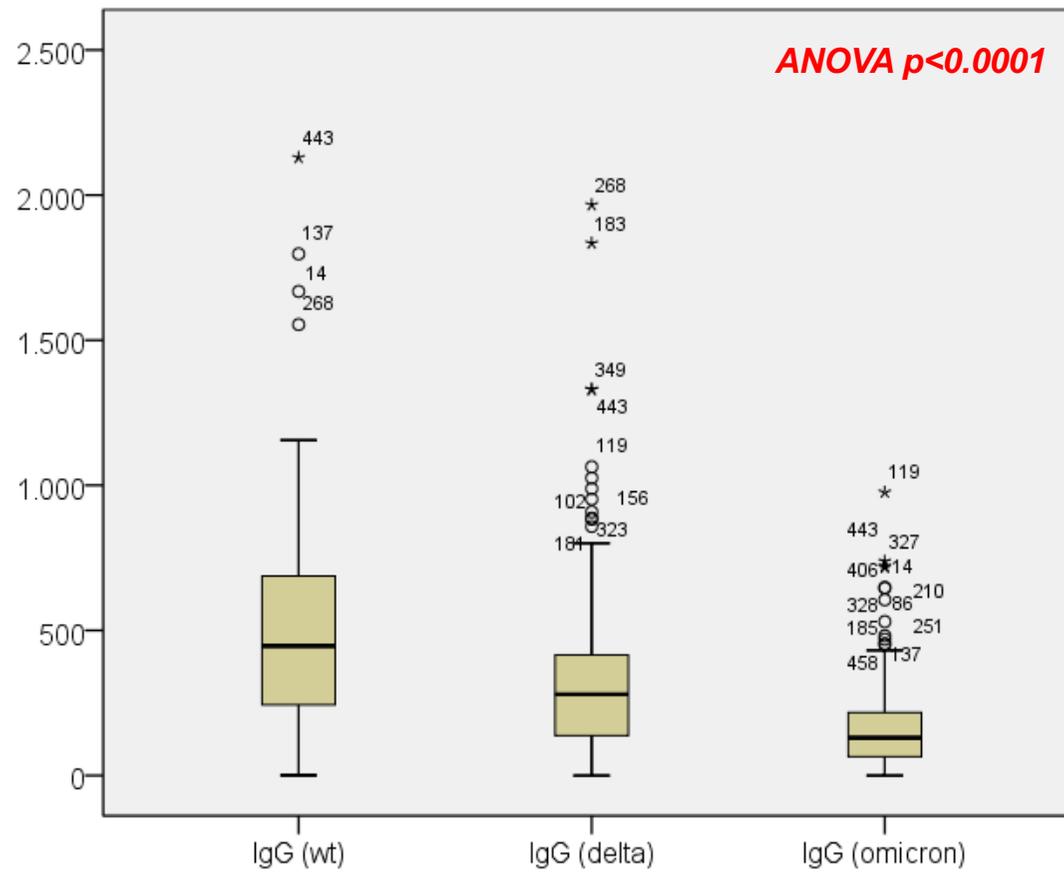
		Frecuencia	Porcentaje	Porcentaje válido
Válido	LOW	126	40,0	47,4
	HIGH	140	44,4	52,6
	Total	266	84,4	100,0
Perdidos	Sistema	49	15,6	
Total		315	100,0	

MULTIVARIATE *

COVARIABLES	OR	95% CI	p value
Age, (continuous)	0.99	0.97 – 1.00	ns
Sex, female (vs male)	2.02	1.24 – 3.30	<0.01
Type of vaccine, (vs Astrazeneca)			
Moderna	4.08	1.49 – 11.14	<0.01
Pfizer-BioNTech	1.98	0.85 – 4.62	ns
Condition, liver disease (vs healthy controls)	0.78	0.46 – 1.32	ns

*Low IgG (omicron) levels as reference value

IgG - 2 wks after 2nd dose (1st for Astrazeneca)

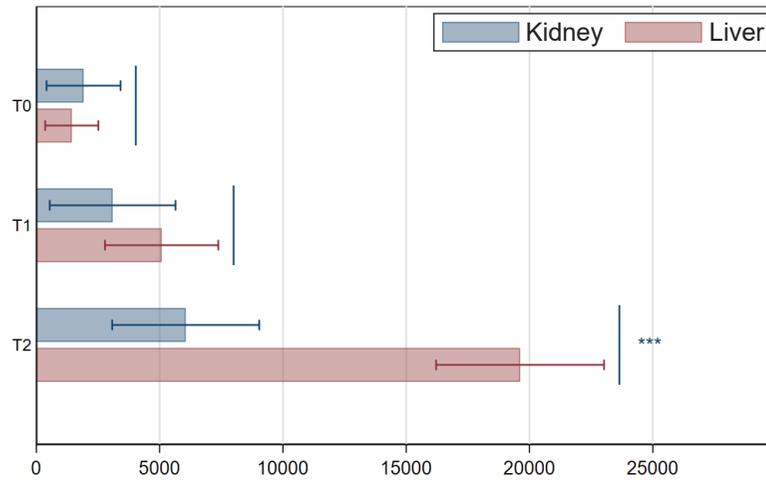


Variables en la ecuación

	B	Error estándar	Wald	gl	Sig.	Exp(B)	95% C.I. para EXP(B)	
							Inferior	Superior
Paso 1^a								
HBV	1,602	1,179	1,844	1	,174	4,962	,492	50,067
HCV	1,124	,882	1,624	1	,202	3,077	,546	17,331
HDV	-,938	1,508	,387	1	,534	,392	,020	7,521
AIH	-21,679	18737,967	,000	1	,999	,000	,000	.
PBC	,347	1,167	,088	1	,766	1,414	,144	13,937
PSC	1,119	1,733	,417	1	,518	3,062	,103	91,423
Alcohol	-,252	,837	,091	1	,763	,777	,151	4,008
NAFLD	,358	,765	,219	1	,640	1,430	,319	6,402
child_pugh_score			,604	2	,739			
child_pugh_score(1)	-,025	,591	,002	1	,966	,975	,306	3,107
child_pugh_score(2)	,884	1,168	,573	1	,449	2,421	,245	23,904
hepatocellular_carcinoma	-,850	,889	,913	1	,339	,427	,075	2,443
vaccine_developer			17,309	2	,000			
vaccine_developer(1)	-4,483	1,278	12,309	1	,000	,011	,001	,138
vaccine_developer(2)	-2,257	,633	12,725	1	,000	,105	,030	,362
Constante	1,162	,950	1,496	1	,221	3,198		

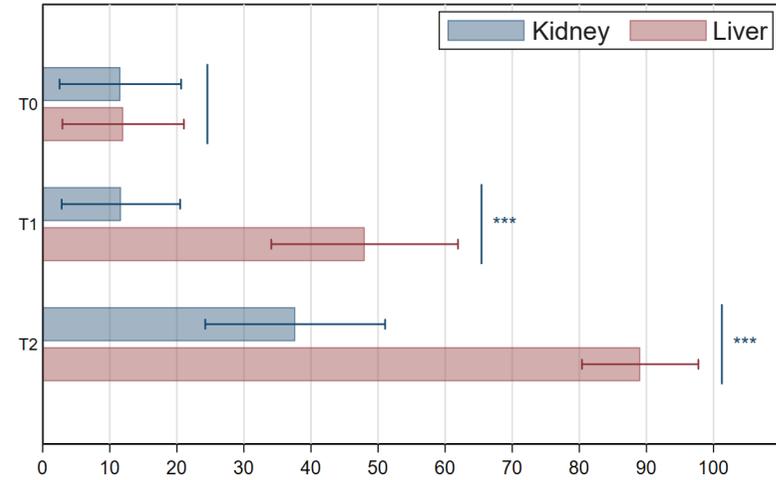
a. Variables especificadas en el paso 1: HBV, HCV, HDV, AIH, PBC, PSC, Alcohol, NAFLD, child_pugh_score, hepatocellular_carcinoma, vaccine_developer.

Dati del nostro centro in collaborazione con il Mount Sinai New York e Stanford University



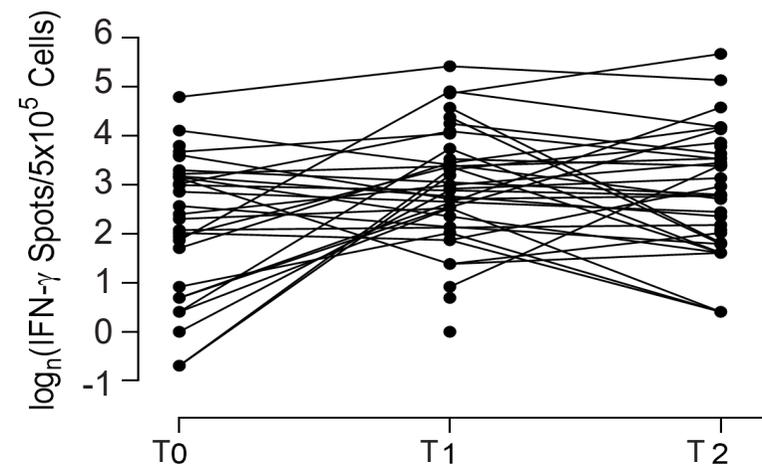
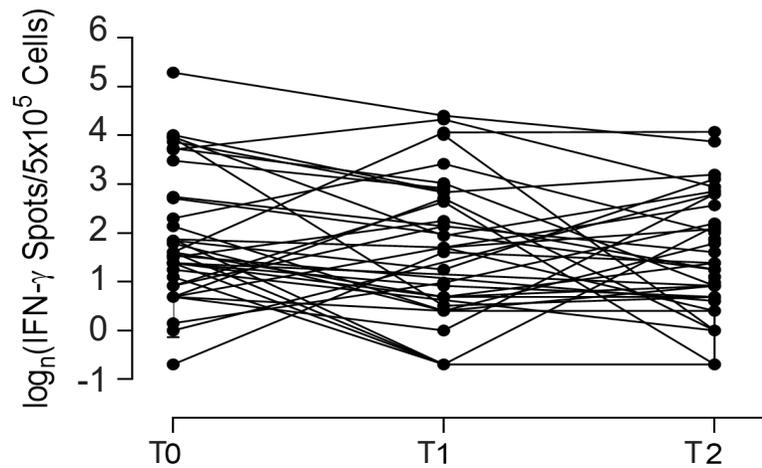
Anti-RBD IgG (MFI)

Kidney



Percentage of anti-RBD positive patients

Liver



Conclusions

- The first wave of pandemic impacted LT across the world differently, especially with detrimental effects on the hit countries.
- The resilience of the entire transplantation network supported liver donation and transplantation.
- High rate of immunization in the waiting list for liver transplantation
- Acceptance rate for COVID-19 vaccination among liver transplant recipients is extremely high
- Benefit of third dose