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Humoral response to different SARS-CoV-2 vaccines in orthotopic liver transplant recipients

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ABSTRACT

Background: The safety and efficacy data of the different types of available vaccines is still needed. The goal of the present analysis was to evaluate the humoral response to the COVID-19 vaccines in orthotopic liver transplant (OLT) recipients.

Methods: Participants were included from February to September 2021. No prioritized vaccination roll call applied for OLT patients. Controls were otherwise healthy people. Blood samples were drawn after 15 days of the complete vaccine doses. The samples were analyzed according to the manufacturer's instructions using the Liaison XL platform from DiaSorin (DiaSorin S.p.A., Italy), and SARS-COV-2 IgG II Quant (Abbott Diagnostics, IL, USA).

Results: A total of 187 participants (133 OLT, 54 controls, median age: 60 years, 58.8% women) were included for the analysis; 74.3% had at least one comorbidity. The serologic response in OLT patients was lower than in controls (median 549 AU/mL vs. 3450 AU/mL, respectively; p = 0.001). A positive humoral response was found in 133 OLT individuals: 89.2% with BNT162b2 (Pfizer-BioNTech), 60% ChAdOx1 nCOV-19 (Oxford-AstraZeneca), 76.9% with CoronaVac (Sinovac, Life Sciences, China), 55.6% Ad5-nCov (Cansino, Biologics), 68.2% Gam-COVID-Vac (Sputnik V) and 100% with mRNA-1273. In controls the serological response was 100%, except for Cansino (75%). In a multivariable model, personal history of COVID-19 and BNT162b2 inoculation were associated with the serologic response, while the use of prednisone (vs. other immunosuppressants) reduced this response.

Conclusion: The serologic response to COVID-19 vaccines in OLT patients is lower than in healthy controls. The BNT162b2 vaccine was associated with a higher serologic response.

Abbreviations: AIH, Autoimmune hepatitis; ALD, Alcoholic liver disease; CI, confidence intervals; COVID-19, coronavirus disease of 2019; COV-2 IgG II, SARS-COV-2 IgG II Quant Receptor-binding domain-Spike; GFR, Glomerular filtration rate; IQR, interquartile range; INCMNSZ, *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán*; mRNA, messenger ribonucleic acid; n, number; NASH, Non-Alcoholic SteatoHepatitis; OLT, orthotopic liver transplant; PBC, Primary Biliary cholangitis; PSC, Primary Sclerosing Cholangitis; RBD, Receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VHC, Hepatitis C Virus.

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1. Introduction

The coronavirus disease of 2019 (COVID-19), the entity caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affects patients differently. In Mexico, the reconstruction of the health care system aimed to prioritize the care to patients with COVID-19. Efficient mRNA vaccines against this pathogen were developed in a record time, a little over a year, and were considered a significant measure to protect individuals and household members. For our population, BNT162b2 (Pfizer-BioNTech) was the first to be available. Over time, other vaccines that used diverse platforms such as replication-deficient viral vectors, inactivated virus, and protein subunits were developed [1]. Nonetheless, solid organ transplant recipients were excluded from pivotal clinical trials, and the safety and efficacy of the different types of available vaccines for this susceptible population is limited and requires additional studies. Concerns regarding COVID-19 vaccines include the lack of long-term safety data, potential reduction in efficacy in immunocompromised patients, unknown durability of the immune response, and potential for vaccine-associated allograft rejection [2]. These concerns are common to all vaccine platforms available.

The major target of most vaccines is the viral Spike protein and its receptor-binding domain (RBD), which interacts with the human angiotensin-converting enzyme-2 and is critical for viral entry into human epithelial cells. Available vaccines stimulate both B- and T-cell responses, engaging humoral and cellular immune pathways [2].

Mexico was among the most affected countries in terms of case numbers, case fatality rate, and population mortality [3,4]. Nevertheless, Mexico was the first country in Latin America where a COVID-19 vaccine was available [5]. Since December 24, 2020, the vaccine was offered to all health care personnel [6], and since February 2020, inoculation of high risk populations, according to age, was initiated [7]. Solid-organ recipients were not considered a particular risk group, and they were included in the vaccination roll call by age group. Different COVID-19 vaccines became available in Mexico. Still, some people traveled to other countries (mainly the United States) to receive a vaccine shot, sometimes with brands not locally available. The goal of the present analysis was to evaluate the humoral response to the COVID-19 vaccines in orthotopic liver transplant (OLT) recipients.

2. Patients and methods

2.1. Study design

From February 2021 to September 2021, vaccines became available for the general population in Mexico. No prioritized vaccination was performed for this subset of patients, and they were included in the regular schedule according to age and place of residency. Due to this, not all OLT recipients receive the same vaccine. All participants completed the full vaccination scheduled proposed for the type of vaccine they received (For Ad5-nCov only 1 dose was applied, and for the other evaluated vaccines a two-dose scheduled were applied with a window frame of 4–6 weeks). Controls were healthy adult volunteers, mainly family members of patients willing to participate. Exclusion criteria included age < 18 years, inability to provide informed consent for the present study, and pregnancy. All the participants signed a written informed consent and were evaluated at the Liver Transplant Clinic of the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (INCMNSZ). The INCMNSZ's Investigation and ethics board approved the study (study number GAS-3678-21-22-1), and the research was performed in accordance with the Helsinki Declaration.

Patients filled a questionnaire for the data concerning the vaccination, and proof of the vaccine was required. Clinical data were obtained from the patient's medical records, and laboratory data were obtained from the laboratories due to the clinical evaluation in the clinic. The estimated glomerular filtration rate was calculated using the Cockcroft – Gault formula, and chronic kidney disease categories were defined according to KDIGO recommendations. For reactogenicity we interviewed for all the adverse effects described to date. Symptoms were classified as mild (those that did not limit the patient's functionality in the daily activities) or severe (as those that required medical monitoring or that impaired the patient functionality) as well as local or systemic.

2.2. SARS-CoV2 antibodies test

Blood samples were taken after a median of 42 days of completion of the vaccine schedule. Samples were collected in gold-capped tubes with separating gel; the samples were centrifuged at 350 rpm for 10 min. Serum samples were aliquoted and stored in a secondary tube at a temperature of −20 °C, until the day of processing. The samples were analyzed according to the manufacturer's instructions using indirect chemiluminescence immunoassay (CLIA) technology, Liaison XL platform from DiaSorin, LIAISON® SARS-CoV-2 S1/S2 IgG reagent to determine antibodies directed against S1 and S2 proteins of the SARS COV virus spike 2 (DiaSorin S.p.A., Italy). For the determination of antibodies type SARS-COV-2 IgG (Nucleocapsid) and SARS-COV-2 IgG II Quant Receptor-binding domain-Spike (COV-2 IgG II), the samples were processed in the ARCHITECT i2000 DE ABBOTT equipment (Abbot Diagnostics, IL, USA), the analysis method used in this equipment was chemiluminescence microparticle immunoassay (CMIA). For the S1/S2 reagent, a participant was considered positive when it had values above 15 AU/mL, and for COV-2 IgG II, it was considered positive with values above 50 AU/mL.

2.3. Statistical analysis

Relative frequencies of nominal variables are expressed as percentages. For the relevant relative frequencies, 95% confidence intervals (CI) were calculated by the adjusted Wald method. Parametric continuous variables are expressed as means with standard deviation (SD). Non-parametric continuous variables are expressed as medians with minimum and maximum or interquartile range (IQR), as correspond. Pearson chi-square or Fisher exact tests were used to assess proportions in nominal variables for bivariate analyses. To compare quantitative variables between two groups, Student *t* test and the Mann-Whitney *U* test were performed in distributions of parametric and non-parametric variables, respectively. A multivariate analysis was created to find the factors associated with serological responses to the SARS-CoV-2 vaccine by a binary logistic regression. Variables putatively associated with serological response to the vaccine were included in the model for adjustment (among them, previous COVID-19 infection, demographic variables, comorbidities and treatments). Adjusted odds ratios with 95% CIs are provided. Corrected ORs were calculated and taken as an approximation of the true relative risk obtained from the regression analysis, with the Zhang and Yu method [8]. The model's fitness was evaluated using the Hosmer-Lemeshow goodness-of-fit test and considered reliable if p was >0.2. All p values are two-sided and considered significant when $p < 0.05$. SPSS

version 20.0 for MAC (SPSS Inc., Chicago, IL.) was used for all calculations.

3. Results

3.1. General characteristics

In all, 187 participants (133 OLT, 54 controls, median age: 60 years, 58.8% women) were included for the analysis (Supplemental Fig. 1); none had a positive nucleocapsid antibody and 74.3% of the participants had ≥1 comorbidities (32.6% diabetes, 31.6% had hypertension, 23% obesity and 7% neoplastic disorders). The median time since last vaccine dose to serological response measurement was 42 days (IQR: 29–76 days) (Table 1) for all participants. By vaccine platforms, 50.3% received BNT162b2 (Pfizer-BioNTech), 16% Gam-COVID-Vac (Sputnik V), 13.9% received ChAdOx1 nCOV-19 (Oxford-AstraZeneca), 10.7% received CoronaVac (Sinovac, Life Sciences, Beijing, China), 7.0% Ad5-nCov (Cansino, Biologics), and 2.1% received mRNA-1273 (Moderna). The global response rate for S1/S2 DiaSorin was 78.6% and 83.4% for COV-2 IgG II.

1. Liver transplant recipients

Among all, 133 patients had an OLT, 54.1% were female (n = 72) with a median age of 61 (IQR: 52.5–66.0), and 115 (86.5%) had at least 1 comorbidity (in 11.3% of patients we found at least 4 comorbidities). Diabetes was present in 40.6%, arterial hypertension in 36.8%; 24.8% had GFR KDIGO stage 3 or higher. The main etiology of cirrhosis was Hepatitis C virus with 31.6%. Up to 18.8% of patients had hepatocellular carcinoma.

After OLT, for immunosuppression, 53.4%, 41.4%, and 5.3% had a single, double or triple scheme, respectively, it mostly consisted of tacrolimus (90.9%), prednisone (27%) and mycophenolate mofetil in 23.3%. In the triple immunosuppression scheme (7 patients), only 5 presented humoral response (median: 14829.73 AU/mL).

No correlation was found between the time from OLT to vaccination initiation (r = 0.121, p = 0.17) or completion of the scheme (r = 0.120, p = 0.17).

a. Antibody titers by type of vaccine in OLT patients

By vaccine brands: 48.9% received BNT162b2 (Pfizer-BioNTech), 16.5% Gam-COVID-Vac (Sputnik V, Russia), 15% received ChAdOx1 nCOV-19 (Oxford-AstraZeneca), 9.8% received CoronaVac (Sinovac, Life Sciences, Beijing, China), 6.8% Ad5-nCov (Cansino, Biologics), and 3% received mRNA-1273 (Moderna). Response rates to the vaccine are available in Fig. 1 and Supplemental Table 1. In all, a median of 56 months (IQR: 36–79) had passed since the OLT to the vaccine administration. To date, no episode of rejection is reported in the cohort. The global response rate in OLT for S1/S2 DiaSorin was 70.7% (median: 76.4 AU/mL) and 77.4% (median: 549 AU/mL) for COV-2 IgG II (Table 2).

None of the OLT presented a COVID-19 infection during the study.

b. Previous COVID-19 infection and Antibody titers

For OLT, up to 18% of patients had previous COVID-19 infection, and a median of 143.5 days (IQR: 98.2–316.7) passed since the documented infection by RT-PCR to the application of the complete scheme of the vaccine. Demographic characteristics of OLT by COVID-19 infection are seen in Table 3.

For values in accordance to previous COVID-19 infection and vaccine brands both in OLT and controls (Table 4, Fig. 2).

Table 1
General characteristics of the population by administered vaccine.

Variable	OLT patients (n = 133)							Controls (n = 54)						
Type of vaccine	All patients	BNT162b2 (n = 65)	ChAdOx1 nCOV-19 (n = 20)	CoronaVac (n = 13)	Ad5-nCov (n = 9)	Gam-COVID-Vac (n = 22)	mRNA-1273 (n = 4)	All controls	BNT162b2 (n = 29)	ChAdOx1 nCOV-19 (n = 6)	CoronaVac (n = 7)	Ad5-nCov (n = 4)	Gam-COVID-Vac (n = 8)	mRNA-1273 (n = 0)
Time since last vaccine dose to serological response measurement, median (IQR)	38 (28–60)	44 (28.5–66)	37 (28.2–58.5)	37 (27.5–52.5)	41 (31.5–72.5)	29.5 (22.5–59)	34.5 (17.5–71.7)	72.5 (31–94)	94 (76.5–97)	32.5 (10.75–51)	36 (29–81)	31 (19.7–38.5)	43.5 (28.2–55)	–
Sex at birth, n (%)														
Male	61 (45.9)	36 (55.4)	7 (35.0)	3 (23.1)	4 (44.4)	9 (40.9)	2 (50)	16 (29.6)	4 (13.8)	2 (33.3)	6 (85.7)	1 (25.0)	3 (62.5)	–
Female	72 (54.1)	29 (44.6)	13 (65.0)	10 (76.9)	5 (55.6)	13 (59.1)	2 (50)	38 (70.4)	25 (86.2)	4 (66.7)	1 (14.3)	3 (75.0)	5 (37.5)	–
Age, median (IQR)	61 (52.5–66)	61 (53–67)	63 (52.7–66)	65 (61–68)	44 (39–53.5)	67 (55 – 66.5)	52 (44.5–67.7)	55 (41.7–65.2)	50 (38–55)	63 (63.7–70.2)	64 (63–69)	41.5 (39.5–5)	58 (61.2–68.7)	–
Comorbidities, n (%)	115 (86.5)	55 (84.6)	19 (95)	11 (84.6)	6 (66.7)	20 (90.9)	4 (100)	24 (44.4)	11 (37.9)	5 (83.3)	3 (42.9)	1 (25)	4 (50)	–
Diabetes	54 (40.6)	27 (41.5)	9 (45)	6 (46.1)	2 (22.2)	10 (45.4)	–	7 (12.9)	3 (10.3)	2 (33.3)	1 (14.2)	0	1 (12.5)	–
Arterial Hypertension	49 (36.8)	24 (36.9)	8 (40)	6 (46.1)	2 (22.2)	8 (36.3)	1 (25)	10 (18.5)	4 (13.7)	3	2 (14.2)	0	1 (12.5)	–
Obesity I	25 (18.8)	11 (16.9)	5 (25)	4 (30.7)	1 (11.1)	3 (13.6)	1 (25)	11 (20.4)	5 (17.2)	3	1 (14.2)	1 (25)	1 (12.5)	–

(continued on next page)

Table 1 (*continued*)

Variable	OLT patients (n = 133)							Controls (n = 54)						
Type of vaccine	All patients	BNT162b2 (n = 65)	ChAdOx1 nCOV-19 (n = 20)	CoronaVac (n = 13)	Ad5-nCov (n = 9)	Gam-COVID-Vac (n = 22)	mRNA-1273 (n = 4)	All controls	BNT162b2 (n = 29)	ChAdOx1 nCOV-19 (n = 6)	CoronaVac (n = 7)	Ad5-nCov (n = 4)	Gam-COVID-Vac (n = 8)	mRNA-1273 (n = 0)
Obesity II	4 (3.0)	2 (3.0)	0	0	0	0	1 (25)	2 (3.7)	2 (6.8)	0	0	0	0	–
Obesity III	0	0	0	0	0	0	0	1 (1.9)	1 (3.44)	0	0	0	0	–
Neoplasia	11 (8.3)	5 (7.9)	2 (10)	2 (15.3)	1 (11.1)	1 (4.54)	0	2 (3.7)	1 (3.44)	0	1 (14.2)	0	0	–
GFR > 3	33 (24.8)	18 (27.6)	5 (25)	6 (46.1)	1 (11.1)	3 (33.3)	0	4 (7.4)	1 (3.4)	0	2 (28.6)	0	1 (12.5)	–
Cirrhosis etiology, n (%)														
NASH	17 (12.8)	11 (16.9)	2 (10)	1 (7.6)	0	2 (9.0)	1 (25)							
ALD	10 (7.5)	4 (6.1)	2 (10)	1 (7.6)	0	3 (13.6)	0							
VHC	42 (31.6)	23 (35.3)	5 (25)	5 (38.4)	2 (22.2)	7 (31.8)	0							
PBC	10 (7.5)	6 (9.2)	0	2 (15.3)	0	2 (9.0)	0							
HAI	14 (10.5)	6 (9.2)	4 (20)	1 (7.6)	0	3 (13.6)	0							
Cryptogenic	20 (15)	10 (15.3)	5 (25)	2 (15.3)	1 (11.1)	2 (9.0)	0							
PSC	4 (3)	1 (1.5)	0	0	0	1 (4.54)	2 (50)							
PBC + AIH	5 (3.8)	2 (3.0)	1 (5)	1 (7.6)	1 (11.1)	0	0							
Other	11 (8.3)	2 (3.0)	1 (5)	0	5 (55.5)	1 (4.54)	1 (25)							
Hepatocelular carcinoma, n (%)	25 (18.8)	12 (18.4)	4 (20)	3 (23.0)	0	6 (27.2)	0							
Immunosuppression used, n (%)														
Single	71 (53.4)	36 (55.3)	10 (50)	9 (69.2)	3 (33.3)	10 (45.4)	3 (75)							
Double	55 (41.4)	25 (38.4)	9 (45)	4 (30.7)	6 (66.6)	10 (45.4)	1 (25)							
Triple	7 (5.3)	4 (6.1)	1 (5)	0	0	2 (9.0)	0							
Type of immunosuppression used, n (%)														
Tacrolimus	121 (90.9)	59 (90.7)	17 (85)	12 (92.3)	9 (100)	20 (90.9)	4 (100)							
Cyclosporine	11 (8.3)	5 (7.6)	3 (15)	1 (7.6)	0	2 (9.0)	0							
Prednisone	36 (27.0)	14 (21.5)	8 (40)	3 (23.0)	5 (55.5)	5 (22.7)	1 (25)							
Mycophenolic acid	31 (23.3)	18 (27.6)	2 (10)	1 (7.6)	1 (11.1)	9 (40.9)	0							
Azathioprine	1 (0.75)	0	1 (5)	0	0	0	0							
Sirolimus	2 (1.5)	2 (3.0)	0	0	0	0	0							
Previous COVID-19 infection, n (%)	24 (18)	10 (15.3)	3 (15)	2 (15.3)	5 (55.5)	3 (13.6)	1 (25)	12 (22.2)	7 (24.1)	0	2 (28.5)	2 (50)	1 (12.5)	–
Time from liver transplantation to vaccine, months, median, (IQR)	56 (36–79)	61 (36–79.5)	58.5 (38.2–95.5)	64 (46.5–98)	45 (28–100.5)	37.5 (21.7–55.2)	68.5 (42–81.5)	–						
Time from COVID-19 to the vaccine, days (IQR)	143.5 (98.2–316.7)	150.5 (131.25–351.5)	423 (163–423)	288 (182–288)	89 (70.5–202)	92 (87–92)	116	169.5 (95–194.2)	186 (116–229)	0	169.5 (155–169)	141.5 (88–141)	–	–
Adverse effects after vaccination, n (%)														
None	91 (68.4)	38 (58.5)	16 (80)	11 (84.6)	7 (77.8)	16 (72.7)	3 (75)	35 (64.8)	20 (69)	4 (66.7)	6 (85.7)	2 (50)	3 (37.5)	–
Mild	42 (31.6)	27 (41.5)	4 (20)	2 (15.4)	2 (22.2)	6 (27.3)	1 (25)	19 (35.2)	9 (31)	2 (33.3)	1 (14.3)	2 (50)	5 (62.5)	–

OLT: Liver transplant recipients, **IQR:** interquartile range, **RBD:** Receptor-binding domain, **NASH:** Non-Alcoholic SteatoHepatitis, **ALD:** Alcoholic liver disease, **VHC:** Hepatitis C Virus, **CBP:** Primary Biliary cholangitis, **AIH:** Autoimmune hepatitis, **PSC:** Primary Sclerosing Cholangitis, **GFR:** Glomerular Filtration Rate.

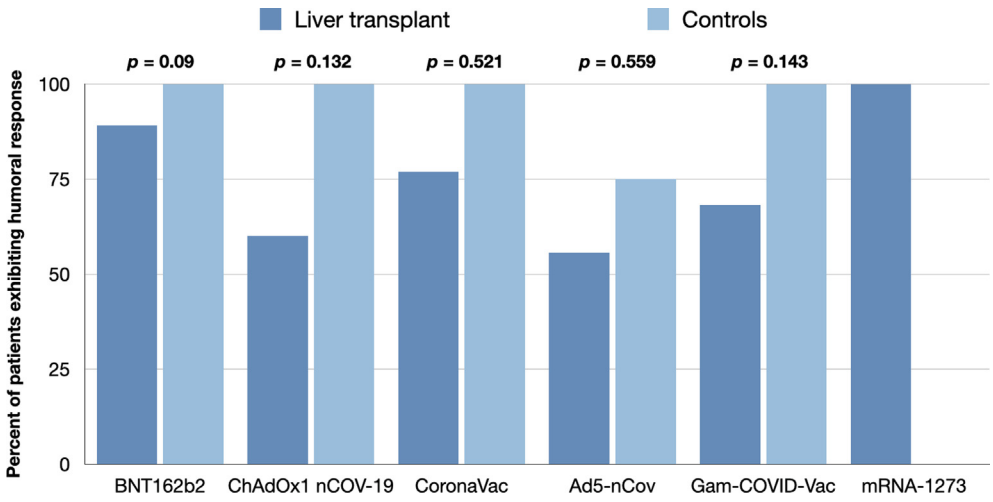

Fig. 1. Humoral response associated with the different types of vaccines in liver transplant patients.

Table 2
Response to the vaccine by a group of patients.

	OLT patients (n = 133)	Controls (n = 54)	p
S1–S2 (DiaSorin), n (%)			
Positive	94 (70.7)	53 (98.1)	< 0.001
Negative	39 (29.3)	1 (1.9)	
COV-2 IgG II (Abbott), n (%)			
Positive	103 (77.4)	53 (98.1)	0.001
Negative	30 (22.6)	1 (1.9)	
S1–S2 (DiaSorin), median AU/mL (IQR)	76.4 (9.36–317)	281.5 (121–400)	<0.001
COV-2 IgG II (Abbott), median AU/mL (IQR)	549.00 (64.4–8739.5)	3450 (1495.7–9606.5)	0.002

OLT: Liver transplant recipients, **IQR:** interquartile range, **RBD:** Receptor-binding domain. **COV-2 IgG II:** SARS-COV-2 IgG II Quant Receptor-binding domain-Spike. **S1–S2 Diasorin:** S1 and S2 proteins of the SARS COV virus spike 2.

Table 3
General characteristics of liver transplant recipients by COVID-19 infection.

	OLT patients (n = 133)	
Variable	COVID-19 (+) (n = 24)	COVID-19 (−) (n = 109)
Sex at birth, n (%)		
Male	13 (54.2)	48 (44)
Female	11 (45.8)	61 (56)
Age, median (IQR)	54 (48.7–60.5)	63 (55–67)
Comorbidities, n (%)		
Diabetes	12 (50)	42 (38.5)
Arterial Hypertension	8 (33.3)	41 (37.6)
Obesity I	6 (25)	19 (17.4)
Obesity II	1 (4.2)	3 (2.8)
Neoplasia	3 (12.5)	8 (7.3)
GFR > 3	4 (16.6)	29 (26.6)
Cirrhosis etiology, n (%)		
NASH	3 (12.5)	14 (12.8)
ALD	0	10 (9.2)
VHC	7 (29.2)	35 (32.1)
PBC	1 (4.2)	9 (8.3)
HAI	4 (16.7)	10 (9.2)
Cryptogenic	2 (8.3)	18 (16.5)
PSC	1 (4.2)	3 (2.8)
PBC + AIH	2 (8.3)	7 (6.4)
Other	4 (16.7)	3 (2.8)
Hepatocelular carcinoma, n (%)	1 (4.2)	26 (23.9)
Immunosuppression used, n (%)		
Single	9 (37.5)	62 (56.9)
Double	15 (62.5)	40 (36.7)
Triple	0	7 (6.4)

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Table 3 (*continued*)

Variable	OLT patients (n = 133)	
	COVID-19 (+) (n = 24)	COVID-19 (−) (n = 109)
Type of immunosuppression used, n (%)		
Tacrolimus	22 (91.6)	99 (90.8)
Cyclosporine	2 (8.3)	9 (8.2)
Prednisone	10 (41.6)	26 (23.8)
Mycophenolic acid	5 (20.8)	26 (23.8)
Azathioprine	0	1 (0.91)
Sirolimus	0	2 (1.83)
Time from liver transplantation to vaccine, months, median, (IQR)	62.5 (45–75)	55 (33–79.5)
Time since last vaccine dose to serological response measurement, median days (IQR)	35.5 (29.2–55)	38 (28–62.5)
Adverse effects after vaccination, n (%)		
None	15 (62.5)	76 (69.7)
Local	9 (37.5)	33 (30.3)

OLT: Liver transplant recipients, **IQR:** interquartile range, **RBD:** Receptor-binding domain, **NASH:** Non-Alcoholic SteatoHepatitis, **ALD:** Alcoholic liver disease, **VHC:** Hepatitis C Virus, **CBP:** Primary Biliary cholangitis**, AIH:** Autoimmune hepatitis, **PSC:** Primary Sclerosing Cholangitis, **GFR:** Glomerular Filtration Rate.

Table 4
Response to the vaccine by patients with previous COVID-19 infection.

	OLT patients (n = 133)		Controls (n = 54)	
	COVID-19 (+) (n = 24)	COVID-19 (−) (n = 109)	COVID-19 (+) (n = 12)	COVID-19 (−) (n = 42)
Type of vaccine, n (%)				
BNT162b2	10 (41.6)	55 (50.5)	7 (58.3)	22 (52.4)
ChAdOx1 nCOV-19	3 (12.5)	17 (15.6)	0	6 (14.3)
CoronaVac	2 (8.3)	11 (10.1)	2 (16.6)	5 (11.9)
Ad5-nCov	5 (20.8)	4 (12.8)	2 (16.6)	2 (4.8)
Gam-COVID-Vac	3 (12.5)	19 (17.4)	1 (8.3)	7 (16.6)
mRNA-1273	1 (4.2)	3 (2.7)	–	–
S1-S2 by type of vaccine, median (IQR)				
BNT162b2	400 (353.3–400)	126 (25.7–299)	366 (246–400)	331 (264–400)
ChAdOx1 nCOV-19	400 (400–400)	9.27 (3.8–27.7)	–	322 (63.7–400)
CoronaVac	115.7 (37.3–115.7)	17.4 (8.7–35.9)	213.3 (54.7–213.3)	64.3 (34.7–109.3)
Ad5-nCov	291 (6.8–392)	3.8 (3.8–4.64)	400 (400–400)	69.9 (3.8–69.9)
Gam-COVID-Vac	400 (218–400)	22.7 (4.24–106)	166	105 (69.3–137)
mRNA-1273	400	202 (130–202)	–	–
COV-2 IgG II by type of vaccine, median (IQR)				
BNT162b2	40,000 (12228.2–40000)	1230.9 (188.9–8658.8)	18,897 (2900–33328.9)	4670.9 (3195.3–9696.5)
ChAdOx1 nCOV-19	20585.1 (9000.2–21016.5)	67.3 (9.3–153.9)	–	4819.2 (411.2–16647.1)
CoronaVac	942.5 (297.9–1587.0)	185.5 (38.9–291.1)	1954.9 (512.7–3397.2)	531 (265–1132.1)
Ad5-nCov	15663.3 (31.75–24701)	4.05 (0.7–9.6)	13754.2 (12723–14785.3)	1230.9 (13.8–1230.9)
Gam-COVID-Vac	10561.4 (6047.5–23583.9)	182.9 (13.3–696.1)	4652.6	1288.4 (567.4–2023.7)
mRNA-1273	22,897	4071.6 (2963.7–5450.4)	–	–

OLT: Liver transplant recipients, **IQR:** interquartile range, **RBD:** Receptor-binding domain, **COV-2 IgG II:** SARS-COV-2 IgG II Quant Receptor-binding domain-Spike. **S1–S2 Diasorin**: S1 and S2 proteins of the SARS COV virus spike 2.

c. Reactogenicity

For reactogenicity, 31.6% of patients reported mild symptoms (fever, headache, fatigue or pain at the site of infusion). No serious adverse reactions were reported (Table 5)**.**

3.2. Control patients

A total of 54 controls were included; 70.4% were female (n = 38) with a median age of 55 (IQR: 41.7–65.2), and 44.2% had at least 1 comorbidity. Obesity was seen in 25.9%; 24.8% had a GFR KDIGO stage 3 or higher, hypertension was present in a 16.6% (Table 1).

a. Antibody titers by type of vaccine in controls

In controls, by vaccine brands: 53.7% received BNT162b2 (Pfizer-BioNTech), 14.8% Gam-COVID-Vac (Sputnik V, Russia), 13% received CoronaVac (Sinovac, Life Sciences, Beijing, China), 11.1% received ChAdOx1 nCOV-19 (Oxford-AstraZeneca), 7.4% Ad5-nCov (Cansino, Biologics), and no participant received mRNA-1273 (Moderna) vaccine. Response rates to the vaccine are available in Fig. 1. For controls, S1/S2 reagent, the response rate was 98.1% (median: 281.5 AU/mL) and 98.1% (median: 3450 AU/mL) for COV-2 IgG II. (Tables 2 and 4).

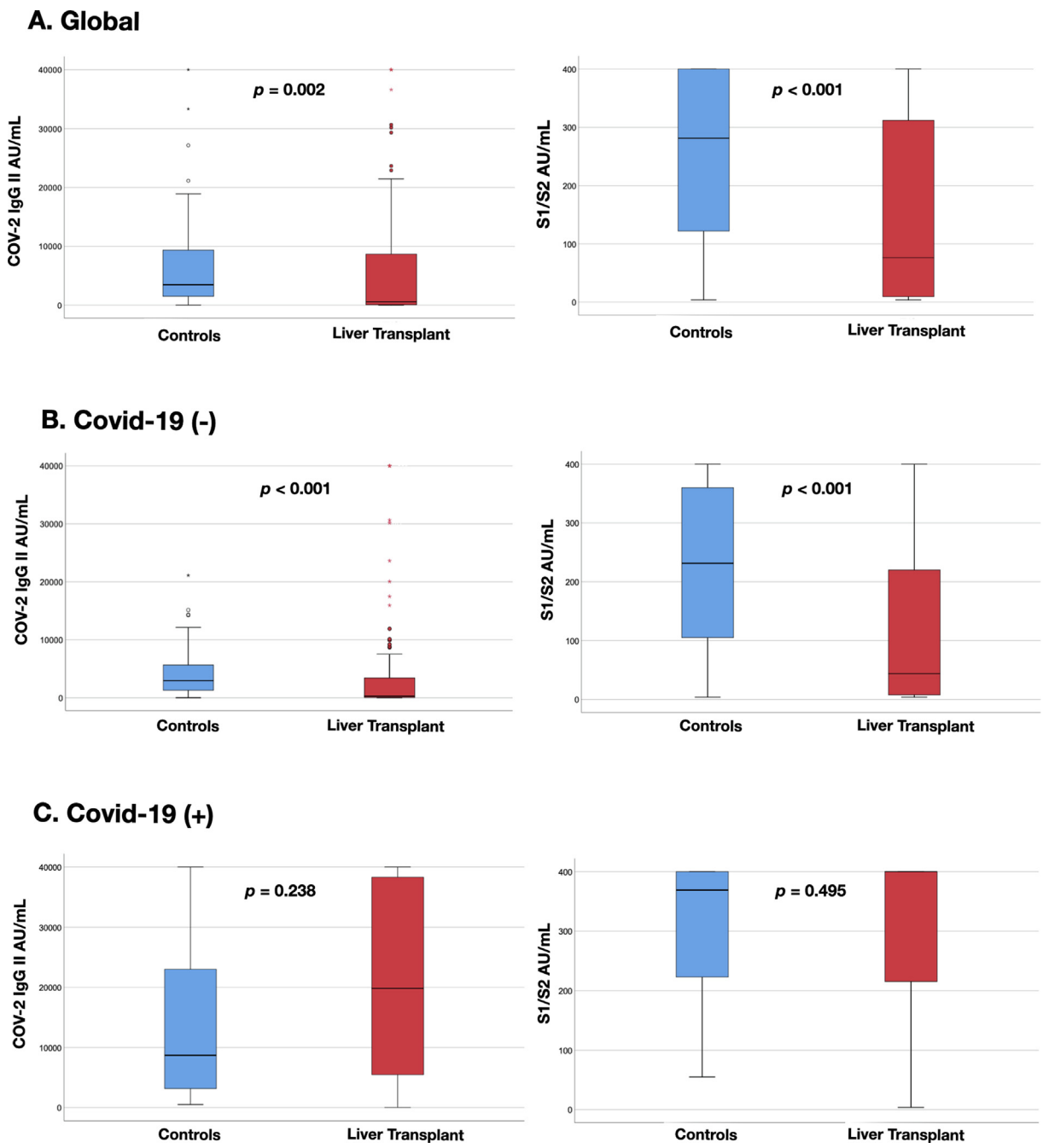


Fig. 2. A. Global quantitative results for COV-2 IgG II S1-RBD antibody test and Anti-S1/S2. B. Response rate for patients without COVID-19 infection (Quantitative results for COV-2 IgG II S1-RBD antibody test and Anti-S1/S2). C. Response rate for patients with previous COVID-19 infection (Quantitative results for COV-2 IgG II S1-RBD antibody test and Anti-S1/S2).

There was a 6.2-fold increase in COV-2 IgG II values in the control group compared to the OLT patients and a 3-fold increase in S1/S2 values in the control vs. OLT group. Among the controls, one patient presented a case of COVID-19 infection after the complete vaccination scheme with mild symptoms.

b. Previous COVID-19 infection and antibody titers

In the case of controls, 22.2% had previous COVID-19 infection, with a median of time of COVID-19 to vaccination of 169.5 days (IQR: 95–194.2). The COV-2 IgG II values were 19823.1 AU/mL (IQR: 5173.75–39151.6) for those who had COVID-19 infection vs. 291.1 AU/mL (IQR: 39.7–3625.7) in the no-COVID population; a 68.1-fold increase in COV-2 IgG II levels. In the case of S1/S2 DiaSorin patients with COVID-19 had a median of 400 AU/mL (IQR: 214.3–400, with 38 participants reaching out the 400 AU/mL maximum detection level of the assay) vs. 43.6 AU/mL (6.7–224) in patients without COVID-19 history, a 9.1-fold increase in S1/S2 values (Table 4, Fig. 2).

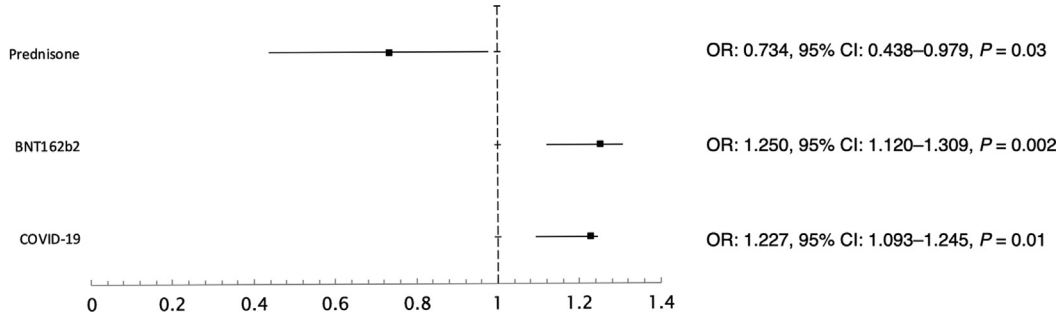
c. Reactogenicity

In the case of controls, 35.2% of patients reported mild symptoms (16.7% with pain at site of injection). No serious adverse reaction was seen (Table 5).

Table 5
Adverse effects after vaccination.

	OLT patients (n = 133)				Controls (n = 54)			
	Pain	Headache	Fever	Fatigue	Pain	Headache	Fever	Fatigue
Type of vaccine, n (%)								
BNT162b2	27 (20.3)	12 (9.0)	16 (12.0)	15 (11.3)	9 (16.7)	2 (3.7)	3 (5.6)	3 (5.6)
ChAdOx1 nCOV-19	4 (3.0)	2 (1.5)	4 (3.0)	3 (2.3)	2 (3.7)	1 (1.9)	2 (3.7)	2 (3.7)
CoronaVac	2 (1.5)	1 (0.8)	1 (0.8)	1 (0.8)	1 (1.9)	0	1 (1.9)	0
Ad5-nCov	2 (1.5)	1 (0.8)	0	1 (0.8)	2 (3.7)	2 (3.7)	0	1 (1.9)
Gam-COVID-Vac	6 (4.5)	5 (3.8)	3 (2.3)	4 (3.0)	5 (9.3)	2 (3.7)	2 (3.7)	2 (3.7)
mRNA-1273	1 (0.8)	0	1 (0.8)	1 (0.8)	–	–	–	–

OLT: Liver transplant recipients.



*Adjusted for age, gender, comorbidities, BMI, type of immunosuppression, type of vaccine used. Multivariate odds ratios (OR) were corrected by the method proposed by Zhang and Y in order to approximate the true risk ratio from the adjusted odds ratios. Hosmer-Lemeshow test for goodness of fit: P = .918, 4 d.f., chi-squared = 0.948.

Fig. 3. Forest plot showing the factors significantly associated with serological response to the SARS-CoV-2 vaccine among patients with orthotopic liver transplant.

3.3. Predictors of serological response in OLT patients

In a multivariable model adjusted for relevant confounders, the antecedent of COVID-19 and BNT162b2, inoculation was associated positively with the serologic response, while the use of prednisone (compared with other immunosuppressants) interfere with this response (Fig. 3).

4. Discussion

Herein we report the humoral response to a complete scheme of vaccines in Mexican OLT patients and controls. We found that independent of the vaccine platform, the serological response to COVID-19 vaccines in OLT patients is lower than in controls. Since we analyzed OLT patients, data regarding seroconversion rates in other solid transplant recipients should be tailored, since the serological response can be heterogeneous due to differences in immunosuppressive regimens. Previous studies have shown a response rate to a mRNA vaccine of 48% [9], 47.5% [10,11] and 44.9% [12] in patients with SOT, response rates significantly lower than that we observed in our OLT cohort (>80% RBD response rate). In the case of mRNA-1273 vaccine, a serological response of 93% [13] was seen vs. 100% in our study, and it is even higher than the liver subset analyzed in a recent SOT *meta*-analysis [12,14]. In the case of CoronaVac, in Uruguay [15], a higher seroconversion rate, as compared with our cohort (36.5% vs. 13%) was observed. To our knowledge, no serological response rate has been previously reported in OLT patients for Sputnik V, PiCoVacc and BBIBP-CorV [16]. When we considered factors for the response rate seen in our population, the BNT162b2 vaccine was positively associated with response rate as seen in SOT *meta*-analysis [12]. Some studies have reported risk ratios for seroconversion of 0.39 in SOT recipients [18].

In the case of controls, the response rate was up to 90% for the mRNA vaccines and the ChAdOx1 nCOV-19 [17]. Even when our controls were different from OLT recipients with respect to age (a difference of 10 years), comorbidities (with more diabetes, hypertension and GFR > 3 in OLT) and time since last vaccine dose to serological response (higher in controls), we found a 100% response rate in this population. A lower vaccine response was seen only for the Cansino vaccine, that is in contrast to the response rate reported by Feng-Cai et al. [19] which can be explained by type of population reported in the study (they excluded major chronic illnesses, they were younger than our population and vaccine dose was higher) which are important in the Mexican population.

Some factors have been associated with seroconversion rate: increased age, sex, deceased donor organ and chronic kidney disease; we did not find them as a risk factor. In the case of immunosuppression, OLT recipients can use a drug dose that is different from that used for other SOT, and it can influence the response rate to the vaccination [10,17]. In our patients, just the use of prednisone contributed to a decrease in the response rate to the vaccine. These data differ from previous observations were antimetabolites have been associated with worse seroconversion rates [12,13,20]. Even with a triple scheme of immunosuppression, we found that 5/7 of our patients had a positive humoral response. Other factors that have been implicated were the time from OLT to vaccination [17]; in our case, a median of 68.5 months were seen in mRNA-1273 and 61 months for BNT162b2.

At the moment, the durability of humoral and cell-mediated immunologic response is still unknown as well as the probability of rejection or allosensitization [2]. In our cohort, no episode of rejection was observed. For reactogenicity, mild adverse events have been reported in other studies [11,13,21] in all of the platforms, and even if new information is still needed in relation to the safety and efficacy of the vaccines in the immunosuppressed population, our results can contribute to patients' acceptance of vaccines.

In the case of OLT recipients with a previous documented COVID-19 infection, there is no data about the level of protection they can acquire from this episode; we saw a 68.1-fold increase in COV-2 IgG II levels, showing a high seroconversion rate. These data is important where limited access to the vaccine is still seen [17]. We are aware that we do not report the T-cell response rate. Still, at the time of the study, only 1 control had a COVID-19 episode after full dose vaccination and none of the controls at a median of 150 days, suggesting that some protection is still present.

With the evolution of COVID-19 new information is available and the reports that a booster dose in SOT patients can increase the serological response rate has been relevant to clinical practice [12,18,22,23].

Our study has limitations, including the small sample size and the lack of T-cell response evaluation. Even though humoral response is accomplished with the complete basic vaccine scheme (one or two shots, depending on the platform), patients should have access to the different boosters available in their country. Moreover, although previous COVID-19 infection was associated with a higher serological response to SARS-CoV-2 vaccines, this should not be interpreted that the natural infection is a valid method to improve the serological response. The maximum detection level of the S1/S2 assay is 400 AU/mL, and since we observed 38 participants reaching this magnitude, it is possible that some differences in S1/S2 antibodies response would fall within this sample proportion, which may lead to underestimation of the groups' differences.

5. Conclusions

Independently of the vaccine brand, the serological response to COVID-19 vaccines in OLT patients is lower than otherwise healthy controls. In these patients, the BNT162b2, vaccine was associated with a higher serologic response. Other variables significantly associated with the humoral response were the COVID-19 antecedent (positively) and prednisone exposure (negatively). At the moment, further analysis is necessary to determine whether this serological response is associated with SARS-COV2 infection or reinfection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ávila-Rojo E, López-Yánez S, Alcaraz-Fuerte C, García Baysa M, López Jiménez J, Márquez Guillén E, Vilatoba M, Cruz Martínez R, Carpinteyro-Espin P, Chávez-Villa M, Romero Morelos R, Torres-del Real D, Uscanga Domínguez F, García-Alanis M, Tapia Sosa R, Servín-Rojas M, collected data, performed the research and reviewed the manuscript.

Del Villar Velasco S, Rivera Monroy S, López Gómez T, Andrés Aguilar J, Balcázar Antonio D, contributed with new reagents and analytic tools and reviewed the manuscript.

Chiquete-Anaya E drafted the manuscript, contributed to the statistical analysis, and reviewed the manuscript.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.08.027.

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