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

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ARTICLE INFO

Article history:
Received 10 March 2022
Received in revised form 17 July 2022
Accepted 15 August 2022
Available online 22 August 2022

Keywords:
Humoral response
Mexico
Vaccines
COVID-19
Pandemia

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.

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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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https://doi.org/10.1016/j.vaccine.2022.08.027
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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 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 (Abbott 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.

2.2. 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 (Abbott 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 response 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
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 31.6%, and 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.

2. Controls

For OLT, up to 18% of patients had previous COVID-19 infection, and a median of 143.5 days (IQR: 29–316.7) 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 (continued)

| Variable                                      | OLT patients (n = 133) | Controls (n = 54) |
|-----------------------------------------------|------------------------|------------------|
|                                               | All patients           |                  |
|                                               | BNT162b2 (n = 65)      |                  |
|                                               | ChAdOx1 nCoV-19 (n = 20) |              |
|                                               | CoronaVac (n = 13)     |                  |
|                                               | Ad5-nCov (n = 9)       |                  |
|                                               | Gam-COVID-19 (n = 22)  |                  |
|                                               | mRNA-1273 (n = 4)      |                  |
| Obesity II                                   | 4 (3.0)                | 2 (3.7)          |
| Obesity III                                  | 0                      | 1 (1.9)          |
| Neoplasia                                     | 11 (8.3)               | 2 (3.7)          |
| Hepatocellular carcinoma, n (%)              | 33 (25.0)              | 4 (7.4)          |
| Cirrhosis etiology, n (%)                    |                        |                  |
| NASH                                          | 17 (12.8)              |                  |
| ALD                                           | 10 (7.5)               |                  |
| VHC                                           | 42 (31.6)              |                  |
| PBC                                           | 10 (7.5)               |                  |
| HAI                                           | 14 (10.5)              |                  |
| Cryptogenic                                   | 20 (15)                |                  |
| PSC                                           | 5 (3.8)                |                  |
| Other                                         | 11 (8.3)               |                  |
| Hepatocellular carcinoma, n (%)              | 25 (18.8)              |                  |
| Immunossuppression used, n (%)               |                        |                  |
| Single                                        | 71 (53.4)              |                  |
| Double                                        | 55 (41.4)              |                  |
| Triple                                        | 7 (5.3)                |                  |
| Type of immunossuppression used, n (%)       |                        |                  |
| Tacrolimus                                    | 121 (90.9)             |                  |
| Cyclosporine                                  | 11 (8.3)               |                  |
| Prednisone                                    | 36 (27.0)              |                  |
| Mycophenolic acid                            | 31 (23.3)              |                  |
| Azathioprine                                  | 2 (1.5)                |                  |
| Sirolimus                                     | 24 (18)                |                  |
| Previous COVID-19 infection, n (%)           |                        |                  |
| Time from liver transplantation to vaccine, months, median, (IQR) | 56 (36–79) | 61 (36–79.5) |
| Time from COVID-19 to the vaccine, days (IQR) | 143.5 (98.2–316.7) | 150.5 (131.25–351.5) |
| Adverse effects after vaccination, n (%)     |                        |                  |
| None                                          | 91 (68.4)              |                  |
| Mild                                          | 42 (31.6)              |                  |

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.

| Vaccine                  | 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

| Variable                          | OLT patients (n = 133) | 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)                |                        |
| Hepatocellular 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)                |                        |

(continued on next page)
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).

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

| Variable                                | OLT patients (n = 133) | COVID-19 (+) (n = 24) | COVID-19 (−) (n = 109) |
|-----------------------------------------|------------------------|-----------------------|------------------------|
| 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 (3.8–69.9) |
|                                         | Gam-COVID-Vac          | 400 (218–400)         | 22.7 (4.24–106)       | 166 (69.3–137) | 105 (69.3–137) |
|                                         | mRNA-1273              | 400 (130–202)         | 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 (2900–33289.9) | 4670.9 (3195.3–9696.5) |
|                                         | ChAdOx1 nCOV-19        | 20585.1 (90002.2–21016.5) | 67.3 (9.3–153.9) | – | 4819.2 (411.2–16647.1) |
|                                         | CoronaVac              | 942.5 (297.9–1587.8)  | 185.5 (38.9–291.1)    | 1954.9 (512.7–3397.2) | 531 (265–1132) |
|                                         | 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 (60475.4–23583.9) | 182.9 (113.3–696.1) | 4652.6 (567.4–20237) | 1288.4 |
|                                         | mRNA-1273              | 22,897 (2963.7–5450.4) | 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.

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).
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 Dia-Sorin 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).
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) interfered 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 the 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]. In the case of CoronaVac, in Uruguay [15], a higher seroconversion rate, as compared with our cohort (36.5% vs. 13%) was observed.

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 where 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.

### Table 5

|                      | 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 et al. in order to approximate the true risk ratio from the adjusted odds ratios. Holm-Sidak test for goodness of fit: P = 918.4 df, 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.
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 serologic 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.

Acknowledgments

Liz Toapanta-Yanchapaxi reports a doctoral scholarship support provided by Consejo Nacional de Ciencia y Tecnología. 

Authors contributions: Toapanta-Yanchapaxi L, García-Juárez I, Valdez Echeverría R designed the report, collected data, performed the research, drafted the manuscript, and reviewed the manuscript.

Ávila-Rojo E, López-Yáñez S, Alcaraz-Fuerte C, García Baysa M, López Jiménez J, Márquez Guillén E, Vilatoba M, Cruz Martínez R, Carpenteyro-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.

Disclosure: The authors of this manuscript have no conflicts of interest to disclose. / Liz Toapanta-Yanchapaxi reports a doctoral scholarship support provided by Consejo Nacional de Ciencia y Tecnología.

Funding: This study has received no funding.

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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