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Pediatric Liver and Kidney Transplant Recipients Demonstrate Greater Serological Response to SARS-CoV-2 Vaccination Than Adults

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Background. Adult solid organ transplant recipients (SOTRs) have decreased responsiveness to severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) vaccination and higher incidence of infection, but there are few data on the serological response in pediatric SOTR. The aim of this study was to determine serological response to SARS-CoV-2 vaccination in pediatric liver (LT) and kidney transplant (KT) recipients and compare it with adult SOTR. **Methods.** A European, prospective, multicenter study was performed. Samples were taken at 7 and 32 wk following COVID-19 vaccination and serological endpoints were measured by ELISA. **Results.** A total of 42 pediatric (16 post-LT and 26 post-KT) and 117 adult (all post-LT) were included. All pediatric participants and 94% adult participants received mRNA vaccines. Paediatric SOTR patients had significantly higher anti-Spike IgG levels than adult participants at week 7 (114 220.7 [59 285.92–220 058.55] versus 8756.7 [5643.69–13 586.71], $P < 0.0001$) and week 32 (46 113.2 [10 992.91–193 436.14] versus 8207.0 [3561.20–18 913.43], $P = 0.0032$). No significant difference in week 7 anti-Spike IgG response was found between pediatric LT and KT (129 434.4 [51 888.64–322 869.69] versus 105 304.5 [39 910.20–277 849.50], $P = 0.9854$). No differences were seen between children and adults in the rate of decline of anti-Spike IgG between weeks 7 and 32 ($P = 0.8000$). Male sex and hemolytic-uremic syndrome or postischemic kidney disease were associated with lower anti-Spike IgG levels at week 7 in pediatric SOTR. **Conclusions.** Paediatric SOTR demonstrate greater SARS-CoV-2 vaccine responses than comparable adult SOTR patients. These data support efficacy and safety of SARS-CoV-2 vaccination in child SOTR and may alleviate vaccine hesitancy in this patient group.

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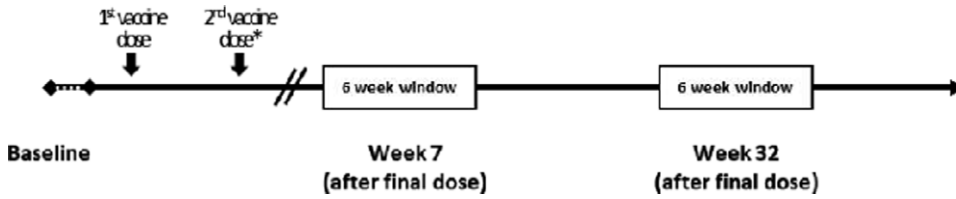

FIGURE 1. Study outline. *Second vaccine dose will be given after 6 wk (±1 wk after initial dose according to the recommendations for mRNA vaccines).

The introduction of vaccines against COVID-19 has reduced the number of infections, hospitalizations and deaths. This applies not only to the general population but also, in particular, to risk groups such as those with liver disease and after transplantation.[1,2] In general, COVID-19 infections in children are often mild.[3,4] The multisystem inflammatory syndrome in children was soon described following a COVID-19 infection. A systemic complication with persistent fever, inflammation, and organ dysfunction is similar to Kawasaki disease.[5,6] Moreover, there is a risk for long COVID-19 with a prevalence up to 25% after infection.[7] Vaccination may lower the risk for developing long COVID-19 in adults.[8] There are good data that COVID-19 vaccines are immunogenic and effective in healthy children and adolescents.[9-11] In May 2021, BNT162b2 COVID-19 vaccine was authorized for the vaccination of 12- to 15-y olds in the European Union (EU).[12] Since November 2021, the vaccine has also been authorized at a lower dose for children aged between 5 and 11 y throughout the EU.[13] However, compared with adults, little is known about the safety and efficacy of COVID-19 vaccines in pediatric patients with underlying medical conditions or who are immunosuppressed. Moreover, children after solid organ transplantation have a high risk for vaccine-preventable infection, but they are often not age-appropriate vaccinated.[14-16]

Even before COVID-19, vaccine hesitancy was a leading cause of underimmunization, both among parents and primary care physicians.[17] Nevertheless, COVID-19 vaccine acceptance in pediatric transplant population is even worse.[18] Many different factors influence COVID-19 vaccine hesitancy; in particular vaccine-specific factors with regard to safety and effectiveness can only be answered by appropriate studies.[19,20]

The primary aim of this study was to determine serological response to severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) vaccination in pediatric patients after liver (LT) or kidney transplant (KT) and undertake comparative analyses with adult patients after liver transplantation. Secondary aims were to evaluate rate of decline of serological response between weeks 7 and 32 in pediatric and adult patients and evaluate factors associated with serological response to SARS-CoV-2 vaccination in the pediatric group.

MATERIALS AND METHODS

Study Design and Participants

COBALT is a European, prospective, multicenter study of SARS-CoV-2 vaccine responses in adult and pediatric patients. Part of the adult data have been previously published.[2] The study design is outlined in Figure 1, and the protocol is available (**Supplemental Material, SDC**). Recruitment for COBALT took place in Italy, Spain, and the United Kingdom. Inclusion criteria for the adult population were age 18 y or older and able to give written informed consent and post-LT (>6 mo) for cirrhosis. Exclusion criteria were history of COVID-19 (polymerase chain reaction–positive episode) or uncontrolled HIV infection. Inclusion criteria for the pediatric population were age between 0 and 17 y, whose parent/legal guardian give written informed consent and SOTR (≥1 y after pediatric LT or KT). Exclusion criteria were parents/legal guardian unable to give written informed consent, participant receiving immunoglobulin supplementation <3 mo, episode of biopsy-proven acute rejection <3 mo, participant receiving high dose steroids <3 mo, episode of posttransplant lymphoproliferative disease <3 mo, uncontrolled HIV infection, diagnosis of combined or severe combined immunodeficiency, or stem cell transplantation. Patients were assessed for eligibility for the study, in clinic or by telephone, at any point until 10 wk after COVID-19 vaccination from May 8, 2021, to September 10, 2021, in the case of adults and from June 14, 2021, to February 3, 2022, for pediatric population with clinical follow-up until June 1, 2024.

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Data Collection and Biological Sampling

The following information was collected at the time of inclusion: demographic data (date of birth, sex, race and ethnicity); medical history (date of onset/diagnosis and etiology of liver or kidney disease); medications and vaccine regimen received by participants (mRNA vaccines—2 doses of BNT162b2 Pfizer-BioNTech or mRNA-1273 Moderna, adenoviral vaccines—1 dose of Ad26.COV2.S Janssen/Johnson & Johnson or 2 doses of AZD1222 Oxford-AstraZeneca or heterologous combinations). Data were entered electronically into a predesigned electronic Case Report Form, maintained by the EF-CLIF Data Management Center.

All participants underwent blood sampling at 7 ± 3 and 32 ± 3 wk following second vaccine dose (or initial vaccine dose for 1-dose regimens) for laboratory analyses. Immunological assays were conducted at the King's College London, United Kingdom. Hematology (full blood count and coagulation) and biochemistry (liver and renal function) profiles were processed at the local center and the results were clinician-reported.

Laboratory Methods

Anti-Spike and Receptor-binding Domain IgG Immunoassays

IgG levels of SARS-CoV-2 spike and SARS-CoV-2 S1 receptor-binding domain (RBD) were determined in serum using electrochemiluminescent immunoassay from meso-scale discovery (V-PLEX COVID-19 CoV Panel 3 Kit, K15399U; Meso Scale Diagnostic, MD). According to the manufacturer's instructions, serum samples were diluted 1:5000 before quantification. Assays were carried out without modification. Before analysis, data were normalized by log10 transformation.

Statistical Analyses

Descriptive Analyses and Humoral Responses to COVID-19 Vaccination

Discrete variables were reported as counts (percentage), continuous variables normally distributed as mean and SD, and not-normally distributed as median and interquartile range (25th percentile–75th percentile). In univariable statistical comparisons, associations between categorical variables were tested using the Pearson chi-square test or Log-linear models depending on data complexity. Concentrations of anti-Spike/RBD IgM, IgG and IgG/IgM ratios at weeks 7 ± 3 and 32 ± 3 following COVID-19 vaccination were normalized by log10-transformation and presented as geometric mean (IU) and 95% confidence interval. The rate of decline was calculated as the difference of the log-transformed antibody levels between weeks 7 and 32. The Wilcoxon-Mann-Whitney or the Kruskal-Wallis tests were used for univariable comparisons between adult and pediatric patients or between LT and KT recipients.

Factors Associated With COVID-19 Vaccine Response

To study independent associations of antibody response in the pediatric population, univariable general linear models were performed including demographic, clinical, drug-related, and biochemical data. Only covariates showing a clinical and statistical significance in univariable models, or participating as a confounding factor for the variable of interest, were included in the final step-wise multivariable models.

Software and Data Quality Assurance

Statistical analyses were carried out using SAS v 9.4, R v 4.1.0, SPSS v26/27 and SIMCA v15/v17 depending on package availability and functionality, with the cutoff for statistical significance set at 0.05.

Research Reproducibility Approach

All analyses were reproducibly performed and were hosted in the EF-CLIF repository, which is publicly available on demand.

Ethics

The study was conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognized by governing laws and EU Directives. The study was approved by ethical review boards at all study sites. Each participant's (including children and their legal guardians) consent to participate in the study was obtained after a full age-appropriate explanation was given. The right of the participant to refuse to participate in the study without giving reasons was respected.

RESULTS

Participants

A total of 42 pediatric SOTR (16 post-LT and 26 post-KT) and 125 adult post-LT recipients were recruited. All pediatric participants received mRNA vaccines (BNT162b2 Pfizer-BioNTech) and 117 (93.6%) adults received mRNA vaccines. Only the 117 adult patients after mRNA vaccination were included in the further analyses. Participant characteristics are presented in Table 1. A total of 56% and 62% of pediatric patients were male with a mean age of 9 (3) and 11 (3) y in the LT and KT groups, respectively, whereas in adult patients, 78% were men with a mean age of 60 (12) y. The vast majority of patients were White. The most prevalent liver disease in LT pediatric patients was biliary atresia (38%) followed by malignancy (19%), whereas the most prevalent kidney disease in KT patients was congenital abnormalities (54%) followed by glomerular disease (31%). The most prevalent etiology of cirrhosis in adults was hepatitis B or C (48%) and alcohol (28%). All LT children, 96% of LT adults and 89% of KT pediatrics received immunosuppressors, being calcineurin inhibitors the most frequently used in all groups (88%, 86%, and 85% in LT and KT, respectively).

Humoral Immune Responses to COVID-19 Vaccination

Pediatric SOTR had significantly higher geometric mean anti-Spike IgG levels than adult participants at week 7 postvaccination (114 220.7 [59 285.92–220 058.55] versus 8756.7 [5643.69–13 586.71], $P < 0.0001$) and week 32 (46 113.2 [10 992.91–193 436.14] versus 8207.0 [3561.20–18 913.43], $P = 0.0032$) (Figure 2A). Similar findings were noted for anti-RBD IgG response at week 7 (107 718.8 [43 358.31–267 615.10] versus 4730.2

TABLE 1.

Baseline characteristics of the study population

Variable	Pediatric SOTR (n = 42)	Pediatric post-LT (n = 16)	Pediatric post-KT (n = 26)	Adults post-LT (n = 117)
Male sex, n (%)	25 (60)	9 (56)	16 (62)	94 (80)
Age (y), mean (SD)	10 (3)	9 (3)	11 (3)	61 (12)***
Race, n (%)				
White	41 (98)	15 (94)	26 (100)	117 (100)
Black or Afro-American	1 (2)	1 (6)	0 (0)	0 (0)
Ethnicity, n (%)				
North European	31 (76)	9 (60)	22 (85)	4 (3)***
Mediterranean	8 (20)	5 (33)	3 (12)	112 (96)
Other	2 (5)	1 (7)	1 (4)	1 (1)
Liver disease, n (%)				
Biliary atresia		6 (38)		
Malignancy		3 (19)		
Cryptogenic		2 (13)		
Hemochromatosis		1 (6)		
Other		2 (13)		
Etiology of cirrhosis				
Alcohol				35 (30)
NAFLD/NASH				9 (8)
Autoimmune				13 (11)
Hepatitis B or C				56 (48)
Other				29 (28)
Years since the diagnosis of liver				
disease		5 (33)		13 (13)
1–5		10 (67)		89 (87)
>5				
Kidney disease, n (%)				
Congenital abnormalities			14 (54)	
Glomerular disease			8 (31)	
Tubulo interstitial			1 (4)	
HUS/Postischemic			1 (4)	
Other			3 (12)	
Immunosuppressors, n (%)	39 (93)	16 (100)	23 (89)	112 (96)
Steroids	15 (36)	4 (25)	11 (42)	13 (11)
Calcineurin inhibitor	26 (86)	14 (88)	22 (85)	99 (85)
Mycophenolate	3 (7)	0 (0)	3 (12)	52 (44)***
AZA or 6-MP	1 (2)	0 (0)	1 (4)	1 (1)
Other	23 (55)	4 (25)	19 (73)^^	19 (16)
Biochemical parameters, mean				
(SD) or median (IQR)	4.2 (3.9–4.5)	3.9 (0.5–4.2)	4.4 (4.2–4.6)^^	4.2 (4.0–4.5)**
Albumin (g/dL)	36 (28–44)	37 (32–44)	30 (25–42)	23 (18–29)***
AST (U/L)	27 (22–42)	28 (22–42)	25 (21–43)	19.5 (14–32.5)*
ALT (U/L)	247 (45)	235 (44)	261 (45)	219.1 (66.9)***
LDH (U/L)	276 (104)	331 (76)	201 (92)^^	106.5 (70.8)***
ALP (U/L)	18 (13–69)	22 (15–55)	17 (13–116)	30 (17–72)
GGT (U/L)	0.4 (0.3–0.7)	0.4 (0.3–0.6)	0.6 (0.5–0.7)	0.7 (0.5–1.1)*
Bilirubin (mg/dL)	0.7 (0.5–1.1)	0.4 (0.3–0.6)	1.0 (0.7–1.4)^^	1.0 (0.8–1.3)***
Creatinine (mg/dL)	8.6 (3.6–75)	6 (3–12)	75 (48–163)	26 (26–26)***
Ferritin (ug/dL)	139 (138–140)	139 (138–139)	139 (138–140)	141 (139–142)***
Sodium (mEq/L)	90 (85–101)	88 (84–98)	92 (86–119)	99 (89–114)*
Glucose (mg/dL)	0.6 (0.6–1.7)	0.6 (0.6–1.7)	—	4.3 (1.2–52.5)*
C-reactive protein (mg/L)	13 (11–13)	13 (12–14)	12 (11–13)^	14.4 (12.4–15.5)
Hemoglobin (g/dL)	5.5 (4.6–7.9)	5.1 (4.0–8.3)	5.7 (4.9–7.8)	5.7 (4.5–7.0)
Leucocyte ($\times 10^9$ cells/L)	2.4 (1.1)	2.4 (1.5)	2.4 (0.9)	1.7 (1.1)
Lymphocytes ($\times 10^9$ cells/L)	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.4 (0.4–0.5)	0.5 (0.4–0.6)
Monocytes ($\times 10^9$ cells/L)	2.7 (1.9–3.5)	2.2 (1.7–3.1)	2.9 (2.0–3.8)	3.2 (2.5–4.3)*
Neutrophils ($\times 10^9$ cells/L)	277 (106)	207 (86)	317 (96)^^	150 (118– 215)
Platelets ($\times 10^3$ cells/L)	1.1 (0.1)	1.1(0.1)	—	1.1 (0.2)
INR	88 (15)	88 (15)	—	94.2 (16.3)
Quick, n (%)				

Significant differences between pediatric and adult LT recipients were expressed as *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Significant differences between pediatric LT and KT recipients were expressed as ^$P < 0.05$, ^^$P < 0.01$, ^^^$P < 0.001$.

6-MP, mercaptopurine; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; AZA, azathioprine; GGT, gamma-glutamyltransferase, gamma-GT; INR, international normalized ratio; IQR, interquartile range; KT, kidney transplant; LDH, lactate dehydrogenase; LT, liver transplant; NAFLD/NASH ; SOTR, solid organ transplant recipient.

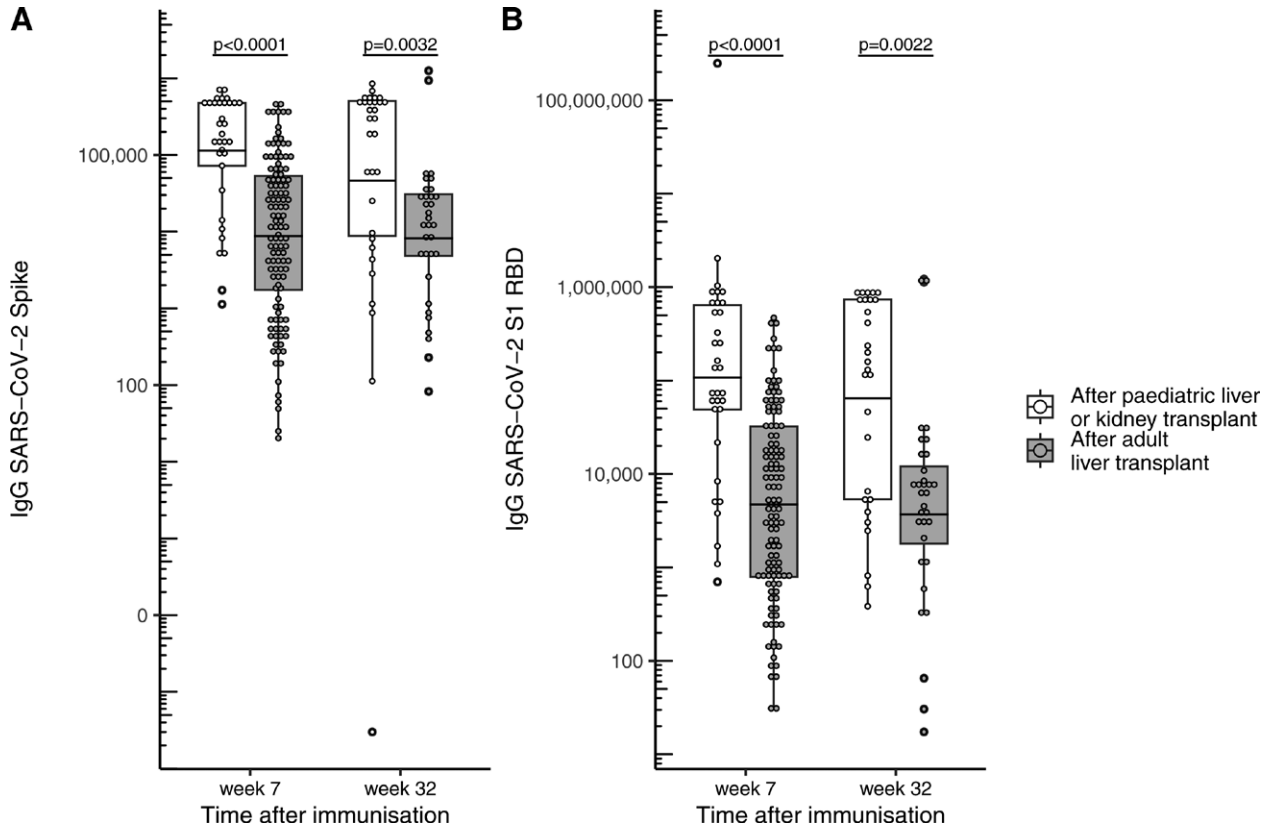

FIGURE 2. Humoral immune responses to COVID-19 vaccination in pediatric and adult patients. Comparison of anti-Spike IgG (A) and anti-RBD IgG (B) levels between pediatric and adult SOTR at weeks 7 and 32 following vaccination. Box plots show geometric mean and interquartile range. The y-axis is scaled logarithmically. RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; SOTR, solid organ transplant recipients.

[3067.76–7293.63), $P < 0.0001$) and week 32 (64 760.8 [23 545.18–178 124.01] versus 3717.3 [1391.62–9929.75], $P = 0.0022$) (Figure 2B).

Within the pediatric cohort, no significant difference in anti-Spike IgG response was found between LT and KT recipients at week 7 (129 434.4 [51 888.64–322 869.69] versus 105 304.5 [39 910.20–277 849.50], $P = 0.9854$) (Figure 3) or week 32 (97 912.0 [26 033.09–368 252.47] versus 32 218.5 [4009.23–258 910.92], $P = 0.8178$) (Figure 3A). Similar findings were noted for anti-RBD IgG response at week 7 (142 814.8 [24 521.05–831 778.51] versus 89 676.4 [29 528.01–272 346.82], $P = 0.9563$) and week 32 (46 422.5 [9617.05–224 086.16] versus 75 822.7 [18 964.97–303 142.27], $P = 0.4103$) (Figure 3B).

Factors Associated With Antibody Levels in Pediatric Patients

Male sex and hemolytic-uremic syndrome or postischemic kidney disease were associated with lower anti-Spike IgG levels at week 7 in pediatric SOTR (Table 2).

Only malignancy as liver disease etiology for liver transplantation in children was associated with anti-RBD IgG levels at week 7 (estimate 1.84; 95% CI, 0.61-3.06; $P = 0.0046$).

Rate of Decline of Serological Response

No differences were seen between children and adults ($P = 0.5849$), pediatric and adult LT recipients ($P = 0.6844$) or between LT and KT pediatric recipients ($P = 0.8017$), in the rate of decline of anti-Spike IgG between weeks 7 and 32. Similarly, no differences were seen between children and adults ($P = 0.9369$), or between LT and KT pediatric recipients ($P = 0.0868$), in the rate of decline of anti-Spike RBD between weeks 7 and 32.

Factors associated with anti-Spike IgG degradation in pediatric SOTR are shown in Table 3. C-reactive protein and treatment with immunosuppressors were associated with anti-Spike IgG decline between weeks 7 and 32 in children. An increase in C-reactive protein was associated with a reduction in the mean difference between weeks 7 and 32 (estimate –0.95; 95% CI, –1.58 to –0.33; $P = 0.0133$). Treatment with immunosuppressors (estimate, –4.24; 95% CI, –6.33 to –2.15; $P = 0.0004$) and more specifically treatment with calcineurin inhibitor (estimate, –3.05; 95% CI, –4.97 to –1.12; $P = 0.0034$) were associated with less anti-Spike IgG degradation between weeks 7 and 32 in pediatric patients.

DISCUSSION

This study, as part of the COBALT initiative, adds to the growing body of evidence regarding COVID-19 vaccination in adult and pediatric SOTRs. These data remain of great importance, even in the postpandemic era, because of the issue of low vaccine coverage and vaccine hesitancy among this patient group and parents/guardians.[18]

The principal finding of this study is robust humoral immune response to initial SARS-CoV-2 vaccination in pediatric SOTRs. Specifically, we observed a significantly higher anti-Spike and anti-RBD IgG response in pediatric SOTRs

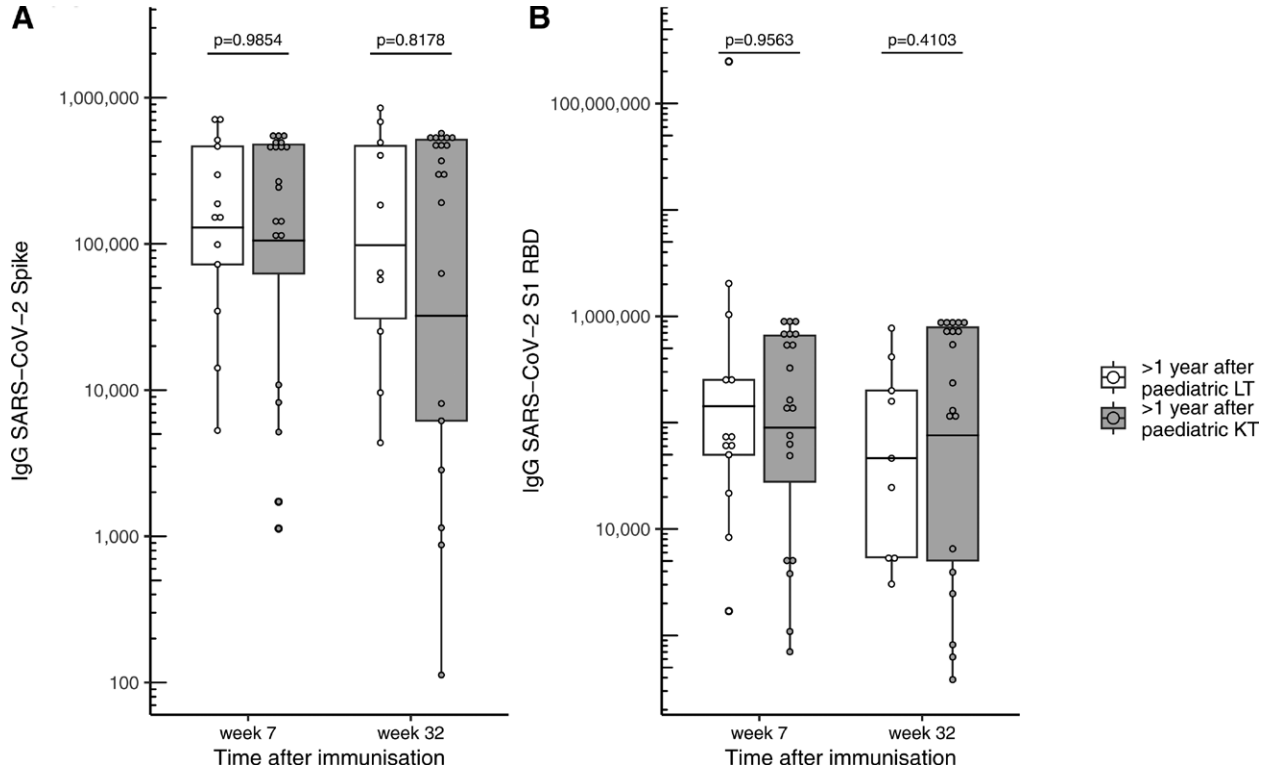

FIGURE 3. Humoral immune responses to COVID-19 vaccination in pediatric liver and kidney transplant patients. Comparison of anti-Spike IgG (A) and anti-RBD IgG (B) levels between pediatric LT and KT recipients. Box plots show geometric mean and interquartile range. The y-axis is scaled logarithmically. KT, kidney transplant; LT, liver transplant; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2.

compared with adult SOTRs at both 7- and 32-wk postvaccination. Both pediatric and adult patients had similar rates of anti-Spike IgG degradation during the follow-up period of 8 mo (32 wk) following initial vaccination. In terms of degree of humoral response to vaccination, male sex and history of hemolytic-uremic syndrome or postischemic kidney disease were associated with decreased anti-Spike IgG levels at week 7. It is notable too that age and maturation of the immune system appears to be the dominant determinant to vaccine response and not the different level of immunosuppression that is used between pediatric liver and kidney recipients.

Very few studies have measured SARS-CoV-2 vaccine responses in pediatric liver transplant recipients, and to our knowledge, this is the first study to compare responses between pediatric and adult liver transplant recipients with similar characteristics. Several studies have evaluated SARS-CoV-2 vaccine responses in pediatric renal transplant recipients; a systematic review of these data demonstrated that rituximab administration, mycophenolate mofetil therapy and lower GFR reduce the vaccination response rates.[21-28] By contrast, there is only 1 published series reporting SARS-CoV-2 vaccine responses in pediatric liver transplant recipients, with no adult comparator group or longitudinal follow-up or response.[29]

Although recommendations for precision medicine approaches cannot be made from the small sample sizes reported here, these data are consistent with greater SARS-CoV-2 vaccine responses seen in healthy children and adolescents compared with adults to mRNA vaccines.[9] Similar findings were also noted in a Chinese study comparing responses to Ad5-vectored SARS-CoV-2 vaccine response in pediatric and adult recipients.[30]

There are several limitations to the current study. First, these data were collected in a real-world observational cohort, and therefore, the analyses are largely descriptive without any prespecified sample size calculation or analysis plan. This also includes that possible COVID-19 infections occurring before or after vaccination may influence the immune response in this observational cohort. As noted earlier, the sample sizes are small, and consequently, recommendations for precision medicine approaches or policy change cannot be made. There is little ethnic or racial diversity among the pediatric cohort, although in older age groups vaccine efficacy has been shown to be similar between races and ethnicities. Finally, there is no efficacy data presented here. Nevertheless, these data are scarce, and represent the only cohort reporting post-LT SARS-CoV-2 vaccine responses in pediatric patients outside China, and the only cohort with longitudinal data collection. Moreover, this is the only study in this patient group to report vaccine responses with a comparable adult cohort recruited alongside.

There remain several areas to research within the field of SARS-CoV-2 vaccination within this pediatric patient group. Specifically, it remains unclear: what is the optimal vaccine schedule for pediatric SOTRs; should booster doses be routinely administered, and if so, when; which immunosuppressive regimens are associated with the best vaccine response; what is the role of cellular immunity in protection against COVID-19 in this population? Nevertheless, these data may shed light on the difference in immune response between children and adults and aid in future development of vaccines for immunocompromised adults and children. This is important to combat vaccine hesitancy and low coverage among SOTR and families for SARS-CoV-2 and potentially future viral pandemics.

TABLE 2.

Factors associated with anti-Spike IgG at week 7 in pediatric SOTR

Variable	Estimate	95% CI	*P*
Male sex	−0.64	−1.17 to −0.11	**0.0200**
Age, y	0.04	−0.03 to 0.12	0.2518
Race, Black or Afro-American	−0.94	−2.59 to 0.72	0.2580
Ethnicity			
North European	0.07	−1.17to1.31	0.9101
Mediterranean	0.32	−1.06to1.69	0.6390
Liver disease			
Biliary atresia	−0.13	−0.88 to 0.61	0.7164
Malignancy	0.82	−0.14 to 1.78	0.0918
Cryptogenic	−1.38	−2.99 to 0.24	0.0919
Hemochromatosis	0.14	−1.55 to 1.83	0.8655
Other	0.17	−1.04 to 1.39	0.7722
Years since the diagnosis of liver disease (1–5)	−0.24	−1.14 to 0.65	0.5584
Kidney disease, n (%)			
Congenital abnormalities	0.11	−0.52 to 0.74	0.7180
Glomerular disease	−0.08	−0.79 to 0.63	0.8203
Tubulo interstitial	0.70	−0.97 to 2.37	0.3999
HUS/postischemic	−1.88	−3.42 to −0.33	**0.0187**
Other	−0.56	−1.76 to 0.64	0.3483
Immunosuppressors, n (%)	0.37	−0.84 to 1.58	0.5372
Steroids	−0.07	−0.68 to 0.55	0.8230
Calcineurin inhibitor	−0.06	−0.95 to 0.82	0.8867
Mycophenolate	0.37	−0.83 to 1.58	0.5311
AZA or 6-MP	0.64	−1.04 to 2.31	0.4430
Other	−0.05	−0.63 to 0.53	0.8584
Biochemical parameters, mean (SD) or median (IQR)	−0.00	−0.23 to 0.23	0.9703
Albumin (g/dL)	−0.01	−0.03 to 0.01	0.3031
AST (U/L)	−0.01	−0.02 to 0.00	0.2015
ALT (U/L)	0.00	−0.00 to 0.00	0.9448
ALP (U/L)	0.00	−0.00 to 0.01	0.6403
GGT (U/L)	0.06	−0.84 to 0.96	0.8888
Bilirubin (mg/dL)	−0.00	−0.17 to 0.16	0.9698
Creatinine (mg/dL)	−0.03	−0.22 to 0.16	0.7432
Sodium (mEq/L)	−0.12	−0.51 to 0.28	0.5041
C-reactive protein (mg/L)	−0.03	−0.08 to 0.03	0.3569
Hemoglobin (g/dL)	0.04	−0.08 to 0.15	0.5358
Leucocyte (×10⁹ cells/L)	0.03	−0.24 to 0.29	0.8395
Lymphocytes (×10⁹ cells/L)	−0.07	−1.24 to 1.10	0.9055
Monocytes (×10⁹ cells/L)	0.09	−0.12 to 0.31	0.3892
Neutrophils (×10⁹ cells/L)	−0.00	−0.00 to 0.00	0.9826
Platelets (×10³ cells/L)	0.39	−4.34 to 5.12	0.8541
INR			

6-MP, mercaptopurine; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; AZA, azathioprine; GGT, gamma-glutamyltransferase, gamma-GT; INR, international normalized ratio; IQR, interquartile range; KT, kidney transplant; LDH, lactate dehydrogenase; LT, liver transplant; NAFLD/NASH ; SOTR, solid organ transplant recipient.
Bold *P* values denote statistical significance, with the threshold for significance set at 0.05.

TABLE 3.

Factors associated with anti-Spike IgG decline between weeks 7 and 32 in pediatric SOTR

Variable	Estimate	95% CI	*P*
Male sex	−0.21	−1,81 to 1.39	0.7895
Age, y	0.11	−0.24 to 0.46	0.5102
Ethnicity			
North European	0.42	−3.69 to 4.53	0.8343
Mediterranean	0.50	−4.13 to 5.12	0.8253
Liver disease			
Biliary atresia	−0.26	−2.61 to 2.08	0.8181
Malignancy	0.55	−1.78 to 2.88	0.6299
Cryptogenic	−2.59	−6.30 to 1.12	0.1617
Years since the diagnosis of liver disease (1–5)	−0.79	−3.36 to 1.78	0.4669
Immunosuppressors, n (%)	−4.24	−6.33 to −2.15	**0.0004**
Steroids	−0.92	−2.47 to 0.63	0.2309
Calcineurin inhibitor	−3.05	−4.97 to −1.12	**0.0034**
Mycophenolate	−0.42	−4.30 to 3.46	0.8258
AZA or 6-MP	−0.38	−4.26 to 3.50	0.8404
Other	−0.87	−2.39 to 0.66	0.2521
Biochemical parameters, mean (SD) or median (IQR)	−0.18	−0.65 to 0.29	0.4236
Albumin (g/dL)	−0.02	−0.06 to 0.01	0.1429
AST (U/L)	−0.01	−0.03 to 0.01	0.4266
ALT (U/L)	−0.00	−0.01 to 0.01	0.7526
ALP (U/L)	−0.00	−0.01 to 0.01	0.6715
GGT (U/L)	0.87	4.09 to 5.84	0.6813
Bilirubin (mg/dL)	0.18	−0.08 to 0.43	0.1715
Creatinine (mg/dL)	0.28	−0.04 to 0.59	0.0823
Sodium (mEq/L)	−0.95	−1.58 to −0.33	**0.0133**
C-reactive protein (mg/L)	0.13	−0.30 to 0.55	0.5457
Hemoglobin (g/dL)	0.02	−0.21 to 0.25	0.8415
Leucocyte (×10⁹ cells/L)	0.08	−0.46 to 0.62	0.7578
Lymphocytes (×10⁹ cells/L)	0.20	−1.92 to 2.33	0.8445
Monocytes (×10⁹ cells/L)	−0.02	−0.41 to 0.36	0.8953
Neutrophils (×10⁹ cells/L)	−0.00	−0.01 to 0.00	0.6130
Platelets (×10³ cells/L)	−9.57	−36.3 to 17.12	0.3367
INR			

6-MP, mercaptopurine; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; AZA, azathioprine; GGT, gamma-glutamyltransferase, gamma-GT; INR, international normalized ratio; IQR, interquartile range; KT, kidney transplant; LDH, lactate dehydrogenase; LT, liver transplant; NAFLD/NASH ; SOTR, solid organ transplant recipient.
Bold *P* values denote statistical significance, with the threshold for significance set at 0.05.

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