Evolution of humoral immune response to SARS-CoV-2 mRNA vaccine in liver transplant recipients – a longitudinal study

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Summary

BACKGROUND AND AIM: Liver transplant recipients show suboptimal vaccine-elicited immune responses to severe acute respiratory coronavirus 2 (SARS-CoV-2) vaccination. This study aimed to assess real-world data on SARS-CoV-2 antibodies after the second and third SARS-CoV-2 vaccination in liver transplant recipients in Switzerland.

METHODS: We enrolled liver transplant recipients who attended regular follow-up visits between 01/07/2021 and 30/04/2022 at the outpatient clinic of the Department of Visceral Surgery and Medicine at Bern University Hospital, Switzerland. Following the Swiss Federal Office of Public Health recommendations, we measured SARS-CoV-2 anti-spike IgG antibodies in 117 liver transplant recipients ≥4 weeks after the second SARS-CoV-2 mRNA vaccination from 07/2021–04/2022. In case of antibody levels of <100 AU/ml, patients received a third vaccination and antibodies were re-measured. Patients with antibody levels of >100 AU/ml were defined as "responders", those with 12–100 AU/ml as "partial responders" and those with <12 AU/ml as "non-responders".

RESULTS: After two vaccinations, 36/117 (31%) were responders, 42/117 (36%) were partial responders and 39/117 (33%) were non-responders. The humoral immune response improved significantly after the third vaccination, resulting in 31/55 (56%) responders among the previous partial or non-responders. A total of 26 patients developed COVID-19, of whom two had a moderate or severe course (both non-responders after three doses).

DISCUSSION: One third of liver transplant recipients showed an optimal response following two vaccinations; a third dose achieved a complete antibody response in more than half of partial and non-responders. We observed only one severe course of COVID-19 and no deaths from COVID-19 in the vaccinated liver transplant recipients.

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Introduction

Liver transplant recipients are considered a vulnerable population in the setting of the coronavirus disease 2019 (COVID-19) pandemic [1–3]. Determining the best vaccination strategy is thus essential to ensure optimal protection against COVID-19 in this population. In Switzerland, the two severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger ribonucleic acid (mRNA) vaccines BNT162b2 (Comirnaty®, Pfizer-BioNTech) [4] and mRNA-1273 (Spikevax®, Moderna) [5] have been licensed since December 2020 and January 2021, respectively. Both vaccines have a high efficacy in preventing severe COVID-19 [6,7] in non-immunocompromised individuals. However, the immunogenicity of these vaccines is reduced in immunosuppressed individuals [8–10].

In the general population, the humoral immune response following COVID-19 [11] or SARS-CoV-2 mRNA vaccine [12] has been assessed by different types of assays, mainly SARS-CoV-2 anti-spike IgG antibodies. In organ transplant patients, suboptimal immunogenicity was observed after the administration of two doses of SARS-CoV-2 vaccine [8,13], with vaccine breakthroughs reported [14]. This prompted public health authorities in Switzerland and other countries to adjust their vaccination strategies for this population. In July 2021, the Swiss Federal Office of Public Health (FOPH) recommended measuring the SARS-CoV-2 anti-spike IgG antibodies as a surrogate of humoral immune response in all immunocompromised individuals 4 weeks after the second vaccination with a SARS-CoV-2 mRNA vaccine. In case of absent antibodies, or antibody titres not in a clear positive range, a third vaccine dose and a repeated measurement of SARS-CoV-2 anti-spike IgG antibodies were recommended. To date, limited data are available on the immunogenicity of the SARS-CoV-2 mRNA vaccine in the liver transplant population after the second and third doses of SARS-CoV-2 vaccine [15–20], mostly from small, cross-sectional studies [15–19]. We evaluated the SARS-CoV-2

anti-spike IgG antibody responses after the second dose of SARS-CoV-2 mRNA vaccine in 117 well-characterised liver transplant recipients in Switzerland and after a third dose in 55 with no or partial response after the second.

Methods

Study design

We enrolled liver transplant recipients who attended regular follow-up visits between 01/07/2021 and 30/04/2022 at the outpatient clinic of the Department of Visceral Surgery and Medicine at Bern University Hospital, Switzerland. We included liver transplant recipients who were aged 18 years or older and had provided written general consent to the Inselspital. The exclusion criteria were a lack of general informed consent, liver transplant recipients who declined SARS-CoV-2 antibody testing and those younger than 18 years. We measured the SARS-CoV-2 anti-spike IgG antibodies of 117 patients ≥4 weeks after the second dose of a SARS-CoV-2 mRNA vaccine. Liver transplant recipients with antibody levels of <100 AU/ml (equivalent to <550 binding antibody units/ml) received a third dose of a SARS-CoV-2 mRNA vaccine, and the SARS-CoV-2 anti-spike IgG antibody measurement was repeated ≥4 weeks after the third dose (figure 1). The Swiss FOPH recommendations changed on 04/11/2021, recommending a third dose of SARS-CoV-2 mRNA vaccine for all immunocompromised persons, regardless of the SARS-CoV-2 antibody levels. Similarly, routine measurement of antibodies was no longer recommended. However, in individual cases, antibody measurements were done later, and we included these additional data in our study.

We defined patients with antibody concentrations under the assay detection limit of 12 AU/ml (equivalent to 33.8 BAU/ml) as "non-responders", those with 13–100 AU/ml (equivalent to 33.8–550 BAU/ml) as "partial responders" and those with >100 AU/ml (equivalent to >550 BAU/ml) as "responders" to the vaccination.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients gave informed consent by signing the general informed consent. The Bern Cantonal Ethics Committee (KEK 2022-00309) approved the study.

SARS-CoV-2 anti-spike IgG immunoassays

Serum samples were analysed by chemiluminescent immunoassay technology (LIAISON® SARS-CoV-2, DiaSorin, Saluggia [VC], Italy) according to the manufacturer's instructions on the LIAISON® XL Analyzer. IgG antibodies against S1/S2 antigens of SARS-CoV-2 were detected in a semi-quantitative assay with a lower limit of detection of 0.3 AU/ml (arbitrary units/ml) and an upper limit for quantitative evaluation of 400 AU/ml at the Institute for Infectious Diseases, University of Bern.SARS-CoV-2 anti-spike IgGantibody measurements performed in an external laboratory (n=32) were also considered in the analysis when reported in BAU/ml. For better comparability with the externally performed measurements, we analysed the serum samples a second time by LIAISON® SARS-CoV-2 TrimericS IgG assay, where the values are given in BAU/ml with a range between 4.81 and 2,080 BAU/ml. A concentration of 2,080 BAU/ml is the upper limit of antibody quantification without dilution of the serum. Therefore, all values of >2,080 BAU/ml were assigned to 2,080 BAU/ml. Since the conversion factor for the DiaSorin S1/2 IgG assay (reported in AU/ml) to BAU per millilitre is not provided by the manufacturer, we determined the conversion factor by performing the LIAISON® SARS-CoV-2 TrimericS IgG assay in addition to the DiaSorin S1/2 IgG assay (figure S1 in the appendix; conversion factor: 5.5). This was comparable to the conversion factor reported in another report [21]. A cut-off of >100 AU/ml (equivalent to >550 BAU/ml) for clear positive results and a cut-off of >12 AU/ml (equivalent to <33.8 BAU/ml) for minimal positive results were used. Therefore, all values of <33.8 BAU/ml were assigned to 33.8 BAU/ml.

Statistical analysis

Continuous baseline variables are reported as medians and interquartile ranges (IQRs), and categorical variables are reported as frequencies. Differences between categorical characteristics of responders versus partial and non-responders were investigated using Fisher's exact test, and the Wilcoxon rank-sum test was applied for continuous variables. The analyses were performed using Stata/SE version 16.0 (StataCorp, College Station, TX, USA), and a statistical significance level of 5% was used throughout. GraphPad Prism (GraphPad Software 9.4.1) and PowerPoint 2019 were used to create the figures.

Figure 1: Study flowchart. Study population. Flowchart of 117 liver transplant (LT) recipients with SARS-CoV-2 anti-spike IgG antibody testing >4 weeks after the second dose of a SARS-CoV-2 mRNA vaccine. A total of 81 LT recipients with antibody levels of <100 AU/ml (equivalent to <550 binding antibody units/ml) received a third dose of a SARS-CoV-2 mRNA vaccine, and SARS-CoV-2 anti-spike IgG antibody measurement was repeated in 55 LT recipients >4 weeks after the third dose.AB: antibodies; NR: non-responder; PR: partial responder; R: responder; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
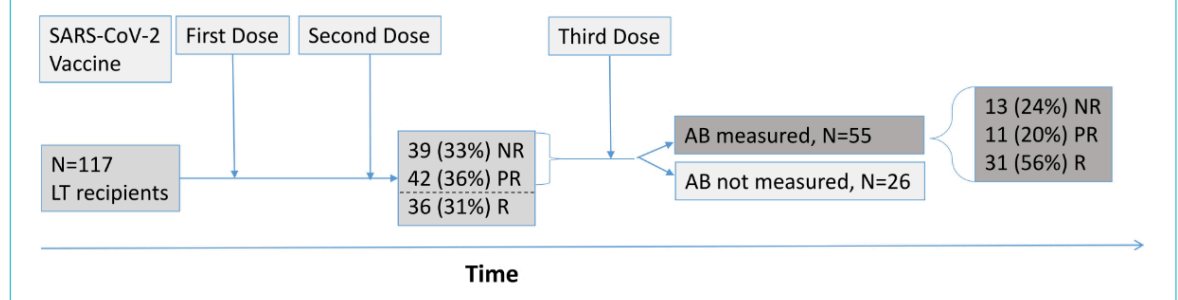
Results

Patients

Out of 119 liver transplant recipients who regularly attended our outpatient clinic, we excluded two who declined SARS-CoV2 antibody testing. The analyses are based on 117 liver transplant recipients, the clinical characteristics of whom are shown in table 1. Of the liver transplant recipients, 46 (39.3%) received the mRNA-1273 vaccine, and 57 (58.7%) received the BNT16b2 vaccine. In 14 patients (12%), no information was available on the vaccine type (mRNA-1273 or BNT16b2). After two doses of vaccination, partial and non-responders were older (p <0.01) than responders.

SARS-CoV-2 anti-spike IgG antibody level after second vaccine dose

The median anti-SARS-CoV-2 anti-spike IgG antibody concentration was 177 (IQR 33.8–780) BAU/ml. We observed 36/117 (31%) responders, 42 partial responders (36%; median 197; IQR 129–305) and 39 non-responders (33%; figures 2 and 3A).

SARS-CoV-2 anti-spike IgG antibody level after third vaccine dose

Of 81 partial and non-responders, 79 received a third dose. Antibody measurements were available for 55/81. Four or more weeks after the third dose, SARS-CoV-2 anti-spike IgG antibodies were detected in 42/55 patients (76%; 31/55 responders, 11/55 partial responders). Thirteen patients (24%) remained non-responders (figures 2 and 3B). The median SARS-CoV-2 anti-spike IgG antibody concentration was 668 (IQR 60.1–2080) BAU/ml.

The proportion of patients classified as responders increased from 31% (36/117) after two vaccines to 56% (31/55) after administering a third vaccine dose to previous partial and non-responders. We observed a downward immune response in two liver transplant recipients at the second antibody measurement compared with the first antibody measurement (figure 3B). This might be explained by changes in the immunosuppressive therapy (intensification at the second measurement in one case; reduction of immunosuppressants at the first measurement in the other case).

Table 1:

Characteristics of 117 liver transplant (LT) recipients at baseline (defined as the last routine visit after the second COVID-19 vaccine and before or at the first SARS-CoV-2 antibody measurement).

	Study population (n = 117)	Vaccine responders* (n = 36)	Partial/non-responders** (n = 81)	p-value
Age, years (median [IQR])	62 (53–69)	55 (44–64)	64 (58–70)	<0.01
Female sex, n (%)	37 (31.6)	16 (36.4)	21 (28.8)	0.31
BMI, kg/m(median [IQR])	25.1 (23.0–29.0)	25.5 (23.5–28.0)	25.1 (22.9–30.0)	0.99
Time since transplantation, months (median [IQR])	48 (24–149)	81 (33–174)	44 (23–143)	0.11
Acute rejection during the year before vaccination, n (%)	3 (2.6)	1 (2.8)	2 (2.5)	0.67
Transplanted organ, n (%)				0.64
– Liver	113 (96.6)	35 (97.2)	78 (96.3)	
– Combined liver and kidney	4 (3.4)	1 (2.8)	3 (3.7)	
Type of immunosuppressive therapy, n (%)				
– Calcineurin inhibitors (tacrolimus, cyclosporin)	76 (65.0)	22 (61.1)	54 (66.7)	0.35
– Antimetabolites (mycophenolate mofetil, azathioprine)	34 (29.1)	9 (25.0)	25 (30.9)	0.34
– mTor inhibitors (sirolimus, everolimus)	47 (40.2)	15 (41.7)	32 (39.5)	0.49
– Steroids	5 (4.3)	1 (2.8)	4 (4.9)	0.51
Regimen of immunosuppressive therapy, n (%)				0.61
– Monotherapy	76 (65.0)	26 (72.2)	50 (61.7)	
– Dual therapy	37 (31.6)	9 (25.0)	28 (34.6)	
– Triple therapy	4 (3.4)	1 (2.8)	3 (3.7)	
Vaccine type, n (%) ***				0.88
– mRNA-1273	46 (39.3)	13 (36.1)	33 (40.7)	
– BNT16b2	57 (58.7)	19 (52.7)	38 (46.9)	
Median leukocyte count (/mm) [IQR]	5.6 (4.4–7.0)	5.5 (4.6–6.6)	5.6 (4.4–7.0)	0.86
Median lymphocyte count (/mm) [IQR]	1.4 (0.9–1.9)	1.7 (1.1–2.2)	1.3 (0.9–1.7)	0.08
COVID-19, n (%)	26 (22.2)	11 (30.6)	15 (18.5)	0.12
– COVID-19 severity, n (%) ****				
– Mild	24 (92.3)	11 (100.0)	13 (86.7)	
– Moderate	1 (3.8)	0	1 (7.1)	
– Severe	1 (3.8)	0	1 (7.1)	
– Death due to COVID-19	0	0	0	

* Patients with antibody levels of >100 AU/ml (equivalent to >550 BAU/ml) were defined as "responders" to the vaccination.

** Patients with values of <12 AU/ml (equivalent to <33.8 BAU/ml) were defined as "non-responders", and patients with values of 13–100 AU/ml (equivalent to 33.8–550 BAU/ml) were defined as "partial responders".

*** In 14 patients (12%), no information was available on the vaccine type (mRNA-1273 or BNT16b2).

**** Severe COVID-19 was defined as admission to intensive care; moderate COVID-19 was defined as admission to a general ward; mild COVID-19 was defined as asymptomatic or mild symptoms (i.e. cough, sore throat, fever) that could be monitored at home.

COVID-19: coronavirus disease 2019; IQR: interquartile range; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

COVID-19

Of the 117 liver transplant recipients, 26 (22%) were diagnosed with COVID-19. Among them, five were diagnosed before the third vaccination, two before any vaccination, one after the first vaccination and two after the second vaccination (clinical characteristics: table S1 in the appendix). Twenty-one patients were diagnosed after the third vaccination (clinical characteristics: table S2 in the appendix), during the Omicron wave of early 2022.

Among the 21 patients who developed COVID-19 after the third dose of SARS-CoV-2 vaccine (median time from third vaccination to COVID-19: 4 months [IQR 2–5]; table S2), 11 (52%) were non-responders, four (19%) were partial responders and six (29%) were responders after the second dose of SARS-CoV-2 vaccine. Of the 10 patients who were retested after the third dose, four (40%) were non-responders, three (30%) were partial responders and three (30%) were responders.

Among the 26 patients who developed COVID-19, only one had severe COVID-19 (admitted to an intensive care unit) in April 2022, one had moderate COVID-19 (admission to a general ward) in February 2022, and 24 had a mild infection, i.e. asymptomatic or with mild symptoms (cough, sore throat, fever) treated in an outpatient setting. Both patients with severe or moderate COVID-19 had no detectable antibodies after the second and third SARS-CoV-2 vaccinations. The patients with moderate and severe courses of COVID-19 were undergoing dual immunosuppressive therapy (cyclosporine and mycophenolate mofetil) and triple immunosuppressive therapy (tacrolimus, mycophenolate mofetil and prednisone), respectively, at the time of the first SARS-CoV-2 antibody measurement. As additional predisposing factors for a moderate or severe COVID-19 course, the patient with moderate COVID-19 had the following factors according to the FOPH criteria list: age >65 years, hypertensive car-

diopathy and multiple cardiovascular risk factors (diabetes mellitus, arterial hypertension, past nicotine use with cumulative 72 package years). The patient with severe COVID-19 had dual organ transplantation (kidney and liver) and two cardiovascular risk factors (arterial hypertension, past nicotine use with cumulative 15 package years). Neither of the two patients with moderate or severe COVID-19 has developed cirrhosis of the graft to date.No death was registered due to COVID-19 among the liver transplant recipients during the observation period.

Discussion

Our study evaluating the SARS-CoV-2 anti-spike IgG antibody responses after the second dose of SARS-CoV-2 mRNA vaccine in 117 liver transplant recipients, and after a third dose in 55 of them with a partial or no response after the second, showed three major findings. First, one third of patients did not develop vaccine-elicited SARS-CoV-2 anti-spike IgG antibodies after two doses of a SARS-CoV-2 mRNA vaccine. The humoral immune response improved significantly after the third vaccination: more than half of the previous partial and non-responders developed SARS-CoV-2 anti-spike IgG antibodies in a clear positive range. Our findings are confirmed by a recent study that observed a significantly improved immune response in liver transplant recipients after a third dose of mRNA SARS-CoV-2 vaccination [22]. Second, despite three vaccine doses, 24% of liver transplant recipients did not develop detectable vaccine-elicited antibodies. This is clinically relevant because these patients might qualify for COVID-19 prophylaxis with monoclonal antibodies or early antiviral therapy (i.e. remdesivir or nirmatrelvir and ritonavir) to prevent a severe course of COVID-19. Furthermore, maintaining surveillance while systematically implementing preventative measures is essential for patients with an absent humoral immune response. Third, we observed only one se-

Figure 2: Distribution of liver transplant (LT) recipients according to SARS-CoV-2 anti-spike IgG antibody levels after the second and third SARS-CoV-2 vaccines. Among the 117 LT recipients who were tested ≥4 weeks after the second dose, 36 (31%) had SARS-CoV-2 anti-spike IgG antibody concentrations of ≥550 BAU/ml. Among the 55 LT recipients who were retested at ≥4 weeks after the third dose, 31 (56%) had SARS-CoV-2 anti-spike IgG antibody concentrations of ≥550 BAU/ml. BAU: binding antibody units; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
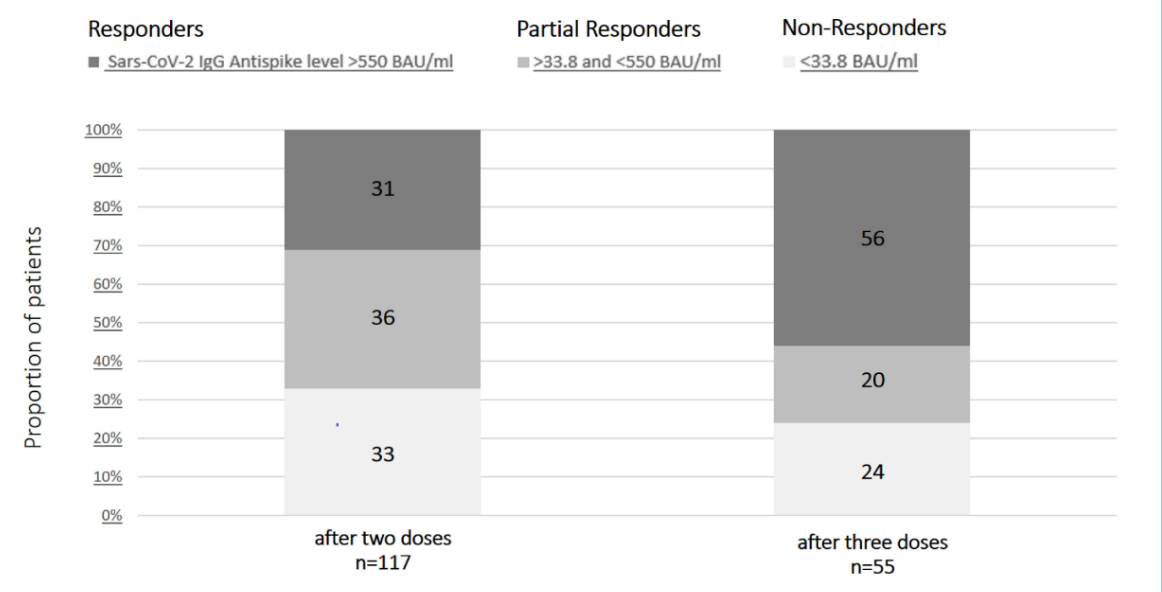
vere course of COVID-19 and no deaths from COVID-19 in our vaccinated liver transplant recipients. Interestingly, the patient who developed severe COVID-19 was a non-responder to the three vaccine doses.

The strengths of our study include the adequate number of well-characterised liver transplant recipients, as well as the measurement of SARS-CoV-2 anti-spike IgG antibod-ies at multiple time points in the same patients. However, we would like to highlight some limitations of this cohort study. We only measured the humoral immune response by analysing SARS-CoV-2 anti-spike IgG antibody levels and did not investigate the T-cell-mediated cellular immune response after SARS-CoV-2 vaccination. We did not measure neutralising antibodies but used anti-spike antibodies as a surrogate [23]. Recent studies have found that individuals boosted with mRNA vaccines exhibited potent neutralisation of Omicron in the general population, suggesting an enhanced cross-reactivity of neutralising antibody responses [24]. However, recent studies in transplant recipients have shown a suboptimal antibody response against the SARS-CoV-2 Omicron variant after a third dose of mRNA vaccine [25, 26]. Therefore, future recommendations for an antibody-driven vaccination strategy for immunosuppressed patients should account for potential differences in inducing neutralising immunity against new variants. Our cutoff of 550 BAU/ml for consideration as a partial responder and receiving a re-vaccination was chosen arbitrarily. However, another study showed that SARS-CoV-2 anti-spike IgG antibodies of 550 BAU/ml are >80% protective in preventing symptomatic COVID-19 [27]. In our study, only monovalent SARS-CoV-2 booster vaccines were administered. Therefore, the results should be cautiously extrapolated to bivalent SARS-CoV-2 booster vaccines. The immune response following mRNA vaccination may vary among different groups of organ transplant recipients. In a recent study [28], the antibody response after the third SARS-CoV-2 vaccination was compared in different groups of solid organ transplant recipients (liver, kidney, lung, heart, combined). Liver recipients but none of the other groups were positively associated with an antibody response in multivariable analysis. Therefore, the results of our study regarding liver transplant recipients should be cautiously extrapolated to other solid organ transplant recipients.

In conclusion, our results underline that a strategy based on antibody measurement after two doses of vaccination, and subsequent administration of a third dose in patients with an absent or partial response, effectively elicited antibody response in the vast majority of patients, with 24% lacking a response after three doses. Knowledge of an inadequate humoral immune response may provide an early opportunity to implement prophylaxis and prevention measures in liver transplant recipients at high risk of severe COVID-19.

Figure 3: Immune responses after SARS-CoV-2 vaccination in liver transplant (LT) recipients. Figure (A) shows the SARS-CoV-2 anti-spike IgG antibody levels in the whole study population (117 LT recipients) after the second dose. Each point represents an individual patient, and horizontal lines indicate the median. The dotted lines indicate the threshold values of 33.8 BAU/ml and 550 BAU/ml, and the black line indicates the median. Values below the detection limit are plotted on the dotted line at 33.7 BAU/ml, and values above the detection limit are plotted on the dotted line at 2,080 BAU/ml. Figure (B) figure shows SARS-CoV-2 anti-spike IgG antibody levels after the second and third doses of SARS-CoV-2 vaccine in the 55 LT recipients who were retested at ≥4 weeks after the third vaccination. Again, each point represents an individual patient's values. Values below the detection limit are plotted on the dotted line at 33.8 BAU/ml, and values above the detection limit are plotted on the dotted line at 2,080 BAU/ml.BAU: binding antibody units; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
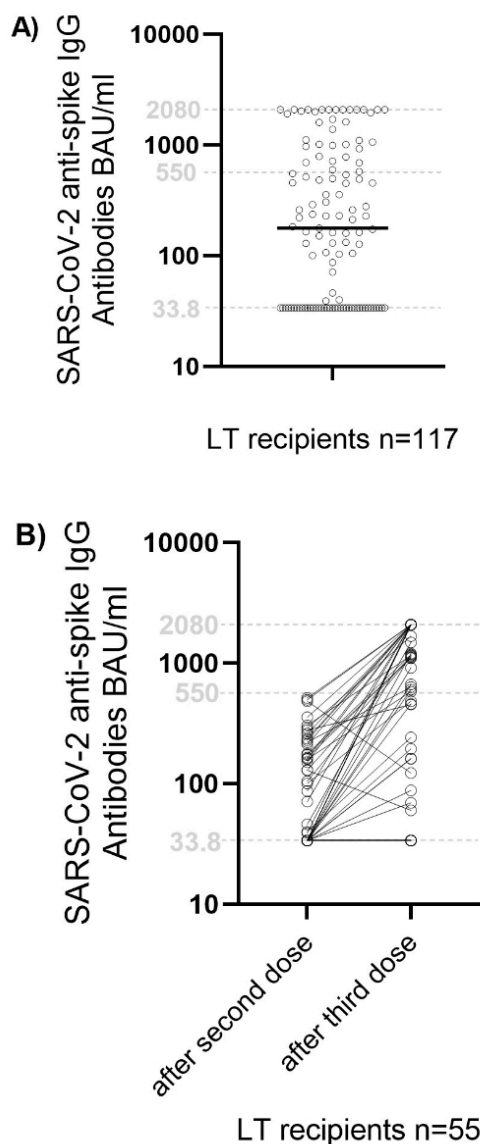
Data availability statement

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants but are available from Annalisa Berzigotti (corresponding author) in consultation with the Bern Ethics Committee's rules and regulations.

writing- review and editing, access and verification of the underlying data

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Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. ICS's institution received a lecture fee from ViiV, outside the submitted work. No other potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Supplementary methods

Figure S1: Correlations among Measurements of SARS-CoV-2 anti-spike IgG Antibodies using different Assays.
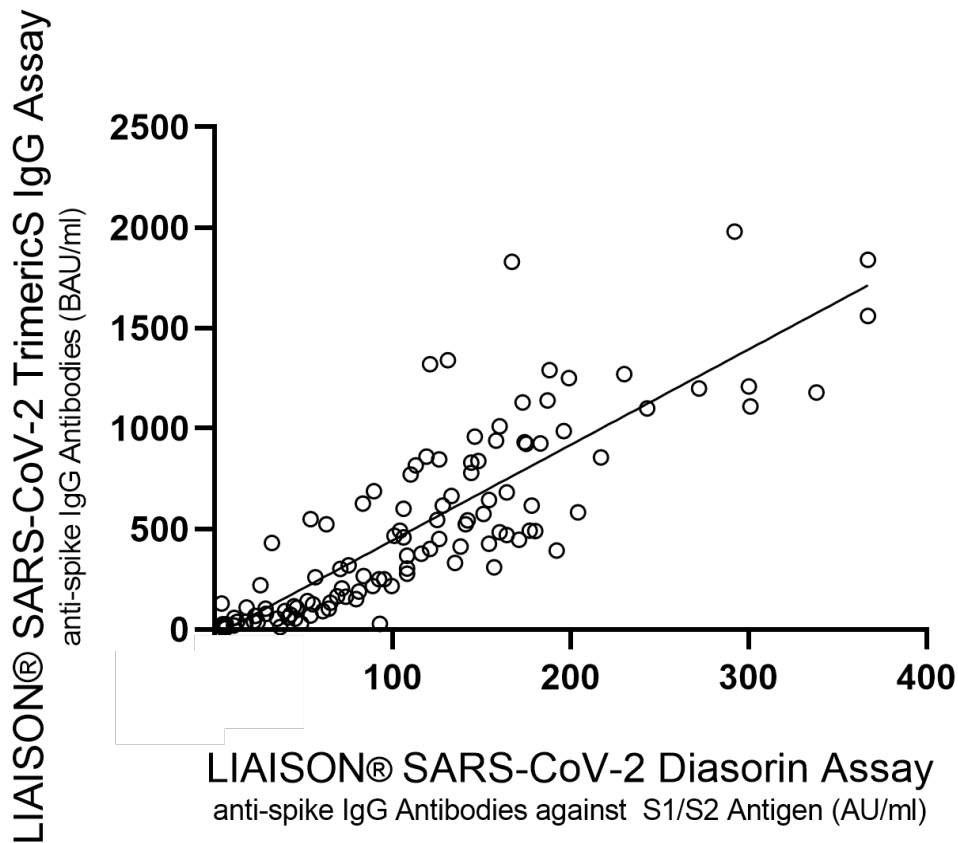
XY scatter plot and fitted linear regression line of SARS-CoV-2 anti-spike IgG Antibodies in BAU/ml detected by LIAISON® SARS-CoV-2 TrimericS IgG assay (**Y-axis**) and anti-spike IgG Antibodies against S1/S2 antigens of SARS-CoV-2 in AU/ml, detected by LIAISON® SARS-CoV-2, Diasorin, Saluggia (VC)—Italy assay (**X-axis**), both measured in 116 serum samples of liver transplant recipients. **Abbreviations.** AU/ml, arbitrary units/mL; BAU/ml, binding antibody units**;** SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

Supplementary results

Table S1. Characteristics of 5 Liver Transplant (LT) Recipients with COVID-19 before Third Dose of Sars-CoV-2 Vaccine at Baseline[1]

LT Recipients (n=117)	COVID-19 before 3. Vaccination (n=5)	No COVID-19 (n=91)
Median age, years (IQR)	55 (45-62)	62 (53-69)
Female sex, n (%)	2 (40.0)	27 (29.7)
Median BMI, kg/m2 (IQR)	23.0 (23.0 -24.0)	26.0 (23.0 -30.0)
Median time since transplantation, months (IQR)	88 (47-182)	51 (25-151)
Acute rejection during the year before vaccination, n (%)	0	2 (2.2)
Transplanted organ, n (%)		
Liver	5 (100.0)	88 (96.7)
Combined liver and kidney	0	3 (3.3)
Type of immunosuppressive therapy, n (%) Calcineurin inhibitors		
(Tacrolimus, Cyclosporin)	4 (80.0)	59 (64.8)
Antimetabolites (Mycophenolate Mofetil, Azathioprine)	0	27 (29.7)
mTor inhibitors (Sirolimus, Everolimus)	1 (20.0)	36 (39.6)
Steroids	0	2 (2.2)
Regimen of immunosuppressive therapy, n (%)		
Monotherapy	5 (100.0)	60 (65.9)
Dual therapy	0 0	29 (31.9))
Triple therapy	0	2 (2.2
Vaccine type, n (%)[2]		
mRNA-1273	2 (40.0)	30 (33.0)
BNT16b2	3 (60.0)	50 (55.0)

Median Leukocyte count (/mm3) (IQR)	5.3 (4.5-6.1)	5.6 (4.4-7.0)
Median Lymphocyte count (/mm3) (IQR)	1.4 (1.1-1.7)	1.4 (1.0 -1.9)
COVID-19, n (%)[3]		
Mild	5 (100.0)	
Moderate	0	
Severe	0	
Death due to COVID-19	0	
Median time between COVID-19 and third vaccination, months (IQR)	11 (6-12)	

Notes. [1]Defined as the last routine visit after the second COVID-19 vaccine and before or at the first SARS-CoV-2 antibody measurement.[2]In 11 patients (12.1%), no information was available on the mRNA vaccine type (mRNA-1273 or BNT16b2).[3]Severe COVID-19 was defined as admission to intensive care; moderate COVID-19 was defined as admission to general ward; mild COVID-19 was defined as asymptomatic or with mild symptoms (i.e. cough, sore throat, fever) that could be monitored at home. **Abbreviations.** COVID-19, coronavirus disease 2019; IQR, interquartile rang; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

Table S2. Characteristics of 21 OLT Patients with COVID-19 after the Third Dose of Sars-CoV-2 Vaccine at Baseline[1]

LT Recipients (n=117)	COVID-19 after 3. Vaccination (n=21)	No COVID-19 (n=91)
Median age, years (IQR)	64 (54-71)	62 (53-69)
Female sex, n (%)	8 (38.1)	27 (29.7)
Median BMI, kg/m2 (IQR)	25.0 (22.8-27.7)	26.0 (23.0-30.0)
Median time since transplantation, months (IQR)	32 (20-106)	51 (25-151)
Acute rejection during the year before vaccination, n (%)	1 (4.8)	2 (2.2)
Transplanted organ, n (%)		
Liver	20 (95.2)	88 (96.7)
Combined liver and kidney	1 (4.8)	3 (3.3)
Type of immunosuppressive Therapy, n (%)		
Calcineurin inhibitors (Tacrolimus, Cyclosporin)	13 (61.9)	59 (64.8)
Antimetabolites (Mycophenolate Mofetil, Azathioprine)	7 (33.3)	27 (29.7)
mTor inhibitors (Sirolimus, Everolimus)	10 (47.6)	36 (39.6)
Steroids	3 (14.3)	2 (2.2)
Regimen of immunosuppressive Therapy, n (%)		
Monotherapy	11 (52.4)	60 (65.9)
Dual therapy	8 (38.1)	29 (31.9)
Triple therapy	2 (9.5)	2 (2.2)
Vaccine type, n (%)[2]		
mRNA-1273	5 (23.8)	30 (33.0)
BNT16b2	13 (61.9)	50 (55.0)
Median Leukocyte count (/mm3) (IQR)	5.8 (4.2-7.3)	5.6 (4.4-7.0)
Median Lymphocyte count (/mm3) (IQR)	1.3 (0.8-2.0)	1.4 (1.0-1.9)
COVID-19, n (%)[3]		
Mild	19 (90.5)	

Moderate	1 (4.8)	
Severe	1 (4.8)	
Death due to COVID-19	0	
Median time between third vaccination and COVID-19, months (IQR)	4 (2-5)	

Notes.[1]Defined as the last routine visit after the second COVID-19 vaccine and before or at the first SARS-CoV-2 antibody measurement. [2]In 14 patients (12%), no information was available on the mRNA vaccine type (mRNA-1273 or BNT16b2). [3]Severe COVID-19 was defined as admission to intensive care; moderate COVID-19 was defined as admission to general ward; mild COVID-19 was defined as asymptomatic or with mild symptoms (i.e. cough, sore throat, fever) that could be monitored at home. **Abbreviations.** COVID-19, coronavirus disease 2019**;** IQR, interquartile rang; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.