ORIGINAL ARTICLE

SARS-CoV-2 vaccination in liver transplant recipients: factors affecting immune response and refusal to vaccine

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KEY WORDS

COVID-19, immunosuppressive agents, liver transplantation, SARS-CoV-2, vaccines

ABSTRACT

INTRODUCTION The effectiveness of SARS-CoV-2 vaccination in liver transplant (LT) recipients varies between reports.

OBJECTIVES In this study, we analyzed the immune response to the SARS-CoV-2 vaccine, factors affecting the response, and reasons for the vaccine refusal.

PATIENTS AND METHODS Among 300 consecutive LT recipients, 75% were vaccinated. The humoral response was assessed by the quantitative determination of antitrimeric spike protein-specific IgG antibodies to SARS-CoV-2. Thirty-four vaccinated patients with prior SARS-CoV-2 infection were analyzed separately.

RESULTS Among 192 LT recipients vaccinated without past natural infection, 69% developed the immune response (median time of 125 days after the second dose). Older age, worse kidney function, and dual immunosuppression negatively affected the humoral response. Mycophenolate mofetil increased the risk of nonresponse (odds ratio [OR], 2.99; 95% CI, 1.45–6.19). The antibody concentration was higher in the first 90 days from the second dose and stable as compared with 90–150 days and over 150 days. LT recipients with prior COVID-19 presented with a robust immune response (100%). The female sex, living in a rural area, lower body mass index, and younger age (all $P < 0.05$) were associated with the refusal of the vaccine.

CONCLUSIONS The lower immune response in the vaccinated LT recipients than in the general population justifies administering the third dose of the vaccine. However, more data are needed to recommend any therapy modification before the vaccination.

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INTRODUCTION The SARS-CoV-2 pandemic has resulted in a profound medical and economic crisis. However, the availability of vaccines with excellent efficacy against SARS-CoV-2, once more in the world history, has become a pivotal factor to control the pandemic.

Experts prioritized vaccination against SARS-CoV-2 in liver transplant (LT) recipients.[1] However, published data highlight a weaker immune response in a large cohort of solid organ transplant recipients.[2] It is postulated that although immunocompromised patients may experience a decreased response to vaccination, there is still a reduction in morbidity and mortality, mainly from severe COVID-19.[3]

The first reports of patients after LT, as well as patients with liver cirrhosis,[4] found a substantially lower immune response to SARS-CoV-2 vaccines than that in the healthy controls.[4,5] Further studies described higher immunogenicity in LT recipients than previously published,[6,7] but still lower than in the general population. However, all available reports assessed the response within the first month after the vaccination,[4-6] and no data for a broader time frame are accessible. The kinetics of the immunogenicity after the infection[8] and the vaccination[9] was reported, but again LT recipients were not investigated. These issues became of critical importance when Bergwerk et al[10] demonstrated that neutralizing

WHAT'S NEW?

Liver transplant (LT) recipients have been prioritized for vaccination against SARS-CoV-2, however, published data highlight a weaker immune response in this group of patients. We found that LT recipients with impaired kidney function or mycophenolate mofetil regimen had an increased risk of nonresponse after SARS-CoV-2 vaccination. Moreover, LT patients with prior SARS-CoV-2 infection presented with a robust immune response after SARS-CoV-2 vaccination. Of the investigated LT recipients, 15% declined the vaccination due to nonmedical reasons. The female sex, living in a rural area, lower body mass index, and younger age were associated with the refusal of the vaccine.

antibody titers in the peri-infection period was associated with the incidence of SARS-CoV-2 infection.

In this study, we analyzed the immune response to SARS-CoV-2 vaccines within 4 months from the second dose in 226 consecutive LT recipients.

PATIENTS AND METHODS Between August and October 2021, we prospectively enrolled 300 consecutive LT recipients, who were supervised by the outpatient clinic of the Medical University of Warsaw, Poland. The inclusion criteria comprised the age of at least 18 years, liver transplantation performed 6 months ago or earlier, and more than 30 days from the second dose of the vaccine.

The study protocol was approved by the Ethics Committee of the Medical University of Warsaw (AKBE/184/2021), according to the ethical guidelines of the Declaration of Helsinki (latest revision, 2013). A written informed consent was obtained from all participants.

The first end point of the study was the immune response of the LT recipients to the vaccine more than 30 days after the second dose. Analyses of the risk factors that may influence the immune response after the vaccine included age, sex, etiology of the primary liver disease, time from LT, time from the second dose of the vaccine, comorbidities, laboratory findings, and treatment regimen. Moreover, the patients with prior COVID-19 were analyzed separately and compared to the vaccinated LT recipients without past natural infection. Further, median concentration of SARS-CoV-2 TrimericS IgG was analyzed with reference to the time from the second vaccination. The patients were divided into 3 subsets: below 90 days, 90–150 days, and above 150 days from the second dose. These time frames were chosen arbitrarily, because the level of circulating SARS--CoV-2 antibodies that renders protection against the infection has not been established.

Finally, we evaluated the differences between the vaccinated patients and those who declined the vaccination due to nonmedical reasons.

Clinical data All patients underwent a clinical examination, and blood samples were drawn from fasted participants. Consecutive LT recipients were enrolled in the study; thus, some of them were not vaccinated due to medical (eg, infection) or nonmedical (eg, personal doubt) reasons. Moreover, some of the patients had had prior COVID-19 confirmed by polymerase chain reaction (PCR) tests, and this subgroup was analyzed separately. The cutoff for the estimated glomerular filtration rate (eGFR) was applied in line with international guidelines, which indicated that an estimated or measured GRF of less than 60 ml/min/1.73 m^2 is considered abnormal for all adults.[11] Therefore, kidney impaired function was defined as eGFR below 60 ml/min/1.73 m^2.

Determination of IgG antibodies to SARS-CoV-2 Evaluation of the immune response to the vaccines was assessed by the quantitative determination of antitrimeric spike protein-specific IgG antibodies to SARS-CoV-2 by LIAISON SARS-CoV-2 TrimericS IgG assay (Diasorin, Saluggia, Italy), which is a chemiluminescence immunoassay, and presented as binding antibody units per milliliter (BAU/ml). According to the manual, the cutoff for positive immune response was at least 33.8 BAU/ml, and the detection ranges were between 4.81 and 2080 BAU/ml.

Statistical analysis Statistical analyses were performed using SPSS (version 27.0, SPSS, Munich, Germany) and GraphPad Prism (version 9.3.0, GraphPad Software, San Diego, California, United States). Data are presented as medians and interquartile ranges (IQR) for continuous variables. Data in figures are presented as medians with 95% CI. A 2-sided *P* value below 0.05 was considered significant. The Shapiro–Wilk test was used to determine distributions. The χ^2 test or, if needed, the Fisher exact test was used to test the difference in dichotomous variables between 2 groups. The *t* and Mann–Whitney or Kruskal–Wallis tests were used to study normally and non-normally distributed parameters between 2 or more groups. The univariable and multivariable logistic regression models were applied to test the associations between the outcome (immune response) and clinical variables.

RESULTS In total, 300 consecutive LT recipients (184 men [61%]; median (IQR) age, 54 [19–74] years; median (IQR) body mass index [BMI], 26 [17–40] kg/m^2) were enrolled. In the entire cohort, 26% of patients had diabetes, and 30% had impaired kidney function. The median (IQR) time after grafting was 3.6 (0.5–21) years, and the main indications for LT were as follows: viral (29%), cholestatic (28%), or alcoholic (19%) liver injury, hepatocellular carcinoma (15%), autoimmune disease (12%), and other reasons (24%). Immunosuppression was based on calcineurin inhibitors in 295 patients (98%); 170 received mycophenolate mofetil (MMF) (57%), 51 prednisolone (17%), and 24 mechanistic target of rapamycin inhibitors (8%). Monotherapy was a regimen implemented in one-third of the patients, whereas 2 or 3 immunosuppressive agents were used in 53% and 15% of the patients, respectively.

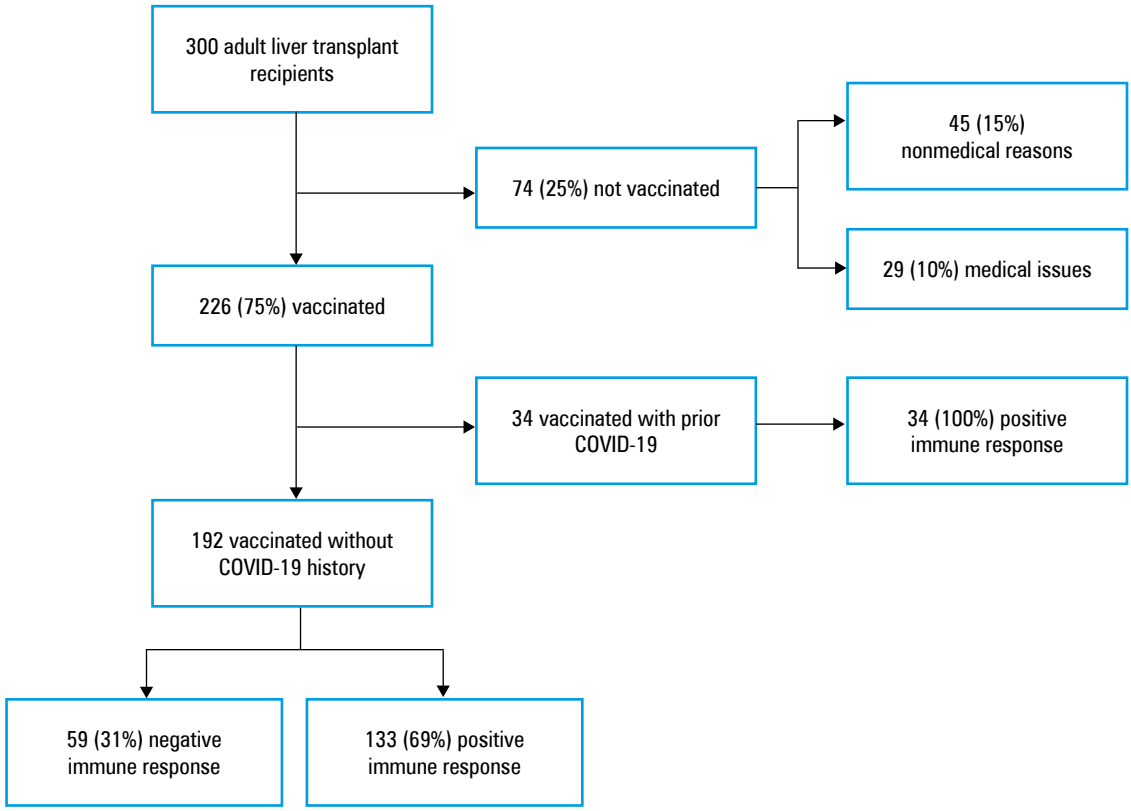

FIGURE 1 Flowchart of the study cohort

A total of 226 patients (75%) were vaccinated, out of which, 206 were vaccinated with BNT162b2 (Pfizer-BioNTech) (91%), 11 with AZD1222 (Oxford / AstraZeneca) (5%), 7 with mRNA-1273 (Moderna) (3%), and 2 with JNJ-78 436 735 (J&J/Janssen) (1%) vaccine. Detailed vaccine type-related results are presented in Supplementary material, *Table S1*. Among the vaccinated patients, 34 (15%) had had prior COVID-19 confirmed by a PCR test, and this subgroup was analyzed separately. Seventy-four individuals (25%) of the entire cohort were not vaccinated; 29 (10%) due to medical reasons, and 45 (15%) due to nonmedical reasons. The study flowchart is presented in FIGURE 1.

Immune response in liver transplant recipients without prior COVID-19 Among 192 LT recipients who were vaccinated without prior COVID-19, a positive immune response was observed in 133 patients (69%), and the clinical characteristics are presented in TABLE 1. The assessment of immunogenicity was performed with a median (IQR) of 125 (31–268) days after the second injection. A comparison of the responders and nonresponders showed that the responders were younger ($P = 0.004$), had higher eGFR, lower creatinine concentration (both $P < 0.001$), and higher hemoglobin concentration ($P = 0.02$), as presented in TABLE 1. Moreover, the responders were more frequently treated with only 1 immunosuppressant (36% vs 15%, $P = 0.002$), in contrast to the MMF regimen, which was more common in the nonresponder subset (75% vs 53%, $P = 0.01$). There were no differences in steroid usage or tacrolimus concentration between the subsets.

Focusing on the comorbidities, impaired kidney function was more frequently diagnosed in the nonresponders ($P = 0.006$), and there was a high prevalence of diabetes in this subset. Further evaluation revealed that the patients with impaired kidney function, defined as eGFR below 60 ml/min/1.73 m^2, had a significantly lower median concentration of TrimericS IgG ($P = 0.002$), as presented in FIGURE 2.

In the univariable analysis, the monotherapy (mainly tacrolimus) was linked to a decreased risk of nonresponse, as shown in TABLE 2. Apart from the immunosuppressive agents, only MMF increased the risk of nonresponse to the vaccination in the univariable model (OR, 2.65; 95% CI, 1.34–5.20; TABLE 2). Furthermore, the impact of MMF on the lack of immune response to the vaccine was also confirmed in the patients with preserved kidney function (ie, eGFR ≥60 ml/min/1.73 m^2); ($P = 0.01$).

Finally, in the multivariable logistic regression model, only impaired kidney function and MMF-based therapy were the risk factors of nonresponse after the vaccination, as presented in TABLE 2. The primary risk factor was MMF, with 3-times greater risk of nonresponse (OR, 2.99; 95% CI, 1.45–6.19; TABLE 2). Sex, etiology of the primary liver disease, and time after LT, as well as time after the vaccination did not show any relationship with the response to the vaccination.

TABLE 1 Clinical characteristics of the vaccinated liver transplant recipients without prior COVID-19

Parameter	Responders	Nonresponders	*P* value
n (%) of the cohort	133 (69)	59 (31)	–
Men, n (%)	88 (66)	35 (59)	0.27
Age, y	52 (21–74)	62 (26–73)	0.004
BMI, kg/m^2	27 (18–36)	27 (19–38)	0.76
Time from LT, y	4.4 (0.5–15)	3.2 (0.5–10)	0.07
Time from the second dose, d	125 (31–268)	125 (31–245)	0.78
Diabetes, n (%)	37 (28)	23 (39)	0.09
Impaired kidney function, n (%)	32 (24)	26 (44)	0.006
AST, U/l (normal <40)	23 (11–136)	24 (13–367)	0.76
ALT, U/l (normal <56)	23 (8–195)	25 (8–355)	0.30
ALP, U/l (normal <126)	82 (21–1050)	91 (40–2321)	0.22
Bilirubin, mg/dl (normal <1.2)	0.6 (0.2–3.1)	0.6 (0.2–6.9)	0.43
INR (normal <1.3)	1.0 (0.8–2.9)	1.0 (0.9–2.5)	0.56
Creatinine, mg/dl (normal <1.1)	1.0 (0.5–2.5)	1.1 (0.6–4.1)	<0.001
eGFR, ml/min/1.73m^2 (normal >60)	81 (18–120)	65 (14–106)	<0.001
Hemoglobin, g/dl (normal 14–18)	14.3 (8.4–18.5)	13.4 (8.4–17.1)	0.02
Platelet count, 10^3/µl (normal 150–400)	161 (32–544)	165 (12–765)	0.99
Tacrolimus, ng/ml	6.0 (3.1–13.7)	6.1 (3.3–11.7)	0.70
CNI, n (%)	131 (98)	59 (100)	0.11
MMF, n (%)	70 (53)	44 (75)	0.01
Steroids, n (%)	20 (15)	8 (14)	0.49
Monotherapy, n (%)	48 (36)	9 (15)	0.002

Values are expressed as median (interquartile range) unless stated otherwise.

SI conversion factors: to convert creatinine to µmol/l, multiply by 88.4, and hemoglobin to g/l, multiply by 10.

Abbreviations: ALP, alkaline phosphatase; ALT, serum alanine aminotransferase level; AST, aspartate aminotransferase; BMI, body mass index; CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LT, liver transplantation; MMF, mycophenolate mofetil

Furthermore, the SARS-CoV-2 TrimericS IgG concentration was higher in the recently vaccinated patients (<90 days from the second dose) than in the other vaccinated individuals (P = 0.03; FIGURE 3). In contrast, there were no differences between the patients vaccinated 90–150 days ago, and more than 150 days ago regarding the serum antibody concentration (P >0.05).

Response in liver transplant recipients with prior COVID-19 Response to the vaccine was robust in the patients who previously developed PCR-confirmed SARS-CoV-2 infection, as compared with the vaccinated recipients without a history of the infection (100% vs 69%; P <0.001), with significantly higher median IgG antibodies concentration (2080 vs 134 BAU/ml; P <0.001; FIGURE 4).

Declining vaccination due to nonmedical reasons Seventy-four patients (25%) were not vaccinated, including 45 (15%) who refused to be vaccinated, and 29 (10%) who chose not to take the vaccine for medical reasons. The medical reasons were identified as infectious complications (such as cholangitis), presumptive acute graft rejection or, in minority, prolonged biliary complications after the LT. The female sex, living in a rural area (village or small town), lower BMI (all P <0.05), and younger age (P <0.001) were associated with the refusal of the vaccine due to nonmedical reasons (all P <0.05). On the other hand, the LT recipients with diabetes (P = 0.002) and impaired kidney function (P <0.001) were more likely to accept the vaccine. In the multivariable logistic regression, only age was linked to the acceptance of the vaccine (OR, 1.03; 95% CI, 1.00–1.06).

DISCUSSION In this study, we investigated a group of 226 LT recipients regarding their immune response and factors that might impact their immunogenicity after the vaccines. Moreover, we analyzed the factors related to the low acceptance of the SARS-CoV-2 vaccines by the study patients. Among the 192 vaccinated patients without past natural infection, 69% had a positive immune response, which is substantially more than the 48% reported by Rabinowich et al,[5] and 63% described by Ruether et al.[4] In contrast, greater humoral response was reported by Guarino et al[6] (75%), Rashidi-Alavijeh et al[7] (79%), and Strauss et al[12] (81%). The differences between studies might be explained by different study cohorts (age and time from the LT), various immunosuppressive treatment regimens, and comorbidities.[13] In line with other studies,[4-6] older age was a common denominator for a nonresponse, which we confirmed in our cohort. In contrast, pediatric solid organ transplant recipients may be able to build more robust immune response following SARS-CoV-2 vaccination.[14]

Impaired kidney function negatively impacted the humoral response in our study (FIGURE 2), which is in line with the published report.[5] The prevalence of impaired kidney function in LT recipients was lower in our study (30%) than in the Israeli[5] (43%) and German[4] (45%) cohorts. The impact of impaired kidney function on the immune response might be caused by an accumulation of uremic toxins in these settings.[15] Moreover, the patients with kidney disease had insufficient erythropoietin and vitamin D levels, which might have affected immunomodulation[16] and negatively impacted their immune response. We found a link between lower hemoglobin level and decreased immune response to the vaccines. The hemoglobin concentration is reduced in most chronic conditions, and anemia is a hallmark of chronic kidney disease. These findings might be explained by the role of erythropoietin in immunomodulation and its effect on lymphocytes.[16]

Finally, we confirmed the positive role of monotherapy and profoundly negative impact of MMF on the response to the vaccine, as shown in other reports.[5-7,12] Interestingly, as LT recipients with kidney failure are usually prescribed MMF, we showed that MMF had a negative impact on the immune response also in the patients without kidney failure. The negative effect of MMF on the immune

TABLE 2 Risk of liver transplant recipients of no immune response after the second vaccination based on the TrimericS IgG

Parameter	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Male sex	0.75 (0.40–1.40)	0.36	–	–
Age ≥65 y	2.09 (1.04–4.20)	0.04	1.95 (0.89–4.27)	0.10
Time from LT >1 y	0.40 (0.12–1.30)	0.07	–	–
Diabetes	1.66 (0.87–3.16)	0.13	–	–
Impaired kidney function	2.44 (1.27–4.67)	0.007	2.09 (1.04–4.19)	0.04
CNI monotherapy	0.32 (0.14–0.70)	0.005	–	–
Any MMF therapy	2.65 (1.34–5.20)	0.005	2.99 (1.45–6.19)	0.003
Triple immunosuppression	1.29 (0.51–2.94)	0.65	–	–

All significant variables from univariable model were analyzed in the multivariable model at $P = 0.05$ based on the Wald test. The 'CNI monotherapy' was excluded from the final multivariable model during the backward elimination.

Abbreviations: see **TABLE 1**

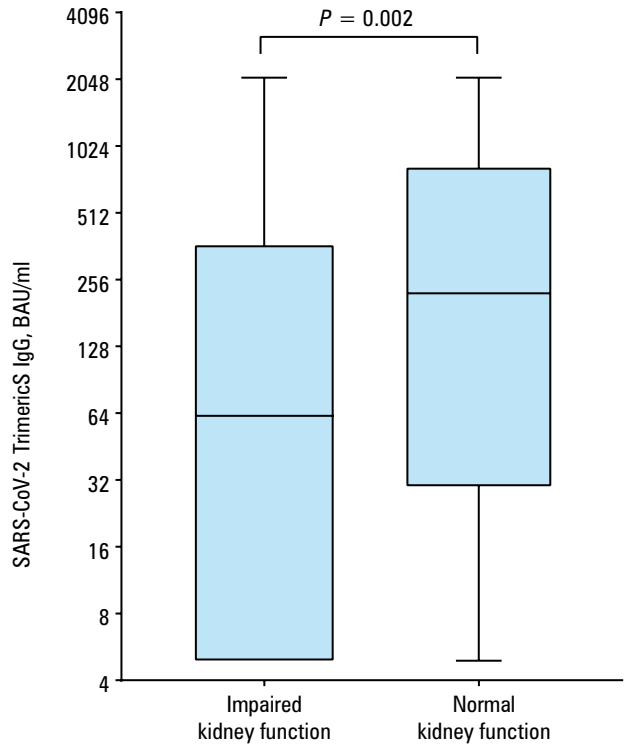

FIGURE 2 Immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients (without prior COVID-19) regarding kidney function (estimated glomerular filtration rate ≥ or <60 ml/min/1.73 m²), presented as median SARS-CoV-2 TrimericS IgG concentration with minimum and maximum values

response might be linked to its potential cytostatic effect on activated lymphocytes. However, despite several recommendations[4], there is still no guideline to suspend or reduce immunosuppressive regimens, particularly MMF, before a scheduled or booster dose of the SARS-CoV-2 vaccine.[17] Finally, in the multivariable model, older age, impaired kidney function, and MMF-based therapy were the risk factors of nonresponse after the vaccination in LT recipients (**TABLE 2**). Unfortunately, we were not able to evaluate the effectiveness of different SARS-CoV-2 vaccines in this specific group; however, the vaccine type-related results are shown in Supplementary material, *Table S1*.

Contrary to previously published data concerning only the first month after the vaccination,[4-6] we assessed in our cohort immune response to the vaccines in a longer period of time (median, 114 days). Since we were not able to perform sequential measurements in each individual, we analyzed the median serum SARS-CoV-2 TrimericS IgG concentration at different time points (ie, <90 days, 90–150 days and >150 days) from the second dose. We found significant differences between the patients assessed before and after 90 days from their second dose, but no difference was noted in individuals 90–150 days and more than 150 days after the second dose (**FIGURE 3**). Certainly, only sequential measurements of the antibodies could elucidate the dynamics of their titers over time. Thus, a stable immune response to the vaccination for a long time after the second dose (ie, 90–150 days vs >150 days) seemed to be crucial, considering the findings of Bergwerk et al[10] that the occurrence of breakthrough infections with SARS-CoV-2 among vaccinated individuals was associated with neutralizing antibody titers during the peri-infection period. It is noteworthy that the vaccinated LT recipients with past natural infection had significantly higher titers than the subset without the infection history, which is in line with previous observations.[18,19] This was also confirmed in the patients after the liver transplantation. However, in this study, the vaccinated population was not tested for SARS-CoV-2 TrimericS IgG before the vaccination, and thus only the subset with positive PCR was named post natural infection. Despite this limitation, the subgroups differed significantly in terms of the antibody concentrations.

Another important finding in our analysis was the high rate of vaccine refusal due to nonmedical reasons, reaching up to 15%. This is more than 7 times higher than that found in an Italian study by Giannini et al[20], who reported that only 2% of patients consciously refused to be vaccinated. We found that the female sex, living in a small town or village, lower BMI, and younger age were associated with

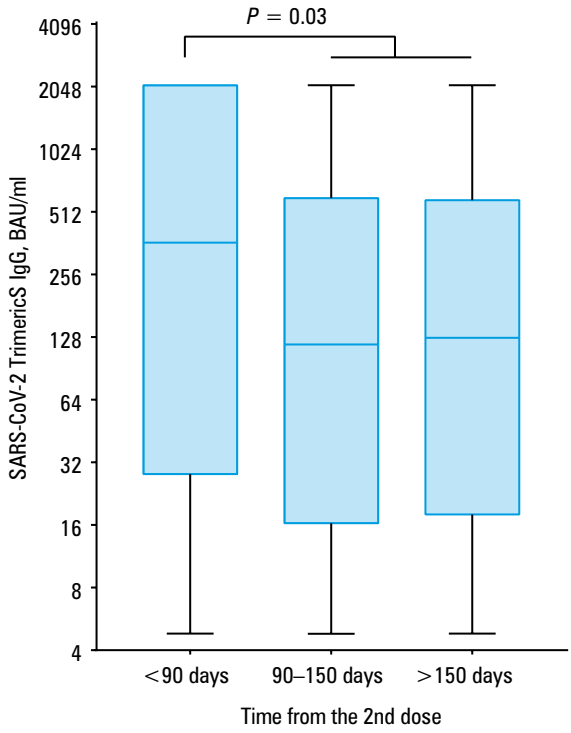

FIGURE 3 Median SARS-CoV-2 TrimericS IgG concentration with minimum and maximum values among liver transplant recipients (without prior COVID-19) in relation to the time from the second dose of the vaccine: below 90 days, 90–150 days, and over 150 days

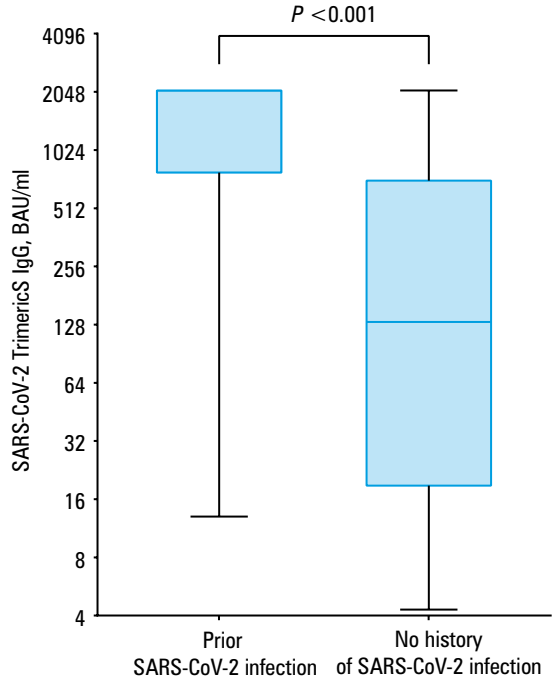

FIGURE 4 Immunogenicity among liver transplant recipients regarding prior COVID-19 presented as median value with minimum and maximum values of SARS-CoV-2 TrimericS IgG concentration

refusal of the vaccine due to nonmedical reasons. These findings are in line with a report regarding patients with inflammatory bowel disease, in whom younger age was associated with increased risk of not being vaccinated against COVID-19.[21] On the other hand, a recently published study, which evaluated the willingness to be vaccinated in 1004 participants from Poland, showed disparate results.[22] In the above-mentioned paper, the participants living in cities were more likely to refuse the vaccination, and there was no link between their sex or age and willingness to be vaccinated.[22] However, our study focused on a specific subset of patients with a chronic condition; therefore, the results may be different from the general population. Moreover, in our study, the LT recipients with diabetes or kidney disease were more likely to choose to be vaccinated. These findings are comparable with an analysis of patients with liver cirrhosis regarding the impact of age, place of living, and comorbidities on their acceptance of the vaccine.[23]

There are numerous causes of this important problem, such as the side effects and effectiveness of the vaccine, available information, and specialist recommendations.[24] Another issue could be widespread misinformation due to a strong and rising antivaccine movement,[25] and the weakness of the general government policy to encourage the society to be vaccinated. However, on the other hand, as 58.9% (as of April 3, 2022) of the Polish population have been fully vaccinated, the 85% vaccination rate in the transplant group may suggest that the transplant community responded well to the vaccination program offered.

In summary, our study, which is one of the largest in a liver transplant cohort to date, showed a moderate response to the COVID-19 vaccine and confirmed previously described negative effects of older age, immunosuppression with MMF, and kidney dysfunction. Moreover, we evaluated the immune response over an extended period of time (ie, <90, 90–150 and >150 days from the second dose), and revealed stable antibody levels after a longer time (90–150 and >150 days) in the patients able to produce antibodies. Novel findings show a much stronger and robust response to the vaccine in individuals who had previous PCR-confirmed SARS-CoV-2 infection; this aspect has not been studied to date. We also addressed the problem of the vaccine refusal in transplant patients, which requires significant attention.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT Conceptualization, PM and JRW; methodology, PM, JRW, and MKJ; formal analysis, JRW and MKJ; investigation, JRW, MKJ, MW, and PM; data curation, JRW, MKJ, MW, and PM; writing—original draft preparation, MKJ; writing—review and editing, JRW, MKJ, MW, and PM; visualization, MKJ; supervision, PM; project administration, PM. All authors have read and approved the published version of the manuscript.

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