Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Accession No. GSE135860) and PRIDE (https://www.ebi.ac.uk/pride/) (Accession No. PXD014908). To access the GEO data, use the password: srqdeykspzmbhor; to access the PRIDE data, use this account: reviewer94895@ebi.ac.uk with password: jf8PgTab. The ribosome profiling and RNA-seq data as well as the SILAC data will be released upon the publication of this study.

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Supplementary data

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Effectiveness of SARS-CoV-2 vaccination in liver transplanted patients: The debate is open!

To the Editor:

Data about the immunogenicity of SARS-CoV-2 vaccination in solid organ transplant recipients are lacking. This population was excluded from clinical trials and lower response to vaccination is a well-known problem in immunocompromised solid organ recipients. In this scenario, we read with great interest the article "Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients" by Rabinowich L. *et al.*[1] recently published in *Journal of Hepatology* evaluating the immunogenicity of the Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine in liver transplant (LT) recipients. They showed that only 47.5% of patients developed neutralizing antibody titers, 10-20 days after receiving the second dose.[1] Similar results have been described in recent reports on SARS-CoV-2 vaccination in solid organ transplant recipients.[2–4]

We would like to share our preliminary results about a prospective study evaluating the effectiveness of SARS-CoV-2 vaccination (in terms of immunogenicity and safety) in a cohort of adult liver transplanted patients regularly followed up at 2 referral hospitals in Southern Italy (Cardarelli Hospital and Federico II Academic Hospital). All liver transplanted recipients had stable graft function prior to vaccination. Participants signed written informed consent. The study was approved by the Federico II Institutional Review Board (n. 214/2021). No patient transplanted during the COVID-19 pandemic received a liver from a SARS-CoV-2-positive donor; however, information about previous SARS-CoV-2 infection in the donors was not available. We enrolled 365 LT patients undergoing Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccination. All patients had a negative history for COVID-19 and tested negative for anti–SARS-CoV-2 antibodies in the 7 days preceding the first dose injection. Four weeks after the second vaccine dose, blood samples were collected for analysis of anti-Spike protein IgG using LIAISON SARS-CoV-2 S1/S2-IgG chemiluminescent assay (DiaSorin, Italy) (range < 3.8 to >400 AU/ml [positive ≥25 AU/ml]). The vaccination was well tolerated, and no major adverse events occurred in

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Table 1. Characteristics of LT recipients stratified according to the serologic response after 2 doses of the BioNTech BNT162b2 SARS-CoV-2 vaccine.

Characteristics	Overall (n = 365)	SARS-CoV-2 seronegative (n = 92)	SARS-CoV-2 seropositive (n = 273)	*p* value
Age, years (mean ± SD)	62.52 ± 12.97	65.01 ± 9.32	61.68 ± 13.9	<0.0001*
<40 years, n (%)	28 (7.6%)	1 (1.08%)	27 (9.8%)	<0.0001**
40-65 years, n (%)	150 (41.1%)	43 (46.7%)	107 (39.2%)	0.071**
>65 years, n (%)	187 (51.23%)	48 (52.17%)	139 (50.9%)	0.036**
Male, sex, n (%)	279 (76.4%)	73 (79.3%)	206 (75.4%)	0.06**
BMI, kg/m^2 (mean ± SD)	26.56 ± 4.52	27.7 ± 7.09	26.77 ± 4.59	0.031*
Time from transplantation, years (mean ± SD)	14.08 ± 8.84	11.94 ± 8.72	14.79 ± 8.77	<0.001*
<1 year, n (%)	7 (1.91%)	5 (5.4%)	2 (0.7%)	<0.0001**
1-5 years, n (%)	69 (18.9%)	22 (23.9%)	47 (17.21)	0.0025**
5-10 years, n (%)	58 (15.89%)	15 (16.3%)	43 (15.75%)	0.058**
>10 years, n (%)	231 (63.21%)	50 (54.3%)	181 (66.3%)	<0.0001**
Immunosuppressive therapy, n (%)				
Calcineurin inhibitor	299 (81.9%)	72 (78.3%)	227 (83.1%)	0.19**
Antimetabolite	132 (36.2%)	49 (53.3%)	83 (30.4%)	<0.0001**
mTOR inhibitor	85 (23.3%)	30 (32.6%)	55 (20.1%)	0.021**
Single immunosuppressive agent, n (%)	218 (59.7%)	34 (36.9%)	184 (67.3%)	<0.0001**
Two or more immunosuppressive agents, n (%)	147 (40.3%)	58 (63.1%)	89 (32.7%)	<0.0001**
Steroids, n (%)	28 (7.6%)	9 (9.8%)	19 (6.9%)	0.07**

LT, liver transplantation.
*Kruskal-Wallis test.
**Chi squared, Fisher exact test

any of the enrolled patients. Protective levels of antibodies were detected in 273/365 patients (74.8%) with a mean value of 214.79 ± 143 AU/ml. In the 92 patients with negative serology, statistically significant associated factors were: older age (>65 years), higher BMI, shorter time from transplantation and immunosuppressive regimens with multiple drugs and antimetabolite therapy (see Table 1 for details). These preliminary results are partially in line with Rabinowich *et al.*[1] who reported negative serologic response in older patients (>63 years), those receiving a high dose of prednisone in the past 12 months, and regimens including antimetabolites and triple immunosuppressive therapy. Furthermore, we compared the serology of LT patients with a control group of 340 healthcare workers with no major comorbidities matched for age and sex (mean age 57.86 ± 8.28; 64% males). In the control group only 5/340 (1.4% *vs.* 26.2%) showed a negative serology 4 weeks after full vaccination, and mean antibodies levels were 314.32 ± 94.1 AU/m, which was statistically higher than in the LT group (p <0.0001).

Our results highlight the decreased humoral response in LT recipients. Moreover, we define the most vulnerable individuals among them (*i.e.*, older, overweight/obese patients, and those receiving multiple drug immunosuppressive regimens and regimens including antimetabolites). Even if these findings were expected, given the known scarce antibody response to other vaccines in immunocompromised patients, we are continuing our study to obtain data about the long-term effectiveness and immunogenicity of SARS-CoV-2 vaccination and the impact of an additional dose, as recently suggested by Werbel *et al.*[5]

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No personal or financial conflicts of interest for all the authors.

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Authors' contributions
M.G., IE, V.C. made substantial contributions to the conception and the design; MG wrote the article; A.F. acquired data; F.M. revised the article critically for important intellectual contribution. All authors read and approved the final version of the article.

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JOURNAL OF HEPATOLOGY

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Reply to: "Effectiveness of SARS-CoV-2 vaccination in liver transplanted patients: The debate is open!"

Time for comprehensive data analysis

To the Editor:

Guarino *et al.* recently published data from 365 liver transplant (LT) recipients receiving 2 doses of the Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine, reporting a positive serological response rate of 74.8%.[1] Earlier this year we published data showing only a 47.5% positive serological response in LT recipients following an identical vaccination protocol.[2] This significant difference in outcomes requires discussion regarding the effectiveness of the SARS-CoV-2 vaccine in LT recipients.

Initial data regarding SARS-CoV-2 vaccination response in LT recipients were limited. A number of recently published studies add valuable information, with reported response rates ranging from 37.5% to 81%.[3–8] Several SARS-CoV-2 vaccination studies

Table 1. Summary of recently published SARS-CoV-2 2nd vaccine studies that included LT patients.

Paper	Number of LT recipients	Type of SARS-CoV-2 vaccine	Positive serological response rate	Antibody titer compared to control group†	Factor related to reduced response rate
Guarino *et al.*[1]	365	Pfizer-Bio-NTech BNT162b2	74.8%	214.79 ± 143 *vs.* 314.32 ± 94.1 AU/ml (p <0.0001)††	Age >65 yr, higher BMI, shorter time from transplantation, immunosuppressive regimens with multiple drugs, antimetabolite therapy
Rabinowich *et al.*[2]	80	Pfizer-Bio-NTech BNT162b2	47.5%	95.41 ± 92.4 *vs.* 200.5 ± 65.1) AU/ml (p <0.001)††	Age, lower eGFR,high dose prednisone in the past 12, triple therapy immunosuppression, MMF
Strauss *et al.*[3**]	161	Pfizer-BioNTech BNT162b2 Moderna mRNA-1273	81%	81.9-250 U/ml, no control‡	Antimetabolite therapy, type of vaccine
Rashidi-Alavijeh *et al.*[4]	43	Pfizer-Bio-NTech BNT162b2	79%	552.7 *vs.* >2,080 BAU/ml (p = 0.0001)††	MMF
Boyarsky *et al.*[5*]	129 (cohort of 658 SOT recipients)	Pfizer-BioNTech BNT162b2 Moderna mRNA-1273	79.8%		For all SOT recipients: age, type of organ, years since transplant, antimetabolite therapy, type of vaccine
Marion *et al.*[6*]	58 (cohort of 367 SOT recipients)	Pfizer-BioNTech BNT162b2 Moderna mRNA-1273	50%		No clinical data
Mazzola *et al.*[7*]	58 (cohort of 143 SOT recipients)	Pfizer-Bio-NTech BNT162b2	37.5%		For all SOT recipients: age >60 yr, type of organ, treated with corticoids, triple-therapy immunosuppression, transplanted <2 yr, diabetic patients

eGFR, estimated glomerular filtration rate; LT, liver transplant; MMF, mycophenolate mofetil; SOT, solid organ transplant.
*Studies including LT recipients in a cohort of SOT patients.
**Patients from this study were included in a previous all organ report.[8]
†Antibody titers provided only for studies exclusive to LT recipients.
††LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay (DiaSorin, Italy).
‡Anti-RBD immunoassay (Roche Elecsys).

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