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.

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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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that included LT recipients are listed in Table 1. We analyzed the available data in order to clarify this wide range of responses to vaccination. Although the response rate differs between the studies, the main factors influencing a negative serological response are consistent and include among others, age, time from transplant and the immunosuppressive regimens[1,2] (Table 1).

The accumulating data supports the notion that the effectiveness of the SARS-CoV-2 vaccine is the result of multiple factors, related to patient and immunosuppression characteristics. To understand the influence of these factors on the vaccination outcome we compared the patient population of our study with that of Guarino *et al.* Some patient characteristics, such as mean age, gender, and BMI are similar between the 2 studies. We noted 2 major differences: time from transplant and immunosuppression regimen. In our group, the mean time from transplant was 6 years, compared to 14 years in the study by Guarino *et al.*[1,2] This most probably had a major impact on exposure to more intense immunosuppression, as well as other immunological processes. Another noteworthy difference is the cumulative use of immunosuppressive medications. In our study only 16.25% of the patients were on a single immunosuppressive agent, while in the data published by Guarino *et al.* the majority (59.7%) were treated with a single agent. Furthermore, in our study, 40 patients (50%) were treated with an immunosuppressive combination that included mycophenolate mofetil (MMF), while the number was 36.2% in Guarino *et al.*'s study.[1,2]

The significant effect of immunosuppression intensity and the use of MMF were also demonstrated in other studies, which reported a reduced rate of response to SARS-CoV-2 vaccination from 79-81% among LT patients in general compared to 45.5-61% among those receiving MMF.[3,4] Preliminary results published by Del Bello *et al.* highlight the negative impact of age, MMF, and dual/triple immunosuppression on vaccination response following a third dose of the SARS-CoV-2 vaccine.[8]

While some of the current studies lack in-depth clinical information and analysis, it is apparent that one of the most influential factors governing vaccination response is the degree of immunosuppression and use of MMF. Thus, managing immunosuppression is a major route to affect vaccine response. Currently we do not have sufficient data to recommend reducing immunosuppression for this purpose, and regardless, these decisions need to be taken on an individual patient basis. Other issues that require further assessment are long term follow-up with regards to clinical outcomes and durability of the antibody response. Given the ongoing pandemic and 3rd vaccination booster programs, further studies with an in-depth data analysis are needed in order to guide us towards a practical recommendation on how to improve the vaccination response in the vulnerable population of LT recipients.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

Liane Rabinowich- concept and writing, Oren Shibolet- writing and review, Helena Katchman- concept and writing.

Supplementary data

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Author names in bold designate shared co-first authorship

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