LETTER TO THE EDITOR

Adverse events after SARS-CoV-2 vaccination in solid organ transplant recipients: A systematic review

To the Editor,

The immunogenicity in solid organ transplant (SOT) recipients against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination is suboptimal.1 However, adverse events including rejection post-vaccination have not been reviewed, which are also of great interest for clinicians taking care of transplant recipients.

We conducted a systematic review on adverse events post SARS-CoV-2 vaccination in SOT recipients and included studies on SOT and SARS-CoV-2 vaccine safety including (a) systemic or local reactions, (b) organ rejection or de novo donor-specific antibodies (DSAs) (eFigure 1). We searched studies published between January 1, 2020 and August 11, 2021 through Medline, Embase, Scopus, Web of Science, CINAHL Plus with Full Text, LitCovid, medRxiv and bioRxiv. Records were downloaded to EndNoteX9, then uploaded to Covidence software for deduplication, screening, and extraction. We assessed studies’ quality and bias using the Mixed Methods Appraisal Tool 2018 (eTable1).

Through the search, we initially identified 74 unique articles. After review, we included 19 articles with 17 studies performing detailed safety assessments (Table 1). The most common side effect was injection-site pain, seen between 52.2% to 90% after vaccination. Fatigue, fever, myalgias, and arthralgias were also reported systemic reactions. Local reactions included pain, erythema, and swelling.

We identified two case reports and three cohort studies reporting organ rejection after vaccination, including one kidney, one liver, one heart transplant recipient, and two nonspecified SOT recipients (Table 2). For three cohort studies, of 1721 recipients, three recipients developed rejection.3,4 Acute cell-mediated rejection was seen at 8- and 11-days post-vaccination in the kidney2 and liver transplant recipient,5 respectively. No documented graft failure was reported. Three/four studies did not identify any de novo or increase in DSA after screening before and within 1–3 weeks of mRNA vaccine doses (Table 1).2–4 One/thirteen kidney transplant recipients developed donor-specific anti-HLA class II antibody 28 days after the second dose of BNT162b2 vaccine which increased after the third dose, without allograft rejection.5

Our study found a very limited number of cases of organ rejection or significant side effects in SOT recipients after SARS-CoV-2 vaccination. The vaccine immunogenicity is still suboptimal in this population.1 On top of this, breakthrough infections have been widely reported. However, SARS-CoV-2 vaccination has a relatively safe profile in SOT recipients, and thus vaccination of this population can be justified.

SOT recipients should still maintain all precautions to prevent infection, such as frequent hand washing, masking, and use of pre-exposure monoclonal antibodies.

There are several limitations in this study. We found a lack of high-quality, controlled studies evaluating rejection episodes after SARS-CoV-2 vaccination, with all published studies being case reports or series. Thus, there could be publication and reporting bias. Furthermore, long-term outcomes were not assessed even in large prospective studies, given the recency of SARS-CoV-2 vaccinations.

In conclusion, even though SARS-CoV-2 vaccine immunogenicity is suboptimal in SOT recipients, given the safety profile, we recommend providing vaccination to SOT recipients in addition to other preventive strategies. Long-term follow-up studies on outcomes including rejection post-SARS-CoV-2 vaccination are warranted in SOT recipients.

Abbreviations: DSA, donor-specific antibodies; SARS-CoV-2, Severe acute respiratory virus syndrome 2; SOT, solid organ transplant.
| First author and year | Study design | SOT patients (N) | Vaccine type and schedule | Follow-up | Local reactions | Systemic reactions | Most common AE | Donor-specific antibodies monitoring |
|-----------------------|--------------|------------------|---------------------------|-----------|----------------|-------------------|----------------|-------------------------------------|
| Boyarsky 2021         | Cross-sectional survey | 187 | mRNA (BNT162b2 or mRNA-1273), one dose | 1 week post-dose | Pain | Fever, Chills, Fatigue, Headache, Vomiting, Diarrhea, Myalgia | Injection-site pain (90%) | NR |
| Cucchiari 2021        | Prospective cohort | 148 | mRNA-1273, two doses | 48–72 h after each dose | Pain | Fever, Fatigue, Chills, Nausea or vomiting, Diarrhea, Myalgia, Arthralgia, Headache | Injection-site pain (86% post dose 1, 75% post dose 2) | DSA tested at baseline and 2 weeks post dose 2: present in five cases at baseline (3.4% of the entire population); no cases of de-novo DSAs observed after dose 2 of mRNA-1273 |
| Grupper 2021c          | Retrospective cohort | 136 | BNT162b2, two doses | 7 days after each dose | Pain | Fever, Chills, Headache, Fatigue, Myalgia, Arthralgia, Nausea, Vomiting, Diarrhea | Injection-site pain (52.2%) | NR |
| Hall 2021a            | Prospective cohort | 127 | mRNA-1273 vaccine, two doses (n = 126 patients) mRNA-1273 vaccine, one dose (n = 1) | Vaccine diary for 7 days after each dose, overall follow-up > = 60 days post-dose 1 | Pain | Fatigue, Myalgia, Headache, Arthralgia, Nausea or vomiting, Chills, Medical visit | Injection-site pain (>60% post dose 1, >20% post dose 2) | NR |
| Hall 2021b            | Randomized controlled trial | 60 | mRNA-1273, three doses (treatment group) | Vaccine diary for 7 days after each injection, overall follow-up > = 4 weeks post-dose 3 | Pain | Fever, Chills, Fatigue, Myalgia, Arthralgia, Headache, Nausea or vomiting, Diarrhea | Injection-site pain (46/60, 76.7%) post dose 3 | NR |
| First author and year | Study design | SOT patients (N) | Vaccine type and schedule | Follow-up | Local reactions | Systemic reactions | Most common AE | Donor-specific antibodies monitoring |
|-----------------------|--------------|-----------------|---------------------------|-----------|----------------|-------------------|---------------|----------------------------------|
| Herrera 2021          | Prospective cohort | 104             | mRNA-1273, two doses      | 48–72 h after each dose | Pain, Swelling   | Fatigue, fever    | Injection-site pain (80%) | No increase in HLA antibodies from baseline to 3 weeks post dose 2 |
| Itzhaki Ben Zadok 2021| Prospective cohort | 42              | BNT162b2, two doses       | Days 21–26 and 35–40 post-dose 1 | Pain, Erythema   | Fatigue, Myalgia, Arthralgia, Headache, Fever | Injection-site pain (71%) | NR |
| Kamar 2021            | Retrospective cohort | 101             | BNT162b2, three doses     | 1 month post-dose 3 | NR              | NR                | NR            | NR                               |
| Marion 2021           | Retrospective cohort | 950             | mRNA (BNT162b2 or mRNA-1273), two doses | 4 weeks post-dose 2 | NR              | NR                | NR            | NR                               |
| Massa 2021            | Prospective cohort | 61              | BNT162b2, three doses     | 72 h after each dose | Injection-site pain, Local paresthesia | Fatigue, Headache, Diarrhea, Fever, Myalgia, Rhinorrhea, Nausea and vomiting, Cough, Hypertension, Anorexia, Vertigo, Abdominal pain, Insomnia | Injection-site pain in 60.7%, 65.6%, and 67.2% (41 of 61 patients) after dose 1, 2, and 3, respectively | Thirteen (21.3%) patients had donor-specific antibodies before vaccination. Only one patient developed de novo donor-specific antibodies, donor-specific anti-HLA class II (DQB1*06:03) antibody 28 days after the second vaccine dose |
| Mazzola 2021          | Retrospective cohort | 143             | BNT162b2, two doses       | 7 days post-dose 1, up to 1 month post-dose 2 | Pain             | Fatigue headache | Injection-site pain (25.7%) | NR |
| Ou 2021a              | Prospective cohort | 609             | BNT162b2, two doses       | 7 days after each dose | Pain, Swelling, Erythema | Fatigue, Headache, Myalgia, Chills, Fever, Diarrhea, Vomiting | Injection-site pain after dose 1 (24% in the non-belatacept group, 22% in the belatacept group). Fatigue after dose 2 (21% in the non-belatacept group, 17% in the belatacept group) | NR |
| First author and year | Study design | SOT patients (N) | Vaccine type and schedule | Follow-up | Local reactions | Systemic reactions | Most common AE | Donor-specific antibodies monitoring<sup>b</sup> |
|-----------------------|--------------|------------------|---------------------------|-----------|----------------|-------------------|---------------|----------------------------------|
| Ou 2021<sup>b</sup>   | Prospective cohort | 741              | BNT162b2; two doses (<i>n</i> = 400) mRNA-1273 vaccination, 2 doses (<i>n</i>-341) | 7 days after each dose | Pain Swelling Erythema | Fatigue Headache Myalgia Chills Fever Diarrhea Vomiting | Injection-site pain (84% after dose 1, 77% after dose 2) | NR |
| Peled 2021            | Prospective cohort | 77               | BNT162b2; two doses | 7 days after each dose | Pain Erythema Swelling | Fatigue Headache Chills Vomiting Diarrhea New or worsening muscle or joint pain Use of antipyretic or pain medication | Injection-site pain in 56% and 49% after dose 1 and 2, respectively | NR |
| Rabinowich 2021      | Case-control   | Liver (<i>n</i> = 71) Controls (<i>n</i> = 21) | BNT162b2; two doses | Survey 7 days post each dose, follow-up until 7-10 weeks post-dose 2 | Pain | Fatigue Headache Myalgias | Injection-site pain in each group following the dose 1 and 2: 43/71, 60.5% (LTR) versus 15/21, 71% (controls); 38/71, 53.5% (LTR) versus 15/21, 71% (controls); respectively | NR |
| Shostak 2021         | Prospective cohort | 168              | BNT162b2; two doses | Median of 68 days (IQR 65–73) post-dose 1 | Pain | Fatigue | Injection-site pain (108/168, 64.29%) | NR |
| Werbel 2021          | Case series    | 30               | Three-dose schedule Initial: BNT162b2; 2 doses (<i>n</i> = 17); mRNA-1273, 2 doses (<i>n</i> = 13) Dose 3: JNJ-78436735 (<i>n</i> = 15), mRNA-1273 (<i>n</i> = 9), BNT162b2 (<i>n</i> = 6) | Survey 7 days post-dose 3, follow-up limited | Pain Erythema Swelling | Chills Headache Fatigue Myalgia Diarrhea | Fatigue in 8/11 (72.73%) of J&J recipients Injection-site pain in 12/12 (100%) of mRNA recipients | NR |

Abbreviations: AE, adverse event; NR, not reported; URI, upper respiratory infection; UTI, urinary tract infection.

<sup>a</sup>References for the table can be found on the Supplement.

<sup>b</sup>The study by Sattler et al. also monitored HLA-specific antibodies with no increase from baseline seen; however no detailed safety assessment was performed.

<sup>c</sup>One patient with undetectable antibody levels despite full vaccination died from severe PCR-proven COVID-19.
TABLE 2  Studies reporting transplant rejection following vaccination in solid organ transplant (SOT) recipients

| Author and year | Patient (type of organ transplant) | Vaccine and schedule | Time from transplant | Time from last vaccine dose to diagnosis | Case | Findings |
|----------------|-----------------------------------|----------------------|----------------------|----------------------------------------|------|----------|
| Del Bello 2021 | Kidney                            | BNT162b2, two doses  | 18 months            | 8 days                                  | Biopsy-proven acute cellular rejection | Detectable donor-specific antihuman leukocyte antigen antibodies (DSAs) against class II antigens, and anti-SARS-CoV-2 spike protein antibodies. Later kidney function improved with steroid pulses. |
| Marion 2021    | SOT (not specified)               | mRNA                | NR                   | NR                                     | Acute cellular rejection               | No biological monitoring               |
| Ou 2021b       | SOT (not specified)               | mRNA, two doses     | NR                   | NR                                     | Acute rejection                         | -                                    |
| Vyhmeister 2021| Liver                             | mRNA-1273 vaccine, one dose | 5.5 months | 11 days                                | Biopsy-proven acute cellular rejection | Presented with newly elevated liver tests, dark urine, fatigue and malaise. Underwent three liver biopsies due to nonresponse to steroids, later improved with antithymocyte globulin. DSA antibodies were negative, antibodies to the antispike protein S1 subunit were present but not to the receptor binding domain. |
| Werbel 2021    | Heart                             | mRNA-1273 vaccine following 2 BNT162b2 doses | NR | 7 days | Biopsy-proven, antibody-mediated rejection | Presented with volume overload, heart function preserved |

Abbreviation: NR, not reported.

References for the table can be found on the Supplement.

AUTHOR CONTRIBUTIONS

AV, YE, and JMR performed the literature search. All authors were responsible for the study design, data interpretation, and writing of the manuscript and are accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Manothummetha K, Chuleerarux N, Sanguankeo A, et al. Immunogenicity and risk factors associated with poor humoral immune response of SARS-CoV-2 vaccines in recipients of solid organ transplant: a systematic review and meta-analysis. JAMA Netw Open. 2022;5(4):e226822. doi: 10.1001/jamanetworkopen.2022.6822

2. Cucchiari D, Egri N, Bodro M, et al. Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. Am J Transplant. 2021;21:2727-2739. doi: 10.1111/ajt.16701

3. Herrera S, Colmenero J, Pascal M, et al. Cellular and humoral immune response after mRNA-1273 SARS-CoV-2 vaccine in liver and heart transplant recipients. Am J Transplant. 2021;21(12):3971-3979. doi: 10.1111/ajt.16768

4. Sattler A, Schrezenmeier E, Weber UA, et al. Impaired humoral and cellular immunity after SARS-CoV2 BNT162b2 (Tozinameran) prime-boost vaccination in kidney transplant recipients. J Clin Invest. 2021;131(14):e150175. doi: 10.1172/JCI150175

5. Massa FCM, Gerard A, Grabsi H, et al. Safety and cross-variant immunogenicity of a three-dose COVID-19 mRNA vaccine regimen in kidney transplant recipients. EBioMedicine. 2021;73:103679. doi: 10.2139/ssrn.3890865

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