Factors Associated With COVID-19 Vaccine Response in Transplant Recipients: A Systematic Review and Meta-analysis

Jiajing Li, MSc,[1] Ibrahim Ayada, MD,[1] Yining Wang, MSc,[1] Caroline M. den Hoed, MD, PhD,[1,2] Nassim Kamar, MD, PhD,[3] Maikel P. Peppelenbosch, PhD,[1] Annemarie C. de Vries, MD, PhD,[1] Pengfei Li, MSc,[1] and Qiuwei Pan, PhD[1,2]

Background. The rapid development and universal access to vaccines represent a milestone in combating the coronavirus disease 2019 (COVID-19) pandemic. However, there are major concerns about vaccine response in immunocompromised populations in particular transplant recipients. In the present study, we aim to comprehensively assess the humoral response to COVID-19 vaccination in both orthotopic organ transplant and allogeneic hematopoietic stem cell transplant recipients. **Methods.** We performed a systematic review and meta-analysis of 96 studies that met inclusion criteria. **Results.** The pooled rates of seroconversion were 49% (95% confidence interval [CI], 43%-55%) in transplant recipients and 99% (95% CI, 99%-99%) in healthy controls after the second dose of vaccine. The pooled rate was 56% (95% CI, 49%-63%) in transplant recipients after the third dose. Immunosuppressive medication is the most prominent risk factor associated with seroconversion failure, but different immunosuppressive regimens are associated with differential outcomes in this respect. Calcineurin inhibitors, steroids, or mycophenolate mofetil/mycophenolic acid are associated with an increased risk of seroconversion failure, whereas azathioprine or mammalian target of rapamycin inhibitors do not. Advanced age, short interval from receiving the vaccine to the time of transplantation, or comorbidities confers a higher risk for seroconversion failure. **Conclusions.** Transplant recipients compared with the general population have much lower rates of seroconversion upon receiving COVID-19 vaccines. Immunosuppressants are the most prominent factors associated with seroconversion, although different types may have differential effects.

(*Transplantation* 2022;106: 2068–2075).

Received 6 April 2022. Revision received 18 May 2022.

Accepted 30 May 2022.

[1] *Department of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands.*

[2] *Erasmus MC Transplant Institute, Erasmus MC-University Medical Center, Rotterdam, The Netherlands.*

[3] *Department of Nephrology, Dialysis and Organ Transplantation, CHU Rangueil, INSERM UMR 1291, Toulouse Institute for Infectious and Inflammatory Disease (Infinity), University Paul Sabatier, Toulouse, France.*

This study is supported by a VIDI grant (No. 91719300) from the Netherlands Organization for Scientific Research (NWO).

The authors declare no conflicts of interest.

J.L. and Q.P.: research design; P.L. and Q.P.: supervision; J.L. and I.A.: data extraction and analysis; J.L.: writing of the article; Y.W. and P.L.: reviewing data as an arbiter; C.M.d.H., N.K., M.P.P., and A.C.d.V.: reviewing and editing. All authors have read and approved the final version of the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

Correspondence: Qiuwei Pan, PhD, Department of Gastroenterology and Hepatology, Erasmus MC, room Na-1005, Wytemaweg 80, NL-3015 CN, Rotterdam, The Netherlands. (q.pan@erasmusmc.nl).

ISSN: 0041-1337/20/10610-2068

DOI: 10.1097/TP.0000000000004256

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a major challenge to healthcare systems across the globe. The rapid development of COVID-19 vaccines, in particular the two mRNA vaccines from Pfizer and Moderna, respectively, and the universal access to these vaccines represent a milestone in combating the current pandemic. However, better protection of vulnerable populations has to be further improved.

Especially with regard to immunocompromised patients, important concerns remain, and specifically in transplantation medicine, the efficacy of COVID-19 vaccination remains in doubt. Transplant recipients constitute a heterogeneous population, roughly divided into solid organ transplant (SOT) and allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients. Such patients usually require lifelong immunosuppressive medication to prevent graft rejection and thus represent an immunocompromised population. In general, these patients have an increased risk of SARS-CoV-2 infection, a more severe disease course, and reduced response to vaccination with a higher rate of breakthrough infections.[1-6] Unfortunately, a precise analysis of the extent of this problem and of the factors associated with driving or counteracting effective COVID-19

<zdoi;10.1097/TP.0000000000004256>

immunization is still lacking, precluding the development of rational strategies of managing the patients involved.

Prompted by the consideration mentioned above, in this systematic review and meta-analysis, we aim to first comprehensively assess the humoral immune response to COVID-19 vaccines in both SOT and allo-HSCT patients. Second, we aim to identify key factors associated with vaccination response in these patients. The findings will facilitate the optimization of vaccination and immunosuppressive strategies aimed at better protecting this vulnerable population against COVID-19.

MATERIALS AND METHODS

Data Sources and Searches

An extensive systematic search was conducted in 5 databases: Embase, Medline ALL, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar. We searched the databases for eligible studies in the English language from inception to December 21, 2021. All searches from these databases were performed by a biomedical information specialist of the medical library, with an exhaustive set of search terms related to transplant recipients and SARS-CoV-2 vaccines (the full search strategies are provided in the Materials, **SDC,** http://links.lww.com/TP/C486). No institutional review board approval was required for this meta-analysis because only published data were included.

Study Selection

Studies were included according to the following criteria: (1) Participants in these studies must be adults and include post-transplant patients without previous and ongoing SARS-CoV-2 infection who have completed 2 or 3 doses of COVID-19 vaccines. (2) The studies contained data about serological responses determined by antibody levels and provided cutoff values. (3) The studies contained characteristics of transplant recipients with and without seroconversion after vaccination. (4) When different studies described the same population, the most recent or the study with the most complete dataset was included.

Studies were excluded according to the following criteria: (1) studies are nonoriginal articles, (2) are human studies, (3) concern SARS-CoV-2 breakthrough infections, (4) contain nonextractable data, and (5) have <10 participants.

Two reviewers (J.L. and I.A.) worked independently to determine whether a study met inclusion criteria, collected information to assess the methodological validity of each candidate study, and extracted data with structured data collection forms. The reviewers resolved discrepancies by jointly reviewing the study in question. If no consensus was reached, a third reviewer (P.L. or Q.P.), unaware of prior determinations, functioned as an arbiter.

Quality Assessment of the Studies

All eligible studies contained seroconversion data and were further divided into 3 types: (1) studies comparing differences of the immune responses to the SARS-CoV-2 vaccine between transplant recipients and healthy controls, (2) studies comparing differences of characteristics between the groups having negative or positive antibody response within the transplant recipient population, and (3) studies only recording the original data of seroconversion in enrolled transplant recipients. All studies included were observational studies, such as prospective cohort studies and retrospective case–control studies. The quality scores of studies were assessed by the NEWCASTLE-OTTAWA quality assessment scale (**Table S1, SDC,** http://links.lww.com/TP/C486). Studies were not excluded on the basis of their quality score to increase transparency and to ensure all available evidence in this area was reported.

Data Extraction and Analysis

For each included study, we independently extracted data using a standardized data extraction form regarding the trial characteristics (study design, study start date, and geographical region), patient characteristics (age, sex, ethnicities, comorbidities, and body mass index), transplant-related parameters (time from transplantation and maintenance immunosuppressive treatment), and the outcomes of vaccination (serological responses determined by antibody levels). For the outcomes of seroconversion, we collected the number of participants with a negative response and positive response and calculated the positive response rate and the risk ratio (RR) of transplant recipients and healthy controls. Corresponding authors were contacted in case clarification was necessary.

Statistics Analysis

For categorical variables in risk factors, analysis was performed by calculating the odds ratio (OR) with a 95% confidence interval (95% CI). For continuous outcomes in risk factors, analysis was performed by calculating weighted mean difference (WMD) and standardized mean difference with 95% CI. Heterogeneity was assessed using the I^2 test, with I^2 >50% indicating the existence of heterogeneity. When there was significant heterogeneity, a random effect model (DerSimonian-Laird method) was used to calculate the pooled effect size; otherwise, the fixed model (Mantel–Haenszel method) was used instead. Possible publication bias was assessed using Harbord's weight linear regression in conjunction with the symmetry of the funnel plot. Sensitivity analysis was assessed using the trim-and-fill method. If the number of included studies in each outcome was <10, the funnel plots was not carried out because of limited power.[7] The process of these analyses was implemented by STATA 15.0.

RESULTS

In total, 510 records were identified through database screening. Of these records, 365 articles were excluded based on title and abstract screening. Consequently, we conducted a full-text review of 145 articles, of which 49 were excluded. As a result, 96 studies were included in the current study (Figure 1).

Among the included studies, 85 studies containing antibody response data after 2 doses of the COVID-19 vaccine were extracted for analysis. Of these, 37 studies also included healthy controls receiving the vaccine. The pooled rate of seroconversion was 49% (95% CI, 44%-55%) of 10 923 transplant recipients (**Figure S1, SDC,** http://links.lww.com/TP/C486), which is much lower than that in 2326 healthy controls (99%; 95% CI, 99%-99%)

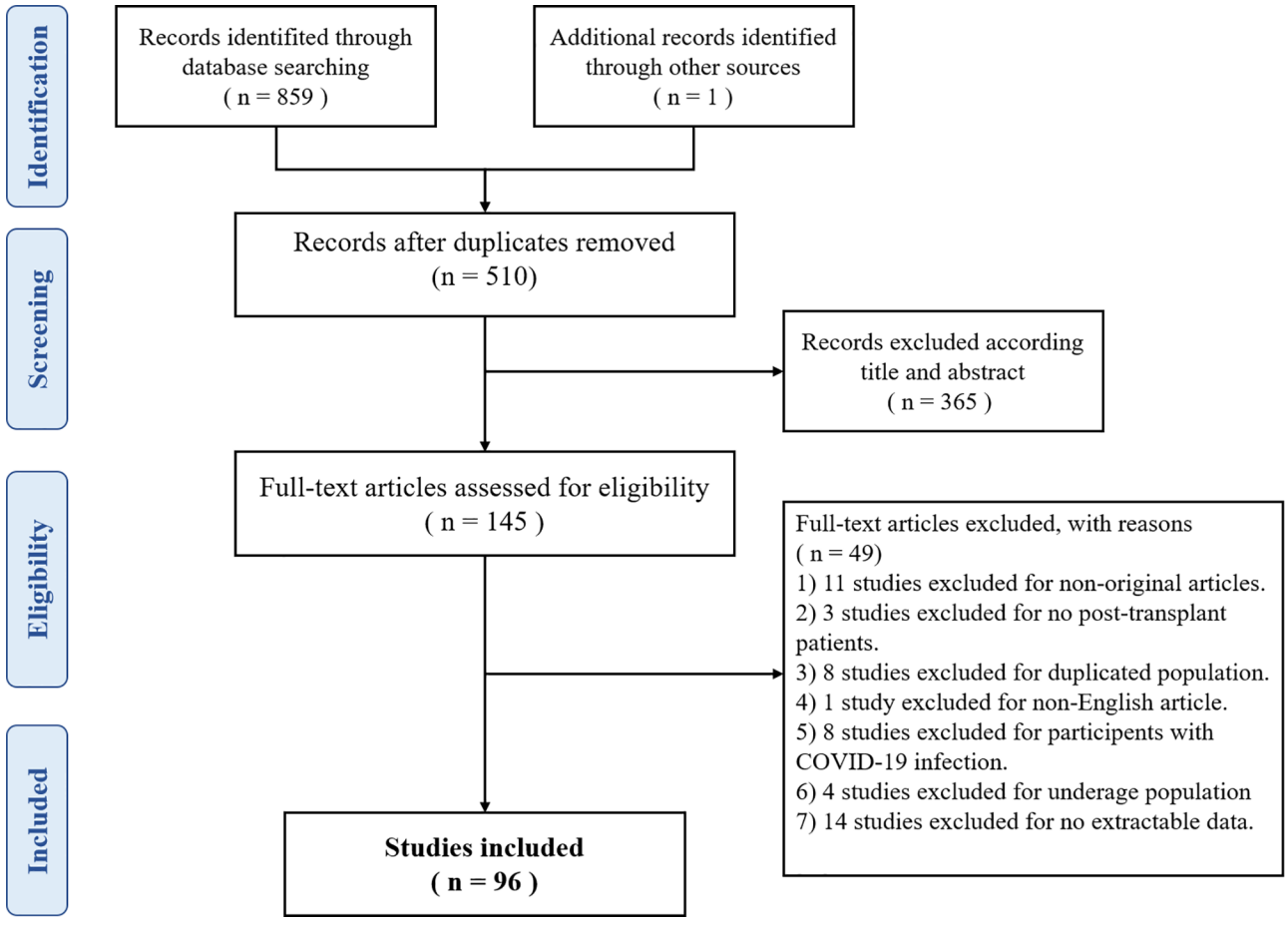

FIGURE 1. Flowchart of studies screening and selection process. COVID-19, coronavirus disease 2019.

(**Figure S2, SDC,** http://links.lww.com/TP/C486). SOT (42%; 95% CI, 37%-47%) compared with allo-HSCT recipients (78%; 95% CI, 74%-83%) had significantly lower response rate (**Figure S1, SDC,** http://links.lww.com/TP/C486). By classifying SOT recipients into different organ types, lung transplant recipients had the lowest rate of seroconversion (29%; 95% CI, 21%-36%), followed by the kidney (37%; 95% CI, 30%-43%) and heart (37%; 95% CI, 23%-51%) transplant recipients, and liver transplant recipients had the highest seroconversion rate (65%; 95% CI, 58%-72%) (**Figure S3, SDC,** http://links.lww.com/TP/C486). No clear difference in the rate of seroconversion was found based on the types of serological tests (**Figure S4, SDC,** http://links.lww.com/TP/C486).

For a further in-depth comparison between the response in transplant recipients and the general population, we specifically analyzed the 37 studies that contained 4071 transplant recipients and their matched healthy controls. The characteristics of these studies are summarized in **Table S2, SDC,** http://links.lww.com/TP/C486. Transplant recipients compared with healthy controls are significantly less likely to have a positive reaction to the COVID-19 vaccine, with an RR of 0.48 (95% CI, 0.42-0.54). Subgroup analysis showed that both SOT (RR, 0.42; 95% CI, 0.37-0.48) and allo-HSCT recipients (RR, 0.82; 95% CI, 0.76-0.89) had a significantly lower rate of humoral response compared with that in healthy controls (Figure 2). The sensitivity analysis and publication bias assessment of these studies are shown in Materials, **SDC,** http://links.lww.com/TP/C486.

We also collected the humoral response data in transplant recipients from 15 studies documenting the third-dose vaccination (characteristics in **Table S3, SDC,** http://links.lww.com/TP/C486). The pooled rate of positive humoral response to the third dose was 56% (95% CI, 49%-63%) (**Figure S5, SDC,** http://links.lww.com/TP/C486). However, only 2 of these studies were in allo-HSCT populations. By excluding these 2 studies and only considering the SOT population, the pooled seroconversion rate was 55% (95% CI, 47%-62%) (**Figure S6, SDC,** http://links.lww.com/TP/C486). Furthermore, there are 9 studies that contained data before and after 3rd dose vaccination. As shown in **Table 1 and Figure S7, SDC,** http://links.lww.com/TP/C486, the seroconversion rates were significantly higher after the 3rd dose (59% [95% CI, 51%-68%]) than those after the 2nd dose (42% [95% CI, 27%-56%]). There are 5 studies that only included the nonresponders of 2 doses of vaccines, and the pooled seroconversion rate of the 3rd dose was 44% (95% CI, 39%-48%).

To identify risk factors of nonresponsiveness to COVID-19 vaccines in transplant recipients, we next analyzed 51 studies that described the characteristics of both responders and nonresponders. Among the basic demographics of the transplant population, gender and body mass index had no significant difference between responders and nonresponders (**Figure 3A, S14 and S23, SDC,** http://links.lww.com/TP/C486). Based on the dichotomous data collected, we found that transplant patients aged ≥60 y were more likely to have a negative response (OR, 1.58;

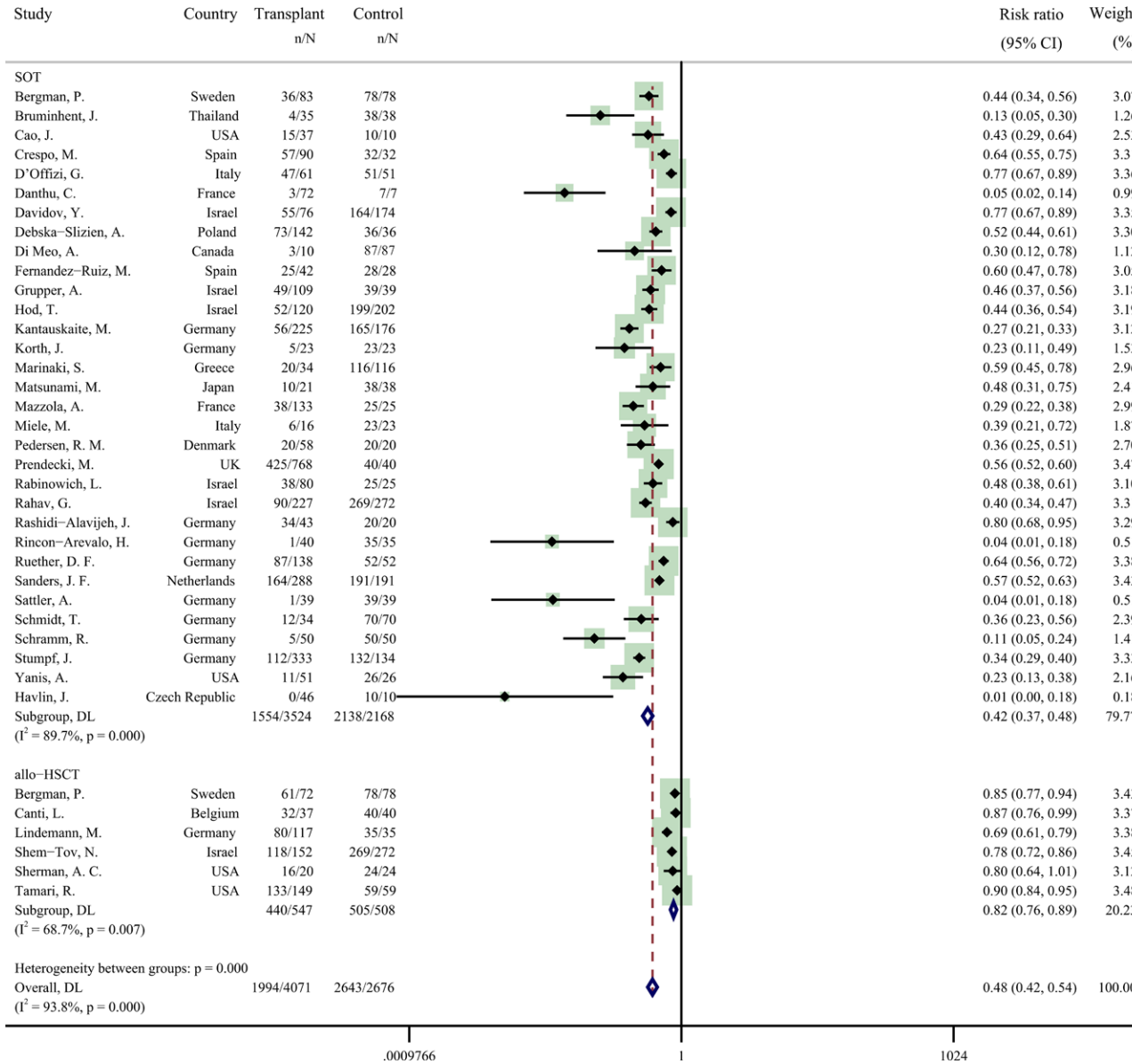

FIGURE 2. Comparing the rates of humoral response to COVID-19 vaccines between transplant recipients and healthy controls. Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells. allo-HSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; COVID-19, coronavirus disease 2019; DL, DerSimonian-Laird; SOT, solid organ transplantation.

95% CI, 1.26-1.98) (**Figure 3A and S15, SDC,** http://links.lww.com/TP/C486). Similarly, on the basis of continuous data collected, the mean age of nonresponders among vaccinated transplant recipients is significantly greater than that of responders (WMD, 4.39; 95% CI, 3.12-5.67) (**Figure 3B and S21, SDC,** http://links.lww.com/TP/C486). Neither mRNA vaccine showed a negative effect on the seroconversion of transplant recipients (**Figure S16, SDC,** http://links.lww.com/TP/C486).

The use of different immunosuppressive medications appears to have a distinct and also a profound impact on the COVID-19 vaccine response. Calcineurin inhibitors (CNI) (OR, 1.60; 95% CI, 1.14-2.24), steroids (OR, 2.13; 95% CI, 1.53-2.96), mycophenolic acid (MPA) and its derivatives (OR, 5.38; 95% CI, 3.76-7.70) were correlated with failure of humoral response, whereas azathioprine (OR, 0.25; 95% CI, 0.15-0.42) and mammalian target of rapamycin (mTOR) inhibitors (OR, 0.62; 95% CI, 0.42-0.93) appear to be associated with favorable response (**Figure 3A and S8–S13, SDC,** http://links.lww.com/TP/C486). Transplant patients with comorbidities, such as diabetes mellitus (OR, 1.44; 95% CI, 1.20-1.73) and hypertension (OR, 1.80; 95% CI, 1.34-2.41), were less likely to have humoral immunity to the vaccines (**Figure 3A and S17, SDC,** http://links.lww.com/TP/C486). Different types of donors, such as living, deceased, and matched unrelated donors (only allo-HSCT population), appear to have no significant impact on the humoral response, and similar results were observed in allo-HSCT recipients with or without graft versus host disease (**Figure 3A and S18–S20, SDC,** http://links.lww.com/TP/C486).

The interval from the time of transplantation to receiving the vaccine was related to vaccine response. As shown in **Figure 3B and S22, SDC,** http://links.lww.com/TP/C486

TABLE 1.

Seroconversion rates of transplant populations completed 3 doses of COVID-19 vaccination

		Before 3rd dose, n			After 3rd dose, n			
Study	Transplant type	Positive	Total	Seroconversion rate (95% CI)	Positive	Total	Seroconversion rate (95% CI)	*P* Value
Transplant populations with data before and after 3rd vaccine dose								
Bertrand et al[14]	Kidney	30	80	38% (27%-48%)	49	80	61% (51%-72%)	
Del Bello et al[15]	SOT	164	396	41% (37%-46%)	269	396	68% (63%-73%)	
Maillard et al	allo-HSCT	538	687	78% (75%-81%)	138	181	76% (70%-82%)	
Marlet et al	Kidney	42	97	43% (33%-53%)	75	160	47% (39%-55%)	
Massa et al	Kidney	27	61	44% (32%-57%)	38	61	62% (50%-74%)	
Masset et al	Kidney	227	456	50% (45%-54%)	94	136	69% (61%-77%)	
Peled et al[16]	Heart	26	96	27% (18%-36%)	64	96	67% (57%-76%)	
Stumpf et al	Kidney	23	68	34% (23%-45%)	9	35	26% (11%-40%)	
Werbel et al	SOT	5	30	17% (3%-30%)	14	30	47% (29%-65%)	
Overall				42% (27%-56%)			59% (51%-68%)	$P < 0.05$
Transplant populations without seroconversion after 2nd vaccine dose								
Benotmane et al	Kidney	0	159	0	78	159	49% (41%-57%)	
Redjoul et al	allo-HSCT	0	42	0	20	42	48% (33%-63%)	
Reindl-Schwaighofer et al	Kidney	0	196	0	76	196	39% (32%-46%)	
Schrezenmeier et al	Kidney	0	24	0	9	24	38% (18%-57%)	
Westhoff et al	Kidney	0	10	0	6	10	60% (30%-90%)	
Overall							44% (39%-48%)	
Only data of 3rd vaccination								
Kamar et al	SOT	NA	NA	NA	578	872	66.3%	

allo-HSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; NA, not applicable; SOT, solid organ transplantation.

the mean of this time interval in nonresponders is smaller than that in responders (WMD −1.40; 95% CI, −2.45 to −0.35). Among the laboratory tests, the mean value of estimated glomerular filtration rate was significantly lower in nonresponders than in responders, whereas the means of serum creatinine, counts of white blood cells, and lymphocytes were not statistically different (**Figure 3B and S24–S27, SDC,** http://links.lww.com/TP/C486). Similar results were observed when analyzing risk factors impeding seroconversion in SOT recipients only (**Figure S28, SDC,** http://links.lww.com/TP/C486).

DISCUSSION

In this systematic review and meta-analysis, we first comprehensively assessed the serological response of COVID-19 vaccines in transplant recipients, both SOT and allo-HSCT patients. In line with overwhelming evidence, we found the response to COVID-19 vaccines in transplant recipients was dramatically attenuated. Here, we quantified that only about half of the transplant recipients developed positive humoral immunity to the 2-dose COVID-19 vaccine, compared with nearly 100% positive rate in the general population. Similarly, a recently published systematic review and meta-analysis also reported a significantly lower likelihood of seroconversion in SOT recipients than in the general population.[8,9] Interestingly, we found that the rate of seroconversion in SOT recipients was significantly lower than that of allo-HSCT recipients, but the underlying mechanisms remain to be further explored. Different types of SOT appear to have slightly different rates of seroconversion with the highest rate in liver transplant recipients, which is consistent with a recently published meta-analysis.[10]

Our analysis was primarily based on the positive rate of seroconversion after vaccination. We did not analyze the levels of anti–SARS-CoV-2 antibodies or neutralizing antibodies. Different studies use different methods for antibody detection and quantification. However, all the included studies have used the US Food and Drug Administration–authorized serology test kits with high sensitivity.[11] Comparative analysis of 3 different methods yielded sensitivities ranging from 98% to 100% among healthcare workers.[12] In transplant recipients, we did not observe clear differences in seroconversion rates with the different assays. Overall, our findings and the literature collectively suggest lower levels of anti–SARS-CoV-2 antibody titers in transplant recipients as compared with the healthy population following vaccination.

The third dose of the COVID-19 vaccine has been rolled out in several countries as a booster dose to consolidate protection against SARS-COV-2 infection. In August 2021, the US Food and Drug Administration issued an emergency use authorization for the third dose of the mRNA-based vaccine for immunocompromised patients, including SOT recipients.[13] Some studies including meta-analysis have shown that the third dose increases the antibody-positive rate in transplant patients.[14-16] The total number of published studies on the third-dose vaccination, however, remains limited and their study designs vary widely hampering meaningful analysis. For example, in 5 of 15 included studies, the third dose was administered only in transplant populations with no seroconversion after 2 doses of vaccine, which were more likely to be nonresponders. There are 9 studies, which compared

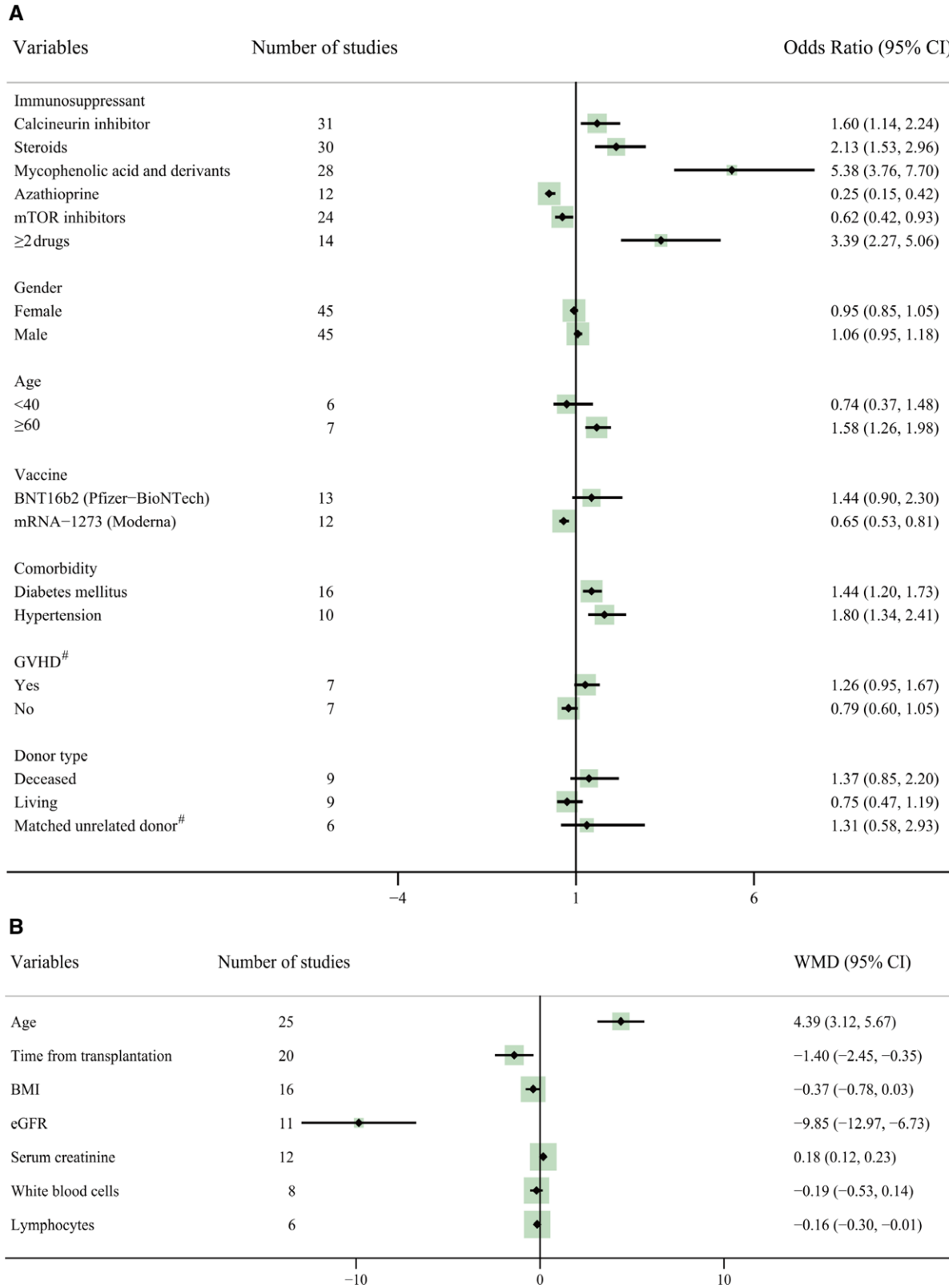

FIGURE 3. Risk factors of failure in humoral response to COVID-19 vaccines in transplant recipients. (A) Dichotomous data; (B) Continuous data. #Only studies describing allo-HSCT populations. BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; eGFR, estimate glomerular filtration rate; GVHD, graft vs host disease; mTOR, mammalian target of rapamycin; WMD, weighted mean difference.

the seroconversion rates before and after the third dose in transplant recipients, and these studies show significant increases in response rates following administration of a third dose. Although it remains difficult to accurately estimate the beneficial effects of a third dose based on currently available data, our findings support booster vaccination for better protection of this vulnerable population from COVID-19.

The key factor of attenuated immune response to the COVID-19 vaccine in the transplant population is inevitably attributed to the universal use of immunosuppressive medications.[17,18] This is in line with our findings that the use of immunosuppressive medication is the most prominent risk factor associated with failure in response to the COVID-19 vaccine. Intriguingly, different types of immunosuppressants appear to have a distinct impact. Similar results were reported in transplant recipients receiving influenza vaccination, with mycophenolate mofetil (MMF) having the most significant negative effect on humoral response rate.[19] A systematic review and meta-analysis showed that the use of antimetabolites was a risk factor for poor antibody response.[8] In our study, we separated the different types of antimetabolites, azathioprine, and MPA/MMF. We found MPA/MMF but not azathioprine is associated with failure of seroconversion. Attributing a large number of included studies, we were also able to identify the use of CNI and steroids as risk factors. The large TRANSFORM Study has demonstrated a lower rate of viral infections in kidney transplant patients using everolimus.[20] In our study, mTOR inhibitors appear to be associated with a favorable effect on seroconversion after vaccination. This is consistent with the findings of the OPTIMIZE trial that the response rates of elderly kidney transplant recipients on the everolimus regimen were significantly higher than those with the standard immunosuppressive regimen after 2 and 3 doses of COVID-19 vaccines.[21]

A general assumption is that the level of immunosuppression irrespective of the types of immunosuppressants affects the response to the vaccine. An experimental study in mice found that immunosuppression reduced the antibody titers in serum and functional antibody response against SARS-CoV-2 spike protein and that temporarily halting immunosuppression improved antibody responses.[22] We were unable to perform a meta-analysis on the impact of immunosuppressant dosage because of the limited number of studies that documented this information. However, a few studies have found that transplant recipients with higher doses of tacrolimus,[23-25] MMF/MPA,[26,27] and steroids[24,28] had a significantly low probability of seroconversion, but another 2 studies found no significant differences.[29,30]

We postulate that the impact of immunosuppressive agents may be also related to their different mode-of-actions.[31] For instance, MPA reduces de novo guanosine nucleotide synthesis by selectively inhibiting the isoform 2 of inosine monophosphate dehydrogenase, mainly expressed by T and B cells.[32,33] CNI inhibits T-cell activation and proliferation, cytokine secretion, and antigen presentation.[34] Steroids function through inhibition of the expression of pro-inflammatory cytokines, reduction of leucocyte trafficking, and induction of T-cell apoptosis.[35] Rapamycin and everolimus target the phosphoinositide 3 kinase–protein kinase B–mTOR pathway to regulate cellular metabolism, growth, and proliferation.[36] We postulate that these immunosuppressants can differentially affect immune responses induced by COVID-19 vaccination, especially in the process of developing antibodies, but the exact mechanisms driving differential response following vaccination obviously require future research. Currently, clinical trials are being carried out in several countries to assess the immunogenicity in transplant recipients after modulation of immunosuppression (The Netherlands, NCT05030974; Israel, NCT04961229; Austria, NCT05338177; the United States, NCT05060991). The results from these trials are expected to help the design of specific immunosuppression protocols for achieving optimal response to vaccines in transplant patients in the near future.

The findings of this study bear essential implications for choosing the specific immunosuppressive medication for transplant patients, to achieve optimal COVID-19 vaccine response. However, these medications can also have other consequences in addition to vaccine response in the context of COVID-19. In hospitalized COVID-19 patients, the use of dexamethasone resulted in significantly lower mortality, which is mechanistically attributed to its anti-inflammatory effect.[37] In experimental models, MPA and ciclosporin have been shown to effectively inhibit SARS-CoV-2 infection in vitro.[38-40] Dexamethasone has been shown to slightly enhance SARS-CoV-2 replication in the lungs of Syrian hamsters.[41] Thus, the optimal choice of immunosuppressive medications for transplant patients amid the COVID-19 pandemic requires the integration of multidimensional evidence, which certainly requires more attention and further research.

Of note, there are some limitations to this study. First, the total number of studies on the allo-HSCT population was limited and the characteristic data were not extensive, which limited our analysis on risk factor identification. Second, there were only 2 studies on the third dose vaccination in allo-HSCT patients. Therefore, we cannot draw any conclusion regarding the response to the third dose in this population. Finally, the vast majority of included studies had participants vaccinated with the Pfizer mRNA vaccine, and there is very limited data on the use of other vaccines. Thus, we were not able to compare the response to different vaccines.

In conclusion, transplant patients compared with healthy populations had dramatically lower rates of humoral response to COVID-19 vaccines. A third dose booster in general further improves the responsiveness, but the response rates remain suboptimal. The use of immunosuppressive regimens is the most prominent risk factor associated with the failure of seroconversion, but interestingly different immunosuppressants have a differential impact in this respect. Furthermore, patients with advanced age, short time from transplantation, or comorbidities are also at higher risk of negative response. These findings are important for developing strategies to optimize COVID-19 vaccine response in transplant patients, and we call future research to better understand the underlying mechanisms of the risk factors affecting vaccine response.

REFERENCES

1. Dęborska-Materkowska D, Kamińska D. The immunology of SARS-CoV-2 infection and vaccines in solid organ transplant recipients. *Viruses*. 2021;13:1879.
2. Fung M, Babik JM. COVID-19 in immunocompromised hosts: what we know so far. *Clin Infect Dis*. 2021;72:340–350.
3. Bergman P, Blennow O, Hansson L, et al. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. *EBioMedicine*. 2021;74:103705.
4. Rahav G, Lustig Y, Lavee J, et al. BNT162b2 mRNA COVID-19 vaccination in immunocompromised patients: a prospective cohort study. *EClinicalMedicine*. 2021;41:101158.

5. Ruether DF, Schaub GM, Duengelhoef PM, et al. SARS-CoV2-specific humoral and T-cell immune response after second vaccination in liver cirrhosis and transplant patients. *Clin Gastroenterol Hepatol*. 2022;20:162–172.e9.
6. Schmidt T, Klemis V, Schub D, et al. Cellular immunity predominates over humoral immunity after homologous and heterologous mRNA and vector-based COVID-19 vaccine regimens in solid organ transplant recipients. *Am J Transplant*. 2021;21:3990–4002.
7. Lau J, Ioannidis JPA, Terrin N, et al. The case of the misleading funnel plot. *BMJ*. 2006;333:597–600.
8. 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:e226822.
9. Marra AR, Kobayashi T, Suzuki H, et al. Short-term effectiveness of COVID-19 vaccines in immunocompromised patients: a systematic literature review and meta-analysis. *J Infect*. 2022;84:297–310.
10. Lee A RYB, Wong SY, Chai LYA, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *BMJ*. 2022;376:e068632.
11. Food & Drug Administration. *EUA Authorized Serology Test Performance*. Available at https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance. Accessed December 3, 2021.
12. Di Meo A, Miller JJ, Fabros A, et al. Evaluation of three anti-SARS-CoV-2 serologic immunoassays for post-vaccine response. *J Appl Lab Med*. 2022;7:57–65.
13. Food & Drug Administration. *Coronavirus (COVID-19) Update: FDA Authorizes Additional Vaccine Dose for Certain Immunocompromised Individuals.* Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised. Accessed August 12, 2021.
14. Bertrand D, Hamzaoui M, Lemée V, et al. Antibody and T-cell response to a third dose of SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant recipients. *Kidney Int*. 2021;100:1337–1340.
15. Del Bello A, Abravanel F, Marion O, et al. Efficiency of a boost with a third dose of anti-SARS-CoV-2 messenger RNA-based vaccines in solid organ transplant recipients. *Am J Transplant*. 2022;22:322–323.
16. Peled Y, Ram E, Lavee J, et al. Third dose of the BNT162b2 vaccine in heart transplant recipients: immunogenicity and clinical experience. *J Heart Lung Transplant*. 2022;41:148–157.
17. Stock PG, Henrich TJ, Segev DL, et al. Interpreting and addressing suboptimal immune responses after COVID-19 vaccination in solid-organ transplant recipients. *J Clin Invest*. 2021;131:151178.
18. Giannella M, Pierrotti LC, Helanterä I, et al. SARS-CoV-2 vaccination in solid-organ transplant recipients: what the clinician needs to know. *Transpl Int*. 2021;34:1776–1788.
19. Karbasi-Afshar R, Izadi M, Fazel M, et al. Response of transplant recipients to influenza vaccination based on type of immunosuppression: a meta-analysis. *Saudi J Kidney Dis Transpl*. 2015;26:877–883.
20. Tedesco-Silva H, Pascual J, Viklicky O, et al; TRANSFORM Investigators. Safety of everolimus with reduced calcineurin inhibitor exposure in de novo kidney transplants: an analysis from the randomized TRANSFORM study. *Transplantation*. 2019;103:1953–1963.
21. de Boer SE, Berger SP, van Leer-Buter CC, et al. Enhanced humoral immune response after COVID-19 vaccination in elderly kidney transplant recipients on everolimus versus mycophenolate mofetil-containing immunosuppressive regimens. *Transplantation*. 2022;106:1615–1621.
22. Paschall AV, Ozdilek A, Briner SL, et al. Modulation of immunosuppressant drug treatment to improve SARS-CoV-2 vaccine efficacy in mice. *Vaccine*. 2022;40:854–861.
23. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients – a prospective cohort study. *Eur J Heart Fail*. 2021;23:1555–1559.
24. Cholankeril G, Al-Hillan A, Tarlow B, et al. Clinical factors associated with lack of serological response to SARS-CoV-2 messenger RNA vaccine in liver transplantation recipients. *Liver Transpl*. 2022;28:123–126.
25. Rozen-Zvi B, Yahav D, Agur T, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect*. 2021;27:1173.e1–1173.e4.
26. Hod T, Ben-David A, Olmer L, et al. Humoral response of renal transplant recipients to the BNT162b2 SARS-CoV-2 mRNA vaccine using both RBD IgG and neutralizing antibodies. *Transplantation*. 2021;105:e234–e243.
27. Hall VG, Ferreira VH, Ierullo M, et al. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. *Am J Transplant*. 2021;21:3980–3989.
28. Grupper A, Rabinowich L, Schwartz D, et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant*. 2021;21:2719–2726.
29. Peled Y, Ram E, Lavee J, et al. BNT162b2 vaccination in heart transplant recipients: clinical experience and antibody response. *J Heart Lung Transplant*. 2021:40:759–762.
30. Shostak Y, Shafran N, Heching M, et al. Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine. *Lancet Respir Med*. 2021;9:e52–e53.
31. Pan Q, Tilanus HW, Metselaar HJ, et al. Virus-drug interactions–molecular insight into immunosuppression and HCV. *Nat Rev Gastroenterol Hepatol*. 2012;9:355–362.
32. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology*. 2000;47:85–118.
33. Eickenberg S, Mickholz E, Jung E, et al. Mycophenolic acid counteracts B cell proliferation and plasmablast formation in patients with systemic lupus erythematosus. *Arthritis Res Ther*. 2012;14:R110.
34. Zaza G, Leventhal J, Signorini L, et al. Effects of antirejection drugs on innate immune cells after kidney transplantation. *Front Immunol*. 2019;10:2978.
35. Lansbury L, Rodrigo C, Leonardi-Bee J, et al. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2019;2:CD010406.
36. Zhou X, Wang Y, Metselaar HJ, et al. Rapamycin and everolimus facilitate hepatitis E virus replication: revealing a basal defense mechanism of PI3K-PKB-mTOR pathway. *J Hepatol*. 2014;61:746–754.
37. Calzetta L, Aiello M, Frizzelli A, et al. Dexamethasone in patients hospitalized with COVID-19: whether, when and to whom. *J Clin Med*. 2021;10:1607.
38. Dittmar M, Lee JS, Whig K, et al. Drug repurposing screens reveal cell-type-specific entry pathways and FDA-approved drugs active against SARS-Cov-2. *Cell Rep*. 2021;35:108959.
39. Wan W, Zhu S, Li S, et al. High-throughput screening of an FDA-approved drug library identifies inhibitors against arenaviruses and SARS-CoV-2. *ACS Infect Dis*. 2021;7:1409–1422.
40. Han Y, Duan X, Yang L, et al. Identification of SARS-CoV-2 inhibitors using lung and colonic organoids. *Nature*. 2021;589:270–275.
41. Yuan L, Zhou M, Ma J, et al. Dexamethasone ameliorates severe pneumonia but slightly enhances viral replication in the lungs of SARS-CoV-2-infected Syrian hamsters. *Cell Mol Immunol*. 2022;19:290–292.