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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Humoral and cellular response of COVID-19 vaccine among solid organ transplant recipients: A systematic review and meta-analysis

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Abstract

Background: We aimed to analyze the humoral and cellular response to standard and booster (additional doses) COVID-19 vaccination in solid organ transplantation (SOT) and the risk factors involved for an impaired response.

Methods: We did a systematic review and meta-analysis of studies published up until January 11, 2022, that reported immunogenicity of COVID-19 vaccine among SOT. The study is registered with PROSPERO, number CRD42022300547.

Results: Of the 1527 studies, 112 studies, which involved 15391 SOT and 2844 healthy controls, were included. SOT showed a low humoral response (effect size [ES]: 0.44 [0.40–0.48]) in overall and in control studies (log-Odds-ratio [OR]: −4.46 [−8.10 to −2.35]). The humoral response was highest in liver (ES: 0.67 [0.61–0.74]) followed by heart (ES: 0.45 [0.32–0.59]), kidney (ES: 0.40 [0.36–0.45]), kidney-pancreas (ES: 0.33 [0.13–0.53]), and lung (0.27 [0.17–0.37]). The meta-analysis for standard and booster dose (ES: 0.43 [0.39–0.47] vs. 0.51 [0.43–0.54]) showed a marginal increase of 18% efficacy. SOT with prior infection had higher response (ES: 0.94 [0.92–0.96] vs. ES: 0.40 [0.39–0.41]; *p*-value < .01). The seroresponse with mRNA-12723 mRNA was highest 0.52 (0.40–0.64). Mycophenolic acid (OR: 1.42 [1.21–1.63]) and Belatacept (OR: 1.89 [1.3–2.49]) had highest risk for nonresponse. SOT had a parallelly decreased cellular response (ES: 0.42 [0.32–0.52]) in overall and control studies (OR: −3.12 [−0.4.12 to −2.13]).

Interpretation: Overall, SOT develops a suboptimal response compared to the general population. Immunosuppression including mycophenolic acid, belatacept, and tacrolimus is associated with decreased response. Booster doses increase the immune response, but further upgradation in vaccination strategy for SOT is required.

KEYWORDS
additional dose immunogenicity, booster, SARS-CoV-2 vaccine, solid organ transplantation

Abbreviations: CI, confidence interval; CNI, calineurin inhibitor; eGFR, glomerular filtration rate; ES, effect size; IQR, interquartile range; MMF, mycophenolic acid; mTOR, mammalian target of rapamycin; NOS, Newcastle-Ottawa scale; OR, log-odds ratio; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus; SOT, solid organ transplantation.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) vaccine is the prime arsenal for battling the ongoing COVID-19 pandemic because of the failure of definitive therapy.[1] Solid organ transplantation (SOT) population is among the most vulnerable groups for high morbidity and mortality in the pandemic.[2,3] To add to the burden, the vaccine response in SOT has not been encouraging. So far, all the large-scale randomized controlled trials[4,5] for various COVID-19 vaccines have excluded SOT. Hence, high-level evidence-based in this context is unavailable. With reports of higher breakthrough COVID-19 cases in SOT,[6,7] a timely and in-depth analysis of vaccine responsiveness becomes imperative. We hereby address this knowledge gap in this systematic review and metanalysis to address the immunogenicity (both cellular and humoral) of different COVID-19 vaccines among SOT. We also interrogated the risk factors for decreased responsiveness and measured the impact of booster dosing in SOT.

2 | MATERIALS AND METHODS

2.1 | Literature search strategy and eligibility criteria

This systematic review and meta-analysis was conducted and reported in accordance with the meta-analyses of observational studies in epidemiology checklist.[8] The study is registered with PROSPERO (registration number: CRD42022300547 on January 6, 2022), which is a validated and recognized database for meta-analysis. We have utilized search engines of PubMed, Google scholar, Medline, and World Health Organization (WHO) COVID-19 research portal with the data published between January 1, 2020 and January 11, 2022 (Table S1). The search included only studies in the English language. There were no other limits or filters. The primary search terms used were COVID, vaccine, transplant. The other search strings used in the search engine included SOT, kidney, lung, pancreas, lung, SARS-CoV-2 vaccine, COVID-19 vaccine, ChAdOx1 nCoV-19, Oxford–AstraZeneca, mRNA vaccines, BNT162b2, and mRNA-1273. We have not included the outcomes studied like immune response, antibody response, seroconversion, or immunogenicity as the MeSH term, to broaden the data retrieved and to avoid any missing report. Preprint materials were not included in this study. Other grey literature published as abstracts in journals and WHO portal for COVID-19 research were also excluded.

The inclusion criteria included studies with the population who had a history of any SOT and studied immunogenicity response (antibody and/or cellular) following a complete schedule of vaccination. The absence of a control group was not a criterion for exclusion. Exclusion criteria were the studies reporting reactogenicity only and studies with a single-dose immune response. The type of articles included was clinical trials, letters, and original articles with cases more than two. Systemic reviews, personal viewpoints, and editorials were excluded. The manual search was performed by two independent reviewers (S.C. and V.B.K.) to reduce bias and to retrieve data from drop-outs of the first search. The manual search was performed by both forward and backward snowballing methods. Two independent reviewers (H.R. and R.D.) independently assessed the validity of the titles, abstracts, and full texts of each publication.

2.2 | Outcome ascertainment and data extraction

The primary outcome was the immunogenicity response (humoral or cellular response measured separately) to the COVID-19 vaccine following complete vaccination among SOT. The antibody response was reported in the following sequence: antispike protein IgG, antireceptor-binding domain protein, or neutralization antibodies. Cellular response rates were analyzed for the available studies. The immunogenicity response was recorded as a binary outcome, and continuous outcomes were not studied, due to wide variability in cut-off titers for different tests performed. Thus, for seroresponse, we have recorded studies reporting a yes or no response, and the same procedure was applied for cell-mediated immunity. And also, we have not assessed quantitative values reported in the studies for humoral or cellular immunity. Two reviewers (H.S.M. and V.B.K.) were involved in the data extraction independently. We also extracted relevant variables, including the patient's age, sex, timing from transplantation to vaccination, type of vaccine, number of doses, time of testing from the last dose, history of prior COVID-19, immunosuppression regimen, and estimated glomerular filtration rate (eGFR) for assessing the risk factors for decreased immune response. We have excluded these variables from our analysis if the reporting is given in univariate or multivariate odds ratios. Any disagreements were resolved through consensus with a third author (S.C). The missing data were not traced to the concerned study investigators for additional information, as the data for primary outcomes of interest were reported in all the included studies. The other outcome was the immunogenicity rates of SOT compared with healthy controls.

2.3 | Quality of study assessment

The quality of the non-randomized controlled trial studies was assessed by two independent reviewers (V.B.K and H.R.) using the Newcastle-Ottawa scale (NOS), which is a widely accepted method of assessing the quality of evidence for observational studies.[9] This tool has a maximum of nine points in three major categories: quality of the selection, comparability, and the outcome of study participants. Studies that reported scores between 7 and 9 points were indicated as having low risk; 4 and 6 points as a moderate risk; and <4 points as high risk for bias. Any conflict in the quality check for a study was resolved from discussion with the third reviewer (RD) and finalized thence. We have not excluded any study based on the lower points in NOS detected.

2.4 | Statistical procedure

Data analysis for the meta-analysis was performed by H.S.M. through statistical software of STATA 16 (Stata Corp, College Station, Texas, USA). Double data checking was performed by the co-investigator (S.C.) before analysis. Categorical outcome was reported as frequencies, and percentages while continuous outcomes were reported as median, mean, standard deviation, interquartile range (IQR), and range as per the availability. To combine two means and standard deviation, decomposition was done and reported by Cochrane's formula.[10] Standard deviation was calculated by dividing IQR by 1.35 and range by 4. To perform meta-analyses of binomial data with no control group, metaprop commands, which is an extension of STATA, was used which allows computation of 95% confidence intervals (CIs) using the score statistic and the exact binomial method. To perform a meta-analysis of binary data with two groups (SOT and control) and continuous outcomes (eGFR and tacrolimus levels), we used the DerSimonian-Laird random effect model as the statistical method. The outcomes were reported as effect size, log odds ratio, and Hegde's g with an accompanying 95% CI. I^2 statistic was used to assess the heterogeneity of the pooled estimate, where a value above 0.5 indicated substantial heterogeneity. For exploring the potential source of heterogeneity in cellular response, we conducted several subgroup analyses for (1) standard or booster vaccination; (2) different vaccine responses. We computed separate effect sizes for humoral response in SOT for (1) organ wise immunogenicity response (2) prior or naïve SARS-CoV-2 infection (3) different vaccine response (4) standard or booster vaccination. We reported the effect sizes of pooled data for the aforementioned subgroups. We have also performed univariate random-effects meta-regression analysis with the use of the following study-level explanatory variables: median age, the number of males, and years of transplantation from vaccination. The rationale for selecting these continuous data variables is their attenuating effect on immune response with COVID-19 vaccine in majority of the studies. Data visualization for the outcomes was completed by forest plots and bubble plots. In the forest plots, the columns are added to show the exact number of cases with a response or no response. Publication bias was described with funnel plots and egger's test. Sensitivity analysis was done for humoral response studies by excluding small sample studies (defined as having cases less than 100 for this purpose). Sensitivity analysis for cellular response studies was done with studies including a sample size of 50 or more. A *p*-value of less than .05 was used as a measure of statistical significance.

3 | RESULTS

We identified 903 potentially eligible studies from PubMed, 80 potentially eligible studies from MEDLINE, 335 potentially eligible studies from Google scholar database, and 182 studies from WHO COVID-19 research database. The detailed search results are shown in Figure 1. The grey literature including preprint studies and conference abstracts were identified and excluded. After removing duplicate articles, a total of 1012 studies were screened. After the exclusion of irrelevant studies, including studies not addressing the outcome of interest and studies only reporting breakthrough cases, reactogenicity, and single dose-response, 112 studies were included in the meta-analysis. A total of 33 reports were excluded in the process. The details of excluded studies with explanatory reasons are summarized in Table S2.

Table S3 shows the baseline characteristics of the studies[11–122] included. For this meta-analysis, a total of 112 studies were finally included, which involved 15391 SOT and 2844 healthy controls. The bulk of the studies originated from European followed by American regions, while only three reports were published from the South-East Asian region. The median (IQR) age of the patients was 59 (55–62) years. There was a disproportionate sex distribution with 8949 (58.1%) males in the study. Table S4 depicts the vaccination strategies and outcomes of the studies. The vaccines reported were BNT162b2, mRNA-1723, ChAdOx1nCoV-19, and inactivated whole virus vaccine. Nineteen studies[17,21,29,30,42,56,59,68,70,76–78,86,90,97,107,113,119,120] have reported and discussed immunogenicity after a booster dose. The testing methods mostly involved anti-spike protein IgG and interferon-gamma release assay for T-cell response against SARS-CoV-2. There was a variation in the timing of response testing after the last dose.

Figure 2 shows the forest plot of humoral response with COVID-19 vaccine in SOT compared to healthy controls. SOT (log odds-ratio: −4.46 [−8.10 to −2.35]; I^2 = 38.43%) had lower chances of showing antibody response compared to controls, and also there was mild heterogeneity for the results. The forest plot of humoral response from all the studies is depicted in Figure S1, which yielded low pooled immunogenicity (ES: 0.44 [0.40–0.48]; I^2 = 95.92%). The forest plots for humoral response for individual organs are depicted in Figures S2–S4. Figure 3 shows the metanalysis assessing humoral response from pooled sample sizes. From 13450 organ transplant patients (kidney: 10588; liver: 1434; heart: 711; lung: 653 and pancreas: 94), the highest humoral response rate was reported for liver (ES: 0.67 [0.61–0.74]; I^2 = 97.42%) followed by heart (ES: 0.45 [0.32–0.59]; I^2 = 93.92%), kidney (ES: 0.40 [0.36–0.45]; I^2 = 95.7%), kidney-pancreas (ES: 0.33 [0.13–0.53]; I^2 = 81.76%), and lung (0.27 [0.17–0.37]; I^2 = 90.41%). The inter-organ difference in humoral response had statistically significant difference (p-value < .01). The meta-analysis for humoral response with neutralization antibodies only showed very less response (Figure S5).

Figure 3 also shows the meta-analysis for standard and booster dose (ES: 0.43 [0.39–0.47] vs. 0.51 [0.43–0.54]; I^2 = 70.6%) with pooled sample size of 15329 and 1693, respectively, was even though statistically significant, showed a nonsatisfactory increase of 18% with booster dose. On subgrouping the humoral response on the basis of prior COVID-19 infection, SOT with prior infection (ES: 0.94 [0.92–0.96] vs. ES: 0.40 [0.39–0.41]; p-value < .01) had exceptionally higher immune response compared to naïve in 2309 and 13430 cases, respectively. The response rate for mRNA-12723 mRNA, BNT162b2 vaccine, ChAdOx1 nCoV-19 vaccine, and inactivated whole-virus arranged in decreasing order of responsiveness was 0.52 (0.40–0.64), 0.43 (0.38–0.48), 0.36 (0.14–0.57), and 0.33 (0.20–0.46). We also computed the

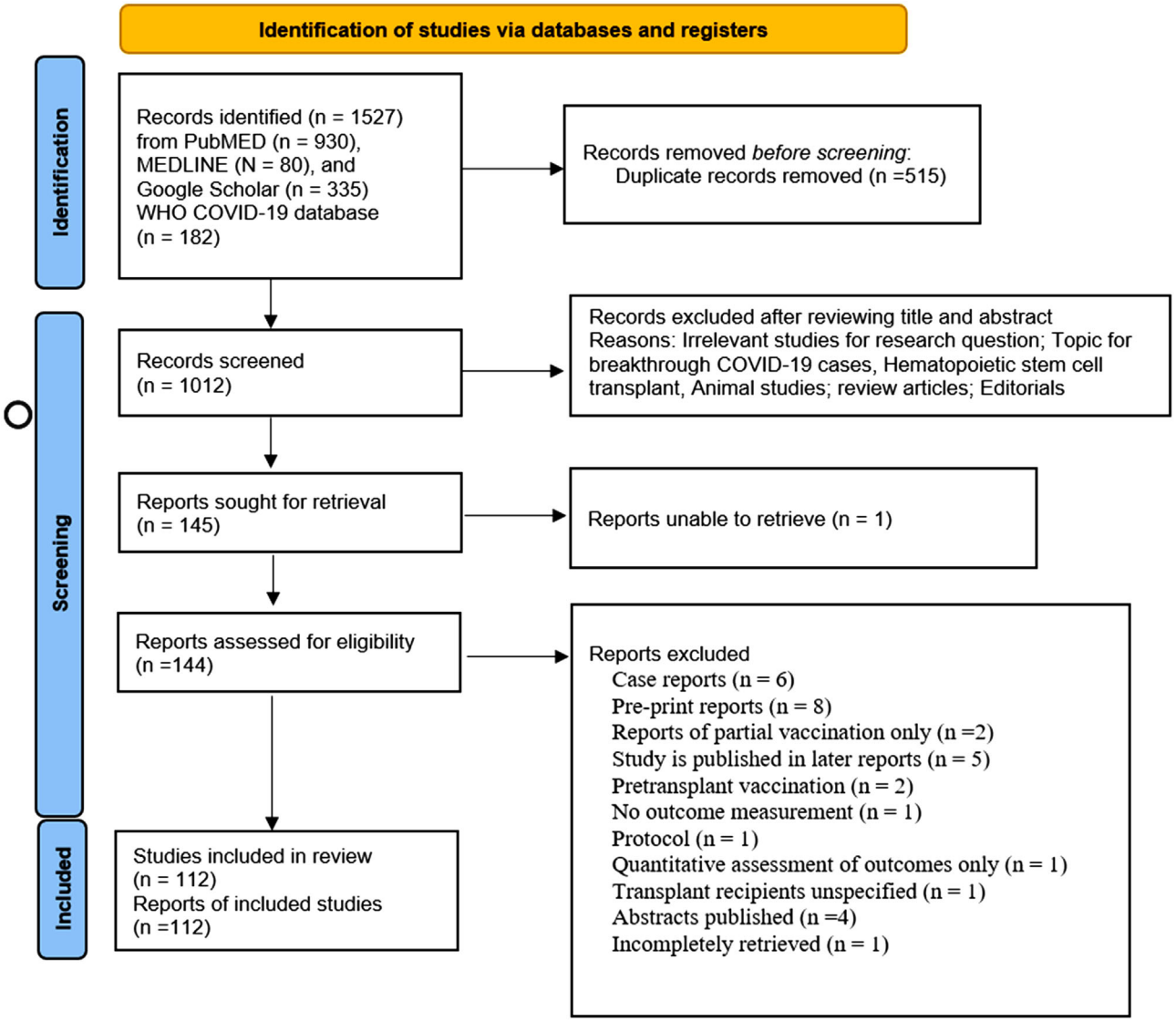

FIGURE 1 PRISMA 2020 flow diagram for the study. *From*: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

risk factors for decreased response. The use of calineurin inhibitor (CNI) (log OR = 0.02 [0.29–0.33]; I^2 = 52.66%) was associated with marginal increased risk of nonresponse (Figure S6). CNI trough levels (Hedges's g = 0.16 [−0.28 to 0.60]; I^2 = 91.59%) were not associated with higher risk of nonresponse (Figure S7). Mycophenolic acid (MMF) (log OR = 1.42 [1.21–1.63]; I^2 = 63.06%) was associated with higher risk for nonresponse (Figure 4). Belatacept (log OR = 1.89 [1.3–2.49]; I^2 = 0.00%) use had highest risk for nonresponse (Figure 5). The presence of triple immunosuppression (log OR = 1.17 [0.83–1.52]; I^2 = 63.34%) was associated with higher risk of nonresponse (Figure 5). The regimen with mammalian target of rapamycin (mTOR) inhibitors (log OR = −0.57 (−0.88 to −0.26); I^2 = 56.71%) had contrarily lower risk of nonresponse (Figure S8). Risk factors like history of recent antirejection therapy was also associated with decreased humoral response (Figure S10). The patients with lower eGFR (Hedges's g = −0.44 (−0.54 to 0.3 5); I^2 = 91.59%) had higher chances of nonresponse compared to a better eGFR (Figure S11).

Figure 6 shows the forest plot for cellular response with COVID-19 vaccine in SOT compared to healthy controls. The cellular response (log OR: −3.12 [−0.4.12 to −2.13] I^2 = 82.33%) was significantly lower compared to controls. All the studies with cellular response reported a lower response rate (ES: 0.42 [0.32–0.52]; I^2 = 96.8%) as shown in Figure S12. Subgroup analysis with standard and booster dosing showed no statistical difference (ES: 0.43 [0.33–0.54] vs. 0.32 [0.01–0.62]; *p*-value = .48) (Figure S13). Subgroup analysis with various types of vaccines including BNT162b2 (ES: 0.42 [0.26–0.57]) and mRNA-1273 (ES: 0.52 [0.32–0.71]) showed higher responsiveness in the latter, but there was no statistical difference between groups (Figure S14).

Study	Solid organ transplantation Seroresponse	Solid organ transplantation No response	Healthy controls Seroresponse	Healthy controls No response	Log odds ratio(95% CI)	% Weight
Affeldt et al,[11] 2021(Antibody)	34	52	27	0	-4.427(-7.257--1.598)	1.84
Ben-Dov IZ et al,[14] 2022	111	141	71	0	-5.201(-7.994--2.409)	1.88
Benning L et al,[16] 2021	41	94	134	0	-6.418(-9.218--3.617)	1.87
Bergman P et al,[19] 2021	38	51	90	0	-5.489(-8.3--2.679)	1.86
Bruminhent J et al,[25] 2021	3	32	38	0	-6.572(-9.572--3.573)	1.69
Cao J et al,[27] 2021	14	23	10	0	-3.527(-6.439--0.616)	1.77
Cassaniti I et al,[28] 2021	36	61	74	0	-5.526(-8.337--2.715)	1.86
Crespo M et al,[36] 2021	57	33	32	0	-3.634(-6.459--0.809)	1.85
Danthy C et al,[38] 2021	3	71	7	0	-5.725(-8.782--2.668)	1.64
Davido Y et al,[39] 2021	55	21	164	10	-1.834(-2.647--1.022)	5.96
Dębska-Ślizień A et al,[40] 2021	95	54	15	0	-2.873(-5.709--0.037)	1.84
Dębska-Ślizień A et al,[41] 2021	73	69	36	0	-4.235(-7.044--1.425)	1.86
D'Offizi G et al,[44] 2021	47	14	51	0	-3.448(-6.295--0.602)	1.83
Erol Ç et al,[49] 2021	35	13	56	0	-3.761(-6.614--0.907)	1.82
Fernández-Ruiz M et al,[50] 2021	13	29	28	0	-4.825(-7.694--1.956)	1.8
Firket L et al,[52] 2021	10	10	19	1	-2.944(-5.138--0.751)	2.63
Grupper A et al,[53] 2021(post-transplant)	49	60	39	0	-4.57(-7.385--1.756)	1.86
Grupper A et al,[54] 2021	51	85	25	0	-4.439(-7.259--1.619)	1.85
Havlin J et al,[60] 2021	28	51	10	0	-3.636(-6.51--0.763)	1.8
Hod T et al,[62] 2021	42	78	197	5	-4.293(-5.256--3.329)	5.51
Kantauskaite M et al,[67] 2021	56	169	165	11	-3.813(-4.494--3.132)	6.34
Karaba AH et al,[68] 2021	34	13	15	0	-2.496(-5.381-0.39)	1.79
Korth J et al,[69] 2021	5	18	23	0	-5.063(-8.022--2.105)	1.72
Kute V et al,[71] 2021	19	12	31	0	-3.698(-6.581--0.816)	1.79
Marinaki S et al,[73] 2021	20	14	116	0	-5.105(-7.963--2.247)	1.82
Matsunami M et al,[79] 2021	10	11	38	0	-4.435(-7.347--1.522)	1.76
Mazzola A et al,[80] 2021	38	95	25	0	-4.84(-7.664--2.017)	1.85
Miele M et al,[83] 2021	6	10	23	0	-4.33(-7.297--1.363)	1.71
Pedersen RM et al,[88] 2021	18	40	20	0	-4.497(-7.356--1.638)	1.81
Peled Y et al,[89] 2021	14	63	134	2	-5.709(-7.22--4.197)	3.99
Prieto J et al,[92] 2021	35	50	44	0	-4.841(-7.661--2.021)	1.85
Rabinowich L et al,[94] 2021	38	42	25	0	-4.031(-6.863--1.198)	1.84
Rahav G et al,[95] 2021	90	136	269	3	-4.909(-6.078--3.74)	4.91
Rashidi-Alavijeh J et al,[96] 2021	34	9	20	0	-2.424(-5.32-0.472)	1.78
Rincon-Arevalo H et al,[99] 2021	1	39	35	0	-7.534(-10.766--4.301)	1.5
Ruether DF et al,[101] 2021	89	49	52	0	-4.062(-6.868--1.255)	1.87
Sanders JF et al,[103] 2021	164	124	191	0	-5.669(-8.455--2.884)	1.89
Sattler A et al,[104] 2021	1	38	39	0	-7.615(-10.846--4.383)	1.5
Schmidt T et al,[105] 2021	12	22	70	0	-5.537(-8.403--2.67)	1.81
Schramm R et al,[106] 2021	5	45	50	0	-6.728(-9.651--3.805)	1.75
Seija M et al,[108] 2021	80	204	82	0	-6.038(-8.83--3.246)	1.88
Stumpf J et al,[112] 2021	140	193	132	2	-4.511(-5.924--3.097)	4.24
Wagner A et al,[118] 2021	14	8	26	0	-3.436(-6.359--0.513)	1.75
Yanis A et al,[121] 2021	11	40	26	0	-5.229(-8.103--2.356)	1.8
Overall					-4.464 (-4.907 - -4.022)	

Heterogeneity: $t^2 = 0.68$, $I^2 = 38.43\%$, $H^2 = 1.62$, $p = 0.01$

Random-effects DerSimonian-Laird model

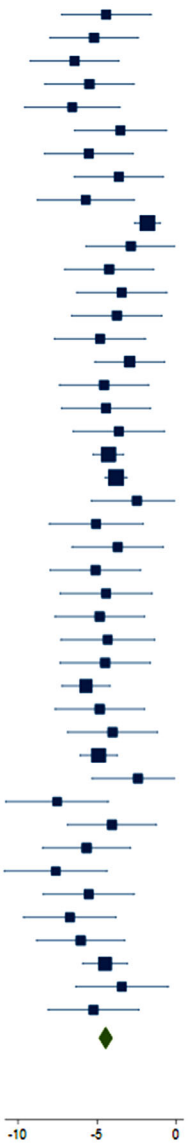

FIGURE 2 Humoral response in solid organ transplantation (SOT) compared to controls

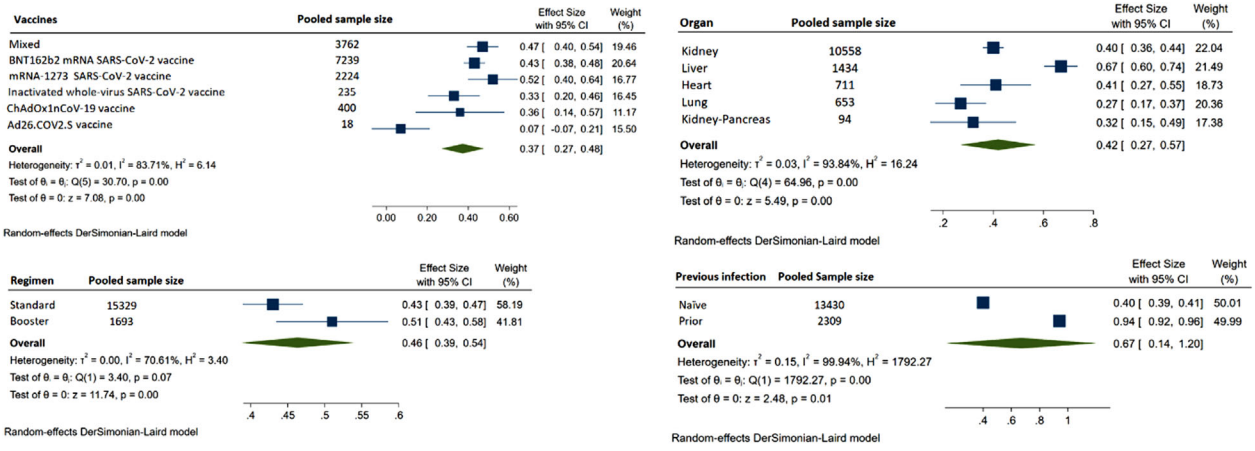

FIGURE 3 Detailed analysis of humoral response in solid organ transplantation (SOT)

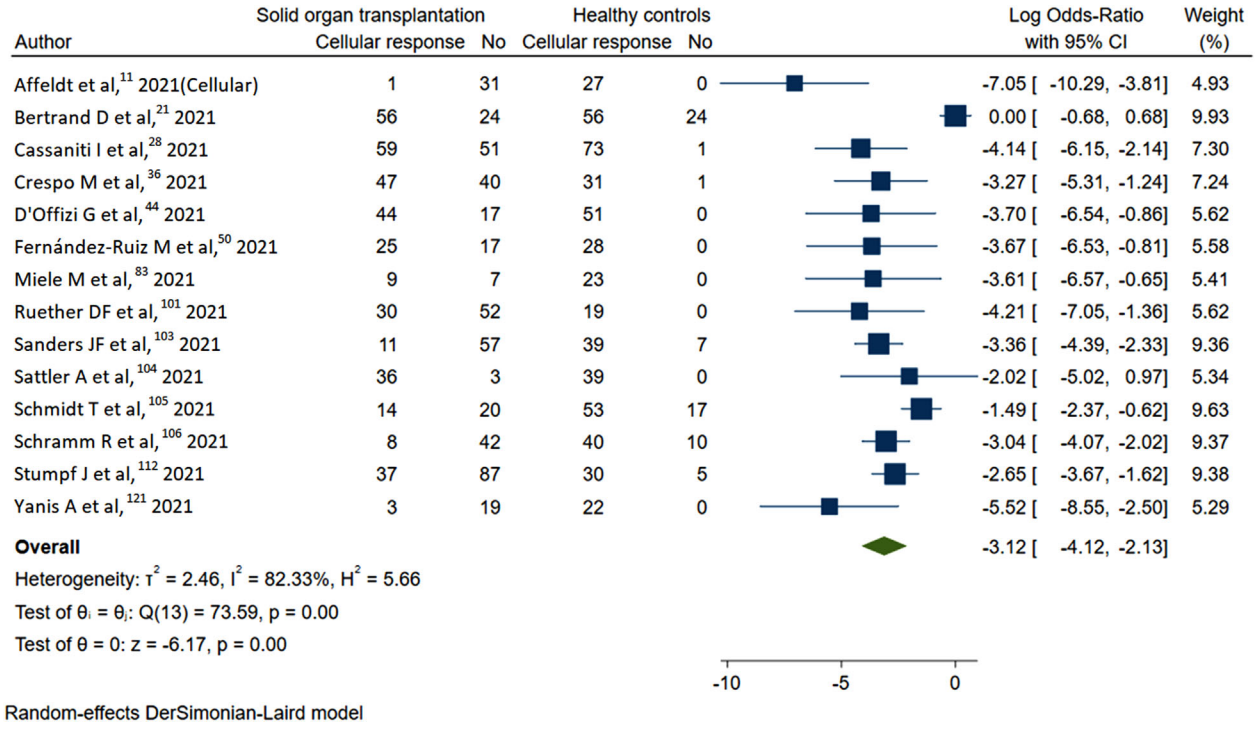

FIGURE 4 Humoral response with mycophenolic acid-based regimen in solid organ transplantation (SOT)

Figure S15 describes the bubble plot for meta-regression analysis. For overall studies assessing humoral response, meta regression analysis for male sex showed a regression coefficient of −0.0001 (95% CI: −0.0002 to 0.0005; *p*-value = .546) with I^2 = 95.6% and R^2 = 7.07%. Meta regression analysis for median age showed regression coefficient of −0.005 (95% CI: −0.008 to 0.001; *p*-value = .012) with I^2 = 96.03% and R^2 = 0.84%. Thus, increasing age was a factor for decreased humoral response. For overall studies with cellular response, male sex showed a coefficient of regression of −0.0008 (95% CI: −0.003 to 0.001); *p*-value = .36 with I^2 = 97.06% and R^2 = 0% in the meta regression analysis. For median age, the coefficient of regression reported was −0.001 (95% CI: −0.021 to 0.018); *p*-value = .84 with I^2 = 96.99% and R^2 = 0%. Thus, there was no impact in cellular response with age and sex as per the analysis. Time from transplantation was not assessed, as the data were unspecified for the concerned sample size. For humoral response, meta regression analysis for years since transplantation to vaccination showed a regression coefficient of 0.008 (95% CI: −0.0022 to 0.018; *p*-value = .127) with I^2 = 96.05% and R^2 = 3.41%. Thus, earlier period of transplantation showed a trend toward lower response, but the difference was not statistically significant. However, in meta-analysis performed with early versus later period of transplant (within 1 year in most studies), there was a significant no-seroresponse in early period of transplant (Figure S9).

Publication bias is demonstrated in Figure S16. The Egger test indicated that there was publication bias for humoral response in our meta-analysis, while no publication bias was detected for cellular response studies. A total of 13, 11, 17, 39, and 26 studies had NOS scores of 5, 6, 7, 8, and 9, respectively (Table S5). The results of the sensitivity analysis for humoral and cellular response are depicted in Figures S17 and S18, which were consistent with that of our primary analysis, hence confirming the robustness of our findings.

4 | DISCUSSION

This systematic review and meta-analysis has many highlights which are as follows: (1) The overall immunogenicity rate in the SOT was only 44% and 42% for both humoral and cellular response, respectively, which is strikingly lower compared to the general population. (2) The immunogenicity rates differ substantially with organs, where liver transplants had a relatively better response compared to kidney and heart. Lung transplant recipients had the lowest humoral response. (3) The booster dosing of vaccines does not induce a full response to vaccines in SOT. (4) SOT showed a comparatively higher response with mRNA-1273 compared to other vaccines. (5) Lower vaccine response was shown with triple-drugs, belatacept, and mycophenolic acid-based regimens. (6) The older age, low eGFR of the SOT is a risk factor for a decreased response, while an early period of transplantation and history of anti-rejection therapy, had a lower response.

Our analysis tested vaccine effectiveness but, protection from infection in the real world among SOT is limited. A recent study demonstrated inferior protection in SOT compared to the general population.[123] Furthermore, in real-world studies, the risk of acquiring post-vaccination COVID-19 was relatively lower with mRNA vaccines compared to the BNT162b2 vaccine[124] This stresses the choice of vaccine used in SOT, as our report also showed varying immunogenicity with different vaccines.

A

Study	No seroresponse Belatacept	No seroresponse non-Belatacept	Seroresponse Belatacept	Seroresponse non-Belatacept	Log Odds-Ratio with 95% CI	Weight (%)
Affeldt et al,11 2021(Antibody)	1	51	0	34	6.50 [-55.51, 68.51]	0.01
Benning L et al,16 2021	2	96	0	36	6.62 [-55.38, 68.62]	0.01
Benotmane I et al,18 2021	4	102	1	97	1.34 [-0.87, 3.54]	7.25
Bertrand D et al,20 2021	10	27	0	8	1.87 [-1.07, 4.81]	4.09
Bertrand D et al,21 2021	11	20	1	48	3.27 [1.16, 5.39]	7.92
Bertrand D et al,22 2021	46	124	2	63	2.46 [1.01, 3.91]	16.87
Chavarot N,30 2021	58	0	4	0	2.56 [-1.47, 6.60]	2.17
Danthy C et al, 38 2021	2	69	0	3	4.47 [-57.54, 66.47]	0.01
Del Bello A et al, 42 2021	17	110	8	261	1.62 [0.75, 2.49]	46.79
Ducloux D et al, 46 2021	4	68	0	81	8.47 [-53.52, 70.46]	0.01
Husain SA et al, 65 2021	6	19	0	7	7.70 [-54.29, 69.69]	0.01
Kantauskaite M et al, 67 2021	5	164	0	56	7.44 [-54.54, 69.43]	0.01
Korth J et al, 69 2021	1	17	0	5	7.99 [-188.02, 204.00]	0.00
Masset C et al, 77 2021(2-dose cohort)	9	220	2	225	1.53 [-0.02, 3.07]	14.84
Ou MT et al, 87 2021	18	0	1	0	-1.71 [-624.60, 621.17]	0.00
Westhoff TH et al, 120 2021	1	3	0	6	12.21 [-607.59, 632.01]	0.00
Yi SG et al et al, 122 2021	2	65	0	38	7.06 [-54.93, 69.06]	0.01
Overall					1.89 [1.30, 2.49]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\theta_i = \theta_j$: Q(16) = 3.37, p = 1.00

Test of $\theta = 0$: z = 6.23, p = 0.00

-500 0 500 1000

Random-effects DerSimonian-Laird model

B

Authors	No seroresponse Triple	No seroresponse non-Triple	Seroresponse Triple	Seroresponse non-Triple	Log Odds-Ratio with 95% CI	Weight (%)
Barrios Y et al,13 2021	4	1	10	10	1.39 [-0.97, 3.75]	1.73
Benotmane I et al,18 2021	46	60	18	80	1.23 [0.59, 1.87]	6.66
Boydarsky et al,23 2021 (Janssen)	6	4	0	2	1.98 [-1.29, 5.24]	1.00
Cholankeril G et al,32 2021	5	31	3	30	0.48 [-1.04, 1.99]	3.26
Danthy C et al, 38 2021	71	0	0	3	6.91 [2.84, 10.97]	0.67
Davido Y et al, 39 2021	2	19	2	53	1.03 [-1.00, 3.05]	2.18
Dębska-Ślizień A et al, 41 2021	57	12	46	27	1.03 [0.24, 1.81]	5.98
Del Bello A et al, 42 2021	102	25	185	84	0.62 [0.11, 1.12]	7.27
D'Offizi G et al, 44 2021	13	1	17	30	3.13 [1.01, 5.25]	2.05
Duni A et al, 47 2021	28	10	7	9	1.28 [0.06, 2.50]	4.16
Grupper A et al, 54 2021	73	12	34	17	1.11 [0.27, 1.96]	5.71
Hod T et al, 62 2021	48	30	19	23	0.66 [-0.10, 1.42]	6.09
Kantauskaite M et al, 67 2021	156	13	28	28	2.48 [1.71, 3.26]	6.04
Mazzola A et al, 80 2021	54	41	13	25	0.93 [0.15, 1.71]	5.98
Midtvedt K et al, 82 2021	99	17	6	19	2.91 [1.86, 3.97]	4.81
Peled Y et al, 89 2021	29	34	3	11	1.14 [-0.23, 2.51]	3.68
Peled Y et al, 90 2021	24	8	52	12	-0.37 [-1.38, 0.65]	4.95
Prendecki M et al, 91 2021(Humoral)	95	248	36	389	1.42 [1.01, 1.84]	7.66
Qin CX et al, 93 2021	5	7	6	27	1.17 [-0.28, 2.62]	3.44
Rabinowich L et al, 94 2021	9	33	11	27	-0.40 [-1.42, 0.62]	4.95
Russo G et al, 102 2021	33	6	26	17	1.28 [0.22, 2.34]	4.76
Seija M et al, 108 2021	167	37	48	32	1.10 [0.53, 1.67]	6.98
Westhoff TH et al, 120 2021	4	0	5	1	6.68 [-55.34, 68.71]	0.00
Overall					1.17 [0.83, 1.52]	

Heterogeneity: $\tau^2 = 0.36$, $I^2 = 63.34\%$, $H^2 = 2.73$

Test of $\theta_i = \theta_j$: Q(22) = 60.01, p = 0.00

Test of $\theta = 0$: z = 6.63, p = 0.00

-50 0 50 100

Random-effects DerSimonian-Laird model

FIGURE 5 Humoral response with belatacept and triple immunosuppression in solid organ transplantation (SOT)

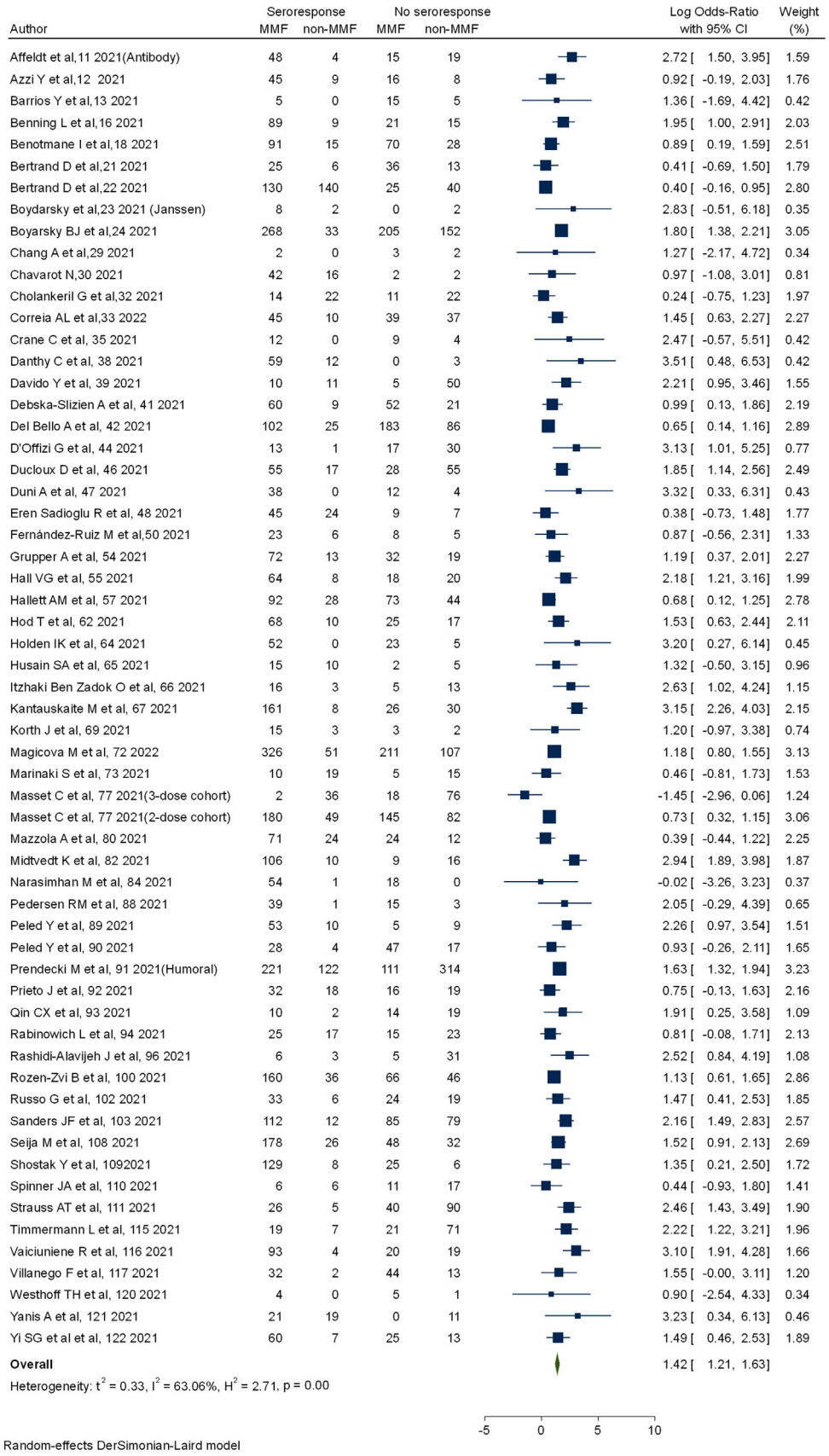

FIGURE 6 Cellular response in solid organ transplantation (SOT) compared to controls

Our report has analyzed humoral response with anti-Spike protein antibodies in the majority of the cases as most studies reported the same, but neutralization antibodies have shown high predictivity for protection from symptomatic COVID-19.[125] However, the protective levels of these antibodies in SOT would be debatable. In our systematic review, SOT has mounted further lower levels of neutralization antibodies (Figure S5) in comparison to spike protein. Thus, the seroprotection would be further diminished than the humoral response reported in our report.

The durability of vaccine effectiveness would be in focus in current practices. A recent meta-analysis[126] has shown a waning of antibody response within 6 months, which further raises an approach of regular booster for SOT. The inter-rim statement of WHO on December 22, 2021 stressed the potential utility of booster dosing in the omicron era. A few reports[127,128] measuring antibody titers following booster dose in SOT showed similar issues with fading of the immune response. Recent data[129] in the general population have confirmed that heterologous vaccine as the booster is inducing a stronger response. Our review had a few reports[78,97,107] with similar observations. The reports of inadequate response, even after vaccination with the third dose, lead to testing of the fourth dose in SOT. In the same context, a recent study[130] tested 18 SOT and showed a response of 28%, 67%, and 83% after the 2nd, 3rd, and 4th dose, respectively. The immune response to COVID-19 vaccine is proven dose-dependent in a recent study that showed higher dose elicits a better immune response in the general population.[131] All these reports open an area of research, which can be explored to increase the immunogenicity of the COVID-19 vaccine among SOT.

In our review, a study[53] reported a marked increase in immune response among pretransplant patients, which bolsters the rationale of immunizing candidates before transplantation. A recent meta-analysis[132] on hemodialysis patients showed around 80% immune response, which is double our report in SOT. This comparison further pushes the rationale to mandate vaccination before transplantation as a policy in transplantation practices.

Our analysis has shown considerably lower response with maintenance therapy of Belatacept and mycophenolic acid; however the rationale to modify these drugs to augment the immunogenicity is tricky and warrants a rigorous safety analysis.

The study has some inherent limitations. Firstly, the majority of the studies had around 4 weeks duration from the last vaccine dose to testing. Still, there was wide variation in the reports. Sero-responsiveness in the SOT host may relate to time from vaccination, and so if serologies were performed early after vaccination, they may be falsely negative. Secondly, there was a wide array of tests performed in different parts of the world to study immunogenicity, which is understandable in the unprecedented era of the pandemic. Thirdly, there could be an overlapping of cases from the same investigating centers, despite our efforts to exclusion of any such studies. Another limitation of our report is that the side effect profiles of vaccines and boosters are not studied, but the rationale was the extensive and ensuring safety reports for COVID-19 vaccines in the general population.[133] A recent study reporting reactogenicity of booster doses in SOT[134] also demonstrated the safety of vaccines, which further supported our exclusion. Also, the data for multiorgan transplant and non-mRNA-based vaccines were less reported, so the results regarding them would be inconclusive.

In a nutshell, our report focuses on continued research for developing a strategy for effective vaccination among SOT for future preparedness for the pandemic.

5 | CONCLUSION

This systematic review and meta-analysis found that patients with SOT had an immunogenicity rate of only around 40%, for both humoral and cellular response. The increase in immune response following a booster dose is important, and additional doses are the need of the hour in SOT. Immunosuppression like mycophenolic acid and belatacept has a significant impact on vaccine response. Immunizing SOT with higher efficacy vaccines, higher doses, heterologous booster doses, and regular dosing are important procedures that can increase the response. Further investigations and research are needed to implement modified vaccine protocols among SOT.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the conception, design of the work, acquisition, analysis, interpretation of data, drafting the work, revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work.

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DATA AVAILABILITY STATEMENT

The data used for meta-analysis will be made available upon request to the corresponding author.

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SUPPORTING INFORMATION

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