BRIEF COMMUNICATION

mTOR inhibitors, mycophenolates, and other immunosuppression regimens on antibody response to SARS-CoV-2 mRNA vaccines in solid organ transplant recipients

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A recent study concluded that SARS-CoV-2 mRNA vaccine responses were improved among transplant patients taking mTOR inhibitors (mTORi). This could have profound implications for vaccine strategies in transplant patients; however, limitations in the study design raise concerns about the conclusions. To address this issue more robustly, in a large cohort with appropriate adjustment for confounders, we conducted various regression- and machine learning-based analyses to compare antibody responses by immunosuppressive agents in a national cohort ($n = 1037$). MMF was associated with significantly lower odds of positive antibody response ($aOR = {}_{0.09}0.13_{0.18}$). Consistent with the recent mTORi study, the odds tended to be higher with mTORi ($aOR = {}_{1.00}1.45_{2.13}$); however, importantly, this seemingly protective tendency disappeared ($aOR = {}_{0.47}0.73_{1.12}$) after adjusting for MMF. We repeated this comparison by combinations of immunosuppression agents. Compared to MMF + tacrolimus, MMF-free regimens were associated with higher odds of positive antibody response ($aOR = {}_{2.39}4.26_{7.92}$ for mTORi+tacrolimus; ${}_{2.34}5.54_{15.32}$ for mTORi-only; and ${}_{6.78}10.25_{15.93}$ for tacrolimus-only), whereas MMF-including regimens were not, regardless of mTORi use ($aOR = {}_{0.81}1.54_{2.98}$ for MMF + mTORi; and ${}_{0.81}1.51_{2.87}$ for MMF-only). We repeated these analyses in an independent cohort ($n = 512$) and found similar results. Our study demonstrates that the recently reported findings were confounded by MMF, and that mTORi is not independently associated with improved vaccine responses.

KEYWORDS
clinical research/practice, immunosuppressant, immunosuppression/immune modulation, infection and infectious agents, infection and infectious agents—viral: SARS-CoV-2/COVID-19, infectious disease

1 | INTRODUCTION

Antibody responses after SARS-CoV-2 mRNA vaccines are substantially attenuated in organ transplant recipients.[1–6] The low vaccine efficacy in this population is primarily attributed to immunosuppression therapy.[2,7,8] Given that several regimens with various levels of potency are used for post-transplant immunosuppression,[9] understanding the impact of immunosuppressive regimens on the immunogenicity of SARS-CoV-2 mRNA vaccines could allow us to enhance vaccine efficacy via immunosuppression adjustments in this high-risk population.

Recently in the American Journal of Transplantation, Netti, and colleagues[10] concluded that mTOR inhibitors (mTORi) provided a beneficial role in mRNA vaccine-induced immunogenicity. However, there were a number of limitations in the design of this study, including[1]: the sample size was only 132, of whom only 28 received mTORi, which limits the ability to account for confounding, and[2] the comparison groups were mTORi-based regimens (where no patients received MMF) versus MMF-based regimens (where no patients received mTORi), thereby fully confounding any conclusions about mTORi by the well-documented negative effects of MMF. This issue needs to be clarified because of its potential profound implications on immunosuppression strategies in trying to improve vaccine responses in transplant patients.

In this study, we aimed to dissect the respective impacts of mTORi, MMF, and other immunosuppressive agents in the immunogenicity of SARS-CoV-2 mRNA vaccines using two independent cohorts of solid organ transplant recipients ($n = 1037$ and 512).

2 | METHODS

2.1 | Study population

We recruited a prospective cohort ("primary cohort") of solid organ transplant recipients with no known history of a positive PCR test for COVID-19 infection from across the United States through an online campaign. The participants reported two congruent SAR-CoV-2 mRNA vaccines, either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna), between December 16, 2020 and May 21, 2021, and were followed up until July 6, 2021. The study was approved by the Johns Hopkins Medical Institutional Review Boards.

This study also included an independent cohort ("secondary cohort") of solid organ transplant recipients at a tertiary transplant center who were vaccinated between January 4, 2021 and May 31, 2021. Those who were vaccinated prior to transplantation, had no medical records of vaccine type or antibody results after the second dose of vaccine, or history of a positive test for COVID-19 infection were excluded from this cohort. Data were collected with a waiver of informed consent approved by the Houston Methodist Research Institute IRB. De-identified data were shared between institutions after approval from both IRBs.

In both cohorts, we excluded those who used belatacept as belatacept use was rare and associated with a substantially lower chance of positive antibody response.[11] A comparison of these two cohorts is presented in Table 1.

2.2 | Antibody response

Antibodies were measured one month after the second dose (median [interquartile range]; 30 [28–33] days) via an electrochemiluminescence immunoassay for antibodies to SARS-CoV-2 spike protein receptor binding domain (Elecsys® Anti-SARS-CoV-2 S, Roche) or an enzyme-linked immunosorbent assay for antibodies to SARS-CoV-2 spike protein (S1 subunit) (EUROIMMUN Anti-SARS-CoV-2 ELISA IgG, EUROIUMMUN). We used the manufacturer-suggested thresholds (0.8 U/ml for Elecsys and ≤1.1 AU for EUROIMMUN) to determine positive antibody responses.

2.3 | Antibody response by immunosuppressive agents

We quantified the association between individual immunosuppressive agents with antibody response after adjusting for age, time since transplant, and vaccine type (mRNA-1273 vs. BNT162b2) using logistic regression. We conducted stepwise model building in which the immunosuppressive agents were gradually included in the model.

2.4 | Antibody response by immunosuppressive regimens

Post-transplant immunosuppression regimen is typically planned as combination therapy of multiple agents, resulting in a strong correlation between the use of each agent. To account for this correlation in a more clinically relevant and methodologically robust way, we repeated the comparison by regimens, that is, the combinations of the immunosuppressive agents. The cohort was divided into seven categories: single therapy (MMF only, mTORi only, and tacrolimus only), double therapy (MMF + tacrolimus, MMF + mTORi, and mTORi+tacrolimus), and others. We simply adjusted for steroids, rather than creating more categories by steroids because the association of steroids with antibody response was consistent even after adjusting for other agents in our previous analysis, implying minimal impacts from correlation (Table 2). A full analysis including steroids as a separate category is presented in the Appendix S1.

2.5 | Variable importance of immunosuppressive agents

We used gradient boosting, a general-purpose machine learning algorithm, to create a prediction model for positive antibody response

TABLE 1 Population characteristics

Characteristic	Primary cohort		Secondary cohort	
	Positive	Negative	Positive	Negative
	(n = 604)	(n = 433)	(n = 220)	(n = 292)
Age, year	59 (45, 68)	62 (47, 68)	62 (52, 69)	60 (51, 67)
Male sex	261 (43.6%)	176 (41.1%)	141 (64.1%)	166 (56.8%)
Non-White race	60 (10.0%)	43 (10.0%)	54 (24.5%)	73 (25.0%)
Organ(s) received				
Kidney	284 (47.0%)	273 (63.0%)	59 (26.8%)	124 (42.5%)
Liver	201 (33.3%)	39 (9.0%)	57 (25.9%)	58 (19.9%)
Pancreas	17 (2.8%)	25 (5.8%)	24 (10.9%)	26 (8.9%)
Heart	98 (16.2%)	56 (12.9%)	20 (9.1%)	24 (8.2%)
Lung	38 (6.3%)	71 (16.4%)	60 (27.3%)	60 (20.5%)
Time since transplant, year	9 (4, 16)	5 (2, 11)	3 (2, 8)	2 (1, 4)
Mycophenolates	260 (43.0%)	372 (85.9%)	134 (60.9%)	250 (85.6%)
Azathioprine	64 (10.6%)	11 (2.5%)	11 (5.0%)	6 (2.1%)
Tacrolimus	469 (77.6%)	380 (87.8%)	198 (90.0%)	266 (91.1%)
Steroids	283 (46.9%)	279 (64.4%)	179 (81.4%)	254 (87.0%)
mTOR inhibitors	105 (17.4%)	49 (11.3%)	66 (30.0%)	36 (12.3%)
Sirolimus	72 (11.9%)	37 (8.5%)	37 (16.8%)	21 (7.2%)
Everolimus	33 (5.5%)	12 (2.8%)	30 (13.6%)	15 (5.1%)
mRNA-1273 (vs. BNT162b2)	311 (51.5%)	167 (38.6%)	116 (52.7%)	113 (38.7%)

Note: This study was conducted in two independent cohorts of solid organ transplant recipients. The cohorts were stratified by antibody response to the two-dose SARS-CoV-2 mRNA vaccine series. Continuous variables are shown in median (interquartile range). Categorical variables are shown in *n* (%).

Abbreviation: mTORi, mammalian target of rapamycin inhibitors.

based on immunosuppressive agents and other clinical factors. During this procedure, the association of each immunosuppressive agent with a positive antibody response is characterized in a flexible and entirely data-driven manner. We then examined these associations using variable importance, a metric for assessing how much contribution each variable had made to the overall prediction ability of the machine learning model. Variables included in the models were immunosuppressive regimen use (MMF, mTORi, tacrolimus, steroids, and azathioprine), age, sex, race, organ(s) received (kidney, pancreas, liver, heart, and lung), time since transplant, number of transplants, and vaccine type (BNT162b2 vs. mRNA-1273).

2.6 | Sensitivity analysis

As antibody titer may wane over time after vaccination,[12] the time interval from vaccination to antibody testing may confound the association of immunosuppressive regimens with antibody response. To assess the impact of this potential confounding, we conducted sensitivity analyses where we repeated the analyses described above after including the time interval from vaccination to antibody testing as an additional covariable.

2.7 | Statistical analysis

We described the population characteristics using median [interquartile range] for continuous variables and *N* (%) for categorical variables. We used a significance level of 0.05 for all statistical testing. Confidence intervals are reported as per the method of Louis and Zeger.[13] All analyses were performed using R version 4.1.2.

3 | RESULTS

3.1 | Study population

The primary cohort included 1037 solid organ transplant recipients. Median (interquartile range) antibody titers were 4.63 (<0.4 to > 250) U/ml among 743 recipients with Elecsys and 1.56 (0.15–7.18) arbitrary units among 294 with EUROIMMUN (Figure S1). Using the manufacturer-suggested thresholds, 604 (58.2%) were classified as positive antibody responders. Compared to those with negative antibody responses, those with positive responses were more likely to have received mRNA-1273 (51.5% vs. 38.6%) and mTORi (17.4% vs. 11.3%), and less likely to be kidney transplant

TABLE 2 Association of individual immunosuppressive agents with positive antibody response to the two-dose SARS-CoV-2 mRNA vaccine series in two independent cohorts of solid organ transplant recipients

	MMF	mTORi	Tac	Steroids
Primary cohort (n = 1037)				
Model 1 (MMF only)	**0.13 (0.09–0.18)**			
Model 2 (mTORi only)		1.45 (1.00–2.13)		
Model 3 (Tac only)			0.70 (0.48–1.03)	
Model 4 (Steroids only)				**0.46 (0.35–0.60)**
Model 5 (MMF and mTORi)	**0.12 (0.09–0.17)**	0.73 (0.47–1.12)		
Model 6 (MMF, mTORi, and Tac)	**0.12 (0.08–0.16)**	**0.57 (0.35–0.92)**	**0.58 (0.36–0.92)**	
Model 7 (MMF, mTORi, and Steroids)	**0.12 (0.09–0.17)**	0.74 (0.48–1.14)		**0.48 (0.35–0.64)**
Model 8 (All four agents)	**0.12 (0.08–0.17)**	**0.58 (0.36–0.94)**	**0.58 (0.36–0.92)**	**0.47 (0.35–0.64)**
Secondary cohort (n = 512)				
Model 1 (MMF only)	**0.36 (0.23–0.57)**			
Model 2 (mTORi only)		**2.14 (1.33–3.50)**		
Model 3 (Tac only)			1.31 (0.68–2.57)	
Model 4 (Steroids only)				0.81 (0.49–1.35)
Model 5 (MMF and mTORi)	**0.41 (0.24–0.70)**	1.32 (0.74–2.35)		
Model 6 (MMF, mTORi, and Tac)	**0.41 (0.24–0.69)**	1.35 (0.75–2.39)	1.48 (0.76–2.97)	
Model 7 (MMF, mTORi, and Steroids)	**0.42 (0.24–0.70)**	1.32 (0.74–2.34)		0.87 (0.52–1.45)
Model 8 (All four agents)	**0.41 (0.24–0.70)**	1.34 (0.75–2.38)	1.47 (0.75–2.95)	0.88 (0.52–1.47)

Note: Estimates represent the adjusted odds ratio (95% confidence interval). Boldface indicates statistical significance. All models included age, time since transplant, and vaccine type (mRNA-1273 vs. BNT162b2) for covariable adjustments. Models 1–4 included each of the immunosuppressive regimens. Model 5 included MMF and mTORi in a bivariate manner. Model 6 included all four immunosuppressive regimens.
Abbreviations: MMF, mycophenolates; mTORi, mammalian target of rapamycin inhibitors; Tac, tacrolimus.

recipients (47.0% vs. 63.0%) or have received MMF (43.0% vs. 85.9%). Other characteristics were generally similar between the two groups (Table 1).

The secondary cohort included 512 recipients. Of those, 220 (43.0%) showed positive antibody responses. Compared to those with negative antibody responses, those with positive responses were more likely to have received mRNA-1273 (52.7% vs. 38.7%) and mTORi (30.0% vs. 12.3%), and less likely to be kidney transplant recipients (26.8% vs. 42.5%) or have received MMF (60.9% vs. 85.6%). Other characteristics were similar between the two groups (Table 1).

3.2 | Antibody response by immunosuppressive agents

When each immunosuppressive agent was modeled separately (Table 2; Model 1–4), MMF (aOR = $_{0.09}0.13_{0.18}$) and steroids (aOR = $_{0.35}0.46_{0.60}$) were significantly associated with lower odds of positive antibody response. On the contrary, mTORI showed a tendency toward higher odds of positive antibody response (aOR = $_{1.00}1.45_{2.13}$), although this tendency did not reach statistical significance. Nonetheless, this potentially protective tendency disappeared after adjusting for MMF (Model 5); in this bivariate approach, mTORi showed a tendency toward lower odds of positive antibody response (aOR = $_{0.47}0.73_{1.12}$) while MMF maintained

a significant association with lower odds of positive antibody response (aOR = $_{0.09}0.12_{0.17}$). We observed similar associations after adding tacrolimus and steroids to the model (Model 6–8). Similar results were observed in a sensitivity analysis that was restricted to kidney transplant recipients (Table S1).

This analysis yielded similar results when repeated in the secondary cohort (Table 2). We observed a statistically significant association of mTORi with higher odds of positive antibody response (aOR = $_{1.33}2.14_{3.50}$) when mTORi was examined by itself (Model 2). However, this association was attenuated and no longer statistically significant after adjusting for MMF (Model 5) and other agents (Model 6–8).

3.3 | Antibody response by immunosuppressive regimens

The crude rate of positive antibody response tended to be higher in MMF-free regimens, including the mTORi only (83.3%), tacrolimus only (87.1%), and mTORi+tacrolimus (73.1%) groups, compared to MMF-including regimens, including the MMF only (58.5%), MMF+tacrolimus (38.4%), and MMF+mTORi (55.6%) groups (Table 3).

Our logistic regression showed similar trends. The MMF+tacrolimus group was the most common regimen (n = 528; 50.9%) and therefore used as the reference group. Compared to the MMF+tacrolimus group, the mTORi only (aOR = $_{2.34}5.54_{15.32}$), tacrolimus only

TABLE 3 Association of immunosuppressive regimens with positive antibody response to the two-dose SARS-CoV-2 mRNA vaccine series in two independent cohorts of solid organ transplant recipients

Category	Positive/total	(%)	aOR (95% CI)
Primary cohort (n = 1037)			
MMF only	31/53	(58.5%)	1.51 (0.81–2.87)
mTORi only	30/36	(83.3%)	**5.54 (2.34–15.32)**
Tac only	216/248	(87.1%)	**10.25 (6.78–15.93)**
MMF + Tac	203/528	(38.4%)	Ref
MMF + mTORi	25/45	(55.6%)	1.54 (0.81–2.98)
mTORi + Tac	49/67	(73.1%)	**4.26 (2.39–7.92)**
Others	50/60	(83.3%)	**5.16 (2.52–11.46)**
Secondary cohort (n = 512)			
MMF only	7/24	(29.2%)	0.57 (0.20–1.46)
mTORi only	6/9	(66.7%)	1.83 (0.44–9.23)
Tac only	31/46	(67.4%)	**3.18 (1.60–6.54)**
MMF + Tac	111/332	(33.4%)	Ref
MMF + mTORi	4/7	(57.1%)	0.80 (0.13–4.89)
mTORi + Tac	44/65	(67.7%)	**2.59 (1.43–4.80)**
Others	17/29	(58.6%)	**3.27 (1.46–7.58)**

Note: Boldface indicates statistical significance. All models included age, time since transplant, vaccine type (mRNA-1273 vs. BNT162b2), and steroid use for covariable adjustments.

Abbreviations: MMF, mycophenolates; mTORi, mammalian target of rapamycin inhibitors; and Tac, tacrolimus.

(aOR = $_{6.78}10.25_{15.93}$), and mTORi + tacrolimus (aOR = $_{2.39}4.26_{7.92}$) groups showed significantly higher odds of positive antibody response, whereas the MMF only (aOR = $_{0.81}1.51_{2.87}$) and MMF + mTORi (aOR = $_{0.81}1.54_{2.98}$) groups did not. We observed similar findings in the secondary cohort (Table 3) and in a sensitivity analysis that was restricted to kidney transplant recipients (Table S2). Lastly, we found congruent results in a full analysis that included steroids as a separate category (Table S3).

3.4 | Variable importance of immunosuppressive agents

MMF showed the highest variable importance (37.4%) among all variables that were used in the machine learning model to predict antibody response in the primary cohort. Steroids (2.8%), tacrolimus (1.2%), and mTORi (0.7%) contributed to much smaller extents to the prediction model.

3.5 | Sensitivity analysis

The time interval from vaccination to antibody testing was similar between those with positive and negative responses (median [interquartile range]; 30 [28–33] vs. 30 [28–32]), likely because the testing was conducted per protocol at one month after vaccination. Accordingly, the results largely remained the same after adding the time interval as a new covariable (Tables S4 and S5).

4 | DISCUSSION

In this analysis of 1549 solid organ transplant recipients, MMF showed a strong association with lower odds of positive antibody response after SARS-CoV-2 mRNA vaccines, which far outweighed the association of mTORi or other immunosuppressive agents with antibody response. While mTORi showed a tendency toward higher odds of positive antibody response (aOR = 1.45), this protective tendency disappeared after adjusting for MMF (aOR = 0.73). When compared by regimens (i.e., combinations of the agents), MMF-free regimens were associated with higher odds of positive antibody response, whereas MMF-including regimens were not, regardless of mTORi use. Lastly, MMF accounted for 37.4% of a machine learning model's ability to predict antibody response, whereas no other immunosuppressive agents did for >3%. Our findings demonstrate that MMF avoidance, but not mTORi use, is independently associated with improved antibody responses to SARS-CoV-2 mRNA vaccines in transplant recipients.

Netti and colleagues[10] recently concluded that mTORi was associated with improved antibody responses to BNT16b2. In this study, the authors compared 28 kidney transplant recipients who received everolimus + tacrolimus + prednisolon to 108 kidney transplant recipients who received MMF + tacrolimus + prednisolon and observed that the everolimus group was associated with a positive antibody response compared to the MMF group (e.g., aHR = $_{1.531}4.254_{11.816}$). Based on these findings, the authors concluded that their result "underlines the potential beneficial role of mTOR inhibitors to enhance the immunogenicity of mRNA BNT162b2 vaccine in kidney transplant recipients".

On the one hand, our findings are highly congruent with those of Netti and colleagues.[10] In our study, the recipients who received mTORi+tacrolimus had significantly higher odds of positive antibody response compared to the recipients who received MMF + tacrolimus (Table 3; aOR = $_{2.39}4.26_{7.92}$). However, more importantly, we also found that[1] the beneficial association of mTORi with antibody responses disappeared after adjusting for MMF,[2] MMF-free regimens showed superior antibody responses to MMF-including regimens regardless of mTORi use, and[3] MMF had substantially greater variable importance than mTORi or any other agents had in a machine learning-based prediction model. These results were replicated in an independent secondary cohort. Our findings support that MMF avoidance, rather than mTORi use, would have been the primary factor that led to Netti and colleague's results.

Due to the observational design of this study, the associations observed in our study do not warrant causal effects. Clinical factors that influence both the exposure (the selection of immunosuppressive regimen) and the outcome (vaccine efficacy) might have confounded the associations observed in our study. To mitigate this concern, we adjusted for age, time since transplant, and vaccine type, which were the major risk factors for negative antibody response.

In conclusion, our three analytical approaches to two independent cohorts of 1549 solid organ transplant recipients have consistently indicated that MMF avoidance, rather than mTORi use, would be the key determinant of the immunogenicity of SARS-CoV-2 mRNA vaccines in this population. As sustaining sufficiently high antibody titer is a central part of protection against SARS-CoV-2 and its variants, continued research on this topic is warranted.

DISCLOSURE
The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. D.L.S. has received consulting and speaking honoraria from Sanofi, Novartis, CLS Behring, Jazz Pharmaceuticals, Veloxis, Mallinckrodt, and Thermo Fisher Scientific. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.