



Brief Communication

Morning administration enhances humoral response to SARS-CoV-2 vaccination in kidney transplant recipients



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ABSTRACT

Although severe acute respiratory syndrome coronavirus 2 messenger ribonucleic acid (SARS-CoV-2 mRNA) vaccines are effective in kidney transplant recipients (KTRs), their immune response to vaccination is blunted by immunosuppression. Other tools enhancing vaccination response are therefore needed. Interestingly, aligning vaccine administration with circadian rhythms (chronovaccination) has been shown to boost immune response. However, its applicability in KTRs, whose circadian rhythms are likely disrupted by immunosuppressants, remains unclear. To assess the impact of vaccination timing on seroconversion in the KTRs population, we analyzed data from 553 virus-naïve KTRs who received 2 doses of messenger ribonucleic acid (mRNA) vaccine. Bayesian logistic regression was employed, adjusting for previously identified predictors of seroconversion, including allograft function, maintenance immunosuppressants, or time since transplantation. SARS-CoV-2 immunoglobulin G (IgG) levels were measured with a median of 47 days after the second dose. The results did not reveal a reliable effect of timing of the first dose but did indicate that earlier timing for the second dose brings a notable benefit—every 1-hour delay in the application was associated with a 16% reduction in the odds of seroconversion (OR 0.84, 95% CI 0.71, 0.998). Similar results were obtained from quantile regression modeling IgG levels. In conclusion, morning vaccination is emerging as a promising and easily implementable strategy to enhance vaccine response in KTRs.

Abbreviations: CI, credible interval; COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; KTRs, kidney transplant recipients; mRNA, messenger ribonucleic acid; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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1. Introduction

Coronavirus disease 2019 (COVID-19) proved to be especially harmful to vulnerable patient groups, including kidney transplant recipients (KTRs).¹ Emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines notably broadened our ability to battle the infection.² However, it soon became clear that although COVID-19 vaccines are effective in KTRs, the protection provided is considerably lower than in the general population.^{3–6} As KTRs are especially prone to the development of serious complications of COVID-19, procedures such as temporary mycophenolate withdrawal or heterologous vaccination were tested to overcome the blunted vaccination response, but with little to no effect.^{7–11} Even repeated booster doses are not the solution, as they do not sufficiently induce neutralization against some variants of concern in KTRs with previously impaired vaccination response.¹²

It has been proposed that circadian rhythmicity could play an important role in the immune regulation of vaccination response and that the timing of vaccine administration could be used to improve vaccine response.¹³ Indeed, the benefits of harnessing circadian rhythms in vaccinology (so-called chronovaccination) have been previously demonstrated in cases of influenza¹⁴ and BCG vaccines.¹⁵ More recently, a large study by Hazan *et al.*¹⁶ showed that morning dosing of the SARS-CoV-2 vaccine was associated with better real-world vaccine effectiveness compared to an afternoon dose. Furthermore, Lin and Hung¹⁷ reported that morning vaccination with an adenovirus-based vector vaccine was associated with improved seroconversion among hemodialysis patients, another vulnerable patient group where vaccination response might be blunted.^{4,18} Thus, morning vaccination may represent an easy-to-implement and cost-effective way of improving vaccine effectiveness even in vulnerable and polymorbid patients. However, it has also been previously shown in humans and in animal models that the use of immunosuppressive drugs such as corticosteroids and calcineurin inhibitors may disrupt circadian rhythmicity,^{19–22} potentially altering or negating the effect of morning vaccination in KTRs specifically compared to other patient populations.

To clarify whether morning vaccination might be beneficial in the specific immunosuppressed patient cohort of KTRs with various levels of kidney dysfunction, we performed a secondary analysis of a prospective observational study (NCT04832841).⁴ The original study examined the determinants of immune response in KTRs following messenger ribonucleic acid (mRNA) COVID-19 vaccination with either Pfizer/BioNTech BNT162b2 or Moderna mRNA-1273. The primary research question of the current study is whether the timing of the first or second vaccine dose influences humoral response measured after the complete course of primovaccination (that is after the application of the second vaccine dose).

2. Methods

2.1. Patients

Patient enrollment took place between March 18, 2021, and June 3, 2021.⁴ Of the 626 virus-naïve KTRs from the primary study, 553 were included in the analysis as they were vaccinated at the local transplant center and therefore the time of their vaccination was known. A KTR was considered as virus-naïve if no previous SARS-CoV-2 infection was recorded. To eliminate reporting bias, all previous SARS-CoV-2 infection records were verified in the official government central registry for infectious diseases,²³ where all positive test results were mandatorily reported from all laboratories throughout the country. This study was approved by the local IRB under No. G-21-07.

2.2. SARS-CoV-2 immunoglobulin G (IgG) measurements, seroconversion definition

SARS-CoV-2 IgG levels against the spike protein were measured using the LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescence immunoassay (DiaSorin S.p.A., Italy) with a cut-off value of 9.5 AU/ml for seroconversion as previously described.⁴ The detection limits of the assay are 3.6 AU/mL (lower limit) and 8000 AU/mL (upper limit). Antibody levels were evaluated after the second vaccine dose (median 47 days, range 14–113 days).

2.3. Statistics

Continuous variables are reported as medians with interquartile ranges, and categorical variables as proportions (%). Intergroup differences were calculated with the Mann-Whitney test, chi-square test, or Fischer test as appropriate.

2.4. Bayesian regression modeling

We decided to use the Bayesian approach as it enables direct incorporation of external knowledge into statistical models (in the form of so-called prior). Because the effect of morning vaccination on seroconversion has been already reported in hemodialysis patients,¹⁷ a similar vulnerable group of patients, we believe that employing a methodology that takes these insights into account can contribute to more informed inferences.

We used Bayesian logistic regression in R software (version 4.3.1) and “brms” package²⁴ to analyze the timing effect of first and second doses of SARS-CoV-2 mRNA vaccines on the seroconversion measured after the second vaccine dose. Data of all 553 patients were entered into the Bayesian models (see full report online²⁵).

Table 1

Patient characteristics.

Characteristic	Unsuccessful seroconversion (n = 341)	Successful seroconversion (n = 212)	P value
Male sex, n (%)	202 (59%)	152 (72%)	.003
Age, y, median (IQR)	67 (58, 72)	63 (56, 71)	.017
Months from transplantation, median (IQR)	55 (20, 115)	100 (42, 170)	<.001
Timing of first dose, median (IQR)	12:09 PM (11:09 AM, 1:22 PM)	12:17 PM (11:20 AM, 1:26 PM)	.4
Timing of second dose, median (IQR)	12:25 PM (11:24 AM, 1:20 PM)	12:19 PM (11:10 AM, 1:11 PM)	.2
Days between the second dose and testing, median (IQR)	43 (28, 67)	49 (31, 66)	.2
Timing of IgG testing, median (IQR)	7:20 AM (6:49 AM, 7:52 AM)	7:22 AM (6:52 AM, 7:47 AM)	.8
Diabetes mellitus, n (%)	104 (30%)	62 (29%)	.8
Body mass index (kg/m ²), median (IQR)	28.3 (24.8, 31.3)	27.7 (24.9, 31.3)	.5
Last eGFR before vaccination (mL/min/1.73 m ²), median (IQR)	43.8 (33, 57.6)	51 (41.4, 67.8)	<.001
Maintenance immunosuppression			
Calcineurin inhibitor, n (%)	306 (90%)	190 (90%)	>.9
Tacrolimus, n (%)	279 (82%)	161 (76%)	.1
Trough level tacrolimus, median (IQR)	6.5 (5.5, 7.6)	6.3 (5.7, 7.4)	>.9
Cyclosporin A, n (%)	27 (7.9%)	29 (14%)	.029
Trough level cyclosporin A, median (IQR)	109 (90, 138)	105 (95, 129)	.8
Mycophenolate mofetil/ mycophenolic acid, n (%)	295 (87%)	131 (62%)	<.001
Mycophenolate mofetil/ mycophenolic acid dose (mg/d), median (IQR)	1000 (875, 1500)	1000 (500, 1500)	.9
Corticosteroid, n (%)	316 (93%)	187 (88%)	.075
T cell depletive immunosuppression year before vaccination, n (%)	22 (6.5%)	2 (0.9%)	.002
Albumin (g/L), median (IQR)	42.4 (40.1, 44.4)	42.6 (40.2, 44.3)	.5

(continued on next page)

Table 1 (continued)

Characteristic	Unsuccessful seroconversion (n = 341)	Successful seroconversion (n = 212)	P value
Lymphocytes (n/ μ L), median (IQR)	1.99 (1.46, 2.47)	2.37 (1.76, 3.13)	<.001
Administered vaccine			
Vaccine BNT162b2, n (%)	333 (97.7%)	203 (95.8%)	.2
Vaccine mRNA-1273, n (%)	8 (2.3%)	9 (4.2%)	
SARS-CoV-2 IgG antibody level (AU/mL), median (IQR)	0 (0, 0)	57 (23, 171)	<.001

eGFR, estimated glomerular filtration rate; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Vaccine timings were primarily used as a continuous variable with linear and additive effects, as there were no significant nonlinearities or apparent interactions between the timing of the 2 doses (Supplementary Fig. S1 and Supplementary Table S1).

Models were adjusted for the effect of other covariates previously shown to influence the probability of seroconversion after SARS-CoV-2 vaccination in hemodialysis patients and KTRs.^{4,17} The covariates included: time after kidney

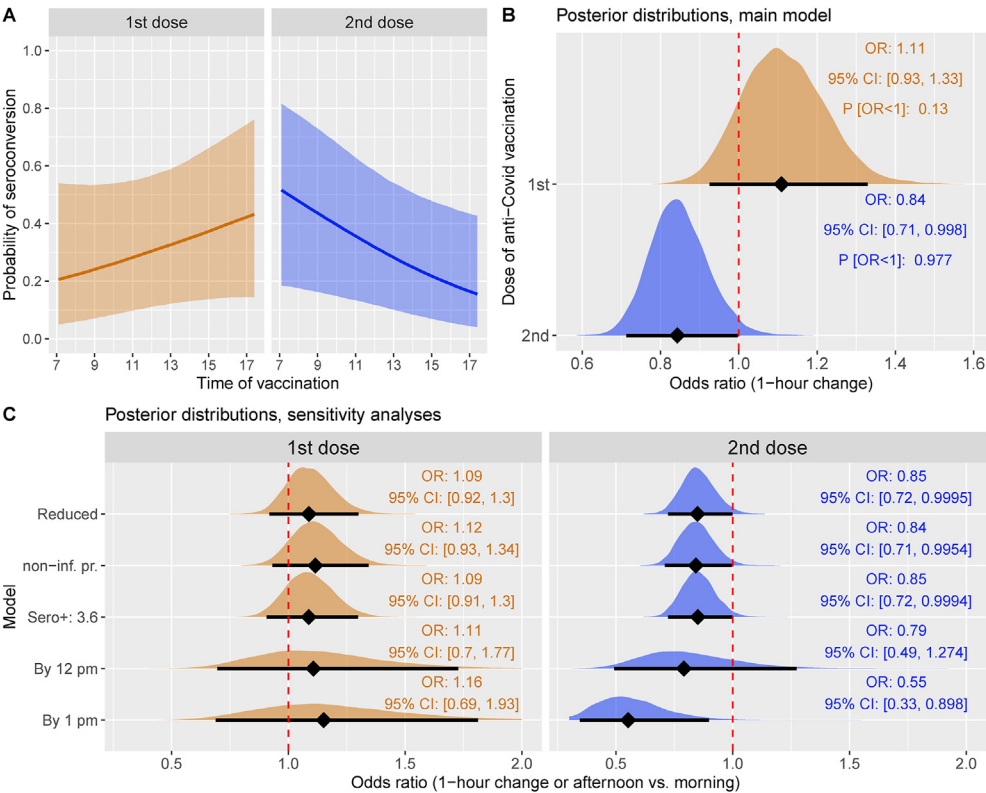


Figure 1. The effects of morning vaccination on seroconversion following SARS-CoV-2 vaccination in kidney transplant recipients. (A) Predicted probability of seroconversion in relation to the timing of vaccine dose administration (first dose in the left panel and second dose in the right panel) and 95% credible intervals (CIs) (shaded regions). The displayed curves show the effects of vaccination times, averaged across binary variables and based on mean values of continuous covariates. (B) Posterior distribution and 95% CI representing the impact of a 1-hour delay in vaccination time on seroconversion according to the main model. The value P [OR < 1] indicates the model-estimated probability that earlier vaccination improves seroconversion (i.e., OR (odds ratio) for time is smaller than 1). (C) Posterior distribution for the effect of a 1-hour delay in vaccination time, or afternoon vs morning vaccination times, based on 5 different sensitivity analyses (reduced = model with reduced covariate adjustments [only variables that differ between seroconverted and not seroconverted patients, as shown in Table 1, were included]; non-inf. pr. = model with a noninformative prior [i.e., a prior that has minimal influence on the inference] for all predictors including vaccination times; sero+: 3.6 = a model where the threshold for antibody positivity was changed to > 3.6 AU/mL [laboratory limit of detection, rather than seroconversion]; By 12 pm = a model with dichotomized vaccination times, the afternoon is defined as later than 12 PM; By 1 PM = a model with dichotomized vaccination times, the afternoon is defined as later than 1 PM). The impact of the timing of the first dose is presented on the left and the second dose on the right. CI indicates bounds of 95% CI. See methods for details and Supplementary Tables S3-S7 for detailed results of sensitivity analyses.

transplantation, the time between the second dose and blood collection (modeled as a nonlinear effect, [Supplementary Fig. S1](#)), age at vaccination, sex, most recent estimated glomerular filtration rate before the first dose (mL/min/1.73 m²), body mass index (kg/m²), serum albumin (g/L), lymphocyte count (n/μL), diabetes mellitus, vaccine type (mRNA-1273 or BNT162b2), and maintenance immunosuppression, namely mycophenolate mofetil or mycophenolic acid, calcineurin inhibitors, and steroids. For Bayesian models, continuous variables were standardized by 2 standard deviations.²⁶

We used Gaussian noninformative priors with $\mu = 0$ (assuming no effect) and $\sigma = 5$ (reflecting a large prior uncertainty) for all covariates except the vaccination time effects. A noninformative prior has minimal influence on the inference and reflects a neutral assumption about the effects. For the administration timing effect, μ was set according to the estimate of Lin and Hung,¹⁷ with $\sigma = 5 \times SE$ of their estimates on day 56 ($\mu = -0.9$, $\sigma = 2$). In our perspective, this prior acknowledges differences in our study population and design, yet informs the statistical models about the already gained insights. Throughout the manuscript, we report odds ratio (OR, median posterior estimate) along with 95% credible intervals (CIs) and probability of direction which is an index (0.5 to 1) representing the certainty that the effect goes in a particular direction.²⁷ We also show a model-estimated probability of the negative effect of a later vaccination time (i.e., the probability that OR is less than 1).

Finally, we conducted additional sensitivity analyses, rerunning models with various adjustments as follows: (1) employing reduced covariate adjustments only with covariates that differed between successful and unsuccessful seroconversion groups (see [Table 1](#)); (2) employing a noninformative prior (i.e., a prior that has minimal influence on the inference) for all the covariates including the vaccination time effect ($\mu = 0$, $\sigma = 5$); (3) the threshold for antibody positivity was changed to > 3.6 AU/mL (laboratory limit of detection, rather than seroconversion); (4) examining dichotomized vaccination times with 2 “afternoon” thresholds at 12 PM and 1 PM; and (5) utilizing quantile regression to model antibody IgG levels as a continuous outcome variable.

The complete statistical procedure and code are available online as a full statistical report with R code.²⁵

3. Results

3.1. Baseline characteristics

We included 553 KTRs who were vaccinated with mRNA vaccines. The baseline demographics are given in [Table 1](#) (categorized by seroconversion) and [Supplementary Table S2](#) (categorized by vaccination times). Seroconverted KTRs were more often men (72% vs 59%; $P = .003$), younger (63 vs 67 years; $P = .017$), longer since transplantation (100 vs 55 months; $P < .001$), had better graft function (51 vs 43.8 mL/min/1.73 m²; $P < .001$), had less often mycophenolate in maintenance immunosuppression (62% vs 87%; $P < .001$), less often T cell depletive immunosuppression year or less before vaccination (0.9% vs

6.5%; $P = .002$), and had higher absolute lymphocyte count on the day of the first vaccine dose (2.37 vs 1.99/μL; $P < .001$). Distribution of vaccination times and SARS-CoV-2 IgG levels in patients with successful seroconversion are shown in [Supplementary Figures S2 and S3](#), respectively.

3.2. Bayesian modeling of morning vaccination

Bayesian models support the beneficial effect of the earlier administration for the second, but not the first vaccination dose.

The result of the main model is shown in [Figure 1A](#), illustrating how the probability of seroconversion changes with each hour later of the day of the vaccine administration. The model does not support the beneficial effect of early vaccination of the first dose for the KTR patients (OR 1.11, 95% CI 0.93, 1.33, [Fig. 1B](#)). In contrast, the model estimated 97.7% probability that earlier administration of the second dose enhances seroconversion, with a 1-hour delay reducing the odds of seroconversion by approximately 16% ([Table 2](#)). However, the magnitude of this effect carries uncertainty (OR 0.84, 95% CI 0.71, 0.998), and the

Table 2

Results of Bayesian logistic regression modeling the probability of seroconversion following mRNA SARS-CoV-2 vaccination.

Parameter	Full model		
	OR	95% CI	PD
Timing of first dose (h)	1.11	0.93, 1.33	0.866
Timing of second dose (h)	0.84	0.71, 0.998	0.977
Male sex	2.02	1.29, 3.2	1.000
Age (10 y)	0.72	0.55, 0.94	0.993
Time since transplantation (10 y)	2.12	1.46, 3.1	1.000
Diabetes mellitus	0.91	0.56, 1.49	0.645
Body mass index (5 units)	0.97	0.77, 1.22	0.611
eGFR (10 mL/min/1.73 m ²)	1.38	1.23, 1.55	1.000
Calcineurin inhibitor	1.79	0.79, 4.11	0.922
Mycophenolate mofetil/ mycophenolic acid	0.12	0.07, 0.21	1.000
Corticosteroid	0.73	0.35, 1.54	0.791
T cell depletive immunosuppression year before vaccination	0.24	0.04, 1.14	0.961
Albumin (g/L)	1.03	0.97, 1.1	0.855
Lymphocyte counts (log[n/ μL])	2.53	1.49, 4.35	1.000
Vaccination with mRNA-1273	1.39	0.39, 4.8	0.703

OR implies odds ratio, an expected fold-change in odds when the predictor changes by the unit defined in parenthesis.

CI, credible interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; PD, probability of direction.

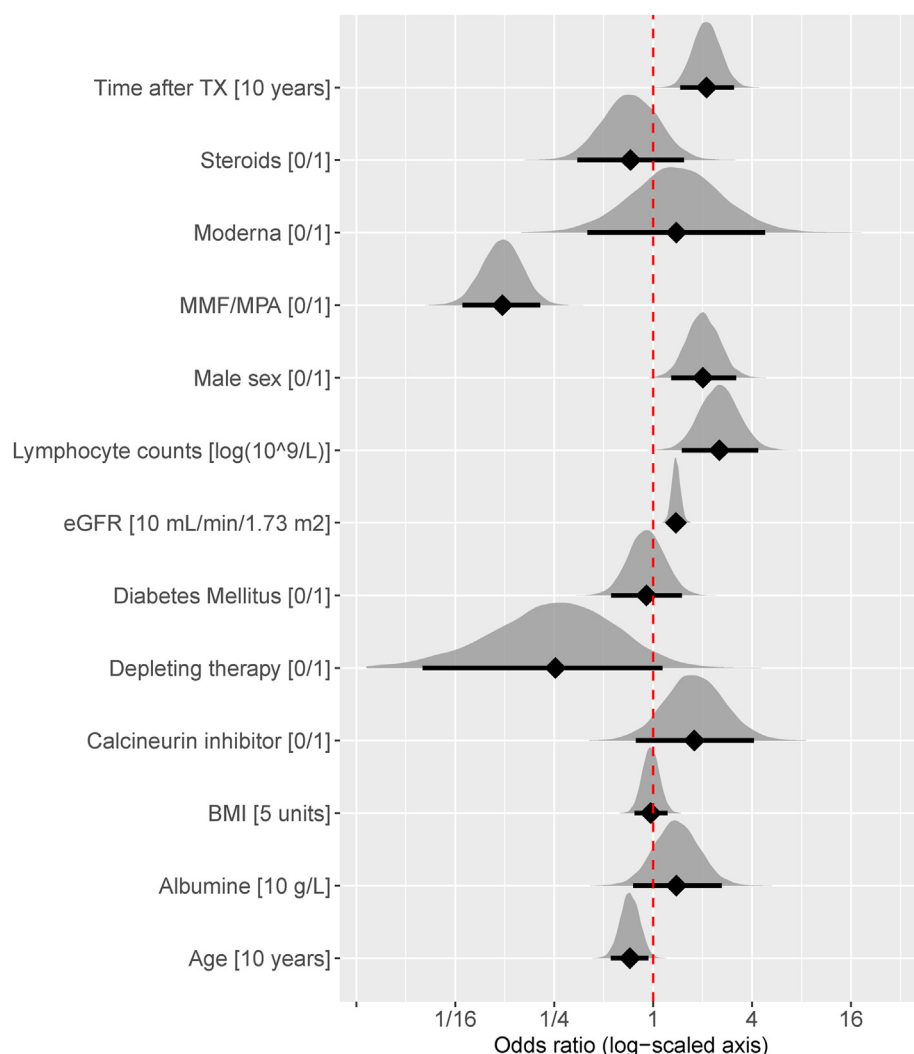


Figure 2. Posterior distributions (gray) and 95% credible intervals (black) for the effects of recorded covariates on odds of seroconversion following SARS-CoV-2 vaccination in kidney transplant recipients. This Figure illustrates in more detail the posterior probabilities of all covariates from the model shown in Table 2. BMI, body mass index; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; TX, transplantation.

actual benefit likely falls into a wide range between 0.2% to 29% decrease in the odds of seroconversion per hour. The effects of other covariates are shown in Figure 2.

The sensitivity analyses generally support our primary findings (Fig. 1C). Variants of models incorporating reduced covariate adjustments, noninformative priors, and using laboratory limit of detection of SARS-CoV-2 IgG antibodies (IgG > 3.6 AU/mL) instead of seroconversion as the outcome variable, all indicate the benefits of early vaccination for the second dose (Supplementary Tables S3–S5). When vaccination times are treated as binary (i.e., “afternoon” vs “morning”), the effect is dependent on the threshold chosen to define “morning” (Supplementary Table S6). Using a 1 PM threshold supports the benefits of morning vaccination (OR for afternoon vs morning 0.55, 95% CI 0.33, 0.898), whereas a 12 PM threshold suggests a smaller and rather uncertain effect (OR 0.79, 95% CI 0.49, 1.274). Lastly, we calculated a quantile regression model where continuous absolute antibody levels were used as the outcome variable (Supplementary Table S7). In this model, each additional hour of vaccination delay was associated with a 4.7% decrease in antibody levels, which also supports the beneficial effect of earlier vaccination time.

4. Discussion

In this study, we found that morning vaccination with an mRNA SARS-CoV-2 vaccine likely improves seroconversion rates in KTRs, despite the well-described blunted vaccination response and the use of immunosuppression potentially disrupting circadian rhythmicity. To our knowledge, this is the first report on the beneficial role of chronovaccination in the specific cohort of KTRs using mRNA vaccines.

We previously reported that shorter time from transplantation, mycophenolate in the maintenance immunosuppression, and worse allograft function were all independently associated with a lower likelihood of seroconversion.⁴ Importantly, in this analysis, we discovered that morning vaccination resulted in higher seroconversion rates independent of all these variables. Taken together, these results suggest that morning vaccination is both an easy-to-implement approach and a cost-effective one and might help offset other factors that negatively affect humoral response.

However, chronovaccination is mechanistically poorly understood. Body functions as a whole, as well as single-cell or subcellular functions are controlled by circadian rhythmicity.^{28,29} Both

adaptive and innate immunity are no exception to these rules.^{29–33} Yet, we can only speculate about the mechanisms underlying chronovaccination.¹³ Among the possible mechanisms are circadian steroid hormone variations,³⁴ variable migration of immune cells to lymph nodes during the day,^{32,35} or intracellular diurnal variation (e.g., protein synthesis following mRNA injection).³⁶

Interestingly, the benefit of morning vaccination was only documented for the second dose and not the first one. We believe that this is a result of enhanced immune response (second dose) following the initial development of immunological memory (first dose). For example, it has been recently shown, that ipsilateral vaccination is associated with better humoral response than contralateral vaccination, suggesting that the immunological memory of immune cells in the regional lymph nodes is of importance.³⁷ Therefore, it is possible, that even the timing of the first dose might be beneficial, but the stronger effect of the second dose overshadows it. Because we did not measure the SARS-CoV-2 antibodies in the time between the 2 doses, we cannot reasonably test this hypothesis and the lack of these measurements is a limitation of our study. The other limitations are the observational design, the fact that we did not investigate the association between morning vaccination and the risk of COVID-19 infection, and the possibility of other unmeasured confounding factors. Lastly, because the upper 95% CI of OR of vaccination time is near 1, some uncertainty in the results remains, especially regarding the magnitude of the effect.

Among the strengths of our study are the large prospective cohort and the use of reliable data for the selection of virus-naïve individuals from the central nationwide registry, where data from all laboratories in the country were mandatorily reported.^{3,23} Furthermore, the Bayesian approach allows the incorporation of previously published data, which provides more realistic estimates.

In conclusion, our analysis indicates that morning vaccination is likely beneficial even for the specific patient population of KTRs. Despite reported circadian rhythmicity disturbances in KTRs due to the use of immunosuppression,^{19–22} morning vaccination can still improve vaccination response and may be considered a simple and cost-effective method of increasing vaccination efficacy in this vulnerable patient population. However, the exact extent of the positive effect seen is still unclear, emphasizing the need for further studies to improve the accuracy of our estimation. Furthermore, the underlying mechanisms of chronovaccination should be further studied and ideally harnessed.

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Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajt.2024.03.004>.

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