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LONGITUDINAL ANALYSIS OF ANTIBODIES IMMUNE RESPONSES IN KIDNEY TRANSPLANT RECIPIENTS AFTER SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

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Long-lived antibodies against SARS-COV-2 emerge after a severe acute respiratory sever in kidney transplant recipients

BACKGROUND

Evaluating the **immune response** of kidney transplant recipients (KTRs) who recover from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the **factors** that may influence it, namely, the role of immunosuppression, is crucial to understanding the quality and durability of the immune response to natural infection.

In this study, we report the **longitudinal antibody kinetics** using two SARS-CoV-2 antigens: the nucleocapsid and the S1 domain of spike protein, anti-N IgG and anti-S1 IgG ratio values, respectively.

METHODS

- All adult KTRs with primary SARS-CoV-2 infection in the absence of vaccination identified at our center between March 04, 2020, and March 8, 2021.
- Patient demographic and clinical characteristics were retrospectively retrieved from the electronic medical records. A severe form of COVID-19 was defined by the need for oxygen therapy.
- We estimated the SARS-COV-2 antibody ratio values over time and their association with several demographic and clinical covariates, using a **structured Bayesian additive regression model for longitudinal data.**

RESULTS

Seventy-seven KTRs with SARS-CoV-2 infection were analyzed, **52** (67.5%) were seropositive for anti-N IgG and **64** (83.1%) were seropositive for anti-S1 IgG.

- The mean age was 57.1 ± 11.6, with 40.3% older than 60 years, and 63.6% were male.
- Only 9 (11.7%) patients had a previous kidney transplant.
- Comorbidities were frequent, with hypertension (84.4%), diabetes mellitus (32.5%), and cardiovascular disease (23.5%) being the most common.
- At diagnosis, all but one KTRs were on low-dose prednisolone, most were treated with CNI (94.8%) primarily tacrolimus (81.8%), antimetabolites (89.6%) mainly mycophenolate (87%) and 90.9% were on triple immunosuppression.
- Regarding COVID-19 disease severity, 52 (67.5%) had non-severe disease.

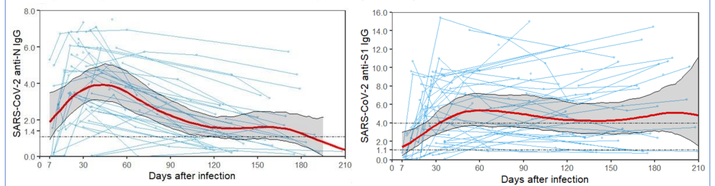

Figure 1. Longitudinal antibodies ratio response of SARS-CoV-2. Observed values (points), trajectories (lines), posterior mean estimates (red line) and 95% credibility intervals (shaded areas) of anti-N/anti-S1 IgG ratio values for the 52/64 seropositive patients (136/157 samples) from the model fit, respectively. The threshold for antibody positivity is represented by a dashed line (sample ratio value < 1.4/1.1, respectively).

Table 1. Clinical factors associated with SARS-CoV-2 anti-N IgG longitudinal antibody kinetics

	Posterior mean	95% CrI	
COVID-19 Severity: severe	**0,12**	0,04	0,20
Sex: male	**0,16**	0,08	0,24
Age, years	-0,01	-0,11	0,00
Tacrolimus trough levels	**-0,02**	-0,04	-0,01
Mycophenolate daily dose: >720 mg	**-0,11**	-0,22	-0,02

Coefficient posterior mean estimates and 95% credibility intervals for the anti-N IgG longitudinal model.
Bolding indicates significant variables.

Table 2. Clinical factors associated with SARS-CoV-2 anti-S1 IgG longitudinal antibody kinetics

	Posterior mean	95% CrI	
COVID-19 Severity: severe	**0,17**	0,07	0,26
Sex: male	0,10	0,00	0,20
Age, years	0,00	-0,01	0,01
Tacrolimus trough levels	-0,01	-0,02	0,01
Mycophenolate daily dose: >720 mg	0,09	-0,04	0,22

Coefficient posterior mean estimates and 95% credibility intervals for the anti-S1 IgG longitudinal model.
Bolding indicates significant variables.

- Posterior mean estimates of anti-N IgG reached their peak by **day 42** after infection with a maximum value of 3.92 (95% CrI, 3.10-4.99) followed by decay with time, reaching the threshold of positivity of 1.4 (95% CrI, 0.64-2.31) by **day 176** (Figure 1 left).
- Patients with severe disease and male patients had significantly higher anti-N IgG over time with adjusted increases of 0.12 (95% CrI, 0.04-0.20) and 0.16 (95% CrI, 0.08-0.24) ratio values compared to non-severe and female patients, respectively (Table 1).
- Conversely, higher TAC through levels at SARS-CoV-2 infection was associated with a small, albeit significant decrease in posterior mean anti-N IgG over time, of -0.02 (95% CrI, -0.04 to -0.01) per 1.0 ng/ml increase in TAC trough levels. Also, higher mycophenolate doses (> 720 mg per day) were associated with lower [-0.11 (95% CrI, -0.22 to -0.02)] posterior mean anti-N IgG over time, compared with lower doses or no mycophenolate use.
- Regarding anti-S1 IgG, posterior mean estimates peaked later, by **day 56** after infection with a maximum value of 5.29 (95% CrI, 3.79-7.17), and then remained relatively stable over time, with minimal decline over the 7th month follow-up period (Figure 1 right).
- Disease severity was the only factor significantly associated with changes in posterior mean anti-S1 IgG over time (Table 2). Patients with severe disease had significantly higher anti-S1 IgG over time, with adjusted increases of 0.17 (95% CrI, 0.07- 0.26) when compared to non-severe patients.

CONCLUSION

In our study, most KTRs seroconverted, and IgG antibodies to the S1 subunit of the spike protein had minimal decline over the duration of the study, mainly after a severe acute respiratory syndrome. Furthermore, at 6 months after infection, the estimated proportion of having anti-S1 ratio values over 4 was 80%, suggesting functional immunity in a substantial proportion of KTRs, for at least 6 months after infection. In contrast, antibodies to nucleocapsid protein fell over time, and by six months after infection the estimated proportion of seropositivity was 37%.

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