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Article

Immune Response to BNT162b2 in Solid Organ Transplant Recipients: Negative Impact of Mycophenolate and High Responsiveness of SARS-CoV-2 Recovered Subjects against Delta Variant

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BNT162b2 vaccination in transplanted patients

Table 1. Demographic and clinical characteristics of enrolled patients.

	Number (%)
Male gender	66 (60%)
Type of transplant	
Heart	22 (20%)
Lung	26 (23.6%)
Kidney	62 (56.4%)
CNIs	
Cyclosporine	22 (20%)
Tacrolimus	83 (75.5%)
No	5 * (4.5%)
Anti-proliferative drug	
Mycophenolate	62 (56.4%)
Everolimus	30 (27.3%)
Mycophenolate and everolimus	6 (5.4%)
No	12 (10.9%)
Steroid level	
Low doses (<5mg/day)	68 (61.8%)
High doses (>5 mg/day)	3 (2.7%)
No	39 (35.5%)
Time after transplant	
Less than 1 year	12 (10.9%)
Between 1 and 5 years	45 (40.9%)
More than 5 years	53 (48.2%)
SARS-CoV-2 positivity at T0	
No	97 (88.2%)
Yes	13 (11.8%)

Legend CNIs: calcineurin inhibitors; T0: baseline time point.* Three patients received sirolimus in place of CNIs.

A total of 110 SOTRs (66 males and 44 females; median age 49, range 23–82) were enrolled at time of SARS-CoV-2 vaccination with BNT162b2 vaccine and samples were
collected the same day of first dose administration (T0) and three weeks after complete vaccination (T2). Serum samples were collected for evaluation of SARS-CoV-2 total and neutralizing antibodies while PBMC were used for quantification of Spike-specific T-cell response.

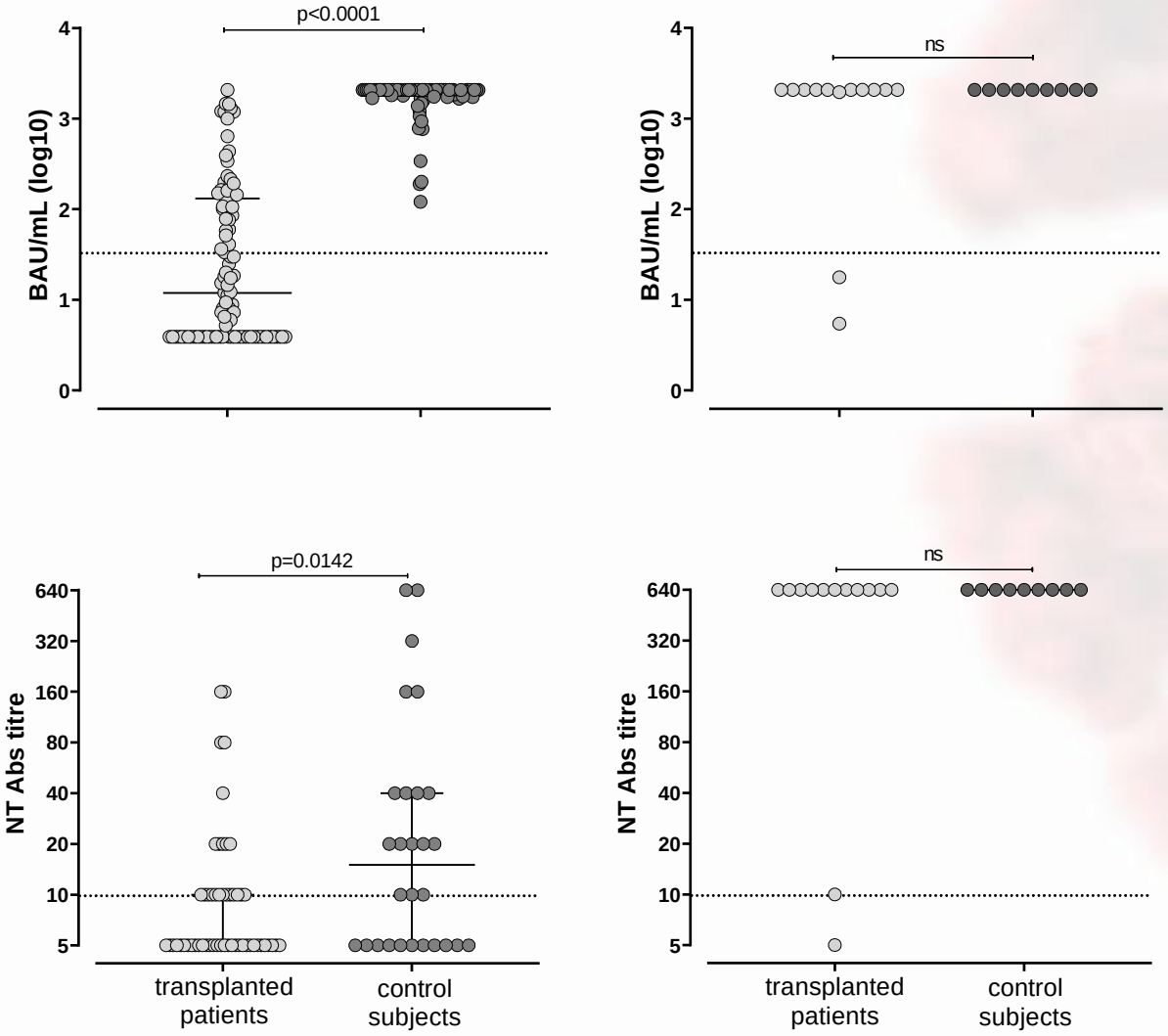
All the patients were enrolled at Fondazione IRCCS Policlinico San Matteo, according to
Helsinki declaration and after approval of local ethical committee “Comitato Etico Pavia”
(P-20210000232) on 10 February 2021.

Cassaniti I et al. Microorganisms 2021

Antibody response toBNT162b2 vaccine in solid organ transplant recipients

SARS-CoV-2-naive

SARS-CoV-2-experienced



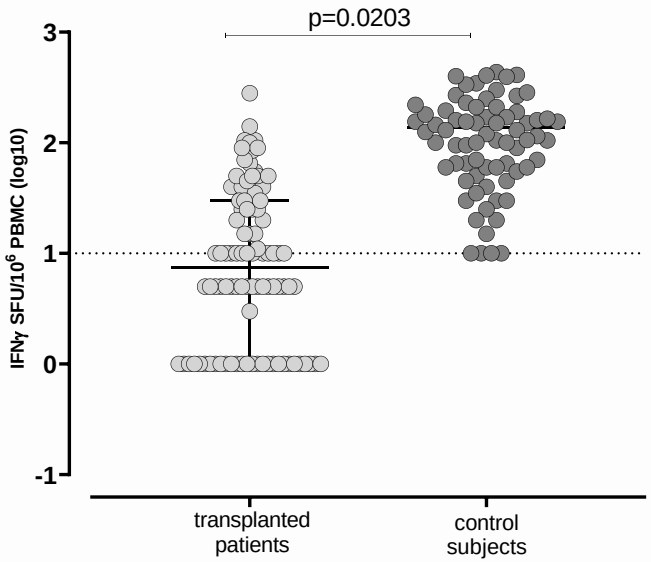
36/97 (37.1%) SARS-CoV-2-naïve SOTR developed anti-S (Trimeric) IgG

46/97 (47.4%) SARS-CoV-2-naïve SOTRs developed SARS-CoV-2 NT Abs

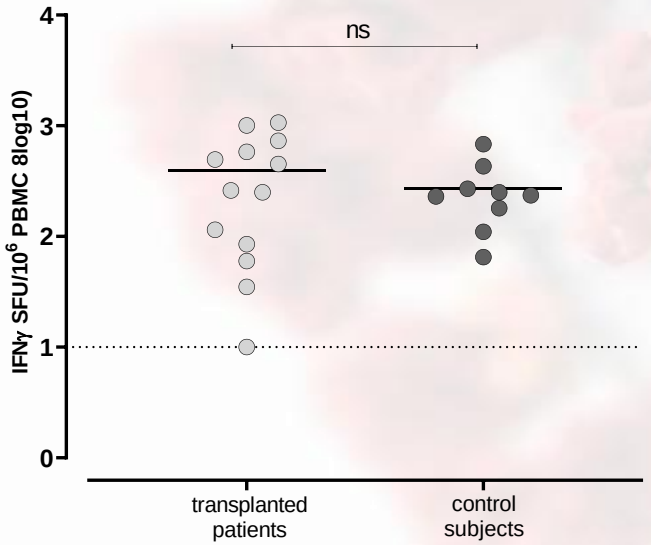
11/13 SARS-CoV-2-experienced SOTR developed high levels of anti-S (Trimeric) IgG and NT Abs similar to healthy controls

T-cell response to BNT162b2 vaccine in solid organ transplant recipients

SARS-CoV-2-naive



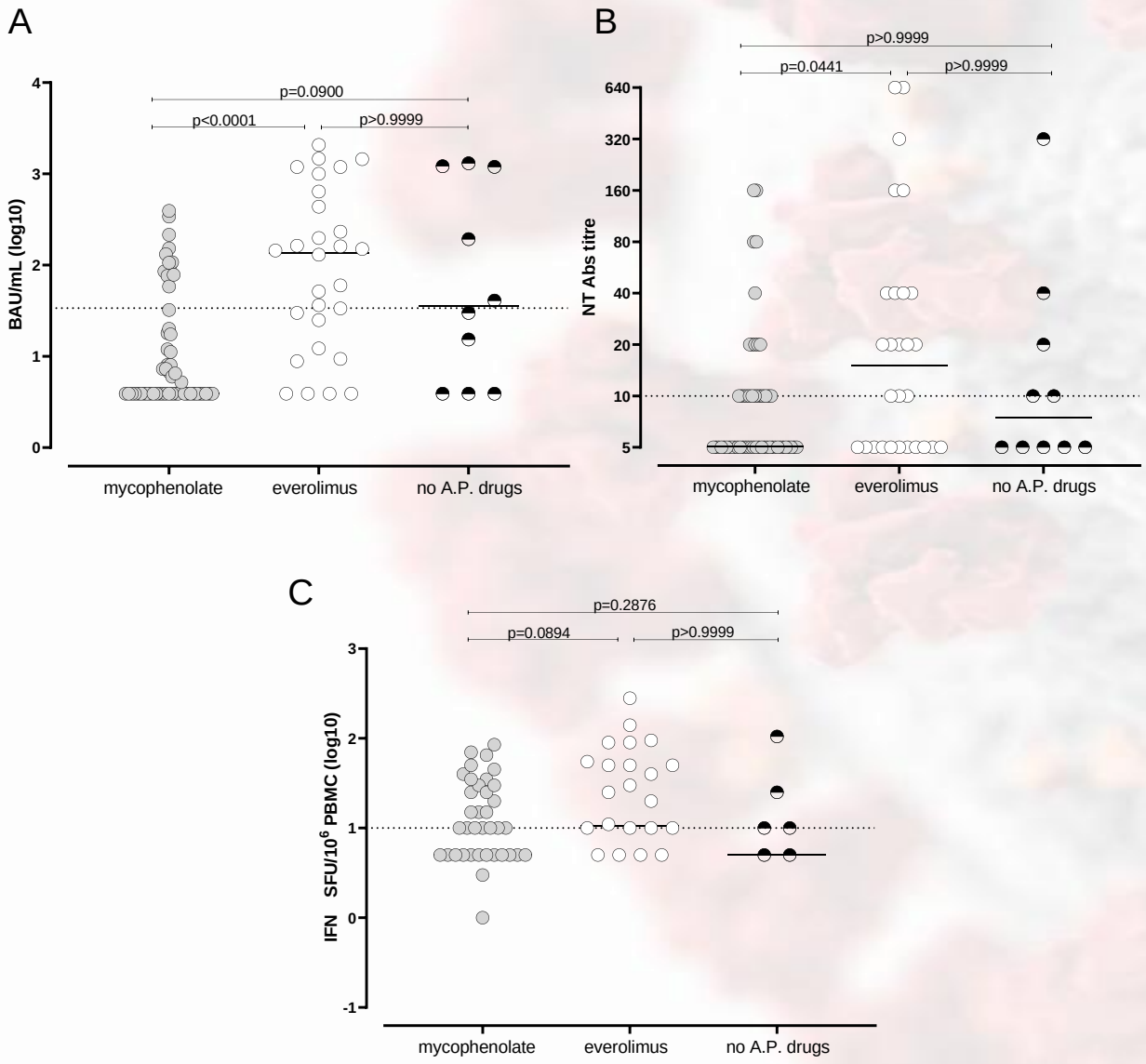
SARS-CoV-2-experienced



49/97 (50.5%) SARS-CoV-2-naïve SOTR developed S-specific T-cell response

All the 13 SARS-CoV-2-experienced SOTR developed S-Specific T-cell response similar to healthy controls

Reduced humoral (and cell-mediated) response in mycophenolate-treated patients



BNT162b2 vaccination in transplanted patients

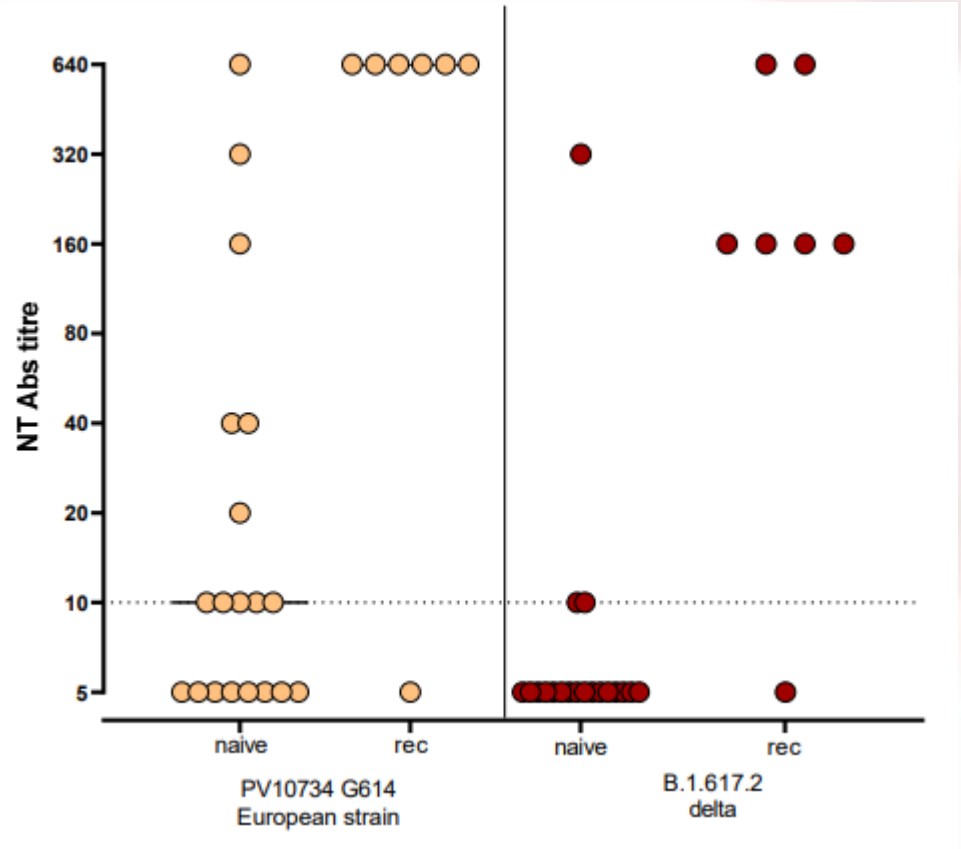
Table 2. Multiple linear regression analysis of factors potentially associated with vaccine response in transplant recipients.

Dependent Variable	Independent Variable	Estimate β Coefficient	95% Confidence Interval	*p* Value
S Trimeric (Log_{10}BAU/mL)	Intercept	2.690	1.903 to 3.468	<0.001
	Age	−0.014	−0.028 to 0.000	0.054
	Time after transplant <18 months	−0.561	−1.030 to −0.091	0.020
	Use of mycophenolate	−0.806	−1.110 to −0.498	<0.001
Nt Abs (Log_{10} titer)	Intercept	1.480	0.930 to 2.030	<0.001
	Age	−0.00437	−0.014 to 0.005	0.380
	Time after transplant <18 months	−0.218	−0.547 to 0.111	0.192
	Use of mycophenolate	−0.264	−0.480 to −0.048	0.017
Spike-specific T cells (Log_{10} Spots)	Intercept	1.280	0.530 to 2.020	0.001
	Age	−0.006	−0.019 to 0.0078	0.407
	Time after transplant <18 months	−0.033	−0.475 to 0.408	0.881
	Use of mycophenolate	−0.200	−0.489 to 0.090	0.174

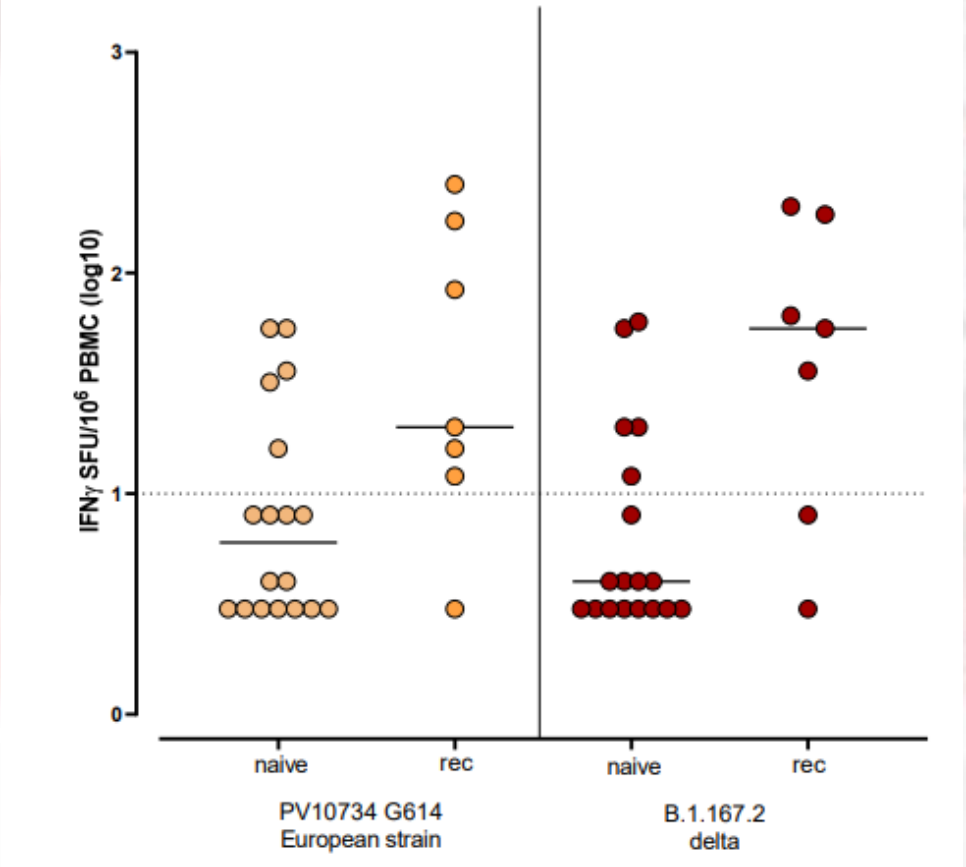
In a multivariate linear regression model including age, time after transplant and use of mycophenolate, we found that the use of mycophenolate was independently associated with a lower IgG antibody level and to a lower NT titer. Association between age and time after transplant was significant with the IgG S Trimeric assay. No factor appeared independently associated with T-cell response.

SARS-CoV-2 immune response against VOC in transplanted vaccinated subjects

SARS-CoV-2 NT Abs

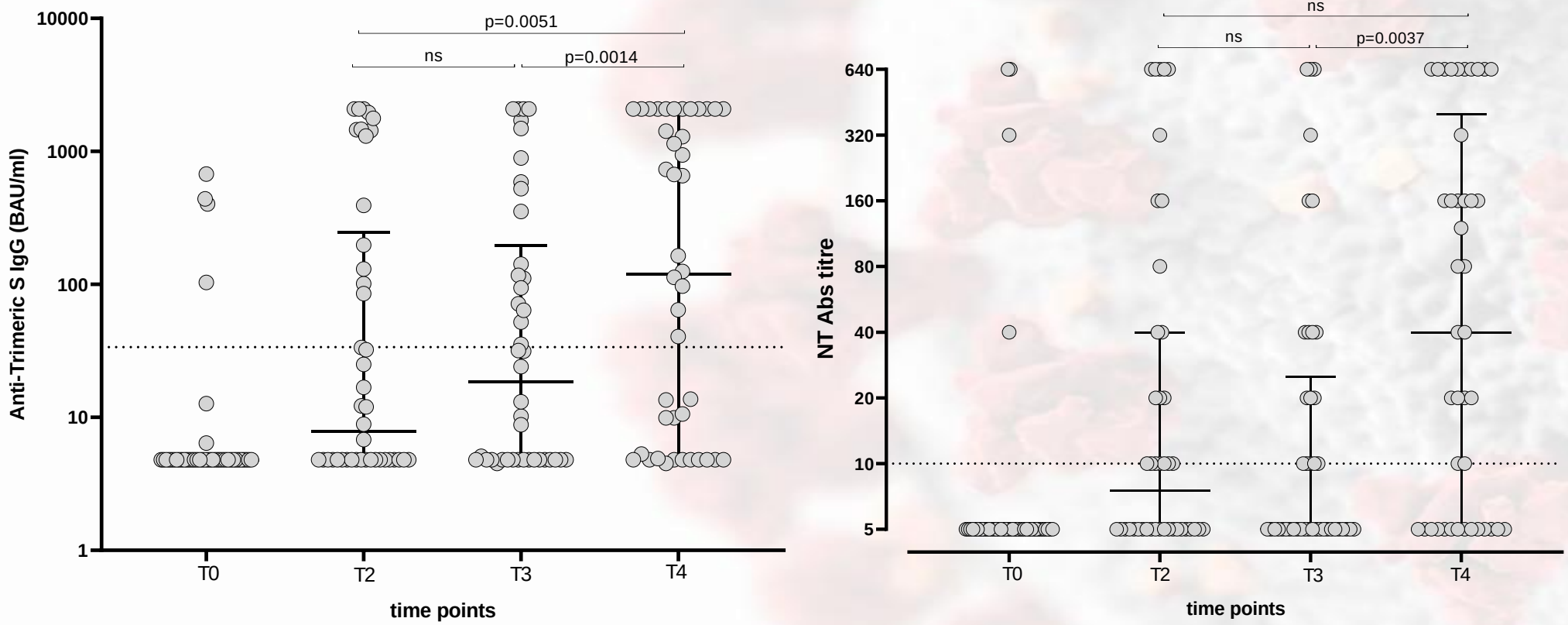


T-cell mediated response



Immunogenicity of third BNT162b2 vaccine dose in transplanted patients

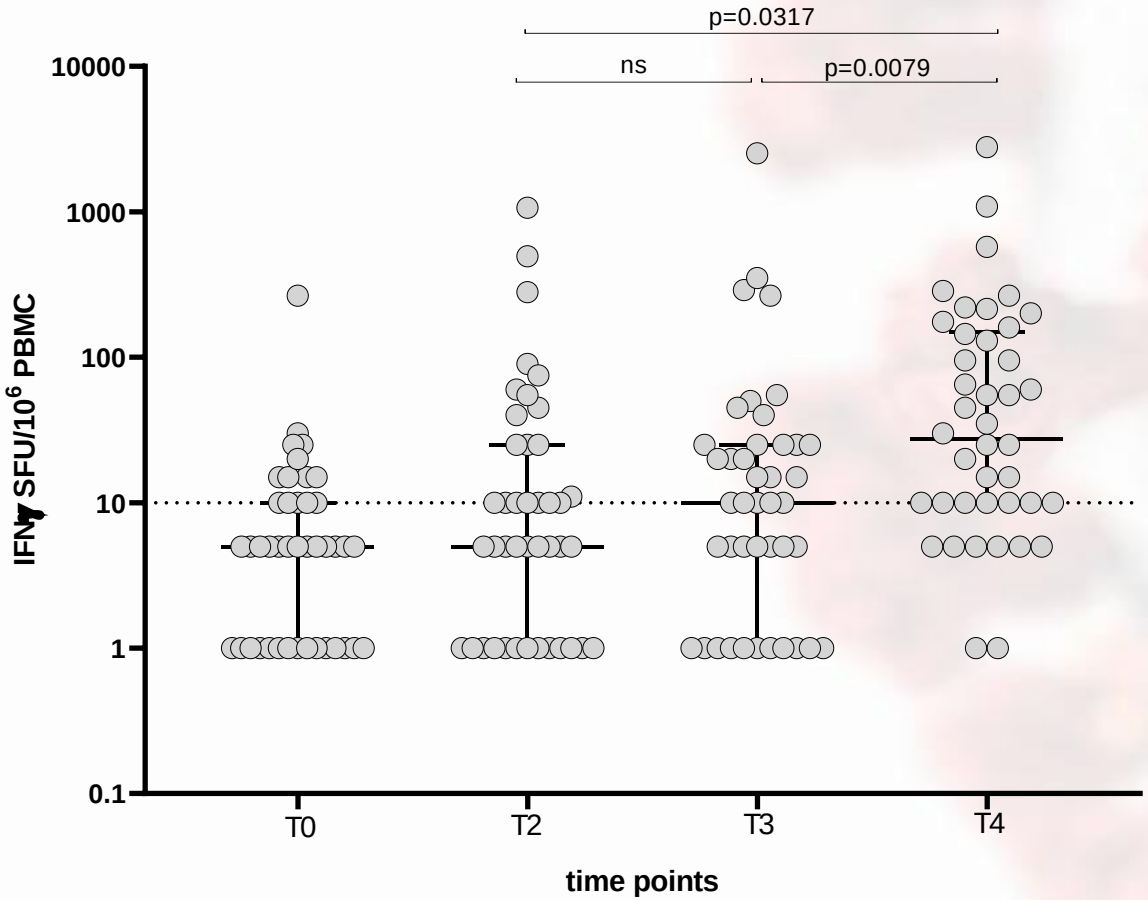
baseline (T0),
2° dose (T2),
six months (T3)
3° dose (T4)



47 kidney transplant recipients were longitudinally monitored for total IgG and SARS-CoV-2 NT Abs. The percentage of responders were 30% and 55% at T2 and T4 for total IgG and 46% and 61% at T2 and T4 for NT Abs

Immunogenicity of third BNT162b2 vaccine dose in transplanted patients

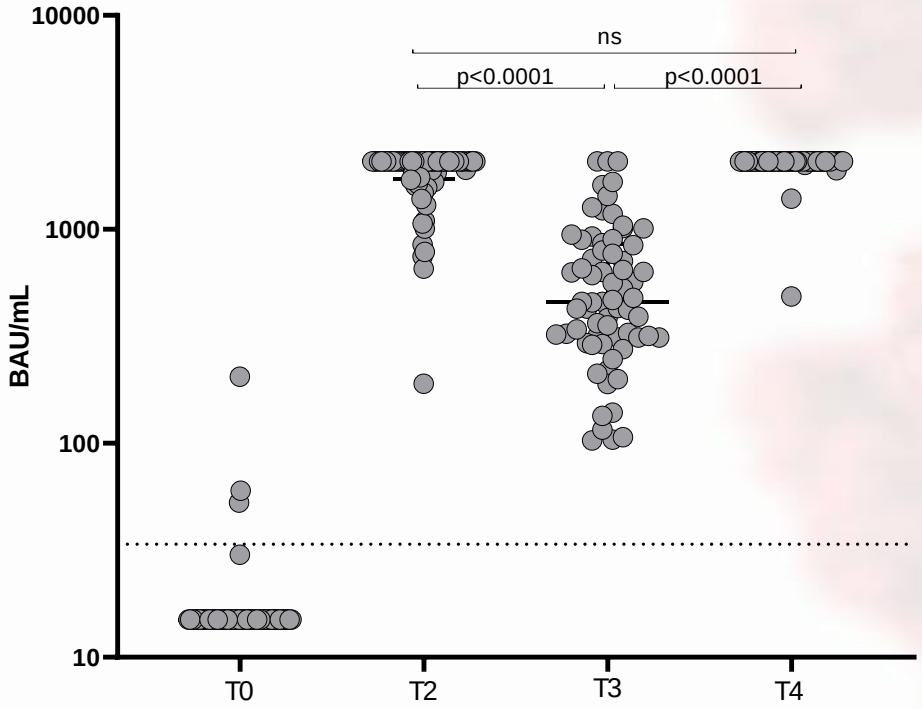
baseline (T0),
2° dose (T2),
six months (T3)
3° dose (T4)

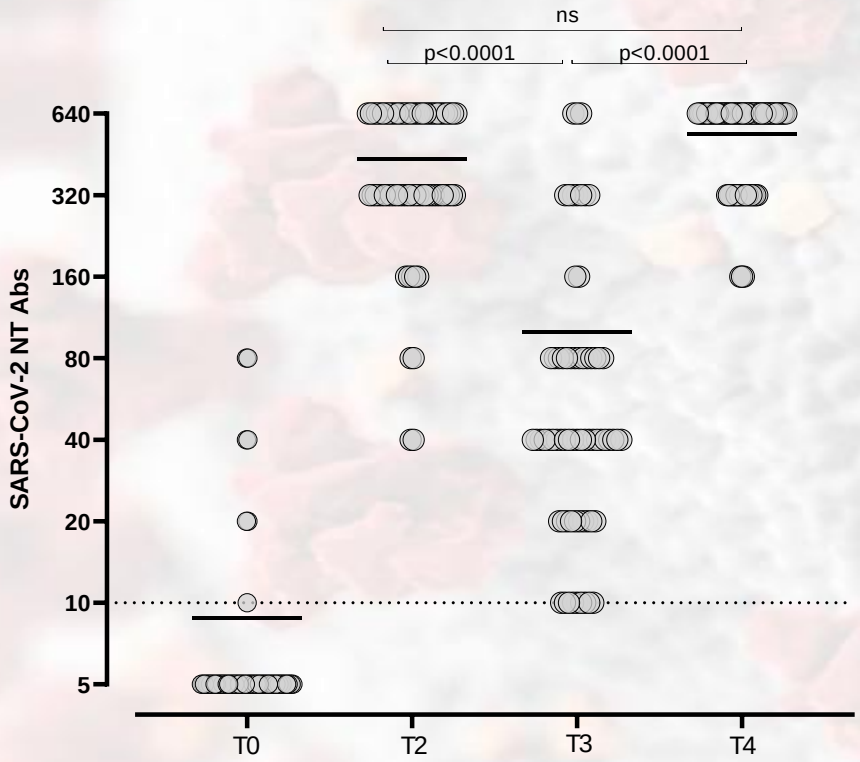


47 kidney transplant recipients were longitudinally monitored for Spike-specific T-cell response.

The percentage of responders was 55% at T2 and 79% at T4

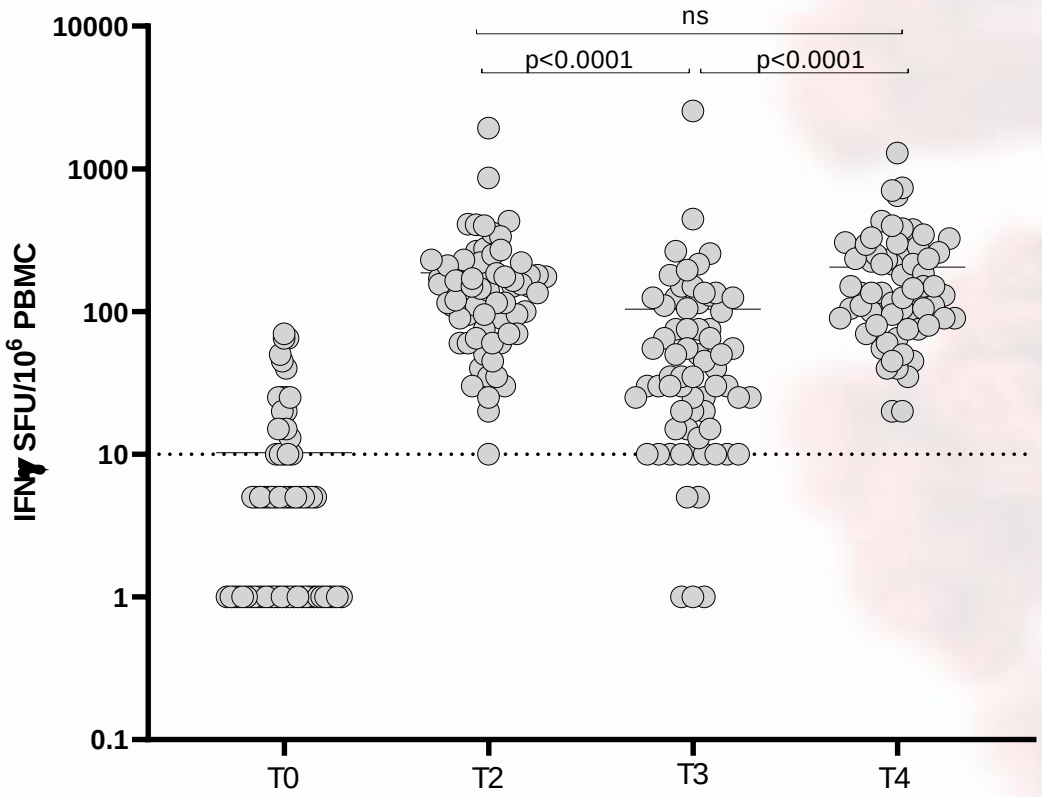
Immunogenicity of third BNT162b2 vaccine dose in healthcare workers





BNT162b2 vaccine immunogenicity was evaluated in 68 HCW at baseline (T0), after II dose (T2), at six months after vaccination (T3) and after third dose administration (T4).

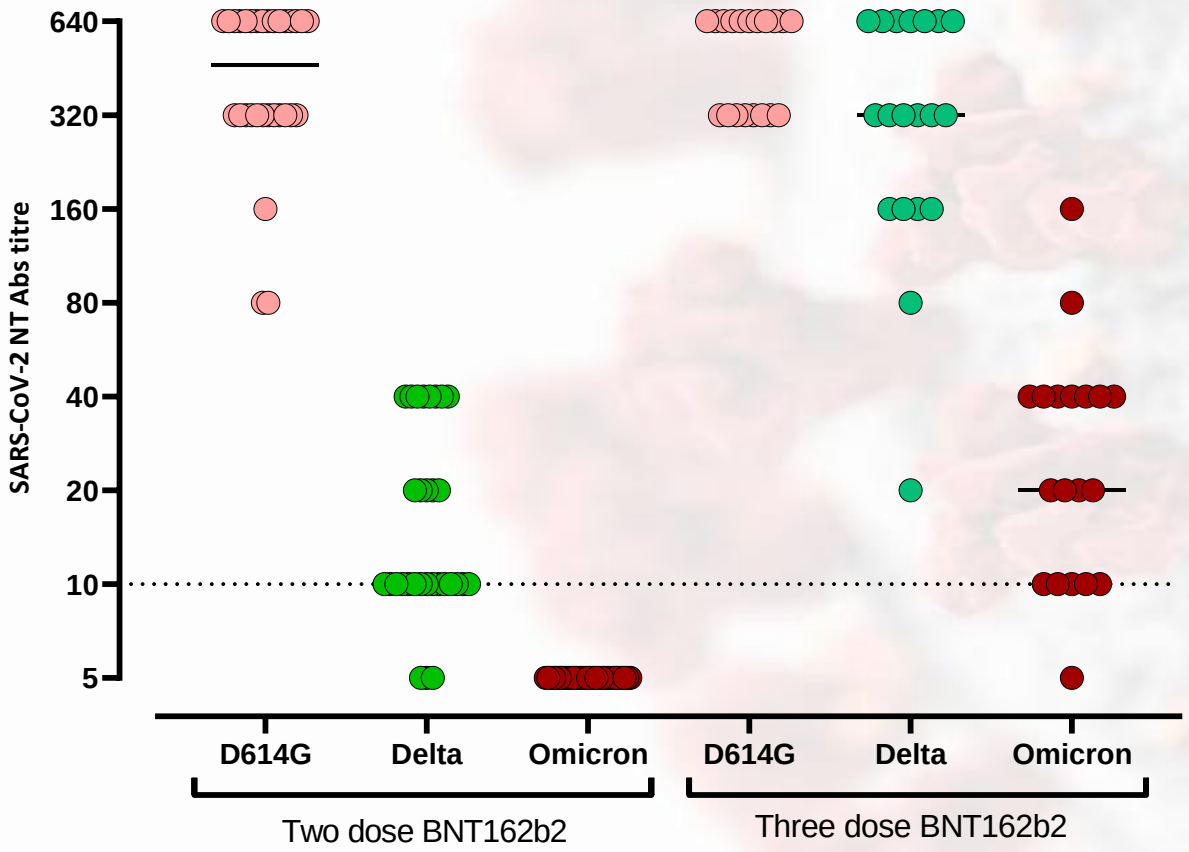
Immunogenicity of third BNT162b2 vaccine dose in healthcare workers



T-cell response elicited by BNT162b2 vaccine was evaluated in 68 HCW at baseline (T0), after II dose (T2), at six months after vaccination (T3) and after third dose administration (T4).

All the subjects were reponders for T-cell mediated response at T2 and T4

SARS-CoV-2 NT Abs response against VOC after third dose



Immunogenicity of third BNT162b2 vaccine dose in transplanted patients

Dependent variable	Independent variable	Estimate β coefficient	95% confidence interval	P value
S Trimeric (Log_{10}BAU/ml)	Intercept	3.442	1.774 to 5.110	<0.001
	Age	-0.011	-0.0374 to 0.015	0.401
	Sex (F)	0.022	-0.669 to 0.624	0.944
	Use of mycophenolate	-0.850	-1.524 to -0.176	0.015
	Use of steroid	-0.653	-1.373 to 0.068	0.075
Nt Abs (Log_{10} titer)	Intercept	3.009	1.709 to 4.310	<0.001
	Age	-0.017	-0.038 to 0.003	0.095
	Sex (F)	-0.049	-0.553 to 0.455	0.845
	Use of mycophenolate	-0.436	-0.962 to 0.089	0.101
	Use of steroid	-0.406	-0.968 to 0.156	0.152
Spike-specific T cells (Log_{10} Spots)	Intercept	3.446	2.246 to 4.646	<0.001
	Age	-0.032	-0.051 to -0.013	0.002
	Sex (F)	-0.088	-0.532 to 0.356	0.689
	Use of mycophenolate	0.118	-0.346 to 0.582	0.609
	Use of steroid	-0.658	-1.184 to -0.132	0.016

In a multivariate linear regression model, we found that the use of mycophenolate was significantly associated with a lower anti-S Trimeric IgG antibody level, while association between use of steroid and a low antibody level was close to significance. Conversely, age and use of steroid were significantly associated with a lower T-cell response. Association between age or use of mycophenolate and a lower Nt Abs titer was close to significance.

11 patients reported SARS-CoV-2 infection after third dose administration (median days after third dose: 106; range 92-117).

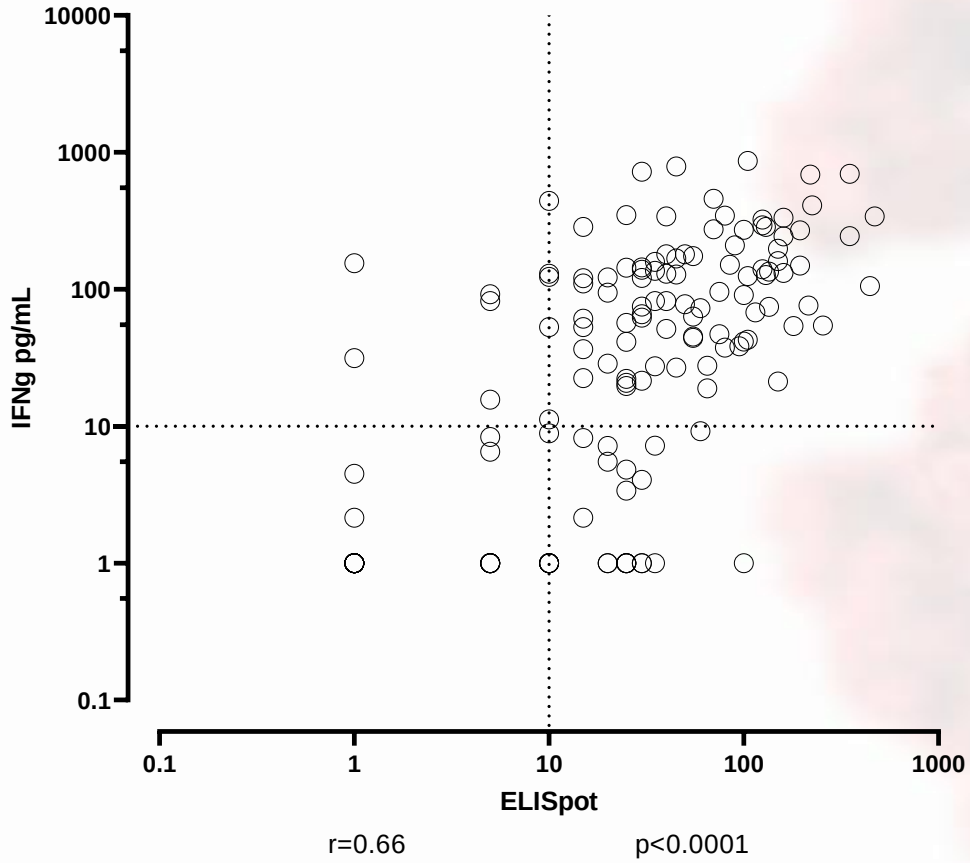
Patient ID	Days*	IgG Abs	SARS-CoV-2 NT Abs	S-ELISpot	Symptoms	Antiviral therapy
#1	92	neg	1:10	10	none	no
#2	117	125	neg	na	cold hoarseness	molnupiravir
#3	103	113	1:10	15	None	no
#4	106	>2080	1:640	575	cold muscolar pain	remdesivir
#5	100	>2080	1:320	65	cough	no
#6	96	neg	neg	neg	cold	MAbs
#7	117	neg	neg	neg	pneumonia, acute respiratory distress and acute kidney injury,	no
#8	110	neg	neg	neg	pneumonia, and acute kidney injury	no
#9	117	neg	1:40	15	ageusia	MAbs
#10	130	183	1:40	na	cough	no
#11	105	neg	neg	25	cold, cough	MAbs

No patient required invasive ventilation and ICU admission and no deaths were observed, confirming that third dose is protective against severe complications and mortality from COVID19

Anti-HLA antibody after third BNT162b2 vaccine dose in transplanted patients

- Anti-HLA antibodies were observed in 7/47 (14.9%) patients.
- DSA antibodies were observed in 3/47 (2.1%) patients.
- No rejection episode was recorded during this follow up period.

Monitoring of SARS-CoV-2 T-cell response: methods

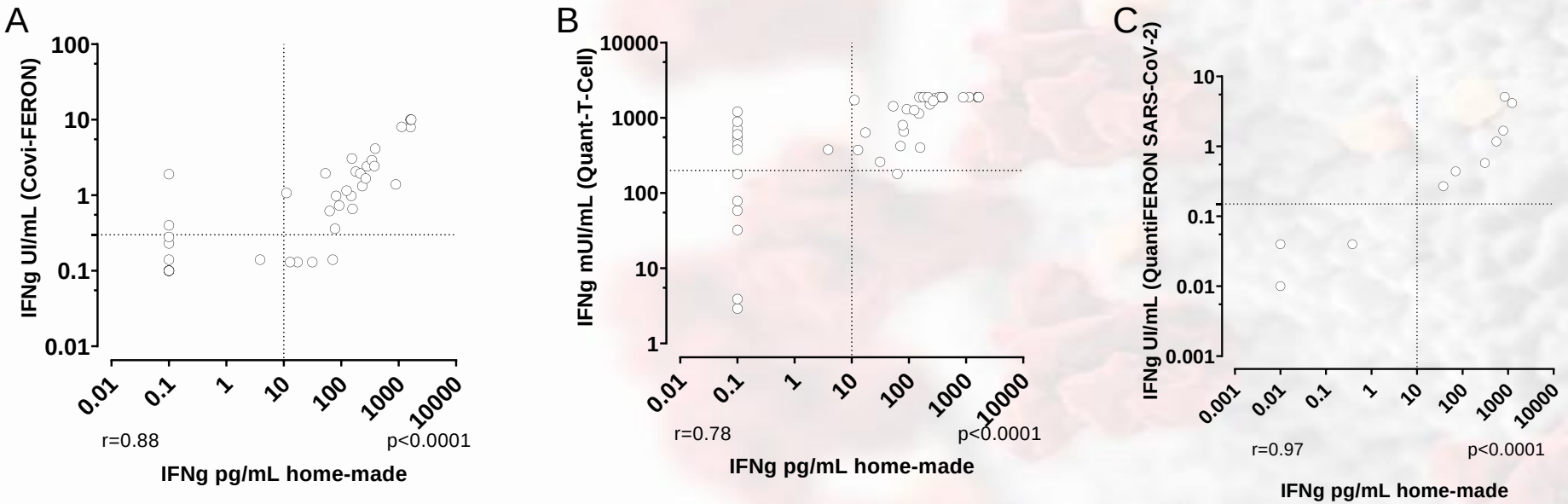


Home-made whole blood stimulation and IFNg release assay was developed and compared with results obtained by ELISpot assay

Results of 150 donors are shown in Figure

	ELISpot		
HM IGRA	positive	negative	total
positive	93	6	99
negative	23	28	51
total	116	34	150

Monitoring of SARS-CoV-2 T-cell response: methods



Three commercial IGRA and results were compared to those obtained by our home-made assay

Vaccination in haemodyalisis patients

Verdier *et al. BMC Nephrology* (2022) 23:189
https://doi.org/10.1186/s12882-022-02751-5

BMC Nephrology

RESEARCH Open Access

Response to three doses of the Pfizer/ BioNTech BNT162b2 COVID-19 vaccine: a retrospective study of a cohort of haemodialysis patients in France

Jean-François Verdier[1*], Sonia Boyer[1], Florence Chalmin[1], Ahmed Jeribi[1], Caroline Egasse[1], Marie France Maggi[2], Philippe Auvray[1] and Tarik Yalaoui[3]

The humoral immune response rate was 82.9% after two injections and 95.8% after three injections

Nephrol Dial Transplant (2021) 36: 1704–1709
doi: 10.1093/ndt/gfab193
Advance Access publication 31 May 2021

High immunogenicity of a messenger RNA-based vaccine against SARS-CoV-2 in chronic dialysis patients

Nathalie Longlune[1], Marie Béatrice Nogier[1], Marcel Miedougé[2], Charlotte Gabilan[1], Charles Cartou[1], Bruno Seigneuric[1], Arnaud Del Bello[1], Olivier Marion[1,3,4], Stanislas Faguer[1,3], Jacques Izopet[2,3,4] and Nassim Kamar[1,3,4]

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The seroconversion rate was 88.7% after two doses.

Due to high immunogenicity and safety of mRNA vaccines, patients waiting for a kidney transplantation should be offered the vaccine before transplantation.

Conclusion

- Transplanted patients with no history of previous SARS-CoV-2 showed a suboptimal response to vaccination. Response to vaccination appears delayed in transplant recipients.
- Third dose increase the number of responders and the level of response.
- We observed a higher level of immunization in terms of cell-mediated response than humoral response. Serological approach alone might underestimate the rate of responder subjects.
- Response to vaccination was reduced in older patients and in those treated with mycophenolate or steroid.
- SARS-CoV-2 vaccination can promote DSA appearance (but with no clinical consequences in our cohort). DSA monitoring after vaccination might be suggested.

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