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Immunogenicity and safety of an inactivated virus vaccine against SARS-CoV-2 in patients with autoimmune rheumatic diseases

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Article

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Abstract

CoronaVac(SARS-CoV-2 inactivated vaccine) has been largely used as the main immunogen for COVID-19 in several countries. However, its immunogenicity in immunocompromised individuals has not been established. This was a prospective controlled study of 910 adult ARD patients and 182 age- and sex-matched control group(CG) who received two doses of CoronaVac in a 28-days interrval. Anti-SARS-Cov-2 IgG and neutralizing antibodies were assessed at each vaccine shot and 6 weeks after the 2nd dose. Vaccine adverse events(AE) were similar in both groups. We observed significant lower anti-SARS-Cov-2 IgG seroconversion(70.4% vs. 95.5%,p < 0.001) and titers[12.1(95%CI 11.0-13.2) vs. 29.7(95%CI 26.3–33.5),p < 0.001], frequency of neutralizing antibodies(56.3% vs. 79.3%),p < 0.001) and median (interquartile range) neutralization activity [58.7(43.1–77.2) vs. 64.5(48.4–81.4),p = 0.013] in ARD patients compared to CG. A significant decline in the number of COVID-19 cases (p < 0.0001) were observed 10 days after the second dose, with a predominant P1 variant. Safety analysis revealed no moderate/severe AEs. In conclusion, CoronaVac has an excellent safety profile and reasonable rates of quantitative serology(70.4%)/neutralization(56.3%) in ARD patients. The impact of this reduced immunogenicity in vaccine effectiveness warrants further evaluation.

Main

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people around the world[1]. Moreover, Brazil is among the countries with the highest numbers of confirmed cases and deaths by SARS-CoV-2[1,2] with a second wave driven by the P.1 coronavirus variant[3], which is considered to be 2.5 fold more contagious than the original strain[4] and possibly associated with higher risk for hospitalization and intensive care unit (ICU) admission in patients younger than 60 years-old[5]. This second peak had a hard-hit in March and April 2021 with more than double of the prior record of coronavirus disease 2019 (COVID-19) cases of the first peak in 2020[6]. Vaccines are therefore essential for reducing COVID-19 mortality and morbidity.

Although phase III clinical trials results are still being consolidated in China, Hong Kong, Indonesia, Brazil, Chile, Philippines, and Turkey[7], CoronaVac, an inactivated virus vaccine against SARS-CoV-2, has received approval for use in several countries. These regions account for at least three of the top six most populated countries in the world and therefore, of great interest for the global control of this disease. By the time of this submission, CoronaVac accounts for approximately 75% of the administered vaccines in Brazil. It can be kept refrigerated[8], a great advantage for deployment in developing countries. In addition, the more traditional technology using the whole virus may have the benefit of a broader immune response compared to the other vaccine platforms using only the Spike protein as the basis for immunogenicity. This may be relevant for the second surge of SARS-CoV-2 variants containing mutations in the Spike protein, also documented in Brazil[3,9]. In fact, cross-reactive immunogenicity for Brazilian variants P.1 and P.2 was achieved in healthy volunteers vaccinated with CoronaVac in a phase III clinical trial conducted in this country, which confirmed the outstanding safety profile[10,11].

However, the reported 50.7% efficacy to prevent mild COVID-19 in the phase III clinical trial[10], raises concerns about its immunogenicity in immunosuppressed patients as they comprise millions of people including those with autoimmune diseases, patients with neoplasia, transplant recipients and patients living with human immunodeficiency virus (HIV) among other groups, with an estimated prevalence in the US of 2.7% of the population[12]. A recent letter reported a greatly reduced anti-spike antibody response (17%) after the first dose of SARS-CoV-2 mRNA − 1273 or BNT162b2 vaccination in 436 solid organ transplant recipients[13]. Immunogenicity improved after the second dose, but 46% still lacked detectable antibody response[14]. In contrast, all patients developed antibody responses in a small group of patients with chronic inflammatory diseases (n = 26), including some with autoimmune rheumatic diseases (ARD) after SARS-CoV-2 mRNA vaccine[15]. Similarly, most patients (91%) with several immune-mediated inflammatory diseases (n = 84), including only 16 with systemic ARD, developed detectable neutralizing activity in a retrospective study with BNT162b2 mRNA SARS-CoV-2 vaccine immunogenicity[16]. Reinforcing this finding, a report with small representation of various ARD without a control group, also observed that anti-RBD antibodies response to the mRNA vaccines was present in 74% of the patients, with distinct patterns according to age and therapeutic regimen[17]. Importantly, immunocompromised patients encompasses a group that have intrinsic factors of high risk for infectious diseases due to disease immune dysregulation itself and current therapy, in addition to high frequencies of comorbidities associated with coronavirus severity[18–20] and therefore, they may fulfill criteria for prioritization in the context of limited vaccine supply[21]. Moreover, immunocompromised state was reported to be associated with a prolonged SARS-CoV-2 shedding[22], reduced SARS-CoV-2 virus clearance, and enhanced viral genomic evolution[23], emphasizing the relevance of the vaccine for this group of patients to reduce transmission and prevent new variants development.

In this context, the present study aimed to prospectively evaluate the immunogenicity (anti-SARS-CoV-2 IgG and neutralizing antibodies) and safety of CoronaVac in a large cohort of ARD patients compared with age- and sex-matched controls without these conditions. We further checked for incident symptomatic cases confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 and the presence of variants of concern (P1, B.1.1.7, and B.1.351 lineages).

Results

Participants

A total of 1418 ARD patients were invited to the study, but 225 were excluded according to the established criteria: 24 cases of acute febrile illness/symptoms compatible to COVID-19 at the day of vaccination or with real-time RT-PCR confirmed COVID-19 less than four weeks before the day of vaccination, 1 demyelinating disease, 25 previous vaccination with any SARS-Cov-2 vaccine, 1 virus vaccine inactivated up to two weeks before, 161 individuals who did not accept to participate in the study, and 13 hospitalized patients. Subsequently, 542 controls were summoned, but 50 individuals refused to participate. The remaining 1193 ARD patients and 492 controls received the vaccine first dose, but 232

(19.4%) ARD patients and 191 (38.8%) controls had positive baseline IgG serology and/or neutralizing antibodies (Nab) and were further excluded from this analysis. The remaining 961 ARD patients and 301 controls with negative serology were then matched in a 5:1 ratio (5 ARD patients:1 control) by age and gender (maximal variation ± 5 years), and 910 ARD patients and 182 control group (CG) comprised the final study groups.

ARD patients diagnoses were: 451 (49.6%) chronic inflammatory arthritis (CIA) [256 (28.1%) rheumatoid arthritis (RA), 106 (11.6%) axial spondyloarthritis (AxSpA) and 89 (9.8%) psoriatic arthritis (PsA)] and 459 (50.4%) other systemic ARD [232 (25.5%) systemic lupus erythematosus (SLE), 66 (7.3%) primary vasculitis, 42 (4.6%) primary Sjögren's syndrome (pSSj), 41 (4.5%) systemic sclerosis (SSc), 41 (4.5%) idiopathic inflammatory myopathies (IIM), and 37 (4.1%) primary antiphospholipid syndrome (PAPS) (Table 1). The CG (n = 182) included hospital cleaning and general maintenance services workers 109 (59.9%), health professionals 45 (24.7%) and hospital administrative services employees or their relatives 28 (15.4%).

Table 1
– Baseline characteristics of autoimmune rheumatic diseases (ARD) patients and control group (CG)

	ARD (n = 910)	**CG (n = 182)**	***p* value**
Demographics			
Current age, years	51 (40–60)	50 (41–60)	0.985
Female sex	700 (76.9)	140 (76.9)	1.0
Caucasian race	482 (53.0)	82 (45.1)	0.051
Comorbidities			
Systemic arterial hypertension	400 (44.0)	55 (30.2)	**0.001**
Diabetes mellitus	106 (11.6)	28 (15.4)	0.161
Dyslipidemia	246 (27.0)	14 (7.7)	**< 0.001**
Obesity	295 (32.4)	58 (31.9)	0.954
Chronic cardiomyopathy	52 (5.7)	3 (1.6)	**0.024**
Chronic renal disease	44 (4.8)	0	**0.001**
Current smoking	84 (9.2)	21 (11.0)	0.461
Chronic obstructive pulmonary disease	13 (1.4)	2 (1.1)	1.0
Asthma	36 (4.0)	6 (3.3)	0.673
Interstitial lung disease	78 (8.6)	0	**< 0.001**
Pulmonary hypertension	13 (1.4)	0	0.142
Hematologic disease	3 (0.3)	0	1.0
Hepatic disease	39 (4.3)	0	**0.001**
Current cancer	8 (0.9)	0	0.365
Stroke	34 (3.7)	0	**0.004**
Current tuberculosis	2 (0.2)	0	1.0
HIV	0	0	-

Results are expressed in medians (interquartile range) and n (%).

ARD – autoimmune rheumatic diseases; CG – control group; RA – rheumatoid arthritis; axSpA – axial spondyloarthritis; PsA – psoriatic arthritis; Other ARD: SLE – systemic lupus erythematosus, primary vasculitis, SSc – systemic sclerosis, pSSj – primary Sjögren syndrome, IMM – Idiopathic inflammatory myopathies, and PAPS – primary antiphospholipid syndrome.

	ARD (n = 910)	CG (n = 182)	*p* value
ARD			
Chronic inflammatory arthritis (RA, axSpA, PsA)	451 (49.6)	-	-
Other ARD (SLE, primary vasculitis, SSc, pSSj, IIM, PAPS)	459 (50.4)	-	-
CURRENT THERAPY			
Prednisone	348 (38.2)	-	-
Prednisone dose, mg	5 (5–10)	-	-
Prednisone ≥ 20mg/day	32 (3.5)	-	-
Immunosuppressive drugs	573 (63.0)	-	-
Biologic therapy	321 (35.3)	-	-
Results are expressed in medians (interquartile range) and n (%).			
ARD – autoimmune rheumatic diseases; CG – control group; RA – rheumatoid arthritis; axSpA – axial spondyloarthritis; PsA – psoriatic arthritis; Other ARD: SLE – systemic lupus erythematosus, primary vasculitis, SSc – systemic sclerosis, pSSj – primary Sjögren syndrome, IMM – Idiopathic inflammatory myopathies, and PAPS – primary antiphospholipid syndrome.			

The 910 ARD patients and 182 CG had comparable median (interquartile range) ages [51 (40–60) vs. 50 (41–60) years, p = 0.985] and female sex (76.9% vs. 76.9%, p = 1.0) (Table 1). Frequencies of comorbidities were significantly higher in ARD, particularly systemic arterial hypertension (44.0% vs. 30.2%, p = 0.001), dyslipidemia (27.0% vs. 7.7%, p < 0.001), interstitial lung disease (8.6% vs. 0, p < 0.001), cardiomyopathy (5.7% vs. 1.6%, p = 0.024), and chronic renal disease (4.8% vs. 0, p = 0.001) (Table 1). Concerning current ARD treatment, 348 (38.2%) patients were under prednisone, mean dose of 8.4 ± 7.3mg/day, 573 (63.0%) were using immunosuppressive drugs and 321 (35.3%) were under biologic therapy (Table 1).

Vaccine immunogenicity

For this analysis we excluded 38 (4.2%) participants (35 ARD patients and 3 CG) with real time RT-PCR confirmed COVID-19 after the first or the second dose of vaccine until D69 and 16/910 (1.5%) patients who did not attend the final visit (D69), including two deaths not related to COVID-19.

Anti-SARS-CoV-2 IgG antibodies

Humoral response parameters against CoronaVac in the remaining 859 ARD patients and 179 controls are shown in Table 2. Analysis of SARS-CoV-2 S1/S2 IgG response revealed that six weeks after vaccine second dose, seroconversion (SC) rates [605 (70.4%) vs. 171 (95.5%), $p < 0.001$], geometric mean titers (GMT) [27.0 (95%CI 24.7–29.5) vs. 67.0 (95%CI 59.8–74.9), $p < 0.001$], and factor increase in GMT (FI-GMT) [12.1 (95%CI 11.0-13.2) vs. 29.7 (95%CI 26.3–33.5), $p < 0.001$] were lower in ARD patients compared to CG (Table 2). Further analysis of disease subgroups revealed that after complete vaccination, SC rates and GMT were reduced in CIA [SC: 70.7% vs. 95.5%, $p < 0.001$ and GMT: 26.3 (95%CI 23.3–29.8) vs. 67.0 (95%CI 59.8–74.9), $p < 0.001$] and other systemic ARD [70.2% vs. 95.5%, $p < 0.001$ and GMT: 27.7 (95%CI 24.3–31.6) vs. 67.0 (95%CI 59.8–74.9), $p < 0.001$] versus CG (Table 2). No differences were observed in immunogenicity parameters between CIA and other systemic ARD ($p > 0.05$).

Table 2
Seroconversion (SC) rates and anti-SARS-CoV-2 S1/S2 IgG titers before and after the first and second doses of CoronaVac vaccination in autoimmune rheumatic diseases (ARD) and Control Group (CG)

	Before vaccine 1st dose	After vaccine 1st dose			After vaccine 2nd dose		
	GMT	SC	GMT	FI-GMT	SC	GMT	FI-GMT
CG, n = 179	2.3 (2.1–2.4)	62 (34.6)	10.3 (8.5–12.5)Ŧ	4.6 (3.9–5.4)	171 (95.5)	67.0 (59.8–74.9)Ŧβ	29.7 (26.3–33.5)
ARD, n = 859	2.2 (2.2–2.3)	161 (18.7)*	5.1 (4.7–5.5)*#	2.3 (2.1–2.5)*	605 (70.4)*	27.0 (24.7–29.5)*#α	12.1 (11.0-13.2)*
CIA, n = 430	2.2 (2.1–2.2)	64 (14.9)*	4.4 (4.0-4.9)*	2.1 (1.9–2.3)*	304 (70.7)*	26.3 (23.3–29.8)*	12.2 (10.8–13.8)*
Other ARD, n = 429	2.3 (2.2–2.4)	97 (22.7)*	5.9 (5.3–6.6)*	2.5 (2.3–2.8)*	301 (70.2)*	27.7 (24.3–31.6)*	12.0 (10.5–13.7)*
Results are expressed in mean (95%CI) and n (%).							
GMT – Geometric mean titers (AU/mL); SC – seroconversion (defined as post vaccination titer ≥ 15 AU/mL - Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy); FI-GMT – factor increase of Geometric mean titers;							
ARD – autoimmune rheumatic diseases; CG – control group; CIA – chronic inflammatory arthritis (rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis); Other ARD– systemic lupus erythematosus, primary vasculitis, systemic sclerosis, primary Sjögren syndrome, idiopathic inflammatory myopathies and primary antiphospholipid syndrome;							
***** - $p < 0.001$ in comparison among ARD and CG at the same time points;							
# - $p < 0.001$ for longitudinal comparisons of GMT in ARD at D28 and D69 *vs.* baseline;							
α - $p < 0.001$ for longitudinal comparison of GMT in ARD at D69 *vs.* D28;							
Ŧ - $p < 0.001$ for longitudinal comparison of GMT in CG at D28 and D69 vs. baseline;							
β - $p < 0.001$ for longitudinal comparison of GMT in CG at D69 vs D28.							

Regarding the dynamics of anti-SARS-CoV-2 IgG response, the minority of participants in both groups developed antibodies after the first dose, with a lower frequency and level in ARD patients compared to CG [161 (18.7%) vs. 62 (34.6%), $p < 0.001$] and FI-GMT [2.3 (95%CI 2.1–2.5) vs. 4.6 (95%CI 3.9–5.4), $p <$

0.001]. The SC rates doubled after the second dose with more than 5-fold increase in GMT (FI-GMT) for both groups (Table 2 **and** Fig. 1**).**

SARS-CoV-2 cPass virus-neutralization antibodies (Nab)

The presence of NAb was analyzed in 859 ARD patients and 179 controls, all with negative anti-SARS-CoV-2 S1/S2 IgG antibodies and Nab pre vaccination (Table 3). After the complete vaccination, Nab positivity was lower in ARD patients compared to controls [56.3% vs. 79.3%, $p < 0.001$) with lower median (interquartile range) neutralization activity [58.7% (43.1–77.2) vs. 64.5% (48.4–81.4), $p = 0.013$]. Analysis of the dynamics of Nab detection disclosed that, after the first dose, the minority of participants had positive antibodies and ARD patients had significantly lower frequencies [177 (20.6%) vs. 65 (36.3%), $p < 0.001$] but with similar median (interquartile range) activity [42.6% (35.8–60.4) vs. 45% (34.5–71.1), $p = 0.490$] compared with CG (Table 3).

Table 3
– Frequency of neutralizing antibodies (NAb) and median percentage of neutralizing activity in positive cases, after the first and second doses of CoronaVac vaccination in autoimmune rheumatic diseases (ARD) in comparison to control group (CG).

	After vaccine 1st dose		**After vaccine 2nd dose**	
	Subjects with positive NAb, N (%)	**Neutralizing activity (%) Median (interquartile range)**	**Subjects with positive NAb, N (%)**	**Neutralizing activity (%) Median (interquartile range)**
CG, n = 179	65 (36.3)	45 (34 .5-71.1)	142 (79.3)	64.5 (48.4–81.4)
ARDs, n = 859	177 (20.6)*	42.6 (35.8–60.4)	484 (56.3)*	58.7 (43.1–77.2) ***
CIA, n = 430	75 (17.4)*	41.4 (33.5–57.2)	230 (53.5)*	57.8 (42.5–72.8) **
Other ARDs, n = 429	102 (23.8)**	44.6 (37.3–60.9)	254 (59.2)*	59.4 (44.2–80)
Results are expressed in median (interquartile range) and n (%). Positivity for Nab defined as a neutralizing activity ≥ 30 % (cPass sVNT Kit, GenScript, Piscataway, USA)				
***p < 0.05, **p < 0.01 and *p < 0.001 in comparison to CG				
ARD – autoimmune rheumatic diseases; CG – control group; CIA – chronic inflammatory arthritis (rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis); Other ARD – systemic lupus erythematosus, primary vasculitis, systemic sclerosis, primary Sjögren syndrome, idiopathic inflammatory myopathies and primary antiphospholipid syndrome.				

Factors associated with lower SC

Analysis of factors associated with lower immunogenicity in ARD demonstrated that patients with negative anti-SARS-CoV-2 IgG after two doses of CoronaVac had older age [53 (45–63) vs. 49 (39–59), $p < 0.001$), with a higher frequency of females [208/254 (81.9%) vs. 452/605 (74.7%), $p = 0.023$] compared to those with positive anti-SARS-CoV-2 IgG. Regarding therapy, frequencies of prednisone [142/254 (55.9%) vs. 188/605 (31.1%), $p < 0.001$], prednisone ≥ 20mg/day [14/254 (5.5% vs. 16/605 (2.6%), $p = 0.037$], immunosuppressants [208/254 (81.9%) vs. 330/605 (54.5%), $p < 0.001$] and biologic therapy [112/254 (44.1) vs. 195/605 (32.2%), $p = 0.001$] were higher in non-seroconverters (Table 4). Multivariate analysis revealed that age more than 60 years old (OR = 0.564, 95%CI 0.401–0.793, $p < 0.001$), prednisone use (OR = 0.500; 95%CI 0.359–0.695, $p < 0.001$), use of immunosuppressive drugs (OR = 0.330; 95%CI 0.225–0.485, $p < 0.001$]) and biologic therapy (OR = 0.627; 95%CI 0.454–0.864, $p = 0.004$) were significantly associated with absence of SC in ARD patients.

Table 4
– Baseline characteristics of ARD patients with and without seroconversion (SC) for anti-SARS-CoV-2 S1/S2 IgG antibodies and with and without neutralizing antibodies (NAbs) after two doses of CoronaVac vaccination

	ARD patients without SC (n = 254)	ARD patients with SC (n = 605)	*p* value	ARD patients without NAbs (n = 375)	ARD patients with NAbs (n = 484)	*p* value
Demographics						
Current age, years	53 (45–63)	49 (39–59)	**< 0.001**	52 (43–62)	49 (39–59)	**< 0.001**
Age ≥ 60years	89 (35)	142 (23.5)	**< 0.001**	122 (32.5)	109 (22.5)	**0.001**
Female sex	208 (81.9)	452 (74.7)	**0.023**	293 (78.1)	367 (75.8)	0.427
Caucasian race	144 (56.7)	312 (51.6)	0.170	213 (56.8)	243 (50.2)	0.055
ARD						
CIA	126 (49.6)	304 (50.2)	0.864	200 (53.3)	230 (47.5)	0.091
Other ARD	128 (50.4)	301 (49.8)		175 (46.7)	254 (52.5)	
CURRENT THERAPY						
Prednisone	142 (55.9)	188 (31.1)	**< 0.001**	185 (49.3)	145 (30.0)	**< 0.001**
Prednisone dose, mg	5 (5–10)	5 (5–10)	0.926	5 (5–10)	5 (5–10)	0.731
Prednisone ≥ 20mg/day	14 (5.5)	16 (2.6)	**0.037**	15 (4)	15 (3.1)	0.476
Immunosuppressive drugs	208 (81.9)	330 (54.5)	**< 0.001**	272 (72.5)	266 (55)	**< 0.001**
Biologic therapy	112 (44.1)	195 (32.2)	**< 0.001**	155 (41.3)	152 (31.4)	**0.003**

Results are expressed in median (interquartile range) and n (%).

ARD – autoimmune rheumatic disease; CIA – chronic inflammatory arthritis (rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis); Other ARD – systemic lupus erythematosus, primary vasculitis, systemic sclerosis, primary Sjögren syndrome, idiopathic inflammatory myopathies and primary antiphospholipid syndrome. SC – seroconversion defined as a positive serology (IgG titer ≥ 15 AU/ml) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for Nabs defined as a neutralizing activity ≥ 30 % (cPass sVNT Kit, GenScript, Piscataway, USA).

Similarly, patients with negative NAb after complete vaccination were older [52 (43–62) vs. 49 (39–59) years, $p < 0.001$] than those with positive NAb. Non-seroconverters were more frequently ≥ 60 years old [122/375 (32.5%) vs. 109/484 (22.5%), $p = 0.001$], under prednisone [185/375 (49.3%) vs. 145/484 (30%), $p < 0.001$], immunosuppressants [272/375 (72.5%) vs. 266/484 (55%), $p < 0.001$] or biologic therapy [155/375 (41.3%) vs. 152/484 (31.4%), $p = 0.003$] (Table 4). Multivariate analysis identified age ≥ 60 years old (OR = 0.613; 95%CI 0.442–0.849, $p = 0.003$), prednisone use (OR = 0.530; 95%CI 0.389–0.721, $p < 0.001$), immunosuppressive drugs (OR = 0.569; 95%CI 0.415–0.780, $p < 0.001$) and biologic therapy (OR = 0.691; 95%CI 0.493–0.969, $p = 0.032$) as associated with absence of neutralizing activity in ARD patients.

Vaccine tolerance and safety

CoronaVac vaccine safety analysis is illustrated in Table 5. No moderate/severe adverse events (AE) related to the vaccine were reported. After the first dose, the most frequent reported vaccine reactions in ARD and CG were pain at the injection site (19.8% vs. 17.0%, $p = 0.388$), headache (20.2% vs. 11.0%, $p = 0.003$) and somnolence (13.6% vs. 10.4%, $p = 0.243$). Overall reactions were more frequently reported in ARD patients than CG (50.5% vs. 40.1%, $p = 0.011$) including arthralgia (13.5% vs. 6.0%, $p = 0.005$), back pain (9.8% vs. 4.9%, $p = 0.037$), malaise (9.5% vs. 4.4%, $p = 0.026$), nausea (6.1% vs. 2.2%, $p = 0.032$) and sweating (5.6% vs. 1.1%, $p = 0.007$). After the second dose, ARD patients significantly reported less local itching (2.7% vs. 5.5%, $p = 0.047$) and more sweating (5.3% vs. 1.1%, $p = 0.010$) (Table 5).

Table 5
Adverse events of CoronaVac vaccination in autoimmune rheumatic disease (ARD) patients and control group (CG)

	After vaccine 1st dose			**After vaccine 2nd dose**		
	ARD (n = 909)	**CG (n = 182)**	p **value**	**ARD (n = 893)**	**CG (n = 181)**	p **value**
No symptoms	450 (49.5)	109 (59.9)	**0.011**	545 (61.0)	118 (65.2)	0.293
Local reactions (at the injection site)	213 (23.4)	36 (19.8)	0.284	154 (17.2)	32 (17.7)	0.888
Pain	180 (19.8)	31 (17.0)	0.388	125 (14.0)	30 (16.6)	0.368
Erythema	25 (2.8)	5 (2.7)	0.998	23 (2.6)	3 (1.7)	0.602
Swelling	43 (4.7)	12 (6.6)	0.294	45 (5.0)	10 (5.5)	0.787
Bruise	28 (3.1)	6 (3.3)	0.878	23 (2.6)	2 (1.1)	0.232
Pruritus	28 (3.1)	4 (2.2)	0.637	24 (2.7)	10 (5.5)	**0.047**
Induration	56 (6.2)	4 (2.2)	**0.032**	41 (4.6)	12 (6.6)	0.248
Systemic reactions	392 (43.3)	61 (33.5)	**0.014**	298 (33.4)	56 (30.9)	0.526
Fever	25 (2.8)	5 (2.7)	0.998	23 (2.6)	7 (3.9)	0.336
Malaise	86 (9.5)	8 (4.4)	**0.026**	80 (9.0)	15 (8.3)	0.772
Somnolence	124 (13.6)	19 (10.4)	0.243	83 (9.3)	15 (8.3)	0.668
Lack of appetite	37 (4.1)	7 (3.8)	0.888	37 (4.1)	7 (3.9)	0.864
Nausea	55 (6.1)	4 (2.2)	**0.032**	58 (6.5)	13 (7.2)	0.734
Vomit	14 (1.5)	1 (0.5)	0.488	11 (1.2)	2 (1.1)	1.0
Diarrhea	56 (6.2)	9 (4.9)	0.527	56 (6.3)	12 (6.6)	0.857
Abdominal pain	44 (4.8)	7 (3.8)	0.562	43 (4.8)	10 (5.5)	0.688
Vertigo	64 (7.0)	9 (4.9)	0.302	46 (5.2)	9 (5.0)	0.921
Tremor	22 (2.4)	1 (0.5)	0.155	20 (2.2)	2 (1.1)	0.562
Headache	184 (20.2)	20 (11.0)	**0.003**	130 (14.6)	33 (18.2)	0.209
Fatigue	99 (10.9)	14 (7.7)	0.196	95 (10.6)	22 (12.2)	0.550
Sweating	51 (5.6)	2 (1.1)	**0.007**	47 (5.3)	2 (1.1)	**0.010**

Results are presented in n (%). ARD – autoimmune rheumatic diseases; CG – Control group

	After vaccine 1st dose			After vaccine 2nd dose		
Myalgia	81 (8.9)	10 (5.5)	0.128	78 (8.7)	17 (9.4)	0.776
Muscle weakness	68 (7.5)	7 (3.8)	0.077	68 (7.6)	11 (6.1)	0.470
Arthralgia	123 (13.5)	11 (6.0)	**0.005**	93 (10.4)	13 (7.2)	0.184
Back pain	89 (9.8)	9 (4.9)	**0.037**	77 (8.6)	19 (10.5)	0.420
Cough	63 (6.9)	8 (4.4)	0.206	57 (6.4)	12 (6.6)	0.902
Sneezing	75 (8.3)	9 (4.9)	0.127	87 (9.7)	18 (9.9)	0.933
Coryza	75 (8.3)	13 (7.1)	0.616	76 (8.5)	17 (9.4)	0.701
Stuffy nose	52 (5.7)	8 (4.4)	0.474	55 (6.2)	11 (6.1)	0.967
Sore throat	67 (7.4)	7 (3.8)	0.084	60 (6.7)	11 (6.1)	0.751
Shortness of breath	29 (3.2)	6 (3.3)	0.941	23 (2.6)	6 (3.3)	0.576
Conjunctivitis	12 (1.3)	0	0.235	9 (1.0)	2 (1.1)	1.0
Pruritus	33 (3.6)	3 (1.6)	0.253	39 (4.4)	6 (3.3)	0.519
Skin rash	9 (1.0)	3 (1.6)	0.433	14 (1.6)	0	0.090
Results are presented in n (%). ARD – autoimmune rheumatic diseases; CG – Control group						

COVID-19 incident cases

Incident cases evaluation period was extended to 10 days (D79) after final immunogenicity analysis (D69). A total of 39 incident symptomatic cases of COVID-19 confirmed by RT-PCR among ARD patients and CG [36/910 (4%) vs. 3/182 (1.6%), p = 0.186] was observed throughout the study period. The frequency of cases occurring from D0-D39 (until 10 days after the second dose) was higher compared to D40-D79 [33/1092 (3.0%) vs. 6/1057 (0.6%), p < 0.0001]. Four ARD patients were hospitalized (< 10 days after second dose) and none deceased for COVID-19. Evaluation of variants of concern revealed that 83.3% (15/18) were P.1 variants, 5.6% (1/18) B.1.1.7 and 11.1% (2/18) had other variants.

Regarding environmental factors associated with high risk of exposure to SARS-CoV-2, ARD patients reported higher adherence to social isolation [620/892 (69.5%) vs. 39/180 (21.7%), p < 0.001], with lower household contact with infected people (4.6% vs. 15.5%, p = 0.0001) and lower use of public transportation [426/893 (47.7%) vs. 147/180 (81.7%), p < 0.001) compared to CG. Number of people living in the same home were alike in both groups [2 (1–3) vs. 2 (1–3), p = 0.648].

Discussion

This large prospective study of SARS-CoV-2 vaccination in ARD patients. CoronaVac vaccine demonstrated an excellent safety profile without any serious/moderate AE related to the vaccine. The vaccine was immunogenic, but at lower levels when compared to the CG.

We prospectively included a large population of ARD patients representing eight systemic ARD fulfilling their respective classification criteria and followed all participants with scheduled face-to-face appointments, telephone, smartphone instant messaging and email contacts, which allowed a more precise monitoring of vaccine induced AEs in this population. In fact, tolerance and safety are a relevant concern for ARD patients, since they have, for instance, an intrinsic risk of thrombosis[24], a rare complication reported for some of the new vaccines[25]. No serious AE related to vaccination was reported including the lack of autoimmune/autoinflammatory manifestations, another relevant problem with adjuvanted vaccines in this already predisposed population[26]. Similar to CoronaVac trials in the healthy population[27], most of the vaccine related AEs were mild and pain at the injection site was the most frequently reported. Interestingly, vaccine related AE, particularly systemic symptoms, were much less frequent in both ARD and CG than those reported with mRNA vaccines[28,29]. We, therefore, confirmed the reported excellent safety profile of CoronaVac[11], and extended this finding to immunocompromised patients.

Age-matching with the CG was essential as seroconversion against CoronaVac may be lower in the older population[10]. This condition was not met by previous studies evaluating SARS-CoV-2 vaccination in ARD patients precluding a definitive conclusion about their findings[15–17]. The lack of assessment of vaccine T-cell responses was a limitation of the present study[30,31].

The current COVID-19 pandemic began in December 2019 in Wuhan, China, and quickly became a global health and economic emergency[32], leading to an unprecedented burden on health systems worldwide. Brazil is the second country with highest mortality by COVID-19 complications, with more than 430,000 deaths registered and the third among the top countries in number of confirmed cases (approximately ~ 15 million cases until May 2021)[1]. Vaccinating this population and particularly the immunosuppressed patients, who were excluded from phase III vaccine trials, is of utmost importance since ARD patients are generally under an increased risk of hospitalization for severe COVID-19[19]. In line with this intrinsic increased vulnerability for more severe COVID-19, we observed herein, a higher frequency of comorbidities such as cardiovascular and chronic respiratory diseases, systemic arterial hypertension and chronic renal disease in ARD than in age- matched CG.

The exclusion of pre-vaccination seropositive patients using two different methods (SARS-CoV-2 IgG antibody and/or Nab) and those with COVID-19 during the study period allowed a more accurate evaluation of CoronaVac. In addition, the concomitant blood collection in two consecutive days for the whole group at each time point precluded the possible confounding non-linear relationship between time elapsed and vaccine response. With this rigid protocol, our findings evidenced a lower CoronaVac immunogenicity in ARD patients, although within the immunologic response standards (SC rates and

GMT) established by European Medicine Agency (EMA) and Food and Drugs Administration (FDA) recommendations for Emergency Use Authorization of pandemic vaccines, such as influenza[33,34]. The 70% SC rate was comparable to the obtained against the pandemic influenza A H1N1 inactivated vaccine (approximately 63%),[35] but lower than the reported for SARS-CoV-2 mRNA vaccine in a very small ARD population,[17] and in a study with patients predominantly under cytokine inhibitors therapy and with small representation of systemic diseases[16]. We further demonstrated a significant increase in immune response parameters after the second dose, reinforcing the importance to observe the full vaccination schedule for optimal vaccine effect. Similar to the anti-SARS-Cov-2 response, the frequency of mean inhibitory neutralizing activity against SARS-CoV-2 (56.4%) was reduced compared to controls and that reported after SARS-CoV-2 mRNA vaccination[15,16]. Again, the second dose was essential to achieve the maximum response for both groups, with a lower neutralization activity in ARD than in CG after the two vaccine doses. The profile of tertiary hospital patients evaluated herein, with high frequency of immunosuppressive/glucocorticoid use, probably contributed to the reduced humoral response observed in ARD group.

We confirmed and extended previous reports with mRNA vaccines that older age and ARD itself negatively influence SARS-CoV-2 humoral response, a finding also observed for CoronaVac[10]. The deleterious impact of immunosuppressive therapy was also observed herein for this latter inactivated vaccine compared to those not on these drugs. This finding is in line with a small sample size ARD study[15] and contrasts with the observed for ARD patients under cytokines inhibitors with a small representation of systemic diseases[16].

Although not the main objective of this study, the data also suggest preliminary encouraging evidence of a short-term efficacy of CoronaVac vaccine in preventing symptomatic cases and an extension period of 12 months observation period for incident cases is already in progress. Importantly, ARD patients and CG were all vaccinated at the same epidemiological week within two days, providing a unique condition of comparable influence of the ongoing COVID-19 epidemiology. Remarkably, the 45% rapid acceleration of COVID-19 cases in Sao Paulo city occurred from mid-March coinciding with the period after 10 days of second dose through the end of April[36]. In this 40 days-interval in which vaccine immunity is already expected, the frequency of COVID-19 cases were significantly lower than the previous 40 days after the first vaccination. The unanticipated overall similar frequencies of SARS-CoV-2 infection in ARD patients, a known vulnerable immunosuppressed population, compared to CG during the study period may be explained by the higher adherence to social isolation and lower household contact with infected people, as well as lower use of public transportation among patients. Or else, it may be related to high exposure of the professional activity of the majority of CG. The small number of new RT-PCR-confirmed COVID-19 cases during the observation period hampers, however, a definitive conclusion on the role of vaccine efficacy. P.1 variant was the dominant strain in line with the virological surveillance in the region, when P.1 represented 90% of all sequenced samples in the state in late April 2021, followed by B.1.1.7 (United Kingdom) and B.1.351 (South Africa) as the other variants of concern[37].

In conclusion, this study provides clear evidence of safety and reduced but acceptable short-term immunogenicity of an inactivated SARS-CoV-2 vaccine in the ARD population. The impact of this diminished humoral response in vaccine effectiveness needs to be determined in future studies.

Methods

Ethics statement

The protocol was conducted according to the Declaration of Helsinki and local regulations and approved by the National and Institutional Ethical Committee of Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil (CAAE: 42566621.0.0000.0068). Written informed consent was obtained from each participant before enrollment.

Study design

This phase 4 prospective controlled clinical trial (clinicaltrials.gov #NCT04754698) was conducted at a single tertiary center in Brazil.

Patients and controls

ARD patients ≥ 18 years old from the Outpatient Rheumatology Clinics at our center were included, with the following diagnosis: RA[38]; SLE[39]; AxSpA[40]; PsA[41]; primary vasculitis[42–43]; pSSj[44]; SSc[45]; IIM[46] and PAPS[47].

After confirming ARD patient's participation, CG were invited, matching by gender and sex (up to ± 5 years differences). None of them were previously vaccinated in the hospital's regular campaign. Well-controlled medical conditions were allowed in the CG, except ARD, use of immunosuppressive drugs or HIV infection.

Overall exclusion criteria were: history of anaphylactic response to vaccine components, acute febrile illness or symptoms compatible to COVID-19 at vaccination, Guillain-Barré syndrome, decompensated heart failure (class III or IV), demyelinating disease, previous vaccination with any SARS-Cov-2 vaccine, history of live virus vaccine up to four weeks before, virus vaccine inactivated up to two weeks before, history of having received blood products up to six months before the study, individuals who did not accept to participate in the study, hospitalized patients, and pre-vaccination positive COVID-19 serology and/or Nab.

After receiving the first vaccine dose, participants with RT-PCR confirmed COVID-19 were excluded from the immunogenicity analysis, but included in the evaluation of incident cases.

Vaccination protocol

The vaccination protocol for ARD patients and GC consisted of a two-dose schedule of the COVID-19 vaccine. The first dose with blood collection was given on February 9-10th 2021 (D0), the second dose with blood collection on March 9th and 10th 2021 (D28) and the last blood collection on April 19th 2021

(D69) at the Hospital Convention Center. This protocol was delayed 4 weeks for participants with incident COVID-19 during the study. Ready-to-use syringes loaded with CoronaVac (Sinovac Life Sciences, Beijing, China, batch #20200412), that consists of 3 µg in 0.5 mL of β-propiolactone inactivated SARS-CoV-2 (derived from the CN02 strain of SARS-CoV-2 grown in African green monkey kidney cells - Vero 25 cells) with aluminum hydroxide as an adjuvant were administered intramuscularly in the deltoid area.

Immunogenicity evaluation

Immunogenicity's primary outcome was assessed by two criteria at D69: seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG and presence of NAb. Secondary immunogenicity criteria were: anti-S1/S2 IgG seroconversion and presence of Nab at D28 (after vaccine first dose); geometric mean titers of anti-S1/S2 IgG and their factor-increase in GMT (FI-GMT) at D28 and D69; and median (interquartile range) neutralizing activity of NAb at D28 and D69. In order to assess these outcomes, blood samples (20mL) from all participants were obtained at days D0 (baseline - immediately before first vaccine dose), D28 (immediately before the second dose), and D69 (six weeks after the second dose). Sera were stored in a -70 ºC freezer.

Anti-SARS-CoV-2 S1/S2 IgG antibodies

A chemiluminescent immunoassay was used to measure human IgG antibodies against the S1 and S2 proteins in the RBD (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Seroconversion rate (SC) was defined as positive serology (≥ 15.0 UA/mL) post vaccination taking into consideration that only patients with pre-vaccination negative serology were included. Geometric mean titers (GMT) and 95% confidence intervals of these antibodies were also calculated at all time points, attributing the value of 1.9 UA/mL (half of the lower limit of quantification 3.8 UA/mL) to undetectable levels (< 3.8 UA/mL). The factor increase in GMT (FI-GMT) is the ratio of the GMT after vaccination to the GMT before vaccination, showing the growth in titers. They are also presented and compared as geometric means and 95% confidence intervals (CI).

SARS-CoV-2 cPass virus-neutralization antibodies (Nab)

The SARS-CoV-2 sVNT Kit (GenScript, Piscataway, NJ, USA) was performed according to manufacturer instructions. This analysis detects circulating neutralizing antibodies against SARS-CoV-2 that block the interaction between the receptor binding domain (RBD) of the viral spike glycoprotein with the angiotensin-converting enzyme 2 (ACE2) cell surface receptor. The tests were performed on the ETI-MAX-3000 equipment (DiaSorin, Italy). The samples were classified as either "positive" (inhibition ≥ 30%) or "negative" (inhibition < 30 %), as suggested by the manufacturer.[48] The frequency of positive samples was calculated at all time points. Medians (interquartile range) of the percentage of neutralizing activity only for positive samples were calculated at all time points.

Vaccine adverse events and incident cases of COVID-19

Patients and control groups were advised to report any side effects of the vaccine and they received on D0 (first dose) and on D28 (second dose) a standardized diary for local and systemic manifestations. Local manifestations included in the diary were local pain, erythema, swelling, bruise, pruritus and

induration at the vaccine site. Systemic reactions included were: fever, malaise, somnolence, lack of appetite, nausea, vomit, diarrhea, abdominal pain, vertigo, tremor, headache, fatigue, myalgia, muscle weakness, arthralgia, back pain, cough, sneezing, coryza, stuffy nose, sore throat, shortness of breath, conjunctivitis, pruritus and skin rash. Vaccine AE severity was defined according to WHO definition[49].

Environmental factors associated with high risk of exposure to SARS-CoV-2 were recorded from all participants, including adherence to social isolation, number of people living in the same house, household contact with infected people and use of public transportation.

Additionally, all ARD patients and controls were instructed to communicate any manifestation associated or not with COVID-19 through telephone, smartphone instant messaging or email. Our medical team was divided to provide a proper follow-up for the assigned group of patients/controls including the need for medical care, hospitalizations, severity of infections, sick days, and treatment. Suspicious cases of COVID-19 were instructed to seek medical care near the residence and if recommended to come to our tertiary hospital to have the PCR exam or in-person visit. If tertiary care was required, the participant was transferred to a referenced Hospital. The standardized diary of adverse events was carefully reviewed with each participant on the day of the second dose (D28) and at the last visit (D69). COVID19 incident cases were followed for 40 days [from D0 to 10 days after the second dose (D39)] and thereafter for the following 40 days [from D40 to D79].

Study data were collected and managed using REDCap electronic data capture tools hosted at our Institution[50,51].

RT-PCR for SARS-CoV-2 and analysis of variants of concern

Clinical samples for SARS-CoV-2 RT-PCR consisted in naso- and oropharyngeal swabs, using a laboratory developed test[52]. Participants with positive samples collected at our hospital were further analyzed for variants of concern using the previously described protocol[53], including the deletion in the NSP6 gene that is observed in the P1, B.1.1.7, and B.1.351 lineages. Distinction of B1.1.7 from P1 and B 1.351 lineages was performed as described[54].

Statistical analysis

The sample size calculation was based on the previous 15% reduction of seroconversion rate after primo vaccination with the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of ARD patients[35]. Expecting seroconversion rates of 63% in the ARD patient's cohort and 78% in the control group, considering an alpha error of 5% and power of 80%, in 5:1 ratio in order to include more ARD patients, the minimum sample required would be 445 ARD patients and 89 healthy subjects, sex-matched and with similar ages. Expecting a higher SC rate of 98% for this vaccine,[27] such sample size had a power greater than 99% to detect a 15% reduction in SC of ARD patients. Due to the peak of pandemics ongoing in Brazil during the vaccination period, we invited more patients and controls, expecting a high incidence of previously infected people and a high rate of infections.

Continuous general data are presented as medians (interquartile ranges) and compared using Mann-Whitney test for intergroup comparisons. Longitudinal analyses within the same group were performed using ANOVA on ranks. Continuous data regarding anti-S1/S2 serology titers are presented as geometric means (95% CI) and compared with the same tests, but in neperian logarithm (ln) transformed data. Categorical variables are presented as number (percentage) and compared using the chi-square or Fisher's exact tests, as appropriate. Multivariate logistic regression analyses were performed using as dependent variables seroconversion or presence of Nab, and as independent variables those with $p < 0.2$ in univariate analysis. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using GraphPad Prism (version 8.0.2–159, serial number GPS-1360936-TLPU-E3F30).

Declarations

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Data availability

All the background information on controls and clinical information for ARD patients in this study are included in Source Data. Additional correspondence and requests for materials should be addressed to the corresponding author (E.B.). Source data are provided with this paper.

Ethics declarations

Competing interests

All authors declare no competing financial interests.

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Contributions

A.C.M.R., N.E.A., C.G.S., E.F.N.Y., T.N.P., S.G.P., E.G.K., and E.B., conceived and designed the study and participated in data collection and analysis, supervised clinical data management, writing of the manuscript and revision of the manuscript. SGRF and PTR organized and supervised blood collection and vaccination. A.J.S.D. and L.A. supervised sera processing, SARS-CoV-2 specific antibody ELISAs/neutralization assays and SARS-CoV-2 RT-PCR. A.C.M.R., N.E.A., C.G.S., E.F.N.Y., T.N.P., S.G.P., E.B, S.R.G.F., P.T.R., R.M.R.P., S.K.S., D.C.O.A., P.D.S.B., C.T.R., G.B.H.D., V.A.O.M., C.A.S., collected epidemiological and clinical data and assisted with the identification of SARS-CoV-2 infection and follow-up of patients. M.H.L. organized and supervised the vaccination protocol. E.C.S. performed the SARS-CoV-2 genotyping of positive RT–qPCR samples and screening of variants of concern. All authors helped to edit the manuscript.

Reporting Summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

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Figures

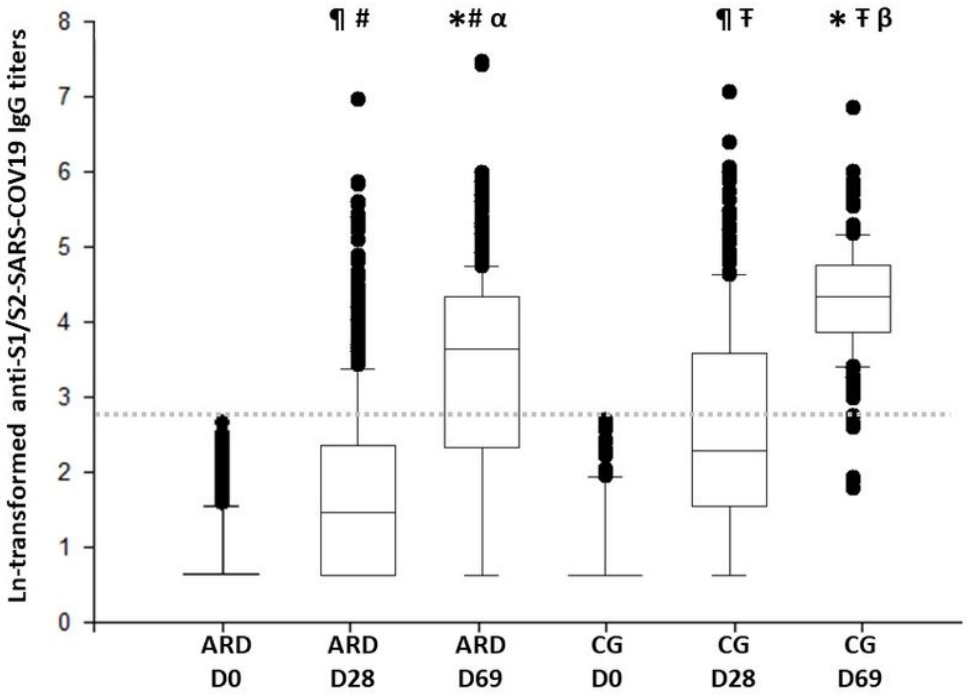

Figure 1

Box plot of neperian logarithm (Ln)-transformed anti-SARS-CoV-2 S1/S2 IgG titers (AU/mL) of 859 autoimmune rheumatic diseases (ARD) patients and 179 subjects in control group (CG) at baseline, D28 and D69. ¶, *- p<0.001 for intergroup comparisons of ARD vs. CG at D28 and D69, respectively; # - p <0.001 for longitudinal comparisons of ARD at D28 and D69 vs. baseline; α - p<0.001 for longitudinal comparison of ARD at D69 vs D28; ₸ - p<0.001 for longitudinal comparison of CG at D28 and D69 vs. baseline; β - p<0.001 for longitudinal comparison of CG at D69 vs D28. Dotted line is the cut-off level for positivity (ln 15 AU/mL = 2.71 - Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy)

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