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Antibody Response before and after the Booster Dose of Inactivated Corona Vaccine in Antibody Deficient Patients

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ABSTRACT

Patients with inborn errors of immunity (IEI) are among the high-risk groups regarding COVID-19. Receiving booster doses (third and fourth) in addition to the standard doses is recommended in these patients. This study investigated the antibody response before and after a booster dose of Sinopharm vaccine in IEI patients.

Thirty patients (>12 years) with antibody deficiencies, referred to Imam Khomeini Hospital and Children's Medical Center in Tehran, were enrolled in this prospective cross-sectional study. All patients were fully vaccinated with the BBIBP-CorV vaccine (2 doses of Sinopharm). Initial measurements of anti-receptor-binding domain (anti-RBD) and anti-nucleocapsid (anti-N) IgG antibody responses were conducted by enzyme-linked immunosorbent assay (ELISA). Subsequently, all patients received a booster dose of the vaccine. Four to six weeks after booster injection, the levels of antibodies were re-evaluated.

Twenty patients with common variable immunodeficiency (CVID), 7 cases with agammaglobulinemia and 3 patients with hyper IgM syndrome were studied. Anti-RBD IgG and anti-N IgG antibodies increased in all patients after the booster.

Our results indicated the need of receiving booster doses of the COVID-19 vaccine in patients with antibody deficiencies, even for enhancing humoral immune response specially in patients with CVID.

Keywords: Antibody deficiency; Booster; COVID-19; Inborn errors of immunity; Primary immunodeficiency; Sinopharm vaccine; Vaccination

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly contagious virus that emerged unexpectedly in 2019 and continues to spread globally.[1,2] The virus possesses four structural proteins: spike protein (S), nucleocapsid protein (N), envelope protein (E), and membrane protein (M).[3] Humoral immune responses to these proteins demonstrate both preventive and diagnostic properties. The evaluation of the immune response in healthy individuals to the SARS-CoV-2 virus reveals a robust interaction among components of the acquired immune system, including B cells, CD4+ T-cells, and CD8+ T-cells. These cells contribute to the induction of antibodies against the S and N proteins of the virus.[4]

The severity of the disease varies widely, ranging from asymptomatic infection to acute respiratory distress syndrome and death due to multi-organ disorders. Elderly individuals and those with underlying diseases or compromised vaccine immune systems often experience more severe clinical conditions and prognoses when infected with Coronavirus disease 2019 (COVID-19).[5,6]

Since the onset of the COVID-19 outbreak, vaccines have emerged as the primary defense against the viruses.[7,8] Studies demonstrate that widespread vaccination against SARS-CoV-2 has been successful in controlling the pandemic and preventing the occurrence of severe disease.[9] COVID-19 vaccines have generated humoral and cellular immune responses in a high percentage of healthy individuals.[10,11] However, most immunocompromised patients struggle to produce effective antibody responses to pathogens or vaccines.[12] This issue has led researchers to focus on the performance of COVID-19 vaccination in patients with Inborn errors of immunity (IEI).

IEI comprises a diverse group of disorders determined by genetic mutations, leading to increased susceptibility to infection, malignancy, autoimmunity, auto-inflammatory, and allergic diseases.[13,14] Severe COVID-19 in IEI patients has been associated with critical pneumonia and comorbidities such as immune dysregulation complications, lung disease, or higher pro-inflammatory responses.[15-17] Due to the vulnerability of IEI patients to the SARS-CoV-2 virus and the potential for severe morbidity and mortality within this specific group, active vaccination and passive immunization become particularly important.[18]

Inactivated and non-live vaccines are generally considered safe for IEI patients, but their effectiveness varies based on the type of immunodeficiency and residual function of the immune response in the patient.[19] Previous studies have indicated that cellular and humoral responses after injecting standard doses of different COVID-19 vaccines in most immunocompromised patients were suboptimal.[20-22]

Even mRNA immunization against the specific receptor-binding domain (RBD) of COVID-19 can be quite beneficial compared to having no protection against the virus in IEI cases. However, studies have shown that in IEI patients, the incidence of severe COVID-19 infection after receiving two doses of mRNA vaccine remains higher compared to healthy vaccinated individuals.[23] Consequently, a booster dose injection is recommended in these patients, especially those with moderate and severe immunodeficiency.[24]

Due to the diversity of IEI and their low prevalence, there is insufficient clinical information about the effectiveness of various vaccines, especially China's BBIBP-CorV (Sinopharm) vaccine, licensed for use in Iran. BBIBP-CorV is an alum-adjuvanted, inactivated whole-virus vaccine, with its safety and immunogenicity established through pre-clinical studies and phase I and II clinical trials.[25] This study aimed to investigate the residual humoral immune response after receiving a booster dose of Sinopharm vaccine in IEI patients with antibody deficiency.

MATERIALS AND METHODS

Study Design

In this prospective cross-sectional study, we enrolled thirty patients with IEI who were referred to Imam Khomeini Hospital and Children's Medical Center in Tehran from October 2021 to October 2022. Given the rarity of IEI diseases, sampling was exclusively conducted through a census, focusing on patients with antibody deficiencies. The clinical diagnosis of IEI was established based on the criteria outlined by the European Society for Immunodeficiencies (ESID).[26] The inclusion criteria comprised patients above the age of 12 who had received two homologous doses of the Sinopharm vaccine. Excluded from the study were patients who did not undergo the antibody test at the scheduled time. In addition, those with heterologous vaccinations, individuals refusing the Sinopharm vaccine booster

dose, and patients currently under immunosuppressive treatment.

Study Timeline

At the study's commencement (T0) and before the booster dose injection, we collected all demographic information, including age, gender, date of receiving the first and second doses of the COVID-19 vaccine, history of COVID-19 based on polymerase chain reaction (PCR) positivity, and other related diseases from the patient's medical record. Additionally, we gathered information through direct patient and/or caregiver questioning. Anti-RBD and anti-N IgG antibody responses were measured for each patient using the enzyme-linked immunosorbent assay (ELISA) method. Following the first measurement, all patients received intravenous immunoglobulin based on their total IgG level within 15-30 minutes interval. After 1-2 days, all patients were vaccinated with the Sinopharm booster dose, prepared from the inactivated whole-virus COVID-19 vaccine (Beijing Bio-Institute of Biological Products Co Ltd)).[27] Four to six weeks after the booster dose injection (T1), we measured the levels of anti-receptor-binding domain (anti-RBD) and anti-nucleocapsid (anti-N) IgG antibodies again (Figure 1). A positive response was defined as an antibody level equal to or greater than 5 Ru/mL.

Statistical Analysis

The statistical analysis was performed by SPSS software version 22 (IBM, Chicago, USA). The quantitative variables were presented as mean ± standard errors (SD), and the qualitative variables as numbers (percentage). Distribution was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. The Wilcoxon Signed Rank test was utilized to compare anti-RBD IgG and anti-N IgG antibody levels before and after the booster dose. Fisher's exact test was employed to compare the frequencies among groups, and a *p*-value less than 0.05 was considered statistically significant.

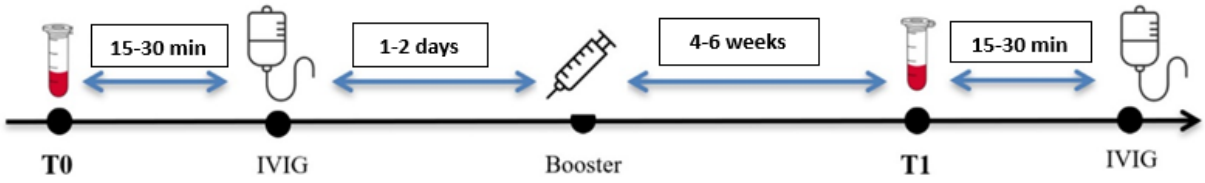

Figure 1. study timeline

RESULTS

Thirty patients with an average age of 30.7±13.6 years (median 29, 12–64 years) participated in this study. Ten patients (33.3%) were female. Based on the diagnosis of IEI type, 20 patients (66.7%),7 patients (23.3%) and 3 patients (10%) had common variable immunodeficiency (CVID), agammaglobulinemia (XLA) and hyper-IgM (HIGM), respectively. Before receiving the booster dosage injection, two patients (P3 and P20) had a documented history of acquiring COVID-19, according to their medical records. Additional details regarding the demographic and clinical presentations are provided in Table 1.

There was a statistically significant difference between the mean anti-RBD IgG level before booster dose injection and four to six weeks post-injection in patients with IEI ($p<0.05$). There was a similar pattern in the subgroups (CVID, XLA, and HIGM). However, the difference in the subgroups was not statistically significant (Table 2).

Table1. Baseline and clinical characteristics of patients during COVID-19 pandemic

Patient code	Diagnosis	Gender (M/F)	Age (Years)	Comorbidity	History of positive COVID-PCR test	Autoimmune diseases	Anti-RBD IgG (Ru/mL)		Anti-N IgG (Ru/mL)		Post Booster Complications
							T0	T1	T0	T1	
P1	**CVID**	F	43	Cataract/ Enteropathy	-	Lichen Planus	2.6	4.2	0.3	1.7	-
P2	**CVID**	M	36	Bronchiectasis	-	Hashimoto's thyroiditis	1.3	>100	1.4	15.8	-
P3	**CVID**	F	40	Sinusitis/ Allergic rhinitis/ Hypothyroidism/ Vitiligo	+ (>4 mo. before booster dose injection)	-	0.4	0.6	2	1.7	Fatigue/ Lethargy
P4	**CVID**	M	28	Nephropathy	-	-	19	21.6	2.1	2.7	Fatigue
P5	**CVID**	F	64	Bronchiectasis	-	Psoriasis/ diabetes insipidus	29.5	34	4.7	6.1	-
P6	**CVID**	F	43	-	-	Celiac	5	6.7	3.5	4	-
P7	**CVID**	M	32	Sinusitis/ Allergic rhinitis	-	-	9.4	0.8	2.8	0.1	-
P8	**CVID**	M	24	-	-	Celiac	22.9	27	4.6	5.2	-
P9	**CVID**	F	14	-	-	Rheumatoid Arthritis	75.6	2.7	1.9	4	-
P10	**CVID**	F	41	Enteropathy	-	Celiac	23.7	24.3	5.9	6.4	-
P11	**CVID**	M	24	Sinusitis/ Bronchiectasis	-	-	0.3	4.2	2.9	3.5	-
P12	**CVID**	M	12	Sinusitis/ Wheat allergy	-	Non-Hodgkin lymphoma	>100	>100	2.2	3	Pain on the site of injection
P13	**CVID**	M	18	Myopathy	-	Rheumatoid Arthritis	31.8	25.2	3.3	3.8	-
P14	**CVID**	M	23	Sinusitis/ Pneumonia	-	-	0.3	0.8	2	2.3	-

Table 1. Continued...

atient code	Diagnosis	Gender (M/F)	Age (Years)	Comorbidity	History of positive COVID-PCR test	Autoimmune diseases	Anti-RBD IgG (Ru/mL)		Anti-N IgG (Ru/mL)		Post Booster Complications
							T0	T1	T0	T1	
P15	**CVID**	F	18	-	-	ITP	11	19.7	4	1	-
P16	**CVID**	M	50	Sinusitis/ Fatty liver	-	ITP	0.1	0.3	1.7	1.6	-
P17	**CVID**	M	54	Sinusitis/ Bronchiectasis	-	-	0.3	0.6	2.9	2.5	-
P18	**CVID**	M	21	-	-	-	3.2	3.4	5.3	5.2	-
P19	**CVID**	F	44	Sinusitis/ Otitis/ Eczema/Chronic diarrhea	-	Rheumatoid Arthritis	3.2	6.2	4.3	6.1	-
P20	**CVID**	M	-	Bronchiectasis	+ (4 ½ mo. before booster injection)	Lichen Planus	3.9	2.8	1.6	1.5	-
P21	**XLA**	M	34	-	-	Celiac	1.64	3.6	1.4	1.8	-
P22	**XLA**	M	18	-	-	-	0.8	0.5	0.6	1.2	-
P23	**XLA**	M	50	-	-	-	1.2	1.5	2.4	3	-
P24	**XLA**	M	29	-	-	-	0.5	0.8	1.6	2.6	-
P25	**XLA**	M	21	-	-	-	0.1	1.4	1.6	2.1	-
P26	**XLA**	M	32	Bronchiectasis/ Cirrhosis	-	-	0.1	1.2	1.9	3.1	-
P27	**XLA**	F	12	-	-	-	3.9	3.9	1.8	1.5	-
P28	**HIGM**	F	17	-	-	-	0.6	2.8	1.4	1.8	Headache
P29	**HIGM**	M	20	-	-	-	3.9	4.2	1.7	1.2	-
P30	**HIGM**	M	29	-	-	-	1.1	1.8	2.1	3.7	-

CVID: Common variable immunodeficiency, XLA: X-linked agammaglobulinemia, HIGM: Hyper Immunoglobulin M syndrome, Anti-N: Anti-Nucleocapsid, Anti-RBD: anti- receptor-binding domain.

Table2. Anti- nucleocapsid IgG and anti-RBD IgG before booster dose injection and four weeks after injection patients

	Total (n=30)	CVID (n=20)	XLA (n=7)	Hyper IgM (n=3)
Anti-RBD IgG T0	11.91±22.82	17.17±26.57	1.17±1.32	1.86±1.77
Anti-RBD IgG T1	13.56±25.36	19.25±29.64	1.84±1.35	2.93±1.2
p	0.013	0.116	0.072	0.109
Anti-Nucleocapsid T0	2.53±1.36	2.97±1.45	1.61±0.54	1.73±0.35
Anti- Nucleocapsid T1	3.34±2.86	3.92±3.33	2.18±0.73	2.23±1.30
p	0.004	0.54	0.32	0.59

CVID: Common variable immunodeficiency, XLA: X-linked agammaglobulinemia, HIGM: Hyper Immunoglobulin M syndrome, Anti-N: Anti-Nucleocapsid, Anti-RBD: anti- receptor-binding domain

Considering the cut-off point of anti-RBD IgG Ab, only 10 patients (33.3%) exhibited anti-RBD IgG antibody response before the administration of the booster dose of the COVID-19 vaccine. All 10 patients suffered from CVID. Following the administration of the booster dose, anti-RBD IgG antibody response was present in all ten patients, with two patients, (P2 and P19), demonstrating no antibody response before injection which was subsequently produced thereafter. Conversely, in two patients (P7 and P9), anti-RBD IgG antibody response was present before the administration of the booster dose, but after the injection, the antibody level diminished below the cut-off point as determined in the present study. The reduction of anti-RBD IgG antibodies was reported in five patients (16.7%) after receiving the booster dosage. Eight patients (26.7%) had an increase in anti-RBD IgG antibody levels that were less than 50%, whereas 15 patients (50%) had an increase that was greater than 50%. The level of anti-RBD IgG antibody did not change in two patients (6.7%). There was no statistically significant difference between CVID, XLA, and HIGM patients' increases in the level of anti-RBD IgG antibody following the booster dose injection (p=0.87).

According to the findings, a statistically significant difference in the average anti-N IgG levels was noted among all the IEI patients, both before and after the administration of booster dose injection during the four to six-week period. Two patients exhibited an antibody response when considering the anti-N IgG Ab cutoff threshold of 5 Ru/ml before injection. After injection, six patients (20%) manifested antibody responses, with each of these cases belonging to the CVID subgroup. Overall, regardless of the specific threshold, the anti-N IgG antibody level experienced a decline in 9 patients (30%) following the administration of a booster dose. A rise of less than 50% was reported in 14 patients (46.7%), while an increase of more than 50% was reported in 7 patients (23.3%). The analysis revealed no statistically significant difference between CVID, XLA, and HIGM subjects concerning alterations in anti-N IgG antibody levels after the booster dose injection.

In this study, 16 patients (53.3%) presented with IEI co-morbidities. The analyses indicated that there was no statistically significant relationship between the response of anti-RBD IgG, anti-N IgG antibodies, and the patients' history of co-morbidities. In the same way, no significant statistical relationship was found between the level of these antibodies (before and 4-6 weeks after injection) with other non-infectious complications. Notably, 14 patients (46.7%) had IEI in addition to autoimmune disorders, and they exhibited a more robust residual response of post anti-RBD IgG and anti-N IgG.

According to the data presented in Table 3, a statistically significant association was identified between the anti-RBD IgG antibody response and the patients' medical histories. Despite the presence of autoimmunity, there was no statistically significant correlation between the anti-N IgG antibody response and a history of autoimmune disorders. Additionally, patients with autoimmune illnesses exhibited considerably higher levels of anti-RBD IgG antibodies than non-autoimmune patients, both before and one week after injection. However, no statistically

significant relationship was observed between the levels of anti-RBD IgG and anti-N IgG antibodies (before injection and 6 weeks after injection) concerning gender and age. It is noteworthy that four patients (13.3%) reported experiencing minor adverse effects after receiving a booster dosage injection, including lethargy, headaches, and soreness at the injection site. Importantly, none of the patients had any acute problems that required medical attention.

Table 3. Relationship between response and changes in Anti-RBD IgG and Anti-Nucleocapsid IgG antibody levels after the injection of a booster dose of the COVID-19 vaccine

Variables	T0		T1		Response	
	Anti-RBD IgG	Anti-N IgG	Anti-RBD IgG	Anti-N IgG	Anti-RBD IgG≥ 5 Ru/mL (T1)	Anti-N IgG≥5 Ru/mL (T1)
Comorbidity						
Yes	14.11±25.47	2.62±1.39	20.42±32.92	3.86±3.6	7 (43.8)	4 (25)
No	9.38±19.9	2.42±1.37	5.71±7.77	2.73±1.46	3 (21.4)	2 (14.3)
p	0.95	0.55	0.42	0.47	0.26	0.65
Autoimmune disease						
Yes	22.30±30.25	2.91±1.63	25.47±33.44	4.42±3.77	9 (64.3)	5 (35.7)
No	2.81±4.94	2.19±1.01	3.13±5.10	2.38±1.20	1 (6.25)	1 (6.25)
p	0.002	0.37	0.001	0.07	0.001	0.072
Gender						
Male	10.09±22.93	2.30±1.10	15.08±30.22	3.29±3.20	5(25)	3(15)
Female	15.55±23.35	2.98±1.75	10.51±11.36	3.43±2.16	5 (50)	3(30)
p	0.1	0.21	0.37	0.65	0.23	0.37

Anti-N: Anti-Nucleocapsid, Anti-RBD: anti- receptor-binding domain

DISCUSSION

Our findings reveal a significant increase in Anti-RBD IgG and Anti-N IgG antibodies in all patients following the booster dose injection. Previous studies on the efficacy of COVID-19 vaccines in patients with immunodeficiency disorders indicate varying serum level changes in patients with mild antibody deficiency, phagocytic defects, combined immunodeficiency, and simple CVID. Despite these differences, the antibody and T cell responses have generally been appropriate. Conversely, patients with XLA and complicated CVID typically exhibit a poor response to vaccines.[16] In our study, CVID patients demonstrated a higher average increase in serum levels of anti-RBD IgG and anti-N IgG antibodies compared to other patients, while XLA patients showed lower changes in the levels of the studied antibodies. According to our findings, approximately 33% of patients exhibited an anti-RBD IgG antibody response before the booster dose injection, and all these patients belonged to the CVID group.

Based on the studies conducted on IEI patients, a relative humoral response has been observed in most patients after receiving the second dose of COVID-19 vaccines.[28-30] However, the effectiveness of the third dose of various COVID-19 vaccines has been reported inconsistently in different studies. In the study by Ainsua-Enrich et al., it was noted that receiving the third dose of the Moderna vaccine induced a relative humoral response in most IEI patients.[17] Additionally, Grenz et al. demonstrated a 100% anti-RBD IgG antibody response in CVID patients after the third dose of the Pfizer or Moderna vaccine.[31] Also, they reported that the third dose of the Pfizer vaccine only caused a 13% increase in the production of Anti-S IgG in CVID patients.[32] Furthermore, a previous study by Nourizadeh et al, in Iran revealed that IEI patients[17] exhibited weaker antibody production and function compared to healthy

controls. Despite this, the study claimed that the reporting of COVID-19-like symptoms in patients with IEI significantly decreased after the first, second, and booster doses of COVID-19 vaccines (Sinopharm, AstraZeneca, and Sputnik).[33]

In contrast to previous studies, our research found no difference in the number of patients with a positive anti-RBD IgG antibody response after booster dose injection. Only two CVID patients who had a negative anti-RBD IgG antibody response before the injection produced the necessary antibody response after the booster dose injection. This suggests that the immunity generated following the third dose of the Sinopharm vaccine may be comparatively weaker than that observed with mRNA vaccines such as Pfizer and Moderna.

In our study, none of XLA and HIGM patients exhibited a positive response in terms of anti-RBD IgG antibody before or after the booster dose injection. This absence of response in XLA patients could be attributed to the lack of B cells, resulting in the non-production of serum antibodies, especially anti-spike and anti-RBD antibodies following vaccination.[28] Consistent with our findings, Squire et al. reported that, among 11 IEI patients who received both doses of the Pfizer or Moderna vaccine, only one patient with XLA failed to generate an antibody response.[34] It has been noted in studies that XLA patients might not be highly susceptible to severe COVID-19, possibly because the deficiency of Bruton tyrosine kinase (BTK) reduces virus-induced IL-6 production by monocytes, thereby potentially lowering the risk of cytokine storm associated with COVID-19.[35]

According to our findings, concomitant diseases had no significant effect on the production of anti-RBD IgG and anti-N IgG antibodies. Notably, Anti-RBD IgG antibody levels before and after injection were higher in patients with autoimmune diseases. Among the 10 patients with positive responses to anti-RBD IgG antibodies, 9 were suffering from autoimmune diseases. In the study by Shin et al., the response of CVID patients to Pfizer and Moderna vaccines was influenced by the patients' history of autoimmune disease .[36] In contrast to the results of our study, Arroyo-Sánchez et al. highlighted the presence of autoimmune disorders as one of the risk factors of a weak response or lack of humoral and cellular response in CVID patients to the COVID-19 vaccine.[29]

In this study, none of the patients reported acute complications after booster dose injection, and only mild cases of fatigue, headache, and pain at the injection site were observed in a small number of patients. Similar to our results, Goda et al.'s study showed that, compared to healthy subjects, patients with CVID exhibited a poorer response to the booster dose of the Pfizer vaccine and experienced fewer systemic complications.[32] Our study did not report acute and rare complications of vaccination, such as myocarditis, immune thrombocytopenia (ITP), and anaphylaxis. It appears that the use of immunoglobulin replacement therapy in IEI patients may reduce the risk of acute and adverse complications associated with the COVID-19 vaccine.

This study had some limitations, including relatively small sample sizes, the absence of healthy controls, and a short follow-up period for patients after the booster injection. Another limitation was that the administration of IVIG to patients may influence the humoral and cellular response induced by the COVID-19 vaccine.

This study demonstrated an increase in anti-RBD IgG and anti-N antibody levels following the administration of a booster dose of the Sinopharm vaccine in IEI patients. However, in the majority of patients, this rise in antibody levels was within a lower range than the standard, leaving uncertainty about how effectively this improvement will protect them from COVID-19 or its duration. It is recommended that future studies, with larger sample sizes and extended follow-ups, re-evaluate the safety and efficacy of Sinopharm's cellular and humoral vaccine in IEI patients.

STATEMENT OF ETHICS

The Ethics Committee of the Tehran University of Medical Science approved this study (IR. TUMS.CHMC.1400.287). Also, written informed consent was obtained from all patients and/or their parents.

FUNDING

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The protocol of study was approved in Tehran University of Medical Sciences (Pajouheshyar ID: 56975).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Tang X, Wu C, Li X, Song Y, Yao X, Wu X, et al. On the origin and continuing evolution of SARS-CoV-2. Nat Sci Rev. 2020;7(6):1012-23.
2. Giardino G, Romano R, Coppola E, Cillo F, Borzachiello C, De Luca M, et al. SARS-CoV-2 infection in the immunodeficient host: necessary and dispensable immune pathways. J Clin Immunol. 2021;9(9):3237-48.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271-80. e8.
4. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell. 2021;184(4):861-80.
5. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood, The Journal of the American Society of Hematology. 2020;136(25):2881-92.
6. Azzi Y, Bartash R, Scalea J, Loarte-Campos P, Akalin E. COVID-19 and solid organ transplantation: a review article. Transplantation. 2021;105(1):37-55.
7. Ma J, Cheng ZJ, Xue M, Huang H, Li S, Fang Y, et al. Investigation of Antibody Levels During Three Doses of Sinopharm/BBIBP Vaccine Inoculation. Fronti Immunol. 2022;13:913732.
8. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA. 2021;326(1):35-45.
9. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. New Eng J Med. 2021;384(15):1412-23.
10. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature. 2021;595(7868):572-7.
11. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. New Eng J Med. 2021;384(5):403-16.
12. Wood P, Stanworth S, Burton J, Jones A, Peckham D, Green T, et al. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. Clin Expe Immunol. 2007;149(3):410-23.
13. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human inborn errors of immunity: 2022 update on the classification from the international union of immunological societies expert committee. J Clin Immunol. 2022;42(7):1473-507.
14. Bousfiha A, Moundir A, Tangye SG, Picard C, Jeddane L, Al-Herz W, et al. The 2022 update of IUIS phenotypical classification for human inborn errors of immunity. J Clin Immunol. 2022;42(7):1508-20.
15. Meyts I, Bucciol G, Quinti I, Neven B, Fischer A, Seoane E, et al. Coronavirus disease 2019 in patients with inborn errors of immunity: an international study. J Clin Immunol. 2021;147(2):520-31.
16. Milito C, Lougaris V, Giardino G, Punziano A, Vultaggio A, Carrabba M, et al. Clinical outcome, incidence, and SARS-CoV-2 infection-fatality rates in Italian patients with inborn errors of immunity. J Clin Immunol. 2021;9(7):2904-6. e2.
17. Ainsua-Enrich E, Pedreño-Lopez N, Bracke C, Ávila-Nieto C, de la Concepcion MLR, Pradenas E, et al. Kinetics of immune responses elicited after three mRNA COVID-19 vaccine doses in predominantly antibody-deficient individuals. Iscience. 2022;25(11).
18. Allan M, Lièvre M, Laurenson-Schafer H, de Barros S, Jinnai Y, Andrews S, et al. The World Health Organization COVID-19 surveillance database. Int J Equity Health. 2022;21(Suppl 3):167.
19. Sobh A, Bonilla FA. Vaccination in primary immunodeficiency disorders. J Clin Immunol. 2016;4(6):1066-75.
20. Bergman P, Blennow O, Hansson L, Mielke S, Nowak P, Chen P, et al. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. EBioMedicine. 2021;74.
21. Delmonte OM, Bergerson JR, Burbelo PD, Durkee-Shock JR, Dobbs K, Bosticardo M, et al. Antibody responses to the SARS-CoV-2 vaccine in individuals with various inborn errors of immunity. J Clin Immunol. 2021;148(5):1192-7.
22. Pulvirenti F, Fernandez Salinas A, Milito C, Terreri S, Piano Mortari E, Quintarelli C, et al. B cell response induced by SARS-CoV-2 infection is boosted by the

BNT162b2 vaccine in primary antibody deficiencies. Cells. 2021;10(11):2915.
23. Di Fusco M, Moran MM, Cane A, Curcio D, Khan F, Malhotra D, et al. Evaluation of COVID-19 vaccine breakthrough infections among immunocompromised patients fully vaccinated with BNT162b2. J Med Eco. 2021;24(1):1248-60.
24. Pham MN, Murugesan K, Banaei N, Pinsky BA, Tang M, Hoyte E, et al. Immunogenicity and tolerability of COVID-19 messenger RNA vaccines in primary immunodeficiency patients with functional B-cell defects. J Clin Immunol. 2022;149(3):907-11. e3.
25. Zhang Y, Belayachi J, Yang Y, Fu Q, Rodewald L, Li H, et al. Real-world study of the effectiveness of BBIBP-CorV (Sinopharm) COVID-19 vaccine in the Kingdom of Morocco. 2022;22(1):1584.
26. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. J Clin Immunol. 2019;7(6):1763-70.
27. Zeng T, Lu Y, Zhao Y, et al. Effectiveness of the booster dose of inactivated COVID-19 vaccine against Omicron BA.5 infection: a matched cohort study of adult close contacts. *Respir Res*. 2023;24(1):246.
28. Salinas AF, Mortari EP, Terreri S, Quintarelli C, Pulvirenti F, Di Cecca S, et al. SARS-CoV-2 vaccine induced atypical immune responses in antibody defects: everybody does their best. J Clin Immunol. 2021;41:1709-22.
29. Arroyo-Sánchez D, Cabrera-Marante O, Laguna-Goya R, Almendro-Vázquez P, Carretero O, Gil-Etayo FJ, et al. Immunogenicity of anti-SARS-CoV-2 vaccines in common variable immunodeficiency. J Clin Immunol. 2022;42(2):240-52.
30. Amodio D, Ruggiero A, Sgrulletti M, Pighi C, Cotugno N, Medri C, et al. Humoral and cellular response following vaccination with the BNT162b2 mRNA COVID-19 vaccine in patients affected by primary immunodeficiencies. Front Immunol. 2021;12:727850.
31. Gernez Y, Murugesan K, Cortales CR, Banaei N, Hoyte L, Pinsky BA, et al. Immunogenicity of a third COVID-19 messenger RNA vaccine dose in primary immunodeficiency disorder patients with functional B-cell defects. J Allergy Clinical Immunol. 2022;10(5):1385-8. e2.
32. Goda V, Kriván G, Kulcsár A, Gönczi M, Tasnády S, Matula Z, et al. Specific antibody and the T-cell response elicited by BNT162b2 boosting after two ChAdOx1 nCoV-19 in common variable immunodeficiency. Front Immunol. 2022;13:907125.
33. Nourizadeh M, Feizabadi E, Mirmoghtadaei M, Mohammadi A, Fazlollahi MR, Moradi L, et al. Antibody production after COVID-19 vaccination in patients with inborn errors of immunity. 2023;20(4):400-9.
34. Squire J, Joshi A. Seroconversion after coronavirus disease 2019 vaccination in patients with immune deficiency. Annals Allergy Asthma Immunol. 2021;127(3):383-4.
35. Delmonte OM, Castagnoli R, Notarangelo LD. COVID-19 and inborn errors of immunity. Physiology. 2022;37(6):290-301.
36. Shin JJ, Par-Young J, Unlu S, McNamara A, Park H-J, Shin MS, et al. Defining clinical and immunological predictors of poor immune responses to COVID-19 mRNA vaccines in patients with primary antibody deficiency. J Clin Immunol. 2022;42(6):1137-50.