



doi • 10.5578/tt.20219612

Tuberk Toraks 2021;69(4):547-560

Received/Geliş Tarihi: 01.08.2021 • Accepted/Kabul Ediliş Tarihi: 01.10.2021

REVIEW
DERLEME

Immunogenicity of SARS-CoV-2 mRNA vaccine in dialysis and kidney transplant patients: A systematic review

Merve AKYOL¹(ID)
Enes ÇEVİK¹(ID)
Duygu UCKU¹(ID)
Cem TANRIÖVER¹(ID)
Barış AFŞAR²(ID)
Asiye KANBAY³(ID)
Adrian COVIC⁴(ID)
Alberto ORTIZ⁵(ID)
Carlo BASILE⁶(ID)
Mehmet KANBAY⁷(ID)

¹ Department of Internal Diseases, Koc University School of Medicine, İstanbul, Turkey

¹ Koç Üniversitesi Tıp Fakültesi, Dahiliye Anabilim Dalı, İstanbul, Türkiye

² Division of Nephrology, Department of Internal Diseases, Süleyman Demirel University School of Medicine, Isparta, Turkey

² Süleyman Demirel Üniversitesi Tıp Fakültesi, Dahiliye Anabilim Dalı, Nefroloji Bilim Dalı, Isparta, Türkiye

³ Clinic of Pulmonary Medicine, Atasehir Medicana Hospital, İstanbul, Turkey

³ Medicana Ataşehir Hastanesi, Göğüs Hastalıkları Kliniği, İstanbul, Türkiye

⁴ Division of Nephrology, Department of Internal Diseases, Grigore T. Popa' University of Medicine, Iasi, Romania

⁴ Grigore T. Popa' Üniversitesi, İç Hastalıkları Anabilim Dalı, Nefroloji Bilim Dalı, Iasi, Romania

⁵ Division of Nephrology, Jimenez Diaz Foundation Health Research Institute, University of Autonoma De Madrid School of Medicine, Madrid, Spain

⁵ Jimenez Diaz Vakfı Sağlık Araştırma Enstitüsü, Autonomia De Madrid Üniversitesi, Nefroloji Bilim Dalı, Madrid, İspanya

⁶ Clinic of Nephrology, Miulli General Hospital, Acquaviva Delle Fonti, Italy

⁶ Miulli Hastanesi, Nefroloji Kliniği, Acquaviva Delle Fonti, İtalya

⁷ Department of Medicine, Division of Nephrology, Koç University School of Medicine, İstanbul, Turkey

⁷ Koç Üniversitesi Tıp Fakültesi, Dahiliye Anabilim Dalı, Nefroloji Bilim Dalı, İstanbul, Türkiye

Cite this article as: Akyol M, Çevik E, Ucku D, Tanrıöver C, Afşar B, Kanbay A, et al. Immunogenicity of SARS-CoV-2 mRNA vaccine in dialysis and kidney transplant patients: A systematic review. Tuberk Toraks 2021;69(4):547-560.

Address for Correspondence (Yazışma Adresi)

Dr. Asiye KANBAY
Department of Medicine, Koc University
School of Medicine,
İSTANBUL - TURKEY
e-mail: kanbaydr@yahoo.com

ABSTRACT

Immunogenicity of SARS-CoV-2 mRNA vaccine in dialysis and kidney transplant patients: A systematic review

Kidney transplant recipients and dialysis patients constitute a risk group for severe COVID-19. They are highly advised to get vaccinated according to the current guidelines. However, data on antibody response, cell responses and protection from events, and factors that might alter this response after a routine full series of vaccination remain incomplete for these populations. The aim of this article was to analyze the antibody responses after a full series of



mRNA-based SARS-CoV-2 vaccination in kidney transplantation and dialysis patients and to define the factors that alter seroconversion status in these populations. In this systematic review, 18 studies investigating the antibody response to full vaccination with two doses of COVID-19 mRNA vaccines in hemodialysis, peritoneal dialysis, and kidney transplant patients were included. Kidney transplant and dialysis patients have a lower seroconversion rate after mRNA-based SARS-CoV-2 vaccination than the healthy population: 27.2% for kidney transplantation, 88.5% for dialysis patients while all healthy control in these studies seroconverted. Moreover, anti-S antibody titers were lower in seroconverted kidney transplantation or dialysis patients than in healthy control in all studies that assessed this variable. Older age and dialysis vintage, immunosuppressive or chemotherapy treatment, and lower serum albumin, white blood cell, lymphocyte and hemoglobin counts were associated with lower/no antibody response to vaccination. Dialysis patients and kidney transplant recipients have lower seroconversion rates after a full series of mRNA-based SARS-CoV-2 vaccination than the general population. Several factors are associated with an altered antibody response. A third dose could be considered in this patient group.

Key words: COVID-19; Biontech BNT162b2; Moderna mRNA-1273; vaccination

ÖZ

Diyaliz ve böbrek nakli hastalarında SARS-CoV-2 mRNA aşısı sonrası immunojenite: Sistemik derleme

Böbrek nakilli ve diyaliz hastaları COVID-19 enfeksiyonu açısından yüksek riskli gruptadırlar. Güncel klavuzlar bu nedenle bu hastaların öncelikli aşılınması gereken grupta olduğunu belirtmişlerdir. Bununla birlikte aşı sonrası antikor yanıtı, koruyuculuğu, hücresel immün yanıt üzerine etkileri net olarak bilinmemektedir. Bu sistematik derlemede mRNA-tipi SARS-CoV-2 aşılamanın böbrek nakli ve diyaliz hastalarında antikor yanıtını ve antikor yanıtını etkileyen faktörlerin araştırılması yapıldı. Bu sistematik derlemeye 18 adet hemodiyaliz, periton diyaliz ve böbrek nakli hastalarında 2 doz COVID-19 mRNA aşısı uygulanan hastaların alındığı klinik çalışma dahil edildi. Çalışmalarda 2 doz COVID-19 mRNA aşısı sonrası böbrek nakli hastalarında %27,2, diyaliz hastalarında %88,5 antikor yanıtı saptanırken sağlıklı insanlarda %100 antikor yanıtı saptandı. İleri yaş, diyaliz süresi, immünsüpresif tedavi, düşük serum albumin, düşük serum lökosit, düşük serum lenfosit, düşük hemoglobin düzeyleri düşük antikor yanıtı ile ilişkili olduğu saptandı. COVID-19 mRNA aşısı sonrası diyaliz ve böbrek nakli hastalarında antikor yanıtı düşüktür. Bu nedenle bu hasta grubunda üçüncü doz aşı uygulanması uygun olabilir.

Anahtar kelimeler: COVID-19; Biontech BNT162b2; Moderna mRNA-1273; aşılama

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, affects multiple organs including the kidneys and has spread to millions of people worldwide (1,2). COVID-19 in dialysis patients and solid organ transplant recipients is associated with a high morbidity and mortality (3-5). The reason is unclear, but it may be related to various immunosuppressive states or to cell and molecular changes secondary to uremia that facilitates virus entry into cells and proliferation. Transplant and dialysis patients are advised to get vaccinated against SARS-CoV-2 according to current guidelines despite the lack of data regarding efficacy in these populations (6-8). However, dialysis and kidney transplant patients present decreased immune responses to various vaccines (9). Furthermore, transplant recipients have not been included in phase 3 trials of SARS-CoV-2 vaccines, and no immunogenicity, efficacy and safety data is available from clinical trials for this vulnerable population (10,11). Therefore, we performed a systematic review, evaluating antibody response among hemodialysis (HD), peritoneal dialysis (PD) and kidney transplant (KT) patients 1-6 weeks after receiving the sec-

ond dose of either one of the two mRNA vaccines (Biontech BNT162b2, Moderna mRNA-1273) currently in the market.

MATERIALS and METHODS

In this systematic review, we performed a literature search through three databases, including PubMed/Medline, Google Scholar, and Web of Science from July 2020 to June 2021 by using the following keywords: "dialysis", "chronic kidney disease", "renal failure", "renal transplant", "kidney transplant", "glomerulonephritis", "COVID-19", "coronavirus", "vaccine", "vaccination", "antibody", "efficacy".

We independently assessed the titles, and the abstracts of each study, discussed and reexamined each article in detail until reaching a consensus if any conflicts were present and also analyzed the references of the selected studies. Following preliminary selection, we independently evaluated the full text versions of the selected studies.

Inclusion criteria for our systematic review were as follows: studies investigating the response to COVID-19 vaccine in HD, PD and KT patients. Studies in

which patients were fully vaccinated with 2 doses of COVID-19 mRNA vaccines, reported antibody response and determined outcomes as seroconverted and non-seroconverted were included.

We excluded studies in which patients were administered a single dose or an extra dose of COVID-19 mRNA vaccines and inactive COVID-19 vaccines. Preprints, editorials, case reports, systematic reviews and meta-analysis were excluded from this study.

Our literature search identified 74 results. After assessing each study according to our inclusion and exclusion criteria, we identified 18 manuscripts. Among the 18 studies, 4 studies included only KT patients (12-15), 10 studies included only HD (16-22) and/or PD patients (23-25) and 4 studies included both KT and HD/PD patients (26-29).

Table 1 shows a summary of the included studies. Table 2 delineates information on the baseline characteristics of KT patients and healthy controls (HC) and seroconversion status following a full series of SARS-CoV-2 vaccination. Table 3 provides information on the baseline characteristics of HD and PD patients and HC and seroconversion status following a full series of SARS-CoV-2 vaccination.

RESULTS

We included, in our final analysis, 18 prospective cohort studies (12-29) (Table 1). One study included KT, HD, PD, HC patients (29). One study included HD, PD, HC patients (25). Two studies included both HD and PD patients (23,24). Three studies included only HD patients (16-18). Four studies included both HD and HC patients (19-22). Two studies included only KT patients (12,14). Two studies included KT and HC patients (13,15). One study included KT and HD patients (27). Two studies included KT, HD and HC patients (26,28). The total number of evaluated patients was 2453 which consisted of 1182 HD, 80 PD, 693 KT and 498 HC patients. All of the included studies used mRNA vaccines. Patients in each study received the BNT162b2 Pfizer-BioNTech mRNA vaccine. In addition, the mRNA-1273 Moderna vaccine was administered to the patients in two studies by Husain et al. (n= 12) and Broseta et al. (n= 100). All studies measured anti-spike protein antibody levels.

Antibody Response in KT Recipients

Table 2 depicts the baseline characteristics, seroconversion rates, comorbidities, primary kidney disease,

and laboratory values of patients having undergone KT. The seroconversion rate in KT patients ranged from 2.5% to 37.5%. The overall seroconversion rate was 27.2% of KT studied. In 5 studies that also included HC, the seroconversion rate for KT ranged from 2.5% to 37.5% (overall 19.7%) and in HC it was 100%. However, the total number of HC (n= 129) was low, and they were generally younger (up to 13 years) than KT patients.

Rozen-Zvi et al. have reported that factors associated with positive antibody response are a higher estimated glomerular filtration rate (eGFR) (odds ratio (OR) 1.025 per mL/min/1.73 m², 95% confidence interval (CI) 1.014-1.037, *p*< 0.001), lower mycophenolic acid (MMF) dose (OR 2.347 per 360 mg decrease, 95% CI 1.782-3.089, *p*< 0.001), younger age (OR 1.032 per year decrease, 95%CI 1.015-1.05, *p*< 0.001) and lower calcineurin inhibitor (CNI) blood levels (14). Husain et al. have observed lower antibody responses in patients on immunosuppressive regimens, especially in those including belatacept and MMF (12). Bertrand et al. have identified a negative impact of the immunosuppressive regimen, particularly tacrolimus or belatacept, on antibody response (27). Korth et al. have reported no differences in age, sex and immunosuppressive drug regimens in patients who were seroconverted and non-seroconverted for anti-S IgG antibodies (15). In contrast, Danthu et al. have reported only 3 KT patients among 74 with a positive antibody response, all of whom were receiving cyclosporine monotherapy (28). However, most non-converters received MMF in their combination therapies. Sattler et al. have observed a non-significant trend for an association of seroconversion with younger age in KT patients (*P*=0.0568) (26). The poor immune response in their cohort has been associated with MMF use by all patients and a high percentage of patients using glucocorticoids. Grupper et al. have listed variables associated with absent antibody response as high-dose corticosteroids in the last 12 months (OR 1.3 [95% CI 1.09-1.86]), older age (OR 1.66 [95% CI 1.17-2.69]), maintenance of triple immunosuppression (OR 1.43 [95% CI 1.06-2.15]), and regimens that include MMF (OR 1.47 [95% CI 1.26-2.27]) (13). It has been concluded that positive antibody response is associated with younger age, shorter maintenance dialysis vintage before transplantation, longer time since transplantation, a higher prevalence of living donors, higher eGFR, higher mean hemoglobin and higher

Table 1. Summary of the 18 included studies. Vaccines are as follow: mRNA-1273 (Moderna), BNT162b2 SARS-CoV- 2 (Pfizer-BioNTech)

Author	Country	Study design	Patient population	Vaccine	Sample size	Outcome/Criteria for positive response	Timing of blood sampling after full vaccination	Seroconversion rate
Agur et al. (23)	Israel	Prospective cohort	HD, PD	Pfizer-BioNTech, 21 days apart	122 HD, 23 PD	Anti-S IgG >50 AU/ml	2-6 weeks	93.44% HD 95.65% PD
Attias et al. (16)	France	Cohort study	HD	Pfizer-BioNTech	52 HD	Anti-S1 IgG signal-to-cutoff >1; gray zone, 0.8-1. Anti-S1-RBD IgG >1 and identification of activated CD4+ 3 weeks after completion of vaccination	Weekly until 3 weeks after second dose	82.69% HD
Broseta et al. (17)	Spain	Prospective cohort	HD	Moderna (100 pt), 28 days, Pfizer-BioNTech (75 pt), 21 days	175 HD	Anti-S, cut-off 15 U/mL	3 weeks	95.42% HD
Frantzen et al. (18)	France	Prospective cohort	HD	Pfizer-BioNTech, 21 days	244 HD	Anti-S IgG ≥50 AU/ml	1 month	90.57% HD
Grupper et al. (19)	Israel	Prospective cohort	HD, HC	Pfizer-BioNTech, 21 days	56 HD, 95 HC	Anti-S IgG ≥13.0 AU/mL	3 weeks	96.43% HD 100% HC
Jahn et al. (20)	Germany	Cohort study/communication	HD, HC	Pfizer-BioNTech, 3-4 weeks apart	72 HD, 16 HC	Anti-S/Control > 1.1	14 days	93.06% HD 100% HC
Longlune et al. (24)	France	Cohort study	HD, PD	Pfizer-BioNTech, 28 days apart	82 HD, 20 PD	Anti-S >29 U/ml	1 month	84.15% HD 85% PD
Simon et al. (22)	Austria	Cohort study	HD, HC	Pfizer-BioNTech, 21 days apart	81 HD, 80 HC	Anti-S1 semi-quantitative index ≥ 1	21 days	72.83% HD 100% HC
Speer et al. (21)	Germany	Cohort study/original article	HD, HC	Pfizer-BioNTech, 19-22 days apart	17 HD, 46 HC	Anti-S	18-22 days	82.35% HD 100% HC
Yanay et al. (25)	Israel	Cohort study/letter to the editor	HD, PD, HC	Pfizer/BioNTech	127 HD, 33 PD, 132 HC			90.0% HD+PD 100% HC
Husain et al. (12)	USA	Prospective cohort	KT	Moderna (12), Pfizer-BioNTech (16)	28 KT	Anti-S IgG	2-6 weeks	KT: 25%
Rincon-Arevalo et al. (29)	Germany	Prospective cohort	KT, HD, PD, HC	Pfizer-BioNTech, 21 days apart	40 HD, 4 PD, 40 KT, 35HC	IgG and IgA anti-S1	7 ± 2 days	70.45% HD+PD 100% HC 2.5% KT
Bertrand et al. (27)	France	Prospective cohort	KT, HD	Pfizer-BioNTech, 3 weeks apart	45 KT, 10 HD	Anti-S >50 AU/mL	1 month	17.78% KT 80% HD
Danthu et al. (28)	France	Prospective cohort	KT, HD, HC	Pfizer-BioNTech, 28 days apart	74 KT, 78 HD, 7 HC	Anti-Trimeric S IgG >13 AU/mL	8 days	80.76% HD 100% HC 4.05% KT
Grupper et al. (13)	Israel	Prospective cohort	KT, HC	Pfizer-BioNTech, 21 days apart	136 KT, 25 HC	Anti-S1/S2 IgG <12.0 AU/mL negative, 12.0 to 15.0 AU/mL equivocal, >15 AU/mL positive	10 and 20 days	37.5% KT 100% HC
Korth et al. (15)	Germany	Prospective cohort	KT, HC	Pfizer-BioNTech, 22.0 +/- 4.6 days apart	23 KT, 23 HC	Anti-S IgG AU/mL <13.0 negative, 13.0 positive	14 days	21.74% KT 100% HC
Rozen-Zvi et al. (14)	Israel	Prospective cohort	KT	Pfizer-BioNTech, 21 days apart	308 KT	Anti-S IgG 50 AU/mL positive	2 to 4 weeks, followed for up to 6 weeks.	36.36% KT
Sattler et al. (26)	Germany	Prospective cohort	KT, HD, HC	Pfizer-BioNTech, 21 days apart	39 KT, 26 HD, 39 HC	Anti-S	8 ± 1 days	84.62% HD 100% HC 2.56% KT

AU/mL: Arbitrary Units per milliliter, HD: Hemodialysis, PD: Peritoneal dialysis, KT: Kidney transplant, HC: Healthy control, Anti-S: Anti-Spike protein of SARS-CoV-2.

Table 2. Factors associated with vaccine response in kidney transplant (KT) patient

		Seroconversion	Patients, n (%)	Age, years	Male, n (%)	MMF n (%)	Corticosteroids n (%)	Tacrolimus n (%)	Cyclosporine n (%)	Belatacept n (%)
Rozen Zvi et al. (14)	Transplant	Yes	112 (36.36%)	53.7	76 (64.0%)	66 (58.9%)	4 (3.6%)	104 (92.9%)	8 (7.1%)	
		No	196 (63.64%)	59.7	121 (61.7%)	160 (81.6%)	22 (11.2%)	181 (92.3%)	15 (7.7%)	
Husain et al. (12)	Transplant	Yes	7 (25%)		NA	2 (29%)	4 (57%)	6 (86%)		0 (0%)
		No	21 (75%)	60	NA	15 (71%)	5 (24%)	15 (71%)		6 (29%)
Bertrand et al. (27)	Transplant	Yes	8 (17.78%)	63.5	23 (51.1%)	37 (82.2%)	21 (46.7%)	24 (53.3%)	8 (17.8%)	10 (22.2%)
		No	37 (82.22%)							
Korth et al. (15)	Transplant	Yes	5 (21.74%)	57.0	2 (40.0%)	3 (60%)	3 (60%)	2 (40%)	2 (40%)	0
	Transplant	No	18 (78.26%)	57.9	9 (50.0%)	15 (83%)	11 (61%)	12 (67%)	2 (11%)	1 (6%)
	HC	Yes	23 (100%)	44.4	9 (39.0%)					
	HC	No	0							
Danthu et al. (28)	Transplant	Yes	3 (4.17%)	64.8	44 (61.1%)		34 (45.9%)			2 (2.6%)
	Transplant	No	69 (95.83%)							
	HC	Yes	7 (100%)	51.6	4 (58.0%)					
	HC	No	0							
Rincon-Arevalo et al. (29)	Transplant	Yes	1 (2.5%)	62.4	28 (70.0%)	39 (97.5%)	37 (92.5%)			
	Transplant	No	39 (97.5%)							
	HC	Yes	35 (100%)							
	HC	No	0							
Sattler et al. (26)	Transplant	Yes	1 (2.56%)	57.4	28 (71.8%)	39 (100%)	38 (97.43%)	22 (56.41%)	14 (35.89%)	
	Transplant	No	38 (97.44%)							
	HC	Yes	39 (100%)	53.0	20 (51.3 %)					
	HC	No	0							
Grupper et al. (13)	Transplant	Yes	51 (37.50%)	54.5	34 (66.6%)	32 (62.7%)	7 (13.7%)			
	Transplant	No	85 (62.50%)	60.9	53 (62.4%)	72 (84.7%)	25 (29.4%)			
	HC	Yes	25 (100%)	52.7	8 (32.0%)					
	HC	No	0							
HC: Healthy control.										

Table 3. Factors associated with vaccine response in dialysis (hemodialysis (HD), peritoneal dialysis (PD) patients and compared with healthy controls (HC)

Author	Population	Seroconversion	Patient number	Age (years)	Male, n (%)	HD/ PD, n	Dialysis vintage (months)	BMI>30 kg/m ² , n (%)	Lymphocyte (10 ³ /mm ³)	Serum albumin (g/dL)
Longlune et al. (24)	HD/PD	Yes	86 (84.3%)	64	56 (65.1%)	69/17	37 ± 36		993 ± 490	
		No	16 (15.7)	70	9 (81.8%)	13/ 3	31 ± 49		1249 ± 664	
Agur et al. (23)	HD/PD	Yes	136 (93.8%)	71	76 (66.7%)	114/22	40 ± 33	29 (25.4%)		3.99 ± 0.35
		No	9 (6.2%)	78	5 (62.5%)	8/1	39 ± 27	2 (25%)		3.41 ± 0.56
Frantzen et al. (18)	HD	Yes	221 (90.6%)	77	158 (71.5%)			51 (23%)		
		No	23 (9.4%)					4 (17%)		
Broseta et al. (17)	HD	Yes	167 (95.4%)	71	111 (66.5%)		67 ± 105		1282 ± 635	4.1 ± 2.6
		No	8 (4.6%)	73	7 (87.5%)		79 ± 53		750 ± 484	3.19 ± 0.62
Bertrand et al. (27)	HD	Yes	8 (80%)	71			3.1 years [0.6-12.6]*			
		No	2 (20%)							
Attias et al. (16)	HD	Yes	43 (82.7%)	68	35 (51.5%)					
		No	9 (7.3%)	83	6 (66.7%)					
Simon et al. (22)	HD	Yes	59 (72.8%)	67	58 (71.6%)					
		No	22 (27.2%)							
	HC	Yes	80 (100%)	49	30 (37.5%)					
		No	0							
Speer et al. (21)	HD	Yes	14 (82.4%)	74	12 (54.5%)		5 years [2-14]*	16 **		
		No	3 (17.6%)							
	HC	Yes	46 (100%)	48	19 (41.3%)					
		No	0							
Grupper et al. (19)	HD	Yes	54 (96.4%)	74	42 (75.0%)		38±37		1500 ± 600	4.0 ± 0.35
		No	2 (3.6%)							
	HC	Yes	95 (100%)	57	26 (27.4%)					
		No	0							
Jahn et al. (20)	HD	Yes	67 (93.1%)	68	41 (56.9%)					
		No	5 (6.9%)							
	HC	Yes	16 (100%)	45	7 (43.8%)					
		No	0							

Table 3. Factors associated with vaccine response in dialysis (hemodialysis (HD), peritoneal dialysis (PD) patients and compared with healthy controls (HC) (continue)

Author	Population	Seroconversion	Patient number	Age (years)	Male, n (%)	HD/ PD, n	Dialysis vintage (months)	BMI>30 kg/m ² , n (%)	Lymphocyte (10 ³ /mm ³)	Serum albumin (g/dL)
Danthu et al. (28)	HD	Yes	63 (85.9%)	73	46 (59%)		5 years ± 6		1200 ± 600	3.54 ±/± 0.47
		No	15 (4.1%)							
	HC	Yes	7 (100%)	52	4 (57.1%)					
		No	0							
Rincon-Arevalo et al. (29)	HD/PD	Yes	31 (70.5%)	69/70	25 (62.5%)/3 (75%)	40/4	5.5 years [2,9]*			
		No	13 (29.5%)							
	HC	Yes	35 (100%)	51	20 (57.1%)					
		No	0							
Sattler et al. (26)	HD	Yes	22 (84.6%)	67	17 (65.4%)		7 years ±5			
		No	4 (15.4%)							
	HC	Yes	39 (100%)	53	20 (51.3%)					
		No	0							
Yanay et al. (25)	HD+PD	Yes	144 (90%)	69	101 (63.1%)	127/33	3 years [2-5]*			
		No	16 (10%)							
	HC	Yes	132 (100%)	50	67 (50.8%)					
		No	0							
*: median, IQR										
**: n= 22										
BMI: Body mass index.										

lymphocyte count (13). Treatment with MMF or triple maintenance immunosuppression has been found less frequent in seropositive than in seronegative patients (13). Rincon-Arevalo et al. have observed a lower antibody response with advanced age in KT patients (29) and reported seroconversion rate as 2.5% in KT, 70% in dialysis and 100% in the HC group (29).

The studies conducted by Korth et al. (15), Arevalo et al. (29) and Grupper et al. (13) have demonstrated a lower antibody titer in patients with KT than in HC: Korth et al. (50.9 \pm 138.7 AU/mL vs. 727.7 \pm 151.3 AU/mL, $p = 0.0001$) (15) and Grupper et al. ($p < 0.001$) (13).

Antibody Response in HD and PD Patients

Table 3 presents seroconversion rates, baseline characteristics, comorbidities, primary kidney disease, immunosuppressive treatment and laboratory values of HD, PD and HC patients. Seroconversion rate in HD patients ranged from 72.83% to 96.43% and in HD+PD patients from 70.45% to 90%. The overall seroconversion rate was 88.5 % of HD and 88.0% of HD+PD studied. In 8 studies that also included HC, seroconversion rate for dialysis patients ranged from 70.45 to 96.43% (85.0% overall) and in HC it was 100%. However, HC were generally younger (up to 23 years) than HD patients.

Longlune et al. have reported that immunosuppressive drug use, especially steroid use, is significantly higher among non-responder dialysis patients [OR 0.075 (95% CI 0.019-0.303), $p = 0.0003$] (24). Agur et al. have observed that younger age (Beta 0.021 per year decrease, 95% CI 0.011-0.031, $p < 0.001$), serum albumin above 3.5 g/dL (Beta 1.039, 95% CI 0.65-1.429, $p < 0.001$), lower intravenous iron dose (Beta 0.002 per mg/week decrease, 95% CI 0.00-0.004, $p = 0.009$) and body mass index under 30 kg/m² (Beta 0.394, 95% CI 0.107- 0.681, $p = 0.008$) are positive predictor factors for antibody response (23). Frantzen et al. have found that older age is associated with a poor antibody response. In addition, it has been found that patients undergoing chemotherapy or who were under immunosuppression are all non-seroconverters (18). In their univariate analysis, Broseta et al. have demonstrated that the use of immunosuppressive treatment ($p < 0.001$), longer dialysis vintage ($p = 0.03$), lower hemoglobin ($p = 0.04$) and lower albumin ($p < 0.001$) concentrations,

and lower white blood cell ($p = 0.04$) and lymphocyte ($p = 0.004$) counts were associated with a lower antibody response (17). Immunosuppressive treatment ($p < 0.001$), lower hemoglobin level ($p = 0.04$), and a lower lymphocyte count ($p = 0.02$) are significant predictors of a negative antibody response in multivariate analysis (17). Attias et al. have observed no difference in patient characteristics between seroconverted and non-seroconverted HD patients (16). Unlike most other studies, they have established that immunosuppression does not alter the seroconversion status (16). Simon et al. have reported that dialysis patients with an antibody response higher than 20 IU/ml to the Hepatitis B vaccine had higher anti-S antibody titers (responders: median = 223.5, IQR = 587; non-responders: median = 159, IQR = 450) (22). Unlike Agur et al. and Frantzen et al., Speer et al. could not detect an age-related difference in antibody levels (21). According to Grupper et al. older age and lower lymphocyte count were associated with a lower antibody response (OD 1.22 per 1-year older; 95% CI, 1.13 to 1.68; $p = 0.03$ and OR, 0.83 per 10³/ml-higher lymphocyte count; 95% CI, 0.58 to 0.97; $p = 0.05$) in the dialysis patients (19). Jahn et al. have revealed that older age is negatively associated with antibody response in HD patients, with significantly lower titers over 60 years (280.0 AU/mL (45.7- 477.0), $p < 0.0001$) (20). Danthu et al. have found a similar association, indicating that those older than 75 years of age were more likely to be non-seroconverters (28). A higher serum albumin and Kt/Vurea levels have been significantly associated with higher seroconversion rate ($p < 0.043$ and $p < 0.019$, respectively) (28). Yanay et al. could not detect a difference in age, sex, dialysis modality, and dialysis vintage between seroconverters and non-seroconverters (25).

In addition to these findings, mean anti-S antibody titer of dialysis recipients has been found significantly lower than in HC in Simon et al. (22), Grupper et al. (19), Jahn et al. (20), Speer et al. (21), Danthu et al. (28), Rincon-Arevalo et al. (29) and Yanay et al. (25).

DISCUSSION

In this systematic review, we analyzed seroconversion rates after SARS-CoV-2 vaccination in KT and dialysis patients and defined the factors that associate with seroconversion status in these populations. The main findings are that the overall seroconversion rate

was 27.2% for KT, 88.5% for dialysis patients, while all HC in these studies seroconverted. Moreover, anti-S antibody titers were lower in seroconverted KT or dialysis patients than in HC in all studies that assessed this variable.

In KT patients, a lower seroconversion rate was associated with older age (13,29), and with immunosuppressive regimen use mostly consisting of MMF (12, 13,26,28,29), but even with glucocorticoids (13,26,29), calcineurin inhibitors (27,29) or belatacept (12,27), higher rate of triple immunosuppressive regimen (13), and higher MMF (13,14) or calcineurin inhibitor dose (14) (Figure 1). On the other hand, a higher seroconversion rate was associated with a higher eGFR (13,14), cyclosporine monotherapy (28), younger age (13,14,26), a shorter dialysis vintage before transplantation (13), a longer period of time since transplantation (13), a higher prevalence of living donor (13), and a higher mean hemoglobin and lymphocyte count (13) (Figure 1). Only Korth et al. found no difference in age, gender and immuno-

suppressive regimen between seroconverted and non-seroconverted groups (15). In general, a more aggressive immunosuppression regimen was associated with lower seroconversion rates, while factors associated with less intense current or past immunosuppression (e.g longer time since transplantation, living donor) or lower exposure to uremia (higher eGFR, shorter dialysis vintage) or its consequences (higher hemoglobin and lymphocyte count) were associated with better antibody responses.

In dialysis patients, older age (18-20,28), current immunosuppressive therapy (17,18,24) or chemotherapy (18), lower serum albumin (17), lower white blood cell (17) or lymphocyte counts (17,19), lower hemoglobin (17) and lower dialysis vintage (17) were identified as indicators of a lower antibody response or non-response (Figure 2). Only Attias et al. failed to find any relation between immunosuppressive therapy and antibody response (16). This could be due to a smaller sample size ($n=52$) than Longlune et al. ($n=97$) (24), Broseta et al. ($n=175$) (17) and Frantzen et

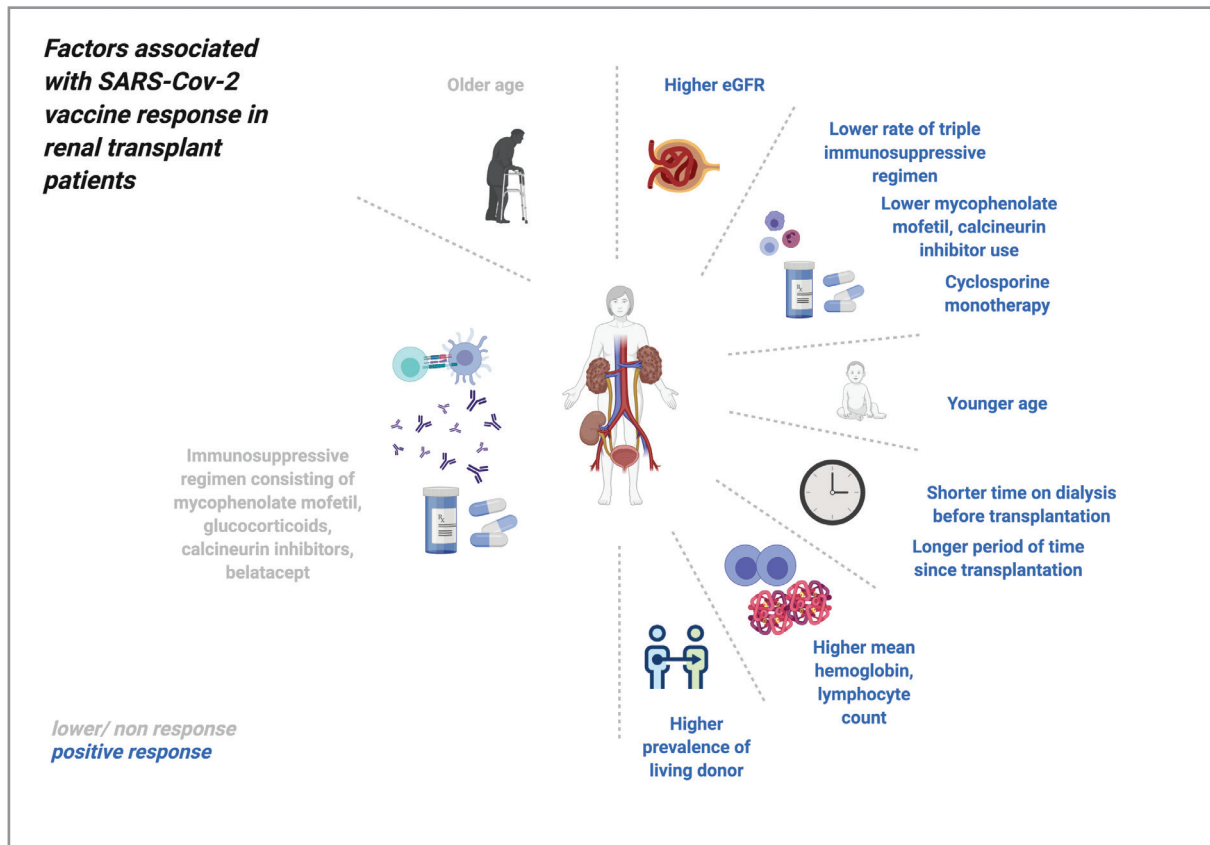


Figure 1. Factors associated with a lower/non-response or a positive response in kidney transplant patients following a full series of SARS-CoV-2 vaccination.

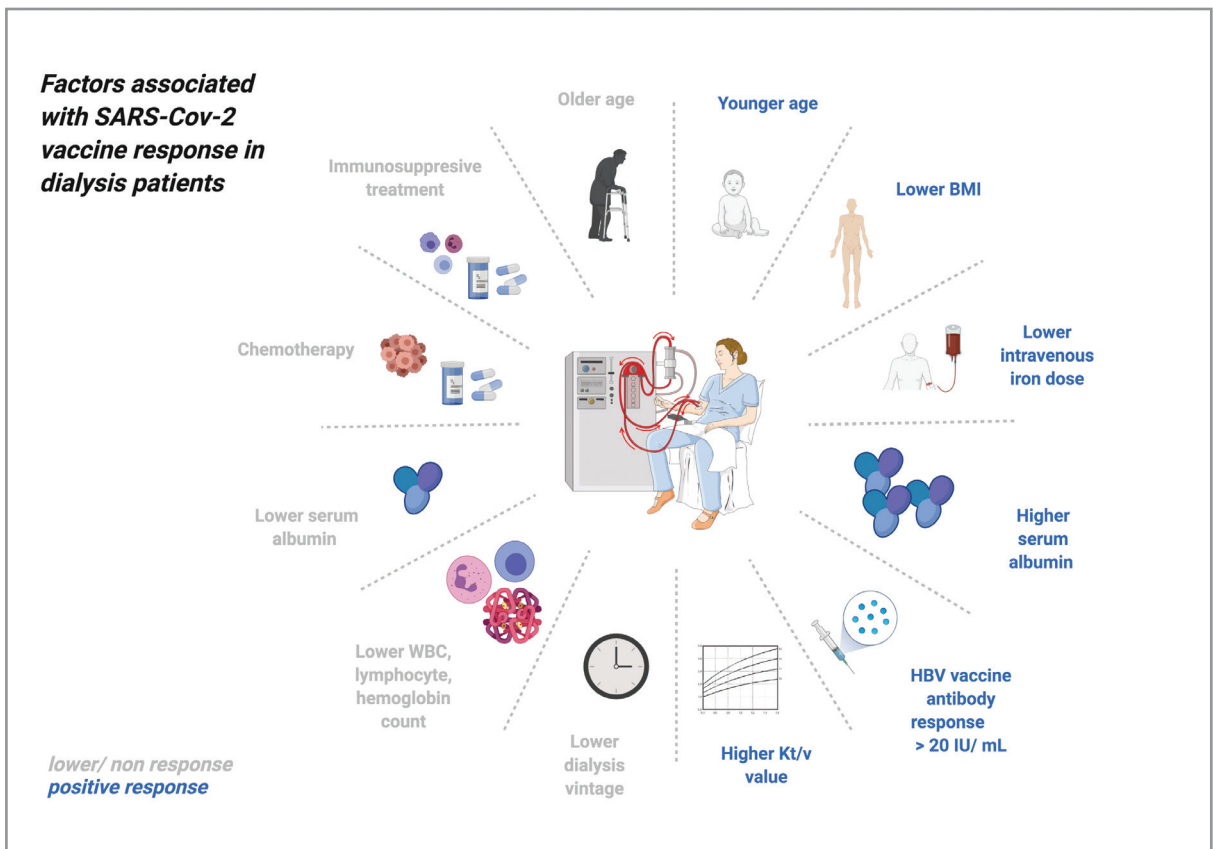


Figure 2. Factors associated with a lower/non-response or a positive response in dialysis patients following a full series of SARS-CoV-2 vaccination.

al. (n= 244) (18). On the other hand, younger age (23), higher serum albumin (23,28), lower intravenous iron dose (23), body mass index $<30 \text{ kg/m}^2$ (23), HBV vaccine antibody response $>20 \text{ IU/mL}$ (22, 28), higher Kt/Vurea value (28) were correlated with higher seroconversion rates (Figure 2). Again, not all studies were concordant, Yanay et al. (25) and Speer et al. (21) could not detect age as a predictor of seroconversion status or confirm some of the above predictors of seroconversion status, while Attias et. al did not observe differences in patient characteristics between seroconverted and non-seroconverted groups (16).

Although seroconversion status was differently reported compared to other articles, Anand et al. also reported outcomes of fully vaccinated dialysis patients (30). In this rather large study, 610 fully vaccinated dialysis patients were divided in three groups according to follow-up antibody titers: absent, attenuated and medium-high antibody titers (30). Longer dialysis vintage and lower serum albumin were asso-

ciated with higher likelihood of absent or attenuated antibody response (30).

Our literature review revealed a relatively poor seroconversion rate and antibody titers in dialysis patients compared to HC. These results are in line with the lower antibody response observed in chronic kidney disease patients compared to the general population. In our study, we additionally reported specific immunosuppressive drugs that might have a supplemental negative impact on the immune response after vaccination. Differently, we included studies that report patient data who received a full series of vaccination (31). Chronic kidney disease impairs both natural and adaptive immune response, which might be the culprit for the lower seroconversion rates seen in dialysis patients (32). Immune dysregulation caused by uremia is characterized not only by immune depression that makes this patient group prone to acquiring COVID-19 during their hospital visits, but also immune activation that predisposes to cardiovascular diseases, placing an additional risk for

severe COVID-19 disease (33). This immune dysregulation was also shown by the study Rincon-Arevalo et al. in which immunophenotyping of dialysis patients revealed predominance of pre-switch and naive receptor binding domain antigen-specific B cells, whereas HC group was dominated by plasmablast and post-switch memory B cell compartments (29). Furthermore, not only chronic kidney disease but dialysis itself may also weaken immune function (34). It compromises chemotactic and phagocytic function of neutrophils (32). Therefore, these patients may have higher risk of severe COVID-19 infection compared to the healthy population and could also be less protected after vaccination.

Similar to dialysis patients, KT patients are likely to develop poor antibody response to SARS-CoV-2 mRNA vaccines. Immunosuppressive treatment can dampen immunological responses; together with a high rate of comorbidities. KT patients do not only have a poor humoral response, but also an impaired cellular response to vaccination against SARS-CoV-2. Rincon-Arevalo et al. have shown that naive and pre-switch B cells were more abundant than post-switch and double negative memory B cells. This was similar to dialysis patients and differed from the HC group (29). Non-responder KT patients had reduced plasmablasts and T cells, as well (29). In addition, Sattler et al. have reported a reduction in the frequency of spike-specific Th cells and almost absence of CD8+ T cell responses among KT patients with impaired cytokine production and memory B cell differentiation (26). Immunosuppressive drug modulation/reduction can be considered to improve vaccination responses. However, in the absence of clinical trials, the optimal duration or intensity prior or post vaccination and the rejection risks associated with this strategy are unknown (35).

In most studies, immunosuppressive drug use was a negative predictor for seroconversion. A negative effect of MMF on antibody response in KT groups was observed almost in all studies (12-14, 26-29). In the study by Sattler et al., most KT patients were on MMF and the seroconversion rate was 2% (26). Similarly, Rozen-Zvi et al. and Grupper et al. have found a statistically significant difference in MMF use among seroconverted and non-seroconverted KT patients (13,14). Furthermore, lower MMF dose was associated with higher antibody titers (14). In line with these findings, the seroconversion rate was

2.5%, 70% and 100% in the KT, dialysis and HC groups, respectively and MMF use was the main differential factor of KT patients (29). MMF inhibits purine nucleotide synthesis in lymphocytes and prevents B cell and plasma cell formation (26), thereby decreasing antibody production. In previous reports, MMF has also been confirmed to decrease responses to influenza and cholera vaccine in a dose-dependent manner (13).

CNI and belatacept were also associated with poor vaccine responses (14,27,29) (12,27,36). CNI inhibit activation and proliferation of adaptive immune cells, namely B cells, CD4+ T cells and Tfh cells (29). Belatacept inhibits T cell activation by binding CD80 and CD86 to prevent their attachment with CD28, a T cell costimulator on multiple other immune cells (37). All these data suggest that MMF, CNI and belatacept might contribute to suppress anti-S antibody responses after vaccination.

Poor antibody response to SARS-CoV-2 mRNA vaccines among dialysis and KT patients might be overcome by a third additional dose which can be offered to the non-seroconverted patients after a full series of vaccination. In this regard 5 of 12 non-seroconverted dialysis patients that received a third dose of BNT162b2 vaccine one month after the second dose seroconverted and maintained anti-S antibody titers at one month-post vaccination without serious adverse effects (24). In another study, 8 of 24 solid organ transplant recipients who had negative antibody response to SARS-CoV-2 vaccination have seroconverted after a third vaccine dose (38). In a further study in 45 seronegative dialysis patients without history of prior COVID-19 infection, a third BNT162b2 dose has improved humoral response in almost all patients (39). These data suggest that a third additional dose could be administered to seronegative dialysis and KT patients.

Some demographic characteristics were also associated with the seroconversion rate. Age was an important factor affecting the seroconversion status in KT and dialysis patients. Older age (13,18-20,28,29) led to lower seroconversion rates in both KT and dialysis patients. This can partially be explained by a reduction in immunologic memory with increasing age as aged T cells produce short-lived inflammatory effector T-cells instead of memory or follicular helper T cells (33). Accordingly, younger age led to a higher seroconversion rate in many stud-

ies (13,14,23,26). In one study, a lower body mass index ($<30 \text{ kg/m}^2$) was associated with a higher seroconversion status (23). In contrast, in several studies did not correlations between seroconversion rates and demographic characteristics such as age, gender, body mass index (15,16,21,25,28). Therefore, further studies are needed to evaluate the relation between demographic data and seroconversion rates in both dialysis and KT patients.

In the majority of studies, the time interval between the first and second dose of vaccine varies between 21 days to 28 days. In several studies, the interval between doses was not reported (12,16,25). In studies with a time interval of 28 days on dialysis patients (24,28), the seroconversion rate ranges from 81% to 83%. On the other hand, the seroconversion rates varied between 73% (22) and 96% (19) in studies with a time interval of 21 days in dialysis patients. These suggest that there is no considerable difference in seroconversion when the interval between the two doses in dialysis patients is 21 to 28 days.

All studies investigated the presence of anti-spike protein IgG antibodies to evaluate the seroconversion status. The timing of blood sampling for antibody detection after a full series of vaccination ranged from seven days to six weeks. Seroconversion rates greatly varied between studies regardless of the time from the last dose to the blood sampling. Simon et al. have reported an additional increase in the seroconversion rates after a 10 week post-vaccination follow up in hemodialysis patients (22). This may warrant further investigations to determine the effect of blood sampling timing after full vaccination on seroconversion status. Among 18 studies, only Husain et al. have used the Moderna mRNA-1273 vaccine in addition to the Pfizer/Biontech BNT162b2 vaccine in KT patients (12). The seroconversion rates were equal (25%) for both. However, only 12 and 16 patients have been immunized with the Moderna mRNA-1273 and the Pfizer/Biontech BNT162b2 vaccines, respectively (12). All other studies only assessed Biontech BNT162b2. Therefore, additional studies with larger sample sizes are needed for the further assessment of efficacy of different mRNA vaccines.

Following SARS-CoV-2 infection, HD patients have a rapid decline in anti-SARS-CoV-2 antibody titers after COVID-19, which appears to be earlier than in general population studies (32). In another study, up to

85% of 136 HD patients who were antibody positive at baseline, maintained serologic evidence of immune responses at 6 months (40). In 8 patients who became seronegative at 6 months, there was evidence of a robust cellular immunity measured by T-cell response to SARS-CoV-2 structural proteins (40). Thus, whether cellular immunity develops in vaccinated seronegative KRT patients and whether this immunity confers clinically significant protection from severe COVID-19 should be studied. Additionally, given the potential shorter duration of seroconversion in KRT, the optimal timing of eventual booster doses of vaccine should be studied in this population.

Future Directions

Seroconversion rates following vaccination in both KT recipients and dialysis patients are suboptimal and this is an unmet clinical need. Future studies should address how to optimize patient management (e.g. immunosuppressive regimens) in order to improve vaccination responses, including assessing the impact of a third dose or optimization of vaccine dosing, as well as studying the best way to assess clinically relevant immunological responses (e.g. are patients with low antibody titers but preserved cellular responses protected from clinically significant diseases?).

CONCLUSION

Dialysis patients and KT recipients have lower seroconversion rates after a full series of mRNA-based SARS-CoV-2 vaccination compared to the general population. Several factors are associated with the altered antibody response in these patients. These potential predictors should be kept in mind and managed during the vaccination of patients on KRT. A third dose could be considered in non-seroconverted patients and in those with early loss of anti-S antibodies.

ACKNOWLEDGEMENTS

MK gratefully acknowledge use of the services and facilities of the Koc University Research Center for Translational Medicine (KUTTAM), funded by the Presidency of Turkey, Presidency of Strategy and Budget. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Presidency of Strategy and Budget.

REFERENCES

- Carriazo S, Kanbay M, Ortiz A. Kidney disease and electrolytes in COVID-19: more than meets the eye. *Clin Kidney J* 2020; 13(3): 274-80.
- Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A, Hassanzadeh G. COVID-19 and multiorgan failure: A narrative review on potential mechanisms. *J Mol Histol* 2020; 51(6): 613-28.
- Chawki S, Buchard A, Sakhi H, Dardim K, El Sakhawi K, Chawki M, et al. Treatment impact on COVID-19 evolution in hemodialysis patients. *Kidney Int* 2020; 98(4): 1053-4.
- Caillard S, Chavarot N, Francois H, Matignon M, Greze C, Kamar N, et al. Is COVID-19 infection more severe in kidney transplant recipients? *Am J Transplant* 2021; 21(3): 1295-303.
- Basile C, Combe C, Pizzarelli F, Covic A, Davenport A, Kanbay M, et al. Recommendations for the prevention, mitigation and containment of the emerging SARS-CoV-2 (COVID-19) pandemic in haemodialysis centres. *Nephrol Dial Transplant* 2020; 35(5): 737-41.
- American Society of Transplantation COVID-19 Vaccination Guidance [Internet]. 02.02.2021. Available from: <https://www.myast.org/sites/default/files/ASTCOVID-info.pdf>.
- Vaccinating Dialysis Patients and Healthcare Personnel [Internet]. CDC. 03.24.2021. Available from: <https://www.cdc.gov/vaccines/covid-19/planning/vaccinate-dialysis-patients-hcp.html>.
- Combe C, Kirsch AH, Alfano G, Luyckx VA, Shroff R, Kanbay M, et al. At least 156 reasons to prioritize COVID-19 vaccination in patients receiving in-centre haemodialysis. *Nephrol Dial Transplant* 2021; 36(4): 571-4.
- Krueger KM, Ison MG, Ghossein C. Practical Guide to Vaccination in All Stages of CKD, Including Patients Treated by Dialysis or Kidney Transplantation. *Am J Kidney Dis* 2020; 75(3): 417-25.
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; 383(27): 2603-15.
- 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. *N Engl J Med* 2021; 384(5): 403-16.
- Husain SA, Tsapepas D, Paget KF, Chang JH, Crew RJ, Dube GK, et al. Postvaccine Anti-SARS-CoV-2 Spike Protein Antibody Development in Kidney Transplant Recipients. *Kidney Int Rep* 2021; 6(6): 1699-700.
- Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M, et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant* 2021 Aug; 21(8): 2719-26.
- Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect* 2021 Aug; 27(8): 1173. e1-1173.e4.
- Korth J, Jahn M, Dorsch O, Anastasiou OE, Sorge-Hadick B, Eisenberger U, et al. Impaired humoral response in renal transplant recipients to SARS-CoV-2 vaccination with BNT162b2 (Pfizer-BioNTech). *Viruses* 2021; 13(5).
- Attias P, Sakhi H, Rieu P, Soorkia A, Assayag D, Bouhroum S, et al. Antibody response to the BNT162b2 vaccine in maintenance hemodialysis patients. *Kidney Int* 2021;99(6):1490-2.
- Broseta JJ, Rodriguez-Espinosa D, Rodriguez N, Mosquera MDM, Marcos MA, Egri N, et al. Humoral and cellular responses to mRNA-1273 and BNT162b2 SARS-CoV-2 vaccines administered to hemodialysis patients. *Am J Kidney Dis* 2021 Jun; 99(6): 1490-2.
- Frantzen L, Cavaille G, Thibeaut S, El-Haik Y. Efficacy of the BNT162b2 mRNA Covid-19 Vaccine in a hemodialysis cohort. *Nephrol Dial Transplant* 2021 Apr 24; gfab165.
- Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. *Clin J Am Soc Nephrol* 2021 Jul;16(7):1037-42.
- Jahn M, Korth J, Dorsch O, Anastasiou OE, Sorge-Hadick B, Tyczynski B, et al. Humoral Response to SARS-CoV-2 Vaccination with BNT162b2 (Pfizer-BioNTech) in Patients on Hemodialysis. *Vaccines (Basel)* 2021; 9(4).
- Speer C, Goth D, Benning L, Buylaert M, Schaefer M, Grenz J, et al. Early humoral responses of hemodialysis patients after COVID-19 vaccination with BNT162b2. *Clin J Am Soc Nephrol* 2021 Jul; 16(7): 1073-82.
- Simon B, Rubey H, Treipl A, Gromann M, Hemedi B, Zehetmayer S, et al. Haemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls. *Nephrol Dial Transplant* 2021 Aug 27; 36(9): 1709-16.
- Agur T, Ben-Dor N, Goldman S, Lichtenberg S, Herman-Edelstein M, Yahav D, et al. Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients - a prospective cohort study. *Nephrol Dial Transplant* 2021 Apr 11; gfab155.
- Longlune N, Nogier MB, Miedouge M, Gabilan C, Cartou C, Seigneure B, et al. High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients. *Nephrol Dial Transplant* 2021 Aug 27; 36(9): 1704-9.
- Yanay NB, Freiman S, Shapira M, Wishahi S, Hamze M, Elhaj M, et al. Experience with SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients. *Kidney Int* 2021; 99(6): 1496-8.

26. Sattler A, Schrezenmeier E, Weber UA, Potekhin A, Bachmann F, Straub-Hohenbleicher H, et al. Impaired humoral and cellular immunity after SARS-CoV2 BNT162b2 (Tozinameran) prime-boost vaccination in kidney transplant recipients. *J Clin Invest* 2021 Jul 15; 131(14): e150175.
27. Bertrand D, Hamzaoui M, Lemee V, Lamulle J, Hanoy M, Laurent C, et al. Antibody and T Cell Response to SARS-CoV-2 Messenger RNA BNT162b2 vaccine in kidney transplant recipients and hemodialysis patients. *J Am Soc Nephrol* 2021 Sep; 32(9): 2147-52.
28. Danthu C, Hantz S, Dahlem A, Duval M, Ba B, Guibbert M, et al. Humoral Response after SARS-CoV-2 mRNA Vaccine in a Cohort of Hemodialysis Patients and Kidney Transplant Recipients. *J Am Soc Nephrol* 2021 Sep; 32(9): 2153-8.
29. Rincon-Arevalo H, Choi M, Stefanski AL, Halleck F, Weber U, Szelinski F, et al. Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients. *Sci Immunol* 2021; 6(60).
30. Anand S, Montez-Rath M, Han J, Garcia P, Cadden L, Hunsader P, et al. Antibody response to COVID-19 vaccination in patients receiving dialysis. *J Am Soc Nephrol* 2021 Oct; 32(10): 2435-8.
31. Carr EJ KA, Graham-Brown M, Abra G, Argyropoulos C, Harper L, Lerma EV, et al. Systematic review of early immune response to sars-cov-2 vaccination among patients with chronic kidney disease. *Kidney Int Reports* 2021 Sep; 6(9): 2292-304.
32. Alcazar-Arroyo R, Portoles J, Lopez-Sanchez P, Zalamea F, Furaz K, Mendez A, et al. Rapid decline of anti-SARS-CoV-2 antibodies in patients on haemodialysis: the COVID-FRIAT study. *Clin Kidney J* 2021; 14(7): 1835-44.
33. Yen JS, Wang IK, Yen TH. COVID-19 vaccination & dialysis patients: Why the variable response. *QJM* 2021 Nov 5; 114(7): 440-4.
34. Reddy S, Chitturi C, Yee J. Vaccination in Chronic Kidney Disease. *Adv Chronic Kidney Dis* 2019; 26(1): 72-8.
35. Stock PG, Henrich TJ, Segev DL, Werbel WA. Interpreting and addressing suboptimal immune responses after COVID-19 vaccination in solid organ transplant recipients. *J Clin Invest* 2021 Jul 15; 131(14): e151178.
36. Ou MT, Boyarsky BJ, Chiang TPY, Bae S, Werbel WA, Avery RK, et al. Immunogenicity and Reactogenicity After SARS-CoV-2 mRNA Vaccination in Kidney Transplant Recipients Taking Belatacept. *Transplantation* 2021 Sep 1; 105(9): 2119-23.
37. Parsons RF, Larsen CP, Pearson TC, Badell IR. Belatacept and CD28 Costimulation Blockade: Preventing and Reducing Alloantibodies over the Long Term. *Curr Transplant Rep* 2019; 6(4): 277-84.
38. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Ann Intern Med* 2021 Sep; 174(9): 1330-2.
39. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after three doses of BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. *Kidney Int* 2021 Sep; 100(3): 702-4.
40. Clarke CL, Prendecki M, Dhutia A, Gan J, Edwards C, Prout V, et al. Longevity of SARS-CoV-2 immune responses in hemodialysis patients and protection against reinfection. *Kidney Int* 2021; 99(6): 1470-7.