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REVIEW

Clinical manifestations of COVID-19 infection in dialysis patients and protective effect of COVID-19 vaccine

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Abstract

Background and objective COVID-19 infection poses a special challenge to patients with dialysis patients. The purpose of this study was to evaluate the clinical manifestations of dialysis patients with COVID-19 and the protective effect of the vaccine.

Methods We included 41 studies based on big data, mainly analyzing the clinical symptoms of dialysis patients with COVID-19, the proportion of severe patients before and after vaccination, and the humoral reaction of vaccine in the body.

Results 6.1% to 35.7% of dialysis patients with COVID-19 developed respiratory distress symptoms and needed to be admitted to an intensive care unit for mechanical ventilation. The incidence and mortality of COVID-19 in dialysis patients before vaccination were 5.5% and 1.1%, respectively, and decreased to 4.5% and 0.6% in breakthrough infected patients. There was no statistical difference in serum conversion rates between dialysis patients and healthy controls, but the neutralizing antibody titer in the control group was 1922 (IQR 533 to 3186) AU/mL, and the neutralizing antibody titer in dialysis patients significantly decreased to 367 (IQR 171 to 1650) AU/mL (P=0.046).

Conclusions Dialysis is associated with an increased risk of severe COVID-19, and generally has a poor seroconversion response to vaccines. It also confirms the protective effect of vaccines on high-risk populations such as dialysis.

Keywords COVID-19 · COVID-19 vaccine · CKD · Dialysis · Mortality

Abbreviations

COVID-19	Coronavirus disease in 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
WHO	World Health Organization
GBD	Global Burden of Disease
KDIGO	Kidney Disease: Improving Global Outcomes
CKD	Chronic kidney disease
KRT	Kidney replacement therapy
ERSD	End stage renal disease
ACE2	Angiotensin converting enzyme 2
ICU	Intensive care unit
EPO	Erythropoietin
LPS	Lipopolysaccharide
DPP-4	Dipeptidyl peptidase-4
Treg	Regulatory T cells
Tconv	Conventional T cell
WBC	White blood cell
EPOR	Erythropoietin receptor
DC	Dendritic cell
APC	Antigen presenting cells
MHC	Major histocompatibility complex
TCR	T cell receptor
BCR	B cell receptor
TLR	Toll-like receptor
ERACODA	European Renal Association COVID-19 database
PD	Peritoneal dialysis
HD	Hemodialysis

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Introduction

At present, the pandemic of novel coronavirus pneumonia has become a major international threat. Globally, as of May 25, 2022, more than 500 million confirmed cases of coronavirus disease in 2019 (COVID-19) have been reported to the World Health Organization (WHO), including 6 million deaths. As of May 23, 2022, 10 billion doses of vaccine had been vaccinated (https://covid19.who.int). The high-risk groups of COVID-19-mediated critical diseases include obesity, diabetes, old age and chronic kidney disease (CKD) [1, 2]. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline group divided CKD into five stages according to the estimated glomerular filtration rate, and further subdivided stage 5 into dialysis dependent and dialysis independent [3]. The Global Burden of Disease (GBD) Collaboration identified CKD as the most common risk factor by estimating the number of people at increased risk for COVID-19 in 188 countries [4, 5]. The proportion of severe patients in patients with different CKD stages and even renal transplantation was higher than that in other groups [6]. Through the analysis of risk factors of death caused by severe COVID-19 on OpenSAFELY platform, it is suggested that the risk ratio of COVID-19-related death increases with the severity of CKD, and advanced CKD is one of the diseases with the highest risk of death [7]. The results of ERA-EDTA (European Renal Association-European Dialysis and Transplant Association) registration also support the high mortality caused by COVID-19 in dialysis and transplantation patients in Europe [8]. It was reported that the mortality rate of hemodialysis patients was 14% compared with that of patients without COVID-19 infection [9]. Although patients with CKD stage 4–5, dialysis or renal transplant are not included in these trials or the number of patients included is small [10], it is still necessary to directly protect CKD patients through rapid vaccination trials, because uremia and immunosuppressants may have a negative impact on vaccination response [11].

Mechanism of increased susceptibility of dialysis patients

CKD, especially end stage renal disease (ESRD), can cause functional defects in innate and adaptive immune cell populations, as well as uremia-related damage to monocytes, neutrophil phagocytosis, T lymphocytes, B lymphocytes and cytokines [12]. Among them, the increase in the level of proinflammatory factors, the imbalance of oxidative stress and inflammatory response, the increased susceptibility to viral infection, and the promotion of viral replication and expansion are the main reasons for the increased risk of pulmonary inflammation [13, 14]. Hemodialysis patients are easily infected with COVID-19 due to other comorbidities, older age and low immune function. At the same time, patients often need to go to the hospital for dialysis, which will increase contact and cannot maintain social distance. The increased risk of symptomatic infections is due to impaired immune status, chronic inflammation, high oxidative stress, accumulated uremic toxins and endothelial dysfunction [15].

Angiotensin converting enzyme 2 (ACE 2), the main receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the human body, is highly expressed in the kidney, so the renal tubules of CKD patients infected with SARS-CoV-2 may be attacked first [16, 17]. Figure 1 describes the mechanism of CKD patients' susceptibility after COVID-19 attacks the human body. Uremic toxins can affect the function of immune cells. For example, the accumulation of phenylacetic acid, indole sulfate and p-cresol sulfate promotes the inflammatory state and oxidative stress of uremia. Among them, the effect of p-cresol sulfate on phagocytes impairs the adaptive immune response of CKD patients. An important immune modulator in patients with renal failure is oxidant and antioxidant. The excessive production of oxidant promotes the expression of proinflammatory cytokines and the recruitment of immune cells. This balance is produced excessively in active oxygen and active nitrogen, and the antioxidant is broken after excessive consumption. Under normal circumstances, the kidney plays an immune regulatory role by producing vitamin D and erythropoietin (EPO). Vitamin D regulates the proliferation and differentiation of immune cells by promoting the tolerance of dendritic cells, promoting the production of anti-inflammatory IL-10, and regulating the production of Th1 and Th2 cytokines. EPO can inhibit effector T cells and memory T cells, and promote the differentiation of regulatory T cells. The lack of vitamin D and EPO in dialysis patients changes the immune status of patients, leading to an increase in proinflammatory effect and a decrease in anti-inflammatory effect [18–20]. The increase of intestinal permeability in uremic patients leads to the transfer of lipopolysaccharide (LPS) endotoxin from intestinal tract to systemic circulation. As an immunostimulator, LPS can promote the release of various proinflammatory cytokines. Some of these immunomodulatory mediators will inhibit innate and adaptive immunity, leading to "immune paralysis", and damaging the specific immune response of patients with renal failure to pathogens [21]. At the same time, COVID-19 will attack some small arteries and capillaries of the kidney. Compared with ordinary people, these factors directly lead to increased damage to the kidney caused by viruses and inflammatory cytokines in the blood [22]. Moreover, biological materials

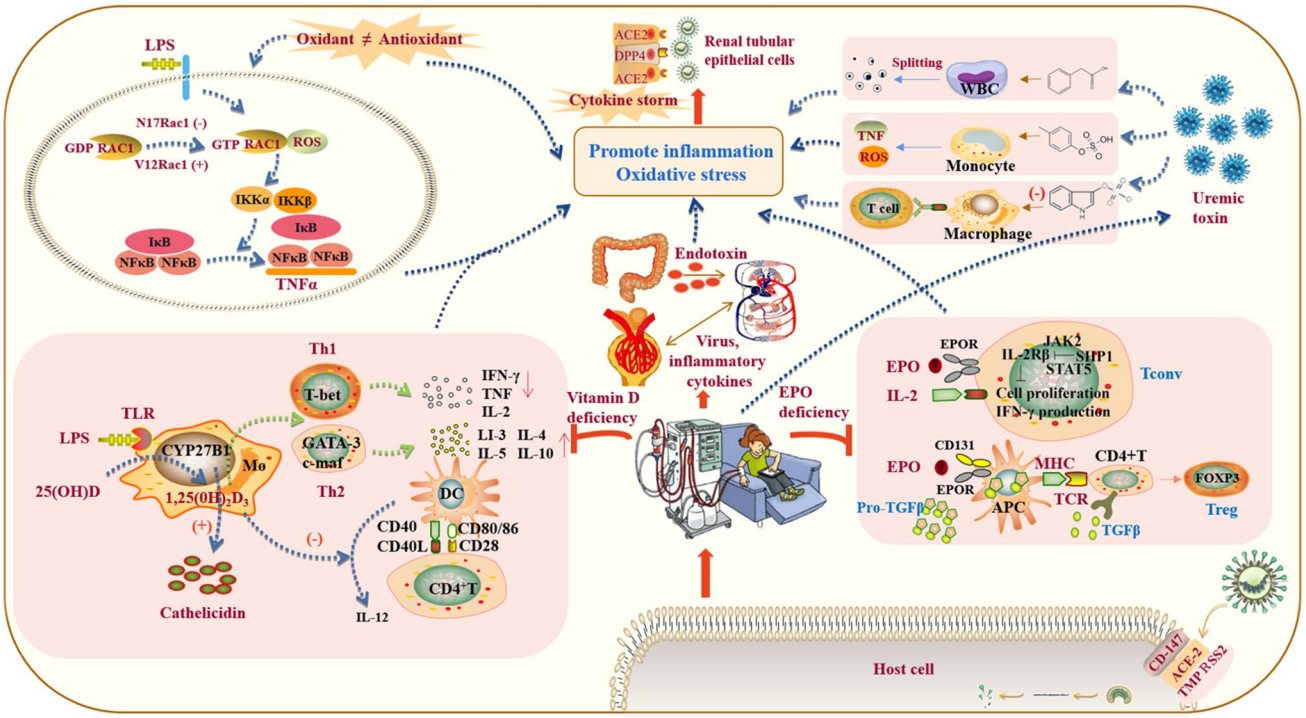

Fig. 1 Mechanism of increased susceptibility of dialysis patients. This figure describes the mechanism of CKD patients' susceptibility after COVID-19 attacks the human body. ACE 2 is the main receptor of human SARS CoV-2, which is highly expressed in the kidney. Therefore, renal tubules of CKD patients infected with SARS CoV-2 may be attacked first. First, the accumulation of uremic toxins such as phenylacetic acid, indole sulfate and p-cresol sulfate, the imbalance between oxidants such as active oxygen, active nitrogen and antioxidants, and the lack of vitamin D and erythropoietin promote the occurrence of cytokine storms, leading to inflammation and oxidative stress, affecting cellular and humoral immunity, and increasing the susceptibility of dialysis patients to neo coronal pneumonia. Secondly, the intestinal permeability of uremic patients increases, leading to endotoxin transfer from the intestinal tract to the systemic circulation. At the same time, neo coronal pneumonia will attack some small arteries and capillaries of the kidney. Compared with ordinary people, these factors directly lead to increased damage to the kidney caused by viruses and inflammatory cytokines in the blood

such as dialysate membranes and replacement fluids of dialysis patients have an impact on cell activation and the secretion of proinflammatory cytokines [23, 24]. In dialysis population, the development of COVID-19 may worsen the damaged renal function, and further lead to rapid deterioration of renal function and even death [22]. The main goal of COVID-19 vaccine is to produce immunity to the virus spike protein, so as to prevent the interaction between the spike protein and ACE2 [25].

Clinical manifestations and severity of disease

Several current studies show that the COVID-19-related mortality rate in the general population is 1.4–8% [26–28]. It is reported that among patients with severely impaired renal function, the risk of COVID-19-related death in patients receiving dialysis and kidney transplantation is three to four times higher than that in the general population [7]. Since the beginning of the pandemic, the study on the prevalence and mortality of dialysis patients has been carried out in the form of isolated observation or small case series. The advantage of our research is that we expanded the search scope to different geographical regions, collected data from multiple national registries, and finally searched 19 reports and analyzed the results of more than 100 dialysis centers registered on the European Renal Association COVID-19 database (ERACODA), and found that the incidence and mortality of COVID-19 infection in dialysis patients were 7.1% and 25.4%, respectively (Table 1) [28–46]. This is comparable to the mortality reported by 207 dialysis centers in Brazil (27.7%), 14 dialysis centers in Poland (30.4%), Scotland (26.7%), the Belgian Nephrological Society (29.6%), the Ontario Renal Reporting System (28.3%) and the British Renal Registry [47–51]. In general, our data are mainly from Asian and European populations, and there are differences in the incidence rate of patients. However, due to the lack of data in some cohorts, we cannot evaluate whether it is statistically significant. Although coming from different regions, the most common clinical manifestations of patients are still fever and respiratory symptoms, as well as the initial

Table 1 Clinical manifestations of COVID-19 infection in dialysis patients

Author	Setting	Dialysis patients, *n* (%)	Fever	Cough	Shortness of breath	Sore throat	Fatigue	Gastrointestinal symptoms	Oxygen therapy	Mechanical ventilation	Admission to ICU	Mortality %	Leave hospital
Jung [29]	South Korea	14 (NA)	NA	50.0	21.4	7.1	28.6	14.3	42.9	14.3	35.7	14.3	64.3
Valeri [30]	New York, Single centre	59 (13)	49.1	38.9	35.6	NA	22.0	15.3	NA	13.6	NA	30.5	69.5
Weiss [31]	New York, Single centre	306 (14.0)	43.8	28.1	NA	NA	19.9	NA	NA	NA	NA	27.8	NA
Goicoechea [28]	Spain, 2 centres	36 (12.8)	66.7	66.7	NA	NA	NA	16.7	100.0	33.3	2.8	30.6	NA
Broseta [32]	Spain	36 (8.4)	69.4	58.3	52.8	NA	NA	25.0	2.8	13.9	22.2	36.1	NA
Sánchez-Álvarez [33]	Spain, Entire country[a]	868[b] (NA)	76	68			NA	23	NA	NA	8	22.8	20.4
Seidel [34]	Germany, 5 centres	56 (7.4)	55.4	46.4	NA	NA	NA	19.6	NA	NA	28.6	26.8	NA
Wu [35]	Wuhan, Single centre	49 (NA)	46.9	NA	44.9	6.1	59.1	NA	83.7	30.6	6.1	14.3	81.6
Zou [36]	Wuhan, Single centre	66 (11.0)	37.9	69.7	16.7	NA	34.8	15.2	6.1	3.0	6.1	27.3	72.7
Xiong [37]	Wuhan, 65 centres	131 (2.2)	51.9	37.4	26.0	7.7	45.0	13.7	NA	19.1	NA	31.3	35.9
Min [38]	Wuhan, Single centre	74 (11.8)	17.6	41.9	14.8	NA	24.2	4.1	NA	NA	NA	18.9	NA
Kocak [39]	Istanbul, Single centre	45 (NA)	60.0	53.3	55.6	4.4	8.9	8.9	62.2	31.1	31.1	31.1	68.8
Yau [40]	Toronto, Single centre	11 (4.6)	9.1	27.3	0	0	NA	NA	45.5	0	18.2	0	NA
Tortonese [41]	Paris, Single centre	44 (NA)	79.5	43.2	29.5	NA	NA	13.6	45.5	27.3	34.1	27.3	58.5
Lano [42]	French, 11 centres	122 (5.5)	66.4	63.1	38.5	NA	NA	17.2	74.6	NA	15.6	27.9	63.1
Alberici [43]	Brescia, 4 centres	94 (15)	68.1	23.4	25.5	2.1	NA	6.4	NA	NA	NA	28.7	13.8
Mazzoleni [44]	Belgium, 3 centres	40 (65)	57.5	42.5			NA	NA	62.5	5.0	7.5	27.5	20.0
Hilbrands [45]	ERACODA[c]	768 (NA)	54.0	45.1	32.0	10.9	NA	10.9	NA	10.0	12.0	25.0	NA
Goffin [46]	ERACODA[d]	1174 (NA)	56	47.1	32.9	12.1	NA	11.3	NA	NA	10.7	23.9	NA

This table summarizes some common clinical manifestations of COVID-19 infection in CKD patients

The data in the table refer to the percentage of patients except the number and age of dialysis patients

COVID-19 coronavirus disease in 2019, *CKD* chronic kidney disease, *n* number, *ICU* intensive care unit, *NA* not applicable

[a]Including 103 health centers nationwide

[b]Data from the COVID-19 registry of the Spanish Society of Nephrology. Dialysis patients accounted for 67%, and transplant patients accounted for 33%

[c]The European Kidney Association COVID-19 database, currently covers 26 countries/regions, mainly distributed in Europe and the northern Mediterranean region, from February 1 to May 1, 2020

[d]The European Kidney Association COVID-19 database, currently covers more than 130 centers from 31 countries (mainly in Europe), from February 1, 2020 to December 1, 2020

manifestations of atypical gastrointestinal symptoms. Bilateral and multifocal exudates are common in chest imaging. Some patients may have pleural effusion. Some patients have respiratory distress symptoms and need to enter the intensive care unit (ICU) and receive mechanical ventilation, which increases the risk of death. No significant difference in mortality was observed in different cohorts.

Most of the patients were not seriously infected, 81% of the cases were mild and 14% were severe [52]. To explore the severity of symptoms of dialysis patients, we listed 10 series of observed dialysis cases in Table 2 [12, 34, 37, 53–59]. The primary diseases of these patients are diabetes nephropathy and hypertensive nephropathy, and most of them are over 50 years. We found that the progression and poor prognosis of COVID-19 are not only related to complex underlying diseases, but also closely related to age and gender, with statistical significance. It has been proved that age is an important risk factor for dialysis patients. After stratified analysis according to different age groups, it is found that the mortality of dialysis patients is significantly higher than that of the general population [13, 14]. Similarly, a report by Jager also confirmed that the mortality rate of dialysis patients in different age groups was significantly different, especially in patients over 75 years, the 28-day mortality rate could be as high as 31.4% [8]. On the contrary, for the general population, the Italian report confirmed that the mortality rate of people aged 70–79 was 12.8%, while the mortality rate of people aged 60–69 was only 3.5% [60]. More than half of dialysis patients diagnosed with COVID-19 are male. Male patients seem to have a higher infection rate, but their progression and prognosis are not clear compared with women. Our results show that in different dialysis cohorts, the positive rate of COVID-19 PCR is as high as 32.8%, and the mortality rate is as high as 31.3%. This was similar to mortality in other smaller cohorts from New York, Spain, and Italy, where mortality ranged from 28 to 31% [28, 30, 43, 61]. Moreover, compared with the European population, the proportion of patients with severe and critical illness in the Asian population is low.

There is little information on the topic of peritoneal dialysis (PD) patients. Although the physiological basis of peritoneal dialysis and hemodialysis is similar, their exposure risks and clinical reactions are different. The main advantage of patients receiving PD treatment is that they can carry out dialysis treatment in their own homes, reduce interpersonal contact, avoid contact with viruses due to taking tools on the way to see a doctor, and reduce the advantage of close contact with medical staff, who may be affected by SARS-CoV-2 infection [62, 63]. Therefore, PD seems to be the best kidney replacement therapy (KRT) for patients with end-stage renal disease during COVID-19 outbreak [63]. SARS-CoV-2 was recently found in PD effluents, but it is not clear whether the virus is likely to replicate [64]. These findings suggest that dialysate is the potential source of the most serious coronavirus strains, so it should be carefully managed [64]. The study of Ronco in Italian dialysis population has confirmed that the incidence of COVID-19 in PD patients is significantly lower than HD [65]. However, there was no statistical difference between the two groups in terms of hospitalization due to SARS-CoV-2 infection, admission to intensive care unit, need for mechanical ventilation and mortality. This was confirmed in Yavuz's research [66]. The prevalence, hospitalization rate and mortality of COVID-19 in HD and PD were 12.7% and 14% ($P=0.83$), 50% and 46.2% ($P=0.79$), 13.0% and 26.1% ($P=0.06$), respectively [66]. In terms of respiratory symptoms of patients, PD removes fluid more continuously than HD, thus reducing the risk of high blood volume to a greater extent, but intraperitoneal fluid perfusion may increase intraperitoneal pressure and may damage lung function [67]. HD is prone to liquid accumulation, which may aggravate the impact on oxygenation [67].

COVID-19 vaccination of dialysis patients

At present, the success of the vaccine depends on the fact that the frequency of breakthrough infection of COVID-19 is lower than that of the unvaccinated population, and the performance is milder (the admission rate and mortality rate are lower) [68, 69]. This is due to the ability of the vaccine to induce the production of antibodies and cytotoxic T cells, which can resist subsequent infection [67]. The mRNA-based vaccine, after producing antigen in the host cell, is presented by antigen presenting cell and triggers the primary immune response. This leads to the differentiation of memory B and T cells, and the long-term protective immunity is achieved through the cytotoxicity mediated by antigen-specific antibody and antigen reactivation (Fig. 2) [70, 71]. The above immune changes in CKD patients interfere with the production of protective immunity during natural infection or after vaccination, which increases the incidence and severity of infectious diseases in these patients (Fig. 2) [18, 70, 71]. So far, few studies have investigated the protective effect of vaccines by estimating the prevention of COVID-19 infection and related hospitalization or mortality. In Table 3 [72–77], after receiving two doses of COVID-19 vaccine, the positive rate of COVID-19 PCR in dialysis patients was 4.5%, and the highest rate was 20.5% in different cohorts. The mortality rate of dialysis patients accounted for 0.6% of the total cohort, and the highest mortality rate among PCR positive patients in different cohorts was 4.3%. The data are heterogeneous, which may be caused by differences in the size of the cohort, the prevalence of complications, the control cohort and vaccination strategy. According to the research report of Canada, one dose of vaccine can reduce

Table 2 Severity of COVID-19 infection in dialysis patients

Author	Country	Patients positive for COVID 19, *n* (%)	Age, years	Male, *n*	Most common causes of CKD	COCID-19 severity				P^a	P^b
						Mild-moderate disease, *n* (%)	Severe-critical disease, *n* (%)	Admission to ICU, *n* (%)	Death, *n* (%)		
Seidel [34]	Germany	56 (7.4)	76	33	Diabetes nephropathy	13 (23.2)	28 (50.0)	16 (28.6)	15 (26.8)	NA	NA
Sahin [12]	Turkey	58 (32.8)	63	32	NA	37 (63.8)	17 (29.3)	9 (15.5)	2 (3.4)	NA	NA
Xiong [37]	China	131 (2.2)	63	75	Diabetes nephropathy/hypertensive nephropathy	101 (77.1)	30 (22.9)	NA	41 (31.3)	> 0.05	> 0.05
Stefan [54]	Romania	37 (NA)	64	19	Diabetes nephropathy/vascular nephropathy	22 (59.5)	15 (40.5)	NA	7 (18.9)	> 0.05	> 0.05
Ahmed [53]	United Arab Emirates	152 (13.0)	53	123	NA	136 (89.4)	16 (10.5)	20 (13.1)	14 (9.2)	< 0.05	NA
Keller [55]	France	123 (9.1)	77	70	Diabetes nephropathy	66 (53.7)	54 (43.9)	7 (5.7)	29 (23.6)	< 0.05	> 0.05
Couchoud [59]	French	1621 (3.3)	72	1034	NA	1442 (88.9)	157 (9.7)	157 (9.7)	287 (17.7)	< 0.05	> 0.05
Turgutalp [56]	Turkey	567 (NA)	63	296	NA	297 (52.4)	270 (47.6)	134 (23.6)	93 (16.3)	< 0.05	> 0.05
Qzturk [57]	Turkey	390 (NA)	64	201	Diabetes nephropathy	225 (57.7)	162 (41.5)	99 (25.4)	63 (16.2)	< 0.05	> 0.05
Qzturk [58]	Turkey	150 (NA)	72	79	NA	67 (44.7)	83 (55.3)	56 (37.3)	40 (26.7)	< 0.05	NA

This table summarizes the nosocomial diagnostic rate of COVID-19 infection in CKD patients, the proportion of severe patients, and the in-hospital mortality

COVID-19 coronavirus disease in 2019, *CKD* chronic kidney disease, *n* number, *NA* not applicable

[a]Association between age and severity of disease

[b]Association between sex and severity of disease

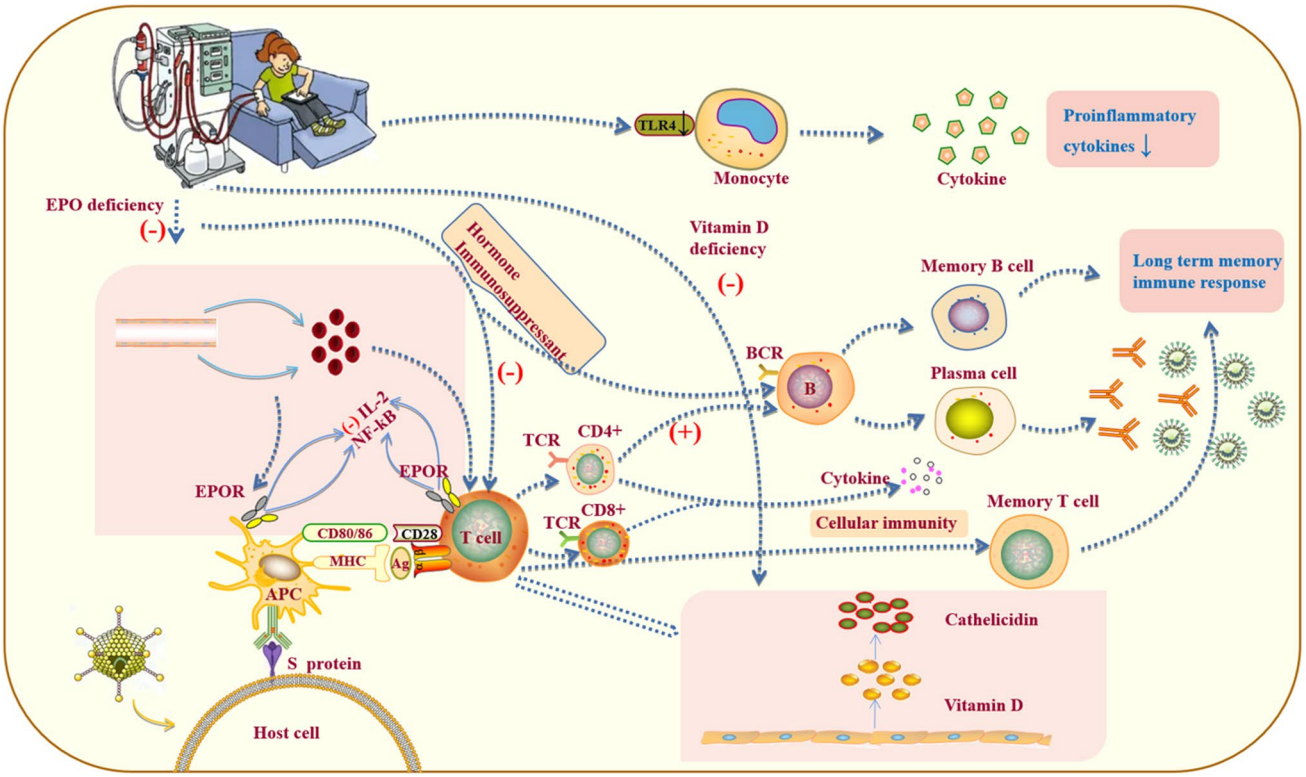

Fig. 2 Immune process of vaccine in dialysis patients. Vaccines play roles in protecting dialysis patients mainly through cellular and humoral immunity, but the lack of erythropoietin (EPO) and vitamin D, the attack from cytokines, and the use of immunosuppressants will affect the immune process of the vaccine

Table 3 Breakthrough infection in dialysis patients after COVID-19 vaccination

Author	2 doses of vaccine, *n*	Age, years	Male, *n*	Dialysis time, mo	Common complication	Breakthrough infection			
						All patients, *n* (%)	Hospitalized patients, *n* (%)	Serious condition, *n* (%)	Death, *n* (%)
Oliver [72]	809	68	NA	24	NA	63 (7.8)	19 (2.3)	19 (2.3)	6 (0.7)
Rodríguez-Espinosa [73]	302	73	197	35	Hypertension	18 (6.0)	4 (1.3)	1 (0.3)	0 (0)
Wand [74]	117	NA	NA	29.6	Hypertension	24 (20.5)	13 (11.1)	11 (9.4)	5 (4.3)
Bell [75]	1933	NA	NA	NA	Diabetes	98 (5.1)	29 (1.5)	NA	7 (0.4)
Medina-Pestana [76]	138	NA	12	NA	Cardiovascular disease	5 (3.6)	3 (2.2)	NA	1 (0.7)
Anand [77]	2563	65	1504	NA	Diabetes	56 (2.2)	25	NA	NA

This table describes the incidence of breakthrough infection and the proportion of severe and dead patients after CKD patients received two doses of COVID-19 vaccine

COVID-19 coronavirus disease in 2019, *RRT* renal replacement therapy, *HD* hemodialysis, *RTP* renal transplantation therapy, *n* number, *mo* month, *NA* not applicable

the risk of infection and serious consequences by 41% and 46%, respectively, compared with hemodialysis patients who have not been vaccinated. The two doses of vaccine reduced the risk of infection and serious consequences by 69% and 83%, respectively. The results of this study suggest that one dose of COVID-19 mRNA vaccine has a moderate effect in preventing COVID-19 infection, and the two doses are very effective in preventing infection and related serious consequences in maintenance dialysis population [72]. According to the report on vaccine types pointed out that the infection

risk of dialysis population was reduced by 31–79% after BNT162b2 vaccine and 49–73% after mRNA-1273 vaccine [78].

In Table 4 [79–86], we compared dialysis patients who received two doses of COVID-19 vaccine with the control group, which refers to healthy people or medical personnel without impaired renal function. To investigate the humoral response of patients to antibodies after two doses of vaccine, we defined seroconversion as an IgG antibody that can detect the receptor binding domain of S1 spinous process antigen (anti-S1-RBD IgG) against COVID-19. Compared with the control group, the response of hemodialysis patients to the vaccine was weaker, the serum conversion rate was lower (73–99% and 94–100%, respectively), and the antibody titer decreased rapidly. Almost all dialysis patients showed seroconversion after vaccination. Although the antibody concentration of patients decreased significantly, it was not as serious as that of renal transplant recipients. Data from vaccine experiments and observational studies showed that the anti-S1-RBD IgG titer of patients decreased with the passage of time, although the magnitude of the decline varied greatly between studies. This is consistent with the large-scale research results of Anand et al. The median index of anti-S1-RBD IgG in dialysis patients who were successfully vaccinated was 91.9 at 14–30 days after the completion of the vaccine. By 5–6 months, the median index value of the whole cohort decreased to 8.4 [87]. In patients with CKD stage 3–5, the main cause of CKD may affect the efficacy of the vaccine on COVID-19, because immunosuppressants may in turn affect adaptive immunity, thus affecting the IgG titer after vaccination [88]. In CKD patients who do not use immunosuppressants, the efficacy of the vaccine may be hindered, because the uremic environment, older age, and lack of vitamin D and erythropoietin (EPO) will change the innate immunity. Vaccines play roles in protecting dialysis patients mainly through cellular and humoral immunity, but the lack of EPO and vitamin D, the attack from cytokines, and the use of immunosuppressants will affect the immune process of the vaccine, which is shown in Fig. 2 [18, 89]. It is speculated that EPO and vitamin D supplementation at different stages of CKD may be crucial to maintain the efficacy of COVID-19 vaccine [90].

The neutralizing antibody against S1 protein can bind to the RBD region of COVID-19, block the binding of RBD to ACE2 receptor, and thus block the virus from invading human cells. Some neutralizing antibodies target the NTD region of S1 protein and may be involved in the interaction with C-type lectin [91]. In addition to being used as a standard to evaluate the effectiveness of vaccines, neutralizing antibodies can also be used as another passive immune weapon, which can block infection and eliminate pathogens, which is crucial for providing long-term immunity [95]. High serum conversion rates were observed within 14 days after infection and the first

Table 4 Humoral response of dialysis patients after COVID-19 vaccination

Author	Patient type	2 doses of vaccine, *n*	Age, years	Dialysis time, mo	Time from the second inoculation to sampling, days (range)	Seropositive reaction		IgG level, AU/ml ($P<0.05$)
						n (%)	*P*	
Grupper [79]	HD	56	74	38	30 (27–34)	54 (96)	> 0.05	2900 (1128–5651)
	Control group	95	57	NA	30 (26–34)	95 (100)		7401 (3687–15,471)
Yanay [80]	Dialysis	160	69	38	NA	144 (90)	< 0.001	116.5 (66–160)
	Control group	132	51	NA	NA	132(100)		176.5 (142–235)
Jahn [81]	HD	72	68	52	17 (15–18)	67 (93)	> 0.05	366.5 (90–606)
	Control group	16	46	NA	13 (13–13)	16 (100)		800 (521–800)
Simon [82]	HD	81	67	NA	21	59 (73)	0.001	171 (478)
	Control group	80	49	NA	21	80 (100)		2500 (944)
Sanders [83]	Dialysis	159	60	31	28	158 (99)	> 0.05	1650 (698–3024)
	Control group	191	59	NA	28	191 (100)		3186 (1896–4911)
Kolb [84]	Dialysis	32	83	36	14 (13–15)	28 (88)	> 0.05	503 (NA)[a]
	Control group	78	84	NA	17	73 (94)		1922 (NA)
Matsunami [85]	HD	70	73	66 (NA)	43 (36–50)	69 (99)	> 0.05	185.5 (95–324)
	Control group	35	75	NA	33 (23–45)	35 (100)		533 (276–1100)
Piscitani [86]	HD	21	68	4 (NA)	NA	NA	NA	429 (NA)
	Control group	15	47	NA	NA	NA		1901 (NA)

This table summarizes the humoral responses of dialysis patients receiving 2 doses of COVID-19 vaccine

COVID-19 coronavirus disease in 2019, *HD* hemodialysis, *n* number, *mo* month, *NA* not applicable

[a]BAU/mL

COVID-19 vaccine inoculation [92]. When given early after diagnosis and/or symptom onset, the effective SARS CoV-2 neutralizing antibody can reduce the risk of disease progression by about 70–80%, and reduce the incidence rate of symptomatic diseases in asymptomatic individuals [93]. Antibody combination can accelerate virus clearance in respiratory tract samples [94]. Subcutaneous use of antibodies also reduced the incidence rate of COVID-19 in uninfected, unvaccinated residents at baseline [94]. Since it has been observed that mutations related to drug resistance occur during single antibody treatment, while the frequency appears to be relatively low during combined treatment, it is necessary to develop new antibodies with cross-variant activity and high escape barrier to provide more options for antibody combination [95, 96].

Prevention of infection

Dialysis patients should reduce going out on non-dialysis days, avoid personal contact, and receive education and publicity about COVID-19 from dialysis institutions [62]. The treatment and waiting area of dialysis institutions should have good air conditioning and ventilation [97]. The temperature should be strictly monitored at the beginning and end of dialysis, and the symptomatic infected people should be identified early [62, 97]. The symptomatic infected people should try to wait in a separate isolation room, otherwise they should wait in a separate isolation room, and receive dialysis in the last shift of the day until the infection is eliminated [62]. The patient should wear an appropriate (surgical or N95) mask to filter 95% < 2.5 μm particles in the exhaled aerosol [97]. If the dialysis center finds a newly diagnosed or highly suspected COVID-19 infection case, it should be disinfected immediately [62]. Under the current global containment, PD and HD are the best methods of KRT which can reduce the transmission rate of SARS-CoV-2 infection. Similarly, for patients undergoing dialysis and kidney transplant recipients, in addition to giving the booster vaccine dose after the immunity of the primary immunization-enhanced vaccination begins to weaken, we also recommend that they receive additional primary vaccine dose to improve their initial vaccination response, and we can also consider temporarily stopping the immunosuppressive drug treatment that has a strong inhibitory effect on vaccine-induced immunity [98, 99]. Some studies have also supported the recommendation of a fourth dose of primary vaccine in such populations [100]. Importantly, compared with BNT162b2, mRNA-1273 vaccine has higher immunogenicity, and additional adjuvants and intradermal vaccine may also improve the immunogenicity of the vaccine [101].

Conclusion

COVID-19 infection presents a special challenge to patients with CKD, especially those with central hemodialysis. By summarizing the relevant literature, this paper summarizes the severity of CKD patients after COVID-19 infection, especially in dialysis population, the mortality and the proportion of severe patients are significantly higher than those without kidney disease. Dialysis is associated with an increased risk of severe COVID-19 infection and usually shows a less favorable seroconversion response to vaccines. Therefore, we summarized observational studies of breakthrough infection after two doses of COVID-19 vaccine and the humoral response of patients to anti-S1-RBD IgG antibody. Finally, the protective effect of the vaccine on high-risk groups such as dialysis was confirmed. With the enhancement of the vaccine dose, a higher proportion of dialysis patients could maintain a higher titer of anti-S1-RBD IgG antibody. Unfortunately, according to the results of big data analysis, this paper cannot better distinguish between HD patients and peritoneal dialysis patients, so our results have certain limitations. At the same time, we also expect more large-scale experiments to be carried out in these two groups.

Author contributions XZ performed the data analysis, wrote the manuscript, and reviewed articles. GX and QC devised the study and revised the manuscript. All authors have read and approved the manuscript.

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Data availability The data supporting the results of this study can be obtained from the corresponding author of Park SH, Husain SA, Goicoechea M, Wu J, Kocak SY, Xiong F, Wald R, Zaidan M, Alberici F, Broseta JJ, Gansevoort RT, Sahin B, Westhoff TH, Zhang C, Ahmed W, Mehedinti AM, Keller N, Arici M, Oliver MJ, Broseta JJ, Cohen-Hagai K, Bell S, Cristelli MP, Anand S, Israel M, Yanay NB, Jahn M, Simon B, Gansevoort RT, Stegbauer J, Matsunami M, Piscitani L, Coritsidis GN, Sánchez-Álvarez JE, Westhoff TH, Zou R, Zhang C, Lano G, Carlier S, Gansevoort RT, Couchoud C according to reasonable requirements.

Declarations

Conflict of interest The author claims that there is no conflict of interest in this article.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

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