Clinical Kidney Journal, 2022, vol. 15, no. 10, 1816–1828

https://doi.org/10.1093/ckj/sfac174
Advance Access Publication Date: 27 July 2022
CKJ Review

CKJ REVIEW

Immune responses to SARS-CoV-2 in dialysis and kidney transplantation

Chiara Cantarelli[1], Andrea Angeletti[2], Laura Perin[3,4], Luis Sanchez Russo[5], Gianmarco Sabiu[6], Manuel Alfredo Podestà[7] and Paolo Cravedi[5]

[1]UO Nefrologia, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy, [2]Division of Nephrology, Dialysis and Transplantation, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [3]GOFARR Laboratory, Division of Urology, Children's Hospital Los Angeles, Los Angeles, CA, USA, [4]Department of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, [5]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [6]Nephrology and Dialysis Unit, ASST Fatebenefratelli Sacco, Università degli Studi di Milano, Milan, Italy and [7]Nephrology Unit, Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

Correspondence to: Paolo Cravedi; E-mail: paolo.cravedi@mssm.edu

ABSTRACT

Despite progressive improvements in the management of patients with coronavirus disease 2019 (COVID-19), individuals with end-stage kidney disease (ESKD) are still at high risk of infection-related complications. Although the risk of infection in these patients is comparable to that of the general population, their lower rate of response to vaccination is a matter of concern. When prevention strategies fail, infection is often severe. Comorbidities affecting patients on maintenance dialysis and kidney transplant recipients clearly account for the increased risk of severe COVID-19, while the role of uremia and chronic immunosuppression is less clear. Immune monitoring studies have identified differences in the innate and adaptive immune response against the virus that could contribute to the increased disease severity. In particular, individuals on dialysis show signs of T cell exhaustion that may impair antiviral response. Similar to kidney transplant recipients, antibody production in these patients occurs, but with delayed kinetics compared with the general population, leaving them more exposed to viral expansion during the early phases of infection. Overall, unique features of the immune response during COVID-19 in individuals with ESKD may occur with severe comorbidities affecting these individuals in explaining their poor outcomes.

LAY SUMMARY

People with end-stage kidney disease, both those on dialysis and the recipients of a kidney transplant, are at high risk of coronavirus disease 2019–related complications. Their lower rate of response to vaccination is a matter of concern and, when prevention strategies fail, infection is often severe. Chronic kidney failure per se and immunosuppressive therapies have been shown to impair their immune responses against the virus. A more in-depth understanding of how their immune system responds to severe acute respiratory syndrome coronavirus 2 infection and vaccination is critical to identify effective prevention and treatment strategies.

Received: 1.6.2022; Editorial decision: 20.7.2022

Keywords: COVID-19, dialysis, infection, organ transplant

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly targets the respiratory tract, leading to a wide range of clinical manifestations, from asymptomatic to mildly symptomatic forms involving the upper respiratory tract, to extremely aggressive cases of acute respiratory distress syndrome (ARDS). Other organs can be affected, including, among others, kidneys, gastrointestinal tract, brain and heart [1]. Over time, improvements in patient management, together with vaccine and antiviral agent availability, have significantly reduced mortality. However, it is estimated that ~1% of infected patients require hospitalization and mortality rates are still >0.1% [2, 3]. Rapid emergence of variants of concern adds more variability to symptoms at presentation and to the disease course.

Viral load, host factors and the presence of multiple comorbidities affect disease severity. Moreover, older age, male gender, obesity and use of immunosuppressive medications are factors associated with severe forms of coronavirus disease 2019 (COVID-19) [4].

Patients with kidney failure on maintenance dialysis and kidney transplant recipients (KTRs) are at higher risk of severe manifestations of COVID-19 due to multiple comorbidities, immunosuppression [5] and reduced response to vaccination [6]. The principal outcomes of SARS-CoV-2-infected patients on dialysis are summarized in Table 1. Most studies report a mortality rate >20–30%, which is significantly higher in patients admitted to the intensive care unit (ICU). No significant differences in mortality rate were found comparing mortality at 28 days and 3 months [7]. Despite the improvements in prevention and supportive care, mortality in patients on dialysis remained significantly higher than in the general population, even after adjustment for comorbidities. Similar outcomes have been reported also for patients on peritoneal dialysis (PD), with mortality rates ranging from 12 to 36% of infected patients [8–12].

These poor outcomes have also been reported for KTRs, with population-based studies and meta-analyses reporting short-term mortality of 19–31% [13–15] (Table 2). National registry data from the USA revealed that 16% of deaths among KTRs was attributed to COVID-19 in 2020 [16]. Moreover, direct comparisons between KTRs and waitlisted patients suggest a higher risk of severe disease and mortality in the former group [17].

Herein we discuss recent insights into the mechanisms at the basis of the altered immune response observed in these patients, which have been suggested to impact SARS-CoV-2 infection outcomes and the response to vaccination.

IMMUNE RESPONSE TO SARS-CoV-2 INFECTION AND VACCINATION

In most cases, SARS-CoV-2 infection elicits an effective innate and adaptive immune response that clears the virus in ≤1 week. In some individuals, however, the virus may elicit an incomplete and/or unrestrained immune response with derangements that involve both the innate and adaptive arms of the immune system, which ultimately drive the more severe clinical manifestations of COVID-19.

Like many other viruses, SARS-CoV-2 triggers innate immunity through the engagement of pattern recognition receptors, such as Toll-like receptor (TLR). Downstream signaling of TLR promotes the transcriptional activation of several proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6) and IL-1, along with the production of type I and type III interferons (IFNs) with antiviral activity [18] (Figure 1). However, SARS-CoV-2 infection has been associated with immune escape and incomplete activation of IFN signaling, resulting in impaired viral clearance and a maladaptive increase in proinflammatory cytokines [19]. Multiple data converge to support a protective role for early type I IFN and $CD8^+$ T cell responses [20] and genetic alterations in genes involved in the type I IFN response [21] or the presence of neutralizing autoantibodies against type I IFN [22] are associated with more severe forms of COVID-19. In severe forms of the disease, serum IFN activity and IFN-stimulated genes are significantly reduced compared with mild and moderate forms, while genes involved in type I IFN signaling are upregulated [23].

In severe forms of COVID-19, the release of proinflammatory mediators can cause a cytokine storm [24], which frequently results in ARDS, pulmonary edema, vascular injury and multiorgan failure. Higher cytokine levels at the time of hospital admission, particularly IL-6 and TNF-α, strongly correlate with disease severity and predict mortality, independent of other factors [25]. Cytokine and chemokine release also amplify the activation of monocytes and macrophages that are recruited at the site of infection, leading to a detrimental amplification loop [26]. Delayed kinetics of humoral and cellular adaptive immune responses early in the disease course have been associated with severe COVID-19 cases, whereas patients with milder infection usually display more prompt responses [27–31].

Lymphopenia and T cell exhaustion are common features of SARS-CoV-2 infection. Typically, T cell exhaustion develops in response to prolonged antigen stimulation, i.e. during chronic or persistent viral infections or in the presence of a high antigen load [32], and leads to reduced effector functions and cytokine production.

Even though the cause of lymphopenia during COVID-19 has not been fully elucidated, a significant association between COVID-19 severity and upregulation of inhibitory immune checkpoint receptors (e.g. PD-1) in cytotoxic T cells has been described. In these patients, the expression of exhaustion-associated gene signatures in $CD8^+$ T cells and in natural killer cells has also been reported [33, 34].

The $CD4^+$ T cell compartment also displays altered responses, with severe COVID-19 featuring a lower frequency of IFN-γ-producing T helper 1 (Th1) cells when compared with milder disease [35, 36]. On the other hand, proinflammatory Th17 cells are increased after SARS-CoV-2 infection, which could partly account for cytokine overproduction [37]. Moreover, severe disease is also associated with a higher proportion of regulatory T cells (Tregs), which can suppress antiviral immunity and contribute to immune dysfunction [38].

Dysregulation of T follicular helper (T_{FH}) cells, a T cell subset that promotes B cell maturation, somatic hypermutation and clonal selection, has also been suggested to contribute to impaired antibody responses and mortality [39, 40]. Subjects with severe COVID-19 produce higher antibody levels than those with mild or asymptomatic disease [41, 42] and remain seropositive for longer time periods than subjects with an initial low antibody titer. In severe infections, however, T_{FH} cells are blocked in their differentiation trajectories and the germinal

Table 1. Incidence and outcomes of SARS-CoV-2 infection in dialysis patients

Reference	Study type	Pts nr	Study period	Follow-up	Incidence	Hospitalization	Mortality	Comments
De Meester *et al.* [11]	Prospective, multicenter	4297 HD, 329 PD	2 March–25 May 25 2020	–	5.31% HD, 1.82% PD, 0.64% general population	60.5% HD, 66.7% PD	29.6% HD, 15.3% general population	Age-standardized cumulative mortality rates 19.9% (95% CI 15.4–25.2) in HD versus 15.3% in the general population
Couchoud *et al.* [137]	Registry	1621 (3.3% HT)	16 March–4 May 2020	–	3%, 0.2% general population	62% (9% ICU)	21%, 19% general population (no systematic screening)	
Xiong *et al.* [138]	Retrospective, observational, multicenter	7154 HD	1 January–10 March 10 2020	–	2.15%, 0.5% general population	–	–	
Ng *et al.* [54]	Observational	408 HD, 11 PD	1 March–27 April 2020	Through 27 May 2020	–		OR 1.38* unadjusted, OR 1.47* adjusted for demographics, OR 1.37 adjusted for demographics and comorbidity	Patients with ESKD were compared with non-ESKD patients hospitalized for COVID-19
Hilbrands *et al.* [139]	Observational	768 (96% HD, 4% PD)	1 February–1 May 2020	28 days	–	70% (12% ICU)	25%	Mortality in nonhospitalized was 5%, mortality risk increased to 33.5% (95% CI 28.2–38.9) in hospitalized patients and 53% if admitted to the ICU

Table 1. Continued

Reference	Study type	Pts nr	Study period	Follow-up	Incidence	Hospitalization	Mortality	Comments
Valeri *et al.* [5]	Retrospective, single center	57 HD, 2 PD	9 March –8 April 2020	Through 29 April 2020	–	14% ICU	31%	
Fisher *et al.* [140]	Retrospective	114 HD	9 March–8 April 2020	Through 22 April 2020	–	13% ICU	28% (87% ICU)	
Kathri *et al.* [51]	Retrospective	128 HD, 588 CKD, 3189 no CKD	2 March–27 August 2020	Through 15 January 2021	–	23–25% ICU	27% HD (56% ICU), 34% CKD (64% ICU), 24% no CKD (56% ICU)	Comparing the first 2 months, mortality for HD, CKD and non-CKD patients was 29%, 35% and 25%, respectively, compared with 13%, 15% and 14%, respectively, over the last 4 months
Hsu *et al.* [141]	Retrospective	7948 HD	17 February–1 June 2020	Through 31 August 2020	5.5%	67.6% ICU	24.9% (32.1% ICU)	

HT, home treatments (home HD, PD).
*Values that reach statistical significance.

Table 2. Mortality in SARS-CoV-2-infected SOT recipients

Reference	Study type	N	Mortality	F-U (days)	Comments
Trapani *et al.* [13]	Retrospective	43 983 SOT	45% in KTR versus 22% in non-SOT	60	Authors compared the 60-days cumulative incidence of mortality in SOT versus non-SOT with COVID-19 in the first pandemic in Italy during the first phase
Ao *et al.* [142]	Meta-analysis	1385 SOT	50% higher in SOT than in non-SOT	NA	More than 80% of SOTs considered were KTRs. In the final total number of SOT recipients, there may be an overlap in which one patient may have been involved in more than one study
Goffin *et al.* [17]	Retrospective	498 KTRs, 1174 HD	2:1 risk in KTR	NA	As a conclusion from this large European study, the authors suggested that postponing transplantations may be justified, especially during the highly active phase of the pandemic. However, kidney transplant programs were not officially postponed in European countries
Pascual *et al.* [94]	Multicenter cohort observational	502 KTRs	45%	60	Of the 502 KTRs considered, 24 patients suffered from COVID-19 during the first 60 days after kidney transplantation, when immunosuppression is more intense and 11/24 died
Requião-Moura *et al.* [143]	Multicenter cohort	1680 KTRs	21%	90	The use of tacrolimus and mycophenolic acid was independently associated with the risk of death
Massie *et al.* [144]	Retrospective comparative	NA	NA	2015–February 2020 versus March 2020–2021	The mortality risk per month between the pre-COVID-19 and COVID-19 eras increased of 41.2%

F-U: follow-up; N/A: not available, RTX: rituximab.

center response is reduced, with plasma cells and memory B cells being mainly of extrafollicular origin [41, 42]. Impaired germinal center responses lead to reduced clonality and affinity maturation of spike-specific B cells, which impacts on the quality of anti-SARS-CoV-2-specific antibodies. In addition, the neutralization potency of anti-SARS-CoV-2-specific antibodies is reduced in patients with severe disease and portends worse outcomes [42]. Impaired cytotoxicity and reduced neutralizing capability of the anti-SARS-CoV-2 antibodies lead to increased viral shedding and potentiate innate immunity activation.

As a link between the innate and adaptive immune response, the complement system is critical in controlling SARS-CoV-2 infection, but its dysregulation produces harmful effects [43]. Complement activation in COVID-19 occurs mainly through the lectin pathway [44], but the other complement pathways can also be activated by anti-spike immunoglobulin G (IgG) and IgM antibodies (classical pathway) or directly by SARS-CoV-2 spike protein (alternative pathway). C3a and C5a release leads to neutrophil and monocyte/macrophage recruitment as well as cytokines release, further amplifying the inflammatory response. Consistently, elevated levels of the complement split products C3a and C5a associate with increased disease severity and mortality risk [45, 46].

The impact of vaccination in the general population has been evident since the development of messenger RNA (mRNA)-based vaccines, which confer protection against severe COVID-19 in >90% of cases. Independent of the platform, most vaccines aim to deliver the spike protein to antigen-presenting cells. This elicits both a cellular and humoral response involving the early induction of virus-specific $CD8^+$ and $CD4^+$ T cells, the latter being necessary for the maturation of high-affinity antibodies [47]. The development of neutralizing antibodies is the hallmark of immune protection, which typically lasts at least 6 months after the primary vaccination and is further increased with subsequent booster doses [48, 49].

SARS-CoV-2 IN INDIVIDUALS ON MAINTENANCE DIALYSIS

Immune response to SARS-CoV-2 infection

In dialysis patients, the impaired immunity and chronic low-grade inflammation associated with the uremic milieu affect inflammatory responses against a broad spectrum of pathogens, making these subjects particularly vulnerable to infections. Although the understanding of immune alterations in kidney failure is limited, particularly for innate response, decreased antigen presentation capabilities of dendritic cells, increased frequency of exhausted and anergic $CD4^+$ and $CD8^+$ T cells as well as hyporeactivity of monocytes and neutrophils all have an adverse impact on the immune response to infections [50]. On the other hand, patients with kidney failure commonly display

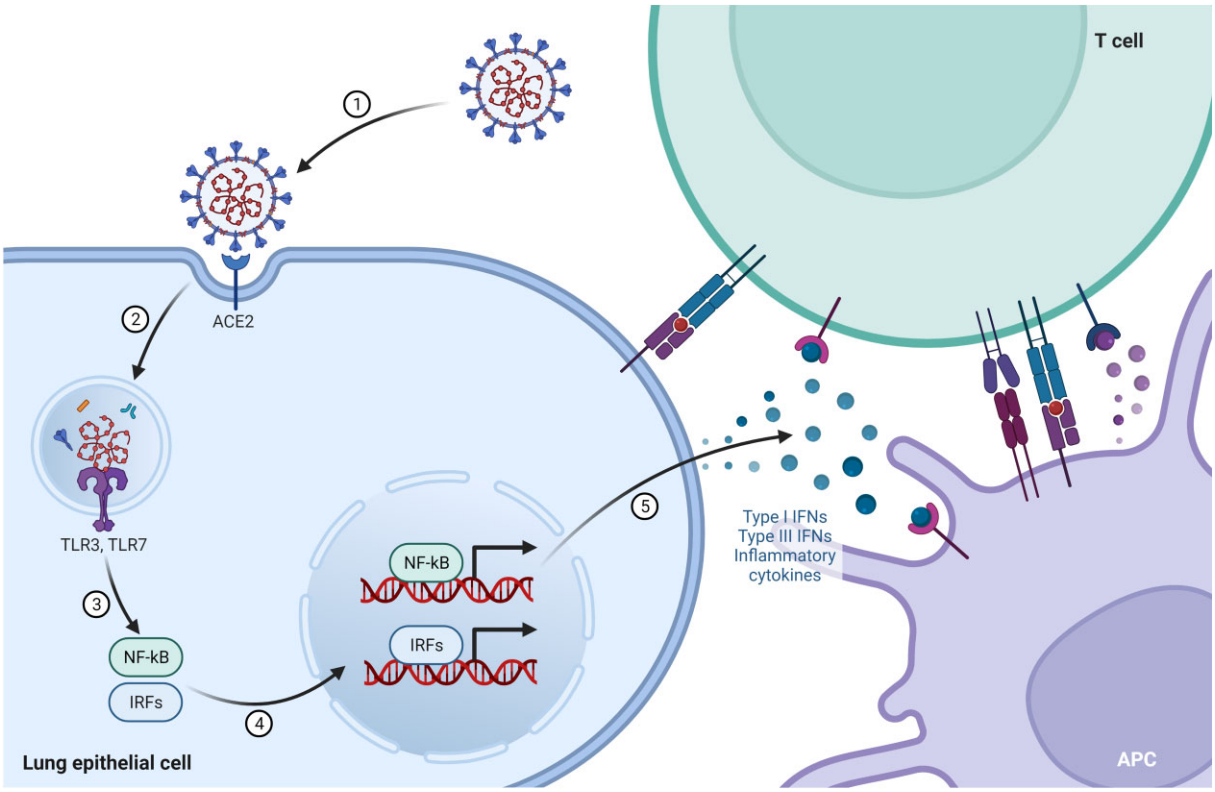

FIGURE 1: Schematic representation of the immune response to SARS-CoV-2. SARS-CoV-2 enters the epithelial host cells through endocytosis or membrane fusion after binding to the angiotensin-converting enzyme 2 (ACE2) receptor (1). Viral components are recognized by Toll-like receptors (2), whose downstream signaling promotes the secretion of type I and III IFNs and proinflammatory cytokines (3–5), which stimulate antigen-presenting cells and induce adaptive immunity. Adapted from 'Acute Immune Responses to Coronaviruses', BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.

high levels of proinflammatory cytokines resulting from decreased renal clearance and increased generation due to oxidative stress and the effect of uremic toxins (Figure 2). In dialysis patients with COVID-19 IL-6 levels were found to be significantly higher compared with subjects with CKD not on dialysis and non-CKD patients [51] and correlated with disease severity and outcomes [5].

The majority of the studies have focused on nonspecific inflammatory markers, showing that patients on maintenance dialysis have higher C-reactive protein (CRP) levels compared with nondialysis patients. CRP levels were also an independent predictor of severe disease and mortality [5, 17, 51–54].

Proteomic analysis of the serum from dialysis patients with COVID-19 identified higher levels of CCL2 and CCL7 during severe disease, which were associated with a lower blood monocytes count and higher inflammatory markers. CCL2 and CCL7 are both chemokines that attract monocytes, and their high expression suggests the recruitment of these innate immune cells into damaged tissues [55].

Patients with kidney failure have increased percentages of exhausted and anergic T cells compared with healthy subjects, which are associated with increased susceptibility to infections. Furthermore, these patients have preserved percentages of T_{FH} but a reduced frequency of the $T_{FH}1$ subset, critical to mount an effective humoral antiviral response [56].

Available data on T cell response in hemodialysis (HD) patients suggest a preserved ability to produce efficient T cell response, with similar percentages of T cells reactive against the different virus-specific proteins and similar cytokine production (IFN-γ, TNF-α, IL-2) compared with patients without kidney failure [57, 58].

Whether the presence of a robust T cell response reflects effective protection against reinfection is still unclear. Recently Klenerman *et al.* [59] did not find any correlation between T cell response, even if robust, and protection from reinfection in 36 HD patients. In keeping with observations from the general population, antibody titers also correlate with the severity of SARS-CoV-2 infection in dialysis patients. However, data demonstrate that patients on dialysis who develop antibodies in response to natural SARS-CoV-2 infection are less protected from reinfection compared with healthy subjects [60–62].

Only a few studies have explored the role of the complement system in patients with COVID-19 on dialysis. One study analyzed serial samples from 49 HD patients and controls with COVID-19, stratifying for disease severity and measuring complement activation split products [63]. Compared with non-COVID-19 subjects on HD, plasma levels of C3a and C5a were significantly increased. C3a levels could also discriminate between severe and nonsevere infections, a feature that was maintained throughout the course of the disease, except for the recovery phase. In sharp contrast, C5a levels increased only before clinical worsening. Overall, C3a and C5a levels directly correlated with CRP values and inversely correlated with lymphocyte count.

Circulating lectin pathway proteins have been also analyzed in HD patients with COVID-19 and directly correlated with

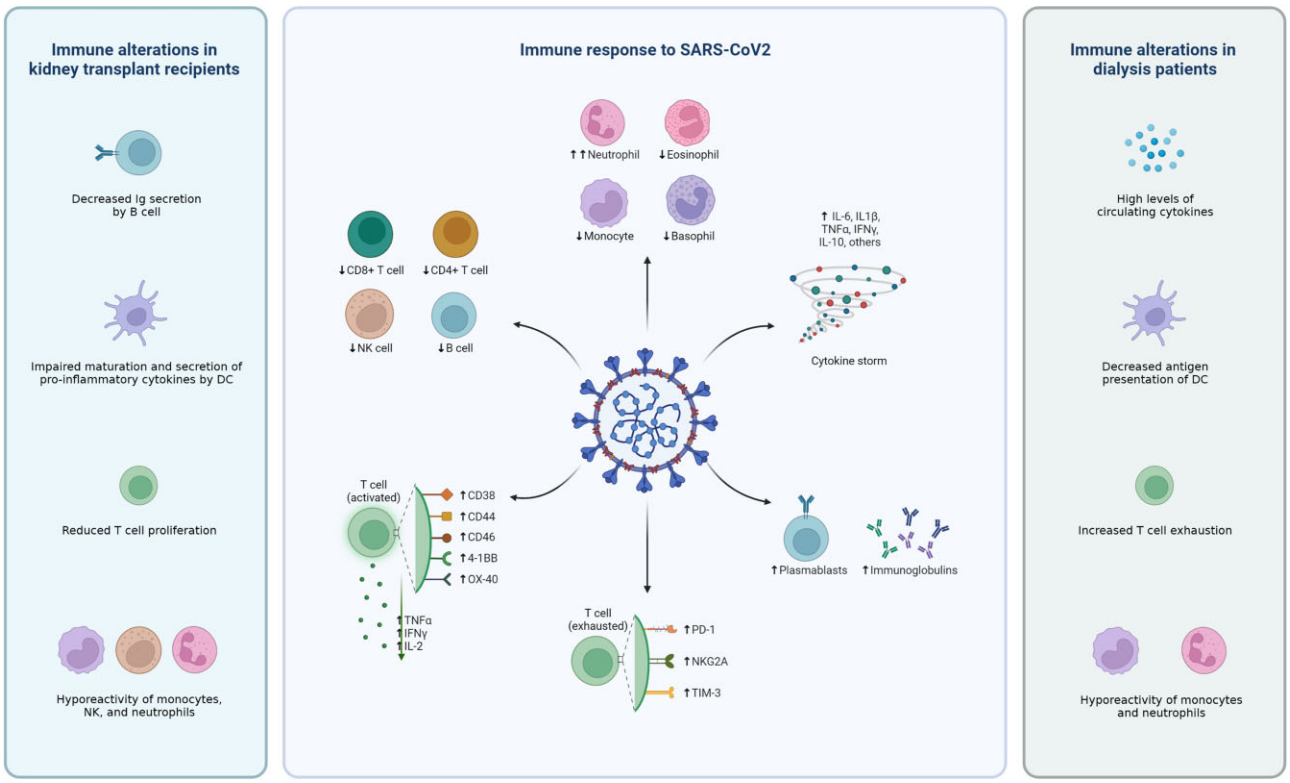

FIGURE 2: Immune responses to SARS-CoV-2 in dialysis patients and KTRs. Summary of immune alterations commonly observed in patients with COVID-19 (central panel) and derangements described in KTRs (left panel) and in patients on maintenance dialysis (right panel). Created with BioRender.com.

disease severity [64], confirming a role for this pathway in response to SARS-CoV-2 infection.

Immune response to SARS-CoV-2 vaccination

Early data after the introduction of SARS-CoV-2 vaccination showed that patients on dialysis have sufficient but delayed responses, significantly reinforced after a second or third dose [65, 66]. Subjects with a prior infection suggested by the presence of anti-receptor-binding domain (RBD) antibodies before vaccination were more likely to have effective vaccine responses compared with anti-RBD antibody-negative subjects, independent of the type of vaccine [67]. The synergistic effect that follows this type of hybrid immunization has also been observed in the general population and has distinctive features, including a greater magnitude and strength of antibody and cellular responses against SARS-CoV-2 [68].

The antibody response is quantitatively and qualitatively higher in subjects with breakthrough infection compared with subjects vaccinated with two doses, but comparable to those of subjects who received three vaccine doses or were vaccinated after a primary infection [69, 70]. This is mainly due to a higher frequency of memory B cells producing potent neutralizing antibodies [68, 71].

Differences in the immunological profiles between COVID-19-recovered and naïve patients have also been identified in dialysis patients and are crucial to establish more effective vaccination policy, particularly in frail populations. A recent French study showed that virus-naïve patients on HD have a lower anti-RBD IgG response after two mRNA vaccine doses compared with control subjects, but this response was higher in virus-recovered patients [72]. Administration of a third dose within 6 months significantly boosted serologic and cellular memory response in HD-naïve patients but not in recovered HD patients, in which it was probably already maximally induced [72]. Similar to what happens after primary infection, the anti-spike antibody titer tends to wane faster after 6 months from vaccination in patients on dialysis and the reduction is particularly pronounced in individuals with impaired initial antibody response [73].

These observations support the indication of a fourth dose to reinforce the antibody protection against new viral variants, as available data suggest inadequate protection against the omicron variant after a three-dose regimen [74, 75]. In addition, a fourth booster dose promoted a median 19-fold increase in anti-spike antibody titer in 45 patients on chronic dialysis (both HD and PD), with no serious adverse events [76], an effect comparable to the one observed in the general population [77].

Data on immune cell responses after vaccination in dialysis patients are still limited. De Vriese *et al.* [78] analyzed the anti-SARS-CoV-2 IFN-γ production in response to two doses of mRNA vaccine, showing that it was significantly lower in 543 HD patients compared with healthy subjects. This result is in line with other studies describing impaired T cell response in patients on dialysis [79–82]. In contrast to the significant increase in antibody titer produced by a booster dose, SARS-CoV-2 reactive T helper and T cytotoxic cells remained stable [75].

Studies comparing the impact of different dialysis modalities on the entity of seroconversion after vaccination confirmed significant associations between higher titers in response to the first or second vaccine dose and factors such as younger dialysis vintage and fewer comorbidities (both with BNT162b2 and mRNA-1273 vaccine). Other parameters like CRP, albumin and

age did not appreciably influence the magnitude of the response [78, 83–87]. Median anti-spike IgG levels were similar between HD and PD, even if patients receiving home treatments usually had fewer comorbidities [67, 88].

Differences between the type of vaccine used recently have been identified, suggesting that the initial high dose of mRNA may help obtain a more durable response, as observed between BNT162b2 and mRNA-1273 recipients [89], and particularly compared with other non-mRNA-based vaccines such as Ad26.COV2.S [73]. Although response is reduced compared with immunocompetent subjects, SARS-CoV-2 vaccination in large populations of chronic dialysis patients limited the incidence and severity of SARS-CoV-2 infection [90, 91].

In a Canadian cohort of 13 759 subjects on maintenance dialysis, COVID-19 vaccination effectively prevented SARS-CoV-2 infection and severe outcomes. In particular, the risk of infection was reduced by 41% after vaccination with one dose and by 69% after two doses compared with the period before vaccination. Furthermore, severe outcomes were reduced by 46% and 83% after one and two doses, respectively [90].

Sibbel *et al*. [91] compared 35 206 vaccinated subjects on HD with 63 243 unvaccinated, finding a reduction in the hospitalization rate for COVID-19 from 43.4% to 28% after vaccination with BNT162b2 and from 45.6% to 37.2% with mRNA-1273. Vaccinated patients also had lower mortality (4.0% for BNT162b2 and 5.6% for mRNA-1273 versus 12.1% and 14.5% in unvaccinated controls). However, compared with the general population, these percentages remain significantly higher (29% for hospitalization and 7% for mortality risk after two doses versus <0.1% after the first dose) [92], confirming the importance of booster doses in this group of patients.

SARS-CoV-2 IN KTRs

Immune response to SARS-CoV-2 infection

Infections are a common cause of morbidity after transplantation and account for a large proportion of deaths with a functioning graft [93]. The use of immunosuppressive drugs to control alloreactivity and prevent rejection is a concern in KTRs exposed to SARS-CoV-2. Some European studies have shown that mortality rates increase significantly when SARS-CoV-2 infection occurs in the first period following kidney transplantation [17, 94, 95], suggesting that the intensity of immunosuppression may impact outcomes. However, the use of stronger conditioning regimens with lymphodepleting agents was surprisingly not associated with mortality [95, 96].

Immunosuppressive regimens used in kidney transplantation may affect the immune system at multiple levels. However, although based on limited available data, early innate responses to SARS-CoV-2 infection seem to be similar between transplant and nontransplant patients. In studies comparing solid organ transplant (SOT) recipients with carefully matched nontransplant cohorts, levels of inflammatory markers and IL-6 were similar among hospitalized patients [97–100]. In KTRs, IL-6 levels correlated with disease severity [101], with scarce prediction of disease progression [101, 102].

Although multiple studies have described profound lymphopenia among SOT recipients with COVID-19, only a few studies have performed a more detailed evaluation of cellular immune responses to SARS-CoV-2 in this population [103]. Candon *et al*. [104] measured the frequency of SARS-CoV-2–reactive T cells by IFN-γ enzyme-linked immune absorbent spot in a small cohort of KTRs who all underwent a reduction of immunosuppression at the time of COVID-19 diagnosis. These patients displayed broadly reactive SARS-CoV-2–specific $CD4^+$ and $CD8^+$ T cells at 2–6 weeks after symptom onset, with frequencies similar to patients on HD. However, due to the lack of controls, the impact of immunosuppression on the robustness of antiviral T cell responses could not be evaluated. More recently, another study confirmed that SARS-CoV-2-specific T cell responses in KTRs were similar to those of patients on dialysis and persisted for up to 10 months from infection, a time point by which the humoral response had completely weaned [105]. Interestingly, a reduction of maintenance immunosuppression did not impact SARS-CoV-2-specific T cell numbers, which persisted up to 3 months from infection even in patients who resumed full immunosuppressive regimens after recovery. Importantly, in KTRs with asymptomatic infection, the percentages of subjects developing a SARS-CoV-2-specific T cell response were significantly lower compared with patients with a mild or severe disease course [106].

Studies conducted at the beginning of the pandemic showed that KTRs are able to generate normal serum levels of total anti-SARS-CoV-2 IgG upon infection [101, 102, 107–109], but the humoral response kinetics are delayed and serum antibody levels decrease more rapidly compared with immunocompetent subjects [101, 107, 110–112].

The first study comparing humoral immune responses to SARS-CoV-2 between kidney transplant and nontransplant subjects reported that most KTRs with COVID-19 exhibited broad activation of B cell subsets (switched, activated and memory) but not T_{FH} cells compared with controls, as well as a robust anti-SARS-CoV-2 nucleocapsid IgM and IgG antibody response. Similar results were also observed in nontransplant patients with COVID-19 [107], and disease severity correlated with the entity of the antibody response at different time points, as in nontransplant patients, with a greater impact compared with other factors like age, sex and type of immunosuppression [106, 113]. Withdrawal of antiproliferative agents (e.g. mycophenolate) at the time of COVID-19 diagnosis did not seem to impact the magnitude of the antibody response [107].

The isotypic distribution of anti-SARS-CoV-2 antibodies in KTRs was recently assessed in a multicenter cross-sectional study. Patients at earlier stages of the infection had lower IgG levels against four distinct spike protein epitopes compared with nontransplanted subjects. However, no difference was observed between controls and kidney transplanted patients at later time points, suggesting a normal, albeit delayed, evolution of the humoral response [114]. The evolution of spike-specific IgA and IgM kinetics was preserved at all time points. The fact that IgG production was impaired during the acute phase of the disease may explain in part the poor outcomes in transplant recipients with COVID-19. Of note, the majority of KTRs considered in the study received a significant reduction or withdrawal of mycophenolate mofetil after infection, which may have had an impact on IgG levels at later time points [114].

The clear impact of immunosuppression on viral response has not been demonstrated thus far [115]. Intriguingly, despite the common procedure of reducing immunosuppression during infection, the acute rejection rate in KTRs with COVID-19 has not increased [116], as well as the incidence of anti–human leukocyte antigen antibodies [117]. This might be due to the emergence of an anti-inflammatory transcriptional program in lymphocytes [118], but the underlying molecular mechanisms are still unclear.

In a recent study, however, the empirical reduction of chronic immunosuppression to favor antiviral T and B cell responses

was associated with increased rejection rates [119], but these contrasting results could be due to the different practice of immunosuppression management across the centers.

Immune response to SARS-CoV-2 vaccination

Similar to patients on maintenance HD, KTRs have been shown to mount less robust immune responses following vaccination compared with the general population. In a prospective observational multicenter study in 368 KTRs the seroconversion rate after SARS-CoV-2 vaccination was 8% after the second dose and 42% after the third booster dose [80]. The kinetics of spike-reactive $CD4^+$ T cells following vaccination demonstrated a relevant delay, with a significant increase occurring only after the booster vaccination. Immunosuppression and type of vaccine were identified as major independent risk factors for a negative seroconversion. In more detail, belatacept, antiproliferative agents and calcineurin inhibitors were associated with higher seroconversion failure rates compared with mammalian target of rapamycin inhibitors and glucocorticoids. The seroconversion rate was almost twice as high with the mRNA-1273 (49%) compared with the BNT162b2 mRNA (26%) vaccine [80].

Grupper *et al.* [120] reported only 40% of seroconversion after two doses in KTRs compared with 98% of the healthy control group. Serological response increased to 76% after the third dose. Of note, every year of age increased the risk of having a negative serology by 5%. In terms of cellular response, levels of anti-spike $CD4^+TNF\text{-}\alpha^+$ and $CD4^+IFN\text{-}\gamma^+$ before the third booster were lower in transplant recipients than in controls. Other studies described a significant reduction in the frequency of total T cells and $CD4^+$ T cells but an increase in the percentage of Tregs and $CD8^+$ T cells postvaccination in kidney graft recipients [121]. Of note, KTRs have a uniquely impaired cellular and humoral response to SARS-CoV-2 vaccination compared with other organ transplant recipients, a phenomenon that is not entirely explained by the different levels of immunosuppression and could be related to uremia-associated immune abnormalities [122].

The impaired immune response developed after one or two vaccine doses in KTRs is responsible for their numerous breakthrough infections and their poor outcomes that are often similar to those of unvaccinated transplant recipients [123, 124]. After three doses, even if the risk of infection remains high, critical cases in KTRs are significantly less frequent, as demonstrated by a reduction in ICU admissions, need for ventilatory support and mortality [125]. However, compared with the general population, disease severity and mortality risk in vaccinated KTRs remains disproportionately higher [125–127].

Also in KTRs, previous SARS-CoV-2 infection allows the generation of a more effective immune response; after two vaccine doses, both serological conversion and specific T cell response were significantly higher in previously infected KTRs compared with naïve patients (97.1% versus 40.1% and 90% versus 9.4%, respectively), apart from patients treated with costimulatory blockade [128].

Available data converge to indicate an increased immune response in KTRs following a third vaccine dose, along with a significant increase in antibody titers for patients who were already seropositive after the second dose [129–132]. However, most recent variants, such as B.1.617.2 (delta) and B.1.1.529 (omicron), are characterized by partial immune escape, rapidly displacing other circulating strains and increasingly leading to breakthrough infections. In an observational cohort study, spike-specific neutralizing antibodies against the B.1.617.2 (delta) variant were present in only 59% of patients after the third vaccine dose [133]. Moreover, vaccine-induced cross-neutralization of the B.1.1.529 (omicron) variant was observed in only 43% of cases. In a similar report, Al Jurdi *et al.* [134] found that even though 67% of KTRs developed anti-spike antibodies after a third booster, the frequency of patients who developed neutralizing responses against the omicron variant increased from 0 to 12%.

In conclusion, a third mRNA vaccine dose significantly improves spike-specific immunity in KTRs. However, neutralizing antibody activity against immune-escape variants is suboptimal even in seroconverted individuals after a third vaccine dose and poses the urgent need to optimize vaccination strategies for this highly vulnerable population. As a therapeutic strategy, a temporary hold of antiproliferative agents for a few weeks could be considered to significantly improve third and fourth vaccination outcomes in KTRs who have not mounted a humoral immune response to previous doses [135].

Immune response during SARS-CoV-2 infection in end-stage kidney disease (ESKD) patients is delayed and presents some unique features, but overall it is preserved. In sharp contrast, the immune response against mRNA SARS-CoV-2 vaccines in HD patients, and even more so in KTRs, is severely impaired. A possible explanation for this discrepancy is that during natural infection, activation of oral dendritic and epithelial cells stimulates a more efficient immune response than vaccine injection in the muscle. Moreover, the vaccine includes only spike protein epitopes, whereas natural infection has 4 structural and 23 nonstructural proteins that are coordinately expressed [136]. Finally, natural infection results in a significant amount of systemic inflammation with TLR activation that is not seen with vaccination, which may also be boosted by a reduction of immunosuppression [114].

CONCLUSIONS

COVID-19 had a significant impact on ESKD patients. Despite a seemingly preserved immune response during acute infection, the high rate of comorbidities largely accounted for the excess mortality in this population in the early phases of the pandemic. After vaccines became available, their lower-than-expected rates of response kept their relative risk higher than in the general population. Understanding the immune mechanisms responsible for the impaired response to vaccination in ESKD patients is critical to optimize prevention strategies and reduce the excess morbidity and mortality in this fragile population.

FUNDING

No funding was received for this article.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Gupta A, Madhavan MV, Sehgal K *et al*. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020;**26**:1017–32.
2. Ulloa AC, Buchan SA, Daneman N *et al*. Estimates of SARS-CoV-2 omicron variant severity in Ontario, Canada. *JAMA* 2022;**327**:1286–8.
3. Nyberg T, Ferguson NM, Nash SG *et al*. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022;**399**:1303–.
4. Williamson EJ, Walker AJ, Bhaskaran K *et al*. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430–6.
5. Valeri AM, Robbins-Juarez SY, Stevens JS *et al*. Presentation and outcomes of patients with ESKD and COVID-19. *J Am Soc Nephrol* 2020;**31**:1409–15.
6. Windpessl M, Bruchfeld A, Anders HJ *et al*. COVID-19 vaccines and kidney disease. *Nat Rev Nephrol* 2021;**17**:291–3.
7. Hemmelder MH, Noordzij M, Vart P *et al*. Recovery of dialysis patients with COVID-19: health outcomes 3 months after diagnosis in ERACODA. *Nephrol Dial Transplant* 2022;**37**:1140–51.
8. Hsu CM, Weiner DE, Aweh G *et al*. Epidemiology and outcomes of COVID-19 in home dialysis patients compared with in-center dialysis patients. *J Am Soc Nephrol* 2021;**32**:1569–73.
9. Savino M, Santhakumaran S, Evans KM *et al*. Outcomes of patients with COVID-19 on kidney replacement therapy: a comparison among modalities in England. *Clin Kidney J* 2021;**14**:2573–81.
10. Jager KJ, Kramer A, Chesnaye NC *et al*. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. *Kidney Int* 2020;**98**:1540–8.
11. De Meester J, De Bacquer D, Naesens M *et al*. Incidence, characteristics, and outcome of COVID-19 in adults on kidney replacement therapy: a regionwide registry study. *J Am Soc Nephrol* 2021;**32**:385–96.
12. Jiang HJ, Tang H, Xiong F *et al*. COVID-19 in peritoneal dialysis patients. *Clin J Am Soc Nephrol* 2020;**16**:121–3.
13. Trapani S, Masiero L, Puoti F *et al*. Incidence and outcome of SARS-CoV-2 infection on solid organ transplantation recipients: a nationwide population-based study. *Am J Transplant* 2021;**21**:2509–21.
14. Kremer D, Pieters TT, Verhaar MC *et al*. A systematic review and meta-analysis of COVID-19 in kidney transplant recipients: lessons to be learned. *Am J Transplant* 2021;**21**:3936–45.
15. Raja MA, Mendoza MA, Villavicencio A *et al*. COVID-19 in solid organ transplant recipients: a systematic review and meta-analysis of current literature. *Transplant Rev (Orlando)* 2021;**35**:100588.
16. Mohan S, King KL, Husain SA *et al*. COVID-19-associated mortality among kidney transplant recipients and candidates in the United States. *Clin J Am Soc Nephrol* 2021;**16**:1695–703.
17. Goffin E, Candellier A, Vart P *et al*. COVID-19-related mortality in kidney transplant and haemodialysis patients: a comparative, prospective registry-based study. *Nephrol Dial Transplant* 2021;**36**:2094–105.
18. Diamond MS, Kanneganti TD. Innate immunity: the first line of defense against SARS-CoV-2. *Nat Immunol* 2022;**23**:165–76.
19. Perico L, Benigni A, Casiraghi F *et al*. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol* 2021;**17**:46–64.
20. Chandran A, Rosenheim J, Nageswaran G *et al*. Rapid synchronous type 1 IFN and virus-specific T cell responses characterize first wave non-severe SARS-CoV-2 infections. *Cell Rep Med* 2022;**3**:100557.
21. Zhang Q, Bastard P, Liu Z *et al*. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020;**370**:eabd4570.
22. Bastard P, Rosen LB, Zhang Q *et al*. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020;**370**:eabd4585.
23. Hadjadj J, Yatim N, Barnabei L *et al*. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020;**369**:718–24.
24. Lucas C, Wong P, Klein J *et al*. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020;**584**:463–9.
25. Del Valle DM, Kim-Schulze S, Huang HH *et al*. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020;**26**:1636–43.
26. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020;**20**:355–62.
27. Lucas C, Klein J, Sundaram ME *et al*. Delayed production of neutralizing antibodies correlates with fatal COVID-19. *Nat Med* 2021;**27**:1178–86.
28. Ren L, Zhang L, Chang D *et al*. The kinetics of humoral response and its relationship with the disease severity in COVID-19. *Commun Biol* 2020;**3**:780.
29. Rydyznski Moderbacher C, Ramirez SI, Dan JM *et al*. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. *Cell* 2020;**183**:996–1012.e19.
30. Tan AT, Linster M, Tan CW *et al*. Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients. *Cell Rep* 2021;**34**:108728.
31. Zohar T, Loos C, Fischinger S *et al*. Compromised humoral functional evolution tracks with SARS-CoV-2 mortality. *Cell* 2020;**183**:1508–19.e12.
32. Klenerman P, Hill A. T cells and viral persistence: lessons from diverse infections. *Nat Immunol* 2005;**6**:873–9.
33. Rha MS, Shin EC. Activation or exhaustion of $CD8^+$ T cells in patients with COVID-19. *Cell Mol Immunol* 2021;**18**:2325–33.
34. Zheng M, Gao Y, Wang G *et al*. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 2020;**17**:533–5.
35. Chen G, Wu D, Guo W *et al*. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;**130**:2620–9.
36. Le Bert N, Clapham HE, Tan AT *et al*. Highly functional virus-specific cellular immune response in asymptomatic SARS-CoV-2 infection. *J Exp Med* 2021; **218**:e20202617.
37. Xu Z, Shi L, Wang Y *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;**8**:420–2.
38. Galvan-Pena S, Leon J, Chowdhary K *et al*. Profound Treg perturbations correlate with COVID-19 severity. *Proc Natl Acad Sci USA* 2021; **118**:e2111315118.

39. Juno JA, Tan HX, Lee WS *et al*. Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19. *Nat Med* 2020;**26**:1428–34.
40. Kaneko N, Kuo HH, Boucau J *et al*. Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19. *Cell* 2020;**183**:143–57.e13.
41. Woodruff MC, Ramonell RP, Nguyen DC *et al*. Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nat Immunol* 2020;**21**:1506–16.
42. Garcia-Beltran WF, Lam EC, Astudillo MG *et al*. COVID-19-neutralizing antibodies predict disease severity and survival. *Cell* 2021;**184**:476–88.e11.
43. Afzali B, Noris M, Lambrecht BN *et al*. The state of complement in COVID-19. *Nat Rev Immunol* 2022;**22**:77–84.
44. Ali YM, Ferrari M, Lynch NJ *et al*. Lectin pathway mediates complement activation by SARS-CoV-2 proteins. *Front Immunol* 2021;**12**:714511.
45. Sinkovits G, Mezo B, Reti M *et al*. Complement overactivation and consumption predicts in-hospital mortality in SARS-CoV-2 infection. *Front Immunol* 2021;**12**:663187.
46. Carvelli J, Demaria O, Vely F *et al*. Association of COVID-19 inflammation with activation of the C5a–C5aR1 axis. *Nature* 2020;**588**:146–50.
47. Moss P. The T cell immune response against SARS-CoV-2. *Nat Immunol* 2022;**23**:186–93.
48. Goel RR, Painter MM, Apostolidis SA *et al*. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. *Science* 2021;**374**:abm0829.
49. Naaber P, Tserel L, Kangro K *et al*. Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study. *Lancet Reg Health Eur* 2021;**10**:100208.
50. Kato S, Chmielewski M, Honda H *et al*. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008;**3**:1526–33.
51. Khatri M, Charytan DM, Parnia S *et al*. Outcomes among hospitalized chronic kidney disease patients with COVID-19. *Kidney360* 2021;**2**:1107–14.
52. Kular D, Chis Ster I, Sarnowski A *et al*. The characteristics, dynamics, and the risk of death in COVID-19 positive dialysis patients in London, UK. *Kidney360* 2020;**1**:1226–43.
53. Kamel MH, Mahmoud H, Zhen A *et al*. End-stage kidney disease and COVID-19 in an urban safety-net hospital in Boston, Massachusetts. *PLoS One* 2021;**16**:e0252679.
54. Ng JH, Hirsch JS, Wanchoo R *et al*. Outcomes of patients with end-stage kidney disease hospitalized with COVID-19. *Kidney Int* 2020;**98**:1530–9.
55. Gisby J, Clarke CL, Medjeral-Thomas N *et al*. Longitudinal proteomic profiling of dialysis patients with COVID-19 reveals markers of severity and predictors of death. *Elife* 2021;**10**:e64827.
56. Hartzell S, Bin S, Cantarelli C *et al*. Kidney failure associates with T cell exhaustion and imbalanced follicular helper T cells. *Front Immunol* 2020;**11**:583702.
57. Anft M, Blazquez-Navarro A, Paniskaki K *et al*. SARS-CoV-2-reactive cellular and humoral immunity in hemodialysis population. *Kidney Int* 2021;**99**:1489–90.
58. De Vriese AS, Van Praet J, Reynders M *et al*. Longevity and correlation with disease severity of the humoral and cellular response to SARS-CoV-2 infection in haemodialysis patients. *Clin Kidney J* 2021;**14**:2446–8.
59. Shankar S, Beckett J, Tipton T *et al*. SARS-CoV-2-specific T cell responses are not associated with protection against reinfection in hemodialysis patients. *J Am Soc Nephrol* 2022;**33**:883–7.
60. Banham GD, Godlee A, Faustini SE *et al*. Hemodialysis patients make long-lived antibodies against SARS-CoV-2 that may be associated with reduced reinfection. *J Am Soc Nephrol* 2021;**32**:2140–2.
61. Cohen DE, Sibbel S, Marlowe G *et al*. Antibody status, disease history, and incidence of SARS-CoV-2 infection among patients on chronic dialysis. *J Am Soc Nephrol* 2021;**32**:1880–6.
62. Clarke CL, Prendecki M, Dhutia A *et al*. Longevity of SARS-CoV-2 immune responses in hemodialysis patients and protection against reinfection. *Kidney Int* 2021;**99**:1470–7.
63. Prendecki M, Clarke C, Medjeral-Thomas N *et al*. Temporal changes in complement activation in haemodialysis patients with COVID-19 as a predictor of disease progression. *Clin Kidney J* 2020;**13**:889–96.
64. Medjeral-Thomas NR, Troldborg A, Hansen AG *et al*. Plasma lectin pathway complement proteins in patients with COVID-19 and renal disease. *Front Immunol* 2021;**12**:671052.
65. Bensouna I, Caudwell V, Kubab S *et al*. SARS-CoV-2 antibody response after a third dose of the BNT162b2 vaccine in patients receiving maintenance hemodialysis or peritoneal dialysis. *Am J Kidney Dis* 2022;**79**:185–92.e1.
66. Garcia P, Han J, Montez-Rath M *et al*. SARS-CoV-2 booster vaccine response among patients receiving dialysis. *Clin J Am Soc Nephrol* 2022;**17**:1036–8.
67. Garcia P, Anand S, Han J *et al*. COVID-19 vaccine type and humoral immune response in patients receiving dialysis. *J Am Soc Nephrol* 2022;**33**:33–7.
68. Crotty S. Hybrid immunity. *Science* 2021;**372**:1392–3.
69. Walls AC, Sprouse KR, Bowen JE *et al*. SARS-CoV-2 breakthrough infections elicit potent, broad, and durable neutralizing antibody responses. *Cell* 2022;**185**:872–80.e3.
70. Altarawneh HN, Chemaitelly H, Ayoub HH *et al*. Effects of previous infection and vaccination on symptomatic omicron infections. *N Engl J Med* 2022;**387**:21–34.
71. Andreano E, Paciello I, Piccini G *et al*. Hybrid immunity improves B cells and antibodies against SARS-CoV-2 variants. *Nature* 2021;**600**:530–5.
72. Attias P, Azzaoui I, El Karoui K *et al*. Immune responses after a third dose of mRNA vaccine differ in virus-naive versus SARS-CoV-2-recovered dialysis patients. *Clin J Am Soc Nephrol* 2022;**17**:1008–16.
73. Hsu CM, Weiner DE, Manley HJ *et al*. Seroresponse to SARS-CoV-2 vaccines among maintenance dialysis patients over 6 months. *Clin J Am Soc Nephrol* 2022;**17**:403–13.
74. Carr EJ, Wu M, Harvey R *et al*. Omicron neutralising antibodies after COVID-19 vaccination in haemodialysis patients. *Lancet* 2022;**399**:800–2.
75. Cinkilic O, Anft M, Blazquez-Navarro A *et al*. Inferior humoral and sustained cellular immunity against wild-type and omicron variant of concern in hemodialysis patients immunized with 3 SARS-CoV-2 vaccine doses compared with 4 doses. *Kidney Int* 2022;**101**:1287–9.
76. Housset P, Kubab S, Hanafi L *et al*. Humoral response after a fourth "booster" dose of a coronavirus disease 2019 vaccine following a 3-dose regimen of mRNA-based vaccination in dialysis patients. *Kidney Int* 2022;**101**:1289–90.
77. Regev-Yochay G, Gonen T, Gilboa M *et al*. Efficacy of a fourth dose of Covid-19 mRNA vaccine against omicron. *N Engl J Med* 2022;**386**:1377–80.

78. Van Praet J, Reynders M, De Bacquer D *et al*. Predictors and dynamics of the humoral and cellular immune response to SARS-CoV-2 mRNA vaccines in hemodialysis patients: a multicenter observational study. *J Am Soc Nephrol* 2021;**32**:3208–20.
79. Espi M, Charmetant X, Barba T *et al*. The ROMANOV study found impaired humoral and cellular immune responses to SARS-CoV-2 mRNA vaccine in virus-unexposed patients receiving maintenance hemodialysis. *Kidney Int* 2021;**100**:928–36.
80. Stumpf J, Siepmann T, Lindner T *et al*. Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: a prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. *Lancet Reg Health Eur* 2021;**9**: 100178.
81. Broseta JJ, Rodriguez-Espinosa D, Rodriguez 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;**78**:571–81.
82. Karakizlis H, Nahrgang C, Strecker K *et al*. Immunogenicity and reactogenicity of homologous mRNA-based and vector-based SARS-CoV-2 vaccine regimens in patients receiving maintenance dialysis. *Clin Immunol* 2022;**236**:108961.
83. Beilhack G, Monteforte R, Frommlet F *et al*. Antibody response and safety after mRNA-1273 SARS-CoV-2 vaccination in peritoneal dialysis patients – the Vienna cohort. *Front Immunol* 2021;**12**:780594.
84. Longlune N, Nogier MB, Miedouge M *et al*. High immunogenicity of a messenger RNA-based vaccine against SARS-CoV-2 in chronic dialysis patients. *Nephrol Dial Transplant* 2021;**36**:1704–9.
85. Agur T, Ben-Dor N, Goldman S *et al*. Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients – a prospective cohort study. *Nephrol Dial Transplant* 2021;**36**:1347–9.
86. Yanay NB, Freiman S, Shapira M *et al*. Experience with SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients. *Kidney Int* 2021;**99**:1496–8.
87. Ducloux D, Colladant M, Chabannes M *et al*. Humoral response after BNT162b2 mRNA COVID-19 vaccination in patients on haemodialysis depends on immune status. *Clin Kidney J* 2021;**14**:2266–7.
88. Patecki M, Merscher S, Dumann H *et al*. Similar humoral immune responses in peritoneal dialysis and haemodialysis patients after two doses of the SARS-CoV-2 vaccine BNT162b2. *Perit Dial Int* 2022;**42**:100–1.
89. Yau K, Chan CT, Abe KT *et al*. Differences in mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) SARS-CoV-2 vaccine immunogenicity among patients undergoing dialysis. *CMAJ* 2022;**194**:E297–305.
90. Oliver MJ, Thomas D, Balamchi S *et al*. Vaccine effectiveness against SARS-CoV-2 infection and severe outcomes in the maintenance dialysis population in Ontario, Canada. *J Am Soc Nephrol* 2022;**33**:839–49.
91. Sibbel S, McKeon K, Luo J *et al*. Real-world effectiveness and immunogenicity of BNT162b2 and mRNA-1273 SARS-CoV-2 vaccines in patients on hemodialysis. *J Am Soc Nephrol* 2022;**33**:49–57.
92. Bell S, Campbell J, Lambourg E *et al*. The impact of vaccination on incidence and outcomes of SARS-CoV-2 infection in patients with kidney failure in Scotland. *J Am Soc Nephrol* 2022;**3**: 677–86.
93. Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 2012;**7**:2058–70.
94. Pascual J, Melilli E, Jimenez-Martin C *et al*. COVID-19-related mortality during the first 60 days after kidney transplantation. *Eur Urol* 2020;**78**:641–3.
95. Thaunat O, Legeai C, Anglicheau D *et al*. IMPact of the COVID-19 epidemic on the moRTAlity of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPORTANT). *Kidney Int* 2020;**98**:1568–77.
96. Cravedi P, Mothi SS, Azzi Y *et al*. COVID-19 and kidney transplantation: results from the TANGO International Transplant Consortium. *Am J Transplant* 2020;**20**: 3140–8.
97. Molnar MZ, Bhalla A, Azhar A *et al*. Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. *Am J Transplant* 2020;**20**:3061–71.
98. Miarons M, Larrosa-Garcia M, Garcia-Garcia S *et al*. COVID-19 in solid organ transplantation: a matched retrospective cohort study and evaluation of immunosuppression management. *Transplantation* 2021;**105**:138–50.
99. Sharma P, Chen V, Fung CM *et al*. COVID-19 outcomes among solid organ transplant recipients: a case–control study. *Transplantation* 2021;**105**:128–37.
100. Alberici F, Affatato S, Moratto D *et al*. SARS-CoV-2 infection in dialysis and kidney transplant patients: immunological and serological response. *J Nephrol* 2022;**35**:745–59.
101. Benotmane I, Gautier-Vargas G, Wendling MJ *et al*. In-depth virological assessment of kidney transplant recipients with COVID-19. *Am J Transplant* 2020;**20**:3162–72.
102. Fava A, Donadeu L, Sabe N *et al*. SARS-CoV-2-specific serological and functional T cell immune responses during acute and early COVID-19 convalescence in solid organ transplant patients. *Am J Transplant* 2021;**21**:2749–61.
103. Phadke VK, Scanlon N, Jordan SC *et al*. Immune responses to SARS-CoV-2 in solid organ transplant recipients. *Curr Transplant Rep* 2021;**8**:127–39.
104. Candon S, Guerrot D, Drouot L *et al*. T cell and antibody responses to SARS-CoV-2: experience from a French transplantation and hemodialysis center during the COVID-19 pandemic. *Am J Transplant* 2021;**21**:854–63.
105. Bertrand D, Hamzaoui M, Drouot L *et al*. SARS-CoV-2-specific humoral and cellular immunities in kidney transplant recipients and dialyzed patients recovered from severe and nonsevere COVID-19. *Transplant Direct* 2021;**7**: e792.
106. Fava A, Donadeu L, Jouve T *et al*. A comprehensive assessment of long-term SARS-CoV-2-specific adaptive immune memory in convalescent COVID-19 solid organ transplant recipients. *Kidney Int* 2022;**101**:1027–38.
107. Hartzell S, Bin S, Benedetti C *et al*. Evidence of potent humoral immune activity in COVID-19-infected kidney transplant recipients. *Am J Transplant* 2020;**20**:3149–61.
108. Prendecki M, Clarke C, Gleeson S *et al*. Detection of SARS-CoV-2 antibodies in kidney transplant recipients. *J Am Soc Nephrol* 2020;**31**:2753–6.
109. Azzi Y, Parides M, Alani O *et al*. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics. *Kidney Int* 2020;**98**:1559–67.
110. Chavarot N, Leruez-Ville M, Scemla A *et al*. Decline and loss of anti-SARS-CoV-2 antibodies in kidney transplant recipients in the 6 months following SARS-CoV-2 infection. *Kidney Int* 2021;**99**:486–8.
111. Burack D, Pereira MR, Tsapepas DS *et al*. Prevalence and predictors of SARS-CoV-2 antibodies among solid organ

transplant recipients with confirmed infection. *Am J Transplant* 2021;**21**:2254–61.
112. Silvano J, Ferreira F, Bustorff M *et al*. Viral clearance and serological response to SARS-CoV-2 in kidney transplant recipients. *Transplant Proc* 2021;**53**:1180–6.
113. Softeland JM, Gisslen M, Liljeqvist JA *et al*. Longevity of anti-spike and anti-nucleocapsid antibodies after COVID-19 in solid organ transplant recipients compared to immunocompetent controls. *Am J Transplant* 2022;**22**:1245–52.
114. Cravedi P, Ahearn P, Wang L *et al*. Delayed kinetics of IgG, but not IgA, antispike antibodies in transplant recipients following SARS-CoV-2 infection. *J Am Soc Nephrol* 2021;**32**:3221–30.
115. Devresse A, De Greef J, Yombi JC *et al*. Immunosuppression and SARS-CoV-2 infection in kidney transplant recipients. *Transplant Direct* 2022;**8**:e1292.
116. Anton Pampols P, Trujillo H, Melilli E *et al*. Immunosuppression minimization in kidney transplant recipients hospitalized for COVID-19. *Clin Kidney J* 2021;**14**:1229–35.
117. Gandolfini I, Zanelli P, Palmisano A *et al*. Anti-HLA and anti-SARS-CoV-2 antibodies in kidney transplant recipients with COVID-19. *Transpl Int* 2021;**34**:596–9.
118. Zhang W, Yi Z, Cravedi P *et al*. A transcriptomic signature in PBMC from kidney transplant recipients at baseline predicts early acute rejection [abstract 406]. https://atcmeetingabstracts.com/abstract/a-transcriptomic-signature-in-pbmc-from-kidney-transplant-recipients-at-baseline-predicts-early-acute-rejection/ (5 August 2022, date last accessed) .
119. Schmidt-Lauber C, Gunster C, Huber TB *et al*. Collateral effects and mortality of kidney transplant recipients during the COVID-19 pandemic. *Kidney360* 2022;**3**:325–36.
120. Grupper A, Rabinowich L, Ben-Yehoyada M *et al*. Humoral response to the third dose of SARS-CoV-2 vaccine in kidney transplant recipients. *Transplant Proc* 2022;doi: 10.1016/j.transproceed.2022.02.011.
121. Al Jurdi A, Gassen RB, Borges TJ *et al*. Non-invasive monitoring for rejection in kidney transplant recipients after SARS-CoV-2 mRNA vaccination. *Front Immunol* 2022;**13**:838985.
122. Furian L, Russo FP, Zaza G *et al*. Differences in humoral and cellular vaccine responses to SARS-CoV-2 in kidney and liver transplant recipients. *Front Immunol* 2022;**13**:853682.
123. Hall VG, Al-Alahmadi G, Solera JT *et al*. Outcomes of SARS-CoV-2 infection in unvaccinated compared with vaccinated solid organ transplant recipients: a propensity matched cohort study. *Transplantation* 2022;**106**:1622–8.
124. Mazuecos A, Villanego F, Zarraga S *et al*. Breakthrough infections following mRNA SARS-CoV-2 vaccination in kidney transplant recipients. *Transplantation* 2022;**106**:1430–9.
125. Villanego F, Vigara LA, Alonso M *et al*. Trends in COVID-19 outcomes in kidney transplant recipients during the period of omicron variant predominance. *Transplantation* 2022;**106**:e304–5.
126. Qin CX, Moore LW, Anjan S *et al*. Risk of breakthrough SARS-CoV-2 infections in adult transplant recipients. *Transplantation* 2021;**105**:e265–6.
127. Maggiore U, Riella LV, Azzi J *et al*. Mortality in solid organ transplant recipients with COVID-19: more than meets the eye. *Am J Transplant* 2021;**22**:1496–7.
128. Magicova M, Zahradka I, Fialova M *et al*. Determinants of immune response to anti-SARS-CoV-2 mRNA vaccines in kidney transplant recipients: a prospective cohort study. *Transplantation* 2022;**106**:842–52.
129. Benotmane I, Gautier G, Perrin P *et al*. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. *JAMA* 2021;**326**:1063–5.
130. Kamar N, Abravanel F, Marion O *et al*. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med* 2021;**385**:661–2.
131. Del Bello A, Abravanel F, Marion O *et al*. Efficiency of a boost with a third dose of anti-SARS-CoV-2 messenger RNA-based vaccines in solid organ transplant recipients. *Am J Transplant* 2022;**22**:322–3.
132. La Milia V, Tonolo S, Luzzaro F *et al*. Humoral and T-cell response to SARS-CoV-2 mRNA BNT162b2 vaccination in a cohort of kidney transplant recipients and their cohabitant living kidney donor partners. *Clin Kidney J* 2022;**15**:820–1.
133. Benning L, Morath C, Bartenschlager M *et al*. Neutralizing antibody response against the B.1.617.2 (delta) and the B.1.1.529 (omicron) variant after a third mRNA SARS-CoV-2 vaccine dose in kidney transplant recipients. *Am J Transplant* 2022;**22**:1873–83.
134. Al Jurdi A, Gassen RB, Borges TJ *et al*. Suboptimal antibody response against SARS-CoV-2 omicron variant after third dose of mRNA vaccine in kidney transplant recipients. *Kidney Int* 2022;**101**:1282–6.
135. Schrezenmeier E, Rincon-Arevalo H, Jens A *et al*. Temporary antimetabolite treatment hold boosts SARS-CoV-2 vaccination-specific humoral and cellular immunity in kidney transplant recipients. *JCI Insight* 2022;**7**:e157836.
136. Gangappa S, Wrammert J, Wang D *et al*. Kinetics of antibody response to influenza vaccination in renal transplant recipients. *Transpl Immunol* 2019;**53**:51–60.
137. Couchoud C, Bayer F, Ayav C *et al*. Low incidence of SARS-CoV-2, risk factors of mortality and the course of illness in the French national cohort of dialysis patients. *Kidney Int* 2020;**98**:1519–29.
138. Xiong F, Tang H, Liu L *et al*. Clinical characteristics of and medical interventions for COVID-19 in hemodialysis patients in Wuhan, China. *J Am Soc Nephrol* 2020;**31**:1387–97.
139. Hilbrands LB, Duivenvoorden R, Vart P *et al*. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant* 2020;**35**:1973–83.
140. Fisher M, Yunes M, Mokrzycki MH *et al*. Chronic hemodialysis patients hospitalized with COVID-19: short-term outcomes in the Bronx, New York. *Kidney360* 2020;**1**:755–62.
141. Hsu CM, Weiner DE, Aweh G *et al*. COVID-19 among US dialysis patients: risk factors and outcomes from a national dialysis provider. *Am J Kidney Dis* 2021;**77**:748–56.e1.
142. Ao G, Wang Y, Qi X *et al*. The association between severe or death COVID-19 and solid organ transplantation: a systematic review and meta-analysis. *Transplant Rev (Orlando)* 2021;**35**:100628.
143. Requiao-Moura LR, Sandes-Freitas TV, Viana LA *et al*. High mortality among kidney transplant recipients diagnosed with coronavirus disease 2019: results from the Brazilian multicenter cohort study. *PLoS One* 2021;**16**:e0254822.
144. Massie AB, Werbel WA, Avery RK *et al*. Quantifying excess deaths among solid organ transplant recipients in the COVID-19 era. *Am J Transplant* 2022;**22**:2077–82.