Post COVID-19 condition imposes significant burden in patients with advanced chronic kidney disease

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Post COVID-19 condition imposes significant burden in patients with advanced chronic kidney disease: A nested case-control study ☆

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ABSTRACT

Background: The burden of post COVID-19 condition (PCC) is not well studied in patients with advanced kidney disease.
Methods: A large prospective cohort of SARS-CoV-2 vaccinated patients with chronic kidney disease stages G4–G5 (CKD G4/5), on dialysis, and kidney transplant recipients (KTR) were included. Antibody levels were determined after vaccination. Presence of long-lasting symptoms was assessed in patients with and without prior COVID-19 and compared using logistic regression. In patients with prior COVID-19, PCC was defined according to the WHO definition.
Results: Two hundred sixteen CKD G4/5 patients, 375 dialysis patients, and 2005 KTR were included. Long-lasting symptoms were reported in 204/853 (24%) patients with prior COVID-19 and in 297/1743 (17%) patients without prior COVID-19 (aOR: 1.45 (1.17–1.78)], $P < 0.001$). PCC was prevalent in 29% of CKD G4/5 patients, 21% of dialysis patients, and 24% of KTR. In addition, 69% of patients with PCC reported (very) high symptom burden. Odds of PCC was lower per 10-fold increase in antibody level after vaccination (aOR 0.82 [0.70–0.96], $P = 0.01$) and higher in case of COVID-19 related hospital admission (aOR 4.64 [2.61–8.25], $P = 0.003$).

☆ A list of RECOVAC collaborators is added in the acknowledgments.

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Conclusions: CKD G4/5 patients, dialysis patients, and KTR are at risk for PCC with high symptom burden after SARS-CoV-2 vaccination, especially if antibody levels are low and in case of hospitalization due to COVID-19.

Introduction

Although the World Health Organization (WHO) ended the global emergency status for COVID-19 on 5 May 2023, reports on long-lasting symptoms after COVID-19 have been emerging. Over 200 long-lasting symptoms affecting various organ systems have been documented in more than 65 million individuals worldwide [1]. These symptoms are referred to as ''long-COVID'', ''post COVID-19 condition'' (PCC) and ''post-acute sequalae of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)''. In a recent observational matched cohort study conducted on the general population, the prevalence of PCC was estimated to be 21% among individuals with prior COVID-19 [2]. In contrast, 9% of matched controls without prior COVID-19 had similar persistent symptoms. The impact of PCC goes beyond compromised individual health and includes potential strains on society, including the economy and the health care system [3]. Moreover, PCC leads to increased healthcare expenditures.

Patients with advanced kidney disease could be more susceptible to develop PCC, since they are at higher risk for a severe disease course during the acute phase of COVID-19 [4]. This can be partially explained by high comorbidity rates and acquired immunodeficiency. Activation of helper T cells may be impaired in patients with CKD G4/5. In dialysis patients, the inflammatory activation of antigen presenting cells during the haemodialysis procedure is associated with diminished T- and B-cell function. Additionally, the use of immunosuppressive drugs hampers protection against severe disease in these patients [5,6]. Indeed, patients with CKD stages G4/5 and dialysis patients showed lower levels of anti-RBD IgG antibodies after receiving the SARS-CoV-2 vaccine [6,7]. Furthermore, a significant proportion of KTR remain serological non-responders even after repeated vaccination [6–9]. Despite this high-risk profile, data on PCC are limited for patients with CKD G4/5, dialysis patients, and KTR. Previous studies were qualitatively limited because they included only hospitalised patients, did not define symptoms according to the WHO clinical case definition, examined a limited number of symptoms, or did not include a control group [10–16]. Furthermore, there are no previous studies that directly compared PCC in patients with CKD G4/5, dialysis patients, and KTR. The prevalence and impact of PCC remains to be determined in these high-risk patients.

We therefore analysed the association between COVID-19 and long-lasting symptoms and its burden in a cohort of patients with CKD G4/5, dialysis patients, and KTR who were vaccinated for COVID-19. The prevalence of PCC and its determinants was assessed by comparing long-lasting symptoms in patients with prior COVID-19 to patients without prior COVID-19

Methods

Study setting

The first COVID-19 case was reported on 27 February 2020 in the Netherlands. Patients with CKD G4/5, dialysis patients, and KTR received their first two vaccinations between March and June 2021. The third vaccine was offered in October 2021 to all patients, except for CKD G4/5 patients without use of immunosuppressive drugs. After the first three vaccinations, repeated vaccination was available every 3–6 months for these patient groups. The mRNA-1273 (Moderna) vaccine was the preferred vaccine for the first two vaccinations, succeeded by the BNT162b2 (Pfizer-BioNTech) vaccine for the third and subsequent vaccination rounds. Patients with CKD G4/5 using immunosuppressive drugs, dialysis patients, and KTR are considered fully vaccinated against SARS-CoV-2 when they have received three doses of an mRNA-based vaccine.

Study design

In this nested case-control study, we surveyed CKD G4/5 patients, dialysis patients, and KTR who were included in the prospective Long-term Efficacy and Safety of SARS-CoV-2 vaccination (LESS-CoV-2) study [17]. Patients were included after the second SARS-CoV-2 vaccination during the first national vaccination campaign in The Netherlands. Patients were asked to collect blood samples through a home-based finger prick set, and fill in a questionnaire 28 d after the second and third vaccination. Serum samples were analysed for the presence of anti-receptor-binding-domain (anti-RBD) IgG antibodies using enzyme-linked immunosorbent assay (ELISA) (Sanquin) [18]. Levels of anti-RBD IgG antibodies were expressed in binding antibody unit (BAU) per milliliter (mL). The serum samples were also analysed for the presence of antibodies induced during prior COVID-19 by using anti-SARS-CoV-2 nucleocapsid protein bridging ELISA. At 12 months after inclusion, we asked for the presence and burden of long-lasting symptoms according to the WHO definition of PCC [19]. This definition follows the presence of any symptom either during acute COVID-19 or within three months after COVID-19 diagnosis, that lasts for more than two months, and cannot be explained by a diagnosis other than COVID-19. For the latter, we asked patients whether they discussed alternative causes of long-lasting symptoms other than COVID-19 with their physician. We excluded patients with COVID-19 diagnosis prior to study inclusion, established by either a self-reported diagnosis or positive anti-nucleocapsid IgG antibodies. This study is conducted and reported in accordance with the STROBE recommendations. Patient representatives were involved in the RECOVAC consortium and composition of all questionnaires.

Data collection

We collected COVID-19 related outcomes through questionnaires at 1 month, 6 months, and 12 months after study inclusion. An additional questionnaire asking for the presence of long-lasting symptoms was collected at 12 months after study inclusion (see supplementary material). Symptoms surveyed were fatigue, dyspnoea, muscle weakness, myalgia, arthralgia, fever, cough, headache, diarrhoea, nausea or vomiting, hair loss, palpitations, anosmia or ageusia, concentration problems, memory loss, sleeping problems, anxiety, and depressive feelings. Patients reported symptom-specific burden on a 5-point Likert scale (1: no burden, 2: little burden, 3: moderate burden 4: much burden, 5: very much burden). Patient characteristics collected were SARS CoV-2 vaccination status, comorbidities, medication use, kidney replacement

modality, ethnic background, body mass index (BMI), smoking status, and alcohol use. Collected comorbidities were cardiovascular disease (including heart failure and cerebrovascular events), diabetes mellitus, hypertension, malignancy treated with chemo- or immunotherapy within the past 5 years, and lung diseases such as chronic obstructive pulmonary disease. Medication use in KTR was surveyed for corticosteroids, calcineurin inhibitors, mycophenolate mofetil, mammalian target of rapamycin inhibitors, or azathioprine from the Dutch Organ Transplantation Registry (NOTR) or from questionnaires if data was missing in the NOTR. Mycophenolic acid was considered equivalent to mycophenolate mofetil. Data on primary kidney disease, estimated glomerular filtration rate (eGFR), and kidney replacement modality were retrieved from the Dutch Renal Registry (Renine) and the NOTR. Socio-economic status was derived from postal code [20]. The dominant SARS-CoV-2 variant at time of COVID-19 diagnosis was determined in correspondence to established periods from the National Institute for Public Health and the Environment. We did not collect data on treatment for COVID-19.

Statistical analysis

We performed descriptive statistics for patients with CKD G4/5, dialysis patients and KTR separately, and according to COVID-19 diagnosis. Continuous variables are presented as mean and standard deviation or median and interquartile range according to data distribution. For categorical variables we used numbers and percentages (%). Differences between the inclusion and exclusion cohort were tested using Student's *t* test or Mann-Whitney U test for normally and non-normally distributed continuous variables, respectively. Categorical variables were compared and tested using chi-squared tests or, if assumptions were violated, Fisher's exact test. Symptom burden was categorised into none, little, moderate, high, or very high, according to the highest symptom-specific burden within each patient.

We estimated the association between prior COVID-19 and long-lasting symptoms by first performing multivariable logistic regression analysis in all patients, and stratified for patient category (CKD G4/5, dialysis, KTR). Confounders were selected based on previous literature and clinical knowledge, and included age, sex, ethnic background (Caucasian versus non-Caucasian), socio-economic status, patient category, BMI, comorbidities, number of immunosuppressive drugs, and eGFR. Second, we performed propensity score stratification in KTR to balance out differences between patients with and without prior COVID-19 to assess adjusted prevalence of long-lasting symptoms, absolute risk reduction, and number needed to harm. Positivity assumption was tested, and if needed, populations were marginally trimmed to guarantee a broad region of common support. We used five strata and within each stratum balance was assessed using a cut-off standardised mean difference of $\leq$0.25.

In patients with prior COVID-19, the most recent available antibody level prior to COVID-19 diagnosis was selected and log-transformed. Antibody levels were analysed for association with PCC using multivariable logistic regression and 3-knot restricted cubic spline regression. We additionally included eGFR as a confounder. Lastly, we estimated the association between COVID-19 related hospital admission and PCC, which was additionally corrected for antibody level and eGFR.

Missing data was handled through multiple imputations by chained equations using 10 iterations to construct 10 imputed datasets. Figures were constructed with GraphPad Prism 5. We used IBM SPSS Statistics 27 for all analyses, except for propensity score stratification and restricted cubic spline, for which we used R version 4.2.2. A significance level (α) <0.05 was considered statistically significant.

Results

Patient characteristics

Out of 4407 patients, 3180 (72%) responded to the survey, and among these respondents, 2596 were included. Within this group of 2596 included patients, 853 had prior COVID-19 and 1743 had not (Figure 1). CKD G4/5 patients had a mean age of 67 $\pm$ 9 years at baseline, while dialysis patients and KTR had mean ages of 64 $\pm$ 11 and 59 $\pm$ 12 y, respectively (Table 1). The distribution of sex and ethnic background was comparable between the patient groups. The eGFR was 23 $\pm$ 10 mL/min/1.73m^2 in CKD G4/5 patients and 51$\pm$19 mL/min/1.73m^2 in KTR. Use of immunosuppressive drugs was reported by 8% of CKD G4/5 patients and 15% of dialysis patients. The median time after the last transplantation was 8 [4–16] y in KTR. Included CKD G4/5 patients had higher eGFR and lower prevalence of lung disease, whereas included dialysis patients less often had diabetes or use of immunosuppressive drugs in comparison to patients who did not respond to the survey. KTR who were included were older than patients who did not respond to the survey (Table S1). COVID-19 diagnosis was established in 56 CKD G4/5 patients, 84 dialysis patients, and 713 KTR (Table 2). CKD G4/5 and dialysis patients with prior COVID-19 had less diabetes, more use of immunosuppressive drugs, and lower median antibody levels after two SARS-CoV-2 vaccinations compared to these patient groups without prior COVID-19 (Table S2).

Long-lasting symptoms

Long-lasting symptoms were reported in 204 of 853 patients (24%) with prior COVID-19, whereas these were reported in 297 of 1743 (17%) patients without prior COVID-19 ($P < 0.001$) (Figure 2). This resulted in an OR of 1.45 (1.17–1.78), $P = 0.001$) after correction for confounders (Table S3). No differences were observed between patients with CKD G4/5, dialysis patients, and KTR ($P = 0.7$). Long-lasting symptoms were present in 24.7% (95% CI: 21.3–28.1) and 18.6% (95% CI: 16.5–20.8) of KTR with and without prior COVID-19, respectively. The absolute risk reduction of long-lasting symptoms in absence of COVID-19 was 5.9% (95% CI: 1.9–9.9). This implies that 1 out of 17 (95% CI: 10–53) KTR with prior COVID-19 develops additional long-lasting symptoms.

Post COVID-19 condition

The majority of COVID-19 diagnoses were due to the SARS CoV-2 Omicron variant (83%). Hospital admission occurred in 7% (4/56) of CKD G4/5 patients, 5% (4/84) of dialysis patients, and 9% (64/713) of KTR. ICU admission occurred in only <1% (3/713) of KTR. The prevalence of PCC was 29% (16/56) in patients with CKD G4/5, 21% (18/84) in dialysis patients, and 24% (170/713) in KTR (P = 0.5). The PCC-related disease burden was experienced as "much" or "very much" in 57%, 72%, and 70%, respectively. The most frequent PCC-related symptoms were fatigue (81%), dyspnoea (57%), and muscle weakness (47%) (Figure S1, Table S4).

Risk factors for post COVID-19 condition

Anti-RBD IgG antibody levels and COVID-19 related hospital admission were identified as potentially modifiable risk factors for PCC. Median anti-RBD IgG antibody levels in KTR with PCC were lower compared to those without PCC (121 vs. 249 BAU/mL, $P = 0.002$). This was not observed in patients with CKD G4/5 (169 vs. 216 BAU/mL, $P = 0.5$) and dialysis patients (875 vs. 941 BAU/mL, $P = 0.8$) (Table S5). For all patients, each 10-fold increase in anti-RBD IgG antibody levels was associated with an 18% lower odds for PCC (aOR 0.82 [0.70–0.96], $P = 0.01$, Figure 3 and Table S6). We

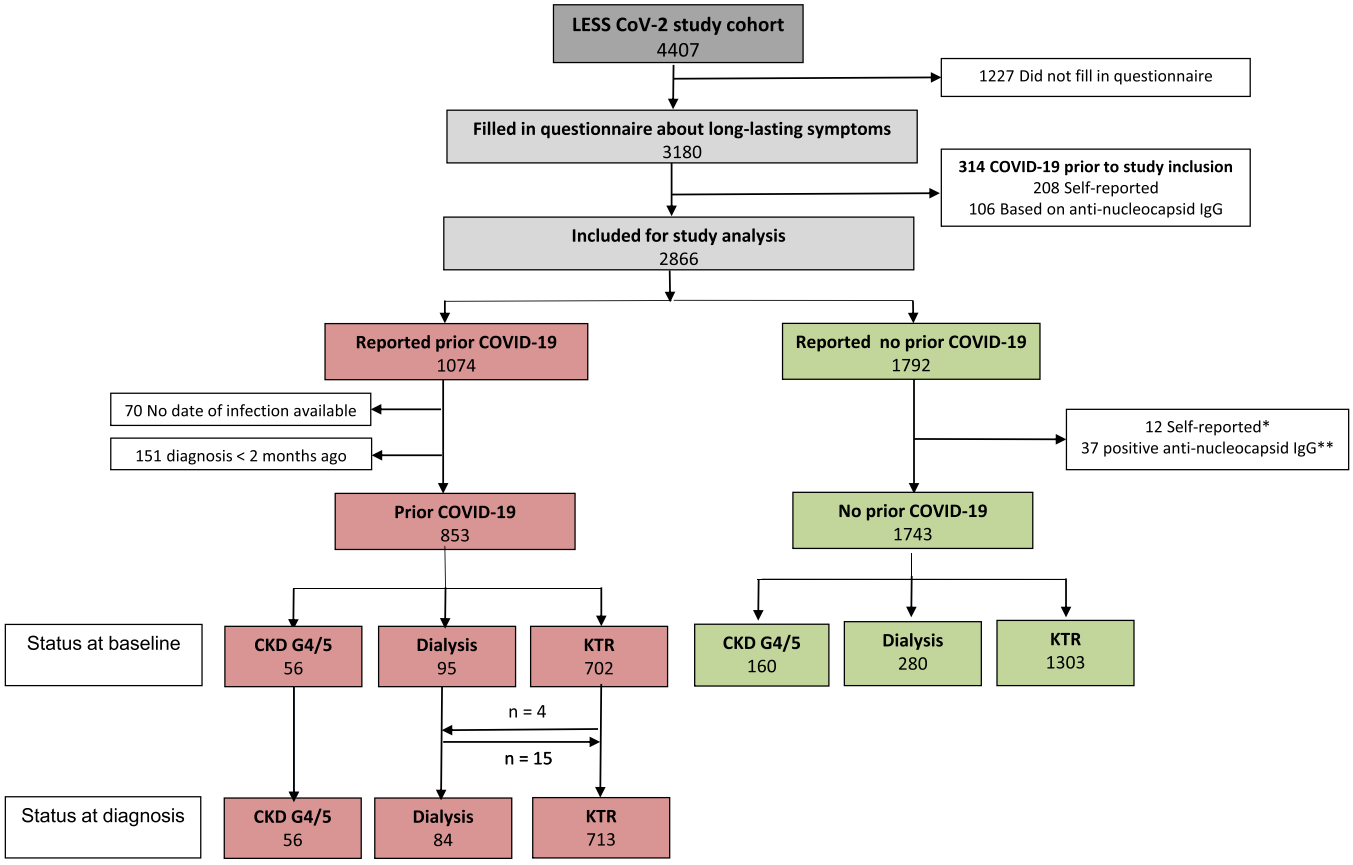

Figure 1. Flowchart. LESS CoV-2 study = long term efficacy and safety of SARS-CoV-2 vaccination in kidney disease patients study, COVID-19 = coronavirus disease 2019, IgG = immunoglobulin G, CKD = chronic kidney disease, KTR = kidney transplant recipient. *Twelve patients reported at twelve months absence of prior COVID-19, however also mentioned prior COVID-19 in a previous questionnaire during follow-up. **Thirty-seven patients who reported no prior COVID-19 did have a positive anti-nucleocapsid IgG test.

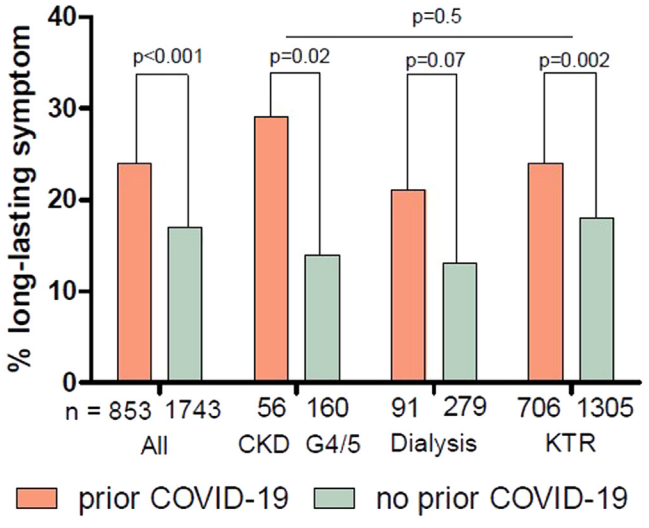

Figure 2. Prevalence of long-lasting symptoms in patients, with or without prior COVID-19. COVID-19 = Coronavirus disease 2019, CKD G4/5 = chronic kidney disease stages G4-G5, KTR = kidney transplant recipients.

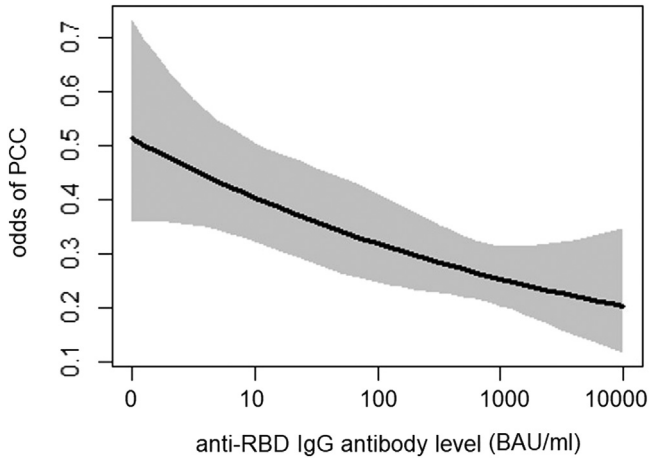

Figure 3. Log-linear association between anti-RBD IgG antibody level after SARS-CoV-2 vaccination and development of PCC. PCC = post COVID-19 condition, anti-RBD IgG = anti-receptor binding domain immunoglobulin G, BAU = binding antibody unit.

found no association between the number of vaccinations prior to COVID-19 diagnosis and the development of PCC. COVID-19 related hospital admission was also associated with PCC (aOR 4.64 [2.61–8.25], $P = 0.003$, Table S7), independently of antibody levels after vaccination.

Discussion

We observed that the risk of long-lasting symptoms was higher in SARS-CoV-2 vaccinated CKD G4/5 patients, dialysis patients, and KTR with COVID-19 diagnosis compared to those without COVID-19 diagnosis. Among those patients with COVID-19 diagnosis, 24%

Table 1
Patient characteristics at baseline.

	CKD G4/5	Dialysis	KTR
	$n = 216$	$n = 375$	$n = 2005$
Age, y, mean (SD)	67 (9)	64 (11)	59 (12)
Sex, male, *n* (%)	124 (57)	233 (62)	1170 (58)
Ethnic background, Caucasian, *n* (%)	196 (91)	312 (83)	1763 (88)
Socio-economic status, median (IQR)	0.043 (−0.36, 0.17)	0.058 (−0.12, 0.18)	0.073 (−0.084, 0.20)
Current smoker, yes, *n* (%)	19 (9)	46 (12)	102 (5)
Alcohol consumption, yes, *n* (%)	93 (43)	111 (30)	863 (43)
BMI, kg/m^2, mean (SD)	29 (6)	27 (6)	26 (4)
eGFR, mL/min/1.73m^2, mean (SD)	23 (10)	–	51 (19)
Primary kidney disease, *n* (%)			
•Diabetes	n.a.	50 (13)	99 (5)
•Hypertension	n.a.	92 (25)	119 (6)
•Glomerulonephritis	n.a.	44 (12)	314 (16)
•Interstitial nephritis	n.a.	22 (6)	94 (5)
•PCKD	n.a.	39 (10)	266 (13)
•Congenital/hereditary	n.a.	7 (2)	266 (13)
•Autoimmune disease	n.a.	34 (9)	72 (4)
•Other	n.a.	31 (8)	445 (22)
•Unknown	n.a.	28 (7)	284 (14)
Previous transplantation, yes, *n* (%)	–	48 (13)	–
Dialysis vintage, y, median (IQR)	–	2 (1–4)	–
Previous dialysis, yes *n* (%)	–	–	1099 (55)
First transplantation, yes. *n* (%)	–	–	1456 (73)
Donor type, Living, *n* (%)	–	–	1031 (51)
Transplantation time, y, median (IQR)	–	–	8 (4–16)
Comorbidities, *n* (%)			
•Cardiovascular disease	73 (34)	143 (38)	412 (21)
•Diabetes mellitus	68 (31)	95 (25)	426 (21)
•Hypertension	144 (67)	212 (57)	1215 (61)
•Lung disease	23 (11)	55 (15)	131 (7)
•Malignancy	12 (6)	28 (7)	58 (3)
Number of immunosuppressive drugs			
•0	190 (88)	299 (80)	0 (-)
•1	11 (5)	31 (8)	211 (11)
•2	3 (1)	16 (4)	992 (49)
•≥3	3 (1)	7 (2)	735 (37)
•Unknown	9 (4)	22 (6)	67 (3)
Type of immunosuppression			
•Corticosteroids	13 (6)	43 (11)	1352 (67)
•Calcineurin inhibitor	5 (2)	24 (6)	1604 (80)
•Mycophenolate mofetil	3 (1)	11 (3)	1124 (56)
•mTOR-inhibitor	1 (<1)	3 (<1)	129 (6)
•Azathioprine	4 (2)	3 (<1)	198 (10)
Anti-RBD IgG Ab level after two SARS-CoV-2 vaccinations, BAU/mL, median (IQR)	1228 (411–2873)	1269 (391–2755)	99 (11–726)
Time between second SARS-CoV-2 vaccination and anti-RBD IgG measurement, d, median (IQR)	33 (29–41)	38 (30–48)	31 (28–39)

CKD G4/5, Chronic Kidney Disease stages G4-G5; BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; anti-RBD IgG Ab, anti-receptor binding domain immunoglobulin G antibody; BAU, binding antibody unit; COVID-19, coronavirus disease 2019; IQR, interquartile range; PCKD, polycystic kidney disease; mTOR, mammalian target of rapamycin

developed PCC, of which the majority experienced a high symptom burden. A lower anti-RBD IgG antibody level after SARS-CoV-2 vaccination, as well as COVID-19 related hospital admission, were associated with PCC.

The observed symptoms from PCC in CKD G4/5 patients, dialysis patients, and KTR in our study is consistent with previous literature. Fatigue was the most common symptom which has been previously reported in dialysis patients and KTR with PCC in the pre-Omicron era [10–12,16,21]. Other PCC symptoms, including both somatic and neuropsychiatric, have also been reported in these patient groups [13,22,23]. A prospective single-centre study found a similar PCC prevalence of 27% in KTR [14]. However, this study defined symptoms according to the NICE guideline, and included more hospitalised (45%) and younger patients (mean age of 48 y) [24]. Another cross-sectional study showed a similar PCC prevalence of 18% in dialysis patients, with also a higher likelihood of PCC after hospitalization. However, an accepted definition of long-lasting symptoms after COVID-19 was not used [15]. Our study firstly investigated PCC in a large cohort of hospitalised and non-hospitalised CKD G4/5 patients, dialysis patients, and KTR. In addition, we compared long-lasting symptoms between patients with and without prior COVID-19, and 83% of COVID-19 diagnoses were due to the SARS CoV-2 Omicron variant. These considerations imply that PCC has been relevant for patients with CKD G4/5, dialysis patients, and KTR in the pandemic after SARS-CoV-2 vaccination has been introduced, and new SARS-CoV-2 serotypes have become dominant.

Patients with CKD G4/5, dialysis patients, and KTR who were hospitalised due to COVID-19 had a 4.6 times higher risk of PCC in our cohort. This suggests that a more severe course of COVID-19 predisposed for PCC in these patient groups. This may be explained by higher comorbidity rates and an immunosuppressive state because of uraemia, inflammation, or use of immunosuppressive drugs in hospitalised patients [4–6,25]. Furthermore, following COVID-19, long-lasting symptoms may be provoked by a chronic inflammatory state or ongoing SARS-CoV-2 viral replication in these patient groups [26,27]. These phenomena fit the several pathophysiological mechanisms of PCC suggested so far, including autoimmunity, persistent inflammation and putative viral reservoirs [28,29]. This is further supported by a study showing that chronic kidney disease was an independent predictor of prolonged SARS-CoV-2 infection [30]. These findings underline how

Table 2
COVID-19 related outcomes during follow-up.

	CKD G4/5 $n = 56$	Dialysis $n = 84$	KTR $n = 713$
COVID-19 diagnosis			
SARS-CoV-2 diagnosis method, *n* (%)			
•PCR	32 (59)	45 (54)	496 (73)
•Antigen test	21 (39)	25 (30)	165 (24)
•Unknown	1 (2)	5 (6)	16 (2)
COVID-19			
Symptoms during COVID-19 episode, *n* (%)	54 (96)	74 (88)	680 (95)
•Little burden	5 (9)	17 (23)	95 (14)
•Moderate burden	17 (31)	19 (26)	158 (23)
•Much burden	14 (26)	21 (28)	194 (29)
•Very much burden	18 (33)	17 (23)	233 (34)
New symptoms within 3 months after diagnosis *n* (%)	1 (2)	2 (2)	39 (5)
COVID-19 related hospital admission, *n* (%)	4 (7)	4 (5)	64 (9)
COVID-19 related ICU admission during COVID-19 episode, *n* (%)	0 (-)	0 (-)	3 (<1)
PCC			
Post COVID-19 condition (WHO definition), *n* (%)	16 (29)	18 (21)	170 (24)
•Little burden	1 (6)	1 (6)	11 (6)
•Moderate burden	6 (38)	4 (22)	40 (24)
•Much burden	6 (38)	6 (33)	71 (42)
•Very much burden	3 (19)	7 (39)	48 (28)
Alternative diagnosis long-lasting symptoms discussed with any doctor, *n* (%)	9 (56)	9 (50)	86 (51)
Underwent further diagnosis or treatment for long-lasting symptoms, *n* (%)	2 (13)	7 (39)	44 (26)

Numbers and percentages can vary because of missing values. CKD G4/5, Chronic Kidney Disease stages G4-G5; KTR, kidney transplant recipients; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; COVID-19, coronavirus disease 2019; ICU, intensive care unit; WHO, World Health Organization; PCC, Post COVID-19 condition

acquired immunodeficiency predisposes patients with CKD G4/5, dialysis patients, and KTR to long-term health damage after COVID-19.

Examining our observations in relation to the prevalence of PCC in the general population, Ballering et al. showed in a large general population-based cohort study that 21% of individuals developed PCC, whereas 9% of individuals without prior COVID-19 reported similar symptoms [2]. This study was conducted in the pre-Omicron era and only 10% of the participants were fully vaccinated by the end of the study. Compared to our vaccinated cohort, we observed that 24% of patients developed PCC. However, in the reference population without prior COVID-19, we found a higher proportion of 17% with long-lasting symptoms. The 5.9% absolute risk difference is lower as compared to Ballering et al., which might be explained by a higher background symptom burden in our patient groups. Since we did not include patients without chronic kidney disease or kidney replacement therapy, we cannot conclude whether or not PCC is more prevalent in patients with advanced kidney disease than in the general population during the Omicron pandemic phase.

SARS-CoV-2 vaccination might provide an effective strategy to protect patients with CKD G4/5, dialysis patients, and KTR against the long-term effects of COVID-19, such as PCC. A large multinational cohort study demonstrated effectiveness of SARS-CoV-2 vaccination against PCC (preprint) [31]. It remains questionable whether this can be extrapolated to patients with chronic kidney disease or kidney replacement therapy. Anti-RBD IgG antibody levels after SARS-CoV-2 vaccination were lower compared to healthy controls in patients with CKD G4/5 and dialysis patients, especially if they were treated with immunosuppressive drugs [6,7]. Notably, SARS-CoV-2 vaccines are poorly immunogenic in KTR, as SARS-CoV-2 specific antibody responses remain impaired or absent after repeated vaccination [7–9]. Recent data showed that higher antibody levels were associated with less COVID-19 breakthrough infection and a less severe disease course in KTR [20]. In the present study, we observed an association between higher antibody levels and lower prevalence of PCC in KTR, suggesting effectiveness of SARS-CoV-2 vaccination to prevent PCC. Each 10-fold increase in anti-RBD IgG antibody levels was associated with an 18% lower odds for PCC. This reveals that patients with an antibody level of 1000 BAU/mL after vaccination have an estimated 54% reduced likelihood of PCC compared to non-responders to vaccination. A clinical implication of these findings may be that repeated SARS-CoV-2 vaccination can induce higher antibody levels which better protects against severe COVID-19 as well as reduces the risk of PCC in KTR.

The main strengths of our study are the large cohort with CKD G4/5 patients, dialysis patients, and KTR as well as the availability of anti-RBD IgG antibody levels after two and three SARS-CoV-2 vaccinations. Unlike other studies examining PCC in these patient groups, we included a control group of patients without prior COVID-19 exposure [10–16]. Furthermore, we included both hospitalised and non-hospitalised patients and we surveyed both somatic and neuropsychiatric symptoms. This allows us to depict a realistic representation of PCC and its associated disease burden. Lastly, no differences in results were observed before and after imputation for missing data. This demonstrates robustness of the findings in this study. This study also has some limitations. The presence of long-lasting symptoms was surveyed over different time periods in patients with COVID-19 compared to patients without prior COVID-19. Patients with COVID-19 reported long-lasting symptoms after COVID-19 diagnosis over a period of 4 months on average. Patients without prior COVID-19 reported long-lasting symptoms since start of inclusion over a period of 28 months on average. This likely resulted in an overestimation of long-lasting symptoms in patients without prior COVID-19. We therefore expect an even larger difference in risk of long-lasting symptoms between patients with prior COVID-19 and those without. It is possible that an increased awareness and media attention about this topic promoted the reporting of long-lasting symptoms after COVID-19. We could not utilise validated questionnaires on PCC since these were not available at that moment. However, we used the WHO definition of PCC for our analysis and we enabled the assistance of patient representatives in formulating the questionnaires. The cross-sectional design potentially induced recall bias. Our findings have limited generalizability to patients with CKD G4/5 and dialysis pa-

tients given the limited sample sizes and the use of immunosuppressive drugs in these groups.

In conclusion, patients with CKD G4/5, dialysis patients, and KTR are at risk for PCC with a high symptom burden, especially if antibody levels after SARS-CoV-2 vaccination are low or if they were hospitalised due to COVID-19. Future research is needed to elucidate the impact on long-term health and which interventions may be effective to reduce the burden of PCC.

Declarations

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Ethical approvals: All patients provided informed consent. Approval to conduct this study was granted by the Medical Research Ethics Committee of the University Medical Center Groningen (EudraCT number: 2021–001,520–18). The study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act.

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Supplementary materials

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References

[1] Davis HE, McCorkell L, Vogel JM, Topol EJ. Author correction: long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;**21**(6):408.
[2] Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet* 2022;**400**(10350):452–61.
[3] Mirin AA. A preliminary estimate of the economic impact of long COVID in the United States. *Fatigue Biomed Health Behav* 2022;**10**(4):190–9.
[4] Gansevoort RT, Hilbrands LB. CKD is a key risk factor for COVID-19 mortality. *Nat Rev Nephrol* 2020;**16**(12):705–6.
[5] Girndt M, Sester M, Sester U, Kaul H, Kohler H. Molecular aspects of T- and B-cell function in uremia. *Kidney Int Suppl* 2001;**78**:S206–11.
[6] Sanders JF, Bemelman FJ, Messchendorp AL, Baan CC, van Baarle D, van Binnendijk R, et al. The RECOVAC immune-response study: the immunogenicity, tolerability, and safety of COVID-19 vaccination in patients with chronic kidney disease, on dialysis, or living with a kidney transplant. *Transplantation* 2022;**106**(4):821–34.
[7] Bouwmans P, Messchendorp AL, Imhof C, Sanders JF, Hilbrands LB, Reinders MEJ, et al. Impact of immunosuppressive treatment and type of SARS-CoV-2 vaccine on antibody levels after three vaccinations in patients with chronic kidney disease or kidney replacement therapy. *Clin Kidney J* 2023;**16**(3):528–40.
[8] Kho MML, Messchendorp AL, Frolke SC, Imhof C, Koomen VJ, Malahe SRK, et al. Alternative strategies to increase the immunogenicity of COVID-19 vaccines in kidney transplant recipients not responding to two or three doses of an mRNA vaccine (RECOVAC): a randomised clinical trial. *Lancet Infect Dis* 2023;**23**(3):307–19.
[9] Osmanodja B, Ronicke S, Budde K, Jens A, Hammett C, Koch N, et al. Serological response to three, four and five doses of SARS-CoV-2 vaccine in kidney transplant recipients. *J Clin Med* 2022;**11**(9):2565.
[10] Och A, Tylicki P, Polewska K, Puchalska-Reglinska E, Parczewska A, Szabat K, et al. Persistent post-COVID-19 syndrome in hemodialyzed patients-a longitudinal cohort study from the north of Poland. *J Clin Med* 2021;**10**(19):4451.
[11] Malinowska A, Muchlado M, Slizien Z, Biedunkiewicz B, Heleniak Z, Debska-Slizien A, et al. Post-COVID-19 sydrome and decrease in health-related quality of life in kidney transplant recipients after SARS-COV-2 infection-a cohort longitudinal study from the north of Poland. *J Clin Med* 2021;**10**(21):5205.
[12] Chauhan S, Meshram HS, Kute V, Patel H, Desai S, Dave R. Long-term follow-up of SARS-CoV-2 recovered renal transplant recipients: a single-center experience from India. *Transpl Infect Dis* 2021;**23**(6):e13735.
[13] Basic-Jukic N, Juric I, Furic-Cunko V, Katalinic L, Radic J, Bosnjak Z, et al. Follow-up of renal transplant recipients after acute COVID-19: a prospective cohort single-center study. *Immun Inflamm Dis* 2021;**9**(4):1563–72.
[14] Amorim CEN, Gomes VLT, Cristelli MP, Viana LA, de Luca Correa H, Lima GBB, et al. High prevalence of long-COVID among kidney transplant recipients: a longitudinal cohort study. *Transplantation* 2022;**106**(12):2408–15.

[15] Belkacemi M, Baouche H, Gomis S, Lassalle M, Couchoud C, registry R. Long-lasting clinical symptoms 6 months after COVID-19 infection in the French national cohort of patients on dialysis. *J Nephrol* 2022;**35**(3):787–93.
[16] Hajibaratali B, Amini H, Dalili N, Ziaie S, Anvari S, Keykha E, et al. Clinical outcomes of kidney recipients with COVID-19 (COVID-19 in kidney recipients). *Transpl Immunol* 2023;**76**:101772.
[17] Bouwmans P, Messchendorp AL, Sanders JS, Hilbrands L, Reinders MEJ, Vart P, et al. Long-term efficacy and safety of SARS-CoV-2 vaccination in patients with chronic kidney disease, on dialysis or after kidney transplantation: a national prospective observational cohort study. *BMC Nephrol* 2022;**23**(1):55.
[18] Vogelzang EH, Loeff FC, Derksen NIL, Kruithof S, Ooijevaar-de Heer P, van Mierlo G, et al. Development of a SARS-CoV-2 total antibody assay and the dynamics of antibody response over time in hospitalized and nonhospitalized patients with COVID-19. *J Immunol* 2020;**205**(12):3491–9.
[19] World Health Organization; A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021: 2021 https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
[20] Messchendorp AL, Sanders JF, Abrahams AC, Bemelman FJ, Bouwmans P, van den Dorpel RMA, et al. Incidence and severity of COVID-19 in relation to anti-receptor-binding domain IgG antibody level after COVID-19 vaccination in kidney transplant recipients. *Viruses* 2024;**16**(1).
[21] Chancharoenthana W, Kamolratanakul S, Leelahavanichkul A, Ariyanon W, Chinpraditsuk S, Saelim R, et al. Gastrointestinal manifestations of long-term effects after COVID-19 infection in patients with dialysis or kidney transplantation: an observational cohort study. *World J Gastroenterol* 2023;**29**(19):3013–26.
[22] Dogas T, Brkovic T, Novak I, Radic J. COVID-19 in kidney transplant recipients; a DALMATIAN single-center experience. *Ther Apher Dial* 2023;**27**(1):107–16.
[23] Dogas T, Novak I, Babic M, Vuckovic M, Tandara L, Radic J. Associations of serum calprotectin, arterial stiffness and long COVID symptoms in dalmatian kidney transplant recipients. *Viruses* 2023;**15**(8):6–7.
[24] Venkatesan P. NICE guideline on long COVID. *Lancet Respir Med* 2021;**9**(2):129.
[25] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**(7821):430–6.
[26] Cobo G, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. *Nephrol Dial Transpl* 2018;**33**(Suppl 3):iii35–40.
[27] Benotmane I, Risch S, Doderer-Lang C, Caillard S, Fafi-Kremer S. Long-term shedding of viable SARS-CoV-2 in kidney transplant recipients with COVID-19. *Am J Transpl* 2021;**21**(8):2871–5.
[28] Mehandru S, Merad M. Pathological sequelae of long-haul COVID. *Nat Immunol* 2022;**23**(2):194–202.
[29] Batiha GE-S, Al-kuraishy HM, Al-Gareeb AI, Welson NN. Pathophysiology of Post-COVID syndromes: a new perspective. *Virol J* 2022;**19**(1):158.
[30] Guo Y, Guo Y, Zhang Y, Li F, Yu J, Zhang Y, et al. Factors affecting prolonged SARS-CoV-2 infection and development and validation of predictive nomograms. *J Med Virol* 2023;**95**(2):e28550.
[31] Català M, Mercadé-Besora N, Kolde R, Trinh NTH, Roel E, Burn E, et al. The effectiveness of COVID-19 vaccines to prevent long COVID symptoms: staggered cohort study of data from the UK, Spain, and Estonia. *Lancet Respir Med* 2024;**12**(3):225–36.