Diplomarbeit

Retrospective quantification of anti-SARS-CoV-2 antibody response after mRNA COVID-19 vaccine in patients treated with peritoneal dialysis

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Abbreviations

ACE-2	Angiontesin Converting Enzyme 2
ACR	Albumin-Creatinine-Ratio
ADPKD	Autosomal Dominant Polycystic Kidney Disease
APC	Antigen Presenting Cell
APD	Automated Peritoneal Dialysis
AU/mL	Antibody Units Per Milliliter
BAU/mL	Binding Antibody Units per Milliliter
BMI	Body Mass Index
CAPD	Continuous Ambulatory Peritoneal Dialysis
CD	Cluster of Differentiation
CFS	Clinical Frailty Score
CGA	Cause GFR Albuminuria
CI	Confidence Interval
CKD	Chronic Kidney Disease
COVID	Coronavirus Disease
COPD	Chronic Obstructive Pulmonary Disease
CRP	C Reactive Protein
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ESAs	Erythropoiesis-Stimulating Agents
ESKD	End Stage Kidney Disease
ESRD	End Stage Renal Disease
EU	European Union
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GMFR	Geometric Mean Fold Rise
GMC	Geometric Mean Antibody Concentration
HA	Hemagglutination Assay
HBs-Antigen	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HD	Hemodialysis
HDF	Hemodiafiltration
HF	Hemofiltration
HI	Hemagglutination Inhibition
HIV	Human Immunodeficiency Virus
IL-6	Interleukin 6
KDIGO	Kidney Disease: Improving Global Outcomes
mRNA	Messenger Ribonucleic Acid
NSAIDs	Non-steroidal Anti-Inflammatory Drugs
PD	Peritoneal Dialysis
PPA	Positive Percent Agreement
PPI	Proton Pump Inhibitor
PPV	Positive Predictive Value
ROS	Reactive Oxygen Species
RRT	Renal Replacement Therapy
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2

SNA	Surrogate Neutralizing Antibodies
TLR	Toll-Like-Receptor
TNF α	Tumor-Necrosis-Factor

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Zusammenfassung

Einleitung

PatientInnen welche Nierenersatztherapieverfahren benötigen sind ein Kollektiv mit einem erhöhten Risiko an *Coronavirus 2019-disease* (COVID19) zu erkranken und infolgedessen auch zu versterben. Im Kampf gegen die COVID19-Pandemie sind Impfungen einer der wichtigsten Ansatzpunkte, um die Mortalitätsrate zu senken. DialysepatientInnen zeigten in vergangenen Studien eine reduzierte Antikörperproduktion im Zuge von Impfungen, wie zum Beispiel Hepatitis B oder Influenza. Antikörpertiter von DialysepatientInnen zeigen typischerweise niedrigere Höchstwerte und einen schnelleren Rückgang im Vergleich zu Kontrollgruppen. Die meisten Arbeiten in diesem Feld fokussieren sich auf HämodialysepatientInnen, es stehen aber nur wenige Daten für das wachsende Kollektiv der PeritonealdialysepatientInnen zur Verfügung. Deshalb ist es von höchster Wichtigkeit, die serologische Antwort auf die relativ neuen Messenger-Ribonucleic-Acid (mRNA) Impfstoffe in dieser Population zu untersuchen.

Methoden

In diese nicht-invasive, retrospektive, Einzelzentrumsstudie wurden 31 PatientInnen der Peritonealdialyseambulanz der Medizinischen Universität Graz eingeschlossen. Den TeilnehmerInnen wurden im Rahmen ihrer Routineversorgung zwei Impfdosen von mRNA-1273 verabreicht und Blutabnahmen durchgeführt. Die Daten für die Analyse wurden retrospektiv aus der elektronischen Krankenakte erhoben. Der primäre Endpunkt war die serologische Antikörperantwort, 28 Tage nach der ersten Impfdosis. Wir untersuchten auch die Titer nach der zweiten Impfdosis und nach einer Follow-up Periode. Weiters erkundeten wir, wie gewisse PatientInnen-Parameter mit der Dynamik der Antikörper assoziiert waren.

Ergebnisse

Vier Wochen nach der ersten Dosis zeigten 80.6% der PatientInnen einen reaktiven Antikörperassay. Ein serologisches Ansprechen, definiert als Binding Antibody Units per Milliliter ≥15/mL (BAU/mL), wurde bei 38.7% der PatientInnen festgestellt. Achtundzwanzig Tage nach der zweiten Dosis, hatten 93.3% reaktive Assays, von denen alle die Schwelle für eine serologisch signifikantes Ansprechen überschritten. Beim Follow-up Termin, nach einem Mittelwert von 202.5 Tagen, hatten 94.7% reaktive Assays. Alle dieser 94.7% zeigten eine serologisch signifikante Antwort.

Bei einem höheren Schwellenwert von 2000 BAU/mL, erreichten nur 40% die Schwelle vier Wochen nach der ersten Dosis und niemand erreichte sie am Follow-up Termin. Der erhöhte Schwellenwert, soll die Aussagekraft des Titers erhöhen.

Wir entdeckten eine signifikant höhere Anzahl an Impfversagen in der Gruppe der PatientInnen, die mit Erythropoese-stimulierende Substanzen behandelt wurden. Weiters gab es eine positive Assoziation zwischen höherer Impfantwort und residueller Nierenfunktion.

Signifikant niedrigere *geometric mean ratios* von Covid-19 Anti-Spike-Antikörpern wurden bei PatientInnen mit immunsuppressiven oder Erythropoese-stimulierenden Substanzen, Hepatitis B Impfversagern und gebrechlichen Patienten beobachtet.

Konklusion

Mit dieser Studie konnten wir zeigen, dass PatientInnen unter Peritonealdialyse in der Lage sind eine adäquate, serologische Antwort auf das verwendete COVID-19 mRNA Vakzin zu zeigen. Weiters konnten wir PatientInnen-Charakteristika identifizieren, welche die Fähigkeit der Antikörperbildung beeinflussen könnten. Diese Informationen könnten helfen PatientInnen zu identifizieren, welche eventuell von erhöhter medizinscher Achtsamkeit oder alternativen Impfstrategien profitieren könnten.

Abstract

Introduction

Patients undergoing renal replacement therapy are a collective with an increased risk of contracting and subsequently dying from COVID-19. In fighting the COVID-19 pandemic, vaccination is one of the most important tools to decrease mortality. Patients undergoing renal replacement therapy have, in the past, exhibited an inferior ability to mount a sufficient antibody response to vaccines, such as the Hepatitis B or Influenza vaccine. Antibody titers in dialysis patients were found to have lower peaks and be shorter-lived, compared to control groups. Most studies in this field have focused on the hemodialysis population, but only limited information is available on the growing number of patients undergoing peritoneal dialysis. Therefore, it is of the utmost importance to investigate the response to the relatively new mRNA COVID-19 vaccines in this population.

Methods

We performed a single-center, non-invasive, retrospective study, where the final analysis included 31 patients of the peritoneal dialysis department of the Medical University of Graz. Patients underwent their routinely scheduled vaccinations and blood for antibody titers was drawn at routine visits, also. Data was gathered in a retrospective chart review. Our primary endpoint was the serologic response 28 days after the first vaccination. We also included the antibody titers after the second dose and after a follow-up period. We explored how certain patient characteristics were associated with the dynamics of the antibody titers.

Results

Four weeks after the first dose, 80.6% of patients showed reactive antibody assays. A serologic response (defined as BAU ≥15/mL), was found in 38.7% of patients. Twenty-eight days after the second shot, 93.3% of patients had reactive assays, while also 93.3% showed a serologic response. At follow-up after a mean of 202.5 days, 94.7% of assays were reactive. All of those 94.7% reached the threshold of serologic response.

When utilizing a cut-off of 2000 BAU/mL, which has been suggested to enhance the positive predictive value for protection against severe disease, only 40% reached the threshold 28 days after the first dose and none at follow-up.

Non-responders were significantly more likely to be treated with ESAs and had a lower residual renal function compared to responders.

Significantly lower geometric mean ratios of SARS-CoV-2-antibodies were observed in patients treated with immunosuppressive drugs or erythropoiesis stimulating agents, for HBV-vaccine low or non-responder and frail patients.

Conclusion

We were able to show, that peritoneal dialysis patients are able to mount a good serologic response to the COVID-19 mRNA vaccine mRNA-1273 . Further, we were able to identify patient characteristics, which were associated with a weaker antibody response. This knowledge may be helpful for identifying candidates in need of increased medical attention or alternative vaccination strategies.

Previous Publications

Kolland M, Riedl R, Bachler B, Ribitsch W, Niedrist T, Meissl AM, et al. Decreased response to the mRNA anti-SARS-CoV-2 vaccine in hepatitis B vaccine non-responders and frail patients treated with peritoneal dialysis. Nephrol Dial Transplant. 2022 May 25;37(6):1188–90.

Introduction

1.1 Chronic Kidney Disease

1.1.1 Definition

Kidney function can be categorized into excretory, endocrine and metabolic functions.
Chronic kidney disease (CKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) initiative as a structural or functional impairment of the kidneys with implications for the health of the individual, lasting for more than three months. The impairment is further characterized as either albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorder, abnormalities detected by histology, structural abnormalities detected by imaging, history of kidney transplantation or a decreased glomerular filtration rate (GFR) (2).
There are structural or functional impairments, which do not alter an individual's prognosis and do not require specific therapies, for example simple kidney cysts. This is reflected in the definition by the addition "with implications for health" (2).

1.1.2 Classification

CKD is most often classified using the so-called CGA-Staging. This classification includes the **C**ause of CKD, **G**FR-category and the **a**lbuminuria-category (2).
GFR is generally accepted to be the best available overall index of kidney-function. The GFR-category is subdivided into six categories (G1, G2, G3a, G3b, G4, G5) (2).
Albuminuria is not only strongly associated with severity of kidney-injury, but also with progression of kidney disease, since albuminuria increases the risk for End Stage Kidney Disease (ESKD) independent of GFR or other cardiovascular risk factors (3). Albuminuria in the CGA-Staging is further subdivided into three categories (A1, A2, A3), characterized by the urine albumin-to-creatinine-ratio (ACR).
Based on GFR and Albuminuria, an individual can be assigned to one of four categories, indicating risk and outcome of the CKD. These categories include low risk, moderately increased risk, high risk and very high risk (2).

1.1.3 Epidemiology

The true prevalence of CKD can only be estimated, as it often is asymptomatic in its earlier stages and resources for early detection are often lacking, especially in the developing

world. Different methods of detection yield vastly different results in terms of CKD prevalence. For example, when defined solely as an estimated GFR (eGFR) < 60mL/min, prevalence is estimated at 2.5-11.2% of the adult population across Europe, Asia, North America and Australia. This prevalence rises drastically to 10.5-13.1%, when albuminuria is also incorporated. Twenty-five to 35 percent of people over the age of 65 meet criteria for CKD, although it is unclear, if this represents true CKD or if it is part of the natural decline in kidney-function (4). Globally, death due to CKD increased by 82.3% in the timespan between 1990 and 2010 (5).

In Austria, only the incidence of patients treated with renal replacement therapy (RRT) is published annually and in 2019, 134 people per one million inhabitants were started on RRT (6).

The common risk factors for incidence and progression of CKD include diabetes mellitus (DM) Type II, hypertension, old age, smoking and dyslipidemia. The rising incidence in CKD can largely be attributed to the increase in the aforementioned common risk factors. Less common factors are immunological diseases, heavy metal exposure, low birth weight with reduction in number of nephrons and toxicity by herbal remedies. The importance of these risk factors varies by location, age of the population and socio-economic status (7).

The most common underlying kidney diseases of all patients starting RRT in Austria in 2019 were type two DM (23.1%), arterial hypertension (22.8%), unknown kidney disease (16%), glomerulonephritis (10.3%), hereditary kidney disease (7.7%), interstitial nephritis and pyelonephritis (5.5%), DM Type I (2.2%) and others (11.5%) (6).

1.1.4 Symptoms and Complications

CKD in its earlier stages is often asymptomatic. Less than 5% of early CKD patients are aware of their disease. Most often, CKD is diagnosed via serum or urine chemistry tests. Patients also may present with hematuria, foamy urine, nocturia, flank pain or decreased urine output. Patients with more advanced CKD might exhibit fatigue, nausea, metallic taste, weight loss, pruritus, altered mental status and signs of hyperhydration, such as dyspnea and peripheral edema (8).

A decrease in kidney function can lead to multiple complications with negative effects on the individuals state of health. These deleterious complications include, but are not limited to cardiovascular disease (9), electrolyte and acid-base disorders (10), decreased cognitive function (11) and dysfunction of the immune system (12). CKD is consistently associated with an increased all-cause-mortality and cardiovascular mortality. Risk of death increases,

as residual kidney-function decreases (13). The mortality rates per 1000 person years for cardiovascular mortality in dialysis patients in the age group of 45-54 has been reported as 34.6, while the general population experiences a rate of 0.7. In the age range of 65-74 the rates are 90.0 for dialysis patients and 6.8 for the general population.

The same rates for non-cardiovascular mortality in the ages of 45-54 are 41.7 and 7.4, while the age range of 65-74 experiences rates of 111.7 and 12.9 (14).

The immune system is affected in multiple ways through CKD. On the one hand, a chronic state of inflammation exists and on the other hand, CKD patients experience immune deficiency. The chronic inflammation leads to atherosclerosis, cardiovascular disease (CVD), anemia and cachexia. The immune dysfunction leads to an increased incidence in infectious diseases and a diminished response to various vaccinations (15).

1.1.5 Management of CKD

The risk of cardiovascular disease in CKD patients is increased greatly, compared to non-CKD patients. Thus, reduction of cardiovascular risk factors plays a major role in CKD management. For example, it is recommended to initiate statin therapy for CKD at stage G3 for patients over the age of 50, regardless of their serum lipid profile, however initiation of statin-therapy for dialysis patients is not universally recommended, as there is no data showing benefit in this patient cohort. KDIGO recommends maintaining systolic and diastolic blood pressure below 140mmHg and 90mmHg respectively for patients in the A1 level of the Albuminuria-category. Smoking cessation is recommended. Control of DM is also a cornerstone of CKD-management. Most guidelines recommend glycemic control of about 7% HbA1c (8), although the current KDIGO guideline on DM in CKD recommends an individualization of the HbA1c goal. Appropriate individual targets may range from 6.5% to 8% HbA1c (16).

Patients should also be advised to avoid intake of unnecessary potential nephrotoxins. Most notably nonsteroidal antiinflammatory drugs (NSAIDs), unregulated herbal preparations, oral or rectal sodium phosphates and PPIs should be avoided, if possible. CKD patients also often require adjusted drug doses, since as renal clearance decreases, patients are at a higher risk of developing adverse drug reactions. Dietary recommendations for CKD-patients are controversial because studies have shown ambivalent results. Lower dietary acid and sodium intake may be advantageous. Patients should be monitored for renal anemia, mineral and bone disorder, electrolyte and acid-base-disturbances at certain intervals, depending on the CKD stage (8).

1.1.6 Erythropoiesis Stimulating Agents in CKD

Renal anemia is a common phenomenon in CKD patients. There is an association between renal anemia, heart failure, exercise tolerance and quality of life. That is why treating the anemia is a crucial part of CKD care (17).

Prevalence of renal anemia in the USA is estimated at 15.4% in all CKD patients. This value increases from 8.4% at CKD stage 1 to 53.4% at CKD stage 5 (18).

There are a multitude of causes for renal anemia, including erythropoietin deficiency, chronic inflammation, decreased lifespan of erythrocytes, increased bleeding, dietary restrictions and reduction of iron supply (19).

Several iron and erythropoietin agents are licensed to treat anemia in CKD patients. In general, the iron stores of patients should be replete, before starting ESA (Erythropoiesis stimulating agents) treatment. Oral or intravenous iron should be administered first, if ferritin levels are decreased. Only when this absolute iron deficiency is corrected, should ESA therapy be initiated. The goal for adult patients receiving ESA therapy is a hemoglobin between 100 and 120 g/L, but this remains controversial (17).

1.1.7 Frailty in CKD

Frailty is a state of vulnerability to physical influences. The cumulative decline and progressive degeneration of many physiological and psychological systems with increased age is the cause of frailty. The homeostatic reserves get continuously depleted, until even minor stressors or events cannot be compensated for accordingly (20).

Frailty is an extremely common phenomenon in the dialysis-dependent CKD population. A US study found the prevalence of frailty to be at 73% amongst patients starting dialysis. Even though frailty is typically associated with old age, 63% of patients under 40 years starting dialysis were considered as frail. Furthermore, frailty was found to be associated with increased mortality in these patients (21).

Reasons for the increased prevalence of frailty in CKD patients may include a reduced dietary intake, leading to sarcopenia, decline in physical activity, increase in pro-inflammatory cytokines, metabolic acidosis, testosterone deficiency, low vitamin D levels and cellular senescence (22).

1.1.8 Renal Replacement Therapy

There is much debate on the topic of timing the start of RRT. ESKD is often defined as a GFR <15mL/min per 1.73m^2 (23). An early initiation of dialysis treatment (residual GFR

of 15-16 mL/min per 1.73 m^2) seems to be associated with a 5.1% lower absolute risk of 5-year mortality, compared to later initiation (residual GFR of 6-7 mL/min per 1.73 m^2). The incidence of major adverse cardiovascular events was 3.3% lower for early initiation. Though early initiation postponed death only about 1.6 months, dialysis would have to be started approximately 4 years earlier. For many patients the reduction in mortality might not outweigh the burden of prolonged time on dialysis (24,25).

Renal transplantation is the gold standard for ESKD, as it completely reinstitutes the functions of the kidneys. Because of the limited availability of donor organs and the many contraindications for performing a transplant surgery, there is still a need for alternative methods of renal replacement (23).

1.1.8.1 Hemodialysis, Hemofiltration and Hemodiafiltration

In Hemodialysis (HD) the clearance of uremic toxins is achieved mainly by diffusion and convection across a semipermeable membrane. While HD is the most common form of RRT, hemofiltration (HF) is a RRT that mainly utilizes convection and a phenomenon called solvent drag, to filter out solutes and hemodiafiltration (HDF) is a combination of HD and HF, that aims to utilize the advantages of both methods of RRT (26). For all these modalities, a venous access needs to be established, either an arteriovenous shunt of graft or central venous access.

1.1.8.2 Peritoneal Dialysis

The peritoneal cavity, composed of a visceral and parietal layer of the peritoneum, is about the size of the body surface area. This space is used to perform Peritoneal Dialysis (PD) and is accessed via a catheter traversing the anterior abdominal wall, with the tip of the catheter laying in the pelvic region. A fluid is instilled into the peritoneal cavity, into which uremic solutes diffuse and excess fluid is osmotically pulled into. The osmotic pressure is most often created, using a hypertonic glucose solution as dialysate.

PD is performed by instilling the dialysate into the peritoneum and allowing it to dwell for a defined time-period, after which the dialysate is removed via the catheter. The PD fluid exchange can be performed manually by the patient three or four times a day, which is termed continuous ambulatory peritoneal dialysis (CAPD). Other methods of PD fluid exchange are performed by a cycler-machine, so called automated peritoneal dialysis (APD). The cycling may be done only at night or continuously throughout the day. Because of interindividual differences in peritoneal blood-flow, muscle mass and residual

kidney-function a patient-specific approach to dialysis intervals and “dwell times” is needed (27).

Studies have shown, that the overall outcome of PD is not inferior when compared to HD. PD seems to exhibit an improved short term prognosis and a comparable long term prognosis (28). A possible explanation for this is the superior preservation of residual renal function in PD. It is hypothesized that dehydration leads to intrarenal ischemia during HD, which negatively impacts renal function (29). Most studies have shown a better relative efficacy of PD in younger patients without other comorbidities (28).

The decision to initiate PD or HD should be made by an interdisciplinary team. An individualized approach is needed to reflect the needs, capabilities and motivation of individual patients. Advantages of PD include preservation of residual renal function, no need for anticoagulation, less risk of bloodstream infections and no need for a vascular access. In general patients on PD also experience less anemia. Another considerable advantage of PD is the compatibility with an active lifestyle and the possibility of home-based therapy – an important consideration during the COVID19 pandemic. PD patients need to exhibit a certain amount of independence, hygiene and functionality when undergoing PD. Disadvantages of PD include an increased risk of peritonitis and encapsulating peritoneal sclerosis. Obesity, hyperglycemia and hyperlipidemia are also possible complications, due to glucose-containing PD-solutions. Especially in elderly patients the risk of malnutrition should be assessed (30).

1.2 Pathophysiology of Immune Dysfunction

The abnormalities of the innate immune system associated with CKD immune dysfunction include a general expansion of monocytes, Toll-like-receptors (TLR), cytokines and an increased production of reactive oxygen species (ROS). This immune state is also characterized by spontaneous activation, granulation, decreased phagocytic capacity and increased apoptosis of granulocytes (31).

A disorder of the pattern-recognition receptor system has also been observed. Monocytes cultured in uremic serum display decreased endocytosis and an impaired maturation (32).

The bactericidal properties of neutrophil granulocytes are reduced in HD patients, when compared with healthy controls, but neutrophilic functionality increased after undergoing HD, which suggest, that some dialyzable substance may play a role in neutrophilic dysfunction (33).

The acquired immune system exhibits a reduction of the CD4/CD8 T-cell-ratio, a depletion of memory T-cells and a diffuse B-cell-lymphopenia. A reduction in the function of regulatory T-cells has also been observed (31).

Uremia also decreases the function of antigen presenting cells (APC). By altering costimulatory molecules, dendritic cells and macrophages are less able to present antigens. It is hypothesized, that a disorder in TLR expression or activity is responsible for the dysfunction of APCs (34).

Hypercytokinemia is a typical finding in uremia, probably due to reduced renal excretion and an increased production of cytokines. The increased production of cytokines is linked to uremic toxins, oxidative stress, volume overload and common comorbidities (15). Anti-inflammatory cytokines as IL-10, as well as pro-inflammatory cytokines such as Tumor necrosis factor α (TNF-α) (35) or Interleukin 6 (IL-6) (36) accumulate.

CKD-associated inflammation is the result of an increased activation of the innate immune system, whereas the depletion of T-cells, B-cells, dendritic cells and dysfunction of granulocytes is the reason for the immunosuppressive aspect of CKD (31).

1.2.1 Infectious Risks

The 2017 report of the United States Renal Data System shows that patients over the age of 65 with CKD exhibit a risk of hospitalization nearly three times higher than patients without CKD. CVD accounted for 23% of hospitalizations, while infections contributed 21% (37).

The major contributing factors to mortality in ESKD are CVD and infections. CVD accounts for up to 50% of deaths and infections account for another 20%. The mortality rate in ESKD patients is about 20% per year (15).

The risk of infectious complications is not only increased in ESKD, but also a mildly decreased GFR indicates a higher susceptibility to infectious diseases. On the one hand due to the aforementioned pathophysiologic changes in CKD, on the other hand due to increased exposure to the health care system and thus a higher exposure to infectious agents. Individuals with an eGFR of 30-59 mL/min have an approximately 50% higher chance of hospitalization because of infections. The risk for patients with an eGFR <30 mL/min per 1.73m^2 is about 2-3 times higher, compared to an eGFR> 60mL/min per 1.73m^2 (38).

Fewer data is available on the influence of the albuminuria category on infectious complications. Though one study found a 7% increase in risk for lower respiratory tract

infections and an almost 30% increase in risk for pneumonia and sepsis in patients with a history of proteinuria (39). An ACR of 30-299 mg/g and >300mg/g also indicates a 1.6 and 2.3 times higher risk of hospitalization because of infectious diseases (40).

ESKD patients also experience more severe courses of infections. The annual percentage mortality due to sepsis is 100 to 300 times higher in dialysis patients, compared with healthy controls. In patients who had received a kidney transplant, the percentage only increased 20-fold (41).

1.2.2 Immune Dysfunction in HD and PD

There seem to be differences in the immunologic profile, depending on the modality of RRT. For patients treated with PD, mainly peritonitis, bio-incompatible solutions and peritoneal catheters may be responsible for induction inflammation, T-cell activation and accelerated aging (42).

Studies have shown contradictory results, relating to whether PD patients exhibit increased levels of IL-6 or C-reactive-protein (CRP) (43,44).

Several studies have also found an inflammation burst due to HD-sessions. Inflammatory marker, such as Pentraxin-3 and lipoprotein-associated phospholipase A2 seem to increase after HD sessions (45,46).

A higher telomerase activity has been observed in PD patients, as compared with HD. This suggests a possible inhibition of telomerase activity, facilitated by HD (42). Cytokines known to be secreted during HD, such as IFN-α, may inhibit telomerase activity in hematopoietic cells (47). Shorter relative telomer length has been associated with increased mortality in CKD patients (48).

In addition to a patients age, the dialysis modality also plays an important role in influencing the proportions of T-cell subsets. A lower frequency of effector cells and a higher frequency of central memory cells among both CD4+ and CD8+ T cells were found in PD patients, compared with HD patients. These differences are hypothesized to exist, due to a different microenvironment in PD and HD patients.

Naïve T cells are a key player in the function of the adaptive immune system. Lower counts of these cells, may lead to poor vaccine responses and increased risk of infections in older primates (49).

Thus, maintaining naïve T cells may be an important goal in ESKD patients. Hemodialysis treatment may cause this accelerated aging of T-cells through decreasing the ability of T cell proliferation, increasing T cell apoptosis and decreasing thymic output of T-cells (50–

52). T cell subsets in HD patients showed an increased tendency to progress from naïve to effector cells, than in PD patients (53).

1.3 Preventing Complications in CKD

As explained above, CKD patients are at an increased risk of complications from infectious diseases, compared to the general population. Thus, methods of prevention are particularly important in this vulnerable cohort. In addition to the standard vaccinations, KDIGO recommends an annual influenza vaccine and the polyvalent pneumococcus vaccine every five years for all CKD patients. Furthermore the Hepatitis B vaccine plays a very important role in CKD and because of that, the response to the vaccine should be serologically confirmed (54).

In 2006 a cross sectional US-study found vaccination rates of 76% for influenza, 73% for Hepatitis B and 44% for Pneumococcus among dialysis patients. As vaccinations are a relatively cheap method of prevention, the need to increase education about and access to these vaccines is well known (55).

It is known from previous studies, that patients with CKD are only able to mount a limited antibody response to other vaccines. They develop antibodies more slowly and reach lower peak values than control groups. This translates to an inferior protection against the diseases and may warrant a modified vaccination regimen, where higher doses or an increased amount of shots are necessary to achieve acceptable immunity (56,57).

1.3.1 Influenza-Vaccination

The hospitalization rate in the general population during the 2009 H1N1 Influenza pandemic was estimated to be around 5-7%. Most healthy people recovered quickly, though 10% of hospitalized patients required intensive care. The overall mortality rate was estimated at 0.2-0.5%. Patients receiving chronic dialysis seem to have had an at least 10-fold higher mortality rate than the general population, making CKD a risk factor for severe courses of illness and warranting research into preventive methods (58).

Themost commonly used trivalent influenza vaccine contains three viral strain antigens: Type A(H1N1), Type A(H3N2) and Type B. The exact composition of the vaccine is altered every year, according to the current epidemiologic situation of influenza (14).

A study from Antonen et al. demonstrated, that patients receiving dialysis exhibited lower antibody titer increases than general population, but an almost comparable percentage

reached a seroprotective antibody level, defined as hemagglutination inhibition (HI) titers ≥40 hemagglutination assay (HA) units, 5 weeks after inoculation (59).

Other studies have found conflicting results, showing an insufficient serologic response, in which only 40% of HD patients exhibited protective levels of antibodies, compared to 65% in control groups. The response rate to the H1 antigen was about half as good in HD patients compared to a healthy control group, one month after vaccination (60).

During the 2009 Influenza pandemic Labriola et al. studied the efficacy of a monovalent adjuvanted influenza A/California/2009 (H1N1) vaccine, where only 64% of HD patients developed seroconversion, compared to a conversion rate of 94% in control groups (56).

Chang et al. evaluated the efficacy of a standard single 15 µg-dose of a non-adjuvanted monovalent pH1N1/09 vaccine, also during the 2009 Influenza pandemic. The serconversion rate of dialysis patients in this study was only 23.4% in adults and 25.4% in the elderly, while healthy control groups exhibited a seroconversion rate of 92.5% in adults and 73.6% in the elderly (61).

Some potential ways to increase Influenza vaccine efficacy have been suggested, for example higher vaccine doses, second annual booster doses or topical imiquimod.

One study in 2014 found, that a higher vaccine dose of 60 µg per strain, induced a significantly higher antibody titer concentration and provided better protection against laboratory confirmed influenza in older adults without dialysis (62).

A meta-analysis concluded, that a booster dose of the Influenza vaccine did not significantly improve immunogenicity in HD patients (63).

Another 2014 randomized controlled trial by Hung et al. found that pretreatment with a topical 5% 250 mg imiquimod ointment, followed by intradermal vaccination significantly improved, accelerated and prolonged antibody response in adults (64).

1.3.2 Hepatitis-B-Vaccination

Hemodialysis patients suffer an increased risk of contracting Hepatitis B, via contaminated surfaces and objects and in the past often also via contaminated blood transfusions. Transmission occurs via percutaneous or permucosal contact with contaminated blood or other fluids containing blood (65).

The Hepatitis B Virus (HBV) is relatively stable and may survive for seven days on surfaces at room temperature (66). Because of the dysfunctional immune system in ESKD, infected individuals may be more likely to develop chronic Hepatitis B (67).

Due to these circumstances, dialysis wards were experiencing a relatively high prevalence of HBV. The prevalence has greatly decreased through the implementation of HBV vaccination programs, ESA, improvement in blood product control, adherence to hygiene programs and routine testing for HBV (54).

In 1974 the incidence of new HBV infections in HD patients in the USA was 6.2%. The incidence of chronic HBV declined from 7.8% in 1976 to 0.9% by 1999 (65,68).

In CKD patients, altered vaccination regimen are suggested in order to increase the seroprotection rate. Forty μg are administered at the time points 0, 1 and 6 months, instead of the usual 20μg (69).

A study in patients with ESKD treated with HD or CAPD found, that after administering the recombinant hepatitis B vaccine (Engerix B, GlaxoSmithKline Biologicals, London, UK) 40 μg at 0,1,2 and 3 months, 64% achieved seroconversion (anti-HBs titer of >10 IU/l), but only 31% reached an anti-HBs titer of >100 IU/l. Of the remaining patients, 57% achieved seroconversion after the first booster dose and another 40% after a second booster dose. Seroprotection rates also decreased relatively quickly, as after a mean of 16 months 62% had a significant reduction in their titers and 26% lost all detectable antibodies. The response rate was relatively similar between HD, PD and predialytic patients (70).

Another study found seroconversion rates after primary vaccination of 87% in HD patients. About 28% of those were weak responders and 59% high responders. After a one year follow-up 18.2% of responders lost their antibodies (71).

Better results may be achieved by using the adjuvanted HB-AS04 (FendrixTM, GlaxoSmithKline Biologicals, London, UK) vaccine. In one study, after the primary vaccination course, the adjuvanted vaccine was able to elicit seroprotection in 91% compared to 84% in the standard vaccine. After 36 months seroprotection was still present in 73% compared to 52% of patients. Significantly fewer people who had received the adjuvanted vaccine required booster shots (57).

Another proposed strategy to improve seroconversion rates is intradermal application of the vaccine, which is supposed to directly stimulate dendritic cells, promoting antigen presentation. A systematic review of 204 dialysis patients found, that intradermal application significantly increased seroconversion rates, as compared to intramuscular application (72).

In summary, the inferior response of CKD patients is thought to be caused by patient factors such as age, gender, obesity, active HCV and HIV infection, blood transfusion history, interleukin genotypes, possession of the major histocompatibility complex

haplotype HLA-B8, SCOI, DR3, insufficient nutritional status and vitamin D deficiency (73).

It appears, that vaccination in the earlier stages of CKD is associated with a better seroconversion rate. Therefore it is recommended, that HBV vaccination is administered early in CKD patients, preferably before initiation of RRT (74).

1.3.3 SARS-CoV-2-Vaccination

Advanced CKD is one of the conditions, that carries the highest risk for COVID19 related mortality. For example, age and eGFR are the two most impactful factors for COVID-mortality in diabetic patients (75).

Additionally, before the introduction of COVID19-vaccines, patients on RRT seemed to suffer from an about 4-fold increase in COVID19-incidence, as well as a 11-fold increase in COVID related mortality. This is thought to be a result of heightened exposure, due to frequent hospital-visits and the fact, that dialysis-patients often suffer from numerous comorbidities (76).

Although the need for vaccinations in these vulnerable groups is self-evident, CKD-patients have been excluded in all but one of the extensive initial studies. Thus, only limited data has been available for this high-risk group (77).

A meta-analysis about immunogenicity of the newly developed Covid-19-vaccines included a total of 4917 patients vaccinated with four different vaccines: JNJ-78436735 [Janssen, Beerse, Belgium], mRNA-1273 [Moderna, Cambridge, USA], BNT162b2 [Pfizer, New York City, USA and BioNTech, Mainz, Germany], and AZD1222 [AstraZeneca, Cambridge, UK]. Patients were receiving either chronic HD or PD treatment. The meta-analysis concluded an overall immunogenicity of 86% after full vaccination with two doses. Immunogenicity after the first and second shot was significantly lower in RRT patients, compared to controls. Response rates further increased after a third booster shot to 94%. DM was significantly correlated with a lower immune response rate (78).

Another meta-analysis comprising 1337 HD patients who received the Pfizer-Biontech-vaccine found humoral response rates after complete vaccination of 87% after one week, 89% after two weeks, 93% after three weeks and 89% after four weeks among HD patients. The response rate of the control groups at the same intervals was 100%, 100%, 100% and 100% respectively. The same study also looked at cellular response and found

rates of 63% and 86%, three and four weeks after completion in the HD group. The control groups exhibited response rates of 93% and 96%, two and four weeks after completion of the vaccine regimen. Cellular immunity was defined as development of spike-stimulated antigen-reactive T-helper cells (79).

The development of SARS-CoV-2-specific T-cells is an essential part of the immune response. These specific T-cells may facilitate viral clearance, may prevent infection without seroconversion, provide immunological memory and mediate recognition of viral particles. These cells are also elicited through vaccination, where they may offer some level of protection from severe courses and death. While antibody levels are relatively easy to detect, cellular response remains more costly and difficult to study (80).

An early cytotoxic $CD^{8}+$ T-cell response, which is typically observed in the first 7 days of symptoms, is associated with better viral clearance and a less severe course of infection. Patients with severe disease exhibit a delayed cellular response and experience a higher degree of systemic inflammation at symptom onset (81).

1.3.3.1 Comparability of SARS-CoV-2 Antibody Assays

The SARS-CoV-2 virus exhibits both anti-spike and anti-nucleocapsid epitopes, which are both targeted by antibody production after an infection. After inoculation with a spike-based-vaccine, only the antibodies against the spike-epitope are present, which allows distinguishing natural immunity from a vaccine response.

A variety of assays to test for anti-spike-antibodies are available. Although these assays show a high sensitivity to vaccination and a high degree of correlation amongst each other (82), the absolute values of antibody titers vary greatly, depending on the assay used. A strategy to combat these discrepancies is the conversion into binding antibody units per milliliter (BAU/mL), although this method does not yield directly interchangeable results (83). The WHO international standard for SARS-CoV-2 immunoglobulin was introduced to convert the results of different assays to BAU/mL, using different conversion factors for the results of the individual assays. The conversion factor for the Roche (Roche Diagnostics, Rotkreuz, Switzerland) Elecsys SARS-CoV-2 S assay used in this study is *1, which is why AU/mL and BAU/mL may be used interchangeably. For the Roche assay a cut-off for reactivity of 0.8 BAU/mL is used to indicate the presence of any amount of antibody response. The manufacturer recommends a cut-off of 15 BAU/mL for seroconversion (84).

Tests based on other principles are also used occasionally. For example, the surrogate neutralizing antibodies (SNA) test determines the inhibition of serum antibodies on the spike protein-angiotensin Converting Enzyme 2 (ACE2) binding ability. It is determined by a plate-based SARS-CoV-2 surrogate virus neutralizing assay (Medac, Wedel, Germany). The test achieves 99.9% specificity and 95–100% sensitivity. The SNA test corresponded with the SARS-CoV-2 inhibition capacity in virus neutralization tests (85).

1.3.3.2 SARS-CoV-2-Vaccination in Peritoneal Dialysis

Tylick et al. described an 86% seroconversion rate for 21 PD patients after the first dose of the Biontech-Pfizer vaccine, compared with 57% in HD patients. After the second dose PD and HD reached a 100% and 97% rate respectively. PD patients were able to produce a median of 93 BAU/mL of anti-spike IgG antibodies after the first dose and a median of 1623 BAU/mL after the second dose. The threshold for seroconversion was set at 15 BAU/mL (86).

Another study evaluated the humoral response of 34 PD patients treated with the Moderna vaccine. Here 62.5% of patients seroconverted after the first dose, while another 34.38% seroconverted after the second dose. One patient did not show a humoral response at all (87).

In another cohort of 41 PD patients, 54% had humoral response after the first dose and 95% after the second dose. The threshold was defined as SNA >1. HD patients exhibited a humoral response of 35% and 85% after doses one and two. PD patients showed no significant difference in SNA to healthy controls after the first vaccination, but had lower SNA levels after the second dose. After a twelve week follow-up, seropositivity decreased to 88% in PD and 77% in HD patients (85).

25 PD patients showed higher post-vaccination IgG titers, when compared with HD patients. PD titers after the first dose were 5.44 AU/ml, while HD patients exhibited titers of 0.99 AU/ml and after the second dose PD and HD patients had titers of 170.43 AU/ml and 65.81 AU/ml respectively. There were no non-responders in the PD group, but 14% of HD patients showed no response. However, PD was not an independent factor for a better response, instead age and comorbidity burden influenced the results (88).

A long-term multicenter study found, that 81.3% of 64 PD patients and 78.8% of 118 HD patients still had anti-spike titers >50 BAU/mL six months after completing vaccination. Mean antibody levels were not influenced by dialysis modality, but they inversely correlated with age in the HD cohort. The age-correlation was not observed in the PD

group (89).

Another study of 58 PD and 232 HD patients found no significant difference in humoral or T-cell response after treatment with mRNA-based COVID-19 vaccines. PD patients experienced a higher rate of side-effects though (90).

1.3.4 Characteristics Influencing Serologic Response

A prospective, multicenter study, in 543 HD patients vaccinated with an mRNA COVID-19 vaccine, conducted a multivariate analysis on which characteristics may predict immune response. It found, that immunosuppressive drugs, low serum albumin, lymphocyte count, hepatitis B vaccine nonresponder status and dialysis vintage are independent risk factors for an inferior response (91).

Another study performed with 205 HD patients was able to identify an association between greater age and immunosuppressive medication with lower antibody titers (92).

In 122 hemodialysis and 23 PD patients younger age, BMI <30, normal albumin level and reduced intravenous iron doses were found to be predictive of a better serologic response following mRNA vaccination (93).

2 Methods

2.1 Study Design

This study has been designed as a retrospective and non-invasive project. The included patients received their scheduled COVID-19-vaccination as part of routine care in spring of 2021. At the time, the participants were vaccinated with the Moderna vaccine, which has been approved by the European Medicines Agency (EMA). Patients underwent the recommended vaccination interval of 28 days between the first two shots.

Blood samples of the patients were drawn as part of their routine care, during control visits for their PD at the PD clinic of the Medical University of Graz. Routine hematology, clinical chemistry tests and titers of SARS-CoV-2 spike and nucleocapsid antibodies were performed with the samples and samples were sent for storage to the Biobank of the Medical University of Graz.

Nucleocapsid antibodies were evaluated, to determine whether a previous infection with SARS-CoV-2 had taken place. Individuals with positive Nucleocapsid titers were excluded from the analysis.

The Biobank in Graz is one of the biggest storage facilities for clinical materials in the world. About 20 million samples of medical fluids and tissue are stored there for research and scientific purposes (94).

The samples were collected at various times, namely before first dose of the vaccine, after first and second dose of the vaccine and as a follow-up in early September of 2021. All patients previously signed informed consent, for storage of their blood samples at the Biobank at the Medical university of Graz.

As primary endpoint the serologic response at 28 days after the first vaccination was chosen. The cutoff for a positive response is determined at >15 arbitrary units per mL (AU/mL), which corresponds to 15 BAU/mL.

As secondary endpoints, geometric mean antibody concentration (GMC), geometric mean fold rise (GMFR) and percentage of subjects with a ≥ 4-fold rise in antibody concentration were considered.

We assessed baseline characteristics such as age, sex, BMI, smoking-status, dialysis-vintage, dialysis-modality, comorbidities, underlying kidney-disease, previous COVID-infection, co-medication, HBV-vaccine-response, current influenza-vaccination and a frailty score via retrospective chart review. Influences of these parameters on serologic response, were determined by performing an explorative analysis.

The collection of data and its subsequent processing was performed in accordance with the current General Data Protection Regulation (GDPR) Regulations of the European Union (EU). Data Management was the responsibility of the Division of Nephrology, Department of Internal Medicine, Medical University of Graz. The participating patients were assigned a number for identification purposes. The participating patients and the clinical samples, which were obtained from the biobank, were identified using these identification numbers. The processed Data and the following statistical analyses were done anonymously. Measures such as deletion or encryption were used whenever possible, in order to protect the identity of participating patients in all presentations and publications as required by local and national requirements.

Ethical approval of the study was obtained from the ethics committee of the Medical university of Graz (EK-Nr: 33-391 ex 20/21).

2.2 Study Population

All PD-patients having received a routine COVID-19 vaccination with the Moderna vaccine were eligible for screening. All participants were screened and selected, using a

retrospective chart review of the documentation system at the PD clinic of the Division of Nephrology at the Medical University of Graz.

Inclusion criteria for the participation in the study included being 18 to 90 years of age, suffering from ESKD and undergoing peritoneal dialysis and being scheduled to receive an approved SARS-CoV-2 vaccine as part of their routinely performed care. Patients must have signed informed consent for the Bio-Bank storage. Only patients fulfilling all inclusion criteria were included.

2.3 Patient Information

All patient information has been acquired through retrospective chart review. The information was entered into the Research Electronic Data Capture (REDCap) program. REDCap is an online, browser-based, Electronic Data Capture software, designed to create databases for clinical research.

The captured general datapoints for each patient included Record ID, Name, Gender (male, female, other), date of birth, height, weight, Body Mass Index (BMI) and Age at first COVID-vaccination. Patients were also characterized by their Clinical Frailty Score (CFS) (95). The CFS is a clinical and judgement-based score, that aims to combine comorbidities, function and cognition into a scale from 1 to 9. The steps of the CFS are Very Fit (1), Fit (2), Managing Well (3), Living with very mild Frailty (4), Living with mild Frailty (5), living with moderate Frailty (6), Living with severe Frailty (7), Living with very severe Frailty (8) and Terminally ill (9) (95). In this study frailty was defined as a CFS ≥ 5.

The starting date of RRT and the Dialysis vintage in days (first day of RRT to first vaccination) were recorded. To assess dialysis quality, the last known spKt/V (single-pool kinetic modeling of Kt/V) was also recorded. The spKt/V is a dimensionless marker, that correlates with the removal of small molecules by a single session of dialysis. K is the urea clearance during dialysis, t represents the time of treatment and V is the patient specific volume of urea distribution (96).

Because the response to the COVD-vaccines, may be similar in other vaccinations, we also recorded the previous serologic response to the HBV vaccine. HBV-vaccine-response was characterized into non-responder (<10 IE/L), low-responder (10-99 IE/L) and normal-responder (>100 IE/L) status.

We also recorded, if the patient had received their Influenza shot in the 2020/2021 season and if a previous SARS-CoV-2 infection had been present.

For comorbidities, we recorded if the patients had had any of the following diagnoses in their doctor's notes: hypertension, coronary heart disease, history of myocardial infarction, stroke/cerebrovascular disorder, peripheral vascular disease, diabetes mellitus, history of liver disease, COPD, history of malignancy, thyroid disorder, anemia, heart failure or nicotine abuse.

Hypertension, coronary heart disease, history of myocardial infarction, stroke/cerebrovascular disorder and peripheral vascular disease were also grouped into one category of cardiovascular disease.

Furthermore, the underlying kidney disease of the ESKD was recorded and categorized into: diabetic nephropathy, hypertensive kidney disease, glomerulonephritis, autosomal dominant polycystic kidney disease (ADPKD) and other or unknown primary kidney disease.

Any form of Vitamin D substitution, use of erythropoiesis-stimulating agents (ESAs), immunosuppressive medications or conditions with the exception of DM were also recorded.

Also, the dates of the first and second dose of the vaccination, dates of collection of blood-samples before and after the vaccinations and date of the follow-up titer were recorded. The level of Spike-Antibodies and Nucleocapsid-Antibodies gathered from the blood-samples were also recorded.

2.4 Antibody Assays

We used the Elecsys® Anti-SARS-CoV-2 Assay, which detects antibodies against the Nucleocapsid antigen (N), and the Elecsys® Anti-SARS-CoV-2 S Assay, which detects antibodies against the receptor-binding-domain of the Spike-protein of the virus. After an infection the immune system produces both Anti-Spike and Anti-Nucleocapsid-Antibodies, as both epitopes are exhibited on the natural COVID-Virus. After vaccination with an mRNA- or other spike-based-vaccines however, only the antibody against the spike-protein will be present. This makes it possible to distinguish natural immunity through infection from immunity acquired through vaccination.

The Elecsys® Anti-SARS-CoV-2 (N-Assay) also correlates with the Virus Neutralization test. The two tests had a 74% positive and 98% negative match. The correlation to the GeneScript®cPass™ Test was even better, at a 96% positive and 98% negative match (97). The Elecsys® Anti-SARS-CoV-2 S Assay correlates very well with the Surrogate Virus Neutralization Assay. A cut-off of 0.8 U/mL exhibits a positive percent agreement (PPA)

of 99.19% and a positive predictive value (PPV) of 96.27%. For this study, we used a higher cut-off of 15U/mL, which exhibits a PPA of 88.97% and a PPV of 99.10% (98).
Sensitivity and Specificity for the Elecsys® Anti-SARS-CoV-2 (N-Assay) was found to be 99.46% and 99.80% by internal Roche data and 98.2% and 99.85% by an external study. Sensitivity and Specificity for the Elecsys® Anti-SARS-CoV-2 S Assay was found to be 98.81% and 99.98% by internal Roche data and 97.92% and 99.95% by an external study. These sensitivity and specificity studies were done ≥14 days after a positive SARS-CoV-2 PCR-test (97,99). Additionally, we utilized a higher cut-off of 2000 AU/mL. According to an observational study by Meschi et al. (100), an antibody response to mRNA vaccines over 2000 AU/mL highly correlates with a virus microneutralization test titer ≥1:80. This cut-off is supposed to represent a more robust surrogate marker of a protective response.

2.5 Statistics

The primary endpoint for this study was chosen to be a seroresponse ≥15 AU/mL, measured by the Elecsys® Anti-SARS-CoV-2 S Assay. As secondary endpoints, the Geometric mean antibody concentration (GMC), Geometric mean fold rise (GMFR), Percentages of subjects with a ≥ 4-fold rise in antibody concentration and Percentages of subjects with SARS-CoV-2 infections after vaccination were chosen.
Geometric means are used when dealing with antibody titers, as the values do not follow linear distribution. Thus, a logarithmic scale is used in geometric means, to offer a better representation of the results. Immunologic data, such as titers, tends to exhibit an asymmetrical distribution with many larger values. Because of this, statistical analysis based on a normal distribution is not applicable to these data sets. This can be addressed by logarithmically transforming the data, which results in a normal distribution for these values. Data transformed in this way is marked as geometric mean concentration or as geometric mean ratio (101).
Exploratory analysis was performed to investigate associations between serological response and baseline parameters, age strata, frailty score and HBV responder-status.
The continuous and binary endpoints are presented and described with descriptive statistics for the different timepoints of vaccination. For the binary parameters, the percentages with two-sided exact 95% confidence intervals (CIs) were calculated and for the continuous parameters descriptive parameters are presented. Geometric mean antibody concentration (GMC) and Geometric mean rise (GMR) are presented with two-sided 95% CIs.

For categorical and continuous parameters, Fishers-exact test and unpaired t-test or Mann-Whitney-U test were used. The goal was to investigate associations between baseline parameters with the serological response (positive or negative at day 28 after first dose) to the SARS-CoV-2 vaccination.

Mixed models were used, to explore any associations between antibody concentrations at different timepoints and baseline parameters. These timepoints were baseline, 28 days after first vaccine, 28 days after the second vaccine and about 180 days after the second vaccine (follow-up). The mixed models included the log10 concentrations as outcome and the timepoints, the baseline parameter and time x parameter interaction as fixed effects.

The geometric mean ratios (GMR) with 95% CIs were calculated using back transformation of the mixed model estimates.

For the statistical analysis the program SAS, version 9.4 (Cary, NC, USA), was used. The cut-off for statistical significance of the p-value was set at <0.05.

3 Results

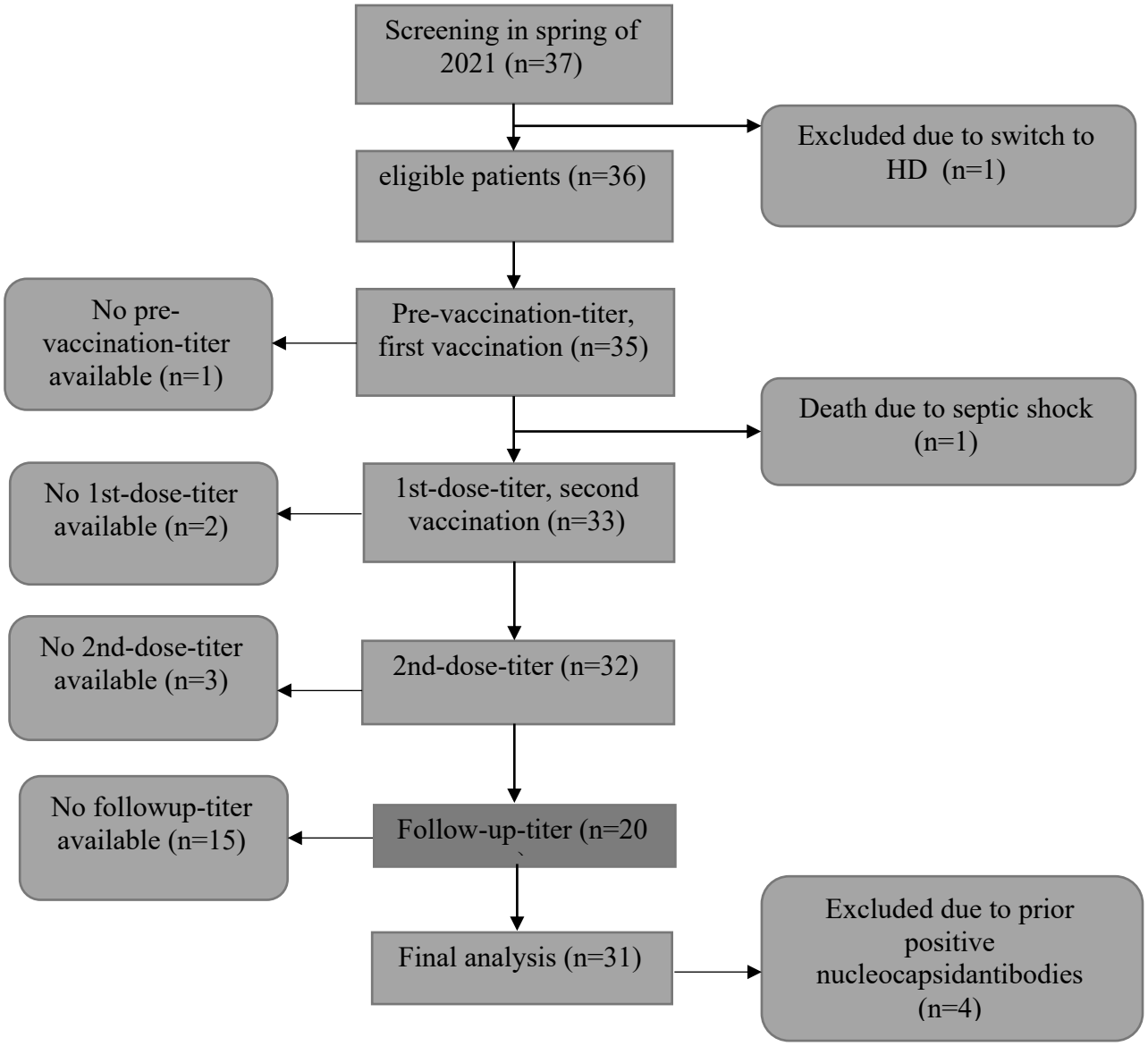
3.1 Population

Thirty-seven patients were selected in spring of 2021, one of which was excluded before the study began, due to a switch in dialysis modality from PD to HD. Of the 36 included patients, 35 pre-vaccination-blood-samples were obtained. For one patient, no pre-vaccination-titer was available. Between the first and second vaccination one patient died due to septic shock (1).

Out of the remaining 35 patients, we were able to obtain blood-samples in 33 patients, 28 days after the first vaccination. No post-first-vaccine titer was available in two patients. The titer about 28 days after the second shot, was available in 32 and unavailable in three patients (1).

The follow-up titer in September was obtained in 20 patients. The 15 patients, who had no follow-up titer available, had received their third dose of the vaccine, before blood-samples could be drawn. Four of the included patients, had had positive Nucleocapsid antibodies, indicating a prior infection with SARS-CoV-2. These patients were removed from the final explorative analysis, leaving a total of 31 patients in the final study, see figure 1 (1).

Figure 1: Flowchart of patient inclusion



3.2 Baseline Characteristics

Among the 31 PD-patients included in the final analysis, the mean age was 62,5 (standard deviation (SD) of 12.6) years. Of all patients, 77% were male and the median dialysis vintage was 839 days (span of 82 to 4218 days). The mean BMI was 26 (SD 5.5) kg/m^2. (1).

Fifteen (58%) patients were undergoing CAPD, 12 (39%) APD and 4 (13%) IPD. Eleven (36%) patients had previously responded normally to the HBV vaccine, while 20 (65%) were low-responders or HBV-vaccine non-responder (1).

Using the CFS, 5 patients (16%) were considered frail with a CFS ≥ 5, while 26 (84%) were not considered frail. Mean frailty score was 3.4 (SD 1.8) (1).

Of all 31 patients, 30 (97%) suffered from some form of cardiovascular disease, 8 (26.0%) from DM, 3 (10%) had a history of liver disease, 5 (16%) from chronic obstructive pulmonary disease (COPD), 7 (23%) had a history of malignancy, 3 (10%) from a thyroid disorder, 9 (29%) from any form of anemia and 4 (13%) were active smokers (1).

Considering the underlying kidney disease, 6 (19%) patients had diabetic nephropathy, 10 (32%) had hypertensive kidney disease, 7 (23%) had a form of glomerulonephritis, 4 (13%) had ADPKD and 8 (26%) had other or unknown kidney diseases. Some patients had more than one disease responsible for their ESKD (1).

Eight (26%) patients had some kind of immunosuppressive medication. Four patients were on tacrolimus and four patients were treated with corticosteroids (1).

Twenty-four (77%) patients received Vitamin-D substitution and 21 (68%) were on ESAs.

Thirty-five vaccine recipients were available to serology after the first dose, 33 after the second dose and 20 individuals for a follow-up-titer (1).

Four patients (11.1%) had a positive Nucleocapsid-antibody at baseline, indicating previous contact with SARS-CoV-2. The four candidates with positive Nucleocapsid-antibodies were excluded from the final exploratory analysis (1).

The baseline characteristics of the 31 patients included in the final analysis are provided in table 1.

Table 1. Baseline characteristics

Characteristics	**All patients** (n=31)
Gender (n, %)	
Male	24 (77.4%)
Female	7 (22.6%)
Age (years) (mean±SD)	62.5 (± 12.6)
<60 years (n, %)	12 (38.7%)
≥60 years (n, %)	19 (61.3%)
BMI (kg/m²) (mean±SD)	26.3 (± 5.5)
Type of PD (n, %)	
APD	12 (38.7%)
CAPD	15 (58.4%)

IPD	4 (12.9%)
Dialysis vintage (days) (median, min and max)	839 (82, 4218)
HBV response (n, %)	
Non or low responder	20 (64.5%)
Normal responder	11 (35.5%)
Frailty (n, %)	
Yes	5 (16.1%)
No	26 (83.9%)
Mean Score (mean±SD)	3.4 (±1.8)
Comorbidities (n, %)	
Cardiovascular disease	30 (96.8%)
Diabetes mellitus	8 (25.8%)
History of liver disease	3 (9.7%)
COPD	5 (16.1%)
History of malignancy	7 (22.6%)
Thyroid disorder	3 (9.7%)
Anemia	9 (29.0%)
Smoking	4 (12.9%)
Underlying renal disease (n, %)	
Diabetic kidney disease	6 (19.4%)
Hypertensive/Vascular	10 (32.3%)
Glomerulonephritis	7 (22.6%)
ADPKD	4 (12.9%)
Other/Unknown	8 (25.8%)
Concomitant medication (n, %)	
Immunosuppression	8 (25.8%)
Tacrolimus	4 (50.0%)
Corticosteroid	4 (50.0%)
Vitamin D Treatment	24 (77.4%)
ESA treatment	21 (67.7%)
Baseline spKt/V (n, %)	
≤1.7	7 (33.3%)
>1.7	14 (66.7%)
Residual renal function (mL/d) median (interquartile range)	1000.0 (200.0, 2500.0)

Frailty was defined as a Clinical Frailty score = or greater than 5, HBV Responder status was defined as following: HBV responder-status (non-responder: HBV titer <10 IE/L, low-responder: HBV titer 10-99 IE/L, responder: anti-HBs titer >100IE/L); BMI Body Mass Index, APD automated peritoneal dialysis, CAPD continuous ambulatory peritoneal dialysis, IPD intermittent peritoneal dialysis, COPD chronic obstructive pulmonary disease, ADPKD autosomal dominant polycystic kidney disease, ESA treatment = treatment with erythropoiesis stimulating agents. P-values were obtained via Fishers exact test, t-test or Mann-Whitney-U test

3.3 Serologic Response

Significant differences in baseline characteristics between responders (i.e. >15 AU/mL after 28 days) and non-responders were, that patients treated with ESAs showed an inferior response (p= 0.021) and patients with better residual renal function showed a better response (p=0.019) (1). Results of baseline characteristic, stratified by serologic response (after 28 days), are shown in Table 2.

Table 2. Baseline characteristics stratified by serologic response

Characteristics	**All patients** (n=31)	**Response after 1st dose** < 15 AU/mL (n=19)	≥ 15 AU/mL (n=12)	**P value**
Gender (n, %)				
Male	24 (77.4%)	14 (73.7%)	10 (83.3%)	0.676
Female	7 (22.6%)	5 (26.3%)	2 (16.7%)	
Age (years) (mean±SD)	62.5 (± 12.6)	63.1 (± 10.9)	61.8 (±15.4)	0.801
<60 years (n, %)	12 (38.7%)	12 (63.2%)	7 (58.3%)	1.000
≥60 years (n, %)	19 (61.3%)			
BMI (kg/m²) (mean±SD)	26.3 (± 5.5)	25.0 (±5.4)	28.5 (±5.3)	0.084
Type of PD (n, %)				
APD	12 (38.7%)	8 (42.1%)	4 (33.3%)	0.681
CAPD	15 (58.4%)	8 (42.1%)	7 (58.3%)	
IPD	4 (12.9%)	3 (15.8%)	1 (8.3%)	
Dialysis vintage (days) (median, min and max)	839 (82, 4218)	860 (146, 3368)	694 (82, 4218)	0.887
HBV response (n, %)				
Non or low responder	20 (64.5%)	14 (73.7%)	6 (50%)	0.255
Normal responder	11 (35.5%)	5 (26.3%)	6 (50%)	
Frailty (n, %)				
Yes	5 (16.1%)	4 (21.1%)	1 (8.3%)	0.624
No	26 (83.9%)	15 (78.9%)	11 (91.7%)	
Mean Score	3.4 (±1.8)	3.6 (±2.0)	3.1 (±1.5)	

(mean±SD)				
Comorbidities (n, %)				
Cardiovascular disease	30 (96.8%)	18 (94.7%)	12 (100.0%)	1.000
Diabetes mellitus	8 (25.8%)	4 (21.1%)	4 (33.3%)	0.676
History of liver disease	3 (9.7%)	3 (15.8%)	0 (0%)	0.265
COPD	5 (16.1%)	3 (15.8%)	2 (16.7%)	1.000
History of malignancy	7 (22.6%)	5 (26.3%)	2 (16.7%)	0.676
Thyroid disorder	3 (9.7%)	1 (5.3%)	2 (16.7%)	0.543
Anemia	9 (29.0%)	5 (26.3%)	4 (33.3%)	0.704
Smoking	4 (12.9%)	2 (10.5%)	2 (16.7%)	0.630
Underlying renal disease (n, %)	6 (19.4%)	4 (21.1%)	2 (16.7%)	1.000
Diabetic kidney disease	10 (32.3%)	5 (26.3%)	5 (41.7%)	0.447
Hypertensive/Vascular	7 (22.6%)	5 (26.3%)	2 (16.7%)	0.676
Glomerulonephritis	4 (12.9%)	2 (10.5%)	2 (16.7%)	0.630
ADPKD	8 (25.8%)	5 (26.3%)	3 (25.0%)	1.000
Other/Unknown				
Concomitant medication (n, %)	8 (25.8%)	6 (31.6%)	2 (16.7%)	0.433
Immunosuppression	4 (50.0%)	3 (50.0%)	1 (50.0%)	
Tacrolimus	4 (50.0%)	3 (50.0%)	1 (50.0%)	
Corticosteroid	24 (77.4%)	16 (84.2%)	8 (66.7%)	0.384
Vitamin D Treatment	21 (67.7%)	16 (84.2%)	5 (41.7%)	**0.021**
ESA treatment				
Baseline spKt/V (n, %)				
≤1.7	7 (33.3%)	6 (50.0%)	1 (11.1%)	0.159
>1.7	14 (66.7%)	6 (50.0%)	8 (88.9%)	
Median residual renal function (mL/d) median (interquartile range)	1000.0 (200.0, 2500.0)	800.0 (500.0,1500.0)	1500.0 (1000.0,2000.0)	**0.019**

Frailty was defined as a Clinical Frailty score = or greater than 5, HBV Responder status was defined as following: HBV responder-status (non-responder: HBV titer <10 IE/L, low-responder: HBV titer 10-99 IE/L,

responder: anti-HBs titer >100IE/L); BMI Body Mass Index, APD automated peritoneal dialysis, CAPD continuous ambulatory peritoneal dialysis, IPD intermittent peritoneal dialysis, COPD chronic obstructive pulmonary disease, ADPKD autosomal dominant polycystic kidney disease, ESA treatment = treatment with erythropoiesis stimulating agents. P-values were obtained via Fishers exact test, t-test or Mann-Whitney-U test

Four weeks after the first vaccination dose 25 (80.6%) patients had reacted and mounted any antibody response (>0.8 AU/mL) to the vaccine, while 6 (19.4%) patients had no serologic response. Twenty-eight (93.3%) patients were able to react and produce antibodies 28 days after the second dose and 18 (94.7%) patients still had reactivity at follow-up (mean 202.5 days ± 6.2 days; n=19) (1).

If the cut-off was set at ≥15 AU/mL, 12 (38.7%) patients exhibited serologic response after 28 days, while 28 (93.3%) patients showed a response 28 days after the second dose. Eighteen (94.7%) patients still had an anti-spike-protein-titer ≥15 AU/mL at follow-up.

Twenty-two (71%) patients experienced an equal or greater than 4-fold rise in antibody concentrations after 28 days. Twenty-eight patients (93.3%) experienced an equal or greater than 4-fold rise 28 days after the second shot. Eighteen (94.7%) maintained their 4-fold-rise at follow-up (1).

Using a higher cut-off of >2000 AU/mL, zero patients had protection after their first shot. Twelve (40%) patients were able to reach this cut-off, after their second shot, but they all were below the protective threshold at follow-up (1).

Median Anti-SARS-CoV-2 S levels (interquartile range) after the first dose, were 5.4 AU/mL (0.9, 82.3) and 1188.5 AU/mL (316.0, 2500.0) after the second dose. At follow-up mean antibody concentrations decreased to 200.0 AU/mL (62.2. 560.0) (1). Results are visually presented in Table 3.

Table 3. Serologic response

Characteristics	**All patients**
Anti-SARS-CoV-2 S reactive (n, %)	
4 weeks post vaccine 1 (n=31)	25 (80.6)
4 weeks post vaccine 2 (n=30)	28 (93.3)
Follow up (n=19)	18 (94.7)
Anti-SARS-CoV-2 S response (n, %)	
4 weeks post vaccine 1 (n=31)	12 (38.7)
4 weeks post vaccine 2 (n=30)	28 (93.3)
Follow up (n=19)	18 (94.7)
Anti-SARS-CoV-2 S ≥4-fold rise (n, %)	
4 weeks post vaccine 1 (n=31)	22 (71.0)
4 weeks post vaccine 2 (n=30)	28 (93.3)

Follow up (n=19)	18 (94.7)
Anti-SARS-CoV-2 S levels (BAU/mL), median (interquartile range)	
4 weeks post vaccine 1 (n=31)	5.4 (0.9, 82.3)
4 weeks post vaccine 2 (n=30)	1188.5 (316.0, 2500.0)
Follow up (n=19)	200.0 (62.2. 560.0)
BAU > 2000/mL (n, %)	
4 weeks post vaccine 1 (n=31)	0 (0.0)
4 weeks post vaccine 2 (n=30)	12 (40.0)
Follow up (n=19)	0 (0.0)

Significantly lower response rates (GMR<1) were observed in patients treated with immunosuppression, ESAs, HBV low or non-responders and frail patients (Table 4).

Table 4. GMC and GMR

Characteristics	**GMC after 1st dose (95% confidence interval)**	**GMR after 1st dose (95% confidence interval)**	**GMC after 2nd dose (95% confidence interval)**	**GMR after 2nd dose (95% confidence interval)**	**p-value for GMR after 1st dose**	**p-value for GMR after 2nd dose**
Immunosuppression						
No	12.73 (6.16 – 26.30)	Reference	908.40 (439.51 – 1877.50)	Reference	0.012	0.040
Yes	2.01 (0.57 – 6.87)	0.16 (0.04 – 0.66)	187.42 (50.27 – 698.78)	0.21 (0.05 – 0.93)		
ESA treatment						
No	34.58 (11.08 – 107.88)	Reference	842.16 (269.98 – 2627.28)	Reference	0.002	0.532
Yes	3.91 (1.78 – 8.58)	0.11 (0.03 – 0.45)	543.00 (242.89 – 1213.93)	0.64 (0.16 – 2.60)		
HBV Response						
No	4.71 (2.10 – 10.57)	0.23 (0.06 – 0.90)	371.50 (162.03 – 851.76)	0.24 (0.06 – 0.94)	0.036	0.041
Yes	20.26 (6.81 – 60.28)	Reference	1558.86 (523.84 – 4638.94)	Reference		
Frailty						
No	9.66 (4.67-19.98)	Reference	888.47 (423.36-1864.53)	Reference	0.174	0.026
Yes	2.78 (0.53-14.57)	0.29 (0.05 – 1.76)	111.38 (21.23- 584.31)	0.13 (0.02 – 0.77)		

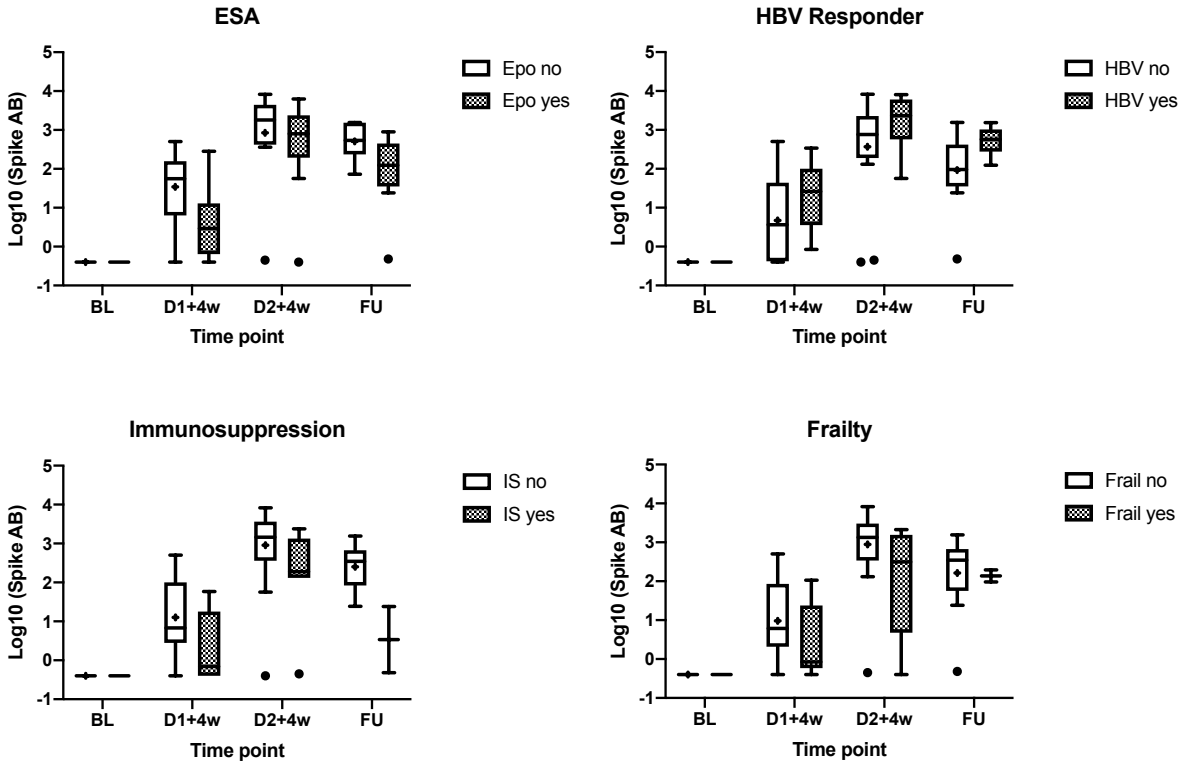
Frailty was defined as a Clinical Frailty score = or greater than 5, HBV Responder status was defined as following: HBV responder-status (non-responder: HBV titer <10 IE/L, low-responder: HBV titer 10-99 IE/L, responder: anti-HBs titer >100IE/L), ESA treatment = treatment with erythropoiesis stimulating agents, GMC Geometric mean antibody concentration, GMR geometric mean ratios. P-values from mixed models including the log10 concentrations as outcome and the timepoints, the baseline parameter and time-parameter interaction as fixed effects.

GMC and GMR values are provided in table 4. Immunosuppression had a significant influence on GMR after the first and second dose (p=0.012, p=0.040). The GMR after the first shot was calculated at 0.11 (95% CI 0.03 – 0.45) for patients receiving ESA treatment (p= 0.002). The GMR increase after the second dose of vaccine did not reach a statistically significant level (1).

The GMR for HBV-non and low-responders after the first dose was calculated at 0.23 (95% CI 0.06 – 0.90) (p=0.036). After the second shot, the GMR for non and low-responders was 0.24 (95% CI 0.06 – 0.94) (p= 0.041) (1).

The GMR of frail patients after their first dose compared to non-frail patients was not statistically significant. After the second dose however, the GMR was found to be 0.13 (95% CI 0.02 – 0.77) with a significant p-value of 0.026 (1).

Figure 2: Logarithmic response by baseline parameters



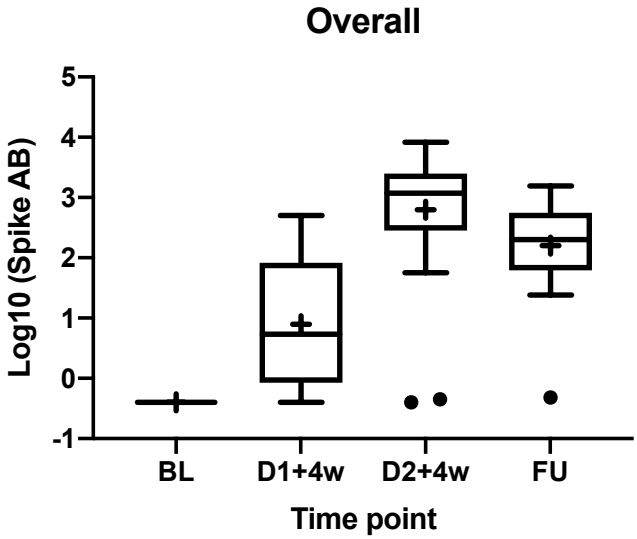
BL=baseline, D1+4w= 4 weeks after the first vaccination, D2+4w= 4weeks after the second vaccination, FU= follow up. Epo= Erythropoietin

Figure 3 shows the overall logarithmic concentrations of spike antibodies in all patients at different time points.

The graphs show the logarithmic concentrations of measured antibodies, using boxplots to differentiate between patient characteristics such as ESA-treatment, Immunosuppression,

HBV-vaccine responder status and Frailty. On the x-axis, the different time points (baseline, 4 weeks after first vaccination, 4 weeks after second vaccination and follow-up) are visualized.

Figure 3: Overall serologic response



Antibody concentration after SARS-CoV2 vaccination. BL=baseline, D1+4w= 4 weeks after the first vaccination, D2+4w= 4weeks after the second vaccination, FU= follow up.

4 Discussion

In this retrospective study, we aimed to elucidate, whether patients treated with peritoneal dialysis respond to the COVID-19 mRNA vaccines and if they exhibit a sustained antibody response.

These findings are important, as PD patients are an at-risk group for infectious complications. This indicates a relative longevity of anti-spike-antibodies.

We also wanted to explore patient characteristics, that may influence the ability to produce a sufficient antibody response.

In summary, we found associations between ESA-treatment, previous HBV-vaccine response, residual renal function, usage of immunosuppressive drugs and frailty with a diminished ability to produce antibodies, following the SARS-CoV-2 vaccination.

We were able to show a good serologic response to SARS-CoV-2 vaccines in PD patients. Patients with frailty, immunosuppression, ESA-treatment and a prior poor response to the HBV vaccine show a significantly inferior antibody response.

The main endpoint showed, that about 38.7% of patients had an antibody titer of >15 AU/mL 28 days after their first vaccination.

The seroconversion rate 4 weeks after the second vaccination was calculated at 93.3% in our study. This seems to be more in line with what other studies found, for example 100% (86), 97% (87) and 95% (85).

4.1 ESA Treatment

We found that significantly more non-responders were being treated with ESAs. This may be important, as patients treated with ESAs, might profit from altered vaccination regimes or adjuvanted vaccines.

ESAs have been suspected of having cellular and humoral immunomodulating characteristics. ESAs increased production of IgM antibodies in a lymphoblastoid cell line and IgG, IgM and IgA production in purified tonsil small resting B cells. This indicates a direct stimulative effect of ESAs on activated and differentiated B cells (102).

ESA treatment has also been linked to increasing the CD4+ and CD8+ cell counts without affecting the CD4+/CD8+ ratio, decreasing natural killer cells and improving phagocytic activity in HD patients (103).

ESAs also enhances mitogenic proliferation of T-cells in vitro, even after a relatively short treatment of 6 weeks (104).

The influence of erythropoietin and ESAs on vaccination response, has been under investigation in the past years, although one recent meta-analysis found no impact of ESAs on the response to the HBV-vaccine (105).

The inferior response to the vaccines in patients with ESA treatment, may be the result of a pro-inflammatory milieu in CKD patients, which leads to a functional iron deficiency, requiring the treatment with ESAs. Though, we are only able to hypothesize about this, as we did not look at inflammatory or iron markers in our patients.

4.2 HBV Vaccine Responder Status

Previous low- and non-responders to the HBV vaccine, also exhibited a diminished serologic response with the SARS-CoV-2 vaccine. This may be of particular importance, as the same pathophysiologic mechanisms, elucidated in the background provided in the introduction section, could be at play and patients with an increased risk of poor response could be identified by their HBV-vaccine-response.

4.3 Residual Renal Function

We found that patients with a better residual renal function, defined as >500mL residual daily diuresis, were more likely to exhibit a serological response. This suggests that not every CKD or ESKD patient is affected in the same way by their morbidities in terms of immunologic response. There may be a positive correlation between residual renal function and ability to produce antibodies after mRNA vaccines. Though another study found no correlation between residual renal function and serologic response in PD patients treated with the Hepatitis B vaccine (106). The patients in this study, had been treated with PD for an average of 34 months, which is about half a year longer, than in our study. Thus, this may lead to the hypothesis, that the patients in this study were, compared to our study, already in a more advanced stage of their CKD and thus unable to mount an antibody response.

4.4 Immunosuppression

Immunosuppressed patients are known to have an impaired response to numerous vaccinations such as the influenza A H1N1/2009 vaccine (107) or the 9-Valent Human Papillomavirus Vaccine (108).

A recent systematic review of COVID-19 vaccines in immunosuppressed patients concluded, that immunosuppressed patients suffer a diminished immunogenicity and an increased rate of breakthrough infections. Patients taking immunosuppressive agents seem to suffer from an inferior immune response to these vaccines. Patients response rates decreased especially drastically with B-cell depleting agents (109).

4.5 Frailty

A study with a trivalent Influenza vaccine, showed that frailty is associated with a decreased HI titer response and also with an increased rate of Influenza and Influenza like illnesses (110).

Another study in 168 patients treated with an Influenza vaccine, came to the same conclusions. They also characterized peripheral blood mononuclear cells of patients and found that frail patients exhibited a reduced expression of genes required for cellular proliferation, translation of proteins, metabolism, antibody production and cytokine expression. Frail patients also showed an increase in oxidative stress, IL-8 signaling and T-cell exhaustion genes. These reduced or altered transcriptional programs in frail patients

likely represent advanced immunosenescence. Thus, total reliance on antibody titers may be insufficient, as these cellular characteristics and the cellular immune response are an important part of protection. Especially in the elderly, antibody titers may not be the best way to assess immunogenicity of vaccines (111).

An alternative might be the enzyme-linked immunosorbent spot (ELISpot) assay. It is a test that, among other things, characterizes the antigen-specific T cells quantitatively (112). A study on the COVID-19 BioNTech mRNA vaccine from 2021, found no association between various frailty scores and inmmunogenic response based on antibody titers (113).

4.6 Cut-offs and Antibody-Assays

A problem in this field of research is that the utilized cut-offs are still not sufficiently validated and the importance of cellular and humoral immunity is also not quite clear yet. The manufacturer of the test recommends a cut-off of 15 AU/mL, which seems to have a PPV > 99% for neutralizing antibodies. This cut-off has only been validated in patients experiencing natural infection, but not vaccination. Although it has been shown, that these assays reliably reflect cellular immunity (114). In addition, the PPV for the presence of neutralizing antibodies has not been specifically studied in ESRD patients.

Comparability of different assays is also limited, as the absolute values of antibody concentrations vary greatly, depending on the assay. When using the standardized BAU/mL comparability improves, but marked differences remain. Larger differences were observed, when higher concentrations of antibodies were present (83).

4.7 Limitations

We acknowledge that our study has several limitations. First is the relatively small sample size, with only 31 patients in the final analysis. Statistically significant results may not have been discovered due to this fact. Furthermore, results may also not be applicable to all patients, since 77.4% of the included patients were male.

In our study, only 38.7% of patients, showed a response with a titer of >15AU/mL 28 days after their first dose. This stands in contrast to previous studies of COVID-vaccines in PD patients. Other comparable studies found seroconversion rates of 86% (86), 62.5% (87) and 54% (85). There seems to be no considerable difference between these and our study in terms of age and BMI. Although in our study, we were only able to recruit 22.6% female patients, while the others had a more equal sex distribution.

Another limitation is the single-center nature of this study and its retrospective, observational and non-interventional design.

As stated above, the comparability of different antibody assays is another problem, which makes it less accurate to compare different studies with each other.

Additionally, we only tested the humoral response to the vaccinations, although the cellular component of the adaptive immune system also plays an important role in preventing infections and lessening the severity of the disease. Although there seems to be some correlation between the humoral and cellular response, this is not explored in this study.

4.8 Future Perspectives

Further research into vaccinations in PD patients is warranted, as CKD and PD represents a risk factor for severe COVID-19 and COVID-related mortality. Analogous to other vaccinations in CKD patients, different strategies to improve efficacy of vaccination should be investigated. Different vaccination regimens, sooner or more booster shots, topical imiquimod, intradermal application, different adjuvants or other improvements might be warranted in these patient collectives.

The epidemiologic situation is constantly changing, with a different vaccination rate, incidence rate and new and different emerging variants of concern. The epidemiologic circumstances of spring and summer of 2021 have to be kept in mind.

Furthermore, the influencing factors, such as HBV-response, ESA-treatment, frailty and immunosuppression should be explored further, in terms of their influence on serologic response.

A robust connection between serologic antibody testing and cellular immunity or immunity in general should be established. Differences in different antibody assay results should also be explored further, so as to make studies on the subject more comparable.

Literaturverzeichnis

1. Kolland M, Riedl R, Bachler B, Ribitsch W, Niedrist T, Meissl AM, et al. Decreased response to the mRNA anti-SARS-CoV-2 vaccine in hepatitis B vaccine non-responders and frail patients treated with peritoneal dialysis. Nephrol Dial Transplant. 2022 May 25;37(6):1188–90.

2. Stevens PE, Levin A. Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. Ann Intern Med. 2013 Jun 4;158(11):825–30.

3. Gansevoort RT, Matsushita K, Velde M van der, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations: A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011 Jul;80(1):93.

4. James MT, Hemmelgarn BR, Tonelli M. Early recognition and prevention of chronic kidney disease. The Lancet. 2010 Apr 10;375(9722):1296–309.

5. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012 Dec;380(9859):2095–128.

6. Kerschbaum J. 2018 and 2019 annual OEDTR report [Internet]. [cited 2022 Feb 16]. Available from: https://oedtr.i-med.ac.at/jahresberichte/

7. Ayodele OE, Alebiosu CO. Burden of Chronic Kidney Disease: An International Perspective. Adv Chronic Kidney Dis. 2010 May;17(3):215–24.

8. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA. 2019 Oct 1;322(13):1294.

9. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease. Circulation. 2021 Mar 16;143(11):1157–72.

10. Dhondup T, Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update. Kidney Dis. 2017 Dec;3(4):136.

11. Hailpern SM, Melamed ML, Cohen HW, Hostetter TH. Moderate Chronic Kidney Disease and Cognitive Function in Adults 20 to 59 Years of Age: Third National Health and Nutrition Examination Survey (NHANES III). J Am Soc Nephrol. 2007 Jul 1;18(7):2205–13.

12. Syed-Ahmed M, Narayanan M. Immune Dysfunction and Risk of Infection in Chronic Kidney Disease. Adv Chronic Kidney Dis. 2019 Jan;26(1):8–15.

13. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic Kidney Disease and Mortality Risk: A Systematic Review. J Am Soc Nephrol. 2006 Jul;17(7):2034–47.

14. Grohskopf LA, Alyanak E, Ferdinands JM, Broder KR, Blanton LH, Talbot HK, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 Influenza Season. MMWR Recomm Rep. 2021 Aug 27;70(5):1–28.

15. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al. Aspects of Immune Dysfunction in End-stage Renal Disease. Clin J Am Soc Nephrol. 2008 Sep;3(5):1526–33.

16. de Boer IH, Caramori ML, Chan JCN, Heerspink HJL, Hurst C, Khunti K, et al. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020 Oct;98(4):S1–115.

17. Mikhail A, Brown C, Williams JA, Mathrani V, Shrivastava R, Evans J, et al. Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease. BMC Nephrol. 2017 Dec;18(1):345.

18. Stauffer ME, Fan T. Prevalence of Anemia in Chronic Kidney Disease in the United States. Moura IC, editor. PLoS ONE. 2014 Jan 2;9(1):e84943.

19. Nangaku M, Eckardt KU. Pathogenesis of Renal Anemia. Semin Nephrol. 2006 Jul;26(4):261–8.

20. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013 Mar;381(9868):752–62.

21. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, Dialysis Initiation, and Mortality in End-Stage Renal Disease. Arch Intern Med [Internet]. 2012 Jul 23 [cited 2022 Sep 1];172(14). Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinternmed.2012.3020

22. Nixon AC, Bampouras TM, Pendleton N, Woywodt A, Mitra S, Dhaygude A. Frailty and chronic kidney disease: current evidence and continuing uncertainties. Clin Kidney J. 2018 Apr 1;11(2):236–45.

23. Fleming GM. Renal replacement therapy review: Past, present and future. Organogenesis. 2011 Jan;7(1):2–12.

24. Fu EL, Evans M, Carrero JJ, Putter H, Clase CM, Caskey FJ, et al. Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. BMJ. 2021 Nov 29;e066306.

25. Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, et al. A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis. N Engl J Med. 2010 Aug 12;363(7):609–19.

26. Rabindranath KS, Strippoli GFM, Roderick P, Wallace SA, MacLeod AM, Daly C. Comparison of hemodialysis, hemofiltration, and acetate-free biofiltration for ESRD: Systematic review. Am J Kidney Dis. 2005 Mar;45(3):437–47.

27. Teitelbaum I. Peritoneal Dialysis. Ingelfinger JR, editor. N Engl J Med. 2021 Nov 4;385(19):1786–95.

28. Heaf JG, Wehberg S. Relative Survival of Peritoneal Dialysis and Haemodialysis Patients: Effect of Cohort and Mode of Dialysis Initiation. Burdmann EA, editor. PLoS ONE. 2014 Mar 10;9(3):e90119.

29. Jansen MAM, Hart AAM, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int. 2002 Sep;62(3):1046–53.

30. Eroglu E, Heimbürger O, Lindholm B. Peritoneal dialysis patient selection from a comorbidity perspective. Semin Dial. 2022 Jan;35(1):25–39.

31. Pahl MV, Vaziri ND. Immune Function in Chronic Kidney Disease. In: Chronic Renal Disease [Internet]. Elsevier; 2015 [cited 2022 Feb 22]. p. 285–97. Available from: https://linkinghub.elsevier.com/retrieve/pii/B978012411602300024X

32. Lim WH, Kireta S, Leedham E, Russ GR, Coates PT. Uremia impairs monocyte and monocyte-derived dendritic cell function in hemodialysis patients. Kidney Int. 2007 Nov;72(9):1138–48.

33. Anding K. The influence of uraemia and haemodialysis on neutrophil phagocytosis and antimicrobial killing. Nephrol Dial Transplant. 2003 Oct 1;18(10):2067–73.

34. Ando M, Shibuya A, Tsuchiya K, Akiba T, Nitta K. Reduced expression of Toll-like receptor 4 contributes to impaired cytokine response of monocytes in uremic patients. Kidney Int. 2006 Jul;70(2):358–62.

35. Stenvinkel P, Ketteler M, Johnson RJ, Lindholm B, Pecoits-Filho R, Riella M, et al. IL-10, IL-6, and TNF-α: Central factors in the altered cytokine network of uremia—The good, the bad, and the ugly. Kidney Int. 2005 Apr;67(4):1216–33.

36. Stenvinkel P, Barany P, Heimbürger O, Pecoits-Filho R, Lindholm B. Mortality, malnutrition, and atherosclerosis in ESRD: What is the role of interleukin-6? Kidney Int. 2002 May;61:S103–8.

37. Saran R, Robinson B, Abbott KC, Agodoa LYC, Albertus P, Ayanian J, et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2017 Mar;69(3):A7–8.

38. Ishigami J, Matsushita K. Clinical epidemiology of infectious disease among patients with chronic kidney disease. Clin Exp Nephrol. 2019 Apr 2;23(4):437–47.

39. McDonald HI, Thomas SL, Millett ERC, Nitsch D. CKD and the Risk of Acute, Community-Acquired Infections Among Older People With Diabetes Mellitus: A Retrospective Cohort Study Using Electronic Health Records. Am J Kidney Dis. 2015 Jul;66(1):60–8.

40. Ishigami J, Grams ME, Chang AR, Carrero JJ, Coresh J, Matsushita K. CKD and Risk for Hospitalization With Infection: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2017 Jun;69(6):752–61.

41. Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int. 2000 Oct;58(4):1758–64.

42. Ducloux D, Legendre M, Bamoulid J, Rebibou JM, Saas P, Courivaud C, et al. ESRD-associated immune phenotype depends on dialysis modality and iron status: clinical implications. Immun Ageing. 2018 Dec;15(1):16.

43. Lambie M, Chess J, Donovan KL, Kim YL, Do JY, Lee HB, et al. Independent Effects of Systemic and Peritoneal Inflammation on Peritoneal Dialysis Survival. J Am Soc Nephrol. 2013 Dec;24(12):2071–80.

44. Cho JH, Hur IK, Kim CD, Park SH, Ryu HM, Yook JM, et al. Impact of systemic and local peritoneal inflammation on peritoneal solute transport rate in new peritoneal dialysis patients: a 1-year prospective study. Nephrol Dial Transplant. 2010 Jun 1;25(6):1964–73.

45. Oldani S, Finazzi S, Bottazzi B, Garlanda C, Baldassarre E, Valaperta S, et al. Plasma pentraxin-3 as a marker of bioincompatibility in hemodialysis patients. J Nephrol. 2012;25(1):120–6.

46. Bitla AR, Reddy PE, Manohar SM, Vishnubhotla SV, Pemmaraju Venkata Lakshmi Narasimha SR. Effect of a single hemodialysis session on inflammatory markers: Inflammatory markers in hemodialysis. Hemodial Int. 2010 Oct;14(4):411–7.

47. Xu D, Erickson S, Szeps M, Gruber A, Sangfelt O, Einhorn S, et al. Interferon alpha down-regulates telomerase reverse transcriptase and telomerase activity in human malignant and nonmalignant hematopoietic cells. Blood [Internet]. 2000 Dec 15 [cited 2022 Mar 15];96(13). Available from: https://pubmed.ncbi.nlm.nih.gov/11110707/

48. Crépin T, Legendre M, Carron C, Vachey C, Courivaud C, Rebibou JM, et al. Uraemia-induced immune senescence and clinical outcomes in chronic kidney disease patients. Nephrol Dial Transplant. 2020 Apr 1;35(4):624–32.

49. Čičin-Šain L, Smyk-Paerson S, Currier N, Byrd L, Koudelka C, Robinson T, et al. Loss of Naive T Cells and Repertoire Constriction Predict Poor Response to Vaccination in Old Primates. J Immunol. 2010 Jun 15;184(12):6739–45.

50. Meier P, Dayer E, Blanc E, Wauters JP. Early T cell activation correlates with expression of apoptosis markers in patients with end-stage renal disease. J Am Soc Nephrol JASN [Internet]. 2002 Jan [cited 2022 Mar 15];13(1). Available from: https://pubmed.ncbi.nlm.nih.gov/11752039/?dopt=Abstract

51. Lisowska K, Dębska-Ślizień A, Jasiulewicz A, Heleniak Z, Bryl E, Witkowski J. Hemodialysis affects phenotype and proliferation of CD4-positive T lymphocytes. J Clin Immunol [Internet]. 2012 Feb [cited 2022 Mar 15];32(1). Available from: https://pubmed.ncbi.nlm.nih.gov/21993694/

52. Meijers RW, Litjens NH, de Wit EA, Langerak AW, van der Spek A, Baan CC, et al. Uremia causes premature ageing of the T cell compartment in end-stage renal disease patients. Immun Ageing. 2012 Dec;9(1):19.

53. Xiaoyan J, Rongyi C, Xuesen C, Jianzhou Z, Jun J, Xiaoqiang D, et al. The difference of T cell phenotypes in end stage renal disease patients under different dialysis modality. BMC Nephrol. 2019 Dec;20(1):301.

54. Haddiya I. Current Knowledge of Vaccinations in Chronic Kidney Disease Patients. Int J Nephrol Renov Dis. 2020 Jul;Volume 13:179–85.

55. Bond TC, Patel PR, Krisher J, Sauls L, Deane J, Strott K, et al. Association of Standing-Order Policies With Vaccination Rates in Dialysis Clinics: A US-Based Cross-sectional Study. Am J Kidney Dis. 2009 Jul;54(1):86–94.

56. Labriola L, Hombrouck A, Marechal C, Van Gucht S, Brochier B, Thomas I, et al. Immunogenicity of an adjuvanted 2009 pandemic influenza A (H1N1) vaccine in haemodialysed patients. Nephrol Dial Transplant. 2011 Apr 1;26(4):1424–8.

57. Chiew Tong NK, Beran J, Kee SANN, Miguel JL, SanNchez C, Bayas JM, et al. Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients. Kidney Int. 2005 Nov;68(5):2298–303.

58. Marcelli D, Marelli C, Richards N. Influenza A(H1N1)v pandemic in the dialysis population: first wave results from an international survey. Nephrol Dial Transplant. 2009 Dec 1;24(12):3566–72.

59. Antonen JA, Hannula PM, Pyhälä R, Saha HHT, Ala-Houhala IO, Pasternack AI. Adequate Seroresponse to Influenza Vaccination in Dialysis Patients. Nephron. 2000;86(1):56–61.

60. Mastalerz-Migas A, Steciwko A, Brydak LB. Immune Response to Influenza Vaccine in Hemodialysis Patients with Chronic Renal Failure. In: Pokorski M, editor. Respiratory Regulation - The Molecular Approach [Internet]. Dordrecht: Springer Netherlands; 2013 [cited 2022 Feb 23]. p. 285–90. (Advances in Experimental Medicine and Biology; vol. 756). Available from: http://link.springer.com/10.1007/978-94-007-4549-0_35

61. Chang YT, Guo CY, Tsai MS, Cheng YY, Lin MT, Chen CH, et al. Poor immune response to a standard single dose non-adjuvanted vaccination against 2009 pandemic H1N1 influenza virus A in the adult and elder hemodialysis patients. Vaccine. 2012 Jul;30(33):5009–18.

62. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. N Engl J Med. 2014 Aug 14;371(7):635–45.

63. Liao Z, Xu X, Liang Y, Xiong Y, Chen R, Ni J. Effect of a booster dose of influenza vaccine in patients with hemodialysis, peritoneal dialysis and renal transplant recipients: A systematic literature review and meta-analysis. Hum Vaccines Immunother. 2016 Nov;12(11):2909–15.

64. Hung IFN, Zhang AJ, To KKW, Chan JFW, Li C, Zhu HS, et al. Immunogenicity of Intradermal Trivalent Influenza Vaccine With Topical Imiquimod: A Double Blind Randomized Controlled Trial. Clin Infect Dis. 2014 Nov 1;59(9):1246–55.

65. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep [Internet]. 2001 Apr 27 [cited 2022 Feb 23];50(RR-5). Available from: https://pubmed.ncbi.nlm.nih.gov/11349873/

66. Bond W. SURVIVAL OF HEPATITIS B VIRUS AFTER DRYING AND STORAGE FOR ONE WEEK. The Lancet. 1981 Mar;317(8219):550–1.

67. Ribot S. Duration of Hepatitis B Surface Antigenemia (HBs Ag) in Hemodialysis Patients. Arch Intern Med. 1979 Feb 1;139(2):178.

68. Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ. Special Article: National Surveillance of Dialysis-Associated Diseases in the United States, 2002: ANNUAL DIALYSIS CENTER SURVEY. Semin Dial. 2005 Jan 21;18(1):52–61.

69. Ma BM, Yap DYH, Yip TPS, Hung IFN, Tang SCW, Chan TM. Vaccination in patients with chronic kidney disease—Review of current recommendations and recent advances. Nephrology. 2021 Jan;26(1):5–11.

70. Bel'eed K. Vaccination against hepatitis B infection in patients with end stage renal disease. Postgrad Med J. 2002 Sep 1;78(923):538–40.

71. Ramezani A, Eslamifar A, Banifazl M, Ahmadi F, Maziar S, Razeghi E, et al. Efficacy and long-term immunogenicity of hepatitis B vaccine in haemodialysis patients. Int J Clin Pract. 2009 Mar;63(3):394–7.

72. Yousaf F, Gandham S, Galler M, Spinowitz B, Charytan C. Systematic review of the efficacy and safety of intradermal versus intramuscular hepatitis B vaccination in end-stage renal disease population unresponsive to primary vaccination series. Ren Fail [Internet]. 2015 Aug [cited 2022 Feb 24];37(7). Available from: https://pubmed.ncbi.nlm.nih.gov/26258528/

73. Fabrizi F, Cerutti R, Dixit V, Ridruejo E. Hepatitis B virus vaccine and chronic kidney disease. The advances. Nefrología. 2021 Mar;41(2):115–22.

74. DaRoza G, Loewen A, Djurdjev O, Love J, Kempston C, Burnett S, et al. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. Am J Kidney Dis. 2003 Dec;42(6):1184–92.

75. ERA-EDTA Council, Ortiz A, Cozzolino M, Fliser D, Fouque D, Goumenos D, et al. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. Nephrol Dial Transplant. 2021 Jan 1;36(1):87–94.

76. Ewelina PR, Alicja DŚ, Bogdan B, Piotr T, Karolina P, Piotr J, et al. Extremely high mortality rates among hemodialysis patients with COVID-19 before the era of SARS-CoV-2 vaccination: results from a large database from the North of Poland. Pol Arch Intern Med. 2021 Jul 30;131(7–8).

77. Windpessl M, Bruchfeld A, Anders HJ, Kramer H, Waldman M, Renia L, et al. COVID-19 vaccines and kidney disease. Nat Rev Nephrol. 2021 May;17(5):291–3.

78. Chen JJ, Lee TH, Tian YC, Lee CC, Fan PC, Chang CH. Immunogenicity Rates After SARS-CoV-2 Vaccination in People With End-stage Kidney Disease: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Oct 28;4(10):e2131749.

79. Swai J, Gui M, Long M, Wei Z, Hu Z, Liu S. Humoral and cellular immune response to severe acute respiratory syndrome coronavirus-2 vaccination in haemodialysis and kidney transplant patients. Nephrology. 2022 Jan;27(1):7–24.

80. Moss P. The T cell immune response against SARS-CoV-2. Nat Immunol. 2022 Feb;23(2):186–93.

81. Bergamaschi L, Mescia F, Turner L, Hanson AL, Kotagiri P, Dunmore BJ, et al. Longitudinal analysis reveals that delayed bystander CD8+ T cell activation and early immune pathology distinguish severe COVID-19 from mild disease. Immunity. 2021 Jun;54(6):1257-1275.e8.

82. Carta M, Marinello I, Cappelletti A, Rodolfi A, Cerrito E, Bernasconi C, et al. Comparison of Anti–SARS-CoV-2 S1 Receptor-Binding Domain Antibody Immunoassays in Health Care Workers Before and After the BNT162b2 mRNA Vaccine. Am J Clin Pathol. 2022 Feb 3;157(2):212–8.

83. Giavarina D, Carta M. Improvements and limits of anti SARS-CoV-2 antibodies assays by WHO (NIBSC 20/136) standardization. Diagnosis [Internet]. 2021 Dec 2 [cited 2022 Mar 12];0(0). Available from: https://www.degruyter.com/document/doi/10.1515/dx-2021-0126/html

84. Perkmann T, Perkmann-Nagele N, Koller T, Mucher P, Radakovics A, Marculescu R, et al. Anti-Spike Protein Assays to Determine SARS-CoV-2 Antibody Levels: a Head-

to-Head Comparison of Five Quantitative Assays. Powell EA, editor. Microbiol Spectr. 2021 Sep 3;9(1):e00247-21.

85. Speer C, Schaier M, Nusshag C, Töllner M, Buylaert M, Kälble F, et al. Longitudinal Humoral Responses after COVID-19 Vaccination in Peritoneal and Hemodialysis Patients over Twelve Weeks. Vaccines. 2021 Oct 4;9(10):1130.

86. Tylicki L, Piotrowska M, Biedunkiewicz B, Zieliński M, Dąbrowska M, Tylicki P, et al. Humoral response to COVID-19 vaccination in patients treated with peritoneal dialysis: the COViNEPH Project. Pol Arch Intern Med [Internet]. 2021 Oct 11 [cited 2022 Feb 24]; Available from: https://www.mp.pl/paim/issue/article/16091

87. Rodríguez-Espinosa D, Broseta JJ, Maduell F, Bedini JL, Vera M. Humoral response of the mRNA-1273 SARS-CoV-2 vaccine in peritoneal dialysis patients. Kidney Int. 2021 Aug;100(2):476–7.

88. Duarte R, Roldão M, Figueiredo C, Luz I, Ferrer F, Gonçalves H, et al. Humoral response to BNT162b2 mRNA COVID-19 vaccine in peritoneal and hemodialysis patients: A comparative study. Ther Apher Dial. 2021 Dec 14;1744-9987.13766.

89. Nacasch N, Cohen-Hagai K, Benchetrit S, Zitman-Gal T, Einbinder Y, Erez D, et al. Comparison of long-term antibody response to mRNA SARS-CoV-2 vaccine among peritoneal dialysis and hemodialysis patients. Nephrol Dial Transplant. 2021 Nov 12;gfab321.

90. Stumpf J, Klimova A, Mauer R, Steglich A, Gembardt F, Martin H, et al. Equivalent humoral and cellular immune response but different side effect rates following SARS-CoV-2 vaccination in peritoneal and haemodialysis patients using messenger RNA vaccines. Nephrol Dial Transplant. 2021 Nov 15;gfab324.

91. Van Praet J, Reynders M, De Bacquer D, Viaene L, Schoutteten MK, Caluwé R, 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 Dec;32(12):3208–20.

92. Broseta JJ, Rodríguez-Espinosa D, Rodríguez N, Mosquera M del M, Marcos MÁ, Egri N, et al. Humoral and Cellular Responses to mRNA-1273 and BNT162b2 SARS-

CoV-2 Vaccines Administered to Hemodialysis Patients. Am J Kidney Dis. 2021 Oct;78(4):571–81.

93. Agur T, Ben-Dor N, Goldman S, Lichtenberg S, Herman-Edelstein M, Yahav D, et al. Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients—a prospective cohort study. Nephrol Dial Transplant. 2021 Jun 28;36(7):1347–9.

94. Abteilung Biobank Graz | [Internet]. [cited 2022 Mar 15]. Available from: https://biobank.medunigraz.at/

95. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the Clinical Frailty Scale. BMC Geriatr. 2020 Dec;20(1):393.

96. Churchill B, Patri P. The nitty-gritties of Kt/V urea calculations in hemodialysis and peritoneal dialysis. Indian J Nephrol. 2021;31(2):97.

97. Elecsys Anti-SARS-CoV-2 | roche.de [Internet]. [cited 2022 Mar 5]. Available from: https://www.roche.de/diagnostik-produkte/produktkatalog/tests-parameter/elecsys-anti-sars-cov-2

98. Olbrich L, Castelletti N, Schälte Y, Garí M, Pütz P, Bakuli A, et al. A Serology Strategy for Epidemiological Studies Based on the Comparison of the Performance of Seven Different Test Systems - The Representative COVID-19 Cohort Munich [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jan [cited 2022 Mar 5]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.01.13.21249735

99. Riester E, Findeisen P, Hegel JK, Kabesch M, Ambrosch A, Rank CM, et al. Performance evaluation of the Roche Elecsys Anti-SARS-CoV-2 S immunoassay. J Virol Methods. 2021 Nov;297:114271.

100. Meschi S, Matusali G, Colavita F, Lapa D, Bordi L, Puro V, et al. Predicting the protective humoral response to a SARS-CoV-2 mRNA vaccine. Clin Chem Lab Med CCLM. 2021 Nov 25;59(12):2010–8.

101. Olivier J, Johnson WD, Marshall GD. The logarithmic transformation and the geometric mean in reporting experimental IgE results: what are they and when and why to use them? Ann Allergy Asthma Immunol. 2008 Apr;100(4):333–7.

102. Kimata H, Yoshida A, Ishioka C, Masuda S, Sasaki R, Mikawa H. Human recombinant erythropoietin directly stimulates B cell immunoglobulin production and proliferation in serum-free medium. Clin Exp Immunol. 2008 Jun 28;85(1):151–6.

103. Huraib S, Abu-Aisha H, Al-Momen A, Al-Wakeel J, Memon N, Al-Tuwaijri A. Effect of recombinant human erythropoietin on lymphocyte phenotyping and phagocyte activity in hemodialysis patients. Am J Kidney Dis. 1997 Jun;29(6):866–70.

104. Shurtz-Swirski R, Kristal B, Shkolnik T, Weissman I, Shapiro G, Shasha SM. Short-Term Effect of Erythropoietin on T-Cell Mitogenic Proliferation in Chronic Renal Failure Patients. Nephron. 1996;72(1):27–9.

105. Fabrizi F, Dixit V, Martin P, Messa P. Erythropoietin Use and Immunogenicity of Hepatitis B Virus Vaccine in Chronic Kidney Disease Patients: A Meta-Analysis. Kidney Blood Press Res. 2012;35(6):504–10.

106. Dacko C, Holley J. The influence of nutritional status, dialysis adequacy, and residual renal function on the response to hepatitis B vaccination in peritoneal dialysis patients. Adv Perit Dial Conf Perit Dial [Internet]. 1996 [cited 2022 Mar 23];12. Available from: https://pubmed.ncbi.nlm.nih.gov/8865927/

107. Crespo M, Collado S, Mir M, Cao H, Barbosa F, Serra C, et al. Efficacy of Influenza A H1N1/2009 Vaccine in Hemodialysis and Kidney Transplant Patients. Clin J Am Soc Nephrol CJASN. 2011 Sep;6(9):2208–14.

108. Boey L, Curinckx A, Roelants M, Derdelinckx I, Van Wijngaerden E, De Munter P, et al. Immunogenicity and Safety of the 9-Valent Human Papillomavirus Vaccine in Solid Organ Transplant Recipients and Adults Infected With Human Immunodeficiency Virus (HIV). Clin Infect Dis Off Publ Infect Dis Soc Am. 2021 Aug 2;73(3):e661–71.

109. Galmiche S, Luong Nguyen LB, Tartour E, de Lamballerie X, Wittkop L, Loubet P, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. Clin Microbiol Infect. 2022 Feb;28(2):163–77.

110. Yao X, Hamilton RG, Weng N ping, Xue QL, Bream JH, Li H, et al. Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine. 2011 Jul;29(31):5015–21.

111. Moehling KK, Zhai B, Schwarzmann WE, Chandran UR, Ortiz M, Nowalk MP, et al. The impact of physical frailty on the response to inactivated influenza vaccine in older adults. Aging. 2020 Dec 31;12(24):24633–50.

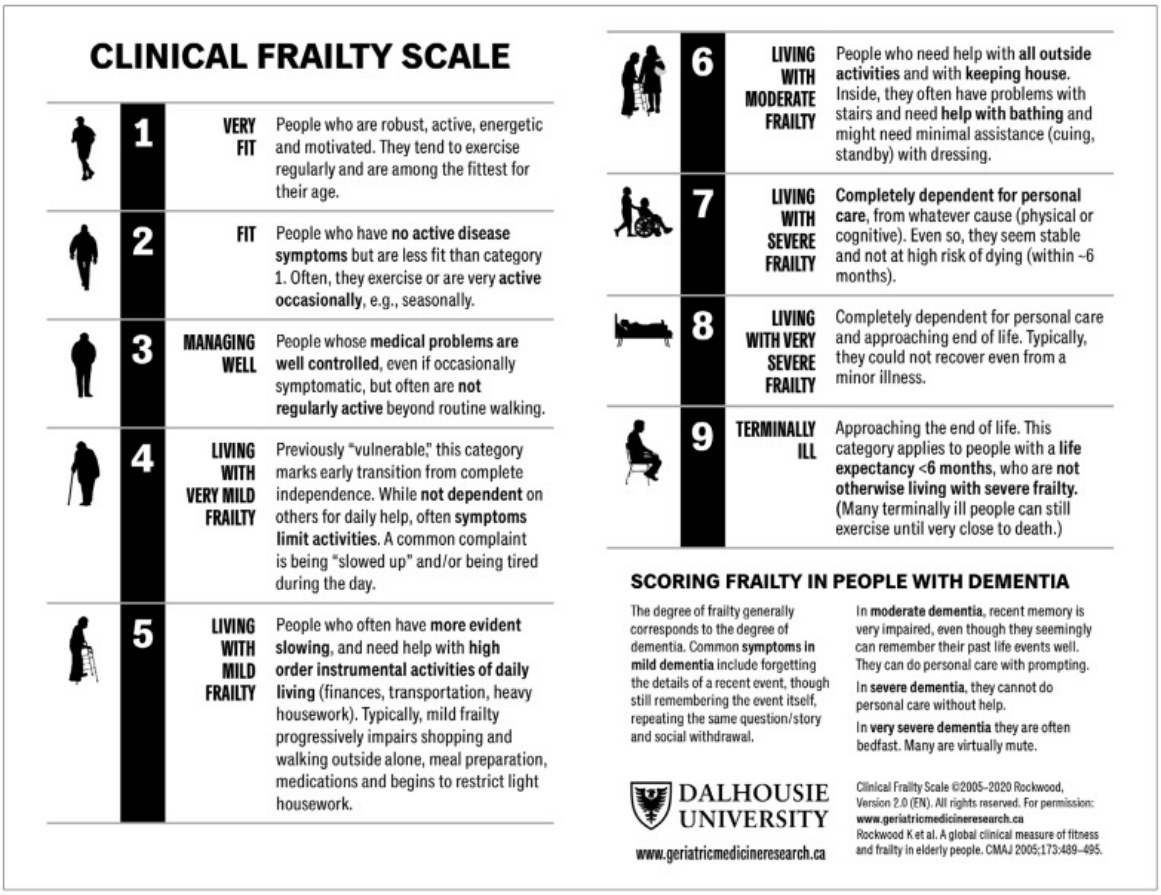
112. Slota M, Lim JB, Dang Y, Disis ML. ELISpot for measuring human immune responses to vaccines. Expert Rev Vaccines. 2011 Mar;10(3):299–306.

113. Salmerón Ríos S, Mas Romero M, Cortés Zamora EB, Tabernero Sahuquillo MT, Romero Rizos L, Sánchez-Jurado PM, et al. Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study. J Am Geriatr Soc. 2021 Jun;69(6):1441–7.

114. Mrak D, Tobudic S, Koblischke M, Graninger M, Radner H, Sieghart D, et al. SARS-CoV-2 vaccination in rituximab-treated patients: B cells promote humoral immune responses in the presence of T-cell-mediated immunity. Ann Rheum Dis. 2021 Oct;80(10):1345–50.

115. Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. Can Geriatr J. 2020 Aug 24;23(3):254–9.

Appendix



CLINICAL FRAILTY SCALE

1 VERY FIT — People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.

2 FIT — People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.

3 MANAGING WELL — People whose **medical problems are well controlled**, even if occasionally symptomatic, but often are **not regularly active** beyond routine walking.

4 LIVING WITH VERY MILD FRAILTY — Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up" and/or being tired during the day.

5 LIVING WITH MILD FRAILTY — People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.

6 LIVING WITH MODERATE FRAILTY — People who need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 LIVING WITH SEVERE FRAILTY — **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

8 LIVING WITH VERY SEVERE FRAILTY — Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.

9 TERMINALLY ILL — Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

In **very severe dementia** they are often bedfast. Many are virtually mute.

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Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

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