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The Final thesis

Covid-19 Infection in Patients with End-Stage Kidney Disease: A Narrative Review

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1 Contents

2 Summary

The following graduation thesis, "Covid-19 infection in patients with end-stage kidney disease: A narrative review," is about the effects of the SARS-CoV-2 pandemic, which started in December 2019, on patients with end-stage renal disease. Therefore, clinical symptoms, pathology, and diagnosing processes were discussed. The major objectives of this thesis were to demonstrate the huge impact of Covid 19 on the quality of life of nephrology patients. Consequently, it was shown the high rates of infection in end-stage renal disease patients, the high rates of mortality among them compared to the healthy population, as well as the enhanced level of severity of the illness in a patient with kidney disease. The other purpose of this thesis is to demonstrate the new challenges for patients with end-stage renal disease and a Covid-19 infection. These are mainly to find in the care of the patients. Therefore, this work investigates the measurements to prevent an infection in the first place and also the pharmacological agents currently used to treat a SARS-CoV-2 infection. For that reason, this works focuses on the management and treatment possibilities in this patient group. The data for this research was gathered using PubMed and Science direct.

3 Introduction

The topic was chosen because of the global pandemic situation that the world has been facing since the start of the year 2019. In December, the first Covid-19 case was identified. The first cluster of patients was related to an animal market in Wuhan, Hubei Province, China (1). The second part of this work is about end-stage renal disease respectively kidney failure (2). Chronic kidney disease is a leading public health problem, and the global prevalence is 13.4%. Patients with kidney failure who need renal replacement therapy are between 4.9 and 7.1 million people. The financial burden of chronic kidney disease will increase in developing and developed countries. The population at risk for chronic kidney disease and end-stage renal disease will increase with an older population and further escalate in diabetes, hypertension, and obesity (3). This work is written to know if there is a connection between Covid 19 patients with end-stage renal disease and higher morbidity and mortality than in the population facing a corona infection without kidney failure. The goal is to show the mechanism and pathology, diagnostic possibilities, and management of patients with end-stage renal disease who are infected with the SARS-CoV-2.

4 Literature research strategy

The literature research for this narrative review was performed using literature published from December 2019 until today. Exemptions are the guidelines for the evaluation and management of chronic kidney

disease, which were released in 2012 by the "kidney disease – improving global outcome" society. Other exemptions are pharmacological information on drugs with potential benefits for patients with Covid-19. The research work was done by using PubMed and ScienceDirect by Elsevier. The research is focused on epidemiology, pathogenesis, diagnosis, treatment of Covid 19 and kidney failure, and the connection between these two diseases. Specific Keywords that were used are "SARS-CoV-2", "Covid-19", "end-stage renal disease," and "epidemiology," or "pathogenesis," or "treatment," or "diagnosis, or "economic burden." Information from websites of different professional association and national or international organization were scoured. Cross-referencing from eligible sources was used to examine relevant information

5 Clinical presentation of disease

5.1 Covid-19 infection

The most common clinical features in patients with a SARS-Cov-2 infection are fever, fatigue, and dry cough. Additionally, there is the possibility of suffering from dyspnea, anosmia or ageusia, and anorexia (4).

Table 1 Clinical characteristics of study subjects (4)

Author	Date(MM/DD)	N	Fever	Cough	Sore throat	Myalgia or fatigue	Sputum production	Headache	hemoptisis	diahrrea	Dyspnoe
WMCHHHPNCI	01/20	136	136	136	-	-	-	-	-	-	136
Chaolin et al.	01/24	41	40	31	0	18	11	3	2	1	22
Li et al.	01/29	425	-	-	-	-	-	-	-	-	-
Chen et al.	01/30	99	82	81	5	11	-	8	-	2	31
Chung et al.	02/04	21	14	9	-	6	-	3	-	-	-
Chen et al.	02/06	29	28	21	-	12	21	2	-	4	17
Wang et al.	02/07	138	136	82	24	138	37	9	-	14	43
Kui et al.	02/07	137	112	66	-	44	6	13	7	11	26
Chang et al.	02/07	13	12	6	-	3	2	3	-	1	-
To et al.	02/12	12	-	-	-	-	-	-	-	-	-
COVID-19 team Australia	02/12	15	14	11	-	-	-	-	-	-	-
Yueying et al.	02/13	63	-	-	-	-	-	-	-	-	-
Li et al.	02/13	24	19	6	-	6	-	4	-	-	2
Feng et al.	02/13	21	18	12	4	11	6	-	-	-	-
Liang et al.	02/14	1590	-	-	-	-	-	-	-	-	-
Zhang et al.	02/15	9	8	5	4	4	-	-	-	-	-
Feng et al	02/17	15	5	1	-	-	-	-	-	-	-
Wang et al.	02/17	34	17	13	-	-	-	-	-	-	-
Xiaobo et al.	02/21	52	51	40	-	6	-	3	-	-	33

The course and severity of the disease depend on the SARS-CoV-2 variant, its virulence, and the host's immune system response. The clinical features of the disease vary from asymptomatic but positive people to patients deteriorating to severe inflammatory syndrome and multiorgan failure. The "National Institutes of health" started a classification system for Covid 19 ranging from asymptomatic to critical (5). The asymptomatic patients tested positive for the virus but have no symptoms that suggest the diagnosis of Covid-19. Affected people with a mild course of the disease encounter the common symptoms, but they do not experience shortness of breath, dyspnea on exertion, or abnormal imaging. In the case of clinical or imaging confirmation of lower respiratory disease with $SpO2 \geq 94\%$, it is a moderate progression of the illness. The criteria for severe illness are $SpO2 < 94\%$, $PaO2/FiO2 < 300$ mmHg, a respiratory rate >30 breaths per minute, or lung infiltrates > 50%. The most severe course of the infection will eventually end in clinical critically ill patients, characterized by septic shock, acute respiratory distress syndrome, cardiac dysfunction, an exaggerated inflammatory response, or exacerbation of underlying comorbidities (6). Severe and critically ill patients are significantly older and male. Another important factor is underlying conditions. Patients with hypertension, diabetes, chronic renal disease, chronic lung disease, chronic heart disease, and malignancy have a higher chance of facing a severe or critical course of the disease (7).

5.2 End-stage renal disease

Patients with chronic kidney disease are often asymptomatic at the beginning of the disease. This is due to the fact that the kidney can adapt to stress. In adaptive hyperfiltration, the filtration rate is increased in the healthy nephrons, and therefore patients often have normal serum creatinine initially, although they suffer from kidney insufficiency. Patients with advanced kidney failure might suffer from volume overload, hyperkalemia, metabolic acidosis, hypertension, anemia, and mineral bone disorders. The last stage of this disease, end-stage renal disease or kidney failure, is characterized by signs of the uremic state. It encompasses central nervous system abnormalities, peripheral neuropathy, pericarditis, vomiting, nausea, and anorexia. Patients who reach this last stage of the disease need kidney replacement therapy with hemodialysis, peritoneal dialysis, or kidney transplantation (8). The international society "Kidney Disease – Improving Global Outcomes" defines chronic kidney disease as abnormalities of kidney function or structure, displayed for more than three months, and affecting patients' health (9). Six categories (G1, G2, G3a, G3b, G4, G5) subdivide the chronic kidney disease patients using the glomerular filtration rate.

Table 2 GFR catgeories in CKD(9)

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≤ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

The rate shows a good overview of kidney function, and other functions decline in parallel with the glomerular filtration rate (9). Kidney failure is determined as GFR <15 ml/min per 1.73 m^2 or treatment by dialysis (2). The KDIGO includes the cause of disease and level of albuminuria in defining chronic kidney disease (10).

Table 3 Albuminuria in CKD (9)

Category	AER (mg/24 h)	ACR approx. equivalent (mg/mmol)	ACR approx. equivalent (mg/g)	Terms
A1	< 30	< 3	< 30	Normal to mildly increased
A2	30 – 300	3 – 30	30 – 300	Moderately increased
A3	> 300	> 30	> 300	Severely increased

6 Discussion

The transmission of the SARS-CoV-2 virus takes place through routes like direct transmission, contact transmission, and airborne transmission. The most common modes of spread are coughing, sneezing, droplet inhalation, and contact with oral, nasal, or eye mucous membranes (11). There is a higher risk spread the virus if the patients suffer a severe course of the disease (12). In their study, Yang et al. showed that the viral load is higher, and the time they are contagious is longer in people with a severe course (13). After transmission, SARS-CoV-2 infects the cells by binding to the S-proteins of the Angiotensin-converting enzyme 2 receptors of the host cells (14). Therefore, the most outstanding symptoms are respiratory disease symptoms because of the high numbers of Angiotensin-converting enzyme 2 receptors in the human lung tissue, including alveolar epithelial cells, bronchiolar cells, and lung vascular cells (15). These target receptors are not only restricted to the human lung tissue but can also be found in other organs. This includes the kidneys, the heart, but also the urinary bladder, esophagus, and ileum, leading to a wide variety of possible complications and symptoms, such as cardiac distress, gastrointestinal manifestations, acute kidney injury, and shock (14). Kidney damage in patients has three potential mechanisms linked to each other. The possible pathways are cytokine damage, organ crosstalk, and systemic effects (16). The cytokine release syndrome can occur in several conditions like hemophagocytic syndrome, sepsis, ad chimeric antigen receptor T cell therapy (17). Still, it has also been

documented in patients with Covid-19 infection since the start of the pandemic (18). Kidney damage in patients with cytokine storms might result from intrarenal inflammation, increased vascular permeability, volume depletion, and cardiomyopathy. Eventually, this can lead to cardiorenal syndrome type 1, including symptoms like intravascular fluid loss, hypotension, pleural effusions, and edema (16). The most causative cytokine in this syndrome is Interleukin-6. In patients with Covid-19, the plasma concentration of interleukin-6 is increased. In their retrospective cohort study, Chaomin et al. showed increased levels of IL-6 in patients with acute respiratory distress syndrome and also that it was significantly connected to death in patients with ARDS (18). Furthermore, extracorporeal oxygenation, invasive mechanical ventilation, and continuous kidney replacement therapy can lead to cytokine production (16). Organ crosstalk is the second pathway that might play a role in the kidney damage mechanism in Covid 19 patients. The study conducted by Anupol Panitchote et al. included 357 patients with ARDS, and 68 % developed acute kidney damage. Other important factors in these patients were diabetes mellitus, older age, greater severity of illness, and positive fluid balance (19). Additionally, cytokine overproduction is also important in both directions of this organ crosstalk. Renal tubular epithelium promotes the increased generation of Interleukin-6, leading to a higher alveolar-capillary permeability and pulmonary hemorrhage in patients with acute kidney injury. ARDS may also provoke hypoxia in the renal medulla, leading to an insult of the tubular cells (20). An additional crosstalk leading to kidney damage in patients with Covid-19 is the heart-kidney axis. This is again connected to the cytokine-releasing syndrome. A CRS cardiomyopathy could contribute to renal hypoperfusion, hypotension, and renal vein congestion, leading to a reduced glomerular filtration rate (16). The third possible mechanism of kidney damage in Covid-19 patients is systemic effects. In ARDS patients, fluid expansion leads to a positive fluid balance increasing the alveolar-capillary leakage, and in AKI, it deteriorates renal vein congestion, resulting in renal compartment syndrome. Moreover, other systemic effects play a key role in kidney damage and hemodynamic instability, like rhabdomyolysis, metabolic acidosis, and hyperkalemia (16).

Table 4 Potential mechanisms of kidney damage in Covid -19 patients(16)

Pathway	Mechanism of kidney damage
Cytokine damage	
Cytokine release syndrome	Direct cytokine lesion
Increased cytokine generation owing to ECMO, invasive mechanical ventilation an or CRKT	
Hemophagocytic syndrome	
Organ crosstalk	
Cardiomyopathy and/or viral myocarditis	Cardiorenal syndrome type 1
Alveolar damage	Renal medullary hypoxia
High peak airway pressure and intra-abdominal hypertension	Renal compartment syndrome
Rhabdomyolysis	Tubular toxicity
Systemic effects	
Positive fluid balance	Renal compartment syndrome

Endothelial damage, third-space fluid loss, and hypertension	Renal hypoperfusion
Rhabdomyolysis	Tubular toxicity
Endotoxins	Septic AKI

In patients with already existing kidney diseases, studies imply a severe course in patients with underlying morbidities like hypertension and diabetes. Wang et al. also showed that these comorbidities lead to higher submission to the Intensive care unit in patients (21). In the case of patients receiving hemodialysis, a study conducted by Cheng et al. showed the severity was mild, but the HD hospitals remained high-risk areas. The probability of infection with SARS-CoV-2 is higher in hemodialysis patients compared with the healthy population (22). Mubarak et al. showed that patients with chronic kidney disease are at a higher risk of severe Covid-19 infection (23). In the event of infection in patients with hypertension, diabetes, heart disease, or old age, these patients likely develop an acute kidney injury, a solid risk factor for developing chronic kidney disease later. Patients with chronic kidney failure have a higher risk of morbidity and mortality in infection cases than the healthy population. Chronic kidney disease stage 3 – 5 is associated with a significantly increased risk of severe illness (24). Kumar et al. conducted a review of 11,419 cases, including highlighting the increased mortality in end-stage kidney disease patients with Covid-19. They showed a strong connection between ESRD and mortality in Covid-19 patients (25). Harrison et al. conducted a study to compare mortality in patients with ESRD and Covid 19 and compared them to historical data from patients with ESRD. In their study, they showed that 13 % of people with ESRD and Covid-19 died, in contrast to 3 % of historical controls. The results of the research demonstrate that Covid-19 increases mortality almost 4-fold (26). Compared to the general population, it is 14 – 16 times higher and also connected to an enhanced risk for a severe course (27). Chronic kidney disease is connected to higher mortality in Covid-19 positive patients (28), and also the severity of the disease is enhanced (29). Therefore, Rastad et al. showed the importance of defining the risk factors connected to the death and the severity of the disease in patients with ESRD and Covid-19. They carried out a retrospective cohort study and investigated the characteristics of survivors and non-survivors. Patients with ESRD and Covid-19 that died were significantly older, more probably to present with a lack of consciousness, oxygen saturation of less than 93%, and receive invasive mechanical ventilation. In the laboratory analysis has been shown that non-survivors had lower lymphocyte count, higher neutrophil count, and higher aspartate aminotransferase concentration compared to survivors. Furthermore, they compared the ESRD patient group with non-ESRD patients infected with SARS-CoV-2 and showed that the risk factors for death, male sex, lack of consciousness, hypertension, diabetes mellitus, cardiovascular disease, and the need for invasive mechanical ventilation were significantly higher in the group of ESRD patients (30).

7 Diagnosis

7.1 Diagnosis of Covid-19

It is essential for the monitoring and prognosis of the disease to have diagnostic tests. Currently, the detection of viral RNA from a clinical sample of SARS-CoV-2 infected patients using the reverse transcription-polymerase chain reaction method is used primarily (31).

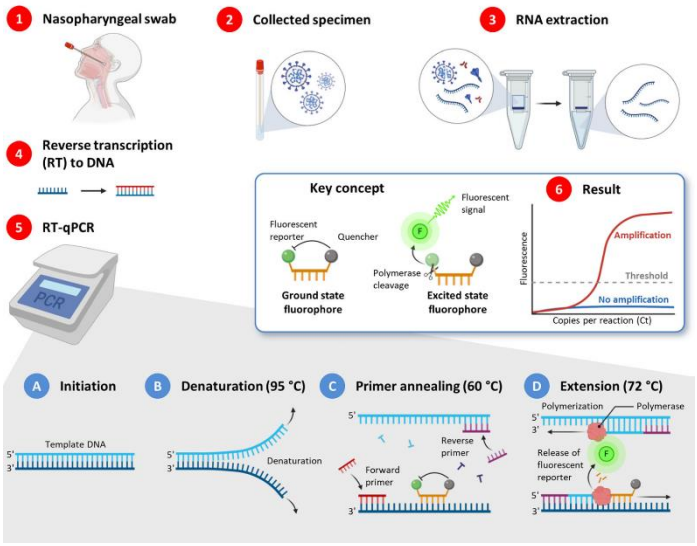

Figure 1 Covid-19 diagnostics through RT-PCR (31)

Nevertheless, other methods like isothermal nucleic acid amplification assays, serological and immunological assays for anti-SARS-CoV-2 antibodies, hybridization microarray assays, and chest CT scans are available (32–34). The biggest challenge is identifying asymptomatic cases to prevent the spread of the disease. Therefore, it is crucial to have accurate diagnostics available. The most important method is the Real-Time Reverse Transcription Polymerase Chain Reaction producing reliable results in a few hours (35). The sensitivity depends on the amount of RNA obtained from each sample. Tested people can be categorized into positive or negative cases. The method has a disadvantage since it shows no information about already recovered patients. Also, cases at the beginning of the disease might respond negatively (36). Serological testing is another diagnostic option. This method detects anti-SARS-CoV-2 antibodies. A standard test is enzyme-linked immunosorbent assays; in this process, IgM, IgA, IgG, or total antibodies can be discovered (37). These tests allow information about the status of the patients if they already had a Covid-19 infection or not. In vaccinated people, this is not easy to interpret. Nevertheless, they are helpful in the case of inconclusive molecular results (38). Another method is the antigen test. Unlike the PCR methods, it detects viral components (M protein, S glycoprotein, released N protein) or the virus without thermal amplification (35). On the downside, likewise, the PCR-technique antigen test gives only information about the ongoing and active infection, not about the recovered

patient. Also, imaging techniques are essential for diagnosing Covid-19. At the pandemic's beginning, they were used because of the lack of other diagnostic tools. In a study conducted by Ai et al., 1014 patients underwent both Chest CT and RT-PCR. They showed that the initial test was positive in 59%, whereas 88% of Chest CTs were positive for Covid-19. The sensitivity of the imaging technique was 97 % with the PCR as a reference. In the group of patients with an initial negative PCR result but positive Chest scan, 48 % were reevaluated as highly likely causes, and 33% were grouped as probable cases. The study showed that imaging techniques like Chest CT have a high sensitivity (39). In the early stages of the disease, the scans showed both bilateral and peripheral ground-glass opacities, while in the late stages irregular-shaped paving patterns are dominant. These abnormal findings are used as a feature for Covid-19 (40,41).

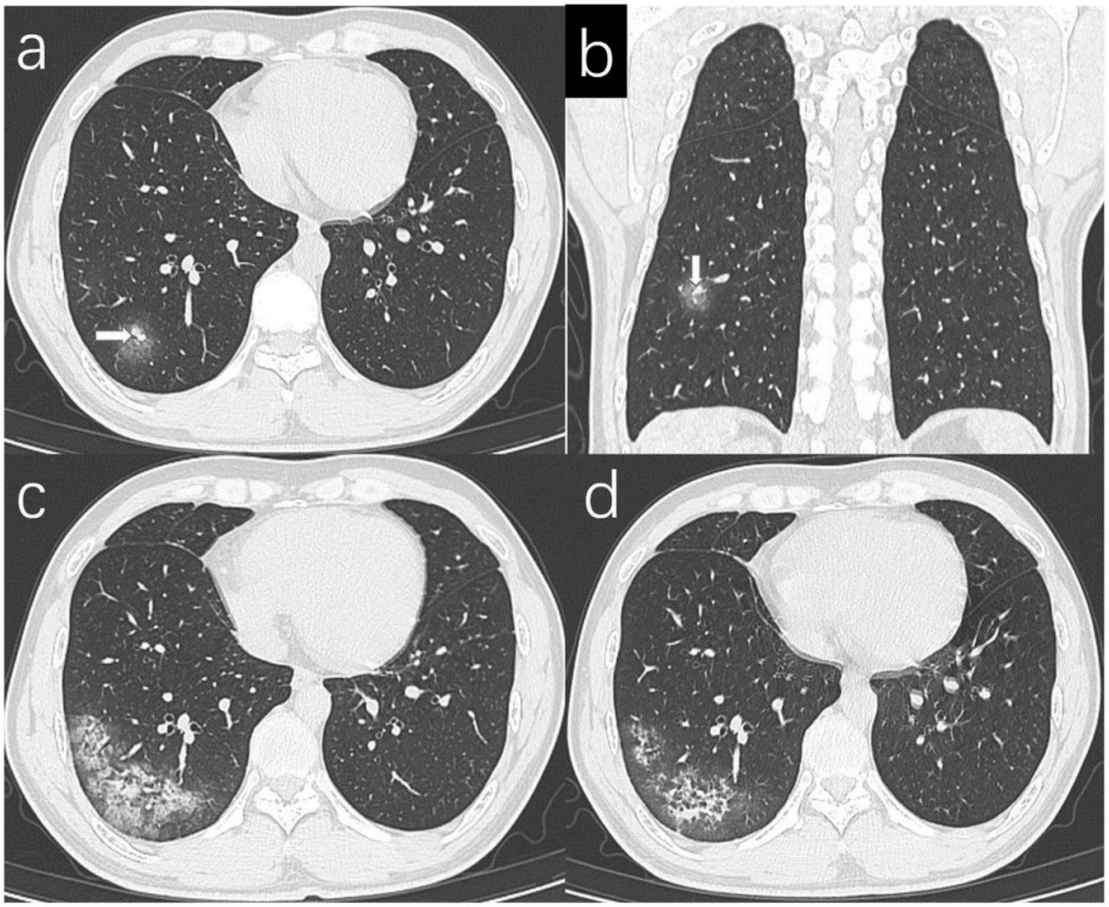

Figure 2 A 29-year-old woman with COVID-19 pneumonia. a, b Axial CT image and coronal CT image showed ground-glass opacification accompanied with thickened small vessels (arrow) in the right lower lobe on day nine after symptom onset; c The first follow-up CT image (5 days after initial CT) showed the ground-glass opacification obviously enlarged mixed with consolidation. d The second follow-up CT image showed the opacification gradually absorbed and the density of the lesion reduced. (41)

7.2 Diagnosis of End-stage renal disease

Diagnostic criteria for chronic kidney disease are a glomerular filtration rate of fewer than 60 ml/min/1.73m^2 and a marker of kidney damage for more than three months. These markers could be

albuminuria, urine sediment abnormalities, or abnormalities because of tubulointerstitial dysfunction, which could be displayed as reduced production of erythropoietin, electrolyte and acid-base imbalances, or retention of nitrogenous wastes. Other criteria include the history of renal transplant, histological abnormalities on a biopsy, and irregularities shown on an image. Chronic kidney disease progression is diagnosed by a fall in renal function resulting in a change in the glomerular filtration rate. A worsening of the status quo is determined as a change to a lower category and a drop of more than 25% in terms of estimated GFR from the baseline (9). End-stage renal disease is diagnosed with an estimated GFR of less than 15 mL/min/1.73m^2. Additionally, there must be a manifestation of uremia that require chronic renal replacement therapy with dialysis or renal transplantation (42). Astor et al. showed in their meta-analysis of 13 studies, including 21688 patients with chronic kidney disease, the importance of eGFR and albuminuria. Both markers are robust independent markers for mortality and progression to end-stage renal disease. In the lower categories of eGFR, the mortality rate was higher. This was also true for albuminuria, with higher mortality rates in patients with more prominent albumin levels. The authors find the same results for the risk and progression of end-stage renal disease. The rates were independently higher for patients with low eGFR and patients with higher levels of albuminuria (43).

8 Management

8.1 Prevention

In their systemic review and meta-analysis, Nopsopon et al. showed that patients with end-stage renal disease have a higher incidence of Covid-19 infection, 3.10%, than the global average of 0.14%. Moreover, they demonstrated a higher case-fatality rate in patients with an end-stage renal disease with renal replacement therapy compared to the worldwide average. In patients with kidney failure, the case-fatality rate was 18.06% compared to 4.98% (44). These high numbers in incidence and mortality might be connected to the changes in the immune system of patients with end-stage renal disease. The progressive loss of the kidneys' function leads to impairments of the innate and adaptive immune systems. In the last stage, this results in a high susceptibility to infections, both bacterial and viral, and weak responses to vaccinations (45). One of the critical mechanisms in the decreased immune response in these patients is uremia. This disease is defined as the retention of nitrogenous compounds and cytokines due to failed kidney clearance (46). This is described as a state of chronic immune activation and chronic immune suppression (47). The altered immune status in these patients shows the importance of measurements to prevent the transmission of SARS-CoV-2. The transportation to the dialysis should be organized. In the case of an infection, facilities must be able to provide dialysis for these patients (48). The facility should train the staff members to minimize the risk of transmitting the infection. This

includes self-monitors symptoms to recognize suspicious signs connected to the Covid-19 condition. In case of contact with a Covid-19 positive person, they should provide this information. To further prevent the infection clusters, sick team members should stay at home. The facility should have trained personnel that can take nasopharynx swabs to detect Covid-19. Patients should remain at home on their non-dialysis days and should reduce their social interaction, especially the interaction with children should be avoided, since they are often transmitting the infection without showing any symptoms. Important information about hygiene should be shared by the facility. The distance in-between the stations should be at least 2 meters. The whole facility must be equipped with a modern ventilation system to remove aerosols sufficiently from the environment. Before and after the treatment, the patient's temperature should be checked. It is crucial that patients with respiratory symptoms are identified by the staff. In case of self-recognition of symptoms, they should inform the hospital before arrival. The treatment should take place in a different area of the hospital, separated from other dialysis patients. After the treatment, the room must be cleaned thoroughly. The team of the department should be divided into working with high-risk and low-risk patients. In the special case of patients which receiving the dialysis treatment at home, it is crucial to avoid hospital visits for as long as possible (48).

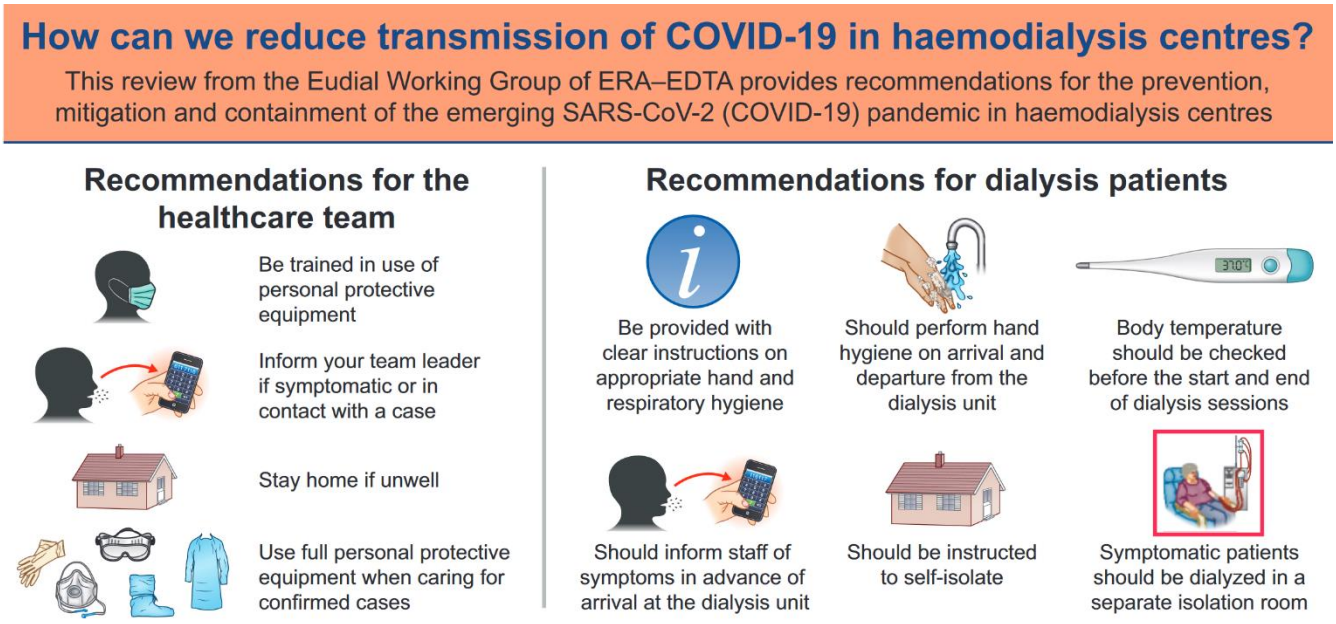

Figure 3 Prevention of transmission of Covid-19 in hemodialysis centers (48)

Studies suggest that patients receiving peritoneal dialysis or hemodialysis at home have a significantly lower risk for Covid-19 infection than patients within center treatment (49). A different form to prevent the illness or a severe course of the disease and its transmission is vaccination. Even though the effect of vaccines in patients with end-stage renal disease is altered (45), it can be an effective measure. Fu et al.

showed in their study the effectiveness of vaccination in terms of severity and mortality in ESRD patients. In their observational study, they divided 303 patients into vaccinated and non-vaccinated. The vaccinated patient group had a significantly lower incidence of severe course (33.8% vs. 69.7%) and also lowered mortality (12.2% vs. 38.7%) compared to the non-vaccinated group (50). Freitas et al. showed the antibody production response to the Pfizer vaccine. Their results indicated that patients on maintenance hemodialysis have a lower response than the general population. Moreover, patients with hemodialysis treatment have a much shorter time of immune protection after receiving the second dose of the vaccine (51). Fu et al. showed that vaccination reduces severity and mortality in ESRD. Nevertheless, patients with chronic kidney disease are still at high risk, regardless of their vaccination status. Therefore, they showed the importance of a scoring system to predict the severity of disease in vaccinated patients with breakthrough infection. Important predictors of the severity, according to this study, are the cyclic threshold value, the white blood cell count, and the absolute lymphocyte count (52).

8.2 Treatment

The pharmacological therapies for the Covid-19 positive patients are limited, but with the expanding knowledge of the virus, potential targets for medications arise. The steps of the viral lifecycle are crucial targets for drug therapy (53).

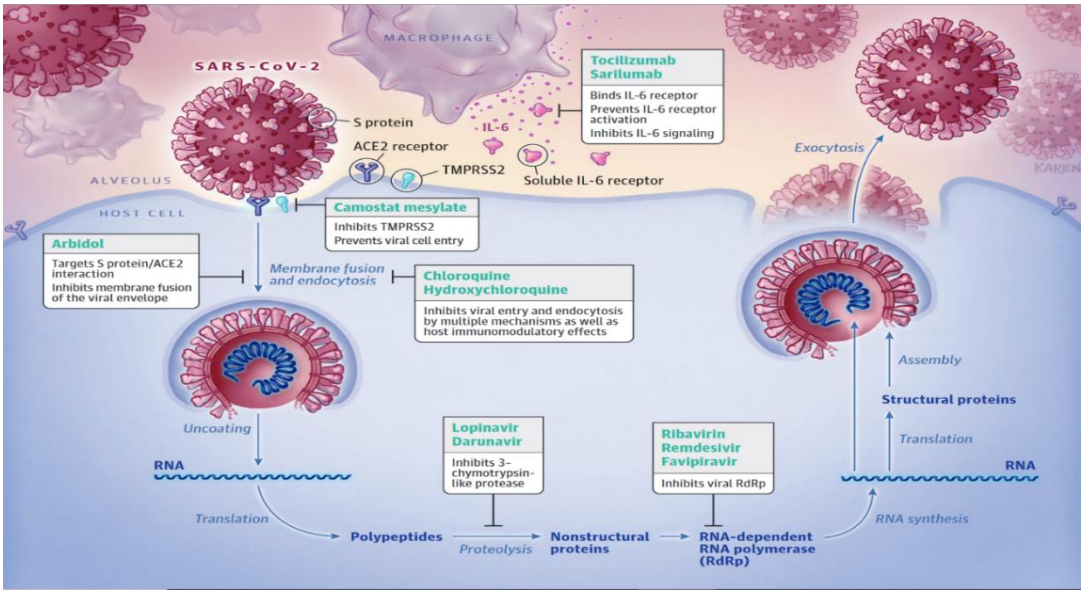

Figure 4 Viral Lifecycle and Potential Drug Targets (53)

As mentioned before, this single-stranded RNA-enveloped virus targets the host cells through a spike protein, which binds to the angiotensin-converting enzyme 2 receptors. The transmembrane serine protease 2 promotes entry(54). Inside the host cell, the virus synthesizes polyproteins that encode the replicase-transcriptase complex. After RNA synthesis, structural proteins lead to the assembly and

release of the particles (55). Possible targets for pharmacological treatment include nonstructural proteins, viral entry, and immune pathways (56). Potential drugs for these targets include but are not limited to hydroxychloroquine, tocilizumab, remdesivir, lopinavir, and favipiravir (53). The main problem for patients with chronic kidney disease with these medications is even less information about their efficiency and safety than in the general population. As most of these drugs are eliminated by the kidneys, the dosage must be adjusted. Furthermore, many of these drugs have adverse effects with potential kidney damage (57). Another problem for this affected population is that the data on the potential drugs is limited, and therefore adjustment of the dosage is difficult (58). Dexamethasone was used in the controlled, open-label trial conducted by "The RECOVERY Collaborative Group" to show the effects of the drug on the mortality of Covid-19 positive persons. The results showed a lower mortality rate in patients receiving invasive mechanical ventilation but not in patients without respiratory support (59). The dosage does not need adjustments in patients with renal diseases, but frequent monitoring is recommended (60). In the case of renal replacement therapy, it is suggested to use the same dosage since it is not significantly impacted by the therapy (61). Lopinavir, a protease inhibitor licensed for HIV treatment, and given together with the booster Ritonavir and is given twice daily with a dosage of 400/100mg. The study by Cao et al. showed no significant benefit for severe cases compared to standard care alone (62). The dosage in the renal patient does not need any adjustments since only 10.4% is cleared by the kidneys (63). Remdesivir is a nucleotide analog metabolized to the pharmacologically active nucleoside triphosphate metabolite. The drug and its metabolite are mainly excreted by the kidney, 49% and 10% (64). Grein et al. concluded a study that showed clinical improvement in 68% (36/53) of patients using Remdesivir. The dosage included a 200mg loading dose and 100mg for ten days (65). Even though the drug was fully licensed (66), it should not be used in patients with a filtration rate below 30 mL/min. There are two possible causes for this. Remdesivir is given together with sulfobutylether-β-cyclodextrin sodium salt (SBECD) because of its limited solubility in water (67). This vehicle accumulates in patients with renal impairments since they have a reduced renal clearance (68). The other possible mechanism is that the metabolite of Remdesivir accumulates in patients with decreased eGFR. Because of this, the drug is not recommended in patients with end-stage renal disease (58). Favipiravir could be compassionately used to treat Covid-19 infection, as Du et al. showed. This is based on the data of its original treatment target, influenza, and its known mechanism of action. The drug works by inhibiting virus replication. (69). The usage in renal impaired patients is not secure, as the drug is excreted by the kidneys (90%). The major part is the metabolites aldehyde oxidase and xanthine oxidase, which accumulate in patients with reduced filtration rates. Furthermore, Mishima et al. showed that the drug increases uric acid levels

in urine. They demonstrated adverse effects in 13 of 30 patients with renal impairment and 110 of 363 patients with normal kidney function (70). Hydroxychloroquine is the most studied drug used in the treatment of Covid-19 infections because of its low costs and accessibility (58). Sinha et al. demonstrated in their study that hydroxychloroquine could have an important influence on the treatment strategy of Covid-19 due to its antiviral mechanisms. This mainly affects the inhibition of Interleukins and the TNF-alpha. The drug shows clinical improvements in patients and decreased viral load (71). Patients with renal impairment should be treated without dose adjustments since different studies showed that the drug is safe for patients with kidney disease. Jallouli et al. showed this already in 2015 in patients with lupus erythematosus. Even though the concentration of hydroxychloroquine was significantly higher, with impaired renal function, it was still in the therapeutic window. Furthermore, the study showed the drug is not affected by dialysis (72). In the case of using the drug for short time treatment of Covid-19, is it rather safe for patients with kidney impairment, but if HCQ is used for long-term use such as in prophylaxis, the risk of retinopathy and cardiomyopathy in patients with chronic kidney disease significantly increases (73). Ribavirin is a drug that affects viral RNA replication and translation by several mechanisms of action (74). Ribavirin is excreted by the kidneys (62%) and in patients with declining renal function the exposure and toxicity of the drug increase. Additionally, the drug is not cleared by dialysis, therefore this drug must be dose-adjusted in patients with renal impairments and renal replacement therapy (58). Tocilizumab is a monoclonal antibody against the interleukin-6 receptor, which is licensed for rheumatoid arthritis and juvenile idiopathic arthritis. As patients with Covid-19 can suffer from a cytokine storm this drug was thought to be useful, but the study by Rosas et al. showed no significant better clinical status of the patients or lower mortality 28 days after infection (75). Anakinra is a drug also licensed for the treatment of rheumatoid arthritis. It is a recombinant human interleukin receptor antagonist, that blocks the pro-inflammatory effects of interleukin-1 (76). Cavalli et al. investigated the effect of Anakinra in Covid-19 infected patients. They demonstrated in their retrospective cohort study that the drug significantly improves the outcome. The survival rate in the patient group receiving high-dose of the anakinra was 90% whereas in the control group the survival was 56%. Another observational finding of the study was the rate of mechanical ventilation-free was higher in the anakinra group. 72% compared to 50% in the standard group (77). The kidney function of the patient is directly connected to the clearance of this drug (78). Therefore, the dosage must be adjusted accordingly. Patients that have an altered renal filtration but the eGFR is above 30mL/min should receive 100% of the dosage. Patients with eGFR below 30mL/min or ESRD, which have a renal clearance of 70% respectively 75% should receive the same dosage but only every second day (58).

9 Conclusion

This thesis aimed to show the impact of Covid-19 in patients with end-stage renal disease. Based on the research that was conducted, it was shown that the SARS-CoV-2 pandemic has a major effect on this group of patients. It was demonstrated that mortality in patients with chronic kidney disease is significantly higher than in the healthy population in the case of Covid-19 infection. Furthermore, the course of the infection is considerably more severe in patients with kidney damage. This work intended to show possible pathological pathways for kidney damage after transmission of and infection with the virus. The thesis also demonstrated the signs and symptoms of both diseases as well as diagnosing criteria and processes. The major part of this work showed the challenges that lie ahead for end-stage renal disease patients. It investigated the measures for prevention. Based on the findings, it would be recommended to develop global guidelines for the treatment of end-stage renal disease patients in this pandemic and for possible similar situations in the future. The pharmacological treatment is currently under investigation in many studies for different agents. This research showed a few promising drugs used in Covid-19 positive patients but also made clear that there are even more challenges for the patients with end-stage renal disease, stretching from dose adjustments up to contraindication of the drug in this patient group. Many drugs are under investigation, but it would be recommended to conduct more research on drug safety in chronic kidney disease patients. International treatment guidelines could improve the work of the physicians and the outcome for the patients in the future to reduce the higher mortality rates in Covid-19 patients with end-stage renal disease.

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