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Abstract of a dissertation

On the topic of:

COVID-19 in patients with end-stage renal disease, complications, risk factors, mortality

for the award of the educational and scientific degree

"Doctor"

Scientific supervisor:

Assoc. Prof. Dr. Alexander Stoyanov, MD

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CONTENTS

ABCRONYMS USED

CKD – Chronic kidney disease

DKD – Diabetic kidney disease

KRT – Kidney replacement therapy

HIV – Human immunodeficiency virus

WHO – World health organization

ARDS - Acute respiratory distress syndrome

RNA - Ribonucleic acid

COPD – Chronic Obstructive Pulmonary Disease

RRF - residual renal function

CVD - cardiovascular diseases

KDIGO - Kidney Disease: Improving Global Outcomes

NKF - American National Kidney Foundation

CGA - KDIGO classification system

eGFR – estimated glomerular filtration rate

YLL - Years of Life Lost

ESRD - End-Stage Renal Disease

ADPKD - autosomal dominant polycystic kidney disease

COVID-19 – coronavirus disease 2019

SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2

VOC - variant of concern

ACE2 - angiotensin-converting enzyme 2

IL-1β – interleukin 1β

IL-6 – interleukin 6

TNF-α – tumor necrosis factor – alpha

PAAC - renin-angiotensin-aldosterone system

CAR-T – chimeric T-cell receptor

mRNA – messenger RNA

POTS - postural orthostatic tachycardia syndrome

CRP – C-reactive protein

HD - Hemodialysis

HDF - Hemofiltration

URR – urea reduction ratio

IDWG - interdialysis weight gain

CRRT - continuous renal replacement therapy

SLED – sustained low-efficiency dialysis

RSV - respiratory syncytial virus

PASC - postacute consequences of SARS-CoV-2 infection

PCR – protein catabolic rate

nPCR – normalized protein catabolic rate

ERA-EDTA – European renal asociation

USRDS - US Kidney Disease Data System

PEW - protein-energy malnutrition

NOS - Newcastle–Ottawa scale

MCO – dialyzers removing molecules with an medium cut-off size

UF – ultrafiltration

INTRODUCTION:

The infection caused by the novel coronavirus SARS-CoV-2 has triggered a global health crisis with profound medical, social and organizational consequences. Since the beginning of 2020, COVID-19 has become one of the most significant challenges facing modern medicine, putting healthcare systems around the world under pressure and requiring the adaptation of clinical practices to the dynamically changing epidemiological environment. Patients with chronic diseases and patients with a compromised immune system have been particularly affected, in whom the risk of severe illness, complications and fatal outcome is significantly higher compared to the healthy population.

Among the most vulnerable groups of patients are patients with end-stage renal disease (ESRD) undergoing chronic hemodialysis. Chronic uremia is associated with complex disorders in the immune system. In addition, patients on chronic hemodialysis are often elderly and have many comorbidities such as arterial hypertension, cardiovascular diseases and diabetes mellitus. All of these factors put them at particularly high risk of exposure to SARS-CoV-2.

Of additional importance is the organizational aspect of dialysis treatment. Patients on hemodialysis are unable to maintain complete home isolation, as they must visit a dialysis center three times a week, where they are in necessary physical contact with medical staff and other patients. This greatly increases the likelihood of infection and makes dialysis units

epidemiologically vulnerable structures. At the same time, COVID-19 can lead to a number of complications specific to hemodialysis patients, including hemodynamic instability, increased blood clotting during and outside the hemodialysis procedure, and missed or shortened procedures, which further compromises their treatment.

International data from numerous cohort studies show that in dialysis patients, COVID-19 is more severe and is associated with higher morbidity and mortality, reaching 20–30% in some countries in the early phases of the pandemic. However, the available data are heterogeneous and highly dependent on the national context, vaccination coverage levels, the organization of the health system, as well as the characteristics of the dialysis population. For Bulgaria, there is a lack of sufficient studies that systematically analyze the characteristics of the clinical course, factors affecting survival, and the impact on the quality of dialysis treatment.

In this context, there is a need for an in-depth study to characterize the impact of COVID-19 on chronic hemodialysis patients in our country, to compare clinical outcomes between patients with and without proven infection, and to identify key predictors of adverse outcome. Of particular interest are indicators of dialysis adequacy, such as URR and Kt/V, as well as their dynamics before and after infection, as they reflect the quality of treatment and can serve as modifiable factors affecting survival.

The present dissertation aims to fill this significant gap in the national scientific literature by presenting a comprehensive analysis of the clinical, epidemiological and dialysis characteristics of hemodialysis patients in the context of the COVID-19 pandemic. The study was conducted on a large cohort of patients treated at the University Hospital "St. Marina" - Varna, and offers a comparative approach based on statistically significant clinical indices and survival indicators. Through its results, the dissertation aims to provide a deeper understanding of the risks to which dialysis patients are exposed, as well as to outline possible directions for improving clinical practice and organizational strategies in future pandemic or epidemic situations.

CHAPTER ONE: PURPOSE AND OBJECTIVES.

Objective: To determine the impact of the COVID-19 pandemic on a population of chronic hemodialysis patients undergoing the same at the University Hospital "St. Marina" in Varna.

Objectives:

1. To study the survival and causes of death in chronic hemodialysis patients with COVID-19.
2. To analyze the demographic characteristics (age, gender) and comorbidities (diabetes, hypertension, cardiovascular diseases) in the monitored dialysis cohort.
3. To investigate the relationship between SARS-CoV-2 infection and vaccination status as predictors of hemodialysis effectiveness and clinical outcome.
4. To determine the relationship between the quality of hemodialysis (measured by URR and Kt/V) and clinical outcomes, including the duration of hospitalization, severity of the course and 6-month survival.
5. To determine whether there is a change in the effectiveness of the dialysis procedure before and after COVID-19 infection, by comparing URR and Kt/V in patients.

CHAPTER TWO. MATERIALS AND METHODS.

2.1. Study design

A retrospective observational cohort study was conducted at the Nephrology and Dialysis Clinic of the University Hospital "St. Marina", Varna, Bulgaria.

The studied cohort included patients on chronic hemodialysis, divided into two groups: with proven COVID-19 infection and without evidence of infection during the pandemic period 2020–2022. Data were extracted from the electronic hospital information system and medical records

2.2. Population and selection criteria

A total of 190 patients were included in the analysis, of which group A - 101 with a positive PCR or rapid antigen test for COVID-19 and group B - 89 without confirmed infection during the follow-up period. Clinical and demographic data were collected from medical records, including: Age and gender, comorbidities (e.g. diabetes, cardiovascular disease), dialysis quality indicators (URR, Kt/V), length of hospital stay due to COVID-19, presence and severity of complications after infection, survival in the period of 6 months after proving COVID-19 infection, vaccination status.

2.2.1. Inclusion criteria

- age ≥18 years;
- proven SARS-CoV-2 infection (PCR or rapid antigen test);

- patients undergoing chronic renal replacement therapy (hemodialysis) for at least 6 months prior to the start of follow-up.

2.2.2. Exclusion criteria

- age < 18 years;
- patients with CKD in the pre-dialysis stage/after kidney transplantation

Thus, a homogeneous cohort was formed, suitable for the analysis of renal complications in COVID-19.

2.3 Statistical analysis

Various statistical analyses were performed. The χ^2 test was used to assess the associations between groups and clinical outcomes, and binomial logistic regression was used to examine factors associated with mortality. Multinomial logistic regression was used to determine the determinants of the various causes of mortality. Kaplan–Meier analysis and Cox regression helped identify independent predictors of mortality.

Statistical processing was performed using Jamovi version 2.2.2. Paired samples T-test and Wilcoxon W test were used for the monitored indicators, and Independent samples T-test and Mann-Whitney U test were used for the remaining variables.

2.4 Laboratory parameters

2.4.1. PCR for SARS-CoV-2 - Gold standard for proving COVID-19 infection; uses reverse transcription and real-time amplification (RT-PCR).

2.4.2. Rapid antigen test for SARS-CoV-2 - Used for screening for active infection and as an additional diagnostic method in symptomatic patients; Immunochromatographic method.

2.4.3. Dialysis adequacy indicators (URR и Kt/V)

Urea Reduction Ratio (URR) and Kt/V are the two main indices for evaluating the effectiveness of hemodialysis. URR is the ratio between the initial and final urea in the serum, while Kt/V also includes parameters such as dialysis clearance, procedure duration, and volume of distribution in the calculation.

CHAPTER THREE. RESULTS.

3.1. Characteristics of the study cohort

The demographic characteristics of the study cohort include a total of 190 chronic hemodialysis patients followed in the period 2020–2022. Of these, 108 were female (56.8%) and 82 were male (43.2%), with a mean age of 62.7 years. The youngest included patient was 32 years old and the oldest was 88 years old, reflecting a wide age range and allowing analysis of both young and elderly dialysis patients. Of all participants, 101 (53.2%) had at least one positive PCR or rapid antigen test for COVID-19 during the pandemic period and were included in group A (COVID-19 positive). The remaining 89 patients (46.8%), in whom no evidence of past or proven SARS-CoV-2 infection was found, constituted group B (COVID-19 negative). This division allows for a direct comparison between the two groups in terms of clinical course, complications and mortality. (Table 1)

A total of 98 deaths were recorded during the follow-up period, representing 51.57% of the entire cohort. Of these, 55 cases (56.12% of deaths) occurred among patients with proven COVID-19 infection (group A) and 43 (43.87% of deaths) in control group B. (Table 1)

These results highlight the high vulnerability of chronic hemodialysis patients and indicate a significant risk of adverse outcome in both COVID-19 infected and uninfected patients, which likely reflects the combined impact of severe comorbidity and the general immunosuppressive environment typical of this population.

Indicator		COVID-19 positive group (Group A)	COVID-19 negative group (Group B)	Total
Number		101	89	190
Age	average	62.7 years	61.9 years	62.7 years
	median	66 years	62 years	64 years
Gender (number)	Men	62	46	108
	Women	39	43	82
Comorbidities (number)	Cardiovascular disease	64	58	122
	Diabetes	32	26	58
Vaccinated (number)		69	64	133
Deaths (number)		55	43	98

Table 1: Demographic and clinical characteristics of patients by COVID-19 status

In group A (COVID-positive), there is a more pronounced cluster of patients in the age range of 60–70 years, with the curve showing a peak around this age. In group B (COVID-negative), the distribution is more even, with a broader distribution in the interval of 50–75 years and several distinct peaks. Although in both groups there is a concentration of patients in the older age range.

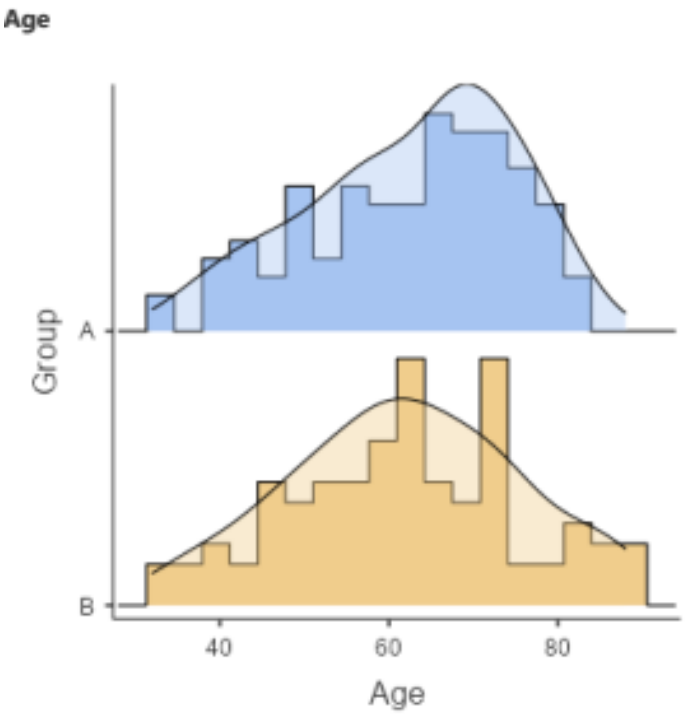

Fig.1: Age distribution in the two monitored groups (A and B)

Figure 2 presents the age distribution of patients by group using a violin plot. The mean age was similar between group A and group B, with a typical clustering of patients in the 60–75 age range in both groups. In group A, the median was approximately 66 years, while in group B it was approximately 62 years. Despite the presence of younger and older patients in both groups, the difference in mean age between them did not reach statistical significance. This suggests that the age profile of the two groups was similar and was not a major confounding factor in the analysis.

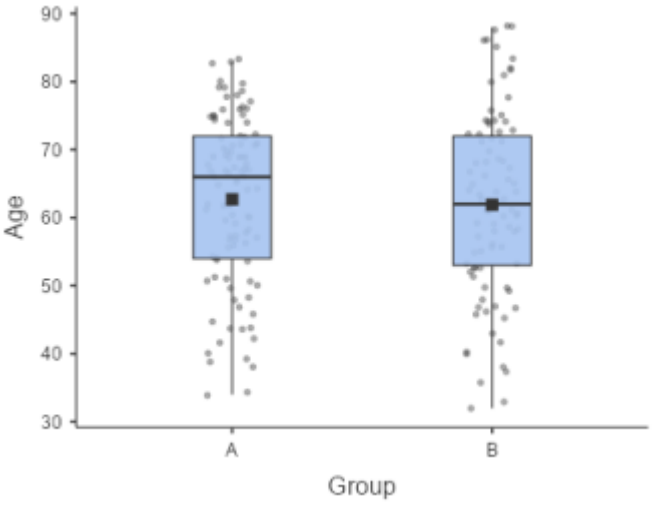

Fig.2: Violin diagram of the age distribution of patients

3.2 Comorbidities

In the studied cohort of 190 patients on chronic hemodialysis, a significant proportion of participants had comorbidities, which is expected given the advanced age and high degree of comorbidity in this population. A total of 123 patients (64.7%) had diagnosed cardiovascular disease, which included conditions such as arterial hypertension, ischemic heart disease, chronic heart failure and rhythm disorders. This highlights the central role of cardiovascular pathology as a leading comorbidity in this group of patients. When distributed by groups, it was found that in the COVID-19 positive group (group A) 64 patients (63.4%) had cardiovascular disease, while in the control COVID-19 negative group (group B) their number was 59 (66.3%). This indicates that the high incidence of cardiovascular disease is relatively evenly distributed between the two groups, which eliminates the possibility that the outcome

results are due solely to an imbalance in the prevalence of this comorbidity. (Table 2)

Diabetes mellitus is also among the significant comorbidities in the cohort, with a total of 58 patients (30.5%) having an established diagnosis. In them, diabetes often appears as a primary cause or contributing factor for the development of chronic kidney disease, as well as for aggravating cardiovascular risk. Of the diabetics, 32 (55.2%) were in the group with confirmed COVID-19 infection (group A), while 26 (44.8%) belonged to the control group (group B). This distribution suggests that diabetics were not spared from the risk of SARS-CoV-2 infection and represent a particularly vulnerable subgroup of dialysis patients. (Table 2)

Statistical analysis using the binomial test showed that the prevalence of cardiovascular disease in the entire cohort (64.2%, 95% CI [57.0–71.0]) was statistically significantly higher than the expected theoretical frequency of 50% ($p < 0.001$). This confirms that cardiovascular pathology is a leading characteristic of hemodialysis patients and that this group of patients is exposed to a particularly high risk of cardiovascular complications and mortality. Conversely, the frequency of diabetes mellitus (30.5%, 95% CI [24.1–37.6]) was statistically significantly lower than 50% ($p < 0.001$), which means that although diabetes is a significant risk factor, it is not a dominant comorbidity in this cohort, but nevertheless has an important impact on clinical outcomes.

These data clearly highlight the burden of cardiovascular disease in hemodialysis patients and emphasize the need for systematic control of cardiovascular risk factors. At the same time, the presence of diabetes, although less common, remains a key risk

feature, especially in the presence of concomitant COVID-19 infection, which requires special attention to the individualized approach in the treatment and follow-up of this high-risk group of patients.

Binomial Test

	Level	Count	Total	Proportion	p
CVD	**1**	122	190	0.642	<.001
	0	68	190	0.358	<.001
Diabetes Mellitus	**0**	132	190	0.695	<.001
	1	58	190	0.305	<.001

Note. H_a is proportion ≠ 0.5

Table 2: Distribution of comorbidities among hemodialysis patients with and without COVID-19

3.3 Causes of death

As for the cause of death, patients were divided into 4 groups: 1 – Died from COVID-19 infection or its complications, 2 – Died from cardiovascular disease and its complications, 3 – Died from other or unknown causes, 0 – Patients who remained alive at the end of follow-up. (Table 3)

Contingency Tables

Group		Cause of Mortality				
		Other	Cardiovascular events	COVID-19	Survivors	Total
A	Observed	22	8	25	46	101
	Expected	25.0	13.8	13.3	48.9	101.0
	% within row	21.8%	7.9%	24.8%	45.5%	100.0%
B	Observed	25	18	0	46	89
	Expected	22.0	12.2	11.7	43.1	89.0
	% within row	28.1%	20.2%	0.0%	51.7%	100.0%
Total	Observed	47	26	25	92	190
	Expected	47	26	25	92	190
	% within row	24.7%	13.7%	13.2%	48.4%	100.0%

χ^2 Tests

	Value	df	p
χ^2	28.4	3	<.001
N	190		

Table 3: Causes of death in hemodialysis patients by COVID-19 status

3.4 Total mortality

The overall mortality rate among hemodialysis patients in the studied cohort (A and B) was high, which highlights the severity of COVID-19 infection and the multifactorial risks in this vulnerable population. During follow-up, more than half of the included patients (51.6%) died, indicating an extremely poor prognosis for dialysis patients. These data fit into the available international literature, which also reports high mortality rates in hemodialysis patients infected with SARS-CoV-2, often reporting values above 30–40%, and in some populations even higher. When considering the distribution by group, it was found that mortality was similar between patients with proven COVID-19 infection (group A) and those without registered infection (group B). In group A, the mortality rate reached 54.5% (55 out

of 101 patients), while in group B it was 48.3% (43 out of 89 patients). Although at first glance a slightly higher mortality rate is observed among patients with proven infection, statistical analysis does not show a significant difference between the two groups ($\chi^2 = 0.714$; $p = 0.398$). This means that belonging to group A or group B cannot be considered as an independent predictor of the risk of fatal outcome. (Table 4)

It is important to note that in both groups the patients were exposed to a number of other risk factors – advanced age, high incidence of cardiovascular diseases and diabetes, as well as long-term dialysis treatment. All of these factors probably contributed to the high mortality rate, regardless of COVID-19 infection. This confirms the concept that the prognosis of dialysis patients is multifactorial and that SARS-CoV-2 infection is only one of many factors that worsen the clinical outcome.

The results of our study (Fig. 3) show that although COVID-19 infection is a significant stress factor for hemodialysis patients, its presence alone is not sufficient to explain the high mortality. Much more important is the interaction with pre-existing comorbidities and limited compensatory mechanisms of these patients. This emphasizes the need for a comprehensive assessment and individualized therapeutic approach that takes into account all risk factors, not just the infectious status.

Contingency Tables

Group		Mortality 1	Mortality 0	Total
A	Observed	55	46	101
	% within row	54.5%	45.5%	100.0%
B	Observed	43	46	89
	% within row	48.3%	51.7%	100.0%
Total	Observed	98	92	190
	% within row	51.6%	48.4%	100.0%

χ^2 Tests

	Value	df	p
χ^2	0.714	1	0.398
N	190		

Table 4: Comparison of mortality in hemodialysis patients according to COVID-19 status

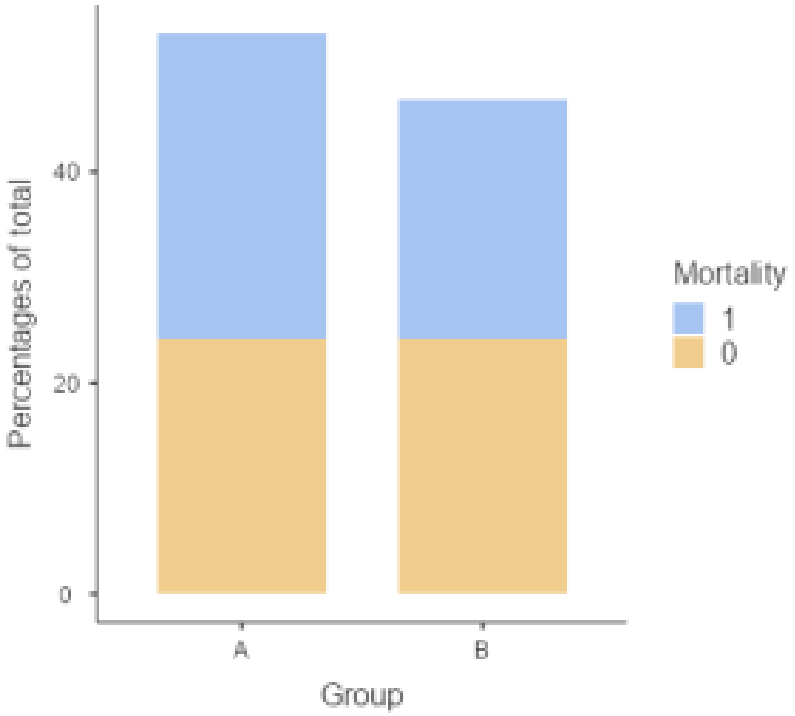

Fig.3 Percentage ratio of survival and lethal outcomes in group A and group B. (0-survivors at the end of follow-up; 1- death due to any cause).

3.5. Mortality factors

The binary logistic regression model used to assess the factors associated with the lethal outcome in the studied cohort clearly showed that two indicators have the most significant and independent impact on mortality. The first of these is the age of the patients – the analysis demonstrated that with increasing age the probability of an unfavorable outcome increases significantly, and this relationship was statistically confirmed ($p = 0.026$). This corresponds to the already well-known trend in

clinical practice and literature, according to which age is one of the strongest and universal risk factors for mortality in patients with chronic kidney disease and in severe infections such as COVID-19. The second factor of distinct importance is the presence of cardiovascular diseases (CVD), which show a very strong association with mortality ($p < 0.001$). Patients with a history of CVD were found to have a clearly higher risk of lethal outcome, regardless of other concomitant conditions. (Table 5)

Binomial Logistic Regression

Model Fit Measures

Model	Deviance	AIC	R^2_{McF}
1	218	232	0.170

Note. Models estimated using sample size of N=190

Model Coefficients - Mortality

Predictor	Estimate	SE	Z	p
Intercept	1.3612	0.9420	1.445	0.148
Age	-0.0315	0.0141	-2.232	0.026
Group:				
B – A	0.2760	0.3336	0.827	0.408
Gender:				
Female – Male	0.0975	0.3431	0.284	0.776
CVD:				
0 – 1	1.6304	0.3731	4.370	<.001
Diabetes Mellitus:				
1 – 0	0.0659	0.3766	0.175	0.861
Vaccination:				

Note. Estimates represent the log odds of "Mortality = 0" vs. "Mortality = 1"

Table 5: Results of binomial logistic regression for mortality in chronic hemodialysis patients with COVID-19.

3.6 Causes of death

The examination of factors associated with mortality in chronic dialysis patients revealed that belonging to group A (COVID-positive) alone is not an independent predictor of risk of fatal outcome (Estimate = 0.276, p = 0.408). This means that the presence of proven SARS-CoV-2 infection is not sufficient to predict increased mortality if other clinical and demographic factors are not taken into account. The strongest and most convincing influence is exerted by the presence of cardiovascular diseases – these patients show a more than fivefold higher probability of fatal outcome (Estimate = 1.630, $p < 0.001$; OR $\approx$ 5.1), which emphasizes the central role of cardiovascular comorbidity in the course of COVID-19 in dialysis patients.

Age also emerged as a significant factor: with advancing years, the risk of death gradually increased (Estimate = -0.0315, p = 0.026), reflecting the accumulation of additional vulnerabilities and a decrease in physiological reserves. Vaccination status, on the contrary, showed a protective effect – vaccinated patients had an approximately 53% lower risk of death compared to unvaccinated patients (Estimate = -0.7587, p = 0.042; OR $\approx$ 0.47). This finding is particularly important from a practical point of view, as it highlights the effectiveness of immunization strategies even in patients with advanced kidney disease and severe comorbidities.

In contrast, the presence of diabetes mellitus (Estimate = 0.0659, p = 0.861) and gender (Estimate = 0.0975, p = 0.776) did not show a statistically significant effect on survival. This suggests that although diabetes and gender are important demographic and clinical characteristics, within the current model they do not

contribute significantly to the risk of death. Overall, the model explained about 17% of the variation in mortality (R^2McF = 0.170), which highlights that in addition to the factors studied, there are likely other determinants of outcome in this high-risk population that were not captured in the current analysis. These results are illustrated in Table 6 and Figure 4.

Contingency Tables

		Cause of Mortality				
Group	Gender	Other	Cardiovascular events	COVID-19	Survivors	Total
A	Male	13	4	18	27	62
	Female	9	4	7	19	39
	Total	22	8	25	46	101
B	Male	15	7	0	24	46
	Female	10	11	0	22	43
	Total	25	18	0	46	89
Total	Male	28	11	18	51	108
	Female	19	15	7	41	82
	Total	47	26	25	92	190

χ^2 Tests

Group		Value	df	p
A	χ^2	1.82	3	0.612
	N	101		
B	χ^2	NaN	3	NaN
	N	89		
Total	χ^2	4.80	3	0.187
	N	190		

Table 6: Distribution of causes of death by group and gender in chronic hemodialysis patients with COVID-19.

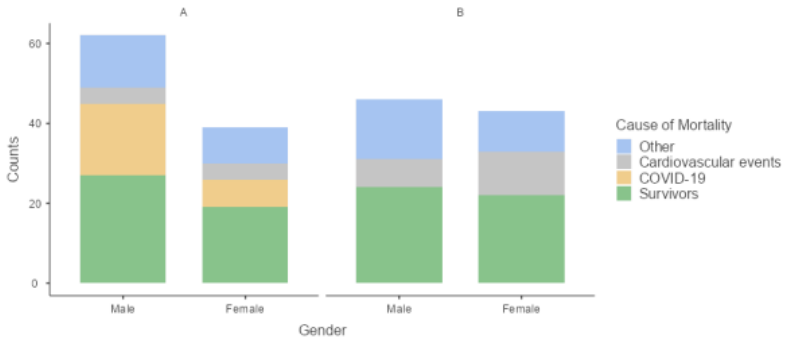

Fig. 4: Distribution of causes of death by group and gender in chronic hemodialysis patients with COVID-19.

3.7 Causes of death – predictors

The multinomial logistic regression model compared the different categories of fatal outcome (infectious complications, cardiovascular events, other/unknown) and allowed the identification of factors that increase the probability of a certain type of death. The analysis highlighted the role of several key predictors:

3.7.1. Cardiovascular disease

Cardiovascular disease emerged as the strongest independent predictor of cardiovascular death. Patients with existing CVD had an approximately six-fold higher risk of dying from cardiovascular causes compared to those without such a history (OR $\approx$ 6.4, $p < 0.001$). This highlights the significant role of concomitant cardiovascular pathology as a dominant risk factor for fatal outcome in dialysis patients, especially in the context of COVID-19.

3.7.2. Vaccination status

Vaccination against SARS-CoV-2 showed a clear protective effect. Unvaccinated patients demonstrated an approximately four-fold higher probability of death related to cardiovascular events (OR ≈ 4.4, p = 0.016). This suggests that vaccination not only reduces overall mortality but also modifies the spectrum of complications, reducing the risk of fatal cardiovascular outcomes.

3.7.3. Age

Age is confirmed as a general predictor of mortality, but in this model it does not show a statistically significant effect in distinguishing the specific cause of fatal outcome. In other words, advanced age increases the overall risk of death, but is not a determining factor in whether the fatal outcome will be infectious, cardiovascular or of another etiology.

3.7.4. Diabetes mellitus:

Diabetes mellitus, although it is among the most common comorbidities in chronic hemodialysis patients, is not confirmed as a statistically significant factor in distinguishing the specific cause of death in this model. Although diabetes is a known risk factor for the development of vascular complications, immune dysfunction and higher susceptibility to infections, its influence seems to be rather generalized – it increases the overall vulnerability of the patient, but does not indicate a predominant probability of a fatal outcome from cardiovascular or infectious etiology. (Table 7, Fig. 5)

Model Coefficients - Cause of Mortality

Cause of Mortality	Predictor	Estimate	SE	Z	p	Odds ratio	95% Confidence Interval	
							Lower	Upper
Cardiovascular events - Other	Intercept	-2.00487	1.5066	-1.331	0.183	0.135	0.00703	2.58
	Group:							
	B – A	0.62838	0.5306	1.184	0.236	1.875	0.66260	5.30
	CVD:							
	0 – 1	-15.54829	5.15e-7	-3.02e+7	<.001	1.77e-7	1.77e-7	1.77e-7
	Diabetes Mellitus:							
	1 – 0	0.40108	0.5307	0.756	0.450	1.493	0.52779	4.23
	Vaccination:							
	0 – 1	0.56697	0.5414	1.047	0.295	1.763	0.61015	5.09
	Age	0.00705	0.0211	0.334	0.738	1.007	0.96633	1.05
	Gender:							
	Female – Male	0.76873	0.5204	1.477	0.140	2.157	0.77785	5.98
COVID-19 - Other	Intercept	-2.07425	1.8821	-1.102	0.270	0.126	0.00314	5.03
	Group:							
	B – A	-17.32846	2.74e-7	-6.33e+7	<.001	2.98e-8	2.98e-8	2.98e-8
	CVD:							
	0 – 1	1.85708	0.7230	2.569	0.010	6.405	1.55277	26.42
	Diabetes Mellitus:							
	1 – 0	0.58731	0.6203	0.947	0.344	1.799	0.53337	6.07
	Vaccination:							
	0 – 1	1.48561	0.6146	2.417	0.016	4.418	1.32449	14.73
	Age	0.01582	0.0264	0.598	0.550	1.016	0.96462	1.07
	Gender:							
	Female – Male	-0.24446	0.5989	-0.408	0.683	0.783	0.24213	2.53
Survivors - Other	Intercept	1.82362	1.1130	1.638	0.101	6.194	0.69922	54.87
	Group:							
	B – A	-0.26292	0.4016	-0.655	0.513	0.769	0.34992	1.69
	CVD:							
	0 – 1	1.85885	0.4892	3.799	<.001	6.416	2.45951	16.74
	Diabetes Mellitus:							
	1 – 0	0.40097	0.4529	0.885	0.376	1.493	0.61465	3.63
	Vaccination:							
	0 – 1	-0.26943	0.4545	-0.593	0.553	0.764	0.31340	1.86
	Age	-0.02867	0.0166	-1.723	0.085	0.972	0.94057	1.00
	Gender:							
	Female – Male	0.21385	0.4091	0.523	0.601	1.238	0.55549	2.76

Table 7: Causes of death by comorbidities, age, gender, vaccination, and diagnosis of COVID-19.

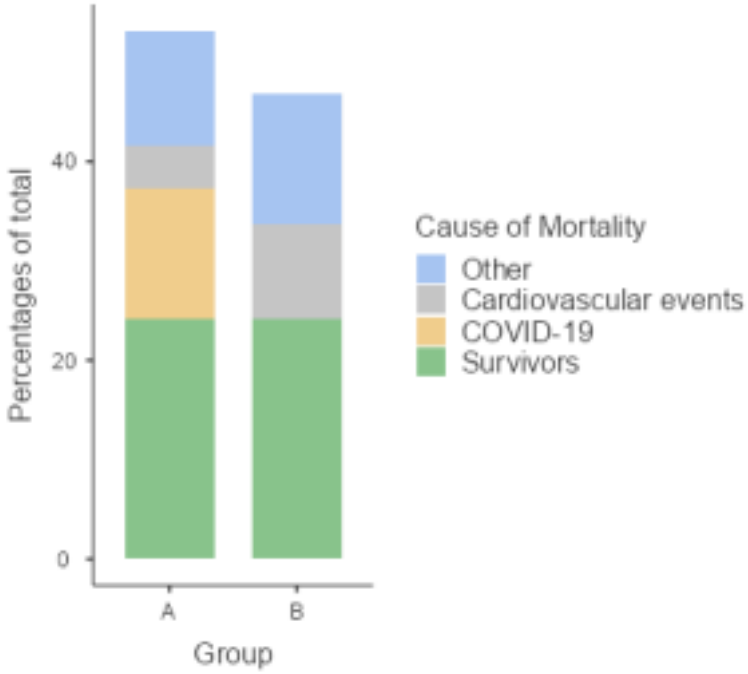

Fig.5: Percentage distribution of causes of death by groups A and B in chronic hemodialysis patients with COVID-19. 0- remained alive at the end of follow-up, 1-COVID 19; 2 – cardiovascular incident (stroke/heart attack); 3 – other/unknown.

3.8. Survival:

3.8.1. Survival by vaccination status

Survival analysis shows a clear role of vaccination as a protective factor in hemodialysis patients with COVID-19. According to Cox regression, unvaccinated patients have an almost twofold higher risk of death compared to vaccinated patients (HR=1.94; 95% CI: 1.29–2.92; p=0.002). Time analysis

confirms this trend – in vaccinated patients, survival remains high in the first months after infection (88.7% at 1 month and 84.2% at 6 months), and even after 2 years, over half (54.1%) are still alive. In contrast, in unvaccinated patients, significantly lower survival is observed at the beginning – 71.9% at 1 month and 61.4% at 6 months – and by 24 months it drops sharply to only 35.1%. (Fig.6) These data highlight the significant benefit of vaccination in reducing mortality and confirm its key role in improving long-term prognosis within the two-year follow-up.

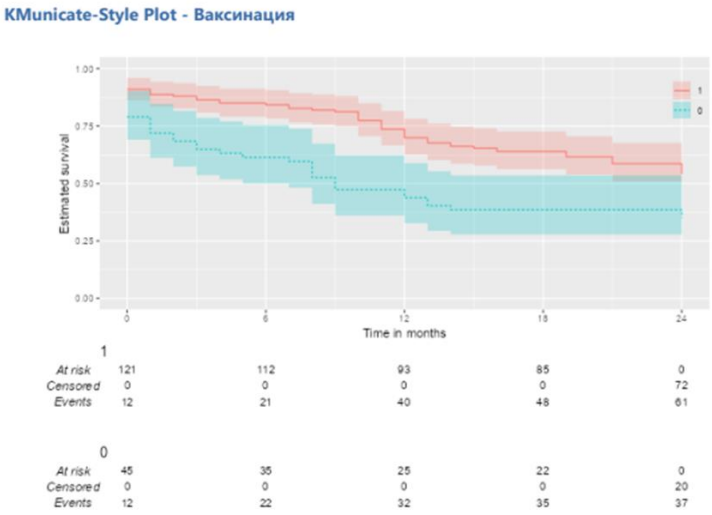

Fig. 6. Kaplan–Meier analysis of survival in chronic hemodialysis patients with COVID-19 depending on vaccination status.

3.8.2 Survival by groups

Survival in both groups of patients showed significant differences in favor of group B, which included COVID 19-negative patients. According to the Cox regression analysis,

patients in group B had a 36% lower risk of death compared to group A (HR=0.64; 95% CI: 0.43–0.95; p=0.027). Kaplan–Meier curves confirmed this trend: in group A, survival decreased from 69.3% at 1 month to 45.5% at 24 months, while in group B it remained 100% at 1 month and 97.8% at 6 months, falling to 51.7% at 24 months. The difference was most pronounced in the first year, when survival in group B reached 76.4% compared to only 49.5% in group A. (Fig. 7)

These results are also consistent with the data from the Cox regression analysis, according to which group B had a 36% lower risk of death compared to group A (HR=0.64; 95% CI: 0.43–0.95; p=0.027).

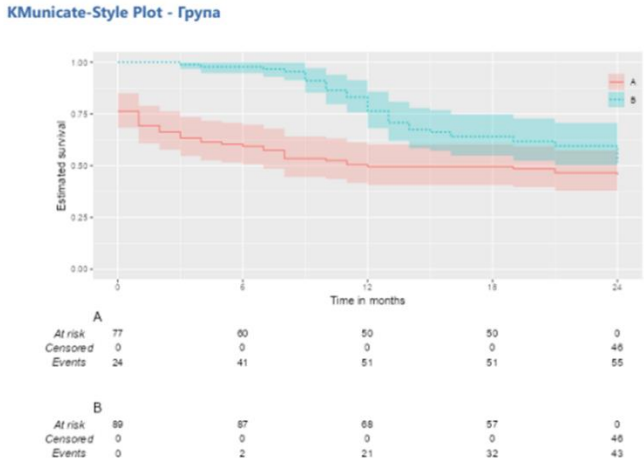

Fig.7 Kaplan–Meier survival curve within 24 months in chronic hemodialysis patients with COVID-19, stratified by groups

The results of the analysis demonstrate that survival in chronic hemodialysis patients with COVID-19 is significantly

determined by both vaccination status and group A or B affiliation. Vaccinated patients have a significantly better survival, with their risk of death being almost two times lower compared to unvaccinated patients (HR=1.94; 95% CI: 1.29–2.92; p=0.002). A similar trend is observed in group B patients, who have an approximately 36% lower risk of fatal outcome compared to group A (HR=0.64; 95% CI: 0.43–0.95; p=0.027). Kaplan–Meier curves confirm these results, clearly showing higher survival in vaccinated and group B patients within the two-year follow-up. These data highlight the importance of vaccination and clinical differences between groups as key factors for the prognosis of this high-risk population.

3.9. Quality of hemodialysis and complications in COVID-19 positive patients.

The study included 88 chronic hemodialysis patients with confirmed SARS-CoV-2 infection by PCR test. They were divided into two subgroups according to the dialysis adequacy indicator: Group A (Kt/V < 1.3) – 34 patients (38.6%) and Group B (Kt/V ≥ 1.3) – 54 patients (61.4%). (Fig.8 and 9) Of all participants, 33 (37.5%) were women and 55 (62.5%) were men. The average age of the study subjects was 64 years (range 35 to 84 years). A Kt/V value of 1.3 was used as a cutoff point because it ensures that all patients with ≥1.3 Kt/V will have good dialysis quality. The patients were followed for a period of 6 months after the positive COVID-19 test.

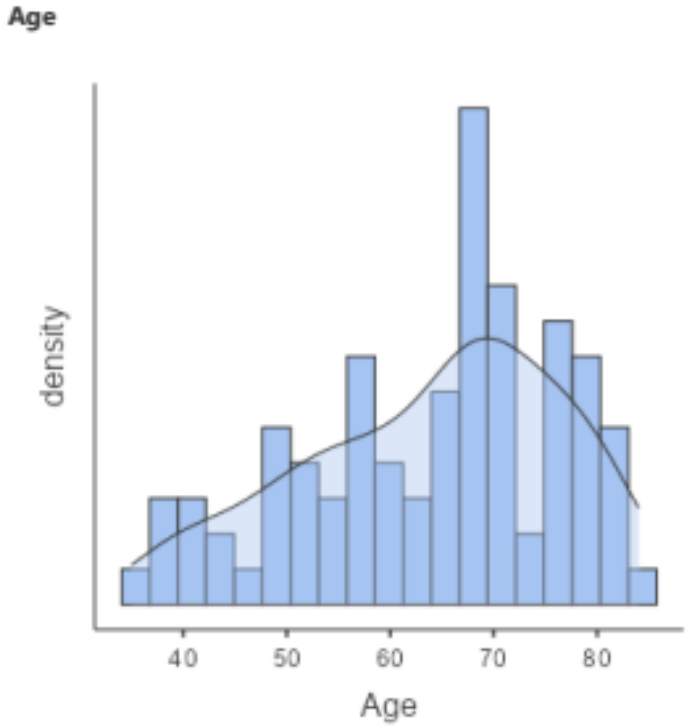

Fig 8: Histogram of age distribution in chronic hemodialysis patients with COVID-19.

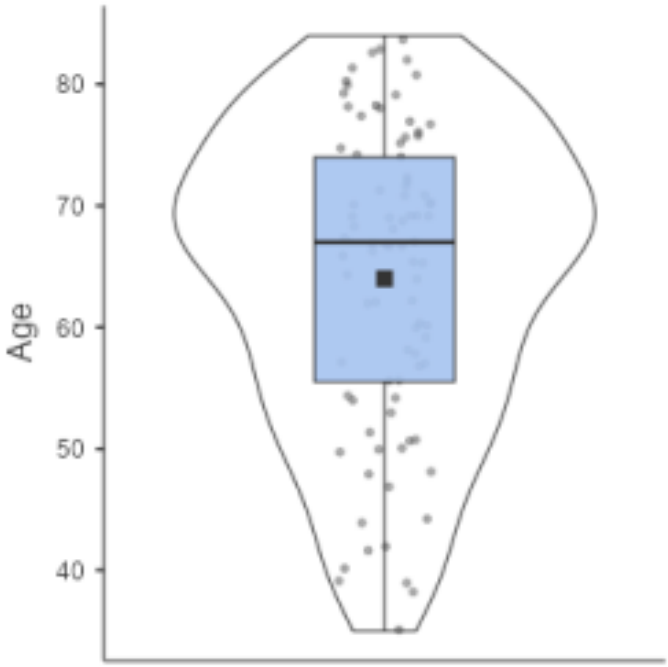

Fig 9: Violin curve of the age distribution of the studied cohort

Patients were followed for complications, including prolonged hospital stay, pneumonia, need for oxygen therapy, and death. The overall incidence of complications was high, with 59 patients (67.0%) developing at least one, while 29 (33.0%) had none. In group A, complications occurred in 27 of 34 patients (79.4%) and in group B, in 32 of 54 (59.3%). The difference was at the border of statistical significance ($\chi^2 = 3.83$; $p = 0.050$), with the relative risk of complications for $Kt/V < 1.3$ being 1.34 (95% CI: 1.01–1.77). (Fig. 10, Table 8)

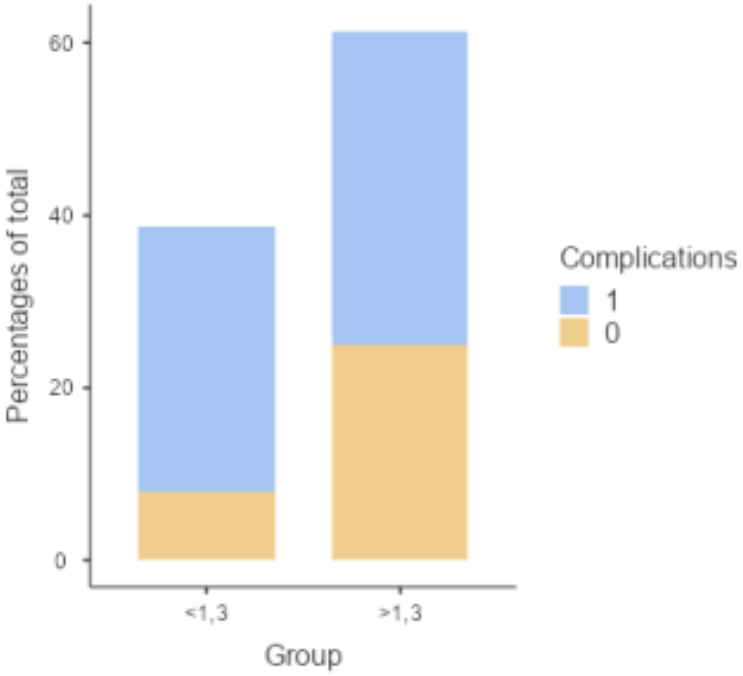

Fig 10: Percentage of complications in both groups

Contingency Tables

Group		Complications 1	0	Total
<1,3	Observed	27	7	34
	% within row	79.4%	20.6%	100.0%
>1,3	Observed	32	22	54
	% within row	59.3%	40.7%	100.0%
Total	Observed	59	29	88
	% within row	67.0%	33.0%	100.0%

χ^2 Tests

	Value	df	p
χ^2	3.83	1	0.050
χ^2 continuity correction	2.98	1	0.084
z test difference in 2 proportions	1.96		0.025[a]
Likelihood ratio	3.99	1	0.046
Fisher's exact test			0.041[a]
N	88		

[a] H_a: Group P(<1,3) > P(>1,3)

Table 8 Relationship between dialysis adequacy (Kt/V) and complication rate in patients with chronic hemodialysis and SARS-CoV-2 infection

The mortality rate for the entire cohort was 36.4% (32 patients). It was higher in group A – 47.1% (16/34), compared to 29.6%

(16/54) in group B. Although the difference did not reach statistical significance ($\chi^2 = 2.74$; $p = 0.098$), there was a trend for increased mortality in patients with lower Kt/V. The relative risk of fatal outcome in group A compared to group B was 1.59 (95% CI: 0.92–2.74). (Table 9)

Contingency Tables

		Mortality		
Group		1	0	Total
<1,3	Observed	16	18	34
	% within row	47.1%	52.9%	100.0%
>1,3	Observed	16	38	54
	% within row	29.6%	70.4%	100.0%
Total	Observed	32	56	88
	% within row	36.4%	63.6%	100.0%

χ^2 Tests

	Value	df	p
χ^2	2.74	1	0.098
N	88		

Table 9: Mortality according to dialysis adequacy (Kt/V) in chronic hemodialysis patients with COVID-19

The analysis of complications showed that patients with lower dialysis adequacy (Kt/V < 1.3) had worse clinical outcomes than those with Kt/V ≥ 1.3. In group A, complications were recorded in 27 of 34 patients (79.4%), while only 7 (20.6%) remained complication-free. In group B, characterized by higher adequacy, complications were observed in 32 of 54 patients (59.3%), and 22 (40.7%) did not develop any. Statistical analysis revealed a significantly higher risk of complications in group A: $\chi^2 = 3.83$; $p = 0.050$. The additional z-test for difference in proportions confirmed the significance ($p = 0.025$), and the results of Fisher's exact test were similar ($p = 0.041$). These findings clearly highlight that lower dialysis efficiency is associated with a higher incidence of complications in chronic hemodialysis patients with COVID-19.

Comparative Measures

		95% Confidence Intervals	
	Value	Lower	Upper
Relative risk	1.59[a]	0.922	2.74

[a] Rows compared

Table 10: Relative risk of mortality in patients with different dialysis adequacy (Kt/V <1.3 vs. Kt/V ≥1.3)

The mortality analysis in the studied cohort showed that a total of 32 out of 88 patients (36.4%) died during the follow-up period. When stratified according to the adequacy of dialysis treatment, clear differences were found between the two subgroups. In group A (Kt/V < 1.3), mortality was significantly higher – recorded in 16 out of 34 patients (47.1%). In comparison, in group B (Kt/V ≥ 1.3) a lethal outcome was

observed in 16 out of 54 patients (29.6%). Although the data show a clear trend for a worse prognosis in patients with lower dialysis adequacy, statistical analysis did not confirm the presence of a significant difference between the two groups ($\chi^2 = 2.74$; $p = 0.098$).

The estimated relative risk (RR) for mortality in group A versus group B was 1.59, with a 95% confidence interval ranging from 0.922 to 2.74. This indicates that patients with $Kt/V < 1.3$ have an approximately 59% higher risk of mortality compared with those with better dialysis adequacy ($Kt/V \geq 1.3$). However, the wide confidence interval, which includes unity, and the lack of statistical significance require that the results be interpreted with caution. (Figs. 11 and 12)

The practical value of these results lies in highlighting the potential clinical relevance of dialysis adequacy as a prognostic factor for survival. Although the present study failed to demonstrate a significant difference, the trend in the results is consistent with published data in the literature, according to which optimization of dialysis dosage is a key component in improving the long-term prognosis in patients on chronic hemodialysis. Further studies with larger samples and a longer follow-up period are needed to clarify the real impact of Kt/V on mortality and to confirm whether the observed trend can achieve statistical significance.

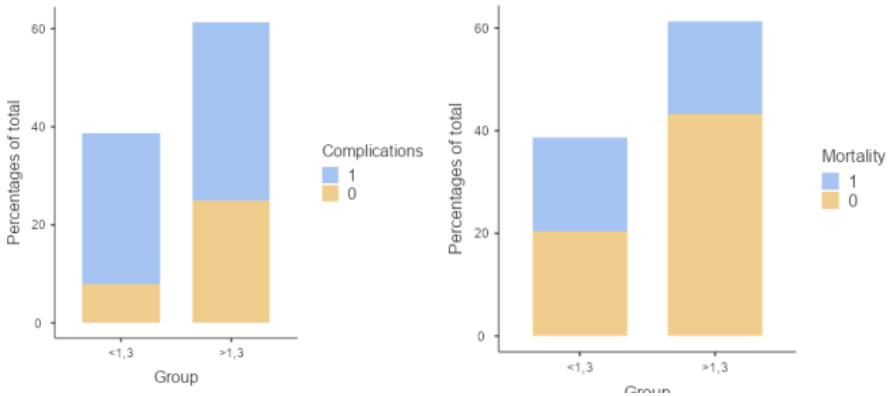

Fig 11 and 12: Distribution of complications and mortality in patients according to dialysis adequacy (Kt/V <1.3 vs. ≥1.3)

The logistic regression model with complications as the dependent variable and group and age as predictors showed that belonging to the group >1.3 versus <1.3 was associated with an odds ratio (OR) = 2.49, p = 0.076. Age was not a significant factor (OR = 0.98, p = 0.407). Although the results did not reach statistical significance, there was a trend towards a higher risk of complications in patients with Kt/V <1.3. The model explained a limited part of the variation in the data (R^2McF = 0.0419), indicating that there are probably other factors that influence the development of complications. (Table 11)

Model Fit Measures

Model	Deviance	AIC	R^2_{McF}
1	107	113	0.0419

Note. Models estimated using sample size of N=88

Model Coefficients - Complications

Predictor	Estimate	SE	Z	p	Odds ratio
Intercept	-0.3165	1.3067	-0.242	0.809	0.729
Group:					
>1,3 – <1,3	0.9109	0.5130	1.776	0.076	2.487
Age	-0.0156	0.0189	-0.828	0.407	0.984

Note. Estimates represent the log odds of "Complications = 0" vs. "Complications = 1"

Table 11: Logistic regression model: association of group and age with the risk of complications

Survival analysis in patients divided according to dialysis adequacy (Kt/V < 1.3 and Kt/V ≥ 1.3) did not show statistically significant differences between the two groups. The median survival remained indeterminate in both cases, as the survival curves did not fall below 50% within the follow-up period. This indicates that despite some trends related to the quality of dialysis, a clear advantage of one group over the other in the context of overall survival cannot be proven. The results of the Cox regression analysis confirm this finding – patients in the Kt/V ≥ 1.3 group have approximately 0.80 times the risk of an adverse event compared to those in the Kt/V < 1.3 group (HR = 0.80; 95% CI: 0.40–1.62; p = 0.539). These data clearly show that the difference is not statistically significant and that higher dialysis adequacy alone is not an independent predictor of better survival in the period under consideration.

The assessment of survival at specific time points also supports these conclusions. The probability of survival at 12 months is similar between the two groups – 82.4% for Kt/V < 1.3 and 81.5% for Kt/V ≥ 1.3. At 36 months, the values remain close: 70.6% for the <1.3 group and 74.1% for the ≥1.3 group. At five-year follow-up (60 months), survival reaches 67.6% for the first group and 70.4% for the second, indicating a similar long-term prognosis. (Table 12)

In summary, the results of the analysis show that the quality of dialysis, measured by Kt/V, although an important parameter for the adequacy of treatment, does not have a decisive impact on survival within the period considered. It is likely that other factors – such as age, cardiovascular diseases, infectious complications and vaccination status – play a more significant role in the final clinical outcomes in this vulnerable population.

					95% Confidence Interval	
Levels	time	Number at Risk	Number of Events	Survival	Lower	Upper
<1,3	12	28	6	82.4%	70.5%	96.2%
<1,3	36	24	4	70.6%	56.8%	87.7%
<1,3	60	23	1	67.6%	53.6%	85.3%
<1,3	120	21	2	61.8%	47.4%	80.5%
<1,3	180	20	1	58.8%	44.4%	77.9%
>1,3	12	44	10	81.5%	71.8%	92.5%
>1,3	36	40	4	74.1%	63.3%	86.7%
>1,3	60	38	2	70.4%	59.2%	83.7%
>1,3	120	38	0	70.4%	59.2%	83.7%
>1,3	180	36	2	66.7%	55.2%	80.5%

Table 12: Survival of chronic hemodialysis patients with COVID-19 according to Kt/V groups and time intervals

Kaplan–Meier analysis illustrates that the dynamics of survival in both groups (<1.3 and >1.3) follow a similar trend throughout

the observation period. Patients with Kt/V <1.3 show a steeper decline in the first 30 days of follow-up, which probably reflects the greater vulnerability of these patients in the acute phase after SARS-CoV-2 infection. After this initial period, the curve stabilizes and in the longer term (at 180 days) survival remains around 60%. This suggests that although patients with lower dialysis adequacy are at higher immediate risk, those who successfully pass the initial critical period have a relatively stable chance of survival in the following months. In the group with Kt/V >1.3, a similar initial decline in survival is reported, but it is less pronounced, and the curve quickly turns into a smoother decline. This reflects some protection associated with better dialysis adequacy. At the end of the 180-day period, survival in this group reached approximately 67%, which is higher compared to the <1.3 group. Despite this visually distinct difference, statistical analysis (Cox regression and log-rank test) did not demonstrate a significant difference between the two curves, which can be explained both by the relatively small number of patients included and by the influence of other concomitant factors such as age, cardiovascular disease and vaccination status. (Fig. 12)

These data suggest that dialysis adequacy, as measured by Kt/V, may be important for early survival dynamics, but does not establish itself as an independent predictor within the six-month period. Despite the lack of statistical significance, the trend for higher survival in patients with Kt/V >1.3 remains clinically important and deserves confirmation in larger and multicenter studies.

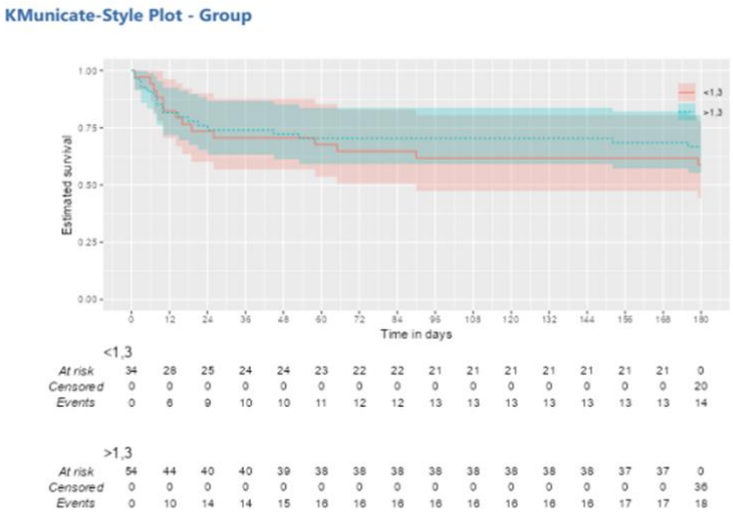

Fig 13: Kaplan–Meier analysis of survival in the two groups of patients.

3.9.1. Comparison of dialysis quality before and after COVID-19 infection

The study included a total of 50 patients on chronic hemodialysis, who made up the observed cohort. Of these, 20 (40%) were women, and the remaining 30 (60%) were men, which reflects a slight male predominance among dialyzed patients.

Regarding the vascular access used for hemodialysis treatment, the following distribution was observed: the largest proportion of patients with arteriovenous fistula (AVF), which is considered the "gold standard" in chronic hemodialysis. There were 23 such patients, or 46% of the entire cohort. In second place in frequency were patients with a permanent tunneled catheter – 22 patients (44% of the sample). A significantly smaller number of

patients performed dialysis through a temporary catheter – only 5 people (10%), which indicates that this access is used mainly as a transitional option or in specific clinical circumstances.

For the purposes of statistical analysis, the different types of vascular access are numerically coded as follows: indwelling catheter is coded "1", arteriovenous fistula is coded "2", and temporary catheter is coded "3". This coding allows for easier data processing and comparison between the different categories when applying statistical models.

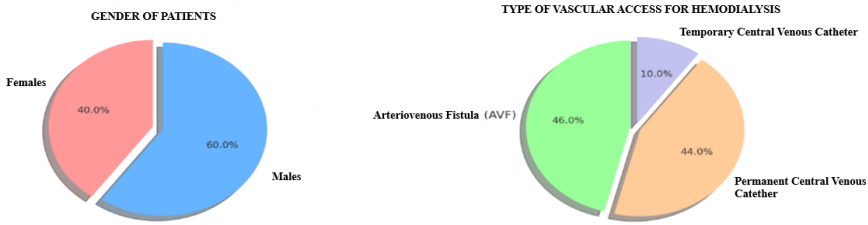

Fig.14 Distribution of patients by gender and types of vascular access in the studied cohort

The age distribution of the patients includes the range between 40 and 84 years. The median age of the cohort is approximately 64 years, which is consistent with the well-known tendency of the chronic hemodialysis population to predominantly affect older patients. When we look at the intermediate values, half of the participants fall into the range between 58 and 70 years, which clearly outlines the main "center of gravity" in the age structure. (Fig.14)

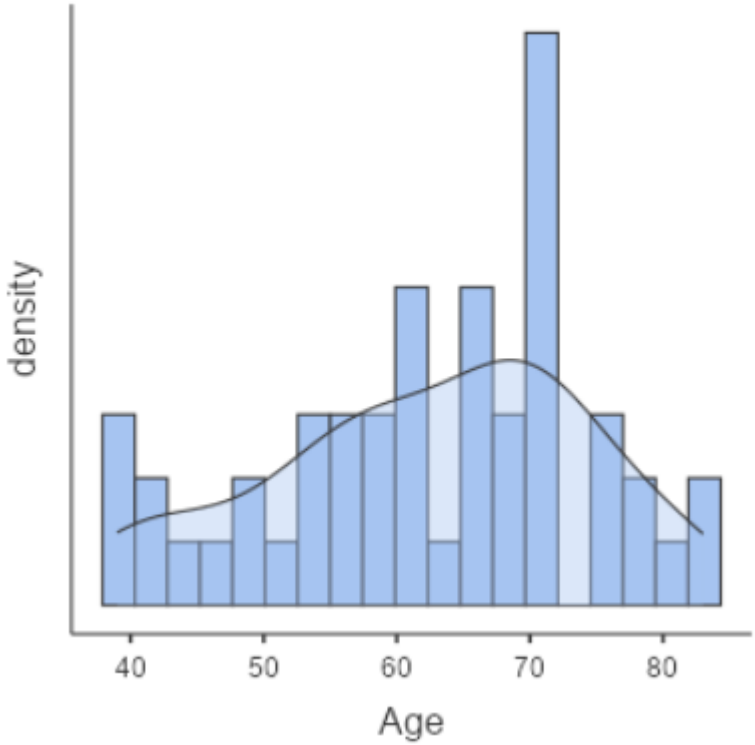

Fig 15: Histogram of age distribution in chronic hemodialysis patients

The highest concentration of patients is observed in the age group 60–70 years, where the incidence is significantly higher than in the other intervals. In the younger age range – under 50 years – the number of patients is significantly lower, which emphasizes the rarity of chronic hemodialysis in younger individuals. On the other hand, patients over 75 years of age also have a limited representation, although this group is particularly vulnerable to complications and increased mortality. Overall, the

distribution shows a relatively even age structure with a distinct clustering in the older ages, which is typical of dialysis populations worldwide. This confirms that age remains one of the most important demographic factors to be taken into account when interpreting clinical outcomes and patient prognosis (Figs. 15 and 16).

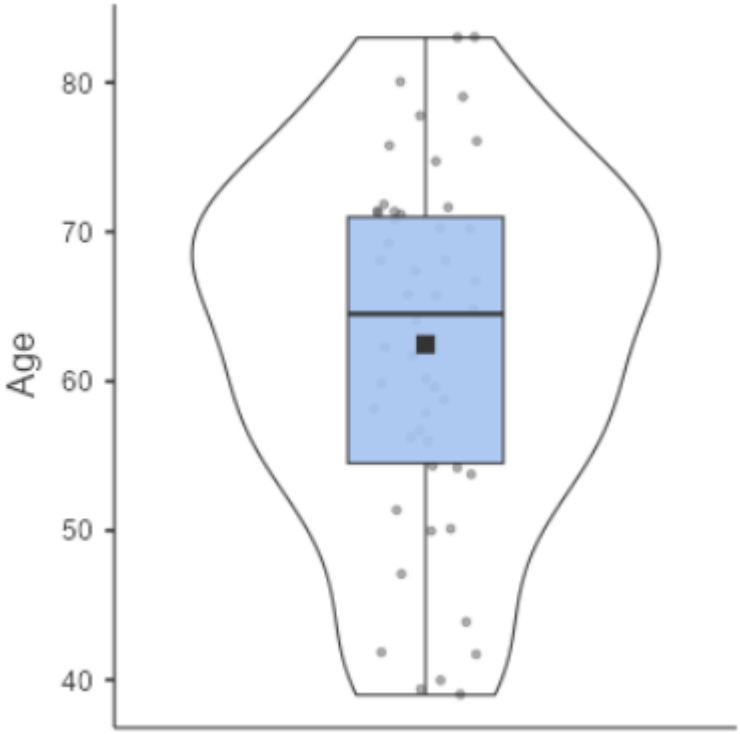

Fig 16: Violin curve for the age distribution of patients

The results of the paired sample analysis show that there is no statistically significant difference in the indicators of dialysis adequacy before and after COVID-19. The mean value of URR before infection is 0.703 (SD = 0.0879), and after it – 0.707 (SD

= 0.0781), with the difference not reaching statistical significance (t = –0.386, p = 0.701). Regarding Kt/V, the mean value before COVID-19 is 1.522 (SD = 0.4544), and after infection – 1.503 (SD = 0.3289), also without significant change (t = 0.329, p = 0.743). These results indicate that in the studied cohort, COVID-19 infection did not lead to a significant deterioration in dialysis adequacy (Table 13).

Paired Samples T-Test

			statistic	df	p		Effect Size
URR before COVID-19	**URR after COVID-19**	**Student's t**	-0.386	49.0	0.701	Cohen's d	-0.0547
Kt/V before COVID-19	**Kt/V after COVID-19**	**Student's t**	0.329	49.0	0.743	Cohen's d	0.0465

Note. H_a $\mu_{Measure\ 1\ -\ Measure\ 2} \neq 0$

Descriptives

	N	Mean	Median	SD	SE
URR before COVID-19	50	0.703	0.708	0.0879	0.0124
URR after COVID-19	50	0.707	0.717	0.0781	0.0110
Kt/V before COVID-19	50	1.522	1.480	0.4544	0.0643
Kt/V after COVID-19	50	1.503	1.495	0.3289	0.0465

Table 13: Comparison of dialysis adequacy indicators (URR and Kt/V) before and after COVID-19 in chronic hemodialysis patients

Group Descriptives

	Group	N	Mean	Median	SD	SE
URR before COVID-19	**M**	29	0.679	0.690	0.0764	0.0142
	F	21	0.736	0.740	0.0939	0.0205
URR after COVID-19	**M**	29	0.689	0.697	0.0782	0.0145
	F	21	0.733	0.740	0.0721	0.0157
Kt/V before COVID-19	**M**	29	1.410	1.400	0.3743	0.0695
	F	21	1.678	1.640	0.5159	0.1126
Kt/V after COVID-19	**M**	29	1.434	1.420	0.3226	0.0599
	F	21	1.597	1.620	0.3212	0.0701

Independent Samples T-Test

		Statistic	df	p		Effect Size
URR before COVID-19	**Student's t**	-2.35	48.0	0.023	Cohen's d	-0.673
	Welch's t	-2.27	37.6	0.029	Cohen's d	-0.662
	Mann-Whitney U	156		0.003	Rank biserial correlation	0.488
URR after COVID-19	**Student's t**	-2.01	48.0	0.050	Cohen's d	-0.577
	Welch's t	-2.04	45.2	0.047	Cohen's d	-0.581
	Mann-Whitney U	196		0.034	Rank biserial correlation	0.356
Kt/V before COVID-19	**Student's t**	-2.13	48.0	0.038	Cohen's d	-0.610
	Welch's t	-2.02	34.6	0.051	Cohen's d	-0.594
	Mann-Whitney U	162		0.005	Rank biserial correlation	0.468
Kt/V after COVID-19	**Student's t**	-1.76	48.0	0.084	Cohen's d	-0.505
	Welch's t	-1.76	43.4	0.085	Cohen's d	-0.505
	Mann-Whitney U	211		0.068	Rank biserial correlation	0.307

Note. H_a $\mu_M \neq \mu_F$

Table 14: Comparative analysis of dialysis adequacy (URR and Kt/V) in men and women before and after COVID-19 infection.

Independent sample analysis showed that there are significant gender differences in the adequacy of dialysis treatment. In women, URR values before COVID-19 infection are significantly higher (Mean = 0.736, SD = 0.094) compared to

those in men (Mean = 0.679, SD = 0.076), with the statistical test confirming the significance of the difference (t = –2.35, p = 0.023; Cohen's d = –0.673). A similar pattern is observed after recovery from COVID-19 – women retain higher values (Mean = 0.733) compared to men (Mean = 0.689). In this case, the difference reaches the limit of statistical significance (t = –2.01, p = 0.050; Cohen's d = –0.577), which again suggests a trend for better dialysis efficiency in women.

A clear distinction is also observed with regard to the Kt/V indicator. Before infection, women showed significantly better values (Mean = 1.678, SD = 0.516) compared to men (Mean = 1.410, SD = 0.374), the difference being again statistically significant (t = –2.13, p = 0.038; Cohen's d = –0.610). After recovering from COVID-19, the average values for Kt/V in women remained higher (Mean = 1.597) compared to those in men (Mean = 1.434), but this time statistical significance was not reached (t = –1.76, p = 0.084), which may be due to greater variability and a limited sample. In summary, the data obtained show that women in the cohort under consideration have higher indicators of dialysis adequacy compared to men. This advantage was most pronounced before COVID-19 infection and partially maintained after it. The observed results are consistent with published data, according to which physiological differences between the sexes – including different body composition and metabolic characteristics – can affect the effectiveness of dialysis treatment.

Independent Samples T-Test

		Statistic	df	p		Effect Size
URR before COVID-19	**Student's t**	0.106[a]	45.0	0.916	Cohen's d	0.0308
	Welch's t	0.107	38.6	0.916	Cohen's d	0.0310
	Mann-Whitney U	246		0.534	Rank biserial correlation	-0.1087
URR after COVID-19	**Student's t**	0.524	45.0	0.603	Cohen's d	0.1529
	Welch's t	0.523	44.7	0.603	Cohen's d	0.1528
	Mann-Whitney U	240		0.444	Rank biserial correlation	-0.1322
Kt/V before COVID-19	**Student's t**	0.363	45.0	0.719	Cohen's d	0.1058
	Welch's t	0.366	40.6	0.717	Cohen's d	0.1062
	Mann-Whitney U	254		0.640	Rank biserial correlation	-0.0815
Kt/V after COVID-19	**Student's t**	0.119	45.0	0.906	Cohen's d	0.0347
	Welch's t	0.119	44.4	0.906	Cohen's d	0.0347
	Mann-Whitney U	263		0.782	Rank biserial correlation	-0.0489

Note. H_a $\mu_1 \neq \mu_2$

[a] Levene's test is significant ($p < .05$), suggesting a violation of the assumption of equal variances

Group Descriptives

	Group	N	Mean	Median	SD	SE
URR before COVID-19	**1**	24	0.712	0.717	0.1016	0.0207
	2	23	0.709	0.709	0.0629	0.0131
URR after COVID-19	**1**	24	0.718	0.730	0.0734	0.0150
	2	23	0.707	0.713	0.0762	0.0159
Kt/V before COVID-19	**1**	24	1.579	1.490	0.5275	0.1077
	2	23	1.531	1.490	0.3578	0.0746
Kt/V after COVID-19	**1**	24	1.530	1.540	0.3129	0.0639
	2	23	1.519	1.500	0.3380	0.0705

Table: 15: Comparative analysis of dialysis adequacy (URR and Kt/V) according to the type of vascular access before and after COVID-19 infection

The results of the independent t-tests for comparison between the two groups of patients according to the type of vascular access (group 1 – indwelling catheter, group 2 – arteriovenous

fistula) show that there are no statistically significant differences in terms of dialysis adequacy indicators (URR and Kt/V) both before and after COVID-19 infection.

The mean URR values before COVID-19 are almost identical between the two groups – 0.712 in group 1 and 0.709 in group 2 ($p = 0.916$), and after COVID-19 there is again no significant difference (0.718 vs. 0.707; $p = 0.603$). Similarly, Kt/V before infection is 1.579 in group 1 and 1.531 in group 2 ($p = 0.719$), and after infection the values are 1.530 vs. 1.519 ($p = 0.906$).

These data indicate that the type of vascular access (indwelling catheter or AV fistula) does not significantly impact dialysis adequacy indicators, either before or after recovery from COVID-19.

CHAPTER FOUR. DISCUSSION.

4.1. Summary of main results

In this study, we examine the impact of COVID-19 on chronic hemodialysis patients in three complementary cohorts, focusing on survival, comorbidities, complications, and dialysis adequacy. Together, the analyses provide a broad perspective on how infection, demographic factors, and treatment variables interact to shape outcomes during the pandemic.

The largest cohort included 190 hemodialysis patients, of whom 108 were female and 82 were male, with a median age of 62.7 years (range 32–88). In this group, 101 patients were diagnosed with at least one confirmed SARS-CoV-2 infection (Cohort A), while 89 remained COVID-negative during follow-up (Cohort B). A total of 98 deaths (51.57%) were recorded: 55 among COVID-positive patients and 43 among COVID-negative patients. Cardiovascular disease was the most common comorbidity, affecting 122 (69.5%) patients, followed by diabetes mellitus in 58 (30.5%) patients. Logistic regression identified older age ($p = 0.026$) and the presence of cardiovascular disease ($p < 0.001$; OR ≈ 5.1) as the strongest independent predictors of mortality, while gender and diabetes were not significantly associated with outcomes. These findings highlight the critical role of age and cardiovascular burden in shaping survival during the pandemic.

Vaccination status emerged as a powerful modifiable factor. Among the 133 vaccinated patients, survival was significantly higher compared to the unvaccinated. Regression analysis showed that vaccination reduced the risk of mortality by approximately 53% (OR ≈ 0.47; $p = 0.042$). Kaplan-Meier

curves confirmed this effect: after 24 months, 54.1% of the vaccinated were alive, compared to 35.1% of the unvaccinated. Furthermore, Cox regression analysis showed that patients in group B (COVID-negative) had a 36% lower risk of death compared to those infected (group A) (HR = 0.64; 95% CI: 0.43–0.95; p = 0.027). These results highlight that survival in dialysis patients during the pandemic was influenced by both immutable factors, such as age and cardiovascular disease, and modifiable factors, such as vaccination and exposure to infection.

The second cohort included 88 patients with PCR-confirmed COVID-19 infection. Patients were stratified by dialysis adequacy using Kt/V values: 34 (38.6%) had Kt/V <1.3, while 54 (61.4%) had Kt/V ≥1.3. The median age was 64 years (range 35–84), with 55 men (62.5%) and 33 women (37.5%). Complications were common, affecting 67% of patients (59 individuals). Group A had a significantly higher complication rate (79.4%) compared with Group B (59.3%), a difference that was borderline significant ($\chi^2 = 3.83$; p = 0.050; Fisher's exact test p = 0.041).

The mortality rate in this cohort was 36.4% (32 patients), with deaths occurring more frequently in the group with Kt/V <1.3 (47.1%) than in the group with Kt/V ≥1.3 (29.6%). Although the difference did not reach statistical significance (p = 0.098), the relative risk of death in patients with low Kt/V was 1.59 (95% CI: 0.92–2.74). Logistic regression suggested that patients with Kt/V <1.3 were more than twice as likely to develop complications (OR = 2.49, p = 0.076). Kaplan-Meier survival curves showed a steeper early decline in Group A, although Cox regression did not identify statistically significant long-term differences. Taken together, these findings highlight that

suboptimal dialysis adequacy was consistently associated with worse clinical outcome, although statistical thresholds were not fully met.

The third analysis focused on 50 patients in whom dialysis adequacy was measured before and after COVID-19 infection. This subgroup included 20 women (40%) and 30 men (60%), with a mean age of 64 years. Regarding vascular access, 23 patients (46%) had an arteriovenous fistula, 22 (44%) had an indwelling catheter, and 5 (10%) had a temporary catheter. Paired-sample testing did not show a significant change in adequacy after infection: the mean URR was 0.703 before and 0.707 after COVID-19 ($p = 0.701$), while the mean Kt/V was 1.522 before and 1.503 after infection ($p = 0.743$). However, subgroup analyses revealed persistent gender-related differences. Women achieved higher adequacy values compared to men both before and after infection: URR was 0.736 versus 0.679 before infection ($p = 0.023$) and 0.733 versus 0.689 after infection ($p = 0.050$), while Kt/V was 1.678 versus 1.410 before infection ($p = 0.038$) and 1.597 versus 1.434 after infection ($p = 0.084$). In contrast, adequacy did not differ significantly by vascular access type, either before or after infection. These results suggest that although COVID-19 itself did not impair long-term adequacy of dialysis treatment, gender-related differences persisted, while access type was not a determining factor.

Taken together, these analyses highlight the multifactorial impact of COVID-19 on the dialysis population. Mortality is primarily determined by age and cardiovascular disease, but vaccination was protective and emerged as the strongest modifiable factor. Among infected patients, inadequate dialysis

dose was consistently associated with more complications and a higher risk of mortality, but infection itself did not appear to significantly affect dialysis adequacy. This is likely due to the study design and the fact that we excluded patients with a change in dialysis access at the same time.

4.2. Analysis and comparison with existing literature

The results observed in our cohorts are consistent with international reports highlighting the disproportionate vulnerability of hemodialysis patients during the COVID-19 pandemic. In various countries, dialysis populations have borne a significantly higher burden of infections, hospitalizations, and mortality compared with the general population [83; 76; 181]. In some cohorts, COVID-19 has been responsible for up to 43.7% of all deaths [141]. Mortality among infected dialysis patients ranges from 20–24% [83; 103], and some long-term analyses have reported rates as high as 35.7% [32]. However, it is important to note that not all additional deaths are directly related to the viral infection—nearly half of these, especially during the early phases of the pandemic, have been attributed to cardiac arrest or pneumonia [85]. Similar patterns were observed in analyses with an overall all-cause mortality rate of ~23%, of which COVID-19 accounted for ~13% [200]. Such trends are consistent with our observation of mortality rates >50% during long-term follow-up—they highlight how the pandemic has exacerbated both infectious and noninfectious risks in dialysis patients. This effect is particularly strong in multimorbid sufferers, for whom ongoing clinical monitoring has become more difficult to achieve in the context of commitment and limited access.

Comorbidities appear to be key prognostic factors. In our analysis, cardiovascular disease and age emerged as the strongest independent predictors of increased mortality—a finding consistent with the international literature, where older age, male gender, and cardiovascular comorbidity dominate the risk profile in patients with COVID-19 on dialysis [103, 69; 95; 205]. Vascular events are a common cause of death in these patients, especially in the context of endothelial dysfunction, thrombo-inflammatory activation, and complement activation induced by SARS-CoV-2 [42, 25, 155]. Clinical series have documented that up to one third of critically ill patients develop macrovascular complications such as venous thromboembolism, myocardial infarction, or stroke [62], while microvascular damage—e.g., thrombotic microangiopathy—contributes to organ failure [89; 23]. In the context of pulmonary vasculopathy, dysregulation of the renin-angiotensin system and neutrophil-induced injury further complicate the pathophysiology [68; 65]. These mechanisms explain the disproportionate cardiovascular mortality observed in hemodialysis patients, especially in the setting of increased stress and systemic inflammation.

Bacterial (or other secondary) infections should not be neglected either — they add additional inflammatory and septic stress and complicate the prognosis, especially in an immunosuppressed group such as dialysis patients [6; 27].

Anticoagulation strategies have been the subject of intensive research in the context of this increased thrombotic risk. Meta-analyses consistently show that anticoagulation can reduce mortality in hospitalized patients with COVID-19 [84], with prophylactic doses often demonstrating a good balance against the risk of bleeding [129], while the use of moderate to

therapeutic doses is associated with an increased risk of bleeding and complications [129; 115]. In the outpatient setting, data suggest that anticoagulation can reduce the risk of hospitalization by up to 43% [74]. In our patients, this highlights the need for strict individualization of therapy, especially in those on dialysis, where the balance between thrombotic and hemorrhagic risk is delicate. Dialysis adequacy is emerging as an important prognostic factor. In our cohort, patients with Kt/V < 1.3 had a significantly higher incidence of complications and mortality, consistent with multiple literature linking inadequate dialysis efficiency to adverse clinical outcomes [178, 13; 57; 66]. In comparative analyses, dialysis patients had an increased risk of in-hospital death (HR ~ 2.07) and combined severe conditions (HR ~ 3.50) compared with patients without CKD [140]. Furthermore, dialysis patients often present with an atypical clinical picture in COVID-19, with less frequent fever, prolonged hospital stay, and adverse outcomes [114]. Our paired analysis did not find a statistically significant decline in dialysis adequacy after infection, which is in contrast to other reports [132; 175; 160]. Studies such as that of Navarrete et al. (2021) showed that Kt/V often normalizes over time (about two months) after acute infection, which is partly consistent with our observations. Interestingly, Karaca et al. (2024) documented cases in which URR and Kt/V improved in patients with dietary restrictions, likely as an adaptive response to metabolic changes.

A key modifiable factor that stands out in our study and in global practice is vaccination. In our cohort, vaccination was associated with an almost twofold reduction in mortality, which is fully consistent with international observations. The efficacy against infection was estimated to be 72–79%, and mortality among vaccinated patients decreased from ~29.5% in unvaccinated

patients to ~6.7% in fully vaccinated patients [126, 184, 130]. Large European cohorts have reported mRNA vaccine efficacy rates of 83.5% against infection and 91.2% against mortality [20]. Booster doses appear to be most critical for maintaining protection—Brković et al. (2023) noted that they confer the strongest and most durable immune protection. This finding is even more significant in the context of countries with low vaccination rates, such as Bulgaria, where excess mortality remains among the highest in the region [147, 75]. The data strongly support vaccination as the most effective strategy for reducing mortality in dialysis patients and highlight its public health importance, especially in regions with under-vaccination coverage.

In addition, modern risk-prediction approaches offer promising avenues for improving clinical care. For example, multinational studies have developed models to predict COVID-19 morbidity and mortality among hemodialysis patients using multiple clinical and laboratory variables—with an AUC of about 0.706 for mortality (0.788 in internal validation) [69].

In another European study (Fresenius NephroCare), modifiable risk factors (e.g., low serum albumin, higher CRP) were found to be statistically significant predictors of 30-day mortality in hemodialysis patients with COVID-19 [165].

When we summarize all of this data, the following key messages stand out:

• Dialysis patients are extremely vulnerable to COVID-19, with much higher mortality and more severe disease than the general population.

• Age, cardiovascular disease, low serum albumin, elevated CRP, and other laboratory markers of inflammation (e.g., ferritin) are reliable prognostic indicators.

• Adequacy of dialysis and good technical support remain fundamental to improve outcome.

• Vaccination is the powerful modifiable factor that can most significantly affect survival.

• Integration of predictive models (including machine learning) can optimize early identification of high-risk patients and target treatment to these groups.

Our study, conducted in Eastern Europe, contributes original data from a region that is often underrepresented in global nephrology. It highlights the need for targeted strategies—prioritizing vaccination, optimizing dialysis, treating cardiovascular risks, and personalized monitoring—to protect one of the most vulnerable patient populations in the post-pandemic era.

4.3. Interpretation of specific analyses

Our analyses of the three cohorts are not only consistent with international reports, but also highlight specific characteristics of our population that help explain the results. While Section 5.2 established how our findings are consistent with the global

evidence base, here we interpret the results in more detail, focusing on demographics, dialysis adequacy, survival modeling, and methodological considerations.

4.3.1 Gender and age

Age was confirmed as a crucial predictor of mortality in our cohort, unlike gender. This confirms the global evidence that advanced age is the most consistent risk factor for severe COVID-19 due to immunosenescence, accumulated comorbidities, and cardiovascular burden [169; 204]. Although many studies have reported higher mortality in men [108; 206], we did not observe this pattern. One possible explanation is that in dialysis populations, the effect of age and cardiovascular disease outweighs gender-related differences. Interestingly, in our cohort of 50 patients, women achieved higher URR and Kt/V values both before and after COVID-19, which is consistent with reports linking gender differences in adequacy to variations in body composition and urea distribution [17; 176]. This suggests that gender affects the effectiveness of dialysis treatment, but not survival.

4.3.2 Hemodialysis adequacy.

Adequacy of dialysis emerged as an important but nuanced factor. In the cohort of 88 patients, those with Kt/V <1.3 had more complications and higher mortality, although the differences were not always statistically significant. These results are consistent with previous evidence showing that suboptimal dialysis dose undermines resilience to systemic stress [178, 58; 196]. The consistency of this trend across studies emphasizes that adequacy of clearance should be considered not

only as a technical measure but also as a determinant of clinical outcomes during infectious crises.

Two methodological features of our study may partly explain why the differences in outcomes were less pronounced compared with international reports. First, all patients were on concomitant antiplatelet therapy, in addition to routine intradialytic anticoagulation. This background treatment likely reduced thrombo-inflammatory complications and contributed to more favorable outcomes, narrowing the survival differences between adequacy groups. Second, in the paired analysis of 50 patients, those with a changed vascular access for hemodialysis were excluded, removing a source of variability often associated with reduced clearance and worse prognosis. These contextual factors may explain the apparent stability of adequacy in our cohort, while reinforcing the broader principle that inadequate clearance adversely affects outcomes.

4.3.3 Residual renal function

Although not directly measured in our study, residual renal function likely contributed to the results. COVID-19 is known to cause acute kidney injury in addition to chronic kidney disease, accelerating the loss of residual clearance [41; 187]. Even modest declines can impair fluid balance, toxin removal, and phosphate control, shifting patients with borderline adequacy into higher-risk categories. The association we observed between low Kt/V and adverse outcomes may therefore partly reflect unmeasured differences in residual function, an area that future studies should explore in more detail.

4.3.4 Survival analysis

Survival modeling confirmed the central role of both infection status and vaccination. Vaccinated patients had significantly lower mortality, consistent with international evidence of improved outcomes in dialysis populations despite impaired immune responses [51; 197; 78, 88, 99, 128]. Similarly, patients who avoided infection (Group B) had a 36% lower risk of death, consistent with registry data documenting high early mortality among infected dialysis patients [135; 81]. Finally, Cox regression analysis confirmed cardiovascular disease as the dominant comorbidity shaping survival, consistent with the mechanisms of vascular injury described in Section 5.2. These findings confirm that outcomes are determined by a combination of unmodifiable factors (age, cardiovascular disease) and modifiable ones (vaccination, adequacy, and potentially antithrombotic strategies).

4.4. Clinical conclusions

The results of this study have several important implications for the care of hemodialysis patients during and after the COVID-19 pandemic. First, the strong association between cardiovascular comorbidity and mortality highlights the need for proactive cardiovascular risk management in dialysis populations. This includes tight control of blood pressure and lipid levels, optimization of anemia therapy, and prevention of thromboembolic events. Cardiovascular events were the predominant cause of death in our cohort, which is consistent with international reports. These results emphasize that cardiovascular protection should remain central to nephrology care, regardless of the pandemic context [58; 70; 136].

Second, our results highlight the importance of dialysis adequacy as a determinant of patient resilience. Patients with lower Kt/V values had more complications and a higher risk of mortality, supporting the principle that adequacy is not simply a laboratory goal but a factor that shapes outcomes during systemic crises. The better outcomes observed in our cohort may have been partly influenced by universal antiplatelet therapy, which could mitigate the thromboinflammatory processes induced by SARS-CoV-2. This suggests that combination antithrombotic strategies deserve consideration in dialysis patients during infectious outbreaks, although careful balancing of bleeding risks is essential [43]. Third, the paired analysis, which did not show a significant decline in adequacy after infection, suggests that dialysis efficiency stabilizes after resolution of the acute illness. However, this stability was likely reinforced by our methodological decision to exclude patients who underwent changes in vascular access during the observation period. Clinically, this highlights the need to reduce unplanned vascular access changes during health crises, as these events can reduce adequacy and worsen clinical outcomes. Therefore, maintaining vascular access stability should be considered a priority in pandemic preparedness planning for dialysis units.

Fourth, our results confirmed the significant survival benefit of vaccination. Vaccinated patients had a significantly lower mortality compared with unvaccinated patients, and this effect was maintained over a 2-year follow-up. These findings reflect global evidence that vaccination remains highly protective, even in the immunocompromised population of hemodialysis patients [51; 197; 78]. In countries such as Bulgaria, where vaccination rates lag behind the European average and mortality rates are

particularly high [147, 75], dialysis units should serve as key sites for targeted vaccination programs, booster dose administration, and education to manage hesitation.

Finally, the study highlights the importance of individualized risk stratification. The prognosis of dialysis patients is shaped by the interaction of unmodifiable factors such as age and cardiovascular disease and modifiable factors, including vaccination, adequacy, and stability of vascular access. Therefore, a one-size-fits-all approach is insufficient. Older patients with cardiovascular disease benefit from closer monitoring, while those with poorer hemodialysis quality require proactive procedures to maintain adequate clearance. Multidisciplinary collaboration between nephrologists, cardiologists, vascular surgeons, and infectious disease specialists is critical to implementing these personalized strategies. In summary, these clinical implications support a multifaceted approach: vaccination campaigns, cardiovascular management, sustained dialysis adequacy, vascular access stability, and judicious use of antithrombotic therapy. Together, these measures provide a framework for improving survival and resilience in hemodialysis patients during pandemics and beyond.

4.5. Strengths and limitations

The key strength of this study lies in its comprehensive design, including three complementary cohorts that together provide a multidimensional perspective on the effects of COVID-19 in dialysis patients. By combining analysis of survival and comorbidities in a large cohort of 190 patients, adequacy and complication data in 88 COVID-positive patients, and paired comparisons of adequacy in 50 patients before and after

infection, the study captures both the immediate and long-term dimensions of the pandemic's impact. The application of robust statistical methods—including logistic regression, Kaplan-Meier survival analysis, and Cox proportional hazards modeling—further enhances the reliability of the results. Another important strength is the detailed stratification of patients by vaccination status, dialysis adequacy, and vascular access type, which allowed for a nuanced exploration of factors influencing outcomes.

The real-world context of this study also enhances its contribution. All patients received routine antiplatelet therapy in addition to intradialysis anticoagulation, reflecting local clinical practice. This may have reduced the variability of thrombo-inflammatory complications and made the results more consistent across subgroups. Similarly, in the analysis of hemodialysis adequacy before and after COVID-19 infection, patients who changed vascular access immediately before the illness or not after it, as well as patients in whom dialysis parameters (dialysis pump speed, filter type change) were changed, were excluded, which reduced the effects of treatment and complications related to the change of access. While these decisions improved the internal consistency of our analysis, they also represent important contextual insights: both routine antithrombotic prophylaxis and stable vascular access may have contributed to more favorable outcomes in our cohort compared with some international reports.

However, several limitations must be acknowledged. First, the single-center, retrospective design limits generalizability, as patient populations, healthcare resources, and treatment protocols vary across regions. Second, although the sample size

of the main cohort was large, subgroup analyses—particularly the 50-patient adequacy cohort—were underpowered to detect smaller differences, and several associations tended toward but did not reach statistical significance. Third, we did not directly measure residual renal function or inflammatory biomarkers, which would have provided better insight into the mechanisms linking infection, adequacy, and survival. Fourth, although the universal use of antiplatelet agents and the exclusion of changes in access improved consistency, these factors also limit comparability with international cohorts where similar practices may not be followed. Finally, vaccination was assessed as a binary variable, without accounting for vaccine type, dosing schedule, or time since last administration, all of which could influence protection against emerging variants.

In summary, the strengths of the study lie in its comprehensive design, methodological rigor, and reflection of real-world practice in an Eastern European setting. Its limitations, including single-center coverage, modest subgroup sizes, and lack of biomarker data, highlight the need for larger, multicenter, prospective studies. Despite these limitations, the study adds valuable evidence in an area where data remain scarce—Eastern Europe—and provides insights directly relevant to clinical practice in resource-limited health systems.

4.6. Future directions

The results of this study highlight several important areas for future research. First, there is an urgent need for larger, multicenter studies that encompass diverse dialysis populations in different health systems. Registry-based initiatives have already provided invaluable data in Western Europe and North America [83,76], but similar efforts are lacking in Eastern

Europe, where mortality rates are among the highest and health systems have faced significant pressure [147,46]. Expanding such registries to include underrepresented regions would strengthen the global evidence base and allow meaningful comparisons between health settings with different resources, vaccination uptake, and patient demographics.

Second, future studies should include appropriate measurements of residual renal function and inflammatory biomarkers. Although our study focused on URR and Kt/V, the lack of data on residual clearance, urine output, protein catabolism rate, or inflammatory markers such as cytokine levels and biomarkers of endothelial injury limited our ability to fully assess the pathophysiological effects of COVID-19. Tracking these parameters over time would clarify whether COVID-19 induces subtle but persistent changes in dialysis patients and would help to distinguish temporary impairments during acute illness from long-term consequences such as chronic inflammation or progressive vascular injury.

Third, our results raise important questions about the role of antithrombotic strategies in dialysis patients with COVID-19. All patients in our cohorts received routine antiplatelet therapy, in addition to intradialysis anticoagulation, which may have contributed to the relatively stable outcomes compared with international cohorts. Meta-analyses have confirmed the benefit of prophylactic anticoagulation [84, 129, 157], but little is known about how combination antiplatelet therapy alters the risks and benefits in dialysis patients. Prospective studies could help determine whether combined antiplatelet and anticoagulant regimens improve outcomes or increase the risk of bleeding, and whether dialysis-specific protocols should be developed.

Fourth, further research is needed on the impact of vascular access stability on adequacy during pandemics. In our study, patients with access changes were excluded from the paired analysis, which likely reduced variability and resulted in more robust adequacy measures. However, in clinical practice, access changes are common and often coincide with hospitalizations, episodes of infection, or lower quality of hemodialysis.

Finally, vaccination remains a research priority. Our results confirmed a strong survival benefit, but further studies are needed to assess the durability of immune responses in dialysis patients, the comparative efficacy of different vaccine platforms, and the role of booster regimens in maintaining protection against emerging variants [51; 197; 78]. Furthermore, little is known about the potential of vaccination to prevent prolonged COVID or mitigate chronic complications in dialysis patients, an area that deserves closer investigation. For Eastern European countries such as Bulgaria, research should also explore strategies to overcome low vaccination rates, including vaccination in dialysis units and adapting community outreach programs.

4.7. Conclusions

1. The overall mortality rate in chronic hemodialysis patients is extremely high (over 50% for the entire follow-up period), which confirms the vulnerability of this population regardless of COVID-19 infection.

2. Although SARS-CoV-2 infection is a significant stress factor, it is not established as an independent predictor of mortality

compared to major comorbidities. The results show that the multifactorial nature of the risk is decisive.

3. Cardiovascular diseases emerge as the strongest independent predictor of fatal outcome. They increase the risk of mortality more than fivefold and are a leading factor for cardiovascular death.

4. Vaccination against COVID-19 is associated with significantly lower mortality and a reduction in the risk of cardiovascular fatal outcomes, which emphasizes the importance of immunization strategies in dialysis patients.

5. Advanced age increased the overall risk of death but was not directly associated with a specific type of fatal outcome (infectious, cardiovascular, or other).

6. Although common in the cohort, diabetes and gender were not established as independent predictors of mortality.

7. Lower dialysis adequacy was associated with more complications and higher mortality but did not reach statistical significance as an independent predictor of survival. However, the trend remains clinically important.

8. Indwelling hemodialysis catheter and AV fistula did not show significant differences in dialysis adequacy, suggesting that other factors have a more significant impact on the results.

CHAPTER FIVE. CONCLUSION.

This study provides a comprehensive assessment of the impact of COVID-19 on chronic hemodialysis patients, integrating survival, comorbidities, complications, dialysis adequacy, and vaccination. Several themes emerged consistently across three complementary cohorts. Mortality was unacceptably high, largely driven by cardiovascular disease and advanced age, highlighting that these are the strongest predictors of poor outcomes. Dialysis adequacy influenced complication rates, with suboptimal clearance being associated with worse trajectories, although differences did not always reach statistical significance. Adequacy did not decline significantly after infection in our paired analysis. Gender differences persisted, with women achieving higher adequacy values, while vascular access type had no measurable effect. Vaccination was the most effective modifiable determinant of survival. Vaccinated patients had significantly lower mortality, consistent with international evidence demonstrating a protective effect of immunization in dialysis populations, despite impaired immune responses. These findings confirm vaccination as a cornerstone for pandemic management in vulnerable groups. Contextual factors such as routine antiplatelet therapy and exclusion of patients with access changes likely contributed to the relatively robust adequacy results in our study, highlighting how local practices can influence outcomes [43].

In addition to their scientific contribution, these findings are of particular relevance to Eastern Europe and Bulgaria, regions heavily affected by the pandemic but underrepresented in the global nephrology literature. Bulgaria has some of the highest mortality rates in Europe, fueled by low vaccination rates and

resource constraints [147; 75; 46]. By situating local evidence in a global context, this study highlights both universal vulnerabilities and region-specific challenges. The results highlight the urgent need for targeted strategies: improving vaccination coverage, strengthening cardiovascular care, maintaining vascular access stability, and ensuring continuous dialysis provision during crises.

In conclusion, COVID-19 has increased the already significant risks faced by dialysis patients, but it has also revealed clear opportunities for treatment and prevention. A multifaceted approach—combining aggressive vaccination programs, proactive cardiovascular disease management, optimizing dialysis adequacy, and access stability—offers the most effective path to improving survival. By providing data from an underrepresented region, this study contributes to the global understanding of dialysis care during pandemics and highlights the importance of building health resilience in vulnerable populations.

Theoretical Contributions

1. The study demonstrates that the high mortality in chronic hemodialysis patients during the COVID-19 pandemic cannot be explained solely by the presence of SARS-CoV-2 infection, but is the result of a complex interaction between age, cardiovascular disease (CVD), vaccination status and dialysis adequacy.

2. CVD is established as the strongest independent predictor of mortality, which emphasizes its dominant importance in the pathogenesis of lethal outcome in dialysis patients.

3. Advanced age is confirmed as a universal risk factor for mortality, without, however, being associated with a specific type of lethal outcome, which complements the knowledge of its generalized impact.

4. Although without statistical significance, the trend for higher mortality in patients with Kt/V < 1.3 outlines a potential dependence that requires confirmation in larger studies and contributes to the scientific debate on the role of dialysis dosing in prognosis.

Practical contributions

1. Our follow-up data show that immunization has a pronounced protective effect, reducing both overall mortality and the risk of cardiovascular mortality. This has direct implications for public health strategies and dialysis programs.

2. The results emphasize the need for aggressive prevention, diagnosis, and treatment of CVD in hemodialysis patients as a core component of the therapeutic approach.

3. Differentiating between different risk factors allows for better stratification of patients according to their vulnerability and the creation of individualized treatment and follow-up plans.

4. The lack of a significant influence of the type of vascular access leads to the conclusion that the choice between indwelling catheter and AV fistula should be determined primarily by technical and clinical considerations, without expecting differences in dialysis adequacy.

5. Although the results do not reach statistical significance, the reported trend for a worse prognosis at $Kt/V < 1.3$ may direct clinical practice towards stricter control and optimization of dialysis treatment.