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„Prof. Dr. Paraskev Stoyanov" - Varna

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Department of Second Department of Internal Medicine

PROSPERITAS VESTRA FINIS NOSTRA!

Dr. Diana Dimcheva Nenova, MD

Adequacy of dialysis treatment and the relationship with achieved quality of life and survival in patients with stage V chronic kidney disease

ABSTRACT

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Assoc. Prof. Dr. Alexandar Stoyanov, MD, PhD

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The dissertation contains 200 standard pages and is illustrated with 24 tables, 43 figures and 1 appendix. The literature includes 379 literary sources, of which 10 in Cyrillic and 369 in Latin.

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External members:
1. Prof. Dr. Boryana Deliyska, PhD, DSc
2. Prof. Dr. Rayna Robeva, PhD
3. Prof. Dr. Boris Bogov, PhD
Spare external member:
1. Assoc. Prof. Dr. Alexandar Osichenko, PhD

Internal members:
1. Prof. Dr. Svetla Staykova, PhD, DSc
2. Assoc. Prof. Kiril Nenov, PhD
Spare internal member:
1.Assoc. Prof. Dr. Rositsa Zorcheva, PhD

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ABBREVIATIONS USED:

RRT- renal replacement therapy
CKD-5D – chronic kidney disease stage 5 on dialysis
OL-HDF- online - hemodiafiltration
HD - hemodialysis
LF-HD – low flux dialysis
HF-HD- high flux dialysis
HDF - hemodiafiltration
UKM – urea kinetinc modeling
AVF- arteriovenosus fistula
PC - permanent catheter
ECA – erythropoetin stimulating agent
IDH – intradialytic hypotension
RT – recovery time
IDWG – interdialytic weight gain
HRQOL – health related quality of life
spKt/v – single pool Kt/V index of dialysis adequancy
URR- Urea Reduction Ratio
PCR - Protein catabolic rate
OCM – Online Clearance Monitor
Qo – convective volume
ERA-EDTA- European Renal Association-European Dialysis and Transplant Association.
KDOQI - Kidney Disease Outcome Quality Initiative
NCDS - National Cooperative Dialysis Study
USRDS - United States Renal Data System
DOPPS -Dialysis Outcomes and Practice Patterns Study
EUDIAL - Европейска работна група по диализа
ERBP - European Renal Best Practice
TBW – total body water
UF - ultrafiltration

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1. Introduction

According to the 2017 annual report of the European Kidney Association - European Dialysis and Transplant Association (ERA-EDTA), at the end of 2016 the total number of people with chronic kidney disease in Europe was 564,638, more than 80% of them on hemodialysis (CKD-5D). Worldwide, the prevalence of sustaining hemodialysis continues to grow, probably due to the growing incidence of diabetes and cardiovascular disease, as well as the widespread use of venous contrast agents in clinical practice. Despite technological advances, unsatisfactory results in the hemodialysis (HD) patient population indicate that improved patient care is still insufficient to increase survival. The question of the need to improve hemodialysis therapies, which has been the subject of research and discussion for many years, remains relevant. Many studies have shown a significant correlation between hemodialysis dose, clinical outcome, and quality of life. It has been found that increasing the time and frequency of dialysis, blood flow rate, lack of recirculation and reducing intradialysis complications are associated with better adequacy of HD. The term "dialysis adequacy" is most often associated with achieving a minimum acceptable Kt/V value and largely does not consider other clinical indicators in patients with CKD-5D. Dialysis adequacy is a much broader concept, and it is appropriate to discuss the dialysis methods used, water quality, volume and blood pressure control, treatment of anemic syndrome and bone-mineral deficiencies, as well as the recovery process and social rehabilitation of patients. Dialysis adequacy needs to include all the measures aimed at increasing patient survival, improving their quality of life, improving cardiovascular outcomes, and other patient-related benefits.

2. Purpose and tasks

2.1 Objective: To study the effect of non-standardized high dialysis dose spKt/V≥1.5, obtained by different dialysis techniques - conventional and convective, on the clinical outcome and to assess its importance for survival and quality of life in patients with CKD-5D.

2.2 MAIN TASKS:

1. To study the objective component of the achieved quality of life in patients with CKD-5D at different dose regimens by assessing the received dialysis dose and its impact on nutritional status, serum hemoglobin levels and average applied weekly erythropoietin dose for a period of five years.
2. To study the importance of vascular access, resp. blood flow (Qb) on the dialysis dose received and the clinical outcome.
3. To determine the influence of different dialysis membranes and techniques on the delivered dialysis dose and the clinical outcome in patients undergoing OL-HDF and HD.
4. To study the influence of the applied convective volume on the above indicators and to evaluate its role as an indicator for evaluating the effectiveness of the conducted convective therapy.
5. To evaluate the influence of convective volume and OL-HDF on episodes of intradialysis hypotension and recovery time.
6. To determine the influence of the received dialysis dose and the different types of dialysis techniques on the annual survival and mortality of the studied population
7. To study the subjective component of quality of life in patients with CKD-5D according to the received dialysis dose and the effect of the applied conventional and convective techniques.
8. To compare the methods of UKM and ionic dialysis for estimation of the received dialysis dose through the results of online monitoring and blood urea clearance in order to develop new therapeutic strategies.
9. **To develop an algorithm for research and treatment with a view to increase survival and quality of life based on the assessment of the researched factors.**

2.3 Working hypotheses:

1. The obtained high non-standardized dialysis dose (through conventional or convective therapies) leads to improved clinical outcome, survival, and quality of life in its two components - objective and subjective.
2. Ionic dialysis provides a reliable estimate of the dialysis dose delivered at high benefit to the patient.

3. Object, methodology and design of the study.

3.1 Object of the research.

The study includes a retrospective part with review and evaluation of medical documentation for the period 2017-2021 per 100 patients undergoing HD in the Clinic of Nephrology and Dialysis, Activity: Dialysis treatment at the University Hospital "St. Marina" in Varna. Several subgroups were formed to perform certain tasks of the study: 87 patients to study the impact of vascular access on indicators of adequacy, nutritional status and anemic syndrome; **41 patients** to study the effect of applied convective therapies on the received dialysis dose, nutritional status and anemic syndrome; **32 patients** to study the relationship between the indicators of adequacy calculated by UKM and the results obtained in online monitoring; **50 patients** for assessment of the achieved individual quality of life, who by 2021 are subject to monitoring for the needs of scientific research.

3.2 Inclusion and exclusion criteria

3.2.1 Including criteria

1. Persons over 18 years of age on chronic dialysis treatment for a period of more than 6 months with depleted residual renal function.
2. Persons who have signed an informed consent to participate in the study.
3. Persons with corrected iron deficiency.

3.2.2 Exclusion criteria

1. Persons under 18 years of age
2. Persons who have not signed an informed consent to participate in the study
3. Uncorrected iron deficiency
4. Active bleeding
5. Malignant process

The research was approved by a protocol of the Commission on Ethics of Research at the Medical University of Varna. The processing, statistical analysis and summarization of the results took place in the period October 2021-January 2022.

3.3 Methods

3.3.1 Documentary method — for analysis of literature sources, guidelines, normative acts, and medical documentation, which describe the researched issues.

3.3.2 Laboratory method - laboratory tests for blood counts and biochemistry are performed using the stop pump technique before and/or after HD, thus avoiding the effect of recirculation and minimizing the effect of urea rebound. (Table 1)

***Table 1* Laboratory method**

INDICATOR	*LABORATORY METHOD*	*REFERRALS*
HEMOGLOBIN	colorimetric method with Sodium Laurilsulfate; hematological analyzer Sysmex XN1000, Siemens.	120-180g/l*
UREA	Conjuged enzymatic reaction (with GLD, UV); kinetic method. Biochemical analyzer ADVIA 1800, Siemens.	3.2-8.2mmol/l
CREATININE	Jaffe Kinetic Method; Biochemical Analyzer ADVIA 1800, Siemens	44-115mmol/l
ALBUMIN	Colorimetric method with selective dye-bromcresol green (BCG); biochemical analyser ADVIA 1800, Siemens.	

**** 110-120g/l are taken as target values of serum hemoglobin in patients with CKD-5D***

3.3.3 Anthropometric methods

Anthropometric data (height and weight) are needed for UKM and nutritional status assessment. The registered difference in body weight before and after HD gives us information about the applied ultrafiltration, resp. the change in volume V in the Daugirdas formula. Watson's standardized formula for total body water (TBW) is used to estimate the volume of urea distribution. The latter uses the patient's body weight after the dialysis procedure or the so-called optimal "dry" weight.

3.3.4 Mathematical method

A validated UKM adequacy calculator (http://www.ureakinetics.org/) calculates dialysis adequacy and nutritional status indicators - spKt/V, URR and nPCR. The calculator is based on mathematical formulas presented in Table 2.

***Table 2* Mathematical methods**

Indicator	Formula
spKt/V	$spKt / V = - \ln (R- 0.008 \times t) + [4 - 3.5 \times R] \times 0.55\ UF / W)$
URR%	$URR\% = 100 \times (1 – C/Co)$
nPCR	$nPCR = 0.22+ \frac{0.36x(Cn-C)x24}{ID}$
Total Body Water (TBW) Men Total Body Water (TBW) Women	TBW = 2.447 - 0.09516 x age + 0.1074 x height + 0.3362 x weight TBW = -2.097 + 0.1069 x height + 0.2466 x weight

t - dialysis time in hours (h), UF - the volume of ultrafiltration in liters. (l), W- post-dialysis weight of the patient in kg., ln - natural logarithm, Co-pre-dialysis urea nitrogen, C-post-dialysis urea nitrogen, Cn-pre-dialysis urea nitrogen from the next HD, R = C/Co, ID - inter-dialysis time in hours. (h), Age - age in years, Height - height in cm, Weight - optimal weight in kg

3.3.5 Sociological method

A direct questionnaire is used to study the achieved individual quality of life of patients with CKD-5D

3.3.6 Statistical methods

Descriptive analysis to establish the average levels and variations in quantitative variables and absolute and relative values in qualitative variables.;

Parametric methods for hypothesis testing (Student's t-test, ANOVA analysis, HSD Tukey post-hoc test);
Non-parametric hypothesis testing methods (Chi square test, Cramer's V test);
Correlation analysis to study the relationship between the observed phenomena (Pearson's r, Spearman's Rho);
Regression analysis;
Survival analysis (Kaplan-Mayer curve, Survival median plot, Cox regression, Relative Risk);
Roc-curve;

The results at $p < 0.05$ are considered statistically significant.
Tabular and graphical method for presenting data - simple and multidimensional tables; line, pie, and pie charts.

Statistical analysis of the data was performed using SPSS v. 20.0.

3.4 Research – design

3.4.1 Retrospective analysis

3.4.1.1 Examination of the objective component of quality of life achieved at different dose regimens in patients with CKD-5D by assessing dialysis dose, nutritional status, serum hemoglobin levels and the mean weekly erythropoietin dose administered over a five-year period.

The medical protocols for performed dialysis procedure are monitored, as well as the medical files for a 5-year period of the studied population. The dialysis procedures are performed with equipment of Fresenius Medical Care series 4008 and 5008 in different dose regimes with average dialysis time - 11.38 ± 1.30h., 15.21 ± 0.40h, 16.1 ± 0.20h with bicarbonate dialysate, at blood flow Qd = 500ml/min and dialysis flow Qb = 200 to 400ml/min, according to the possibilities of the used vascular access and polysulfone dialyzers - Etropal, Diadema, Ashahi, F7, F70 with a surface standardized with the patient's body surface. For the purposes of the study, the results of the above-mentioned laboratory tests, the parameters for dialysis adequacy and nutritional status calculated on the basis of UKM, as well as data on the applied average weekly ESA dose (UI/week) were used; the optimal weight of the patient in kilograms; the applied volume of UF in liters (l); the duration of the procedure in hours (h); Permeability/Clearance of the used dialyzer in ml/min; Qd in ml/min and Qb in ml/min. Patients were randomized into three groups according to the delivered dialysis dose: inadequate spKt/V≤1.19, adequate standardized according to the criteria of KDOQI 2015 - spKt/V = 1.2-1.49 and high (non-standardized) -spKt/V≥1.5, examining the presence of the lack of connection between the received dialysis dose and the studied indicators, objectifying the clinical result and the achieved quality of life.

3.4.1.2 Five-year mortality and survival study in patients with CKD-5D

For the indicated 5-year period, the total annual mortality and survival are registered, assessing their relationship with the delivered dialysis dose in the total sample and the formed groups with analysis of the relative risk of death and expected survival.

3.4.1.3 Study of the importance of vascular access, respectively blood flow (Qb) on the received adequate dialysis dose.

For a two-year period (08.2017 - 08.2019), 87 patients undergoing dialysis were monitored, randomized into two groups: group 1 - patients with arteriovenous fistula/AVF/-45 patients, group 2 - patients with permanent tunneled vascular catheter/PC/- 42 patients. To assess the effect of vascular access on the adequacy of HD, URR and spKt/V, serum albumin, nPCR as well as the values of achieved hemoglobin levels, average weekly ESA dose, morbidity and mortality, reflecting the physical aspect and the objective component of the achieved quality of life in the study population. Dialysis was performed under the same conditions: low flow polysulfone dialyzers, surface 1.8-2.1m2, relative to the individual body surface and Qd = 500ml/min and Qb = 280 ± 52ml/min in conventional dialysis regimen with a weekly dose of 12 ± 0.40h and at initial randomization in the groups, patients were on an identical dose of ECA - 47UI / kg.

3.4.1.4 Investigation of the effect of different dialysis membranes and regimens on clinical outcome in patients undergoing online hemodiafiltration (OL-HDF)

For a two-year period, 41 patients were monitored, randomized into two groups, group 1 - conducting HD and group 2 - conducting OL-HDF. Fresenius Medical Care 4008 and 5008 devices were used, as group 1 performed conventional HD with low flux polysulfone dialyzers, and group 2 - OL-HDF in post-dilution mode with high flux dialyzers F70 and applied high convective volume Qo > 20l session. Qd = 500ml/min and Qb = 300 ± 42ml/min were administered to both groups of patients. In the second year, in 8 of the patients with OL-HDF, the Qo was changed to <20l per session while maintaining the remaining conditions. For the purposes of the study, the above indicators were evaluated, considering the frequency of episodes of intradialysis hypotension, as well as the recovery time reported by patients. The importance of the applied Qo as a criterion for efficiency and dosing of the performed OL-HDF is evaluated, as well as its influence on the achieved clinical result and objective quality of life.

3.4.1.5 Study the relationship between the Dialysis Adequacy indicators determined by UKM and those registered in online monitoring.

The values for spKt/V and URR, calculated by UKM based on routine blood tests in the Clinic and recorded in online monitoring (onKt/V) for the same sessions, reflected in the files of the examined patients are monitored. For this purpose, Fresenius Medical Care 5008 series devices were used, which determine the received dialysis dose based on ionic dialysis by OSM (Online Clearance Monitor). HD are according to a conventional scheme with Diadema polysulfone dialyzers with low flow and surface, consistent with the patient's body size at Qb = 300 ± 48ml/min and Qd = 500ml/min with a set temperature of 37 ° C and without sodium profiling in the dialysis solution in order to exclude interference of the result. In each patient, 4 measurements were performed in parallel sessions, excluding from the sample patients with problematic vascular access (with impaired flow and / or recirculation) and data on hyperhydration for complete reliability of the result.

3.4.2 Prospective analysis of the achieved quality of life in patients with CKD-5D

It is carried out through a direct survey based on a variant of the standardized questionnaire SF-36 for quality assessment of quality of life in patients with CKD at different stages, conducted among 50 respondents of HD, who are a representative sample of the observed in the retrospective part of the study group by 2021. The questionnaire is divided into 5 components, reflecting the achieved quality of life and a section for general information. Based on the survey conducted among the respondents, a correlation is sought between the studied indicators and the received dialysis dose and the type of dialysis technique to develop optimized therapeutic strategies and improved clinical results.

4. Own results

4.1 Evaluation of the indicators for the objective component of the achieved quality of life and their connection with the delivered dialysis dose

Figure 1 shows the distribution of the studied population according to their main disease, and Table 3 - their distribution by age, sex, and duration of dialysis treatment:

Table. 3 ***Population structure by sex, age and age of HD***

Year	Patients Count	Female	Men	Age	Duration
2017	100	40	60	58,55±11.84	5,27±3.72
2018	91	37	54	58.56±11.82	5,61±3.77
2019	84	36	48	58,26±11,29	6,84±3.82
2020	80	33	47	58.71±11.25	7.96±3.86
2021	66	24	42	58.38±11.30	8.95±3.94
Total	50	21	29	56.90±11.23	9.46±4.15

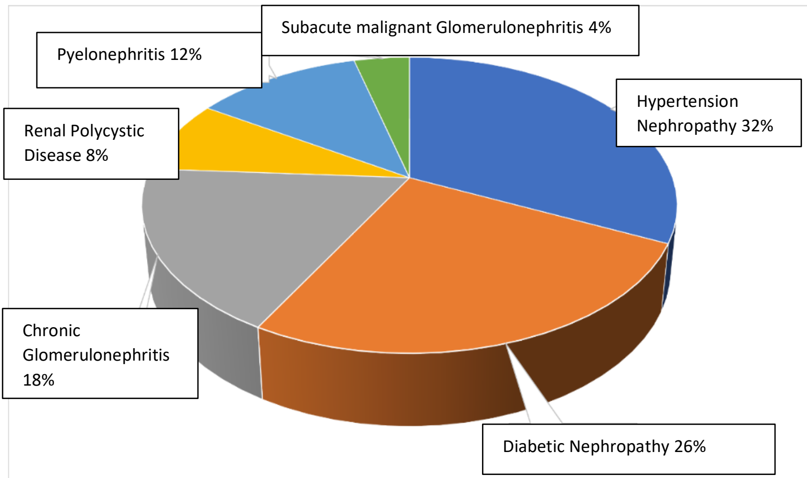


FIG. 1 Percentage distribution of the studied patients according to the main disease that led to CKD-5D (n = 100)

Table 4 present the results of the variation and ANOVA analysis of the indicators of adequacy, nutritional status, serum hemoglobin and applied average weekly erythropoietin (ESA) dose for the period under review, which reflect the achieved objective physical component of quality of life.

<u>Table 4</u> ANOVA results and five-year variation analysis

	2017	2018	2019	2020	2021	ANOVA
spKt/V	1.25±0.20	1.34±0.15	1.39±0.20	1.54±0.31	1.59±0.32	F=27.42986 P < 0.0001
URR%	65.59±7.23	71.12±5.70	71.06±6.32	73.02±7.62	73.57±7.26	F= 19.25779 P < 0.0001
nPCR (g/kg/d)	1.09±0.14	1.16±0.12	1.18±0.12	1.21±0.15	1.22±0.14	F =12.57039 P < 0.0001
Alb (g/l)	34.38±4.71	36.64±4.18	37.46±4.53	37.73±5.14	37.02±4.34	F = 7.90568 P < 0.0001
Hgb (g/l)	100.51±10.2	104.38±6.04	105±6.87	105.81±7.95	106.73±8.25	F=7.90939 P < 0.0001
ECA (UI/week)	9210±3036	8802±4222	7571±2983	7469±3217	7230±4050	F = 5.9666 P < 0.0001
Count	400	364	366	320	264	

The tendency to increase the dialysis dose, expressed by spKt/V and URR at the beginning of the study with mean values of 1.25 ± 0.20 and 65.59 ± 7.23% and at the end of the 5-year follow-up period with values of 1.59 ± 0.32 and 73.57 ± 7.26 is impressive. %. There was also a trend towards improvement in nutritional status with a mean nPCR at the beginning of the study of 1.09 ± 0.14 and 1.22 ± 0.14 at the end. Regarding serum albumin and hemoglobin after the increase in the first year of the study, no significant change was observed after the second year. It is impressive that despite the stabilization of the levels to the target value for the dialysis population, with increasing dialysis dose there is a tendency to reduce the average weekly erythropoietin dose - at the beginning of the period 9210 ± 3036UI and at the end 7230 ± 4050UI.

Table 5 presents the data from the post-hoc Tukey analysis (Post Hoc Tukey HSD - Honestly significant difference). Regarding spKt/V, significant differences in dose were observed after the third year of the study with intensification of treatment to spKt/V> 1.3. Regarding the recorded average annual values for nPCR, serum albumin and hemoglobin after the second year, no statistically significant difference was found in the result. However, the trend towards improved nutritional status cannot be ignored, especially in the last two years of the study (T2: T4 Q = 3.42, p = 0.11169; T2: T5 Q = 3.74, p = 0.06419). increases and approaches a p-value value close to the significant one.

***Table 5** Results of the post-hoc Tukey test for a five-year period*

Q p value	spKt/V	URR %	nPCR (g/kg/d)	Alb (g/l)	Hgb (g/l)	ECA UI/week
T_1:T_2	Q = 3.10 (p = .18354)	Q = 7.35 (p = .00000)	Q = 4.61 (p = .01048)	Q = 4.47 (p = .01458)	Q = 4.38 (p = .01784)	Q = 1.10 (p = .93738)
T_1:T_3	Q = 5.05 (p = .00365)	Q = 7.27 (p = .00000)	Q = 6.39 (p = .00008)	Q = 6.10 (p = .00020)	Q = 5.07 (p = .00343)	Q = 4.41 (p = .01655)
T_1:T_4	Q = 11.01 (p = .00000)	Q = 9.87 (p = .00000)	Q = 8.04 (p = .00000)	Q = 6.63 (p = .00004)	Q = 5.99 (p = .00027)	Q = 4.69 (p = .00883
T_1:T_5	Q = 12.34 (p = .00000)	Q = 10.61 (p = .00000)	Q = 8.35 (p = .00000)	Q = 5.22 (p = .00233)	Q = 7.02 (p = .00001)	Q = 5.33 (p = .00176)
T_2:T_3	Q = 1.94 (p = .64451)	Q = 0.07 (p = .00000)	Q = 1.78 (p = .71834)	Q = 1.63 (p = .77862)	Q = 0.70 (p = .98813)	Q = 3.31 (p = .13368)
T_2:T_4	Q = 7.91 (p = .00000)	Q = 2.52 (p = .38404)	Q = 3.42 (p = .11169)	Q = 2.16 (p = .54543)	Q = 1.61 (p = .78489)	Q = 3.59 (p = .08448)
T_2:T_5	Q = 9.23 (p = .00000)	Q = 3.26 (p = .14543)	Q = 3.74 (p = .06419)	Q = 0.75 (p = .98382)	Q = 2.65 (p = .33459)	Q = 4.23 (p = .02446)
T_3:T_4	Q = 5.96 (p = 0.00029)	Q = 2.60 (p = .35378)	Q = 1.65 (p = .77122)	Q = 0.53 (p = .99578)	Q = 0.92 (p = .96678)	Q = 0.28 (p = .99968)
T_3:T_5	Q = 7.29 (p = .00000)	Q = 3.33 (p = .12943)	Q = 1.97 (p = .63467)	Q = 0.87 (p = .97217)	Q = 1.95 (p = .64111)	Q = 0.92 (p = .96689)
T_4:T_5	Q = 1.32 (p = .88239)	Q = 0.74 (p = .98531)	Q = 0.32 (p = .99944)	Q = 1.40 (p = .85833)	Q = 1.03 (p = .94929)	Q = 0.64 (p = .99124)

T_1-2017 T_2-2018 T_3-2019 T_4-2020 T_5-2021

Post-hoc analysis also confirmed the established dependence on the administered erythropoietin dose. There was a significant decrease in the administered dose after the third year of the study with the intensification of the dialysis prescription, after which the levels stabilized in a similar range.

However, the fact that at the end of the study there was a significant tendency to increase the difference from the start (T1: T5 Q = 5.33, p = 0.00176; T2: T5 Q = 4.23, p = 0 .02446) should not be neglected.

The results of the correlation analysis demonstrate dependencies of different nature between the delivered dialysis dose and the studied indicators presented in fig 2 and 3. First of all, it is important to consider the fact that despite the established moderate negative correlation between the age of the patients and spKt/V (r = -0.5023, p = 0.000018, R^2 = 0.2523) a moderate positive correlation between the duration of dialysis treatment and spKt/V (r = 0.4108., p = 0.000629 R2 = 0.17), which is probably related to the good level of rehabilitation and is objectified by the achieved clinical result. A strong positive correlation was found between spKt/V and patient nutritional status indicators - nPCR (r = 0.7689, p <0.0001; R^2 = 0.5912) and serum albumin (r = 0.7473, p = <0.0001, R^2 = 0.5585) (fig. 2 and 3).

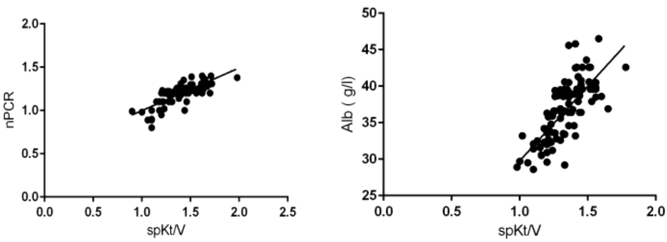


Fig. 2 Correlation between spKt / V and nPCR, serum albumin.

Regarding the anemic syndrome, there is a moderate positive correlation with serum hemoglobin levels (r = 0.5952. P = <0.0001, R^2 = 0.4543) and a strong negative correlation with the applied erythropoietin dose (r = -0.7414 p = <0.0001, R^2 = 0.5497).

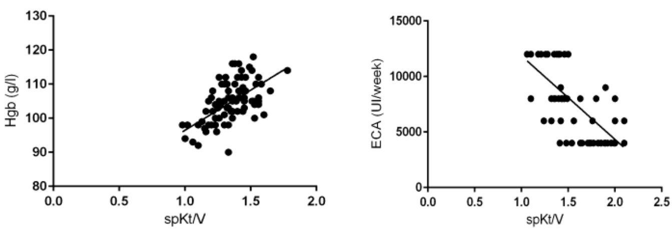


Fig.3 Correlation dependences between spKt / V and serum Hgb, mean weekly ECA dose.

The data from the analysis of variance according to the obtained dialysis dose are presented in table 6 and 7

Table 6 Data from ANOVA dose analysis.

				2017			2018			2019			2020			2021
	category	n	%		n	%		n	%		n	%		n	%	
spKt/V	1.20-1.49	46	46	1.323±0.091	62	68.1	1.33±0.0835	48	57.1	1.325±0.0884	27	33.3	1.36±0.1982	22	33.3	1.37±0.086
	≥1.50	13	13	1.58±0.0473	16	17.6	1.56±0.0701	26	31.0	1.615±0.1042	42	54.2	1.81±0.1427	33	52.7	1.88±0.174
	≤1.19	41	41	1.074±0.1173	13	14.3	1.1±0.0682	10	11.9	1.087±0.0851	11	12.5	1.092±0.0716	11	14.0	1.13±0.0475
URR	1.20-1.49	46	46	68.347±2.921	62	68.1	71.25±3.8203	48	57.1	70.221±0.0851	27	33.3	70.75±5.4146	22	33.3	70.83±3.080
(%)	≥1.50	13	13	76.179±2.771	16	17.6	78.17±1.691	26	31.0	77.323±1.992	42	54.2	78.56±2.9564	33	52.7	79.47±3.063
	≤1.19	41	41	59.145±5.456	13	14.3	61.78±2.2551	10	11.9	58.82±3.7022	11	12.5	59.84±3.1173	11	14.0	60.13±3.933
nPCR	1.20-1.49	46	46	1.16±0.096	62	68.1	1.16±0.0975	48	57.1	1.179±0.0811	27	33.3	1.18±0.1075	22	33.3	1.18±0.0686
	≥1.50	13	13	1.22±0.07	16	17.6	1.22±0.0654	26	31.0	1.235±0.063	42	54.2	1.32±0.0924	33	52.7	1.33±0.0906
	≤1.19	41	41	0.98±0.11	13	14.3	1.02±0.0864	10	11.9	0.965±0.0957	11	12.5	0.95±0.0737	11	14.0	0.98±0.0636
Alb	1.20-1.49	46	46	36.30±3.45	62	68.1	36.77±3.6302	48	57.1	36.837±3.2093	27	33.3	36.98±4.7259	22	33.3	36.50±3.405
(g/l)	≥1.50	13	13	39.19±3.15	16	17.6	40.6±2.4372	26	31.0	41.535±2.2611	42	54.2	40.12±3.9679	33	52.7	39.837±3.035
	≤1.19	41	41	30.71±3.5964	13	14.3	31.16±1.7061	10	11.9	29.88±2.7145	11	12.5	30.07±2.0069	11	14.0	30.337±1.97
Hgb	1.20-1.49	46	46	105.52±7.34	62	68.1	104.94±5.3496	48	57.1	103.958±5.44	27	33.3	104.38±7.5228	22	33.3	104.895±6.51
(g/l)	≥1.50	13	13	107.77±9.88	16	17.6	108.19±5.2943	26	31.0	110.231±5.19	42	54.2	114.80±5.1411	33	52.7	115±5.7595
	≤1.19	41	41	92.585±7.563	13	14.3	97.08±3.7961	10	11.9	96.4±6.2218	11	12.5	93.33±5.2915	11	14.0	96±6.5247
ECA	1.20-1.49	46	46	8065.22±2594.03	62	68.1	8096.77±2665.56	48	57.1	8062.5±2724.25	27	33.3	8916.67±3119.60	22	33.3	9000±2687.42
(UI/week)	≥1.50	13	13	5384.62±1709.70	16	17.6	5062.5±1611.16	26	31.0	5192.31±1442.75	42	54.2	5358.97±1739.44	33	52.7	5100±1936.05
	≤1.19	41	41	11707.32±1308.51	13	14.3	12000±0.0	10	11.9	11400±1897.37	11	12.5	11333.3±2000	11	14.0	11500±1414.21
Duration	1.20-1.49	46	46	5.543±4.0863	62	68.1	5.85±4.0442	48	57.1	6.896±3.7882	27	33.3	6.708±2.9559	22	33.3	8.053±3.4395
(years)	≥1.50	13	13	5.462±3.9289	16	17.6	6±3.4254	26	31.0	7.5±4.2919	42	54.2	8.923±4.3127	33	52.7	10.633±4.3746
	≤1.19	41	41	2.463±2.3569	13	14.3	4±2.582	10	11.9	4.9±2.079	11	12.5	6.667±3.4278	11	14.0	7.625±3.0677

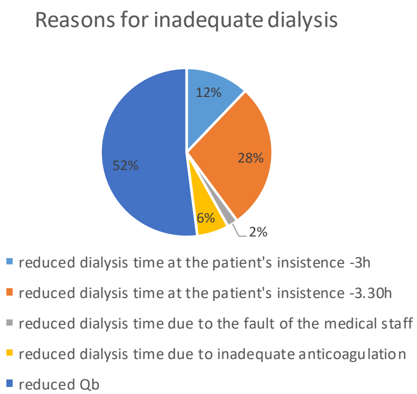
The gradual increase in the proportion of patients receiving a high dialysis dose of spKt/V ≥1.5 over the years and the steady downward trend in the number of patients receiving a low dialysis dose are noteworthy. All patients receiving high dialysis dose have good nutritional status covering the recommendations of KDOQI 2015, with a tendency to increase it, along with increasing the dialysis dose in the group to values close to the target nPCR = 1.4, a goal difficult to achieve in severely impaired conditions and an aging dialysis population. For the entire five-year follow-up period, only 12% of all patients on high-dose therapy had nPCR <1.2, all of whom were representatives of the upper age group (64-79 years). Of the adequate dialysis dose (spKt/V = 1.2 - 1.4), varying in the range 1.16 and 1.17, they remain too low compared to the recommendations. Although a significant difference in nPCR in the two groups was not found until after the third year of the study, it was present throughout the period for serum albumin levels that were consistently higher in the spKt/V group ≥1.5. No significant differences in hemoglobin levels were observed during the first three years of the study between the high and standard dialysis dose ($p > 0.05$), but a significant difference in the mean weekly dose of ECA ($p < 0.05$) was observed throughout the follow-up period. The latter is significantly lower in the spKt/V≥1.5 group.

<u>Table 7</u> Data from post-hoc Tukey test by dose regimen

Q p value		2017	2018	2019	2020	2021
spKt/V	T1:T2	Q = 7.89 (p = .00000)	Q = 7.39 (p = .00000)	Q = 8.91 (p = .00000)	Q = 10.61 (p = .00000)	Q = 11.04 (p = .00000)
	T1:T3	Q = 8.35 (p = .00000)	Q = 8.22 (p = .00000	Q = 8.26 (p = .00000	Q = 8.14 (p = .00000	Q = 7.99 (p = .00000)
	T2:T3	Q = 9.86 (p = .00000)	Q = 9.65 (p = .00000	Q = 9.91 (p = .00000)	Q = 11.61 (p = .00000)	Q = 11.25 (p = .00000)
URR	T1:T2	Q = 7.41 (p = .00000)	Q = 7.28 (p = .00000)	Q = 7.35 (p = .00000)	Q = 7.32 (p = .00000)	Q = 7.21 (p = .00000)
(%)	T1:T3	Q = 8.36 (p = .00000)	Q = 8.24 (p = .00000)	Q = 8.30 (p = .00000)	Q = 8.29 (p = .00000)	Q = 8.26 (p = .00000)
	T2:T3	Q = 10.28 (p = .00000)	Q = 9.86 (p = .00000)	Q = 10.22 (p = .00000)	Q = 9.98 (p = .00000)	Q = 9.87 (p = .00000)
nPCR	T1:T2	Q = 3.42 (p = .11169)	Q = 3.24 (p = .15563)	Q = 3.82 (p = .0611)	Q = 5.52 (p = .00258)	Q = 5.63 (p = .00146)
(g/l)	T1:T3	Q = 6.52 (p = .00011)	Q = 6.43 (p = .00021)	Q = 6.99 (p = .00003)	Q = 7.02 (p = .00001)	Q = 6.48 (p = .00018)
	T2:T3	Q = 10.21 (p = .00000)	Q = 10.15 (p = .00000	Q = 11.26 (p = .00000	Q = 11.21 (p = .00000	Q = 11.10 (p = .00000
Alb	T1:T2	Q = 7.21 (p = .00000)	Q = 7.23 (p = .00000)	Q = 7.99 (p = .00000)	Q = 7.25 (p = .00000)	Q = 7.14 (p = .00000)
(g/l)	T1:T3	Q = 8.37 (p = .00000)	Q = 8.84 (p = .00000)	Q = 8.26 (p = .00000	Q = 8.64 (p = .00000)	Q = 8.57 (p = .00000)
	T2:T3	Q = 9.46 (p = .00000)	Q = 9.63 (p = .00000)	Q = 10.97 (p = .00000)	Q = 9.59 (p = .00000)	Q = 9.48 (p = .00000)
Hgb	T1:T2	Q = 3.26 (p = .14543)	Q = 3.33 (p = .12943)	Q = 3.73 (p = .0622)	Q = 5.51 (p = .00255)	Q = 5.62 (p = .00152)
(g/l)	T1:T3	Q = 7.58 (p = .00000)	Q = 6.10 (p = .00050)	Q = 6.27 (p = .00041)	Q = 7.62 (p = .00000)	Q = 6.28 (p = .00042)
	T2:T3	Q = 7.59 (p = .00000)	Q = 7.41 (p = .00000)	Q = 7.38 (p = .00000)	Q = 10.42 (p = .00000)	Q = 10.21 (p = .00000)
ECA	T1:T2	Q = 8.66 (p = .00000)	Q = 8.91 (p = .00000)	Q = 8.82 (p = .00000)	Q = 10.58 (p = .00000)	Q = 11.27 (p = .00000)
UI/week	T1:T3	Q = 9.24 (p = .00000)	Q = 9.18 (p = .00000)	Q = 9.28 (p = .00000)	Q = 9.97 (p = .00000)	Q = 9.82 (p = .00000)
	T2:T3	Q = 11.03 (p = .00000)	Q = 10.14 (p = .00000)	Q = 10.58 (p = .00000)	Q = 11.15 (p = .00000)	Q = 10.46 (p = .00000)
Duration	T1:T2	Q = 3.33 (p = .12943)	Q = 3.31 (p = .13368)	Q = 1.95 (p = .64111)	Q = 1.61 (p = .78489)	Q = 1.78 (p = .71834)
(years)	T1:T3	Q = 7.27 (p = .00000)	Q = 3.26 (p = .14543)	Q = 2.52 (p = .38404)	Q = 1.95 (p = .64111)	Q = 1.94 (p = .64451)
	T2:T3	Q = 7.18 (p = .00000)	Q = 3.59 (p = .08448)	Q = 2.65 (p = .33459)	Q = 1.97 (p = .63467)	Q = 2.16 (p = .54543)

T1-spKt/V=1.2-1.49 T2-spKt/V≥1.5 T3-spKt/V≤1.19

The main methods used to increase the dialysis dose for the five-year period were extension of the dialysis time from 3.30 hours per session to 4 hours in 28% of patients, from 3 hours to 4 hours in 12% and from 4 hours to 4.30 hours in 6% of patients, the rest received a standard dialysis time of 4 hours per session; performing emergency dialysis procedures in 22% of patients; the introduction in the conventional dialysis scheme of high-flow dialyzers - once a week in 38% of patients and twice a week in 19% of patients; increasing the blood flow rate from 280 ml/min to 400 ml/min in an average of 32% of patients, with the percentage varying between 19% and 46% according to the possibilities of vascular access; the introduction of online HDF in the treatment regimen in the last two years of the study in 21% of patients. The mean blood flow at the beginning of the study was 268 ± 36ml/min and the end at 352 ± 43ml/min. The mean dialysis time increased from 3.10 ± 0.2h to 4.15 ± 0.3h
The main reasons for inadequate dialysis spKt/V≤.19 for the period under consideration are presented in Figure 4.



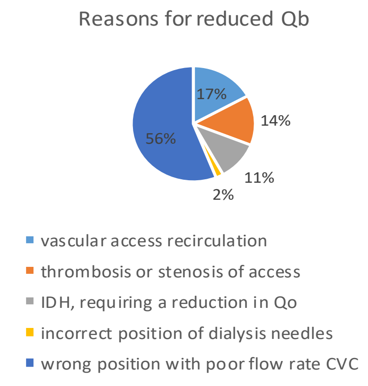
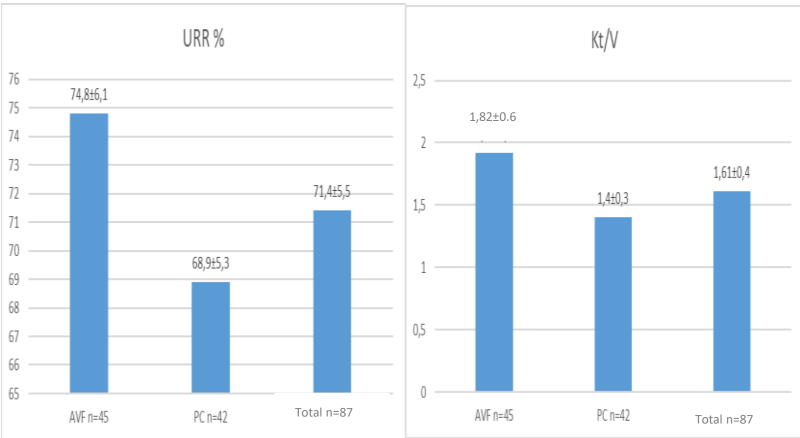


Fig. 4. Causes of inadequate dialysis and decreased Qb

4.2 Influence of vascular access on the adequacy of dialysis treatment.

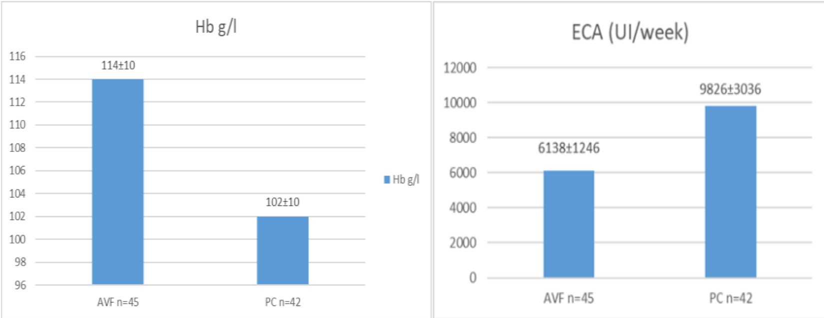
The age of the studied population was on average 59.8 ± 5.1 years, and no statistically significant difference was found in the received dialysis dose by age groups ($p = 0.103$). The figure 5 presents the data from the variation analysis and Student's T-test for URR and spKt/V in the studied groups, as a significantly better result is found in group 1. Inadequate dialysis dose (URR <65% and Kt/V <1.2) was found in only 3.1% of patients, mostly from group 2, at the expense of group 1, where the registered percentage is 0.8%. The most common cause of inadequate dialysis in group 2 was catheter dysfunction, followed by catheter-associated infections, and in group 1, anastomotic recirculation.



t = 6.267, p <0.0001 ***t = 8.632, p <0.0001***

Fig. 5- Influence of permanent vascular access on HD - adequacy ratios URR and Kt/V.

Figure 6 presents the data from the variation analysis and Student's T-test for serum hemoglobin (g/l) and the mean weekly ECA dose (UI / week) administered to patients in both groups. It is noteworthy that despite the randomization of patients with an identical dose of fast-acting ECA (47 IU / kg) at the start of the study, at the end of the period hemoglobin levels in the AVF group were significantly higher with a significant reduction in ECA dose compared to the PC group. (p <0.05).



t=7.21, p<0.0001 ***t=7.54, p<0.0001***

Fig. 6 Influence of constant vascular access and dialysis dose on the achieved Hb levels (g/l) when applying the same dose of fast-acting ECA.

The reported overall mortality in the study group was 6.3%, with a significantly higher mortality - 9.1% reported in the PC group (χ^2 = 12.867, p = 0.002) due to complications from catheter-associated sepsis, while the mortality in the AVF group was 2.3 %. Analysis of the data showed that the relative risk of death in the PC group was 4.29 times higher (RR 4.29; CI95 0.4989-36.8151, p<0.001). The most common cause of death in patients with AVF was cardiovascular events, which were and a leading cause of death in the dialysis population. The figure 7 shows the most common complications in both groups for the two-year follow-up period:

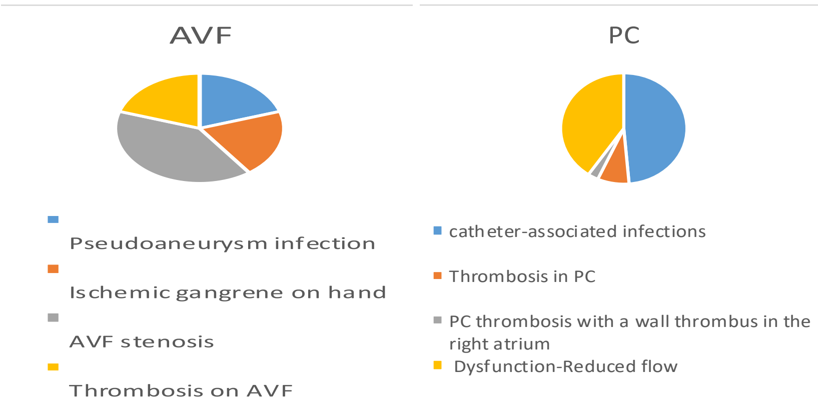


Fig. 7 Complications in patients using AVF and PC for a period of two years.

4.3 OL-HDF and its effect on the clinical outcome and prognosis of the patient. Convective volume (Qo).

On the table 8 the data from the variational analysis and Student's T-test for a two-year period are presented.

Table 8

Indicator X±SD	2020 OL-HDF n=22	2020 HD n=19	2020 t -test P value	2021 OL-HDF n=21	2021 HD n=14	2021 t -test P value
Age	53.9±11.96	56.63±11.07	t=-0.734 p=0.467	55.6±11.78	55.64±11.12	t=-0.738 p=0.465
spKt/V	1.82±0.12	1.3±0.11	t=14,52 p<0.00001	1.83±0.25	1.37±0.08	t=7.54 p<0.00001
URR %	79,46±1.45	69.01±5.8	t=7.647 p<0.00001	79.21±3.56	71.86±2.99	t=6.36 p<0.00001
nPCR (g/kg/d)	1.28±0.12	1.16±0.11	t=3.215 p=0,003	1.31±0.12	1.2±0.05	t=3.48 p=0.0024
Alb (g/l)	38.90±5.4	35.74±3.19	t=2.275 p=0. 029	38.17±3.96 4.05	36.64±2.98	**t=1.20289 p=0. 238**
Hgb (g/l)	111.64±4.43	102.32±5.19	t=6.20 p<0.00001	112.15±6.86	104.14±4.73	t=3.64 p<0.00001
ECA (UI/week)	5681±1742	9947±2328	t=6.53 p<0.00001	6142±2080	9714±1749	t=-4.01 p=0.000162

There was a significant difference (p <0.05) in the studied indicators in the two groups, except for the registered levels of serum albumin in the second year of observation (t = 1.20289, p = 0.238). The results show significantly higher values of dialysis adequacy and nutritional status in patients with OL-HDF, as well as higher values of serum hemoglobin in the group, achieved at significantly lower erythropoietin dose.

Table 9 presents the results of the study groups in terms of applied ultrafiltration (UF), convective volume (Qo) and episodes of intradialysis hypotension (IDH) with the time required for recovery (RT) of patients.

Table 9

Indicator X±SD	2020 OL-HDF n=22	2020 HD n=19	2020 t -test P value	2021 OL-HDF n=21	2021 HD n=14	2021 t -test P value
UF (l)	3905±413	4042±414	t=-1.061 p=0.295	3890±274	3743±408	t=1.146 p=0.265
Qo (l)	24.73±0.98	-	-	22.57±4.31	-	-
RT (h)	2.86±2.61	5.79±4.52	t=-2.58 p=0.014	1.53±0.59	5.57±5.78	t=-2.51 p=0.026
IDH (%)	27%	42%	**t=-0.986 p=0.165**	4.8%	35.8%	**t=-1.753 p=0.043**

The obtained results show significantly shorter RT in the OL-HDF group compared to HD and although in the first year of observation the difference was not statistically significant (t = -0.986, p = 0.165), at the end of the study demonstrated the pronounced effect of convective therapies on hemodynamics (t = -1.753 p = 0.043) with secondary improved recovery time. This effect is a result of the correction of the applied convective volume (Table 10), which stands out as the main factor determining the clinical outcome.

Table 10 Frequency of IDH after Qo correction

OL-HDF X±SD	2020 n=22	2021 n=21	t -test P value
Qo (l)	24.73±0.98	22.57±4.31	t =2.23053 p=0.015623
RT (h)	2.86±2.61	1.53±0.59	t=2.29736 p=0.013388
IDH (%)	27%	4.8%	**t =1.74939, p=0.044257**

The data from the analysis of variance by age are presented in table 11:

Table 11 ***Mean values of the studied indicators for different age groups conducting OL-HDF and HD***

X±SD	2020			2021		
	T1 32-47 years	T2 48-63 years	T3 64-79 years	T1 32-47 years	T2 48-63 years	T3 64-79 years
Therapy	Online HDF					
spKt/V	1.84±0.10	1.9±0.12	1.73±0.04	2.0±0.10	1.96±0.08	1.57±0.24
URR %	79.55±0.82	80.15±2.02	79.01±0.72	81.16±1.13	81.46±1.86	75.73±3.13
nPCR (g/kg/d)	1.38±0.04	1.34±0.07	1.14±0.07	1.4±0.06	1.36±0.07	1.17±0.05
Alb (g/l)	42.53±0.60	41.35±4.18	32.9±3.37	42.48±2.02	39.65±2.43	33.98±7.73
Hgb (g/l)	112.5±4.03	112.8±4.83	109.75±4.65	111.4±6.84	116±6.27	108.5±6.54
ECA (UI/week)	4666±1032	4666±1032	7000±1511	4800±1095	4625±1767	8500±3338
Qo	24.5±1.22	24.6±1.03	24.8±0.99	25±0.70	25.37±0.74	18.25±4.52
IDH	0%	0%	75%	0%	0%	12.5%
RT	1.16±0.40	1.5±0.54	5.5±2.72	1.12±0.21	1.25±0.46	2.13±0.35
Therapy	Conventional HD					
spKt/V	1.35±0.07	1.27±0.11	1.28±0.13	1.39±0.03	1.34±0.09	1.41±0. 07
URR %	71.4±3.97	67.16±6.61	69.48±5.98	72.84±2.27	70.02±3.12	73.26±2.83
nPCR (g/kg/d)	1.21±0.02	1.10±0.10	1.21±0.11	1.2±0.01	1.16±0.05	1.25±0.05
Alb (g/l)	36.98±1.23	33.68±2.85	37.43±3.5	37.28±1.3	33.88±3.15	39.28±0,33
Hgb (g/l)	105.6±6.58	98.5±2.07	104.6±3.98	104.4±3.84	101.8±4.6	108.4±6.51
ECA (UI/week)	8400±2509	11125±1642	9666±2658	9200±1643	10600±1949	9000±1732
IDH	0%	87%	16.5%	20%	90%	4%
RT	3.8±2.68	7.87±5.30	4.66±3.98	4.0±2.23	9.8±8.67	2.2±0.44

Patients in the upper tertile (64-79 years) have a significantly higher frequency of IDH when applying a high convective volume - Qo> 20 liters ($t = -3.03489$, $p = 0.004457$) Reduction of the latter ($t = 4.04289$, $p <0.0001$) at these patients leads to improved tolerability of the procedure and shortened recovery time, which is at the expense of the achieved clinical result (Table 12)

***Table 12** Comparative analysis of the achieved result in patients aged 64-79 years performing HDF for a two-year follow-up period*

Indicator	2020	2021	t-test p value
Qo (l)	24.87±0.99	18.25±4.52	t=-4.04289, p<0.0001
IDH	75%	12.5%	t=-3.03489 , p=0.0044
RT (h)	5.5±2.72	2.12±0.35	t=3.4733, p=0.002
Kt/V	1.73±0.04	1.57±0.24	t=1.7975, p=0.04
URR (%)	79.01±0.72	75.73±3.13	t=-2.877, p=0.006
nPCR	1.14±0.07	1.17±0.05	**t=-0.979, p=0.17**
Alb (g/l)	32.9±3.37	33.98±7.73	**t=0.80, p=0.218**
Hgb (g/l)	109.75±4.65	108.5±6.54	**t=0.44, p=0.333**
ECA (UI/week)	**7000±1511**	**8500±3338**	**t=1.15, p=0.13**

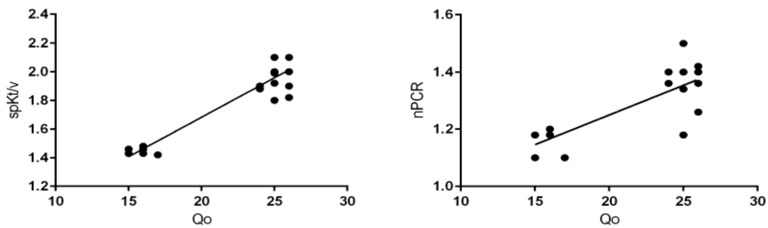
The results of the Student's T-test did not reveal a statistically significant difference (p> 0.05) in the above indicators between the first and second year of the study in the other age groups of OL-HDF-first (32-47 years) and second tertile (48-63 years). This has not been proven for any age group within the conventional HD

It should not be neglected that after correction of Qo the obtained average values for spKt/V (t = 1.37, p = 0.09) and URR (t = 1.43, p = 0.08) in the third tertile are completely comparable with those in the same age group. conducting HD (table 13). A significant difference was found only in the parameters of nutritional status -nPCR (t = -2.59, p = 0.01) and serum albumin (t = -6.64, p <0.001), which are significantly higher in the group of HD, as the latter is also associated with better hemodynamic stability and recovery time in patients in the third age tertile

***Table13.* Comparative analysis of the results achieved in patients with HDF and HD in the age group 64-79 for a two-year follow-up period**

Indicator X±SD	2020 OL-HDF	2020 HD	t-test p value	2021 OL-HDF	2021 HD	T- test P value
Qo (l)	**24.87±0.99**	-	-	**18.25±4.52**	-	-
IDH	**75%**	**16.5%**	t=2.44, p=0.015	**12.5%**	**4%**	t=0.77, p=0.23
RT (h)	5.5±2.72	2.66±1.98	t=3.483, p=0.018	2.12±0.35	2.2±0.44	t=-0.33, p=0.37
Kt/V	1.73±0.04	1.28±0.13	t=8.61, p<0.0001	1.57±0.24	1.41±0. 07	t=1.37, p=0.09
URR (%)	79.01±0.72	69.48±5.98	t=4.52, p=0.0003	75.73±3.13	73.26±2,83	t=1.43, p=0.08
nPCR	1.14±0.07	1.21±0.11	t=-1.35, p=0.10	**1.17±0.05**	**1.25±0,05**	**t=-2.59, p=0.01**
Alb (g/l)	**32.9±3.37**	**37.43±3.5**	**t=-2.43, p=0.015**	**33.98±7.73**	**39.28±0.33**	**t=-6.64, p<0.001**
Hgb (g/l)	109.75±4.65	104.6±3.98	t=2.14, p=0.026	108.5±6.54	108.4±6,51	t=0.02, p=0.48
ECA (UI/week)	7000±1511	9666±2658	t=-2.38, p=0.017	8500±3338	9000±1732	t=-0.3,p=0.38

While in the first year of the study, when using a standard Qo> 20 liters, no correlations were found with the studied parameters (r = 0.0001 p> 0.05), despite the high dialysis dose achieved, after its adaptation according to the individual characteristics of the patient in the second year strong positive correlation of Qo with spKt/V (r = 0.91, p <0.0001, R^2 = 0.86) and nPCR (r = 0.74, p <0.0001, R^2 = 0.68) and regression with high predictive value (Fig. 8)



Y = 0.05507*X + 0.5803 ***Y = 0.02072*X + 0,8351***

***Fig 8* Regression dependence of Qo with spKt/V and nPCR.**

A moderate positive correlation was also reported with serum albumin levels (r = 0.68, p <0.0001, R^2 = 0.48) and hemoglobin (r = 0.55, p <0.0001, R^2 = 0.30). A high negative correlation was found for the administered erythropoietin dose (r = -0.7143, p <0.001, R^2 = 0.51) (fig.9)

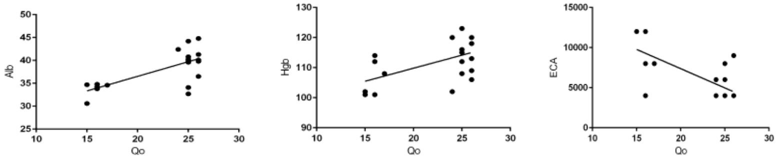


Fig. 9 Relationship between Qo (l) and serum albumin levels (g/l), hemoglobin (g/l) and administered weekly ECA dose (UI/week)

The obtained results also show significant differences in the annual mortality rates for 2020 for the group of OL-HDF - 4.5%, and for HD - 26% (χ^2 = 18.478 V = 0.521 p = 0.001) For 2021 for OL-HDF - 14.3%, and in HD - 42.8% (χ^2 = 13.147, V = 0.513, p = 0.001) It was found that the relative risk of death in the group of HD is 3.6 times higher (RR 3.59; CI 95% 1.2531 - 10.2467, p <0.001) compared to OL-HDF. At the end of the period, the registered two-year survival in patients with OL-HDF was 87.7%, while in the group of HD significantly lower - 57.2%.

The figure 10 shows the Roc-curves for determining the main predictors of deteriorating clinical outcome and death in both groups for the two-year follow-up period.

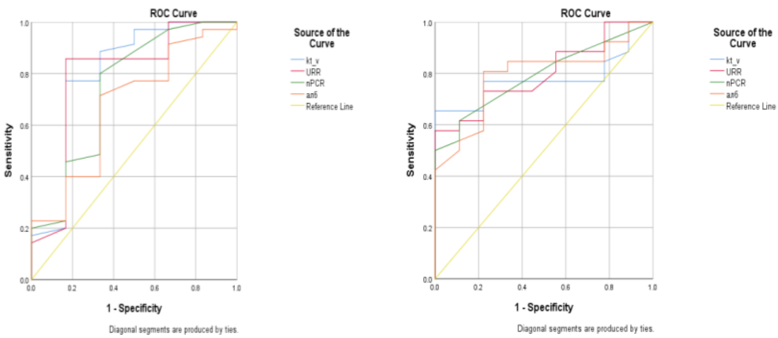


Fig. 10 Roc-curves for estimating the predictors of deteriorating clinical outcome in HD (1) and OL-HDF (2).

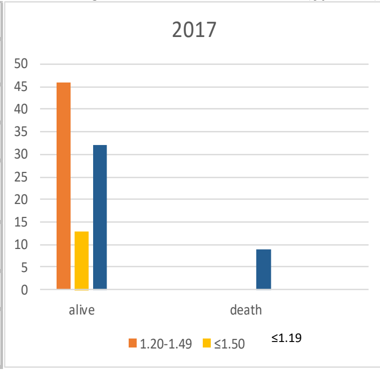
Roc-analysis demonstrates that in the group of HD the main predictors of deteriorating clinical outcome are spKt/V (AUC = 0.805, 95% CI: 0.567-1.00, p=0.018) and URR (AUC= 0.790, 95% CI: 0.552- 1.00, p = 0.024) with critical values respectively spKt/V <1.25 with sensitivity of 88.6% and specificity of 33.3% and URR <70.25% with sensitivity of 85.7% and specificity of 16.7%. nPCR and serum albumin did not show statistical significance as predictors of death in our sample. The results of Roc-analysis in the group of OL-HDF show that in addition to spKt/V (AUC = 0.780, 95% CI: 0.629-0.931, p = 0.013) and URR (AUC = 0.799, 95% CI: 0. 652- 0.946, p = 0.008), as the main predictors of deterioration and death are the indicators of nutritional status - nPCR (AUC = 0.793, 95% CI: 0.644-0.941, p = 0.010) and serum albumin (AUC = 0.793, 95%). CI: 0.637-0.949, p = 0.010) with a predictive value above 7. The registered critical values for the studied indicators in the sample are spKt/V <1.4 (sensitivity 76.9%; specificity 22.2%), URR <74.4% (sensitivity 73.1%); specificity 22.2%), nPCR <1.2 (sensitivity-61.5%; specificity-11.1%) and serum albumin <34.75g/l (sensitivity 84.6%; specificity 33.3%). Despite its high negative predictive value, the lowest sensitivity of the studied indicators is nPCR. Given the negative predictive value of nPCR and serum albumin and the data from the analysis of variance with age, caution should be exercised in patients of the third age group performing OL-HDF.

4.4 Survival and dialysis adequacy.

An important aspect and a key determinant for assessing the quality of dialysis is the achieved survival. For 2017 at an average annual delivered dose of spKt/V = 1.25 ± 0.20 the results show the highest survival rate of the total sample in the group of standard dialysis dose -50.5% and although for the group of high dialysis dose it is only 14.3% and at first glance it seems significantly lower than the other two groups, we must keep in mind that this is due to the sample size. In practice, the survival rate in both subgroups for standard and high dialysis was 100%. Test x2 demonstrates a strong association between mortality and dialysis dose spKt/V <1.19. ($\chi^2 = 14.2$, p <0.001) (table 14)

Table 14 Relationship between mortality and dialysis dose delivered (χ^2 test)

χ^2=14.2, p<0.001		2017г			
		1.20-1.49	≤1.50	≤1.19	total
alive	count	46	13	32	91
	%	50.5%	14.3%	35.2%	100.0%
death	count	0	0	9	9
	%	0.0%	0.0%	100.0%	100.0%
total	count	46	13	41	100
	%	46.0%	13.0%	41.0%	100.0%



Based on Cox regression analysis for proportional risk, it was estimated that the risk of death in the spKt/V≤1.19 group was 2.11 higher than the standard dialysis dose (HR 2.11 CI 95% 1.32-3.39, p = 0.002), while in the group of high dialysis dose, the same is without statistically significant difference - HR 1.03 (CI95% 0.55-1.93, p = 0.917).

Expected survival curves were constructed according to the Kaplan-Mayer method, which clearly demonstrate that for the 2017 sample, the greatest advantage in terms of expected survival is the standard dialysis dose group spKt/V 1.2-1.49 with an average expected survival of 18 months, and in the second place the group of the high dialysis dose with an expected survival of 16 months is outlined (Fig. 11). from the treatment in contrast to the group of the standard dialysis dose, where the slope of the curve is significantly steeper in the first 12 months, which appear to be critical for the occurrence of an event, after which its stabilization is observed.

2017

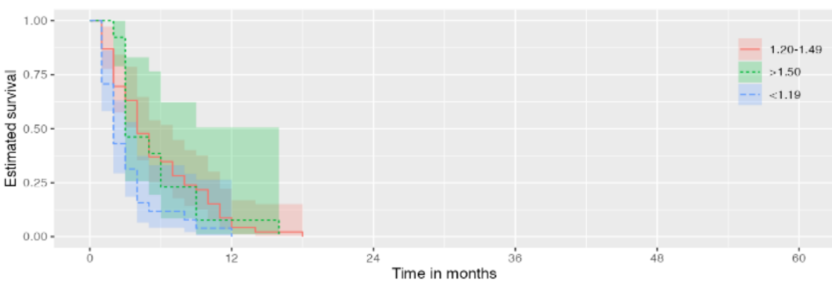


Fig. 11 Curves of the expected survival at different dose regimens of HD for 2017.

The results of the analyzes for 2018 (χ^2 = 31.6, p <0.001) and 2019 (χ^2 = 31.1, p <0.001) did not differ significantly from the first year of the study, despite the increase in the average annual dialysis dose of spKt/V = 1.34 ± 0.15 and spKt/V = 1.39 ± 0.20, with patients with a standard dialysis dose having the best prognosis for survival, life expectancy and risk of death. The results of the Survival analysis have changed significantly in the last two years of the study with the increase of the average total annual dialysis dose for 2020 - spKt/V = 1.54 ± 0.31 and for 2021 spKt/V = 1.59 ± 0.32.

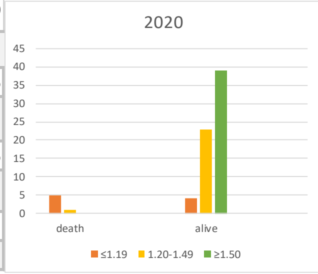
As for the same period the annual mortality rate in the observed cohort showed a significant jump at the expense of COVID-19 infection and its complications, which as a respiratory infection does not show dependence on the delivered dialysis dose (p> 0.05), for objectivity of the Survival analysis, the relevant events were removed from the sample.

Analysis χ^2 again demonstrates the strong association of mortality with low dialysis dose, but it is noteworthy that as the latter increases, survival is already in favor of high dialysis dose. (p <0.001) (table 15). On the one hand, this is related to the increase in the duration of dialysis treatment and increased rehabilitation of patients, as pointed out between the last and delivered dialysis dose there is a weak positive correlation (r = 0.41, p = 0.01), and on the other hand is a manifestation of the long-term effect of increasing the dialysis dose and the introduction of the OL-HDF methodology in the weekly dialysis schedule.

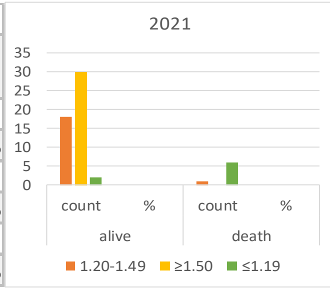
Cox regression analysis for 2020 confirmed that patients receiving a high dialysis dose of spKt/V≥1.5 had better survival at a significantly reduced risk of death - HR 0.60 (0.35-1.02, p = 0.051) compared to the standard dialysis dose. The result is similar for the 2021 sample with a reduced risk for spKt/V≥1.5 of HR 0.59 (0.32-1.08, p = 0.054). This is also evidenced by the Survival curves for the respective period, which clearly demonstrate the significantly higher expected survival in the high dialysis dose group.

Table 15 ***Achieved survival levels for 2020 and 2021 (χ^2 - test)***

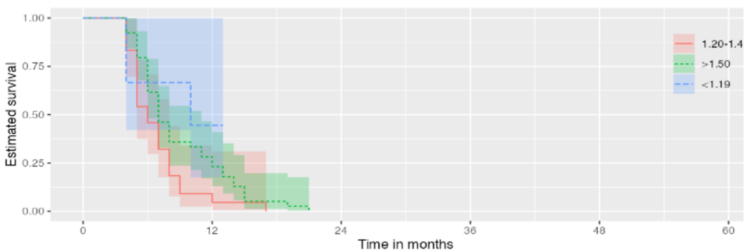
χ^2=30.4, p<0.001		spKt/V			2020
		≤1.19	1.20-1.49	≥1.50	total
death	count	**5**	1	**0**	6
	%	**83.3 %**	16.7 %	**0.0 %**	100.0 %
alive	count	**4**	23	**39**	66
	%	6.1 %	34.8 %	**59.1 %**	100.0 %
total	count	9	24	**39**	72
	%	12.5 %	33.3 %	54.2 %	100.0 %



χ^2=32.1, p<0.001		spKt/V			2021
		1.20-1.49	≥1.50	≤1.19	total
alive	count	18	**30**	2	50
	%	36.0 %	**60.0 %**	4.0 %	100.0 %
death	count	1	0	**6**	7
	%	14.3 %	0.0 %	**85.7 %**	100.0 %
total	count	19	30	8	57
	%	33.3 %	52.6 %	14.0 %	100.0 %



2020



2021

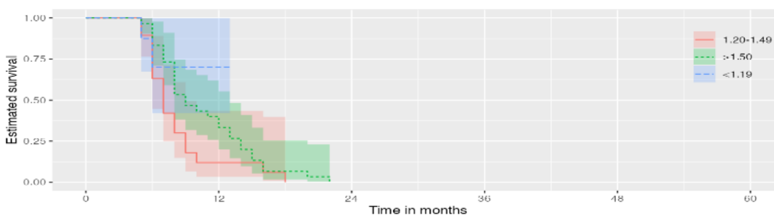


Fig. 12. Curves of the expected survival at different dose regimens of HD for 2020 and 2021.

From the analysis of the curves (fig. 12), it is noteworthy that with increasing dialysis dose, the expected survival in the spKt/V≥1.5 group increased to nearly 24 months compared to the expected 12-16 months in the first three years of the study. Therefore, it can be concluded that the long-term effect of increasing the dialysis dose on survival is manifested after the third year and significantly improves the prognosis of patients.

Roc curves (fig.13) for the high and standard dialysis groups also outline the main predictors of death in the sample. It is noteworthy that for the standardized dialysis dose the main predictors of death are spKt/V (AUC 0.81, 95% CI: 0.581-1.00 p = 0.01) and URR (AUC 0.782, CI: 0.541-1.00 p = 0.021) with critical values of spKt/V <1.21 with sensitivity of 85.7% and specificity of 33.23% and URR <70.8% with sensitivity of 82.9% and specificity of 16.7%. In the group of high dialysis dose to risk factors except spKt/V (AUC = 0.798, 95% CI: 0.668-0.952, p = 0.006) and URR (AUC = 0.779 95% CI: 0. 632-0.916, p = 0.011) nutritional status parameters were added - nPCR (AUC = 0.791, 95% CI: 0.654-0.936, p = 0.010) and serum albumin (AUC = 0.794, 95% CI: 0.657-0.938, p = 0.012), which did not show statistical significance for the adequate dialysis group. The registered critical values for the studied indicators in the sample are spKt/V <1.41 (sensitivity 76.9%; specificity 33.3%), URR <75.1% (sensitivity 65.4%; specificity 22.2%), nPCR <1.2 (sensitivity 62.4%; specificity 11.6 %) and serum albumin <35.2g/l (sensitivity 80.8%; specificity 33.3%).

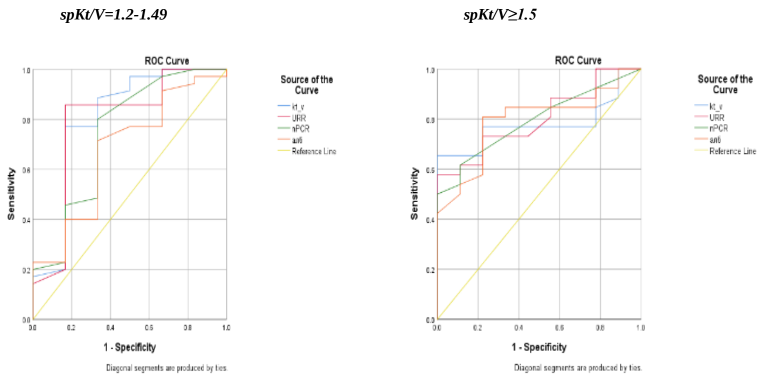


Fig.13 Roc-curves for evaluation of the predictors of deteriorating clinical outcome at spKt / V = 1.2-1.49 and spKt / V≥1.5.

The main causes of mortality in the studied population are presented in Fig,14

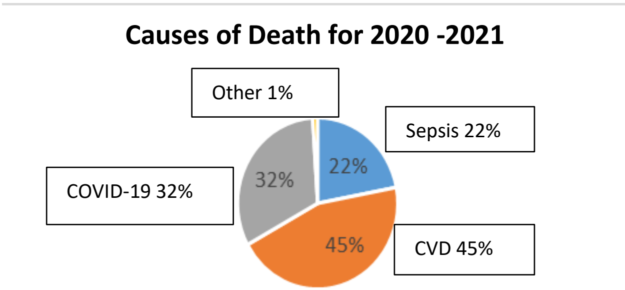


Fig. 14 Main causes of death for a five-year follow-up period.

As mentioned above, the last two years of the study showed a significant jump in annual mortality rates (Fig. 15) As a result of COVID 19 infection. The analysis of the results shows that the latter severely affects the dialysis population and reaches over 50% of the total annual mortality. For 2020 COVID 19 mortality is 67.2% of the total mortality in the sample, and for 2021 - 66.3%.

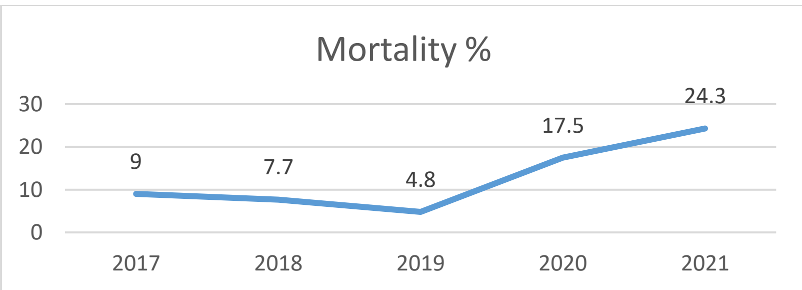


Fig. 15 Registered total mortality for the period 2017-2021

The figure 16 shows the overall mortality adjusted for COVID-19 in the sample

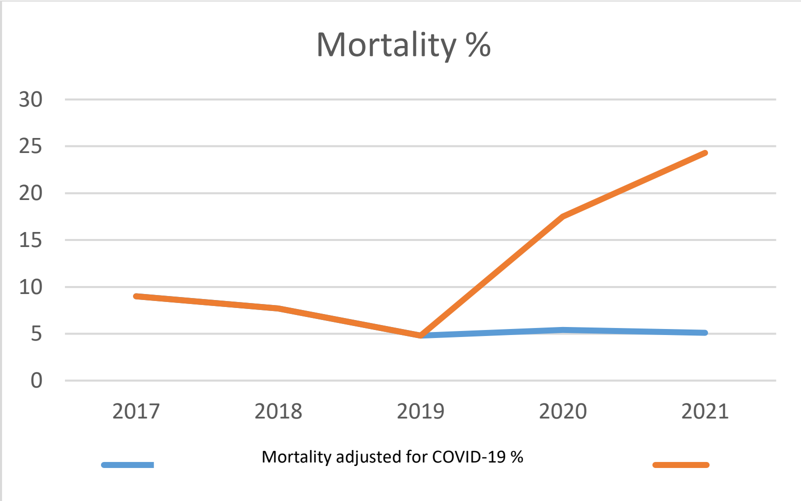


Fig.16 Corrected mortality curve for the period 2017-2021

4.5 Results for achieved individual quality of life and connection with the dialysis prescription.

The study was conducted among a representative sample of 50 respondents of the observed population with a mean age of 57.14 ± 11.84 years (range 33-80 years) and a mean duration of dialysis treatment of 9.04 ± 4.27 years (range 4-25 years). 54% of the respondents were men (n = 27) and 46% were women (n = 23). 62% have secondary education, 15.3% have primary education and 22.7% have higher education. For the one-year period under consideration, patients received a mean dialysis dose of spKt/V = 1.64 ± 0.32 (range 1.06-2.10), with 32 performing conventional HD with low-permeability dialyzers, and 18 of them on OL-HDF. Of these, 54% received a high dialysis dose-spKt/V≥1.5, 36% received an adequate dialysis dose-spKt/V = 1.2-1.49 (standardized by KDQOI) and 10% received a low dialysis dose-spKt/V≤1.19. The low percentage of patients in the last category is due to their more damaged general condition and unwillingness to participate in the survey.

The results of the study of the physical component of HRQQL (table 16) show that for the last year most patients describe their health as good (73.5%) and 4.1% as excellent and feel its improvement (36%) or hospitalization. 36%). The rest of the patients (22.4%) describe their condition as unsatisfactory. It is noteworthy that 36% of patients feel limited in their daily activities and, contrary to the fact that 62% of them do not feel it, report approximately the same percentage that they have reduced their time, other commitments, and the ability to perform various tasks.

The results of the tests performed on Pearson Chi-Square and Cramer's V demonstrate the dependence of the tested components in relation to the received dialysis dose. It is noteworthy that a higher percentage of patients who self-described their health as good (46.9%) and improved in the last year (32.0%) received a high dialysis dose of spKt/V≥1.5 (table 16). Only 4% of patients in the same group describe their condition as unsatisfactory and worse than a year ago. (Tables 1 and 2) Statistically significant dependence was also found with respect to the therapy. (χ^2 = 12.867, V = 0.507, p = 0.002) The majority of patients with OL-HDF-34% reported an improvement in their health in the last year, and 14% did not report such a change. In the group of HD, the percentage of patients who reported improvement or stationary condition is the same - 12%, and 28% feel worse in the last year. No OL-HDF patients reported deterioration in their health.

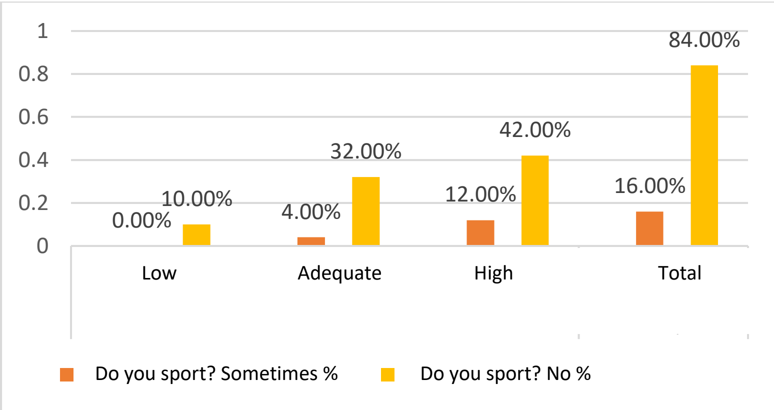
It is also noteworthy that low-dialysis patients feel limited in their daily activities, while almost all high-dialysis patients do not experience this change. The result for the group with adequate dialysis dose is different, represented by an approximately equal percentage in both categories.

Regarding the type of therapy, a significant dependence was also found (χ^2 = 12.579, V = 0.502, p = 0.002). A similar percentage of patients on both therapies, 28% for HD and 34% for OL-HDF, reported not being affected in their daily activities, but the proportion of patients experiencing such a restriction in the HD group was significantly higher - 34 % against only 2% in OL-HDF.

Table 16 ***Results for an own perception of physical health***

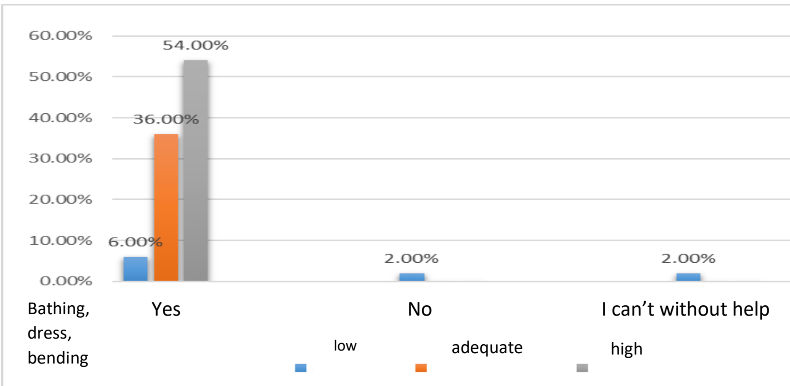
			Low dosage	Adequate dosage	High dosage	Total	X^2 test Cramer's V P-value
You determine your health such as:	**Excellent**	count	0	0	2	2	*X2*=18.742 V=0.43 p= 0.001
		%	0.00%	0.00%	4.10%	4.10%	
	good	count	0	13	23	36	
		%	0.00%	26.50%	**46.90%**	73.50%	
	unsatisfactory	count	4	5	2	11	
		%	8.20%	10.20%	**4.10%**	22.40%	
Compared to a year ago, how would you rate your health right now?	**better now**	count	0	2	16	18	*X2*=20.376 V=0.451 p < 0.0001
		%	0.00%	4.00%	**32.00%**	36.00%	
	same as a year ago	count	1	8	9	18	
		%	2.00%	16.00%	18.00%	36.00%	
	worse now than a year ago	count	4	8	2	14	
		%	8.00%	16.00%	**4.00%**	28.00%	
Does your health limit your daily activities household, shopping, lifting, driving?	**Yes**	count	5	10	3	18	*X2*=19.434 V=0.441 p =0.001
		%	10.00%	20.00%	6.00%	36.00%	
	Not	count	0	8	23	31	
		%	0.00%	16.00%	**46.00%**	**62.00%**	
	I cannot determine	count	0	0	1	1	
		%	0.00%	0.00%	2.00%	2.00%	
Total		count	5	18	27	50	
		%	10.00%	36.00%	54.00%	100.00%	

The figures 17, 18, 19, 20 show the results and the derived dependencies in terms of walking distance, climbing stairs, sports, and self-service. The connection with the delivered dialysis dose is not established only in terms of sports activity



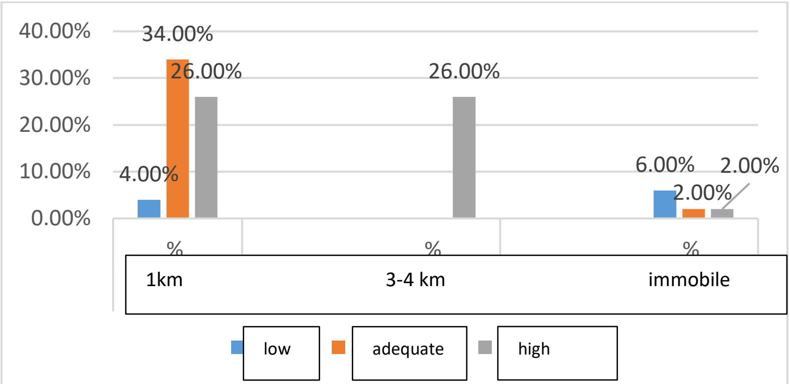
χ^2 = 2.050, V = 0.202, p = 0.359

Fig.17 Influence of the delivered dialysis dose on the sports activity.



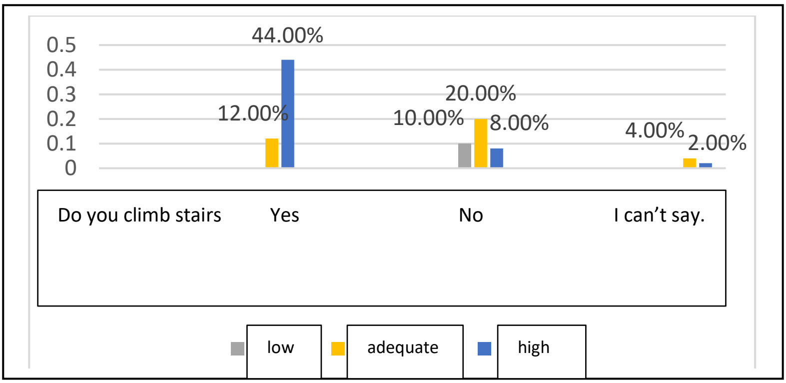
χ^2 = 18.750, V = 0.433, p = 0.001

Fig 18 Influence of the delivered dialysis dose on the ability to self-care.



$\chi^2 = 29.117$, V = 0.540, p <0.0001

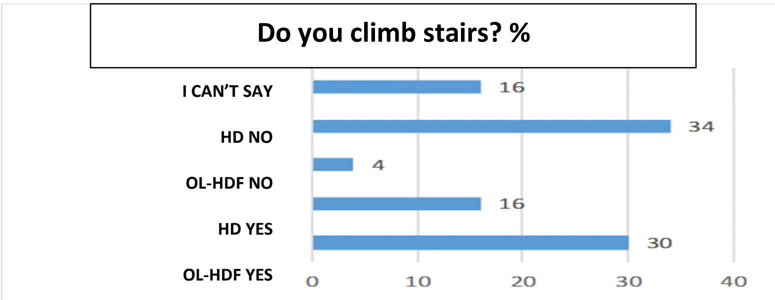
Fig.19 Influence of the delivered dialysis dose on physical activity in the form of walking distance.



$\chi^2 = 19.240$, V = 0.439, p = 0.001

Fig.20 Influence of the delivered dialysis dose on physical activity in the form of climbing stairs.

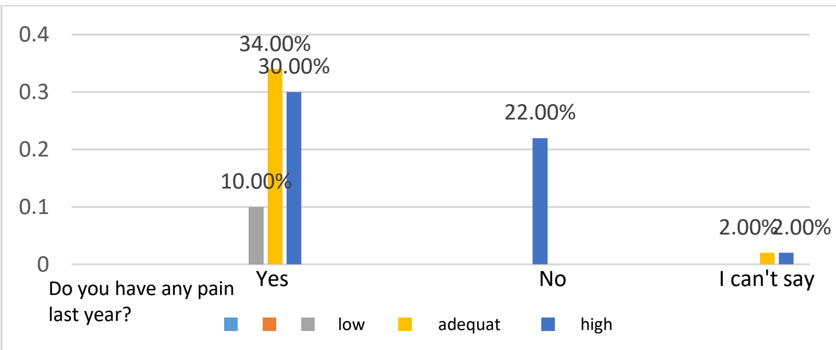
Significant dependence on the applied therapy of the listed components is established only in the ability to climb stairs ($\chi^2 = 9.113$, V = 0.427, p = 0.011). The percentage of patients with HD who cannot climb stairs is significantly higher. % versus only 4% for OL-HDF. Climbing is easy for 30% of patients with OL-HDF versus 16% for HD. The remaining 16% of patients cannot determine (fig.21).



χ^2 =9.113, V=0.427, p=0.011

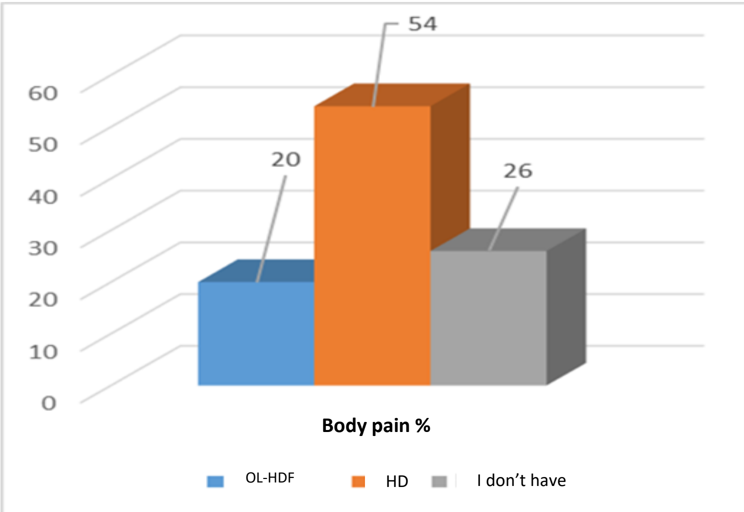
Fig. 21 Dependence of the type of therapy with the ability to climb stairs.

Unfortunately, the percentage (total -74%) of patients suffering from chronic pain to varying degrees remains very high and a reliable dependence on the delivered dialysis dose is established (Fig. 22).



χ^2 = 12.400, V = 0.352, p = 0.015
Fig. 22 Effect of dialysis dose on chronic pain.

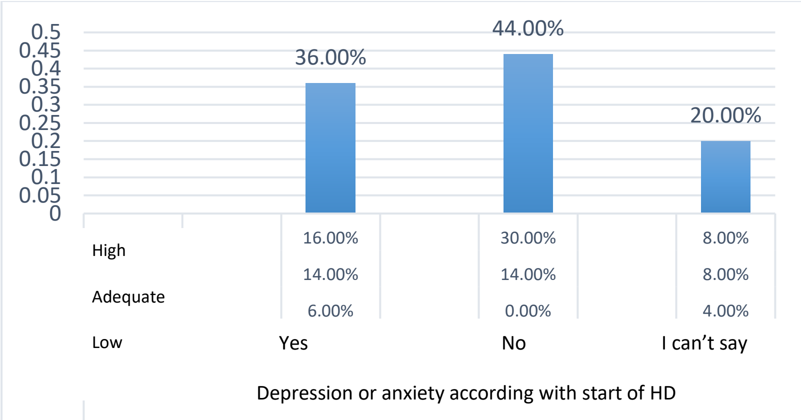
At first glance, the proportion of patients in the low dialysis dose range seems low compared to the standard and high dialysis doses, but in practice these are 100% of the patients in the spKt/V≤1.19 group. A connection is also established with the type of dialysis therapy (χ^2 = 8.858, V = 0.421, p = 0.012). The percentage of patients with HD experiencing physical pain is significantly higher - 54%, compared to 20% for OL-HDF (fig23).



χ^2 =8.858, V=0.421, p=0.012

Fig 23 Dependence of the feeling of body pain on the type of dialysis therapy.

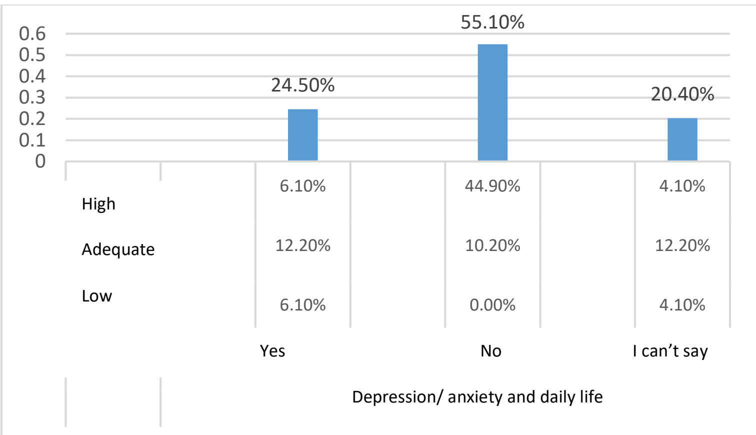
A highly underestimated component of HRQQL is emotional health. The results show that a significant proportion of patients (36%) report feelings of anxiety, depression, irritability associated with the inclusion of dialysis, and it should be borne in mind that the percentage is higher (20% of respondents categorized the emotional component with the answer: "I cannot determine") (fig. 24).



χ^2 = 5.680, V = 0.238, p = 0.224

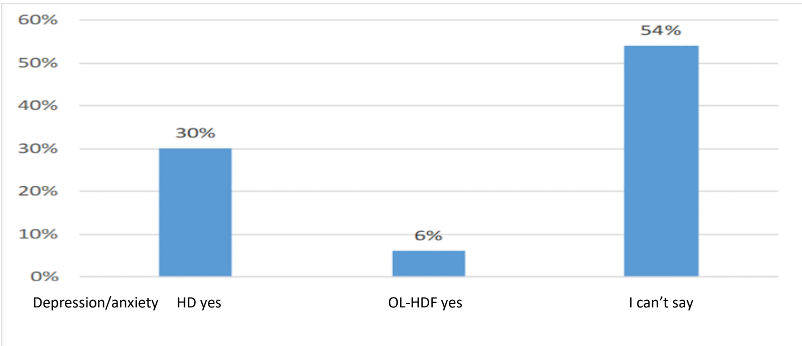
Fig 24 Overall distribution of the patients studied according to their feelings of depression or anxiety.

Figure 25 shows the effect of the emotional component of quality of life on daily life and conducting dialysis procedures.



χ^2 = 18.582, V = 0.616, p = 0.001
Fig.25 Influence of emotional health on everyday life. Distribution in the total sample and according to the delivered dialysis dose.

The analysis of the results (fig.26) demonstrated an increased level of depression and anxiety in the HD group - 30% versus 6% for OL-HDF (χ^2 = 13.147, V = 0.513, p = 0.001), and in 18.4% of patients on conventional dialysis their negative effect on daily life (χ^2 = 6.441, V = 0.363, p = 0.04), but such is not reported on the course of procedures (χ^2 = 5.680, V = 0.238, p = 0.224)



χ^2 =13.147, V=0.513, p=0.001

Fig. 26 Dependence of emotional health on the type of dialysis therapy.

An important aspect in the evaluation of HRQOL is one's own perception of kidney disease. 66% of respondents report that their kidney disease does not interfere with their lives, and only 28% are disappointed with their coping. The picture of the symptoms associated with hemodialysis procedures is diverse (Fig. 27) and reported by patients.

It is noteworthy that the higher frequency of any of the above symptoms is directly associated with the type of therapy. Regarding the manifestations of thoracic oppression, the ratio is 32% for patients with HD versus only 4% for OL-HDF (χ^2 = 6.151, V = 0.351, p = 0.046). It was also found that pronounced anorexia was observed only in the group of HD (24%), and all patients in the group of OL-HDF (36%) reported that they had a good appetite. The percentage of patients with HD without eating problems was similar (40%) (χ^2 = 7.031, V = 0.375, p=0.03). Significantly more frequent are the manifestations of hemodynamic instability in the group of HD - dizziness and more frequent collapses occur in 24% of patients with HD against only 2% for OL-HDF (χ^2 =6.138, V=0.350, p=0.046). The other patients in both groups were hemodynamically stable. A statistically significant difference was also reported for cramps episodes, which were significantly more common in the HD group - 42% versus 12% for OL-HDF (χ^2 = 8.858, V = 0.421, p = 0.012).

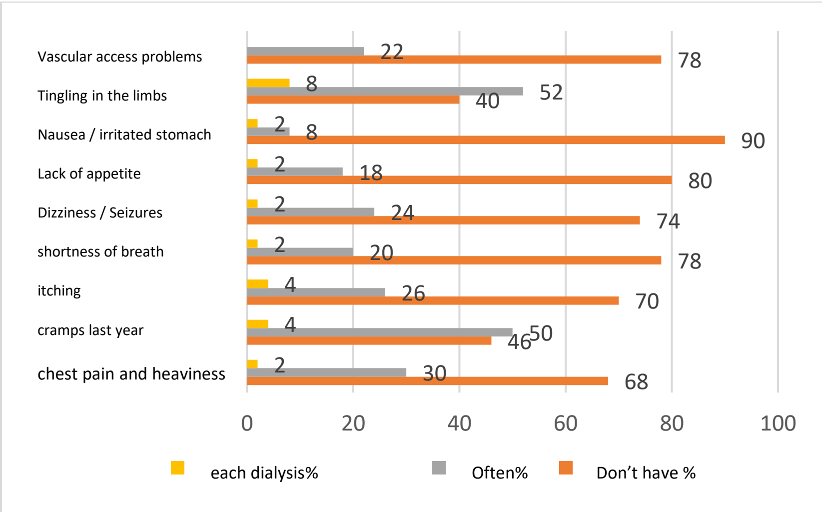


Fig 27. Total distribution of the studied patients according to the reported symptoms.

Dialysis dose dependence was found for pruritus manifestations, which were significantly lower in the high dialysis group - 48% of patients denied pruritus and only 6% reported itching. (χ^2 = 10.323 V = 0.391 p = 0.035) Although at first glance the percentage of patients with pronounced pruritus in the group of low dialysis dose - 8% seems low, this is 90% of patients in the group, which is a total of 10 % of the whole sample. With an adequate dialysis dose, the percentage of patients without and without symptoms is approximately equal. There is also a moderate negative correlation with the delivered dialysis dose, with increasing dose the likelihood of itching decreases. (Rho = -0.397, p = 0.004).

The analysis shows that episodes of chest pain and heaviness occur in 100% of inadequately dialysis patients, who are 10% of the sample, and in half of patients with adequate dialysis dose a total of 18% with varying frequency.

Most patients who received a high dialysis dose of 50% of a total of 54% for the entire sample did not have such symptoms. (χ^2 = 18.478 V = 0.521 p = 0.001), finding a moderate negative correlation with the delivered dialysis dose. (Rho = -0.526, p = 0.0001). High link strength is a manifestation of peripheral polyneuropathy in the low and adequate dialysis dose groups. (χ^2 = 35, 604 V = 0.568 p = 0.0001) Numbness of the dialysis was reported in all patients receiving a low dialysis dose (10% in total) and 90% of patients in the standard dialysis dose group for a total of 30% of all patients in the 36% group size. from the whole sample. There is also a strong negative correlation with the dialysis dose. (Rho = -0.573, p = 0.0001).

Regarding the manifestations of the gastrointestinal tract, it is noteworthy that their manifestation is strongly associated with the low degree of dialysis and is almost not observed in other groups (Table 17).

Table 17 Gastrointestinal manifestations in patients with CKD-5D

			Have	often	In each dialysis	Total	X^2 test Cramer's V Spearman Rho P-value
Lack of appetite	Low dose	count	0	5	0	5	X^2=24.714
		%	0.00%	**10.00%**	0.00%	**10.00%**	V=0.548
	Adequate dose	count	13	**4**	**1**	18	p=0. 0001
		%	**26.00%**	8.00%	2.00%	36.00%	
	High dose	count	26	1	0	27	Rho= -0.551
		%	**52.00%**	2.00%	0.00%	**54.00%**	p=0.0001
Total		count	39	10	1	50	
		%	78.00%	20.00%	2.00%	100.00%	
Nausea or irritated stomach	Low dose	count	1	4	0	5	X^2=28.789
		%	2.00%	**8.00%**	0.00%	**10.00%**	V=0.480
	Adequate dose	count	16	1	1	18	p=0.0001
		%	**32.00%**	2.00%	2.00%	36.00%	Rho= - 0. 483,
	High dose	count	27	0	0	27	p=0.0001
		%	**54.00%**	0.00%	0.00%	54.00%	
Total		count	44	5	1	50	
		%	88.00%	10.00%	2.00%	100.00%	

Rho = -0.554, p = 0.0001) This is confirmed by the negligibly low frequency of episodes in the high dialysis group - only 2% with a total sample rate of 54%. In the other groups there was an equalization of the frequency of accidents compared to hemodynamically stable patients (χ^2 = 17.183, V = 0.499, p = 0.002)

The cognitive component was not affected in most respondents, but more than half reported sleep disorders (Fig. 28).

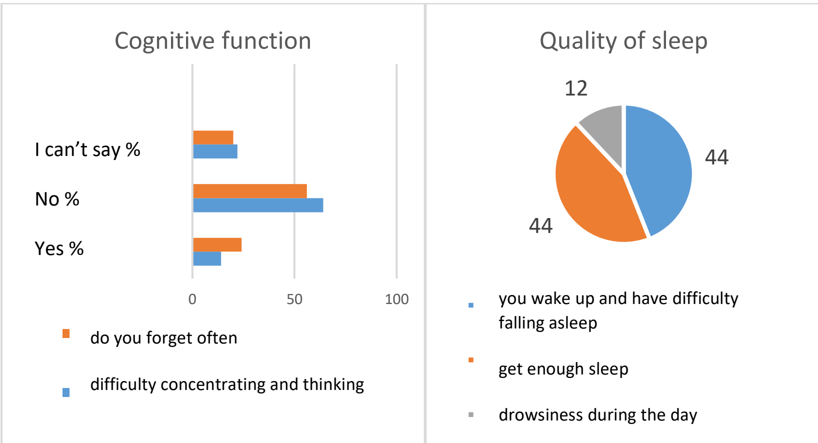


Fig .28 Changes in the quality of sleep and cognitive function of patients.

No reliable dependence of these components on the delivered dialysis dose has been established. (χ^2 = 8.593, V = 0. 293, p = 0.072). However, increased sleep quality was observed in the group of OL-HDF (χ^2 = 14.226, V = 0.533, p = 0.001). While 48% of patients on conventional dialysis reported disturbances in the form of frequent awakenings with difficulty falling asleep (40%) and daytime drowsiness (8%), only 8% of OL-HDF patients reported poor sleep. No association of the conducted therapy with the cognitive function was established (χ^2 = 1.844, V = 0.192, p = 0.398).

A very important indicator for both HRQOL and as an indicator of dialysis adequacy is the recovery time after dialysis sessions (fig.29). The results reported by the respondents show that the average recovery time achieved in the examined patients is 4 hours (in 60% of the respondents) only 26% report the need for one day. Significant dependence was found with the type of therapy (χ^2 = 25.541, V = 0.715, p <0.0001). Recovery time 1-2 hours after the session was reported mainly in the group of OL-HDF - 28% against only 6% in HD. It has been found that HD patients need 4 hours or more to return to their daily activities. At 20% it takes between 2-4 hours, at 12%> 4 hours, and at 26% about a day. In the OL-HDF group, only 6% of patients reported a need between 2-4 hours and only 2% - over 4 hours. None reported recovery time of 24 hours or more. The analysis of the data also showed a strong negative correlation between the recovery time and the delivered dialysis dose. (Rho = -0.762, p = 0.0001). As spKt/V increases, the recovery period shortens significantly. This is evidenced by the fact that patients receiving a high dialysis dose have an average recovery time of 4 hours (50% of patients studied in the group size of 54% of the total sample). day to return to everyday life (χ^2 = 34.628, V = 0.758 p = 0.001)

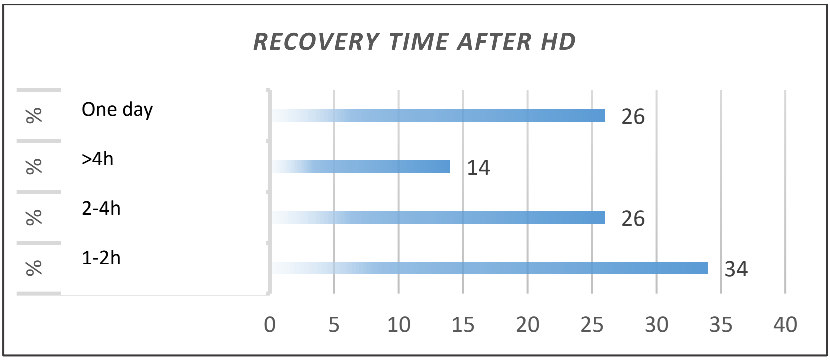
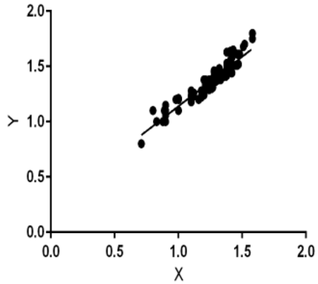


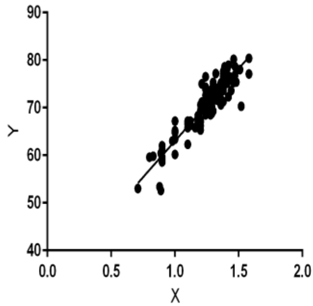
Fig 29. Characteristics of patients according to the recovery time after HD

As the biggest difficulties in their life with kidney disease, patients report the need for fluid restriction in the first place (90%), in second place diet (56%), in third place are the limited ability to travel (54%) and dependence on medical equipment and staff (52%). No reliable dependence of the delivered dialysis dose was established. ($\chi^2 = 8.593$, V = 0.293, p = 0.072) and the type of therapy ($\chi^2 = 1.844$, V = 0.192, p = 0.398). Regarding the satisfaction with the medical care, most of the patients have given a positive assessment to the treatment team and the applied therapy, and no reliable dependence with the delivered dialysis dose has been established. ($\chi^2 = 5.640$, V = 0.218, p = 0.223) and the type of therapy ($\chi^2 = 2.483$, V = 0. 223, p=0.289)

5.6 Comparability of ionic dialysis with the classical indicators of dialysis adequacy.

The results of the variation analysis for the 128 measurements of the classical indicators of dialysis adequacy by UKM, show that the obtained average value of spKt/V is 1.36 ± 0.16 with a variation of 0.02533, and the average value of URR is 70.54 ± 5.58% with a variation of 31.15 The mean value for parallel measurements by ionic dialysis onKt/V is 1.25 ± 0.17 with a variation of 0.02793. The results of the Pearson correlation analysis show a statistically significant correlation between the indicators measured by online monitoring and those by UKM -spKt/V (r = 0.9419 p <0.00001 $R^2 = 0.8872$) and URR (r = 0.9114 p <0.00001 $R^2 = 0.8306$) Regression analysis revealed a straight linear regression between the studied indices (Fig. 30 and 31) This shows that the measured values of onKt/V have a strong predictive value for spKt/V and URR%, and the same can be calculated based on the derived regression equations for spKt/V - Y = 0.8971 * X + 0.2427, and for URR - Y = 30.43 * X + 32.58 without the need for additional blood tests to verify the result fig .... Despite the high value at a coefficient of determination of 83%, the calculation of URR based on ionic dialysis is of less clinical significance due to several shortcomings of URR as an indicator for assessing dialysis adequacy. Despite the high degree of correlation, the fact that the values of onKt/V can underestimate the value of spKt/V should not be overlooked - the measured values of onKt/V are 8% lower, as the Student's T-test for addicts' variables show a statistically significant difference between the two indicators (t = -23.031832, p <0.00001)





----------- regression line

• Observed values

Y = 0.8971 * X + 0.2427, R2 = 0.8872

Y = 30.43 * X + 32.58, R2 = 0.8306

Fig 30 Regression between spKt / V (Y) and onKt / V (X). Linear regression equation: Y=0.8971*X + 0.2427 at a statistically significant slope from the horizontal F=991.5, DFn, DFd =1.126, p<0.0001 (R^2=0.89, Sy.x =0.054).

Fig 31 Regression between onKt / v (X) and URR% (Y). Linear regression equation: Y=30.43*X + 32.58, at a statistically significant slope from the horizontal F=618.0, DFn, DFd =1.126, p < 0.0001 (R^2= 0.83, Sy.x 2.306).

5. Discussion

5.1 Assessment of the indicators for the objective component of the achieved quality of life and their connection with the delivered dialysis dose

Dialysis adequacy and the achieved quality of life are two invariably related concepts, between which a balance must be sought to improve the clinical outcome, as well as ensuring social and physical existence close to that of the average disease-free individual. Of course, these are extremely difficult to achieve, especially in the conditions of increasing age and polymorbidity of the dialysis population. Regarding the objective component of the achieved quality of life in the studied patients for a five-year observation period, it is noteworthy that at the beginning of the study the percentage of patients with standardized dialysis dose according to KDOQI 2015 criteria (spKt/V = 1.2-1.4) dominated - 46% of the sample, with a relatively high percentage of patients receiving inadequate dialysis (spKt/V≤1.2) - 41% of the sample. Data representing the typical dialysis population worldwide (245). It can be seen that with the gradual increase of the average dialysis time, the introduction in the dialysis prescription of high flux dialyzers in different treatment regimens - once or twice a week, as well as with the average increase in blood flow of 268 ± 36ml/min in at the beginning of the study up to 352 ± 43ml/min the delivered dialysis dose significantly increased from spKt/V = 1.25 ± 0.20 to spKt/V = 1.59 ± 0.32 in 2021, as the data from the post hoc analysis demonstrate that this effect is manifested in the third year of the study. This in turn led to a significant change in the structure of the studied population. There was a significant increase in the percentage of patients receiving a high dialysis dose of spKt/V≥1.5 of 13% at the beginning of the study at 52.7% at the end of the five-year period, while a significant decrease in inadequately dialysis patients was observed at 14%. The main reason for inadequate dialysis in our study is the reduced blood flow, while the second place is occupied by the shortened dialysis time due to lack of compliance on the part of patients. Unfortunately, the trend of more frequent use of permanent tunneled catheters as vascular access is also worrying, which is emerging as a major factor in impaired blood flow in 56% of cases, followed by recirculation of access in 17% of cases. Our results are consistent with studies by Nafar et. al (2016) and

Fernandez et al. (2017), who also reported reduced blood flow and access dysfunction as the main reasons for inadequate dialysis (109, 242).
The effect of the long non-standardized dialysis dose (spKt/V≥1.5) on the clinical outcome and prognosis of patients with CKD-5D has been the subject of long-standing debate among the nephrology community. The results obtained by us demonstrate a significant benefit of increasing spKt/V≥1.5 on the achieved clinical result - there is a significant improvement in the parameters of nutritional status - nPCR and serum albumin, as well as better control of renal anemia with significant reduction of ECA dose, , effects that occur after the second to third year of intensification of the dialysis prescription .About nPCR and serum hemoglobin levels, the difference reached statistical significance compared to the standard dialysis dose only after the third year. It should be noted that the nutritional status of high dialysis patients is adequate and not only meets the KDOQI criteria for good clinical practice nPCR> 1.2, but also shows a long-term trend to reach the target value of 1.4, while although adequately dialyzed, standard dialysis patients still have unsatisfactory nutritional status nPCR <1.2. A beneficial effect of the high dialysis dose is also reported with respect to serum albumin, whose average value for the period under consideration is significantly higher than the other groups. These results not only demonstrate the improved nutritional status of patients but are also a predictor of a favorable prognosis - hypoalbuminemia is a proven independent risk factor for death in the dialysis population. Although the results of the HEMO and FHD studies (64, 102, 175, 211) do not show an increase in dialysis dose on dietary indices, a study by Tentori et al (2012) showed good agreement between high dialysis dose and clinical outcome, especially for serum albumin and anemic syndrome. Our results contradict the study of Perez -Garcia et al. (2019) (260), but the same uses a different methodology to evaluate the result and has a high average age of the sample. The second fact to note is that despite the lack of a significant difference in hemoglobin levels between standard and high dialysis doses in the first three years of the study, this was found in the administered erythropoietin dose, which was significantly lower at spKt /V≥1.5. This, in turn, can be considered in two aspects - the reduction of ESA dose, significantly reduces the systemic effects of erythropoietin, which are associated with high blood pressure, increased risk of vascular accidents, and on the other - in purely economic terms leads to a significant reduction of the financial cost to the community.

The lack of a significant difference in hemoglobin levels at the standard and high dialysis dose, we attribute rather to the need to keep them in a certain target range - between 110 and 120g/l, above which the risk of thrombotic events increases and although after the third-year values in patients on intensive dialysis are significantly higher, from a clinical point of view the difference is negligible. Our relationship between dialysis dose and anemic syndrome has been confirmed by studies by by studies of Stoyanov (2002), Movilli et al. (2001), Bowry et al. (2011), Ayesh et al. (2014), Somdji et al. (2020), Yamamoto et al (2021), (10, 22, 43, 238, 307, 374), but rejected the results of Ornt et al. (251).

In summary, we believe that the effects of high dialysis dose spKt/V≥1.5 on objective indicators of clinical outcome and achieved quality of life are not to be ignored. Of course, we do not deny that it is possible that high numerical values differ from the clinical result and in significantly more damaged patients we register a "perfect" dialysis dose. This requires the latter to always be evaluated in relation to nutritional status, which is one of the most powerful predictors of the result and prognosis of the patient.

6.2 Vascular access and dialysis dose

Properly functioning and efficient vascular access is essential to deliver an adequate dialysis dose. Unfortunately, vascular access can also be defined as the "Achilles' heel" of hemodialysis procedures. The reason for this is still the high incidence of complications, especially in permanent catheters, which remains one of the leading causes of morbidity and mortality in patients with CKD-5D, which is confirmed by our results.

Their analysis demonstrated the significant superiority of AVF, both in terms of dialysis dose received and in terms of survival, incidence of complications, and quality of life in patients with CKD-5D. Significantly higher values of dialysis adequacy-spKt/V and URR, higher serum hemoglobin levels with lower erythropoietin dose, lower incidence and lower mortality in the AVF group , which confirms the report of Karkar et al (2014), Canaud et al. (2019), Ethier et al. (2008), Momeni et al (2018), Wu et al (2021) (51, 106, 170, 232, 371but contradicts those reported by Mutavelic et al. al (2015) Vojinovich et al (2018) and Zamani et al.(2021) results (241, 355, 377), according to which there is no significant difference, both in the received dialysis dose and in the other studied indicators. Our results are confirmed by a study by Staykova from 2020 (7).

The reported incidence of inadequate dialysis is not high but is observed mainly in patients with PC. The reason for this and the significantly lower rates in patients in group 2 were catheter dysfunction - inability to reach a flow rate above 250 ml/min. (6, 7, 213). The latter is most often associated with its incorrect position at the time of its placement, and in the long run can be caused by stenosis, thrombosis, due to improper filling with heparinized serum, twisting or breaking of the PC in the area of the subcutaneous tunnel. (1, 6, 7, 136). Catheter-associated infections were another reason for the lower dialysis dose recorded in patients in group 2. They often require replacement with temporary vascular access, which usually provides lower blood flow. AVF stenosis. The latter together with thrombosis are the most common complications of vascular anastomoses and in any case their frequency is not comparable to that of complications in PC, which is confirmed by our results and by all authors (7, 70, 103, 104, 146, 189, 197, 232, 371).

It should be borne in mind that some complications may occur only in patients with AVF such as the development of pseudoaneurysms - a rare complication that can lead to dysfunction, rupture or infection, skin necrosis due to frequent use of the same puncture sites (they may complicated by life-threatening bleeding), ischemia of the hand with subsequent development of gangrene, hyperdynamic syndrome due to increased blood flow through the anastomosis and subsequent development of heart failure (40, 232, 259). As we have already pointed out, these are rare complications of AVF, but they require the placement of a temporary CVC, which usually provides a lower flow rate, respectively a lower dialysis dose and worsens the clinical outcome.

Significantly higher incidence of complications in patients with PC is confirmed by all authors and inevitably leads to an increased rate of hospitalizations and mortality in the group on the one hand due to access events, and on the other hand the reflex effect on dialysis should be considered. adequacy associated with deteriorating clinical outcome, potentiation of malnutrition, chronic inflammation, and immune dysfunction (189, 241, 277). Some studies deny a link between the type of vascular access and the control of anemic syndrome, a problem that is the subject of widespread debate precisely because of the inconsistency of the outcome. The analysis of the data obtained from us demonstrates not only improved hemoglobin levels, but also a lower applied erythropoietin dose in patients with AVF with strong statistical significance of the relationship. Better control of the anemic syndrome in group 1 patients was found because of the higher dialysis dose received. On the other hand, it should not be overlooked that the higher incidence of infections in PC patients, the maintenance of chronic inflammation, and the blood loss associated with frequent extracorporeal clotting in catheter dysfunction also contribute to persistently lower hemoglobin levels. levels in group 2 and determine the need for significantly higher erythropoietin doses to achieve the target value.

In addition to the benefits of AVF so far, such as vascular access and its contribution to improved dialysis adequacy, attention should be paid to the significantly higher survival it is associated with (11, 25, 144, 189, 274). The analysis of the results demonstrates a significant difference in the registered mortality rates in the two groups. The reason for this was the combined effect of the lower dialysis dose delivered in patients with PC and the high frequency of catheter-associated sepsis, which is the main cause of death in this group. It is noteworthy that in the AVF group, the main cause of death was cardiovascular complications. This undoubtedly proves the strong link between the type of vascular access used and mortality, not only as a side effect of the dialysis dose received, but also directly through its complications. The causes of reported PC mortality are mainly related to access infection, while AVFs do not differ from those in the general dialysis population. In this aspect, it can be concluded that patients in group 2 are at additional risk of death directly related to access, which is 4 times higher than patients in AVF.

The trend in recent years for the mass placement of permanent tunneled catheters is worrying, data confirmed by the USRDS report for 2019 (291). To date, only 30% of patients in the clinic are dialyzed for fistulas. It should not be overlooked that higher dialysis doses in patients with AVF, control of anemia, as well as lower incidence of complications and related hospitalizations have a beneficial effect not only on the objective purely physical component of quality of life., and positively affects the subjective emotional component, reflecting the self-esteem of the physical and mental sensations of the individual. Frequent flow problems, infections, the need for repositions, temporary catheters, and the inability to perform a normal dialysis procedure significantly impair patients' quality of life, make them aggressive,

nervous, and in many cases cause depression or anxiety. This further worsens their condition and leads to a vicious circle in which patients lose motivation to commit to their own health and well-being.
Despite the latest KDOQI 2019 vascular access guidelines (213), which overshadow the Fistula First principle and recommend an individualized approach that includes, among other things, the patient's personal subjective preferences, we believe that AVF should be preferred in every possible case. This requires its promotion as a vascular access of choice, educating patients about the emerging risks and benefits, and developing a multidisciplinary approach with an updated algorithm for designing, servicing AVF, early diagnosis and timely therapeutic intervention of complications. We also believe that it is necessary to develop an algorithm for nursing care that unifies the processing and maintenance of vascular access in order to maximize its preservation and prevent infections. As is well known, there are significant differences between different dialysis centers and even between individual healthcare professionals in maintaining vascular access. For this reason, we believe that the standardization of the procedure would lead to increased quality not only of medical services, but also of significantly improved clinical outcome.

5.3 OL-HDF and its effect on clinical outcome and prognosis for the patient

Despite technological advances more than 40 years after its introduction as a method of RRT, the real benefits of OL-HDF, even with the use of high convective volume, are still under discussion. Three large randomized controlled trials compared survival outcomes in patients receiving HD or OL-HDF after dilution and reported conflicting results. Meta-analyzes of published studies are also not able to give a clear and definitive answer about the possible benefits of choosing one treatment over another. The reported overall mortality, anemia, phosphate control and small molecule clearance do not appear to be sufficiently affected by the treatment. On the other hand, cardiovascular mortality, hemodynamic stability, and clearance of protein-bound molecules are better performed in patients treated with OL-HDF (206). The evidence currently available is not yet strong enough to prove that OL-

HDF is associated with better clinical outcomes than conventional HD, and that medicine is an evidence-based science.
The results of our two-year follow-up demonstrate significantly higher values of the studied indicators of dialysis adequacy and nutritional status in patients undergoing OL-HDF. The difference was not only observed for serum albumin levels at the end of the study, which was probably associated with loss during the procedure. A positive effect of OL-HDF was also noted for the anemic syndrome with improved hemoglobin levels at reduced erythropoietin dose. It is noteworthy that the recorded mean values of spKt/V = 1.82 ± 0.12 and URR = 79.46 ± 1.45 are significantly higher in the group of OL-HDF and although these characteristics are representative of the purification of low molecular weight molecules , and not the medium molecules to which OL-HDF is directed, the results obtained by us demonstrate a significant effect in terms of diffusion clearance, which is consistent with the reports of Piccoli et al (2018) (265) According to Cornelis et al. (2014). The clearance of urea and small molecules (<500 Da) is slightly higher in OL-HDF and should not be the only reason for choosing OL-HDF as a method for RRT. The authors did not find a significant difference in the removal of serum phosphates (71).
Regarding nutritional status, we found that despite the acceptable KDOQI (2015) nPCR with a range of 1.16 at the beginning to 1.2 at the end of the study in patients with HD, significantly higher values were found in the group of OL-HDF - nPCR = 1.28 at the first year and nPCR = 1.31 at the end of the observation. This, in our opinion, is due to the increased clearance of uremic toxins, not only low molecular weight, but also medium molecules, as well as some of the serum protein, which significantly improves appetite and gastrointestinal manifestations of uremia. The results recorded by us for the OL-HDF group are in contradiction with the data of Piccoli et.al (2018), which report significantly lower values for nPCR in OL-HDF, corresponding to deteriorating nutritional status (265). We report the same discrepancy in the results with respect to serum albumin levels, which in our study were significantly higher than reported. However, it should be borne in mind that the study by Piccoli et.al (2018) is aimed at elderly patients. When adjusting our results for age, we found that in the upper age tertile, patients with OL-HDF tend to have poor nutritional status with nPCR <1.2 and moderately decreased serum albumin, which is confirmed by the above study. This is most likely due to the loss of albumin with OL-HDF, which is a well-known effect

of the procedure. The clinical effect of albumin loss is usually negligible and is offset by patients' improved appetite along with hepatic protein synthesis, but in elderly patients it has a significant effect and should be considered as a potential risk. It should be borne in mind that the loss of albumin in OL-HDF is non-selective, i.e., not only the fraction associated with uremic toxins (so-called toxic albumin) is lost and despite the opinion of some authors that the clearance of toxic albumin should be increased, but our opinion is also that serum albumin levels below 35g/l should be increased. avoid. It should not be overlooked that the loss of the latter is also a marker for the loss of other useful nutrients, including vitamins, and may further contribute to malnutrition and poor clinical outcome (264).

Opinions about the effect of OL-HDF on the control of anemia also remain conflicting. Our results demonstrate a strong correlation between the conducted convective therapy, both with the achieved hemoglobin levels, which are significantly higher than those in patients with HD, and with the applied ECA dose, which shows a lasting tendency to decrease compared to conventional HD. This is probably due to the improved purification of medium molecular weight erythropoiesis inhibitors, as well as the use of ultrapure dialysate produced by online technology. Unlike the parameters of the nutritional status, no reliable age dependence was found here. Several small and uncontrolled studies as well as a small, randomized study (198, 206) confirm our results by reporting an improvement in the control of anemia after the transition from standard low-flux HD (LF-HD) to the use of high-permeability (HF-HD) and biocompatible membranes. Ok et. al (2013) in the Turkish Hemodiafiltration Study (206, 249) also reported that the applied dose of ECA was significantly lower in the OL-HDF group, which is in line with our results, but nevertheless did not show a significant difference in in relation to the achieved hemoglobin levels. At the same time, data from Maduell et al (2013) from the Spanish study ESHOL as well as a meta-analysis from 2013 of 65 studies comparing convective therapies with conventional HD did not show a significant improvement in serum hemoglobin levels and erythropoietin dose (206, 317). Similar data were reported by Schneider et al (2012) in the MINOXIS study (293), as well as Panichi et al. (2014) in the REDERT study (256), the latter reporting only a significantly higher administered ECA dose in the HD group, which is consistent with our data (206).

This is probably due to the different design of the studies - control and treatment group, the size of the applied convective volume, different area, and permeability of the dialyzer. Based on the results achieved, our opinion is that high-volume OL-HDF contributes to better control of renal anemia at lower erythropoietin doses. This is on the one hand related to the improved clinical outcome and quality of life of the patient, and on the other hand to the reduced financial cost of erythropoietin therapy. On the other hand, the secondary effect of controlling renal anemia should not be neglected, namely reduced cardiovascular risk, and reduced incidence of associated hospitalization and death. Therefore, despite the higher cost of the procedure, the improved clinical outcome ultimately leads to a lower total cost of treatment.

There is a debate in the literature as to whether OL-HDF can improve hemodynamic stability. Some studies by Maduell et al (2013) and Locatelli et al (2010) demonstrate a beneficial effect of OL-HDF compared to HD in this regard (207, 216). Four meta-analyzes from 2013 and 2014 also report the positive effect of convective techniques to improve hemodynamic stability (236, 247, 317, 358), conclusions that are consistent with our results. Our study demonstrated a significantly lower incidence of episodes of intradialysis hypotension with improved recovery time in patients undergoing OL-HDF, which is particularly pronounced at the end of the two-year follow-up period ($p < 0.05$). Although in the first year the result was contradictory and no advantage of convective therapies was found in terms of hemodynamic stability ($p > 0.05$), which was reported by some studies (71, 234, 305), we found that after adjusting the convective volume (Qo) according to individual characteristics of the individual, there is a significant reduction in episodes of IDH from 27% in 2020 to 4.8% in 2021 ($t = 1.74939$, $p = 0.044257$) and secondary improved recovery time

Our study also found age dependence of tolerance to the procedure - patients in the upper age tertile have difficulty tolerating high convective volumes Qo> 20l and respond with pronounced hemodynamic instability and prolonged recovery time, which is surprisingly not observed in the relevant age group. After correction and reduction of Qo on average to 16-18l per procedure there is a significant reduction in the manifestations of IDH and shortening the time required for recovery from an average of 5.5 ± 2.72 h in 2020 to 2.12 ± 0.35 h in 2021 ($p < 0.05$) however, to neglect that this reflects on the clinical outcome, which becomes comparable to that of adult patients undergoing HD. In our opinion, this requires strict refinement and individual approach in the choice of therapy for this fragile population of patients in whom the pursuit of high efficiency of therapy and improved clearance of uremic toxins can significantly impair quality of life through hemodynamic instability and prolonged RT. Our results are inconsistent with some studies by Cornelis et al (2014), Morena et al (2017), Smith et al. (2017), which do not demonstrate the benefits of OL-HDF on hemodynamic stability (71, 234, 305).

The data reported so far on the effect of OL-HDF on mortality are contradictory. Only one (216) of five (134, 207, 216, 234, 249) recent randomized - including three (134, 216, 249) specifically designed to test mortality as a primary endpoint [35, 59, 60] - showed better patient survival. of OL-HDF compared to HD. According to Grooteman et al (2012) in the CONTRAST study the overall mortality rate was not affected by the type of therapy used, although subgroup analysis suggested the benefit of high-volume OL-HDP (Qo> 20l) (HR 0.66; p = 0.03). However, a post hoc analysis of the Turkish OL-HDF study showed that OL-HDF with Qo> 17.4l was associated with a 46% reduction in overall mortality (p = 0.02) and a 71% reduction in cardiovascular mortality (p = 0.003) compared to with HD (206, 249). As already mentioned, ESHOL (216) is the only randomized study that shows a significant advantage of OL-HDF in terms of overall mortality, mortality from cerebrovascular and cardiovascular events and mortality related to infections and this is the study with highest achieved convective volume -22.9–23.9l per session.

Our results, like those presented so far, demonstrate an association of OL-HDF with improved patient survival. There was a significant difference in the recorded overall mortality rates between the two groups, with the analysis showing a 3.6-fold higher risk of death (RR 3.59; OR 4.88; CI 95% 1.2531 - 10.2467, p <0.001) in the conventional HD group. At the end of the period, the two-year survival rate in patients with OL-HDF was 87.7%, while in the group of HD significantly lower - 57.2%. Data from the Roc-analysis of total mortality show that for the group of conventional HD, the main predictors of poor outcome and death were spKt/V <1.25 and URR <70.25%. In the group of OL-HDF, as predictors of death and deterioration are the parameters of nutritional status - spKt/V <1.4, URR <74.4%, nPCR <1.2 and serum albumin <34.75g/l. This clearly shows that in the conditions of high dialysis dose and convective therapies, the assessment of dialysis adequacy and risk stratification should always be complex with an emphasis on the parameters of nutritional status. Although serum albumin did not show statistical significance as a negative predictor of Roc analysis for the HD group, our opinion is that it should be interpreted as a proven independent risk factor for death in any periodic dialysis patient.

Several meta-analyzes of Susantitaphong et al. (2013) (317), Nistor et al. (2014) (247) and Wang et al. (2014) for the possible benefits of OL-HDF on patient survival do not prove an advantage of the studied convective therapies, both in terms of overall and in terms of cardiovascular mortality and are in contrast to our results.

In summary, we believe that despite the small number of studies and the inconsistency of the data currently reported, OL-HDF shows an advantage both in terms of clinical outcomes and in terms of patient prognosis. Of course, it should not be overlooked that our study has some limitations due to its retrospective nature and small sample size (due to the small number of devices providing the study), which did not allow to study the clearance of medium molecules such as beta-2 microglobulin, which is not routinely examined at the Clinic and is not included in the standard for Dialysis Treatment of the Republic of Bulgaria (2), which remains a future prospect for research. We are aware that despite the reported encouraging results - increased dialysis dose, improved nutritional status, control of anemic syndrome with reduced erythropoietin dose, better hemodynamic stability, further studies are needed to clarify some of the unresolved issues outlined above, which are reported and in world literature. Of course, despite the seeming many benefits of OL-HDF, we realize that this is not an ideal therapy for every patient, which shows that we must put the individualized approach to medicine first. In our opinion, the choice of therapy in elderly patients should be strictly specified, because dialysis adequacy is not only embodied in the digital values of generally accepted indicators but is a much broader concept and should ensure a balance between clinical goals and quality. of the patient's life. At the same time, this does not mean that OL-HDF is only suitable for young patients. The choice of therapy should weigh very well the benefits and risks for the individual in the name of better clinical outcome, and not be based solely on the choice of "new" and "modern".

5.4 OL-HDF - convective volume (Qo). Measure of effectiveness

Online hemodiafiltration is the most effective RRT, which allows enhanced removal of small and large uremic toxins by combining diffusion and convective transport of solutes. Although the aim of OL-HDF is to provide greater clearance of solutes with a preference for medium molecules, the European Dialysis Working Group (EUDIAL) believes that this should not be at the expense of reduced clearance of small uremin toxins, which should be at least the same as for HD. As we already know, the latter is quantified by UKM and spKt/V. However, there is no validated indicator for assessing the convective clearance of the solute. Theoretically, the latter can be calculated based on the screening coefficient of the dialyzer-KoA and the applied volume of convection – Qo (218). The EUDIAL Group therefore takes the view that convective volume is the key quantitative indicator for OL-HDF in addition to standard adequacy measures. Although primary analyzes of the three large randomized controlled trials (71, 216, 249) showed inconclusive results, post hoc analyzes of these and other studies comparing OL-HDF after dilution with HD showed that the risk of overall and cardiovascular mortality was lowest in patients which are treated with Qo> 20l. Therefore, the size of the convection volume seems crucial and can be considered as a "dose" for OL-HDF.

Our study in practice considers only high-volume OL-HDF with its effect on clinical outcome and survival, results which were thoroughly discussed in a previous section of this dissertation. There is no doubt about the advantage in terms of achieved diffusion clearance levels expressed by spKt/V and URR, as well as in terms of nutritional status expressed by nPCR and serum albumin levels. However, are these parameters indicative of the conducted OL-HDF and are they sufficient to assess its effectiveness? As already pointed out, EUDIAL is of the opinion that the diffusion clearance of small uremic toxins should not be reduced at the expense of increased clearance of medium molecules (321). Our results confirm that high-volume OL-HDF not only does not reduce, but on the contrary enhances the purification of small molecules, a claim supported by other studies (217, 265). The recorded values of spKt/V and URR in OL-HDF for the two-year follow-up period are significantly higher than in HD and are in the range of the high dialysis dose spKt/V≥1.5, which is the subject of increased interest from the nephrology community in recent years, although according to the recommendations of KDOQI from

2015 and a dose above 1.2 is quite sufficient to provide quality treatment (245). This, together with the improved nutritional status and control of the anemic syndrome, demonstrates the undeniable advantage of high-volume OL-HDF in terms of dialysis adequacy. It should be borne in mind that despite many studies on this issue, there is no clear criterion for prescribing and dosing the applied convective volume. In the analysis of our results, it is noteworthy that in the first year of the study, when all patients received a high convective volume Qo = 24.73 ± 0.98, the latter did not show good agreement with any of the studied indicators. On the contrary, its use in some patients has led to an increase in IDH episodes and prolonged recovery time compared to other patients in the group. These are mainly patients in the upper tartar of the age distribution who find it difficult to tolerate the procedure, data confirmed in a comparative study by Piccoli et al (2018) (265). It is noteworthy that after the correction of na Qo with respect to age and hemodynamics, a strong correlation was found with spKt/V and nPCR. This was also found with serum hemoglobin and albumin levels, but the strongest predictive value of convective volume was in terms of dialysis dose delivered and nutritional status. This dependence demonstrates that the correctly selected convective volume, according to the individual characteristics of the patient, can be a measure of the dose and quality of OL-HDF, and that one dose, however effective, is not suitable for everyone. Dialysis adequacy and clinical outcome do not simply have to meet a set criterion that must be met at all costs. They are a much broader concept, in which the principle of "Primo non nocere" is in the first place. Ultimately, the goal of any therapy is the well-being of the patient, therefore deteriorating quality of life

The results obtained by us show that the criterion for high efficiency of the conducted convective therapy is Qo> 20l, which is confirmed by most clinical studies. (52, 218, 237). It is significant that when the volume was reduced to 16-18 l per session, significantly lower values were observed for both adequacy and serum hemoglobin levels, which are fully comparable to those achieved with conventional dialysis, which is also confirmed by the study of Piccoli et al (2018) (264, 265). Of interest is the fact that although no significant difference in nutritional status is found in low-volume OL-HDF, there is a tendency to improve it, which is probably related with the fact that large convective volumes lead to significantly greater albumin loss (114, 151, 309, 353). This indicates that high-volume HDF should always be used under

strict control of serum albumin and should not be used in patients with initially poor nutritional status. Data from the Roc analysis show that Alb values <34.75 g/l are critical for deterioration and risk of death. Therefore, the latter also emerges as a dose meter, along with Qo. Of course, it should be borne in mind that our results are retrospective, and the use of low convective volumes is observed mainly in patients in the upper age tertile, which requires further study in younger patients for complete objectivity of the result.
Like most trials (53, 151, 216, 247, 255, 302, 317, 358), we also found a benefit of Qo> 20l in terms of survival, which is significantly higher in the group of high-volume OL-HDF compared to conventional HD, results discussed in detail in another section of this dissertation. As the sample of patients with lower convective volume was too small and limited in a certain age group, the survival score was not comparable and did not reach statistical significance.
In conclusion, despite some limitations of our study, we believe that Qo> 20l per session can be considered as a measure of high efficiency and quality of convective therapy. Our opinion is that the dose of convection should be adapted to the individual characteristics of the patient, paying special attention to age, hemodynamic stability, and levels of serum albumin, which we also accepted as a dose measure. At Alb <34.75 g/l, the convective volume should be refined, or the dialysis regimen should be modified due to a significant increase in the risk of deterioration and death. Therefore, although OL-HDF is at the forefront of modern dialysis technology, it is not an ideal therapy for every patient and additional large-scale and randomized studies are needed to confirm the main indications, dose regimen, risks, and benefits of use.

6.5 Survival and dialysis adequacy

Recorded survival and mortality rates are the most important determinant of quality of life and dialysis adequacy in the growing population of CKD-5D patients and should always be interpreted in conjunction with validated clinical outcome indicators. Life expectancy in patients with end-stage renal disease is gradually improving, with the 2018 USRDS report for patients starting dialysis in 2011, the adjusted five-year survival was 42% (69, 111, 340). Currently, as a threshold for adequate dialysis, spKt/V> 1.2 is defined, and in recent years more intensified HD regimens have been discussed, which can significantly improve survival (245). Similar results have been reported in patients performing nocturnal HD with significantly higher spKt/V values obtained at the expense of prolonged dialysis time, as well as in patients performing home dialysis (58, 223, 246, 283, 289, 298, 325, 334). In addition to increasing the duration of the procedure, other factors that may improve the outcome have been discussed in recent years, such as the frequency of dialysis treatment, volume control and UV rate, and improved clearance of medium molecules (245).

As already mentioned, the effect of long-standing discussion in the nephrology community is the effect of high dialysis dose spKt/V≥1.5 on patient survival and quality of life. There are also authors (62, 192, 260) who associate extremely high Kt/V values (> 1.5) or URR (URR between 75% and 79%) with reduced survival and increased relative risk of death. According to them, the high values of spKt/V are "illusory" and are the result of malnutrition and increased protein catabolism - a decrease in V volume in the formula of Daugirdas, which is the basis of increased mortality despite high dialysis dose (31, 142). However, it has been found that with the isolated use of urea clearance Kt with volume neglect as an alternative measure of dialysis adequacy, the risk of death not only does not increase, but on the contrary, decreases by 2% for each liter of clearance increase (108,142,219, 270). This shows that the assessment of dialysis adequacy should not be based on isolated, although generally accepted indicators, but a complex multifactorial approach is needed, assessing the corrected risk in the individual patient.

The results of our study show a good agreement of survival with the high dialysis dose spKt/V≥1.5. Survival analysis demonstrated that as the dialysis dose received over the 5-year follow-up period, the expected survival rate increased significantly from 12-16 months to the third year of the 24-month study at its end, with an increase in the mean total annual dialysis dose in the sample from spKt/V = 1.25 ± 0.20 to spKt/V = 1.59 ± 0.32. The persistent increase in the percentage of patients in the high dialysis group in the last two years of follow-up should also be noted. Based on this, we believe that the objective result of the intensification of dialysis therapy on patient survival can be expected after the third year. Evidence of the changes already considered because of dose intensification, both in nutritional status and in the case of anemic syndrome, are two independent predictors of death in the growing population of patients with CKD-5D. All this leads to a cumulative effect on the achieved levels of survival and significantly improves the prognosis of patients and their quality of life. Of course, its manifestation takes time, and we cannot expect an immediate result, the insufficiently long follow-up period is probably one of the reasons why some authors deny the benefit of a higher than standardized dialysis dose for the prognosis of patients (62, 64, 102, 211, 260). It should also not be overlooked that in the last two years of monitoring the intensification of therapy is at the expense of the introduction of OL-HDF in the treatment regimen of part of the cohort. During the first three years of the study, the intensification was mainly based on prolonging the dialysis time, performing emergency dialysis, increasing the blood flow rate, and introducing high-flow dialyzers into the treatment regimen once or twice a week.

It should also be borne in mind that a high dialysis dose can be defined as such only with optimal nutritional status. In any other case, regardless of the numerical value of spKt/V≥1.5, it is inadequate. This is also confirmed by the constructed Roc-curves, which clearly show that in the conditions of high dialysis dose with cut-off value of spKtV <1.41, as predictors of death are nPCR <1.2 and serum albumin <35.2 g/l. Fereira et al reported a significant difference in serum albumin levels, in which individuals with HD ≥40.0g/l had a significantly lower risk of death HR 0.230 (95% CI 0.097-0.541) (111) and a 10-year cohort a 2013 study by Kato, Castro and Natarajan demonstrated a higher risk of death in patients with serum albumin ≤38 g/l. (172) According to Teixeira et al. (2015) albumin is independently associated with low survival (323), and Msaad et al. (2019) reported that 77.27% of deceased patients have decreased serum albumin (239). A study by Ebhahimi et al. (2019) reported that for every 10g/l increase in serum albumin, the survival time in patients with HD increases by approximately 23% (100). In conclusion, hypoalbuminemia is considered an indicative marker of malnutrition and a strong predictor of death in patients with CKD-5D. However, serum albumin levels should be used with caution as markers of nutritional status, as low levels in HD patients may be an expression of increased protein catabolism due to chronic inflammation, breakdown, and some other complications of CKD (15,111,172). Therefore, a positive predictive value of spKt/V in terms of patient survival can only be interpreted by considering nutritional status parameters. It should also be borne in mind that patients in the high dialysis group have improved their results not only in terms of the latter, but also in terms of control of anemic syndrome. Although renal anemia did not show statistical significance as a predictor of death from the Roc analysis, it should

be borne in mind that its inadequate control is associated with increased cardiovascular risk.
Analysis of the underlying causes of death confirmed the literature and outlined cardiovascular disease (CVD) as the leading cause of death, followed by catheter-associated sepsis, most caused by staphylococcal infections (63, 69, 129, 142). Many studies report that while there is a decline in cardiovascular mortality in the general population, no such trend is observed in patients with HD - approximately 50% of deaths are due to CVD (63, 69, 230). This discrepancy is due in part to high comorbidity and old age in HD patients — approximately 40% are diabetic; the mean age is approximately 60 years and approximately 20% are> 75 years, most patients have mainly CVD and have evidence of severe left ventricular hypertrophy at enrollment (17, 74, 128, 142, 154, 187, 196). Hyperlipidemia, control of arterial hypertension, hyperphosphatemia with secondary hyperparathyroidism should also not be neglected. The influence of the above factors and their predictive value in terms of survival has been rigorously studied and confirmed by Liabeuf et al. (2019) within the EURODOPRS study, which is part of the international cohort study Dialysis Outcomes and Practice Patterns Study (DOPPS) (111, 200).
The analysis of our results demonstrates that spKt/V≥1.5 appears to be a threshold value that improves patient prognosis. The results of Cox regression analysis showed 2 times higher risk of death for inadequately dialysis patients HR 2.11 (CI95% 1.32-3.39, p = 0.002) and its significant reduction in the group of high dialysis dose HR 0.60 (CI95% 0.35-1.02, p=0.051). The reported decline in mortality with increasing average dialysis dose should also not be overlooked. As already noted, in contrast to the other results, the overall mortality rates in the sample have risen significantly over the last two years of the study. At first glance, this would mean an increased risk of death with the intensification of dialysis therapy. However, it should be noted that over 50% of deaths are due to COVID-19 infection and its complications, which is a new risk factor that does not exist until 2020, regardless of the dialysis dose. (p> 0.05) In a corrected mortality model, the beneficial effect of the high dialysis dose on the achieved survival and mortality rates for the studied cohort is clearly visible. Although our results contradict the data from the HEMO study (64, 102, 211), which finds no advantage in either intensified dialysis therapy or the use of high-flow dialyzers, both in terms of both primary and secondary

results, many studies in recent years prove our claims. Data from Tomo et al (2021) from a Japanese study within the DOPPS study, as well as the results of Marshal et al (2016) in a study of mortality in the HD population of Australia and New Zealand favor intensified regimens and the pursuit of high dialysis as a predictor of improved clinical outcome and survival (223, 334).
In conclusion, our opinion is that the aspiration of the modern nephrological community should be aimed at achieving a high dialysis dose of spKt/V≥1.5 in view of improved clinical outcome and prognosis for the patient. The extension of the dialysis time, the increased frequency of dialysis procedures, the use of high-flow dialyzers, the inclusion of OL-HDF in the dialysis scheme must be adapted to the needs and individual characteristics of the patient. As already mentioned, the assessment of dialysis adequacy is complex and is not just a numerical value of an isolated indicator - spKt/V. In interpreting the result, stabilization of the nutritional status nPCR> 1.2 and strict monitoring of serum albumin as an independent risk factor for death are essential to achieve the therapeutic goal, especially in elderly patients with age-dependent difficulty compensating for protein catabolism. Our results demonstrate that the effect of high dialysis dose is lasting, but to achieve it requires time, perseverance, and precise control not only of the adequacy indicators, but also of all concomitant complications of CKD-5D. This comprehensive approach in therapeutic strategy would lead to improved clinical outcome with reduced financial cost to the community and improved quality of life and prognosis for the patient.

5.6 Dialysis adequacy and individual quality of life

Patients with CKD-5D have a worse health related quality of life (HRQOL) compared to the general population, as evidenced by numerous studies in recent years (139, 153, 284, 376), factors affecting HRQOL in patients with CKD-5D remain underappreciated. Previous research has focused mainly on the effects of ESA, exercise, the impact of different types of RRT, but the impact of dialysis adequacy remains somewhat neglected. A small number of studies have examined the effect of the latter on the achievement of HRQOL. An uncontrolled study demonstrated that an increase in spKt/V by an average of 0.2 resulted in improvement in six of the eight components of HRQOL SF-36. Numerous studies have described a strong correlation between dialysis dose and clinical outcomes, with the result that dialysis adequacy is now considered a strong predictor of morbidity and mortality in patients with CKD-5D (67, 139, 284, 376).

The physical component of HRQOL includes three subscales, namely physical activity, limiting the role in everyday life and physical pain. Several previous studies have reported that it is an independent predictor of both hospitalization and death. This also argues for the need to improve it in dialysis patients - a change that is expected to effectively reduce the risk of death and recurrent hospitalization at a lower cost to the community (139, 221, 222).
Unfortunately, the results of our study still show a low result in terms of the physical component of HRQOL. This is in line with the relevant findings reported for European and American patients in the DOPPS study (269). Similar data are reported from studies by Hasan et al. (2021) and Staykova (2018) (6, 139).

As mentioned, it is very impressive that 36% of the patients surveyed in our study feel limited in their daily activities. At the same time, 62% do not feel such a limitation, but report in approximately the same percentage that they have reduced their time for work, other commitments, and the ability to perform various tasks, which shows that patients do not have a real criterion for self-assessment. This is to some extent related to the social status of patients, as well as the low level of education - mostly secondary. Proof of this is the self-assessment of their own health as "good" in 2/3 of patients, although the objective condition and purely clinical evaluation criteria show the opposite. However, we should not underestimate the fact that the subjective feeling of improved health is the result of good collaboration between the medical team and the patient, which is confirmed by the results of the component for satisfaction with the provided health service. The effect of psychosocial support on patient self-esteem and disease control is confirmed by studies by Theofilou et al (2012; 2013; 2015) (326, 327, 328, 329, 330).
Unfortunately, despite the development of modern technology, the limitation in the physical scale remains significant. Most patients, although they have retained their ability to self-care and perform routine activities, are not complete in terms of physical acivity, which, as the results show, is relatively light and is limited to walking no more than 1 km per day and moderate

difficulty climbing stairs. Of interest is the fact that with the intensification of the dialysis dose spKt/V≥1.5 there is a significant improvement in all aspects of the physical scale of HRQOL, which is consistent with the data of Hasan et al. (2021), Theofilou et al. (2015) и El Sheikh et al. (2016) (103, 139, 330), but denies the results of Ayoub et al. (2013) (23), which do not establish such a relationship. It is also worrying that the percentage of patients suffering from physical pain is still too high - 74% of the total sample, and the results show a strong link between its improvement, both with increasing the dialysis dose and with the implementation of OL-HDF, which is objectified by other authors.

Given the importance of the physical component of HRQOL as a predictor of death and hospitalization, it is imperative to develop strategies for its optimization. Exercise has been the subject of interest in many (158, 162, 185, 204). A systematic review of 29 clinical trials reported improvement in HRQOL's physical scale after aerobic exercise as well as cardiopulmonary circulation, anemia, hyperlipidemia, chronic inflammation, blood pressure, insulin resistance, anxiety, and depression (139, 158). Although exercise in dialysis patients has many beneficial effects and should be a mandatory part of rehabilitation, it is not yet part of routine clinical practice. Unfortunately, our study confirms the literature on the high incidence of emotional disturbances in the form of depression and anxiety in the dialysis population (76, 110, 252, 324, 326, 376). It should be borne in mind that the mental state of patients is closely linked to their social status, which is greatly altered by the disease and often leads to their inability to work, respectively to receive adequate financial security. In the conditions of the Bulgarian reality and social insurance 80% of the patients with CKD-5D rely on a social pension, which is extremely insufficient to ensure their existence. As a result, these patients often lose their self-esteem and feel disabled, even in good physical health. At the same time, HD can also cause mood and sleep disorders, which further aggravate mental suffering (76, 139).

Our study found a significant relationship, both in terms of dialysis dose delivered and in terms of the type of therapy performed with the emotional component of HRQOL. Our results demonstrate its significant improvement with an increase in the delivered dialysis dose spKt/V≥1.5, as well as with the introduction of OL-HDF in the dialysis prescription, which is confirmed by other authors (139, 330). Very often, in addition to the purely physiological effect of the above measures, patients "seeing", clinical and laboratory results are ambitious in their fight against the disease.

Although the emotional component is often underestimated as a predictor of HRQOL, it is one of the most important factors in the complex therapy of patients with CKD-5D. Our opinion is that by ensuring the emotional health of patients, we not only improve their self-esteem and social existence, but also create an opportunity to improve their physical condition. Only an individual who is in harmony with himself and his disease could have a quality compliance with the therapy, dietary regime and actively participate in both the prevention and treatment of complications associated with the disease. In our opinion, the main points for improving the mental health of patients should include training patients for timely communication in case of anxiety, use of group therapy, enabling them to feel that they are not alone in fighting the disease and the burden of dialysis (87). Here the role of both the nephrologist and qualified psychologists is extremely important, which is necessary to ensure the comfort of the patient, to predispose him to "teamwork" and cooperation to overcome the problem and prevent it from affecting both everyday life, and on the desire to deal with the disease. More extreme but necessary measures in many cases include the use of antidepressants in GFR-compliant doses (139, 141).

Of interest are the results of the component related to kidney disease and its objective manifestations. A strong association of high dialysis dose $spKt/V \geq 1.5$ with improvement in uremic symptoms by type of negative correlation ($p < 0.001$) was found. Any increase in dialysis dose was associated with increased HRQOL with respect to renal disease, and the dependence was verified for all subscales of this component. This finding is also confirmed by the publications of Hasan et al. (2021), Theofilou et al. (2015), El Sheikh et al. (2016), Babu et al. (2018) и Kalender et al. (2014) (24, 103, 139, 165, 330). of the low and standard dialysis dose and although some authors such as Gabbay et al. (2010) and Grove et al (2018) deny the effect of high-dose HD ($spKt/V \geq 1.5$) on uremic symptoms(121, 135). It should be borne in mind that some subscales take time to show the true effect of dose escalation. Of interest is the discrepancy of some of the results with the objective complaints of patients during dialysis procedures. For example, on average about 70% of respondents deny shortness of breath and thoracic oppression, but the clinical examination during the dialysis procedure showed objective evidence of hyperhydration and difficulty breathing in a significantly higher percentage of respondents due to HDR disorders. On the other hand, the opposite trend is observed regarding reported cramps and their objective manifestation during the dialysis session - 54% of respondents report cramps during procedures with different frequency (often 50% and 4% for each dialysis). Objectively, however, this frequency is lower. This is largely because during the years of dialysis treatment, patients are "trained" in the symptoms needed to gain optimal weight.

Regarding the conducted OL-HDF, we found a reliable dependence only for some subscales as statistically significant lower incidence of chest pain and depression, improved appetite, hemodynamic stability with low incidence of cramps. Several cross-sectional studies support the beneficial role of OL-HDF in improving the quality of life in these patients (3, 13, 9,10). Our results are confirmed by studies by Shifl et al. (2007), Karkar et al. (2015) and Kantartzi et al. (2013). Other authors such as Steffanson et al. (2012), Mazairac et al. (2013), Morena et al. (2017), Suwabe et al (2018), do not report a statistically significant difference in quality of life in patients undergoing HD and OL-HDF (275, 284).

Although we did not find a statistically significant difference ($p > 0.05$) with respect to the observance of dietary regime reported by the respondents at different dialysis doses and therapies, it is worth noting that this is a serious problem that not only hinders patients but also objectively clinically worsens their condition. Most of them deny dietary errors and excessive fluid intake, but objective data show otherwise - in 60% of patients we objectively observe excessive interdialytic weight gain (IDWG), and in most patients - clinical data on hyperkalemia. IDWG seems to be a new predictor of HRQOL (284). Taskapan et al (2005) (319) reported that higher IDWG adversely affected the viability and social function of HRQOL. Their results also reflect that depression, the presence of one or more comorbidities, and low satisfaction with perceived social support are associated with higher IDWG. In addition, the latter is associated with longer recovery times, which is a predictor of deteriorating HRQOL (275, 284, 319). It should be borne in mind that high weight gain is often the cause of IDH, cramps and early termination of procedures with shortened dialysis time, which invariably reflects on the received dialysis dose. In this way, a vicious circle is formed, in which the result is a deterioration in HRQOL. This requires that adequate measures be taken to educate patients, as well as the inclusion of a nutritionist in the team to properly control uremia and prevent malnutrition.

In conclusion, it can be said that dialysis adequacy is an important predictor of HRQOL. Our results demonstrate that the high dialysis dose of spKt≥1.5 achieved by conventional HD or OL-HDF appears to be a major prospect for improving patients' HRQOL in all its aspects and, despite conflicting opinions, should be a major goal of dialysis treatment. However, in addition to dialysis prescriptions, there are several problem areas of deteriorating performance that offer opportunities to improve HRQOL Our opinion is that in addition to purely therapeutic intervention in terms of clinical and laboratory data of patients, attention should be paid to their emotional satisfaction and the achieved subjective quality of life. Improving physical and emotional functioning can be an important perspective for changing the perception of the disease and reducing its damage. This requires an interdisciplinary approach involving physiotherapists, psychologists, and nutritionists to encourage the patient to be independent and committed to the disease and ongoing therapy. An ongoing HRQOL evaluation plan needs to be developed and timely action taken, where necessary, to improve it. Early diagnosis of inadequate dialysis is a cornerstone in this aspect and should be corrected immediately, as it would have a beneficial effect on patients' abilities as productive members of society. We believe that only with joint efforts, both on the part of the team and the patient, can the goal be achieved, namely improved HRQOL in its two components - objective and subjective.

6.7 Ionic dialysis - a modern perspective for assessing dialysis adequacy

In clinical practice, the adequacy of dialysis is monitored by spKt/V once every 3 months, and the most common follow-up is once a month. Based on this, it is assumed that the same dialysis dose will be delivered for all sessions if the dialysis prescription does not change. However, data from the HEMO study (64, 102, 211) show that 21% of patients prescribed target spKt/V of 1.3 had spKt/V <1.2 at some point. In this respect, more frequent measurements of spKt/V may be more useful, but not practical due to the cost and effects of frequent blood sampling in this patient population. Dialysis adequacy, measured by online ionic dialysis monitoring, is a new reliable technique that allows real-time dialysis dose quantification without the need for blood tests and allows for timely therapeutic intervention to achieve the target dialysis dose. (21) However, for its routine implementation in clinical practice, additional studies are needed to confirm its reliability as a methodology, as well as its comparability with generally accepted indicators of dialysis adequacy.

The analysis of our results proves a high correlation between the validated indicators of dialysis adequacy (spKt/V; URR) and those registered with online monitoring by ionic dialysis (onKt/V), while considering a significant difference between the two methods, based mainly of the anthropometric formulas used to estimate the volume. This finding has been objectified by and by other authors in previous publications (14, 21, 73, 93, 94, 122, 127, 186, 203, 210, 235, 272, 281).

Despite the high strength of the connection, the values recorded by us for onKt/V are 8% lower compared to the results using UKM. Therefore, onKt/V as an indicator of evaluation can underestimate the dialysis dose received. Various factors have been reported as the reason for this and have been discussed by some authors as a possible source of error in the study. Differences of 2-5% in instantaneous conductivity measurements reported by several previous studies have been associated mainly with differences in urea and sodium diffusion coefficients, as well as with different effects on the dialysis membrane (such as charge), and inadequate correction of ultrafiltration. According to Gotch et al. (2004) spKt/V may be underestimated because of systemic salt loading during measurements, resulting in a reduced diffusion gradient of the conductivity through the dialyzer, especially when the urea clearance is> 150 ml/min (132).

To ensure maximum comparability of the result, our study was conducted by eliminating possible additional factors affecting the obtained dialysis dose such as permeability and dialyzer surface, Qb and Qd velocity, problematic vascular access with poor flow and / or recirculation, duration of HD, sodium profiling (possible interferences with conductivity), with measurements taken within the same session i.e. each of the above factors would affect both methodologies equally. The main reason for the underestimation of the dialysis dose obtained in onKt/V was the use of anthropometric formulas for estimating the volume of distribution (V) of urea - Watson's formula for total body water. It should be borne in mind that the latter is based on anthropometric data from healthy individuals and may overestimate the total body water in chronodialysis patients due to depletion of muscle mass and poor nutritional status, and does not consider postdialysis urea rebound, opinion confirmed by other authors (14, 94, 127, 203, 281, 372).

Studies by McIntyre et al (2003) and Alayoud et al. (2012) consider that overestimating V by anthropometric formulas causes ionic dialysis to show better agreement with the dpKt/V double pool, which is inconsistent with the results of Di Filippo et al (2001) (93), who demonstrated significantly higher values for Kt/V measured by ionic dialysis compared to dpKt/V. This inconsistency in the reported results can be explained by differences in the characteristics of the studied populations and the nature of the conductivity methods used (21, 235).

For the purposes of online monitoring and estimation of the volume of distribution, UKM can also be used for indirect calculation of theoretical urea clearance, which, however, may be significantly lower than the actual one. The most common reasons for this are recirculation, low blood flow velocity and thrombosis of capillary fibers in the dialyzer in suboptimal heparinization. Therefore, this method requires strict tracking and correction of errors single-pool modeling. effective urea clearance. This leads to an overestimation of its in vivo efficacy, which creates conditions for error in estimating V, like Watson's formula, which is confirmed by Wuepper et al. (2003) (372) the actual volume of urea distribution, as well as that measured by bioimpedance -Vimp and contradicts the data of Koubaa et al (2010) (186), according to which Vukm demonstrates a high correlation with the latter. may be affected by errors in blood sampling, urea rebound rate, and residual renal function (203). According to Alayoud et al (2012) correcting these factors makes Vukm much closer to Vimp. At present, the bioimpedance is most closely aligned with TBW and the actual volume of urea distribution, however, the results differ depending on the applied impedance frequency, as well as the position and contact of the electrode (14, 281).

Our results demonstrate a very good agreement of onKt/V with the dialysis dose indicator validated by the KDOQI recommendations - spKt/V and despite the registered statistically significant difference between the two indicators, the strength of the correlation between them is very high. ($r = 0.91$, $p < 0.0001$) data reported in recent studies by Rodrigez et al. (2021), Churchill et al. (2021), Raiman et al. (2020), Mohamed et al. (2018), Creput et al. (2013) and Locatelli et al. (2013) (66, 73, 210, 231, 272, 281). Our study confirmed the findings of other authors that OCM can underestimate the dialysis dose received - the results for onKt/V are 8% lower than spKt/V. The main reason for this was the use of Watson's anthropometric formula. Theoretically, it is possible that this difference is due to convective transport of sodium during the dialysis procedure, which would also lead to a change in the reported conductivity and interference of the result. This is because the OCM methodology does not consider convection, unlike UKM. It should also be borne in mind that our study found a much better agreement between onKt/V and the one-dimensional model than the data reported so far. Most authors such as Alayoud et al (2012), Marsenic et al (2011) report a better correlation of online monitoring with the double-pool model, precisely because of the effect of anthropometric volume estimation (14, 203, 224, 227). This proved how important its accurate assessment is when only anthropometric data are used. It is extremely important for the clinician to consider the presence of hyperhydration, the nutritional status of the patient, the loss of muscle mass, as well as to make an accurate assessment of the actual optimal weight. The latter is often overestimated due to non-cooperation of patients, excessive use of fluids with overweight between dialysis sessions, high levels of ultrafiltration, and hence frequent episodes of IDH and inability to achieve it. However, it should be borne in mind that even the most accurate anthropometric estimation of the volume of urea distribution cannot reach the agreement of the bioimpedance methodology, which remains the subject of our future research.

Despite some shortcomings of the method, its high degree of correlation with the received dialysis dose is promising for new perspectives in the concept of dialysis adequacy and optimal clinical outcome. The regression equation derived by us makes it possible to estimate the actual dialysis dose obtained by correcting the influence of the anthropometric component, i.e., at any time based on the values for onKt/V, the corresponding value of spKt/V obtained by UKM can be recalculated. In addition, it should be borne in mind that, although generally accepted, spKt/V itself has several disadvantages. In this aspect, even underestimating to some extent the dialysis dose received, online monitoring makes it possible to assess dialysis adequacy in real time without the need for blood tests before and after the dialysis session. This demonstrates the advantage of the method compared to the classic UKM - on the one hand in a purely financial aspect, and on the other, which is undoubtedly much more important, is the strict quality control of the dialysis dose. Tracking it at longer intervals in routine practice creates a precondition for missing important events leading to inadequate dialysis and worsening the result. Effective ionic dialysis provides reliable, real-time, non-invasive, and inexpensive dialysis dose measurement during the current dialysis session. It allows the clinician to take the necessary interventions as well as to directly assess their impact. For example, in case of data for a much higher than prescribed dialysis dose, respectively. Reaching the latter early in 1-2 hours, in patients without concomitant malnutrition (volume reduction V) with normal or even high body mass index, recirculation of access should be considered, even in the absence of clinical data. The reason for this phenomenon is that the greater the recirculation of the extracorporeal chain, the faster the concentration of uremic toxins decreases, respectively that of sodium required for OCM. In other cases, OCM records persistently low dialysis results, which are a sign of inadequate prescriptions, problematic access, or inadequate anticoagulation with a risk of coagulation of the extracorporeal system, factors that can be identified early and with each procedure. In addition to the above benefits, our observations show that online monitoring has a positive, purely psychological impact on patients. As we know, one of the most common causes of inadequate dialysis is the shortened dialysis time initiated by patients, as well as the omission of dialysis sessions at their request. We found that real-time dialysis dose monitoring motivates the patient to adhere to and even prolong dialysis time.

In conclusion, we confirmed that OCM is a practical non-invasive tool for daily use, which complements the classic indicators of UKM by helping to deliver an adequate dialysis dose with increased benefit to the patient and minimal cost of financial resources. The difference of 8% reported by us is negligibly low in clinical terms, especially considering the ability to monitor the dialysis dose in each session without the need for blood tests. In addition, based on our relationship between the two methods, the ionic dialysis result can be adjusted at any time to the value corresponding to the standardized spKt/V in UKM. Our opinion is that future research, development, and implementation of OCM in routine clinical practice creates an opportunity for strict control of dialysis adequacy in each session, timely recognition of the causes of inadequate dialysis and therapeutic intervention on the factors causing deteriorating clinical outcome. However, it should be emphasized that the clinical picture of the patient is above any formula and methodology and should be leading in the prescription for dialysis adequacy in view of improved survival and optimal quality of life.

5.8 Diagnostic - therapeutic algorithm for dialysis prescription

Based on the analysis and evaluation of the available literature, reflecting the specifics and significance of the problem, as well as the results of this study with a strict assessment of the risks and benefits of its application, an original diagnostic-therapeutic algorithm for dialysis was developed to improve clinical outcome, survival, and quality of life in patients with CKD-5D.
The latter is illustrated in fig 32.

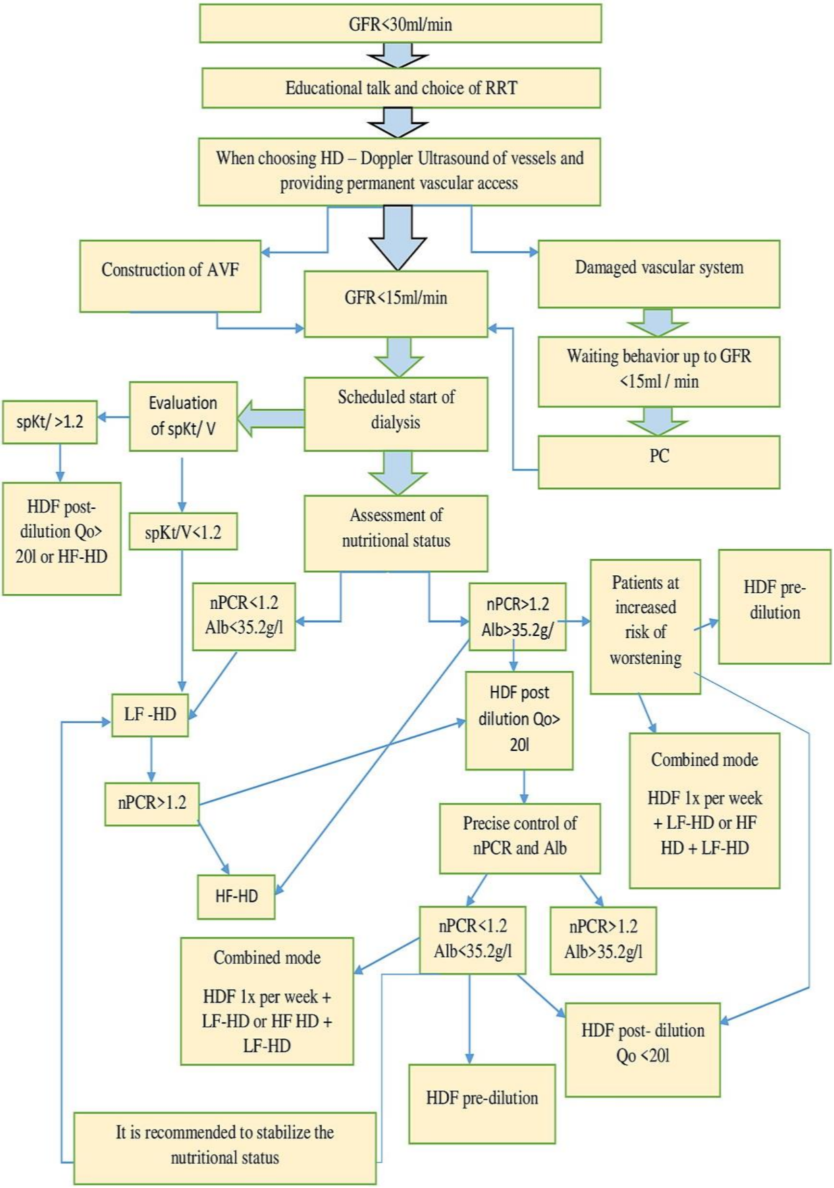


Fig. 32 Diagnostic-therapeutic algorithm for dialysis prescription.

6. Conclusions

1. Ionic dialysis is a new non-invasive tool for daily use with high correlation and predictive value in relation to the classic indicators of dialysis adequacy - spKt/V and URR, which allows cheap assessment of the delivered dialysis dose in real time without the need for blood tests.

2. Despite conflicting opinions in the literature on the high dialysis dose of spKt/V≥1.5 and its effect on clinical outcome, the latter leads to a significant improvement in nutritional status, anemic syndrome, and quality of life in patients with CKD-5D, with a lasting effect. manifests itself in the third year of intensification of therapy.

3. The beneficial effect of high dialysis dose on nutritional status is indisputable in young and middle-aged patients, but is unsatisfactory for elderly patients who, despite good rehabilitation, have age-related weight loss and malnutrition with high comorbidity.

4. High-dose dialysis therapy spKt/V≥1.5 is associated with improved survival, reduced risk of death HR 0.60 (CI 95% 0.35-1.02, p = 0.051) and a significant increase in life expectancy compared to other groups, while the critical period for stabilization and survival is significantly shorter.

5. In the conditions of the non-standardized high dialysis dose achieved by conventional (HD) or convective therapies (OL-HDF) the nutritional indices have a stronger predictive value for poor performance, as in OL-HDF the serum albumin is of special importance due to the expressed his loss during the procedure

6. AVF significantly outperforms other types of vascular access in terms of dialysis dose and control of anemic syndrome, achieved survival with reduced risk of death (4 times lower than the use of PC) with a significantly lower incidence of complications and related with them hospitalizations.

7. OL-HDF after dilution provides significantly higher values of the delivered dialysis dose and nutritional status, better control of the anemic syndrome with stable hemodynamics and shortened recovery time.

8. The use of a convective volume Qo> 20 l per session has been proven to be the main measure for dose and high efficiency of the conducted OL-HDF. At volumes below the indicated value, the clinical effect is comparable to that of conventional dialysis.

9. The high volume Qo> 20 l is not a universal dose for every patient, despite the higher efficiency, which is evidenced by the derived correlation dependencies after its adaptation to the individual.

10. In elderly patients, high convective volumes are associated with hemodynamic instability, prolonged recovery time, and poor nutritional status with significantly lower nPCR, and serum albumin values compared to the same age group performing conventional dialysis, requiring strict precision. of dialysis prescription schemes.

11. Online HDF is associated with better survival than HD patients (87.7% vs. 57.2% at the end of the two-year period), with the latter being almost four times more likely to die (RR 3.59; CI 95% 1.25 - 10.24 p <0.001)

12. Despite advances in dialysis technologies with increased membrane biocompatibility and high clearance of uremic toxins, patients have shown low scores on the physical and emotional component of HRQOL, which directly correlates with the dialysis dose delivered and the type of dialysis therapy

7. Contributions

The contributions from the present dissertation are of theoretical and practical nature.

7.1 Theoretical contributions:

1. The relationship between the achieved survival, quality of life and different doses and techniques of dialysis treatment was studied with a thorough review of the literature data on the problem
2. The association of high dialysis dose spKt/V≥1.5 with improved patient survival and reduced risk of death compared to standard dialysis dose has been demonstrated, a controversial statement in the world literature.
3. Vascular access as a factor determining the clinical outcome and the dialysis dose obtained has been studied, confirming the advantage of AVF as the vascular access of choice.
4. For the first time in our country the effect of convective therapies that are not routinely applied in clinical practice on the achieved dialysis dose, the parameters of the nutritional status and the control of the anemic syndrome has been studied and evaluated.
5. For the first time in our country the convective volume was studied as an indicator for dosing of OL-HDF and the threshold value for the effectiveness of the therapy was established.
6. The connection of high-volume OL-HDF with the selected survival and significantly reduced risk of death compared to conventional HD has been proven, and the main predictors of death in both groups have been assessed.
7. For the first time in our country, ionic dialysis has been studied as a method for estimating the dialysis dose

7.2 Practical contributions:

1. The main risk groups for conducting OL-HDF are assessed and approaches to risk reduction are proposed.
2. The strong connection of high-dose HD spKt/V≥1.5 and OL-HDF with the achieved quality of life has been proven and approaches for its improvement have been proposed.
3. The high comparability and benefit of ionic dialysis compared to the classical indicators of UKM has been proven and its routine implementation in clinical practice is proposed in view of improved clinical outcome and reduced cost of treatment.

4. An original algorithm for therapeutic behavior and choice of dialysis regimen in patients with CKD-5D has been developed and proposed - a basis for a complex and individualized approach in patients for improved quality of life and survival.

8. Publications in connection with the dissertation:

• Petrov A., Benkova-Petrova M., Staykova Sv., Petrov P., **Nenova D**. Dimieva-Dineva J., Koleva T, Zhelyazkov K., Damyanova D., Ivanova B., Ahmed E., Koleva R., "Distribution of CKD among the population of Varna, Valchi dol municipality and Avren municipality", Actual Nephrology, issue 1, volume 13, 2019, p.16

• **Nenova. D.,** AV-fistula – the gold standard for the adequacy of hemodialysis treatment and achieved quality of life in patients with ESRD, Actual Nephrology, issue 1, volume 15 2021, p. 11.

• **Nenova D.,** Atanasova S., Staykova Sv. - Analysis of the achieved quality of life in patients with end-stage CKD undergoing ONLINE Hemodiafiltration, Actual Nephrology, issue 1, volume 15, 2021, p. 39.

• **Nenova D.** - Effective ionic dialysis - a modern perspective for assessing dialysis adequacy, Varna Medical Forum, vol.1, 2022, Online First