

Research Article

Association of Continuous-Equivalent Urea Clearances with Death Risk in Intermittent Hemodialysis

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Background. Several reports describe favorable results from frequent hemodialysis, but due to the lack of unequivocal dose measures it is not clear whether the benefits are due to more efficient toxin removal or other factors. **Methods.** The associations with death risk of six continuous-equivalent urea clearance measures were compared in 57 conventional in-center hemodialysis treatment periods of 51 patients, together 114 patient years. The double pool dose measures were calculated with the Solute-Solver program and separately scaled to urea distribution volume or normalized with body surface area. **Results.** Mortality associated significantly with equivalent renal urea clearance (EKR) scaled to urea distribution volume (V) ($p = 0.033$) and with EKR normalized with body surface area (BSA) ($p = 0.044$) but not with V -scaled ($p = 0.059$) nor BSA-normalized ($p = 0.183$) standard clearance (stdK). Women had significantly higher normalized protein catabolic rate (nPCR), EKR/ V , and stdK/ V than men but slightly lower BSA-normalized dose measures and lower mortality. Protein catabolic rate and dialysis dose correlated positively with each other and with survival. **Conclusions.** The prognostically most valid continuous-equivalent clearance in the present material was EKR/ V , calculated from double pool urea generation rate, distribution volume, and time-averaged concentration.

1. Introduction

Survival correlates with urea-based hemodialysis session dose in many large registry studies (Lowrie et al. [1]: 43,334 patients, Port et al. [2]: 84,936 patients, and Miller et al. [3]: 88,153 patients) in conventional thrice-weekly schedule, but in the randomized controlled HEMO trial mean equilibrated Kt/V (e Kt/V) 1.53 did not result in a significantly better outcome than 1.16 [4].

Intermittent hemodialysis treatments can be compared to each other by the session dose measures URR, Kt , Kt/V , and e Kt/V only if the treatment frequency is equal. Several observational studies, referred to in [5, 6], and the randomized controlled FHN trial [7] describe positive results from frequent (“daily”) hemodialysis. However, the role of solute removal efficiency remains obscure.

Urea distribution volume (V) is an essential variable in kinetic modeling and can be used as a representative

of patient size, a scaling factor. However, it may have also an independent effect on outcome [1, 8], which weakens the value of Kt/V as a prognostic factor. BSA has recently been recommended for scaling of dialysis dose similarly as in expressing the glomerular filtration rate [9]. V -scaled dosing may result in suboptimal outcome in women and children.

Equivalent renal urea clearance (EKR, Casino and Lopez) [10] and standard clearance (stdK, Gotch) [11, 12] take treatment frequency and residual renal function (RRF) into account and they were intended for use in comparing dialysis doses in different schedules and for continuous dialysis and renal function [13, 14].

RRF may contribute significantly to the total weekly solute removal [14] but only minimally (usually <1%) to the delivered Kt/V or URR measured from blood samples. Renal clearance (K_r) can be added mathematically to session Kt/V [15–17]. Continuous-equivalent clearance based on UKM

TABLE 1: Association of patient characteristics and dialysis dose measures with death risk in 57 hemodialysis treatment periods of 51 patients.

		Mean	SD	Min	Max	<i>p</i>	Univariate OR	95% CI
Age	Years	61.6	15.5	16.7	91.6	0.103	1.038	0.993–1.085
Weight	kg	75.1	18.2	44.2	123.6	0.525	0.989	0.957–1.023
BMI	kg/m ²	26.1	5.5	16.3	43.7	0.198	0.924	0.819–1.042
BSA	m ²	1.84	0.25	1.31	2.34	0.872	0.823	0.078–8.727
V	L	31.8	6.7	20.5	50.3	0.637	1.021	0.936–1.113
nPCR	g/kg/day	1.15	0.24	0.73	1.74	0.058	0.065	0.004–1.095
nK _r	mL/min/1.73 m ²	1.7	1.4	0.0	6.0	0.861	0.963	0.631–1.469
nEKR	mL/min/1.73 m ²	12.5	1.3	8.4	16.4	0.044	0.611	0.379–0.988
nstdK	mL/min/1.73 m ²	8.5	1.0	6.2	12.2	0.183	0.638	0.330–1.235
nEKRant	mL/min/1.73 m ²	15.1	2.3	8.3	20.3	0.113	0.806	0.617–1.053
nstdKant	mL/min/1.73 m ²	10.2	1.6	6.1	14.3	0.232	0.785	0.527–1.168
EKR/V	/week	4.35	0.64	2.36	5.82	0.033	0.326	0.117–0.912
stdK/V	/week	2.93	0.39	1.73	3.88	0.059	0.205	0.040–1.060
fr	/week	2.9	0.3	2.0	3.7	0.413	0.503	0.097–2.606
t _d	h/week	13.5	2.3	7.7	18.4	0.077	0.786	0.602–1.027

TABLE 2: Hemodialysis treatment period durations and reasons for discontinuation.

	N	%	Duration (years)			
			Mean	SD	Min	Max
Continuing	19	33.3	2.5	1.7	0.4	5.8
Death	16	28.1	2.3	1.6	0.6	6.9
Transplantation	8	14.0	1.4	1.3	0.6	4.6
Transfer to another unit	8	14.0	1.3	1.2	0.3	3.8
Transfer to peritoneal dialysis	3	5.3	2.1	1.4	0.7	3.5
Decision	3	5.3	0.8	0.3	0.6	1.1

The numbers include hemodialysis treatment periods ongoing on January 1, 1998 (from that date on), and incident periods during the nine-year observation time until December 31, 2006 (unless terminated earlier).

includes K_r automatically. Renal function is “qualitatively” better than dialysis with equal urea clearance [18].

In theory, the continuous-equivalent average clearance based on double pool UKM and including RRF is fine, but the best measure is the one most closely associated with outcome. Only few earlier reports correlate mortality directly with ECC [7, 19–22]. The aim of the present preliminary study was to compare the prognostic value of different continuous-equivalent urea clearances as dialysis dose measures.

2. Subjects and Methods

The study is a retrospective registry analysis from a hospital providing adult hemodialysis services in a district with a catchment area of some 50,000 inhabitants in Eastern Finland. The observation time was nine years, from January 1, 1998, to December 31, 2006. The material comprises 57 conventional in-center hemodialysis treatment periods of 51 patients, in total 114 patient years. Periods lasting under 90 days are not included. Patient characteristics are described in Table 1. Table 2 presents the characteristics of the dialysis treatment periods. “Decision” refers to a unanimous decision

by patient and physician to discontinue renal replacement therapy.

Dosing of dialysis, including treatment frequency, was prescribed by the first author on multiple criteria (weight, hydration status, predialysis plasma urea concentration, and other laboratory values, eKt/V targets, and patient’s preferences). Renal diagnosis, comorbidity, functional status, waiting for transplantation, age, anticipated survival time, and protein catabolic rate (PCR) were not used as dosing criteria. The patients were encouraged by a dietician to use a diet containing protein 1.2 g/kg/day, but the actual dietary protein intake was not controlled.

Urea kinetic modeling with interdialysis urine collection was performed monthly. K_r was interpolated from previous and next measurements if urine collection occasionally failed. RRF was detected in 68% of UKM sessions. In 15% of them, K_r was interpolated. The numbers describing the patient characteristics and dialysis dose measures are means of each treatment period.

Double pool UKM calculations were conducted with the Solute-Solver program version 1.97 (July 2, 2010, with source code) [23], accessed November 12, 2015: <http://www.ureakinetics.org/>.

Dialyzer mass area coefficient (K₀A) reported by the dialyzer manufacturer is used in Solute-Solver in calculating dialyzer clearance (K_d) from Q_b and Q_d with Michaels’ equation [24].

Six double pool continuous-equivalent urea clearance measures were compared:

EKR/V (/week).

nEKR (mL/min/1.73 m²).

nEKRant (mL/min/1.73 m²).

stdK/V (/week).

nstdK (mL/min/1.73 m²).

nstdKant (mL/min/1.73 m²).

TABLE 3: Dialysis treatment periods divided into two groups with approximately equal mean nPCR.

		EKR/V				<i>p</i> value
		Low	SD	High	SD	
Age	Years	Mean	SD	Mean	SD	
		60.8	13.2	62.5	17.7	0.668
Weight	kg	77.1	21.2	72.9	14.7	0.393
BMI	kg/m ²	26.5	6.5	25.7	4.4	0.595
BSA	m ²	1.86	0.27	1.81	0.22	0.441
V	L	33.7	7.5	29.8	5.1	0.024
nPCR	g/kg/day	1.19	0.28	1.12	0.19	0.283
nK _t	mL/min/1.73 m ²	2.0	1.4	1.4	1.4	0.102
nEKR	mL/min/1.73 m ²	12.1	1.5	13.0	1.0	0.005
nstdK	mL/min/1.73 m ²	8.3	1.1	8.7	0.9	0.240
nEKRant	mL/min/1.73 m ²	14.2	2.4	16.2	1.7	0.001
nstdKant	mL/min/1.73 m ²	9.8	1.7	10.7	1.3	0.023
EKR/V	/week	3.99	0.59	4.72	0.45	<0.001
stdK/V	/week	2.75	0.38	3.12	0.30	<0.001
Treatment frequency	/week	2.8	0.4	3.1	0.2	0.006
Treatment time	h/week	12.6	2.5	14.4	1.7	0.003
Treatment periods	<i>n</i>	29		28		
Women	%	31.0		46.4		0.233
Diabetics	%	37.9		46.4		0.516
Ending with death	%	37.9		17.9		0.092
Patient years	<i>n</i>	49.8		64.5		
Deaths	<i>n</i>	11		5		
Mortality	/1000 py	221		78		0.049

Their definitions are described in the Appendix. EKR is based on time-averaged urea concentration; stdK is based on average peak concentration. All include diffusion, convection, and renal clearance.

2.1. Statistical Methods. Continuous variables are expressed as means with standard deviations (SD) and minimum and maximum values. Categorical variables are expressed as percentages.

Univariate and multivariable binary logistic regression analyses were performed to identify variables associated with death. Variables with a univariate *p* value < 0.10 were entered into the multivariable models. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported.

Linear regression analysis was used to evaluate the interaction of dialysis dose and nPCR (Figure 1) and the material was split into two groups on the basis of EKR/V and nPCR (Table 3).

SPSS 22.0 and STATA 13.1 were used in statistical calculations. The graph was drawn with Excel 2007.

3. Results

The overall mortality was 140 per 1,000 patient years. The main results are shown in Table 1. Mortality was significantly associated only with EKR/V and nEKR. In multivariable analysis, EKR/V was the only variable having an association with death risk (OR = 0.326, CI = 0.117–0.912, and *p* = 0.033).

Figure 1 illustrates the linear regression between nPCR and EKR/V. To eliminate the confounding effect of nPCR

on the dose-mortality relationship, the material was split into two groups with approximately equal mean nPCR but different mean EKR/V. The line separating the groups is depicted in Figure 1. Table 3 shows that the difference in mortality between the low and high dose groups is still significant.

Men had lower nPCR, EKR/V, and stdK/V and higher mortality than women (Table 4). Diabetics had higher weight, BMI, and BSA but did not differ significantly from nondiabetics in mortality (Table 5).

Correlations between some patient characteristics and continuous-equivalent clearances are shown in Table 6. All clearances correlate with each other.

4. Discussion

The association of six continuous-equivalent urea clearance measures with death risk was evaluated by statistical analysis. The most significant predictor in univariate analysis and the only significant one in multivariable analysis was EKR/V, calculated from TAC (*p* = 0.033). The *p* value of stdK/V (from PAC) was 0.059. In the old NCDS, TAC had a closer correlation with outcome than PAC [25]. The stdK concept is compliant with the peak concentration hypothesis [26], not supported by the present results.

Normalizing with BSA was tested by the variables nEKR and nstdK, with mL/min/1.73 m² (or L/week/1.73 m²) as their unit. nEKR was significantly associated with death risk, but nstdK was not. In the present study, K_d was derived from Q_b, Q_d, and K_{0A} reported by the dialyzer manufacturer.

TABLE 4: Dialysis treatment periods by gender.

		Women		Men		<i>p</i> value
		Mean	SD	Mean	SD	
Age	Years	63.3	14.5	60.6	16.1	0.529
Weight	kg	65.2	15.3	81.2	17.4	0.001
BMI	kg/m ²	25.7	5.9	26.3	5.3	0.694
BSA	m ²	1.66	0.17	1.95	0.22	<0.001
V	L	26.1	3.6	35.3	5.7	<0.001
nPCR	g/kg/day	1.23	0.23	1.10	0.24	0.043
nK _r	mL/min/1.73 m ²	1.9	1.4	1.6	1.4	0.467
nEKR	mL/min/1.73 m ²	12.4	1.1	12.7	1.5	0.401
nstdK	mL/min/1.73 m ²	8.2	0.7	8.7	1.1	0.066
nEKRAnt	mL/min/1.73 m ²	14.8	1.9	15.4	2.6	0.349
nstdKAnt	mL/min/1.73 m ²	9.8	1.2	10.5	1.7	0.082
EKR/V	/week	4.64	0.57	4.17	0.62	0.005
stdK/V	/week	3.07	0.36	2.85	0.39	0.036
Treatment periods	<i>n</i>	22		35		
Ending with death	%	13.6		37.1		0.055
Patient years	<i>n</i>	50.6		63.7		
Deaths	<i>n</i>	3		13		
Mortality	/1000 py	59		204		0.040

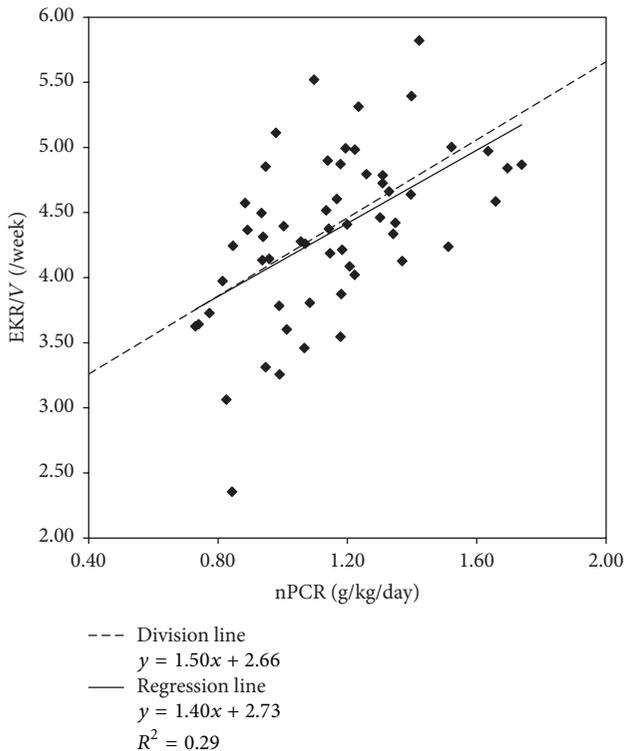


FIGURE 1: Linear regression between nPCR and dialysis dose (EKR/V) and the line separating the groups of Table 3.

Calculated with Michaels' equation [24], a 50% error in K_0A causes an error of some 10% in K_d with usual Q_b and Q_d . Errors in K_d cause in UKM proportional errors in V and G .

In EKR/V and stdK/V, the errors cancel each other out, but not in nEKR and nstdK.

Two other BSA-normalized continuous-equivalent clearances nEKRAnt and nstdKAnt were calculated applying the method of Daugirdas et al. described in the Appendix [9, 27]. The anthropometric total body water is usually larger compared to the kinetic V . Thus, nEKRAnt and nstdKAnt are higher than the simple BSA-normalized values. They are UKM-based continuous-equivalent hemodialysis dose measures, where the possible errors in K_d are eliminated, normalized with two anthropometric measures of body size and with mL/min/1.73 m² as unit. However, normalizing with BSA with either method did not improve the predictive value of EKR/V and stdK/V.

In the HEMO trial, the age-adjusted mortality did not differ significantly between genders, but women did benefit from higher dose [28]. In the present study, women had lower mortality and got higher EKR/V and stdK/V but slightly lower BSA-normalized doses (Table 4). Comorbidity other than diabetes was not analyzed.

The rather wide range of dialysis doses in the present study is probably due to the opportunistic aspect: more may be better, but with large patients it is not easy to achieve a high dose (Table 6). In Table 3, the distribution volume and the proportion of men were higher in the low dose group. Men had higher mortality and volume and lower V -scaled dialysis dose (Table 4).

The patient characteristics and dialysis dose measures have multiple correlations or dependencies (Table 6). Figure 1 shows the linear regression between nPCR and EKR/V. PCR is a function of EKR/V or stdK/V ((B.3) and (B.4) in Appendix). Thus, mathematical coupling is inevitable. It is also possible that nPCR depends on the dialysis dose

TABLE 5: Dialysis treatment periods by diabetic status.

		Diabetes				<i>p</i> value
		Yes	SD	No	SD	
Age	Years	Mean	SD	Mean	SD	
Weight	kg	61.2	14.9	62.0	16.1	0.842
BMI	kg/m ²	81.7	18.5	70.2	16.7	0.018
BSA	m ²	28.1	6.3	24.6	4.4	0.016
V	L	1.92	0.22	1.78	0.25	0.037
nPCR	g/kg/day	32.9	6.3	30.9	6.9	0.260
nK _t	mL/min/1.73 m ²	1.16	0.23	1.14	0.26	0.739
nEKR	mL/min/1.73 m ²	1.5	1.0	1.9	1.6	0.243
nstdK	mL/min/1.73 m ²	12.7	0.9	12.4	1.6	0.356
nEKRant	mL/min/1.73 m ²	8.6	0.8	8.4	1.1	0.350
nstdKant	mL/min/1.73 m ²	15.8	1.9	14.6	2.5	0.055
EKR/V	/week	10.7	1.3	9.9	1.7	0.047
stdK/V	/week	4.43	0.47	4.29	0.74	0.427
Treatment periods	<i>n</i>	2.99	0.27	2.89	0.46	0.360
Ending with death	%	24		33		
Patient years	<i>n</i>	25.0		30.3		0.660
Deaths	<i>n</i>	54.3		60.0		
Mortality	/1000 py	6		10		
		110		167		0.439

TABLE 6: Spearman’s correlations, significant at the 0.01 level (2-tailed).

	Weight	BMI	BSA	V	nPCR	nEKR	nstdK	nEKRant	nstdKant	EKR/V	stdK/V
Weight	1	0.854	0.950	0.748			0.352	0.453	0.530		
BMI	0.854	1	0.658	0.455				0.393	0.427		
BSA	0.950	0.658	1	0.817			0.364	0.430	0.521		
V	0.748	0.455	0.817	1			0.436			-0.475	-0.354
nPCR					1			0.493	0.519	0.535	0.609
nEKR						1	0.929	0.694	0.711	0.566	0.631
nstdK	0.352		0.364	0.436		0.929	1	0.569	0.686	0.351	0.509
nEKRant	0.453	0.393	0.430		0.493	0.694	0.569	1	0.962	0.821	0.850
nstdKant	0.530	0.427	0.521		0.519	0.711	0.686	0.962	1	0.706	0.809
EKR/V				-0.475	0.535	0.566	0.351	0.821	0.706	1	0.961
stdK/V				-0.354	0.609	0.631	0.509	0.850	0.809	0.961	1

(causality) or that dosing of dialysis is guided by urea concentrations or adjusted for protein catabolic rate [29] as recommended by Gotch et al. [12, 30, 31] (reverse causality). All these factors may have a role in the present study, but their separate contribution could not be specified. In the HEMO trial, the effect of dose on nPCR and the role of mathematical coupling were estimated to be small [32].

PCR reflects dietary protein intake, which correlates with nutritional status and outcome [33]. In a recent large registry material mortality decreased with increasing nPCR until 1.3 g/kg/day [34]. Table 3 shows that in the present study EKR/V had a significant association with mortality, although nPCR was slightly higher in the low EKR/V group. nPCR is associated with mortality directly and with the dialysis dose through the “fear of high urea concentrations” effect—an example of the mechanisms possibly underlying the dose-targeting bias [35]. nPCR and dialysis dose may have a synergistic effect on survival.

A limitation of the present study is the small number of patients, which prevents robust conclusions. On the other hand, different dosing definitions were compared in the same material—a response to the challenge presented by Debowska et al. [36].

In summary, EKR/V and nEKR were significantly associated with mortality but stdK/V and nstdK were not. Normalizing with BSA [9, 37] did not improve the significance of the ECC measures.

Appendix

A. Continuous-Equivalent Clearance (ECC)

EKR (ECC_{TA}) and stdK (ECC_{PA}) are based on the definition of clearance (K):

$$K = \frac{E}{C}. \tag{A.1}$$

In steady state, the removal rate (E) equals the generation rate (G), and thus

$$K = \frac{G}{C}. \quad (\text{A.2})$$

In EKR, C is the time-average concentration (TAC) and, in stdK, it is the average predialysis concentration (peak average concentration, PAC):

$$\text{EKR} = \frac{G}{\text{TAC}}, \quad (\text{A.3})$$

$$\text{stdK} = \frac{G}{\text{PAC}}. \quad (\text{A.4})$$

The unit is, for example, mL/min or L/week. Both may be scaled to body size by dividing by urea distribution volume V and expressed as EKR/V and stdK/V :

$$\text{EKR}/V = \frac{\text{EKR}}{V}, \quad (\text{A.5})$$

$$\text{stdK}/V = \frac{\text{stdK}}{V}. \quad (\text{A.6})$$

G , V , TAC, and PAC are determined by kinetic modeling, in the present study with Solute-Solver. TAC and PAC are whole-body water concentrations and V is the postdialysis total volume V_t . The most practical unit of EKR/V and stdK/V is /week.

$n\text{EKR}$ and $n\text{stdK}$ are ECC values (ECC_{TA} and ECC_{PA}) normalized with body surface area analogically to glomerular filtration rate or renal clearance, with mL/min/1.73 m² as the unit:

$$n\text{EKR} = \frac{\text{EKR}}{\text{BSA}} * 1.73, \quad (\text{A.7})$$

$$n\text{stdK} = \frac{\text{stdK}}{\text{BSA}} * 1.73.$$

Daugirdas et al. have developed a method to get a BSA-normalized $\text{stdK}t/V$ [9, 27]:

$$\text{SAn-stdK}t/V = \text{stdK}t/V * \frac{\text{Vant}}{\text{BSA} * 20}, \quad (\text{A.8})$$

where Vant is anthropometric TBW in liters, BSA is in m², and the constant 20 is the mean of V/BSA (L/m²) in their material. Similarly, $n\text{EKRant}$ and $n\text{stdKant}$ can be calculated by using a combined anthropometric scaling factor Vant/BSA (=TBW/BSA):

$$n\text{EKRant} = \text{EKR}/V * \frac{\text{Vant}}{\text{BSA}} * 1.73, \quad (\text{A.9})$$

$$n\text{stdKant} = \text{stdK}/V * \frac{\text{Vant}}{\text{BSA}} * 1.73, \quad (\text{A.10})$$

with appropriate unit conversion factors. Vant/BSA takes gender into account. In the present material, its average value was 18.7 (18.3–20.3) L/m² for women and 21.9 (20.2–24.5) L/m² for men.

B. nPCR

By definition (see (A.4) and (A.6)),

$$G = \text{stdK}/V * \text{PAC} * V. \quad (\text{B.1})$$

In hemodialysis, nPCR is generally calculated by the Borah equation [38] with Sargent's modification [39]:

$$n\text{PCR} = \frac{(9.35 * G + 0.294 * V)}{(V/0.58)}, \quad (\text{B.2})$$

where nPCR is expressed in g/kg/day, G is expressed in milligrams of urea-N/min, and V is expressed in L. By substituting G from (B.1) and using appropriate unit conversion factors we get

$$n\text{PCR} = 0.0151 * \text{stdK}/V * \text{PAC} + 0.171, \quad (\text{B.3})$$

where nPCR is in g/kg/day, stdK/V is in /week, and PAC is in mmol/L. V will be eliminated. nPCR is high if concentration (PAC) is high despite high or normal clearance (stdK/V). stdK/V and PAC can be substituted with EKR/V and TAC:

$$n\text{PCR} = 0.0151 * \text{EKR}/V * \text{TAC} + 0.171. \quad (\text{B.4})$$

nPCR is inevitably correlated with stdK/V and EKR/V . The body surface area-normalized ECC measures are not so closely associated with nPCR.

Abbreviations

BMI:	Body mass index = weight/height ²
BSA:	Body surface area
C:	Concentration
ECC:	Continuous-equivalent clearance
EKR:	Equivalent renal clearance = G/TAC
EKR/V :	EKR scaled to V
eKt/V :	Equilibrated Kt/V
fr:	Dialysis session frequency
G :	Generation rate
K_d :	Dialyzer clearance
K_r :	Renal clearance
K_0A :	Dialyzer mass area coefficient
Kt :	Clearance * session time
Kt/V :	Kt scaled to distribution volume = $K_d * t_d/V_t$
nEKR:	EKR normalized with BSA (mL/min/1.73 m ²)
nEKRant:	EKR normalized with BSA and Vant (mL/min/1.73 m ²)
nK_r :	K_r normalized with BSA (mL/min/1.73 m ²)
nstdK:	stdK normalized with BSA (mL/min/1.73 m ²)
nstdKant:	stdK normalized with BSA and Vant (mL/min/1.73 m ²)
nPCR:	PCR scaled to normal body weight = $\text{PCR}/(V/0.58)$ (g/kg/day)

PAC:	Average predialysis concentration, peak average concentration
PCR:	Protein catabolic rate (g/day)
py:	Patient years
Q_b :	Dialyzer blood flow
Q_d :	Dialysate flow
RRF:	Residual renal function
spKt/V:	Single pool Kt/V
stdK:	Standard clearance = G/PAC
stdK/V:	stdK scaled to V
TAC:	Time-averaged concentration
TBW:	Total body water (Watson) = Vant
t_d :	Dialysis session duration
UF:	Ultrafiltration volume (positive, if fluid is removed)
UKM:	Urea kinetic model
V:	Distribution volume
Vant:	Anthropometric V = TBW
V_t :	Postdialysis V.

Ethical Approval

The study was based on an analysis of register data collected and utilized during the routine care of patients and conducted with the permission of the medical director of the hospital. There was no control group or randomization. The study was not presented to an ethics committee because there were no interventions and, according to Finnish law, registry reports are not subject to evaluation by ethics committees. The patient data were anonymized and deidentified prior to analysis.

Competing Interests

The authors declare that they have no competing interests.

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