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Ultrafiltration rate and diabetes as useful indicators of cardiovascular-related death in hemodialysis patients below 60 years of age*

Wskaźnik ultrafiltracji i cukrzyca jako użyteczne czynniki predykcyjne zgonów z przyczyn sercowo-naczyniowych u chorych hemodializowanych poniżej 60 roku życia

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: The survival rate of elderly hemodialyzed (HD) patients is commonly thought to be poor. In a prospective, single center, non-interventional, observational study, the cause of all-cause and cardiovascular (CV) and heart failure (HF) mortality in this patient group were examined and compared with a younger cohort (below 60 years).

Material/Methods: The study included 223 patients (90 women and 133 men) with age ranging from 34.5 to 75.0 years treated with HD. Median duration of HD was 70.0 months (24.0-120.0). Mortality data was collected over a period of six years. We divided patients into groups: <60 (n=123), ≥60 years (n=100), and with (n=33) and without DM type 2 (n=190).

Results: During a six-year follow-up, 100 patients (44.8%) died, including 83 (37.2%) patients who died due to CV reasons. Median follow-up was 2015.0 days (946.0-2463.0) with the median time to death of 1166.0 days (654.5-1631.0). The factors negatively affecting patients' survival in univariate Cox regression analysis included for all-cause mortality were: inter-dialytic weight gain (IDWG) (hazard ratio [HR]=1.60; p=0.01), ultrafiltration (UF) rate (HR=3.63; p=0.012) for group <60 years; for CV death: UF rate (HR=4.20; p=0.03), DM (HR=5.11; p=0.002) for group <60 years; for HF death: mellitus type 2 (DM) (HR=2.93; p=0.027) for group ≥60 years). In a multivariate Cox regression analysis for patients <60 years, the UF rate was the only independent predictor of all-cause mortality (HR 3.63 (1.34-9.67); p=0.011). Both DM (HR 4.91 (1.71-14.10); p=0.003) and UF rate (HR 3.62 (1.04-12.61); p=0.044) were independent predictors of CV-related mortality in patients <60 years.

Conclusions: The UF rate can be a simple, useful indicator of higher long-term all-cause and CV mortality in HD patients <60 years of age. Also, DM may be a predictor of CV–related mortality in younger HD patients.

Keywords: all-cause mortality • cardiovascular mortality • hemodialysis • diabetes • ultrafiltration rate

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Introduction

In hemodialyzed (HD) patients, high interdialytic weight gain (IDWG), a high ultrafiltration rate (UFR), and short session duration have been associated with poor outcomes [16]. The major causes of death are cardiovascular (CV) and infectious [17,27]. CV complications are related to coronary artery disease, congestive heart failure (HF), arrhythmias and sudden cardiac death (SCD) [3,11]. In the study by Go et al. [11], the risk of adverse CV events was 43% higher in patients with an estimated glomerular filtration rate (eGFR) between 45 and 59 ml/min and 343% higher in those with end stage renal disease (ESRD) as compared to the control group with a normal GFR. The presence of either baseline or progressive left ventricular hypertrophy (LVH) is strongly associated with adverse outcomes.

To prevent volume overload (hypertension, LVH) and to maintain the fluid balance, even 5-6 liters of fluid have to be removed during each HD session. Rapid fluid removal or ultrafiltration (UF) during a short period of time can lead to intradialytic hypotension (IDH) in 25-50% of patients [10]. Moreover, IDH has been associated with myocardial stunning, cerebral atrophy as well as an increased risk for coronary and cerebral ischemic events, and vascular access thrombosis. Also, it is a major cause of morbidity in elderly HD patients and those with CV complications [10,20]. The impact of HD parameters on outcomes in younger patients is less established.

HD patients with diabetes mellitus (DM) have higher rates of several comorbidities and experience poorer clinical outcomes compared with patients without DM [18]. In a study conducted by Rhee et al. [24] higher HbA1C levels were significantly associated with higher rates of CV mortality and MI in a large cohort of HD patients with DM. Increased mortality and morbidity are reported in association with high UFR, IDWG, with long dialysis recovery time and diabetes [16,18,22,33]. However, the association between parameters of HD session in patient group above and below 60 years and in DM patients and without DM has not been studied yet.

The aim of the our prospective, observational study was to assess the effect of HD parameters: IDWG, UF rate, dry weight, duration of the dialysis session, blood flow, HD vintage and age, DM on all-cause, CV- and HF- related mortality in HD patients <60 years of age during six-year follow-up.

Materials and Methods

The study included 223 patients (90 female and 133 male), age from 34.5 to 75.0 years, treated with long-term regular thrice-weekly HD for at least six months due to CKD. Patients with stroke, myocardial infarction (MI) or limb ischemia in the previous six months or who had chronic atrial fibrillation or morbid obesity (body mass index >40 kg/m^2) were excluded. Then patients were prospectively followed for six years and the data on all-cause, CV- and HF-related mortality was collected. Patients who received a kidney transplant during the observation period were only followed up to successful treatment. CV mortality was defined as death due to MI or stroke. HF-related mortality was defined as death related only to HF. The date and cause of death was determined based on patients' hospital records. The researcher who collected the mortality data was blinded to the results of laboratory tests and clinical data.

Clinical data

The following variables were collected at baseline: age, sex, CKD patients with diagnosis of type 2 DM and without DM, HD parameters: IDWG between HD session, UF rate, dry weight, duration of the dialysis session, blood flow and HD vintage.

The UF rate is the rate of volume removal at dialysis, expressed in ml/h/kg body weight, measured by the weight change per duration of HD treatment using the post HD weight as a denominator. The value of UF rate used in the analysis was the mean UF rate for each patient over the first 12 months of the study.

Dry weight was clinically determined using the standard protocol and reflects the lowest weight the patient can tolerate without intradialytic symptoms and hypotension in the absence of overt fluid overload and was modified by the attending doctor as needed.

Blood flows were the mean values for each patient over the first 12 months of the study.

Absolute IDWG was abstracted from patients' history documentation and was defined as predialysis weight from one treatment minus postdialysis weight from the prior treatment, which represents fluid accumulation between dialysis treatments (1 kg weight gain equals approximately 1 liter fluid accumulated). The value of IDWG used in the analysis was the mean IDWG for each patient over the first 12 months of the study. Relative IDWG was calculated as a percentage of postdialysis weight. It described the amount of fluid accumulated between dialysis treatments as a function of the patient's body size. Median duration of HD was 70.0 (24.0-120.0) months.

The study was approved by the Bioethics Committee of the Jagiellonian University and all patients signed an informed consent for their participation.

Statistical methods

Results were presented as numbers (percentages) of patients or medians (inter-quartile range) where applicable. Differences between groups were tested using the chi-square test and Fisher's exact test for dichotomous variables and the Mann–Whitney U test or the Kruskal-Wallis test for continuous variables. Survival curves were computed using the Kaplan–Meier method. Associations between clinical/HD-related factors and all-cause, CV, HF-related death during follow-up were estimated using univariate Cox regression analysis. In addition, multivariate Cox proportional hazard regression analysis was performed to find independent predictors of all-cause, CV, and HF-related death. Forward selection with a probability value for covariates to enter the model was set at the 0.05 level. The following covariates were tested: gender, presence of diabetes mellitus, HD-related factors (IDWG, relative IDWG, UF rate, duration of HD session, blood flow, HD vintage). Analysis was conducted separately for patients aged <60 years and ≥60 years. Results of univariate and multivariate analyses were presented as hazard ratios (HR) with 95% confidence intervals [95%CI].

In addition, the risk of all-cause, CV and HF-related death in patients with vs. without DM was presented as odds ratios (OR) with 95%CI. The Breslow-Day test was used to compare the homogeneity of the ORs between age groups.

All tests were two tailed and a p value of <0.05 was considered to be statistically significant.

All statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics and HD parameters are presented in Table 1.

During a six-year follow-up, 100 patients (44.8%) died, including 83 (37.2%) patients who died due to CV causes in 64 (28.7%) patients and 19 (8.5%) patients who died due to HF (Table 2). The median follow-up was 2015.0 days (946.0-2463.0) with the median time to death of 1166.0 days (654.5-1631.0). The median time to kidney transplantation was 978.5 days (452.5-1735.0).

We divided patients into groups according to age: <60 (n=123), >60 years (n=100), and according to DM presence: with (n=33) and without DM (n=190). The factors negatively affecting patients' survival in univariate Cox regression included: for all-cause mortality: the IDWG (HR=1.60; p=0.01), UF rate (HR=3.63; p=0.012) for group <60 years (Table 3); for CV death: UF rate (HR=4.20; p=0.03), DM (HR=5.11; p=0.002) for group <60 years

Table 1. Study group characteristics

Variable	Maintained HD patients (n=91)	Patients who died (n=100)	P value*
Male	49 (53.8%)	61 (61.0%)	0.38
Age [years]	55.0 (47.5-63.5)	66.0 (55.5-75.0)	<0.001
Age ≥60 years	29 (31.9%)	68 (68.0%)	<0.001
DM	11 (12.1%)	20 (20.0%)	0.17
Dry weight [kg]	65.0 (54.5-74.5)	62.5 (55.3-72.8)	0.60
IDWG [kg]	3.4 (2.7-3.9)	3.3 (2.8-4.0)	0.55
Relative IDWG [%]	5.2 (4.2-6.1)	5.3 (4.4-6.4)	0.72
UF rate [mL/kg/h]	1.3 (1.0-1.5)	1.3 (1.1-1.6)	0.33
Duration of the dialysis session [minutes]	240.0	240.0 (210.0-240.0)	0.29
Blood flow [mL/min]	250.0	250.0 (250.0-250.0)	0.25
HD vintage [months]	70.0 (24.0-120.0)	43.5 (20.0-120.0)	0.14

HD- hemodialysis, DM- diabetes mellitus, KTx- kidney transplant, UF- ultrafiltration, IDWG- inter-dialytic weight gain; *Values are presented as numbers (percentages) or medians (inter-quartile range)

Table 2. Mortality

	All (n=223)	Age <60 (n=123)	Age ≥60 (n=100)	p value	DM (-) (n=190)	DM (+) (n=33)	p value
All cause	100 (44.8%)	32 (26.0%)	68 (68.0%)	<0.001*	80 (42.1%)	20 (60.6%)	0.049
CV	64 (28.7%)	17 (13.8%)	47 (47.0%)	<0.001*	47 (24.7%)	17 (51.5%)	0.002
HF	19 (8.5%)	2 (1.6%)	17 (17.0%)	<0.001*	9 (4.7%)	10 (30.3%)	<0.001*

CV- cardiovascular, HF-heart failure, DM-diabetes mellitus; * differences statistically significant

Table 3. Univariate Cox regression analysis for all-cause death

Variable	All (n=223)		Age <60 years (n=123)		Age ≥60 years (n=100)		DM (-) (n=190)		DM (+) (n=33)	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Male vs. female	1.17 (0.78-1.75)	0.44	1.21 (0.60-2.44)	0.59	0.92 (0.56-1.51)	0.75	1.31 (0.83-2.07)	0.25	0.77 (0.32-1.86)	0.56
Age (per 1 year)	1.06 (1.04-1.07)	<0.001*	1.04 (1.00-1.09)	0.08	1.07 (1.03-1.10)	<0.001*	1.07 (1.05-1.09)	<0.001*	1.02 (0.98-1.05)	0.34
Age ≥60 vs. <60 years	3.17 (2.08-4.83)	<0.001*	-	-	-	-	3.69 (2.32-5.87)	<0.001*	1.22 (0.44-3.36)	0.70
DM vs. no DM	1.40 (0.86-2.29)	0.18	2.43 (0.93-6.31)	0.07	0.78 (0.44-1.38)	0.38	-	-	-	-
Dry Weight [kg]	1.00 (0.98-1.01)	0.53	0.99 (0.97-1.03)	0.96	0.99 (0.97-1.00)	0.12	0.99 (0.98-1.01)	0.39	1.00 (0.96-1.03)	0.79
IDWG [kg]	1.04 (0.85-1.27)	0.73	1.60 (1.11-2.31)	0.012*	0.88 (0.69-1.13)	0.31	1.07 (0.85-1.35)	0.57	0.92 (0.62-1.38)	0.69
Relative IDWG [%]	1.00 (1.00-1.00)	0.75	0.99 (0.99-1.01)	0.74	1.01 (0.86-1.19)	0.90	1.00 (0.99-1.01)	0.74	0.99 (0.74-1.32)	0.94
UF rate [mL/kg/h]	1.50 (0.90-2.52)	0.12	3.63 (1.34-9.87)	0.011*	1.26 (0.69-2.30)	0.46	1.55 (0.86-2.78)	0.15	1.32 (0.45-3.87)	0.62
Duration of the dialysis session [minutes]	1.00 (0.99-1.00)	0.21	1.01 (0.99-1.02)	0.36	0.99 (0.99-1.00)	0.10	1.00 (0.99-1.01)	0.55	0.99 (0.98-1.01)	0.35
Blood flow [mL/min]	0.99 (0.98-1.00)	0.28	1.00 (0.99-1.02)	0.61	0.98 (0.97-1.00)	0.040*	1.00 (0.99-1.01)	0.50	0.98 (0.95-1.02)	0.34
HD period [month]	1.00 (1.00-1.00)	0.28	1.00 (0.99-1.00)	0.22	1.00 (1.00-1.00)	0.72	1.00 (1.00-1.00)	0.73	0.99 (0.97-1.01)	0.17

HD- hemodialysis, DM- diabetes mellitus, UF- ultrafiltration, IDWG- inter-dialytic weight gain; *p<0.05; data presented as hazard ratio (HR) with 95% confidence interval (95%CI)

(Table 4); for HF death: DM (HR=2.93; p=0.027) for group ≥60 years (Table 5). In multivariate Cox regression analysis for patients <60 years, UF rate was the only independent predictor of all-cause mortality (HR 3.63 (1.34-9.67); p=0.011). Both DM (HR 4.91 (1.71-14.10); p=0.003) and UF rate (HR 3.62 (1.04-12.61); p=0.044) were predictors of CV-related death in HD patients <60 years.

However, in the overall population age ≥60 years was the only independent predictor of all-cause (HR 3.37 (2.21-5.14); p<0.001) and CV mortality (HR 4.40 (2.52-7.67); p<0.001). On the other hand, age ≥60 years (HR 10.09 (2.28-44.63), p=0.002), DM (HR 4.33 (1.72-10.87), p=0.002) and IDWG (HR 0.54 (0.31-0.93), p=0.026) were independently associated with HF-related death.

Kaplan-Meier survival curves stratified by age group and DM status for all-cause, CV and HF-related mortality are presented in Figures 1 and 2 respectively. The crude rates of all-cause, CV- and HF-related mortality stratified by age and DM status is shown in Figure 3. A significant interaction between age group and impact of DM on mortality was confirmed only for CV death. DM increases the risk of CV mortality only in the sub-

Table 4. Univaria te Cox regression analysis for CV death

	All (n=223)		Age <60 years (n=123)		Age ≥60 years (n=100)		DM (-) (n=190)		DM (+) (n=33)	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Male vs. female	0.96 (0.58-1.57)	0.86	1.03 (0.40-2.66)	0.96	0.73 (0.41-1.30)	0.28	1.08 (0.61-1.94)	0.79	0.69 (0.27-1.80)	0.45
Age, years	1.07 (1.05-1.09)	<0.001*	1.04 (0.98-1.11)	0.18	1.09 (1.05-1.14)	<0.001*	1.09 (1.06-1.12)	<0.001*	1.01 (0.98-1.05)	0.43
Age ≥60 years	4.07 (2.34-7.10)	<0.001*	-	-	-	-	5.40 (2.80-10.41)	<0.001*	0.98 (0.35-2.79)	0.97
DM vs. no DM	2.01 (1.15-3.50)	0.014*	5.11 (1.80-14.54)	0.002*	0.93 (0.48-1.80)	0.83	-	-	-	-
Dry weight [%]	0.99 (0.97-1.01)	0.38	1.00 (0.96-1.04)	0.96	0.98 (0.96-1.00)	0.08	0.99 (0.97-1.01)	0.27	0.99 (0.96-1.03)	0.57
IDWG [kg]	0.99 (0.77-1.28)	0.95	1.57 (0.95-2.59)	0.08	0.87 (0.65-1.17)	0.35	0.96 (0.71-1.30)	0.80	1.04 (0.69-1.56)	0.86
Relative IDWG [%]	1.00 (0.98-1.01)	0.81	1.00 (0.99-1.01)	0.82	1.04 (0.86-1.25)	0.69	1.00 (0.98-1.02)	0.84	1.11 (0.82-1.50)	0.49
UF rate [mL/kg/h]	1.71 (0.91-3.23)	0.10	4.20 (1.09-16.19)	0.037*	1.54 (0.77-3.07)	0.22	1.60 (0.75-3.39)	0.23	1.91 (0.60-6.03)	0.27
Duration of the dialysis session [minutes]	0.99 (0.98-1.00)	0.024*	1.00 (0.98-1.02)	0.82	0.99 (0.98-0.99)	0.035*	0.99 (0.98-1.00)	0.07	1.00 (0.98-1.01)	0.58
Blood flow [mL/min]	0.99 (0.98-1.01)	0.26	1.00 (0.97-1.02)	0.77	0.99 (0.97-1.00)	0.12	1.00 (0.98-1.01)	0.50	0.99 (0.95-1.02)	0.44
HD period [months]	1.00 (1.00-1.00)	0.42	1.00 (0.99-1.01)	0.44	1.00 (1.00-1.01)	0.77	1.00 (1.00-1.01)	0.76	0.99 (0.97-1.01)	0.21

HD- hemodialysis, DM- diabetes mellitus, UF- ultrafiltration, IDWG- inter-dialytic weight gain; *p<0.05; data presented as hazard ratio (HR) with 95% confidence interval (95% CI)

Table 5. Univariate Cox regression analysis for HF death

	All (n=223)		Age <60 years (n=123)		Age ≥60 years (n=100)		DM (-) (n=190)		DM (+) (n=33)	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Male vs. female	0.86 (0.28-1.67)	0.40	0.96 (0.06-15.44)	0.98	0.48 (0.18-1.23)	0.13	0.59 (0.16-2.21)	0.44	0.77 (0.22-2.66)	0.68
Age, years	1.15 (1.09-1.21)	<0.001*	1.08 (0.86-1.35)	0.50	1.17 (1.09-1.26)	<0.001*	1.20 (1.11-1.30)	<0.001*	1.05 (0.99-1.12)	0.11
Age ≥60 years	12.81 (2.96-55.48)	0.001*	-	-	-	-	15.23 (1.90-122.00)	0.010*	3.63 (0.46-28.66)	0.22
DM vs. no DM	6.05 (2.46-14.90)	<0.001*	12.20 (0.76-196.89)	0.08	2.93 (1.13-7.59)	0.027*	-	-	-	-
Dry weight [kg]	0.97 (0.93-1.00)	0.08	0.83 (0.66-1.04)	0.11	0.97 (0.93-1.00)	0.08	0.94 (0.88-1.00)	0.046*	0.97 (0.92-1.02)	0.21
IDWG [kg]	0.58 (0.36-0.94)	0.027*	0.34 (0.08-1.50)	0.16	0.64 (0.38-1.07)	0.09	0.40 (0.19-0.82)	0.013*	0.81 (0.45-1.47)	0.49
Relative IDWG [%]	0.85 (0.63-1.14)	027	0.89 (0.37-2.14)	0.79	0.93 (0.66-1.29)	0.65	0.77 (0.50-1.19)	0.24	1.03 (0.69-1.53)	0.89
UF rate [mL/kg/h]	1.25 (0.38-4.10)	0.72	5.80 (0.11-299.45)	0.38	1.34 (0.41-4.39)	0.63	0.71 (0.12-4.35)	0.71	1.82 (0.40-8.25)	0.44
Duration of the dialysis session [minutes]	0.98 (0.96-0.99)	0.002*	0.96 (0.92-1.01)	0.13	0.98 (0.97-1.00)	0.015*	0.97 (0.95-0.99)	0.014*	0.99 (0.97-1.01)	0.42
Blood flow [mL/min]	0.98 (0.96-1.01)	0.18	0.98 (0.92-1.05)	0.56	0.97 (0.93-1.01)	0.15	0.98 (0.95-1.02)	0.28	0.99 (0.95-1.04)	0.70
HD period [months]	0.98 (0.97-1.00)	0.012*	0.97 (0.91-1.03)	0.29	0.99 (0.97-1.00)	0.05	0.98 (0.97-1.00)	0.07	1.00 (0.97-1.02)	0.61

HD- hemodialysis, DM- diabetes mellitus, UF- ultrafiltration, IDWG- inter-dialytic weight gain, *p<0.05; data presented as hazard ratio (HR) with 95% confidence interval (95%CI)

group of younger patients. HF-related death was higher in patients with than without DM only in patients ≥60 years of age. However, the lack of a significant interaction between age group and impact of DM on HF-death may suggest some harmful effect of DM also in younger patients.

Discussion

In our prospective, observational study 223 HD patients were followed up for six years. We considered factors particularly associated with HD parameters, which may affect mortality in patients <60 years of age. We showed that in HD patients <60 years, the factors negatively affecting mortality are IDWG and UF rate (for all-cause mortality) and UF rate and DM (for CV death). To our knowledge, the association between parameters of HD session in the patient group above and below 60 years and in DM patients and without DM has not been studied yet.

More importantly, most of these parameters are modifiable factors and thus these results may identify possible room for improvement of the prognosis of patients with CKD.

According to earlier reports, CV disorders lead to death in about 46-60% of patients with renal failure treated with HD [31]. CV diseases are the most frequent cause of death in incident (37.9%) and prevalent HD (42.3%) patients. The strongest influence of mortality is exerted by acute MI, congestive heart failure (CHF), arrhythmia, cardiac arrest and cerebrovascular accidents [15]. According to the European Renal Registry [5], patients aged 65-74 years, which is the commonest age group starting dialysis, can expect to live about five years, 50% less than those in the same age group in the general population. For younger dialysis patients, <45 years of age, CV mortality is even higher, exceeding 100 times [15]. The primary cause of CV death in ESRD patients is SCD. According to Dialysis Outcomes and Practice Patterns (DOPPS) SCD constitute 33% of HD deaths in the United

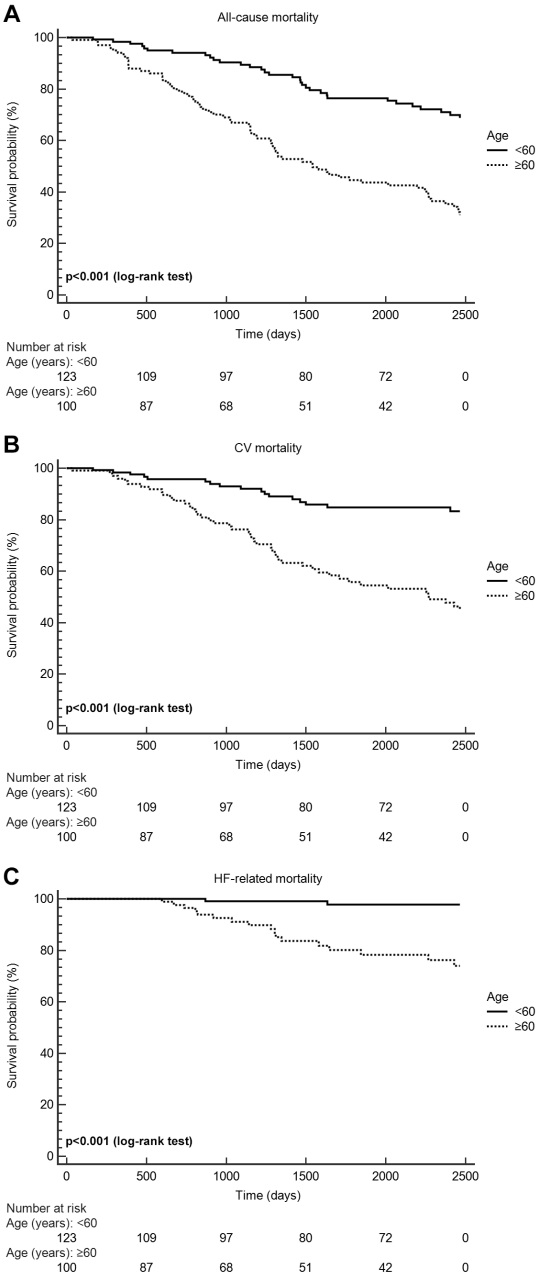

Fig. 1. Kaplan-Meier survival curves by age groups (age <60 years, solid line; age ≥60 years, dotted line) for all-cause death (A), cardiovascular death (B) and heart failure-related death (C)

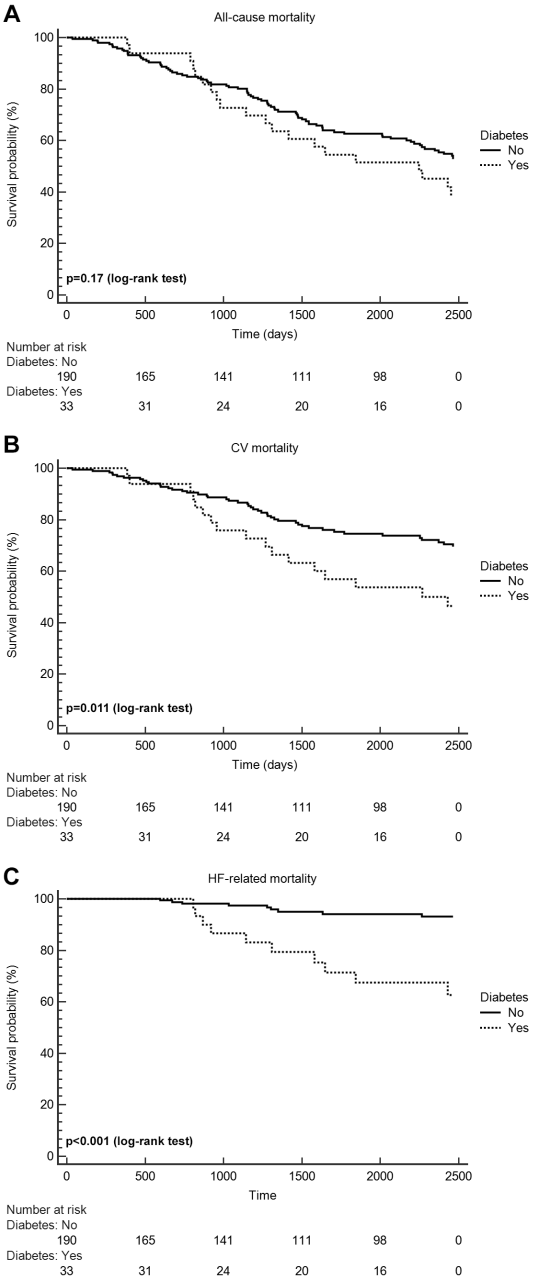

Fig. 2. Kaplan-Meier survival curves by diabetes status (no diabetes mellitus, solid line; diabetes mellitus, dotted line) for all-cause death (A), cardiovascular death (B) and heart failure-related death (C)

States, 23% in Japan, 19% in Australia/New Zealand and 18% in Canada [23]. The lack of SCD in our study is probably related to the incorrect eligibility of SCD in the diagnosis of acute MI. In our study, the median time to death was three years.

In fact, the HD procedure itself has been recognized to induce myocardial stunning and contractile dysfunction, endothelial dysfunction and oxidative stress. Eckard et al. [7], thought that initiation of dialysis triggers CV event. The author has shown that the immediate period following dialysis initiation is a very high CV risk period, characterized by a much higher rate of major CV events than the remainder of the first two years. Incidence rates that were at least three- and up to eight-fold higher than during the second year on dialysis were found for CV events. The first-year CV event rate (30.2/100) greatly exceeded the second-year rate (19.4/100). About one-third of all strokes in dialysis patients were found to occur during or shortly after HD treatment.

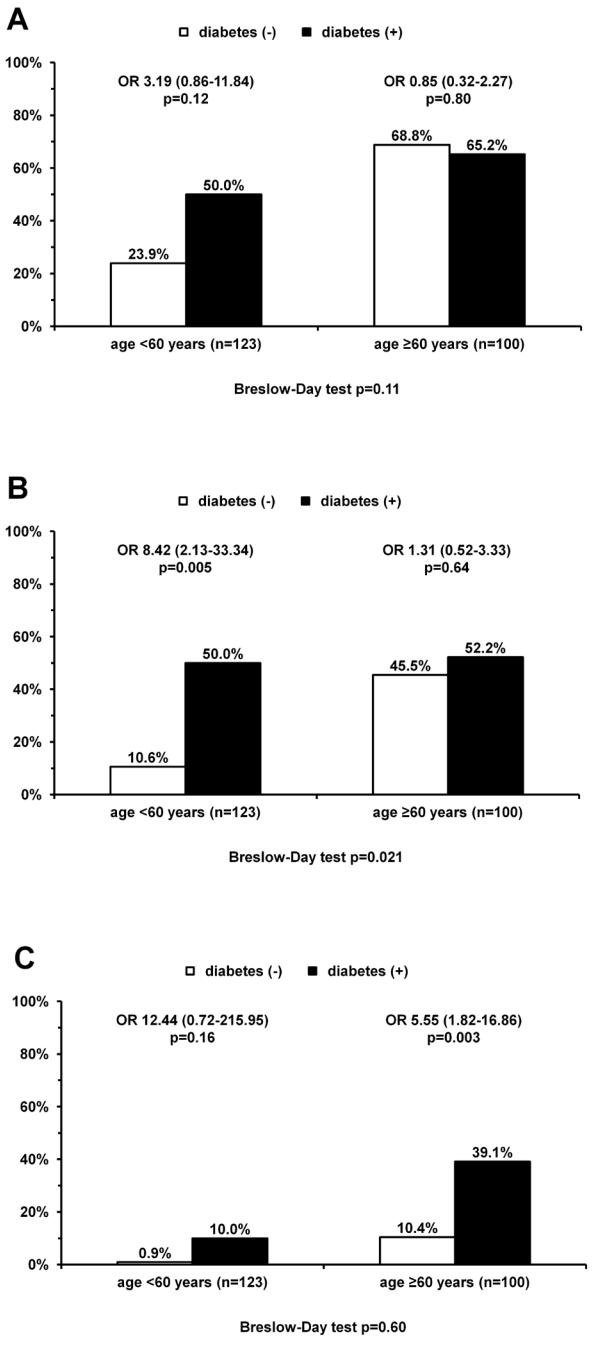

Fig. 3. All-cause (A), cardiovascular (B) and heart failure-related mortality (C) stratified by age and diabetes status

DM is the main cause of initiation renal replacement therapy in the world, and is considered as an independent risk factor for mortality in patients with ESRD. That was confirmed by studies from Schneider et al. [26], who identified more than 27,000 CKD patients with diagnosis of type 2 DM. During nine-year follow-up, 693 patients developed angina pectoris, 1069 CHF, 508 MI, 970 stroke, and 578 transient ischemic attacks. Diabetic patients whose serum creatinine doubled during follow-up had increased risks of CHF, MI, and stroke, as compared with patients whose serum creatinine did not double. Age, diabetes and dialytic age have a strong relationship with the occurrence of CV disease in patients treated with HD [15]. Among HD patients, the observed risk of death from DM is higher as compared to the general population [29]. In patients with DM treated with HD over a twenty-year period a lower survival rate was observed in comparison to patients with glomerulonephritis and adult polycystic kidney disease [28]. Data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) showed that in type 1 DM, HR of death was 1.64 and in type 2 DM it was 1.13 as compared to patients with ESRD but without DM [25,32]. We revealed that DM significantly increases the risk of CV death in patients <60 years of age and HF-related mortality in the subgroup of older patients. Our research presented that DM was an independent predictor of CV-related death in young HD people. Probably, both CV calcification, arterial stiffness and autonomic dysfunction frequently observed in diabetic young HD patients could increase all-cause and CV mortality in this group [25]. Also, high UF rates affect intradialytic hypotension and could be associated with increased mortality [33]

According to earlier reports [21], patients with poor glucose control showed worse survival than patients with HbA1c <8%. A subgroup analysis for patients stratified by age revealed that HbA1c ≥8% was a predictor of mortality in patients from the age <55 and age 55–64 groups but not in the age ≥65 group. In this study, dialysis and age, poor glucose control negatively affected survival only in the age <55 years group among HD patients. Subgroup analysis dividing cases by age revealed that glycemic control was not associated with mortality in patients >65 years old. Similarly, Adler et al. [1] investigated DM patients on HD, and found that HbA1c levels exceeding 8.5% were associated with poorer survival only in patients <60 years of age.

Also, Cea Soriano et al. [3] in a huge cohort of 57,946 patients with type 2 DM showed high overall incidence rates of death (mean follow-up time of 6.76 years), MI (6.64 years) and stroke (6.56 years) - 43.65, 9.26 and 10.39 cases per 1000 person-years, respectively. A CKD stage 4 was associated with an increased risk of death, MI and stroke. Other predictors of death, MI and stroke included age, longer duration of DM, poor control of diabetes, hyperlipidemia, smoking and history of CV events. High UF rates can result in intradialytic hypotension and are associated with increased mortality [22].

Reduced kidney function has been proposed as a risk factor for the deterioration of prevalent HF as well as a risk factor for incident HF [31]. CV events are not only restricted to ESRD; early CKD stages are also associated with variable degrees of HF as underlined in the Atherosclerosis Risk in Communities (ARIC) population study [14]. Statistical analysis found an increase in HF in subjects with an eGFR <60 ml/min/1.73 m^2. Cox regres-

sion analysis demonstrated a relative hazard of incident HF of 1.10 in subjects with a GFR range of 60-89 ml/min/1.73 m^2 and of 1.94 in those with a GFR <60 ml/min/1.73 m^2 [14,31]. CV events and mortality in CKD patients may be related to severity and persistence of LVH, which is typical feature of CKD- related cardiomiopathy. Eccentric or asymmetric LV development up to LV fibrosis can result from activation of the renin-angiotensin system, inhibition of nitric oxide synthesis, intravascular volume expansion, secondary anemia, and the presence of arteriovenous fistulas [6,31].

It is worth noting that our patients had no history of CV events in the previous six months before the start of the study. Foley et al. [9] demonstrated that even HD patients without previous cardiac diseases can develop LVH associated to the time on dialysis. An increased LV mass volume index was observed in 62% of patients after 18 months of incident HD and 49% of them developed overt LV failure. However, Charytan et al. [4] reported that 79-85% of patients beginning dialysis had LVH at the time of inauguration.

In our study, the death of HF has been closely related to age, IDWG and duration of the dialysis session. During a six-year observation period, 19 (8.5%) patients died due to HF, including only 2 patients <60 years and 17 >60 years.

Both volume overload and aggressive fluid removal can induce circulatory stress and multi-organ injury. Cabrera et al. [2] demonstrated that IDWG was associated with higher CV morbidity and mortality. Also, in our study IDWG plays an important role. IDWG and higher net UF during dialysis were associated with all-cause mortality during the observation period in patients under 60 years. A high UF rate during HD is associated with a biochemical evidence of myocardial injury. Flyth et al. [8] showed that higher UF rate (approximately 3.5 liter removed over four-hour HD) was associated with increased risk of CV mortality (HR = 1.71) over against lower UF rate (approximately 2.8 liter removed over four-hour HD) with HR = 1.59. In our study higher UF rate was the independent associated with increased all-cause and CV mortality in younger patients, <60 years of age. Also Mavrakanas et al. [19] showed that high UF, high IDWG, and the duration of the dialysis session, were associated with troponin I elevation and was associated with a higher risk of mortality and major adverse CV events. While high UF rate is closely associated with interdialytic hypotension (IDH), which is a frequent complication of HD and, it is associated with increased CV events. Episodes of IDH result from: a reduction of circulating blood volume due to ultrafiltration, rapid decrease in extracellular osmolality associated with urea and sodium removal and coexisting imbalance between ultrafiltration and fluid refling. Episodes of IDH can be correlated with the presence of CV diseases for example: atherosclerosis, ischemic heart disease, LVH, cardiomyopathy, congestive HF, numerous ventricular arrhythmias and vascular and valvular calcification [12,30]. On the other hand, CV diseases increase the number of episodes of hypotension. A study of Kalanter-Zadeh et al. [13] demonstrated that IDH is related to IDWG, which has been associated with a higher risk of all-cause and CV mortality over the range from 1.0-1.49 to >4.0 kg of fluid weight gain. In another study [2] relative IDWG >3.5 % body weight was independently associated with MI, CV mortality and were consistent among patients with and without DM, and with and without baseline HF. Absolute IDWG >3 kg was associated with outcomes other than MI. On an unadjusted basis, higher absolute IDWG was associated with a greater risk of hospitalization for HF/volume overload. Similarly, significant adjusted associations were observed for all-cause mortality (7 % greater risk), and HF/volume overload (14 % greater risk).

Summarizing, better glycemic control in DM patients, smaller IDWG and UF rate can improve prognosis in young, CKD patients treated with HD.

Limitations of the study

The main limitation of our study is the limited number of patients included. Therefore, a multicenter trial may result in a better revaluation of this aspect of HD patients.

Acknowledgments

We are grateful to all the patients who participated in this study.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by the Bioethics Committee of the Jagiellonian University and all patients signed an informed consent for their participation.

Informed consent: Informed consent was obtained from all individual participants included in the study.

All authors read and approved the final manuscript

Conclusions

UF rate can be a simple, useful indicator of higher long-term all-cause and CV mortality in HD patients <60 years of age. Also, DM may be predictor of CV–related death in younger HD patients.

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