

Original Article

Factors associated with mortality in patients new to haemodialysis

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Abstract

Background. Patients receiving dialysis therapy for end-stage kidney failure have a high cardiovascular mortality that can only be partially explained by traditional risk factors.

Methods. This study was a *post hoc* analysis of a prospectively gathered data set from a randomized trial comparing outcomes in new haemodialysis patients treated with sevelamer or calcium-containing phosphate binders. Patients were followed from the time of enrollment until death or censor on 31 December 2005. Median follow-up was 3.6 years. Demographics, cardiovascular risk factors, laboratory data, medication use and severity of vascular calcification were available at baseline and over the first 18 months of dialysis.

Results. Baseline predictors of mortality included age, creatinine, heart rate, iPTH, C-reactive protein (CRP), coronary and aortic calcium scores and the presence of aortic valve calcification. Over the first 18 months, averages of diastolic blood pressure, BUN, creatinine, albumin, phosphorus, iPTH and CRP were all significantly different between survivors and non-survivors. A stepwise multivariable adjusted Cox regression model demonstrated that low BUN and albumin and high CRP along with the use of calcium-containing phosphate binders (rather than sevelamer) were the strongest predictors of mortality in patients new to haemodialysis.

Conclusions. These findings suggest that non-traditional risk factors, such as inflammation and malnutrition measured during the first 18 months of dialysis, are important determinates of survival in new dialysis patients. In addition, the unique risk factor for dialysis patients, the use of calcium-containing phosphate binders, was associated with a higher mortality rate in patients new to dialysis.

Keywords: ESRD; malnutrition inflammation; mortality; phosphate binders; haemodialysis; vascular calcification

Introduction

Patients receiving dialysis therapy for end stage renal disease (ESRD) have a high cardiovascular mortality that can only be partially explained by traditional risk factors such as age, diabetes, hypertension and lipid disorders [1]. Observational analyses of several large dialysis provider databases suggest that non-traditional risk factors such as albumin, creatinine and markers of inflammation are associated with outcome in this patient population [2–4]. In addition, disorders of mineral metabolism have gained increased recognition as potentially modifiable risk factors in ESRD [5]. This includes serum calcium and phosphorus concentrations, active vitamin D sterol use, intact parathyroid hormone levels, as well as the extent of coronary artery and vascular calcification [6–8]. The purpose of the present study was to evaluate the association between baseline demographic, laboratory data and coronary and aortic calcification, as well as laboratory data and medication use in the first 18 months of dialysis and mortality in a cohort of patients new to haemodialysis who had been randomized to sevelamer or calcium-containing phosphate binders. Results from this *post hoc* analysis are intended to be hypothesis generating and statistically significant findings need to be confirmed by prospective trials.

Methods

One hundred and twenty-seven patients enrolled in a prospective trial of sevelamer vs calcium-containing phosphate binders who underwent baseline electron beam computed tomography (EBCT) scans served as the study population. The baseline characteristics of the study population, the effects of phosphate binder choice on

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the progression of vascular calcification, and the results of the prospective randomized trial on all-cause mortality have been previously reported [9–11].

Subjects

Adults >18 years of age who were new to haemodialysis therapy were enrolled from September 2000 to December 2002. Exclusion criteria were prior history of dialysis, kidney transplant, coronary artery bypass graft, weight >300 lbs, atrial fibrillation, or life expectancy <6 months. Written informed consent was obtained from all subjects for the prospective trial and Investigational/Ethical Review Board approval was obtained for the follow-up mortality data in adherence with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects. The study was closed on 31 December 2005 at which time patients were recorded as alive, dead, censored due to transplantation or lost to follow-up [11].

Laboratory and imaging techniques

Routine biochemical laboratory measurements were obtained at baseline (study entry) and at monthly or quarterly intervals as previously reported [10]. EBCT scans for imaging of coronary artery, aorta and valvular calcification were performed within the first 90 days of starting dialysis as previously described [10]. Coronary artery calcium scores (CCS), aorta calcium scores (ACS) and valvular calcium scores were calculated according to a standard method as previously described [10].

Statistical analysis

Baseline and the first 18 month characteristics were compared between the patients alive/censored at the conclusion of the study *vs* those who died using a two-sided *t*-test for continuously distributed data and the Fisher's exact test for categorical data. Since the EBCT CCS and ACS were not normally distributed, median scores were used for comparisons using the non-parametric Mann–Whitney U-test. Univariate Cox modelling was performed on individual variables. Due to the large number of significant variables and the small number of events (34), a factor analysis was performed on the 16 potential covariates. Five factors were retained, using a minimum eigenvalue of 1.0 as the criterion for retention. The five factors were then rotated to a varimax criterion of simple structure. One variable was selected from each factor for inclusion in the proportional hazards model. For those factors defined by more than one variable, the selection was made on the basis of the magnitude of the variable's loading on the factor. The factor analysis was followed by a stepwise Cox regression model with the selected variables and the binder randomization. Modelling results were scaled to clinically meaningful increments, for example, age per 10 years rather than age per year. Scaling does not change the statistical significance or *P*-value of a variable, only its relative hazard ratio.

Missing data points were imputed as the mean value. All *P*-values were two-tailed. *P*-values <0.05 were considered

statistically significant. Analyses were performed using GraphPad Prism version 4.02 (San Diego, CA, USA) and SAS version 8.2 (Cary, NC, USA).

Results

Baseline data

Baseline demographics, laboratory data and CCS and ACS based on outcome are shown in Table 1. Baseline characteristics based on binder randomization have been previously published [11]. Patients who died were older (66 ± 11 *vs* 54 ± 15 years, $P < 0.0001$), had lower serum creatinine (480 ± 183 *vs* 587 ± 229 $\mu\text{mol/l}$; $P = 0.015$), lower iPTH (25 ± 23 *vs* 42 ± 35 pmol/l ; $P = 0.0048$) and higher high-sensitivity C-reactive protein (hsCRP) (6.62 *vs* 4.08 , $P = 0.002$) and heart rate (85 ± 14 *vs* 78 ± 13 , $P = 0.0121$) than those alive/censored. Median CCS and median ACS were significantly higher in those who died compared with patients alive at follow-up (CCS: dead *vs* alive, 472 *vs* 12, $P < 0.0001$; ACS: dead *vs* alive, 1107 *vs* 72, $P = 0.0002$). The prevalence of aortic valve calcification was also higher in non-survivors.

Follow-up data

Outcome data were available for all 127 patients. The median follow-up was 3.6 years. Nine patients in both the sevelamer and calcium-treated groups were censored at the time of kidney transplant. Two patients randomized to sevelamer and one patient randomized to calcium were lost to follow-up. Laboratory data and dialysis treatment information on patients over the first 18 months of dialysis therapy are shown in Table 2. Diastolic blood pressure, serum albumin, serum creatinine, BUN, serum phosphorus and iPTH were all lower in patients who died compared with those alive/censored. The hsCRP was significantly greater in patients who died than in those alive at the end of study ($P = 0.014$). There was a significantly greater use of calcium-containing phosphate binders in patients who died *vs* those alive/censored (68 *vs* 47%, $P = 0.047$). The use of vitamin D analogues was borderline significant between groups with 83% use in the survivors *vs* 65% use in non-survivors ($P = 0.051$).

Predictive models

Predictors of all-cause mortality in a univariate Cox model are shown in Table 3. Among baseline characteristics, older age ($P = 0.0020$), lower BUN ($P = 0.0256$), higher hsCRP ($P = 0.0474$), higher CCS ($P < 0.0001$) and the presence of aortic valve calcification ($P = 0.0403$) were associated with mortality. During follow-up, lower time averaged serum levels of albumin, BUN, creatinine, phosphorus, iPTH and higher hsCRP as well as lower diastolic blood pressure were associated with increased mortality. The choice of phosphate binder and the use of vitamin D analogues

Table 1. Baseline demographics^a

	Alive/Censored (n = 93)	Dead (n = 34)	P-value
Age (years)	54 ± 15	66 ± 11	<0.0001
Gender			0.8372
Men (%)	62	59	
Women (%)	38	41	
Race			0.4820
Black (%)	33	29	
White (%)	39	47	
Hispanic (%)	24	15	
Other (%)	4	9	
Current smoker (%)	17	24	0.4479
Diabetes (%)	65	55	0.4184
Hypertension (%)	98	94	0.2943
MI (%)	8	18	0.1107
CHF (%)	13	24	0.1742
Angina (%)	7	9	0.7015
ASCVD (%)	21	15	0.4585
Hypercholesterolaemia (%)	32	32	1.0000
Baseline laboratory data			
Weight (kg)	77 ± 18 (92)	74 ± 16	0.3801
Height (cm)	170 ± 12 (92)	169 ± 10	0.6317
SBP (mmHg)	150 ± 21 (91)	148 ± 24	0.6652
DBP (mmHg)	81 ± 15 (91)	79 ± 11	0.4825
Heart rate (min)	78 ± 13 (92)	85 ± 14	0.0121
Pulse press (mmHg)	70 ± 15 (91)	70 ± 19	0.9550
Haemoglobin (gm/l)	119 ± 19	115 ± 23	0.4069
Creatinine (μmol/l)	587 ± 229	480 ± 183	0.0154
Albumin (gm/l)	36 ± 6	35 ± 5	0.1708
Corrected calcium (mmol/l)	2.3 ± 0.2	2.4 ± 0.2	0.0719
Phosphate (mmol/l)	1.7 ± 0.5	1.6 ± 0.5	0.2109
iPTH (pmol/l)	42 ± 35 (86)	25 ± 23 (32)	0.0048
Cholesterol (mmol/l)	4.1 ± 1.0 (89)	4.0 ± 0.9 (32)	0.4264
LDL (mmol/l)	2.0 ± 0.7 (84)	1.9 ± 0.8 (32)	0.7536
hsCRP (mg/l) median	4.08 (90)	6.62 (32)	0.0024
Baseline EBCT scans			
Coronary Calcium Score			
Mean ± SD	311 ± 693	1373 ± 2034	
Median	12.4	472	<0.0001
Aorta Calcium Score			
Mean ± SD	1194 ± 2522	2151 ± 2793	
Median	72.0	1107	0.0002
Aortic value calcification (%)	16.1	38.2	0.0142
Mitral value calcification (%)	21.5	32.4	0.2453

^aNumbers in parentheses are number of observations.

P-values in bold print are statistically significant.

MI, myocardial infarction; CHF, congestive heart failure; ASCVD, atherosclerotic cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; iPTH, intact parathyroid hormone; EBCT electron beam computed tomography.

were borderline significant in this model. Results of the rotated factor solution are shown in Table 4. Stepwise multivariate Cox regression model including binder randomization (sevelamer *vs* calcium) and the five factors identified by the size of the variable's loading in the factor model are shown in Table 5. The analysis demonstrated that lower BUN and serum albumin and higher hsCRP averaged over the first 18 months of dialysis, along with the use of calcium-containing

Table 2. First 18 months of follow-up data

	Alive/Censored (n = 93)	Dead (n = 34)	P-value
SBP (mmHg)	151 ± 14 (91)	147 ± 16 (33)	0.2208
DBP (mmHg)	82 ± 10 (92)	75 ± 9	0.0007
Heart rate (min)	76 ± 9 (91)	79 ± 9 (33)	0.1519
Pulse press (mmHg)	69 ± 11 (91)	72 ± 12 (33)	0.2056
Haemoglobin (gm/l)	123 ± 7 (91)	123 ± 13 (33)	0.7248
Creatinine (μmol/l)	760 ± 230	566 ± 1.59	<0.0001
BUN (mmol/l)	20.3 ± 5.0	17.1 ± 4.6	0.0007
Kt/V	1.6 ± 0.3 (91)	1.5 ± 0.4	0.6906
Albumin (gm/l)	39 ± 3 (91)	37 ± 4 (33)	0.0129
Corrected calcium (mmol/l)	2.4 ± 0.2 (91)	2.4 ± 0.1 (33)	0.3923
Phosphate (mmol/l)	1.7 ± 0.3	1.5 ± 0.3 (33)	<0.0001
iPTH (pmol/l)	32.1 ± 17.6	23.6 ± 13.2 (33)	0.0056
Cholesterol (mmol/l)	4.01 ± 0.88 (80)	3.85 ± 0.96 (25)	0.4809
LDL (mmol/l)	1.97 ± 0.70 (77)	1.99 ± 0.67 (24)	0.7845
hsCRP (mg/l) median	6.28 (80)	9.69 (25)	0.0141
Medication use during 18 months of follow-up			
Calcium-based binders (%)	47	68	0.0471
HMG Co-A reductase (%)	43 (91)	27 (33)	0.1455
ACE-I (%)	65 (91)	52 (33)	0.2127
β-Blocker (%)	59 (91)	52 (33)	0.5384
CCB (%)	48 (91)	39 (33)	0.4196
Vitamin D analogues (%)	83	65	0.0509
Warfarin (%)	12 (91)	24 (33)	0.1553

Numbers in parentheses are number of observations if less than the total *n*.

P-values in bold print are statistically significant.

ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blockers; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

phosphate binders, were the four variables predictive of mortality.

Discussion

This is the first study to evaluate factors present at the initiation of haemodialysis including coronary artery and aorta calcification, laboratory data and medication use during the first 18 months of dialysis care to determine their association with all-cause mortality. This study finds that binder choice and the first 18 month time-averaged hsCRP and BUN are predictive of mortality. A low serum albumin was also predictive of mortality while the baseline aortic calcification score and the use of vitamin D analogues were dropped from the model. In the baseline analysis [9], ACS was inversely correlated with the baseline serum albumin and this may explain this finding. These findings are consistent with previously published literature suggesting that malnutrition and inflammation are important determinants of outcome in dialysis patients. [2–4]. The finding that the use of sevelamer was associated with a survival advantage over calcium-containing phosphate binders after

Table 3. Univariate Cox proportional hazard model for all-cause mortality

Variable	P-value	Unit scaling	Hazard ratio
Age	0.0020	10 years	1.533
Diabetes	0.5428		
Albumin-B	0.1532		
Albumin-M	0.0044	10 g/l	0.303
BUN-B	0.0256	3.6 mmol/l	0.801
BUN-M	0.0001	3.6 mmol/l	0.615
Creatinine-B	0.0869		
Creatinine-M	<0.0001	88 mmol/l	0.701
Cholesterol-B	0.4167		
Cholesterol-M	0.4895		
Haemoglobin-B	0.1721		
Haemoglobin-M	0.3833		
hsCRP-B	0.0474	5 mg/l	1.196
hsCRP-M	0.0110	5 mg/l	1.208
Kt/V-M	0.5300		
LDL-B	0.6502		
LDL-M	0.9015		
Phosphate-B	0.4191		
Phosphate-M	0.0374	<1.13, 1.13–1.78, >1.78	0.446
iPTH-B	0.0825		
iPTH-M	0.0103	<15.8, 15.8–31.5, > 31.5	0.513
DBP-B	0.7436		
DBP-M	0.0111	10 mmHg	0.631
SBP-B	0.7503		
SBP-M	0.2453		
Heart rate-B	0.0857		
Heart rate-M	0.3481		
Vitamin D	0.0587	Yes/No	0.506
CCS	<0.0001	1000	1.381
ACS	0.1437		
AVC	0.0403	Yes/No	2.063
MVC	0.3516		
Phos binder	0.0638	Calcium vs sevelamer	1.977
β-Blocker	0.7617		
ACE-I	0.2012		
Calcium channel blocker	0.7953		
HMG Co-A reductase inhibitor	0.1791		
Warfarin	0.0201	Yes/No	2.610

Hazard ratio only reported for variables with *P*-value <0.05. If the *P*-value >0.05 the hazard ratio is not statistically different from 1.0. hsCRP, high-sensitivity C-reactive protein; B, baseline value; P-values in bold print are statistically significant. M, time averaged over first 18 months of dialysis; CCS, coronary calcium score; ACS, aorta calcium score; AVC, aortic valve calcification; MVC, mitral valve calcification; ACE-I, angiotensin-converting enzyme inhibitor.

adjustment for the first 18 months of laboratory values including hsCRP, BUN and albumin, strengthens the previously published findings of the randomized prospective trial showing improved survival in new dialysis patients treated with sevelamer compared with calcium-containing phosphate binders which adjusted only for differences in baseline characteristics [11].

It is interesting to note that a large number of variables at baseline or during the first 18 months of dialysis were associated with poor survival in univariate analysis. Many of these variables were not significant when other factors were included in the model including age, lower diastolic blood pressure,

Table 4. Rotated factor analysis: all variables scaled as shown in Table 3

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
ACS	0.82248	−0.07018	0.04210	−0.04516	0.05124
Age	0.75883	−0.16849	−0.11505	−0.12547	0.10553
AVC	0.66972	0.11254	−0.10953	0.02055	0.01950
CCS	0.55779	−0.18367	−0.10007	−0.37026	−0.24913
DBP-M	−0.66953	0.34822	0.11793	0.01665	−0.18241
BUN-M	−0.04788	0.66782	−0.01588	0.23168	−0.18144
Phos-M	−0.29228	0.65897	−0.12694	−0.01800	−0.08200
Creat-M	−0.33729	0.60328	0.29145	0.44970	−0.04788
Pulse-B	−0.10104	−0.61280	−0.11658	0.05584	−0.31855
Vitamin D	−0.06833	−0.08209	0.81643	0.09398	−0.08498
iPTH-M	−0.14816	0.12005	0.79214	−0.04579	−0.17619
Albumin-M	0.06682	0.26003	−0.07816	0.77171	−0.22050
MVC	0.44710	0.04080	0.20579	−0.57514	0.08790
DBP-B	0.06912	0.02151	−0.38004	−0.64660	−0.20071
hsCRP-M	0.18605	0.03703	−0.04679	−0.09160	0.77166
Warfarin	−0.05778	−0.14189	−0.37817	0.03865	0.65460

Values in bold signify factors with the strongest loading value.

Table 5. Stepwise Cox regression model for all-cause mortality utilizing five variables identified by factor analysis (bold variables in Table 4) and binder randomization

Variable	Scaling	Parameter estimate	SE	P-value	Hazard ratio
Binder	Ca vs Sev	0.84654	0.37886	0.0255	2.332
BUN-M	3.6 mmol/l	−0.52897	0.13980	0.0002	0.589
Alb-M	10 gm/l	−0.88576	0.43989	0.0441	0.412
hsCRP-M	5 mg/l	0.16946	0.07399	0.0220	1.185

Ca, calcium binder; Sev, sevelamer; M, time averaged over first 18 months of dialysis.

phosphorus and iPTH, and the administration of vitamin D analogues for a least 1 month during their first 18 months of dialysis. The large number of factors predictive of poor outcome in univariate analysis that were not significant in multivariable analysis is consistent with multiple reports in the literature and warns against the oversimplification of our understanding of factors responsible for the high mortality rate in ESRD patients. This notion again underlines the need for randomized controlled interventional trials in ESRD.

Limitations

This study was a *post hoc* analysis of a well-characterized cohort of new dialysis patients [9]. Due to the small sample size and small number of events (deaths) a factor analysis was utilized to identify five reasonably independent covariates for use in the Cox modelling. Furthermore, the relatively small size of the study may have resulted in negative results where true differences existed. This is particularly true for some of the traditional mortality risk factors such as diabetes which has been shown to correlate with outcome in

many large database analyses [1,2]. For example, our sample size provides us with an 80% probability of finding a significant association with mortality if diabetes conferred a 2-fold increased risk of death in this incident dialysis population. The fact that diabetes did not show significance suggests a possible type II statistical error, not finding a difference when one truly exists. This is a known problem with small sample sizes and may explain some of the negative findings in this study.

Our study design measured laboratory values only for the first 18 months of dialysis. A potential limitation of this trial is that variables may change over time resulting in increased or decreased risk. However, the finding that variables measured early in the dialysis lifetime of patients are predictive of future events gives added weight to these variables.

Conclusion

We demonstrated that many non-traditional risk factors such as malnutrition (low time-averaged BUN and low albumin) and inflammation (high time-averaged hsCRP and low albumin) appear to play a role in outcomes of new dialysis patients. Finally, the use of sevelamer and the avoidance of calcium-containing phosphate binders offered a survival benefit to new dialysis patients. The finding that variables present at baseline and during the first 18 months of dialysis are predictive of mortality suggests that trials designed to intervene early in the dialysis treatment course may prove more effective than interventions started after several years of dialysis treatments. This study further suggests that randomized trials designed to reduce inflammation, improve nutrition and minimize calcium loading in new dialysis patients may prove beneficial for the long-term survival of dialysis patients.

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