SERUM CYSTATIN C DOES NOT PREDICT MORTALITY OR TREATMENT FAILURE IN PERITONEAL DIALYSIS: A PROSPECTIVE STUDY

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◆ **Background:** Small solute clearance, especially that derived from residual renal function (RRF), is an independent risk factor for death in peritoneal dialysis (PD) patients. Assessment of solute clearance is time-consuming and prone to multiple errors. Cystatin C is a small protein which has been used as a glomerular filtration rate (GFR) marker. We investigated whether serum cystatin C concentrations are related to mortality in patients receiving PD.

◆ **Methods:** New and prevalent PD patients ($n = 235$) underwent assessment of Kt/V_{urea} , RRF, weekly creatinine clearance (C_{Cr}), normalized protein catabolic rate (nPCR) and a peritoneal equilibration test (PET) at intervals. Blood was collected simultaneously for cystatin C measurement. Patients were followed for a median of 1,429 days (range 12 to 2,964 days) until death or study closure. Cause of death was recorded where given. Cox regression was performed to determine whether cystatin C had prognostic value either independently or with adjustment for other factors (age, sex, dialysis modality, diabetic status, cardiovascular comorbidity, Kt/V , C_{Cr} , RRF, nPCR or 4 h dialysate to plasma creatinine ratio (4 h D/P_{Cr}) during the PET). The primary outcomes were all-cause mortality and treatment failure.

◆ **Results:** There were 93 deaths. Increasing age and 4 h D/P_{Cr} ratio, decreased RRF and presence of diabetes were significantly [$p < 0.05$] negatively associated with survival and treatment failure. Serum cystatin C was not related to either outcome.

◆ **Conclusions:** Serum cystatin C concentration does not predict mortality or treatment failure in patients receiving PD.

KEY WORDS: Cystatin C; dialysis adequacy; kidney failure; peritoneal dialysis; residual renal function; survival analysis.

Prospective studies from the early 1990s (1,2) identified total small solute clearance as an independent risk factor for death in patients with end-stage renal disease (ESRD) treated with peritoneal dialysis (PD). Residual renal function (RRF) is identified as being of primary importance compared to peritoneal clearance and is independently associated with survival (3–5).

The quantification of the effective delivered dose of dialysis that a patient receives is typically derived from an estimation of the clearance of the small solutes urea and creatinine from blood into spent dialysate and urine. Tests of adequacy and RRF are typically routinely performed at 6 – 12 monthly intervals (6). These assessments are time-consuming and cumbersome and are confounded by the numerous measurements that are necessary to calculate small solute clearances, contributing to poor day-to-day reproducibility (7). A simple and more convenient marker of clearance (e.g. serum cystatin C) would be of benefit.

Cystatin C is a 13 kDa protein that has been proposed as a more sensitive marker of glomerular filtration rate (GFR) in non-dialysis patients (8,9). Cystatin C is readily measured from a single blood sample using reliable and reproducible assays. Serum cystatin C concentrations in PD patients are primarily influenced by renal clearance (10–12). We (13,14) and others (15) have previously reported a relationship between serum cystatin C and RRF in PD patients and the use of cystatin C to estimate RRF has been proposed (16,17). In the present study, we have investigated whether serum cystatin C may be an improved marker of mortality in patients receiving PD compared to the currently used markers of PD adequacy and renal elimination (weekly creatinine

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clearance (C_{Cr}), Kt/V_{urea} and RRF) in a large cohort of PD patients.

METHODS

New and prevalent adult patients receiving PD ($n = 235$) were recruited to the study. Inclusion criteria were that the patient must have at least 1 cystatin C measurement during the study period.

Exclusion criteria included known current malignancy, rheumatoid arthritis (18,19) cognitive impairment and age < 18 years. Our center's policy is that all patients undergoing PD as chronic renal replacement therapy have a peritoneal adequacy test once they are established on dialysis, ideally after 6–8 weeks, and this is repeated at varying intervals to guide therapy. Between 1 February 2003 and 6 April 2009 all patients having peritoneal adequacy tests were invited to participate in the study. No patients refused to participate in the study. Ethical approval was obtained (LREC no: EK214/11/02) and all patients gave written informed consent.

During the study period, a further 151 patients entered the PD program but did not have an adequacy assessment undertaken for a variety of reasons, including early switch to hemodialysis ($n = 29$) or transplantation ($n = 16$), death ($n = 34$), severe cognitive impairment ($n = 8$) and other reasons ($n = 64$), including recovery of renal function, poor compliance, loss from follow-up, terminal cancer and age < 18 years). An additional 17 patients consented to participate in the study but no cystatin C measurement was recorded, due to lost or spoiled samples. The 168 patients that were not entered into the study comprised 103 males and 65 females with a mean age of 60 years; 21% were diabetic.

Patients underwent an adequacy assessment (Kt/V_{urea} , RRF and weekly C_{Cr}) in addition to normalized protein catabolic rate (nPCR) and a peritoneal equilibration test (PET) in line with national guidance. A 4-h dialysate to plasma creatinine ratio (4 h D/P_{Cr} ratio) was calculated during the PET. These parameters were calculated using Adequest (Baxter Healthcare Ltd., UK) with V being calculated using the Watson method (20). Residual renal function was calculated from the mean of urea and creatinine clearances. Both RRF and C_{Cr} were adjusted to a standardized body surface area of 1.73 m^2 . Blood was collected by venepuncture simultaneously and serum stored at -80°C for subsequent cystatin C measurement: the stability of cystatin C under these conditions is well established (8). Thereafter, samples were stored for cystatin C measurement at each adequacy study.

Baseline demographic details were collected on each patient at entry into the study including height, weight,

age, primary renal disease, time on PD, PD modality, presence of diabetes or cardiovascular disease (including myocardial infarction, peripheral vascular disease, atrial fibrillation, electrocardiographic abnormalities, left ventricular hypertrophy, hypertension, cerebrovascular disease, ischemic heart disease, heart failure, peripheral vascular disease). Patients were followed until death or study closure (15 March 2011). Cause of death was recorded where given.

Cystatin C was measured by a particle-enhanced nephelometric immunoassay on a BN Prospec analyser (Siemens HealthCare Diagnostics, <http://www.healthcare.siemens.co.uk>). The laboratory reference range was 0.54–1.06 mg/L (21) and between-day imprecision was 3.5% and 1.9% at concentrations of 2.3 and 5.6 mg/L, respectively. The assay used calibrators provided by the manufacturer. Samples were assayed in several batches over the study period. Urea and creatinine in dialysis fluid and urine were measured using enzymatic methods that avoid problems of interference in creatinine measurement due to high glucose concentrations.

DATA ANALYSIS

The relationship between cystatin C and components of adequacy (Kt/V , C_{Cr} , RRF and nPCR) and transport (4 h D/P_{Cr} ratio) was tested using non-parametric (Spearman rank) correlation analysis.

The sample size was determined based on detecting a difference in the probability of survival of 0.4 in people with cystatin C concentrations greater than the median and 0.6 in those with concentrations below the cystatin C median, at the 5% level of significance with the power estimated to be greater than 90%. Univariable and multivariable Cox regression was performed to determine whether cystatin C had prognostic value either independently or with adjustment for other factors (age, sex, dialysis modality (continuous ambulatory peritoneal dialysis [CAPD] or automated peritoneal dialysis [APD]), diabetic status, cardiovascular comorbidity, Kt/V , C_{Cr} , RRF, nPCR or 4 h D/P_{Cr} ratio). The primary outcomes were all-cause mortality or treatment failure (death or transfer to hemodialysis). Analysis was undertaken with censoring of patients who received a transplant during the study. Cystatin C and other predictor variables were treated as time-varying covariates in the Cox regression analysis. This had the advantage of allowing the risk of death at any time to vary as the characteristics of the patients varied. A disadvantage of this method was that there were missing values for several variables at some time points, so some data points were omitted from the analyses as a result of this.

Data were presented as hazard ratios with 95% confidence intervals. Two approaches were taken to this analysis: in each analysis, cystatin C was considered firstly as a continuous variable and secondly as a categorical variable, split into 2 categories by the median value. Note that this was based on the median of all of the individual measurements included in the study rather than the median 'average' value for each patient. Each analysis was performed in 2 stages. Initially the effect of cystatin C and the other factors upon survival times was examined separately in a series of univariate analyses. The second stage of the analysis jointly examined the effect of the various factors together in a multivariable analysis. Only factors showing slight evidence of an association with mortality in the univariable analyses ($p < 0.2$) were included in the multivariable analysis. In the multivariable analysis, cystatin C was considered as a continuous variable. Before the multivariable analysis was performed, the collinearity between predictor variables was assessed using variance inflation factors. A backwards selection procedure was used to retain only the statistically significant variables by removing non-significant variables, one at a time, until all remaining variables were statistically significant. As cystatin C was the main variable of interest, this variable was retained in the analyses, regardless of statistical significance.

Analyses were undertaken using Analyse-It (Analyse-It Software Ltd., Yorkshire, UK) and Stata version 9.2 (StataCorp LP, College Station, TX, USA) statistical packages. A p value < 0.05 was considered significant.

RESULTS

STUDY CHARACTERISTICS

Clinical and biochemical characteristics of the patients are given in Table 1. Of the total cohort, 110 patients (47%) entered the study within 3 months of commencing PD and 125 (53%) were prevalent patients.

The median time in the study was 1,429 days (range 12 to 2,964 days). The median time on PD after study entry was 774 days (range 12 to 2,708 days). There were 528 cystatin C measurements during the study: patients had a median of 2 cystatin C measurements each (range 1 to 7 measurements).

During the study, 93 patients died. Causes of death were: cardiovascular ($n = 14$), malignancy ($n = 7$), peritonitis/septicemia ($n = 14$), pneumonia ($n = 2$), miscellaneous ($n = 4$; hypoglycemic coma, perforated bowel, subdural hematoma, primary autonomic failure), withdrew from treatment ($n = 9$) and not recorded ($n = 43$). During the study, 90 patients switched to hemodialysis

and 48 patients ceased PD because they had received a renal transplant. A further 9 patients received a transplant after switching to hemodialysis.

RELATIONSHIP BETWEEN CYSTATIN C AND PATIENT CHARACTERISTICS

At study entry, there were no significant unadjusted associations between serum cystatin C concentration and age, body mass index, hemoglobin, 4 h D/P_{cr} ratio or nPCR. Cystatin C was inversely related to RRF ($r_s -0.66$, $p < 0.001$), C_{cr} ($r_s -0.58$, $p < 0.001$), and total Kt/V_{urea} ($r_s -0.33$, $p < 0.001$). There was a positive relationship between duration of time on PD and serum cystatin C concentration ($r_s 0.34$, $p < 0.001$).

UNADJUSTED RELATIONSHIPS BETWEEN CYSTATIN C AND PATIENT OUTCOMES

There was no evidence ($p < 0.05$) that cystatin C was significantly associated with overall survival, when assessed on either a categorical or continuous scale (Table 2). In addition to the overall effects of cystatin C, the interaction between cystatin C and both patient type (new/prevalent patient) and modality (CAPD or APD) were examined. The results (not presented) suggested no evidence of an interaction between cystatin C and either of these two variables. These results suggest that the effects of cystatin C upon survival did not vary by patient type or by modality.

Some other variables (increasing age, presence of diabetes or cardiovascular disease) were associated ($p < 0.05$) with increased risk of death. Higher values of RRF and nPCR were associated with a reduced risk of death. Conversely, higher values of 4 h D/P_{cr} ratio were associated with an increased risk of death. Other factors such as patient type (new or prevalent), dialysis modality, gender, body mass index, smoking status, hemoglobin, and C_{cr} were not found to be significantly associated with patient survival (Table 2).

There was no evidence ($p > 0.05$) that cystatin C was significantly associated with technique survival when assessed on a continuous scale but when studied on a categorical scale patients with higher (> 5.3 mg/L) cystatin C concentrations had a 65% higher ($p = 0.01$) risk of technique failure.

The analysis confirmed that higher values of RRF, hemoglobin and total weekly creatinine clearance were associated with a reduced risk of technique failure ($p < 0.05$). Conversely, higher values of 4 h D/P_{cr} ratio and the presence of diabetes were associated with an increased risk of technique failure ($p < 0.05$) (Table 2).

TABLE 1
Descriptive Characteristics^a of the Patients at Baseline^b

Age, years	61 (18–84)
Male:female, <i>n</i> (%)	145:90 (62:38)
Body mass index, kg/m ²	25.8 (15.2–45.0)
Primary cause of renal failure (<i>n</i>)	Diabetes mellitus (39), glomerulonephritis (15), adult polycystic kidney disease (24), IgA nephropathy (18), renovascular disease (13), hypertensive nephropathy (10), focal segmental glomerulosclerosis (10), obstructive nephropathy (10), vasculitis (6), myeloma kidney (4), stone disease (4), interstitial nephritis (4), membranous nephropathy (3), chronic pyelonephritis (5), Alport disease (3), reflux nephropathy (3), systemic lupus erythematosus (2), AL-amyloid (2), hemolytic-uremic syndrome (2), ciclosporin toxicity, medullary sponge kidney, malakoplakia, congenital renal dysplasia, Goodpasture disease, Joubert syndrome, surgical (1 each), unknown (51)
Diabetes, <i>n</i> (%)	55 (23)
Cardiovascular disease, <i>n</i> (%)	157 (67)
Smokers, <i>n</i> (%)	47 (20)
CAPD:APD (CCPD or NIPD), <i>n</i> (%)	188:47 (80:20)
Time on dialysis at study entry, days	111 (2–4,174)
nPCR, g/kg/day (<i>n</i> =219)	0.86 (0.43–1.55)
Weekly C _{cr} , L/week/1.73 m ² (<i>n</i> =223)	81 (13–191)
Kt/V _{urea} (<i>n</i> =224)	2.26 (1.03–4.50)
4 h D/P _{cr} (<i>n</i> =209)	0.78 (0.47–1.00)
RRF, mL/min/1.73 m ² (<i>n</i> =224)	3.5 (0.0–15.5)
Anuric patients, <i>n</i> (%)	11 (5)
Blood hemoglobin, g/dL (<i>n</i> =227)	11.7 (7.3–16.4)
Serum cystatin C, mg/L (<i>n</i> =214)	5.15 (2.28–8.54)
Serum creatinine, μmol/L (<i>n</i> =230)	637 (248–1,742)
Serum urea, mmol/L (<i>n</i> =229)	16.9 (8.2–31.9)

CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; CCPD = continuous cyclic peritoneal dialysis; NIPD = nightly intermittent peritoneal dialysis; nPCR = normalised protein catabolic rate; C_{cr} = creatinine clearance; 4 h D/P_{cr} ratio = 4 h dialysate/plasma creatinine ratio during a peritoneal equilibration test; RRF = residual renal function.

In some cases baseline data were absent: unless stated otherwise data refer to the entire cohort (*n* = 235).

^a Median and range unless otherwise stated.

^b Study entry.

MULTIVARIABLE ANALYSIS OF THE RELATIONSHIP BETWEEN CYSTATIN C AND PATIENT OUTCOMES

Due to collinearity between RRF and total weekly creatinine clearance, only RRF was included in the multivariable analysis, as this variable was most strongly associated with survival from the univariable analyses. Multivariable analysis indicated that older patients, those with diabetes, and higher 4 h D/P_{cr} ratio values had an increased risk of death, whilst patients with higher RRF values were at a reduced risk of death. The same predictor variables were associated with technique survival (Table 3). After adjusting for the significant variables, there was still no evidence that cystatin C was significantly associated with either overall or technique survival. Analyses with cystatin C on a categorical scale found no significant association with either overall survival or technique survival.

DISCUSSION

The purpose of this study was to explore whether serum cystatin C concentrations were associated with outcome in PD patients. Correlations between serum cystatin C and both RRF, (13,15,16) a known predictor of outcome in PD, (1,2) and GFR (14,22) in PD patients have been reported previously. The present study, a prospective longitudinal study in a relatively homogenous Caucasian population, has indicated that the serum concentration of the middle molecule cystatin C does not predict mortality or treatment failure in PD patients. However, the anticipated associations of diabetes, age, transporter status and RRF with survival hold firm in this population.

Peritoneal clearance of cystatin C was not measured in our cohort although it has previously been shown

TABLE 2
Univariate Analysis of Parameters Associated with Primary Outcomes

	Time to death		Outcomes	
	HR (95% CI)	<i>p</i>	Time to treatment failure HR (95% CI)	<i>p</i>
Predictor variables				
Cystatin C (continuous)	1.01 (0.81, 1.24)	0.95	1.12 (0.94, 1.32)	0.18
Cystatin C (categorical, >5.3 mg/L vs ≤5.3 mg/L)	1.16 (0.72, 1.87)	0.54	1.65 (1.12, 2.43)	0.01
Continuous variables				
Age, years ^a	1.76 (1.45, 2.14)	<0.001	1.13 (0.99, 1.28)	0.07
BMI, kg/m ² ^b	0.92 (0.75, 1.14)	0.45	1.04 (0.89, 1.21)	0.62
Hb, g/dL	1.01 (0.86, 1.19)	0.89	0.83 (0.74, 0.94)	0.004
nPCR, g/kg/day ^c	0.88 (0.80, 0.97)	0.01	0.93 (0.86, 1.00)	0.05
Weekly C _{cr} , L/week/1.73 m ² ^a	0.94 (0.86, 1.03)	0.16	0.91 (0.85, 0.98)	0.01
4 h D/P _{cr} ratio ^c	1.42 (1.13, 1.78)	0.002	1.36 (1.13, 1.64)	0.001
Kt/V _{urea}	0.76 (0.51, 1.13)	0.17	0.76 (0.55, 1.05)	0.10
RRF, mL/min/1.73 m ²	0.88 (0.81, 0.96)	0.006	0.88 (0.82, 0.94)	<0.001
Categorical variables				
Patient type (new vs prevalent)	0.73 (0.47, 1.12)	0.15	0.72 (0.51, 1.00)	0.05
Peritoneal dialysis modality (CAPD vs other)	0.91 (0.57, 1.46)	0.70	1.18 (0.81, 1.70)	0.39
Gender (male vs female)	0.98 (0.64, 1.51)	0.94	1.25 (0.89, 1.78)	0.20
Diabetes	1.77 (1.13, 2.78)	0.01	1.53 (1.06, 2.22)	0.02
Cardiovascular comorbidity (present vs absent)	1.68 (1.01, 2.79)	0.04	1.44 (0.98, 2.11)	0.06
Smoker (yes vs no)	1.22 (0.76, 1.95)	0.41	1.27 (0.86, 1.85)	0.22

HR = hazard ratio; CI = confidence interval; BMI = body mass index; Hb = hemoglobin; nPCR = normalized protein catabolic rate; C_{cr} = creatinine clearance; 4 h D/P_{cr} ratio = 4 h dialysate/plasma creatinine ratio during a peritoneal equilibration test; RRF = residual renal function; CAPD = continuous ambulatory peritoneal dialysis.

The figures presented are the size of effect of each variable upon patient survival, given in the form of HR together with corresponding CI. When cystatin C is measured on a continuous scale, this represents the change in the hazard (or occurrence) of death for a 1-unit (1 mg/L) increase in cystatin C. When cystatin C is measured on a categorical scale, the HR represents the hazard of death at any time in the category with cystatin C >5.3 mg/L compared to the hazard of death in the baseline category (cystatin C ≤5.3 mg/L). A HR of greater than 1 would imply an increased risk of death, whilst a HR below 1 would imply a decreased risk of death. The HRs for the other continuous variables are given for a 1-unit increase in that variable, except when 1 unit was either a very small or very large amount, when results for different sized increases are reported (see footnote). Each predictor variable was treated as a time-varying covariate. Significant values are indicated in bold.

^a HR present for a 10-unit increase in explanatory variable.

^b HR present for a 5-unit increase in explanatory variable.

^c HR present for a 0.1-unit increase in explanatory variable.

to contribute minimally to overall cystatin C clearance (11). However, it is possible that peritoneal (23) and other non-renal (24) sources of cystatin C loss which are unlikely to be related to patient survival are responsible for the lack of relationship between cystatin C and outcomes. Davies *et al.* reported that peritoneal transport characteristics predict survival of PD patients independently of RRF (25). The patients in our study had a median

4 h D/P_{cr} of 0.78 and therefore the majority would have been categorized as high or high-average transporters. Although cystatin C correlates with RRF (13) it does not provide information about free water clearance, which would typically be reduced in individuals with fast transporter status. The effect of transport status may have negated the effect of RRF and in turn confounded any association with cystatin C in this population.

TABLE 3
Multivariable Analysis of Parameters Associated with Mortality

Predictor variable	Time to death		Outcomes	
	HR (95% CI)	<i>p</i>	Time to treatment failure HR (95% CI)	<i>p</i>
Cystatin C, mg/L	0.96 (0.71, 1.31)	0.81	0.95 (0.74, 1.21)	0.68
Age, years ^a	2.06 (1.57, 2.70)	<0.001	1.27 (1.08, 1.50)	0.005
4 h D/P _{cr} ratio ^b	1.42 (1.10, 1.84)	0.008	1.34 (1.09, 1.66)	0.006
RRF, mL/min/1.73 m ²	0.83 (0.73, 0.94)	0.005	0.89 (0.81, 0.98)	0.02
Diabetes (present vs absent)	1.91 (1.08, 3.36)	0.03	1.63 (1.02, 2.61)	0.04

HR = hazard ratio; CI = confidence interval; 4 h D/P_{cr} ratio = 4 h dialysate/plasma creatinine ratio during a peritoneal equilibration test; RRF = residual renal function.

The figures presented are the size of effect of each variable upon patient survival, adjusted for other significant variables, given in the form of HR together with corresponding CI. Predictor variables were treated as time-varying covariates.

^a HR present for a 10-unit increase in explanatory variable.

^b HR present for a 0.1-unit increase in explanatory variable.

Our PD population was fairly typical of such populations in the UK in terms of age, gender and diabetes prevalence (26). Peritoneal dialysis patients who did not enter the study were of a similar demographic to those that did. The long follow-up of our population saw an event occurring for many patients, either death or change in modality, again at a rate considered usual amongst such populations. The study was adequately powered across the whole population to show a difference in outcome and the required number of patients were recruited. All of the patients in the present study were assessed as receiving adequate dialysis as described by small solute clearances. There were very few anuric patients (5%).

Our study has limitations. Cystatin C was measured a variable number of times and at varying frequencies between patients, representing real-life clinical practice. Nevertheless, one would expect the availability of extra measurements in many patients to have increased the strength of any potential association between cystatin C and outcome over and above that obtained from study of the biomarker at baseline only. Furthermore, the relationship with death held true for RRF and transporter status in our multivariable analysis despite the similarly variable frequency of these measurements. One of our primary outcomes, transfer to hemodialysis, may reflect social and other factors in addition to failure of PD. A further limitation of the study was that despite considering a number of survival variables, we did not systematically collect data on inflammatory status (C-reactive protein), lipid concentrations, surrogate markers of bone turnover, or medication history. The patient population in Kent is predominantly Caucasian and therefore we cannot extrapolate our

findings to non-Caucasian populations. We included both incident and prevalent patients and patients receiving both CAPD and APD in our study cohort: however we found no evidence to suggest an interaction between survival and either patient type or modality. Unfortunately cause of death reporting was poor and data were unavailable for many patients. This precluded specific mortality analysis, i.e. all-cause compared to cardiovascular death. A large number of individuals ($n = 168$) who were under the care of the dialysis program during the period of the study were not included in the study for a variety of reasons including death in 34 individuals. Given that death was the outcome of interest, this clearly represents a limitation, although it is inherent in the nature of such studies.

CONCLUSIONS

In a predominantly Caucasian population serum cystatin C concentration did not predict death or treatment failure in PD patients despite the association with RRF. We find no evidence to alter standard practice in the assessment of RRF in patients receiving PD treatment.

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DISCLOSURES

None of the authors of this study have conflicts of interest to declare.

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