The effect of serum sodium with survival in patients treated by peritoneal dialysis in the UK

AsmaaAl-Chidadi[1]MRCP, Dorothea Nitsch[2] MRCP, Andrew Davenport[3] FRCP

[1]Department of Nephrology, Broomfield hospital, [2]London School of Hygiene & Tropical Medicine, [3]UCL Centre for Nephrology, Royal Free Hospital, University College London Medical School, London NW3 2PF, UK

Word count

Abstract	294
Body	3296
References	24
Figures	2
Tables	4
Appendix	2 tables

Key words peritoneal dialysis sodium mortality albumin age diabetes

short title – serum sodium and peritoneal dialysis patient outcomes

the authors have no conflict of interest

Abstract

Background

Studies in haemodialysis patients suggest that hyponatraemia is associated with increased mortality, however, results from peritoneal dialysis (PD) patients are discordant. We wished to establish whether there was an association between serum sodium and mortality risk in PD patients.

Methods

We analysed 3108 PD patients enrolled at day 90 of renal replacement therapy (RRT)

into the UK Renal Registry data base with available serum sodium measurements (in 3 groups: ≤137, 138-140, ≥ 141 mmol/l) who were then followed up until death, or the censoring date (31st Dec 2012). Analysis used Cox-regression with adjustment for age, sex, year of starting RRT, primary renal disease, serum albumin, smoking, and co-morbidities.

Results

Unadjusted mortality rates were 118.6/1000 person years (py), 83.4/1000 py, and 83.5/1000 py for the lowest, middle and highest serum sodium tertiles, respectively. After adjustment for covariates, patients in the lowest serum sodium group had almost 50% increased risk of dying compared to those with the highest serum sodium (HR 1.49, CI:1.28-1.74), with a graded association between serum sodium and mortality. The association of serum sodium with mortality varied by age (p interaction <0.001), and whilst this association attenuated after adjustment for confounding variables in the older age groups (55 – 64, and >65 years), it remained in the younger age group of 18-54 years (HR 2.24(1.36-3.70) in the lowest compared to the highest sodium tertile).

Conclusions

Lower serum sodium concentrations at the start of RRT in PD patients are associated with increased risk of mortality. Whilst this association may well be due to confounding in the older age groups, the persistent strong association between hyponatraemia in the younger age group after adjustment for the available confounders suggests that prospective studies are required to assess whether active intervention to maintain serum sodium changes outcomes.

Introduction

Hyponatraemia in the general population is well recognised to be associated with an increased risk for mortality [1]. Hyponatraemia is the commonest electrolyte disorder encountered in hospitalised patients and may develop due to increased renal

water retention secondary to vasopressin release (e.g. in patients with chronic liver disease and cardiac failure), or a failure to adequately excrete water as in cases of inappropriate vasopressin secretion, which may be drug induced, or alternatively due to polydipsia and reduced dietary sodium intake excessive water or beer ingestion, and also due to increased sodium losses associated with hypovolaemia from diuretics and purgatives [2]. Inflammatory states with increased secretion of IL-6 and C reactive protein (CRP) have also been documented to be associated with hyponatraemia due to vasopressin release [3].

Patients with chronic kidney disease may also develop hyponatraemia from either a relative excessive water intake to sodium, or relative greater loss of sodium compared to water. As with the general population there are several large observational studies reporting that pre-haemodialysis hyponatraemia is independently associated with increased risk of mortality for haemodialysis patients [4,5]. Whether this risk for mortality is directly attributable to hyponatraemia, and reduced body sodium stores, or whether hyponatraemia is acting as a surrogate for an inflammatory state and increased endothelial permeability remains to be determined. Although there are studies reporting no increased mortality with lower pre-haemodialysis serum sodium values [6]. However the situation is less clear for peritoneal dialysis patients, with one recent report suggesting an increased risk for mortality for prevalent peritoneal dialysis patients with a lower time-averaged serum sodium [7], whereas two others did not find any statistically significant association between lower serum sodium concentrations at either the start of peritoneal dialysis or intermittent episodes during treatment with peritoneal dialysis and mortality [8,9] . The one previous study reporting increased overall mortality with lower time averaged serum sodium concentrations potentially had a number of confounding factors, ranging from patient selection bias, through to censoring patients transferring from peritoneal dialysis, and statistical analysis. As such we wished to investigate whether hyponatraemia in peritoneal dialysis patients is associated with an increased mortality risk by using data from the UK Renal Registry.

Methods

In the UK data is collected on dialysis patients from the 71 National Health Service dialysis centres in England, Wales and Northern Ireland by the UK Renal Registry after patients have been treated by dialysis for 90 days. This 90 day cut off follows the USRDS data collection designed to exclude cases of acute kidney injury. We analysed data for incident peritoneal dialysis (PD) patients starting dialysis between 2000 and 2012 from centres reporting to the UK renal registry (UKRR). We restricted the analysis to those dialysis centres which had > 85% completeness of serum sodium data at the time of enrolment into the UKRR database. The lack of returns of serum sodium data for a subset of centres relates to their local data extraction routines.

Data from 14,920 patients starting any form of renal replacement therapy (haemodialysis, PD and transplantation) in the UK were collected including age at start of renal replacement therapy, sex, cause of primary renal disease, ethnic group, serum albumin, serum sodium, date of death, smoking status and comorbidity data (angina, non-coronary angioplasty, claudication, chronic obstructive airways disease, diabetes not causing end stage kidney disease, ischaemic and neuropathic ulcers, chronic liver disease, malignancy, previous myocardial infarction both within the last 3 months or more than 3 months from the date of enrolment, previous coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI), amputation for peripheral vascular disease (PVD) and symptomatic cerebrovascular disease. We also collected data on the dates of when dialysis started and ended, and changes in treatment modality. Cardiac disease as a co-morbidity variable was created by combining angina, previous myocardial infarction within the last 3 months, previous myocardial infarction more than 3 months ago, previous CABG or PCI. Peripheral vascular disease as a co-morbidity was created by combining non-coronary angioplasty, claudication and ischaemic or neuropathic ulcers.

552 out of the 14,920 patients died before completing 90 days on haemodialysis, peritoneal dialysis or transplantation and were therefore were removed

from analysis. We then restricted the data analysis to only those patients treated by PD at the time of enrolment by the UKRR, which left 3108 patients (Figure 1).

Rather than predefining patients according to serum sodium concentrations we grouped patients into 3 groups based on the distribution of their serum sodium concentrations; ≤137, 138-140, and ≥ 141 mmol/l.

Patients were then followed up from enrolment at 90 days after starting dialysis until death, or the censoring dates (either the last day these patients observed or the date the cohort was censored on the 31st of December 2012). Patients transferring modality to transplantation or to other UK renal dialysis centres were not censored to prevent introducing a selection bias towards unfit patients (those who are not transplanted).

Serum sodium measurements across different UK health care facilities are routinely standardised through the UK national external quality assessment body (NEQAS) for clinical chemistry laboratories, using an indirect potentiometer method. The UKRR collected serum sodium results electronically within the first quarter once patients had been established on peritoneal dialysis for 90 days, and the first serum sodium result after day 90 was used for this study...

Statistical Analysis

Descriptive analysis was conducted to determine the association between different potential predictors of mortality at baseline. The Chi square ($\chi 2$) test was used to assess associations between binary and categorical variables. Linear regression was used to examine the association of continuous explanatory variables (age and serum albumin) with the main exposure (serum sodium). In cases of missing data across categories of serum sodium and death, a missing data indicator variable was created for each missing data entry. The Z test was used to compare proportions of missing data within "dead" and "alive" groups of the outcome variable. The distribution of missing data across the main exposure categories was described after performing cross tabulation with missing indicator variables for each covariate.

Kaplan-Meier graphs (log rank test) were used to analyse patient survival according to serum sodium group. A Cox-regression model was used to examine the relationship between mortality and serum sodium concentration, while accounting for facility clustering effect using robust standard errors with time-on-study as the time-scale and baseline age as a covariate. Proportional hazard assumption for Cox model was investigated using two methods. Firstly graphs of -log (-log (survival)) against the log of time for each explanatory variable were plotted, and secondly Poisson models were fitted with interaction term between these explanatory variables and follow-up time obtained from lexis expansion. The graphical methods showed non-proportionality for the Cox hazard assumption for the serum sodium concentration and significant interaction with the follow-up time in the Poisson model, but when interaction terms between age and cause of kidney failure and age and comorbidities were included the hazard proportional assumption was valid (interaction between follow-up time and sodium disappeared) which justified the use of cox models. In total seven models were used, with each model building on the previous version (model 1: crude association of serum sodium with mortality; model 2: adjusted for sex and age, model 3: adjusted for period of starting PD, model 4: adjusted for primary renal disease, model 5: adjusted for serum albumin, model 6: adjusted for smoking and also including an interaction term between age and cause of primary renal disease while adjusting for age as continuous variable to account for potential residual confounding, and finally model 7: adjusted for comorbidities. Analysis was initially undertaken on the full cohort, and then restricted to the Caucasian cohort to avoid any potential bias due to patients from the ethnic minorities. Not all variables were recorded in every patient and sequential restrictions were implemented to ensure that comparison of hazard ratios were reviewed between similar cohorts albeit with some loss of power. Models with similarly available data on primary renal disease, serum albumin, smoking and co-morbidities were compared to understand the confounding effects of these covariates in similar cohorts. As age showed a significant interaction with serum sodium, then results were stratified by age categories. Statistical significance was taken at the $p<0.05$ level.

Ethical Approval

The UK Renal Registry has a UK wide ethical approval granted by the UK government secretary of state for health, through the UK patient information advisory group to collect patient data without individual patient consent. The study was approved by the London School of Tropical Medicine & Hygiene research ethics committee reference number 7565.

Results

The mean serum sodium for the 3108 new starters to peritoneal dialysis was 138.5±3.7mmol/l (range 120- 149). Patients were divided into tertiles, according to their serum sodium concentration (table 1). There were more proportionally more women and diabetics in the group with the lowest serum sodium concentrations, and relatively more patients starting PD between 2005 and 2009, than other eras. The serum albumin was also lower in the lower serum sodium tertiles, mean 36.5 g/l (95% confidence limits 35.4-35.8), compared to 37.4 g/l (37.2-37.6) in the middle sodium group and 38.3g/l (38.1-38.5) in the highest serum sodium group, $p<0.001$. However, there were no obvious association of serum sodium with age, or different types of co-morbidity.

The median follow up time was 3.2 (range: 0-12.7) years, with a total survival time of 11,872 person-years. Survival time after enrolment was greater for those patients in the highest and middle serum sodium cohorts, compared to those in the lowest cohort (figure 2). Estimated crude mortality rate was 118.63 per 1000 person years in the lowest serum sodium cohort, 83.36 per 1000 person years in the middle serum sodium cohort and 83.49 per 1000 person years in the highest serum sodium cohort. Patients with the lowest serum sodium group had around 50% increased risk of dying compared to those with the highest serum sodium cohort (HR 1.49, CI:1.28-1.74) while those who were in the middle serum sodium cohort had only 6%, non-significant increased risk of death (HR1.06, CI:0.90-1.26). As expected mortality was also associated with increasing age, male sex, diabetic nephropathy as primary renal disease,

co-morbidities, Caucasian ethnicity, and earlier era of starting dialysis, smoking and lower serum albumin (table 2).

There was a strong interaction between sodium categories and age (p value for interaction <0.001). Mortality rate decreased by 17% for each 3.6 mmol/l increase in serum sodium ((HR: 0.83 (CI 0.76-0.90). On crude analysis when sodium was entered as a continuous variable, there was a very strong evidence of association between mortality and serum sodium level (p<0.001). Results are shown in each age stratum separately (table 3). For the youngest age group, the association of a lower serum sodium with increased risk for mortality remained after adjusting for sex, era starting PD, primary renal disease, serum albumin, smoking and co-morbidities. However, when adjusting for these variables amongst middle and older aged groups the association of serum sodium with mortality was markedly attenuated, but remained significant (Hazard ratio 0.97, p=0.02).

To exclude any potential effect by diabetes, we then re-analysed the data by excluding patients who had diabetic nephropathy as their cause of renal disease. The association between a lower serum sodium, whether modelled as a continuous or categorical variable remained and mortality remained strongly significant (table 4).

Additional tables of analyses are presented in the on-line appendix.

Discussion

Our study reports an increased mortality rate associated with hyponatraemia in PD patients at the time of enrolment into the UKRR. There was a 3% reduction in mortality for each 3.6 mmol/l increase in serum sodium. This association between mortality and hyponatraemia was modified by age, with our younger age group having more than a twofold increased risk of death, even after adjusting for age and other covariates associated with mortality. Whereas some studies have reported an increased mortality with increasing serum sodium [10], we found a relative protective effect of higher serum sodium concentrations, in keeping with the DOPPS report in haemodialysis patients [6] and one smaller study in peritoneal dialysis patients [11].

Hyponatraemia is a recognised risk factor for mortality in the general population and patients admitted to hospital [1]. Traditionally this risk has been ascribed to underlying co-morbidity, such as congestive cardiac failure, cirrhosis and tumour induced inappropriate ADH syndrome. The situation for patients with chronic kidney disease may be somewhat more complex, with reports of both hyponatraemia and also hypernatraemia associated with increased mortality [10], and although there are reports of increased risk for mortality in hyponatraemic haemodialysis patients [4,5], these reports are biased towards more co-morbid patients because they censored patients who were transplanted from the analyses. Our analyses were more conservative – if we had censored the patients who were transplanted we would have biased our sample to the more ill population, and similarly if we had removed all patients with technique failure from the mortality outcome analysis we would have biased our sample to a more healthy population. Incident haemodialysis patients, who were hyponatraemic after adjusting serum sodium measurements for diabetic control were reported to have an increased risk for death [12], whereas others have reported that hyponatraemia does not confer any additional risk for mortality [6] and also in non-haemodialysis diabetic patients [13]. Similarly some studies in haemodialysis patients reported that mortality reduced for each 4 mmol/l increase in serum sodium [4], although others reported no survival advantage once the serum sodium reached 145 mmol/l [6].

We found that the mortality risk associated with hyponatremia was greatest for the younger age group, compared to the older and middle age groups, whereas other studies have not reported any age effect [7,8]. There was also a higher proportion of patients in the lowest serum sodium cohort in the younger age group (45%) compared to the middle (21%) and older (34%) age groups. The higher effect estimate and the higher proportion of hyponatraemia in the younger age group might be partially explained by the higher proportion of patients with diabetic nephropathy in this group (50%) compared to middle (24%) and the older (25%) age groups. There has been debate as to the effect of increasing glucose concentrations on the measurement of serum sodium using indirect potentiometer and flame photometry [14], and potential

correction factors for adjusting serum sodium for glucose, with some studies reporting no difference in serum sodium concentration between diabetic and non-diabetic dialysis patients [6, 15]. Previous observational studies have suggested greater inter-dialytic weight gains in diabetic patients [16], and greater ratio of extracellular to total body water in diabetic peritoneal dialysis patients [17], suggesting that hyponatraemia in diabetic dialysis patients may have an over hydration component, perhaps due to increased thirst. However, when we repeated our analyses after excluding those patients who had diabetes as the primary cause of end-stage kidney disease, the association between lower serum sodium and mortality remained, as did the effect of age. As such this association cannot simply be explained by diabetes.

As expected co-morbidity increased with age, being highest in the older age group (53%) compared to the middle (25%) and the younger (22%), whereas serum albumin fell with increasing age. Previous studies in hyponatraemic patients reported an association with lower serum albumin and malnutrition [8,18] and relative extracellular water over-hydration [19] due to loss of intracellular water and body cell mass [20,21]. The UKRR does not collect data on nutritional status or body composition, even so our data would support a role for inflammation and malnutrition in inducing hyponatraemia, as serum albumin concentrations were lowest in the lowest serum sodium cohort, although we have no corroborating measures of inflammation in terms of C reactive protein or body composition data, relating either to extracellular water excess or loss of lean body tissues. Studies of acutely ill peritoneal dialysis patients admitted with peritonitis have reported an association between lower serum sodium in the acute situation and worse outcomes [22].

When adjusting for co-morbidities [23], there was a greater increase in HR for lower sodium and mortality in the younger patients and to a lesser extent for the older age group, suggesting a confounding effect of increasing comorbidity with age. Mortality rate was higher in the young age groups, which was only partially explained by the higher proportion of diabetes as a cause of primary renal disease among the younger age group and its associated ill health and social deprivation [24]. This effect

modification of age and confounding by covariates, in particular diabetes and albumin, may help to explain the discordant results from other studies in peritoneal dialysis patients, recently reported in studies from Korean and Taiwan [7,9].

As with any retrospective observational study, our study has a number of limitations. Outcome data was missing in 5.6% of cases, but this was equally distributed between the three sodium concentration cohorts, and coupled with similar distribution of follow up time across the cohorts it is unlikely to have biased the results. We adjusted for comorbidities, as they are important predictors for mortality, to enable a less biased conclusion to be reached. Some subgroup analyses were small and had wide confidence intervals, however the size and direction of effect estimates remained consistent. The UKRR does not collect data on the type of peritoneal dialysis solutions used by patients, and as such we were unable to adjust for icodextrin usage [19]. However, icodextrin would only be a potential confounder if icodextrin usage had been restricted to the younger patients. Similarly the UKRR does not collect data on residual renal function, or the prescription of diuretics and anti-hypertensives. We cannot exclude that restoration of haemoglobin concentrations in patients starting PD might be associated with restoration of other nutritional parameters. However as the vast majority of patients starting PD in the UK have pre-dialysis nephrology care with access to erythropoietin stimulating agents (ESAs), and clinical guideline targets for haemoglobin concentration, makes this less likely. As the UKRR does not collect data on ESA usage or iron administration; we were unable to determine erythropoietin resistance, and as such cannot exclude an association with hyponatraemia and mortality due to an association with serum albumin.

In studies which have reported on time averaged serum sodium, lower serum sodium is associated with lower residual renal function and increased peritoneal ultrafiltration [8]. Whether this association is due to changes in peritoneal dialysis prescription and exposure to higher glucose peritoneal dialysates remains to be determined. Even if we had data on type of dialysate prescription over time the issue is that adjusting the associations for changes in prescription over time would be adjusting for variables on the causal pathway. We were also not able to determine volume status, but previous

studies have reported that only a minority of peritoneal dialysis patients with hyponatraemia are overhydrated [7,8]. Similarly we were unable to access data on dietary sodium intake, and the UKRR does not collect data on hydration status of peritoneal dialysis patients. Compared to previous studies which used time averaged serum sodium [22], we chose only to analyse the first serum sodium measured after starting peritoneal dialysis to reduce bias from changes in residual renal function, peritoneal dialysis prescription and censoring due to modality changes. More importantly time averaged serum sodium is likely to be biased by hospital admissions with acute inter-current illnesses, as these are more likely to be associated with a lower serum sodium values, and also increased number of measurements.

Our study shows that lower serum sodium concentrations at the start of renal replacement therapy in peritoneal dialysis patients is associated with increased risk of mortality. As with any observational study causality cannot be established, however the persistent strong association between hyponatraemia in the younger age group after adjustment for the available confounders requires more investigation. Prospective studies are required to determine whether active interventions designed to sustain serum sodium concentrations improve patient outcomes.

Funding Royal Free Hospital

Acknowledgement: We thank all the UK renal units for providing data to the UK Renal Registry.

Disclaimer: Any views or opinions expressed are solely those of the authors and do not necessarily represent those of the UK Renal Registry.

No author has any conflicts of interest

References

1. Asadollahi K, Beeching N, Gill N. Hyponatraemia as a risk factor for hospital mortality. Quart J Med. 2006; 99: 8677-80
2. Davenport A. The brain and the kidney-organ cross talk and interactions. Blood Purif 2008; 26: 526-536
3. Horn EJ, Zietse R. Hyponatraemia revisited: translating physiology into practice. Nephron Physiol. 2008;108: 46-59
4. Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in maintenance haemodialysis. Am J Med. 2011; 124:77-84
5. Iseki K, Uehara H, Nishime K, Tokuyama K, Yoshihara K, Kinjo K, Shiohira Y, Fukiyama K, Impact of the initial levels of laboratory variables on survival in chronic dialysis patients. Am J Kid Dis. 1996:28;541-54
6. Hecking M, Karaboyas A, Saran R, Sen A, Horl WH, Pisoni R, Robinson B, Sunder-Plassmann G, Port F, Predialysis Serum Sodium Level, Dialysis Sodium, and Mortality in Maintenance Haemodialysis Patients: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2012; 59(2): 238-248.
7. Chang TI, Kim YL, Kim H, Ryu GW, Kang EW, Park JK, Yu T-H, Shin SK, Kang S-W, Choi KH, Han DS, Han SH. Hyponatraemia as a Predictor of Mortality in Peritoneal Dialysis Patients. PLoS ONE 2014; 9(10):e111373. doi:10.1371/journal.pone.0111373
8. Kang SH, K.H.C., Park JW, Yoon KW, Do JY. Characteristics and Clinical Outcomes of Hyponatraemia in Peritoneal Dialysis Patients. Nephrology (Carlton), 2013; 18: 132-137

9. Chen K-H, Chen C-Y, Lee C-C, Weng C-M, Hung C-C. Baseline hyponatraemia does not predict two-year mortality in patients with chronic peritoneal dialysis. Ren Fail. 2014: 1-5
10. Kovesdy CP, Lott EH, Lu JL, Malakauskas SM, Ma JZ, Molnar MZ, Kalantar-Zadeh K. Hyponatraemia, hypernatraemia, and mortality in patients with chronic kidney disease with and without congestive heart failure. Circulation. 2012: 125, 677–684.
11. Kim HW, Ryu GW, Park CH, Kang EW, Park JT, Han SH, Yoo TH, Shin SK, Kang SW, Choi KH, Han DS, Chang TI. Hyponatremia Predicts New-Onset Cardiovascular Events in Peritoneal Dialysis Patients. PLoS One. 2015 ;10(6):e0129480
12. Nigwekar SU, Wenger J, Thadhani R, Bhan I. Hyponatremia, mineral metabolism, and mortality in incident maintenance haemodialysis patients: a cohort study. Am J Kidney Dis. 2013;62(4):755-62
13. Sahin OZ, Asci G, Kircelli F, Yilmaz M, Duman S, Ozkahya M, Dogan C, Odabas AR, Cirit M, Ok E. The impact of low serum sodium level on mortality depends on glycemic control. Eur J Clin Invest. 2012;42(5):534-40
14. Persaud J, Thomas M, Davenport A. Indirect ion selective electrode methods potentially overestimate peritoneal dialysate sodium losses. Ther Apher Dial. 2014;18(4):321-5
15. Davenport A. Interdialytic weight gain in diabetic haemodialysis patients and diabetic control as assessed by glycated haemoglobin. Nephron Clin Pract. 2009;113(1):c33-7
16. Davenport A, Cox C, Thuraisingham R. Blood pressure control and symptomatic intradialytic hypotension in diabetic haemodialysis patients: a cross-sectional survey. Nephron Clin Pract. 2008;109(2):c65-71
17. Davenport A, Willicombe MK. Does diabetes mellitus predispose to increased fluid overload in peritoneal dialysis patients? Nephron Clin Pract. 2010;114(1):c60-6

18. Zevallos, G., D.G. Oreopoulos and M.L. Halperin, Hyponatremia In Patients Undergoing CAPD: Role Of Water Gain And/Or Malnutrition. Peritoneal Dialysis International, 2001. 21(1):. 72-78
19. Davies SJ, Garcia Lopez E, Woodrow G, Donovan K, Plum J, Williams P, Johansson AC, Bosselmann HP, Heimburger O, Simonsen O, Davenport A, Lindholm B, Tranaeus A, Divino Filho JC. Longitudinal relationships between fluid status, inflammation, urine volume and plasma metabolites of icodextrin in patients randomized to glucose or icodextrin for the long exchange. Nephrol Dial Transplant. 2008;23(9):2982-8
20. Davenport A, Willicombe MK. Comparison of fluid status in patients treated by different modalities of peritoneal dialysis using multi-frequency bioimpedance.Int J Artif Organs. 2009, 32(11):779-86
21. Davies SJ, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int. 2014;86(3):489-96
22. Tseng MH, Cheng CJ, Sung CC, Chou YC, Chu P, Chen GS, Lin SH. Hyponatremia is a surrogate marker of poor outcome in peritoneal dialysis-related peritonitis. BMC Nephrol. 2014;15:113. doi: 10.1186/1471-2369-15-113
23. CollierTR. Steenkamp R Tomson CRV, Caskey F, Ansell D, Roderick P, Nitsch D, Patterns and effects of missing comorbidity data for patients starting renal replacement therapy in England, Wales and Northern Ireland. Nephrol Dial Transplant, 2011. 26(11): 3651-8.
24. Nitsch D, Burden R. Steenkamp R, Ansell D, Byrne C, Caskey F, Roderick P, Feest T. Patients with diabetic nephropathy on renal replacement therapy in England and Wales. QJM, 2007. 100(9):. 551-60

Figure 1: Flow diagram to show patient study recruitment

Figure 2: Patient Kaplan Meier survival graph

Table 1: Patients divided according to serum sodium at enrolment by UK Renal Registry after day 90 of peritoneal dialysis. Age and other variables at the time of enrolment, patients were also divided according to age and era of starting peritoneal dialysis. . Results as number, percentage (%), mean and 95% confidence limits) unless otherwise stated. Diabetic nephropathy (DN), Co-morbidities : cardiovascular disease (CVS), peripheral vascular disease (PVD), chronic obstructive airways disease (COPD), chronic liver disease (CLD), diabetes mellitus (DM) not causing renal failure, symptomatic cerebrovascular disease (CerebVD), Co-morbidity (Comorbid). *p value for association

Variable		N (%)	Serum Sodium			
			<138 mmol/l	138-140 mmol/l	> 140mmol/l	*p value
Patients		3,108	1061 (35.5%)	1006 (33.6%)	925 (30.9%)	
Age yr		3,108	58.4(57.4-59.3%)	58.5(57.5-59.5%)	58.2(57.2-59.4%)	0.924
	18-54 yr	1164(37.5%)	401(37.8%)	378(37.6%)	346(37.4%)	0.992
	55-64 yr	676(21.8%)	230(21.7%)	215(21.4%)	206(22.3%)	
	≥65 yr	1268(40.8%)	430(40.5%)	413(41.1%)	373(40.3%)	
Sex	Male	1949(62.7%)	607(57.3%)	628(62.4%)	648(70.1%)	<0.001

	Female	1159(37.3%)	453(42.7%)	378(37.6%)	277(30.0%)	
ethnicity	Asian	131(4.4%)	56(5.5%)	46(4.8%)	25(2.8%)	0.098
	Black	60(2.0%)	17(1.7%)	18(1.9%	23(2.6%)	
	White	2751(92.4%)	925(91.6%)	891(92.1%)	829(93.3%)	
	Other	37(1.2%)	12(1.2%)	13(1.3%)	12(1.4%)	
Era	2000-2004	774(24.9%)	570(25.8%)	642(29.3%)	433(22.4%)	<0.001
	2005-2009	1616(51.9)	1248(56.4%)	1129(51.6%)	1107(57.2%)	
	2010-2012	718(23.1%)	394(17.8%)	418(19.1%)	396(20.5%)	
Primary Renal	DN	551(18.7%)	266(26.7%)	146(15.1%)	110(12.6%)	<0.001
Disease	Other	2404(81.3%)	732(73.4%)	822(84.9%)	766(87.4%)	
Smoking	Nonsmoker	1488(86.3%)	497(84.5%)	534(86.7%)	414(87.5%)	0.332
	Smoker	237(13.7%)	91(15.5%)	82(13.3%)	59(12.5%)	
CVS	Absent	1458(83.3%)	498(83.8%)	515(83.1%)	405(83.3%)	0.935
	Present	293(16.7%)	96(16.2%)	105(16.9%)	81(16.7%)	
PVD	Absent	1664(95.3%)	558(94.3%)	591(95.3%	466(96.3%)	0.298
	Present	83(4.7%)	34(5.7%)	29(4.7%)	18(3.7%)	
COPD	Absent	1666(95.9%)	562(95.3%)	571(95.9%)	467(96.9%	0.396
	Present	71(4.1%)	28(4.8%)	25(4.1%)	15(3.1%)	
DM	Absent	1640(94.4%	555(94.1%)	576(93.7%)	462(95.5%)	0.420
	Present	98(5.6%)	35(5.9%	39(6.3%	22(4.6%)	
CLD	Absent	1723(98.6%)	582(98.3%)	612(98.9%)	478(98.6%)	0.712
	Present	24(1.4%)	10(1.7%)	7(1.1%)	7(1.4%)	
Cancer	Absent	1582(90.6%)	542(91.4%)	562(90.8%	432(89.3%)	0.474
	Present	165(9.4%)	51(8.6%)	57(9.2%)	52(10.7%)	
CerebVD	Absent	1618(93.0%)	547(92.9%)	575(93.0%)	449(93.0%)	0.993
	Present	122(7.0%)	42(7.1%)	43(7.0%)	34(7.0%)	
Comorbid	Absent	1114(63.4%)	375(63.0%)	393(63.2%)	314(64.3%)	0.890
1 or more	Present	642(36.6%)	220(37.0%)	229(36.8%)	174(35.7%)	

Table 2 : Multivariable analysis (adjusted for age and sex only): Association of covariates with mortality in the cohort of patients on peritoneal dialysis at start of renal replacement therapy (RRT) adjusted for sex and age. Serum sodium (sodium), age at start of RRT (age), Diabetic nephropathy (DN) as primary cause or renal disease. Hazard ratio (HR).

Variable	category	Rate	time per 1000 patient yrs	HR (95 % CI)	P value
Sodium	continuous			0.95(0.93-0.97)	<0.001
Sodium	<138	118.63	3.87	1.49(1.28-1.74)	<0.001
mmol/l	138-140	83.36	3.99	1.06(0.90-1.26)	
	> 140	83.49	3.57	1	
Albumin g/l	continuous			0.92(0.91-0.94)	<0.001
RRT start	2000-2004	107.0	4.4	1	0.002
	2005-2009	93.0	6.4	0.80(0.68-0.93)	
	2010-2012	75.7	1.1	0.63(0.50-0.82)	
Age yrs	18-54	34.06	5.31	1	<0.001
	55-64	88.80	2.67	2.72(2.18-3.39)	
	≥65	187.16	3.89	5.68(4.57-7.07)	
Sex	Male	103.88	7.4	1	<0.001
	Female	84.51	4.51	0.82(0.73-0.92)	
Ethnicity	White	91.54	10.70	1	<0.001
	Asian	59.45	0.52	0.84(0.60-1.17)	

	Black	32.11	0.28	0.50(0.23-1.10)	
	Other	37.96	0.16	0.72(0.52-0.99)	
DN	Absent	86.86	9.65	1	<0.001
DN	Present	126.06	1.90	1.66(1.29-2.15)	
Smoker	No	75.94	6.11	1	0.130
	Yes	92.38	0.91	1.33(0.92-1.91)	
No co-morbidity	Absent	50.25	4.76	1	<0.001
≥ 1 co-morbidity	Present	135.38	2.39	1.82(1.35-2.45)	

Table 3: Crude and sequentially adjusted hazard ratios (HR) with 95% confidence intervals of serum sodium on long-term survival after 90 days from the start of peritoneal dialysis, stratified by age category. Model 1 – adjusted for age as a continuous variable and sex, Model 2 – additionally adjusted for year of starting renal replacement therapy, Model 3 additionally adjusted for primary renal disease, Model 4 additionally adjusted for serum albumin, Model 5 additionally adjusted for smoking, Model 6 additionally adjusted for co-morbidity

Patient age			Serum	Sodium	mmol/l	
18-54years	No patients	No of patients with the event	< 138	138-140	>140	p value
unadjusted	1125	111	2.18(1.48-3.22)	1.04(0.58-1.86)	1	<0.001
Model 1	1125	111	2.20(1.49-3.23)	1.03(0.55-1.91)	1	<0.001
Model 2	1125	111	2.18(1.48-3.20)	1.02(0.54-1.91)	1	<0.001
Model 3	1073	102	1.77(1.18-2.65)	1.03(0.56-1.91)	1	<0.001
Model 4	1057	99	1.53(1.01-2.32)	0.93(0.48-1.83)	1	0.009
Model 5	611	45	1.99(1.20-3.29)	1.43(0.75-2.74)	1	0.007

Model 6	609	45	2.24(1.36-3.70)	1.52(0.80-2.88)	1	0.002
55-64years						
Unadjusted	651	164	1.45(1.01-2.07)	1.02(0.65-1.58)	1	0.103
Model 1	651	164	1.46(1.01-2.12)	1.03(0.65-1.61)	1	0.047
Model 2	651	164	1.44(1.01-2.06)	1.00(0.64-1.57)	1	0.034
Model 3	619	151	1.18(0.86-1.61)	0.95(0.63-1.44)	1	0.261
Model 4	614	148	1.05(0.78-1.44)	0.87(0.53-1.43)	1	0.571
Model 5	347	62	1.02(0.50-2.08)	1.35(0.75-2.44)	1	0.368
Model 6	346	62	1.00(0.48-2.08)	1.28(0.69-2.38)	1	0.462
65+years						
Unadjusted	1216	452	1.32(1.12-1.55)	1.10 (0.93-1.30)	1	<0.001
Model 1	1217	452	1.30(1.12-1.52)	1.07 (0.90-1.26)	1	0.002
Model 2	1217	452	1.28(1.10-1.49)	1.05 (0.90-1.23)	1	0.003

Model 3	1150	422	1.30(1.11-1.53)	1.11 (0.94-1.31)	1	0.007
Model 4	1139	418	1.12(0.95-1.33)	1.06 (0.87-1.27)	1	0.399
Model 5	693	219	1.14(0.92-1.42)	1.10 (0.87-1.39)	1	0.491
Model 6	693	219	1.20(0.95-1.52)	1.11 (0.88-1.39)	1	0.327

Footnote: models adjusted for comorbidities included an interaction term between comorbidities and age, models adjusted for primary renal disease (PRD) included an interaction term for PRD

Table 4: Multivariable analysis (adjusted for age and sex only) in patients without a diagnosis of diabetes

Variable	category	Rate	time per 1000 patient yrs	HR (95 % CI)	P value
Sodium (continuous)				0.95 (0.93-0.97)	<0.001
Sodium (categorical -mmol/l)	<120-137	114.8	2.83	1.54 (1.30-1.81)	<0.001
	138-140	97.0	3.30	1.13 (0.92-1.38)	
	≥ 141-149	75.5	3.12	1	
Albumin g/l (continuous)				0.95 (0.93-0.96)	<0.001
RRT start	2000-2004	100.11	3.62	1	0.008
	2005-2009	84.95	5.11	0.78 (0.64-0.95)	
	2010-2012	74.15	0.88	0.66 (0.50-0.87)	
Age yrs	18-54	23.93	4.30	1	<0.001
	55-64	76.27	2.12	3.35 (2.64-4.24)	
	≥65	187.85	3.17	8.20 (6.09-11.04)	
Sex	Male	99.65	5.85	1	0.037
	Female	74.12	3.75	0.80 (0.79-0.99)	
Ethnicity	White	84.91	8.66	1	<0.001
	Asian	48.01	0.35	0.78 (0.58-1.05)	
	Black	23.04	0.26	0.46 (0.20-1.10)	
	Other	7.28	0.14	0.20 (0.04-0.93)	
Smoker	No	70.0	4.93	1	0.524
	Yes	69.18	0.69	1.13 (0.78-1.62)	
No co-morbidity	Absent	45.19	4.12	1	<0.001
≥ 1 co-morbidity	Present	134.58	1.60	1.78 (1.30-2.45)	