Chapter 17: Survival on renal replacement therapy: associations with albumin, urea reduction ratio and phosphate

Background

The development of the Renal Registry provides the opportunity for UK nephrologists to examine the outcomes for patients with ESRF. Previous studies from the USA (Lowrie 1990, Owen 1993, Collins 1994) have shown that survival on renal replacement therapy is associated with certain biochemical variables.

A number of studies have reported that hypo-albuminaemia is powerful predictor of subsequent mortality in ESRF patients (Lowrie 1990, Owen 1993). The precise role of comorbidity, inflammatory/infective conditions and poor nutrition in the hypo-albuminaemia and the increased mortality rate is uncertain (Kaysen 1995). There are no prospective studies demonstrating a reduction in mortality following interventions which raise serum albumin.

Retrospective (Lowrie 1990) and uncontrolled (Hakim 1994, Parker 1994) prospective studies have shown that higher urea reduction ratios (URR) are associated with improved patient survival in haemodialysis. The current HEMO study in the USA is examining in a prospective fashion the effect of differing doses of dialysis based on urea removal (Eknoyan 1996).

In the 1998 report the relationship between serum phosphate and mortality was explored. It was found that lowest mortality risk was associated with phosphate concentrations of 1.71-2.11mmol/l. Over 2.11mmol/l the risk of death increased in accordance with the findings of Block et al (Block 1998). Further analysis of this data has been performed including adjusting phosphate for serum creatinine. The purpose of this was to try to account for low muscle mass to determine whether phosphate had a direct effect on mortality or whether this was mediated through nutritional considerations.

Patient Selection and Statistical Methods

The sample consisted of patients who were on dialysis at the start of the 1/1/1998 who were:-

1. receiving treatment at one of the 11 centres on the Renal Registry database
2. were known definitely to have been on dialysis for >1year
3. had quarterly data for 1997.

Not every centre had a complete set of data for each parameter therefore it was not possible to use a uniform sample for each analysis. The details of the excluded patients, reasons for exclusions and the final sample size are given for each variable. For albumin, the HD and PD patients are considered separately because of the difference in albumin ranges between the two forms of therapy.

A Cox Proportional Hazards Model was used to analyse the relationship between each variable and risk of death over the one year period, adjusting for age, length of time on RRT, whether the patient had a primary diagnosis of diabetes and treatment centre. Age and length of time on RRT were entered into the model as continuous variables. The length of time on

RRT was measured in days on the 1/1/1998 and its log transform was used in the model. Patients with a primary diagnosis of 'Not sent' were excluded from the adjusted analysis, as were patients who had been on RRT for an unknown duration. Patients were categorised at the centre where they were receiving treatment on the 1.1.1998 even if they transferred out to a different Renal Registry Centre during the year.

Patients were censored if they transferred out from a Renal Registry Site to a non Renal Registry Site or if they had a transplant in 1998. The 'number of days at risk' was calculated according to the methods described on page 39 of the 1999 Report. Note that if a patient died on the day of transplant, then the death has not been counted. If a patient transferred out and had a transplant, then the patient was censored on the date of the first event. Note that all patients who were still under follow up on the 31/12/1998 were censored on this date.

The results from the Cox Proportional Hazards Model can be interpreted using hazard ratios. The hazard ratio is the ratio of the estimated hazards, where the hazard is the risk of dying at time t given that the individual has survived until this time. The underlying assumption of a proportional hazards model is that this ratio between 2 groups remains constant throughout the follow up period under consideration.

Serum Albumin

Sample size

Patients receiving treatment at Centres E and N were excluded from the analysis due to the lack of albumin data from these centres. Patients receiving treatment at Centre H were excluded from the analysis, as this centre measures their albumin using the BCP method. This resulted in a sample of 1,684 PD and 1768 HD patients. Note that patients receiving treatment at Centre G were included in the analysis, although in this centre some HD patients at satellite units had albumin measured by the BCP method.

Patients were included in the analysis, regardless of their previous treatment and transplant history. The analysis only considered patients who had been on PD/HD throughout the last quarter of 1997. This reduced the sample size to 512 PD patients, of which 454 patients had albumin data and 1172 HD patients of whom 1063 had albumin data.

Methods

Albumin from the last quarter of 1997 was considered in the analysis. The albumin was not laboratory harmonised. The analysis was first carried out categorising albumin as < 35g/L and ≥ 35g/L. This categorisation was chosen since it coincides with the cut-off used in the Renal Registry Report. The analysis was repeated categorising the albumin into quintiles which were defined by albumin concentration (g/L) as:-

	PD	HD
1st quintile	<31	<36
2nd quintile	32-34	37-38
3rd quintile	35-37	39-40

4th quintile	38-39	41-42
5th quintile	>40	>42

The adjusted and unadjusted survival analysis was stratified by centre. Stratifying by centre enables a separate underlying hazard to be estimated at each centre although assumes that the effect of albumin and confounding variables on the hazard to be the same at each centre. In the adjusted model, an interaction was fitted between survival time and whether the patient had a primary diagnosis of diabetes. This was because the assumption of proportional hazards did not seem reasonable for this factor.

Results

PD patients

Categorising albumin as < 35g/L and ≥ 35g/L.

Albumin	Unadjusted Analysis (n = 454) Hazard Ratio [95% CI]	Adjusted Analysis (n = 432) Hazard Ratio [95% CI]
< 35g/L	3.09 [1.92 – 4.98]	2.95 [1.75 – 4.97]
≥ 35g/L	REF	REF
X^2	23.2	17.9
p-value	<0.0001	<0.0001

NB: Although the term 'Unadjusted Analysis' has been used, the analysis was stratified by centre.

Categorising albumin into quintiles.

Albumin	Unadjusted Analysis (n = 454) Hazard Ratio [95% CI]	Adjusted Analysis (n = 432) Hazard Ratio [95% CI]
≤ 31g/L	8.72 [3.37 – 22.58]	6.85 [2.31 – 20.26]
32 – 34g/L	2.68 [0.92 – 7.79]	2.38 [0.73 – 7.75]
35 – 37g/L	2.69 [0.99 – 7.30]	1.97 [0.64 – 6.04]
38 – 39g/L	1.24 [0.33 – 4.65]	1.30 [0.32 – 5.32]
≥ 40g/L	REF	REF
X^2	43.5	31.3
p-value	<0.0001	<0.0001

In the unadjusted analysis, the association between albumin and risk of death could be explained by a linear relationship ($X^2 = 39.2$, d.f = 1, $p < 0.0001$), such that moving up one albumin category was associated with a decrease in hazard of 0.56 [95% CI: 0.46 – 0.68].

In the adjusted analysis, the association between albumin and risk of death could also be explained by a linear relationship ($X^2 = 28.2$, d.f = 1, $p < 0.0001$), such that moving up one albumin category was associated with a decrease in hazard of 0.57 [95% CI: 0.46 – 0.71].

Fitting Albumin into the Model as a Continuous Variable.

Since some evidence for a linear relationship was found, when albumin was categorised into quintiles, it was decided to fit albumin into the model as a continuous variable. This has the advantage over fitting the categorised albumin as an ordinal variable, in that the results and hence their interpretation are not dependent upon the scores given to the categories.

In the unadjusted analysis, a statistically significant association with albumin was found ($X^2 = 46.6$, d.f. = 1, $p<0.0001$), such that an increase in 1g/L of albumin was associated with decrease in the hazard of death of 0.86 [95% CI: 0.83 – 0.90].

In the adjusted analysis, a statistically significant association with albumin was found ($X^2 = 37.3$, d.f = 1, $p<0.0001$), such that an increase in 1g/L of albumin was associated with decrease in the hazard of death of 0.86 [95% CI: 0.83 – 0.90].

HD patients

Categorising albumin as < 35g/L and ≥ 35g/L.

Albumin	Unadjusted Analysis (n = 1063) Hazard Ratio [95% CI]	Adjusted Analysis (n = 1028) Hazard Ratio [95% CI]
< 35g/L	1.74 [1.15 – 2.63]	1.27 [0.82 – 1.96]
≥ 35g/L	REF	REF
X^2	6.2	1.1
p-value	0.0128	0.3039

Categorising albumin into quintiles.

Albumin	Unadjusted Analysis (n = 1063) Hazard Ratio [95% CI]	Adjusted Analysis (n = 1028) Hazard Ratio [95% CI]
≤ 36	4.09 [2.18 – 7.71]	2.56 [1.33 – 4.93]
37 – 38	4.48 [2.37 – 8.47]	3.16 [1.65 – 6.07]
39 – 40	2.09 [1.06 – 4.13]	1.81 [0.91 – 3.59]
41 – 42	1.10 [0.50 – 2.47]	0.87 [0.38 – 1.99]
≥ 43	REF	REF
X^2	48.7	26.7
p-value	<0.0001	<0.0001

In the unadjusted analysis, the association between albumin and risk of death could be explained by a linear relationship ($X^2 = 41.7$, d.f = 1, $p < 0.0001$), such that moving up one albumin category was associated with a decrease in hazard of 0.68 [95% CI: 0.60 – 0.77].

In the adjusted analysis, the association between albumin and risk of death could not be completely explained by a linear relationship, since although a statistically significant linear trend was found ($X^2 = 18.7$, d.f = 1, $p < 0.0001$), there was also a statistically significant departure from trend ($X^2 = 8.0$, d.f = 3, $p = 0.0467$).

Fitting Albumin into the Model as a Continuous Variable.

Since some evidence for a linear relationship was found, when albumin was categorised into quintiles, it was decided to fit albumin into the model as a continuous variable. This has the advantage over fitting the categorised albumin as an ordinal variable, in that the results and hence their interpretation are not dependent upon the scores given to the categories.

In both the unadjusted and adjusted analysis, a statistically significant quadratic effect was found. Whether this effect is an anomaly due to a few outlying observations, or whether it is valid for these data has not been investigated further at this stage.

Urea Reduction Ratio

Sample size

Patients known to be dialysing once, twice, or four times a week in the last quarter of 1997 were excluded from the analysis, although patients dialysing at an unknown frequency were included in the analysis. Patients on home HD were included in the analysis (unlike the analysis of URR data in the 1999 Report). This resulted in a sample of 1,352 patients of which 845 patients had URR data. Patients receiving treatment at Centres E, T V W and V were excluded from the analysis since less than 75% of patients had URR data from these centres. This resulted in a sample of 872 patients, of which 754 patients had URR data.

Statistical Methods

The URR from the last quarter of 1997 were included in the analysis. The analysis was first carried out categorising the URR as <65% and ≥65% to coincide with the Renal Association Standard and was repeated categorising the URR into quintiles. For this sample, the quintiles were defined as follows: ≤60, 61-64, 65-68, 69-72 and ≥ 73%.

Results

Categorising URR as < 65% and ≥ 65%.

URR	Unadjusted Analysis (n = 754) Hazard Ratio [95% CI]	Adjusted Analysis (n = 713) Hazard Ratio [95% CI]
< 65	1.79 [1.26 – 2.55]	1.56 [1.07 – 2.27]
≥ 65	REF	REF
X^2	10.6	5.4
p-value	0.0011	0.0199

4.3.2. Categorising URR into quintiles.

URR(%)	Unadjusted Analysis (n = 754) Hazard Ratio [95% CI]	Adjusted Analysis (n = 713) Hazard Ratio [95% CI]
≤ 60	2.30 [1.31 – 4.05]	1.90 [1.04 - 3.45]
61 – 64	0.93 [0.49 – 1.76]	0.75 [0.38 – 1.48]
65 – 68	0.99 [0.53 – 1.85]	0.86 [0.45 – 1.66]
69 – 72	0.65 [0.32 – 1.32]	0.64 [0.31 – 1.32]
≥ 73	REF	REF
X^2	25.5	18.8
p-value	<0.0001	0.0008

The association between URR and risk of death was non-linear in the unadjusted and adjusted analysis.

Serum Phosphate

Sample size.

The same sample as previously used was considered for the analysis published in the 1998 report.

Method

A logistic regression analysis was used to analyse the association between phosphate from the first quarter in 1997 and risk of death in 1998(adjusting for age, length of time on RRT, whether the patient had a primary diagnosis of diabetes, treatment centre on the 1/1/1998 and serum creatinine. The patient's creatinine from the first quarter of 1997 was used in the

analysis regardless of the treatment modality at that time. The creatinine was included in the model as a continuous variable with no transform applied to it.

The analysis was carried out categorising the phosphate as ≤ 1.70, 1.71 – 2.10 and ≥ 2.11 mmol/L, and was repeated categorising the phosphate into quintiles.

The predicted probabilities from the adjusted analysis have been calculated for someone with average patient characteristics (according to those factors considered in the model). Note that these values will vary for patients with different characteristics, i.e. they will depend upon the age of the patient, length of time on RRT, whether the patient has diabetes and treatment centre. The main reason for giving odds ratios rather than predicted probabilities is that odds ratios are not dependent upon the patient characteristics.

Results

Unadjusted Analysis.

Phosphate (mmol/l)	N	No. died in 1998	Proportion of patients who died
≤ 1.7	584	105	0.180 [95% CI: 0.150 – 0.212]
1.71 – 2.10	353	43	0.122 [95% CI: 0.090 – 0.159]
≥ 2.11	391	67	0.171 [95% CI: 0.136 – 0.211]

Adjusted Analysis.

Phosphate (mmol/l)	Predicted probability of dying in 1998 (estimated from logistic regression model)	Odds ratio
≤ 1.7	0.145 [95% CI: 0.117 – 0.178]	ref
1.71 – 2.10	0.105 [95% CI: 0.078 – 0.142]	0.72
≥ 2.11	0.169 [95% CI: 0.134 – 0.212]	1.17

Odds ratio for unadjusted and adjusted analysis and for creatinine correction

Phosphate(mmol/l) from First Quarter of 1997	Unadjusted Analysis (n = 1328) O.R. [95% CI]	Adjusted Analysis (n = 1299) O.R. [95% CI]	Adjusted Analysis + creatinine (n = 1291) OR [95% CI]
≤ 1.70	REF	REF	REF
1.71 – 2.10	0.63 [0.43 – 0.92]	0.70 [0.46 – 1.03]	0.78 [0.52 – 1.17]
≥ 2.11	0.94 [0.67 – 1.32]	1.20 [0.84 – 1.72]	1.42 [0.97 – 2.09]
p-value	0.0475	0.0367	0.0227

5.3.4. Odds ratio for adjusted analysis by quintile

Phosphate from First Quarter of 1997	Adjusted Analysis (n = 1291) OR [95% CI]
≤ 1.47mmol/L	1.18 [0.74 – 1.88]
1.48 – 1.73mmol/L	REF
1.74 – 1.96mmol/L	0.76 [0.43 – 1.36]
1.97 – 2.23mmol/L	1.37 [0.80 – 2.33]
≥ 2.24mmol/L	1.48 [0.90 – 2.45]
X^2	7.2
p-value	0.1276

Discussion

In PD patients, albumin is a powerful predictor of subsequent mortality even after adjustment for age, diabetes mellitus, length of time on RRT and treatment centre. There was a statistically significant continuous inverse relationship between serum albumin and re risk of death such that rise in albumin of 1g/L was associated with a decrease in risk of death of 0.86(95% CI 0.83-0.90). For HD patients, the relationship was less consistent. After adjustment for cofactors there was no difference in outcome between those with serum albumin above or below 35g/L. There was an increased risk with an albumin in the lower two quintiles but no continuous relationship was identified.

There was an increased risk of death in those patients with URR < 65%. This difference was explained by an increased risk of death in those patients with URR < 60% with no apparent improvement in survival with URR above this level. Although similar observations have been made before (Parker 1994), it would be unwise to draw firm conclusions about the optimal URR from this data. The data is retrospective, blood sampling techniques for post-dialysis urea varied and methods for determining dialysis prescription also varied among different centres. For instance, some units had a minimum dialysis time of 4 hours leading to higher average URR. Smaller patients prescribed a standard dialysis time will have a high URR but if malnourished or ill through co-morbid conditions may have limited survival. The importance of body weight as a marker of survival and the complex interaction between body weight, dialysis prescription and achieved urea clearance (URR or calculated Kt/V) has recently been the subject of much debate (Chertow 1999, Lowrie 1999). The HEMO study (Eknoyan 1996) in the USA is likely to provide important data on the optimal dialysis dose in terms of urea clearance.

Phosphate showed an association with mortality which appeared to follow a J shaped distribution. When categorised into 3 groups the lowest mortality was associated with the middle range of phosphate 1.71-2.10mmol/l and was statistically more significant after adjusting for other risk factors and serum creatinine. When categorised by quintiles there was a trend to increasing mortality in the higher quintiles. The precise mechanism whereby hyperphosphataemia may increase mortality is unclear. Block et al suggested the adverse effects could be mediated by hyperparathyroidism or by vascular/cardiac ectopic calcification (Block 1998).

The incomplete data from some centres has made it difficult at present to perform a multiple regression analysis of survival taking into account a range of biochemical, haematological and physiological parameters (e.g. blood pressure, weight). However, as the registry database expands and data completeness and accuracy improves, it will be possible to perform such analyses. These can be used to generate hypothesis to be tested in prospective interventional studies. The continued high mortality of patients on dialysis highlights the need for further improvements in the treatment of this group of patients.

References

Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic haemodialysis patients: a national study. Am J Kid Dis 1998;31:607-617

Chertow GM, Owen WF, Lazarus JM, et al. Exploring the reverse J-shaped curve between urea reduction ration and mortality. Kidney Int 1999;56:1872-1878

Collins AJ, Ma JZ, Umen A, Keshaviah P. Urea index and other predictors of haemodialysis patient survival. Am J Kid Dis 1994;23:272-282

Eknoyan G, Levey A, Beck G, et al. The hemodialysis (HEMO) study: rationale for selection of interventions. Semin Dial 1996;9:24-33

Hakim RM, Breyer J, Ismail N, Schulman G. Effects of dose on dialysis morbidity and mortality. Am J Kid Dis 1994;23:661-669

Kaysen GA, Rathore V, Shearer GC, Depner TA. Mechanisms of hypoalbuminaemia in haemodialysis patients. Kidney Int 1995;48:510-516

Lowrie EG, Lew NL. Death risk in haemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kid Dis 1990;15:458-482

Lowrie EG, Chertow GM, Lew NL, et al. The urea {clearance x dialysis time} product (Kt) as an outcome-based measure of haemodialysis dose. Kidney Int 1999;56:729-737

Owen WF, Lew NL, Liu Y, et al. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing haemodialysis. N Eng J Med 1993;329:1001-6

Parker TF III, Husni L, Huang W, et al. Survival of hemodialysis patients in the United States is improved with a greater quantity of dialysis. Am J Kid Dis 1994;23:670-680