Prognostic markers in older patients starting renal replacement therapy

S. V. Jassal¹, J. F. Douglas² and R. W. Stout¹

¹Department of Geriatric Medicine, The Queen's University of Belfast, and ²Department of Nephrology, Belfast City Hospital, Northern Ireland

Abstract
Aims. We assessed all patients starting renal replacement therapy during a 1-year period to identify factors influencing 1-year survival in older and younger dialysis patients.

Methods. Data was collected from 113 patients. Twenty-four possible prognostic factors were introduced into a multivariate, time-based analysis.

Results. Hazard ratios, and hence risk of mortality, were increased with increasing alcohol consumption, cardiac dyskinesis, age at onset of dialysis, serum phosphate, number of comorbid illnesses, and Karnofsky score (listed in decreasing order of risk). Risk of death within 1 year was reduced in patients with normal serum albumin and higher Barthel scores at the time of commencing dialysis. No age interactions were found. In the elderly age group the risk of death was also increased if left ventricular dilatation was present. Comorbidity and the age of onset were not independent risk factors in patients aged over 65 years at the time of starting dialysis.

Conclusions. All factors listed above increase the 1-year mortality of elderly patients. Factors known to increase medium-term morbidity in dialysis patients including diabetes mellitus, ischaemic heart disease, and hypertension do not appear to be important in the short-term survival of older patient on dialysis.

Key words: morbidity; prognosis; dialysis; ageing

Introduction

The number of patients presenting with advanced renal disease is increasing rapidly. The greatest increase is in the population aged 65 years or more at the time of presentation. Over the past decade the number of elderly patients being referred for and started onto renal replacement therapy has increased correspondingly [1]. With changing management structures in the National Health Service in the United Kingdom, the appropriate allocation of resources is important. The identification of older patients who would benefit from short-term dialysis is often based upon clinical judgement and studies carried out in younger age groups highlighting the need for a study designed specifically to look at the problems of elderly patients. This study set out to ascertain whether the factors influencing short-term survival are similar in older patients to those in younger patients. We also sought to identify which clinical, biochemical and functional markers best predict 1-year survival.

Subjects and methods

The study was approved by the Queen's University of Belfast Research Ethical Committee. All patients aged 40 years or more and commencing dialysis in the Belfast City Hospital between September 1991 and 31 July 1992 were recruited. After informed consent had been obtained patients aged less than 65 years at the time of their first dialysis were placed in group 1 while those aged 65 years or more at the time of their first dialysis were placed into group 2. Dialysis prescription was initiated by and modified by the supervising clinician. Dialysis was routinely performed on a twice-weekly regime and modified by the clinician in charge of the programme as necessary. No clinical intervention was made by the study organizers although all data collected was made available to the clinical staff.

Each patient was seen and assessed by SVJ at the time of first dialysis and at 3-month intervals. Demographic details recorded included the age at time of first dialysis, date of first dialysis, gender, and the cause of and type of renal disease (whether acute or chronic presentation). Underlying renal disease was defined by the clinical physician in charge of the case. Non-biopsied cases of glomerulonephritis were identified using clinical criteria, urinary sediment, and laboratory findings. Vascular causes of renal failure were defined as radiographically proven renal-artery stenosis or widespread atheromatous disease with no other cause for renal disease detectable.

Clinical details included whether there was a past medical history of hypertension, diabetes mellitus, cardiac disease, cerebrovascular disease, respiratory or gastrointestinal disease or other comorbid condition. The average weekly consumption of alcohol was defined as heavy if more than 14 g per week. An assessment of the patient’s clinical condition...
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at the time of presentation and at the time of first dialysis included symptoms of dyspnoea, nausea, limb cramps, restlessness, pruritus, and tiredness, mental state, pulse rhythm, blood pressure measured using a random-zero sphygmomanometer, clinical fluid state, and peripheral circulatory condition. Cardiac state, in particular cardiac function, and evidence of ischaemia or infarction was assessed using a standard 12-lead electrocardiograph tracing and M-mode and 3D echocardiography. Nutritional state was assessed using the dry weight and scapular and biceps skinfold thickness. Biochemical analysis included serum urea, creatinine, fasting lipids including triglycerides, serum albumin, calcium, and phosphate.

Using pre- and post-dialysis urea values the Kt/V was calculated using the formula [2]:

\[
Kt/V = 1.18 \times [-\log R] 
\]

where \( R = \) the ratio of post dialysis urea/predialysis urea

The degree of independence was measured using the mini-mental state [3] and the Barthel [4] and Karnofsky [5] scores. Depression was sought using the Geriatric Depression Score [6].

Patients were followed up for 1 year or until death or withdrawal from the dialysis programme.

Statistical analysis

All information collected was stored on computer files, using a database program (Paradox 4.0, Borland). A validation check was carried out, after data collection was complete, to ensure that all variables had values. The integrity of the data was confirmed using logical checks; for instance, if records contained a negative or zero value. Values at the extremes of ranges were also verified.

Descriptive analysis was carried out to identify any differences between groups 1 and 2, and to assess the spread and symmetry of the data. Where discrete categories were compared the chi-squared test with Pearson's coefficient was used. The distribution of continuous variables was first assessed and if normally distributed the students \( t \)-test was carried out. If the data was found to be skewed the Mann-Whitney U test was used [6]. A probability level of 0.05 was accepted as significant.

As time to outcome varied, a time-based analysis, in this instance Cox's regressional model was used [7]. Survival time was calculated as the time from first dialysis to the time of death. Patients who survived longer than the 1-year follow-up period or who were withdrawn from the study because of transplantation were treated as censored data from the time of withdrawal. Putative risk factors were initially tested separately using Kaplan–Meier survival curves and the log-rank test. Those showing significance were then introduced into the Cox's regressional model. The backward stepwise method was used with a significant level for removal from the model of \( P > 0.05 \). The proportional hazards model identified those factors which predict death within 1 year of starting dialysis and calculated a hazard ratio with 95% confidence intervals. The hazard ratio equates to a death rate per unit time and a value of 1 equals no increase in the risk of death due to the variable in question.

To identify prognostic factors for 1 year mortality all data were fitted to the above statistical model and then compared to a second model derived only from the data taken from patients in group 2. To assess specific prognostic variables associated with age, each significant variable was introduced as an interaction between age and the variable and the log likelihood ratio test used to assess significance. A level of \( P<0.01 \) was considered as significant. All statistical analyses were performed on the SPSS for Windows package (SPSS Inc, Chicago, IL, USA).

Results

Data was collected from 109 patients. Of these 10 patients were not included in the final analysis because they recovered renal function within 60 days. Four patients were initially approached but not included in the study because they did not commence dialysis. Of these four, two died while awaiting dialysis and two were felt to be unsuitable for acceptance onto the renal replacement programme. Forty-six patients were aged less than 65 years at the time of starting dialysis (group one) and fifty-three aged greater than or equal to 65 years (group 2). Thirty-two of the 99 patients (32.3%) included in the final analysis were being followed by a nephrologist. The mean duration of follow up, prior to dialysis, of these 32 patients was 802±117 days in group 1 and 575±157 days in group 2 (\( P = 0.4 \), \( n = 18 \) and 14 respectively).

Demographic details are given in Table 1. The most common causes of disease was secondary to hypertension, vascular disease, and diabetes mellitus. Patients from group one had a greater prevalence of advanced renal disease of unknown aetiology. Fifteen patients had diabetic nephropathy, of whom seven had insulin dependent diabetes. The mean duration of dialysis was 3.9 h (±0.3 h). All patients were dialysed using a SCE 135 dialysis membrane and bicarbonate-buffered solution. Dialysis adequacy measurements showed the mean Kt/V to be 1.10 (on a twice-weekly dialysis schedule) over the 1-year follow-up period. No significant difference was found between the Kt/V in older and younger patients (\( P = 0.78 \)).

In total 34 of the 99 patients included in the analysis died (Table 1). Causes of death included sudden death secondary to a presumed cardiac event (\( n = 1 \) and \( n = 10 \) in groups 1 and 2 respectively), fluid overload (\( n = 2 \), group 2), cachexia (\( n = 3 \) and 2 respectively) and sepsis (\( n = 3 \), group 2). A total of six patients died after dialysis was withdrawn. Other causes included terminal hepatic failure, pulmonary embolus, and uraemic encephalopathy and seizures in spite of dialysis therapy. Of the 11 patients who died suddenly, four
had predialysis potassium levels greater than 5.7 mmol/l on more than 50% of occasions. Eleven patients were transplanted, 10 with cadaver kidneys and one after a live donor kidney was retrieved.

Biochemical assessment showed that predialysis serum urea was greater in the older patients while serum albumin was lower (urea 24.4 mmol/l and 33 mmol/l; \(P = 0.004\), albumin 36.1 mmol/l and 31.8 mmol/l; \(P = 0.0002\) in groups 1 and 2 respectively). No significant differences were found between the groups in the remaining biochemical measures (Table 2).

Clinical assessment showed that elderly patients were likely to have more comorbid illnesses \((P = 0.02)\), but a similar frequency of hypertension and diabetes mellitus. Left ventricular hypertrophy was detected on ECG in 48% of all cases while only 12% showed evidence of ischaemia. No significant differences were detected between groups. Echocardiography results are given in Table 3. No significant difference was seen in the frequency of cardiac dyskinesis, left ventricular hypertrophy as measured by echocardiography, left ventricular dilatation, or the ejection fraction. Four patients drank more than 14 g of alcohol per week (2 from each group).

Functional scores are listed in Table 3. Differences, between the two groups were noted in the mean Barthel and Karnofsky scores and the mental score predialysis. As expected, older patients had an increased incidence of mild cognitive impairment and reduced functional scores predialysis when compared with those from the younger group.

In the overall group univariate analysis identified 14 factors influencing outcome (Table 4). When introduced into a multivariate analysis model only eight factors were derived. These included, in order of importance, a history of heavy alcohol intake, cardiac dyskinesia, age at the onset of dialysis, increased serum phosphate, reduced serum albumin, the number of comorbid diseases, and the functional score. Significance levels and hazard ratios with 95% confidence limits are given in Table 5. Age did not influence the hazard ratio for each individual factor after the model was tested for interactions.

The model derived for the older patient (Table 6) shows that cardiac function in the form of cardiac dyskinesia and left ventricular dilatation, functional state, and serum albumin and phosphate are important factors in the outcome of older patients. Heavy alcohol intake, the number of comorbid diseases, and the age

### Table 2. Blood results predialysis for groups 1 and 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (Young patients)</th>
<th>Group 2 (Older patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean serum albumin (mmol/l (SD))</td>
<td>36.1 (5.68)</td>
<td>31.76** (6.10)</td>
</tr>
<tr>
<td>Mean predialysis creatinine (mmol/l (SD))</td>
<td>836 (47)</td>
<td>873 (49)</td>
</tr>
<tr>
<td>Mean predialysis urea (mmol/l (SD))</td>
<td>24.4 (8.8)</td>
<td>33.0* (17.3)</td>
</tr>
<tr>
<td>Mean serum phosphate (mmol/l (SD))</td>
<td>2.11 (0.76)</td>
<td>3.20 (7.24)</td>
</tr>
<tr>
<td>Mean serum triglyceride (mmol/l (SD))</td>
<td>1.88 (0.83)</td>
<td>2.08 (1.78)</td>
</tr>
</tbody>
</table>

\* \(P = 0.004\), \* \(P = 0.0002\).

### Table 3. Echocardiographic, functional assessment and mental state details

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (Young patients)</th>
<th>Group 2 (Older patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Mean ejection fraction (SD)</td>
<td>55.5 (17.7)</td>
<td>50.6 (13.7)</td>
</tr>
<tr>
<td>Percentage with left ventricular hypertrophy</td>
<td>63</td>
<td>53</td>
</tr>
<tr>
<td>Percentage with left ventricular dilatation</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Percentage with localized or generalized dyskinesia</td>
<td>28</td>
<td>44</td>
</tr>
<tr>
<td>Mental score median (quartiles)</td>
<td>10 (2.5–10)</td>
<td>8.75 (0–10)</td>
</tr>
<tr>
<td>(n) with mental score less than 8</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Barthel index at start of dialysis (median (quartiles))</td>
<td>95 (5–100)</td>
<td>70 (0–100)</td>
</tr>
<tr>
<td>Karnofsky index at start of dialysis (median (quartiles))</td>
<td>80 (60–90)</td>
<td>60 (40–80)</td>
</tr>
<tr>
<td>(n) Patients living in own home (%)</td>
<td>36 (80)</td>
<td>44 (81)</td>
</tr>
</tbody>
</table>
The results show that short-term survival is consider-
ably less in elderly patients and that poor outcome can be predicted by clinical assessment of cardiac function, functional state, and selected biochemical measures. This group was not included in the analysis as they often have multiple complex problems and are at high risk from coexistent respiratory compromise. Other studies examining the question of survival on dialysis and prognosis in elderly patients fail to include detailed information on biochemical parameters, nutritional state, and cardiac function and identify only psychosocial factors as influencing prognosis [8,9]. We identified several other factors which are of short-term prognostic value in particular cardiac dyskinesis, left ventricular dilatation, functional state, and altered serum albumin and phosphate.

Age is often quoted in the literature as a major limiting factor in the prognosis of patients starting dialysis [10–16]. The data from this study confirms that older patients undoubtedly have a poorer prognosis than those commencing renal replacement therapy at a younger age. However, when survival is compared within older patients, age is of lesser significance. In most cases one may propose that the poorer outcome seen in older dialysis patients is due to age-associated conditions such as cardiac dysfunction and reduced functional independence, which alter prognosis.

The finding that cardiac dyskinesis is related to an increased chance of death within 1 year is an exciting observation. Ejection fraction, left ventricular wall thickness, and end-diastolic volume, measured using echocardiography, have all been shown to relate to survival on renal replacement therapy [17–20]. However, the use of echocardiography for the assessment of dynamic cardiac function, particularly the calculation of ejection fraction, has been criticised in the dialysis-dependent subject because of rapid shifts between the intravascular fluid compartment and the extracellular fluid compartment [21]. Cardiac dyskinesis is seen on echocardiography as a defect in regional wall motion, and is usually associated with ischaemic damage. Although ejection fraction is not always impaired, overall cardiac function is usually affected.

In this study both ejection fraction and the presence of cardiac dyskinesis were identified, on univariate analysis, as factors contributing to death within the 1-year follow-up period. After correction for the presence of cardiac dyskinesis, however, the ejection fraction did not remain a significant prognostic factor, suggesting that cardiac dyskinesis is a more accurate marker for myocardial dysfunction. Interestingly, in subset analysis within the older age group studied, cardiac dilatation was also a significant prognostic factor although confidence limits were wide.

Biochemical factors also play a complex role in the prognosis of both older and younger dialysis patients. The observation that serum albumin and phosphate affect prognosis is not unexpected. Previous studies have shown both biochemical measurements form a U-shaped curve when plotted against mortality [22,23]. We observed a relationship with mortality and
increased serum phosphate and low serum albumin only, but few patients, enrolled in the study, had increased serum albumin or decreased serum phosphate. Both malnutrition and renal bone disease can affect serum phosphate and serum albumin metabolism and thus make it difficult to interpret the results accurately. In an attempt to exclude malnutrition as a factor, skinfold thickness and dry weight were recorded at the onset of dialysis and found not to be of significance in prognosis. An increase in dry body-weight or skinfold thickness over 3 or more months on dialysis does correlate well with prognosis [24] but cannot be regarded as a prognostic factor, as an increase in body-weight cannot be identified at the time dialysis is started. It is recognized that both dry weight and skinfold thickness provide only crude measures of nutritional state.

Measurements of functional ability have only recently been recognized as important markers for prognosis in elderly patients starting renal replacement therapy. Husebye et al. [8] suggested that clinical factors were not of significance, although the study did not adjust for differences in the comorbidity, type of disease (i.e. acute on chronic), or cardiac function. We used both Barthel and Karnofsky scores to measure functional ability. Although both are similar in their objectives, and correlate with each other, the Karnofsky index [5] is a subjective measure of the disability caused by disease while the Barthel score [4] objectively measures the amount of assistance required for activities of personal care. Another difference lies in the scoring method used—the former was scored by the patient as a subjective measure while the latter was assessed by the investigator. Karnofsky scores at the onset of treatment are lower in this series than those from published data, suggesting that the patients accepted for dialysis were in poorer health than in other studies. Both indices appear to correlate with an increased risk of death when interpreted on a univariate model. However, after multivariate analysis the Karnofsky score shows an inverse relationship, suggesting that a lower Karnofsky score (and hence increased disability) correlates with a reduced risk of death. Barthel scores show a more usual relationship, with an increased degree of dependence being associated with increased mortality. Possible explanations for the sudden hazard reversal may be that patients who were at an increased risk of death had less insight into their functional impairment or that individuals who had higher Karnofsky scores complained of increased symptoms and thus received increased medical and nursing attention, giving them a survival advantage.

The relationship between alcohol intake and early death on dialysis has not previously been documented. However, the 95% confidence intervals are wide, suggesting that this may be a coincidental factor. As only four patients were in this category the results must be interpreted with caution.

Factors previously described as important in the outcome of dialysis patients (regardless of age), for example ischaemic heart disease, hypertension, and diabetes mellitus were not found to be strongly linked to outcome in this study after correction for age and other factors [10-12,15,16,25-28]. Two possible explanations exist. Firstly the population studied had a greater mean age than comparable studies. Secondly the follow-up period was limited to 1 year (in comparison to longer follow-up periods in other studies).

Limitations of the study do exist. The population studied was very heterogeneous in the aetiology of disease, reflecting clinical practice, but reducing the exactness of the results. Secondly, data was taken from all patients aged over 40 years, and statistical tools were used to tease out relationships between age and other factors. Although this depends upon the statistical method used, it allows for inaccuracies resulting from the clinical variation in the biological and chronological ages of patients. In the renal setting this may be of increased importance as patients with chronic disease often have impaired functional ability at a younger age. Lastly the authors accept that twice-weekly dialysis is known to be insufficient and is associated with a high mortality. Criticism may be directed toward the unexpectedly high mortality rate, the high serum creatinine, and the low Kt/V values.

In Northern Ireland the expansion of dialysis facilities has not yet matched the increasing recognition of clinical need. The current presentation rate is about 80 per million of population per annum, and of about 200 patients on haemodialysis, under 25% were on thrice-weekly treatment at the time of the study. Following the report of the Department of Health and Renal Review in 1995, it is hoped that the percentage on thrice weekly dialysis treatment will increase to greater than 80% by 1997 or 1998. We believe there are many centres where, as in Belfast over the period of the study, haemodialysis was given to all patients rather than optimal dialysis for a chosen few. The findings of this study may help those centres direct their limited resources towards a patient population most likely to benefit.

Conclusion

All patients, regardless of age, should be individually assessed for suitability for renal replacement therapy. Cardiac dyskinesis, left ventricular dilatation, high serum phosphate levels, low functional state (as measured by the Barthel score) and low serum albumin levels all increase 1-year mortality of elderly patients on dialysis. Factors known to increase medium-term mortality, including age, diabetes mellitus, ischaemic heart disease, and hypertension do not appear to be important in the short-term survival of the older patient on dialysis therapy.
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