Quantifying comorbidity in peritoneal dialysis patients and its relationship to other predictors of survival

Simon J. Davies, Louise Phillips, Patrick F. Naish and Gavin I. Russell

Department of Nephrology, North Staffordshire Hospital Trust, Stoke-on-Trent, UK

Abstract

Background. Comorbidity is the single most important determinant of outcome in patients on renal replacement therapy. The aims of this study were to evaluate a semi-quantitative approach to comorbidity scoring in predicting survival of patients commencing peritoneal dialysis (PD), and to establish the interaction between this and other known predictors of patient outcome, in particular membrane function, residual renal function (RRF) and plasma albumin.

Methods. Comorbidity was recorded in a prospective, single centre cohort study of 303 patients commencing on PD. Using seven disease domains, chosen to reflect the dominance of cardiovascular morbidity in the end-stage renal failure population, comorbidity was graded as '0' when absent, '1' when one or two, and '2' when three or more conditions were present. The Wright comorbidity index, which includes age within the scoring method, was also evaluated. RRF, plasma albumin and peritoneal solute transport were measured every 6 months. Patients were censored at death.

Results. Median survival according to grade of comorbidity was 105, 42 and 29 months, respectively (P = 0.0001), with good separation of the actuarial survival curves. Using Cox regression, the addition of age and the grade of comorbidity to Kt/V urea, solute transport and plasma albumin increased the predictive power of the model. All were independent predictors of outcome with the exception of albumin. The Wright comorbidity index also enhanced the Cox model, although was not as powerful as when age and comorbidity were considered independently. At baseline, RRF was not different according to comorbidity unless diabetes was considered separately. Diabetics started with higher RRF, but after 6 months on PD this was the same as non-diabetic patients. Otherwise, initial rate of decline of RRF was similar across the comorbid grades, although the impact of higher drop-out due to earlier loss in patients with more comorbidity may have disguised earlier loss in these patients. Peritoneal solute transport tended to be higher in patients with increased comorbidity at baseline, $\chi^2 = 13.8, P = 0.032$, and this was sustained with time on treatment.

Conclusion. Comorbidity has a quantitative effect on survival that is independent of age, RRF and membrane function in PD patients. Comorbidity also appears to be associated with increased solute transport at the start of treatment, which is sustained. With the exception of diabetes, grade of comorbidity does not have a profound effect on loss of RRF.

Keywords: age; diabetes mellitus; ischaemic heart disease; left ventricular dysfunction; peripheral vascular disease; residual renal function; solute transport; Stoke PD Study

Introduction

Comorbid disease is now recognised as the most important determinant of clinical outcome, in terms of both survival and morbidity, for patients receiving renal replacement therapy [1,2]. The desire to take a semi-quantitative approach to assessing comorbidity stems from several objectives. First, patients often have more than one comorbid disease, and a descriptive system that takes this fact into account makes good sense. Secondly, there is an increasing need to improve adjustment for case-mix to allow fair comparisons to be made between treatment modalities, centres and costs. Thirdly, precisely because comorbidity is so important in determining outcome, there is a need to gain better understanding of both its mechanisms, e.g. inflammation [3], and its interactions with other known predictors of outcome.

To date, a number of scoring systems have been developed, which range from complex and detailed questionnaires to a simple tally of comorbid conditions [4–8]. In 1990, the Stoke Peritoneal Dialysis (PD)
Study was set up to establish prospectively the factors determining clinical outcome in PD patients, with particular reference to the roles of nutrition and peritoneal membrane function. A simple index of comorbidity conditions was developed at that time for this study, as none other was then available. It enables patients to be graded according to their comorbidity load: 0 (low risk), 1–2 comorbidities (medium risk), and 3 or more (high risk) [9,10]. Seven separate comorbidity domains were identified, selected to reflect the high prevalence of cardiovascular disease in the end-stage renal failure population. In particular it allows differentiation between the patients with less versus more generalized atheromatous disease, cardiac end-organ damage, with or without diabetes. The weighting, therefore, is within the choice of disease domains themselves, rather than a sum of individually rated scales for each comorbidity condition. This makes the process of scoring the patient very simple. Including detailed grading for each comorbidity, although intuitively making sense and being important in predicting the outcome of the individual patient, does not appear to improve the prediction of how populations behave [8].

In this paper, we report the prospective validation of this approach to comorbidity scoring in PD patients. It includes the prediction of patient survival, how it adds to other known predictors of survival, and the relationship between comorbidity and these factors, both at baseline and longitudinally. Direct comparison is also made with the Wright comorbidity index.

Subjects and methods

Patient population and study design

The Stoke PD Study population and the details of data collection have been described in detail elsewhere [11]. This description includes the demographics of the population, the period of data collection (1990–1998), the prevalence of comorbidity and its relationship to the mode of death. It is a single centre, prospective, observational study comprising 303 incident patients in which, for the most part, no systematic interventions were made to account for the decline in residual renal function. However, between 1995 and 1998, patients who had become malnourished on peritoneal dialysis had an increase in delivered peritoneal Kt/V of 25%, resulting in an achieved increase of 18%. The details of this intervention and its outcome (a modest improvement in nutritional parameters mostly in patients without comorbidity disease) has also been published [12].

Comorbid disease

Comorbidity scoring was performed prospectively by a single clinician (S.J.D.), familiar with the patient case-history, utilising the medical and nursing case records and investigation results, e.g. ECG and echocardiograms. The approach to identification of significant comorbid disease has been described previously, where it has been shown to predict patient survival in cross-sectional analyses [9,10]. Certain general principles apply. For each comorbid domain evidence of disease, not its severity, is required. To be counted, comorbidities must either be considered active or still present, or currently controlled by on-going treatment. For example, a patient with a history of suicidal depression who is currently well and on no treatment would not register. A woman with breast cancer successfully removed but still taking Tamoxifen several years later would be considered as having active malignancy. If doubt exists, then advice on cure from the relevant specialist should be sought. The following seven domains of active comorbidity disease are considered.

Malignancy. Active, non-cutaneous disease, e.g. myeloma, breast cancer.

Ischaemic heart disease. As evidenced by previous myocardial infarction, angina pectoris, positive coronary angiography or other diagnostic procedure (e.g. exercise test, thallium or dobutamine stress test) or the presence of ischaemic changes on the resting ECG (as distinct from left ventricular hypertrophy).

Peripheral vascular disease. To include distal aortic, renovascular, lower limb and cerebrovascular disease. Includes either symptomatic disease in these vascular territories (e.g. CVA, claudication, amputation) or significant stenoses (>50%) on vascular imaging or Doppler ultrasound.

Left ventricular dysfunction. Defined as clinical evidence of pulmonary oedema, not attributable to errors in fluid balance, and/or moderate to severe left ventricular dysfunction on echocardiography.

Diabetes mellitus. The presence of either type 1 or type 2 as comorbidity.

Systemic collagen vascular disease. For example, systemic vasculitis, rheumatoid arthritis and systemic sclerosis, either active or requiring treatment.

Other significant pathology. A condition severe enough to have an impact on survival in the general population. Examples include: severe chronic obstructive airways disease, cirrhosis, psychotic illness. Treatable conditions (e.g. peptic ulceration) or non-life threatening diseases such as severe osteoarthritis would be excluded.

The comorbidity score for each patient is simply the number of these domains affected, giving a theoretical maximum of seven (although more than five has not been observed in our patients). The grade of comorbidity is derived directly from this score. Grade 0 (low risk) is a zero score, grade 1 (medium risk) is a score of 1–2, and grade 2 (high risk) a cumulative score of ≥3.

Patients were also graded by the method devised by Wright [6] and validated further by Khan et al. [13,14]. This system includes age within its weighting: grade 0 (low risk), age <70 years, no comorbidity disease; grade 1 (medium risk), age 70–80 years, or any age with one comorbidity disease, or <70 years with diabetes mellitus; grade 2 (high risk), age >80 years, or any age with two comorbidities, or any age with cardiorespiratory disease, or any age with visceral cancer.

Measures of solute clearance, membrane function and blood biochemistry

Dialysis dose and residual renal function (RRF), peritoneal solute transport and plasma albumin were measured at baseline and every 6 months while the patients remained on PD. These methods have been described previously [11]. Briefly, the dialysis dose and RRF was calculated as the weekly Kt/Vurea from the 24 h urinary and dialysate clearance, by direct measurement of urea in urine and each dialysate
Comorbid survival in peritoneal dialysis patients

Statistical methods

Between-group comparisons of RRF, solute transport and plasma albumin were made using analysis of variance (ANOVA). The relationship between solute transport category and grade of comorbidity within 1 month of the start of treatment was made using a $\chi^2$ test. Actuarial survival rates were calculated according to the method of Kaplan and Meier, using the log-rank test to compare survival between comorbid groups. The Cox proportional hazards method was used to evaluate the influence of comorbidity grade when combined with other established predictors of survival. This was achieved by adding age and comorbid grade (or the Wright index alone, as it includes age) to the previously published model for this patient group. This model used the total urea clearance, plasma albumin and peritoneal solute transport at 6 months. The two resulting models were compared using the $\chi^2$ test.

Results

Univariate analysis

Data on 303 consecutive patients commencing PD were available for analysis. As PD is usually a planned treatment, patients experiencing early mortality were not excluded. During the follow-up period there were 106 deaths, of which 58% occurred whilst still of PD, the rest after transfer of modality. Sixty-five patients switched to haemodialysis (HD) and 72 patients were transplanted. Many of the characteristics of this population, including actuarial survival, numbers of patients remaining on PD at each time-point, longitudinal changes in RRF, solute transport and plasma albumin, technique failure rate, causes of technique failure, mode of death and its relation to comorbid diseases, have been reported previously [11]. The numbers of patients with comorbidity, according to each of the seven domains, is shown in Table 1. It can be seen from the proportions surviving at 2 and 5 years that this is decreased in each case when compared with the rest of the population, although this is not significant on univariate analysis for patients with systemic collagen vascular disease. It is also noted that the influence of diabetes on survival is marginal.

Relationship between RRF, solute transport and plasma albumin comorbidity at baseline

RRF at baseline does not differ significantly according to grade of comorbidity (Kt/V for grade 0, 0.87; grade 1, 0.78; grade 2, 0.93; ANOVA $P = 0.26$). Diabetic patients started treatment at a significantly higher level of RRF when compared with all other patients, (Kt/V 1.09 vs 0.76, $P = 0.006$). Plasma albumin is significantly higher in patients without comorbidity (grade 0, 38.9 g/l; grade 1, 34.7 g/l; grade 2, 34.7 g/l; ANOVA

<table>
<thead>
<tr>
<th>Comorbid domain</th>
<th>$n$ (%)</th>
<th>Survival (%) at 2 years</th>
<th>Survival (%) at 5 years</th>
<th>$P$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>23 (7.5)</td>
<td>54</td>
<td>10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IHD</td>
<td>67 (22)</td>
<td>70</td>
<td>5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVD</td>
<td>61 (20)</td>
<td>68</td>
<td>10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVF</td>
<td>36 (12)</td>
<td>63</td>
<td>14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM</td>
<td>45 (15)</td>
<td>68</td>
<td>40</td>
<td>0.07</td>
</tr>
<tr>
<td>SCVVD</td>
<td>18 (6)</td>
<td>70</td>
<td>50</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Univariate 5-year survival (log rank) compared with the rest of the population.

IHD, ischaemic heart disease; PVD, peripheral vascular disease; LVF, left ventricular function; DM, diabetes mellitus; SCVVD, systemic collagen vascular disease.

The influence of grade of comorbidity is shown in Figure 1 and summarized in Table 2. There is clear separation in the actuarial survival curves according to grade of comorbidity, with a highly significant median survival period, log rank statistic 69.83, $P < 0.0001$. Patients with no comorbidity were more likely to receive a transplant (72/151) than those with grade 1 (14/119) and grade 2 (0/33) comorbidity ($P < 0.001$).

Multivariate analysis

The effects of grade of comorbidity on survival, in the context of other known predictors, were explored using Cox regression. For this population, the influence of Kt/V, solute transport and plasma albumin at 6 months on patient survival has been published (see Table 3A). To this baseline model we added, in a step-wise manner, age and comorbidity grade in the case of the Stoke score (Table 3B), and comorbidity risk category alone for the Wright score (as this includes age; Table 3C). In each case, the additions increased the predictive power of the model significantly, giving final $\chi^2$ values of 47.4 and 21.9, respectively. In the former, both age and grade of comorbidity were independent predictors of survival, indicating that these have an additive impact on survival, in part explaining the greater predictive power of the model. In both cases, plasma albumin, which has been a borderline predictor in the baseline model, became less predictive.
Solute transport also varies according to comorbidity (grade 0, 0.608; grade 1, 0.65; grade 2, 0.65; ANOVA $P<0.03$). As shown in Table 4, as the grade of comorbidity increases there is a shift in the distribution of solute transport characteristics. The proportion of patients with high solute transport increases, whereas in those with low transport this decreases. There is a tendency for patients with greater comorbidity scores to be diabetic, with 27% of grade 1 and 47% of grade 2 patients affected. However, the effect could not be explained by diabetes alone, as the total comorbidity load had an additional impact.

Longitudinal changes in RRF, solute transport and plasma albumin according to grade of comorbidity

These are summarized in Figure 2. The initial fall in RRF appears similar in all three comorbid groups and is significant ($P<0.03$, paired $t$-test). Despite the fact that diabetics started treatment with a higher level of residual function, by 6 months this was not different compared to non-diabetics. RRF is relatively well preserved over the subsequent 30 months in patients without comorbidity. Whilst this also appears to be the case in patients with severe comorbidity, the number of patients with well preserved RRF beyond 2 years is small. It is likely that there is a powerful effect of patient selection operating at this stage.

Following an initial increase in solute transport seen in all patient groups, it remains very stable in patients with no comorbidity, at least until 4 years of treatment. In patients with comorbid disease, the initial higher solute transport is sustained with time of treatment. This is despite an increased drop-out rate due to death and modality transfer, associated with high transport, in these patient groups. Plasma albumin remains low throughout treatment in the patients with comorbidity. There is a gradual but significant fall in plasma albumin with time on treatment in those without comorbidity ($P<0.01$, paired $t$-test at 4 years).
Discussion

This study reports the use of a prospective, semi-quantitative approach to comorbidity scoring in a well-characterized cohort of patients commencing renal replacement therapy with peritoneal dialysis. It demonstrates that global survival can be stratified according to comorbid load and shows how comorbidity interacts with other predictors of survival. Whilst age, RRF and membrane function remain important factors, plasma albumin loses its predictive power.

This is not the first report to indicate that a semi-quantitative approach to comorbidity improves prediction. Khan et al. [14] used the Wright index to show that this type of approach was more effective than systems using diabetes and age alone. Beddhu et al. [16] found the modified Charlson index to be a powerful predictor of mortality, morbidity and of health-associated costs. Chandna et al. [8] took a similar approach, finding that prediction could be enhanced further by the addition of measures of functional performance such as the Karnofsky scale. Foley et al. [7] used a comorbidity score to predict early (6 month) mortality on dialysis. It is of interest that all of these semi-quantitative approaches end up with a risk stratification of usually only three, or occasionally four, categories.

If the broad findings of this approach are not markedly different, what are the relative advantages of the different scoring systems? Undoubtedly simplicity of execution is important. The earlier scoring systems, such as the Endstage Renal Disease Severity Index, apart from including dialysis-related complications, are too complex for the functions defined here, and are better suited as a research tool to evaluate the impact of renal disease [4]. The problem of using a complex instrument has been illustrated by the validation of the ‘Form 2728’ used to quantify comorbidity in the CHOICE (Choices for Healthy Outcomes in Caring for ESRD) study [17]. Significant under-reporting of diseases occurred with relatively poor sensitivity, on a form that includes 17 categories of comorbid disease. The Wright index is far simpler, recognising five main

\[
\chi^2 = 13.8, \ P = 0.032. \ LA, \ low \ average; \ HA, \ high \ average.
\]
categories—cardiovascular, malignant, hepatic, pulmonary and diabetes—and was found to be easy to apply in a large retrospective study [6,14]. The Stoke Comorbidity Score was developed with simplicity and ease of scoring in mind, and generally takes only a few minutes of clinician time to complete.

Another problem associated with complexity is the relative weight given to comorbid categories. It is clear that congestive cardiac failure and peptic ulcer disease are likely to have different implications for both mortality and morbidity, and yet these have equal weight in the Charlon index, originally designed to identify risk factors for post-operative complications [5]. It is important to recognise that the types of comorbid disease experienced by patients with renal failure are predominantly cardiovascular in nature. It is not uncommon for patients to experience ischaemic heart disease, peripheral vascular disease and impaired left ventricular function, and yet using the Wright score, patients with any combination of these will have the same comorbidity score. In designing the Stoke score, an attempt was made to account for these problems by limiting the choice of comorbid categories to those likely to influence outcome, but providing an extended range of cardiovascular domains. The weighting, therefore, is in the choice of disease types rather than the more complicated approach of attempting to grade each domain separately. In this prospective study with prolonged follow up, the univariate analysis indicates that each of the domains, with the exception of systemic collagen vascular disease, is associated with a worse outcome. It could be argued that this exception should lead to a reduction in its relative weighting, although the number of patients affected was small, and further validation in a larger patient population should be performed first. The choice of comorbid conditions is not dissimilar to that adopted by Foley et al. [7], which also includes age, acuity of onset of renal failure and recent ventilation. They used their approach to correct for PD vs HD survival data for comorbidity, but have not performed an analysis from a categorical perspective [18].

A further difficulty in designing a comorbid disease index is whether to include age, or to keep this as an independent variable. Age and comorbidity are clearly linked, but from an ethical stand-point clinicians are rightly anxious to show that their decision making process is not prejudiced by this. It is also clear that the impact of age and comorbidity is additive, enhancing the predictive power of the multivariate analysis in our patients when compared with the Wright index. In the recently published study of clinical outcomes and quality of life in the elderly, both age and comorbidity predicted survival. Quality of life, however, was not different to age-matched controls [19]. There are, therefore, a number of reasons for separating age from comorbidity when categorising risk and predicting outcome in patients on renal replacement therapy.

As with any scoring system, even when tested prospectively, there is a need for further validation by other investigators. For example, the decision to split the severity of comorbidity into three grades, according to 0, 1–2 and ≥3 diseases, does result, when PD patients are considered, in a relatively small group in the worst category. In the pilot of the NECOSAD study, which used the Stoke comorbidity score as one of its measures, only 7% of patients (equally distributed between PD and HD) fell into the severe category [20]. Whilst the presence of comorbidity was a predictor of survival, independent of age, the lack of patients in the severe category meant that a semi-quantitative approach to grading could not be taken. One possibility would be to split the middle category into two groups, keeping the simple relationship to number of disease domains. This approach does give separation in the survival curves in our PD population, but does not add to the predictive power of the Cox model (data not shown). In our experience, HD patients tend to have higher comorbidity scores, so it might be anticipated that the current approach would also be a good predictor in these patients (a preliminary analysis of our own data would suggest this). The Stoke Score was also recently prospectively validated in a head-to-head comparison with the Charlson comorbidity index [21]. When combined with age, the Stoke score was equivalent in predicting survival, better at predicting inpatient stay, and easier to perform than the Charlson index.

We were interested to examine the relationship between severity of comorbidity and other known predictors of survival, in particular RRF, solute transport and plasma albumin. RRF was not different at baseline, and appeared to fall equally in all three groups, at least initially. The problem with interpreting this data is the phenomenon of informative censoring [22]. If a variable has an important influence on survival, as RRF does in PD patients, then there may be differential effects according to grade of comorbidity, resulting in a variable selection pressure. As RRF can only be measured in patients still on PD, one possible interpretation is that the equal rate of decline across grades masks a faster decline in some patients with more comorbidity, who stop dialysis early due to death or transfer. If this is correct, then it emphasises the importance of preserving RRF. The relative preservation of RRF in patients without comorbidity between 18 and 30 months of treatment cannot be explained in this way, and may represent a true effect of comorbid disease. The finding that diabetics started treatment with significantly higher RRF, which by 6 months was similar to non-diabetics, suggests that rate of loss of RRF in these patients is more rapid, in keeping with the recent observations of Moisted al. [23].

The finding that there is a relationship between solute transport and comorbidity at the start of treatment is of interest. Diabetics in the CANUSA study had higher solute transport [24], and the phenomenon in our patients is, in part, due to the increased proportion of diabetics as comorbidity grade increases. It is possible that comorbid disease, and in particular the associated inflammation or tissue damage, results in altered peritoneal membrane morphology and
function. Data from the Peritoneal Biopsy Registry has shown that the peritoneum in the uraemic individual is thickened compared with healthy controls (Dr Nick Topley, personal communication, data awaiting publication), indicating that uraemia may also play a part. As treatment continues, transport remains stable in patients without comorbidity, and those with comorbidity have sustained increased transport. Longitudinal, paired data analysis did not show a different rate of change in membrane function with time in the presence of comorbidity when corrected for baseline transport characteristics. Again, due to informative censoring and increased drop out of patients with comorbidity and high solute transport, this difference could be underestimated. The Cox regression would suggest that both comorbidity and solute transport are important in determining clinical outcome, as was the case in the CANUSA study [24].

The relationship of comorbidity to plasma albumin was expected, although the lack of a 'dose-dependent' effect was surprising. Patients with moderate and severe grades had similar plasma albumin at the start and throughout their time on treatment. Yet again, the effect of informative censoring may be masking a true difference. There are many determinants of a low plasma albumin in PD patients, including age, comorbidity, acute and chronic inflammation, high solute transport and under-nutrition [25]. All are associated with worse outcome, and it is of interest that when they are included with albumin in the Cox regression, it ceases to be a significant predictor. This would suggest that albumin is a powerful predictor, but not an independent determinant of outcome, reinforcing the observations of others [26].

In summary, we have shown how a semi-quantitative score of comorbidity can be used to enhance prediction of clinical outcome, independent of age, in a prospective cohort of PD patients. The scoring approach is simple, but requires further validation, particularly in HD patients and in the multicentre setting. Further refinement is possible, but it may be more useful to add alternative measures of outcome rather than making the scoring system more complicated. For example, other measures of physical functioning or inflammation may add more to the clinical picture [3]. By adding the Karnofsky physical functioning scale, Chanda et al. [8] were able to improve the predictive power of their own comorbidity score. Objective measures of physical function can be performed quite simply and quickly, e.g. sit-to-stand test, hand-grip, and markers of inflammation such as C reactive protein can be measured easily.

Acknowledgements. We are very grateful to all those who have made this study possible. These include Rod Hunt (Computer Software), Professor Peter Jones (Statistics), Gill Savage (Nurse and Unit Manager), Janet Bryan who co-ordinated data collection between 1991 and 1993, and in particular Sister Val Rowley and her primary PD Nursing Team. We also express our gratitude to all the patients involved, who have willingly given their time. We gratefully acknowledge the financial support of the Renal Division of Baxter UK (supporting LP).

References


Received for publication: 16.5.01
Accepted in revised form: 16.1.02