# Chapter 18: Co-morbidity in Incident Patients

## *Summary*


- There is a pressing need for the Registry is to improve the returns of comorbidity data for patients starting renal replacement therapy. Previous Registry reports have demonstrated a marked difference in survival between units, after both 90 days and 1 year of treatment. These differences are, however, not consistent and show no obvious correlation with background population mortality. At least part of the variation in survival will be explained by differing comorbidity among incident patients. Only by correcting for such comorbidity can the impact of differences in the process of care be clarified.

- This first analysis has shown the impact of comorbidity upon the survival of UK patients and therefore the importance of adjusting survival analyses for comorbidity. Without good comorbidity data, the value of survival analysis and a comparative audit of groups of apparently similar patients will be greatly reduced.

- Including the 7.3% of patients with diabetes registered as a comorbidity rather than the primary cause of renal failure, diabetic patients account for 24% of the incident patients starting renal replacement therapy.

- An analysis of bias in patient survival and comorbidity reporting indicates that the Registry comorbidity returns currently underestimate the true level of comorbidity in the renal replacement therapy population

- Multivariate analysis shows that the four comorbidity factors with the greatest adverse effect on survival in the first year after 90 days are age, ischaemic ulcers, malignancy and smoking.


## *Co-morbidity data*

The Registry has defined 15 'yes' (present) or 'no' questions relating to comorbidity and asks clinicians to complete this record at the time of starting renal replacement therapy (RRT). As an example, the screen made available to renal units using the CCL Proton system is shown in Figure 18.1. A patient may therefore have a fully completed screen recording no co-morbid conditions to be present. Null entries are considered missing data rather than 'no'.

Beginning in 2003, the presence or absence of heart failure will also be recorded. Definitions for each comorbidity are given at the end of this chapter.

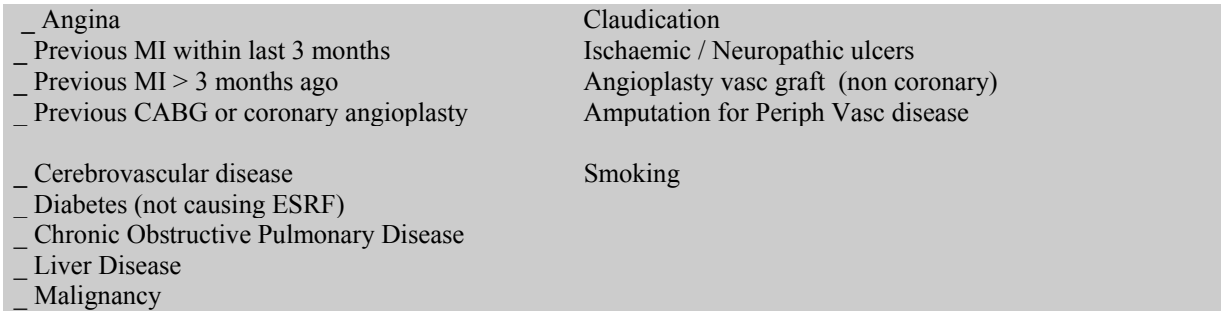


**Figure 18.1: Comorbidity entry screen for the CCL Proton system**

## *Co-morbidity returns by renal unit*

The return of comorbidity data for incident patients in 2001 remains very incomplete, although it has increased from previous years. Prior to 1999, comorbidity data were rarely returned to the Registry. In 1999, at least one item of comorbidity was reported for 20.8% of those patients registered as starting RRT that year. In 2000, 31.9% of incident patients, and in 2001 33.4% of incident patients, had at least one item of comorbidity data returned. When all incident patients ever notified to the Registry are considered, 18.9% have comorbidity data registered, representing 2854 incident patients. The returns by unit and year of starting RRT are shown in Table 18.1.

| Treatment centre | 1999 | | 2000 | | 2001 | |
|---|---|---|---|---|---|---|
| | No. incident | % Return comorbidity | No. incident | % Return comorbidity | No. incident | % Return comorbidity |
| Bradford | – | – | 39 | 48.7 | 61 | 91.8 |
| Bristol | 117 | 88.9 | 147 | 93.2 | 149 | 83.2 |
| Cambridge | – | – | 64 | 0 | 48 | 0 |
| Cardiff | 135 | 0 | 134 | 0 | 136 | 0 |
| Carlisle | 26 | 46.2 | 28 | 35.7 | 25 | 4.0 |
| Carshalton | 108 | 10.2 | 116 | 10.3 | 118 | 12.7 |
| Coventry | 91 | 0 | 88 | 0 | 101 | 0 |
| Derby | 25 | 0 | 40 | 0 | 49 | 0 |
| Exeter | 82 | 28.0 | 72 | 34.7 | 99 | 18.2 |
| Gloucester | 59 | 1.7 | 46 | 97.8 | 49 | 87.8 |
| Guys | 119 | 0 | 120 | 0 | 103 | 0 |
| Heartlands | 82 | 0 | 86 | 0 | 64 | 0 |
| Hull | 64 | 1.6 | 81 | 2.5 | 75 | 0 |
| Leeds LGI | 62 | 25.8 | 68 | 85.3 | 74 | 70.3 |
| Leicester | 158 | 80.4 | 171 | 76.6 | 174 | 86.8 |
| Livrpool | – | – | 154 | 31.2 | 182 | 35.2 |
| Notts | 128 | 24.2 | 113 | 71.7 | 121 | 64.5 |
| Oxford | 134 | 0 | 132 | 1.5 | 163 | 0 |
| Plymouth | 67 | 0 | 60 | 0 | 63 | 0 |
| Portsmouth | – | – | 104 | 0 | 141 | 39.7 |
| Preston | 104 | 0 | 116 | 0 | 134 | 0 |
| Reading | 45 | 0 | 54 | 0 | 72 | 0 |
| S Cleveland | 90 | 0 | 87 | 70.1 | 81 | 90.1 |
| Sheffield | 133 | 17.3 | 134 | 78.4 | 150 | 84.7 |

| Treatment centre | 1999 | | 2000 | | 2001 | |
|---|---|---|---|---|---|---|
| | No. incident | % Return comorbidity | No. incident | % Return comorbidity | No. incident | % Return comorbidity |
| Stevenage | – | – | 103 | 0 | 126 | 0 |
| Southend | 43 | 2.3 | 39 | 2.6 | 35 | 20.0 |
| St James | 79 | 86.1 | 91 | 93.4 | 86 | 76.7 |
| Sunderland | 45 | 0 | 45 | 0 | 35 | 0 |
| Swansea | 83 | 26.5 | 90 | 58.9 | 110 | 40.0 |
| Truro | – | – | 38 | 7.9 | 35 | 37.1 |
| Wolverhmtn | 75 | 0 | 77 | 0 | 77 | 0 |
| Wordsley | 43 | 0 | 40 | 0 | 34 | 0 |
| Wrexham | 51 | 0 | 55 | 0 | 36 | 0 |
| York | 51 | 74.5 | 40 | 92.5 | 36 | 77.8 |
| Totals | 2299 | 20.8 | 2872 | 31.9 | 3042 | 33.4 |

**Table 18.1: Comorbidity data returns, by centre, at the start of RRT**
Total number of patients registered each year and percentage of total incident patients with comorbidity returned.

## *Frequency of co-morbidities returned*

| Comorbidity | Age <65 years | | Age >65 years | | Total incidence |
|---|---|---|---|---|---|
| | No. pts | % | No. pts | % | |
| Angina | 1543 | 13.3 | 1288 | 29.7 | 20.8 % |
| MI in past 3 months | 1542 | 2.1 | 1285 | 3.4 | 2.7 % |
| MI >3 months ago | 1545 | 6.2 | 1283 | 16.3 | 10.8 % |
| CABG/angioplasty | 1543 | 4.1 | 1284 | 6.2 | 5.0 % |
| Cerebrovascular disease | 1548 | 8.2 | 1289 | 17.8 | 12.5 % |
| Diabetes (not as cause of ERF) | 1530 | 5.1 | 1281 | 9.8 | 7.3 % |
| Diabetes as primary disease | 1557 | 20.0 | 1297 | 12.8 | 16.7 % |
| Diabetes of either category | 1557 | 25.0 | 1297 | 22.5 | 23.9 % |
| COPD | 1548 | 4.3 | 1288 | 9.6 | 6.7 % |
| Liver disease | 1546 | 3.0 | 1286 | 1.6 | 2.4 % |
| Malignancy | 1538 | 6.8 | 1284 | 15.3 | 10.7 % |
| Claudication | 1541 | 7.1 | 1288 | 16.9 | 11.6 % |
| Ischaemic/neuropathic ulcers | 1538 | 4.8 | 1285 | 4.6 | 4.7 % |
| Angioplasty/vascular graft | 1546 | 2.5 | 1281 | 5.1 | 3.7 % |
| Amputation | 1549 | 2.9 | 1286 | 2.6 | 2.8% |
| Smoking | 1504 | 24.7 | 1258 | 17.1 | 21.3 % |

**Table 18.2: Frequency of comorbidity at the time of starting RRT**

Total number of patients with data entered for each comorbidity and percentage of total incident patients with each comorbidity present.
MI, myocardial infarction; CABG, coronary artery bypass grafting; ERF, established renal failure; COPD, chronic obstructive pulmonary disease.

The frequency of each of the co-morbid conditions at the time of starting RRT in all 2854 incident patients who have comorbidity recorded on the Registry are shown in Table 18.2. In a small number of these patients, some of the items were left blank, and it is not known whether this indicated that this co-morbid condition was not present or that the data were unknown. Smoking was the category that centres found most difficult to complete and was

returned for 2762 of the 2854 patients. Altogether, comorbidity categories had between 17 and 92 patients with missing data.

Diabetes occurred as a co-morbid condition in 7.3% of patients. When included with the category of diabetes as the primary cause of established renal failure, this increased the frequency of diabetes to 24% of all incident patients.

## *Co-morbidity reporting selection bias*

It is possible that those patients with comorbidity reported to the Registry were not representative of the distribution of comorbidity within the total incident RRT population. Patients with completed comorbidity data may be those who had little comorbidity (so details were easier to complete), had survived longer than 90 days on RRT or had greater comorbidity (more important to fill in) than other patients on RRT.

To analyse the possibility of selection bias, the patients registered by the four units (Bristol, Leicester, St James's and York) who had the most complete comorbidity returns in both 1999 and 2000 were studied. The 1 year survival of patients from these four centres was compared with the that from centres with a low rate of comorbidity data. The 2001 comorbidity data returns could therefore not be included in this analysis as 1 year survival data were incomplete. This analysis for bias does not adjust for any difference in practice in reporting between renal units. The results are displayed in Tables 18.3 and 18.4.

| | **High return units *with* comorbidity registered** | | **High return units *no* comorbidity registered** | |
|---|---|---|---|---|
| | **<65 years** | **>65 years** | **<65 years** | **>65 years** |
| 90 day survival | 97.1% | 88.7% | 89.0% | 65.6% |
| 95% CI | (95.7–98.6) | (85.9–91.5) | (81.9–96.2) | (56.1–75.1) |
| Patients | n=530 | n=488 | n=76 | n=96 |
| 1 year + 90 day survival | 90.4% | 79.7% | 81.3% | 54.8% |
| 95% CI | (87.1–93.8) | (74.8–84.6) | (69.6–93.0) | (39.7–69.8) |
| Patients | n=318 | n=261 | n=44 | n=42 |

**Table18.3: Survival at 90 days and 1 year + 90 days with high comorbidity returns**

| | **Low return units *with* comorbidity registered** | | **Low return units *no* comorbidity registered** | |
|---|---|---|---|---|
| | **<65 years** | **>65 years** | **<65 years** | **>65 years** |
| 90 day survival | 97.3% | 88.3% | 95.0% | 84.9% |
| 95% CI | (96.1–98.6) | (85.5–91.0) | (94.1–95.8) | (83.5–86.3) |
| Patients | n=640 | n=532 | n=2563 | n=2506 |
| 1 year + 90 day survival | 95.3% | 86.4% | 89.9% | 73.9% |
| 95% CI | (92.8–97.8) | (81.8–91.0) | (88.3–91.4) | (71.5–76.2) |
| Patients | n=283 | n=216 | n=1533 | n=1329 |

**Table18.4: Survival at 90 days and 1 year + 90 days with low comorbidity returns**

Those patients in whom comorbidity had been returned (as either present or absent) appear to have better survival, at both 90 days and 1 year later, than those in whom comorbidity was not recorded. This is true for renal units with either a high or a low rate of comorbidity reporting. The implication is that comorbidity is more likely to be reported to the Registry for relatively

healthy uncomplicated patients or those patients who survive long enough for the centres to complete the process of comorbidity registration.

Therefore the reported incidence of comorbidity is likely to be an underestimation of the total burden of comorbidity in patients starting RRT in the UK.

## *Survival and co-morbidity*

### *Inclusion criteria*

In the years up to the end of 2001, there were 2854 incident patients with comorbidity data recorded on the Registry. Those patients starting RRT between 1 January 1999 and 30 September 2001 were included in the 90 day survival analysis. Patients incident in 1998 with comorbidity recorded were excluded from the analysis as the overall return was low. By necessity, 1 year survival analysis excludes patients incident in 2001, as 1 year of follow-up was incomplete. Patients with no comorbidity recorded were excluded from the analyses.

### *The impact of co-morbidity on patient survival at 90 days*

The effect of each individual comorbidity upon patient survival was assessed by univariate analysis. The effect of each comorbidity category was assessed for all patients recorded as having that condition irrespective of whether or not they also had another comorbidity recorded.

For each co-morbid condition, a **co-morbidity hazard** is quoted. This is the risk of death for those with the comorbidity in question (irrespective of whether or not they have other comorbidity recorded), compared with those in the same age group with no comorbidity. A patient aged over 65 years with claudication has, for example, an increased hazard of death by 90 days that is 1.3 times greater then that of someone aged over 65 without claudication. This compares with an increased hazard of death of 4.9 for a patient aged under 65 with claudication, compared with a patient in the same age group without claudication. The results are shown in Table 18.5.

| **Co-morbidity** | **Co-morbidity hazard** | |
|---|---|---|
| | **<65 years** | **>65 years** |
| Angina | 2.6 | 1.6 |
| Heart disease* | 2.4 | 1.7 |
| Vascular disease** | 4 | 1.6 |
| Diabetes (not as cause of ERF) | 3.0 | 1.7 |
| Diabetes as primary disease | 1.6 | 1.7 |
| Diabetes of either category | 1.7 | 1.7 |
| COPD | 2.1 | 2.0 |
| Liver disease | 10.9 | 3.2 |
| Malignancy | 1.6 | 2.1 |
| Claudication | 4.9 | 1.3 |
| Ischaemic/neuropathic ulcers | 7.3 | 2.4 |
| Smoking | 1.2 | 1.7 |

**Table 18.5: Univariate analysis, co-morbidity hazards of death by 90 days**
*At least one of angina, myocardial infarction at any time, angioplasty/vascular graft

**At least one of cerebrovascular disease, claudication, ischaemic/neuropathic ulcer, angioplasty/vascular graft, amputation.
ERF, established renal failure; COPD, chronic obstructive pulmonary disease.

The combined effect of age and each of the individual co-morbidities upon 90 day patient survival after starting RRT was examined by Cox regression analysis. Variables considered in the model were: age, angina, myocardial infarction (MI) in previous 3 months, MI more than 3 months ago, coronary artery bypass grafting (CABG)/angioplasty, cerebrovascular disease, diabetes of either category, chronic obstructive pulmonary disease (COPD), liver disease, malignancy, claudication, ischaemic/neuropathic ulcers, angioplasty/vascular graft, amputation and smoking. Those variables found to be significantly important in the model are shown in Table 18.6.

| Variable | Chi squared | *p*-value | Hazard ratio | 95% Confidence interval | |
|---|---|---|---|---|---|
| Age | 69.9 | <0.0001 | 1.07 | 1.06 | 1.09 |
| Liver disease | 21.4 | <0.0001 | 4.67 | 2.43 | 8.98 |
| Ischaemic/neuropathic ulcers | 15.0 | 0.0001 | 2.90 | 1.69 | 4.96 |
| Smoking | 5.6 | 0.02 | 1.59 | 1.09 | 2.34 |
| MI in past 3 months | 4.8 | 0.03 | 2.23 | 1.09 | 4.56 |
| Malignancy | 5.7 | 0.02 | 1.64 | 1.09 | 2.47 |

**Table 18.6: Cox regression survival analysis of the first 90 days of RRT**

This multivariate analysis shows that those factors with the greatest influence on survival at 90 days are age, liver disease, the presence of malignancy or limb ulcers, be they neuropathic or ischaemic in origin, smoking habit and the occurrence of an MI within 3 months of starting RRT. The 95% confidence interval for liver disease is wide, mainly because of the low number of patients with this disease; therefore the importance of liver disease may be overestimated (or underestimated!).

### *The impact of co-morbidity upon survival at 1 year after 90 days*

As for survival at 90 days, the effect of each individual comorbidity upon patient survival was assessed by univariate analysis, and a hazard risk was calculated. The results are displayed in Table 18.7.

The impact of each individual comorbidity is greater in the under-65 age group because those without comorbidity in this age group might be expected to have a good prognosis. Once again, liver disease and ischaemic or neuropathic ulcers are seen to have a high hazard of death. As one might expect, malignancy likewise carries a high hazard of death by 1 year after 90 days, in contrast to the hazard of death at 90 days.

| Co-morbidity | Co-morbidity hazard | |
|---|---|---|
| | <65 years | >65 years |
| Angina | 7.0 | 2.2 |
| Heart disease* | 7.3 | 2.5 |
| Vascular disease** | 9.3 | 2.0 |
| Diabetes (not as cause of ERF) | 8.0 | 3.4 |
| Diabetes as primary disease | 6.6 | 2.8 |
| Diabetes of either category | 6.8 | 3.0 |
| COPD | 14.7 | 2.1 |

| Co-morbidity | Co-morbidity hazard | |
|---|---|---|
| | <65 years | >65 years |
| Liver disease | 12.3 | 2.4 |
| Malignancy | 10.5 | 3.5 |
| Claudication | 11.1 | 2.4 |
| Ischaemic/neuropathic ulcers | 13.0 | 5.2 |
| Smoking | 6.5 | 2.4 |

**Table 18.7: Univariate analysis, co-morbidity hazards of death by 1 year after 90 days**

*At least one of angina, MI at any time, angioplasty/vascular graft.

**At least one of cerebrovascular disease, claudication, ischaemic/neuropathic ulcer, angioplasty/vascular graft, amputation.

ERF, established renal failure.

Multivariate analysis was also performed to examine the effect of the same variables upon survival at 1 year after 90 days. Those variables found to be significantly important in the model are shown in Table 18.8.

| Variable | Chi squared | *p*-value | Hazard ratio | 95% Confidence interval | |
|---|---|---|---|---|---|
| Age | 43.2 | <0.0001 | 1.04 | 1.03 | 1.05 |
| Ischaemic/neuropathic ulcers | 30.4 | <0.0001 | 3.71 | 2.33 | 5.91 |
| Malignancy | 12.3 | 0.0004 | 1.94 | 1.34 | 2.80 |
| Smoking | 8.0 | 0.005 | 1.63 | 1.16 | 2.28 |

**Table 18.8: Cox regression survival analysis of the 1 year after 90 days of RRT**

This multivariate analysis of survival in the year after 90 days following the start of RRT shows that those factors with the greatest influence on survival are age, the presence of malignancy or limb ulcers and smoking habit.

## *Appendix to Chapter 18*

### *Important changes to co-morbidity definitions 2002*

The non-coronary angioplasty group has been widened to include other vascular grafts and arterial stents. The new definition is given below:

***Angioplasty, stenting, vascular graft (all non-coronary)***

This category now includes vascular grafts (e.g. aortic bifurcation grafts) and arterial stents.

***Episode of heart failure (right or left)***

This is whether or not it was only the result of fluid overload.

(This item has now been included as there is new evidence that heart failure caused by fluid overload is a bad prognostic sign. It was previously excluded as it was difficult to define whether or not it was the result of fluid overload).

## *Comorbidity definitions*

### *Angina*

A history of chest pain on exercise with or without ECG changes, exercise tolerance test, radionucleotide imaging or angiography.

### *Previous MI within the past 3 months*

MI diagnosed by ST segment elevation, Q waves in relevant leads, a rise in enzyme levels of more than twice the upper limit of normal (or a rise in creatine kinase-MB above the local reference range).

### *Previous MI more than 3 months ago*

From the time of the start of RRT.

### *Previous CABG or coronary angioplasty*

### *Episode of heart failure (right or left)*

This is whether or not it was only caused by fluid overload.

### *Cerebrovascular disease*

Any history of strokes (of whatever cause) and including transient ischaemic attacks caused by carotid disease.

### *Diabetes (not causing established renal failure)*

This includes diet-controlled diabetics.

### *Chronic obstructive pulmonary disease*

This is defined as a slowly progressive airways disorder characterised by obstruction of the expiratory airflow, which does not change markedly over several months, may be accompanied by airway hyper-reactivity and may be partially reversible.

N.B. Chronic bronchitis and emphysema may occur in the absence of airflow obstruction. Asthma patients may rarely develop airflow obstruction that does not improve with steroids.

### *Liver disease*

Persistent enzyme evidence of hepatic dysfunction *or* biopsy evidence *or* hepatitis B e antigen- or hepatitis C antigen (polymerase chain reaction)-positive serology.

### *Malignancy*

Defined as any history of malignancy (even if curative), for example the removal of a melanoma; excludes basal cell carcinoma.

### *Claudication*

Current claudication based on a history, with or without Doppler or angiographic evidence.

### *Ischaemic/neuropathic ulcers*

The current presence of these ulcers.

***Angioplasty, stenting, vascular graft (all no- coronary)***

This category now includes vascular grafts (e.g. aortic bifurcation grafts) and renal artery stents

***Amputation for peripheral vascular disease***

***Smoking***

Being a current smoker or having a history of smoking within the previous year.