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Can we measure quality and performance in renal services using routine data?

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Abstract

Disease registries are important resources in reporting incidence and prevalence of disease, and are in the position to identify and suggest best practice in an attempt to improve outcomes, minimise harm or reduce cost. The UK Renal Registry (UKRR) has missing data, lacks information on hospitalisation and associated events and contains errors.

This project links UKRR data to Hospital Episode Statistics (HES) data, collected by hospitals to describe amongst other things admissions, diagnoses, procedures and deaths. This linkage dramatically reduces missing data enabling comprehensively adjusted and inclusive centre specific measures of performance for renal centres.

Previous perceived differences between centres with regard to survival are largely explained, however large differences in admission rates persist using multivarate adjustment techniques. Rates of admission are similar to those published by other national disease registries despite the perception that renal replacement therapy outcomes in the UK were superior to other nations.

The study goes on to determine the ability of HES to identify events which have previously been restricted to studies employing manual case note review, and finds similar incidence and prevalence suggesting HES could be employed to perform more detailed study in these areas. Epidemiological associations are trialled with plausible results. Finally the combination of these datasets is evaluated against standards set by the North American Association of Central Cancer Registries and potential areas for further study suggested.

Contents

Abbreviations

ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
CABG	Coronary Artery Bypass Graft
CCS	Clinical Classification Scheme
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
DGF	Delayed graft function
DOPPS	Dialysis Outcomes and Practice Patterns Study
ERA-EDTA	European Renal Association - European Dialysis and Transplant Association
ERF	Established Renal Failure
HCUP	Healthcare Cost and Utilization Project
HD	Haemodialysis
HES	Hospital Episode Statistics
HRG	Health Resource Group
HSMR	Hospital Standardised Mortality Ratio
ICD9/ICD10	International Classification of Diseases Version 9/10
IMD	Index of Multiple Deprivation
ISPD	International Society for Peritoneal Dialysis
IQR	Interquartile range
LSOA	Lower Super Output Area
MINAP	Myocardial Ischaemia National Audit Project
NA	Not available / Not applicable
NAACCR	North American Association of Central Cancer Registries
NECOSAD	Netherlands Cooperative Study on the Adequacy of Dialysis
NHS	National Health Service
NRD	National Renal Dataset
ONS	Office of National Statistics
OPCS	Office of Population Censuses and Surveys
OR	Odds Ratio
PD	Peritoneal Dialysis
PMP	Per million population
RCP	Research Capability Programme
RMSE	Root Mean Square Error
ROC	Receiver Operator Characteristics
RRT	Renal Replacement Therapy
SES	Socio-economic status

SHMI	Summary Hospital Mortality Index
UKRR	UK Renal Registry
USRDS	United States Renal Data System

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There are aspects of all of you in the pages herein.

Chapter 1 *Introduction*

Kidney Disease – an international problem

Kidney disease is a worldwide health problem. Using the broadest classification which includes low kidney function, blood or protein in the urine or structural problems the prevalence of kidney disease is 13.5% in the UK(Roderick et al. 2011), and is similar in other developed countries(Hallan et al. 2006). Kidney disease is not just a western problem, with developing countries identified as having an evolving health need as the prevalence of type II diabetes increases(El Nahas et al. 2005).

Established renal failure (ERF) represents the lasting failure of the kidneys to function adequately to support life without significant symptoms. It forms part of the chronic kidney disease (CKD) stage 5 group, defined by having an estimate glomerular filtration rate of less than 15ml/min/1.73m^2. Patients can enter this stage acutely and then recover kidney function however the entry into ERF is generally long term (greater than 90 days).

Treatment options exist when a patient develops ERF. Haemodialysis, peritoneal dialysis and kidney transplantation (collectively referred to as renal replacement therapy (RRT)) have evolved over the last fifty years to be commonplace therapies for this group of patients. Additionally a proportion of patients ahead of or when they arrive at ERF choose not to receive RRT. This is referred to as conservative care.

Incidence and prevalence of Established Renal Failure

Established renal failure requiring long term kidney support in the form of renal replacement therapy (RRT) affects approximately 53,000 patients in the UK, with 6,800 patients starting therapy each year(Gilg et al. 2013; Shaw et al. 2013). The risk for starting ERF treatment is a combination of surviving competing causes of death, reaching kidney failure, being offered RRT, and accepting RRT(Hallan et al. 2006). The incidence of ERF requiring RRT is 108 patients per million population (pmp), having increased steadily over the course of the preceding two decades and plateaued over the last five years. The age adjusted incidence (100.2 pmp) in the UK is comparable to other developed countries. The USA has the highest at 348 pmp (non-age-adjusted), despite similar prevalence of CKD stages to other European countries(Hallan et al. 2006). Inferior US pre-dialysis care, different prevalence of risk factors such as diabetes and a higher proportion of patients living below the poverty line in the US are some of the possible explanations. Elsewhere within Europe, rates in France (128.1 pmp),

Greece (157.6), Spain (93.1 – 123.8 pmp), Norway (99.5 pmp) and the Netherlands (107.1 pmp) are more comparable(ERA-EDTA Registry 2011). Importantly, the uptake of conservative care is not fully captured.

The prevalence of ERF requiring RRT in the UK is 842 per million (0.1%), highlighting the differences in incidences across the stages of CKD and that the majority of individuals with milder forms of CKD do not progress to ERF. Due to improvements in survival on RRT, the prevalence of ERF in the UK has climbed steadily over the last six years by four percent per year(Shaw et al. 2013). Prevalence in the US is 6,068 per million(Collins et al. 2012), but due to the differences in ethnicity and recognised survival advantages of other ethnic groups over whites (discussed below), European countries may be more comparable. France (1085 pmp), Greece (1103), Spain (948 – 1202 pmp), Norway (874 pmp) and the Netherlands (961 pmp) are again fairly close to the UK(ERA-EDTA Registry 2011), which itself shows little variation across its constituent countries when compared to the above.

Morbidity on renal replacement therapy

The burden of morbidity for patients receiving RRT for ERF is large. Many patients arrive on the therapy with a number of co-existent medical problems which may or may not relate to the reason they have ERF. Twenty-five percent of patients starting RRT in the UK do so due to diabetic nephropathy(Gilg et al. 2013), with this proportion climbing to 45% in the US(Collins et al. 2012). Diabetes in combination with ERF is associated with incidences of peripheral vascular disease as high as 19%, and ischaemic heart disease of 22%(Helve et al. 2011). Renovascular disease is associated with a similarly high burden of comorbidity due to the underlying aetiology of the disease. Cardiac disease accounts for 22% of deaths in UK RRT patients(Steenkamp et al. 2013), with 12.6% of patients having had a myocardial infarction and 10.8% having had a cerebrovascular incident prior to starting RRT. These numbers are reported to be as high as 53.8% and 25.6% respectively in US dialysis patients, where diabetes is more prevalent(Liu et al. 2009).

The evolution of morbidity once receiving dialysis is considerable and is largely down to cardiovascular disease. The loss of kidney function has wider implications than the capacity to excrete excess fluid and toxins in the urine. Interruption of vitamin D metabolism and reduced or absent urinary excretion of calcium and phosphate (Moe et al. 2008) results in accelerated calcification of blood vessels contributing to cardiovascular risk (Block et al. 2004), and a high incidence of peripheral vascular disease and associated ulceration (O'Hare et al. 2002).

Fluid overload and anaemia lead to cardiac remodelling (Levin et al. 1999), increasing the risk of cardiac failure or arrhythmia (Saravanan et al. 2010) (Foley et al. 1995). The risk of the latter is increased by exposure to elevated levels of potassium, due to inadequate dialysis, longer periods without dialysis built into the haemodialysis schedule or missing a dialysis treatment session (Roberts et al. 2011). In the US, the rate for admissions for cardiovascular disease is 0.54/year, compared to 0.47/year for infections and 0.11/year for dialysis access related infections (Collins et al. 2012).

Transplantation, offering partial or complete restoration of the CKD mineral bone disease axis, only partially ameliorates this association (Foley et al. 1998). Immunosuppressive therapies such as prednisolone and calcineurin inhibitors promote the development of new onset diabetes after transplantation (up to 20% in the first year post-transplant) by suppressing insulin production and reducing insulin sensitivity (Jardine et al. 2011).

Importantly, the high cardiovascular risk burden may be modifiable, and the capacity to modify it can vary at a centre level. Attainment of targets for calcium and phosphate set by governing bodies are associated with improved survival and reduced hospitalisation at a patient level(Plantinga et al. 2007) (Rocco et al. 2006).

The risk of infection related admission for a dialysis is ten times higher than the general population (Naqvi et al. 2006), and again compared to the general population is associated with a 100-300 times increase in the risk of death (Sarnak et al. 2000). The cumulative annual incidence of infection related hospitalisation in the US is 31% in adults receiving dialysis(Chavers et al. 2007). These associations are exacerbated by haemodialysis catheter use which is associated with a five times increase in hazard for bacteraemia (Thomson et al. 2007). Thirty percent of patients in the UK and sixty-four percent of patient in the US start haemodialysis with a intravascular dialysis catheter and significant variation across dialysis providers has been noted(Castledine et al. 2011) (U S Renal Data System 2011). Recipients of kidney transplants are also at greater risk of infection related morbidity, with the admission rate due to infection in prevalent patients in the US running at approximately 22 per 100 patient years for over a decade(U S Renal Data System 2011).

Hospitalisation and resource use in renal replacement therapy

The cost of managing these patients on RRT should not be understated. The provision of haemodialysis in the UK annually is approximately half a billion pounds, accounting for over half of total CKD care bill (Kerr et al. 2012). In the US, $32.9 billion is spent of RRT care each year, with 12.5 billion spent specifically on inpatient care (U S Renal Data System 2011). The same data shows a steady increase in these costs as the RRT population has expanded, with no reduction in hospital costs in absolute or relative terms.

Mortality on renal replacement therapy

The development of ERF requiring RRT shortens life expectancy by 55% compared to the general population, making its impact worse than many regionalised cancers (Nordio et al. 2012). In absolute terms, of all patients starting RRT in the UK, 51.8% survived to five years. Outcomes do continue to improve, with patient survival for the first year climbing from 88% to over 90% between 2005 and 2010(Steenkamp et al. 2013), with similar improvements seen longer term.

At any time point, the cause of death for an RRT patient is most frequently cardiovascular in origin. In the UK, cardiovascular disease accounts for 21% of deaths on RRT with infections accounting for a further 19% (Steenkamp et al. 2013). The cardiovascular mortality risk of a twenty-five year old on dialysis is comparable to an eighty-five year old without kidney disease (Foley et al. 1998). Treatment withdrawal (the cessation of dialysis for instance) is the explanation given in 16% of cases for cause of death, but a number of factors or events can precede this including the above.

Survival on RRT is influenced by the case-mix of the individual and by the prevention and management of morbidity accrued whilst on treatment. Having diabetes when starting RRT inferred an 80% increase in risk of death in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)(Schroijen et al. 2011). Factoring other comorbid conditions and primary renal disease, Liu et al used US Renal Data Service data to show that diabetes was associated with a 34% increase in death in dialysis patients, similar to that seen with heart failure (34%), and higher that that observed in peripheral vascular disease (22%) and cancer (22%)(Liu et al. 2009). These risks are all the more pertinent when one considers the reported incidence of these conditions (diabetes 47.5%, heart failure 55%, peripheral vascular disease 44.5%, cancer 12.2%). The impact of comorbidity may not be the same across age-groups. Nitsch et al identified that the increase in risk of death in diabetic patients below 55 years of age was twice that of the increase in diabetic patients compared to non-diabetic patients over the age of 65(Nitsch et al. 2007).

A number of studies in both the UK and internationally have highlighted that Caucasian patients fare less well on RRT than their South Asian and Black counterparts(Pei et al. 2000; Kucirka et al. 2011). A number of explanations are offered including more severe comorbidity in Caucasian patients compared to other ethnic groups(Szczepura et al. 2008). The speed at which different ethnic groups arrive at RRT after CKD is a possible explanation(Barbour et al. 2010) (Derose et al. 2013), with the slower progression of CKD in Caucasian patients resulting in a longer time at risk to develop an unmeasured burden of vascular comorbidity associated with uraemia. Selection bias in favour of more healthy patients to receive treatment in the non- Caucasian groups has also been proposed(Mehrotra et al. 2008). This survival advantage may not be constant across age groups, with a recent paper identifying that the superior survival in non-hispanic Blacks is reserved to patients above the age of 30(Yan et al. 2013), however the hazard ratio for death overall was 0.87 compared to non-hispanic Whites. Causasian patients do gain an advantage from increased transplantation rates, an intervention associated with a survival advantage(Wolfe et al. 1999; Malek et al. 2011). The explanation for differing transplant rates is multifactorial and currently being explored in observational work.

In addition to the contribution socioeconomic status (SES) has to the risk of developing ERF needing RRT, SES affects survival once the patient starts treatment. Measured by income or segregation, lower measures of SES are associated with worse outcomes and are often interrelated with disparities in outcomes within ethnic groups (Kimmel et al. 2013). The evidence of this association is strongest from American data, but has been reported in UK studies from the UK Renal Registry (Caskey et al. 2006). In the latter late referral was lowest in the least deprived group, and an interaction between age and SES was observed, with the worse comparative outcomes seen in the most deprived patients under the age of 65. The adverse effect of SES (hazard for in most deprived group compared to the least deprived 1.20, 95% CI 1.07 – 1.35) was attenuated dramatically by the inclusion of comorbidity in the model (0.86, 95% CI 0.65 – 1.15) despite little effects of SES on the prevalence of individual conditions.

Referral to a nephrologists late (classically taken as within 90 days of starting RRT) or an unplanned start of RRT (precipitated by a sudden decline in renal function in a patient already known to renal services) has an adverse impact on hospital resource utilisation (Arora et al. 2000) and doubles the relative risk for mortality (Chan et al. 2007). As late referral is classically considered outside the nephrologists' control it would ideally be adjusted for in centre-based comparisons. Late referral is also associated advanced age, with ethnicity, and a greater burden of comorbidity (Farrington et al. 2007). This association may be confounded by the fact that these are associated with more rapid CKD progression (Anderson et al. 2009) and put

patients at a greater risk of acute kidney injury (Leblanc et al. 2005), thereby leaving less time available to be referred.

A patient's survival is also modified by their RRT modality. Wait-listing a 45 year old male for a deceased donor kidney is associated with an increase in survival of 2.4 years (Wong et al. 2012). If a wait-listed patient is transplanted they gain approximately 7.2 years of life (Schnitzler et al. 2005) (Wolfe et al. 2008). Although the survival advantages associated with transplantation are accepted, differences between the dialysis modalities of haemodialysis and peritoneal dialysis are not. More recent studies have found following adjustment for patient case-mix, outcomes are comparable between the two modalities (Mehrotra et al. 2011) (Yeates et al. 2012), whereas more historical studies or those without as comprehensive adjustment have generally found a survival advantage with peritoneal dialysis (Weinhandl et al. 2010). Suggested explanations for residual differences include the adverse effects associated with haemodialysis catheters (Perl et al. 2011) and the statistical impact censoring for renal transplantation as it represents a competing risk(Noordzij et al. 2012). In addition the length of time a patient is exposed to the therapy may be a factor, with superior outcomes noted in patients who remained on haemodialysis for greater than one year in the Australia and New Zealand Dialysis and Transplant Registry (McDonald et al. 2009), and two years when compared to peritoneal dialysis in the NECOSAD study(Termorshuizen et al. 2003).

The country in which you receive dialysis affects mortality; however comparisons are often challenging based on available and comparable data. Using Dialysis Outcomes and Practice Patterns Study (DOPPS) data, authors were able to report multivariate adjusted mortality comparing Japan, Europe and the US. Crude mortality at one year was 6.6%, 15.6% and 21.7% respectively. Following adjustment, the hazard for death in the US was 3.78 and Europe was 2.84 compared to Japan. Data on more recent patient cohorts (2002 – 2008) suggests continued differences internationally, particularly in early death within the first 120 days (Robinson et al. 2013). The UK for instance has similar mortality rates throughout the first 12 months, whereas Japan's mortality rate for the first 120 days is three times the rate of the rest of the year. Explanations for international differences in mortality include background cardiovascular mortality rates in the general population (Yoshino et al. 2006), differences in dialysis access usage (Rayner et al. 2004), dialysis treatment time (Tentori et al. 2012) and missed dialysis sessions (Saran et al. 2003).

The renal centre managing a patient's care appears to have an influence on several clinical outcomes, despite adjustment for some of the variables listed above. One could stratify factors that influence outcomes into levels: geographical or ecological (e.g the influence of the part of

the country the patient lives in) would be at the top. At the bottom would be individual patient factors (e.g. the influence of being diabetic or elderly). In between these levels would be the influence of the healthcare provider and the organisational elements within. This influence is often referred to as the centre effect, and can have positive or negative influence on patient outcomes(Hodsman et al. 2011). There is temptation to class this as abstract and perhaps intangible, representing the influence of the overall influence of being cared for by a particular healthcare provider. However, depending on the method of estimation or adjustment this influence may be directly measurable, or represent an arrogation of a number of organisational factors which themselves might be directly quantifiable with the application of the correct modelling process. For instance the application of clustered logistic regression was used to determine that an increased frequency of patient-physician contact (a centre level organisational factor) was associated with the achievement of a number of clinical performance targets in dialysis care (Plantinga et al. 2005). A centre effect may be the manifestation of how a particular group of patients is managed or responsed to that management (non-constant risk (Nicholl 2007)). The centre effect can be attributed to measured or unmeasured clinical influence rather than chance by the centre in question being an outlier for an extended period.

Given the morbidity, mortality and associated resource use associated with RRT, having tools and resources to identify best practice and detect poor clinical care are important for the health service and the patient. Renal disease registries represent an important resource with the potential to achieve this.

Renal registries

Purpose

Renal registries most commonly cover the collection and analysis of standardised data relating to the incidence, clinical management and outcome of renal disease(The UK Renal Registry 2013). This enables registries to report changes over time and across providers of information (be these geographical areas or participating renal centres). By collecting clinical management they are in the position to identify and suggest best practice in an attempt to improve outcomes, minimise harm or reduce cost. Through comparison they can provoke investigation and encourage quality improvement.

Scope & coverage

Most of the renal registries internationally primarily focus on the management of patients with ERF, however some are able to report on patients with milder stages of CKD. Coverage of

patients is generally from the point where a patient starts RRT, and as a result research is often limited to events during or after this period. The format and level of detail collected varies, but most developed registries collect information on co-existent disease (comorbidity), cause of renal failure (primary renal disease), demography (age, sex, ethnicity, socioeconomic status) and treatment related information. The latter could include laboratory variables, dialysis technique and dose, and transplantation events. The US Renal Data System (USRDS) is in the position to collect Medicare hospitalisation information as patients are eligible to access this health provision once they start RRT, however it precludes them from using it prior to this date. Inclusivity has been a priority, both at a patient and centre level, with most registries now claiming to cover all RRT patients for the country they cover.

History and Examples

One of the longest running renal disease registries is the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) (McDonald et al. 2013). Their first report was produced in 1978 and contained information as far back as 1971, highlighting incidence rates of between 27 and 30 pmp. Data collection is now via a web-based form. The duration of follow-up for their patients and their comprehensive information on peritoneal dialysis related outcomes has resulted in a high research output.

The USRDS published their first report in 1988. Like many other disease registries it is informed by electronic downloads from participating centres, but gains additional information from financial claims data. Capitalising on the fact that physicians need to complete paperwork in order to be remunerated when a patient starts dialysis in the US, the demographic information this provides means the USRDS is more complete than other renal registries (U S Renal Data System 2011). This access to claims data informs many other aspects of the USRDS report, including rates of cardiovascular events and infections, all cause admissions and healthcare costs. Through this linkage and the population size, the USRDS has been extremely successful in its research output.

Coverage of multiple countries is also possible. The European Renal Association / European Dialysis and Transplant Association (ERA-EDTA) moved to its current home in Amsterdam in 2000, and capitalised on national or large regional registries which had high quality data for the preceding decade(Stengel et al. 2003). In order to allow compatibility across the different informing registries, the format of the ERA-EDTA registries is less elaborate than those which inform it. One such informing registry is the UK Renal Registry.

The UK Renal Registry (UKRR) was commissioned by the Renal Association in 1995. UKRR has roles serving clinicians, patients and commissioners, aiming to improve equity of access to care, adequacy of facilities, availability of important but high-cost therapies and the efficient use of resources(The UK Renal Registry 2013). It is informed by informed from downloads of clinical information from renal centres throughout the UK, which is largely inputted by clinicians or information staff. It is subject to extensive data validation and cleaning prior to analysis (Ansell et al. 2009). It is funded by a £19 capitation cost per patient which is paid by the submitting renal unit, who in turn receive centre-specific analyses enabling comparison other centres and national averages in the form of an annual report and an interactive website (Chaudhry et al. 2011). This is unique to UKRR compared to other national renal registries.

Strengths, Weaknesses, Opportunities and Threats

To successfully employ renal registries monitor trends, identify best practice and detect poor clinical care a broad understanding of the characteristics, informing data and landscape in which renal registries lie is important. Given what they are potentially able to achieve, one might view existing outputs as falling short of this.

Using information distilled from reviewing literature generated by renal registries and extensive discussion regarding the landscape in which the UKRR operates in various meetings during the course of this research project, Table 1-1 highlights the strengths, weaknesses, opportunities and threats of Renal Registries, but can generally be applied to most national disease registries. Understanding these paradigms informs the maximum potential a renal registry can achieve and what steps are required.

Strengths & opportunities

Renal registries have the capacity to identify trends illustrated by the UKRR showing a reduction in late referral for RRT care following the introduction of CKD guidelines (Gilg et al. 2013). Despite the encouragement by many renal bodies to improve fistula usage in haemodialysis patients based on research from the USRDS amongst others highlighting a strong association between dialysis catheters and admissions for dialysis related infections (Ishani et al. 2005), infection rates have not reduced (U S Renal Data System 2011). Residual differences in type of first access at centre level have been identified, noting a centre specific range of 51 – 94% of haemodialysis patients starting with definitive haemodialysis access (Castledine et al. 2011).

UKRR has identified inequity in access to transplantation (Ravanan et al. 2010), resulting in subsequent larger more detailed study. The identification that longer haemodialysis treatment

Table 1-1 : A Strengths, Weaknesses, Opportunities and Threats analysis of renal registries

Strengths	Weaknesses	Opportunities	Threats
Identify trends *e.g. The rising prevalence of RRT in the elderly* **Benchmarking and variation reduction** *e.g. Setting audit standards and the variation in achieved rates of arterio-venous fistula use* **Original research** *e.g. Hypothesis generation and testing* **Country specific & relevant** *e.g. USRDS recognises and accounts for differing healthcare insurers* **Credibility** *e.g. High quality staff and techniques producing important outputs*	**Missing or inaccurate data** *e.g. Incomplete comorbidity information, or all patients reported as no comorbidity* **Absent variables** *e.g. Vascular access formation and use not collected by UKRR* **Clinically abstracted** *e.g. Analysts without regular clinical contact fail to account for relevant clinical considerations* **Inflexible specification** *e.g. Addition of new variables laborious with poor centre uptake* **Timeliness** *e.g. Many disease registries take two years to report data* **Statistical and analytical limitations** *e.g. Comorbidity only recorded at one time point*	**Collaborative research partner** *e.g. Power calculations, recruitment estimates and endpoint collection* **Inform commissioning** *e.g. Matching incident or prevalence with healthcare provision* **Drive quality improvement** *e.g. Identifying need and monitoring changes post-intervention* **Identify best practice** *e.g. AV fistula use and improved survival on haemodialysis* **Generate hypotheses and clinical trials** *e.g. Identify good practice necessitating proper exploration in the trial setting* **Improve healthcare value** *e.g. Identify centre specific high resource use and stimulate change* **International collaboration** *e.g. Combining datasets for international comparison* **Linked datasets** *e.g. New endpoints and less missing data*	**Scepticism** *e.g. "The information about my centre is wrong"* **Misinterpretation & Abuse** *e.g. Use of data by inadequately trained, reader failing to understand context behind centre specific variation* **Heterogeneous supplied data** *e.g. Some centres only provide patients who have survived 90 days on RRT*

time is associated with improved survival (Marshall et al. 2006) justifies the increase in treatment time between 1996 and 2008(Tentori et al. 2012).

Data collected by UKRR has enabled high-quality commissioning, for instance geographical analysis for appropriate development of satellite dialysis units (Roderick et al. 1999). A number of centres have tackled individual areas of weakness identified by UKRR reports with subsequent improvement. Many of the Renal Registries listed above have credibility due to their volume of research output and are run by a committee from larger governing bodies with experience and clinically relevant concerns.

Weaknesses and Threats

The negative aspects of renal registries start with the data that informs them. Previous work has highlighted that the date of first RRT was incorrect in approximately 16.5% of patients starting RRT in nine selected centres in the south west of England (Ford et al. 2010). Likely explanations relate to the interpretation of the definition as to when a patient starts RRT, suggesting issues with interpretation may exist elsewhere within the dataset. Missing data affects 50.7% of comorbidity returns, and has not significantly improved in recent years (Webb et al. 2011). Issues with missing or inaccurate data are not limited to the UKRR, or renal registries in general. A quarter of cases from the National Trauma Data Bank were excluded due to missing data on age, sex and length of stay (Zehtabchi et al. 2011). The comparison between a hospital discharge database and cardiology database noted disagreements of up to 57% for comorbidities and 47% for applicable patients (Merry et al. 2009). The ANZDATA registry compared newly reported cancer diagnoses to a cancer registry, and found similar prevalence but approximately 24% disagreement (Webster et al. 2010).

In order to maintain broad compatibility with the systems and sources which inform them, renal registries often have comparatively limited data collection fields. The ERA-EDTA receives information from 44 national or large regional renal registries covering 30 countries to inform its reports, and as a result only utilises five tables. Changes information specifications necessitates engagement from IT suppliers before the collection of patient information can begin, meaning that for some exercises such as recording the first form of dialysis access for a one year period it is easier to supply a spread sheet for completion (Briggs et al. 2013). Delays in the completion of the informing data by renal units, and error checking / validation mean that often the annual reports describe data from two years ago. All of these issues contribute toward scepticism regarding the accuracy of centre level data. Centres with worse than expected results use inaccuracy or inadequate case-mix adjustment as an excuse (Tomson

2012). Contextual interpretation of registry information is important, and the audience is often diverse in its prior understanding of RRT and statistics.

Clearly renal registries are in a position to identify variation at a centre or regional level, and use this variation to drive improvement, recommend best practice or stimulate further investigation. However, issues surrounding data quality and completeness have the capacity to devalue the registry, its research or resultant impact. Improving data quality and completeness, and broaden the scope of the data collected has the capacity to address these issues.

Data linkage

The combination of datasets has the capacity to improve data completeness or enable new analyses. The USRDS routinely links to the Medicare database to enhance the comorbidity information completed by physicians on the Medical Evidence form when a patient starts RRT. Due to incomplete Medicare coverage prior to starting RRT, the USRDS use diagnosis codes from the first nine months of RRT to inform their subsequent analyses (Liu et al. 2009). This linkage is employed to report the trends in admissions for infection or cardiovascular disease highlighted above. Using infection-related hospitalisation from Medicare as a reference point, Dalrymple et al identified that in the 90 days following discharge there was an 18% increased risk in cardiovascular events (Dalrymple et al. 2011). Using the haemodialysis weekly schedule identified from the USRDS, Foley et al showed twice the number of cardiovascular admissions identified from Medicare data after the two day break in three time a week haemodialysis than the following six days(Foley et al. 2011).

Linkage between disease registries and other types of source has also been employed. Linking clinical trial data to a national transplant registry, the investigators comparing different induction regimes for kidney transplantation were able to report five-year outcomes despite ceasing data collection through the trial case report form (Brennan et al. 2008). By linking UK Transplant Registry data to cancer registries in England, Scotland and Wales, Collett et al showed that the ten-year incidence of de-novo cancer in transplant recipients was twice that of the general population, and further characterise which malignancies were subject to the greatest increases (Collett et al. 2010).

Dataset linkage occurs outside nephrology. Hospital performance is routinely measuring in the UK by linking Hospital Episode Statistics of Office of National Statistics death registrations to obtain information on hospital associated mortality out to 30 days following discharge (Campbell et al. 2012). Hospital Episode Statistics have been linked to the National Cancer Data

Repository to show that increasing hospital volume and increasing resection rates for oesophageal and gastric cancer were associated with a survival advantage at one year (Coupland et al. 2013).

Hospital episode statistics

Hospital Episode Statistics (HES) are routinely collected information on secondary care activity in England. HES data became mature and encompassed the majority or secondary inpatient care in 1989-1990, and began covering outpatient activity in April 2003. In addition to generating routine activity statistics, HES has evolved to inform the remuneration of NHS trusts in England using payment by results tariff costing (Allen 2009) (Sinha et al. 2013).

The HES dataset collects information on reason for admission and any associated comorbid conditions or intercurrent illness, procedural activity, location and length of stay and inpatient mortality. It also includes demographic information on age, sex, ethnicity and socioeconomic status. It records this information separately for each period under a different consultant (episode) for each period of time in a separate hospital (spell) (Aylin et al. 2007).

Several agencies use HES to routinely benchmark hospital performance for a range of measures (CHKS 2010) (Aylin et al. 2010) (Campbell et al. 2012). A high profile example is hospital standardised mortality ratios. For each hospital admission the probability of dying is calculated from clinical information in the HES record based on the death rate for all hospitals being monitored. The sum of these probabilities is compared to the sum of the deaths that actually occurred, with high values suggesting poor clinical care. These indicators have subsequently identified a number of under-performing trusts which have been investigated revealing serious clinical issues (Francis 2010) (Spiegelhalter 2013), and their derivation is discussed in the following chapter. Many regard HES as the key information source in more recent government commitments to monitor outcomes (Spencer 2012).

HES have been used in a number of research settings. Operative delay of greater than one day in the repair of fractured neck of femur was associated with a 27% increase in mortality by Bottle et al (Bottle et al. 2006). The same group found the mortality with elective surgery was increased by 44% and 82% if performed on a Friday or a weekend compared to the rest of the week (Aylin et al. 2013). Following the introduction in smoke-free legislation in England, HES data was used to demonstrate a 2.4% reduction in admissions for myocardial infarction (Sims et al. 2010).

Information pertaining to the diagnoses associated with and procedures performed during the hospital admission are documented by clinical coders, rather than the medical staff who

may have identified these diagnoses or performed the procedure. Concerns about the agreement between HES data and clinical events documented in patient notes have prompted a number of reviews. The most recent quotes an 80% diagnostic accuracy and an 84% procedure accuracy. Improvements in both have been observed since 2002 when Payment by Results were introduced, with the accuracy quoted as 96% for diagnoses for this period (Burns et al. 2012). HES data has been shown to perform similarly to national clinical databases (cardiac surgery, vascular surgery and colorectal cancer) in predicting death (Aylin et al. 2007).

The capacity to link other information sources to HES has only recently been developed, as information governance barriers precluded this. HES were only released to researchers in anonymised form, or at best with a pseudo-anonymised identifier which enable subsequent updates and comparisons of patients across years.

Other high profile routine data sources exist within the National Health Service that are largely disease specific. National audits produce a large amount of original research, covering coronary events and diabetes care (Birkhead et al. 2004) (Morris et al. 1997). These too may represent suitable linkage targets for understanding specific disease processes.

The study

Renal registries have an important role in monitoring trends, identifying best practice and detecting poor clinical care. However, limitations in the completeness, quality or included data items has limited what the UKRR has previously been able to achieve, and introduced scepticism from the renal community regarding the conclusions on centres specific performance. A broader range of data collection items and enhanced completeness and validity of existing items would be required to achieve this. Linkage to other existing data sources may have the capacity to achieve this. Would linkage to the HES dataset offer an important opportunity to meet some of these goals?

Study aims

This study aims to link the UKRR dataset to the HES and ONS datasets for a cohort of patients in order to:

- Establish if patients within the UKRR dataset can have their associated hospitalisation and mortality data obtained through the HES and ONS datasets.
- To determine if the combination of these datasets reduces missing data.
- To explore if the variation in incident survival is explained by case-mix inadequately captured by previous data sources.

- To use linked data can enable the generation of new, informative measures of performance.
- To establish if following adjustment for demography the variation in these new measures is reduced.
- Offer suggestions as to where such a linked dataset could be applied.

Thesis overview

Chapter 2 – Literature Review: Reviews comorbidity scoring systems previously derived and employed in the general population and renal patients, and explores hospitalisation associated performance measures and the statistical techniques that underpin them.

Chapter 3 - Methodology: Details the research governance, data linkage and subsequent processing along with statistical methods employed subsequently.

Chapter 4 – Linkage and variable generation: Assessment of linkage strength, data validity and the generation of new variables or enhancement of existing incomplete variables.

Chapter 5 – Mortality on RRT: Adjustment of existing UKRR centre specific survival for new variables and derivation of hospital associated mortality measure.

Chapter 6 – Hospital associated events in haemodialysis: Centre specific admission rates for the first year of haemodialysis and an exploration of admissions according to weekly haemodialysis pattern.

Chapter 7 – Admission rates in peritoneal dialysis patients: Centre specific admission rates for the first year of peritoneal dialysis, with specific exploration of peritonitis events and catheter insertions.

Chapter 8 – Hospital-related events in kidney transplantation: Centre specific length of stay, delayed graft function, surgical complication and admission rates in the first year following kidney transplantation.

Chapter 9 – Discussion and conclusion: Includes an assessment of the quality of the generated linked dataset against existing standards and recommendations for future work with similar linked datasets.

Summary and Conclusions

Recognising the morbidity and mortality associated with RRT, and taking examples from other Renal Registries, the sources of information informing UK specific analyses need to be broadened and existing data improved to fully describe current practice, adequately adjust existing and future measures of performance, and perform cutting edge research. Linkage of the UKRR to HES data has the capacity to overcome some of the existing barriers.

Chapter 2 *Literature Review*

The proposed linkage between the UKRR, HES and ONS datasets greatly expands what it is possible to adjust for and report for English RRT patients and renal centres. To address the former, relevant comorbid conditions (historically dictated by the UKRR dataset specification) and their measurement or identification from the informing sources needs to be understood.

Hospital Episode Statistics captures hospital related activity. This activity can be beneficial to the patient (e.g. being admitted for a kidney transplant which subsequently functions) or detrimental (prolonged or recurrent hospitalisation, perhaps ending with mortality). The appropriate method for identifying, quantifying, adjusting and reporting hospital related events and their assignment to the appropriate renal centre is essential to ensure the validity of centre specific measures and epidemiological conclusions.

This literature review chapter is divided into a review of comorbidity assessment in established renal failure, with a specific focus on measures which can be derived from observational or routine data sources, and a review of previously reported hospitalisation measures and the statistical processes employed to enable multivariate adjustment for patient level case mix.

Review of the literature surrounding comorbidity measurement in established renal failure

Introduction and review methods

Recording comorbidity allows fair comparisons between treatments, healthcare providers and costs, as the presence of comorbid conditions generally has a negative impact on outcomes and healthcare utilisation. Recording comorbid conditions also enables us to estimate of the burden of disease and identify subgroups of patients with specific conditions for more focused analyses. The presence of a comorbid condition allows the study of how patients with this condition are subsequently managed. Failure to collect comorbidity information can lead to inappropriate conclusions regarding the performance of providers or treatments, or fail to detect differing treatment effects such as Simpson's paradox.

This portion of the literature review used PubMed searches. Terms employed included "comorbidity AND mortality" but filtered for hospitalisation/hospitalization/inpatient in order to tailor searches to indices which were informed from hospitalisation data. Manual reference tracking references to relevant papers from other published works was one of the most fruitful and time efficient methods employed. Unique comorbid measurement methods were then

identified and reviewed in detail. Systems developed in the general population but then subsequently applied to ERF patients were included along with those developed primarily on the group of interest. Comorbidity can generally be adjusted for in two ways: One method is to assign the presence of individual conditions scores (weights), and add these together to get an overall score reflecting the burden of overall comorbidity. This would then be included in the subsequent models as a continuous or categorical variable. Alternatively, the presence of individual conditions can be included separately in the model as categorical variables. The methods to derive weights for individual conditions or recalibrate historical scores will be covered, and finally the strengths and weaknesses of these methods will be highlighted.

General population measures

The majority of comorbidity scores in the general population are designed to predict hospital associated mortality (Pine et al. 2007) (Aylin et al. 2010), or have been derived from the longitudinal study of patients enrolled in observational studies or trials. A recent systematic review exploring comorbidity scores applied to administrative data highlights that the Charlson and Elixhauser measures are the most widely published, and failed to detect any other generalizable measures (Sharabiani et al. 2012). These two measures are presented below.

The Charlson index

The Charlson Index is based on 19 different conditions, each of which is assigned a weight for their presence and then summed to generate a score representing the overall burden of comorbidity. The Index is the most popular and well recognised measures of comorbidity in the medical literature. It has been applied to and is continually reported for a wide range of medical conditions, scenarios and endpoints. It has been adapted for use with routine data using ICD9 and ICD10 codes (Sundararajan et al. 2004), with the codes and weights listed in appendix 2a. Designed to be analysed as a continuous score, the original score was designed to be amalgamated with weights derived from the age of the patient (Charlson et al. 1987), however most authors factor the age of the individual separately. Originally reported in 1987, the Charlson Index is based predicting on year mortality on 607 acute medical admissions and subsequently tested on 685 women with histologically proven breast cancer predicting mortality out to then years (Charlson et al. 1987).

This measure has been applied to both Incident dialysis patients (both HD and PD) by Hemmelgarn(Hemmelgarn et al. 2003) in a single centre study of survival in 237 patients out to as much at 800 days. Rather than apply the scores associated with the presence of individual conditions originally derived from Charlson's original 1987 paper, new scores for the presence

of each condition were derived using Charlson's weighting methodology described later in this chapter (termed re-weighting). Notably, this investigation found individuals with scores of three had better survival than those with scores of two with small sample size being blamed. In order to maximise the Charlson's predictive ability, the weights of the individual conditions were re-calculated using methods detailed later in this chapter. For example, the weight for previous myocardial infarction increased from one in the original Charlson paper to two in Hemmelgarn's analysis. As a result of this the model's predictive ability measured by the C-statistic (detailed in Chapter 3) improved from 0.73 to 0.74. Hemmelgarn did not determine if this improvement was meaningful in terms of predicting an individual's survival, and does not mention the inclusion of other variables such as age, primary renal disease or dialysis modality. The C-statistic is generally higher than others reported in this setting and may be due to the single centre having uniform practice and therefore more uniform outcomes when compared to a multi-centre disease registry.

Subsequent studies have looked at peritoneal dialysis patients(Fried et al. 2001) and transplant patients (Grosso et al. 2012) in isolation, finding that even in the presence of many other explanatory variables the Charlson's Index added statistical power. As many studies these were based on single centre data and were unable to assess the influence on centre comparisons. Again the impact of comorbidity as a predictor in these studies may have been understated as scores for individual Charlson conditions were not re-weighted. Jassal et al demonstrated the superior predictive power of the Charlson using original weights from the original 1987 paper compared to scored derived from the re-weighting performed by Hemmelgarn when it was applied to transplanted patients(Jassal et al. 2005). This would argue that re-weighting is often specific to the cohort or the dataset the analyses is being performed on. Importantly, when applying the Charlson Index to administrative data, some of the ICD10 codes used to imply the presence of peripheral vascular disease in most recognised method (Quan et al. 2005) can also be used to imply the presence of an arterio-venous fistula or graft for dialysis access.

In analyses of RRT patients detailed above the scoring for chronic kidney disease (CKD) is appropriately excluded, and when used in conjunction with re-calibrated weights could be considered an applicable measure in patients with CKD. When used to adjust for hospital associated mortality rates in the general population, it is generally not modified to account for the reason the patient is admitted and could be fallible to the phenomenon that codes pertaining to the primary reason for admission spill over into secondary codes observed in the Elixhauser method (detailed below).

The Elixhauser measure

The comprehensively specified Elixhauser measure does not generate a score, but rather represents a list of 30 comorbidities to be adjusted for as individual variables(Elixhauser et al. 1998), listed in appendix 2b. The presence of these conditions are supposed to be factored individually in a model predicting healthcare utilisation or outcomes. Derived from routine hospitalisation data in the US Medicare database, the Elixhauser score is based on ICD9 codes. Quan et al have published updated codes for the ICD10 system(Quan et al. 2005). Further work has been done in combining the score with laboratory data to enhance the predictive capacity with modest results (Pine et al. 2007).

Although less widely employed than the Charlson, some analyses are more detailed or informative. Previous work highlighted the phenomenon whereby codes pertaining to the primary admission manifest in the secondary diagnosis fields in an attempt to describe the admission more adequately. In the Medicare database at this time there was no way of differentiating conditions that were present on admission or subsequently acquired in hospital, as is currently the case with the English HES database. This led Elixhauser to exclude comorbid conditions which could reflect complications of the primary admission; for instance a patient with an acute myocardial infarction could not score for the presence of ischaemic heart disease in a secondary diagnosis field. Undoubtedly more robust in nature, this exclusion method has not been applied to other measures like the Charlson Index. Often when using the Elixhauser score outside the Medicare setting the primary/secondary diagnosis rule is not applied.

In an earlier paper from the same group, the counterintuitive protective nature of some codes was identified (Jencks et al. 1988). Certain chronic conditions when coded as part of an admission were found to be associated with lower short term mortality, despite their adverse impact in other longitudinal studies. Only when looking further post discharge were they found to be associated with reduced survival. Jencks et al postulate that in more complicated admissions or when the primary reason for admission is severe, codes representing this spill over into the secondary code positions and more chronic conditions are not coded. In UK HES data this has also been observed, with the weighted Charlson Index detailed in the Dr Foster Hospital Standardised Mortality Ratio (HSMR) methodology document assigning a score of minus one for diabetic complications (Aylin et al. 2010).

Renal replacement therapy population specific measures

Due to a relatively high level of engagement with data and informatics, the renal community has developed new and recalibrated existing measures of comorbidity. Often these measures are defined by the format of the data routinely collected or existing data collection specifications, especially in the case of disease registries (Liu et al. 2009) (Feest et al.). A summary of comorbidity measures is detailed on the next page. Inevitably the aim is for a newer measure to outperform the previous one; however in reality only marginal gains are realised.

Disease registry measures

Disease registries often record comorbid conditions for the reasons previously highlighted. Important in adjusting provider based survival analyses, the presence of individual conditions can highlight changes in population demographics over time, explain differences in patient management across providers and allow international comparisons.

Often these measures are informed by clinicians indicating the presence of particular conditions via healthcare computer systems or claims forms. Specifications between disease registries differ, so often international comparisons are limited by the data collected. Depending on the process or incentivisation involved in determining comorbidity, some patients may have missing data.

United States Renal Data Services (USRDS)

The USRDS obtains comorbidity data on patients via the Medical Evidence Report form (11 conditions) which is completed when the patient commences RRT and is necessary for reimbursement of the healthcare provider, or during inpatient claims within the first 6 months of treatment(Liu et al. 2009). In order to obtain the additional six comorbid conditions enabling Liu et al to compare the measure to the Charlson, the patient must have survived to nine months. The medical system in the United States precludes usage of data prior to the start of RRT, as Medicare only covers select groups of patients during this time (principally patients over the age of 65). Once on RRT however, all patients are covered and use of this routine data becomes appropriate. The additional conditions only a marginal predictive power.

Details on the individual conditions collected are listed in Table 2-3.

The form of adjustment used was to compute an overall score using the coefficients from co-variates in a Cox regression model based on the presence or absence of individual comorbid conditions. Calibration on one cohort and testing on another was employed, with the latest dated 2001 allowing appropriate follow-up duration. The index was analysed alongside other

important demography: age, sex, ethnicity and primary renal disease. The distribution of scores in incident patients was less skewed than other measures. Several measures of model predictive performance exist, including the C-statistic (explanation in chapter 3), which was quoted as 0.6709 for the USRDS measure and 0.6623 for the Charlson score, although the latter was not reweighted.

UK Renal Registry (UKRR)

The collection of information by UKRR on the comorbidities of patients starting RRT in the UK relies on clinicians in the participating renal centres entering this data into their clinical computer systems from where it is electronically collected (Ansell et al. 2009). Again the conditions are pre-determined like the USRDS method, with fourteen being reported (Table 2-3). There is no financial necessity to complete this data resulting in completion rates of 44 – 52% per annum, less than the USRDS medical evidence form (Webb et al. 2011). Due to poor data completeness their data are only analysed for 15 UK centres to perform adjusted survival (Castledine et al. 2011), with some excluded centres returning no comorbidity information for the six years in question. Analyses do highlight the difference age has on the impact of comorbidity, with conditions having different hazards in patients above and below 65 years of age. Early mortality also attributes different hazards to individual conditions.

International Comparisons using Registry Data

Using ERA-EDTA registry data van Manen highlighted that adjustment for age, gender, primary renal disease, modality and country accounted for 14.4% of the R-squared(R-squared explained in chapter 3) in their model which predicted mortality(van Manen et al. 2007). Comorbidity accounted for an additional 1.9% of the R-squared. A possible explanation for this relatively low percentage is the correlation between general population mortality of the area and the dialysis population of the area(van Dijk et al. 2007), particularly the general population atherosclerotic cardiovascular mortality(Yoshino et al. 2006).

Due to the different specifications of the datasets being combined adjustment was only performed with five conditions. There were significant differences in the hazard associated with individual conditions depending on which country the patient originated from, and could result in the constant risk fallacy, elaborated on later (Nicholl 2007). The inclusion of country in the model goes some way to negate this.

Cohort studies and single centre scores

Khan Method

This method is the first of two which use categories of comorbidity burden, and was derived from renal centres in Aberdeen and Dundee (n=375) to stratify mortality risk. Patients are categorised into three different tiers of risk (Khan et al. 1993) detailed in according to age and the presence of certain comorbid conditions.

Early (pre-90 days) mortality was excluded, and the model identified two years survival of 86, 60 and 35% in the low, medium and high risk groups respectively (). No comparable statistical measure of predictive ability such as the C-statistic mentioned above was reported.

Table 2-1 : Risk categories for the Khan method

Risk Group	Inclusion Criteria	Proportion in group
Low	Age < 70 years and no co-morbid illness	40.5%
Medium	Age 70 – 80 years OR Age < 80 with any of: Angina, Previous myocardial infarction, cardiac failure, chronic obstructive airways disease, pulmonary fibrosis, or liver disease (cirrhosis, chronic hepatitis) OR Age <70 with diabetes	36.5%
High	Age >80 years OR Any age with two or more organ dysfunctions OR Any age with diabetes and cardiopulmonary disease OR Any age with visceral malignancy	23%

Stoke-Davies Method

This measure again uses categorisation of risk, and was derived in a single centre analysis of peritoneal dialysis patients(Davies et al. 2002) to determine mortality, but in addition to understand the role of peritoneal function. The number of conditions (unweighted) places the patient into Low (0), Medium (1-2) and High (>2). The conditions included are summarised in Table 2-3 but somewhat vaguely include a category of “other significant comorbid conditions”.

The resulting grade was treated as a continuous variable alongside age, and measures of peritoneal dialysis membrane transport and adequacy in Cox models. The log-rank test was highlight significant for survival between groups but no other methods of prediction are quoted. Of note, diabetes had a relatively marginal impact on survival when compared to other conditions in univariate analyses. The Stoke-Davies index has subsequently been applied to haemodialysis patients where is was compared to the Charlson and Khan indices and found to perform similarly(Miskulin et al. 2004) with a C-statistic of 0.68 based on multi-centre data from one national dialysis provider.

Netherland Co-operative Study Adequacy of Dialysis (NECOSAD)

The NECOSAD cohort study involving 1,205 patients across 35 Dutch dialysis centres used 15 conditions and gave assessors the opportunity to grade the presence of some conditions (angina thresholds, diabetes duration, heart failure grade etc) to form a new measure. The main role of the published work is to compare this measure to the Khan, Charlson and Davies methods (van Manen et al. 2002). To make the analysis more comparable, the Charlson and the newly derived measure were categorised in a similar fashion to the Khan and Davies methods, resulting in low, medium and high risk. Age was dealt with differently across the measures, as the Khan and classical Charlson include age in the measures but this new measure did not. Therefore age was added separately for all analyses and represented twice for Charlson and Khan measures.

The bespoke measure had the highest C-statistic of 0.75, followed by the Charlson (categorised) with 0.74. It isn't clear if the final grades are treated as categorical or continuous variables. It did however highlight the importance of adjusting for comorbidity in addition to age, quoting the C-statistic for modelling age alone as 0.66.

Dialysis Outcomes and Practice Patterns Study (DOPPS)

The DOPPS is a prospective observational study of prevalent haemodialysis patients across seen countries. The presence or absence of a select 25 conditions collected by DOPPS were analysed in 8,615 patients of varying dialysis duration (Goodkin et al. 2003). Relative risks of various conditions are reported, and the authors highlight the varying impact of certain comorbidities between continents. Strictly this is not an analysis of a comorbidity measure, but is designed to highlight differences in outcome between continents once comorbidity is adjusted for.

A subsequent paper highlights that 17 of the 45 conditions collected by the DOPPS dataset accounted for 96% of the explained variance if all conditions were included in the model (Miskulin et al. 2009). The appendix argues for the removal of many conditions as they were: (1) highly correlated with other conditions with greater prognostic value, (2) too vague in definition or (3) not considered to be prognostic (Miskulin et al. 2009).

Table 2-2 : Comparison of comorbidity scores and applications for Haemodialysis (HD) and Peritoneal Dialysis (PD) patients

Investigation	Data Source	Incident/Prevalent, n	Model	Performance	Comments
Charlson-ERF(Hemmelgarn et al. 2003)	ERF Database Notes Review	Incident HD & PD N=237	18 Conditions (renal removed) Revised weighting, Age excluded	Original c=0.73 Reweighted c=0.74	Logistic model to end of FU (variable), recalibration using Cox Regression
Charlson-PD(Fried et al. 2001)	ERF Database Format unclear	Incident PD N=268	See Above	chi-square 43.3 *P*=0.0001	10 Year incident period – improvements during study
Davies-PD(Davies et al. 2002)	Single centre PD Study	Incident PD N=303	7 conditions incl. "other" present at start of RRT, mapped to 3 tier risk stratification based on number of conditions	chi-square 47.4 P<0.0001	Diabetes had marginal influence
Khan (Khan et al. 1993)	Two Scottish centres	Incident HD & PD N=375	3 tier risk stratification based on combination of age and specific conditions	Not formally reported	Important to note inclusion of age, with stratification based on certain age/condition combinations
DOPPS(Goodkin et al. 2003)	Multicentre HD Observational Study	Prevalent HD N=16,720	25 conditions collected at enrolment Overall burden not indexed	Accounted for 9% of the variation between countries	Co-morbidity not necessarily present at start of RRT (prevalent analysis). Risk for comorbid conditions varied
EDTA-Registry(van Manen et al. 2007)	5 national registries	Incident HD, PD & Tx N=15,571	5 conditions at start of RRT	All significant, accounted for 2% of variation in survival	Extensive loss of co-morbidity data due to differing registry formats, PRD: 2.7% of variance, comorbidity 1.6%
USRDS(Liu et al. 2009)	ERF Database Med. Evidence form	Incident Develop 33,077 Test 33,166	13 conditions within 9m of start, weighted according to cox regression coefficient	C=0.6685	Survival beyond 9 months required for inclusion. Conditions might be in centres control
Charlson/Khan/Davies NECOSAD(van Manen et al. 2002)	Cohort study Clinician completed	Incident HD & PD N=1,205	15 co-morbidities collapsed into existing indices See above definitions	Charlson c=0.74 Khan c=0.72 Davies c=0.73 Bespoke c=0.75	Original dataset includes severity grading (not used)

Table 2-3 : Comorbid Conditions comprising each method

Condition	Charlson	Elixhauser	Davies	Khan	USRDS	DOPPS	UKRR
Angina			O		O	X	X
Blood Disorders	X	X					
Cardiac Other (Arrhythmias)		X			X	X	
Cardiomegaly						X	
Carpal Tunnel Syndrome						X	
Cerebrovascular Disease	X				X	X	X
Congestive Cardiac Failure	X	X	X	X	X	X	
Coronary Artery Bypass Graft							X
Coronary Artery Disease	X		X	X	X	X	X
Deep venous thrombosis						X	
Dementia	X						
Diabetes Mellitus	X	X	X	X	X	X	X
Dyspnea						X	
Gastrointestinal Bleeding		X			X	X	
Hepititis B/C	O			O		X	
HIV/AIDS	X	X				X	
Hypertension		X				X	
Hypothyroidism		X					
Left Ventricular Hypertrophy						X	
Liver Disease	X	X		X	X		
Lung Disease	X	X	O	X	X	X	X
Malignancy	X	X	X	X	X		X
Neurologic Disease	X	X				X	
Obesity		X					
Other			X				
Peptic Ulcer Disease	X	X				X	
Peripheral Vascular Disease	X	X	X		X	X	X
Psychiatric Disorder		X	O			X	
Recurrent Cellulitis/Gangrene						X	X
Smoking						X	X
Collagen vascular disease	X	X	X				
Vision disturbances						X	
β_2-microglobulin disease						X	
Includes Age	X			X			

X – Condition included, O – Condition included under another heading

Comorbidity score weighting

In measures which report an overall score, the presence of the individual conditions which inform them need to be assigned a weight. It is not reasonable to assume that all conditions have similar impact on the outcome of interest, and this is supported by the poorer performance of "count of conditions" methods compared to weighted scores (Sharabiani et al. 2012).

The use of existing weights does have the advantage of instilling trust in the reader, but there are many reasons why reuse of a weight which was derived in one setting should be accompanied by re-weighting. Disease outcomes will change over time, as will the impact of the condition depending on the length of follow-up. Depending on the population studied, the impact of a condition will vary.

Two statistical methods of determining weights (either when a measure is first derived or when it is updated with a process of re-weighting) predominate in the literature, often demonstrated with the Charlson Index, but also employed in deriving new measures (Gagne et al. 2011).

Logistic Regression weighting

Originally proposed by Schneeweiss (Schneeweiss et al. 2003), this method has been used elsewhere (Gagne et al. 2011). Using a multivariate logistic regression model incorporating the conditions proposed to inform the index plus age and sex, authors took the logistic regression coefficient for each condition (log(Odds Ratio)) and assigned one point per 0.3 increase in this statistic. In the Gagne study (Gagne et al. 2011) where they combined conditions from the Charlson and Elixhauser measures one-year mortality in patients over the age of 65 who were admitted and had Medicare coverage was analysed. For 30 day and one year mortality the C-statistics for these models were 0.839 and 0.778 respectively. Also of interest is the distribution of scores (Figure 2-1) as previous investigations by The School of Health and Related Research (ScHARR) have been hampered by a large number of admissions with a comorbidity score of zero (Campbell et al. 2012).

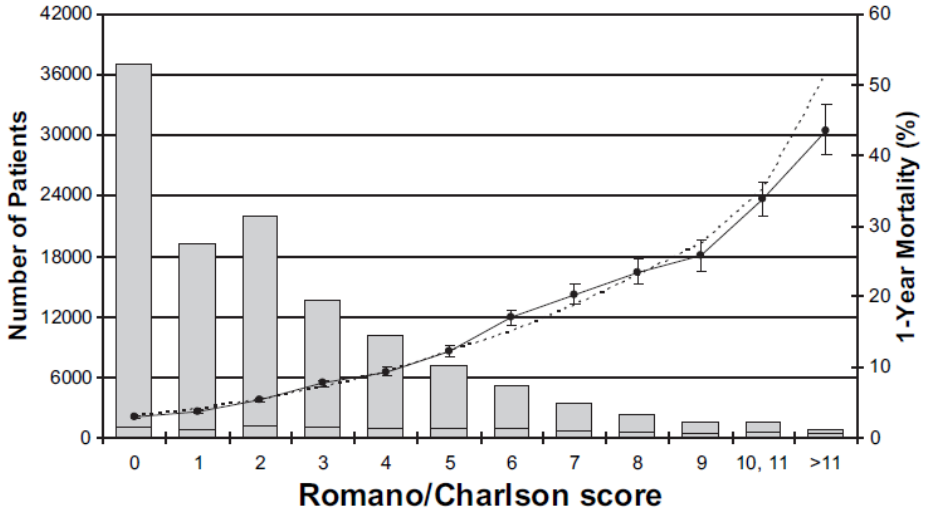


Figure 2-2 : Re-calibrated Charlson score and percentage one year mortality in elderly patients following Cox regression re-weighting, reproduced with permission from Gagne et al. Solid line represents proportion observed mortality, dotted predicted mortality from the model used to derive the re-calibrated weights.

Cox regression weighting

In data with varied follow-up and censoring, the Cox regression method originally applied by Charlson and use other authors including Quan et al(Quan et al. 2011) can prove useful. In this paper the method was applied to both 30 day mortality and mortality at one year following admission, adding and removing the relevant comorbidity alongside age and sex. It is not clear if they dropped variables depending on their significance, or added and removal variables to assess the impact of their presence on other conditions weights. Weights were assigned as follows: hazard 1.2 - <1.5 : 1, ≥1.5 - <2.5 : 2, 2.5 - <3.5 : 3, ≥3.5 - <4.5 : 4, ≥6 : 6 (no hazards were observed in the range ≥ 4.5 - < 6). Interestingly they then applied these scores in a logistic regression model rather than a Cox regression to predict mortality in six other external databases. C-statistics generally improved the further from the measure was assessed from admission, but there was a large range of model performance depending on the international data used (Japan 0.727 – France 0.878). Using the individual conditions in the model generally performed better (Canada calibration dataset – score 0.881, individual conditions 0.884). The wide range of C-statistics for different international datasets highlights either the varying quality of the datasets with regard to coding co-morbidities or the need to calibrate on dataset you intend to predict for.

Summary and Conclusions on comorbidity Evaluation

Due to positive publication bias, new measures of comorbidity are frequently compared to pre-existing measures and always seem to improve (Sharabiani et al. 2012). This may be because authors do not choose to recalibrate the older measures with weights derived from the dataset in question, and that the methods used to compare centres where these measures are reported need to be explained in a peer reviewed setting to inspire confidence in the renal community.

At the outset, age should be considered separately as comorbidity and age are linked. A measure which combines both could mask the individual contributions of comorbidity and age, and prevent their individual influence to vary when applied to different patient groups.

Reviewing the methods, a clear group of comorbidities suitable for analysis present themselves assuming the incidence of the condition is sufficient to make adjustment for it relevant. The precise incidence of the condition is not reported, but previous UKRR reports have generally excluded conditions present in less than two percent of patients when starting RRT. Once relevant conditions are selected, a decision has to be made about including individual conditions as variables, or calculating an overall score either as a continuous variable or risk groups. The former may offer the greatest predictive power, but the latter allows indexing of overall comorbid burden to compare patient groups (e.g. late presenters, ethnic groups) and individual centres.

Risk stratification (Khan) or score categorisation (Davies) may result in improved predictive power, and these measures seem to perform well when applied to the same data (van Manen et al. 2003). Scores derived from test statistics (logistic and Cox regression methods (Gagne et al. 2011) (Schneeweiss et al. 2003)) and resulting in an index to be treated as a continuous variable may have a less linear relationship with mortality further up the scale. More likely is that scores with a skewed distribution experience a degree of leverage by the transition between early more frequent scores, reducing the precision at higher scores. When evaluating the Summary Hospital Mortality Index, categorised Charlson scores like those applied in the NECOSAD investigation outperformed a continuous score(Campbell et al. 2011). A pragmatic approach would be that the method with the greatest performance should be employed.

The wide range of C-statistics seen when quoted and summarised in Table 2-2 highlights the relatively poor performance of some more recent and lauded measures. The USRDS method has a much poorer C-statistic than others reported, but was marginally better than the Charlson when applied to the same dataset. This suggests that for this particular cohort there

exist other factors that are not being accounted for, be they comorbid conditions or other factors such as late presentation or socioeconomic status. A weight of evidence would suggest that following adjustment for comorbidity, socioeconomic status needs not be adjusted for (Caskey et al. 2006). The reverse may also be true when comparing centre outcomes – is adjustment for SES or comorbidity alone enough? Centre specific outcomes could be influenced by a variety of factors beyond patient-specific factors and risks, including centre specific variables involving staffing, infrastructure, resources as well as healthcare environment. For instance having in excess of one "sit-down patient care round" (similar to multi-disciplinary team meetings in the UK) per month was shown to reduce the risk of hospitalisation by 32% and mortality by 29% (Plantinga et al. 2005). When interviewed on the subject, nurses, community nephrologists, medical directors and dialysis opinion leaders were able to identify staffing levels, staff training and the components of a multi-disciplinary team that they believed contributed to better clinical outcomes(Desai et al. 2008).

The importance of individual conditions will alter in survival analyses as other important factors such as late presentation are included, however comorbidity may be a an easier variable to collect than an accurate date when a patient was first referred to a nephrologist. Rationalisation of the number of comorbidities needed to see similar model performance or discriminatory power may also evolve out of the inclusion of other variables which are associated with comorbidity, such as late referral (Farrington et al. 2007). The main focus of many papers is small improvements in predictive ability, but there has been no report on which clinical conditions are important to adjust for when comparing provider outcomes. Only two or three conditions in conjunction with other demography may be all that is required identify differences in outcomes between centres, as was highlighted with cross country comparisons(van Manen et al. 2007).

Review of the literature surrounding hospital-associated measures of performance in patients receiving renal replacement therapy

Introduction and methods

Inpatient care accounts for 41% of the cost of ERF care in the United States, mostly from bed costs and inpatient dialysis(Bruns et al. 1998). Hospitalisation has a significant negative impact on quality of life in dialysis patients(Evans et al. 1985). On average, eight percent of the first year on dialysis is spent in hospital(Metcalfe et al. 2003). Understanding hospitalisation and reducing it therefore has significant advantages, to the health service and the patient.

Dialysis care is novel in that a nephrologist essentially cares for a population of patients both whilst in hospital and during their outpatient care. The quality of outpatient care may be reflected in the inpatient measures such as frequency of admission. In order for the performance of renal services in England with regard to hospitalisation and associated outcomes to be reported, either primary data collection would need to begin or linkage to HES as suggested would need to occur.

This sub-chapter summarises existing literature relating to hospital-associated measures of performance. In addition to pubmed searches for relevant terms, renal registries and healthcare quality agency annual reports, website and monitoring tools were examined. In settings where hospitalisation data has routinely been available, the published literature has focused on hospital associated mortality, frequency of admission and length of stay. The following is broadly categorised into these areas.

Frequency of Admission

The strong association between ERF and morbidity often necessitates admission to hospital. Admission rates in RRT have been the subject of a number of analyses, focused broadly on trends in hospitalisation, the impact of different clinical practices on their rates and more recently comparing providers. As with many chronic conditions associated with hospitalisation, some hospitalisation is avoidable, through different processes of care (for instance outpatient delivered services) or better management of the underlying disease process. As with other clinical measures, hospitalisation is influenced by the underlying case-mix of the patient, and requires appropriate methods of adjustment to allow fair comparison between centres.

Reported admission rates (national and centre specific)

Due to its routine linkage to the Medicare database which funds dialysis care in the USA, the USRDS regularly reports summary measures of hospitalisation. These analyses are primarily focused on temporal trends in overall and cause specific admission rates for the entire US RRT programme. Due to the nature of the USA healthcare system, Medicare has incomplete coverage of admissions prior to the start of RRT in patients under the age of 65, and as a result analyses on admissions prior to the start of RRT are less frequent. USRDS analyses generally report that the admission rate has stayed fairly constant over the period USRDS reports, although hospitalised days per year has reduced. These analyses do highlight different admission rates across the modalities of RRT, with transplant patients understandably having fewer admissions that their dialysis counterparts (Figure 2-3). Many reports are limited to the admission rates per annum and do not give insight into admission rates according to time on RRT or rates within the first year.

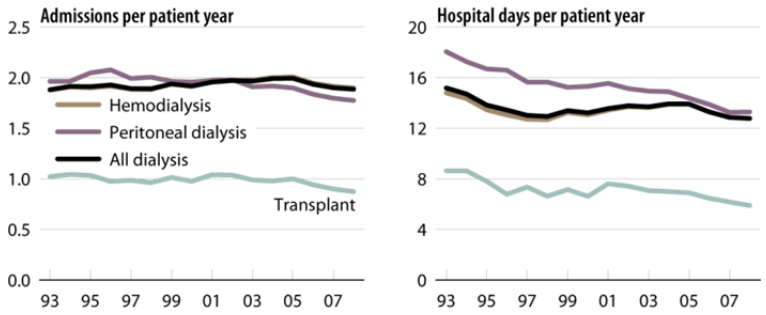


Figure 2-3 : Annualised admission rates generated by the USRDS

Admission rates nationally have been reported for the UK along with comparisons to other countries as part of the DOPPS (Rayner et al. 2004). Patients included in these studies are again prevalent, and note an admission rate of 1.0 per patient year for the UK compared with France, Germany, Italy and Spain (1.43, 1.07, 0.72 and 0.75 per patient year respectively). In order to adjust for differences in case mix, a time to first hospitalisation analysis was performed using a multivariate cox model. Using Germany as the comparator country, the risk ratio for first hospitalisation the UK was 0.81 (95% CI 0.70 – 1.23), the lowest of the countries included. These analyses could be confounded by bed availability, the appropriateness of admission and high admissions rates after a delayed first admission. In the same paper, Rayner reports admission rates for *vascular access-related admission not associated with infection* in UK patients to twice that of other countries. One interpretation of this could be that all cause admission rates may be suppressed by low rates of admission for conditions that can if necessary be managed in the community, which access-related problems generally cannot.

Centre specific admission rates have more recently been generated by dialysisreports.org, which is administered by Arbor Research Collaborative, in conjunction with other measures of performance also reported by UKRR. These are subsequently reported on the Medicare website itself (http://www.medicare.gov/dialysisfacilitycompare). Their methods are openly reported and summarised under statistical modelling. They report a "traffic light" system where the rate ratio is portrayed across a range of safe, better and worse than expected values. The size of the facilities is often small and the number of patients suitable to include limited to issues surrounding the claims required to have been processed before the patient is suitable for inclusion. As a result the confidence limits for the individual providers are extremely wide.

Cause specific admission rates and patterns of admission

In a similar fashion to the above all cause admission rates, the USRDS reports trends in hospitalisation for various conditions over time. Examples of these are illustrated in Figure 2-4. Individual centre specific measures of these rates are not routinely generated.

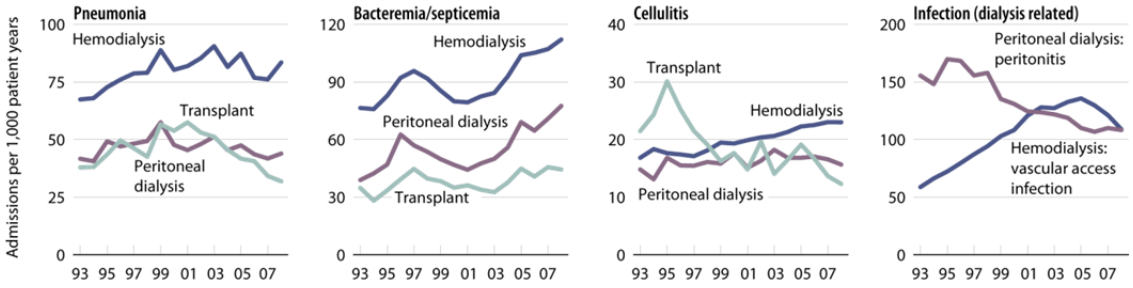


Figure 2-4 : Annual cause specific admission rates for different RRT modalities, generated by the USRDS

Despite an adjusted hospitalisation rate ratio in the DOPPS analysis of 0.81, admission rates for access related problems were higher in the UK than other European countries. The UK had the highest rates of access-related hospitalisations complicated by infection (0.08 per patient year compared to 0.01 – 0.03) which was largely attributed to high rates of line usage (25% vs an overall average of 9%). This compares to a vascular access infection rate in the USRDS reports of 0.11 per patient year for the same period.

Although the bacteraemia/septicaemia rates in haemodialysis patients appear higher than in PD patients, following case mix adjustment using propensity scores rate of infection-related hospitalisation were in fact higher in PD patients in an analysis by Lafrance et al (Lafrance et al. 2012). Recognising the importance of infective episodes, the International Society for Peritoneal Dialysis (ISPD) has released guidance on the auditing and reporting of rates for centres (Li et al. 2010). These include a censoring period where repeat infections with the

same organism within four weeks are classed as relapses, and ways of summarising rates which will be explored below. Bacteraemia rates in haemodialysis patients have audit standards from the Renal Association, but unlike in Peritoneal Dialysis specifications on their derivation have not been issued (Fluck et al. 2011).

Patterns of admission have been studied in a range of RRT modalities. A large body of work has been performed on understanding admission rates after the two day break in three times a week haemodialysis. The largest study by Foley et al highlighted the fact that admission rates from any cardiovascular event were 44.2/100 person-years after the two day break compared to 19.7/100 patient-years across the rest of the week (Foley et al. 2011). Conference posters highlight that and increase in all cause admissions was observed from 141 admissions per 100 patient years to 210 admissions per 100 patient years (Roberts et al. 2012). An increase in mortality rate from 18.0 to 22.1 deaths per 100 person-years was also observed as per other studies (Zhang et al. 2012) (Bleyer et al. 1999) (Genovesi et al. 2009). Increases in admission rates were observed in all groups of patients, particularly in patients with greater comorbidity such as diabetes, cardiovascular disease and those not transplant wait-listed.

Admission frequency has been modelled in on single centre study from the New England Medical Centre(Arora et al. 2000), and highlighted an increase in hospitalisation within the first three months compared to beyond the first three months (4.3 admissions per year vs 1.9 admissions per year), and noted some small differences in the variables predictive of the rate in these two periods. These observations are a likely explanation for some of the methods employed by the Facility Compare service reported by Medicare which analyse separate periods of time according to how long the patient has been on haemodialysis.

Case-mix and admission rates

The presence of comorbidity and the events leading up to the start of RRT influence admission rates. The best example of this in the United Kingdom was work performed by Metcalfe et al based on Scottish Renal Registry data combined with primary data collection following 526 patients and their associated hospitalisation in the first year (Metcalfe et al. 2003). Median admission rates were three per year consuming a median of 13 bed days per year, and cause specific admission counts for the cohort are provided highlighting high admission rates for access related procedures and infections. It notes a 13% increase in admission rates per unit increase in Charlson comorbid score and a 78% increase in admission rates in patients presenting in an unplanned fashion. Of note, age was not a significant predictor for frequency of admission. USRDS reports mirror these findings, with age having little impact on admission rates (1.89 – 2.01 admissions per year from age 20 to 75+), however

the Foley paper mentioned above does find a strong association in the cardiovascular admission rate analysis they presented in their interdialytic gap paper (Foley et al. 2011), with smaller differences observed in all cause admissions (formal numbers not reported in either) (Roberts et al. 2012). Diabetes as primary renal disease has a higher all cause admission rate of 2.08 compared to other PRD groups (1.58 – 1.80) in USRDS reports.

Admission rates after transplantation in the short term have been explored by McAdams-DeMarco et al who looked at 32,961 transplants over a six year period(McAdams-DeMarco et al. 2012). Thirty-one percent of patients had one or more admission in the 30 days post-transplant. Strong associations between age, race, cardiovascular disease, respiratory disease and donor factors were all significant. The authors reported the standardised admission rate ratio for the centres included in the analysis, but adjusted for a number of factors within the centres control making the interpretation of this as a quality indicator questionable. This study identified 36% of admissions relating to "Kidney, ureter, prostate, bladder procedure".

Many studies have compared haemodialysis and peritoneal dialysis admission rates in an attempt to ascertain which modality is superior. However these studies are generally over a decade old and current thoughts are that differences in outcomes including hospitalisation and mortality are due to case-mix. An observational Canadian study highlighted higher hospitalisation rates (as measured as days admitted per 1,000 patient days) in haemodialysis patients in "an intention to treat" analysis (PD 0.85 compared to HD, 95% CI 0.82 – 0.87), which was reversed when modality at 90 days was compared (PD 1.31 compared to HD, 95% CI 0.82 – 0.87). USRDS reports note similar rates between modalities in prevalence patients (Figure 2-3).

Statistical modelling

Before we can fit models to the data, they must be appropriately formatted to consider the appropriate time at risk. An important point when considering multiple events (and well demonstrated by USRDS analyses) is that once in hospital you are not at risk for further admissions, but you are at risk for further hospital days (Rayner et al. 2004; Bethesda 2006). The patient is always at risk of death, irrespective of the setting.

Centre specific hospitalisation rate ratios published by Medicare stratify a patient's follow-up time into different windows of observation and make predictions within these windows for individual patients (Arbor Research Collaborative for Health 2013). This has the advantage of coefficients for adjustment variables being specific to the period in question. They then employ Cox-regression to predict and event within this period, and one assumes that events and time at risk beyond this period is not considered.

A review by Glynn and Buring highlights statistical methods for repeated events around this for fixed and variable follow-up(Glynn et al. 1996), and encourages the avoidance of the Poisson distribution in favour of negative-binomial distributions. The negative-binomial distribution has been used elsewhere in fixed follow-up studies of emergency department attendances(Tsai et al. 2007). However it seems more likely that for any particular study the investigator may need to try fitting several models(Glynn et al. 2001). Previous attempts to adjust for case-mix to compare admission frequencies have used Poisson regression(Murphy et al. 2000) and linear regression(Kassam et al. 2011) disregarding the issues highlighted above.

Length of Stay

Few papers have been published on length of stay in the context of RRT. Part of this relates to the fact that a distinct event or reason for admission needs to be identified in order to be analysed. Previously published DOPPS analyses on UK patients reported mean length of stay per admission in prevalent haemodialysis patients as 8.7 days, lower than the European average of 11.0 day, but this was not stratified by reason for admission(Rayner et al. 2004). Some studies have used total hospitalized days as a measure however this would be skewed by patients who had no admissions having no length of stay. In reality most "for cause" admissions have associated positive length of stay and it is difficult to see how this is generalizable to the modelling of an individual admission.

Published data exists on the length of stay during renal transplantation. An analysis performed on Medicare data highlighted the importance of comorbid conditions on increased length of stay, with each additional Charlson condition contributing 2.94% to length of stay and eleven individual conditions contributing a five percent increase in length of stay or more (Machnicki et al. 2011). Donor specific variables most predictive of prolonged length of stay were donor age and cold ischaemia time in excess of 36 hours. Extended criteria or deceased cardiac death organs were associated with a 10-15% higher length of stay. No formal measures of model performance were reported.

In an older single centre study using similar statistical methods, mean length of stay was approximately ten days and highlighted two comorbid conditions (chronic obstructive pulmonary disease and previous cerebrovascular incident), deceased donor status, obesity and mismatch to contribute to prolonged length of stay in both uni- and multivariate analyses (Johnson et al. 1999). Delayed graft function was also highly predictive, adding five days to the admission duration. Further analysis on length of stay for transplantation and its effect on graft survival was reported due to concerns that driving down length of stay may be associated with adverse outcomes(Lin et al. 2006). Both shorter (less than four days) and longer (greater than

two weeks) admission lengths were associated with poorer outcomes although shorter length of stay ceased to be significant once patient and donor factors were adjusted for.

Statistical modelling

Length of stay is frequently skewed and is subject to long tails(Kulinskaya et al. 2005). Commonly authors have tried to transform length of stay to attempt to get a normal distribution, the most common being a log transformation and in the case of Kulinskaya et al with trimming and truncated regression employed(Kulinskaya et al. 2001; Kulinskaya et al. 2005) . These transformations allow better analysis using general linear models, however in principle several generalized linear models and survival models are applicable.

Austin et al compared seven different strategies for modelling length of stay following coronary artery bypass surgery: Linear regression; linear regression with log-transformed length of stay; generalized linear models with the following distributions: Poisson, negative binomial, normal, and gamma; and semi-parametric survival models (Austin et al. 2002). The premise behind the range of models proposed is that hospital days can be treated as a count rather than a continuous variable and time to discharge can be treated as a survival. Although different variables proved to be statistically significant across the models their performance was similar with the exception of Cox regression which was worse.

Hospital associated mortality

As previously mentioned, RRT patients are often considered as a cohort and followed longitudinally. As a result, mortality associated with hospitalisation has not been explored. Hospital mortality, particularly as a performance measure, is well studied in unselected admissions or cohorts in the form of Hospital Standardised Mortality Ratios (HSMRs).

In the UK since their introduction in 1998, HSMRs have been used as one of the high level performance indicators for in-hospital care (Jarman et al. 1999). UK HSMRs are usually informed by HES data. These routinely collected commissioning data contain demographical, diagnostic, procedural and outcome data for all admitted care in England (2009). The observed number of deaths within a provider for a given period of time is compared to the number of deaths expected based on a statistical model factoring the patient's demography is reported (Aylin et al. 2010). Hospital associated mortality measures have stimulated investigation in NHS trusts which have subsequently highlighted systematic failures to provide quality healthcare. Mid-Staffordshire(Healthcare Commission 2009) and Basildon and Thurrock(BBC News 2009) are two high profile examples. With this interest has come scepticism and criticism:

Diagnosis Coding

Within the HES record exists a primary diagnosis code used to classify why the patient was in hospital, and secondary codes to reflect other conditions and comorbidity. The Dr Foster methods only includes certain reasons for admission and adjusts for the use of palliative care codes(Aylin et al. 2010), both of which are open to manipulation. The quality of secondary diagnosis coding directly impacts on the Charlson Score and is associated with provider HSMRs (Aylin et al. 2009). As coding quality is not uniform, NHS trusts are not compared equally.

Association with quality of care

Despite the importance placed on hospital mortality rates, there is limited evidence of their association with the quality of care delivered. In a systematic review Pitches et al found that a positive correlation with mortality rate and process of care was found in half published literature at the time(Pitches et al. 2007). This association may be stronger in a more refined cohort such as those cared for by renal services.

Hospital mortality indicator calculation methods

Due to the issues highlighted above, and a lack of confidence in the transparency of HSMR calculation methodology, the Department of Health undertook a technical appraisal and development of a new indicator, the Summary Hospital Mortality Index (SHMI) (Keogh 2010) (Campbell et al. 2012). The specification and key variables adjusted for by the Dr Foster HSMR and the SHMI are detailed in Table 2-4.

Table 2-4 : Methodology and adjustment variables for the Dr Foster and Department of Health mortality indicators

	Department of Heath Summary Hospital Mortality Index	**Dr Foster Hospital Standardised Mortatlity Ratio**
Indicator	Mortality up to 30 days post dischage	In-hospital mortality
Proportion of deaths reported	100% of deaths	Admissions from 56 of 259 diagnostic groups accounting for 83% of in-hospital deaths
Excluded admissions	Daycases	Daycases
Variables	Candidate variables: Age & Sex Admission method Year of discharge Deprivation Co-morbidity Number of admission in previous 12 months	Age & Sex Admission method Month of admission Year of discharge Deprivation Co-morbidity Number of emergency admission in previous 12 months Paliative care Ethnicity Source of admission
Missing values	No exclusion in order to maintain 100% of deaths	Exlusion of spells with missing age, sex, admission method and year of discharge
Deaths in admissions spanning hospitals	Assigned to last admitting hospital	Assigned to all hospitals involved in admission

Importantly, how this measure is calculated does effect which providers are outliers. In a recent paper by Shahian et al(Shahian et al. 2010), four vendors were supplied 2.5 million discharges from Massachusetts acute hospitals over a three year period. Although not detailing the methods utilised by each vendor, the paper highlights important differences. The number of admissions used to calculate the mortality rate varied between 28 and 95% of the total, and the correlation between different measures was never greater than 0.70 and often much less. Reassuringly, significant outlying hospitals persisted across the measures.

Admission population & Reason for Admission

As highlighted above, different methods result in the usage of different proportions of the admitted population, the key factor being which reasons for admission are used for the numerator and denominator. The Dr Foster method uses 56 pre-specified reasons for admission by mapping the primary reason for admission to a recognised grouping scheme(Healthcare Cost and Utilization Project (HCUP) 2009). These 56 diagnostic groups account for 82% of the deaths in hospital although only 42% of admissions were used in the Shahain comparison (Shahian et al. 2010). The SHMI indicator was specified to include all hospital associated deaths out to thirty days post discharge (Campbell et al. 2012).

Modelling methods

Logistic regression is generally applied for each reason for admission allowing diagnosis specific coefficients for variables (Aylin et al. 2010), however some methods use a single logistic regression for all admissions (Thomson-Reuters) (Shahian et al. 2010). The former has the advantage of the coefficients for demography can vary within each diagnostic group.

Assignment of Mortality

Although a patient dies in one institution or following the immediate discharge from one provider, several different providers may have been responsible for the care prior to death. Dr Foster assigns deaths to all providers associated with a period of care within several hospitals (Aylin et al. 2010), although this only occurs when the numerator and denominator are being calculated from the constituent diagnostic groups and not when the logistic regression is being performed. Other methods including the SHMI just assign death to the last admitting hospital (Whalley 2010).

In-hospital death vs 30 day mortality

Hospital associated death can occur during the admission or beyond it. It is possible to censor time during the admission, for instance looking only and 30 days from admission with deaths beyond this not being observed. This method has been adopted by NHS Scotland for their indicators (NHS Scotland 2011), but does allow in hospital deaths for which the institution is responsible to go uncounted. Any in-hospital death appears more appropriate and is easy to calculate for both assurance bodies and the hospitals themselves as in general they have access to their own inpatient death rates via their administration system.

Some deaths are inevitable, and recognising this some patients are discharged home to die in surroundings familiar and comfortable for them. Some deaths at hospital may relate to premature discharges, or reflect poor care leading to a recognisable and inevitable death.

These deaths would be unobserved using an in-hospital measure, and is an argument to use a more difficult to obtain 30 day mortality measure. Office of National Statistics records have been linked to HES records and highlight little difference between in-hospital and 30 day mortality (correlation coefficient 0.936) (Campbell et al. 2011), and similar correlations have been found in the trauma setting (Moore et al. 2011).

Adjustment factors

A fundamental principle in comparing providers is that adjustment should be undertaken for factors outside the centre's control. Therefore, adjustment should not be undertaken for factors that are (Mainz 2003). Examples include Health Resource Group (HRG) codes that adjust for complications (some of which may relate directly to care), or adjustment for procedures over and above reason for admission. Information on factors in a providers control can be of use: beyond comparison of providers, unit or centre based factors (e.g. organisational elements, practice patterns) can be included as explanatory factors in appropriately specified multi-level models (previously discussed in *the centre effect* section of introduction).

Discussion and Conclusions

Despite the previously identified heavy burden of hospitalisation in ERF patients, analyses specific to UK patients are lacking, and the small amount of information that does exist highlights that the UK may have lower all-cause admission rates than other European countries, but higher rates for access related admissions (Rayner et al. 2004). Admission-specific rates appear to be a recognised and accepted method of determining events, primarily because, short of clinical studies, the recording of events is not generally performed in a comparable fashion across centres.

The influence of case-mix on hospitalisation is evident from the above papers, and existing measures attempt to adjust for it. It is currently unknown how these comorbid conditions individually contribute to understanding outlying centres for measures of hospitalisation. Hospitalisation for specific events as a performance measure has not been reported and may highlight differing organisation of care between centres. The rate of peritonitis is the sum of the admitted peritonitis rate and the outpatient peritonitis rate, assuming the events do not overlap and represent failed treatment as the ISPD guidelines (Li et al. 2010). Thresholds to admit may vary across centres and patient demography, with potential advantages and disadvantages to the healthcare system and the patient.

Differing analytical techniques have been observed, but the most obvious is the censoring of repeated events with the employment of the Cox method to look at admission rates (Arbor Research Collaborative for Health 2013). Given that the standardised admission rate looks at a period of as much as two years and the prevalent population admission rate for haemodialysis patients is two per year (U S Renal Data System 2011) a large proportion of the time at risk might to be censored and result in unobserved admissions. Length of stay analyses in transplantation have failed to take into account the skewed distribution observed in other causes for admission which may have inflated associations or led to inaccurate predictions. Following on from the index transplantation admission, admissions due to complications of care in transplantation (for instance surgical complications) have generally not been reported despite a high proportion of admissions at 30 days being due to this group of reasons for admission (McAdams-DeMarco et al. 2012).

Hospital mortality rates give us the opportunity to glimpse the contribution of inpatient care (measured by HSMRs) and outpatient care (a potential proxy of which is the attainment of audit measures in ERF) to overall incident survival. Not all death occurs in hospital (Campbell et al. 2012), although location of death in haemodialysis patients does not appear to have been explored. Given the high admission and mortality rates seen after the two day gap in three times a week haemodialysis this should be understood in order to determine if clinical care is worse over this period or the implied impact of the gap in accumulation of toxins and fluid is to blame (Foley et al. 2011).

The intense discussion surrounding the utility and caveats of HSMRs offers up potential methods to understand the variation in outcomes across centres during the adjustment process. Non-constant risk and its explanations offer supportive evidence when understanding residual outlying centres, be it coding errors, population susceptibility or clinical care associated with the variable of interest (Nicholl 2007).

Chapter 3 *Methodology*

Introduction

This study is designed to test whether the UKRR dataset can be linked to the HES dataset in order to allow fairer comparisons between renal centres and report new hospital related measures of performance. The methods adopted are sympathetic to the data sources and the nature of the observed patients.

Study design

Cohort

This is a cohort study of "incident" RRT patients (patients starting RRT for the first time) in England between 1/1/2002 and 31/12/2006. Patients who started RRT in centres covered by UKRR outside England were excluded as HES only covers England. Some centres within England did not submit information to the Registry at this time (e.g. Stoke and Manchester) and therefore data for patients starting in these centres during this time are not presented. However, information on patients who started in included centres but subsequently transferred into a centre which was not submitting patients between 2002 and 2006 but is at the time of transfer would be included. Therefore a centre like Manchester which performs kidney transplants and receives patients from other non-transplanting centres who were submitting patients between 2002 and 2006 would have information on transplants occurring in this centre.

The selection of the period 1/1/2002 – 31/12/2006 was driven by the following:

NHS number completeness – Patients starting RRT in more recent years have greater completeness of NHS numbers, especially with the advent of the NHS batch tracing service.

Duration of lead-up and follow-up – In order to obtain comorbidity information from admissions preceding the date of first RRT, sufficient time between the widespread adoption of HES by NHS trusts needs to have passed. Additional advantages of a later cohort are the improved quality associated with coding as the routine reporting of comorbidity adjusted hospital mortality measures (Chapter 2) encouraged coders to document comorbid conditions more comprehensively. The adoption of Payment by Results should in theory have encouraged more uniform coding practices.

Drawbacks of a prevalent cohort - Using a prevalent cohort would complicate any appropriately adjusted survival analysis as some patients will have started RRT prior to the introduction of HES and therefore not have pre-RRT admissions from which to derive pre-RRT comorbidity. Using RRT admissions prior to the period of interest (for instance reporting mortality of prevalent patients 2002-2003) may have avoidable comorbid conditions which have developed whilst receiving RRT. In addition, survivor biasing may confound analyses.

Research governance

Stakeholders

This research project was suggested and overseen by the UKRR following original negotiations between the researcher and the Chair of the UKRR Dr Charlie Tomson, and the Medical Director Dr David Ansell. The UKRR's involvement has continued in the analysis and reporting of aspects of this research through regular meetings and the presentation of preliminary findings through Dialysis and Transplant study groups. These groups have representative clinicians and researchers from renal units and universities across England.

Funding

This project was funded by the award of a Kidney Research UK clinical training fellowship to the candidate (reference TF1/2010). The outline application was to link to the hospital episode statistics dataset to do the following:

- Describe the pattern of hospitalisation of patients in the period prior to starting renal replacement therapy and within the first year (number of episodes, causes, lengths of stay, hospital transfers) and at the end of life, with a view to identifying best practice.

- To analyse hospitalisation episodes in conjunction with morbidity, mortality and its relation to the quality markers of care for patients receiving RRT. To use these data to develop a case mix adjustment model.

- To compare the patent outcomes between UK renal centres and NHS Trusts with and without renal services using this model of case-mix adjustment, to highlight variation and stimulate change.

- To evaluate the use of routinely collected data in studying the epidemiology of kidney disease.

Salary for three years, plus university tuition fees and a consumables allowance was awarded in April 2010 following panel shortlisting and interview.

Information governance

HES data is collected within hospitals at patient level including patient identifiers, however these identifiers are not available to researchers to perform linkage against. HES data is normally released to researchers anonymised following an application via the Integrated Research Application System that includes ethical considerations and information governance.

The research capability programme

In response to a UK Clinical Research Council report recommending the initiation of pilots to link datasets(UKRCR 2007) , the Department of Health developed the Research Capability Programme (RCP). Designed to allow researchers access to a wide range of healthcare data, it was operating in pilot phase during the inception and early part of this study, subsequently becoming part of the Clinical Practice Research Database. Due to their familiarity with handling large datasets including HES data, Northgate Information Solutions housed the various datasets which healthcare researchers were able to link to.

Authorisations

Due to the novelty of the programme, the RCP engaged in obtaining ethical approval and information governance from the South East Research Ethics Committee for all participating studies in the programme, as they would have to receive all the relevant datasets. This was granted on the 13th of October 2010 (appendix 3a, REC reference 10/H1102/63).

The release of Office of National Statistics (ONS) death registrations which included location of death in the form of a coded list of healthcare institutions required the researcher to obtain ONS approved researcher status, specific to this investigation. In order to perform comparisons of geographically derived socioeconomic status measures and to derive catchment areas, Lower Super Output Area (LSOA) were obtained from both postcode data supplied by UKRR and the HES data the study would be receiving. The release of geographical data at this granular level necessitated additional approval from the ONS to release a "Controlled Access Microdata Sample". Evidence of the research teams understanding of handling sensitive items, suppressing small numbers and conventional rounding was supplied to inform these applications.

Clinical information collected by the UKRR is done so under their existing National Information Governance Board section 251 approval to obtain and store patient information

without the express consent of the individual. External transfer of data from the UK Renal Registry was authorised by their committee.

Conflict of Interest

The author, secondary supervisor and various members of the UKRR study groups are clinical nephrologists who work in renal centres in England. To this end they have a conflict of interest with regards to the clinical outcomes including survival and hospitalisation that are attributed to the centres in which they work. The author largely worked using the UKRR centre codes for renal centres rather than their full name and location. When the impact of adjustment was interpreted using graphs with centres numbered rather than named. There are no financial arrangements between the author and dialysis providers.

Acquisition and linkage of data

Northgate operating for RCP had already taken receipt of the HES dataset from April 1996 to February 2011, and Office of National Statistics death registrations over a similar period, as part of a range of information sources researchers could link to. These sources had additional NHS number tracing to ensure validity of numbers supplied and obtain numbers when they were missing. UKRR data on incident patients starting RRT between 1/1/2002 and 31/12/2006, including demographical, laboratory and treatment related data were exported in an agreed format and specification. Five tables were generated with a common identifier across them, compressed and password protected. The UKRR already perform batch NHS number tracing to obtain NHS numbers for 97.4% of the cohort sent to RCP. This data was then transferred to Northgate using the NHS Secure File Transfer System and linkage was performed.

Having identified corresponding records across the three sources, a new unique patient identifier specific for this cohort was generated and appended to each record. The dataset, now eight tables (five UKRR, two HES, one ONS) was compressed and password protected, and transferred to UKRR and The University of Sheffield for analysis. The structure of the linked dataset is summarised in Figure 3-1:

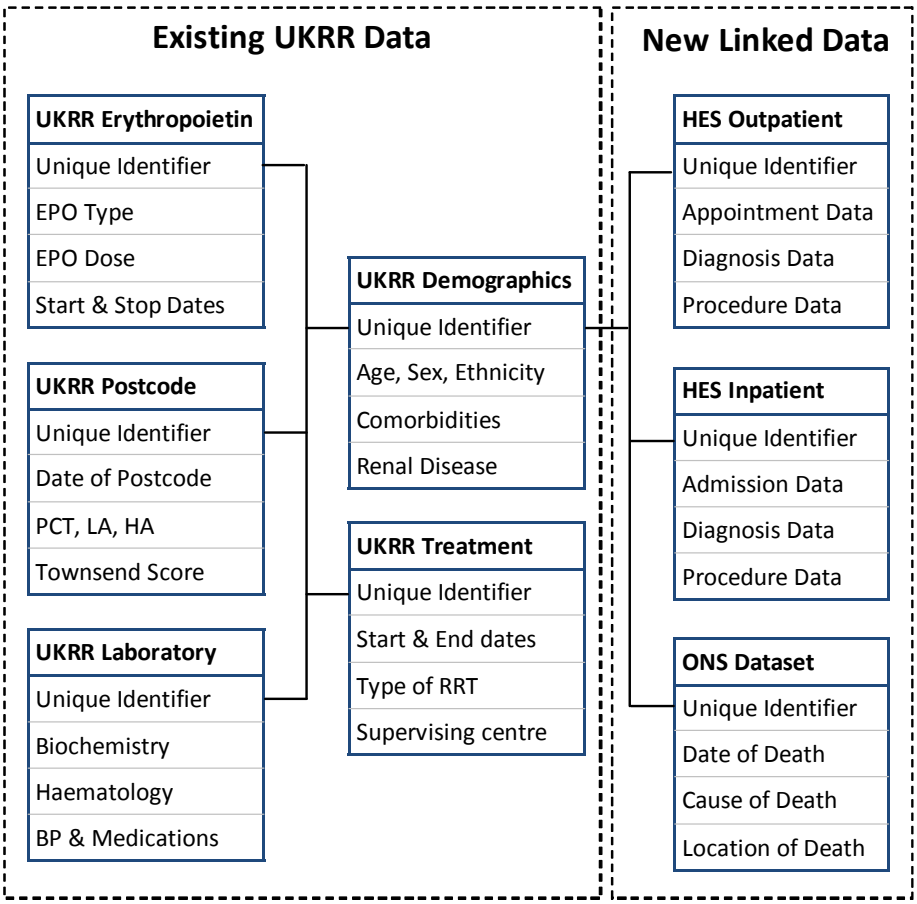


Figure 3-1 : A diagram explaining the multirelational structure of the combined dataset and linkage field. Each box represents a table summarising the items contained within this table. Abbreviations: PCT – Primary care trust, LA – Local authority, HA – health authority, EPO – Erythropoeitin, BP – Blood pressure.

Data processing

UKRR data was loaded directly into Microsoft Access 2010, with the exception of the treatment timeline table, where periods of treatment were assigned a date when they ended based on the occurrence of the next treatment period. HES data was processed in SPSS prior to import into Microsoft Access 2010.

Spells and Superspells

The HES dataset specification is detailed in appendix 3b, summarised in Figure 3-1, with greater detail available on the NHS Information Centre website. Briefly, HES records activity in the unit of the consulting episode. One admission to a particular hospital (spell) can potentially comprise of several consultant episodes. Patients move between hospitals for the same clinical problem, thereby generating more than one spell. A continuous inpatient stay which spans hospitals is referred to as a superspell. This is visualised below:

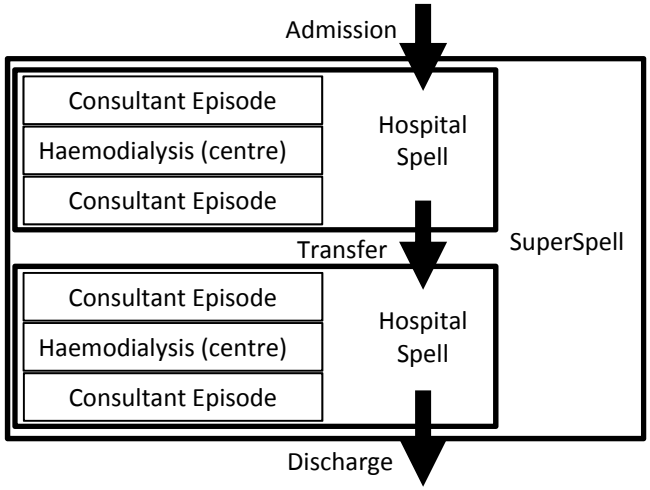


Figure 3-2 : The derivation of an episode, spell and superspell

Haemodialysis attendance and how it manifests further complicates how HES data should be interrogated. Haemodialysis units (nurse led outpatient facilities for purely receiving haemodialysis) are subunits of renal centres (secondary care institutions with inpatient and outpatient facilities staffed by nephrologists etc), and can be located in the community or within the hospital grounds of other hospitals that do not have renal centres. A proportion of centres or the units under their supervision were subsequently identified as recording haemodialysis attendance through HES (detailed in chapter 4). There is a tendency to complete this haemodialysis attendance information automatically, thereby failing to accurately reflect where the patient originated from or is discharged to after haemodialysis is performed. The ward from which the patient originates does record this transfer information, starting a new episode when the patient returns with the same coding information as other episodes earlier in the spell. The sending dialysis unit does not indicate that they are discharging to a ward, and could be operated by the Primary Care Trust resulting in it having difference provider code than the secondary care hospital, despite perhaps physically being on the same grounds. Failure to factor these issues can result in the following:

Example: A patient is admitted for a myocardial infarction, reflected by the ICD10 code *I21* in the position of diagnosis 1, moved from the cardiology ward to the haemodialysis unit and back again three times whilst an inpatient and then was discharged.

1. Counting the number of *I21* codes in the primary position would yield four consulting episodes. However, only one myocardial infarction actually occurred.
2. Counting the number of spells where any of the episodes have *I21* in the primary position would yield four spells, as the movement between the secondary care trust and the

dialysis unit counts as different hospitals, even though the dialysis unit may actually be on the hospital grounds.

3. Counting the number of superspells where any of the episodes have *I21* in the primary position would yield four superspells, as the dialysis unit fails to record that the patient is transferred back to the hospital ward but rather suggests that they are discharged home. Some methods for grouping spells into superspells rely on the marriage of discharging and originating codes to ensure transfer occurred.

To obtain robust measures of event rates (both accurate admission counts and the occurrence of disease), a method which is sympathetic to these issues is needed. The following steps were performed to derive spells and superspells:

Spell Derivation: (HES Inpatient Dataset ordered by patient identifier, admission date, episode start date, episode order)

- If previous episode patient and hospital identifiers match, and this is not the first episode within a spell, this episode is part of the same spell as the previous.
- Otherwise, this episode is a new spell.

Superspell Derivation: (HES Inpatient Dataset ordered by Spell identifier)

- If previous spell identifier matches current spell identifier, this is part of the same superspell.
- If the spell identifier differs from the previous, but the patient identifier matches, and the preceding spell discharge date is within one day of the spell admission day and the admission source suggests a *Transfer of any admitted patient from another hospital provide*r then this is part of the preceding superspell.
- Otherwise generate a new superspell.

Inevitably there will be scenarios where admission inflation persists, for instance where the dialysis unit does not identify that the patient was transferred for dialysis from another trust. Some movement for dialysis isn't documented at all by wards, however ordering by the spell admission date at the spell derivation stage should prevent a dialysis attendance bisecting a series of episodes resulting in the generation of two spells.

Admission definitions

The HES specification classifies admissions into different classes. Most admissions are *"ordinary"*, be they emergency or elective activity. Haemodialysis attendance should be

classified as classification 3 or 4 (*regular day or regular night attender*), and this definition was adopted for preliminary analyses, however data suggested that some trusts failed to make this distinction. Routine haemodialysis attendances which were incorrectly classified as ordinary admissions were defined as less than a day in length, were elective, and had haemodialysis procedural information in the first procedure code position. An elective admission was classified as method of admission codes 11, 12, or 13 (Elective: from waiting list, booked or planned). All other were classed as emergency. Other classes or types of admission are dealt with within the specific chapters that report them.

There are several ways of classifying reason for admission, largely based on the diagnosis and procedural information present in individual episodes or the first admitting episode. The Healthcare Cost and Utilisation Project (HCUP) is an American agency responsible for developing and maintaining the International Classification of Disease version 10 (ICD10) Clinical Classification Scheme (CCS) (Healthcare Cost and Utilization Project (HCUP) 2009). This scheme maps the primary diagnosis associated with the admission (DIAG_01 in the case of HES) to a grouped reason for admission. There are 260 reasons for admission groupings which map to the 8,800 ICD10 codes routinely employed. Dr Foster's HSMR (56 diagnosis groups with highest mortality accounting for 82% of hospital death) and the NHS Information Centre SHMI (260 reasons for admission regrouped into 142 groups accounting for 100% of hospital death) routinely use CCS to group diagnoses for subsequent statistical modelling. Of note these methods to not involve procedural information, the argument being that for a given diagnosis, subsequently doing a procedure involves a clinical decision. Adjusting for procedure is adjusting for a factor in a centre's control.

Other similar methods of grouping reasons for admission have been developed. In response to the exclusion of some diagnosis groups from the HSMR, Lakhani et al derived their own high level mortality indicator to compare trusts(Lakhani et al. 2005). Of note, this excluded deaths related to cancer as the authors argued that these were not modifiable so some groups of admissions were still excluded.

Health Resource Groups (HRGs) were primarily implemented to facilitate remuneration through the Payment by Results system. Using an algorithm the NHS Information Centre derives a HRG for each spell using the combination of diagnosis and procedural information. This combination means a larger range of HRGs (approximately 1500 in 2011/2012). In order to capture and remunerate for activity, HRGs have the capacity to reflect complications associated with challenging cases or complications that may or may not be as a result of poor

care. For this reason many of the summary level mortality statistics reported do not standardise across these measures.

Where possible, reasons for admission were derived with the CCS grouping scheme for the reasons highlighted above. Where shortcomings were identified (such as a large proportion of patients being coded as Chronic Kidney Disease, the HRG for that Spell was explored. CCS groups were derived from mappings available from the HCUP website. HRGs were derived using the NHS information centre grouper software available on their website, to the 2010/2011 specification.

Comorbidity

The presence of comorbid conditions at a given time point (before starting RRT, before transplantation, at the beginning of a haemodialysis week etc) was informed from diagnosis and procedure coding from admissions; the admissions that precede the date in question. When the event for which comorbidity is informing is an admission, only secondary codes not pertaining to the reason for admission were used, as the primary reason may be factored elsewhere in the model (Aylin et al. 2010). Codes are mapped to comorbidity schemes detailed in chapter 4. Comorbid schemes derived from routine data only permit the presence of a comorbid condition once. Limitations on diagnosis and procedure coding exist: There is no differentiation between cancers which have been cured or operated on, or type I and type II diabetes. Specific reasons for amputations are not implicitly coded (in that the procedure code itself does not routinely reflect why it was performed).

Renal replacement therapy modality and supervision

The UKRR treatment timeline codes the type of RRT modality a patient is receiving along with a supervising or submitting centre for this information. The treatment timeline often does not have dates terminating different periods of treatment on a particular modality or under a particular centre, but rather the date of the start of the next treatment period or centre is used to indicate the previous has finished. Dates for the end of treatment periods were computed by back-filling the treatment end date with the treatment start date from the next entry. Where there were no further entries, the date of the 31/12/2009 (end of follow-up) was used. In all analyses the date of death was used as the end of follow-up if it occurred prior to this computed date, and death was not always imputed in the timeline as a field for this exists in the demography table. Primary renal disease codes were mapped from the ERA-EDTA codes to the classification grouping routinely reported by UKRR using look-up tables provided by UKRR.

Modality was mapped to the three RRT modalities using agreed UKRR EDTA codes provided by UKRR, however varieties of dialysis within modalities (e.g. continuous ambulatory vs automated peritoneal dialysis) were not differentiated. Satellite haemodialysis centres were mapped to their associated supervising centres. Although modality is linked to specific complications on dialysis and is associated with differences in patient survival and hospitalisation, adjustment for modality was avoided wherever possible. The rationale is as follows:

1. **Variables in a centre's control**

   Many of the patient level factors adjusted for in performance indicators relate to patient demography at the time they start RRT. Patient selection for a dialysis modality is partly as a result of an informed patient making an independent choice and partly as a result of the attitudes regarding which modality is superior and which is suitable for a given patient(Castledine et al. 2013). If demography correlated perfectly with modality there would be no need to adjust for modality in the presence of this demography and concerns regarding differing centre attitudes would be unfounded. Residual variation in the use of home based dialysis therapies has been identified elsewhere(Castledine et al. 2012).

2. **Patients selection**

   Adjustment for the transition between modalities may be appropriate given the hospitalisation burden associated with it; however failure to tolerate haemodialysis or peritoneal dialysis may be as a result of poor patient selection. In patients who present late or in an unplanned fashion there may not have been adequate time to prepare a patient for their chosen modality and for this reason some analyses look at the modality at 90 days from start as the definitive modality for the year in question.

3. **Centre attitudes**

   Some centres treat the first episode peritoneal dialysis peritonitis as a treatment failure and switch patients to haemodialysis at that time. The association between duration of peritoneal dialysis therapy and risk of complications such as encapsulating peritoneal sclerosis(Johnson et al. 2010) may influence clinicians to electively transfer patients to haemodialysis but no formal guidance exists.

4. **Morbidity necessitating modality change**

   Patients who develop haemodynamic instability on haemodialysis due to heart failure may be switched to peritoneal dialysis, however the development of this complication could be in part as a result of suboptimal fluid management.

Explanatory variables

Existing literature on predicting survival and hospital related events was reviewed to ensure appropriate variables were included in the statistical models detailed in the next section. The introduction reports many of the patient level characteristics which are recognised to influence incident survival on RRT, and the method by which comorbid conditions adjusted for is detailed in Chapter 5. There are patient level factors recognised to influence survival which despite the combination of datasets are not possible to derive and therefore adjust for (e.g. Obesity).

Statistical methods

Descriptive methods

Analysis of the relationship between a continuous variable and a dependent variable to determine linearity or logical categorisation was performed with smoothed spline function (Hastie et al. 1990). The application of splines in this study was to generate a moving average of the dependant variable (representing a proportion in categorical variables or a mean in continuous variables) based on observations in the region around the predictor variable.

Rate calculations

For rates measured over time where time at risk may be variable due to death or changes in modality, time at risk was adjusted as follows:

Hospitalisation measures

For all-cause admissions, time whilst in hospital was subtracted from time at risk. This was adopted as once a patient is admitted, they cannot be admitted again. However, the admitted patient can spend further days in hospital assuming another censoring event does not occur. For this reason where rates for admitted days are reported, time in hospital is still included.

For cause-specific admissions where secondary coding is also scrutinised, time in hospital is subtracted from time at risk only when the admission matches the specific cause. For instance, when a patient is admitted with a myocardial infarction, they are still at risk of getting an infection. Therefore an admission for myocardial infarction without infection is still

time at risk for developing infection and these hospital days are not subtracted. A patient specific rate is determined from:

$$\text{Patient Rate} = \frac{\text{Total number of events}}{\text{Total Treatment Time at Risk} - \text{Excluded time}}$$

Equation 1

Grouped rates

The rate for a group is reported as the total number of events for the group in univarate analyses, divided by the unit of time. This method is adopted in contrast to other potential method as:

1. In events which are infrequent, and a proportion of patients may have zero counts, using the mean or median individual patient rate will skew the result.
2. The confidence limits around a grouped rate conform to standard statistical distributions, whereas mean and median results are not necessarily bounded at the lower limit by zero.

The Breslow-Day test for homogeneity (Breslow et al. 1994) was used to identify interactions in rate ratios between demographic groups. Here, a chi-squared value χ^2_{s-1} was determined from the following formula where IRR_i is the incidence rate ratio for a given group, IRR_{direct} directly standardised incidence rate for the whole group, V_i is the variance for the incident rate ratio of group in question and s is the number of groups.

$$\chi^2_{s-1} = \sum_{i=1}^{s} \frac{[\text{IRR}_\text{i} - \text{IRRdirect}]^2}{V_i}$$

Equation 2

Centre-specific rates

Most centre specific rates are derived from grouped rates unless reported as adjusted. When adjusted unless stated otherwise, the variable of interest (rate, proportion etc…) is predicted using the centre population demography using a multivariate model which has been calibrated on data from all centres. Multivariate modelling techniques are detailed below. These predicted values for the centre are then compared to observed values to report a rate ratio. This represents indirect standardisation. A centre specific unadjusted rate is determined by the following, where *i* indexes the data for the centre in question:

$$\text{Centre Rate } = \frac{\sum_i (\text{number of events})}{\sum_i (\text{Treatment Time at Risk} - \text{ Hospitalised time})}$$

Equation 3

Hospital standardised mortality ratios

For the derivation of HSMRs, the specification for existing measures detailed in chapter 2 was broadly applied. For an individual admission, the probably of death at 30 days from discharge was calculated from a multiple logistic regression model calibrated on all admissions across all hospitals. This process can also be performed on a subgroup of admissions, for instance for one particular reason for admission. This has the advantage of allowing the coefficients for the predictor variables to vary across the diagnoses. The sum of logistic regression model predictions is equal to the sum of the observed events. For a given hospital or renal centre, the sum of the events is compared to the sum of the predicted probabilities for admissions attributed to this provider. The ratio represents the HSMR, and is essentially indirect standardisation detailed below.

Standardisation

Two methods of population standardisation exist, direct and indirect (Barker et al. 1976). Briefly, in direct standardisation, the stratified (e.g. age group) rates within the unit of interest (i.e. a hospital) are applied to a standard population (i.e. national) to calculate a rate which can be compared in absolute terms to the observed national rate. Using the same example, indirect standardisation applies rates derived from national statistics to the age groups observed within a hospital. Both methods are essentially weighted averages over the potential confounder but the weights for direct standardisation are fixed, so that if the stratum specific rates are all the same across hospitals then direct standardisation gives the same stratum specific rates, but this is not necessarily true for indirect standardisation.

The strength of direct standardisation is that it is more robust against Simpson's paradox. The phenomenon of Simpson's paradox is where rates within different subgroups are masked by the headline statistic. One individual trust could be under the impression they were delivering good care with a low hospital standardised mortality ratio, however reasonable performance in large groups of patients could easily mask poor performance in smaller groups.

Often the overall statistic is confounded by a variable or subgroup which as a different association. Direct standardisation requires adequate rates within all groups in all observed populations. For instance sufficient numbers of patients would needed in all age groups in our hospital of analysis. It is also difficult to deal with a number of potential confounders, and it

cannot be done if the confounder is continuous. As standardisation may require adjustment for a number of variables, rates within subgroups would be required (for instance the rates for diabetic and non-diabetic within a specific age-group). For this reason direct standardisation is not practical and in these analyses indirect standardisation is employed. Experience has shown that the results of direct and indirect standardisation often agree.

With both methods the influence of another hospital's mortality rates on the standardised mortality of one hospital could generate a paradox: other hospitals care could improve whilst the hospital in question's crude mortality remains constant. As the expected mortality for this hospital goes down the observed/expected ratio goes up and the perception is mortality has worsened in this hospital whilst in reality it has stayed the same.

Modelling techniques

Statistical modelling was employed to determine the effect size of variables of interest and that their influence persisted in the presence of other confounders. More fundamentally once a model for an outcome of interest was derived using the techniques outlined below, it was used to predict the outcome for a given individual. As the models are derived on the entire dataset, the application of the model result to individual patient level data which is combined to give an overall centre rate represents indirect standardisation. Therefore if a centre has a group of patients who are more likely to be admitted to hospital for instance, the model recognises these characteristics and their associated coefficients and reports a higher expected admission rate. As a result the adjusted admission count for a centre will reflect this by being higher.

Calibrating a model is using data to determine the influence of individual variables on the outcome of interest. This can be performed on the whole dataset as is often done with institutional comparisons (e.g. HSMR, SHMI, UKRR mortality analyses), or with a subset of the data. The latter has advantages in that it is more resistant to over-fitting, a phenomenon which can manifest with amongst other things poor model performance due to attempts to fit outlying data, or with a failure to make accurate predictions in other datasets(Babyak 2004). Given that mortality rates have been shown elsewhere to improve over time, and that other aspects of clinical care and coding are likely to evolve, alongside the weight of evidence that comorbid scores should be recalibrated for the dataset or outcome of interest, the author argues that using the entire dataset for calibration is a more recognised approach to the standardised reporting of institutional performance. The statistical modelling techniques employed in this project are outlined below:

Linear regression explores the association between a dependent continuous variable and independent continuous or categorical variables. For one independent variable an equation would resemble:

$$E(y) = \beta_0 + \beta_1 x$$

Equation 4

where $E(y)$ is the expectation of the dependent variable y, β_0 is the intercept, β_1 is the regression coefficient, and x is a given value of the independent or predictor variable. The values of β_0 and β_1 is derived using the least squares method, which minimises the sum of the squares of the deviations from observed data to predicted values (residuals). The assumption of the linear regression method is that the residuals are normally distributed.

Cox regression was employed to analyse survival time adjusting for multiple predictors. Having established a reference probability of dying at a particular point in time ($h_0(t)$) having survived up until time t, it determines the proportional hazard (how much greater the hazard for death is in the presence of the predictors $X_{i1} \ldots X_{ij}$ compared to their absence) from the exponentiated value of the regression coefficients contributing to the overall time-specific hazard $h_i(t)$ using equation:

$$h_i(t) = h_0(\mathrm{t})\exp(\beta_1 X_{i1} + \cdots + \beta_j X_{ij})$$

Equation 5

In cases when the survival probability of a patient is predicted at a specified time point t, the reference hazard $h_0(t)$ is obtained, with the application of hazard ratios associated with the demography of the patient in question applied to give the overall patient specific hazard, $h_i(t)$. In its current form this model operates with fixed effects, and does not account for clustering. When looking at the impact of a variable across centres, the observations are clustered with these centres. To account for this a 'frailty' parameter is included, which acts on the hazard rate for all individuals within centre *k* and is denoted by ε_i (Andersen et al. 1999).

$$h_{ij}(t) = h_0(\mathrm{t})\exp(\beta_1 X_{i1} + \cdots + \beta_j X_{ij} + \sigma\varepsilon_k)$$

Equation 6

Now σ is a constant and ε is a random variable which is the same for all individuals in a centre with expectation 0 and variance 1. Thus var(σε)=σ^2 and the model will estimate σ^2 which is the variance associated with the frailty.

When predicting a count response (number of admissions to hospital over a one year period for example), the Poisson and negative binomial regression are often employed. The Poisson distribution assumes that the variance of the count being predicted is equal to the mean(Hilbe 2011). Extending this to comparing subgroups (such as diabetic vs non-diabetics), the mean for diabetics should be the same as the variance. Employing the Poisson distribution count P has the density defined by the following equation:

$$P(X = x) = \frac{e^{-\lambda}\lambda^{x}}{x!}$$

Equation 7

Where x is the observed value and λ is the mean value. The above formula assumes that the period over which the count is being observed is constant, but can be adapted for various follow-up time t using:

$$P(X = x) = \frac{e^{-t\lambda}(t\lambda)^{x}}{x!}$$

Equation 8

Biological data does often not conform to the equidispersion needed to employ the Poisson distribution, with outlying values or excess zeros meaning the variance does not equal the mean. The negative binomial distribution is more broadly parameterised and therefore is more robust to over-dispersion. It can be described as the probability of observing k failures before the rth success in a series of Bernoulli trials where p is the probability of success in this trial. A Bernoulli trial is an experiment with two possible outcomes, like a coin toss. The probability mass function is modelled with the following equation:

$$P(k; r, p) = \Pr(X = k) = \binom{k + r - 1}{k} p^{r}(1 - p)^{r}$$

Equation 9

However, the negative binomial distribution is still relatively fallible to excess zero counts. Zero inflated models allow a zero count to be predicted from variables that are the same or different from those that predict the positive count. The probability of a zero count can be predicted at the first stage (using a logit) and then if the chance of a zero count is low, the positive count is calculated using by negative binomial count model itself. The derivation of a logit is detailed in the explanation of Logistic regression below.

Logistic Regression was employed for the multivariate analysis and prediction of a binary outcome, for instance mortality at 30 days from discharge. A logit is predicted, representing the natural log of the odds ratio of the binary outcome of probability P with the equation:

$$logit(P) = \ln\left\{\frac{P}{1-P}\right\} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_m X_m$$

Equation 10

Where β_m is a constant, and X_m are the independent or predictor variables. It can be shown that the odds ratio for the binary outcome for the presence of X_m or a unit increase in X_m is exp(β_m) (Campbell 2008).

Model performance

C-statistics were used to analyse model performance in the case of logistic regression models, advantageous as they could be informed by several different models (for instance when modelling individual diagnosis groups then identifying how prediction was for all groups). The C-statistic is analogous to the area under a Receiver Operator Characteristics (ROC) curve, which plots sensitivity against 1-specificity. It functions using ranking, as in the proposed setting the value of the C-statistic is equivalent to the probability that predicted risk is higher for a randomly selected case than a randomly selected non-case. Prefect prediction would report a C-statistic of 1, no better than chance would report 0.5 (Cook 2007).

Root Mean Square Error (RMSE) is average difference or error between the observed continuous variable and that predicted from a model. The process of squaring the errors, producing a mean then performing a square root of the result is to make all values positive. The RMSE is relative to the scale of the observed values and does not indicate the direction of error.

R squared values are produced for linear regression and Cox regression. It represents the proportion of total variance of the outcome variable explained by the model. In the case of linear regression where predicted values are being assessed compared to their observed values, R squared can be calculated by the following:

$$R^2 = 1 - \frac{sum\ of\ squares\ of\ residuals}{total\ sum\ of\ squares} = 1 - \frac{\sum_i (y_i - f_i)^2}{\sum_i (y_i - \bar{y})^2}$$

Equation 11

Where y_i is the observed value, $\bar{y}$ is the mean of observed values, and f_i is the predicted value.

There are relative merits of each of these assessment techniques. Firstly it is important to recognise that some of the outcomes of interest can be modelled using several statistical methods, each with their own intrinsic model performance output in standard statistical packages. In addition, some predictions are the product of multiple models (e.g. zero inflated models and model per diagnosis group logistic regression for HSMR). C-statistics and RMSE have the advantage of having the capacity to be generated by the user using the predicted values after the model has been run. The C-statistic is bounded between 0 and 1 and therefore is interpretable in a wide range of settings by a range of readers, however it is derived by the ranking of the probabilities and would be insensitive to the movement of all of the predictions higher, lower or them separating. The direct relationship to the scale of variable of interest in accessing the accuracy of the model predictions is a strength of RMSE, in that it would report the average error of a model predicting admissions in admission counts. However, it does not indicate if this error is generally negative (observed count is less) or positive (observed count is more).

Funnel plots

The presentation of centre specific statistic (mean or proportion), associated confidence limits and an overall mean or proportion as previously discussed lent itself to the generation of Caterpillar plot, which is often ordered by the centre specific statistics. This presentation of data is often interpreted as a ranking, despite the fact that this ranking is extremely difficult to quantify (Hodsman et al. 2011). The funnel plot, originally developed to identify publication bias in meta-analyses, has been used in other studies and in UKRR reports. They are recommended method of comparing institutional performance. Their structure and derivation comprise four elements (adapted from (Spiegelhalter 2005), with a clinical example added):

1. An indicator Y (For instance the proportion of patients surviving to three years on RRT for a centre)
2. A target θ_0 for Y which specifies the desired expectation (e.g. overall survival for all centres)
3. A precision parameter p that determines the accuracy of indicator Y. (e.g. the standard error on a proportion surviving to three years for the target θ_0)
4. Control limits, where the chance of exceeding the limits for a centre in control (at θ_0) is for instance p = 0.025, 0.975 and p = 0.001, 0.999 representing two and three standard deviations or errors from the target θ_0.

Using limits derived from two and three standard errors has been widely adopted, generally with the selection of the latter from work by Shewhart on process control(Shewhart 1925). The precision parameter is generally determined from the number of patients in a centre, becoming narrower as the number of patients increases. As a result the control limits resemble a funnel when the indictor Y is plotted against the number of observations or sum of observations within the centre (Figure 3-3). The statistical distribution employed to derive the control limits of each funnel plot is detailed in the individual chapter, but generally is Binomial for an adjusted or unadjusted proportion and Poisson for a rate ratio.

Subsequent work by Spiegelhalter details how to handle over-dispersion of institutions or centres (Spiegelhalter 2005). This paper suggests that over-dispersion represents observed variability which cannot be attributed to change and a few divergent institution. For instance insufficient model adjustment or the sum of a number of institutional factors that do not related to poor quality of care. Some tests for over dispersion exist, for instance the conditional variance of a count exceeding the conditional mean when applying the Poisson distribution.

Options to deal with over-dispersion include grouping similar institutions (e.g. transplanting centres), using a range as a target θ_0 rather than a discrete value (thereby widening the funnel) or estimating an over-dispersion factor. There is a danger that the very institutions one is trying to detect could be masked by such an approach. Factoring overdispersion by excluding a proportion of centres can be performed by trimming the observations to a defined value, for instance the 95% centile. This known as winsorising, and may leave a large number of dispersed outliers if the number of centres is small. The subsequent over-dispersion factor is large and wide control limits are drawn. The result can mean many or all centres appear in control. Given the small number of centres and the lack of strong evidence of centre-level over-dispersion, these methods were not employed.

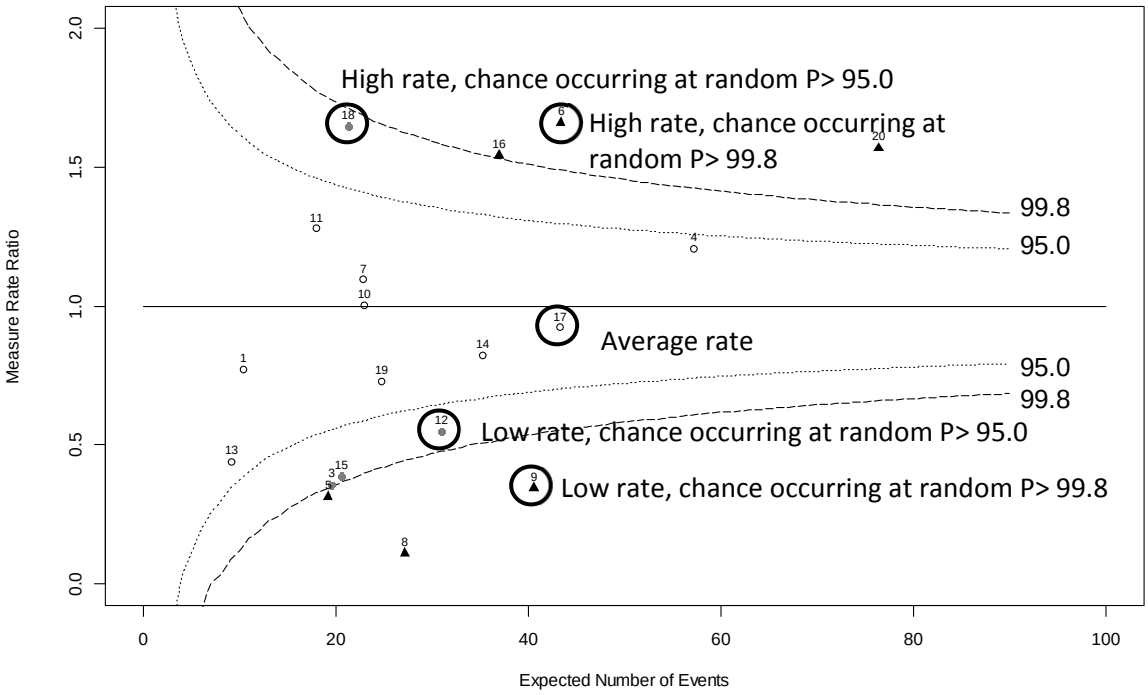


Figure 3-3 : Funnel plot based on Poisson distribution with class of outliers marked

Chapter 4 *Dataset linkage success, completion of existing variables and generation of new variables*

Background

As with many disease registries(Merry et al. 2009; Webster et al. 2010; Zehtabchi et al. 2011), the UK Renal Registry (UKRR) has significant problems with missing data. In addition to allowing the description of new endpoints and measures of performance, data linkage allows the completion of missing data if both sources contain information in comparable formats.

In addition to data being missing, there are existing concerns regarding the inaccuracy of data collected by UKRR. One study which reviewed laboratory values before patients started RRT identified improvements in kidney function before the date reported that treatment commenced (Ford et al. 2010). Following detailed analysis they found that 14% of patients had in fact been exposed to dialysis therapies before the reported start of RRT.

Reasonable agreement needs to be established across sources for a sensible analysis, and new variables should be tested for robustness against other sources where possible**.**

Aims and Objectives:

- To determine the strength of linkage between the HES and UKRR datasets.
- To establish a research cohort suitable for further study.
- To determine the agreement for specific variables between UKRR and HES data sources.
- To establish if the combination of data from HES and UKRR can improve data completeness on demographic and comorbidity variables.
- To determine the validity of variables derived from HES or combined sources with a view to inclusion in further analyses.

Analysis specific methods

Identification of analysis cohort

Patients with multiple UKRR entries as determined by NHS Number tracing, patients who reside outside of England according to the Primary Care Trust code for the postcode residence in either source, or patients with no linked HES data will be excluded from this and subsequent analyses.

Classification of patient ethnicity

HES and UKRR differ in how they classify Ethnicity, and these groupings are detailed along with their mappings in Appendix 4a. HES ethnicity is supposed to be patient reported and therefore was used as the primary source for derivation of ethnic group for the analysis cohort, and cases with missing HES derived ethnicity queried against the UKRR dataset. When HES reported ethnicity differed across the dataset the preference was given to the older, broader grouping method to aid further grouping of the HES 1996 – 2001 specification into the groups of White, Black, South Asian and Other.

Derivation of centre incident catchment area

Centre catchment area was determined for the 46 centres which were contributing incident patients to UKRR between 2002 and 2006 using middle super output areas for patient postcodes around the time of starting renal replacement therapy. The centre with the greatest proportion of incident patients from the Middle Super Output Area was assigned this geographical unit as part of their catchment area. Individual geographical units were merged according to centre to form an overall catchment area.

Derivation of catchment areas for centres which began contributing patients to the UKRR after the incident period, which may feature in analyses due to patients transferring into them from the 46 original centres (six additional centres) is not possible. Their geographical catchment areas are absorbed by neighbouring centres who will receive the occasional patient from these areas.

Geographical socioeconomic status and its application to patients

The postcode derived variable of Lower Super Output Area (LSOA) was available for both data sources following additional information governance authorisation from the ONS. First released in 2004, LSOAs are geographical areas generally representing a population of one thousand to three thousand residents. The LSOA was matched to the index of multiple

deprivation (version 2004) from the UKRR dataset from postcodes completed before the start of RRT to up to 6 months after starting, and HES admissions from 6 months before to 6 months after starting RRT. The derivation method does differ from perhaps how UKRR might choose to obtain postcode data, as more historically reported postcode data submitted to UKRR years prior to the start of RRT, when the patient first came into contact with the submitting centre might have been used. The proposed method enables a more accurate understanding of how the reporting sources might have differed during the same catchment period.

The ONS ranks LSOAs from most deprived equalling 1 to least deprived equalling 32,844, according to various domains including income, employment, education and crime informing the index of multiple deprivation (IMD). Area level socioeconomic status measures like the IMD have been shown to correlate reasonably with individual level socioeconomic status and that this correlation has been similar across a range of area sizes(Reijneveld et al. 2000).

As both sources contain LSOAs mapped to the patient's address and the patient can move within the period suggested, there is the capacity for different ranks of deprivation to be reported. In these scenarios the least deprived (highest rank) was employed. Patients can change residence during the 12 months period studied. For analytical purposes the comparison between sources on geographical accuracy is limited to those patients whose returned postcode from each course did not alter during this period.

Identification of patient level comorbidity

The reported comorbidity in this chapter includes the comorbidity reported to UKRR via renal unit computer systems compared to the accrued comorbidity from HES admissions leading up to the date of first dialysis as defined by the first RRT in the UKRR treatment timeline. When comparisons between sources are made only those with complete data from UKRR and in whom survival is beyond 90 days are reported. Overall and centre specific agreement is defined as the number of individual conditions present in both sources where presence or absence of the condition agree. Therefore there will be ten opportunities for agreement per patient. Complete agreement (both sources reflect the presence or absence of all ten comorbid conditions) is not reported. Agreement between individual conditions was assessed with the Chi Squared test. The existing comorbidity schemes defined by Charlson and Elixhauser were identified using existing ICD10 codes from published literature. The UKRR comorbid scheme was translated into ICD10 codes where the comorbid condition in question was not covered by the Charlson and Elixhauser schemes, and is reported in appendix 4b.

Coding depth measurement

Average coding depth per centre was defined as the mean number of diagnosis codes utilised for the first episode of each spell for admissions of patients under the centre in question. As the length of admission may reflect its complexity and the complexity of the admitted patient and as there is a high prevalence of zero length of stay admissions, coding depth per centre is reported for zero and non-zero length of stay admissions was analysed separately.

Primary renal disease

ICD10 diagnoses associated with PRD were determined from admissions in the 12 months around the start of RRT in patients with PRD completed in the UKRR dataset. Non-specific codes such as those that span several PRD groups or reflect hypertension were excluded. In patients who survive over 90 days with PRD coded as missing or unknown, a HES derived PRD was assigned if an appropriate ICD10 code was identified over the same period. Due to the need for admissions around the start of RRT, this analysis was limited to patients who survive 90 days (n=19,525).

Ascertainment of the date first seen by a nephrologist

The HES outpatient dataset was introduced in April 2003, and therefore could only be used to understand nephrology care in the outpatient setting in patients starting renal replacement therapy from six months after this. Outpatient and inpatient activity was analysed in HES, looking for speciality code 361 (nephrology) in either the main or treating speciality fields.

Coding practice for individual centres was scrutinised to determine if there were changes in coding practice over the period studied, which could thereby alter the perceived date of first contact with a nephrologist. If the speciality code 361 (nephrology) was identified and this pre-dated existing information on earliest contact this was flagged and difference in days computed. In situations where no date of first nephrology contact was submitted the new date was substituted. The time difference from the date first seen by a nephrologist and the date of first RRT was then calculated and categorised into no documented contact, < 90 days, 90 days to six months and > six months.

Agreement between sources was assessed in a limited cohort in whom UKRR date first seen was returned and beyond the period where the outpatient dataset was deemed as valid (six months after its introduction).

Renal replacement therapy activity identification

The date of first RRT for the purposes of UKRR analyses is the earliest recorded RRT modality in the treatment timeline. This was compared to the earliest HES recorded dialysis (as defined as OPCS code X401-X409), in patients whom the UKRR dataset suggested started on dialysis. Cases were flagged where procedure codes indicated dialysis was performed prior to the UKRR reported date of first RRT.

The validity of HES to record elective outpatient haemodialysis frequency was determined by comparing the amount of dialysis time recorded in the UKRR timeline to the amount of dialysis activity recorded in HES, defined as elective planned same day/night activity with procedure codes that indicate haemodialysis was performed.

A peritoneal dialysis catheter insertion was defined using catheter insertions coded in procedure fields using the following codes occurring in the 12 months prior to the first incidence of peritoneal dialysis for a patient. The codes for catheter insertion used were X41 and X42 (permanent and temporary peritoneal dialysis catheter insertion groups).

Transplantation activity was compared using codes for the donor specific procedure of transplantation (M012 – M019) in HES and transplant activity in the UKRR timeline. Donor type was determined in cases where either source was missing from the other source, and secondary OPCS coding that can indicate donor type (Y014-Y016 & Y991-Y994) was employed to further enhance data completeness. Date of transplantation from HES was defined as the procedure date from the corresponding field where the transplant procedure code was identified, unless this was missing where date of admission was substituted.

Sources of date of death

There are four fields within the UKRR linked dataset where date of death could be recorded. UKRR receive manually inputted dates of death from renal units via the electronic downloads which inform other aspects of their analyses. In addition, staff at UKRR submits patient demographical data to the NHS tracing service to validate NHS number and this also returns if the patient has died. The Office of National Statistics linked file records all deaths linked to the UKRR, date and location of death, and cause of death. Finally HES records if a patient has died using the variable *DISMETH*, with a value of 4 in this field to signify discharged dead.

As HES recorded date of death only captures death in hospital, only the three fields of Units submitted, NHS traced and ONS reported date of deaths were compared using deaths before 31/12/2009. NHS traced followed by ONS and finally UKRR sources were hierarchically

used for the combined date of death used for subsequent analyses. Hospitalisation data were compared to derived dates of death to test validity, as admissions beyond the date of death would suggest an error in a data source.

Results

Linkage, data and cohort

Having sent UKRR extracted data to the research capability programme, linkage was performed as reported in chapter 3. Data were returned to the University of Sheffield via the NHS Secure File Transfer Service, decrypted and expanded. It was then loaded into Microsoft Access in accordance with the agreed file format detailed in appendix 3b. Table 4-1 shows the counts for individual records.

Table 4-1 : Record counts for eight linked tables describing the cohort within the linked dataset

Table Name	Description	Record update frequency	Number of Records
Demographics	Age, Gender, Ethnicity, Comorbidity and Primary Renal Disease	One row per patient	21,633
Laboratory	Haematology, biochemistry and sending hospital	One row per 3 months per patient	295,295
Treatment	Modality, supervising centre and dialysis location	One row per change in treatment	61,513
Erythropoietin	Dose, frequency and type of erythropoietin	One row per dose change	251,129
Postcode	Postcode derived fields of Super output area, health authority and IMD	One row per address change in patients address where supplied	32,543
ONS	Location, date and cause of death, plus other conditions	One row per death	11,547
HES Inpatient	Location, date, diagnosis and procedure plus demography	One row per consulting episode	2,818,193
HES Outpatient	Location, date, diagnosis and procedure plus demography	One row per outpatient attendance	1,485,071

Using additional information supplied by RCP summarising the linkage strength decisions regarding the appropriateness of inclusion of patient for further analysis were made. As shown above, 21,633 patients were supplied to RCP by UKRR to be linked. 571 of these patients had

no NHS number supplied by UKRR. Subsequent tracing attempts by RCP against the NHS batch tracing service were able to trace 21,139 of the total cohort, leaving 504 patients with missing or unverified NHS numbers. In these cases unverified NHS numbers were used for linkage or name/ date of birth as per the RCP specified linkage methodology in chapter 3.

Twelve records accounted for six patients, and these duplicates were excluded. Patients with non-English residences accounted for 201 patients who were excluded, as admissions may occur to hospitals outside England. Patients with no HES data linked at any time were excluded. One linked ONS record reported a death in 2000, before the patient started RRT and was deemed erroneous and excluded.

The final cohort is detailed in Figure 4-1including a breakdown of HES record counts in the final analysis cohort which numbered 21,271 patients.

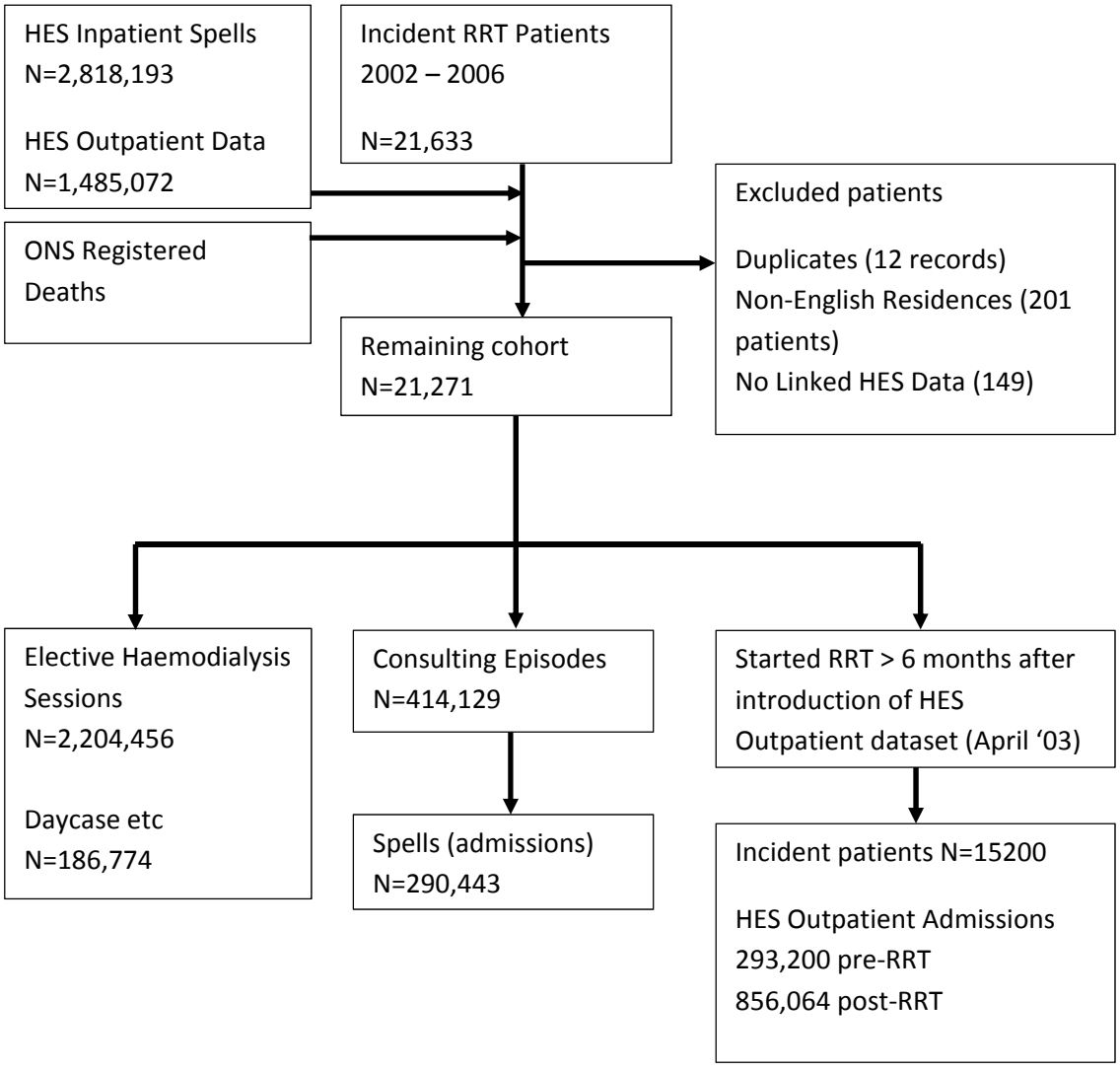


Figure 4-1 : Patients, hospital records and death registrations in the linked cohort

Haemodialysis attendances as defined by HES *CLASSPAT* 3 or 4 with zero length of stay accounted for 78.6% of consulting episodes supplied. 21.2% (61,612 of 290,443) of ordinary admissions (spells) were composed of one episode and 3.2% (9,093 of 278,498) continuous inpatient admissions comprised of more than one spell.

Ethnicity

Overall data completeness for ethnicity in the UKRR dataset for the analysis cohort was 85.5%, below the 95% completeness generally regarded as appropriate for inclusion in multivariate analyses(Hofferkamp 2008). For all ordinary admissions in the same patients, HES data completeness for ethnicity was 84.8% (244,979 out of 288,780 spells). Due to the presence of multiple admissions per patient, ethnicity could be determined from all episodes in the HES dataset in 20,646 (97.1%) of patients. Agreement across admissions was also assessed and noted 1,941 patients of the 20,646 patients (9.4%) with HES derived ethnicity had multiple ethnic classifications across the HES dataset using the proposed mapping. This improved to 1563 (7.5%) once the analysis regrouping was applied to HES derived ethnicity.

17,802 patients had data from both sources. Disagreement between HES and UKRR ethnicity data using the analysis regrouping occurred in 1,284 (7.2%) patients with data from both sources, and was primarily between UKRR patients who were reported as white which HES indicated were another ethnic background (2.5%), or HES derived Other in another group according to UKRR (4.9%). Agreement between the sources is shown in Table 4-2.

Table 4-2 : Agreement between sources for patient ethnicity

		UK Renal Registry Ethnicity Data				
		White	**Black**	**South Asian**	**Other**	**Total**
HES Ethnicity Data	**White**	79.3%	0.2%	0.0%	0.5%	80.1%
	Black	0.6%	5.0%	0.2%	0.3%	6.1%
	South Asian	0.1%	0.0%	6.6%	0.2%	7.0%
	Other	1.7%	0.7%	2.5%	1.8%	6.8%
Total		81.8%	5.9%	9.4%	2.9%	100.0%

Table 4-3 : Change in distribution of ethnicity following the addition of UKRR to HES data

	White	Black	South Asian	Other	Missing
UKRR Alone	70	5.0	8.0	2.0	14.5
UKRR + HES	80.4	5.6	6.4	6.4	1.1

The proportion of patients with ethnicity missing in the UKRR according to the final derived ethnicity suggests that there is greatest under-reporting of the White ethnic group of 14.8% of cases ultimately coded as white not being reported to UKRR compared with 7.2% Black, 6.6% South Asian and 10.5% Other(Chi Squared=129.5, df=3, P<0.001 n= 21,027).

Centre specific rates of ethnicity varied in a predictable manner. The Figure 4-2 demonstrates the variation in the proportion of patient coded as white across renal centres, highlighting significant variation. Reviewing this variation on a map emphasises the geographical areas with lowest White incident patients (e.g. central London, Birmingham), with the centres included in this work superimposed for reference, along with their catchment areas.

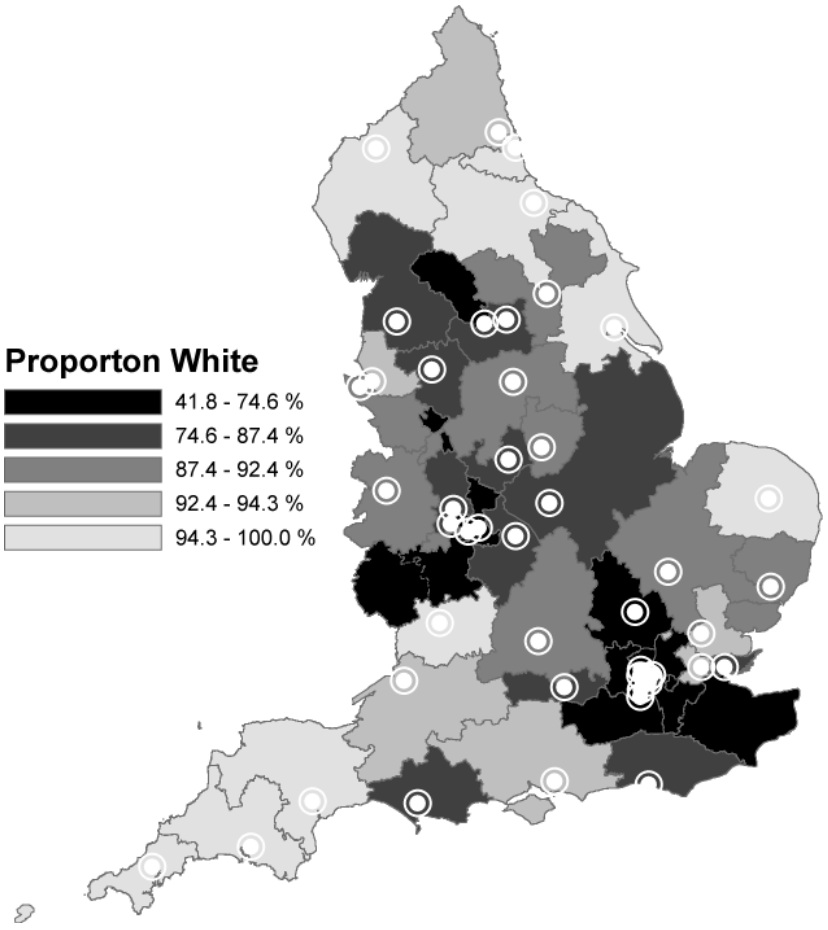


Figure 4-2 : Geographical variation in ethnicity in England by renal unit catchment area.

Renal centres identified by white ringed circles.

Socioeconomic status

Using admissions and UKRR postcode entries from 6 months before to 6 months after UKRR reported data for first RRT, lower super output area could be identified for 20,590 patients (96.8%) using HES data and 16,751 patients (78.8%) using UKRR data. The combination of these accounted for 98.6% of the cohort. 10.3% of cases returned more than one LSOA through HES, and 5.5% returned more than one LSOA via UKRR. Patients with one return via both accounted for 14,427 (67.8%) of the analysis cohort.

Agreement between the two sources in the single response group was high at 14,022 cases (97.2%), with a Spearman's correlation of 0.967 for the reported socioeconomic status rank ($P<0.001$). In the 405 cases where LSOAs differed, the IMD rank difference was on average 6,541 of 32,482 positions, or 20.1% of the range of the measure. Using the division of IMD rank into five groups as we will do in subsequent categorical analyses the agreement between sources was 38.5% for those with differing LSOAs, bringing total agreement for all cases to 98.3%.

In the case of HES, in the 2,196 cases where multiple admissions during the period around the start of RRT reported differing LSOAs, the mean difference between the highest and the lowest ranks was of 6,515 positions, or 20.0% of the range the measure scores across.

The scatter in Figure 4-3 may perhaps suggest that the UKRR returned IMD rank score reads lower than the HES score when the two sources do not agree. The absolute mean difference between the sources when they disagree is 216 in the direction of UKRR reading more deprived.

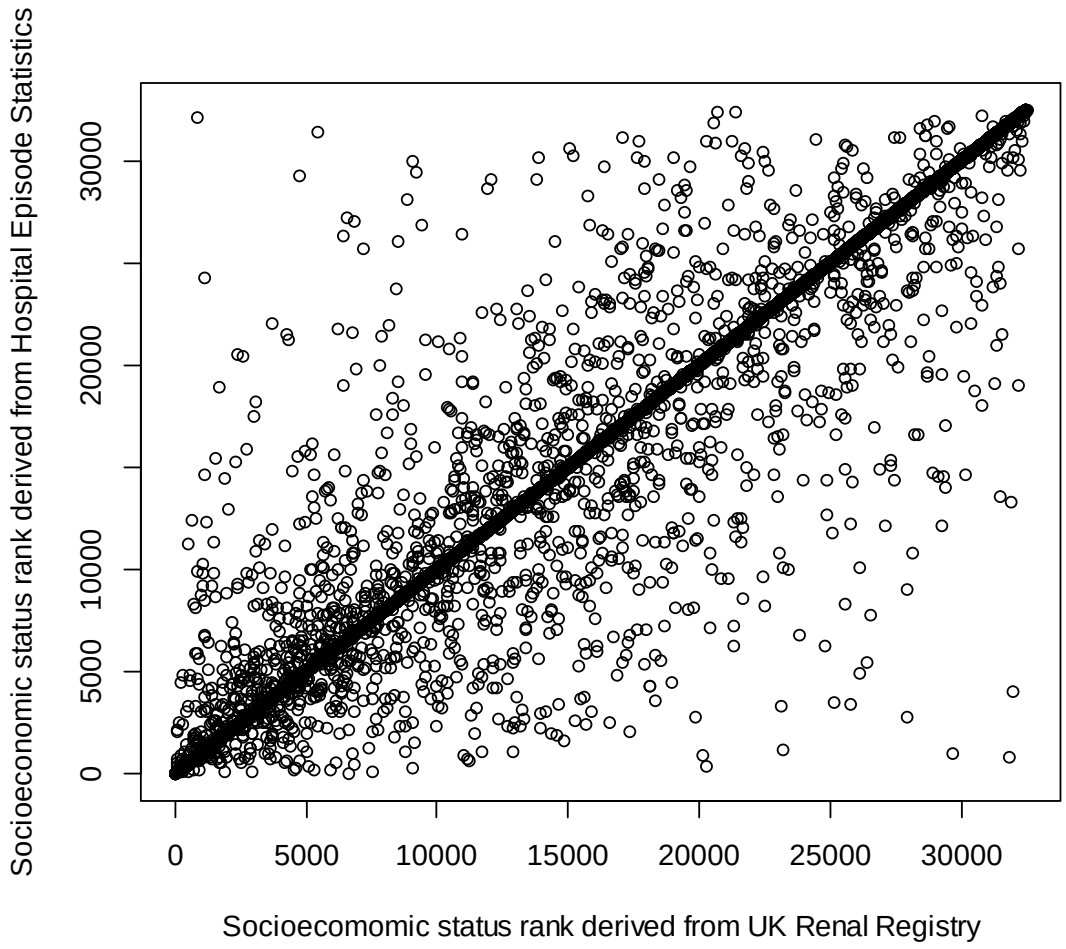


Figure 4-3 : Agreement between linked data sources for socioeconomic status rank.

Comorbidity

Comorbidity was completed in the UKRR dataset for 53.7% of the cohort, with no improvement between 2002 and 2006 (53.0% complete in 2002, 50.4% in 2006). The proportion of patients with UKRR comorbidity complete varied across centre (centre specific range 0.8%-98.7%).

There were 19119 patients (97.6%) surviving 90 days or more with admissions prior to starting RRT to inform the HES derived comorbidity measure. Of the Charlson, Elixhauser and UKRR measures, a total of 30 distinct comorbid conditions were identified. Their prevalence and centre specific range of prevalence is shown in Table 4-4.

Twenty conditions had a prevalence of two percent or more. Notable conditions which often were not identified in any patients within individual centres were depression and connective tissue disease, despite having an overall prevalence greater than two percent. The conditions with the greatest range of prevalence were diabetes, angina, and previous heart failure.

Specifically reviewing the UKRR conditions to enable an assessment of HES accuracy, the prevalence of ten UKRR conditions in patients with UKRR data, HES derived in those with UKRR data and HES derived in those without UKRR data is shown in Figure 4-4.

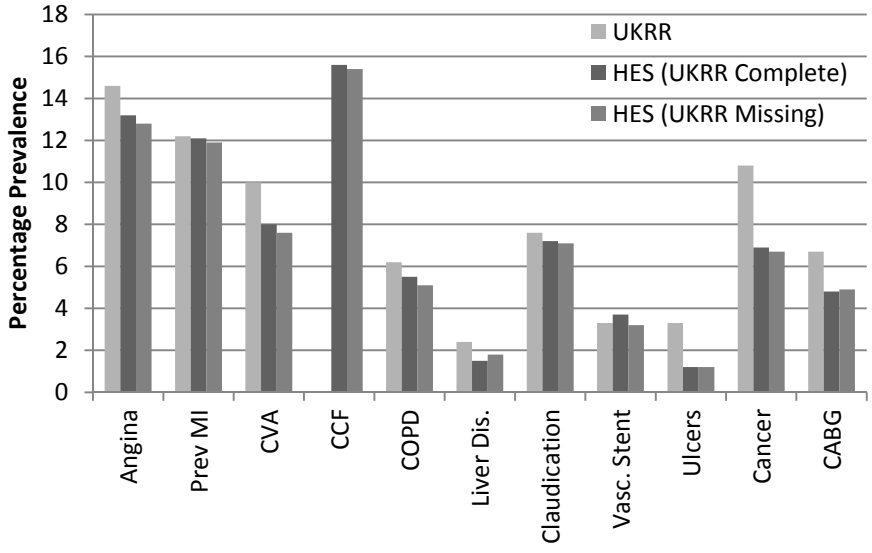


Figure 4-4 : Prevalence of comorbidities according to data source and data completeness.

Table 4-4 : The prevalence of comorbid conditions from three comorbid schemes prior to starting renal replacement therapy, informed from Hospital Episode Statistics data.

	Condition	Overall Prevalence	Centre Specific Range of Prevalence
UK Renal Registry	Angina	13.0%	6.3 - 22.6%
	Previous Myocardial Infarction	11.8%	6.8 - 19.4%
	Previous Heart Failure	15.2%	8 - 25.5%
	Stroke	7.6%	3.2 - 16.1%
	Diabetes	31.5%	23.9 - 45.2%
	Chronic Obstructive Pulmonary Disease	5.2%	1.6 - 12.9%
	Liver Disease	1.6%	0 - 6.5%
	Claudication	7.1%	2.5 - 14.5%
	Ulcers	1.2%	0 - 2.7%
	Cancer	6.8%	4.5 - 14.5%
	Previous Coronary Artery Bypass Graft	4.9%	0.9 - 9.9%
	Non-cardiac Vascular Intervention or Stent	3.4%	1.2 - 7.1%
Elixhauser	Alcohol Dependences	1.3%	0 - 6.5%
	Arrhythmia	3.5%	1.3 - 8.1%
	Coagulopathy	2.0%	0.5 - 4.8%
	Depression	2.3%	0 - 4.8%
	Drug Abuse	0.5%	0 - 1.6%
	Hypothyroid Disease	5.0%	1.9 - 11.9%
	Lymphoma & Myeloma	3.4%	1 - 6.8%
	Neurological Disease	3.7%	1.2 - 11.3%
	Obesity	3.1%	0.4 - 9.7%
	Pulmonary Cardiac Disease	1.7%	0.4 - 4.8%
	Psychiatric Disorder	0.6%	0 - 1.5%
	Peptic Ulcer Disease	3.5%	0.6 - 8.5%
	Valvular Heart Disease	3.7%	1.1 - 10%
Charlson	Connective Tissue Disease	3.4%	0 - 6.1%
	Dementia	0.3%	0 - 1.1%
	Human Immunodeficiency Virus	0.2%	0 - 2.3%
	Paralysis	1.8%	0 - 8.1%
	Pulmonary Disease	11.8%	4.9 - 21%

Overall agreement between UKRR and HES for the ten UKRR comorbid conditions was 92.9% (95,409 out of 102,670 opportunities to agree). The prevalence of UKRR comorbid conditions derived by HES in those with and without UKRR data was not statistically different. Of the conditions not included in the UKRR scheme, the prevalence of lymphoma/myeloma and depression where greater in those without UKRR comorbidity data compared to those with UKRR comorbidity completed (lymphoma/myeloma 3.9% vs 3.0%, P<0.001, depression 2.6% vs 2.1%, P=0.009). In the case of myeloma where survival on dialysis is relatively short patients may die before there is time to return comorbidity through UKRR.

Codes to indicate smoking exist with the ICD10 scheme and are utilised variably within HES, with 6.6% of patients are coded as having tobacco exposure in admissions prior to starting RRT. Prevalence increased to 13.2% if admissions after starting RRT are included. For patients with UKRR comorbidity returned in the incidence of smoking is 15%, with the agreement between this data and smoking ever being identified through HES at 84.9%.

The overall burden of comorbidity and issues with non-constant risk suggesting differing management strategies or coding accuracy will be measured across centres and reported in chapter 5.

Coding depth

Coding depth varied over time and across centres. The mean coding depth for all centres improved from 3.30 in 1996 to 6.11 in 2010, and is plotted in Figure 4-5.

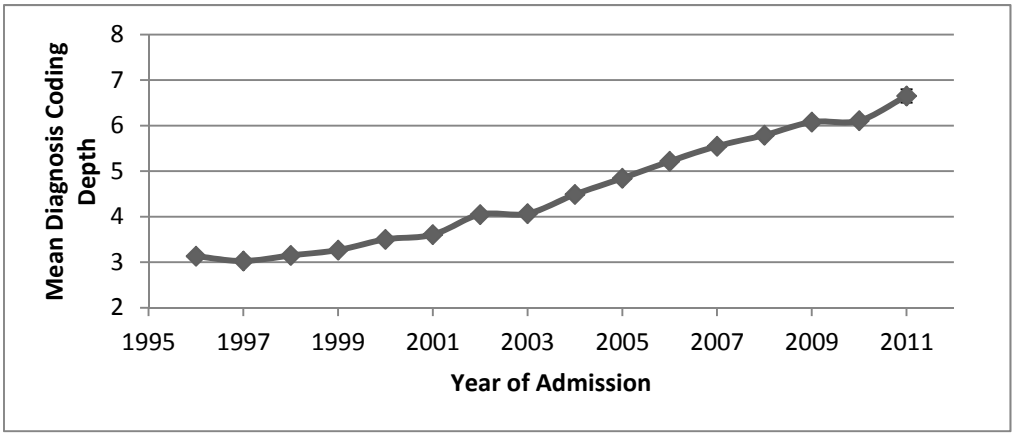


Figure 4-5 : Mean diagnosis code utilisation (depth) according to year of admission for Hospital Episode Statistics data

There was variation in the proportion of ordinary admissions lasting less than one day across centres (range 6.6% – 42.8%), suggesting mis-coding of haemodialysis attendances. Excluding these admissions increased coding depth from 4.81 (95% CI 4.79 – 4.83) codes per

admission to 4.99 (95% CI 4.97 – 5.01) codes per admission, and as a result in the variation in zero length of stay admissions affected centres differently. Two centres with noticeably altered coding depth overall had a high prevalence of zero length of stay (42.8% and 32.4% from left to right in Figure 4-6), again suggesting mis-coding of haemodialysis attendances in these centres.

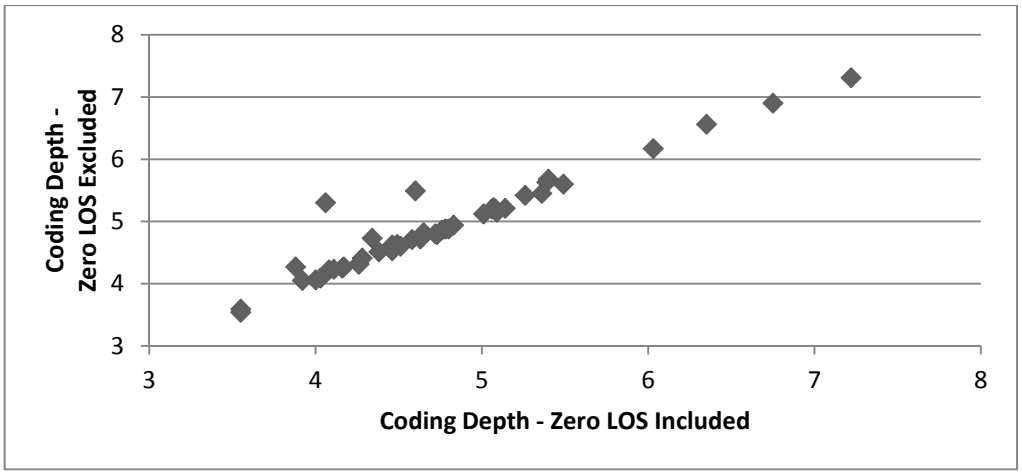


Figure 4-6 : The effect of the exclusion of zero length of stay admissions on centre-specific coding depth, showing two centres suspected of coding haemodialysis attendances as general admissions

Coding depth significantly deepened after starting RRT, increasing from 3.88 to 5.35 codes per admission (difference 1.47, 95% confidence interval 1.44 - 1.48, P<0.001), logically as codes to reflect ERF would now be employed accrued comorbidity on dialysis documented. Centre specific coding depth rates have been published from this work elsewhere (Fotheringham et al. 2012).

Primary renal disease

Prior to enhancement with HES data 73.8% of patients were coded with a primary diagnosis of renal disease (14,417), with 3.4% missing and 22.8% uncertain. In this cohort with primary renal disease completed, 18,066 cases (92.5%) had admissions in the 12 month period around the start of renal replacement therapy, and 48 ICD10 codes were identified as likely candidates to represent primary renal disease. Crosstabulation of the primary renal disease returned to the registry and candidate codes further clarified likely EDTA groupings these codes could belong in, with subsequent groupings specified by UKRR in appendix 4c.

Excluding diabetes as a cause of PRD, 3,299 patients (16.9%) had a HES derived PRD identified using the above method, with 79 cases (0.4%) having multiple PRD groups identified.

Table 4-5 highlights that of the cases identified as having specific primary renal diseases by HES, a proportion of them have other causes of kidney disease defined by UKRR. Excluding UKRR reported cases of PRD due to hypertension and diabetes, and where cases with UKRR primary renal disease complete and a HES PRD identified (n=3179), 75.7% of these cases were identified correctly by HES.

Repeating this process separately with only diabetes, we noted that 3518 of the 3815 patients (92.2%) who had diabetes as a PRD and were admitted in the 12 month period around the start of RRT where identified as diabetic. Repetition of this process for hypertensive nephropathy is not appropriate as many ERF patients will be hypertensive without necessarily having hypertension as their cause of ERF.

Recognising that a 16.9% pick up rate for any PRD is too low to allow HES to be the sole source, the method of using HES derived PRD in cases where the UKRR PRD is missing or absent yielded the results in Table 4-6. As expected there is a reduction in the number of cases coded as missing and uncertain from 5,108 to 4,656, representing overall reduction in these groups from 26.2 to 23.9%. The use of diabetes as a PRD identified a further 800 cases reducing the prevalence of these groups to 19.7%

Centre Specific prevalence of missing and unknown PRD continue to vary following the reduction in these groups with the use of HES data, even with diabetes inferring PRD (Figure 4-7.

Table 4-5 : The proportion of cases providing valid data with agreement between Hospital Episode Statistics and UK Renal Registry data sources for primary renal disease. The cases where both sources agreed are highlighted in bold. Percentages quoted are of the UKRR primary renal disease row.

	HES Primary Renal Disease				
UKRR Primary Renal Disease	**Glomerular**	**Other**	**Polycystic**	**Pyelonephritis**	**Renovascular**
Diabetes	4.30%	11.70%	34.00%	29.80%	20.20%
Hypertension	13.20%	13.20%	34.00%	11.30%	28.30%
Glomerular	**58.60%**	24.20%	10.20%	4.50%	2.50%
Other	1.20%	**80.80%**	7.00%	9.80%	1.20%
Polycystic Disease	0%	0.10%	**99.60%**	0.10%	0.20%
Pyelonephritis	0.80%	2.40%	3.80%	**92.60%**	0.40%
Renovascular	7.80%	13.80%	12.90%	5.20%	**60.30%**

Table 4-6 : Primary renal disease (PRD) prevalence before and after HES augmentation

UKRR PRD Group	Pre HES Augmentation (%)	HES Augmentation, no diabetes (%)	HES Augmentation, diabetes (%)
Missing	3.4	2.8	1.9
Diabetes	20.8	20.8	24.9
Glomerular	10.9	11	11
Hypertension	6	6	6
Other	15	15.8	15.8
Polycystic	6.9	7.7	7.7
Pyelonephritis	7.7	8.1	8.1
Renovascular	6.7	6.8	6.8
Uncertain	22.8	21.1	17.8
Total	100	100	100

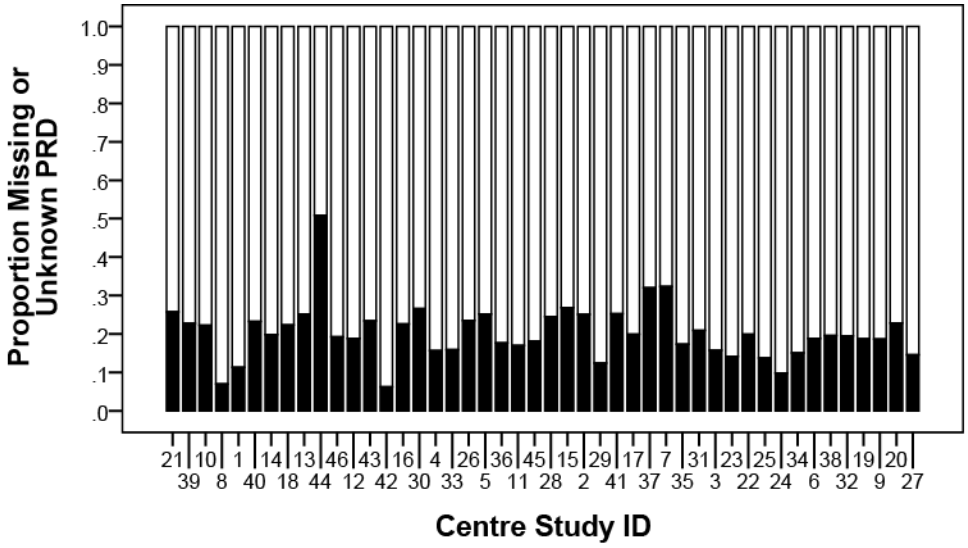


Figure 4-7 : Centre specific variation in patients with "missing" or "unknown" primary renal disease

Date first seen by a nephrologist

Reviewing the proportion of admissions and outpatient attendances coded under nephrology within each centre identifies eight centres which changed their coding practices during the period of study. A visual representation of these centres coding practices and the overall rate of the other centres is shown in Figure 4-8.

If we restrict the cohort to those starting RRT in October 2003 to ensure at least a six month period prior to starting RRT to capture nephrology activity from the introduction of the HES outpatient dataset and exclude centres with changes in coding practice, we found 13,598 patients were suitable for analysis. Using any earlier contact based on HES data to replace date first seen by a nephrologist, 8,231 patients had new dates computed in place of existing UKRR reported dates, including 587 patients in whom the UKRR reported date first seen matched the date of first dialysis. Importantly, 107 patients were documented as having no contact with renal services at any time and 1,251 patients had still had no contact at 30 days from starting RRT.

The proportion of patients referred late as defined as less than 90 days before starting RRT reduced over time, with the sharpest decline seen in the first 12 months of the incident study period (Figure 4-9). Some residual variation in the timeliness of referral persisted following enhancement in the 36 centres appropriate for study (Figure 4-10).

When we compare the date first seen from the HES record compared with the date from the UKRR, two distinct groups emerge (Figure 4-11). One group of patients (group A) have contact with nephrology according to HES very early on after the outpatient dataset is introduced, suggesting they were being seen prior to April 2003. These patients have date first seen from UKRR which is later than that reported from HES, the clustering of which generates a vertical line arising from April 2003 on the X axis. The second group have similar dates from both sources, generating a diagonal line arising from 2003 and terminating at 2007 (Group B).

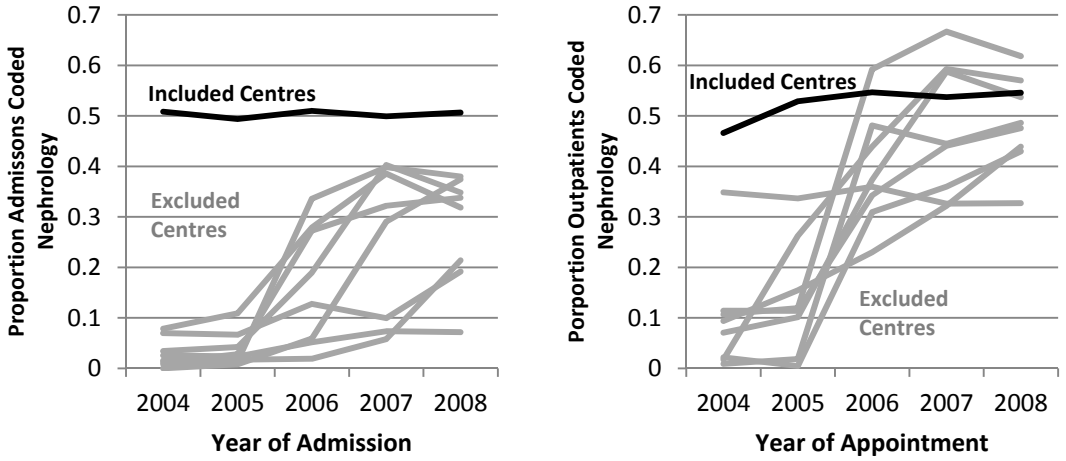


Figure 4-8 : The proportion of admissions (left) and outpatient appointments (right) coded as nephrology over time in centres selected and excluded for "date first seen" analyses

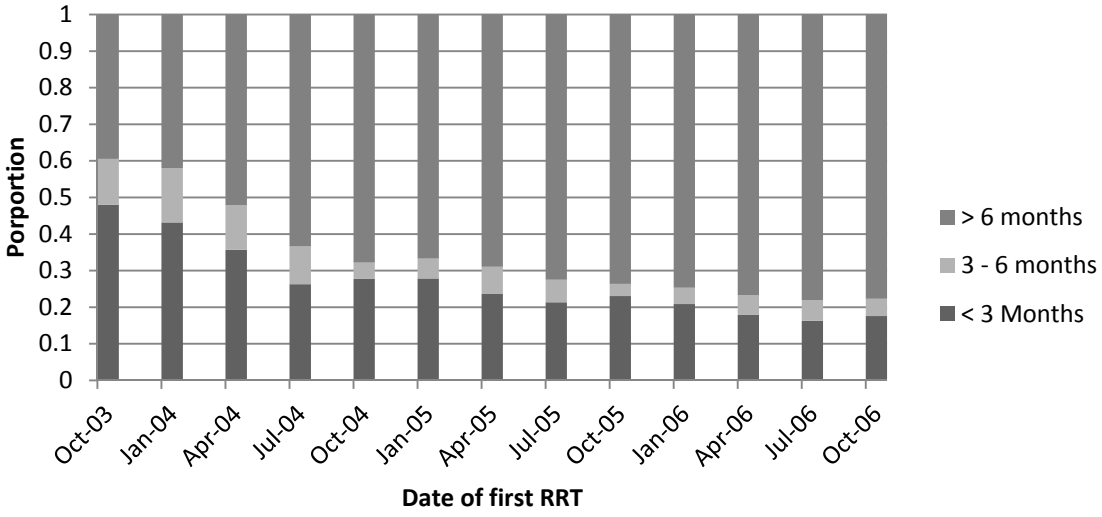


Figure 4-9 : Change in the time from first seen by nephrology to start of RRT over the incident period

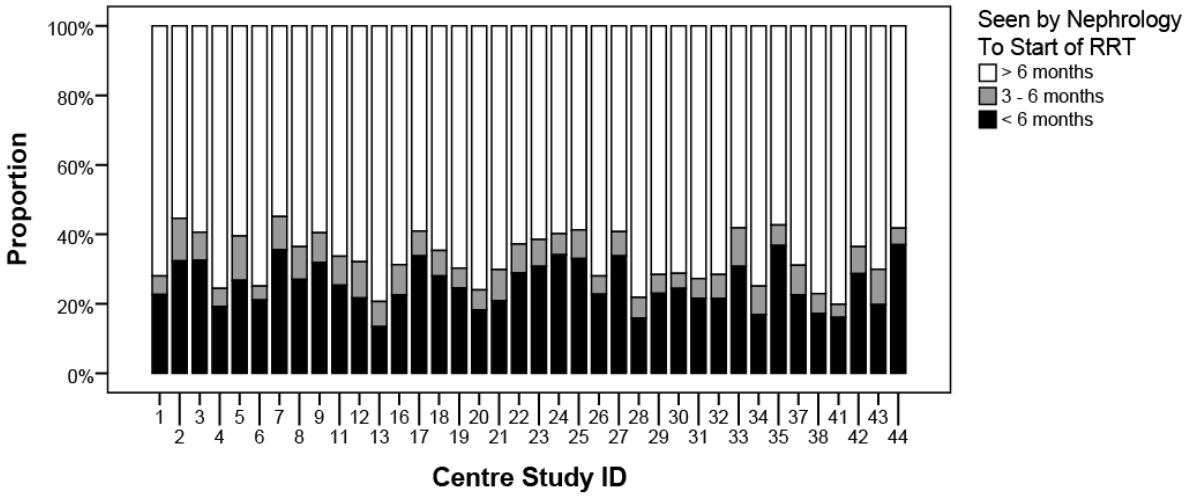


Figure 4-10 : Centre specific variation in time form first seen by nephrology to start of RRT

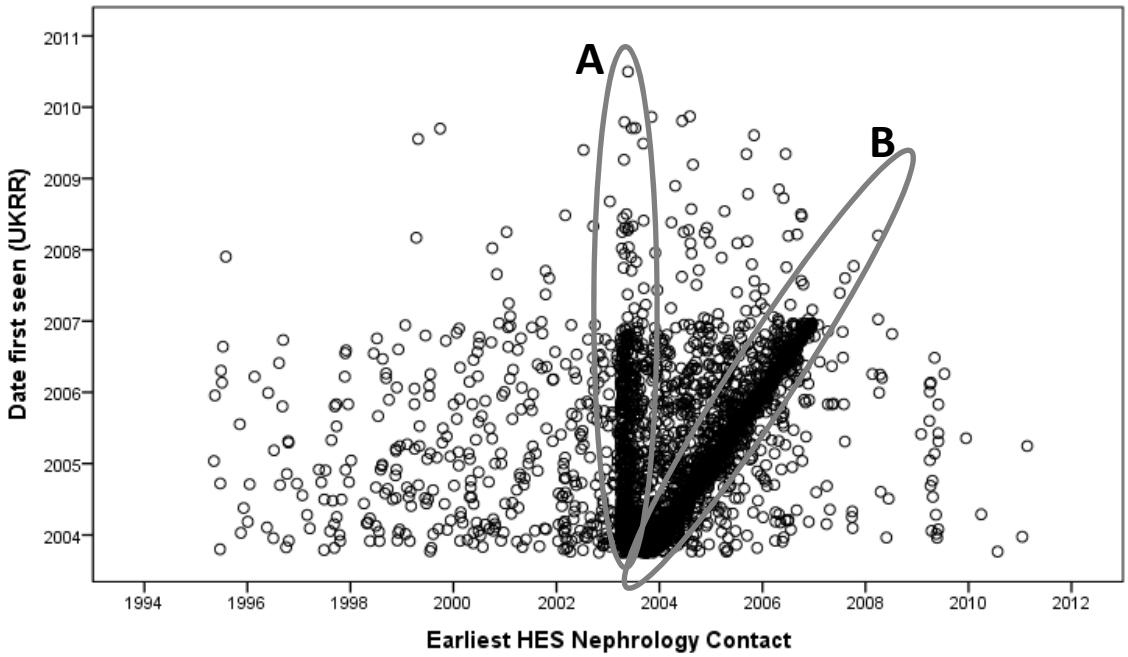


Figure 4-11 : Agreement between data sources for date first seen by nephrology, highlighting a group being identified as been first seen by nephrology around the introduction of the HES outpatient dataset (A) and a group where both sources agree (B).

Of the patients in group B, with dates from both sources within 30 days of each other (n=2121), only 11.6% (246) go on to report UKRR date of first dialyses the same as the date first seen, and could be used as a representative approximation of the proportion of patients who genuinely start dialysis urgently having never seen a nephrologist before.

Within those cases in the group with HES dates first seen soon after the introduction of the HES outpatient dataset defined as with 3 months of April 2003 (n=446, vertical line from the X axis, group A), 38.6% (172 cases) go on to report UKRR date of first dialyses the same as the date first seen. This figure is much higher than the 11.6% who seem to start RRT around the same time as being first seen in those with close agreement (Group B). This suggests that at least two thirds of those identified in group A are due to systematic coding of the date first seen as the date of first dialysis.

Overall the date of first contact using this method differs by more than 30 days from both sources in 2144 of 4265 cases (50.3%).

Renal replacement therapy activity

The date of first dialysis

Based on HES procedure codes a HES derived date of first dialysis could be determined in 14,448 cases starting on dialysis who survived beyond 90 days (76.8%). 3.6% of RRT cases which had a first UKRR modality was a form of dialysis (654 of 18,821) had HES coded dialysis treatment 90 days before the UKRR reported date. 47.2% (8880 cases) had HES coded dialysis within 90 days of the UKRR reported date. The difference in reported dates in patients surviving 90 days or more is visualised in Figure 4-12, with the omission of 4,373 of cases (23.2%) where dialysis was the first modality and no HES dialysis activity was identified. Pre-emptive transplantation is dealt with separately.

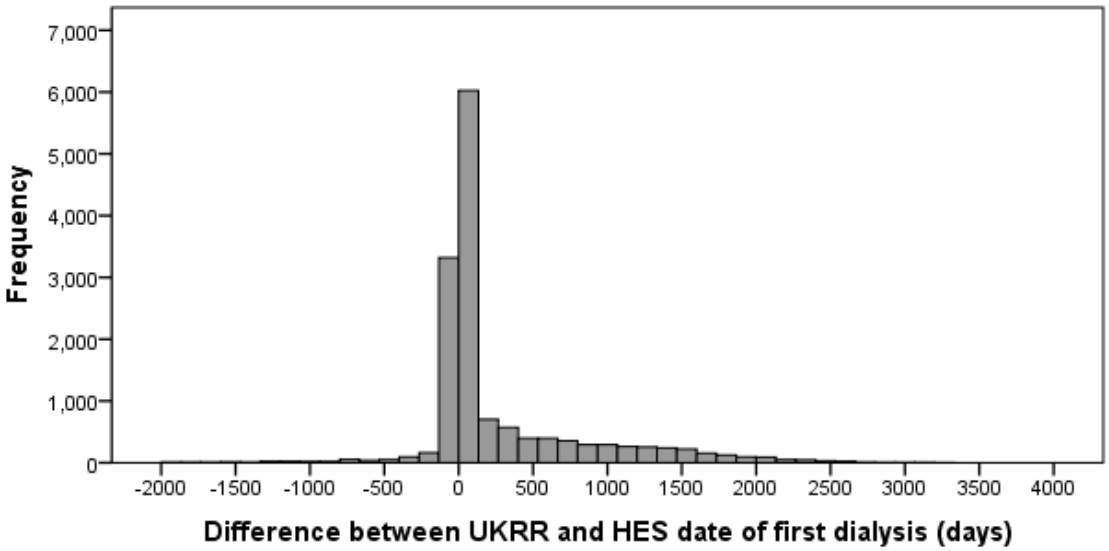


Figure 4-12 : Differences between sources for date of first dialysis

Patients starting on haemodialysis were detected earlier by HES than those starting on peritoneal dialysis. This is shown in **Table 4-7**, where by 90 days 57.7% of patients starting on haemodialysis have had haemodialysis procedural information identified, compared to 29.9% of peritoneal dialysis patients. Of the patients who were recorded as starting on haemodialysis, 5.8% had coded exposure to PD prior to this.

Table 4-7 : The detection of first dialysis activity by HES compared to UKRR

HES vs UKRR Date of first dialysis	> 90 days before	90 – 30 days before	Within 30 days	30 – 90 days beyond	Ever
Haemodialysis	3.8%	3.3% (7.1%)	47.4% (54.5%)	3.2% (57.7%)	(80.1%)
Peritoneal Dialysis	2.6%	2.7% (5.4%)	20.8% (26.2%)	3.7% (29.9%)	(66.8%)

Cumulative in brackets

Haemodialysis

Within the UKRR timeline 44,969 patient-years of haemodialysis were recorded. Using the 1,934,178 attendances for haemodialysis in the identified cohort, this equates to 0.83 attendances for dialysis per week. Once time in hospital is excluded the attendance rate overall is 0.88 per week.

The ratio of outpatient elective haemodialysis attendance to weeks dialysed varied across renal centres, but within centre the ratio was relatively constant over time. Table 4-8 reports the ratios of haemodialysis attendances to weeks available to receive HD of haemodialysis patients between 2002 and 2009, organised by coded location. The variation in these ratios highlights centres appropriate for analysis on haemodialysis attendance, frequency and pattern. Given the three times a week nature of most haemodialysis, the ratio of haemodialysis attendances to haemodialysis weeks should exceed two allowing for time admitted.

Peritoneal dialysis

For first treatments with peritoneal dialysis in the analysis cohort (n=6,259), 5,351 cases (85.5%) had a peritoneal dialysis catheter inserted according to HES in the 12 months prior to their first exposure according to the UKRR treatment timeline (mean 31 days, standard deviation 38.1 days before first exposure, median 21 days). The implications of catheter insertion timing and centre specific practice variation will be explored in chapter 8.

Transplantation

Limiting the analysis to patients identified in the cohort identified in Figure 4-1 and first transplants, we identify 4,642 first transplants as coded by HES, and 4,945 first transplants identified by the UKRR timeline, with 4,591 cases existing in both sources. Limiting analysis to those cases within 90 days of each other we are left with 4517 cases for analysis, 91.3% of cases identified by UKRR alone (Figure 4-13)

Within the cohort of cases where sources agreed with 90 days (n=4,517), comparing the HES procedure coded date of transplant to the UKRR reported date of transplant yielded an agreement of 81.5% (3682 cases), climbing to 95.9% (4333 cases) for sources within a day of each other. Of the cases where UKRR indicated that a transplant had occurred but there was no corresponding HES transplant procedure (354 cases), 37% were in hospital at the time (130 cases).

Table 4-9 describes the improvements in completion rates for donor type observed using combined sources.

Table 4-8 : Centre specific ratio of haemodialysis attendance coded by HES to treatment weeks recorded by UKRR

	Ratio of Haemodialysis Attendances to Weeks Haemodialysed, by Location			
Parent Renal Centre	**Unknown**	**Home**	**Hospital**	**Satellite**
Basildon	1.74	NA	2.76	NA
Birmingham - Heartlands	0.35	0.05	2.68	2.91
Birmingham - QEH	0.12	0.16	2.49	0.09
Bradford	0.00	NA	0.02	0.00
Brighton	0.00	0.00	0.01	0.37
Bristol	1.20	0.06	2.09	2.52
Cambridge	1.40	0.03	2.28	2.51
Canterbury	0.13	NA	0.33	0.00
Carlisle	0.50	2.61	2.65	2.67
Carshalton	0.57	0.00	0.38	0.34
Chelmsford	0.16	NA	0.01	NA
Colchester	N/A	NA	0.00	NA
Coventry	0.73	0.00	0.01	NA
Derby	0.00	0.00	0.00	NA
Doncaster	0.02	NA	0.06	NA
Dorchester	0.58	NA	0.23	0.09
Dudley	1.54	0.01	2.61	0.03
Exeter	0.10	0.08	1.99	0.10
Gloucester	2.14	NA	2.79	NA
Hull	0.01	0.00	0.00	0.00
Ipswich	0.31	0.00	0.00	0.00
Leeds	0.01	0.00	0.00	0.00
Leicester	0.02	0.00	0.00	0.00
Liverpool - Aintree	1.89	0.07	2.46	2.43
Liverpool - RI	0.11	0.05	0.68	0.09
London - Barts	0.01	NA	0.00	0.00
London - Guys	0.13	0.00	2.00	1.06
London - Kings	0.08	0.00	0.39	0.03
London - RFree	0.64	0.09	2.51	2.72
London - St G	2.46	NA	2.25	0.95
London - West	0.01	0.00	0.01	0.00
Manchester	2.97	0.00	2.72	2.76
Middlesbrough	0.02	0.00	0.00	0.00
Newcastle-upon-Tyne	0.00	NA	0.00	NA
Norwich	2.27	0.00	2.76	2.75
Nottingham	1.08	0.01	0.01	0.00
Oxford	0.49	0.55	1.61	0.94
Plymouth	1.39	0.00	0.12	0.00
Portsmouth	0.00	0.00	0.34	0.01
Preston	0.26	0.10	2.28	1.51
Reading	0.33	NA	2.61	2.93
Salford	2.08	1.11	2.58	2.80
Sheffield	0.23	0.16	2.81	2.87
Shrewsbury	1.47	0.00	0.12	0.93
Southend-on-Sea	0.11	NA	0.00	NA
Stevenage	0.01	NA	0.00	0.00
Stoke-on-Trent	1.40	NA	2.76	2.66
Sunderland	0.00	0.00	0.00	0.01
Truro	1.19	0.17	2.55	1.32
Wirral	1.02	0.04	0.06	1.71
Wolverhampton	0.85	0.77	2.35	0.14
York	0.00	0.00	0.00	0.00
Overall	**0.22**	**0.14**	**1.05**	**0.75**

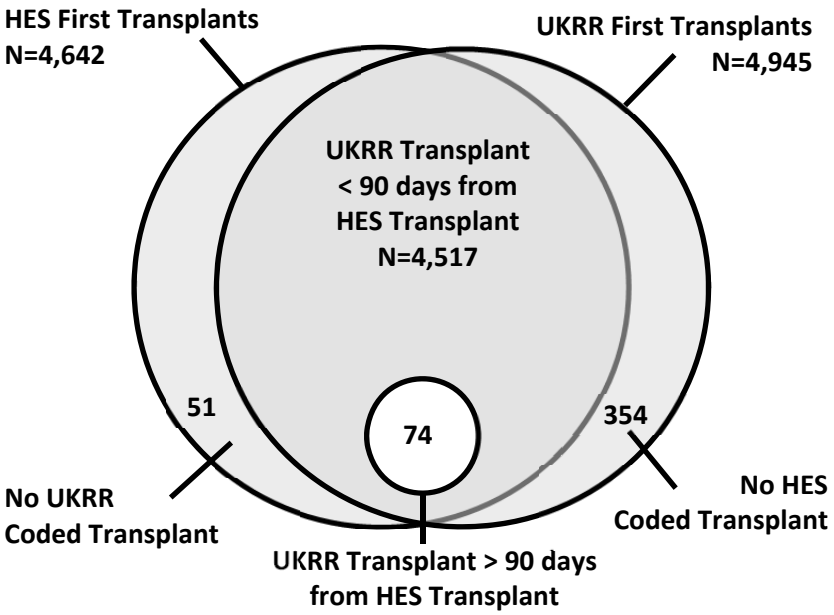


Figure 4-13 : Venn diagram reporting agreement between data sources for date of first kidney transplant

Table 4-9 : Agreements between data sources on donor type for first transplant

	HES Donor Type					
UKRR Donor Type	**Unknown**	**Deceased Heart Beating**	**Deceased Non-heart Beating**	**Deceased Donor (either)**	**Living Donor**	**Total**
Unknown	*13*	125	157	381	305	*981*
Deceased Donor (HB or NHB)	80	248	199	1,591	**316**	2,434
Living Donor	3	0	0	**11**	876	890
Deceased Non-heart Beating	2	**1**	147	62	0	212
Total	*98*	374	503	2,045	1497	4,517

Disagreements in bold, underlined only one source

Cases in underlined italics represent an additional 1,053 cases where donor type was identified but where it was unknown using the analysis of only one data source. Cases where the sources disagreed accounted for 328 transplants, highlighted in bold (7.3%). We can use the data on whether an admission was elective or emergency to determine if a case was a live donor or deceased donor respectively in situations of disagreement. This identified that 247 of the 316 cases where HES derived live donors and UKRR coded deceased were coded as elective, arguing that HES may have been correct in these cases. However, only 5 out of 11 cases where HES suggested a deceased donor were coded as emergency when UKRR suggested a live donor.

Date of Death

For the 21,271 cases classed as appropriate for on-going analysis in this study, the number of deaths identified by each source of the four sources is depicted in Table 4-10, and stratified by year.

Similar numbers are observed across the three inclusive sources of UKRR, UKRR Traced via NHS and ONS. Overall, 10,775 unique deaths were identified before 31/12/2009, accounting for 50.7% of the analysis cohort. For the entire period, Figure 4-14 below shows how these sources correlate with regard to identifying a patient has died at any time-point.

Table 4-10 : Numbers of deaths each year according to data source. Note HES only covers deaths in inpatients (IP)

	Date of Death Source			
Year	**UKRR**	**UKRR Traced NHS**	**ONS**	**HES IP**
2002	431	424	424	335
2003	941	929	937	739
2004	1,250	1,262	1,253	932
2005	1,614	1,676	1,681	1,232
2006	1,865	1,936	1,925	1,395
2007	1,646	1,738	1,732	1,247
2008	1,403	1,456	1,444	989
2009	1,079	1,146	1,130	779
Overall 2002 - 2009	10,229	10,567	10,526	7,648

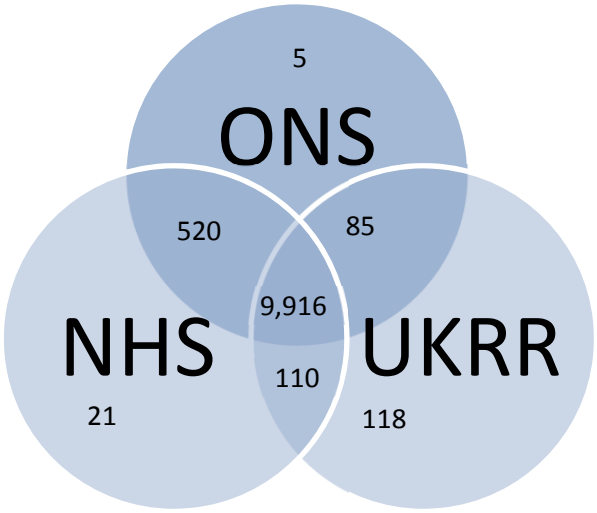


Figure 4-14 : Venn diagram depicting agreement between sources for death occurring

This figure would suggest that of the total unique deaths, beyond the information which the UKRR already had (NHS traced and their own reported), only an additional five were identified by linkage to ONS. Discrepancies between UKRR and Traced UKRR deaths are likely to represent the data loaded into the UKRR database at the time.

There was near perfect agreement between ONS and UKRR Traced dates where both sources had dates reported (10,431 of 10,436 cases with a date from both sources before 2010, 99.9% agreement, all differences less than four days). Agreement between UKRR data and the other two sources was less accurate. NHS traced date of death and UKRR reported date of death agreed 84.6% of the time; however sources were within 2 days of each other in 9,607 out of 10,026 cases (95.8%). Further widening this to 30 days improved accuracy to 9,931 of 10,026 cases (99.1%). Given the close agreement between NHS traced and ONS traced dates of death, analyses comparing ONS and UKRR data were similar. Importantly, there were discrepancies of greater than 3 months between the UKRR data and other sources in 47 cases (0.5%).

Confirming the validity of derived date of death from all sources, 46 patients were identified as having HES inpatient activity after the combined date of death. Thirty of these cases had dates of death agreeing across all three sources, suggesting that the HES attendance may be erroneous. Sixteen cases had HES activity after HES itself suggested the patient had died with a preceding admission with a *DISMETH* coded as 4 (discharged dead). In eleven cases the HES activity was electively planned haemodialysis attendance, suggesting an automated system for reporting dialysis activity for commissioning activity.

Summary of variable completeness and source agreement

Data completeness has generally been improved by the linkage of these two datasets. In situations where significant improvements have been observed, the capacity to change summary statistics (e.g. the proportion with diabetes or late referral) exists. The following table summarises improvements in data completeness, source agreement and any notable changes in summary statistics.

Table 4-11 : Summary of completeness and agreement between HES and UKRR data sources

Variable	Completeness or Improvement	Comments
Comorbidity	Completeness 53.7 to 97.6% Agreement 92.9%	Similar distributions of individual conditions with the exception of lymphoma / myeloma (3.9% vs 3/0%, P<0.001) and depression (2.6% vs 2.1%, P=0.009)
Ethnicity	Completeness 85.5 to 97.1% Agreement 92.8%	Largest proportion of missing data was observed in patients of White ethnicity, with their prevalence increasing from 70% to 80.4%.
Socioeconomic status	Completeness 78.8 to 98.6% Agreement 97.2%	Mean rank SES differed by 0.6% of the range, 10% had differing SES ranks provided by multiple admissions from HES
Primary Renal Disease	Completeness 73.8 to 80.3% Agreement 75.7%	Excellent agreement in PKD patients identified by UKRR, however low agreement in renovascular, and a number of HES polycystic cases were identified in other UKRR PRD groups
Transplantation and transplant type	91.3% UKRR transplants coded by HES Transplant type improved from 78.3 to 92.4%. Type agreement 92.7%	Missing rate similar to other HES procedure studies. 37% of those not coded by HES were in hospital at time of UKRR reported transplant Disagreement between live donor recipients in 11.5%, of which 78% where elective procedures.
Haemodialysis attendance	29.3% of dialysis time reflected by HES coded HD	Strong centre effect with 21 centres representing 98% of cases suitable for analysis.
Peritoneal dialysis catheter insertion	85.5% of PD catheters coded in 12 months before RRT start	PD catheter exposure without PD reported in chapter 6.
Date first seen	60% of suitable patients had earlier or new date first seen determined	Agreement poor at 50%. Using HES, number of patients who start dialysis acutely without having previously seen a nephrologist is 11.6%

Discussion

An essential function of any chronic disease registry is to accurately compare across provider centres hard outcomes such as survival and hospitalisation. Patients maintained on RRT have high morbidity and mortality and for a valid comparison we need to make adequate adjustment particularly for comorbid diseases, ethnicity and socioeconomic factors. In response to the problem of missing data and the absence of morbidity and hospitalisation data within the UK Renal Registry dataset, we linked 21,633 UKRR incident patients to HES data. Subsequent analysis was possible in 98.3% of patients. It enabled significant improvements in Ethnicity (85.5% to 97.1%), Socioeconomic status (78.8% to 96.8%) and comorbidity (53.7% to 97.6%), but yielded small amounts of additional information on primary renal disease (73.8% to 76.1%) and renal replacement activity. Disagreement between sources existed, in some cases in 20% of returns (socioeconomic status).

Our analysis to date demonstrates a high rate of linkage, with only 149 patients (0.07 percent) resident in England having no linked HES data. There are theoretical reasons why an English RRT patient may have no HES data but the employed linkage method is strongest when NHS number is complete, and ensuring this would facilitate future linkages. Beyond the linkage validity, routine data has limitations. Issues relating to incorrect data may persist and even be masked by the use of HES data. Morbid or comorbid conditions cannot be classed as missing in the HES dataset, but simply that there are no comorbid conditions, unlike the UKRR dataset. Outpatient haemodialysis attendance, date first seen by a nephrologist and primary renal disease are only appropriate for certain centres, and continue to limit the inclusiveness of some measures in reporting centre-specific measures of performance. Differences in how NHS trusts code admissions may hamper cause specific admission reporting. Since these data were collected guidance has been issued on how activity in renal centres should be captured with HES (NHS Kidney Care 2011). Standardisation and consensus are needed to allow the greatest utility from a HES-UKRR combined dataset.

Coding practice has been shown elsewhere to have improved over the period in question at a similar rate(Robinson 2010). Coding depth is around two codes greater for RRT patients than the national average, and it is no surprise that there are centres who code deeper than others.

There is clearly scope for further improvement in HES coding, both in the routine documentation of primary renal disease as part of admissions, and the agreement across admissions with regard to ethnicity. The proportion of cases with unknown primary renal disease following enhancement with HES (17.8% including diabetes as a PRD) exceeds what is

formally reported in the USRDS (3.7%)(U S Renal Data System 2011) and ANZDATA (7%)(ERA-EDTA Registry 2012). The limited window adopted to identify primary renal disease is designed to protect against the detection of new renal disease in transplanted individuals. Despite this, 34% of cases labelled hypertensive or diabetic were identified as polycystic by HES, revealing potential inaccuracies in UKRR. The change in ethnicity specification with regard to mixed race may be a major factor in disagreement between sources and across time, and the variable return rate for ethnicity across centres may confound assumptions regarding the reporting completeness within ethnic groups given our increased understanding of the mix in ethnicity across England.

The accuracy of HES can again be called into question based on the coding of haemodialysis attendances and based on the variation in zero length of stay rates and attendances/week ratio across centres, and agreement between sources with regard to transplantation activity. Systematic reviews on HES procedural coding activity summarise that in 2010 HES was 90% accurate (Burns et al. 2012), which may explain the nine percent of cases where transplantation codes were not identified. The proportion of patients who were admitted at the time UKRR reports them as being transplanted but who have no transplant coded argue for HES undercoding in this 37% of patients. Remaining differences could be errors in either source, and additional understanding could be obtained with linkage to NHS Blood and Transplant data.

Potential areas of improvement aside the high rates of completeness achieved through linkage are important, both for some standards posed by other disease registries for data items (discussed more comprehensively in chapter 9) and what a high level of completeness enables. Generally, coverage and completeness exceeding 95% meets the standards set by the North American Association of Central Cancer Registries for case completeness(Hofferkamp 2008). Having met this standard it would seem reasonable to begin the process of reporting performance for renal centres adjusted for the multiple variables listed above.

Chapter 5 *Mortality on Renal Replacement Therapy*

Introduction

The cornerstone of centre specific reporting is uniform data quality and completeness, and variation in these has prevented the UKRR from generating comprehensively adjusted and inclusive centre specific performance indicators. The UKRR has previously shown variation in incident survival across renal centres (Steenkamp et al. 2013) and other authors have demonstrated that case-mix influences survival on RRT for the individual(Liu et al. 2009), arguing for case-mix adjustment when comparing centres. Reporting of outcomes without adequate adjustment for case mix may increase or decrease the apparent variation in performance between centres, and may result in providers being inappropriately labelled as delivering poor care. The combined nature of the UKRR-HES dataset has the potential to enable multivariate adjustment when comparing centre specific survival for the first time.

Hospital standardised mortality ratios published by agencies such as Dr Foster and The NHS Information Centre are established methods of comparing hospital performance in the UK. In addition, they allow insight into subgroups of conditions that may influence overall outcomes. Paired with incident survival they may represent a valuable tool to understand the factors behind centre specific location and rate of death.

Aims and Objectives

- To determine the independent influence of comorbid conditions derived by HES on survival to three years, accounting for other demographical characteristics.
- To use the hazard for death for individual comorbid conditions to create a comorbid index or score for ease of comparison of comorbid burden across patient groups and centres.
- To use comorbid conditions along with other demography to determine centre specific adjusted survival to three years.
- To determine the consistency of risk associated with individual comorbid conditions and comorbid scores across centres.
- To identify the location of death for patients and compare the variation of this across centres.
- To derive hospital standardised mortality ratios for appropriate renal replacement therapy patients and compares these centre measures with incident survival measures.

Analysis specific methods

Cohort

For incident survival, only patients with complete data for age, sex, ethnicity, socioeconomic status and comorbidity who survived beyond 90 days from the date of first RRT were analysed. The 90 day limit was chosen because of issues with variable centre reporting of patients dying within 90 days(Castledine et al. 2011). In addition patients must meet the HES analysis criteria specified in chapter 3.

Hospital standardised mortality ratios (HSMRs) were generated using all admitted patients who had survived 90 days. Although crude mortality rates per admission were determined for transplant recipients, the rate of death was so low that they were excluded.

Patients and their associated admissions in which socioeconomic status and ethnicity could not be derived were excluded from both analyses. Although this differs from some current measures of hospital performance(Campbell et al. 2012), the numbers that necessitated exclusion were sufficiently small (guideline less than five percent) so that their exclusion should make no difference.

Variables

The fact that we had no missing values meant we did not need a separate 'missing' category.

Comorbid conditions were determined at the start of renal replacement therapy for the incident cohort from admissions prior the date of first dialysis as described in chapter 4. For hospital admissions the same process was used, however the admissions used to inform comorbidity were extended beyond the date of first dialysis and included the admission in question. Modality at the time of admission was determined from the UKRR timeline. For hospital associated mortality, location of death was categorised into three groups:

- Out of hospital with no contact within 30 days,
- Out of hospital having had contact within 30 days (inpatient or outpatient),
- In hospital; an acute admitting NHS trust (as defined by the NHS information centre and Dr Foster acute trusts definition).

Hospital associated mortality in hospital or up to 30 days from discharge was assigned to the last admitting acute trust. Due to issues with the quality of information on late referral, only the 36 centres identified in chapter 4 were used to explore the influence of late referral.

Reason for admission was initially determined using the Clinical Classification Scheme. Recognising that a high proportion of admissions were assigned chronic kidney disease or codes pertaining to primary renal disease for the primary diagnosis which do not necessarily infer the underlying reason for admission but rather are the most financially beneficial, additional regrouping based on Health Resource Groups (HRGs) was performed. Informed by the combination of diagnosis and procedure codes, HRGs can group according to whether a complication has occurred. The development of a complication may be related to the hospital or centre's underlying performance, and would contribute to the risk of death. Therefore adjusting for a complication may distort the measurement of the true performance, and to prevent this similar reasons for admission with and without complications were grouped. The grouping algorithm is described in appendix 5a.

Statistical methods

Survival was modelled using Cox proportional hazards in R(R Development Core Team). Although the UKRR has historically not censored for transplantation in order to ensure a fair comparison between centres (Steenkamp et al. 2012), the impact of censoring and its impact on centre performance was explored.

The variables age, gender, ethnicity, socioeconomic status and comorbid conditions of greater than two percent prevalence(listed in chapter 4) were added to determine an appropriate model, with statistically significant variables being retained. To determine renal centre specific survival for a model, patients were standardised to be white, male, of the most deprived socioeconomic group, have started RRT in 2002, and with no comorbidities present. The underlying baseline survival of the cohort with specific proportional hazards of a standardised patient with the above characteristics and centre in question was used to determine the proportion of standard patients alive at three years. Accelerated failure time models were also tested to see if these fitted the data better, with outputs from the different models compared with a Bland-Altman plot. The basic conclusions were unaltered between these two and the results from these are not presented. The Interactions between age and diabetes(Nitsch et al. 2007), age and ethnicity (Yan et al. 2013), diabetes and cardiovascular disease and ethnicity and diabetes was explored with interaction terms where age was categorised into <40 years, 40 – 65 years and > 65 years at the start of RRT. Testing for the constant risk fallacy (Nicholl 2007) was performed by fitting an interaction between centre and the candidate comorbid conditions, in addition to age, ethnicity, socioeconomic status and year of start. If the interaction term was significant, it suggested the mortality risk of a comorbid condition was not constant across all renal centres. Model performance was

assessed using the area under a receiver operator curve (comparable to the c-statistic in other models) comparing observed mortality at three years to the hazard predicted by the model for each individual patient, and R squared statistic with confidence intervals determined using 1,000 bootstraps. The mean comorbid score was compared with the independent T test.

To index the overall comorbid burden per patient to allow a simple comparison between centres, weights for the presence of individual conditions were determined from a Cox proportional hazards model factoring age, sex and the presence or absence of statistically significant candidate comorbidities predicting incident survival. Multivariate hazard ratios for comorbid conditions were converted into scores as described by(Quan et al. 2011). The scores were summed to create an overall score using the following bandings and weights: hazard 1.2 - <1.5 : 1, ≥1.5 - <2.5 : 2, 2.5 - <3.5 : 3, ≥3.5 - <4.5 : 4. Conditions with a hazard of less than 1.2 were assigned zero. Due to apparent variation in the difference in comorbid burden derived from these weights between dialysis modalities when comparing centres suggesting varying attitudes to modality selection, modality was not included in incident survival analysis.

Mortality at 30 days is a binary outcome (0 or 1), and is traditionally modelled using logistic regression when censoring is not an issue (Shahian et al. 2010). Within existing hospital mortality measures, two different ways of employing logistic regression predominate:

One model method: One model is run on the entire dataset, with all explanatory factors included as variables within this model. This would include diagnosis on admission as a categorical variable. The advantage of this method is that it uses all the data to get high precision estimates of the effect of the explanatory variables, statistical programming may be easier and the model performance easier to assess as it will be intuitively reported by the statistical software. Employing this method results in fixing the influence of the explanatory variables for all scenarios (for instance age would have the same influence irrespective of different reasons for admission). This can be overcome by employing interaction terms which would allow the influence of a variable to change according to the presence of another. All the data needs to be stored and analysed within the memory of the statistics package which can present problems.

Method per diagnostic group: A logistic regression model is run the data for each diagnostic group or reason for admission. This means that for data with 23 reasons for admission, 23 models will be run with the coefficients varying for each explanatory variable for each group of diagnoses. Predicted survival for all patients needs to then be calculated and the results combined. Allowing these coefficients to vary could enhance the overall predictive power of the combination of models, but has a risk of overfitting of the data in diagnosis

groups with small numbers of patients. Combining the predictions of the individual models can be challenging, and then some form of model fit needs to be derived.

Due to the number of admissions in the analysis dataset, grouping by CCS diagnostic group as per other performance indicators (Aylin et al. 2010; Campbell et al. 2012) would mean small numbers of admissions per group. Grouping across several diagnostic groups allows adequate numbers of admissions, but leads to more heterogeneous diagnoses within each group. The Dutch mortality indicator includes the CCS group specific 30 day mortality rate as a variable in diagnostic groups where multiple CCS groups exist(Israëls et al.). This means that for a given CCS diagnosis the 30 days mortality is calculated based on all cases with this diagnosis and then added to individual records with this diagnosis so it can be included as a variable alongside additional demographic variables such as age and ethnicity in subsequent analyses.

As renal centres vary in the number of incident patients they take on across England and the number of patients they admit, a funnel plot was used to determine whether a centre was deemed to have better or worse survival than the average. For incident survival, the proportion of patients alive at three years derived from the Cox proportional hazards model for a centre was plotted against the size of the centre. The outlier limits of 95% and 99.8% were derived using the binomial distribution, with centre outlier status explored on the funnel plot with the addition of individual variables (Spiegelhalter 2005). For hospital associated mortality, the ratio of the sum of observed deaths at 30 days post-discharge to expected deaths calculated from a logistic regression for each centre was plotted against the sum of the expected deaths. The 95% and 99.8% limits were derived using a Poisson distribution for the observed deaths. This ratio was plotted on a funnel plot drawn using the Poisson distribution.

Results

Adjusted incident patients survival

Cohort, unadjusted survival and potential censoring events

Between 2002 and 2006 in England 19,585 patients survived to 90 days of which 18,798 (96.2%) had admission HES data prior to the start of RRT and no missing data for ethnicity and socioeconomic status following dataset combination. The distributions are given in Figure 5-1.

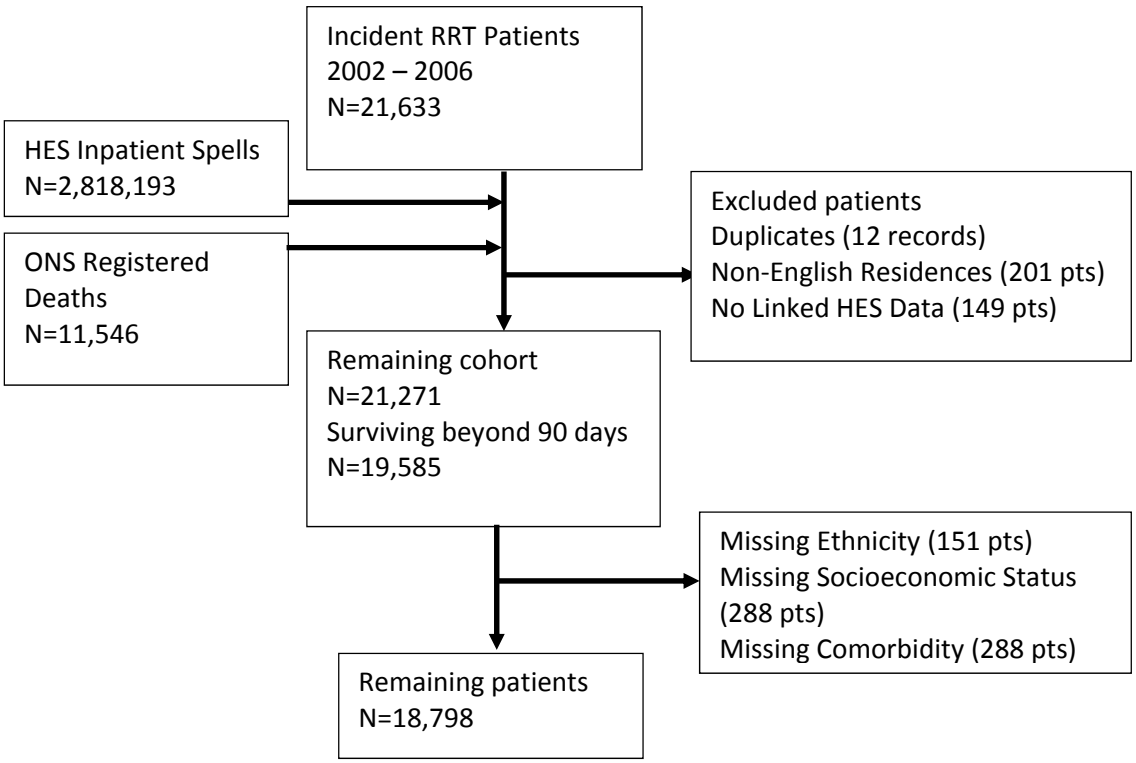


Figure 5-1 : CONSORT Diagram of patients included in incident survival analysis

Survival of this cohort was 68% to three years. 6,292 patients (33.5%) were transplanted during the three year follow-up period used to assess incident survival. Transfers between renal units affected 11.1% of patients, although excluding transfers for transplantation this number reduced to 4.4%.

Location of death

Of the 6,021 patients who died, 65% died in an acute admitting hospital, in which renal centres can reside. Deaths outside of hospital having been admitted under an acute provider in the preceding 30 days accounted for 14.2%, with 20.8% died without having had a hospital admission in the last 30 days. There was centre variation in the proportion of patients within these groups, with six centres with higher and three centres with lower than expected proportions of death in hospital as demonstrated by the funnel plot in Figure 5-2.

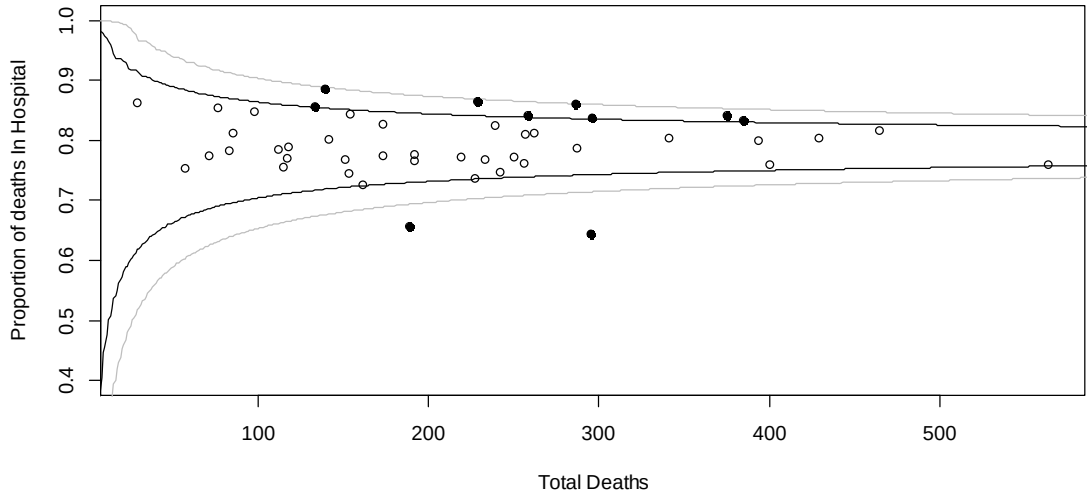


Figure 5-2 : Funnel plot of the proportion of patients dying in acute admitting trusts by parent renal centre

Factors contributing to the mortality of incident patients

Demographic variables included in analyses for the patient cohort are shown in Table 5-1, along with the range of centre prevalence's and number of outlying centres for prevalence of individual conditions. The proportion surviving at three years adjusted to age 65 was 74.5% (95% CI 73.7 – 75.4%) in those with UKRR comorbidity completed and 64.3% (95% CI 63.2 – 65.3%) in those with UKRR comorbidity missing. A number of centres are shown to have greater or fewer than average prevalence for individual conditions. The conditions with the greatest variability across centres are diabetes (23.9 – 45.2%), stroke (3.2 – 16.1%), and heart failure (7.8 – 25.0%) suggesting these may be important to adjust for. Variation in ethnicity according to centre and it's visualisation on catchment area are illustrated in Chapter 4.

Table 5-1 : Demographics of 18,798 patients included in incident survival analysis, plus centre specific characteristics

	Prevalence (%)	Centre Specific Prevalence Range (%)	Outliers (centres high/centres low, out of 46)
Age (mean, range)	60.1 (18 - 94)	-	-
Sex (female)	37.2	-	-
Race		-	-
White	81.4	-	-
Black	5.6	-	-
South Asian	6.5	-	-
Other	6.5	-	-
Comorbid Conditions			
No comorbid conditions	39.2		
COPD	5.2	1.6 – 12.9	5 / 7
Arrhythmia	3.6	1.3 – 8.1	3 / 2
Heart Failure	14.9	7.8 – 25.0	4 / 5
CABG	4.9	0.9 – 9.8	5 / 4
Depression	2.4	0 – 4.8	1 / 1
Stroke	7.7	3.2 – 16.1	5 / 6
Myocardial Infarction	11.9	6.8 – 19.4	5 / 4
Lymphoma	3.4	1.0 – 6.8	2 / 1
Neurological Disease	3.8	1.2 – 11.3	3 / 3
Vascular Procedure	3.5	1.2 – 7.1	3 / 4
Valvular Heart Disease	3.7	1.1 – 10.0	5 / 5
Cancer	6.8	4.5 – 14.5	2 / 2
Connective Tissue Disease	3.4	0 – 6.1	3 / 1
Peptic Ulcer Disease	4.7	1.7 – 8.5	6 / 2
Claudication	7.1	2.5 – 14.5	7 / 6
Diabetes	31.6	23.9 – 45.2	7 / 5

COPD – Chronic Obstructive Pulmonary Disease, CABG – Coronary Artery Bypass Graft

The influence of patient level factors on incident survival as analysed using a cox-proportional hazards model are detailed in Table 5-2.

Table 5-2 : Univariate and multivariate hazards associated with mortality at three years from starting renal replacement therapy, plus comorbid score derived from hazard ratio.

Variable		Hazard Ratio for Death (Univariate) (95% CI)	Hazard Ratio for Death (Adjusted) (95% CI)	Comorbid Score
Age (per decade)		1.27 (1.25 - 1.28)	1.23 (1.22 - 1.24)	
Sex (female)		0.98 (0.93 - 1.03)	1.05 (1.00 - 1.11)	
Race	White	1 (ref)	1 (ref)	
	Black	0.44 (0.38 - 0.51)	0.55 (0.47 - 0.64)	
	South Asian	0.67 (0.59 - 0.75)	0.78 (0.69 - 0.88)	
	Other	0.52 (0.46 - 0.59)	0.65 (0.57 - 0.74)	
Socioeconomic Status				
1 - Most Deprived		1 (ref)	1 (ref)	
2		1.0 (0.92 - 1.08)	0.95 (0.88 - 1.03)	
3		1 .0 (0.92 - 1.09)	0.88 (0.81 - 0.95)	
4		1.12 (1.03 - 1.21)	0.92 (0.85 - 1)	
5 - Least Deprived		1.03 (0.95 - 1.12)	0.85 (0.78 - 0.93)	
Year	2002	1 (ref)	1 (ref)	
	2003	0.96 (0.88 - 1.05)	0.98 (0.90 - 1.07)	
	2004	0.92 (0.85 - 1)	0.89 (0.82 - 0.97)	
	2005	0.87 (0.8 - 0.94)	0.8 (0.74 - 0.88)	
	2006	0.83 (0.76 - 0.9)	0.78 (0.71 - 0.84)	
Comorbid Conditions				
COPD		2.19 (2.01 - 2.39)	1.34 (1.23 - 1.47)	1
Arrhythmia		1.87 (1.67 - 2.08)	1.16 (1.04 - 1.3)	0
Heart Failure		2.27 (2.14 - 2.41)	1.39 (1.3 - 1.48)	1
CABG		1.23 (1.11 - 1.37)	0.81 (0.72 - 0.91)	0
Depression		1.54 (1.34 - 1.77)	1.55 (1.34 - 1.79)	2
Stroke		1.77 (1.64 - 1.92)	1.26 (1.16 - 1.36)	1
Myocardial Infarction		1.95 (1.83 - 2.08)	1.2 (1.11 - 1.29)	1
Lymphoma & Myeloma		3.85 (3.51 - 4.23)	3.48 (3.16 - 3.83)	3
Neurological Disease		1.43 (1.27 - 1.6)	1.52 (1.35 - 1.71)	2
Vascular Procedure		2.1 (1.89 - 2.34)	1.27 (1.13 - 1.42)	1
Valvular Heart Disease		1.9 (1.71 - 2.12)	1.3 (1.16 - 1.45)	1
Cancer		1.95 (1.8 - 2.11)	1.39 (1.28 - 1.51)	1
Connective Tissue Disease		1.25 (1.1 - 1.43)	1.34 (1.18 - 1.53)	1
Peptic Ulcer Disease		1.7 (1.54 - 1.87)	1.17 (1.06 - 1.29)	0
Claudication		2.03 (1.88 - 2.2)	1.19 (1.09 - 1.29)	0
Diabetes		1.47 (1.4 - 1.55)	1.44 (1.36 - 1.52)	1

The univariate analyses showed the highest hazard for mortality in White patients compared to all other ethnic groups, although the difference was slightly reduced in the multivariate model. The relationship between age and hazard ratio as a linear term is shown in Table 5-2, and by decade represented in Figure 5-3.

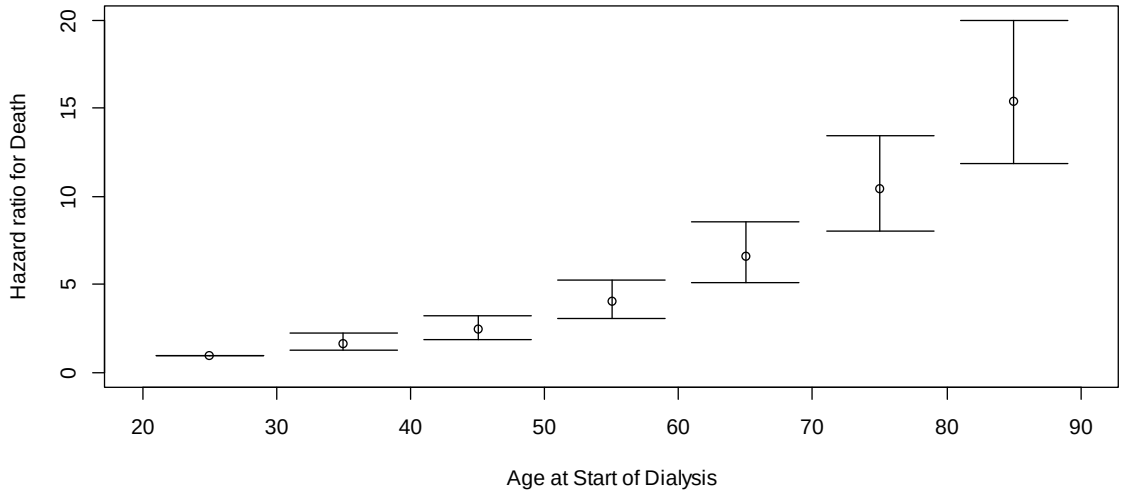


Figure 5-3 : The impact of age on hazard ratio for death (compared to 18 - 30 years of age, 3 years follow-up)

Socioeconomic status appears to only begin to significantly alter survival in the least deprived fifth of the range, and once other variables are included in the model. There is fairly linear improvement in survival over the period of time covered by the study.

Of the 18 comorbid conditions originally determined suitable for inclusion in the analysis, 16 conditions remain statistically significant in the multivariate model, with hypothyroidism being non-significant and pulmonary disease overlapping with COPD. As expected the influence of individual conditions is reduced in the presence of other factors, with CABG becoming paradoxically protective.

Interactions between diabetes and age (classified as less than 55, 55 to 65 and greater than 65 years) revealed greater hazard for death in patients under the age of 55 with diabetes than those older age groups with diabetes (<55 yrs HR 2.85, CI 2.46 – 3.32 compared to >65 years). In the presence of diabetes, the hazard associated with previous acute myocardial infarction was reduced by 15.5% (hazard for the presence of both 0.85, 95% CI 0.74 – 0.96). In the presence of diabetes, being South Asian was associated with an additional hazard of 1.33 (95% CI 1.03 – 1.71).

Comorbid score

Of the 16 conditions found to have a statistically significant influence on survival in the presence of other factors, 12 had a hazard exceeding 1.2 allowing them to score on the comorbid index. The distribution of comorbid scores across patients is shown in Figure 5-4.

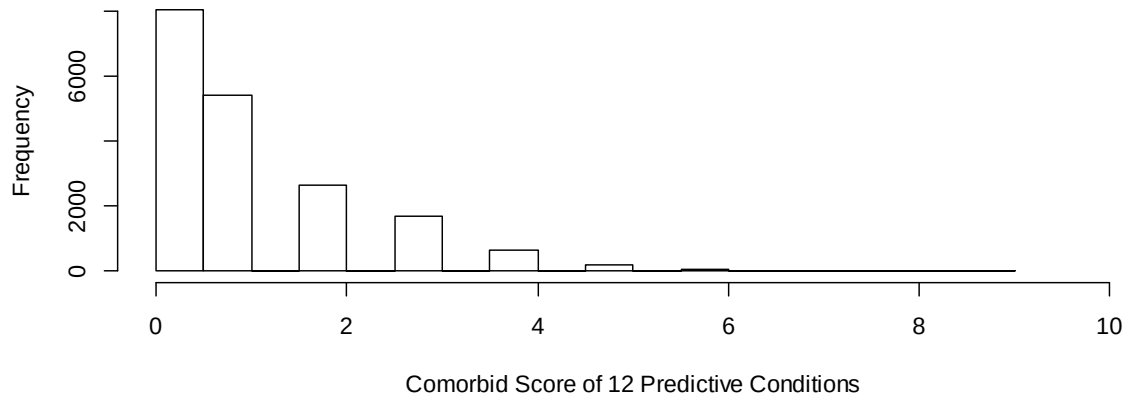


Figure 5-4 : Histogram of the frequency of comorbid score derived from 12 comorbid conditions at the time of starting renal replacement therapy

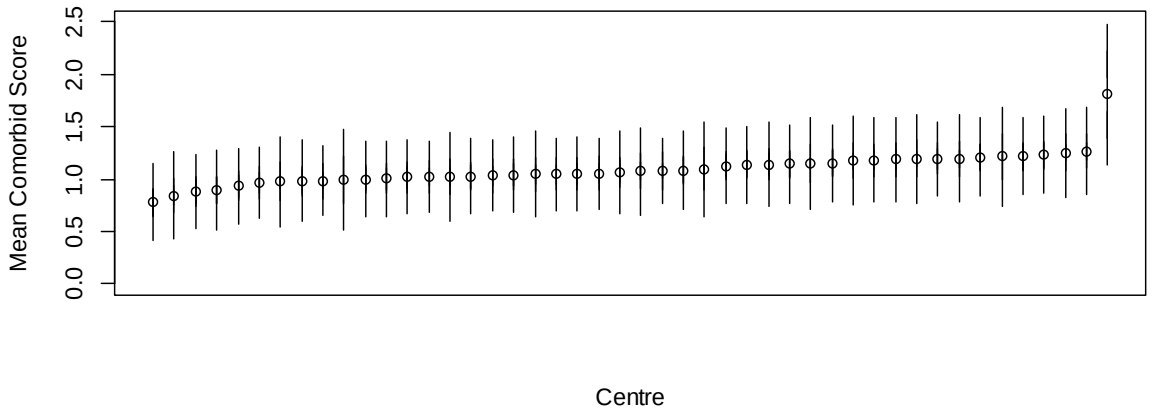


Figure 5-5 : Centre-specific mean comorbid score per patient derived from weights of 12 comorbid conditions

The mean comorbid score was 1.073 (standard deviation 1.254), suggesting a skewed distribution as 39.2% of cases had none of the 16 comorbid conditions highlighted as predictive above (Table 5-1). Mean comorbid score for patients included in the survival cohort across centres is illustrated in Figure 5-5, and would suggest that comorbid score across centres was largely uniform. Given the survival disadvantage seen with White ethnicity, comorbid scores across ethnic groups are shown in Table 5-3, along with the prevalence of individual comorbid conditions within these ethnic groups. The overall burden of comorbidity is less in Black patients than in other groups, but as the persistent influence of ethnicity in multivariate model which informs the scores would suggest any survival advantage in other groups is independent of the comorbid burden.

Table 5-3 : Variation in comorbidity by ethnic group

	All Patients (18,798)	White (81.4%, 15,309)	Black (5.6%, 1,054)	South Asian (6.5%, 1,214)	Other (6.5%, 1,221)
Comorbidities					
Diabetes **	31.6 (5,944)	28.6	39.5	49.7	45.2
Myocardial infarction **	11.9 (2,229)	12.1	5.8	13.6	12.3
CABG **	4.9 (919)	4.7	1.8	8.2	7.3
Heart Failure	14.9 (2,803)	14.7	14.5	16.8	15.4
Claudication **	7.1 (1,344)	7.9	3.3	3.8	5
Valvular Heart Disease *	3.7 (697)	3.9	2.3	2.8	3.1
Stroke	7.7 (1,446)	7.7	7.5	7.9	7.2
COPD **	5.2 (978)	5.8	0.9	3.3	3.8
Comorbid Score (mean, 95% CI)	1.11 (1.09 - 1.13)	1.12 (1.1 - 1.14)	0.99 (0.91 - 1.07)	1.11 (1.05 - 1.17)	1.15 (1.07 - 1.23)

* P < 0.05, ** P < 0.001 for variation in prevalence across ethnic groups

As previously identified in chapter 4, lymphoma/myeloma and depression were more common in patients who had missing UKRR data for comorbidity. These increases were sufficient to separate the comorbid score: the mean comorbid score was 1.10 in those with UKRR comorbid data vs 1.22 in those without (CI on the difference 0.08 – 0.15, P<0.001).

Comorbidity burden worsened as the age of RRT start increased, but then plateaued and marginally improved (illustrated in Figure 5-6), suggesting a preference for less comorbid burden when considering an elderly patient for RRT. Between 2002 and 2006 the burden of comorbidity increased in incident patients, despite the incident population age staying constant around a mean of 60 years. Comorbid score increase linearly from 0.990 in 2002 to 1.171 in 2006 (95% CI of difference 0.121 – 0.240, P<0.001). This is associated with an increase in coding depth as reported in chapter 4.

Patients who started on haemodialysis had more comorbid conditions than those starting on peritoneal dialysis (1.23 vs 0.809, CI on the difference 0.382 – 0.465, P=<0.001), however the size of this difference varied across centres suggesting differing attitudes to who constituted an appropriate patient for each modality (Figure 5-7). Patients who were transplanted within the three year follow-up period were less comorbid than those who were not, as shown in Table 5-4.

Table 5-4 : Comorbid score derived from 12 conditions by dialysis modality and subsequent transplantation

Modality and transplantation	Number of patients	Mean comorbid score (CI)
Haemodialysis, not transplanted	9,882	1.376 (1.345 – 1.403)
Haemodialysis, transplanted	3,470	0.924 (0.885 – 0.963)
Peritoneal dialysis, not transplanted	2,759	0.985 (0.942 – 1.028)
Peritoneal dialysis, transplanted	1,746	0.519 (0.480 – 0.558)
Transplantation by 90 days	850	0.374 (0.323 – 0.425)

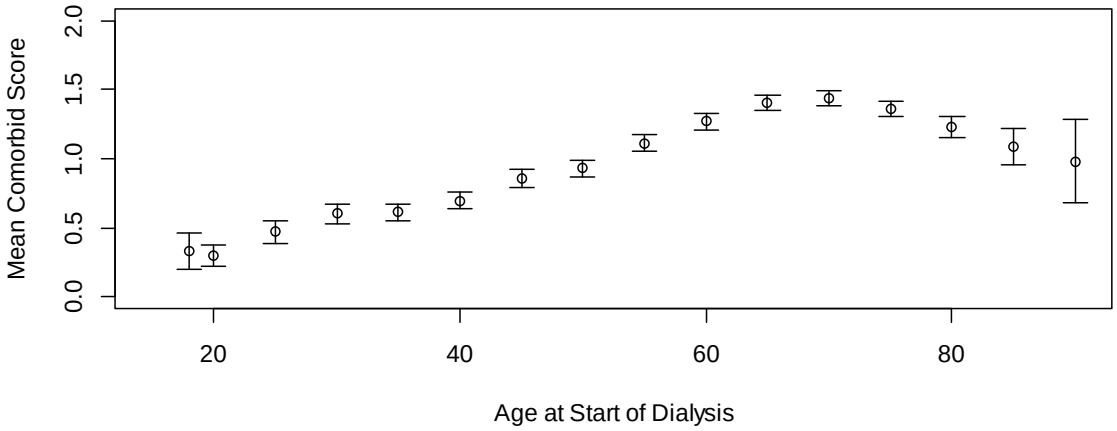


Figure 5-6 : The increase in comorbid score with age at first dialysis

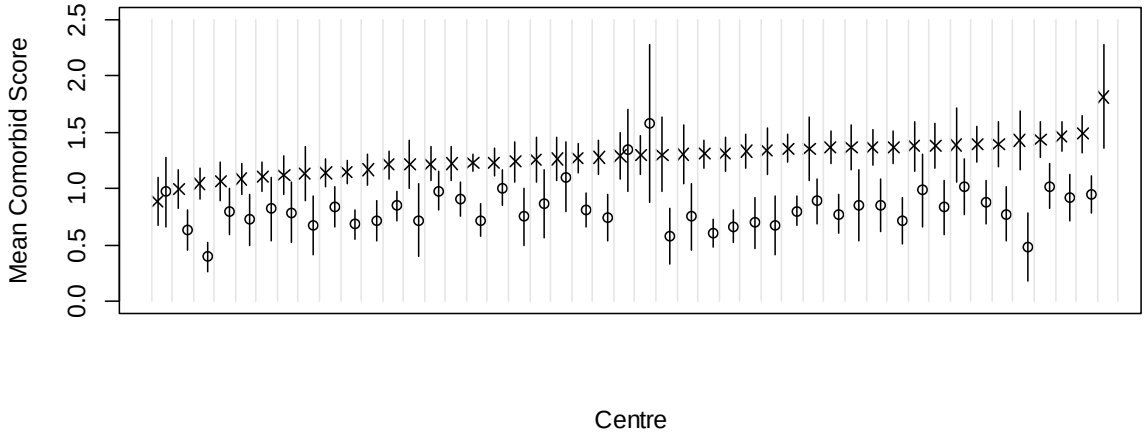


Figure 5-7 : Comorbid score according to dialysis modality (HD – cross, PD – circle) at 90 days by renal centre

Late referral

In the 36 centres suitable for analysis of late referral impact, 16,857 patients were suitable for analysis. Late referral as defined as no prior nephrology exposure within the 90 days before starting RRT, with patients seen between 90 and 180 days also analysed as separate group. Patients had a greater hazard for death out to three years if they were seen less than 90 days (1.417, 95% CI 1.340-1.500) and between 90 and 180 days (1.338, 95% CI 1.205-1.486). Following adjustment for age, sex, socioeconomic status, year of start and comorbidity, the hazard for being first seen less than 90 days was reduced to 1.350 (95% CI 1.270 - 1.436) when compared to greater than 180 days. The other variables previously identified as predictive remained so in the presence of late referral.

Primary renal disease

Using primary renal disease with additional diagnoses derived from HES, varying survival is seen across the six groups routinely used by UKRR to measure survival. The hazard for mortality is represented in the presence of purely age in Table 5-5. Different primary renal diseases were associated with different rates of late referral as would be expected given their varying progression rates and risk of developing acute kidney injury (chi-squared P<0.001, Table 5-6).

Table 5-5 : Hazard ratio for death associated with primary renal disease when compared to patients with polycystic kidney disease, adjusted for age.

Primary Renal Disease	Hazard Ratio (95% CI)
Polycystic Kidney Disease	1.000 (reference group)
Diabetes	3.370 (2.901 - 3.914)
Glomerular Disease	1.255 (1.050 - 1.500)
Hypertension	2.168 (1.807 - 2.602)
Pyelonephritis	2.139 (1.799 - 2.544)
Renovascular Disease	4.487 (3.812 - 5.282)
Other	3.341 (2.863 - 3.898)
Uncertain	2.987 (2.563 - 3.481)

Table 5-6 : The proportion of patients seen for the first time by a nephrologist within and beyond six months from starting RRT, stratified by primary renal disease

Primary renal disease	First seen within 6 months	First seen beyond 6 months
Diabetes	37.1%	62.9%
Glomerular Disease	35.4%	64.6%
Hypertensive Disease	44.8%	55.2%
Polycystic disease	26.8%	73.2%
Pyelonephritis	36.5%	63.5%
Renovascular Disease	45.2%	54.8%
Other	51.7%	48.3%
Uncertain PRD	44.1%	55.9%
Overall	40.7%	59.3%

Model performance

As one would expect, model predictive performance improved with the addition of variables. These measures are derived and quoted without centre in the model. A significant improvement in R squared was observed with the addition of comorbidity, accounting for an additional 10.6% of variance explained (Table 5-7).

Table 5-7 : Sequential improvement of model performance with addition of variables

Model Number	Variables	Model receiver operator characteristic (95% CI)	Model R squared (95% CI)
1	Age & Sex	0.721 (0.713 – 0.729)	0.245 (0.232 – 0.265)
2	Age, Sex & Ethnicity	0.726 (0.719 – 0.734)	0.256 (0.241 – 0.274)
3	Age, Sex, Ethnicity & SES	0.728 (0.720 -0.735)	0.259 (0.244 – 0.278)
4	Age, Sex, Ethnicity, SES & Year of Start	0.729 (0.722 – 0.737)	0.261 (0.247 – 0.280)
5	Age, Sex, Ethnicity, SES, Year of Start & Comorbidity	0.775 (0.769 – 0.782)	0.367 (0.352 – 0.387)
Cohort suitable for analysis of time from referral to start of RRT			
6	Age, Sex, Ethnicity, SES, Year of Start, Comorbidity	0.777 (0.763 - 0.792)	0.370 (0.354 – 0.393)
7	Age, Sex, Ethnicity, SES, Year of Start & Comorbidity and Primary renal disease	0.782 (0.768 – 0.797)	0.383 (0.368 – 0.407)
8	Age, Sex, Ethnicity, SES, Year of Start & Comorbidity, Primary renal disease and Late Referral	0.784 (0.770 – 0.798)	0.389 (0.375 – 0.413)

Experimental models

Recognising the questionable validity of the diagnosis of primary renal disease and the time from referral to starting RRT, the model performance of these variables are reported on a select number of centres accounting for 16,857 patients (89.7% of the cohort), starting with model 5 above for these centres and adding primary renal disease and late referral. The improved model fit for the same model with fewer centres is explained by less variation by centre being unexplained by the model. A further 1.9% of R-squared is explained by the addition of these two variables.

Detecting outlying centres for three year survival

Using the variables which inform model 5 (age, sex, ethnicity, socioeconomic status, year of start and comorbid conditions as a categorical variables), the impact of the sequential additions of these variables to outlier status is demonstrated in Figure 5-8. With adjustment purely for age and sex, mean centre-specific survival at three years adjusted to age 65 and male gender was 69.7% (range 60.2 – 78.7%) and identifying six centres with worse than expected survival. With the addition of ethnicity (predicted as White), socioeconomic status (least deprived) and year of start (2002), the mean centre-specific survival was 67.9% (range 60.5 – 75.02%) and four centres with worse than expected survival remained. Following the addition of the 16 statistically influential comorbid conditions mean centre-specific survival at three years was 78.8% (range 72.9 – 86.3%) and one centre with worse than expected survival remained.

In order to evaluate the impact of late referral and comorbidity, analysis from the point of adding comorbidity was repeated but with centres inappropriate for late referral study excluded. As before, one centre was identified as outliers for survival at three years. With the addition of late referral and primary renal disease the numbers of centres with lower than expected survival were three and one respectively. The same centre one centre was identified as an outlier across all three analyses.

The inclusion of COPD, previous myocardial infarction, congestive cardiac failure and the Diabetes-Age interaction in addition to age, ethnicity, socioeconomic status and year of start of RRT were sufficient to result in no outlying centres, masking the worse than expected survival in one centre identified with the comprehensive model including all comorbid conditions. The comorbidities of previous myocardial infarction, valvular heart disease and claudication showed statistically significantly different hazard ratios for different centres when modelled with age, ethnicity, socioeconomic status and year of start. However following the

addition of the conditions of stroke, congestive cardiac failure, COPD and the diabetes-age interaction term non-constant risk persisted in valvular heart disease only.

Censoring for transplantation

The existing practice of UKRR was not to censor time beyond the date of first transplantation. Using the model excluding late referral and primary renal disease, a model censoring for transplantation resulted in censoring for 6,277 cases, and worsened model fit from an R-squared of 0.367 without censoring to 0.298 with censoring. One additional centre to the centre previously highlighted was identified. Both these centres were non-transplanting centres. The C-statistic was increased from 0.775 to 0.783, but this is a less robust measure due to the much greater degree of censoring which results in fewer observed deaths and follow-up time.

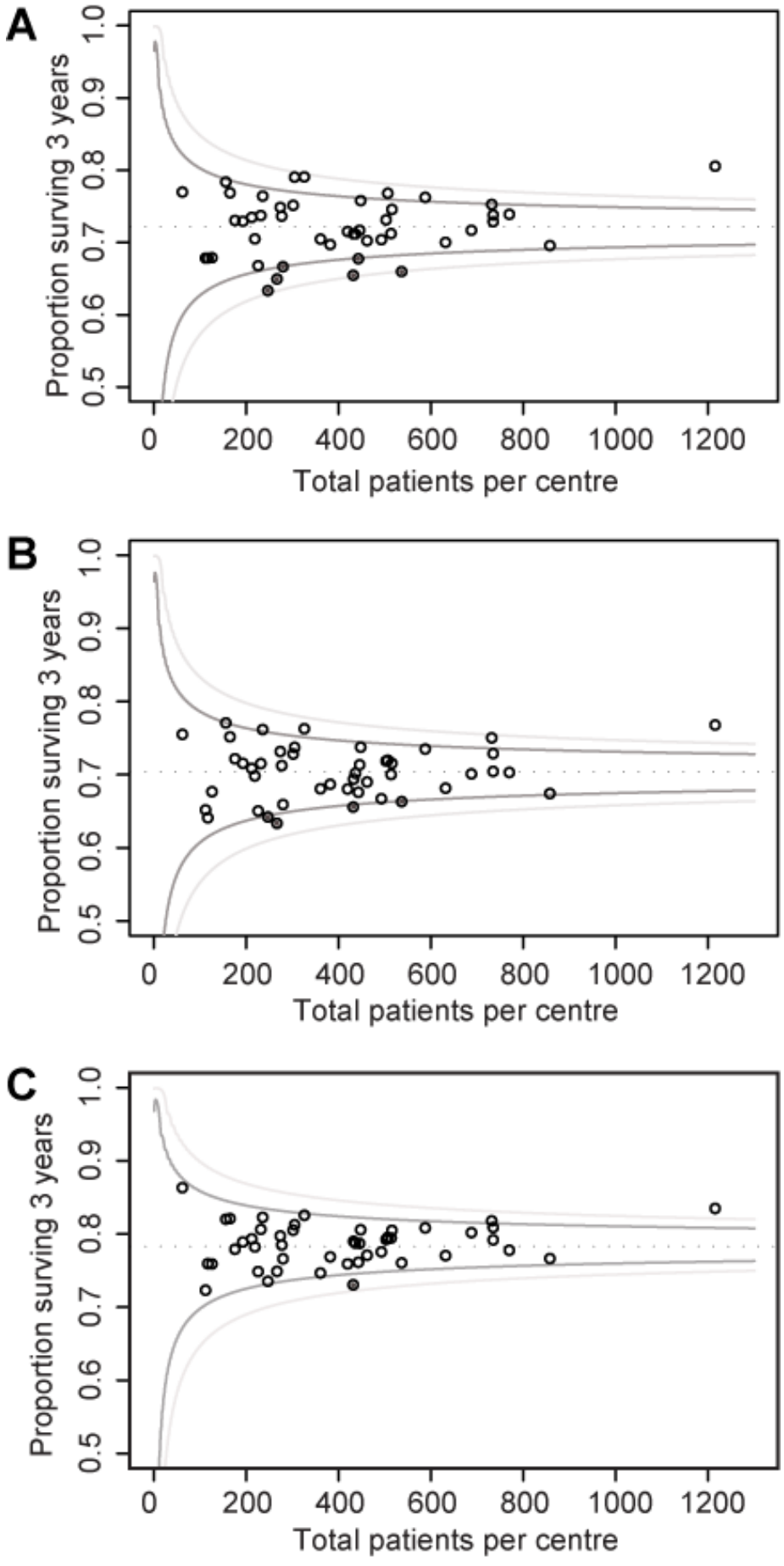


Figure 5-8 : Funnel plots detailing centre specific three year survival following adjustment for

A) Age and sex, B) Age, sex and demography, C) Age, sex, demography and comorbidity

Standardised hospital mortality rates

Admissions, variables and missing data

Limiting analysis to admissions beyond 90 days in acute admitting NHS trusts, 135,577 admissions were identified between 1/4/2002 and 31/12/2009 for analysis. The sequential selection process of admissions is detailed in Figure 5-9.

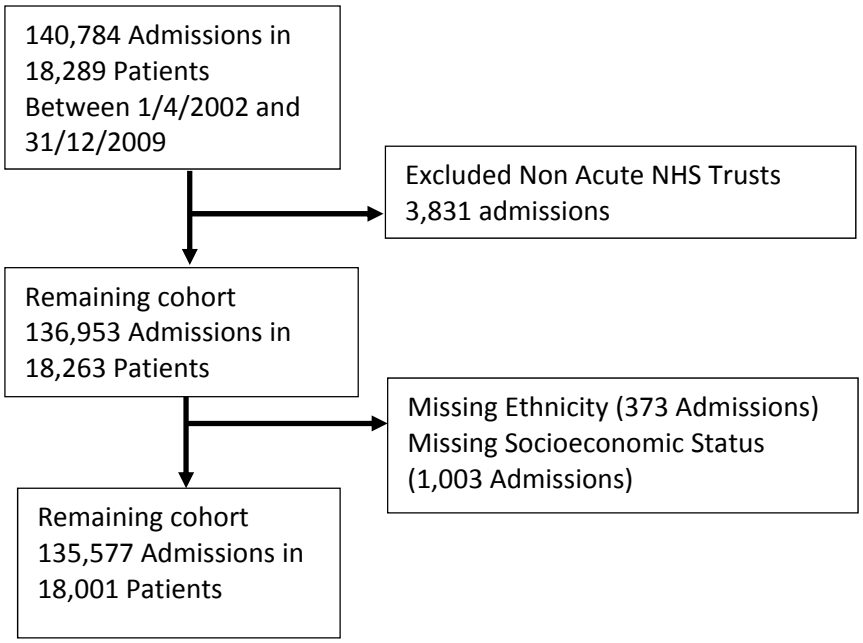


Figure 5-9 : Selection of admissions for analysis of hospital associated mortality

Mortality in hospital and at 30 days

Excluding non-acute trusts, the 30 day from discharge mortality rate was 5.2%. At this early stage the mortality rate per modality was calculated and is displayed below, along with number of admissions. Due to the much lower mortality rate in transplant recipients these patients were excluded from subsequent analysis.

Table 5-8 : Mortality rate 30 days from discharge according to renal replacement modality

Modality	Number of Admissions	Mortality Rate per admission (%)	95% Confidence Interval
Haemodialysis	96,553	5.97%	5.82 – 6.12
Peritoneal Dialysis	23,490	4.76%	4.48 – 5.03
Transplant	15,534	0.94%	0.78 – 1.09

Influence of adjustment variables on 30 day mortality

Age & sex

Increasing age was strongly associated with risk of in-hospital mortality, in a similar distribution to that seen in survival on incidence renal replacement therapy (Figure 5-10A).

The mortality rate in males was 5.31% whereas the mortality rate was 4.98% in females (odds ratio for males 1.07, 95% CI 1.02 – 1.12).

Ethnicity

As we discovered for incident survival on RRT, worse survival was observed in patients of a White ethnic background. Table 5-9 shows 30 day mortality for the ethnic subgroups applied to ethnic group information from the combined datasets. The odds ratio for death in white patients compared to the other ethnic groups was 1.74 (95% CI 1.63 – 1.87)

Table 5-9 : Mortality rate (proportion died) 30 days from discharge according to ethnic group

Ethnic Group	Number of Admissions	30 Day Mortality Rate (%)	95% Confidence interval
White	107,588	5.66	5.52 – 5.79
Black	8,930	2.75	2.41 – 3.09
South Asian	8,811	4.19	3.77 – 4.60
Other	10,248	3.14	2.80 – 3.48

Socioeconomic status

Perhaps contrary to what would have been expected, there were lower mortality rates in patients who were more deprived, demonstrated in Figure 5-10B. These differences were significant when socioeconomic status was grouped by the visible kink in the smooth-spline plot, with the 40% most deprived having an odds ratio for mortality of 0.81 (95% CI 0.77 – 0.85) compared to the 60% least deprived.

Comorbid score

Figure 5-10C shows a linear association between mortality and comorbid score. The odds ratio for 30 day mortality increases by 29.8% per increase in the admission comorbid score (95% CI 28.2 – 31.5).

Time on renal replacement therapy (vintage)

A linear association between vintage and 30 day mortality was observed although the effect size was small (Figure 5-10D). The odds ratio increased by 7.5% (95% CI 5.9 – 9.2%) for every additional year on dialysis.

Year of discharge and month of admission

There has been no discernible improvement in unadjusted 30 day mortality over the admission period that this study reports. Figure 5-11A would suggest that the proportion of deaths year on year has remained static as confidence limits are overlapping, however treating year as a continuous variable in a logistic regression model identifies a small increase in hospital associated mortality. Per year the odds ratio for death increased by 4.4% (95% CI 3.0 – 5.8%).

Unadjusted analysis of month of admission would suggest there is slightly lower mortality during the summer months (more specifically May to October) compared to the winter months (Figure 5-11B). This becomes more apparent when months are grouped by this specification. The period November to April has an odds ratio of 1.16 (95% CI 1.11 – 1.22) compared to May to October.

Emergency or elective admission

Thirty day mortality rate was 2.1% in elective admissions and 7.6% in non-elective admissions (Odds ratio 3.78, 95% CI 3.52 – 4.07).

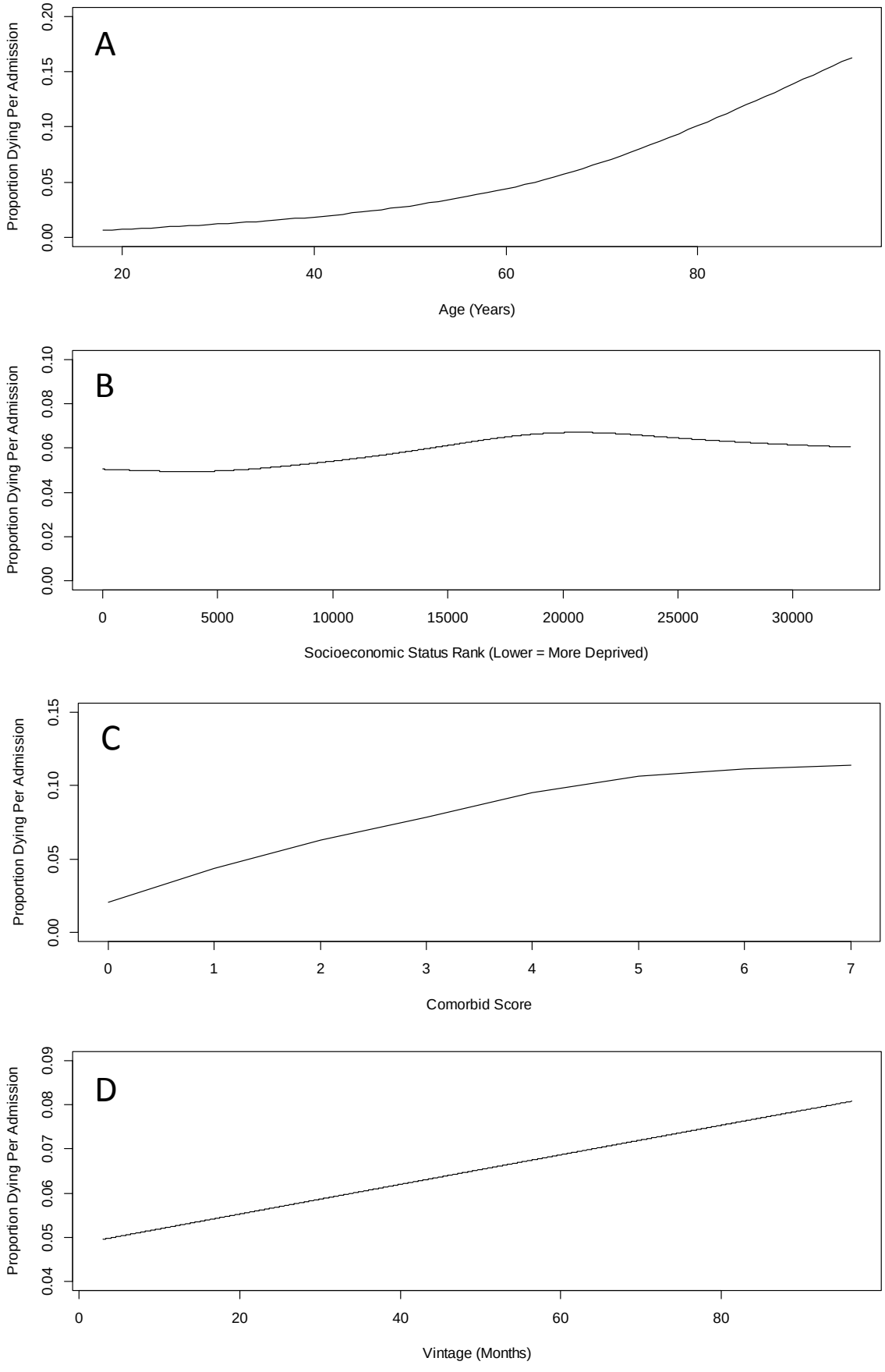


Figure 5-10 : Per admission, the proportion of patients dead at 30 days post discharge is positively influenced by a) increasing age b) lower socioeconomic status c) increasing comorbid score and d) longer time since starting dialysis. Graphs generated using a smoothed spline function.

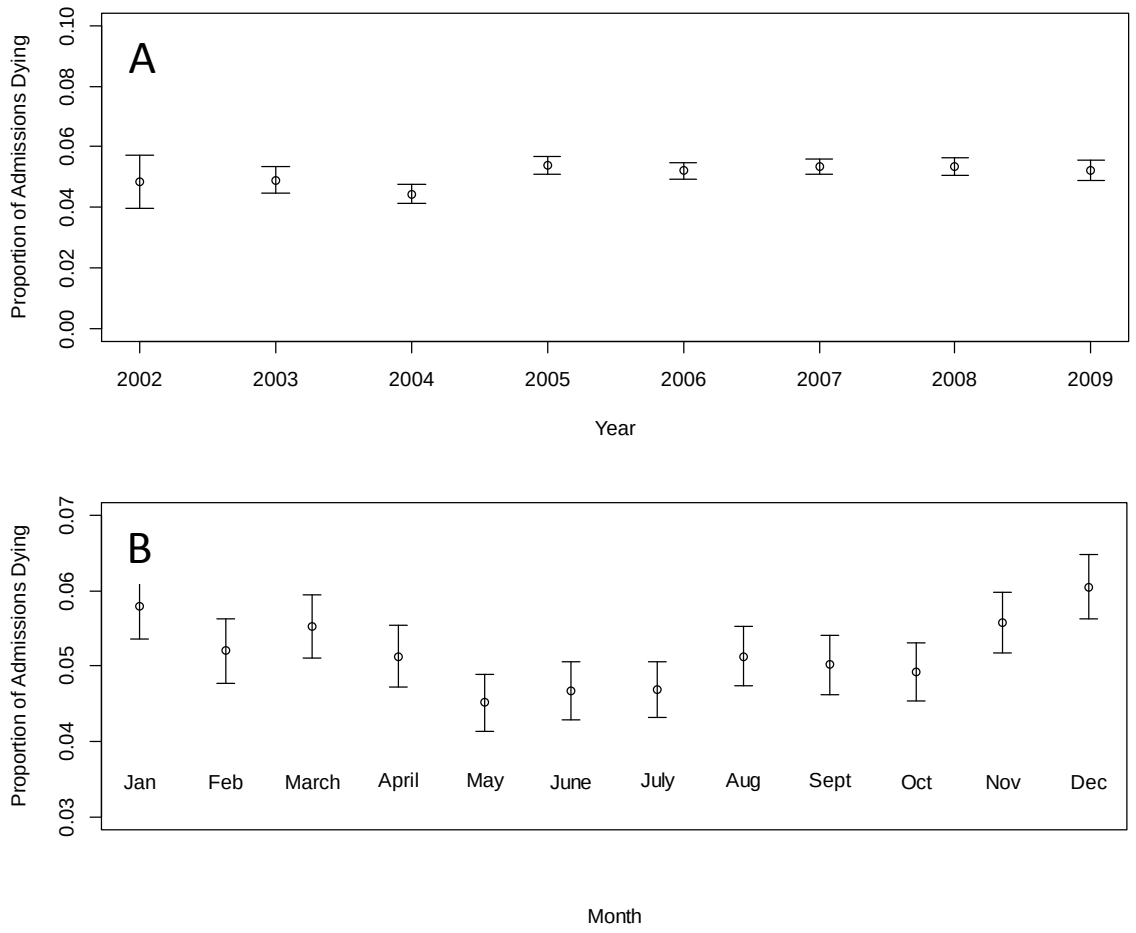


Figure 5-11 : Proportion of patients dead at 30 days post discharge by a) unadjusted by year of discharge appears largely constant b) month of admission shows seasonal variation.

Reasons for admission

Most existing hospital standardised mortality ratios factor reason for admissions in some way or other. Application of the existing ICD10 CCS grouping on primary diagnosis on admission resulted in 237 diagnostic groups. Thirty percent of admissions were groups with 50 deaths or less. The diagnostic groups of *Chronic Renal Failure* and *Hypertension with Complications* accounted for 28.1% of admissions, and primarily reflected coders use of ERF or PRD to reflect the reason for admission when subsequent procedural activity relating to ERF was recorded in the procedural codes. These two vague groups accounting for 34,060 admissions were explored using HRGs which utilise both primary diagnosis and procedure codes. 73.1% were coded as HRGs pertaining to dialysis delivery or care (for instance *Chronic Kidney Disease with length of stay 1 day* and *Renal Replacement Peritoneal Dialysis Associated Procedures*), with 10.6% pertaining to access for dialysis. Importantly, thirty-day mortality varied considerable across the HRGs which the CCS diagnostic groups of *Chronic Renal Failure* and *Hypertension with Complications* encompassed (0 – 27% in HRGs with greater than 100

admissions, average 4.0%). Transplantation episodes were identified from this cohort and excluded from centre specific analysis due to issues with assignment of this event to the appropriate parent renal centre (3,748 admissions).

Manual regrouping of CCS groups and HRGs by clinical cause and factoring thirty-day mortality resulting in the creation of 23 specific groups. This included a generic CKD/Dialysis care group accounting for 26.7% of admissions. 7.6% of admissions did not logically fall into these groups and were placed in a miscellaneous group. The titles of these groups, numbers of admission and 30 day mortality and modality split are listed in Table 5-10.

Table 5-10 : Diagnosis specific admission counts, modality distribution , 30 day mortality rate for all admissions and the range of 30 day mortality for the CCS diagnosis groups within the diagnosis grouping for admissions beyond the first 90 days of renal replacement therapy.

Diagnostic Regrouping	Total Admissions	Percentage Haemodialysis	30 Day Mortality Rate	Range of CCS subgroup mortality
CKD/Dialysis Care	32078 (26.72%)	80.74%	4.29%	0 - 7.3%
Dialysis Access	20518 (17.09%)	82.43%	2.38%	2.7 - 6.6%
Ischaemic Heart Disease	7929 (6.61%)	81.99%	10.67%	1.6 - 43.3%
Bronchitis	5623 (4.68%)	88.96%	4.96%	2.2 - 6.6%
High Risk Sepsis	4744 (3.95%)	87.86%	19.08%	4.4 - 71.4%
Gastroenteritis	4306 (3.59%)	76.31%	4.62%	3.4 - 9.8%
Transplantation	3748 (3.12%)	62.57%	1.01%	0 - 22.2%
Fracture or Trauma	3532 (2.94%)	88.99%	7.42%	0 - 23.5%
Overload	3302 (2.75%)	80.50%	7.39%	3.3 - 17.1%
Chest Pain	2683 (2.24%)	85.58%	1.90%	1.9 - 3.9%
Syncope & Collapse	2623 (2.19%)	85.89%	3.89%	0.8 - 6.8%
Neurological	2510 (2.09%)	86.33%	6.89%	0 - 31.5%
Low Risk Sepsis	2431 (2.03%)	86.67%	3.87%	0 - 8.6%
Abdominal Pain	2403 (2%)	74.24%	4.41%	0 - 10.3%
Biochemical Derangement	2276 (1.9%)	81.41%	5.40%	0 - 10.6%
Urinary Tract Infection	2045 (1.7%)	82.74%	2.69%	1.7 - 6.7%
Cancer	1940 (1.62%)	84.85%	21.55%	0 - 66.7%
Peritonitis	1781 (1.48%)	9.66%	5.50%	5.5 - 5.5%
Urinary Procedures	1458 (1.21%)	82.65%	0.62%	0 - 6.6%
Gastrointestinal Bleed	1102 (0.92%)	85.84%	7.89%	7.8 - 10.6%
Cerebrovascular Incident	1057 (0.88%)	83.44%	32.17%	32.2 - 32.2%
Hernia	849 (0.71%)	47.94%	1.18%	1.2 - 4.6%
Misc	9105 (7.58%)	79.40%	6.32%	0 - 45.5%

These statistics emphasise extremely high mortality rates for cerebrovascular accidents (32.2% thirty-day mortality). One would expect that admissions for access related procedures would be low risk, as many are done with a local anaesthetic block. A 30 day mortality rate of 2.38% would seem high.

The range of 30 day mortality rates for each CCS group within a newly grouped renal diagnosis group is extreme, with some CCS groups having no deaths (cancer for instance, 0 – 67%).

Late referral

Based on the centre inclusion criteria defined in chapter 4, 71,525 admissions were suitable for analysis (59.6% of the analysis cohort excluding admissions in transplant patients). The odds ratio for 30 day mortality was 1.15 (95% CI 1.07 – 1.23) in patients first seen less than 90 days before starting RRT compared to those seen beyond 90 days (no difference between 90-180 days and greater than 180 days). This risk varied with time, with the impact of late referral lessening with increasing dialysis vintage. For admissions in the first year the odds ratio was 1.43 (95% CI 1.25 – 1.62), lessening to 1.10 (95% CI 0.95 – 1.27) in the second and 1.09 (95% CI 0.93 – 1.28) in the third year.

Primary renal disease

Exploration of the risk of death at thirty days would suggest patients broadly fall into two groups – those with low risk primary renal diseases (polycystic kidney disease, glomerular disease) and those with higher (all other groups). Renovascular disease is notable as having the highest risk of death at 30 days from discharge and may relate to other comorbid burden.

Table 5-11 : Mortality at 30 days from discharge according to primary renal disease, polycystic kidney disease as reference group, adjusted for age.

Primary Renal Disease	Odds Ratio	95% Confidence Interval	P
Polycystic Kidney Disease	1 (Reference Group)		<0.001
Glomerular Disease	1.072	0.918 - 1.251	0.382
Diabetes	1.723	1.515 - 1.959	<0.001
Hypertension	1.55	1.322 - 1.818	<0.001
Other	2.015	1.763 - 2.304	<0.001
Pyelonephritis	1.466	1.261 - 1.706	<0.001
Renovascular Disease	2.596	2.248 - 2.998	<0.001
Uncertain / Missing	2.017	1.768 - 2.302	<0.001

Multivariate models

The sequential addition of the predictive variables of age and sex, reason for admission, ethnicity, socioeconomic status, emergency/elective admission, comorbidity and seasonal factors is described below, stratified by modelling technique. In the model-per diagnosis method, reason for admissions in factored from the outset. Table 5-12 details the incremental improvements in model performance as variables are added. Adjustment for reason for admission alone gives a model c-statistic of 0.689 in both modelling methods. From the addition of age, the model per group method reports a superior C-statistic, however confidence limits overlap across many of the reported models.

To obtain further predictive power within the 22 renal diagnosis groups, 30 day mortality as a proportion for the CCS groups within these renal diagnosis groups was calculated and included in the model. Further improvements in model performance were observed. The inclusion of all the above factors results in a model performance c-statistic of 0.800 using the single model method and 0.813 in the model per group technique.

Table 5-12 : Hospital associated mortality model performance as measured by C-statistic for one model with diagnostic group as a factor, and a model per diagnostic group with the addition of predictor variables.

Variable	C-statistic (One Model)	C-statistic (Model Per Group)
Diagnostic Group	0.689 (0.676 - 0.702)	0.689 (0.676 - 0.702)
Age (per decade) & Gender	0.743 (0.731 - 0.755)	0.745 (0.733 - 0.757)
White Ethnic Group	0.746 (0.734 - 0.758)	0.748 (0.737 - 0.76)
Socioeconomic Status (40% most deprived)	0.746 (0.734 - 0.758)	0.749 (0.737 - 0.761)
Emergency Admission	0.774 (0.763 - 0.785)	0.782 (0.771 - 0.792)
Comorbid Score (per unit increase)	0.786 (0.775 - 0.797)	0.794 (0.784 - 0.804)
Vintage (per year on RRT)	0.786 (0.776 - 0.797)	0.795 (0.784 - 0.805)
Modality	0.786 (0.776 - 0.797)	0.796 (0.786 - 0.806)
Year of discharge (per year, 2002-2009)	0.786 (0.776 - 0.797)	0.797 (0.787 - 0.807)
Winter Period	0.787 (0.776 - 0.797)	0.797 (0.787 - 0.808)
CCS Group Mortality Rate	0.800 (0.79 - 0.811)	0.813 (0.803 - 0.823)
Late Referral Applicable Cases		
Above Model	0.799 (0.786 - 0.813)	0.813 (0.800 - 0.826)
Plus Late Referral	0.800 (0.786 - 0.813)	0.814 (0.801 - 0.827)
Plus Primary Renal Disease	0.800 (0.786 - 0.814)	0.818 (0.805 - 0.83)

Odds ratios associated with the included variables are reported in Table 5-13, with univariate and multivariate results displayed. Of note, the previously noted increase in hospital associated mortality year on year and the protective effect of being on peritoneal dialysis is reversed following multivariate adjustment. The multivariate mean predicted risk of death per

admission (with year excluded from the model) increased from 4.8% in 2002 to 6.8% in 2009. The impact of the inclusion of CCS group mortality is most notable in the Cerebrovascular Accident group where any associated risk is neutralised compared to the generic CKD admission group (odds ratio 10.59 (95% CI 9.21 - 12.18) to 0.71 (95% CI 0.48 - 1.04)). This is due to only one CCS group existing within the Cerebrovascular Accident renal reason for admission group.

Adding an interaction between Diagnosis Group and Emergency admission (therefore allowing the risk associated with Diagnosis Group to vary according to whether it was an emergency or elective admission) improved the C-statistic to 0.806 (0.795 - 0.816). Additional inclusion of the less robust variables in the form of late referral and primary renal disease centres had varying impact according to modelling method. No improvements were seen in the single model method, but a modest improvement was seen in the model per group method.

Table 5-13 : Univarate and multivariate odds ratio for 30 day mortality and statistical significance for the one model with diagnostic group as a factor method

Variable	Univariate Odds Ratio	Multivariate Odds Ratio
Age (per decade)	1.55 (1.52 - 1.58)	1.48 (1.44 - 1.51)
Male Gender	1.07 (1.02 – 1.12)	1.09 (1.03 - 1.15)
White Ethnic Group	1.79 (1.67 – 1.93)	1.49 (1.38 - 1.61)
Socioeconomic Status (40% most deprived)	0.81 (0.77 – 0.85)	1.01 (0.96 - 1.07) *
Year of dischage (per year, 2002-2009)	1.04 (1.03 - 1.06)	0.96 (0.95 - 0.98)
Winter Period	1.16 (1.11 – 1.22)	0.86 (0.82 - 0.91)
Emergency Admission	3.78 (3.52 – 4.07)	3.45 (3.19 - 3.73)
Comorbid Score (per unit increase)	1.30 (1.28 - 1.32)	1.22 (1.2 - 1.24)
Modality (Peritoneal Dialysis)	0.81 (0.76 - 0.87)	1.10 (1.03 - 1.19)
Vintage (per year on RRT)	1.08 (1.06 - 1.09)	1.05 (1.03 - 1.08)
CCS Group Mortality	125.9 (96.5 - 163.3)	26.96 (16.41 - 44.29)
Diagnosis Groups		
CKD/Dialysis Care	1 (comparator)	1 (comparator)
Abdominal Pain	1.03 (0.84 - 1.26) *	1.57 (1.19 - 2.07)
Access	0.55 (0.49 - 0.61)	1.66 (1.19 - 2.32)
Biochemical Derangement	1.28 (1.06 - 1.54) ¥	0.97 (0.73 - 1.29) *
Bronchitis	1.17 (1.02 - 1.33) ¥	2.00 (1.45 - 2.78)
Cancer	6.13 (5.43 - 6.92)	1.35 (1.01 - 1.82) ¥
Urinary Procedures	0.14 (0.07 - 0.27)	1.52 (1.10 - 2.09) ¥
Chest Pain	0.43 (0.33 - 0.57)	0.29 (0.14 - 0.58)
Cerebrovascular Incident	10.59 (9.21 - 12.18)	0.71 (0.48 - 1.04) ¥
Fracture or Trauma	1.79 (1.56 - 2.05)	1.31 (0.94 - 1.84) ¥
Gastroenteritis	1.08 (0.93 - 1.26) *	1.60 (1.19 - 2.16) ¥
Gastrointestinal Bleed	1.91 (1.53 - 2.40)	1.54 (1.14 - 2.09) ¥
Hernia	0.27 (0.14 - 0.50)	1.93 (1.36 - 2.74)
Ischaemic Heart Disease	2.67 (2.44 - 2.92)	0.61 (0.31 - 1.21) *
Low Risk Sepsis	0.90 (0.73 - 1.11) *	1.67 (1.26 - 2.23)
Neurological	1.65 (1.40 - 1.95)	2.38 (1.79 - 3.16)
Overload	1.78 (1.55 - 2.05)	1.46 (1.06 - 2.00) ¥
Peritonitis	1.30 (1.05 - 1.61) ¥	1.64 (1.21 - 2.22)
High Risk Sepsis	5.26 (4.81 - 5.76)	2.33 (1.66 - 3.27)
Syncope & Collapse	0.90 (0.74 - 1.11) *	2.05 (1.53 - 2.75)
Urinary Tract Infection	0.62 (0.47 - 0.81)	1.12 (0.80 - 1.56) *
Miscellaneous	1.51 (1.36 - 1.66)	1.44 (1.02 - 2.02) ¥

¥ 0.05 < P > 0.001, * P > 0.05

Table 5-14 : Variables with statistical significance in predicting 30 day mortality for individual reasons for admission (Variable statistical significance: ○ – P<0.05, ● – P<0.001)

	Age	Sex	Elective	CCS Group Mortality	White	IMD	Vintage	Modality	Comorbid Score	Year	Season
CKD/Dialysis Care	●	○	●	●	●		○	●	●		○
Access	●		●	○	●		○	●	●		
Ischaemic Heart Disease	●		●	●			○		●	●	○
Bronchitis	●			●					○		
High Risk Sepsis	●	○	○	●	●		○	●	●	○	○
Gastroenteritis	●			○	○				●		
Fracture or Trauma	●	○		●					●	●	
Overload	●			●	○				●		
Chest Pain	●								●		
Syncope & Collapse	○			○	○				○		
Neuro	●			●					○		
Low Risk Sepsis	●	●		●					●		
Abdominal Pain	●		●	●					●		
Biochemical Derangement	●		●	●	●				○		
Urinary Tract Infection	●			○							
Cancer	●		●	●							
Peritonitis	●	●			○		●	○	●		
Urinary Procedures			○	○							
Gastrointestinal Bleed	●										
Cerebrovascular Incident	●										
Hernia	○		○								
Misc	●		●	●	●				●		

When we review the predictor variables for each model in the model per diagnostic group method (Table 5-14), it is apparent which variables would be important to retain if one were specifying a model with a limited number of predictors. Age is predictive in nearly all models, with CCS group mortality and comorbid score also featuring heavily. Reducing the model from eleven variables to the seven variables of age, reason for admission, emergency admission, CCS group mortality, ethnicity, modality and comorbid score results in a model C-statistic of 0.810 (95% CI 0.801 – 0.820) compared to 0.818 (95% CI 0.805 - 0.830) for all eleven variables, and the Pearson correlation coefficient for the predicted risks was 0.986.

A scatterplot of risk determined from the fully specified single model and multiple model methods is shown below, showing the groups of cancer and peritonitis obtain the most notable differences in risk of death. The Pearson correlation for the risks was 0.958 (P<0.001).

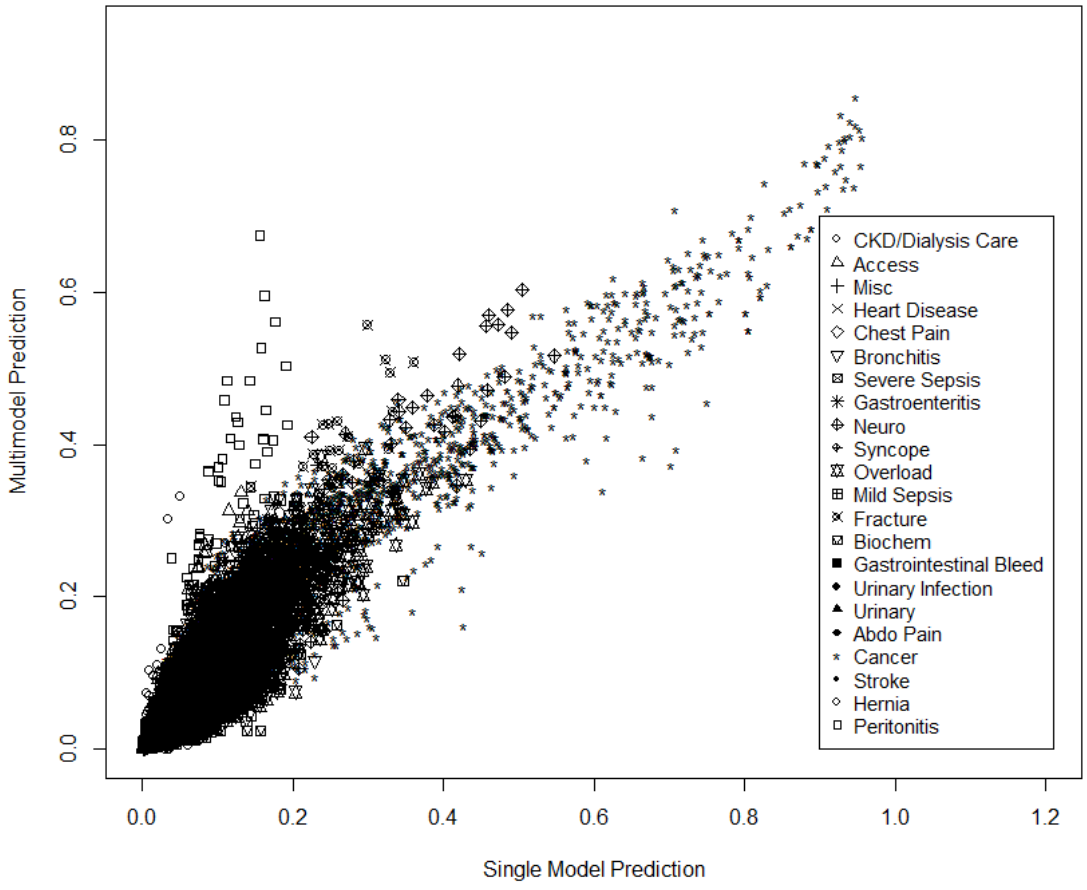


Figure 5-12 : Comparison of predicted risk for 30 day mortality using two methods: X axis – single model for all admissions with reason for admissions as a variable, Y axis – a model per individual reason for admission.

Centre-specific Hospital Standardised Mortality Ratios

Observed/expected death rates to compare centre mortality with adjustment for age, sex and diagnostic group identified 12 of the 46 centres with higher than expected hospital mortality, of which three centres were beyond the 99.5% limits. Following adjustment for all eleven variables, four centres remained outside the 95% control limits, of which one centre was beyond the 99.5% limit (Figure 5-13). Adjustment for seven variables identified the same four outliers as the eleven variable model. A similar distribution of outliers was seen following adjustment with the single model technique (11 outliers adjusted for age, sex and diagnosis, 4 outliers following adjustment for 11 variables). Of note, one centre beyond the 99.5% limit on the model per group method was between the 95% and 99.5% limits on the single model method.

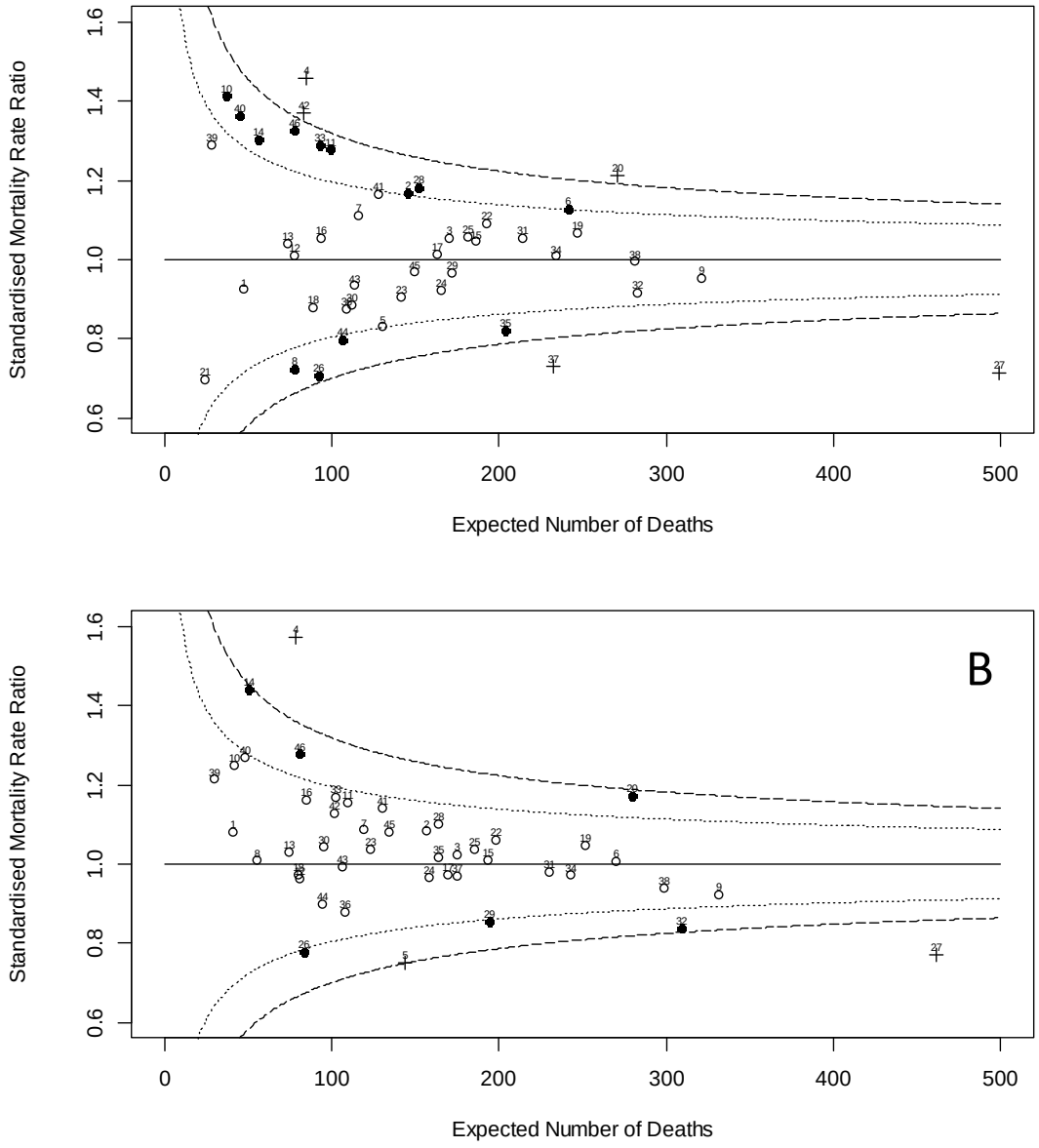


Figure 5-13 : Funnel plots for standardised hospital mortality adjusted for A) Age, sex and diagnosis B)

Eleven predictive variables of hospital mortality

Hospital standardised mortality according to day of the week

Admission rates were lowest on Friday, Saturday and Sunday. Standardised mortality rates were uniform across all days of the week with no one day having a HSMR higher or lower than expected. The same was not the case for day of the week according to discharge. A much lower number of discharges occurred on a Sunday. In addition, the HSMR for Sunday was 1.83 (95% CI 1.63 – 2.06), and along with Saturday were the two days with higher than expected deaths. Discharges on a Friday were less likely to die in hospital or at 30 days (HSMR 0.80, 95% CI 0.74 – 0.87). Similar finds were observed limiting analyses to haemodialysis only (HSMR Friday 0.75, 95% CI 0.61 – 0.92, HSMR Sunday 1.65, 95% CI 1.23 – 2.2) and peritoneal dialysis only (HSMR Friday 0.82, 95% CI 0.75 – 0.89, HSMR Sunday 1.85, 95% CI 1.62 – 2.10).

Table 5-15 : Standardised hospital mortality according to day of the week

	Admissions			**Discharges**		
	Number	**Crude Mort. (%)**	**HSMR (95% CI)**	**Number**	**Crude Mort (%)**	**HSMR (95% CI)**
Mon	21,207	5.73	0.98 (0.90 - 1.06)	14,957	6.26	1 (0.92 - 1.10)
Tue	21,039	5.55	0.96 (0.89 - 1.04)	19,204	5.41	0.92 (0.84 – 1.00)
Wed	19,141	5.21	0.96 (0.88 - 1.05)	18,860	5.73	0.97 (0.90 - 1.06)
Thu	18,175	5.62	1.00 (0.92 - 1.09)	19,584	5.38	0.94 (0.86 - 1.02)
Fri	15,210	6.69	1.05 (0.96 - 1.15)	22,290	4.74	0.80 (0.74 - 0.87)
Sat	11,234	7.01	1.07 (0.97 - 1.19)	14,179	6.13	1.10 (1.00 - 1.22)
Sun	10,286	6.15	1.02 (0.92 - 1.14)	7,218	11.15	1.83 (1.63 - 2.06)

Comparisons between survival indicators

Assuming similar proportions of deaths occurring in hospital across centres and equally robust standardisation across measures, as incident survival decreases hospital standardised mortality would increase. The correlation between incident survival transformed into a ratio to allow the same proportionality shows a relationship approximating this (Figure 5-14). The centres with a high proportion or a low proportion of their total deaths occurring in hospital or within 30 days from discharge are highlighted. Centres with a high proportion of deaths in hospital may be perceived to be performing badly and therefore have a high hospital standardised mortality and a low incident survival. Conversely they may keep their patients out of hospital due to good care and then when impending unavoidable death presents itself the patient is admitted. This would manifest with a high incident survival and a high hospital standardised mortality. The Pearson correlation coefficient between incident survival and hospital standardised mortality was -0.508 ($P<0.001$)

The NHS Information Centre SHMI uses similar methodology to the hospital standardised mortality ratio presented here. Comparing the observed / expected ratios for the SHMI for general population admissions during the period 2005 -2009 to the dialysis standardised hospital mortality shows largely a linear increase across the two measures. Plot points in Figure 5-15 are weighted for size to demonstrate that some of the more outlying results are due to small numbers of observations. The Pearson correlation coefficient between the SHMI and the dialysis HSMR was 0.384 (P=0.009).

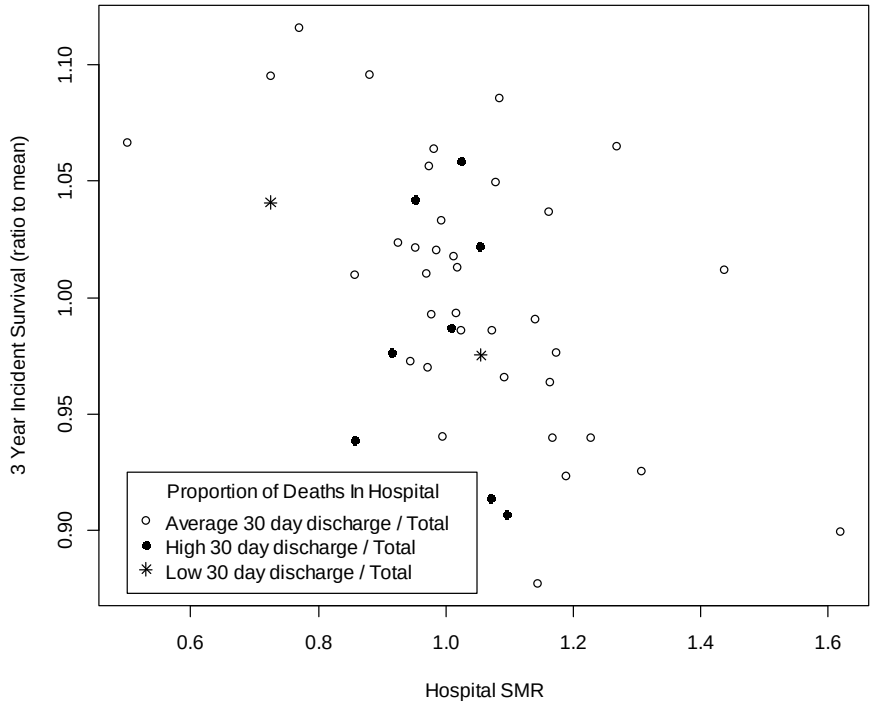


Figure 5-14 : Comparison between hospital standardised mortality and incident survival in RRT patients

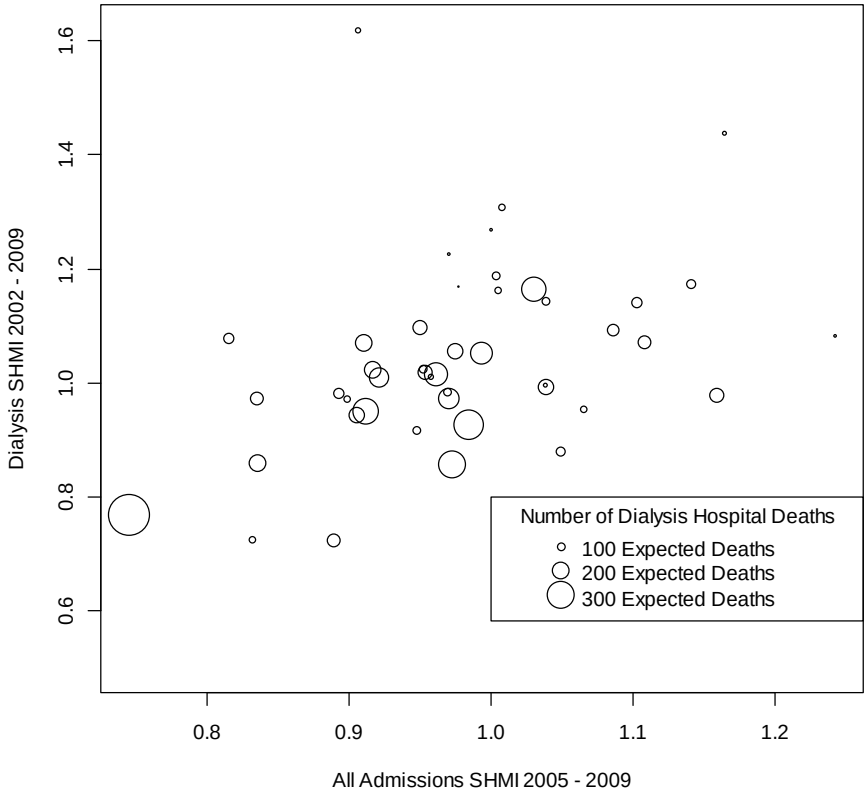


Figure 5-15 : Comparison between dialysis hospital standardised mortality and all patient standardised mortality (SHMI)

Discussion

Using linked data to reduce missing data as previously detailed, it was possible for the first time to report centre-specific incident survival for English renal centres, showing that following adjustment for demography and 16 comorbid conditions the number of outlying centres was reduced to one. Despite these similar outcomes residual differences existed for hospital standardised mortality. There did not appear to be a correlation between these two measures, however following multi-variate adjustment improvements over time were seen in both, despite an increase in crude hospital associated mortality.

When considering centre specific adjusted reporting, one could argue a demographic characteristic or comorbid condition should be adjusted for if it has an impact on survival, is outside the control of a centre, and it varies across centre, it. The ability to report a composite measure of comorbidity has allowed us for the first time to compare the case-mix of patients accepted onto RRT across England. The similar centre specific mean comorbid score across centres argues against variation in the type of patient taken on by an individual centre, for instance due to resource constraints and subsequent rationing of dialysis services(Mulkerrin 2000). Other registry reports show a greater burden of comorbidity in those arriving late or in an unplanned start (Webb et al. 2011), and adjustment for comorbidity may represent a surrogate for this, and employing an index of comorbidity would allow comorbid burden to vary with time in models where this was relevant. The variation in ethnicity and its established impact on survival (Pei et al. 2000) (Kucirka et al. 2011) mirrored in this study highlights the importance of ethnicity as an adjustment variable, however variation in relative risk between ethnic groups across age groups tested for by interactions was not identified (Yan et al. 2013). The variation and impact of ethnicity on centres mandates a high level of data completeness to enable adjustment. As per previous studies using UKRR data, inferior survival in the most socioeconomically deprived patients was observed, with the modest response perhaps explained by a limited impact on patients over 65 years of age(Caskey et al. 2006).

Van Manen reported in her analysis of ERA-EDTA registry data the variables of age, gender, primary renal disease, modality and country accounted for 14.4% of the variance in mortality, with comorbidity only adding a further 1.9% (van Manen et al. 2007). Perhaps the converse would also be true: that in addition to comorbidity, primary renal disease would add a similarly small amount. Additional explanations for the observation by van Manen exist, some within her discussion and some from other literature. The correlations between variables such as age and primary renal disease and comorbidity mean that indirectly comorbidity is already partially factored. The inclusion of country may account for some of the differences in national rates of cardiovascular disease as previously shown by Yoshino et al(Yoshino et al. 2006). Within the 16

comorbid conditions found predictive for incident survival in this investigation, diabetes, connective tissue disease and myeloma overlap with primary diseases, and patients with previous myocardial infarctions, vascular procedures and CABGs are likely to have renovascular disease as well.

Despite the possibility that adjusting for case-mix may have limited impact on centre specific survival, the influence of case-mix adjustment for the individual should not be understated. Using the proposed model 70% of white patients with diabetes aged 65 survive to three years whereas 76% (difference 6%, 95% CI of difference 2-9%) of South Asians with the same case-mix survive to the same time point. If the patients had a previous myocardial infarction and cardiac failure three year survival drops to 55% in the white and 63% in in the South Asians (difference 8%, CI of difference 2-13%) at three years. In addition, a degree of model precision is required to identify or explain outlying centres. Although the variables used for adjustment differ, our model prediction performance (C-statistic excluding centre 0.775, CI 0.769 – 0.782) is superior to that reported at three years using US data (0.669) (Liu et al. 2009), and one year using Canadian data (0.765). The residual variation in risk associated with some cardiovascular diseases such as myocardial infarction, valvular heart disease and claudication may imply a difference in how these conditions are managed in these renal centres or surrounding NHS trusts. Such non-constant risk may be explained by genuine differences in the hazard for mortality in the geographical areas that these renal centres serve (Nicholl 2007). A more likely explanation is the variation in the coding quality across NHS trusts in England. HES data quality has been the subject of discussion for some years, with a body of work claiming reasonable accuracy (Burns et al. 2012) and predictive ability (Aylin et al. 2007). An increase in coding "quality" manifested by the number of coding fields used per admission was observed in this study over time (chapter 4), and some of the improvements seen in the hazard for death for year of start of RRT is likely to reflect this over and above improvements in clinical care. This study has been able to recommend a minimum adjustment specification to adequately explain or identify outliers: The inclusion of COPD, previous myocardial infarction, congestive cardiac failure and the Diabetes-Age interaction in addition to age, ethnicity, socioeconomic status and year of start of RRT were sufficient to result in no outlying centres. Fortunately these conditions all exist within the UKRR comorbidity dataset, although congestive cardiac failure was not reported during the period this study covers.

New insight into institutional performance is gained from the analysis and reporting of hospital standardised mortality ratios. Importantly, even with the adoption of narrower control lines derived from the Poisson distribution compared with a random effects model, only four of the 46 centres reported in this analysis are outliers for hospital mortality following

adjustment for the seven variables of age, reason for admission, emergency admission, CCS group mortality, ethnicity, modality and comorbid score. Model performance in this setting reported a c-statistic of 0.810, which is inferior to the SHMI (0.913) and Dr Foster HSMR (mean c-statistic across diagnostic groups of 0.83), and the relatively high proportion of centres in control may be a factor of the low numbers of expected deaths (a factor of admission numbers) in each centre. One might hope that the high frequency of admission experienced by dialysis patients might mean that for a given admission, the mortality risk would be lower than the general population. The overall mortality of 5.2% exceeds that of general population admissions (which include kidney admissions) of 4.3% for males and 4.5% for females(Campbell et al. 2012). This increased risk needs to be put in context for the age of the cohorts. For the dialysis cohort, women were less likely to die per admissions than men(5.3% in males, 5.0 in females). For general population admissions between 45 and 84, the 30 day mortality rate in women was 4.9% compared to 5.4% in men, almost identical to that found in RRT patients.

The counterintuitive finding of greater levels of socioeconomic deprivation being protective for hospital mortality were found both in the SHMI (3.9% for the most deprived quartile vs 4.6% for the remaining quartiled groups) and this investigation. The most likely explanation for both these findings is the underlying admission rate for the most deprived groups. If more deprived patients are admitted more frequently for the same clinical condition as their less deprived counterparts(Saxena et al. 2006) but If the true underlying risk of death for the condition is the same, this will weaken the mortality risk in the more deprived cohort. Investigation into the impact of deprivation on admission rates forms part of subsequent work in this study.

The Office of National Statistics has highlighted increased mortality for the general population of 15% over the winter months, more specifically October to March(Office of National Statistics 2012). Findings here suggest a similar timing of this winter increase, but that perhaps the increase persists until later into the spring season.

Interrogation of the influence of other predictor variables offers some surprises and reassurances. The fact that unadjusted hospital mortality increases during the study period, but this association is reversed following multivariate adjustment (four percent increase per year became a four percent decrease per year) coupled with the increase in predicted mortality from 4.8% to 6.8% between 2002 and 2009 suggests an increase in severity of admissions. However, a reduction in low risk admissions may similarly be an explanation. The reversal of the odds ratio for thirty day mortality associated with peritoneal dialysis from 0.81

(95% CI 0.76 - 0.87) to 1.10 (95% CI 1.03 - 1.19) should be interpreted with caution as the latter model includes reasons for admission which are modality specific. The same odds ratio (OR) for mortality associated with PD in the one-model technique will be applied across all diagnostic groups and modality specific reasons for admission may apply undue leverage. Table 5-14 reveals that within the reason for admission groups mortality only differs significantly between modality in four of the twenty two diagnostic groups (access mortality OR for PD 2.03, sepsis OR 1.46, CKD/Dialysis Care OR 0.74 and peritonitis OR 0.43). Underlying differences in the coding of admissions between these modalities and their admission rates are likely explanations. A lower admission rate seen in the literature for PD patients coupled with the better social or community coping mechanisms(Plantinga et al. 2010). These could result in unmeasured or inadequately factored differences in severity compared to their haemodialysis counterparts when peritoneal dialysis patients are admitted. Indeed the issue identified with socioeconomic status may contribute as uptake of peritoneal dialysis has been found to be lower in more deprived groups(Briggs et al. 2013).

That thirty day mortality following discharge is greater in patients who are referred late, but that this affect is attenuated with time seems logical. Admission rates are certainly higher in the first 3 months of RRT, and previous studies have shown late referral does not influence admission rates beyond this(Arora et al. 2000). The combination of these two factors is most concerning; in hospital more often, and more likely to die as a result; a multiplicative effect. That the inclusion of this variable identifies two further outlying centres for incident survival following its inclusion, only to have them explained by the inclusion of primary renal disease may be explained by the differing rates of underlying progression and varying acute kidney injury risk associated with primary renal disease. Together they add comparatively little in terms of model performance of identification of new outliers.

The correlation between incident survival, thirty day mortality post discharge and the SHMI would suggest that these measures are registering similar outcomes. There appears to be little pattern to how location of death influences the relationship. The one centre with lower than expected incident survival had hospital mortality within the 95% confidence limits and higher than expected proportion of deaths occurring in hospital or within 30 days of admission than other centres. Aside from the role of chance, this could argue for residual issues in either of the two models. The coding of reason for admission or coding regrouping may fail to accurately reflect the true underlying hospitalisation risk (and indeed this could be the case with a number of other variables). Problems with the incident survival model may fail to adjust this centres survival appropriately. Overarching all of this are concerns raised by other authors that there is no definitive correlation between hospital standardised mortality

rates and clinical care(Pitches et al. 2007). Perhaps the differing outlying centres between these measures add weight to this argument.

In summary, this chapter determined:

- Comorbid burden across renal centres was largely similar.
- Ethnicity was a powerful predictor of incident survival and hospital standardised mortality, with Caucasian patients having higher mortality despite similar comorbidity.
- Centres with worse than expected incident survival were reduced from four to one following comprehensive adjustment for demography and comorbidity.
- Despite a worsening of crude hospital associated mortality and increasing comorbid burden over the study period, standardised hospital mortality improved. This was also observed with incident survival.
- There was no clear correlation between centre specific incident survival and hospital associated mortality.

Chapter 6 *Events associated with hospitalisation and the dialysis pattern in patients receiving haemodialysis*

Background

Haemodialysis (HD) involves removal of toxins and excess water directly from the patient's blood circulation using a machine, which pumps the blood out of the patient and passes it across a membrane. Differences in the concentration of toxins allow their removal by diffusion or convection. A difference in pressure across the membrane regulated by fluid removal within the dialysis circuit allows removal of excess fluid.

Access to the circulation can be gained in a number of ways. When time allows, the joining of an artery to a vein allows the vein to enlarge and thicken, allow the repeated insertion of needles into the vessel to extract and return blood. When this arterio-venous fistula is not possible, the insertion of a plastic catheter into a large blood vessel allows access to the blood supply for a temporary or more sustained period of time depending on the technique of insertion. Both forms of access are susceptible to problems such as thrombosis (the build-up of blood clot) (Hodges et al. 1997) or infection(Butterly et al. 2000), with dialysis catheters generally being associated with a higher incidence of problems and inferior patient outcomes(Rayner et al. 2004). As a result an arterio-venous fistula is considered the gold standard of care (2006).

Haemodialysis is most commonly delivered as an outpatient in the hospital or satellite dialysis unit setting. The most common practice is for the patient to attend for dialysis three times a week, with treatments taking upwards of three hours. The hospital setting normally represents a haemodialysis ward or unit on the physical grounds of an acute admitting hospital. This is therefore associated with easier access to medical input and as a result attracts a different mix of patients (for instance older (Roderick et al. 2004)) or those early on in their haemodialysis career when problems are most likely to arise.

Haemodialysis can also be delivered at home by the patient themselves or an appropriately trained relative or friend, following the installation of necessary equipment. Home HD was the original format in which patients were offered RRT when it became mainstream in the UK. This allows patients to vary and often increase their dialysis frequency, resulting in better control of the metabolic consequences of ERF (for instance calcium and phosphate accumulation (Ayus et al. 2007)), and survival(Weinhandl et al. 2012). There are

also quality of life advantages, and a degree of flexibility often enabling patients to return to employment.

In the UK 4996 of the 6,835 (73.1%) people who started RRT in 2011 commenced treatment on H, joining the 22,706 patients already receiving haemodialysis(Gilg et al. 2013; Shaw et al. 2013). Review of the literature highlights the strong association with case mix and admission rates (Metcalfe et al. 2003), and that admission rates themselves vary with time on haemodialysis (Arora et al. 2000) and the pattern of haemodialysis over the week (Foley et al. 2011). Centre specific hospitalisation rates exist for US dialysis providers, but have not been developed in the UK setting and may fail to adjust for repeated events within observation periods. Variation of admission patterns across the haemodialysis week between centres has not been explored.

Aims and Objectives

- To derive centre and patient specific admission rates for haemodialysis patients.
- To identify variables necessary for adjustment for centre specific admission rates.
- To reveal centres with outlying admission rates.
- To identify patterns in admission rates according to haemodialysis attendance pattern.
- To derived a centre specific measure of dialysis quality according to admission pattern.

Analysis specific methods

Admission rate in first year

Cohort and treatment time

Patients included in the analysis of admission rates in the first year had survived beyond 90 days of starting RRT, were on haemodialysis on their 90th day receiving RRT and were in an English centre receiving their treatment. Patients who transferred out before 90 days, received a transplant or ceased therapy were excluded. Patients who began on other modalities but moved to haemodialysis before the 90th day are included but differences in these subgroups are explored separately. Beyond 90 days, if a patient was transplanted or died before the end of the first year then time and events prior to these events were included and analysed with adjustment for variable follow-up. Patients were assigned to the centre they first received RRT.

Statistical methods

Time in hospital was subtracted from time at risk as described in chapter 3 with an offset included in the model for varying time at risk. Recognising the existence of an interaction between age and diabetes in the existing literature and in the survival analyses presented herein, an interaction term was specified between these variables, allowing the influence of the presence of diabetes on admission rates to vary according to age.

All admissions were included up until admission for transplantation, irrespective of whether they were or emergency or elective in nature. A unit which underperforming in the vascular access it generates and maintains may manifest with a large number of elective admissions to intervene on arterio-venous fistula. The unit of admission was the superspell, with admissions spanning hospitals counting as one admission.

All cause admission rates in year one were modelled using negative binomial regression (with and without zero inflation, explained in Chapter 3) with model performance analysis and centre specific standardisation. Modelling the first three months separately to the subsequent nine months and combination of these as a predictive method was compared to modelling the full 12 months as a block. In cases where there was zero time at risk in either block of the combined model, cases were excluded. Model performance was assessed using observed/expected centiles, where improvements manifest with the centiles increasingly clustering around the value of 1.0. Recognising that in cases where observed counts were zero, ratios would be zero irrespective of the predicted (or expected) counts, root mean squared error was also reported (see chapter 3).

Admission pattern analysis

Cohort and variables

For the admission pattern analysis, any patient receiving haemodialysis having survived ninety days from first RRT treatment was initially included. Patients were analysed per treatment week, with exclusions of weeks where dialysis activity ceased or the patient was admitted for the entire week.

Treatment weeks were determined using the UKRR treatment timeline. Weeks were retained if patients were receiving treatment in a centre with adequate coding of haemodialysis, were attending three times a week and were not in hospital for the entire week. Prolonged periods with no haemodialysis attendance were excluded from the analysis. For weeks were there was some time in hospital, days in hospital were subtracted from the

time at risk when calculating admission rates for days of the week. Where modalities were changed the week during which this occurred was excluded, however if death occurred it was retained.

For the admission pattern analysis, comorbid information, age and time on dialysis were updated for every analysis week. Laboratory variables were taken from the most recent of the two quarters preceding the analysis week. If both quarters had no data the laboratory data was treated as missing. Continuous laboratory variables were grouped into four equal groups unless clinical best practice targets or guidelines suggested alternative grouping (e.g. haemoglobin or urea reduction ratio).

Dialysis pattern, admissions and mortality

Haemodialysis attendance was determined from elective admissions with the coding of the CLASSPAT variable in HES reflecting plans same day/night activity. Only admissions during period when the patient was receiving haemodialysis according to the UKRR timeline were analysed (see chapter 3). A given attendance was assigned the relevant day of the week for treatment week it occurred in. The attendance day of the weeks were then assigned a pattern based on two one day gaps and one two day gaps. For each individual patient neighbouring treatment weeks were analysed to determine if patterns were similar and minor deviations due to non-attendance or periods with hospitalisation were assigned patterns from neighbouring weeks. Scanning forward, when a new "three times a week" pattern was established for 4 weeks or more this pattern was adopted and retrospectively applied to the first occurrence of this pattern.

Admissions and deaths for each week were assigned days of the week and then these were copied across to a unified pattern which fitted all possible "three times a week" templates, the three most common of which are illustrated in Table 6-1:

Table 6-1 : Common haemodialysis schedules on for patients recieveing haemodialysis three times a week

Pattern	**HD1**	**HD1a**	**HD2**	**HD2a**	**HD3**	**HD3a**	**HD3b**
	Dialysis Session	1 Day Gap	Dialysis Session	1 Day Gap	Dialysis Session	2 Day Gap	
Mon/Wed/Fri	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Tue/Thu/Sat	Tue	Wed	Thu	Fri	Sat	Sun	Mon
Sun/Tue/Thu	Sun	Mon	Tue	Wed	Thu	Fri	Sat

Zero length of stay elective admissions were excluded due to concerns over the mis-coding of dialysis attendances as ordinary admissions rather than ordinary day-night attenders. The

unit of admission counted was the superspell, with the definition of a superspell and admission type is explained in Chapter 3. The location of death was determined using the *DISMETH* variable in HES, where a patient who died whilst in hospital was coded as discharged dead.

Statistical methods

Confidence limits for event rates were determined with the Poisson distribution. To determine if there were differences between groups with regard to the relative increase in events between HD1 and the rest of the week, the rate ratio interaction test was employed (detailed in Chapter 3 and Equation 2). Longitudinal assessments of the ratio of HD1 to the rest of the week were performed by categorising dialysis weeks into groups relative to the start of dialysis and the date of death. Sensitivity analyses were performed to determine if the cohort from centres where dialysis attendance was coded was generalizable to the entire cohort and if methods to identify suitable dialysis weeks biased the analysis. This was performed as hospital based dialysis units may code more than satellite centres, and patients in the latter are less comorbid. The demography of the selected and excluded patients was compared at the start of RRT, and admission, hospitalisation (admitted days) and mortality rates for the selected and unselected across days of the week (Monday to Sunday, no translation for haemodialysis attendance pattern) were compared.

Results

First year admission rate analysis

Cohort and Demographics

Of the 21271 cases who began RRT and were suitable for analysis, 13185 survived 90 days and were treated with haemodialysis throughout this period. 285 patients started on PD but were subsequently transferred to HD and will also be included in this analysis. 728 patients who started on HD but were converted to PD will be analysed in the PD chapter. The demographics of the cohort treated on HD by day 90 are shown in Table 6-2:

Table 6-2 : Demographic information on incident cohort

Age At Start of RRT		62
Gender (Male)		62.8%
Ethnicity	White	79.2%
	Black	6.5%
	South Asian	7.1%
	Other	7.1%
Socioeconomic Status Fifth	Most Deprived	21.5%
	2	22.0%
	3	20.6%
	4	18.9%
	Least Deprived	17.0%
Chronic Obstructive Pulmonary Disease		6.4%
Comorbid Conditions (See chapter 4)		
Arrhythmia		3.9%
Congestive Cardiac Failure		17.4%
Coronary Artery Bypass Graft		5.2%
Depression		2.7%
Cerebrovascular Accident		8.5%
Acute Myocardial Infarction		13.2%
Lymphoma		4.2%
Neurological Disease		4.1%
Vascular Stent		4.0%
Valvular Heart Disease		4.1%
Cancer		8.2%
Connective Tissue Disease		3.6%
Peptic Ulcer Disease		5.3%
Claudication		8.0%
Diabetes		33.2%

Admission Rate and Influence of Demography

The admission rate for the overall cohort for the first year of haemodialysis was 2.52 (95% CI 2.49 – 2.55). The highest admission rates were observed at the start of renal replacement therapy, with patients subsequently establishing themselves on treatment. The high admission rate is emphasised in Figure 6-1.

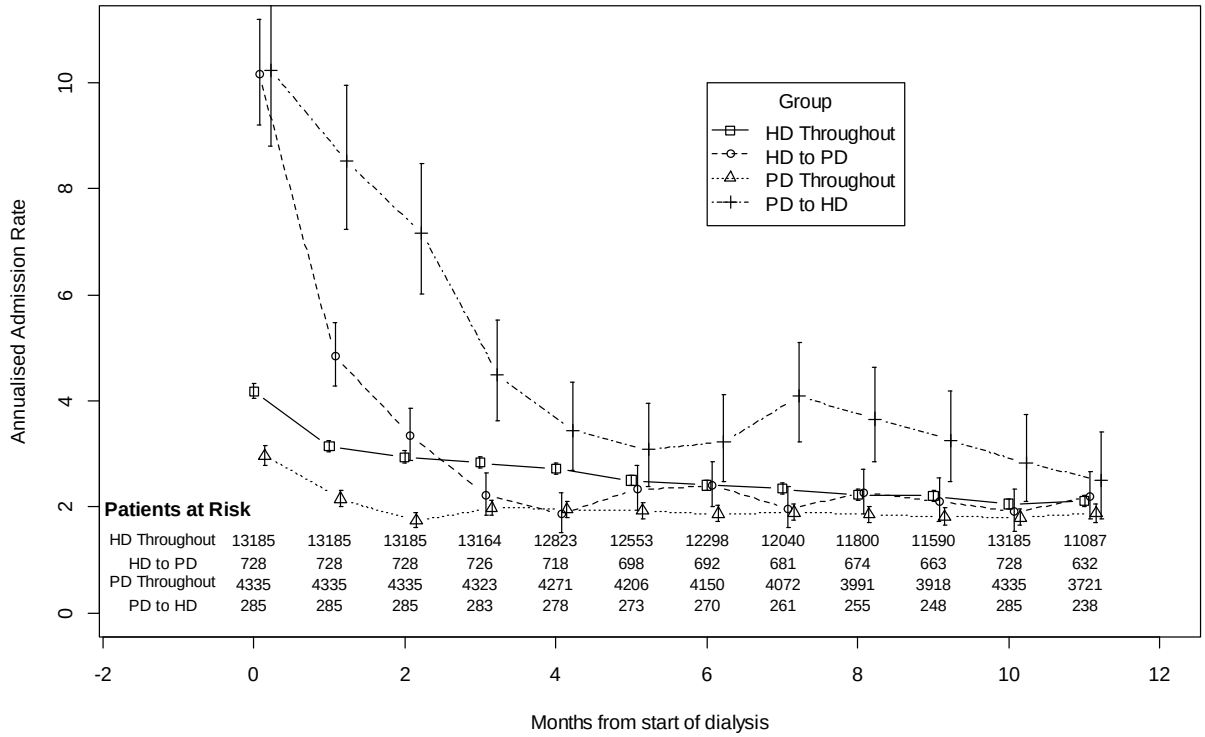


Figure 6-1 : Annualised monthly admission rates for the first year of dialysis according to modality at 90 days. Patient numbers at risk for admissions are detailed at the bottom.

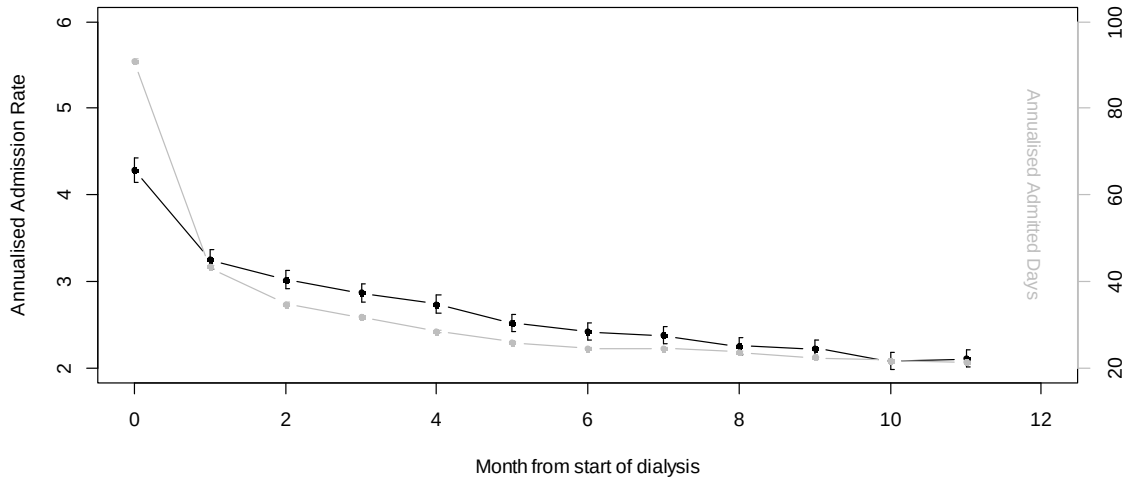


Figure 6-2 : Admitted days and admission rate by month for the first year of haemodialysis

When reviewed per month for the first year of haemodialysis, the days admitted drops quicker (falling to a third of the first month by month three) than the admission rate which has a more gradual decline (Figure 6-2). This could be interpreted as a reduction in length of stay per admission with greater time established on therapy.

Generally, demographics of individual patients contributed to admission rates. The impact of age on admission rates had little impact, with the only marked differences in the rates being in

youngest and oldest age-groups as illustrated in

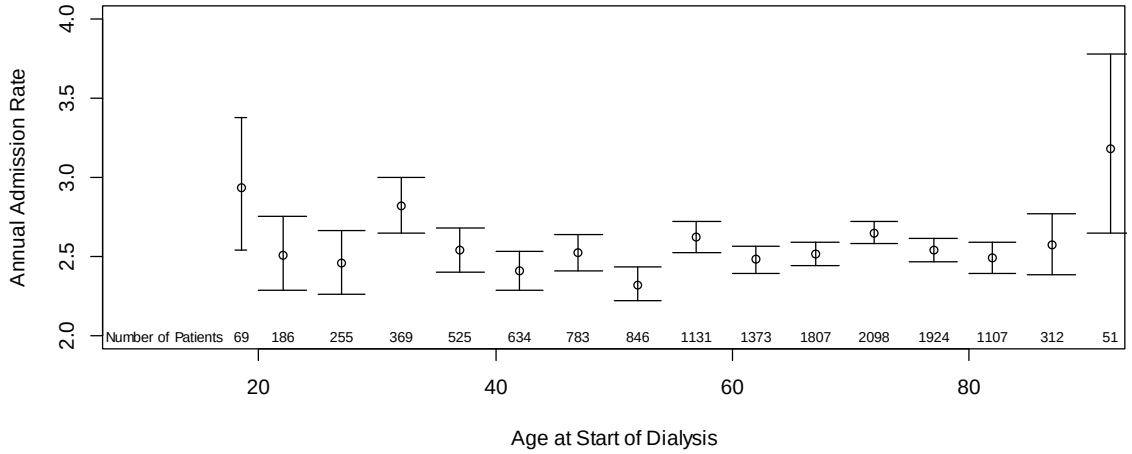


Figure 6-3. Using wider age-bands of <40, 40-65 and >65 we find rates of 2.61 (95% CI 2.53 – 2.70), 2.48 (95% CI 2.44 – 2.53) and 2.56 (95% CI 2.53 – 2.60) respectively, maintaining the U-shaped distribution.

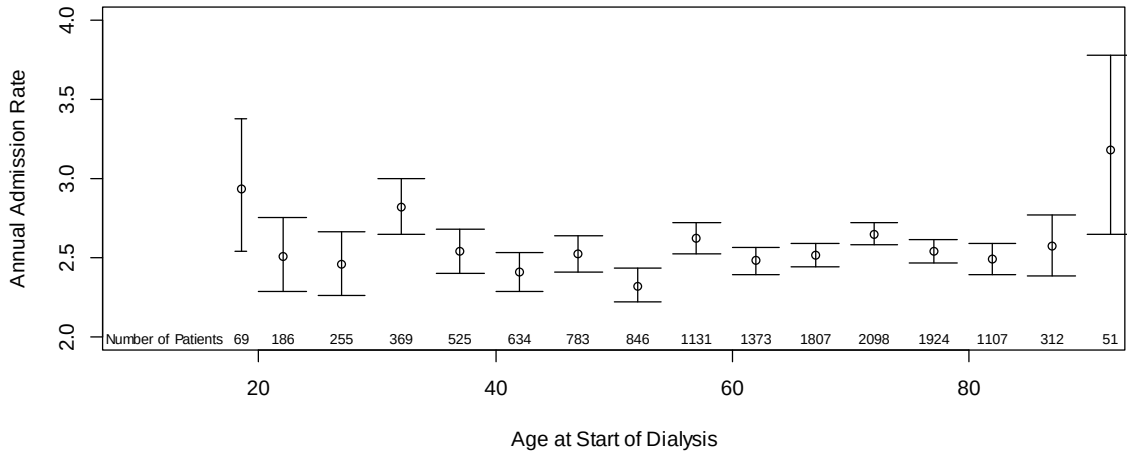


Figure 6-3 : Admission rate in the first year according to age.

Women were more likely to be admitted than men over the entire period (2.67/year vs 2.46/year, rate ratio 1.08, 95% CI 1.06 – 1.11), with a similar increase seen across the first three months and the latter nine months (rate ratio 1.09 across both periods).

The ethnic group of the patient was predictive of admissions in the first year, with the highest admission rates seen in white patients (2.625 per year, 95% CI 2.593-2.658) compared to Black (2.192 per year, 95% CI 2.094-2.294), South Asian (2.189 per year, 95% CI 2.095-2.287) and Other (2.294 per year, 95% CI 2.197-2.395). Socioeconomic status had an almost linear association with admission rate, with the highest rate (2.787, 95% CI 2.707 – 2.870) seen in the most deprived tenth, and the lowest seen the least deprived (2.353, 95% CI 2.253 – 2.457), illustrated in Figure 6-4.

Comorbidity, defined as the presence of absence of individual conditions, generally accounted for an additional one admission in the first 12 months following the start of RRT (2.03 admissions vs 2.83 admissions per year, rate ratio 1.40, 95% CI (1.36 – 1.42).

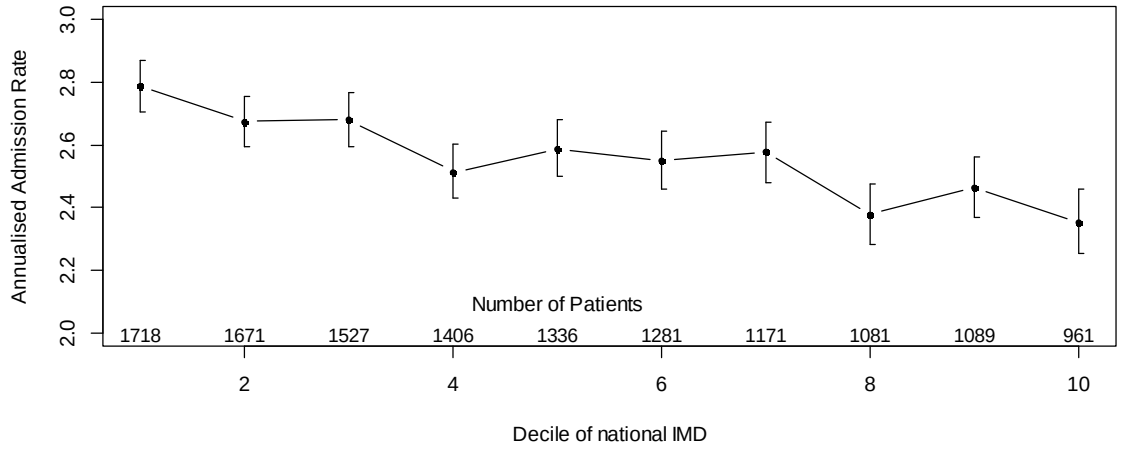


Figure 6-4 : The decline in admission rates in the first year of haemodialysis associated with decreasing socioeconomic deprivation. Patient numbers within socioeconomic centiles are detailed at the bottom of the graph.

The influence of individual conditions compared to patients without this condition is shown in Figure 6-5. Comorbidity as a continuous indexed variable as described in chapter 5 was associated with increasing admission rates as demonstrated in Figure 6-6, although the number of cases in higher comorbid groups is small with only 6.7% of patients having a

comorbid score of four or more.

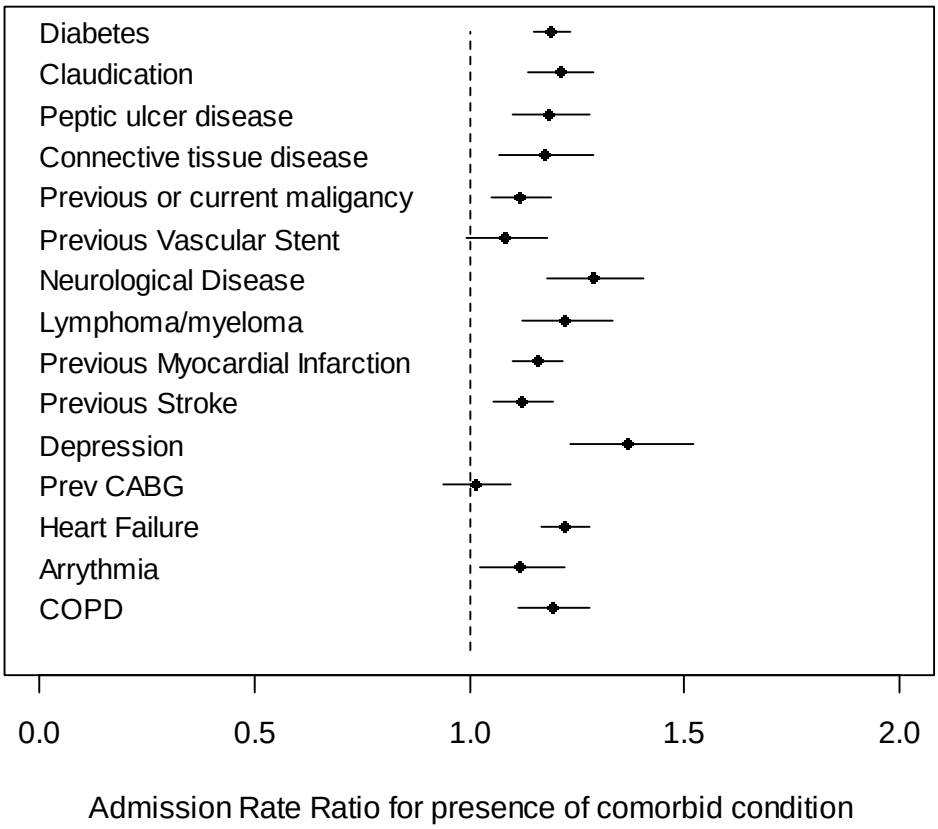


Figure 6-5 : The influence of comorbid conditions on admissions in the first year of haemodialysis

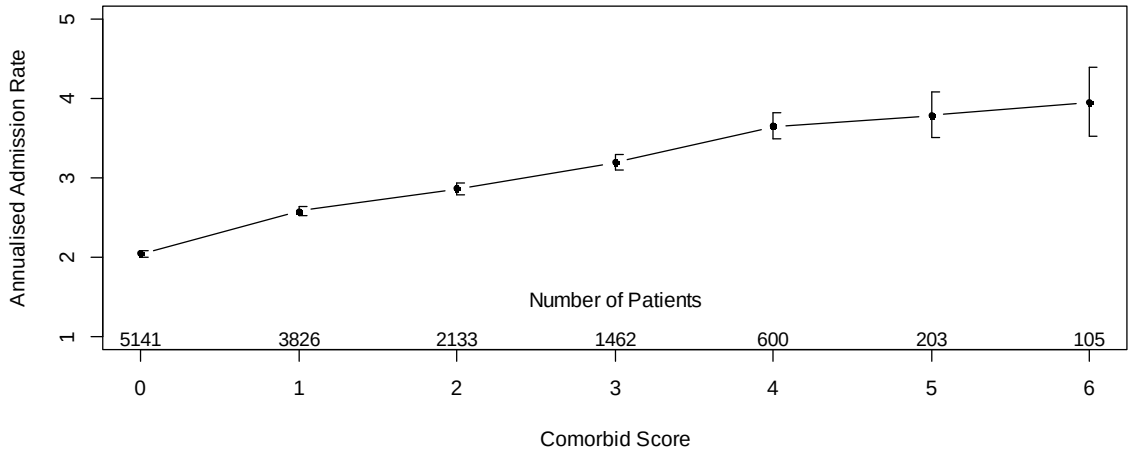


Figure 6-6 : The increase in admission rates in the first year associated with greater comorbid burden as measured by comorbid score (derivation detailed in Chapter 5)

Patients who transferred from peritoneal dialysis to haemodialysis in their first 90 days had lower comorbid burden than patients who remained on haemodialysis throughout, and were less comorbid than those staying on peritoneal dialysis (see chapter 7). Patients who

transferred from peritoneal dialysis to haemodialysis had a greater comorbid burden compared to those remaining on haemodialysis and peritoneal dialysis throughout (Table 6-4).

Primary renal disease had an influence on admission rates in patients from centres where it could be robustly analysed (Table 6-3). If uncertain and missing were excluded conditions with notable rates include Diabetes and Other (>2.90 admissions/year) and Polycystic disease (1.94 admissions per year). Diabetes accounts for the PRD in 25.6% of cases in this cohort.

Late referral in the patients for whom an analysis was possible according to the recommendations we made in the "date first seen by a nephrologist" section of Chapter 4 accounted for a 19% increase in admissions (2.81 vs 2.36, 95% CI on ratio 1.16 – 1.22) in patients seen from 6 months from first treatment. The effect of earlier referral is seen in Figure 6-7, revealing a larger difference from 6 months or less.

Table 6-3 : The influence of primary renal disease on admission rates in the first year of haemodialysis

Primary Renal Disease	Admission Rate in First Year	95% Confidence Interval
Missing	2.36	2.17 - 2.57
Diabetes	2.90	2.84 - 2.96
Glomerular disease	2.17	2.09 - 2.25
Hypertensive	2.20	2.1 - 2.31
Polycystic	1.94	1.85 - 2.04
Pyelonephritis	2.60	2.50 - 2.70
Renovascular Disease	2.58	2.48 - 2.68
Other	2.94	2.86 - 3.01
Uncertain	2.17	2.11 - 2.23

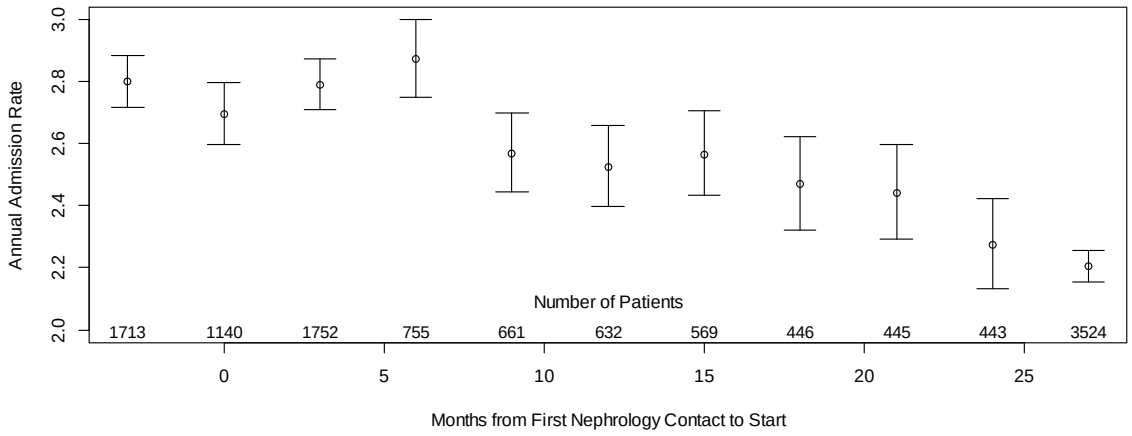


Figure 6-7 : The decline in admission rates associated with increasing time from first nephrology contact to start of dialysis

Changing modality heavily influenced the number of hospitalisations in the first year, with the majority of hospitalisations being clustered around the UKRR reported first date of change in modality, as illustrated in Figure 6-8. Haemodialysis patients who changed to peritoneal dialysis were admitted earlier for switches than those changing from peritoneal dialysis to haemodialysis. Rates of hospitalisation are already higher than the overall cohort in the months prior to the switch.

Admission rates in haemodialysis patients improved over the study period, despite an increase in the comorbid burden of patients increased over the same period (Table 6-5).

Table 6-4 : The influence of changing dialysis modality on admission rates in the first year

Modality	Number of patients	Annualised admission rate (95% CI)	Mean comorbid score (95% CI)
HD Throughout	13185	2.50 (2.47 – 2.53)	1.2356 (1.2127 - 1.2586)
HD to PD	728	2.83 (2.71 – 2.96)	0.9808 (0.8920 - 1.0695)
PD Throughout	4335	1.87 (1.82 – 1.90)	0.7811 (0.7495 - 0.8126)
PD to HD	285	4.26 (4.02 – 4.52)	0.9509 (0.8223 - 1.0794)

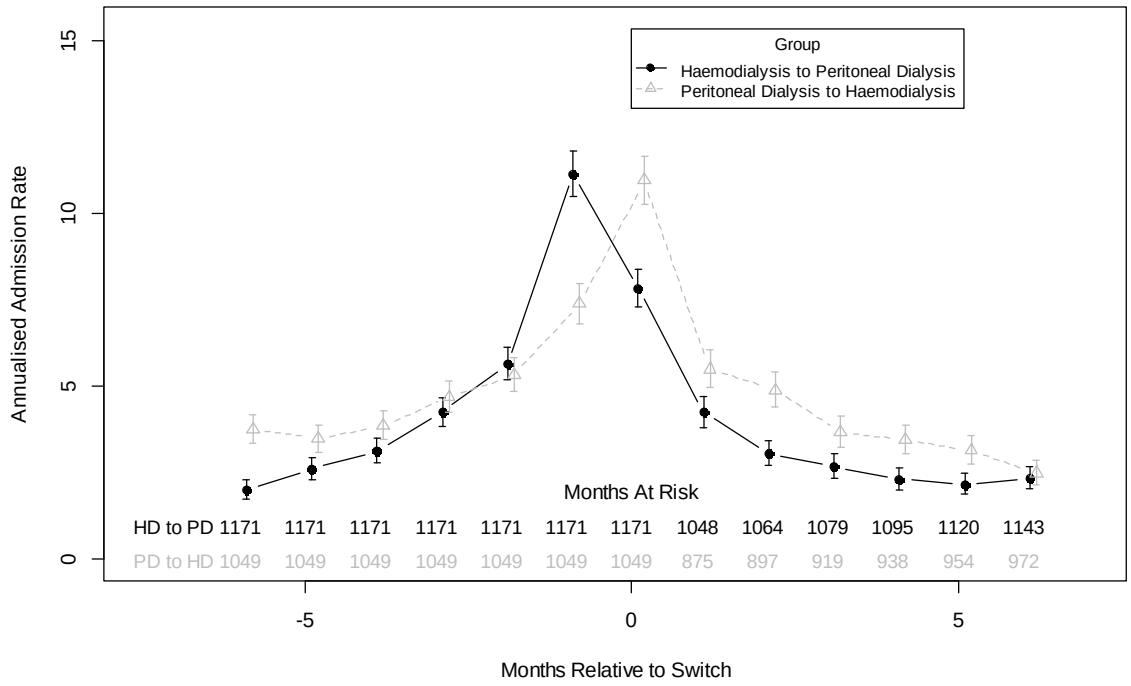


Figure 6-8 : The increase in admission rates per month seen approaching modality change within the first year of dialysis. Patient months at risk are reported at the bottom of the graph

Table 6-5 : The decline in admission rates between 2002 and 2006

Year of start	Comorbid Score	Age of Start of RRT	Admission Rate
2002	1.102 (1.045 - 1.159)	63.177 (62.509 - 63.845)	2.770 (2.695-2.848)
2003	1.142 (1.089 - 1.195)	62.281 (61.632 - 62.93)	2.699 (2.629-2.771)
2004	1.219 (1.17 - 1.268)	62.664 (62.086 - 63.242)	2.542 (2.481-2.604)
2005	1.266 (1.217 - 1.315)	62.62 (62.059 - 63.181)	2.524 (2.467-2.583)
2006	1.337 (1.29 - 1.384)	62.426 (61.897 - 62.955)	2.311 (2.258-2.364)

Lengths of stay for individual admissions vary across individuals and centres, a graph of annualised centre admission rate compared to admitted days per years is shown in Figure 6-9. Assuming similar lengths of stay for each admission, there should be a linear association between centre admission rate and hospitalised days per annum. One centre is highlighted with extremely high bed usage, consuming approximately three times the length of stay for its admission rate.

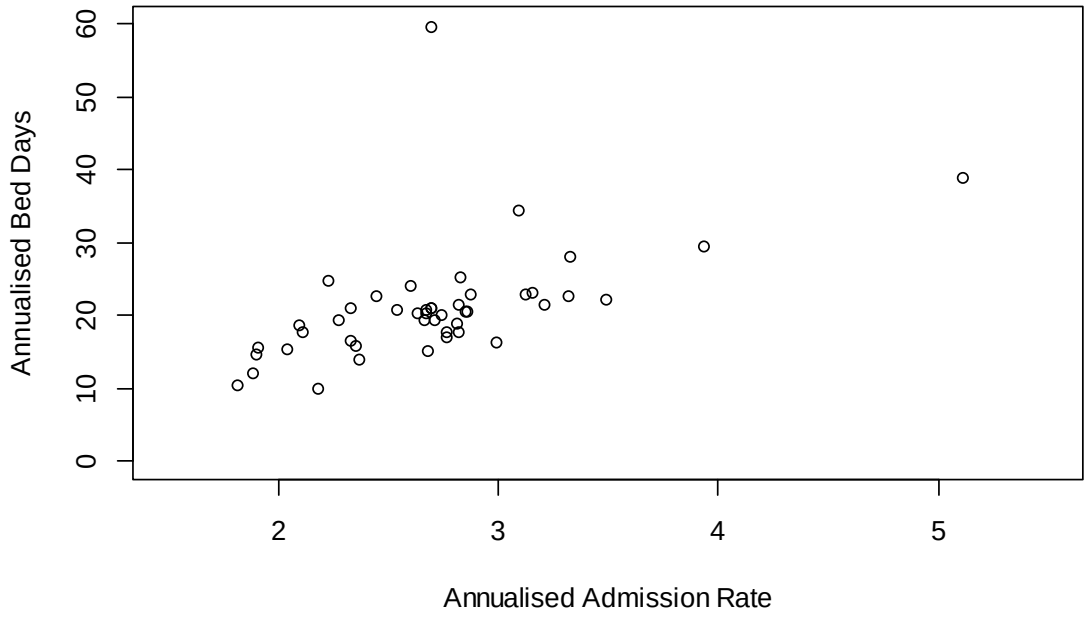


Figure 6-9 : Centre-specific admission rate and admitted days in the first year

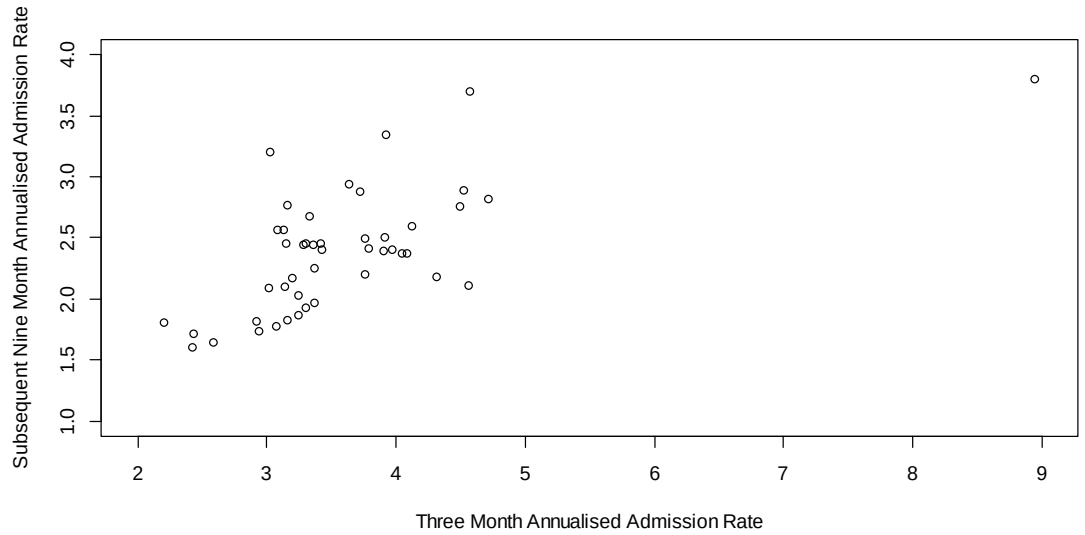


Figure 6-10 : Annualised admission rates in the first three months and subsequent nine months of haemodialysis

The relationship between early admission rates within three months and admission rates later in the year was fairly linear. In general centres with high admission rates early on in the haemodialysis treatment have sustained high rates in the final nine months of the year. Figure 6-10 shows one centre with high rates for both periods, and a group of centres towards the upper left of the graph who have proportionately higher rates of admission in the latter nine months than early on.

Multivariate modelling and modelling methods

Model types and influential variables

Centre specific reporting of frequency of admission by other authors has primarily used time to first event analysis, and during the observation period in question the analysis has excluded subsequent events. The following table illustrates the number of patients in whom admissions would go unobserved if this method was adopted, including full year analysis and stratification by within the first three months and thereafter.

Table 6-6 : The proportion of patients experiencing two or more admissions, potentially censored by time to first admission analyses

Model Period		Percentage
First three months	Zero Admissions	50.7%
	One Admission	29.1%
	Two or More Admissions	20.2%
Subsequent nine months	Zero Admissions	31.1%
	One Admission	24.7%
	Two or More Admissions	44.1%
Full twelve months	Zero Admissions	21.7%
	One Admission	22.2%
	Two or More Admissions	56.1%

A substantial proportion of patients, as much as 56% if the full twelve months were modelled, would have events excluded from the analysis if a time to first event method was adopted. Statistically significant variables in multivariate analysis of factors contributing to admission rates in the first twelve months are identified below including stratification by normal negative binomial and zero inflated methods and prediction within and beyond the first three months. In summary comorbidity remains strongly predictive for the count side of zero-inflated models, but less predictive of zero admissions. Interactions were tested for between diabetes, gender, age and ethnicity were explored in all modelling techniques, with positive interactions between age and diabetes. Interactions were specified for these variables for the remainder of the analysis. Model prediction performance of the non-inflated and zero-inflated methods are detailed using observed/expected ratios in appendix 6a and reported with sequential inclusion of age, socioeconomic status and ethnicity, and finally with the inclusion of significant comorbidities as categorical variables. An improvement in the root mean square error (RMSE) from 2.65 days to 2.54 days is seen with the addition of all predictive variables. The centiles for observed/expected ratios became more clustered around one suggesting improved model performance. In a sub-analysis of centres with adequate quality late referral data in a cohort starting RRT beyond October 2003 late referral is predictive, adds marginal improvement of RMSE by a 0.07 days and the influence of other

demographic variables largely persists (appendix 6a). The best RMSE is seen with the stratified three month / nine month zero inflated negative binomial method. It is likely that this is due to unobserved improvement in predictions of observations where observed counts are zero, as there is a decline in observed/expected ratios in the 50th and 75th centiles. Understanding how these different modelling techniques have manifested in their precision is important, as using different techniques but adjusting for the same variables could result in differing outlying hospitals. Given the issue with zero counts masking changes in prediction performance, the RMSE may be a better judge of overall performance. The stratified (three month / nine month) zero inflated negative binomial has the lowest RMSE and a reasonable O/E at the 50th centile and is therefore taken forward.

Table 6-7 : Statistical significance of predictor variables in a range of modelling strategies

Model	Negative Binomial	Zero Inflated Negative Binomial				Zero Inflated Negative Binomial	
Period	0 - 12m	0 - 3m		3 - 12m		0 - 12m	
	Count	Zero Inflation	Count	Zero Inflation	Count	Zero Inflation	Count
Age	●*		○		●		●*
Sex	●		●	●	○	●	●
Ethnicity	●		●	○	●		●
Socioeconomic Status	●		○	○	●	○	●
Year of Start	●		●	○	●	○	●
Comorbid Conditions:							
COPD	○		○		○	○	●
Arrhythmia							
Cardiac Failure	●		●		●	○	●
CABG					○		
Depression	●		●		●		●
Stroke							○
Myocardial Infarction	○			●	○	○	○
Lymphoma/Myeloma	●		●	●	●	●	●
Neurological Disease	●		○	○	●	○	●
Vascular Disease					○		
Valvular Heart Disease	○					○	
Cancer	●		○	○	●	●	●
Connective Tissue Disease	●		○	○	●		●
Peptic Ulcer Disease	●				●		●
Claudication	●		○		●	○	●
Hypothyroidism	○						
Diabetes	●		●	●	●	●	●

*Age/Diabetes interaction (e.g. differing admission rates in younger vs. older diabetes patients, persisting after multivariate adjustment), ○ – P<0.05, ● – P<0.001

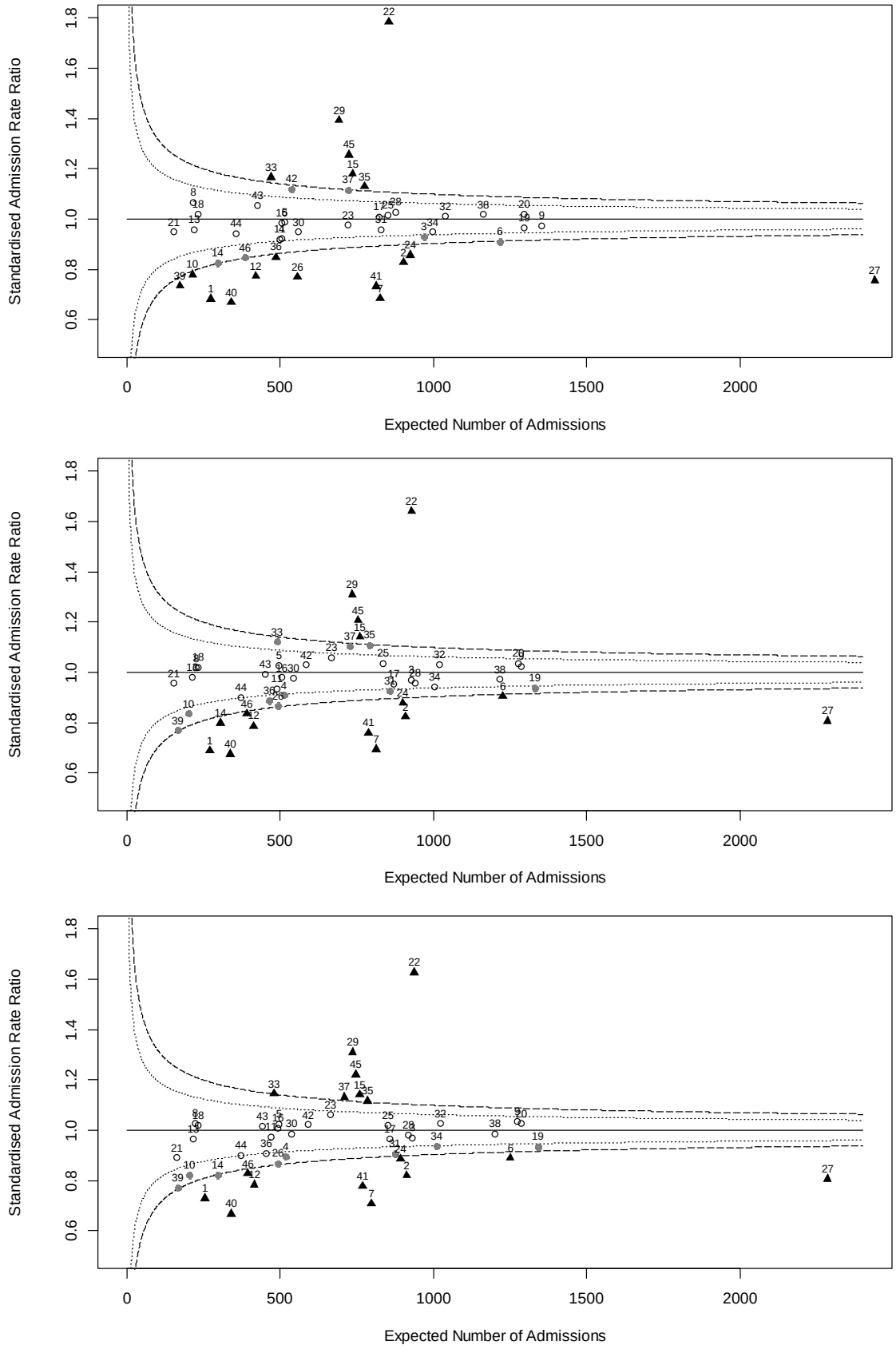


Figure 6-11 : Funnel plots of centre specific standardised admission rates in the first year of haemodialysis identifying outliers following adjustment. Top: Adjustment solely for age. Middle: Adjustment for age and demography. Bottom: Adjustment for age, demography and comorbidity. Outlying centres are largely unchanged by comprehensive multivariate adjustment.

The significance of case-mix adjustment on centres is demonstrated on the following funnel plots on the previous page (Figure 6-11). Adjustment purely for age and sex highlights eight centres with higher than expected admission rates. Following adjustment for socioeconomic status, ethnicity and year of start seven centres persist with higher than expected admission rates (three beyond the 95% control line and four beyond the 99.8% control line). Following adjustment for comorbidity the original seven centres remain with higher than expected admission rates, all beyond the 99.8% control line.

In the selected centres where late referral can be utilised (previously identified issues in chapter 4), following adjustment for age, sex, ethnicity, socioeconomic status, year of start and comorbidity, four centres are outliers using Poisson control limits. The addition of late referral and primary renal disease identifies one additional outlier.

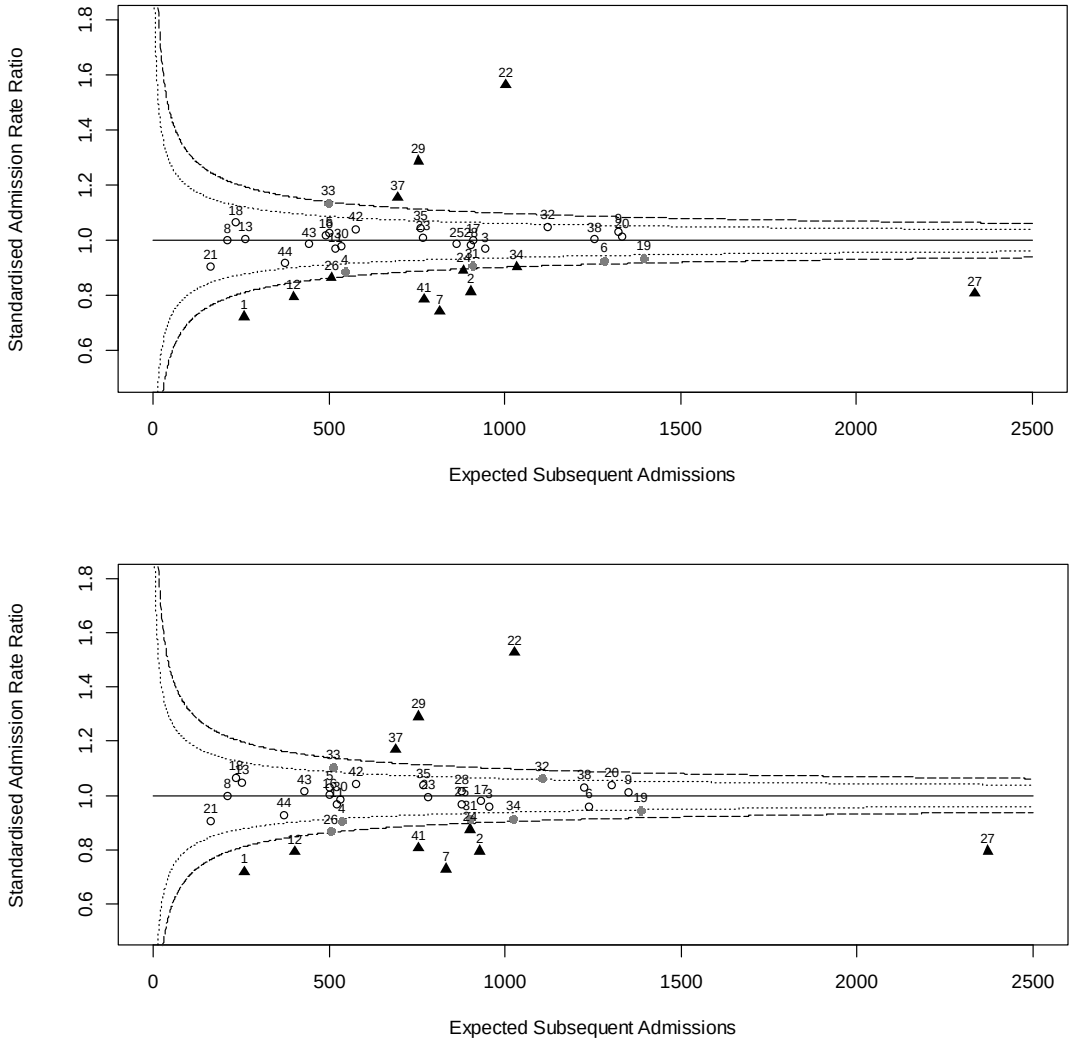
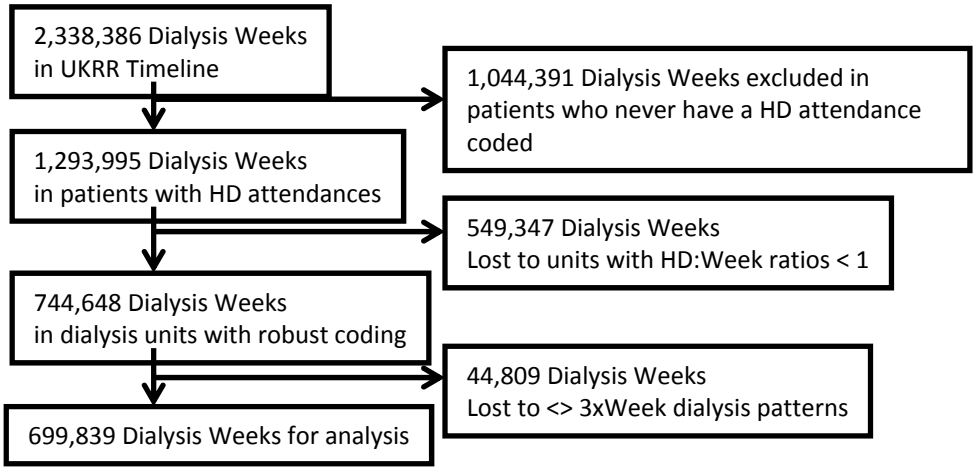


Figure 6-12 : Funnel plots for centre specific admission rates for first year of haemodialysis following previous adjustment for age, demography and comorbidity (top) and additional adjustment for primary renal disease and late referral (bottom) in suitable centres

Admission pattern analysis

From the UKRR timeline 2,379,120 weeks of dialysis activity were identified in 18,246 unique patients. Following the exclusion of patients who never had dialysis coded, centres who did not adequately record haemodialysis attendance and deviation or failure to establish a three times a week haemodialysis pattern 699,839 weeks of dialysis activity in 4770 patients was left available for analysis. The process of exclusion of cases is shown below. The excluded patient-weeks were retained for sensitivity analysis.



Admission pattern

Overall and type specific admission rates and ratios

The admission rate overall for the pattern cohort was 2.87 admissions per year (95% CI 2.84 –2.90), with the elective admission rate accounting for 1.39 admissions (95% CI 1.37-1.41) and the emergency admission rate accounting for 1.48 (95% CI 1.46-1.51) per year. The admission rate per dialysis day of the week was highest on HD1 for both emergency (2.28, 95% CI 2.21 - 2.35) and elective (2.53, 95%CI 2.45 – 2.60) admission types when compared to the rest of the week (2.44, 95% CI 2.52- 2.58) and 1.35, 95% CI 1.33 – 1.37 respectively). The ratio between HD1 and the rest of the week was 1.88 (95% CI 1.84 – 1.93) overall, with ratios of 2.11 (95% CI 2.04 – 2.18) and 1.69 (95% CI 1.63 – 1.74) observed for elective and emergency admission types respectively. These groups of admissions are observed in Figure 6-13.

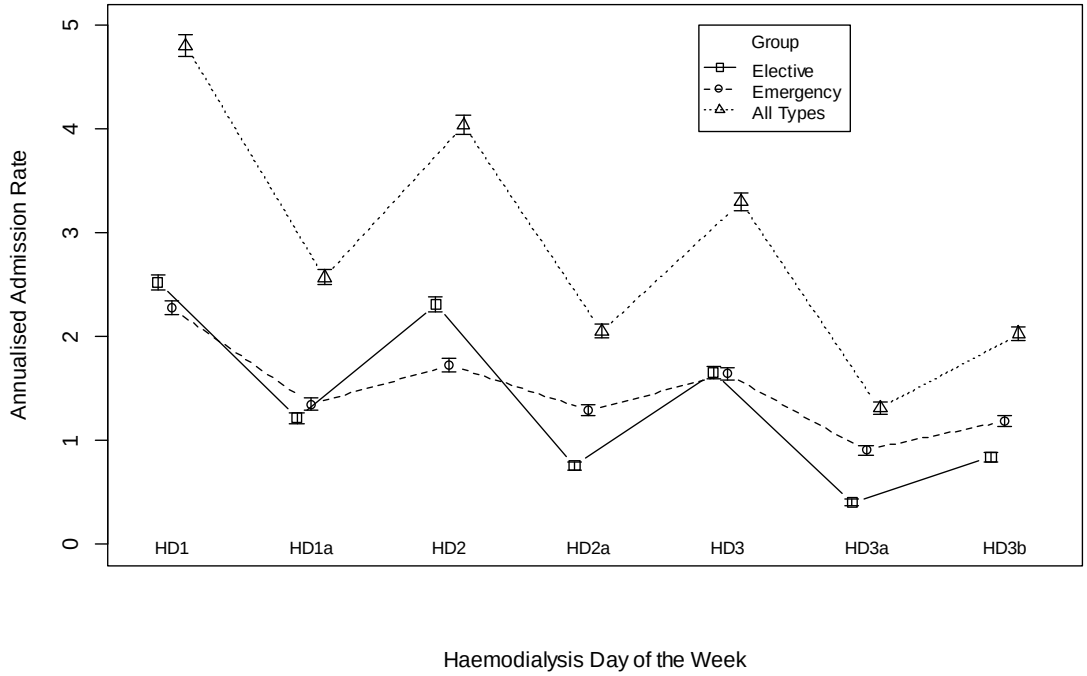


Figure 6-13 : Annualised admission rate according to dialysis day and admission type

Profiles of emergency and elective admission rates are different. Elective activity shows a greater difference between rates on days when dialysis is being administered to days off, with a downward slope towards the end of the week. Explanations for this include patients being admitted for elective activity following their routine haemodialysis, and that most elective activity is loaded towards the beginning of the week to reduce non-essential bed occupancy over the weekend. Emergency admissions are uniformly distributed across the week with the exception of HD1 where there is a spike in emergency admissions.

Admission rates by case-mix and ratios

Case mix affected the overall rate of admission and the ratio of HD1 to the rest of the week. Patient demographic factors are detailed in Table 6-8 showing the overall rate of admission for HD1, the rest of the week and the ratio between the two. The presence of comorbid conditions strongly predicts admission rates (see admission in first year analysis) in this cohort; however the variation in case-mix has a less marked impact on the ratio of HD1 to the rest of the week. Conditions with notable impact are congestive cardiac failure (shown separately and reporting overall increase in admission rates and the increase in HD1, Figure 6-14) and chronic obstructive pulmonary disease.

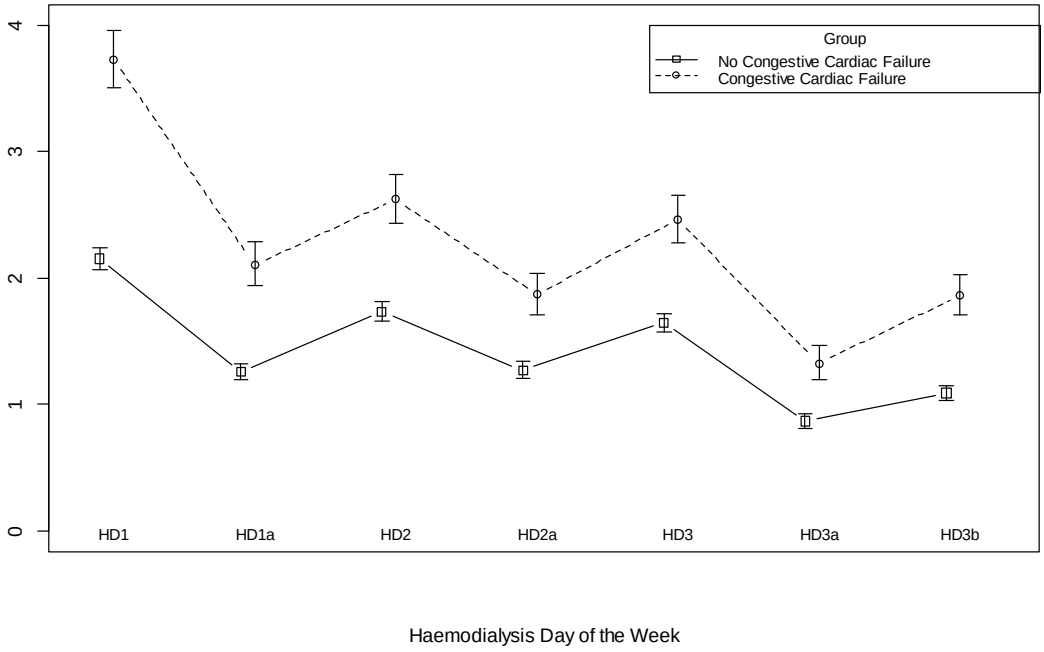


Figure 6-14 : Admission rates over the dialysis week according to the presence of absence of congestive cardiac failure

Laboratory attainment values associated with performance which the UKRR routinely report on also had some effect on admission patterns, however missing data limited some of the inference which could be drawn from this. Patients with a pre-dialysis blood pressure in excess of 150mmHg had significantly higher admission rates and excess admissions after the long gap than those with lower blood pressures. A summary of these associations can be found in Table 6-9.

Table 6-8 : Admission rates and rate ratios for HD1 and the rest of the week by demography and comorbidity on admission

	Group	Overall	HD1	Rest of Week	Ratio
Age At Admission	Under 40 years	1.46 (1.39 - 1.54)	1.96 (2.42 - 1.35)	1.35 (1.28 - 1.42)	1.61 (1.43 - 1.82)
	40 - 65 years	1.43 (1.4 - 1.47)	2.05 (2.28 - 1.32)	1.32 (1.28 - 1.35)	1.64 (1.55 - 1.75)
	Over 65 years	1.52 (1.49 - 1.55)	2.28 (2.48 - 1.38)	1.38 (1.35 - 1.41)	1.72 (1.64 - 1.8)
Ethnicity	White	1.49 (1.47 - 1.51)	2.22 (2.38 - 1.36)	1.36 (1.34 - 1.39)	1.69 (1.63 - 1.76)
	Black	1.42 (1.34 - 1.5)	1.88 (2.42 - 1.3)	1.3 (1.22 - 1.39)	1.64 (1.43 - 1.89)
	South Asian	1.41 (1.33 - 1.49)	1.93 (2.48 - 1.28)	1.28 (1.2 - 1.37)	1.72 (1.49 - 1.97)
	Other	1.56 (1.46 - 1.65)	2.06 (2.68 - 1.43)	1.43 (1.33 - 1.53)	1.65 (1.43 - 1.91)
Time on RRT	RRT less than 1 year	1.8 (1.76 - 1.84)	2.73 (3.03 - 1.63)	1.63 (1.58 - 1.67)	1.77 (1.67 - 1.87)
	RRT greater than 1 year	1.36 (1.34 - 1.39)	1.98 (2.14 - 1.25)	1.25 (1.23 - 1.28)	1.64 (1.58 - 1.72)
Angina	Absent	1.39 (1.36 - 1.41)	2.04 (2.19 - 1.27)	1.27 (1.25 - 1.29)	1.66 (1.6 - 1.73)
	Present	1.96 (1.91 - 2.02)	2.94 (3.31 - 1.78)	1.78 (1.72 - 1.84)	1.75 (1.64 - 1.88)
Previous myocardial infarct	Absent	1.38 (1.36 - 1.4)	2.03 (2.18 - 1.26)	1.26 (1.24 - 1.28)	1.67 (1.61 - 1.74)
	Present	2.06 (2 - 2.12)	3.05 (3.44 - 1.87)	1.87 (1.81 - 1.93)	1.73 (1.62 - 1.86)
Congestive Cardiac Failure	Absent	1.35 (1.33 - 1.37)	1.97 (2.12 - 1.24)	1.24 (1.22 - 1.26)	1.64 (1.58 - 1.71)
	Present	2.11 (2.05 - 2.17)	3.23 (3.62 - 1.9)	1.9 (1.84 - 1.96)	1.8 (1.69 - 1.92)
Stroke	Absent	1.4 (1.38 - 1.42)	2.07 (2.21 - 1.28)	1.28 (1.26 - 1.31)	1.67 (1.6 - 1.73)
	Present	2.18 (2.11 - 2.26)	3.27 (3.76 - 1.97)	1.97 (1.89 - 2.04)	1.78 (1.65 - 1.93)
Diabetes	Absent	1.32 (1.3 - 1.35)	1.99 (2.16 - 1.2)	1.2 (1.18 - 1.23)	1.73 (1.65 - 1.81)
	Present	1.85 (1.81 - 1.89)	2.64 (2.91 - 1.7)	1.7 (1.66 - 1.74)	1.63 (1.55 - 1.72)
COPD	Absent	1.44 (1.41 - 1.46)	2.11 (2.25 - 1.32)	1.32 (1.29 - 1.34)	1.66 (1.6 - 1.72)
	Present	2.22 (2.13 - 2.31)	3.47 (4.1 - 1.97)	1.97 (1.88 - 2.06)	1.92 (1.74 - 2.11)
Arrythmia	Absent	1.47 (1.44 - 1.49)	2.18 (2.33 - 1.34)	1.34 (1.32 - 1.36)	1.68 (1.62 - 1.75)
	Present	1.96 (1.87 - 2.05)	2.77 (3.39 - 1.78)	1.78 (1.69 - 1.88)	1.72 (1.54 - 1.93)
Connective Tissue Disease	Absent	1.49 (1.47 - 1.51)	2.22 (2.37 - 1.36)	1.36 (1.34 - 1.38)	1.69 (1.63 - 1.75)
	Present	1.81 (1.69 - 1.93)	2.4 (3.21 - 1.65)	1.65 (1.53 - 1.78)	1.69 (1.44 - 1.98)
Claudication	Absent	1.41 (1.38 - 1.43)	2.09 (2.24 - 1.29)	1.29 (1.26 - 1.31)	1.68 (1.62 - 1.75)
	Present	2.35 (2.27 - 2.44)	3.39 (3.96 - 2.14)	2.14 (2.05 - 2.23)	1.72 (1.57 - 1.87)
Overall		1.48 (1.46 - 1.51)	2.22 (2.36 - 1.36)	1.36 (1.33 - 1.38)	1.69 (1.63 - 1.74)

Table 6-9 : Admission rates and rate ratios for HD1 and the rest of the week by laboratory values for bloods performed in the preceding 3 to 6 months

	Group	Overall	HD1	Rest of Week	Ratio
URR	<=65	1.73 (1.67 - 1.79)	2.67 (2.49 - 2.86)	1.58 (1.52 - 1.64)	1.69 (1.56 - 1.83)
67.1% Complete	65.1 - 70	1.36 (1.30 - 1.41)	2.11 (1.93 - 2.29)	1.23 (1.18 - 1.29)	1.70 (1.55 - 1.87)
	70.1 - 75	1.31 (1.26 - 1.36)	2.06 (1.90 - 2.22)	1.19 (1.14 - 1.24)	1.73 (1.58 - 1.88)
	>75	1.17 (1.13 - 1.22)	1.80 (1.65 - 1.94)	1.07 (1.03 - 1.12)	1.68 (1.53 - 1.83)
Potassium	<4.0	1.26 (1.14 - 1.37)	1.67 (1.34 - 2.06)	1.19 (1.07 - 1.32)	1.41 (1.11 - 1.77)
10.3% Complete	4.0 - 4.5	1.39 (1.26 - 1.54)	2.22 (1.78 - 2.73)	1.26 (1.12 - 1.41)	1.76 (1.39 - 2.23)
	4.6 - 5.2	1.34 (1.23 - 1.46)	1.88 (1.53 - 2.28)	1.26 (1.14 - 1.38)	1.50 (1.20 - 1.86)
	>5.2	1.35 (1.22 - 1.49)	2.02 (1.61 - 2.50)	1.25 (1.11 - 1.39)	1.62 (1.28 - 2.07)
Haemoglobin	<10.5	2.04 (1.99 - 2.09)	3.27 (3.11 - 3.44)	1.84 (1.79 - 1.89)	1.78 (1.68 - 1.89)
85.3% Complete	10.5 - 12.5	1.31 (1.27 - 1.34)	1.99 (1.89 - 2.10)	1.20 (1.16 - 1.23)	1.67 (1.57 - 1.76)
	> 12.5	1.12 (1.08 - 1.17)	1.63 (1.50 - 1.78)	1.04 (1.00 - 1.09)	1.57 (1.43 - 1.72)
Albumin	< 33	2.13 (2.08 - 2.18)	3.36 (3.19 - 3.54)	1.93 (1.88 - 1.99)	1.74 (1.64 - 1.85)
85.3% Complete	33 - 37	1.35 (1.31 - 1.39)	2.09 (1.96 - 2.23)	1.23 (1.19 - 1.27)	1.70 (1.58 - 1.83)
	37.1 - 40	1.26 (1.21 - 1.30)	1.90 (1.75 - 2.05)	1.15 (1.11 - 1.20)	1.64 (1.51 - 1.79)
	> 40	1.08 (1.04 - 1.12)	1.62 (1.48 - 1.76)	0.99 (0.95 - 1.03)	1.63 (1.49 - 1.80)
Bicarbonate	< 21	1.44 (1.39 - 1.48)	2.24 (2.09 - 2.39)	1.31 (1.26 - 1.35)	1.71 (1.59 - 1.85)
79.8% Complete	21 - 24	1.39 (1.35 - 1.43)	2.06 (1.94 - 2.19)	1.28 (1.24 - 1.32)	1.61 (1.51 - 1.72)
	24.1 - 26	1.50 (1.45 - 1.55)	2.40 (2.22 - 2.58)	1.36 (1.30 - 1.41)	1.77 (1.62 - 1.92)
	>26	1.65 (1.59 - 1.71)	2.70 (2.50 - 2.91)	1.48 (1.42 - 1.54)	1.82 (1.67 - 1.99)
Pre-HD Systolic BP	< 129	1.51 (1.46 - 1.56)	2.28 (2.12 - 2.46)	1.38 (1.33 - 1.44)	1.65 (1.52 - 1.79)
66.4% Complete	129 - 145	1.28 (1.23 - 1.33)	1.85 (1.70 - 2.01)	1.19 (1.14 - 1.24)	1.56 (1.42 - 1.71)
	146 - 165	1.37 (1.32 - 1.41)	2.20 (2.05 - 2.36)	1.23 (1.18 - 1.28)	1.79 (1.65 - 1.94)
	> 165	1.61 (1.55 - 1.67)	2.63 (2.43 - 2.84)	1.44 (1.38 - 1.50)	1.82 (1.67 - 1.99)
Post-HD Systolic BP	< 129	1.34 (1.30 - 1.38)	2.03 (1.91 - 2.15)	1.23 (1.19 - 1.27)	1.65 (1.54 - 1.76)
59.9% Complete	129 - 145	1.41 (1.35 - 1.46)	2.19 (2.01 - 2.38)	1.28 (1.23 - 1.34)	1.70 (1.55 - 1.87)
	146 - 165	1.52 (1.45 - 1.58)	2.50 (2.30 - 2.73)	1.36 (1.29 - 1.42)	1.85 (1.68 - 2.04)
	> 165	1.85 (1.76 - 1.95)	3.04 (2.72 - 3.39)	1.66 (1.56 - 1.76)	1.83 (1.62 - 2.07)
Overall		1.48 (1.46 - 1.51)	2.29 (2.22 - 2.36)	1.36 (1.33 - 1.38)	1.69 (1.63 - 1.74)

Variation in excess admissions with time

Although emergency admissions start out higher and drop to a baseline rate of approximately 1.5 admissions per year, the ratio of excess admissions after the long gap persists and indeed is relatively constant throughout this entire period.

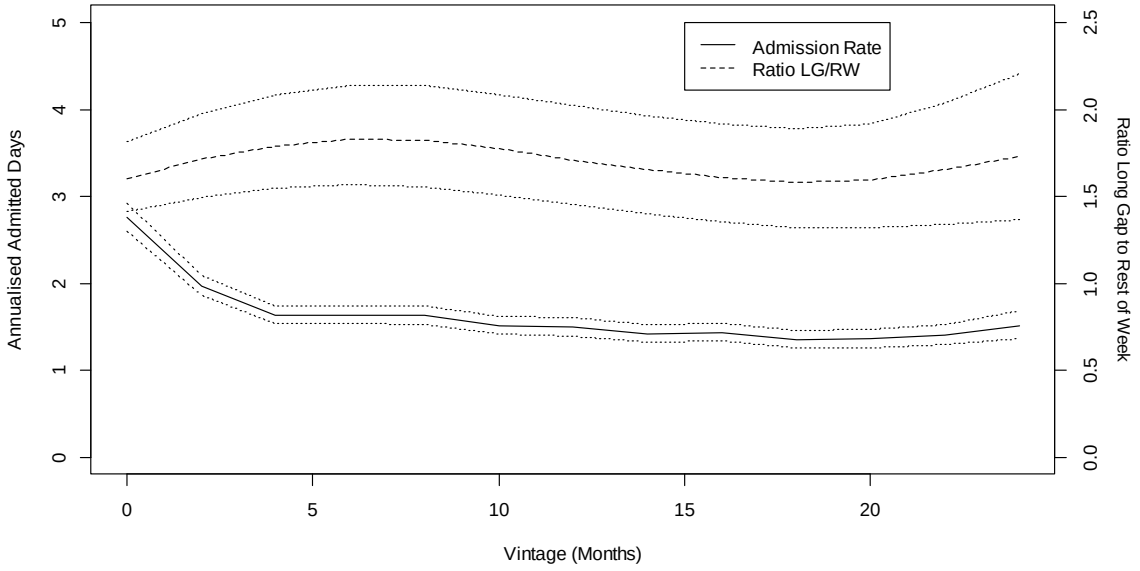


Figure 6-15 : The ratio between admissions on HD1 and the rest of the week with time on dialysis. Admissions are highest in the first three months but the relative increase over the long gap (LG) compared to the short gap (SG) is constant.

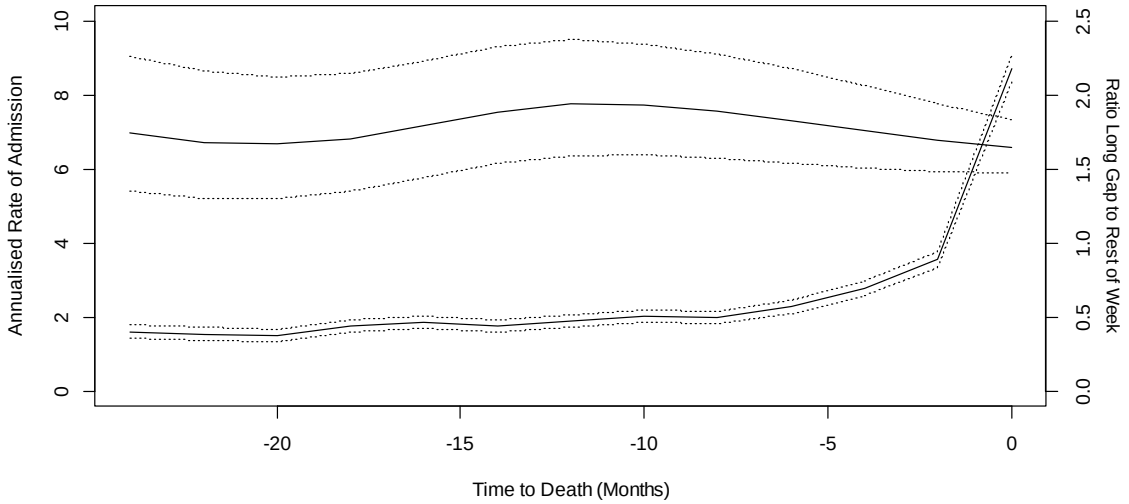


Figure 6-16 : The consistency of the ratio between admissions on HD1 and the rest of the week approaching death. Admissions sharply increase but the the relative increase over the long gap (LG) compared to the short gap (SG) is constant.

In patients who died the emergency admission rate climbs exponentially in the last 6 months of life, but again the ratio of excess admissions after the long gap stays fairly constant. Note the narrowing of the confidence intervals for the ratio as the number of observed admissions increases.

Centre Specific Rates and Ratios

The limited impact of case mix on the ratio of HD1 to the rest of the week and comparable comorbidity across centres in England may negate case mix adjustment for this measure.

Variation in emergency admission rates across centres exists, but ratios of admissions on HD1 to the rest of the week across most centres appear similar. One centre had ratios of HD1 to the rest of the week higher than the overall mean. The majority of centres had HD1:Rest of week ratios between 1.0 and 2.0.

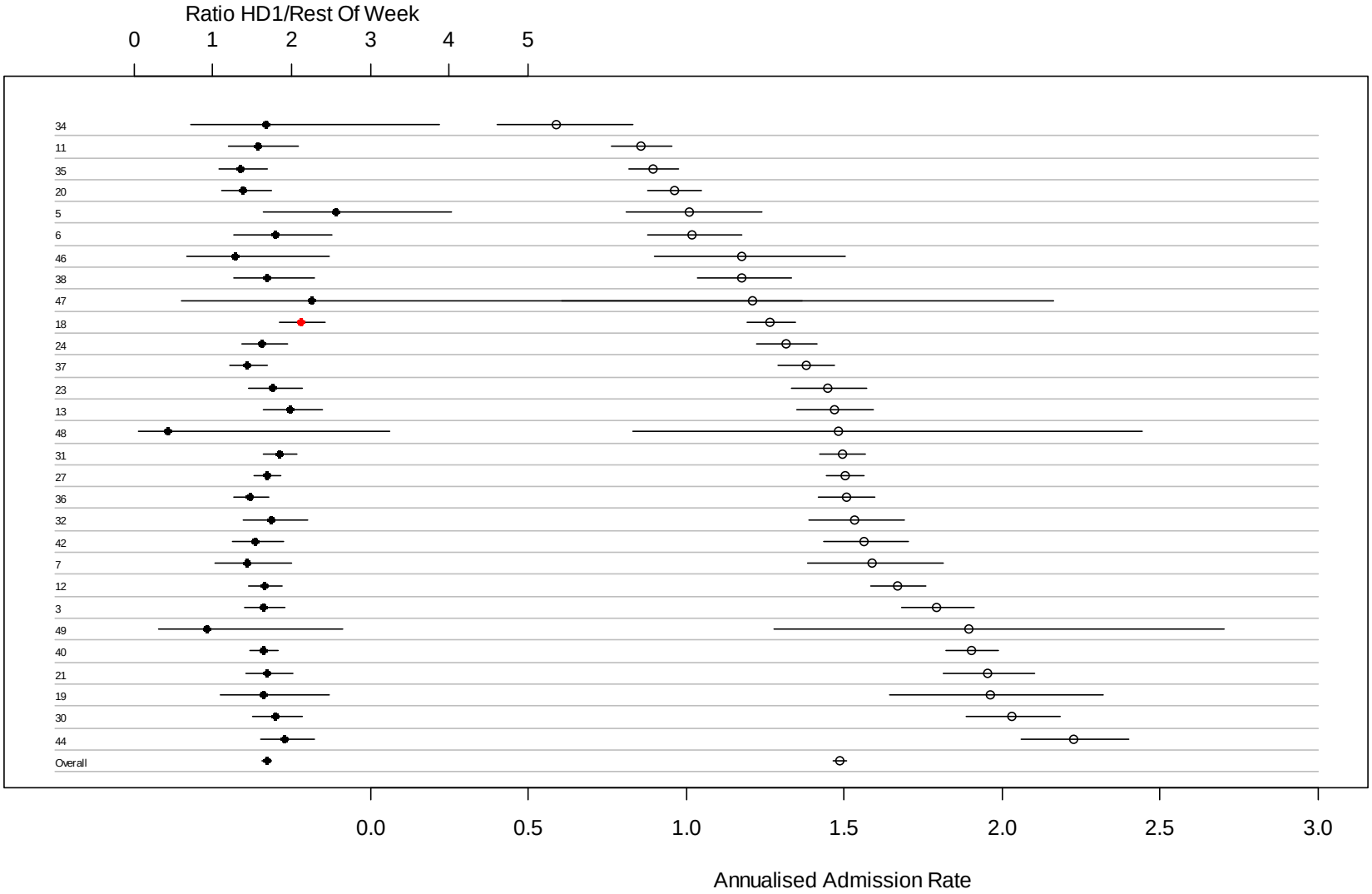


Figure 6-17 : Centre specific emergency admission rates and the ratio between HD1 and the rest of the week. One centre has a higher than average increase in admissions over the long gap

Mortality pattern

The mortality rate over the entire week was 16.1 deaths per 100 dialysis patient years (95% CI 15.4 – 16.7). These rates varied across the dialysis week with highest mortality rates observed in HD1 (20.5 vs 16.8 for the rest of the week, ratio 1.22, 95% CI 1.08 - 1.38). The mortality rate according to location of death differed according to dialysis day. Significant increases in haemodialysis mortality were observed in out of hospital mortality only, with a ratio of HD1 the rest of the week of 1.51 (95% CI 1.25 – 1.82) compared to a ratio of 1.05 (95% CI 0.91 – 1.21) for those who died in hospital. These differences are shown in Figure 6-18, and were identical in Monday/Wednesday/Friday and Tuesday/Thursday/Saturday dialysis patients.

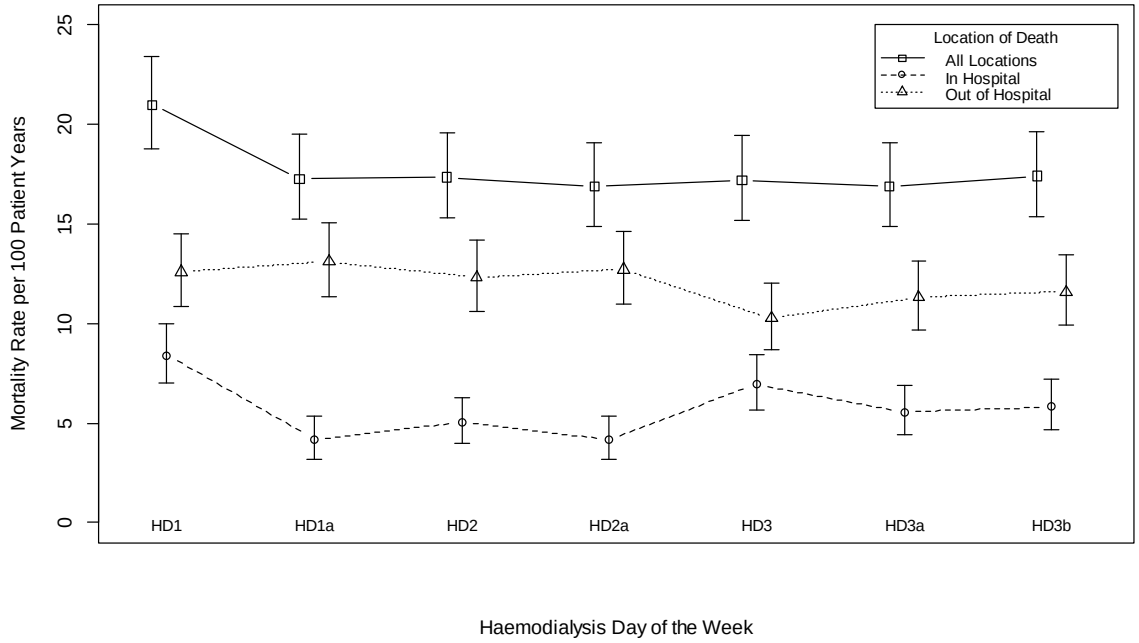


Figure 6-18 : Location of death (in hospital or out of hospital) is influenced by dialysis day of the week

Stratifying mortality rate by cause, the rate of death on HD1 compared to the rest of the week was higher in cardiovascular causes (7.15 vs 5.03 per 100 patient years, ratio 1.42, 95 % CI 1.18 – 1.71) but not significantly higher in non-cardiovascular causes (11.4 vs 10.6 per 100 patient years, ratio 1.08, 95% CI 0.93 – 1.24).

The number of observed deaths in each centre was insufficient to allow centre specific comparison of deaths on dialysis days of the week. Demographic and laboratory variables were associated with differing excess mortality over the two day gap but the number of patients limited statistical significance. These are reported in appendix 6b. The above methods show that the excess mortality rate is only present in patients of a Caucasian background, with the combination of Black, South Asian and Other ethnic groups have a flat profile of mortality

(Caucasians: mortality rate ratio 1.26, 95% CI 1.11 – 1.43 compared to non-Caucasians 0.898, 95% CI 0.59 – 1.37), despite having comparable admission rates and ratios.

Sensitivity analysis

Comparison between the selected and unselected dialysis weeks suggest similar case mix at the start of RRT, with statistically significant differences in baseline demography noted in age to be marginally higher in the selected cohort. The comparison between groups is detailed in Table 6-10.

Table 6-10 : The demography of patients included and excluded from the admission pattern analysis

	Excluded from study	**Included in study**	**P**
Age	63.60 years	64.56 years	0.001
Ethnic Group			
White	78.95%	85.41%	<0.001
Black	6.55%	4.71%	
South Asian	7.20%	5.20%	
Other	7.30%	4.68%	
Angina	18.55%	20.42%	0.008
Myocardial infarction	19.39%	19.60%	0.762
Previous heart failure	21.87%	22.94%	0.150
Cerebrovascular accident	12.81%	14.14%	0.028
Diabetes	34.54%	34.91%	0.664
Chronic obstructive pulmonary disease	8.89%	9.40%	0.315
Arrhythmia	6.53%	6.93%	0.365
Connective tissue disease	4.12%	3.94%	0.608
Claudication	11.39%	11.30%	0.865

Emergency admission rates were overall slightly higher in the unselected cohort (1.59 vs 1.46 per year, P<0.001), but demonstrated a parallel trajectory over the course of the dialysis week. Mortality rates were statistically higher in the unselected group (20.0 deaths per 100 dialysis years in the unselected vs 16.0 per 100 dialysis years in the selected cohort, p<0.001), but again showed similar trajectories and highlighted greater out of hospital mortality rates on Monday and Tuesday (the most common days for HD1 to fall on) compared to the rest of the week. Admitted days per year were significantly higher in the unselected group (22.2 per year vs 7.1 per year, P<0.001). Graphs of the differences in mortality and admission rates are presented below.

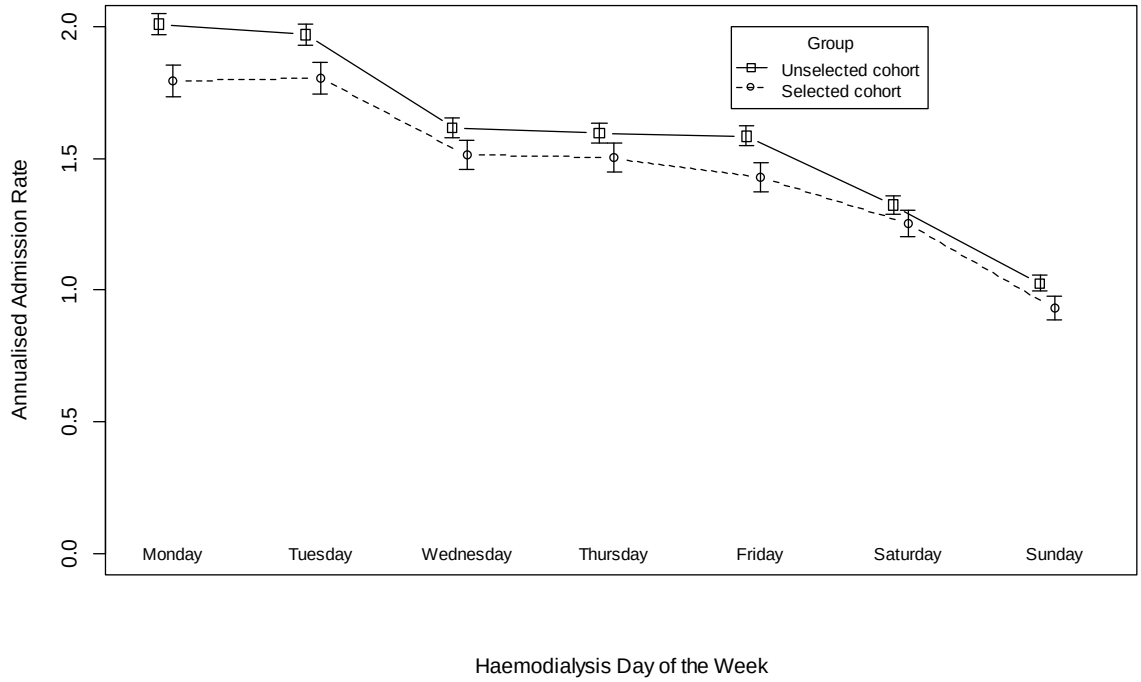


Figure 6-19 : The difference in admission rates by dialysis day of the week in selected and unselected patient weeks

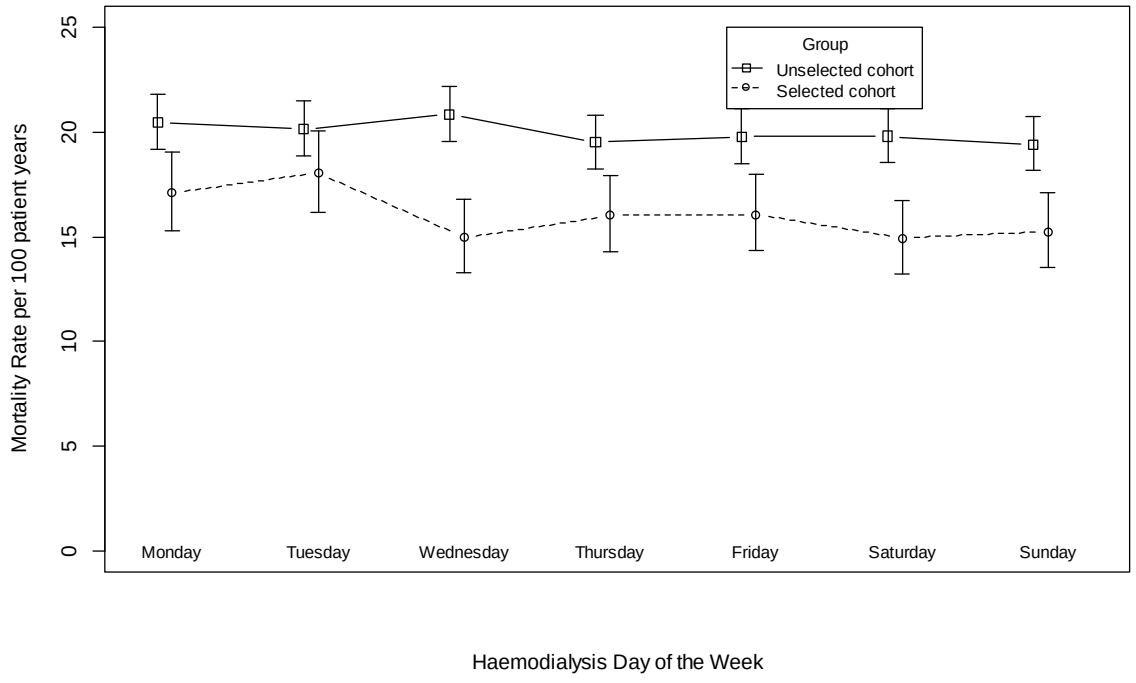


Figure 6-20 : The difference in mortality per day of the dialysis week in selected and unselected patient weeks

Discussion

This linked dataset has been able to report for the first time centre specific admission rates for renal centres in England, and highlighted important patterns and associations which potentially deserve more understanding. Patients are admitted approximately twice a year in the first year of haemodialysis, but those patients who start on peritoneal dialysis and have moved to haemodialysis experience some of the highest admission rates seen at over four admissions in the first twelve months. Comorbidity is one of the strongest predictors for admission rates; however following adjustment for this centres with higher than expected centre specific admission rates persist. The two day gap in three times a week haemodialysis has an increase in admissions, and excess mortality that is driven by out of hospital death. Patients with higher blood pressures and congestive cardiac failure had a greater increment in admissions over the long gap, whereas we were unable to identify a strong association with achieved clearance of solutes as measured by urea reduction ratio, and missing data precluded much inference associated with potassium levels.

These findings have allowed us for the first time to compare more contemporary rates of admission to those found by other renal registries. Although presented differently, admission rates in England are as high as or even higher than those seen in the USRDS analyses, both in their report(U S Renal Data System 2011) and in material pertaining to admission rates over the two day gap(Foley et al. 2011). Although England has previously been shown to have preferable rates of admission when compared to other European countries(Rayner et al. 2004) this may not be the case, and given the supporting evidence that patients in the USA have greater comorbid burden than those seen in this cohort(Liu et al. 2009), it may suggest greater investment in understanding high admissions rates and their prevention are required.

The admission counts seen here and elsewhere support an adjustment method which can deal with repeated events. However despite zero inflation methods these appear poor at predicting zero counts. In general there are fewer predictors for the zero count part of models, and the RMSE for most models is driven by the difference between the conditional mean and those patients who were not admitted. Earlier analyses suggest that comorbidity across centres is largely similar and the fairly poor explanation of outlying centres with regards to admission rates may be explained by insignificant variation in the underlying comorbidity. Ethnicity does vary across centres, and is associated with small differences in admission rates. The poorer survival associated with White RRT patients(Kucirka et al. 2011) may be responsible for the increased admission rate, as we have identified that 65% of patients die within an acute secondary care organisation (chapter 4) and that admission rates exponentially increase in the months before death, not immediately prior. Given that differences between all class

admissions in White and Non-white groups (2.62 vs 2.32) and purely emergency admission (1.50 admissions per year for both groups), one might assume that greater elective activity in White patients is responsible. Residual unexplained differences in admission rates across centres are likely to reflect centre specific practices and organisational factors, not appropriate to include in a performance indicator but worthy of explanation as numerous other authors have previously published.

The variation in admission rates across centres is quite different to the centre specific admission rate ratios between the two day gap and the rest of the week. The admission rate ratio masks the difference in underlying admission rates between centres. The relatively small numbers in each centre may offer some explanation, or that more fundamental processes are at play. The above analysis finds similar differences in the mortality rate to the Foley analysis (rate rato 1.22 vs 1.23 in US), despite higher overall mortality rates (20.5 and 16.8 vs 22.1 and 18.0). Admission rates may not be comparable as it is not clear how elective activity was dealt with. One might expect less of a difference due to lower comorbid burden the longer dialysis treatment times(Tentori et al. 2012) the UK patients are exposed to. Another explanation is the standardisation process Foley et al performed to make his cohort more comparable to the USRDS population.

That the increase in death rates associated with the two day break is driven by out of hospital death raises several questions. Firstly, the high incidence of sudden death in haemodialysis patients is likely to manifest with deaths at home, and this finding supports those of other authors that sudden death is highest on a Monday(Karnik et al. 2001; Bleyer et al. 2006). Many have postulated that this is merely due to the day of the week and not the dialysis schedule itself, and supported by the same authors reporting that sudden deaths were still higher on a Monday in patients who dialysed on Tuesdays, Thursdays and Saturdays. Like the Foley analysis, we show an identical pattern of mortality between the Monday/Wednesday/Friday and Tuesday/Thursday/Saturday regimes, with statistically significant increases in out of hospital mortality only in both groups. Due to low numbers we are unable to learn much about how case-mix influences these results, or if higher potassium levels are associated with greater mortality (including specifically sudden death) as identified elsewhere(Karnik et al. 2001) (Bleyer et al. 2006; Kovesdy et al. 2007). The excess of deaths on HD1 in white patients is not sufficient to explain their overall increased mortality as the annualised mortality of the rest of the week still far exceeds that of the Non-white patients. Statistical significance using the rate-ratio interaction test between HD1 and the rest of the week between Caucasian and non-Caucasian patients was not observed, primarily due to a low baseline mortality rate as seen in chapter 5, and small numbers overall (20.8% of the cohort).

Once admitted patients often deviate significantly from their established dialysis pattern with alternate day and daily treatments often applied. For this and reasons of intercurrent illness hospitalised patients are not generalizable to the outpatient haemodialysis setting where most patients receive their treatment. This is a partial explanation for the more uniform profile of the mortality rates in the unselected patient weeks demonstrated in the sensitivity analysis.

In summary, this chapter determined:

- National admission rates in the first year of haemodialysis allowing international comparison.
- Centre specific admission rates in patients receiving haemodialysis, identifying some centres with unexplained high admissions rates.
- Revealed a 69% increase in admissions after the two day gap in three times a week haemodialysis, with the greatest increases in patients with hypertension, cardiac failure and pulmonary disease.
- Identified a 22% increase in mortality after the two day gap, an increase purely driven by out of hospital death and only seen in White patients.

Chapter 7 *Admission rates in peritoneal dialysis patients*

Introduction

Peritoneal dialysis (PD) is a therapy generally administered at home that involves draining osmotically active fluid into the peritoneal cavity. The peritoneal cavity represents the physical space formed by the blood supply to the bowel, the peritoneum. This vascularity enables movement of fluid and toxins out of the circulation and into the instilled fluid. The fluid is left in the peritoneal cavity for several hours to allow the passive diffusion and osmosis to take place then drained out(Mattocks et al. 1971). Drainage in or out of the peritoneal cavity is generally via a peritoneal dialysis catheter, a plastic tube which runs from the abdominal surface through the peritoneum onto the cavity. Like their haemodialysis counterparts the peritoneal dialysis access is associated with infections in both the tunnel leading from the abdominal surface to the peritoneum and in the fluid itself which then inflames the peritoneal surface (Li et al. 2010). The latter is referred to as peritonitis, and is treated by instilling dialysis fluid mixed with antibiotics into the peritoneum (Li et al. 2010).

In 2011 20.4% of patients starting RRT commenced treatment on peritoneal dialysis (Gilg et al. 2013). Complications associated with the peritoneal dialysis catheter, peritonitis and patients' tolerance of delivering their own dialysis therapy at home results in 20% of patients leaving the therapy each year (Shen et al. 2013). The uptake of peritoneal dialysis therapy is less than that of haemodialysis (71.4% starting RRT (Gilg et al. 2013)). Many potential explanations for this difference exist including changes in the RRT population over the past two decades resulting in an older population with more comorbidities who are less likely to accept peritoneal dialysis, and difficulties in some centres to initiate this therapy quickly should the need to start dialysis present itself suddenly. Exponents of the therapy argue that with appropriate patient selection, hospitalisation and quality of life are superior on peritoneal dialysis.

Peritonitis is the major cause of morbidity, hospitalisation and treatment failure on peritoneal dialysis. Single centre experiences have been reported but no national comparison has been conducted. Variation in catheter function across centres has been emphasised in a recent UKRR audit(Briggs et al. 2013), but the impact of catheter insertion timing has not been explored.

Aims and Objectives

- To determine the utility and validity of HES data in determining admission rates in the first year of peritoneal dialysis.
- To determine the utility and validity of HES data in reporting peritonitis rates in accordance with the International Society of Peritoneal Dialysis guidelines.
- To derive centre specific adjusted admission rates and hospitalised peritonitis rates for English renal centres supervising peritoneal dialysis patients.
- To determine catheter insertion rates and timing for patients receiving dialysis, determining their variation and impact on hospitalised peritonitis.
- To determine outcomes after hospitalised peritonitis episodes.

Analysis specific methods

Cohort

Incident RRT patients whose first therapy was peritoneal dialysis were identified from the UKRR timeline for an all-cause frequency of admission analysis. In addition, to explore the validity of the UKRR timeline, patients who had peritoneal dialysis catheter insertions prior to starting RRT but were documented as only ever receiving haemodialysis were identified.

Both incident RRT patients whose first substantial treatment modality was peritoneal dialysis and those starting peritoneal dialysis following exposure to other modalities such as haemodialysis or transplantation were identified for the determination of peritonitis rates. For analyses specifically looking at peritonitis rates in a patient's first exposure to peritoneal dialysis, periods on different modalities lasting less than 30 days were not classed as modality switches and treatment periods beyond this were still classed as the first peritoneal dialysis exposure period. Comorbidity, time on dialysis and age were determined at the start of each peritoneal dialysis treatment period as per methods specified in Chapter 3, which also details the specification of a superspell.

Event identification

All Cause admission

Admissions of any type (emergency or elective) during the periods when the UKRR treatment timeline indicated peritoneal dialysis therapy was being administered were classed as an all cause admission. The unit of reporting is the superspell. Recognising the practice of assisted automated peritoneal dialysis can be performed in hospital, patients with elective

stays lasting one day at a frequency of one admission per fortnight or more were excluded from the analysis.

Peritonitis admission

Due to varying methods of coding peritoneal dialysis peritonitis, a broader range of codes were employed than simply using "peritonitis" to define an event. As previously highlighted, some centres use the primary diagnosis field to reflect that the patient has end stage renal failure or the primary renal disease. For this reason, secondary fields were scrutinised as well as primary diagnosis fields. All twenty diagnosis fields in admission episodes during the peritoneal dialysis periods specified above were scrutinised to identify peritoneal dialysis peritonitis events. Peritoneal Dialysis peritonitis is not a chronic comorbid condition and therefore its presence in a secondary field should still represent an event. Peritoneal dialysis peritonitis can arise whilst the patient is already admitted, and this can reflect issues with clinical care, giving additional reasons to use codes in secondary fields for the analysis. The following codes and their descriptions were used to screen all hospital episodes for a peritoneal dialysis peritonitis event:

- Infection & inflammatory reaction due to other internal prosthetic devices, implants & grafts (T857)
- Peritonitis, unspecified (K659)
- Acute peritonitis (K650)
- Acute reaction to foreign substance accidentally left during a procedure (T816)
- Infection and inflammation reaction due to other cardiac vascular devices, implants & grafts (T827)
- Other peritonitis (K658)
- Other disorders of the peritoneum in infectious diseases EC (K678)

Although on first impression these may seem vague or not totally applicable, preliminary examination of events using narrower specifications revealed centres with modest sized programmes with extremely low peritonitis rates warranting more comprehensive examination of the codes employed during the peritoneal dialysis timeline.

The presence of coding for organisms alongside the event of peritoneal dialysis peritonitis was done by looking for the codes listed in appendix 7a.

Where possible, the International Society of Peritoneal Dialysis (ISPD) guidelines on peritoneal dialysis peritonitis were adhered to (Li et al. 2010), with special consideration for

how rates should be reported. The terminology for peritonitis events as defined by the ISPD is detailed in Table 7-1, with comments specific to this analysis.

Table 7-1 : International Society of Peritoneal Dialysis definitions of peritoneal dialysis peritonitis

Term	ISPD Definition
Recurrent	An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism
Relapsing	An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or 1 sterile episode
Repeat	An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism
Refractory	Failure of the effluent to clear after 5 days of appropriate antibiotics
Catheter-related peritonitis	Peritonitis in conjunction with an exit-site or tunnel infection with the same organism or 1 site sterile

Relapsing episodes should not be counted as another peritonitis episode when calculating peritonitis rates; recurrent and repeat episodes should be counted.

As patients could develop the condition at any point during the admission and recommended therapy duration is 14 days (Warady et al. 2012), the window during which further events cannot be counted is 42 days (14 days of therapy plus 28 days post completion). Sensitivity analyses with 42 days from admission (assuming that peritoneal dialysis treatment commences on admission) and 28 days from discharge (assuming treatment is completed prior to discharge) are also presented along with the number of events removed by the three techniques.

Statistical methods

Group rates as derived using the patient rate formula below are presented for specific case mix variables. Statistical adjustment using the negative binomial distribution with and without zero inflation was employed. The sequential addition of variables previously identified as predictive of survival was performed, and if a variable was predictive it was retained in the model. Standardised peritoneal dialysis peritonitis rates calculated using observed vs expected rates and presented on a funnel plot. Variable time at risk due to changes in modality and death were adjusted for using an offset in the model defined as the natural log of the days at risk for events. Patients who following dataset generation had zero time at risk due to early hospitalisation and modality switch/death were excluded from the analysis.

The impact of centre specific coding depth was explored with Spearman's correlation and the inclusion of coding depth in a multivariate negative binomial model.

Centres with small programmes as defined by five patients or less were excluded from standardised analyses as robust comparisons could not be generated. Follow-up was ceased at change in modality according to the UKRR timeline or death according to the joint sources.

The ISPD guidelines for reporting peritonitis rates are as follows:

Methods for Reporting Peritoneal Dialysis-Related Infections (Peritonitis, Exit-Site Infections)

1. As rates (calculated for all infections and each organism):
    a. Months of peritoneal dialysis at risk, divided by number of episodes, and expressed as interval in months between episodes
    b. Number of infections by organism for a time period, divided by dialysis-years' time at risk, and expressed as episodes per year
2. As percentage of patients who are peritonitis free per period of time
3. As median peritonitis rate for the program (calculate peritonitis rate for each patient and then obtain the median of these rates)

Relapsing peritonitis (see Table 7-1 for the definition) should be counted as a single episode.

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Hospitalisation time is excluded from time at risk only for admissions where peritoneal dialysis peritonitis is identified. The patient is still at risk of peritonitis when admitted without peritonitis.

Method 2 was employed to explore the association between peritonitis free survival and catheter insertion timing, using a Cox proportional hazards model with influential variables taken from the peritonitis rate models and the time measured as between catheter insertion and start of peritoneal dialysis therapy. As patients are clustered by centre, a frailty term for centre was included. Censoring events were death or change to another modality. The length of stay for this first peritonitis admission and modality at 30 days from discharge were derived from the HES dataset and the UKRR timeline combined with date of death information respectively.

Results

Cohort

Following exclusion of patients classed as unsuitable for analysis in Chapter 4, and whose supervising centre had a small programme (less than five patients) the following patient cohort was identified. Five Patients were excluded as they belonged to a centre with a programme size so small that reporting centre specific rates was inappropriate. Using peritoneal dialysis catheter insertion procedural data, an additional 438 patients who did not have haemodialysis during their first year were identified as having peritoneal dialysis catheters inserted prior to starting RRT. This increased the rate of failure of peritoneal dialysis before three months from 6.2% to 14.3%. Eighty-eight of these additional patients were accounted for by one centre, with the remaining cases being evenly distributed across centres. The demography of this cohort is given in Table 7-2:

Table 7-2 : Demography of cohorts included in peritoneal dialysis (PD) analyses

Demographic Variable		**All PD Treatment Episodes**	**First PD Treatment Episodes**	**Incident PD Patients (First Year)**
Number of patients		6,256	6,256	5,063
Number of PD treatment episodes		7,525	6,256	5,063
Patient Years of follow-up		12,683	11,171	4,864
Age (years)		55.42	55.84	55.7
Male Gender		60.7%	60.7%	61.2%
Socioeconomic Status centile (0 = most deprived)		51.0	51.2	50.9
Ethnicity	White	83%	82.9%	83.5%
	Black	5.3%	5.2%	4.8%
	South Asian	5.4%	5.6%	5.5%
	Other	6.2%	6.4%	6.2%
Diabetes		28.5%	29.0%	29.0%
Previous MI		10.1%	9.8%	8.9%
Stroke		6.5%	6.3%	5.8%
Chronic obstructive pulmonary disease		3.3%	3.1%	2.5%
Comorbid Score		1.03	1.02	0.81
Previous Modality	Haemodialysis	30.2%	22%	0%
	Peritoneal Dialysis	3.5%	0%	0%
	Transplant	2.5%	1.2%	0%
	Pre-RRT	63.8%	76.7%	100%

All cause admission rates

Admission rates in the incident peritoneal dialysis cohort were 2.00/year (95% CI 1.96 – 2.04), and varied according to patient demography. The largest increases were seen in patients with increasing comorbidity and age greater than 85 years, along with those who changed modality from haemodialysis to peritoneal dialysis in the first three months of renal replacement therapy (see chapter 5). Some of the increases in seen in the elderly may relate to shortened time at risk rather and similar admission counts at the start of therapy, rather than a sustained elevation in admission rate. Greatest increases in admission rates were associated with the primary renal diseases of renovascular disease or diabetes. South Asians had a large increase in admissions in the first three months of starting peritoneal dialysis compared to the subsequent nine months (88% annualised increase compared to 35-67% for other ethnic groups), as did those patients without comorbidity (79% compared to 54-65% for other groups) primarily due a very low admission rate beyond three months. In patients starting RRT in appropriate centres for analysis, shortened time from first seeing a nephrologist to start of RRT (in this case defined as less than 180 days) was associated with an increased admission rate of 25% over those who were under follow-up for longer (rate ratio 1.25, 95% CI 1.20 – 1.30). 31.6% of patients had no admissions within the first year.

Influence of case-mix

The influence of patient demography on hospitalised peritonitis rates is shown in Table 7-3, with specific examples of the influence of age in Figure 7-1.

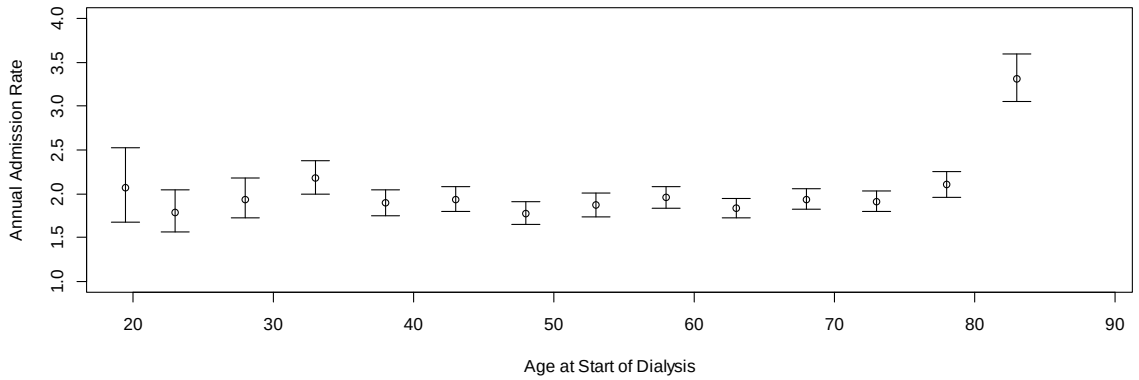


Figure 7-1 : The influence of age on the annualised admission rate in the first year of peritoneal dialysis

Table 7-3 : The influence of demography on admission rates in the first year of peritoneal dialysis, stratified by period

Demography		**Annual Admission Rate**	**Annualised First 3 months**	**Annualised Subsequent 9 months**
Age Group (years)	<40	1.97 (1.88-2.06)	2.98 (2.76-3.22)	1.91 (1.80-2.02)
	40-65	1.87 (1.82-1.92)	2.88 (2.75-3.02)	1.73 (1.67-1.80)
	>65	2.22 (2.15-2.3)	3.68 (3.49-3.88)	2.15 (2.06-2.24)
Sex	Male	2.02 (1.97-2.08)	3.22 (3.09-3.35)	1.88 (1.82-1.94)
	Female	1.96 (1.90-2.03)	3.06 (2.90-3.22)	1.93 (1.86-2.01)
Ethnic Group	White	2.05 (2.00-2.09)	3.26 (3.15-3.37)	1.95 (1.90-2.00)
	Black	1.92 (1.75-2.10)	2.48 (2.09-2.92)	1.83 (1.64-2.05)
	South Asian	1.84 (1.68-2.01)	3.32 (2.89-3.79)	1.76 (1.57-1.96)
	Other	1.62 (1.48-1.77)	2.26 (1.93-2.63)	1.51 (1.35-1.69)
Socioeconomic Status	Most Deprived	2.08 (1.97-2.18)	3.26 (3.00-3.54)	2.07 (1.95-2.20)
	2	1.98 (1.89-2.07)	3.16 (2.93-3.40)	1.89 (1.78-2.00)
	3	1.98 (1.90-2.07)	3.27 (3.05-3.50)	1.82 (1.72-1.92)
	4	2.15 (2.06-2.24)	3.38 (3.16-3.60)	2.04 (1.94-2.15)
	Least Deprived	1.87 (1.79-1.96)	2.87 (2.67-3.08)	1.75 (1.66-1.85)
Diabetes	Non-diabetic	1.81 (1.76-1.85)	2.93 (2.81-3.05)	1.66 (1.61-1.71)
	Diabetic	2.52 (2.44-2.61)	3.81 (3.60-4.02)	2.54 (2.44-2.65)
Myocardial Infarct (MI)	No previous MI	1.96 (1.92-2.00)	3.10 (3.00-3.21)	1.85 (1.81-1.90)
	Previous MI	2.61 (2.45-2.76)	3.96 (3.59-4.37)	2.52 (2.35-2.71)
Primary Renal Disease	Diabetes	2.45 (2.35-2.55)	3.48 (3.25-3.72)	2.29 (2.18-2.41)
	Glomerular	1.59 (1.49-1.69)	2.78 (2.52-3.05)	1.36 (1.25-1.47)
	Hypertension	1.93 (1.78-2.09)	3.16 (2.77-3.60)	1.60 (1.44-1.78)
	Renovascular	2.51 (2.31-2.72)	4.13 (3.61-4.70)	2.09 (1.87-2.32)
	Polycystic	1.30 (1.19-1.41)	1.93 (1.67-2.21)	1.16 (1.04-1.28)
	Pyelonephritis	1.63 (1.50-1.77)	2.25 (1.94-2.59)	1.53 (1.38-1.70)
	Other	2.34 (2.22-2.47)	3.64 (3.34-3.96)	2.14 (2.00-2.29)
	Uncertain	2.06 (1.97-2.15)	3.06 (2.85-3.29)	1.85 (1.76-1.96)
Comorbid Score	0	1.59 (1.54-1.64)	2.53 (2.41-2.66)	1.42 (1.36-1.47)
	1	2.16 (2.08-2.23)	3.18 (2.99-3.37)	2.06 (1.97-2.15)
	2	2.60 (2.45-2.74)	4.30 (3.94-4.69)	2.74 (2.56-2.92)
	3+	3.19 (3.03-3.36)	5.38 (4.96-5.83)	3.27 (3.07-3.48)
Time from first seen to start of RRT	< 90 days	2.24 (2.16-2.32)	3.67 (3.46-3.89)	1.95 (1.86-2.04)
	90 – 180 days	2.53 (2.35-2.71)	3.87 (3.44-4.34)	2.27 (2.07-2.48)
	> 180 days	1.84 (1.79-1.89)	2.68 (2.55-2.80)	1.69 (1.63-1.75)

Multivariate models

To determine the necessity to employ count models, the categorised number of admissions within the first three months, latter nine months and the whole twelve month period is shown below. Using methods which only count one admission would miss the repeated admissions of 43.9% of the cohort who are admitted a second time during the first year. As highlighted previously the greatest rate of admissions is seen in the first three months, illustrated by the proportion admitted being similar for the three month period being similar to the nine month period.

Table 7-4 : The proportion of patients experiencing two or more admissions in the first twelve months of peritoneal dialysis potentially censored by time to first admission analyses

Model Period		Percentage
First 3 months	Zero Admissions	58.4%
	One Admission	26.4%
	Two or More Admissions	15.2%
Subsequent 9 months	Zero Admissions	48.0%
	One Admission	23.2%
	Two or More Admissions	15.8%
Full 12 months	Zero Admissions	31.7%
	One Admission	24.5%
	Two or More Admissions	43.9%

Using a negative binomial and also a zero-inflated negative binomial model, including a stratification of first three months and latter nine months, the statistical influence of the variables of age, sex, ethnicity, socioeconomic status, year of start and comorbid conditions of greater than two percent prevalence at the start of RRT are shown in Table 7-5. In the presence of other variables there was an improvement in admission rates with the standardised admission rate dropping from 1.07 to 0.92 between 2002 and 2009, evidenced by the year of start being significant in all models and persisting in the presence of late referral which has been noted to have improved over the same time-period.

The addition of demographic variables and comorbid conditions improved the performance of the models in terms of predicting admission rates as determined by root mean squared error by approximately 0.05 of a day (appendix 7b). With the inclusion of comorbid conditions the RMSE of the zero inflated method was 2.48 days, better than the standard negative binomial of 2.53 and comparable to that of the zero-inflated method modelling the first 3 months and the latter 9 months separately (RMSE 2.47 days). The addition of late

referral and primary renal disease in a cohort where these were applicable added additional precision as measured by RMSE of 0.01 of a day in the zero-inflated models.

The failure of the models to predict patients with larger numbers of admissions (more than 4 per year) is evidenced by the positively skewed nature of the observed / expected ratios, primarily due to the 31.7% of patients who are not admitted and therefore will have an observed /expected of zero irrespective of the predicted value. The RMSE climbs linearly with observed counts greater than 4, suggesting that these outlying counts are predicted values similar to the cohort mean.

Table 7-5 : Statistical significance of predictor variables in a range of modelling strategies

Model	**Negative Binomial**	**Zero Inflated Negative Binomial**				**Zero Inflated Negative Binomial**	
Period	0 - 12m	0 - 3m		3 - 12m		0 - 12m	
	Count	Zero Inflation	Count	Zero Inflation	Count	Zero Inflation	Count
Age	●*		○	○*	●		●*
Sex							
Ethnicity		○	○				○
Socioeconomic Status						○	●
Year of Start	●		●		○	○	●
Comorbid Conditions:							
COPD	●		○		○		●
Arrhythmia				○			
Congestive Cardiac Failure	●		●	○	○	○	●
CABG			○		○		○
Depression	●				●		●
Cerebrovascular Accident			○			○	
Myocardial Infarction							○
Lymphoma/myeloma	●		●		●		●
Neurological Disease	●		○		●		●
Vascular Disease							○
Valvular Heart Disease	●		●		○		●
Cancer							○
Connective Tissue Disease	○			○		○	○
Peptic Ulcer Disease	●			○			●
Claudication	○				○		
Hypothyroidism							
Diabetes	●*	○	○	●*	○	●	●*

*Age/Diabetes interaction (e.g. differing admission rates in younger vs. older diabetes patients, persisting after multivariate adjustment), ○ – P<0.05, ● – P<0.001

Standardised centre-specific admission rates

Using the 12 month zero-inflated negative binomial model derived above, the influence of case-mix adjustment on the outlier status of centres is shown in Figure 7-2. Adjusting purely for age, eleven centres are outside the 95% control limit (six > 99%, five < 99% > 95%). With adjustment for socioeconomic status, ethnicity and year of start, one centre between the 95% and 99% limits is explained. Further adjustment for fourteen comorbid conditions identifies one additional centre beyond the 99% limit, once centre beyond the 95% limit and explains one centre between the 95% and 99% limits.

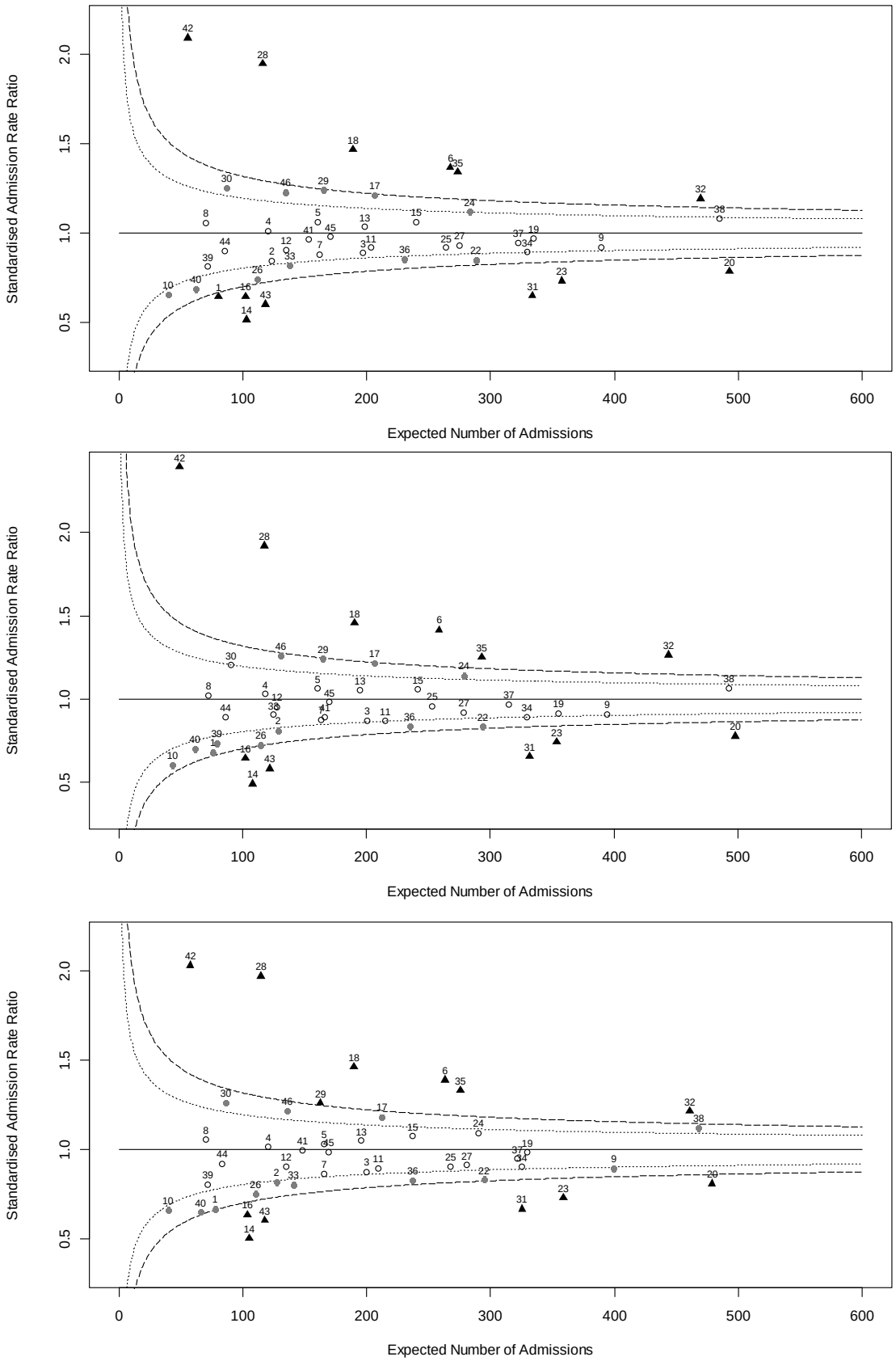


Figure 7-2 : Centre specific standardised admission rates in the first year of peritoneal dialysis, adjusted for age (top), age, ethnicity, socioeconomic status & year of start (middle) age, ethnicity, socioeconomic status, year of start and comorbidity(bottom).

Comparison of centre specific admission rates between modalities

The correlation between standardised haemodialysis and peritoneal dialysis admission rates are poor (Pearson correlation coefficient 0.20, P=0.188), with only two centres identified as outliers beyond the 95% control line in both measures (Figure 7-3).

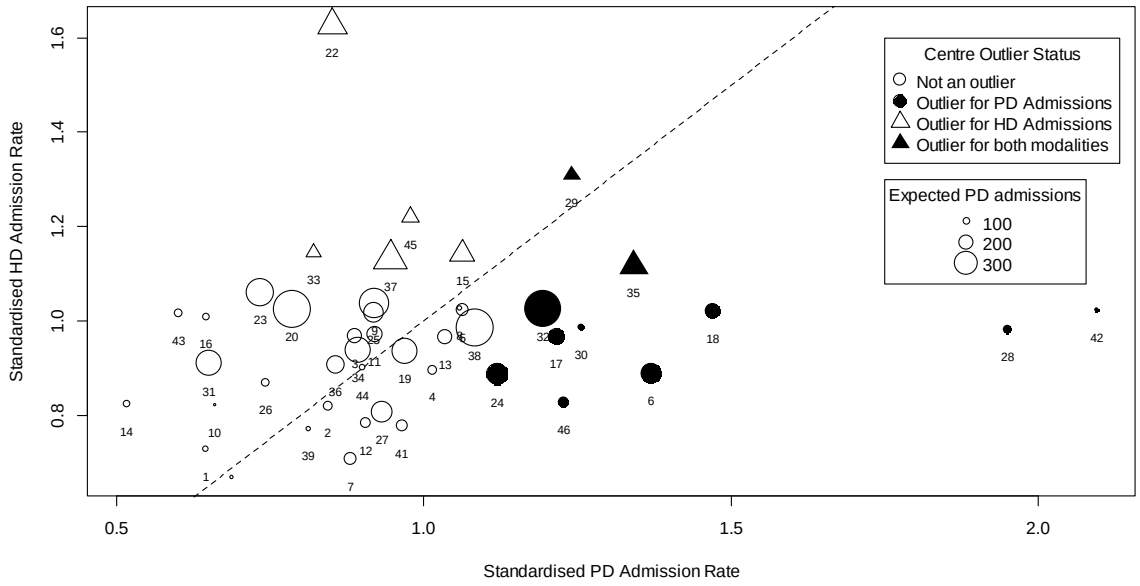


Figure 7-3 : Standardised centre-specific haemodialysis and peritoneal dialysis admission rates (line = equal standardised rates for both modalities)

The smaller programme size of peritoneal dialysis may lead the eye to believe there is greater variation in admission rates for peritoneal dialysis when compared to haemodialysis. Comparing the ratio of the variances for the P-value of observed/expected ratio for haemodialysis and peritoneal dialysis, the ratio is 0.899 (95% CI 0.494 – 1.636, P=0.726) suggesting the variance is greater in peritoneal dialysis, but not significantly.

Catheter insertion admissions

Of the 6,259 patients experiencing their first treatment identified above, 5,906 were documented as having a peritoneal dialysis catheter inserted. 520 of these were beyond the first 30 days of treatment, and 35 of these were greater than 12 months before the first exposure to peritoneal dialysis. These may represent catheters inserted which did not function and patients were then exposed to haemodialysis for a period of time. The timing across centres of the remaining 85.5% of the peritoneal dialysis exposed cohort with catheters inserted between 12 months before to 30 days after first exposure is emphasised in Figure 7-4. The time between catheter insertion and date of first peritoneal dialysis was a mean of 31 days, median of 21 days, with an interquartile range of 14-35.

There were 438 patients who had peritoneal dialysis catheters inserted prior to starting RRT who were never coded as receiving peritoneal dialysis.

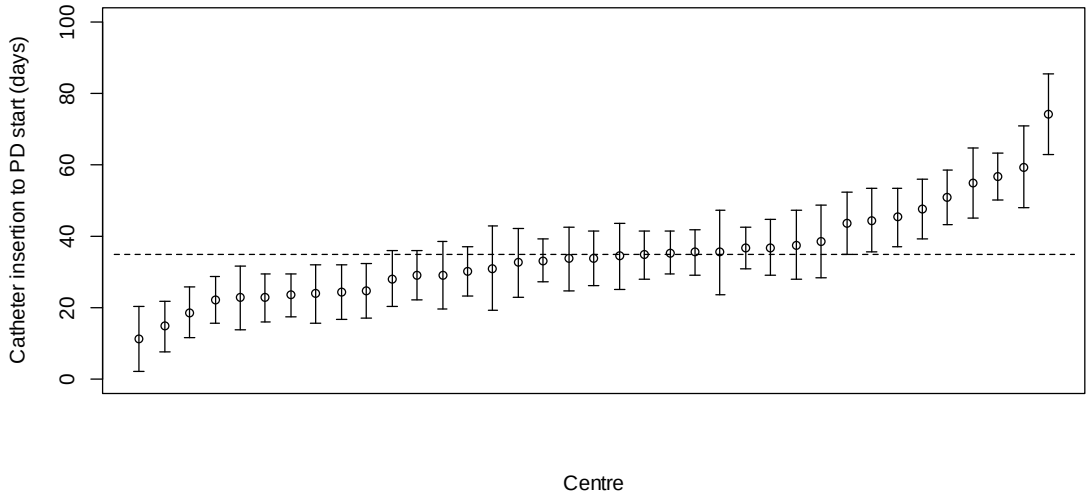


Figure 7-4 : The variation in time from PD Catheter insertion to starting dialysis across centres, adjusted for late referral and previous modality

Peritonitis rates

Raw rate

Across all periods of peritoneal dialysis treatment, 6,259 hospitalised peritonitis events occurred. Using the various censoring methods for repeated admissions reduced this number to 4,894 (78.2%) for repeated admissions within 42 days from discharge, 4,965 (79.3%) for repeated admissions within 42 days of admission and 5,112 (81.7%) for repeated admissions 28 days from discharge. 12,718 patient years of follow-up were available for analysis.

51.5% of patients experienced no peritonitis during their follow-up period, with 29.7% experiencing one event and 18.8% experiencing more than one event. Peritonitis complicated 22.1% of admissions in patients receiving peritoneal dialysis.

The overall admitted peritonitis rate was 38.9/100 patient years using the 42 days from discharge method. Patient case mix influenced admission rates, with higher rates associated with increasing age, worsening socioeconomic status and increasing comorbidity as demonstrated in Table 7-6. Patients who had previously been on haemodialysis had a 34% increase in admitted peritonitis rate compared to patients who had arrived at peritoneal dialysis without experiencing dialysis or from a kidney transplant.

Multivariate standardised rates

Using the zero-inflated negative binomial model, multivariate analyses were performed to determine independently predictive variables in order to perform standardisation. Using forward selection, a model with age and year of start to predict zero inflated coefficients and socioeconomic status, ethnicity, previous modality, year of start, comorbid score (not including diabetes) and diabetes was employed. The root mean squared error for this model was 0.68 admissions and was constant between observed counts of 0 and 1 (representing 85% of the dataset). This is in contrast to an unadjusted rate RMSE of 1.75, also constant between 0 and 1. Excluding year of start from the model allowed the analysis of improvements over time. The standardised admitted peritonitis rate ratio stayed static over the observation period (2002: rate ratio 1.02, 95% CI 0.92 – 1.13; 2006: rate ratio 1.01, 95% CI 0.92 – 1.11), alongside a constant mean age of start and a constant comorbid burden suggesting no changes in rates with time.

Event coding issues

As highlighted above variation in coding and resulted in a broadening of the criteria by which episodes of peritoneal dialysis peritonitis are identified. Nationally for all admissions and within renal patients there is variation in coding depth, which could be interpreted as a variation in the quality of coding being performed. Table 7-7 shows the number of admissions per centre stratified by the ICD10 codes used to identify events. Centre specific employment of these codes is detailed in Appendix 7c.

The primary diagnosis position identified the peritonitis admission in 86% of cases with the majority of centres exceeding 90% of cases being identified this way; however one centre only had 29% of cases identified in the primary position with 27% and 38% of cases being identified in the second and third diagnosis positions respectively. Scrutiny of position tables at centre level, and reviewing all centre coding position, the first three positions (DIAG_01, DIAG_02 and DIAG_03) cover 95.8% of the admissions.

Information on organisms was available in 37.9% of peritonitis episodes. Staphylococcus caused 21.6% of episodes (10.3% of which was Staphylcoccus aureus), gram negative organisms caused 9.9% and streptococcal organisms 5%. Fungal organisms caused 1.3% or episodes with 0.1% other organisms and 62.1% undocumented.

Table 7-6 : The influence of demographics on hospitalised peritonitis rates

Demographic Variable		Rate/100 patient years and 95% CI	
Age	<40	35.6	(33.1 - 38.2)
	40-60	38.2	(36.5 - 40.1)
	>60	40.7	(39.0 - 42.3)
Sex	Male	39.6	(38.2 - 41.1)
	Female	37.8	(36.1 - 39.5)
Ethnic group	White	39.4	(38.2 - 40.6)
	Black	40.0	(35.3 - 44.9)
	South Asian	34.8	(30.7 - 39.2)
	Other	35.9	(31.9 - 40.1)
Socioeconomic Status	Most Deprived	42.4	(39.8 - 45.1)
		40.9	(38.5 - 43.5)
		37.4	(35.1 - 39.9)
		37.8	(35.5 - 40.3)
	Least Deprived	36.2	(33.9 - 38.6)
Diabetes	No DM	37.2	(35.9 - 38.5)
	DM	45.4	(43.1 - 47.7)
Chronic obstructive pulmonary disease	No COPD	39.2	(38.1 - 40.4)
	COPD	48.0	(40.8 - 55.8)
Previous Myocardial Infarct	No MI	39.0	(37.8 - 40.2)
	Prev MI	44.0	(40.3 - 47.9)
Comorbid Score	0	34.8	(33.3 - 36.2)
	1	40.3	(38.1 - 42.6)
	2	45.2	(41.7 - 48.9)
	3	48.5	(43.5 - 53.7)
	>4	47.3	(42.7 - 52.2)
Previous Modality	HD	47.9	(45.5 - 50.4)
	Transplant	34.2	(27.7 - 41.7)
	First RRT	35.8	(34.6 - 37.1)
Overall Rate		38.9	(37.8 – 40.0)

Table 7-7 : The overall frequency of codes employed to describe peritoneal dialysis peritonitis

ICD10 Name	ICD10 Code	Percentage using code
Infection & inflammatory reaction due to other internal prosthetic devices	T857	47.1%
Peritonitis, unspecified	K659	18.7%
Acute peritonitis	K650	14.0%
Acute reaction to foreign substance accidentally left during a procedure	T816	10.0%
Infection and inflammation reaction due to other cardiac vascular devices	T827	6.2%
Other peritonitis	K658	0%
Other disorders of the peritoneum in infectious diseases EC	K678	4.0%

Centre specific peritonitis rates

Due to patients moving between centres there were a greater number of reporting centres available than incident peritoneal dialysis analyses. If a patient moves into a centre which was not providing data to the registry during the incident period, but was towards the end of the observation period they will be included. Forty-five centres were suitable for standardised reporting. The mean centre-specific rate of hospitalised peritonitis was 40.1 per 100 patient years, with a range of 14.8 – 79.2 per 100 patient years.

Standardised admitted peritonitis event rates unadjusted displayed in Figure 7-5, identifying six centres with higher than expected admitted peritonitis rates, and 21 centres with lower than expected rates. Following adjustment for age, socioeconomic status, ethnicity, previous modality, year of start, comorbid score (not including diabetes) and diabetes, nine centres were identified with higher than expected admitted peritonitis rates and twelve with lower than expected admission rates. The improvements in modelling appear to be at predicting low counts which tend to explain centres with low rates.

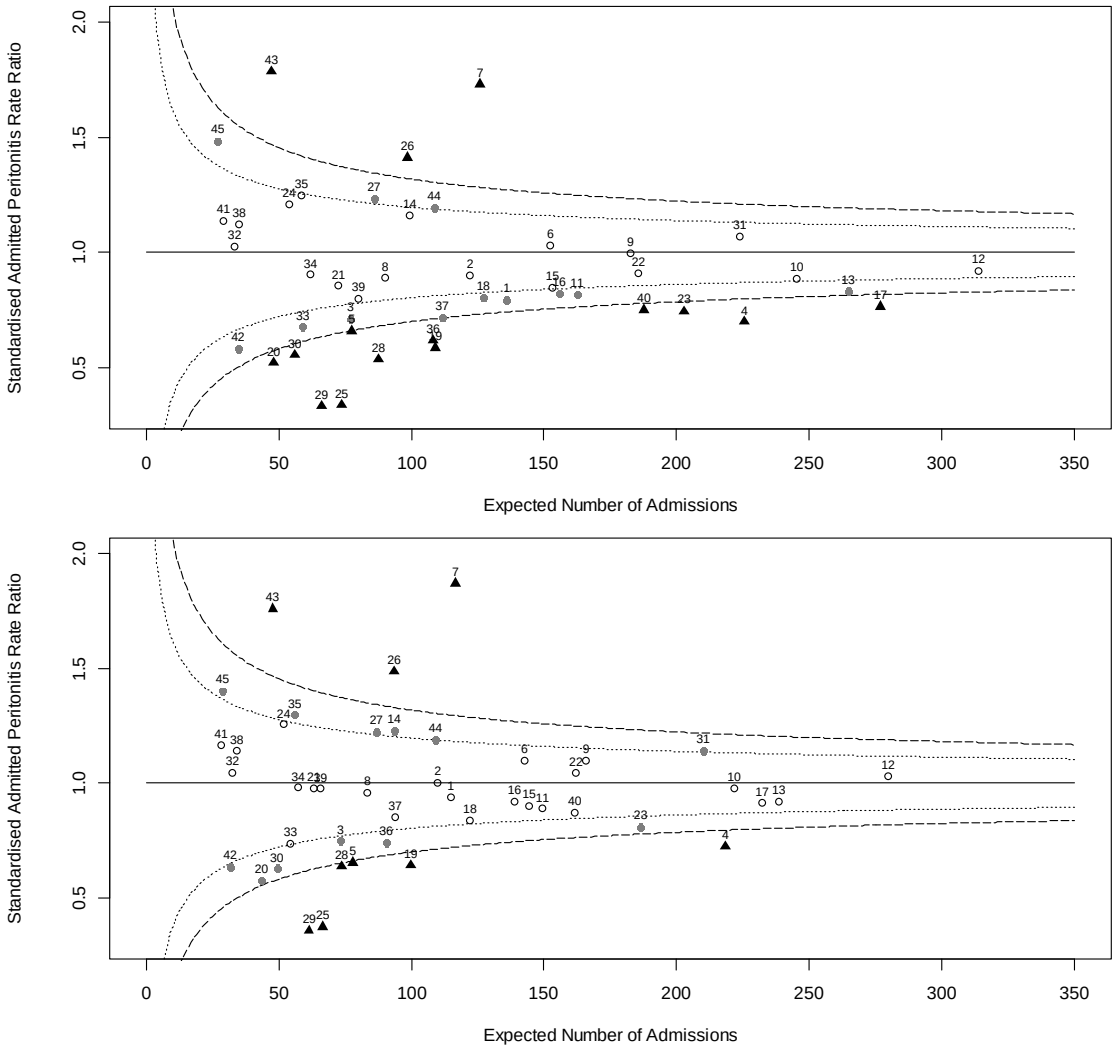


Figure 7-5 : Standardised admitted peritonitis rates for the patients on peritoneal dialysis at any time adjusted purely for age (above) and after (below) multivariate adjustment

Using a multi-level zero inflated negative binomial model, the impact of centre size on peritonitis rates was explored. Categorising the centres into <100, 100 - <200 and >=200 patients and adjusting for age, socioeconomic status, previous modality, comorbidity and year of start, there was no impact on being managed in a small, medium or large centre on individual patients' peritonitis rates (P=0.25).

In the 45 centres which have standardised admission rates and standardised admitted peritonitis rates, there was a strong correlation between the two measures. The correlation coefficient was 0.66 (P<0.001). Three centres were outliers for both measures. Two centres with higher than expected admitted peritonitis rates had normal all cause admission rates. The relationship between the two measures is shown in Figure 7-6, with plot points scaled to expected admission count (expected counts for all cause admissions and peritonitis admissions were extremely closely correlated at 0.97, P=0.001).

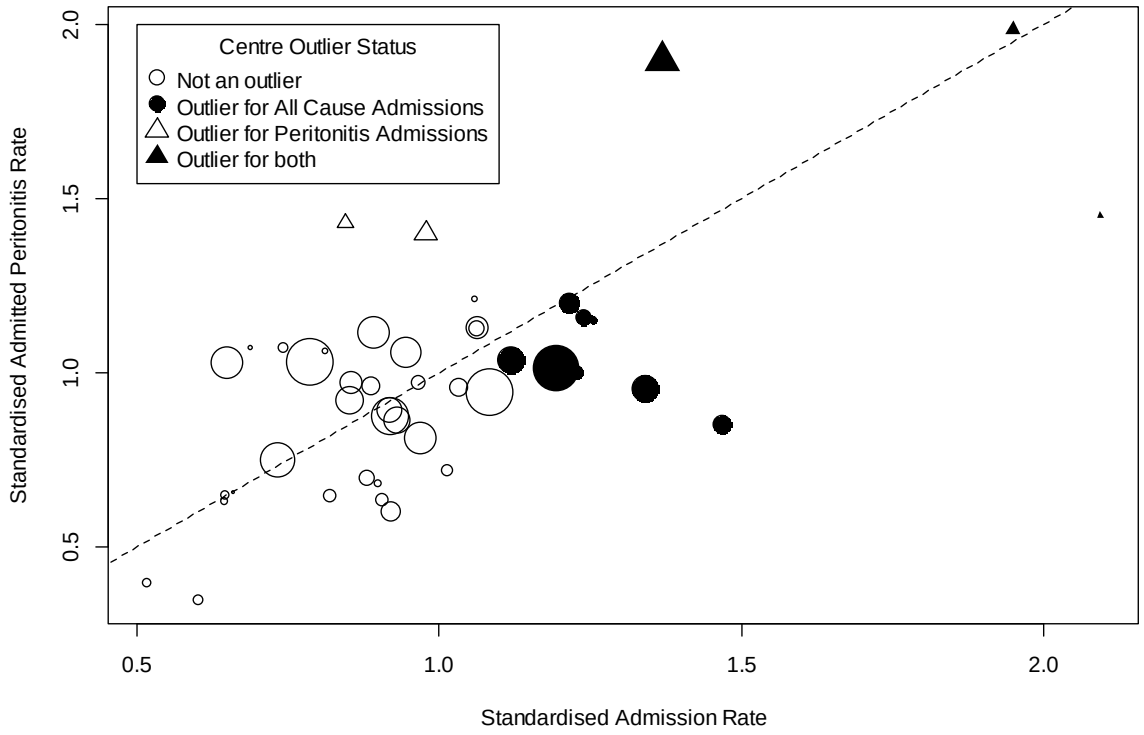


Figure 7-6 : The correlation between centre specific all cause admission rates and peritonitis rates

Catheter Timing and Admitted Peritonitis

Recognising the variation in catheter insertion timing across centres, the potential impact of catheter insertion timing in an individual's peritonitis risk was explored using Cox regression and peritonitis free survival for a patient's first peritonitis treatment exposure. Censoring at one year, 30.5% of the cohort were censored prior to this without having an event, and 25.7% of the total cohort experienced peritonitis. Significant factors in the regression were socioeconomic status, comorbid score and previous modality, with time from catheter insertion to episode of first peritonitis categorised into <15 days (1108 patients), 15-30 days (3107 patients), 31-60 days (670 patients) and >60 days (466 patients). Compared to <15 days, the hazard ratio associated with catheter insertion >60 days before starting therapy was 1.28 (95% CI 1.05 – 1.55, P=0.014). As the centre specific mean time from catheter insertion to start of treatment varies, a clustered survival analysis using a frailty model which included centre as a random effect was performed, and showed no significant impact on catheter insertion timing on peritonitis rates (Table 7-8). The hazard ratio for >60 days was reduced to 1.139 (95% CI 0.926 – 1.402).

Table 7-8 : The influence of demography and catheter timing on time to first peritonitis admission

		Standard Model		**Centre Clustered Frailty Model**	
Variable		Hazard, (95% CI)	P	Hazard, (95% CI)	P
Age	<40	1 (comparator)		1 (comparator)	
	40-65	1.0776	0.336	1.075	0.350
	> 65	1.0386	0.629	1.067	0.410
Socioeconomic Status	Most Deprived	1 (comparator)	0.012	1 (comparator)	0.017
	2	0.9540		0.931	
	3	0.8074		0.762	
	4	0.8162		0.769	
	Least Deprived	0.8167		0.746	
Comorbid Score	Per unit	1.0695	<0.001	1.069	<0.001
Previous Modality	Haemodialysis	1 (comparator)		1 (comparator)	
	Transplant	0.6251	0.110	0.621	0.110
	First RRT	0.750	<0.001	0.744	<0.001
Catheter Insertion	<15 days	1 (comparator)		1 (comparator)	
	15-30 days	1.1021	0.158	1.006	0.930
	31 – 60 days	1.0855	0.307	0.998	0.990
	> 60 days	1.2777	0.014	1.139	0.220

Post-peritonitis outcomes

Reviewing the patient's status at 30 days from discharge following first peritonitis event, 66.6% were still on therapy at 30 days, 24.2% had been transferred to haemodialysis, 7.2% had died with 0.9% having their therapy withdrawn, 1.1% had been transplanted. Mean length of stay for the first peritonitis episode was 10.7 days, and primarily driven by changing to haemodialysis (mean length of stay 18.3 days) and patients who subsequently died (mean length of stay 31.0 days).

The centre specific proportion of patients remaining on peritoneal dialysis or transplanted (the two most preferable outcomes) varied from 40.1% to 86.0%, with eight centres with higher than expected rates of peritoneal dialysis failure at 30 days, and six centres keeping greater than expected numbers of patients on peritoneal dialysis. There was no clear correlation between centre specific rates of remaining on peritoneal dialysis or being transplanted and admitted peritonitis rates (correlation coefficient 0.002, P=0.991).

Discussion

Hospital associated peritonitis events have not previously been described in England. Despite adjustment for a number of patient level factors, there remains a four-fold difference in the rates of all cause hospitalisation in the first year and patients admitted with peritonitis across centres.

The importance of the finding that 484 of the 21271 patients starting RRT between 2002 and 2006 have catheters inserted but never recorded as receiving peritoneal dialysis should not go understated. The increase of peritoneal dialysis failure rate at three month from 7.4 to 16.0% still places it below the regions of 20-25% seen in the US, and Netherlands Cooperative Study on the Adequacy of Dialysis (Jaar et al. 2009) (Kolesnyk et al. 2010).

In addition to allowing us to compare English centres for admission rates and peritonitis rates, it has been possible to compare English peritoneal dialysis outcomes to those internationally. Admission rates for peritoneal dialysis patients have been approximately two per year in the US for the last decade, a similar rate to that seen in this study. Closer to home, Brown et al reported peritonitis rates for 10 adult units in Scotland over an 8 year period(Brown et al. 2011), determining a rate of one episode per 20 months, a figure similar to that observed by the North Thames group's performance over a two year period(Davenport 2009). Our rate of one episode per 30 patient months is more comparable to those seen by the US and Canada (32.7 and 27.6 patient months respectively), and more comparable to Korea and Hong Kong (30 months and 36-45 patient-months respectively) (Li et al. 2002; Kim et al. 2004; Mujais 2006). The high mortality rate and technique failure (7% and 24.2% respectively) observed in this study should be interpreted with caution, as hospitalised peritonitis represents a more severe phenotype than that in the analyses by Brown et al where mortality at 30 days was 2.8% and technique failure was 14.9%. Organism data falls below what would be expected both as a renal association standard (culture-negative rate less than 20%) and seen in clinical practice (19.4%), especially in context of the greater severity and therefore greater likelihood of identifying a causative organism.

The linear association between all cause admission rates and peritonitis admission rates showed in Figure 7-6 can be interpreted in a number of ways, and one could argue this linearity between measures suggests that a hospitalised peritonitis rate is a robust measure and it aligns with companion indicators of centre performance. Assuming a comparable medical complication rate (peritonitis and other dialysis related problems) across centres, the lack of community facilities to treat peritonitis and intervene on other dialysis related medical problems (for instance fluid overload or drainage issues(Ellam et al. 2011)) may manifest

proportionally. Alternatively poor clinical care offered by centres extends through training of patients(Chow et al. 2007) (a large determinant of peritonitis rates) to the prevention of access related complications (Briggs et al. 2013), fluid balance issues and cardiovascular events(Woodrow 2011). Fortunately, this association was not driven by centre size, as we were unable to demonstrate a volume/centre size association between either peritonitis rates or admission rates as previously seen in analyses of other healthcare services.

Despite a wide variation in catheter placement timing, the impact of inserting a peritoneal dialysis catheter <15 days, 15-30 days, 31 – 60 days or > 60 days once clustering of patients within centres is factored appears to be non-significant. There may be additional factors absorbed by the model which explain why centres have such varying catheter insertion timing. For instance, late presentation and unplanned dialysis starts would necessitate later catheter insertion, and is associated with increasing age, increasing comorbidity and ethnicity(Gilg et al. 2011; Gilg et al. 2013).

The influence that comorbid conditions and age have on peritonitis rates may not reflect an increased risk of developing peritonitis per se, but rather reflect the individual patients capacity to tolerate the same degree of infection, or a healthcare professional's attitude towards the treatment of the patient in the community. Frailer patients may become more systemically unwell necessitating admission and monitoring, and the clinician's prior beliefs and experience of this phenomenon will contribute to the likelihood of admission. The fact that rates of peritonitis have stayed stable is in keeping with Scottish and American disease registries(Brown et al. 2011; U S Renal Data System 2011). It has been shown elsewhere that the comorbidity of patients has increased during this period; however the adjustment for this in the above multivariate model would imply that no underlying clinical improvement has been observed.

In summary, this chapter as determined:

- National and centre-specific admission rates in the first year for patients receiving peritoneal dialysis.
- Variation in the rate of hospitalised peritonitis across centres, suggesting differing thresholds at which patients are admitted.
- Variation in the timing of PD catheter insertion, but no strong association between the timing and subsequent admitted peritonitis rate.

Chapter 8 *Hospital-related events in kidney transplantation*

Successful surgical insertion of the kidney from another person (generally referred to as a donor) can return a patient's kidney function to approaching that of someone without kidney disease (Hariharan et al. 2002). Transplanted kidneys can come from a number of types of kidney donor. Kidneys can be donated after death from patients who have suffered brain death as a result of trauma or neurological events such as strokes or intra-cerebral bleeding (Hauptman et al. 1997). More recently the practice of removing kidneys from patients who have suffered more conventional cardiac death has become more widespread(Mandell et al. 2007).

Living donor kidneys can be donated by individuals close to a patient who is approaching ERF or is on dialysis. The donor surgery is performed in conjunction with the recipient being surgically prepared to receive the kidney. Prior to surgery in all these settings investigations are performed to ensure that the donor organ is compatible with the proposed recipient (for instance screening for antibodies directed at red blood cells and other human tissue that can cause rejection) and that there are no underlying medical reasons in the donor precluding them from donating a kidney (the presence of kidney disease or malignancy in the donor, or surgical issues with the anatomy of the kidney) (Davis et al. 2005).

Not all renal centres perform kidney transplants, as demonstrated by the presence of 46 parent renal centres in previous analyses and 20 in this chapter. Many transplanting renal centres are responsible for listing patients for a deceased donor kidney or coordinating the living donor work-up and surgery for neighbouring renal centres. The referral to transplanting centres is generally initiated by the centre supervising the CKD or dialysis care. Concerns about equity have previously been raised(Pruthi et al. 2013) (Ravanan et al. 2010).

Receiving a kidney transplant does not mean that kidney function is normalised, or that the transplanted kidney will last as long as healthy native kidneys. Some kidneys do not work immediately after insertion (delayed graft function), or function at levels which remain in a category associated with chronic kidney disease (Hariharan et al. 2002). Transplantation services in the UK have primarily been focused on kidney transplant and patient survival, and the attainment of laboratory targets (Webb et al. 2011). These measures have been derived and reported by agencies like the UK Renal Registry and NHS Blood and Transplant.

Meanwhile bodies within the surgical arena have developed additional measures encompassing a broad range of surgical activity, but have yet to venture into kidney

transplantation. The Royal College of Surgeons directs clinicians and patients to a range of measures in other surgical procedures including nephrectomy, thyroidectomy and aortic valve replacement (3,000, 3,690 and 4,860 per annum respectively, compared to 2,000 kidney transplants per annum) (Health and Social Care Information Centre 2013). Short-term measures are likely to be more reflective of surgical performance and may represent an earlier warning sign that patient or graft survival.

Aims and Objectives

- To report case-mix variation across transplanting centres in England.
- To report HES derived incidences of surgical complications and delayed graft function, and compare these to existing literature to determine validity.
- To explore the influence of patient level factors on the above, along with length of stay for transplanting admissions and frequency of subsequent admissions.
- To report centre specific rates of surgical complications, delayed graft function, length of stay and frequency of subsequent admission, adjusted for demography.

Analysis specific methods

Only first renal transplants were included in this study. The reasons for these are as follows:

1. The nature of the incident RRT cohort is such that the number of patients who were transplanted, subsequently had a graft failure and were then re-transplanted only occurred in 234 patients.

2. Re-transplanted patients are subject to additional factors that may influence the measures reported herein. Examples include the immunological effect of the previous transplant on the host and the development of antibodies.

First transplantation episodes as defined as the earliest OPCS coded renal transplant in the linked dataset were compared to the earliest transplantation in the UKRR dataset using the methods in Chapter 3 and as reported in Chapter 4. Patients were also excluded if they had no linked HES data and resided outside England, as per the linkage consort diagram in Chapter 4.

Comorbidity at the time of transplantation was determined from the diagnosis and procedure codes for hospitalisations prior to the date of first transplantation as per Chapters 3

and 4. Comorbid conditions were counted with weighting, with the presence of diabetes being modelled separately.

Age was defined as the age a patient was admitted for transplantation, with time on dialysis measured in months from the date of first dialysis reported to UKRR to the date of admission for transplantation. Preceding RRT modality was defined as the previous recognised RRT modality from the UKRR timeline (either haemodialysis, peritoneal dialysis or not on RRT, hereby referred to as pre-emptive transplantation). Socioeconomic variables from the time of RRT start were employed in the form of IMD rank.

Assignment of transplantation centre was performed by reviewing parent renal centre immediately prior to transplantation, reported transplanting centre and the NHS trust which performed the transplant according to HES. Derivation of this is available in appendix 8a.

Length of stay was modelled using linear regression on log-transformed lengths of stay, with zero lengths of stay excluded. A 95% trim was performed to avoid distortion of the model by extreme outliers. A sensitivity analysis was performed to determine the impact of trimming and transformation on model performance. Standardisation was performed on all data excluding zero length of stay patients. This includes long stay patients whose LoS was trimmed. The log predicted length of stay was transformed back and compared to true length of stay. Centres were plotted on a control plot with the X axis reflecting the sum of the expected length of stay and the Y axis being the difference between the observed and expected counts. Control limits of two standard deviations of mean difference in the observed and expected counts limits are plotted above and below the mean and centres beyond these limits are classed as outliers. Length of stay analyses was performed on superspells rather than spells.

Frequency of admission was determined as per the common methods in chapter 3, with time in hospital excluded from time at risk for further admissions. Standardisation of frequency of admission was performed by using zero inflated negative binomial regression on admission counts, incorporating an offset for variable follow-up. The predicted counts from this model were compared to observed counts. For comparative purposes to demonstrate the impact of case-mix and factoring the skewed nature of the dataset median counts for admission rates are presented alongside group specific rates as defined as the total number of admissions divided by the total time at risk. Confidence internals for the latter are determined from the Poisson distribution.

As the HES dataset extends beyond the UKRR dataset, admissions and surgical complications can be derived from a period beyond where the UKRR dataset stops. Therefore

for these hospitalisation measures the last transplant in the UKRR dataset (up to the 31st of December 2009) can be included for analysis. For graft specific outcomes (graft survival and function), a more limited cohort of patients being transplanted up to the 31st of September 2008 would have to be used, enabling sufficient follow-up time for these endpoints to be collected (a three month laboratory window would also be included).

Surgical complications were specified by review of diagnosis and procedure codes during the admission and within the first 12 months following transplantation. Those likely to be as a result of surgery were identified and supplied to a Transplant Surgeon for confirmation. OPCS and ICD10 codes were strictly examined so that routine events such as protocol biopsies and stent removals which are pre-specified activity and do not relate to suboptimal care were not included. Codes were placed into seven broad groups to aid description and enable comparison to the existing literature. The presence of multiple complication groups was permitted for descriptive purposes. The overall modelling of surgical complications was performed on the occurrence of any surgical complication as there is some overlap between the pertinent codes (for instance nephrectomy and laparotomy). The presence of a surgical complication at any NHS trust was assigned to the parent renal centre. Established rates of surgical complications were determined from literature provided by the same collaborating transplant surgeon.

Delayed graft function (DGF) was defined as the use of a dialysis modality (X40, with specific incidences of codes within this) in the procedure field of the HES coded as having occurred after the date of transplantation. Dates for both the transplantation procedure and the dialysis activity were determined from the HES procedure dates from the super-spell during which the transplantation occurred.

Stent usage was defined as the removal of a ureteric stent in the post-operative period in patients who did not have a nephrectomy or die early in the post-operative period (as defined as the first six weeks). If the patient died the stent extraction would effectively be censored, and transplant nephrectomies early in the post-transplant period could result in stent removal at that time, negating the need for a subsequent elective stent removal. Both inpatient and outpatient procedure fields were scanned for procedure code M293 (Endoscopic removal of tubal prosthesis from ureter).

Admission rates where possible were compared to those reported from other kidney disease registries.

Logistic regression was used for the multivariate analysis of predictors of surgical complications and delayed graft function, with indirect standardisation for centre specific comparison performed using observed over expected ratios. The role of coding depth was evaluated as this indicator was more susceptible to coding quality than other performance measures such as subsequent admission and length of stay. Coding depth was defined as the centre specific mean number of diagnosis codes employed per admission for the year the transplant occurred (detail in chapter 4). As some transplanting centres were not routinely supplying incident patients to UKRR during the study period, the coding depth for three centres were not available for inclusion and the mean coding depth of the entire group was substituted.

Cut-points for continuous variables where appropriate were determined from smoothed spline plots. Variables were included for standardisation if they were found to have an impact on patient level rates of admission, length of stay or surgical complications. The impact of variable inclusion was determined on outlier status on a funnel plot as defined as a centre being above or below the 95% upper or 95% lower limits.

Results

There were 4,517 first transplants identified with date of transplant within 90 days of each other from both sources. Twenty transplanting centres were contributing during this time, performing transplants for an additional 26 non-transplanting renal centres who were supervising CKD or dialysis care. The cumulative incidence of transplantation episodes gradually climbs as patients start RRT and then plateaus as the number available for transplantation stabilises (Figure 8-1). This observation limits outcome analyses to the early post-transplant period.

Descriptive statistics of the cohort are detailed below, and show a relatively short dialysis vintage prior to transplantation and an over-representation of living donor and pre-emptive transplants, when compared to a more prevalent analysis of all patients transplanted in England during this period.

Table 8-1 : Demographic differences between 4,517 patients transplant from within and outside transplanting centres

Demographic Variable		Overall	Transplanting Parent Renal Centre (56%)	Non-transplant parent renal centre (44%)	P
Age at Transplant (years)		45.52	45.38	45.69	0.431
Male (%)		62.2	61.1	63.5	0.094
Ethnicity (%)	White	82.6	81.1	84.4	0.005
	Black	5.3	5.7	4.8	
	South Asian	5.4	6.1	4.6	
	Other	6.7	7.1	6.1	
Time on dialysis (months)		23.41	21.6	25.72	<0.001
Pre Transplant Modality (%)	Haemodialysis	48.9	45.5	53.3	<0.001
	Peritoneal Dialysis	36.9	33.1	41.7	
	Pre-emptive	14.1	21.4	4.9	
Living Donor (%)		31.9	35.6	27.1	<0.001
Diabetic (%)		20.1	18.7	21.9	0.007
Comorbid Score (%)	0	59.7	62.3	56.4	<0.001
	1	23.6	22.7	24.7	
	2+	16.7	15	19	
IMD Rank (lower more deprived)		16194	16455	15861	0.035

Missing data: Socioeconomic status – 71 cases

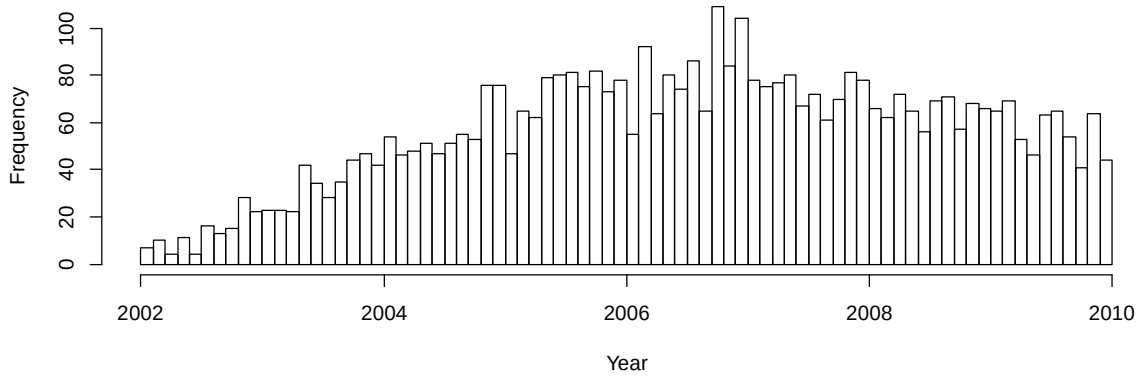


Figure 8-1 : The number of first kidney transplants being performed during the follow-up period

Scrutiny of the demographical differences between patients transplanted by their own centre or those who have to transfer in, showed that those transferring in are older, of increasing dialysis vintage, more likely to receive a deceased donor kidney and more comorbid. These baseline differences may confound some conclusions regarding the outcomes in patients transplanted from other centres.

Centre specific demography

Centre specific variation in baseline demography is shown in Figure 8-2. It is most evident in donor type, socioeconomic status and time on dialysis. There was little variation in donor age (not shown).

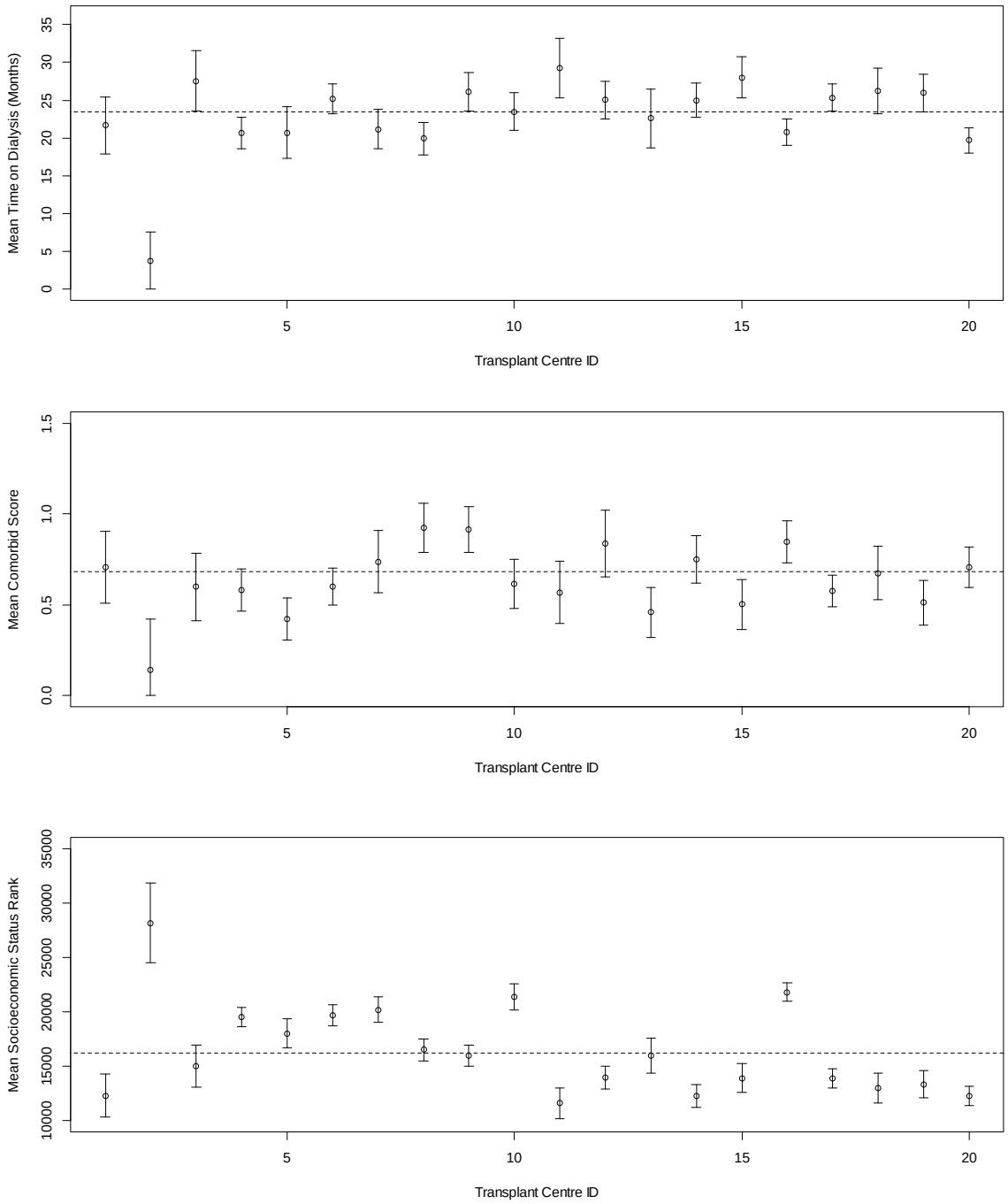


Figure 8-2 : Top: Centre specific mean time on dialysis (months), Middle: Centre specific mean comorbid score calculated using weighted conditions derived in chapter 4, Bottom: Centre specific socioeconomic status rank (lower number = more deprived).

Delayed graft function & surgical complications

The overall DGF rate was 13.2%, and the surgical complication rate was 22.3%. Event incidence was influenced by the case-mix of the recipient in a predictable manner. Higher rates of DGF and surgical complications were seen with increasing age, longer time on dialysis, increasing comorbidity and being the recipient of a deceased donor kidney (Table 8-2). The relationship between the continuous variables of age, time on dialysis, comorbid score and coding depth and the measures of DGF and surgical complication in the lower ends where the majority of the data lied was fairly linear (Figure 8-3).

Table 8-2 : The influence of demography on the incidence of surgical complication and delayed graft function

Demographic Variable		**Surgical Complication (%, (95% CI))**	**Delayed Graft Function (%, (95% CI))**
Age group	<40	19.5 (17.5 - 21.5)	9.5 (8.0 – 11.0)
	40-60	22.1 (20.4 - 23.9)	13.6 (12.2 – 15.0)
	>60	28.6 (25.4 - 31.8) ¥	19.2 (16.4 – 22.0) ¥
Sex	Male	22.5 (21.0 – 24.0)	14.0 (12.7 - 15.3)
	Female	22.1 (20.1 – 24.0)	11.8 (10.2 - 13.3) *
Ethnicity	Non-White	21.6 (18.7 - 24.5)	11.5 (9.3 - 13.7)
	White	22.5 (21.2 - 23.8)	13.5 (12.4 - 14.6)
Pre-transplant modality	Haemodialysis	22.9 (21.2 - 24.7)	16.9 (15.4 - 18.5)
	Peritoneal Dialysis	23.0 (21.0 – 25.0)	12.2 (10.6 - 13.7)
	Pre-emptive	18.6 (15.6 - 21.6)	2.7 (1.4 - 3.9) ¥
Time on RRT	<1 year	19.0 (17.1 - 20.9)	6.7 (5.5 - 7.9)
	1 -2 Years	23.9 (21.2 - 26.6)	10.6 (8.7 - 12.5)
	>2 Years	24.4 (22.5 - 26.4) ¥	20 (18.2 - 21.8) ¥
Donor Type	Deceased Donor	23.7 (22.2 - 25.2)	17.6 (16.3 - 19)
	Live Donor	19.5 (17.5 - 21.6) ¥	3.6 (2.6 - 4.6) ¥
Diabetes	No Diabetes	21.1 (19.8 - 22.5)	13.3 (12.2 - 14.4)
	Diabetic	27.2 (24.3 - 30.1) ¥	12.8 (10.6 - 14.9)
Comorbid score	0	20.5 (19.0 – 22.0)	11.5 (10.3 - 12.7)
	1	24.1 (21.5 - 26.7)	14.3 (12.2 - 16.4)
	2	26.4 (23.2 - 29.5)	17.5 (14.8 - 20.2)
Socioeconomic status	Most Deprived	23.5 (20.4 - 26.5)	13.6 (11.2 - 16.1)
	2	21.4 (18.7 - 24.2)	16.1 (13.6 - 18.5)
	3	23.2 (20.5 - 25.8)	11.4 (9.3 - 13.4)
	4	22.9 (20.1 - 25.6)	12.4 (10.2 - 14.5) *
	Least Deprived	21.0 (18.5 - 23.6)	12.1 (10.1 - 14.2)

¥ P < 0.001 * P< 0.05

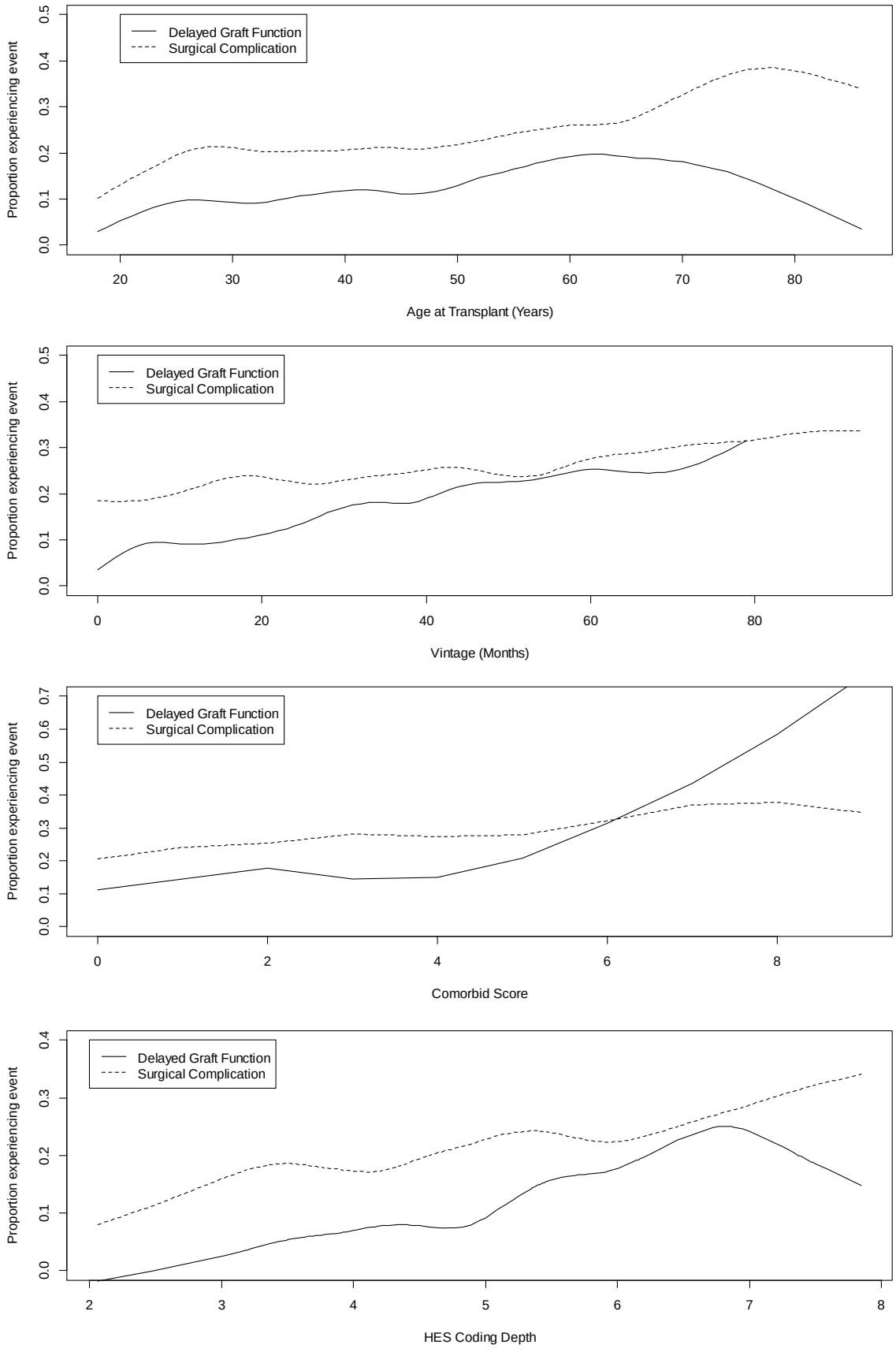


Figure 8-3 : Spline plots illustrating the association between surgical complications and delayed graft function with 1) Age, 2) Time on dialysis, 3) Comorbidity, 4) Coding depth.

Some of the sudden deviations from previously observed linear associations should be interpreted with caution as small numbers of patients exist in the groups with greater age and comorbid burden. It is feasible that residual renal function is less in patients with all these demographic findings, and may explain the higher rate of delayed graft function as the patient's native kidneys would produce sufficient urine to prevent the need for dialysis.

Table 8-3 : Outcome from multiple logistic regression with all listed variables included for delayed graft function and surgical complications according to case mix.

Demographic Variable		Delayed Graft Function Odds Ratio	Surgical Complication Odds Ratio
Male Sex		0.873 (0.721 - 1.058)	0.979 (0.845 - 1.133)
Age (per year)		1.009 (1.002 - 1.016)	1.011 (1.005 - 1.017)
Living Donor		0.222 (0.165 - 0.301)	0.875 (0.742 - 1.033)
Coding Depth (per extra code)		1.458 (1.328 - 1.602)	1.224 (1.137 - 1.317)
Year of transplant (per year compared to 2002)		0.968 (0.901 - 1.039)	0.926 (0.876 - 0.979)
Comorbid Score		1.061 (0.98 - 1.148)	1.094 (1.025 - 1.166)
Vintage (per month)		1.012 (1.005 - 1.018)	1.005 (1 - 1.01)
Modality	Pre-emptive	1 (comparator)	1 (comparator
	Haemodialysis	3.058 (1.811 - 5.165)	1.066 (0.826 - 1.376)
	Peritoneal Dialysis	2.136 (1.258 - 3.629)	1.114 (0.861 - 1.441)
Non-transplanting parent centre		0.86 (0.715 - 1.033)	1.063 (0.918 - 1.231)
Non-White Ethnicity		0.693 (0.537 - 0.895)	0.951 (0.785 - 1.153)

Coding depth remains predictive of complications with a narrow effect size, with year of transplant showing no influence. The variable reflecting whether a patient originates from a non-renal centre is no longer statistically significant when adequate case-mix is accounted for.

The performance of the multivariate models detailed above (following the removal of non-predictive variables) is as follows:

Delayed Graft Function: Adjustment variables: Age at transplant (continuous), donor type, coding depth, time on dialysis (months), pre-transplant modality, ethnicity (white or non-white), C-statistic 0.755 (95% CI 0.716 – 0.793)

Surgical Complication: Adjustment variables: Age at transplant (decade, as a categorical variable) interacting with Diabetes, Coding Depth, Donor Type, C-statistic 0.599 (95% CI 0.559 – 0.639).

HES coding depth and time

Coding depth (the average number of diagnosis codes used to describe an admission) has increased with time, and is variable across centres. We have seen that coding has improved over the period studied (chapter 4), and the delayed graft function rate has increased (Figure 8-4). However, due to the nature of the cohort, patient level characteristics have also altered. As no new patients are taken on to RRT beyond the end of 2006, and those who started earlier than 2006 and are subsequently transplanted will have longer time on dialysis, the proportion transplanted who have been on dialysis for greater than one year climbs rapidly. With increasing time on dialysis comes increasing comorbidity and a greater depth of coding associated with trying to record it. Surgical complication rates on the other had remain largely static across the period analysed.

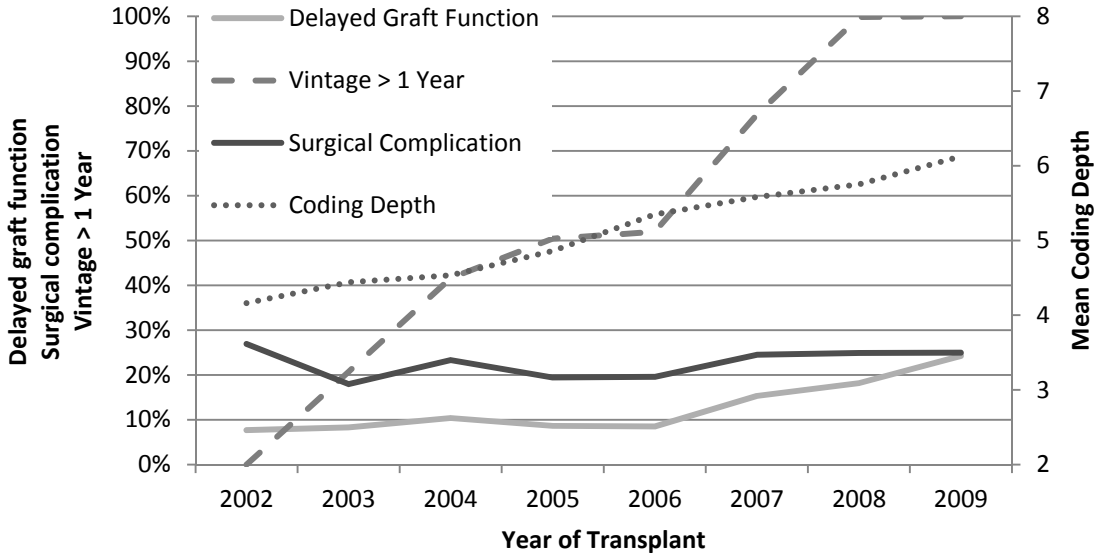


Figure 8-4 : Changes in coding depth, time on dialysis, delayed graft function and surgical complication rates during the study period

Delayed Graft Function and Modality

Haemodialysis patients have higher DGF rates as defined as dialysis use after transplantation. Exploring potential data reasons why this might occur, there may be coding bias towards capturing haemodialysis activity (including continuous therapies administered on the intensive care unit) compared to peritoneal dialysis activity. However, peritoneal dialysis patients could utilise haemodialysis and peritoneal dialysis post-transplant. The usage of dialysis modalities immediately post-transplant is shown in Table 8-4.

Table 8-4 : Coded dialysis modalities in the post-transplant period used to define delayed graft function

	Haemodialysis post-Transplant	Peritoneal Dialysis post-Transplant	Unknown RRT post-Transplant	Any dialysis post-Transplant
Codes Employed	X403, X404, X407	X402, X405, X406	X401, X408, X409	X401 – X409
Haemodialysis	13.2%	0.5%	3.4%	16.9%
Peritoneal Dialysis	8.4%	2.8%	1.3%	12.2%
Pre-emptive	2.2%	0.0%	0.5%	2.7%

As expected there is negligible peritoneal dialysis activity in the post-transplant period in haemodialysis, and significantly more haemodialysis than peritoneal dialysis usage in patients who were on peritoneal dialysis prior to admission.

Cause specific surgical complication rates

Following exploration of diagnosis and procedure codes frequently employed in the 12 months post transplantation, seven groups of surgical complications were specified by 49 ICD10 and OPCS codes, available in appendix 8b. The incidence of these complications compared to existing literature is compared below.

Table 8-5 : Incidence of derived cause specific surgical complications compared to rates from literature. Ranges represent the highest and lowest incidence reported for the specific group.

Complication Group	HES Derived Incidence	Incidence from Literature
Ureteric Complication	7.0%	2 - 10%
Vascular Complication	3.1%	2 - 10%
Complication requiring nephrectomy	3.9%	7%
Wound Complication	5.3%	5 – 10%
Complication requiring exploration	5.1%	Not available
Venous Thrombosis Event	1.3%	1 - 5%
Complication not otherwise specified	4.8%	Not available
Overall Complication Rate	22.3%	5 - 34%

Literature sources: (Humar et al. 1998), (Hernandez et al. 2006), (Humar et al. 2005), (Wilson et al. 2005), (Secin et al. 2003)

Similar incidences are identified as previously published for most complications. Note that overall complication rate is not the sum of the HES derived incidence groups, as some patients might have had more than one class of complication.

Numbers of events occurring within some complication groups prevented analysis of the underlying predictors of individual classes of surgical complications.

Stent usage

Having removed patients who did not experience transplant nephrectomy or die early in the post-operative period (223 exclusions), 62.2% of cases had a documented stent removal in the post-operative period from the inpatient dataset. Including outpatient procedure codes identified an additional 75 cases increasing the total proportion to 64%. Centre specific variation existed (Figure 8-5), with a large proportion exceeding 75% in their patients and perhaps reflecting the coding inaccuracies of the dataset.

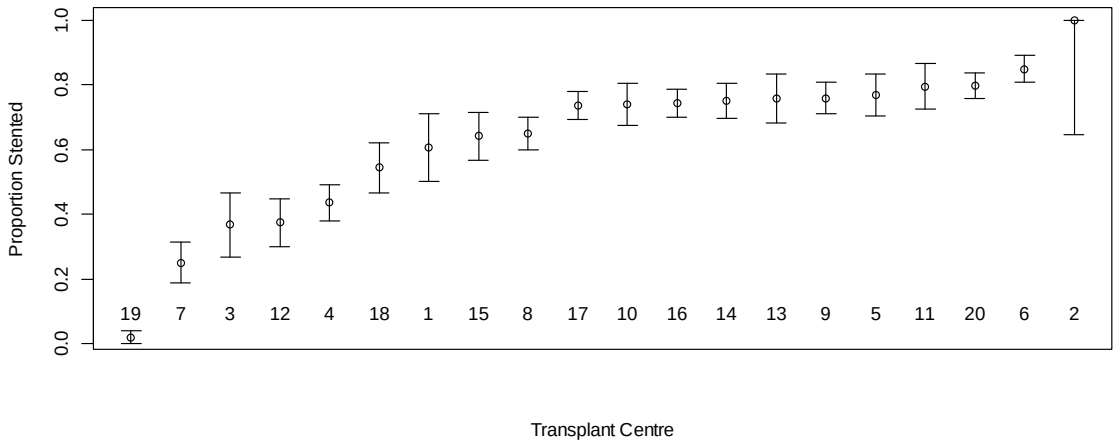


Figure 8-5 : Centre-specific stent rates as defined by subsequent stent removal

The purpose of stent insertion is to prevent major ureteric complications (Wilson et al. 2005). In the 4,278 patients who survived six weeks and did not have a nephrectomy, the rate of ureteric complications in the un-stented group was 7.6% compared with 6.5% in the stented group, however this failed to reach statistical significance (cluster model P=0.795).

Surgical Complications and Delayed Graft Function

In incidence of surgical complications and delayed graft function was strongly correlated, both overall and within individual surgical complication groups. Some authors believe that the causality works both ways, with DGF increasing the risk of surgical complications (Hernandez et al. 2006). The overall surgical complication rate was 36.4% in those with DGF and 20.2% in those without DGF. Alternatively the rate of DGF was 21.4% in those with a surgical complication and 10.8% with those without a surgical complication (P<0.001).

Table 8-6 : The association between surgical complication and delayed graft function (DGF)

Complication Group	DGF rate with	DGF rate without	P
Ureteric Event	16.1%	12.9%	0.067
Vascular Event	18.4%	13.0%	0.059
Nephrectomy	31.2%	12.4%	<0.001
Wound Event	26.2%	12.4%	<0.001
Exploration	23.3%	12.6%	<0.001
Not otherwise specified	18.0%	12.9%	0.031
Venous Thromboembolism	25.4%	13.0%	0.005
Any Complication	21.4%	10.8%	<0.001

As illustrated previously there are a number of predictors for DGF which contribute to the risk of a surgical complication which may confound the association, and therefore the association may not be as strong as that shown in Figure 8-3. We see in Table 8-6 the association exists independently of this, with the odds ratio reducing from 2.252 (95% CI 1.871 – 2.707) in a univarate analysis to 2.010 (95% CI 1.650 – 2.446) in a multivariate regression.

Centre specific delayed graft function rates

Unadjusted rates of delayed graft function are shown in the first plot of Fig 8.6 and identify four centres with higher than expected delayed graft function rates and six with lower than expected rates. The results following adjustment for the above variables, the extreme centres are moved toward the centre, but they still remain outside the 99.9% control limits.

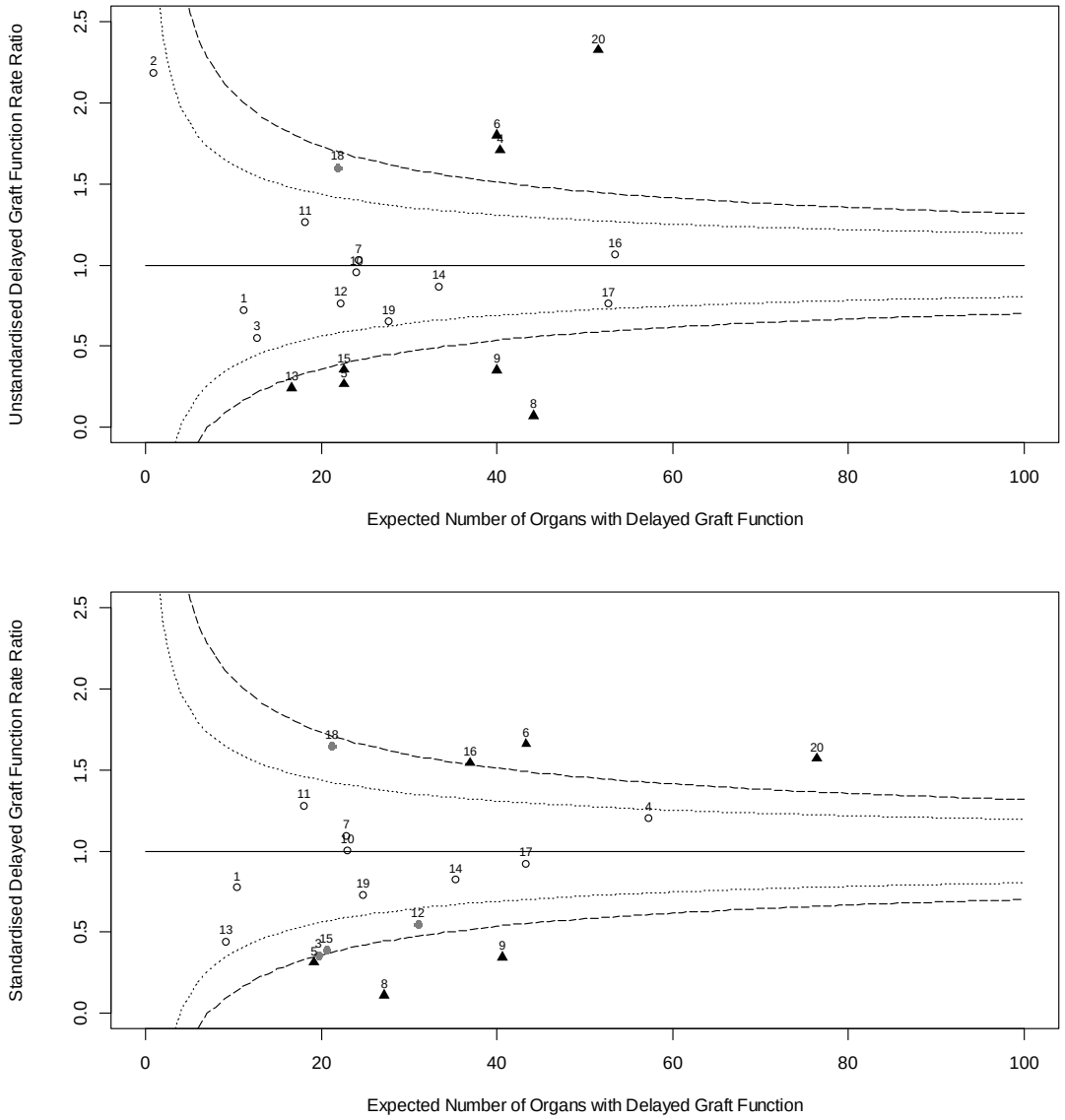


Figure 8-6 : Centre specific standardised delayed graft function rates before (top) and after (bottom) multivarate adjustment for donor type, time on dialysis, ethnicity, recipient age and coding depth.

Clinical factors include how the donor and recipient are managed in the peri-transplant period and thresholds at which issues with fluid overload and biochemical abnormalities would warrant dialysis. Following the accounting for coding factors and demographic factors it may be reasonable to assume the residual differences in centre specific rates would relate to clinical decisions or donor factors.

Standardised centre specific surgical complication rates

Prior to adjustment the funnel plot in Figure 8-7 identifies four outlying centres with higher than expected surgical complication rates, and four centres with lower than expected surgical complication rates.

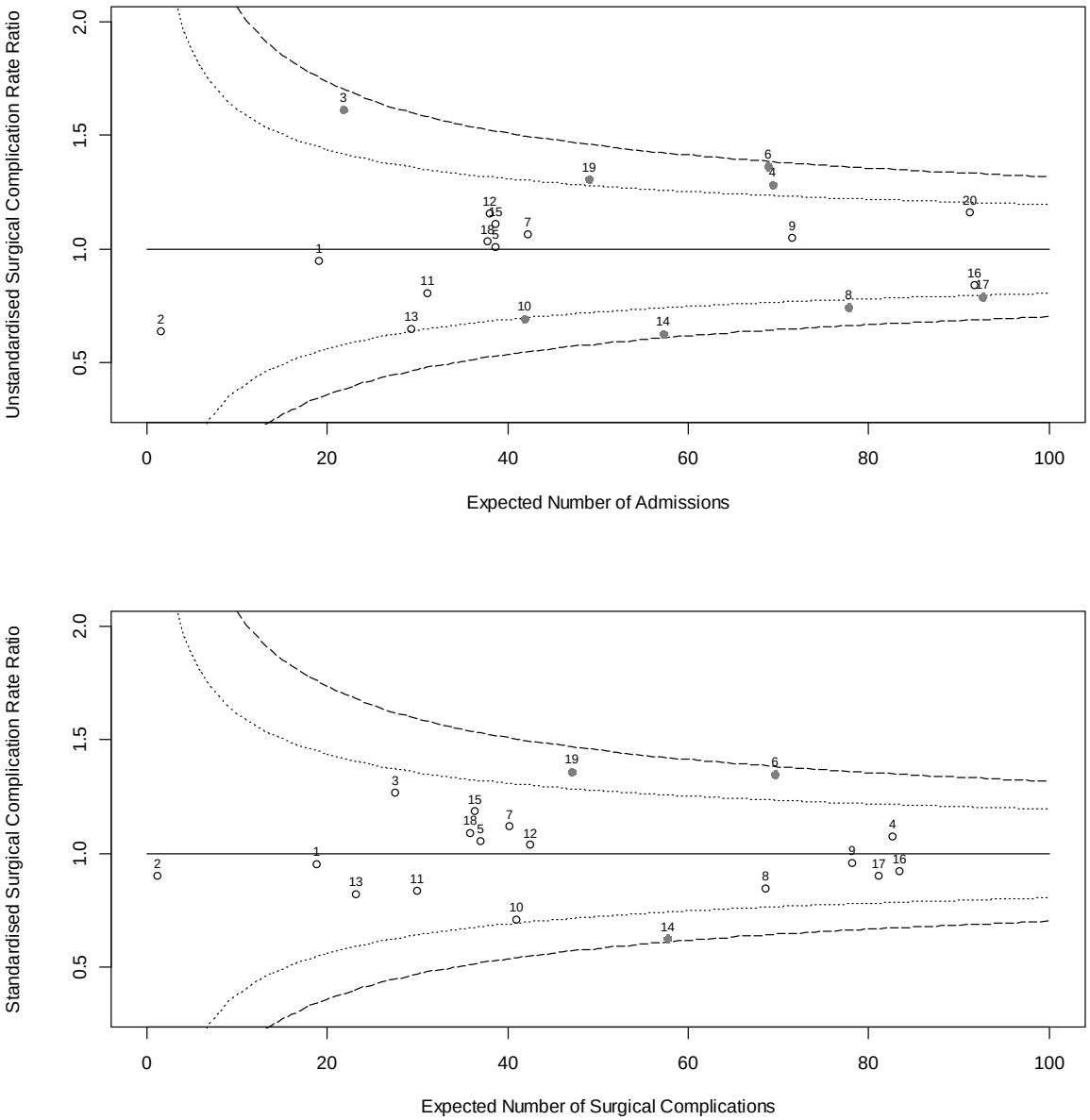


Figure 8-7 : Standardised centre-specific surgical complication rates before (top) and after (bottom) multivariate adjustment

Following adjustment for age, donor type, diabetes and coding depth two centres with higher than expected and one centre with lower than expected surgical complication rates persist.

Length of Stay

Of the 4,517 first transplant admissions, 4,501 admissions had suitable dates available to define the beginning and end of the admission. It was not possible to derive lengths of stay for 16 cases due to uncertain end-dates for spells and/or superspells.

The distribution of length of stay is shown in Figure 8-8 below. The mean was 13.6 days, median 10 days with 4.9% patients having an admission lasting longer than 30 days. Admissions terminated with the patient dying accounted for 0.9% of the first transplants, with 0.5% of all admissions spanning more than one trust.

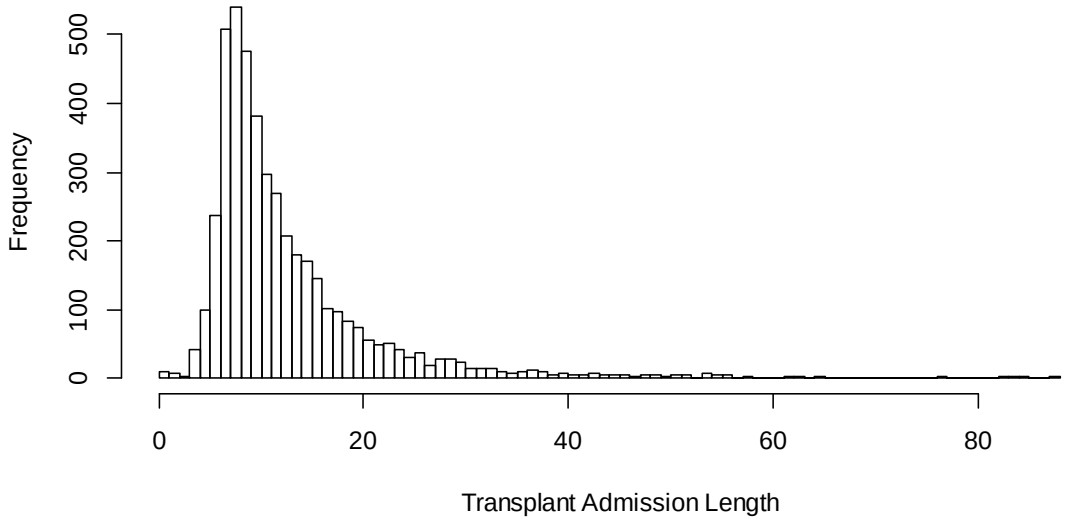


Figure 8-8 : Histogram of transplant admission length (censored at 90 days)

The mean length of stay for all transplants as reported by the NHS Information Centre has decreased during the study period (Table 8-7) however it stayed constant in this cohort. It is likely that the proportion of patients receiving a live donor kidney transplant is initially high in the linked cohort, but then drops as those patients which a suitable donor are transplanted. Those left on the deceased donor waiting list are then transplanted in later years with an associated greater length of stay. In addition the patients will have become older and more comorbid. The proportion of living donor kidney transplants and demography of the prevalent dialysis population represented by the NHS information centre data will remain constant, therefore better reflecting changes in clinical care.

Table 8-7 : Comparison between NHS Health and Social Care Information Centre reported length of stay and UKRR-HES derived length of stay

	NHS IC HES Episode Length of stay			HES-UKRR Incident Cohort Episode Length of stay		
	Mean	**Median**	**Number**	**Mean**	**Median**	**Number**
2002/2003	14.4	11	1,318	13.0	11.5	130
2003/2004	14.6	11	1,279	14.1	11	338
2004/2005	14.3	11	1,280	14.2	11	548
2005/2006	13.5	10	1,409	13.7	10	718
2006/2007	13.2	10	1,600	13.2	10	813
2007/2008	12.8	10	1,699	14.1	10	738
2008/2009	12.6	10	2,008	12.7	10	655
2009/2010	12.6	10	2,150	13.6	10	561

Case-mix influences first transplant length of stay as detailed in Table 8-8 and Figure 8-9 for continuous variables. Both mean and median statistics are reported due to the skewed nature of length of stay.

Linear associations with vintage, socioeconomic status are observed using the spline plots, along with clinically logical associations between demographic variables and length of stay. Age has a greater impact as the recipient gets older, with a steepening of the graph beyond 55 years of age. Delayed graft function increases length of stay by approximately five days.

The influence of demography on length of stay

Table 8-8 : The influence of patient demography on length of stay for first transplantation

Demography		Transplantation Admission Length (days, median and IQR)	Subsequent Admission Rate (per year, median and IQR)
Age Group	<40 ¥	10 (8 - 15) ¥	1 (0 - 2) ¥
	40-60	10 (8 - 15)	1 (0 - 2)
	60+	11 (8 - 18)	1 (0 - 3)
Sex	Male	10 (8 - 15)	1 (0 - 2)
	Female	10 (8 - 15)	1 (0 - 3)
Ethnicity	White	10 (8 - 15)	1 (0 - 2)
	Black	10 (8 - 16)	1 (0 - 3)
	South Asian	11 (8 - 15)	1 (0 - 3)
	Other	10 (8 - 14)	1 (0 - 3)
Diabetes at Tx	No Diabetes	10 (8 - 14) ¥	1 (0 - 2) ¥
	Diabetes	13 (9 - 20)	2 (0 - 3)
Comorbid Score	0	10 (8 - 14) ¥	1 (0 - 2) ¥
	1	12 (8 - 17)	1 (0 - 3)
	2+	12 (9 - 19)	1 (0 - 3)
Donor Type	Deceased Donor	11 (8 - 16) ¥	1 (0 - 3) ¥
	Living Donor	10 (8 - 13)	1 (0 - 2)
Socioeconomic Status	Most Deprived	11 (8 - 16) ¥	1 (0 - 2)
	2	11 (8 - 16)	1 (0 - 2)
	3	10 (8 - 15)	1 (0 - 3)
	4	10 (8 - 15)	1 (0 - 2)
	Least Deprived	10 (7 - 14)	1 (0 - 2)
Pre-transplant Modality	Haemodialysis	11 (8 - 16) ¥	1 (0 - 2) ¥
	Peritoneal Dialysis	10 (8 - 14)	1 (0 - 3)
	Pre-emptive	10 (8 - 14)	1 (0 - 2)
Vintage (Years)	<1 year	10 (8 - 14) *	1 (0 - 2) ¥
	1-2 Years	11 (8 - 16)	1 (0 - 2)
	2 or more years	11 (8 - 16)	1 (0 - 3)
Delayed Graft Function	No DGF	10 (8 - 14) ¥	1 (0 - 2) ¥
	DGF	15 (11 - 22)	1 (0 - 3)
Surgical Complication	No complication	10 (8 - 14)	1 (0 - 2) ¥
	Surgical Complication	13 (9 - 21)	2 (1 - 4)
Parent Centre	Same Centre	10 (8 - 15) *	1 (0 - 2)
	Difference Centre	11 (8 - 16)	1 (0 - 2)

¥ P<0.001 * P<0.05, IQR – Interquartile range

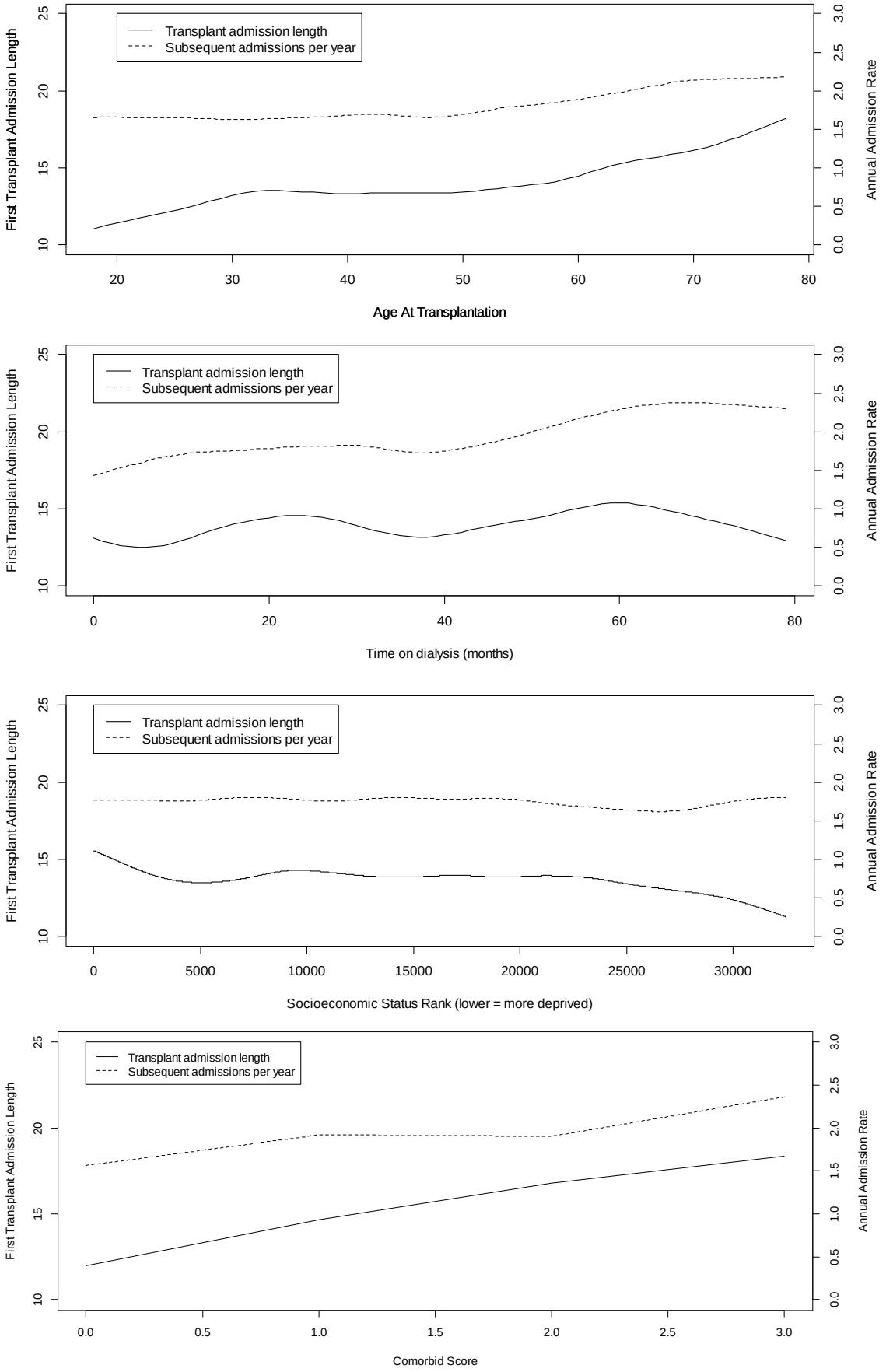


Figure 8-9 : Association between first transplant admission length in days and annualised admission rate with 1) Age, 2) Time on dialysis, 3) Socioeconomic status 4) comorbid score, demonstrated with a smoothed spline plot

A number of variables are correlated with each other. Since length of stay is highly skewed, we decided to log transform it, to make the distribution more symmetrical. Figure 8-10 shows a histogram with unadjusted data and transformed data overlaid, plus the theoretical normal distribution based around the transformed mean. Zero length of stay values (n=3) were excluded for the transformation process. The log transform is successful in rendering the distribution more symmetric.

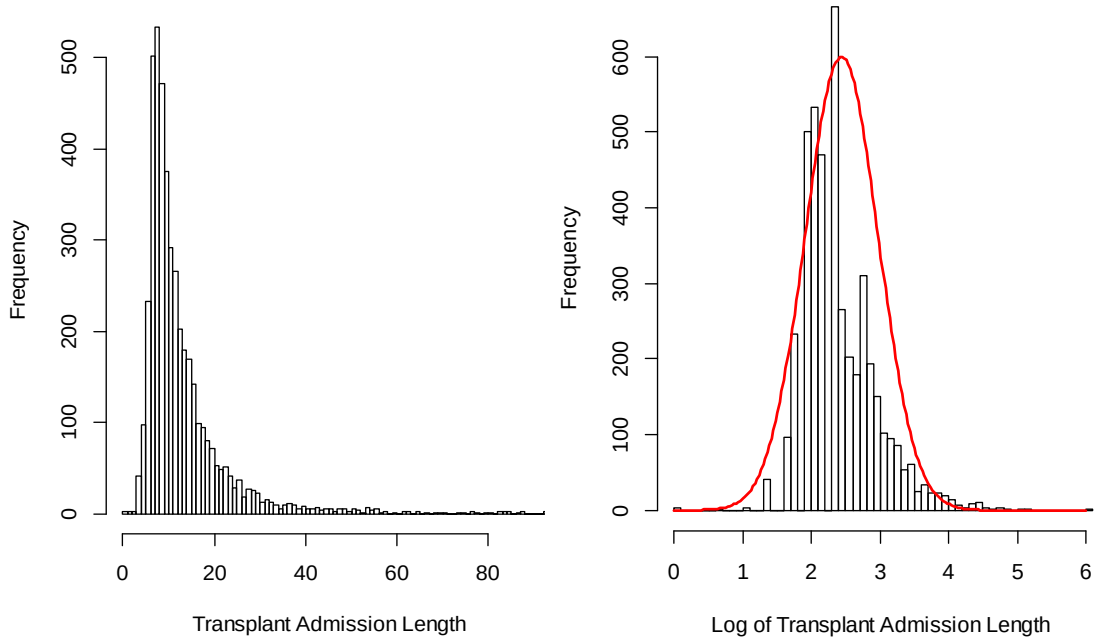


Figure 8-10 : A histogram of transplant admission length before (left) and after (right) log-transformation to achieve normality

Using the transformed data, a multivariate analysis was performed to determine independent predictors. Extreme outliers as defined as those beyond the 95% upper centile were trimmed to this centile (30 days), with comparisons of model performance with trimming at 99.5% and untrimmed data. Following transformation linear associations between the predictors of age, socioeconomic status and vintage with the log transformed length of stay were maintained.

Model R squared was 0.074, dropping to 0.067 with the exclusion of socioeconomic status as this has greatest proportion of missing data, necessitating the exclusion of an additional 71 cases. There was no significant alteration in length of stay as age increased from approximately 30 to 50 years of age, but outside this range length of stay increased linearly with age. To reflect this in the model a smoothed spline function (previously described and employed in graphs herein) was employed, creating a variable which reflected this “kinked” association such that between 30 and 50 years of age the variable did not increase. Employing the transformed age improved the performance of the demography alone model to an R squared

of 0.077. Significant interactions were identified in the demography only model between Age, Donor Type and Diabetes, including all combinations of the three. Inclusion of these interactions further improved the model to an R squared of 0.090.

Table 8-9 : The influence of patient demographic variables on log-transformed length of stay

Variable	B (change in log Length of stay)	P
Age at Transplant (Years)	0.0025	<0.001
Vintage (Months)	-0.0008	0.0575
Diabetes	0.2024	<0.001
Additional Comorbid Conditions	0.0491	<0.001
Live Donor Transplant	-0.0713	<0.001
Socioeconomic Status Rank (Per %)	-0.015	<0.001
White Ethnicity	0.0596	0.001
Previous Modality Peritoneal Dialysis	-0.0669	<0.001
Different Transplanting Centre	-0.0139	0.322

Truncated regression with truncation at zero and at log of 30 was performed to identify superior fit, but R-squared of the models were identical to that obtained with non-truncated models. Modelling living donor and deceased donor admissions separately failed to improve the model.

The extremely predictive nature of events of delayed graft function and having a surgical complication are highlighted below, with a significant improvement in the R-squared to 0.160. These variables are at least in part under a centre's control and therefore should not be used for adjustment but offer explanation for why variation in length of stay may persist. The exponentiated coefficients for DGF and surgical complications were 1.4 and 1.3 days respectively suggesting these additional days length of stay in the presence of these events, adjusting for other predictive factors.

In addition to improvements in model performance, the sequential additions of variables brought the observed/expected ratios closer to the median (Table 8-10). This was more apparent in both long and short stay patients with the exception of extreme outliers.

Table 8-10 : The influence of demographic variables and patient outcomes of model performance

		Observed/expected estimates by percentiles							
Model Parameters	**R squared**	**Min**	**5%**	**10%**	**25%**	**50%**	**75%**	**95%**	**Max**
Demography	0.0738	0.080	0.516	0.580	0.708	0.918	1.316	2.291	3.501
Demography & Interactions	0.0902	0.080	0.512	0.587	0.711	0.919	1.312	2.273	3.458
Above plus DGF	0.1401	0.083	0.515	0.595	0.721	0.925	1.289	2.212	3.632
Above plus Surgical Comp.	0.1781	0.088	0.521	0.591	0.730	0.937	1.284	2.123	3.762

Although the means of the predicted and observed datasets are aligned, two factors result in some distortion in the back-transformation. Firstly the mild asymmetry in the residuals around mean due to a tail of positive residuals, demonstrated by the histogram of residuals not being centred around zero. Secondly when these are transformed back, the positive residuals have a much greater effect than the negative residuals (for instance residual of -1 is 0.37 days, whereas a residual of 1 is 2.72 days). These differences will manifest when centre specific adjustment is performed.

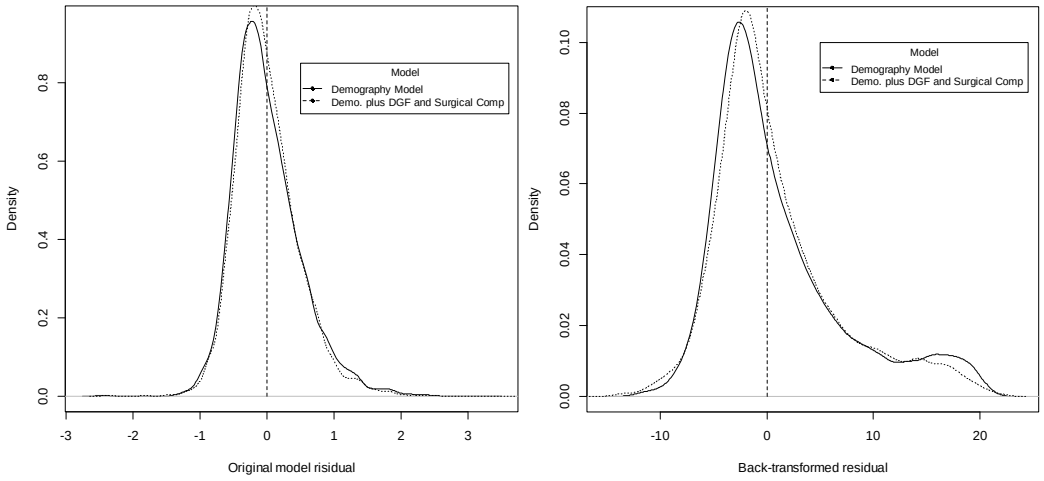


Figure 8-11 : Histogram of the residuals before (left) and after (right) back-transformation

Centre Specific Length of Stay

Box-whisker plots of length of stay by transplanting centres are shown in Fig 8-12 below. They show considerable variation between centres. A number of centres have significantly different medians from the overall median value of 10 days stay (Kruskal-Wallis P<0.001).

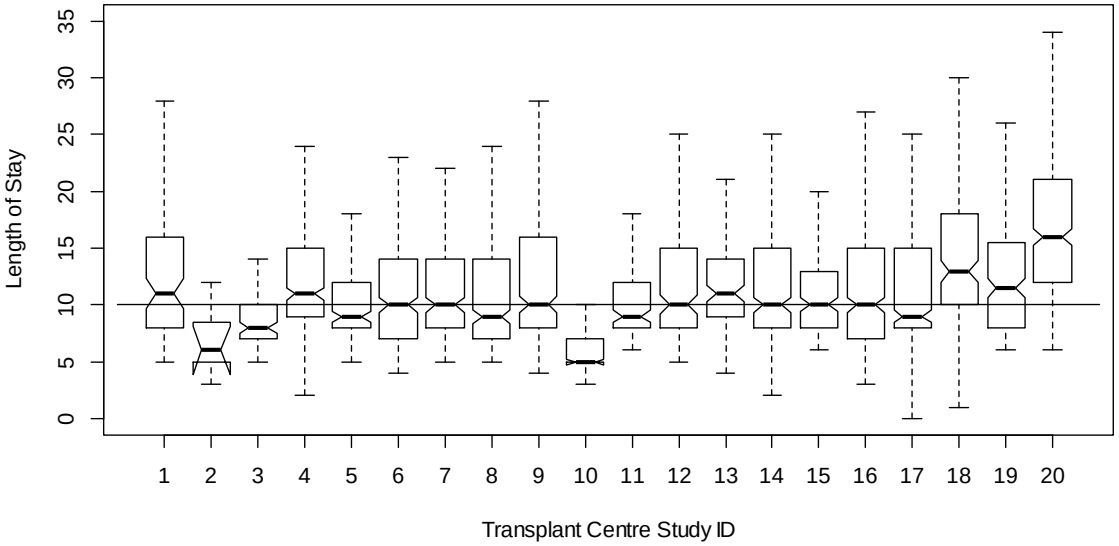


Figure 8-12 : Centre specific length of stay for first kidney transplantation

Using the models derived above, centre specific adjusted length of stay was determined. In unadjusted analyses transplant centre number 20 was identified as having a length of stay higher than the median. Two other centres (numbers 4 and 18) were also identified. The plot in Figure 8-13 reveals that 20 is the only centre identified prior to adjustment using a control plot, and persists as an outlier with demographic adjustment, age transformation using splines, inclusion of interactions and the inclusion of delayed graft function and surgical complications.

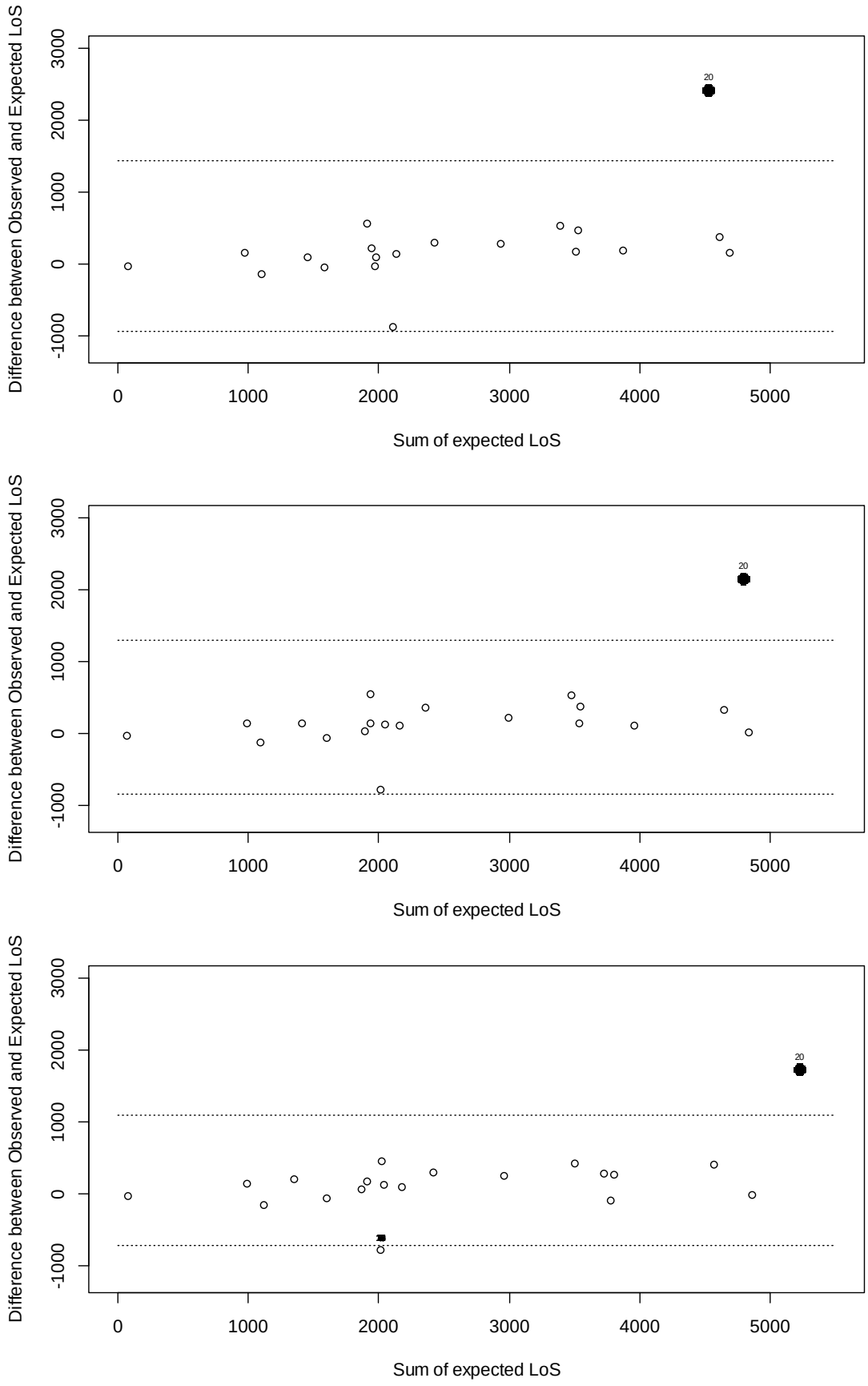


Figure 8-13 : Control plot of length of stay before adjustment (top), following adjustment for demography (middle) and after adjustment for demography, delayed graft function and surgical complications (bottom). Control limits are two standard deviations from the mean difference in observed and expected length of stay.

Frequency of Subsequent Admission

Admission frequency from twelve months post discharge varied across demographic groups and transplanting centres. There were 7,882 admissions identified across 4,465 patients receiving first transplants with 4,272 patient years follow-up. Patients with no admissions once zero length of stay admissions and stent removals lasting one day or less were excluded, and these accounted for 32.2% of the cohort. The mean admission rate was 1.85 (95% CI 1.80 - 1.89) admissions with a median of one admission. Forty-five patients (1%) had zero time at risk for subsequent admissions, which largely relates to death during the primary transplant admission. Patients consumed a median of three hospital days in the first twelve months (interquartile range 0 – 12), highlighting a skewed distribution as shown below in Figure 8-14. This suggests a zero-inflated model for subsequent admissions.

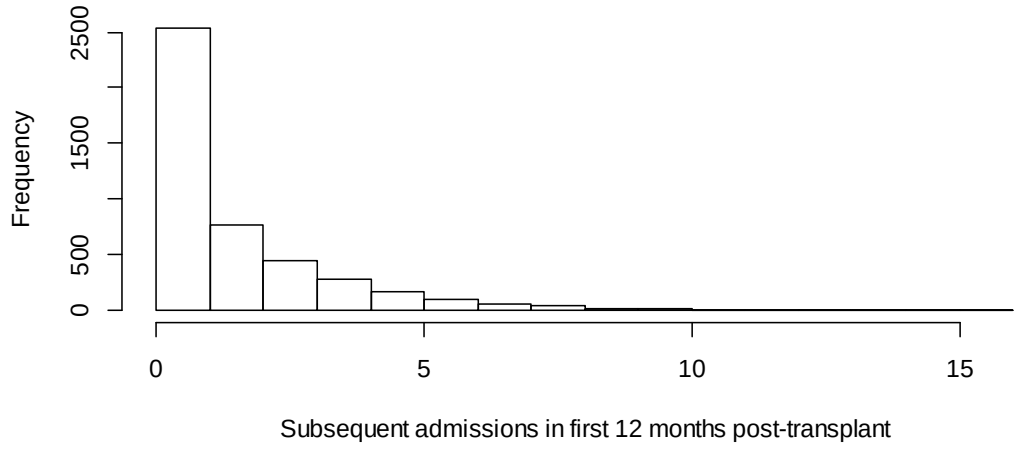


Figure 8-14 : Histogram of admission frequency in the first twelve months following first kidney transplant

Clinically logical associations between demography and admission rate were observed between patient groups. The skewed distribution above lends itself to the reporting of both means and medians (Table 8-8). As time at risk exceeded 300 days in 95% of patients the medians reported are derived from raw counts rather than adjusted rates. The group rate is determined from total events within that group divided by total time at risk, and is more robust to outliers.

A linear association with vintage and no association with socioeconomic status are observed. The association with age only becomes apparent at age 45 years. For this reason a spline function was fitted to aid model fit with a view to better prediction.

Table 8-11 : Statistical influence of patient case mix on various admission rate models

	Standard Negative Binomial		Zero-inflated Negative Binomial			
			Zero Count Prediction		Subsequent Count Prediction	
Variable	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**
Age At Transplant (Years) - Spline Transform	0.700	<0.001	0.567	<0.001	-4.146	0.074
Diabetes	1.595	0.003	1.554	0.003		
Number Comorbid Conditions Excl Diabetes	0.101	<0.001	0.103	<0.001		
Female	0.111	0.002	0.111	0.008		
Living Donor	-0.196	0.002	-0.197	<0.001		
Vintage (Months)	0.003	0.000	0.005	<0.001	0.030	0.012
Age-Diabetes interaction	-0.710	0.019	-0.690	0.020		

Due to the high prevalence of zero admissions, modelling was performed with both standard and zero inflated negative binomial models (Table 8-1). Model performance improvements were observed with an age spline function, and fitting an interaction between age and diabetes. Delayed graft function was not predictive of subsequent admissions in the presence of other demographic variables. Surgical complications were predictive of admissions, with the interaction term for diabetes and age ceasing to be significant in the presence of this added variable. Zero inflated models identify all variables being strongly predictive of zero admissions, but only age and vintage proving predictive of the frequency of admissions beyond zero. Model performance as defined as Observed/Expected ratio centiles, previously employed in chapters 6 and 7 for frequency of admission counts in haemodialysis and peritoneal dialysis therapies are reported for both methods in Table 8-12:

Table 8-12 : Centile of observed/expected estimates for subsequent frequency of admission according to modelling technique. Centiles of 0 and 25 where identical due to the high prevelance of zero counts and are reported together.

	Percentiles for ratios of observed/expected estimates				
Analysis	0 & 25	50	75	90	95
Negative Binomial Model					
Demography	0.000	0.635	1.459	2.591	3.607
Demography, Interactions & spline age	0.000	0.649	1.453	2.627	3.577
Above plus surgical complications	0.000	0.718	1.506	2.611	3.548
Zero-inflated Negative Binomial					
Demography	0.000	0.636	1.465	2.593	3.576
Demography, Interactions & spline age	0.000	0.648	1.448	2.612	3.574
Above plus surgical complications	0.000	0.724	1.506	2.601	3.578

The high prevalence of zero admissions seen does not affect the observed/expected ratios up to the 25th centile, as observed counts are unaffected by the modelling used. The zero inflated method marginally outperforms the standard negative binomial model as shown by the percentile ratios either side of fifty being brought closer to one. Comparing unadjusted to demographically adjusted funnel plots for the zero-inflated and standard models there is no difference in outlier distribution beyond the 95% limit.

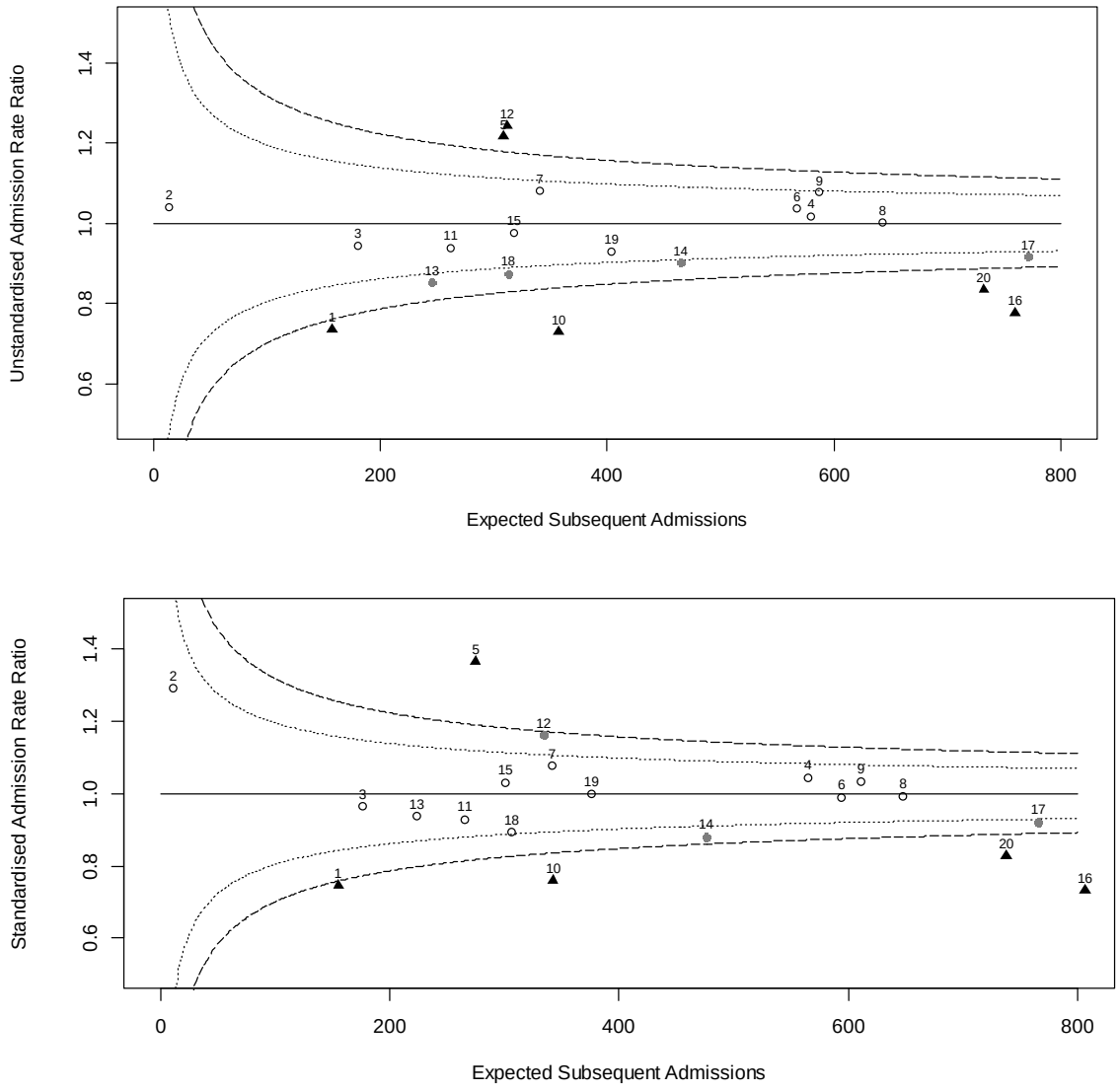


Figure 8-15 : Centre-specific frequency of admission before (top) and after (bottom) case mix adjustment

Prior to adjustment two centres are identified with higher than expected admission rates, and eight with lower than expected admission rates. Following adjustment the two centres with higher than expected rates persist, and five centres with lower than expected admission rates are identified as shown in Figure 8-15.

Summary and Discussion

This chapter shows that HES data can identify transplantation related events at similar frequency to existing literature obtained from detailed case-note review. An individual patient's demography is predictive of transplantation episode length of stay, frequency of admission in the twelve months after transplantation and surgical complications in the post-operative period, but despite adjustment there remain some outlying centres whose performance is not explained by these factors.

Given the powerful influence of case-mix on the rates that inform these measures, one would expect greater impact of adjustment for the demographic variables. Logical explanations for these findings relate to uniformity in patient case-mix across centres, or poor model parameterisation. There was almost no variation in the mean age at transplantation across centres, and although there was some difference in comorbidity and time on dialysis, these small differences may be insufficient to account for differences in outcomes. We can see that model fit is an issue with a number of measures, but reviewing the distribution of the funnel plots, often the outlying centres are extreme at the outset.

The modelling of these measures is dependent on the distribution of the outcome and the variables available for adjustment. Recognising the proportion of patients who have no relevant admissions in the twelve months after transplantation, zero-inflation was explored for this measure and found to perform no better than its non-inflated negative-binomial counterpart. Length of stay was transformed to aid modelling, but this process in itself amplifies small differences in admissions which exceed the predicted values when the inverse exponential transform returns the estimates to the original scales.

Interactions between variables were explored but with available data, factors that may predict these measures are missing. Patient, donor and retrieval factors influence the risk of developing DGF (Perico et al. 2004), as defined in this study as dialysis use post-transplant. Aside from the donor being living or deceased other relevant factors such as cold ischemia time (Quiroga et al. 2006) and peri-retrieval hypotension (Ho et al. 2008) are absent. These may interact with recipient demography, in that a hypotensive donor into a diabetic recipient may have a higher risk of DGF that the sum of the risks of the presence of these to variables in isolation (Parekh et al. 2010). Understanding the deceased donor allocation system (Johnson et al. 2010) strengthens and weakens the argument for donor variable adjustment. Preferential allocation occurs to minimise age differences between donor and recipient, potentially making adjustment for recipient age sufficient. Assignment to reduce travel time

affects ischemia time theoretically making ischemia time similar across centres, but centres covering larger, less populated areas will have longer travel times regardless.

Sensitisation (the presence of antibodies to non-self tissue, resulting from previous transplantation and blood transfusion) and match (the differences in tissue type between donor and recipient) predict future rejection rates (Reisaeter et al. 1998; Dunn et al. 2011). These events are often treated with therapies which necessitate admission and adjustment for these variables might reduce unexplained variation. Surgical complication rates have been found to be influenced by sensitisation and donor factors (Hernandez et al. 2006). The relationship between surgical complications and DGF has previously been identified, with authors postulating an increase in vascular events may be the result of haemodynamic instability, inflammatory response or interstitial oedema attributed to severe acute tubular necrosis (Hernandez et al. 2006). It is more likely that surgical complications impair graft function necessitating dialysis.

Time on dialysis and the transplantation of a patient with a live donor are largely in the centres' control in that recipients and donors are generally selected by surgeons and physicians and the duration of time this takes can be dictated by organisational factors. More challenging is how to account for this when a patient originates from a non-transplanting centre that may be responsible for this process. The time it takes for a patient to be transplanted may relate to blood-group incompatibility (Glander et al. 2010) or sensitisation (Sanfilippo et al. 1992), but other studies have highlighted variation in the time taken to list a patient for a deceased donor transplant (Ravanan et al. 2010), above and beyond these barriers.

The assumption that comorbidity is outside the transplanting centres control may be flawed in those patients already under follow up in the centre in question. The incidence of certain conditions such as cardiac events and type II diabetes may be influenced by control of CKD mineral bone disease (Slinin et al. 2005) (Sampaio et al. 2011) and the use of immunosuppressive therapy in glomerulonephritis (Turnbull et al. 2009). Measures such as incident survival are arguably more tolerant of this.

Although socioeconomic status looks distributed evenly across the range of recipients, the skewed distribution of the overall incident RRT population (chapter 4) means that there is underlying imbalance. Access to transplantation is outside the remit of this project, but a transplantation rate would likely show that the underlying rate is lower in the more deprived than in other groups, and indeed this may vary across centres. Unlike other frequency of

admission analyses within, deprivation was not shown to be predictive of admission rate. This may reflect patient selection.

Underpinning the ability to identify events and adjust for is the reliance on coding quality. Firstly, we have shown that the incidence of surgical complications, both overall and within specific complication groups, is similar to the existing literature (Hernandez et al. 2006) (Humar et al. 2005) (Secin et al. 2003) (Wilson et al. 2005). The definition for delayed graft function varied across the literature, but using the definition of the use of dialysis within the first week of transplantation, comparable cohorts have reported incidences of 16-21% for haemodialysis patients and 12-15% for peritoneal dialysis patients (Snyder et al. 2002) (Molnar et al. 2012), similar to those found in this study.

The fact that coding depth is positively correlated with surgical complication rates is logical, and may be lessened by the possible relationship between coding quality and the quality of clinical care (Aylin et al. 2009). Centres which value data quality may perform better in other aspects of clinical care, and therefore have a "true" surgical complication rate which is less than other centres where coding is worse. However, prior to adjustment the centre specific rates could be reversed. The opposite could occur in length of stay and frequency analyses, where the measure counts are accurate, but the coding for adjustment factors is variable across centres. The association between a variable such as diabetes and length of stay will be weakened by centres poorly coding diabetes and having longer length of stay or more frequent admissions.

Delayed graft function was proven to have the most predictive variables of those events scrutinised using multivariate methods, but residual differences in centre specific rates and rates across demographic groups need explaining. The lower rate observed in peritoneal dialysis patients has been identified elsewhere to a similar proportion and could be explained by the differences in residual renal function (Snyder et al. 2002) or volume status prior to transplantation(Molnar et al. 2012). The proportion of peritoneal dialysis patients receiving this therapy for DGF may be under-representative of the true rate; however post-operative factors often prevent the usage of peritoneal dialysis e.g. peritoneal damage, concern regarding infection. Other associations between DGF, increasing comorbidity, donor type and lengthening time on dialysis are established (Irish et al. 2010). The association with recipient age is less clear but as deceased donor allocation schemes attempt to minimise age differences between donor and recipient the established association between donor age and DGF may be manifesting here.

Reliable coding of dialysis usage DGF rates by centres in the future in conjunction with guidance on surgical complication coding and linkage with NHS Blood and Transplant data could overcome some of the issues highlighted above, however future epidemiological analysis on factors influencing events and practice patterns could be performed using cluster analysis and instrumental variable methods on the existing data. These methods are not appropriate when reporting centre specific rates.

In summary, this chapter has determined:

- Comparable rates of delayed graft function and surgical complications to existing literature.
- Demography influences delayed graft function and surgical complication and should be considered when listing a patient for transplantation.
- That the rates of these events along with admission rate and length of stay vary across transplanting centres.
- Coding-depth influences surgical complication rates, adding doubt to its reliability as a comparative performance measure.
- This study was unable to demonstrate that ureteric stenting prevented ureteric complications post-transplant.

Chapter 9 *Discussion and Conclusions*

This study has taken information on incident patients starting renal replacement therapy in England between 2002 and 2006 and linked it to hospitalisation information. Following data processing we have a dataset of 21,271 patients from 46 centres. With this enhanced information on admissions, diagnoses and procedures it has been able to describe and explore aspects of RRT in England for the first time.

Better quality, linked data

- Ninety-eight percent of patients submitted for linkage were returned with linked data and did not necessitate exclusion for other reasons
- Data completeness improved: 85.5% to 97.1% for ethnicity, 78.8% to 98.6% for socioeconomic status and 53.7% to 97.6% for comorbidity
- Data completeness reached 96% for variables enabling multivariate adjusted comparison between centres
- Differences in the reported timing of the initiation of RRT and exposure to other RRT modalities before the first reported therapy were found.

S**urvival on RRT**

- Sixteen comorbid conditions were identified as predictive for incident survival.
- These conditions allowed reporting of comorbidity across centres (largely similar).
- Previously identified centre outliers for incident survival have been largely explained, with six centres with worse than expected survival being reduced to one.
- The opportunity to study hospital associated practice patterns and measure their impact is aided with hospital standardised mortality ratios.

Haemodialysis

- Seven centres were beyond the 99.8% control limit for admission rate in the first 12 months of HD despite adjustment for demography and comorbidity.
- Increased rates of admission and mortality were identified over the two day break in three times a week haemodialysis (rate ratio 1.64 and 1.22 respectively when compared to the rest of the week).
- Despite longer dialysis treatment times and lower burden of comorbidity compared to the US, admission rates and unadjusted mortality rates were similar.

- Admissions appear primarily driven by issues surrounding fluid with patients with congestive cardiac failure or hypertension being the most susceptible. Mortality over this two day gap was driven by deaths at home.

Peritoneal dialysis

- There were 438 patients (69% of those receiving a PD catheter) were never coded as starting PD by UKRR.
- Extremely high admission rates (4.26 admissions in the first 12 months) were observed in patients switching from HD to PD in the first three months of therapy.
- Eleven centres were identified with higher than expected admission rates in the first 12 months of PD.
- The correlation between peritonitis admission rates and all cause admission rates suggest high peritonitis rates represent a globally poorly performing PD programme, or failure to support PD in the community.

Transplantation

- The incidence of surgical complications following first kidney transplantation identified through HES is similar to that seen in studies performed by manual case-note review (22.3%).
- Surgical complications represent a surgeon-specific benchmark of care which the transplant community has so far lacked, and two outlying hospitals for this measure were identified.
- Measures reveal outlying centres for length of stay (one) and frequency of admission post transplantation (two).
- Using routine data we were unable to show that ureteric stenting prevented transplant ureteric complications.

This investigation has addressed the study aims specified in Chapter 1. With regard to the project funded by KRUK as part of the authors Clinical Training Fellowship, the work presented within this thesis has not tackled the issue of the impact of the presence of renal services in admitting NHS trusts.

This chapter will now explore the findings of this study in a structured fashion, first evaluating the linkage and informing data, then reviewing the statistical techniques employed. It will review the themes identified with adjustment variables and centre measures, and ends with suggestions for future work.

Linkage

This study capitalised on the evolving landscape within health research in the UK at the time. The RCP were actively seeking studies to perform pilot data linkage during the lead-in phase for this study, and did not charge for the service. Since this first linkage other agencies now offer a similar product, however unrestricted access to HES data is still beyond the reach of most researchers. The Health and Social Care information Centre, formally the NHS Information Centre, allows researchers to submit data to link to HES and the Office of National Statistics death registrations via its Data Linkage and Extract Service. The Secure Anonymised Information Linkage (SAIL) Databank has access to a wider range of data sources (mostly Wales specific) and includes the Welsh and English HES data. RCP evolved into the Clinical Practice Research Database which continues to have access to HES along with general practitioner health information for a proportion of general practices enrolled in the system. All these agencies provide data in anonymised form, potentially necessitating processing of historical and well as new data with subsequent data cycles. Bespoke agreements could be arranged.

Clearly HES in its purest form only captures one aspect of clinical activity – that delivered by secondary care. Furthermore outpatient information is somewhat limited in that it does not routinely reflect the purpose of the attendance or clinical decisions. Linkage to other sources may shed light on these processes, and include coverage of countries beyond England.

Data validity, accuracy and uniformity

Although combining sources has the capacity to reduce missing data, it does uncover other data issues. Sources disagreed on comorbidity, socioeconomic status and potentially most worryingly ethnicity, although the latter may relate to the mapping employed between the three schemes (UKRR, HES pre-2001 and HES post-2001). Regrettably it is challenging to determine which source is correct when it comes to demography. What is more informative is the clinical activity either source is missing. Peritoneal Dialysis catheters were inserted in 438 patients who never received PD. Fifty one transplant procedures were performed in patients who never had a transplant and although presumably known by UKRR prior to this study, and 1,478 patients died in whom renal centres did not report a death.

As discussed in chapter 4, these problems are not unique to this study, the UKRR or renal registries overall. Disease registries celebrated for their capacity to inform have similar problems with varying degrees of severity (Larsson et al. 2012). The SWEDEHEART registry has missing data sufficient to exclude 11-15% of patients in their multivariate models (Szummer et al. 2010) (Lawesson et al. 2012). The Surveillance, Epidemiology and End Results registry run by the US National Cancer Institute has reported 12 of the 45 variables it collects routinely to

have greater than 50% missing data (Kim et al. 2011). Closer to home the Myocardial Ischaemia National Audit Project has missing data for age, sex and socioeconomic status however this is far less than seen the submitted UKRR data (Gale et al. 2011).

A recent review article by Couchoud et al, begins by summarising the purpose of RRT registries and then identifies realms where the quality of a RRT registry can be measured(Couchoud et al. 2013). No formal guidance exists specifically for RRT registries, but authors apply of guidance from the North American Association of Central Cancer Registries (NAACCR) to suggest standards which are applicable to the end product from this data linkage (Hulstrom 2002) (Hofferkamp 2008). The dimensions of data quality are as follows:

Attainment of disease registry standards

Case and Events Completeness

Percentage coverage of relevant units – Target: 100%

Beyond the two centres identified as not submitting information to the Registry during the incident period, it is important to highlight this study was only able to report on patients receiving RRT in England. The UKRR reports on 67 centres across England, Scotland, Wales and Northern Ireland. The Scottish Renal Registry produces its own report, arguing perhaps that there should be a more detailed report on hospitalisation measures in this publication. Other linkage agencies such as SAIL now offer Welsh HES data, but a solution for Northern Ireland is yet to be identified. If repeated, excluding Scotland and linking to Welsh HES, coverage of units would be 92% (57 / 62 units).

Percentage of case completeness – Target: 95%

This linkage was not designed to identify additional patients who had not been captured by UKRR, although access to unanonymised unlinked HES data has the capacity to do this. UKRR believes its coverage exceeds the recommended 95% in patients surviving beyond 90 days from the start of RRT.

Completeness of the items – Target: <2% for any individual data item

Prior to data linkage UKRR met this standard for age and sex, but failed to meet this target for many other demographical variables. Following linkage the less than two percent target was met by socioeconomic status and narrowly missed by comorbidity (97.6%) and ethnicity (97.1%). Donor type was complete in 99.7% of included cases although disagreement existed. This level of completeness would reach a silver standard under the NAACCR guidance

(Hofferkamp 2008). There are other areas where the completeness of items is much worse. For instance potassium completion rates in the six months preceding any individual haemodialysis week in Chapter six were approximately ten percent, and mirrored by completion rates of ten percent in the laboratory file overall. This related to the introduction of potassium data submission late on in the period of study.

Prevention of duplicates – Target: < 1/1,000

Following submission of the UKRR data to RCP, patients were checked against the NHS batch tracing service. Six patients accounted for twelve patient records, therefore making the duplicate rate 6 / 21,627 (0.0003%), far below the NAACCR standard (0.001%). Information on how many duplicates were excluded prior to the UKRR dataset being transmitted to RCP is not available.

Beyond patient level duplicates are admission level duplicates. Admission inflation by the movement of patients between the inpatient ward and the dialysis unit, and misclassification of elective inpatient admissions and outpatient haemodialysis attendances are potential concerns and this study has gone to lengths to reduce this. In practical terms it is a challenge to identify these examples, but one solution would be to screen trust supplied spell identifiers for duplicates. In this dataset two percent of ordinary admission episodes were supplied with this field blank.

Validity and accuracy of the items – Target: <1% errors

Re-abstraction is the process of extracting the same information from the case notes and comparing the coded data to that already in the disease registry (Hofferkamp 2008). In the setting of this study, validity and accuracy has largely been assessed by comparing separate data sources.

Agreement between sources for comorbidity was 92.9%, 92.8% for ethnicity and 97.2% for socioeconomic status. Donor type agreed in 94.6% of first transplant cases suitable for analysis. Other disease registries have performed similar cross-source exercises. The ANZDATA registry compared its records of cancer diagnoses to that in the Central Cancer Registry, and identified agreement of 96.3%(Webster et al. 2010), compared to the HES-UKRR cancer agreement of 92.3%. The sensitivity for detecting acute myocardial infarction in the Masstricht cardiovascular registry was 84% when compared to hospital discharge summaries. This compares to a sensitivity of 58.4% in this study. The relatively low prevalence of an individual

comorbidity often results in a high level of agreement between both sources reporting no condition.

Within source agreement assessed by re-abstraction was assessed by the NAACCR group, and found to be 95% for 13 demographic and primary disease fields(Thoburn et al. 2007). Using data from four clinical trials the National Institute on Drug Abuse Clinical Trials Network identified an error rate of 14 per 100,000 fields(Nahm et al. 2008). The USRDS performed a re-abstracting audit, finding agreement for 50 items in 1,692 incident patients was 91.1%(USRDS 1992).

UKRR routinely checks the data submitted to its database with methods appropriate for one source of information, however linkage such as that described herein does offer additional checks which could prompt communication with the submitting centre. The burden of additional activity involved may offset the potential advantage, but movement into other measures of performance such as peritoneal dialysis treatment survival or catheter function(Briggs et al. 2013) would be heavily influenced by the additional events identified above.

Comparability

Couchoud recommends "formal documentation describing (i) the definitions to be used for recording and reporting of the specific items, (ii) the details of all changes to the database storage structure or (iii) major coding revisions". In isolation the UKRR dataset meets these recommendations. For wider adoption of a programme of linkage to HES, specifications of data items collected via hospitalisation data would need to be written and align with the other demands of HES data (specifically HRG coding algorithms).

Clearly this study has identified differences in how centres report outpatient haemodialysis activity, with approximately 30% of haemodialysis time reflecting three times a week HES coded attendance. Examination of data supplied separately from UKRR suggests that between April 2010 and March 2011, approximately 960,000 weeks of dialysis treatment were delivered in England, however only 1,400,000 regular day and night attender episodes were recorded by HES (The NHS Information Centre 2011). Assuming all these were haemodialysis attendances this still represents a third of haemodialysis activity. Explanations for this include locally negotiated remuneration for dialysis services, and the intention to collect this information from the National Renal Dataset (NRD). Examples of how this would interact with the HES dataset published in guidance from NHS kidney care (NHS Kidney Care 2011). The NRD has the capacity to better reflect outpatient haemodialysis and peritoneal dialysis activity due to a

more tailored specification. If the collection of haemodialysis activity is phased out, collection via the registry in existing underutilised fields or linkage to the NRD would be necessary to derive dialysis patterns.

Usefulness

Questionnaires assessing if various registry reports or publications on quality improvement have helped them be more effective have been suggested. A large part of the work herein has been presented without revealing individual renal units and therefore an assessment of this is probably premature. In addition for quality improvement to be assessed timely data is advantageous.

Timeliness: Target – < 23 months

A number of measures have been suggested, with the steps of documentation, upload and analysis. NAACCR suggest that within 23 months, a registry should have received 95% of its projected cases(Hofferkamp 2008). The UKRR and HES datasets currently operate with these margins independently, with more recent UKRR reports aiming to be issued within 12 months, a move which will greatly aid the assessment of quality improvement. HES operate differently, having the capacity to be reported on quarterly. The linkage itself adds a delay beyond those seen with the information governance hurdles, with the data having to be fully loaded and error-checked before linkage can occur.

Asynchrony between the periods available was evident within this study, with UKRR approximately fourteen months behind the most recent HES data at the time of linkage. If findings within this study prompted quality improvement initiatives shorter cycles of reporting would be important to who changes in centre specific measures.

Hospital Episode Statistics data quality

Issues of coding that are often raised when discussing HES data. We have seen that coding depth varied across centres, improved during the study period and was correlated with post-transplant surgical complication rates, arguably the measure most sensitive to differences in coding patterns. In addition, how speciality was reflected changed in eight centres necessitating their exclusion from *date first seen* analyses. The accuracy seen with diagnosis coding (93% for comorbidity) and procedure coding (91% for transplantation, assuming UKRR accurate) are similar to that seen in more recent analyses of discharge coding accuracy performed by the audit commission for 2009-2010 data of 87% and 90% respectively (Audit Commission for Local Authorities 2010).

As previously mentioned in Chapter 5, the non-constant risk for comorbid conditions across centres may suggest differences in coding, variation in susceptibility to the condition in question for the particular population, or differences in how these conditions are managed by the centres. The application of interaction terms or inclusion of other demographic variables identified as varying across centres largely explained non-constant risk.

Primary and secondary diagnoses

The primary reason that patients are admitted is often opaque, and examples given by NHS Kidney Care guide exemplify this (NHS Kidney Care 2011), promoting the continued usage of end-stage renal failure or primary renal disease codes in the HES primary diagnosis field in certain circumstances. The application of existing admission classification schemes employed by other agencies highlight that method such as the Clinical Classification Scheme fail to capture the heterogeneity of an admission in an RRT patient, with the HRG system generally performing better.

There are examples where the primary diagnosis could have better reflected what occurred to the patient. Using PD peritonitis as an example, 86% of cases of peritonitis were identified from the primary diagnosis, with 4% having a primary renal disease of code reflecting CKD in the primary position and 2% reflecting generic complications pertaining to access or dialysis care.

The capacity to make an endpoint disappear using different coding strategies makes a measure highly fallible. An example of cases where this already occurs is the Dr Foster HSMR which only includes 82% of deaths representing approximately 40% of admissions (Shahian et al. 2010). Many other measures of surgical performance are derived from endpoints reported by the surgeons themselves. Centres were unaware that the hospitalisation data they were collecting during the period analysed was to be used for such a measure, so the incentive to mask such events did not exist. Indeed for preferable Payment by Results remuneration there may be an incentive to code surgical complications to get a “with complications” HRG.

One potential method of avoiding coding issues altogether in the short term is limiting analyses to purely hospitalisation, as admissions are accurately captured even if their underlying reason or the events occurring once admitted were not. This discards a huge amount of information which could potentially be used by an agency such as UKRR for adjustment of other measures or endpoint identification.

Statistical issues

A number of multivariate statistical models were employed in these analyses, generally selected as they were appropriate for the scenario and were supported by previous comparable analyses. Predictive ability from these models generally seemed reasonable. More intelligent methods of modelling data undoubtedly exist but methods must be trusted by stakeholders in the end result, the performance measure. Many nephrologists will be familiar with some of the modelling techniques from their own research and audit projects. The ability for healthcare organisations to reproduce measures using their own data has been a recommendation in other settings(Whalley 2010).

Specific guidance for the generation of such models is thin. Looking elsewhere, the methodological recommendations surrounding risk prediction models offers some direction. Authors recommend the following (adapted from (Royston et al. 2009))

- Selecting clinically relevant candidate predictors for possible inclusion in the model.
- Evaluating the quality of the data and judging what to do about missing values.
- Data handling decisions.
- Choosing a strategy for selecting the important variables in the final model.
- Deciding how to model continuous variables.
- Selecting measure(s) of model performance or predictive accuracy.

Where possible, through literature review and available data items candidate predictors have been appropriately selected. Notable omissions persist, especially when considering the performance status of the patient as employed in other studies and comorbidity measures(Miskulin et al. 2004). Variables under a centre's control were excluded. Incidence and prevalence of variables and endpoints were found to be comparable to other published studies and reports, and continuous variables were plotted using spline plots for categorisation where appropriate.

In addition, many would recommend the use of a derivation dataset (where the models are calibrated and coefficients determined) and a testing dataset (where the model is applied and its predictive ability assessed). It is standard practice within performance indicators to model and report on the same data as it is this cohort you are benchmarking. This process does leave models susceptible to over-fitting, especially when outlying observations are present. This study is generally predicting events in large numbers of patients, where the

endpoint in question is frequent (in general occurring in greater than 20% of patients within the analysis cohort).

The majority of these analyses accounted for patient level factors only, an appropriate technique when comparing centres. Further exploration of patient level factors might have been aided by clustering by renal centre. A good example of this would be the location of death as part of the long gap mortality analyses in chapter 6, as we have highlighted location of death varies according to centre. Issues with the format and amount of data (a large number or dialysis weeks and a comparatively low frequency of death) that informed this analysis precluded the adoption of this technique. Clustering by centre was employed when exploring stent usage in transplant recipients and the effect peritoneal dialysis catheter insertion timing on hospitalised peritonitis, and is these methods that would be employed in future work exploring practice patterns and their impact on outcomes. Linked data can also inform the practice patterns as well as collecting the relevant endpoints. Instrumental Variable analyses performed frequently by the DOPPS group, where unmeasured confounders are adjusted for by a measure of physician preference (for instance the proportion of patients receiving a treatment within a centre) are now possible.

Many comparative analyses of centres were performed without the adoption of overdispersion. As stated in our methods, one of the more widely accepted methods of accounting for overdispersion is removing or trimming outliers then estimating a dispersion factor (Spiegelhalter 2005). When the number of centres included in the analysis is small, only a small number of outliers will be removed. This appears to lead to very wide control limits and few or no outliers. Existing publications by the UKRR do not adopt these measures; however some applications of funnel plots in UKRR reports describe a distribution around a recommended range (for instance haemoglobin levels suggested by the National Institute of Clinical Excellence). Speigelhalter does suggest using “an interval as a target” when accounting for overdispersion and it may be that UKRR could consider adopting these strategies. Caution should be applied when considering the application of these methods however, as a centre which may at some fundamental level be underperforming could be interpreted as “in control” if the control limits are widened by the application of overdispersion techniques. Even with the most stringent of control limits there may be centres who are inappropriately labelled as “in control”, due to but not exclusively as a result of differing variable coding practices or accuracy of informing data across centres.

Implications for renal centres

This study has allowed the inclusive comparison of demography across centres. Key themes include the broadly similar comorbid burden across renal centres, but the variation in attitudes towards modality. In general a centre's incident haemodialysis patients are more comorbid than their incident peritoneal dialysis patients and this normally driven by clinical necessity. Despite this, several of the forty-six centres have peritoneal dialysis programmes that have a higher prevalence of patient comorbidity than the national average, or potentially have a higher comorbid prevalence than haemodialysis programmes within the same centre. In contrast to this, some centres only pick relatively healthy patients for their peritoneal dialysis programme. In line with other researcher's findings, this suggests the modality you are offered may be heavily influenced by centre level characteristics in addition to patient level characteristics (Castledine et al. 2013). Similarly differences in the demography of transplant recipients (with the exclusion of age) are also notable, and are the subject of further investigation by the Access to Transplant and Transplant Outcome Measures study.

Ethnicity does vary significantly across centres, and given the protective impact of non-Caucasian ethnicity on incident survival (hazard for Causcasian's adjusted for age 1.50, 95% CI 1.40 – 1.60) adjustment for this and potentially other measures of performance should be adopted where possible.

Despite adjustment for this and other predictive conditions, one renal centre remained beyond the 95% control line for three year survival. In the context of the 46 centres analysed, it is likely that two centres would be outliers. The UKRR reports have noted less dispersion in survival at one year adjusted for age in the funnel plots they include in their reports for the years 2006-2009 and 2007-2010. This observation in combination with the multi-varate adjustment presented may result in no outliers.

Sadly this homogeneity in performance across centres is not observed with admission rates. Eight centres for haemodialysis and eleven centres for peritoneal dialysis were beyond the 95% control lines for admissions within the first year of treatment. There is some reassurance for centres that the correlation between standardised haemodialysis and peritoneal dialysis admission rates are poor (Pearson correlation coefficient 0.20, P=0.188), with only two centres identified as outliers beyond the 95% control line in both measures (Figure 7-3 and Table 9-1).

Table 9-1 - The outlier status for measures reported in this study for the 46 centres included in the analysis

	Mortality		Haemodialysis		Peritoneal Dialysis		Measures Outlying (High/Low)	Transplantation		
Centre Number	Incident survival	HSMR	Admit Rate	Long gap admissions	Admit Rate	Peritonitis Rate		Surgical complication	Length of stay	Admit Rate
1			□		○		0 / 2			
2			□		○		0 / 2			
3						○	0 / 1	●		
4		■	○			□	1 / 2			
5		□				□	0 / 2			
6			□		■		1 / 1			
7						■	1 / 0	●		
8							0 / 0			
9					○		0 / 1			
10			○		○		0 / 2			
11							0 / 0			
12			□				0 / 1			
13							0 / 0			
14		●	○		□	●	2 / 2			
15			■				1 / 0			
16					□		0 / 1			
17			□		●		1 / 1			
18				●	■		2 / 0			
19			○			□	0 / 2			○
20		●			□	○	1 / 2			■
21							0 / 0			
22			■		○		1 / 1			
23					□	○	0 / 2			
24			□				0 / 1			
25						□	0 / 1			
26	○	○	○		○	■	1 / 4			□
27	□	□	□			●	1 / 3			
28	●				■	□	2 / 1			
29		○	■		■	□	2 / 2		●	□
30					●	○	1 / 1			
31			○		□	●	1 / 2			
32		○			■		1 / 1			□
33			■		○		1 / 1			●
34			○				0 / 1			
35			■		■	●	3 / 0			
36					○	○	0 / 2			
37			■				1 / 0			
38	○				●		1 / 1			
39			○				0 / 1			
40			□		○		0 / 2			
41			□				0 / 1			
42					■	○	1 / 1			
43					□	■	1 / 1			
44						●	1 / 0			
45			■			●	2 / 0			
46		●	□		●		2 / 1			

● Outside 95% limits high, ■ Outside 99.5% limits high, ○ Outside 95% limits low, □ Outside 99.5% limits low

Factors that could be driving these high admission rates include transitions between modalities which are not adjusted for. The spike in admissions seen around modality changes is clinically logical, and in order to form appropriate dialysis access potentially unavoidable (although this study excluded day-case activity which for certain forms of access is often used). The argument against adjustment for modality change is that appropriate patient selection for a modality is under a centre's control, and illustrated by the variation in comorbidity between modalities within a centre. There are many appropriate reasons why a patient should transition between modalities and identification of electively planned transition could be performed using the combination of UKRR timeline data and elective dialysis access activity.

In theory, once the patient is admitted we have another metric by which we can measure performance: hospital standardised mortality. As previously mentioned, the one centre which was an outlier for incident survival was not an outlier for hospital associated mortality. A potential explanation for this would be a high out of hospital mortality rate; however this centre is beyond the 95% limit for higher than expected deaths in hospital, which persists when deaths out to 30 days are included. It is challenging to see how the combination of these factors can produce such a phenomenon.

Beyond the perception that survival will vary between centres is the perception that it may vary according to other healthcare factors. The admission day of the week was not associated with any increase in mortality unlike other analyses performed on all cause admissions (approximately 7.5% mortality for Mon-Fri compared to 8.5% at the weekend (Intelligence 2011)) or reason specific admissions (11% mortality on a Sunday compared with 8.9% for the rest of the week in Stroke patients (Palmer et al. 2012)). There was an increase in hospital mortality in patients discharged over the weekend, particularly on a Sunday (HSMR 1.84, 95% CI 1.63 – 2.06). There is likely to be biasing in the unmeasured case-mix of patients who remain in hospital over the weekend. Their conditions are likely to be more severe than those who were fit enough to be discharged during a week day as there is interest for the patient and the workforce to minimise inpatient numbers over the weekend. However, it may raise concerns about the care of the already admitted, deteriorating patient.

One perception from many international studies was that the UK was delivering dialysis care in a superior fashion to the USA. This study does not add to any comparisons of incident survival, however admission rates reported by the USRDS group across the dialysis week are almost identical to those seen in Chapter 6 (Roberts et al. 2012). Despite a lower burden of comorbidity, longer treatment times and the perception of superior pre-dialysis care the proportional increase in admissions and deaths after the long gap are similar. Also, despite the

variation in haemodialysis admission rates across English centres, the rates of admission over the two day gap in three times a week haemodialysis seem fairly constant across centres. This might suggest a greater "class effect" associated with this haemodialysis schedule patterns that is less influenced by international differences, clinical practice patterns and patient demography.

That the mortality rate in hospital is also not affected by the dialysis schedule, but is coupled with an increase in emergency admissions of approximately 69% could be interpreted as reassuring. This increase in admission workload is not associated with an increase in short term hospital associated mortality. Additional conclusions could be drawn from the unremarkable mortality rates over the weekend considering other analyses in general population admissions showing an increase in mortality in admissions over the weekend from approximately 7% to 8.5%(Intelligence 2011). Further supporting evidence to support uniformity of delivered care across the week is that dialysis hospital associated mortality does not vary according to day of the week (Chapter 5). This latter measure does adjust for reason for admission, and therefore if a more severe group of admissions presented on a Monday or Tuesday associated with the long gap, their severity would be masked by the adjustment process.

Themes distilled from adjustment variables

Many of the analyses therein have used a core group of recognised adjustment variables to explain the differences between event rates and outcomes in different centres or patient groups. From these variables the following themes have emerged:

Age

Beyond the unsurprising association between age and mortality, both in incident analyses and HSMRs, some themes emerge. Firstly, we see that as age increase so does the comorbid burden at the time of starting dialysis, up until age 70, where it plateaus and then slightly falls. This perhaps reflects the renal community's conservatism when evaluating the elderly and comorbid patient for RRT. Age had perhaps less of an impact on admission rates that expected, with less than 0.1 admissions per year separating the youngest and oldest age groups. USRDS data showed greater differences in admission rates when their long gap analysis was reported (approximately 18 admissions per 100 patient years after the two day gap in those under 40 years of age compared to 70 admissions per year in those over 65) (Foley et al. 2011). Again this may be a manifestation of the lower comorbid burden in elderly patients (both in

comparison to the young and internationally), or differing approaches to the healthcare system.

Sex

Although females live longer in the general population, we were unable to demonstrate this in RRT patients. With similar admission rates and HSMR, these support comparative mortality in the incident survival analysis. Women were more likely to be admitted than men in the first year of dialysis (2.67/year vs 2.46/year).

Ethnicity

A greater description of the differing outcomes in patients of varying ethnicity was enabled by superior data completeness and a range of new endpoints. Having again demonstrated a survival advantage for non-White patients in incident analyses, we have then gone on to demonstrate comparable admission rates across the dialysis week. This would suggest that once in hospital, non-White patients are less likely to die, a hypothesis supported by the HSMR analysis. What is precipitating what might be perceived as an excess of admissions in a patient group who are being admitted with a less severe phenotype of medical problem, manifesting in an odds ratio of 1.74 (95% CI 1.63 – 1.87) for White patients compared to non-White for 30 day mortality? Differing socioeconomic status may off some explanation (discussed below), or differing rates of late presentation in this group (associated with an increase in admissions of 19%).

Despite a 69% increase in admissions after the two day break in three times a week haemodialysis like their White counterparts, Non-Caucasian patients had lower mortality rates without the increase seen after the two day break across the dialysis week. This may represent the same susceptibility to fluid overload but a comparative resistance to high potassium or other factors influencing sudden death.

Socioeconomic Status

Socioeconomic status is often cited as outside a centres control and demonstrating significant geographical variation across the country. Themes highlighted from this work support analyses by other authors that often find counterintuitive associations. Socioeconomic status only became predictive for incident survival once other variables were included, and even then it was only the least deprived fifth which saw a protective effect. Increasing deprivation was associated with a 19% reduction in the odds of thirty day hospital associated mortality, although this association was normalised following multivariate adjustment. Admission rates were certainly higher in patients who were more deprived in haemodialysis

patients. This association for all cause admissions in peritoneal dialysis patients was less marked (only the least deprived fifth had lower admission rates), but a strong trend was observed with peritonitis associated admissions. It is likely that these findings relate to our own clinical judgements regarding how to manage a patient with identical demography and clinical presentation from varying socioeconomic backgrounds. As alluded to in Chapter 5 and previously shown by Plantinga et al, the availability of greater social support at home is protective against admissions (Plantinga et al. 2010). However, the study was limited on how it could relate social support to socioeconomic status, showing greater support was associated with marriage and white race, but finding no association between high school graduation and employment. The same group were able to link unemployment to social support when examining inpatient haemodialysis initiation (Crews et al. 2010). Clinicians directly or indirectly assess social support when determining whether to admit someone, asking simple questions such as "who do you have at home that could care for you". This means that for the same comorbid patient suffering the same acute medical condition, someone with greater social support would be less likely to be admitted. Assuming greater social support and lower deprivation are associated, this unmeasured confounding explains the greater mortality in less deprived patients and the higher admission rate in the more deprived. Social support would be even more relevant in the community observation and treatment of a patient with peritoneal dialysis peritonitis.

Vintage

The amount of time a patient has been receiving RRT influences a number of measures. Admission rates are highest in the first three months of dialysis, but then settle down to a baseline rate, best demonstrated in haemodialysis analyses. This admission rate of approximately one and a half acute admissions stays static until approximately four months before death, where is begins to climb.

Increasing vintage and declining residual kidney function are closely correlated (McKane et al. 2002). Our assumption that fluid related issues drive admissions after the two day break is not supported by the fact that the increase in admissions is uniform for the first two years of haemodialysis treatment. An association between increased DGF rates (as measured by the need for dialysis in the post-operative period) in the transplant analyses and increasing vintage may suggest that higher levels of residual kidney function negate the need for urgent dialysis when the transplanted kidney is slow to function. More direct measures of residual kidney function would aid our development of individualised dialysis.

Year of start / year of analysis

Improvements in most measures have been observed over the incident period (2002-2006) and prevalent period (2002 – 2009) studied. The UKRR reports an improvement in survival of approximately four percent per year, and this study suggests this is independent of the case-mix accepted onto RRT programmes in England. Hospital mortality has also improved, although if this represents a genuine improvement in care or expansion of care of the dying patient into the community. What was identified was an increase in unadjusted hospital mortality over time, reversed by multivariate adjustment, likely reflecting the increasing age and comorbid burden of the cohort with the passage of time. A simple cohort effect in this more prevalent patient focused analysis may also explain improvements.

Despite a less preferential case-mix associated with increased vintage and comorbid burden, surgical complication rate remained constant between 2002 and 2009. This increase in average coding depth from four to six codes per admission may again be the manifestation of increasing comorbid burden rather than greater coding accuracy. One interpretation is that underlying surgical complication rates have improved as the complication rate has remained constant despite a likely increase in diagnostic coding accuracy and higher risk cohort being transplanted. This may also explain a failure to demonstrate a shortening in length of stay after transplantation over time.

Comorbidity

Wider, more inclusive comorbidity data enabled greater analyses than previously possible with available UKRR data. The perception of the renal community was that comorbid burden across centres varied, and that in some way this was an explanation for varying outcomes. The explanatory power of adding comorbidity was significant for the individual (an improvement in R squared from 0.261 to 0.367) and greater than seen in other studies. However, a large part of the variation between centres had already been explained by other variables prior to the inclusion of comorbidity in centre specific survival analyses. Probing this observation revealed similar levels of comorbidity in RRT patients as measured using a weighted comorbid score across centres in England.

The theme of strong effects on the individual by less on the centre was carried forward in admission rate analyses, where the presence of a comorbid condition generally increased your admission rate from two per year to three per year. Despite this, again there was little movement in outlying renal centres when comorbid conditions were used to adjust admission rates in the first year in either haemodialysis or peritoneal dialysis modalities. The increase in admissions associated with an individual comorbid condition was not uniform across the

haemodialysis week: for instance the addition of congestive cardiac failure to no comorbidity increased the acute admission rate from 1.35 to 2.11 per year, but in addition the relative increase after the long gap increased from 1.64 to 1.80. These observations may aid the tailoring of haemodialysis to the individual patient based on their comorbid conditions.

Using the presence of individual conditions, the prevalence of comorbidity information in the UKRR dataset was similar in those with and without it completed once HES was able to measure it. Given survival in those with UKRR comorbidity missing is worse; one might have expected differing levels of comorbidity to explain this. When comorbidity was assessed with a score the difference between these groups was more apparent, demonstrating the usefulness of such a measure when a number of conditions could be contributing to an overall effect. Within incident survival analyses, three comorbid conditions collected by UKRR were shown to result in similar levels of centre specific adjustment to that obtained using sixteen comorbid conditions, with only a minor reduction of model performance (R squared 0.285 compared to 0.367 for the proposed final model).

Shortcomings and areas for improvement

There are aspects of these analyses which were hampered by statistical issues, data issues and available time. Recognising these shortcomings are important for interpretation of some aspects of the analyses and inform those considering future analyses with a similar linked dataset.

Data issues

Beyond the issues of coding and data completeness highlighted above, there are other data hurdles that prevent certain analyses. The current frequency with which UKRR download laboratory data is quarterly, with may preclude a better understanding of the association between variables such as potassium and other endpoints. I understand that individual results will be downloaded in the future. Dialysis access is still complicated by the fact that the formation of a fistula or the insertion of a dialysis catheter does not necessarily mean they are being used for dialysis access. The NHS is looking to introduce a haemodialysis tariff with different remuneration according to the type of dialysis access employed, informed by the national renal dataset, which also has the capacity to collect interventions for malfunctioning access. We propose that linkage with the national renal dataset would enable high quality epidemiological analysis of dialysis access. Indeed current proposals suggest the national renal dataset will in part be informed by UKRR data (NHS Health and Social Care Information Centre 2010).

The presence of a comorbid condition is likely to have a differing effect according to how long it has been present for. For example, the longer a patient has diabetes the more likely they are to have microvascular and macrovascular complications. The longer a patient survives from their first diagnosis of cancer, the greater likelihood that the patient experienced a curative intervention. However, the converse may also be true if a patient has had curative surgery. The observation window offered by HES prior to starting RRT was not sufficient to enable these forms of analysis but the concept of "comorbid conditions as a continuous variables" would warrant exploration if a linked dataset was sufficiently mature.

The gold standard for evaluating these linked data sources, beyond their agreement with each other, is their agreement with the source – the patient and their notes. Due to the anonymisation process and the period of time in some cases between clinical activity, death of the patient and the receipt of the linked dataset, identification and access to patient case notes was not practical. Should further linkage via a less anonymised process become available this would be a recommended process in a selection of centres with low coding depth or outlying incidences of coding-reliant events.

Analysis and scope

Appropriately given the novelty of the undertaken linkage, a proportion of research time was assigned to the derivation and validation of data items and identification of appropriate cohorts which were repeated used during subsequent analyses. These aspects and organising the linkage itself took time which one might have preferred was invested into understanding centre specific practices and applying them to clinical outcomes. We would argue that a comprehensive understanding of what HES adds to UKRR what it has the capacity to enable is an important pre-requisite and will supply UKRR and the authors with important knowledge to perform these analyses in the future. In addition, the methods applied here and identified adjustment variables serve as a framework to perform practice pattern analysis.

As highlighted by the thesis structure, analyses have been largely modality specific rather than condition specific. Further questions could be answered within specific groups of patients, such as those identified as referred late or which a particular primary renal disease. Some analyses may be better answered with a different structure of linkage such as an analysis of prevalent patients.

Suggestions for future analysis

The strengths and weaknesses of the product of this linkage have been reported. With consideration for these, suggested future analyses with and without HES data are broadly detailed:

Location of care

Despite its potential weaknesses in describing admissions, HES does robustly inform researchers on where patients are admitted. This is a product of patient case-mix, clinical indication, geography and centre specific practice patterns and policies. The impact on clinical outcomes such as mortality could be determined using the HSMR analysis format which adjusts for patient case-mix and clinical indication, and apply centre level practices using either multi-level models or with an instrumental variable, widely applied by DOPPS. Existing analyses by the Aintree Health Outcomes Partnership (Abraham et al. 2012) have categorised trusts by their provision of renal services which could inform this proposed work.

Procedures and interventions following specified events

The impact of cardiac intervention such as coronary artery bypass grafting (CABG) or angioplasty and various time-points (before RRT, for cardiac optimisation for transplant, after a coronary event etc) would be easy to perform, but clouded by confounding by indication. This aside the seemingly protective impact of CABG on incident survival following multivariate adjustment warrants further understanding in a UK setting.

Early warning tools

Existing UKRR reports include reporting of prevalent survival, which seems more likely to identify early the impact of poor care on survival. The application of the methods herein to prevalent patients may enable the identification of changes in outcomes earlier. Moreover, the use of hospital mortality tools and location of death analyses may enable a greater understanding of where in the healthcare system problems exist.

The interdialytic interval

This work postulates that conditions or parameters which suggest volume overload drive excess admissions and that biochemical abnormalities drive mortality (mainly inferred from location of death and existing research) over the two day break. These findings need further validation, and an intervention explored. Similar sources with better potassium completeness and other forms of dialysis clearance measurement (thereby offering potential therapeutic interventions) should be identified. A clinical study either intensively monitoring clinical and

laboratory parameters or removing the long gap with alternate day dialysis could offer insight but would be expensive to conduct and difficult to statistically power to the endpoints reported in this study.

Elective modality change timing

Currently the UKRR treatment timeline specification is based on the ERA-EDTA Registry specification for RRT treatment modalities and outcomes. This shows changes between modalities but not their indication or if they are planned. It is recognised that prolonged exposure to peritoneal dialysis can cause the debilitating and life-threatening complication of encapsulating peritoneal sclerosis (Johnson et al. 2010). Using elective access formation as a surrogate for planned modality change this could inform varying practices towards duration of time on peritoneal dialysis and such outcomes. Encapsulating peritoneal sclerosis is not specifically coded by ICD10, and information from death certificates or HES coding for adhesions from a prevalent cohort may be required.

Linkage to other datasets

The linkage between HES and UKRR has enabled a number of new analyses, it is recognised that there are many questions that cannot be answered with this dataset. Using the power of linked datasets, examples of other potential linkages and supported outputs are offered:

Comparative safety and efficacy of induction regimes in transplantation

As immunosuppression for transplantation has evolved, lower and lower rates of early rejection have been achieved. With these low levels of immunity comes susceptibility to infection, as evidenced by persistent or increasing levels of infectious admissions over the last decade(U S Renal Data System 2011). Despite superior survival compared to dialysis, transplant recipients still have a heavy burden of cardiovascular disease(Jardine et al. 2011). The UKRR does not have details on immunosuppression regimes, and exploring UK trial data or NHS Blood and Transplant information linked to HES data and potentially cancer registries and cardiac registries (discussed below) could offer insight into tailored immunosuppression to minimise morbidity.

Community based care

Activity in primary care remains un-captured, and in the broader setting of chronic kidney disease represents a large proportion of delivered clinical care (Kerr et al. 2012). Understanding the contribution and clinical impact of primary care on patients with CKD who may go progress to ERF, and what the experience and outcomes are associated with the decision to receive conservative care could inform treatment decision making. Linkage

between the General Practice Research Database which covers approximately 9% of general practices in England and Wales could offer insight.

Myocardial ischaemia national audit project (MINAP)

With cardiovascular disease being the leading cause of mortality in RRT patients, and patients with advanced CKD generally being excluded from large interventional studies there is a knowledge gap regarding the optimal management of ERF patients with acute myocardial events. Although purely observational, MINAP data could enable many analyses on outcomes which have previously been limited to single centre (Birkhead et al. 2004). The current MINAP dataset format classifies patients as CKD (definition: creatinine > 200 micromol/L) and the renal function at presentation as measured by one value of creatinine. Additional information on RRT status (inadequately captured with this specification) would be required via data linkage to understand outcomes in this cohort.

Suggestions for coding practice

Some analyses (particularly cause specific admissions) were hampered by coding issues. Recognising that the Payment by Results system is underpinned by HRGs, and that generating new or altering existing HRGs has the capacity to extend beyond nephrology, the following recommendations are tempered by this, and the forthcoming National Renal Dataset.

Admissions

Wherever possible, an ICD10 code reflecting the reason the patient was admitted should reside in the primary diagnosis.

Haemodialysis

The attendance of patients for haemodialysis is to be collected in summary form by the National Renal Dataset, which enables a broader description of the conditions under which a patient is dialysed (NHS Kidney Care 2011). However, it does not reflect the dialysis pattern the patient is receiving (NHS Health and Social Care Information Centre 2010). Rather than suggest haemodialysis attendance should be recorded by HES, it may be appropriate to add this to a UKRR laboratory field, as the dialysis time is currently (but incompletely) documented. This solution does not allow missed dialysis sessions to be captured.

Peritoneal dialysis

When a patient was admitted with peritoneal dialysis peritonitis, secondary coding only yielded organisms in 38% percent of admissions. Uniform coding for a peritoneal dialysis peritonitis event, preferably in the primary position (as 86% were identified in this study) with

organism data would be achievable. The absence of organisms would infer culture negative peritoneal dialysis peritonitis. Outpatient datasets or day-case records could reflect activity in those not admitted.

Catheter insertions were incompletely recorded, but proved extremely valuable in identifying patients who may have trialled peritoneal dialysis. Coding of all catheter insertions and removals is encouraged.

Transplantation

The National Renal Dataset has the capacity to report greatly enhanced information on blood grouping, but this is largely informed by existing NHS Blood and Transplant fields. There is no information on recipient blood group, or that the transplant was explicitly ABO incompatible. The OPCS cede Y994 details ABO incompatibility. Highly sensitised patients are not defined in this or the National Renal Dataset and linkage with NHS Blood and Transplant may be required. The routine coding of the use of dialysis (as evidenced in Chapter 8) after transplantation gives an important insight into delayed graft function and should be encouraged.

Can we measure quality and performance in renal services using routine data?

We have shown that the performance of renal centres as measured by survival is greatly aided by using routine data to reach adequate levels of data completeness for multivariate adjustment and enable robust comparisons between centres. Routine data in the form of Hospital Episode Statistics data enables the derivation of new measures of performance in haemodialysis, peritoneal dialysis and kidney transplantation. This routine data source appears to detect an event rates similar to those seen in the literature following manual notes review. However, some measures reliant of coding practices or quality should be interpreted with caution when comparing centres. Should routine linkage become standard practice to inform existing analyses and report new measures, guidance from the reporting body should be issued to standardise coding practices. This would ensure the renal centres identified as under-performing, as often found in this study, are correctly targeted. Evidence herein suggests that centres with previous poor survival may have been targeted inappropriately.

Chapter 10 *Appendices*

The following appendices are numbered with reference to the referring chapters.

Appendix 2a: Charlson Conditions and ICD10 diagnosis codes(Aylin et al. 2010)

New codes reflect updated weighs employed by Dr Foster for the Hospital Standardised Mortality Ratio, compared to the original derived by Charlson.

	Condition Name	**ICD10 Coding**	**New**	**Old**
1	Acute myocardial infarction	I21, I22, I23, I252, I258	5	1
2	Cerebral vascular accident	G450, G451, G452, G454, G458, G459, G46, I60-I69	11	1
3	Congestive heart failure	I50	13	1
4	Connective tissue disorder	M05, M060, M063, M069, M32, M332, M34, M353	4	1
5	Dementia	F00, F01, F02, F03, F051	14	1
6	Diabetes	E101, E105, E106, E108, E109, E111, E115, E116, E118, E119, E131, E131, E136, E138, E139, E141, E145, E146, E148, E149	3	1
7	Liver disease	K702, K703, K717, K73, K74	8	1
8	Peptic ulcer	K25, K26, K27, K28	9	1
9	Peripheral vascular disease	I71, I739, I790, R02, Z958, Z959	6	1
10	Pulmonary disease	J40-J47, J60-J67	4	1
11	Cancer	C00-C76, C80-C97	8	2
12	Diabetes complications	E102, E103, E104, E107, E112, E113, E114, E117, E132, E133, E134, E137, E142, E143, E144, E147	-1	2
13	Paraplegia	G041, G81, G820, G821, G822	1	2
14	Renal disease	I12, I13, N01, N03, N052-N056, N072-N074, N18, N19, N25	10	2
15	Metastatic cancer	C77, C78, C79	14	3
16	Severe liver disease	K721, K729, K766, K767	18	3
17	HIV	B20, B21, B22, B23, B24	2	6

Appendix 2b: Elixhauser comorbidities and Odds Ratios for conditions(Elixhauser et al. 1998)

Comorbidity	% Prevelance	Odds Ratio for In-hospital mortality
1. Congestive heart failure	4	2.3
2. Cardiac arrhythmias	6.8	1.4
3. Valvular disease	1.8	0.7
4. Pulmonary circulation disorders	0.3	1.9
5. Peripheral vascular disorders	2.6	1.2
6. Hypertension	17.9	0.6
7. Paralysis	1.8	1.7
8. Other neurological disorders	2.7	2.8
9. Chronic pulmonary disease	9.9	1.2
10. Diabetes, uncomplicated	7.8	NS
11. Diabetes, complicated	4.1	1.1
12. Hypothyroidism	2.7	0.7
13. Renal failure	3.3	2.1
14. Liver disease	1.3	1.9
15. Peptic ulcer disease excluding bleeding	0.8	0.8
16. Acquired immune deficiency syndrome (AIDS)	0.4	3.2
17. Lymphoma	0.5	1.8
18. Metastatic cancer	2.4	3.1
19. Solid tumor without metastasis	6	NS
20. Rheumatoid arthritis/collagen vascular diseases	1.2	NS
21. Coagulopathy	1.5	4.1
22. Obesity	2.3	0.5
23. Weight loss	1.1	3.2
24. Fluid and electrolyte disorders	13.3	2.7
25. Blood loss anemia	1.6	0.9
26. Deficiency anemias	7.3	NS
27. Alcohol abuse	2.9	1.1
28. Drug abuse	1.5	NS
29. Psychoses	1.4	1.2
30. Depression	1.5	0.6

Appendix 3a: Ethical and Scientific Approval for Proposed Study

NHS
National Research Ethics Service
South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall
Aylesford
Kent
ME20 7NJ

Telephone: 01622 713012
Facsimile: 01622 885966

26 October 2010

Mr Christian Newsome
Department of Health
Quarry House
Desk 4E56
Leeds
LS2 7UE

Dear Mr Newsome

Title of the Database: **Pilot Health Research Support Service (HRSS)**
REC reference: **10/H1102/63**

The Research Ethics Committee reviewed the above application at the meeting held on 13 October 2010.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research database on the basis described in the application form and supporting documentation.

Duration of ethical opinion

The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research database.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
CV: Peter Knight		
Overarching Governance Framework	1.8	25 August 2010
REC application		24 September 2010
Covering Letter		24 September 2010
List of Pilot HRSS Data Sources		
PPI Co-Ordination Group	0.7	24 August 2010
Pilot HRSS Table of Studies		

This Research Ethics Committee is an advisory committee to South East Coast Strategic Health Authority

Appendix 3b: Structure of Datasets Provided to the Research Capability Programme

Uk renal registry fields

Demographic table variables

Ethnic Group code (Read code) 9S - 9T	Weight at 1st ERF treatment	Claudication
Adult Height	EDTA primary renal disease code	Ischaemic/Neuropathic ulcers
Weight	Angina flag	Angioplasty, vascular graft, aneurysm, stent (non-coronary)
Date first seen by Renal Physician	Previous MI with last 3 months	Amputation for PVD
Creatinine when first seen	Previous MI > 3 months ago	Date of last creatinine prior to start of ERF
Date of Death (as recorded by Renal unit)	Previous CAGB or Coronary angioplasty	Last creatinine prior to start of ERF
Date of death NHS tracing	Episode of Heart failure (either right of left)	Date of last haemoglobin prior to start of ERF
Cause of death 1 EDTA	Smoking	Last haemoglobin prior to start of ERF
Cause of death 2 EDTA	Chronic Obstructive Pulmonary Disease	Age at 1st RRT
Cause of death text	Cerebrovascular disease - symptomatic	Date of start of CKD5
Date 1st ERF treatment	Diabetes - not causing ERF	eGFR at start of CKD5
1st ERF Centre	Malignancy	Sex / Gender
1st ERF Treatment	Liver disease	Claudication

Postcode derived table variables

Start date of Postcode	Local Authority code (current)	Deprivation score townsend (current)
Lower Super Output Area	Ward (current)	Deprivation score/rank IMD (current)
Health authority code (current)	PCT code (current)	

Erythropoietin treatment table variables

Start date of period (EPO00)	EPO drug name	EPO administration route

End date of period (EPO01)	EPO dosage per week	EPO frequency

Laboratory table variables

Start & End date of period (QUA00)	Cholesterol	Post dialysis Diastolic BP
Detailed treatment modality code	iPTH pmol/l	Urea reduction ratio
Treatment centre code	% Hypochromic red cells	EPO Y/N
Treatment supervision code	MCH (QUA29)	Serum Potassium
Sending Hospital code	Calcium	Times per week Dialysis
Allocated Renal Centre code	Corrected Calcium	Length of time on Dialysis in minutes
Stat Analysis	Phosphate	Statin drug use
Creatinine	Bicarbonate	Ace Inhibitor
Urea	Sodium	Renagel
Hb	Systolic BP	Lanthanum
Ferritin	Diastolic BP	Cinacalcet
Albumin	Weight	Calcium based binder
HbA1c %	Post dialysis Systolic BP	Alucaps

Renal replacement therapy treatment table variables

Date start treatment	Treatment site/centre code - may be satellite centre	TreatCen
Date end treatment	Supervision of haemodialysis	
Treatment modality code - see code table	Sending Hospital code	

Office of National Statistics Fields

Date of Death	Cause of Death	Location of Death Code	Location of Death Type

Hospital Episode Statistics Fields (abridged)

In-patient Fields

Augmented care period end date	Main specialty	Intended management
Augmented care period number	Method of admission	Episode order
Augmented care period start date	Method of discharge	Date episode started
Number of augmented care periods within episode	Primary diagnosis - 4 characters	Date episode ended
Number of organ systems supported	Provider code - 5 character	Episode status
Augmented care location	Hospital provider spell number	Beginning of spell
Birth status	Diagnosis Code 1-20	Health Authority of residence
Delivery method	Operative Procedure 1-24	Patient's Primary Care Trust of residence
Length of gestation	Source of admission	Patient's Primary Care Trust of residence
Neonatel level of care	Treatment specialty	Local authority district / Current electoral ward
Well baby flag	Age at start of episode	Lower Super Output Area
Date of admission	Age at end of episode	IMD Overall Rank
Date of discharge	Ethnic category	Intensive care level days
Dates of operation	Sex of patient	High-dependency care level
Destination on discharge	Patient classification	Augmented Care Period Data Quality Indicator

Outpatient fields

Age on day of appointment	Diagnosis Code 1 - 12	Health authority of residence
Appointment date	Priority type	Primary care trust of residence
Attended or did not attend	Provider code	Primary care trust of residence
Ethnic category	Referral request received date	Local authority district of residence
First attendance	Service type requested	Current electoral ward
IMD Overall Ranking	Sex of patient	Lower super output area
Main specialty	Source of referral	
Operative Procedure 1 -23	Treatment specialty	

Appendix 4a: Ethnicity Mapping

UKRR Ethnicity Coding to HES Pre 2001 Coding mapping

UKRR Ethnicity Code	UKRR Ethnicity Group	HES Pre 2001 Code	HES Pre 2001 Group
9S1..	White	0	White
9S2..	Black Caribbean	1	Black - Caribbean
9S3..	Black African	2	Black - African
9S4..	Black / other / non-mixed origin	2	Black - African
9S41.	Black British	3	Black - Other
9S42.	Black Caribbean	1	Black - Caribbean
9S43.	Black North African	2	Black - African
9S44.	Black – other African country	2	Black - African
9S45.	Black East African Asian	2	Black - African
9S46.	Black Indian sub-continent	3	Black - Other
9S47.	Black – other Asian	3	Black - Other
9S48.	Black Black - other	3	Black - Other
9S51.	Other Black - Black/White orig	8	Any other group
9S6..	Indian	4	Indian
9S7..	Pakistani	5	Pakistani
9S8..	Bangladeshi	6	Bangladeshi
9S9..	Chinese	7	Chinese
9SA..	Other ethnic non-mixed (NMO)	8	Any other group
9SA1.	Brit. ethnic minor. spec.(NMO)	8	Any other group
9SA4.	North African Arab (NMO)	8	Any other group
9SA6.	East African Asian (NMO)	8	Any other group
9SA7.	Indian sub-continent (NMO)	5	Pakistani
9SA8.	Other Asian (NMO)	5	Pakistani
9SA9.	Irish (NMO)	0	White
9SAA.	Greek Cypriot (NMO)	8	Any other group
9SAB.	Turkish Cypriot (NMO)	8	Any other group
9SAC.	Other European (NMO)	8	Any other group
9SAD.	Other ethnic NEC (NMO)	8	Any other group
9SB..	Other ethnic / mixed origin	8	Any other group
9SB1.	Other ethnic / Black/White orig	8	Any other group
9SB2.	Other ethnic / Asian/White orig	8	Any other group
9SB3.	Other ethnic / mixed white orig	8	Any other group
9SB4.	Other ethnic / other mixed orig	8	Any other group

HES Post 2001 Ethnic Code	HES Post-2001 Ethnic Group	HES Pre 2001 Ethnic Code	HES Pre-2001 Ethnic Group
A	British (White)	0	White
B	Irish (White)	0	White
C	Any other White background	0	White
D	White and Black Caribbean (Mixed)	8	Any other group
E	White and Black African (Mixed)	8	Any other group
F	White and Asian (Mixed)	8	Any other group
G	Any other Mixed background	8	Any other group
H	Indian (Asian or Asian British)	4	Indian
J	Pakistani (Asian or Asian British)	5	Pakistani
K	Bangladeshi (Asian or Asian British)	6	Bangladeshi
L	Any other Asian background	8	Any other group
M	Caribbean (Black or Black British)	1	Black - Caribbean
N	African (Black or Black British)	2	Black - African
P	Any other Black background	3	Black - Other
R	Chinese (other ethnic group)	7	Chinese
S	Any other group	8	Any other group

Appendix 4b: UK Renal Registry Comorbid Conditions Mapped to ICD10 and OPCS codes

UKRR Comorbid Condition	ICD10 or *OPCS* code
Angina	I200, I201, I208, I209
Myocardial Infarction	I21X, I22X, I23X, I252 & I258
Coronary Artery Bypass Graft	*K401 – K 471, K483, K491 – K511, K75X*
Previous Heart Failure	I110, I119, I130, I132, I50X
Cerebrovascular Accident	G45X, G46X, I60X – I69X
Diabetes	E10X – E14X
COPD	J44X, J438 & J439
Liver Disease	K73X, K74X, K702, K703, K717, K766, K767, B16X, B170, B171, B180-B182
Claudication	I738 & I739
Vascular Angiogram / Angioplasty	*J104, J111, L134, L135, L261, L262, L311, L391, L416, L431, L471, L541, L631, L665, L694, L711, L972*
Vascular Stent	*J152, J152, L032, L136, L265-L267, L27X, L28X, L314, L435, L474, L544, L635, L662, L667, L695, L76X, L793, L804, L898, L899, O03X, O032, O20X*
Vascular Graft / Prosthesis	*J153, J233, J236, J291, L548, L549, L56X – L60X, L62X, L63X, L664, L683, L684*
Ulceration	R02X
Cancer	*C00 – C76, C97*

Appendix 4c: Mapping of ICD10 codes to Primary Renal Disease Codes

Glom	N036	Chronic nephritic syndrome dense deposit disease
Glom	N038	Chronic nephritic syndrome other
Pyelo	N119	Chronic tubulo-interstitial nephritis unspecified
Polyc	N281	Cyst of kidney acquired
Glom	N017	Diffuse concentric glomerulonephritis
Glom	N062	Diffuse membranous glomerulonephritis
Glom	N073	Diffuse mesangial proliferative glomerulonephritis
Glom	N025	Diffuse mesangiocapillary glomerulonephritis
Glom	N011	Focal and segmental glomerular lesions
OtherL	D593	Haemolytic-uraemic syndrome
OtherH	M310	Hypersensitivity angiitis
Diab	E100	Insulin-dependent diabetes mellitus with coma
Diab	E107	Insulin-dependent diabetes mellitus with multiple comps
Diab	E103	Insulin-dependent diabetes mellitus with ophthalmic comps
Diab	E106	Insulin-dependent diabetes mellitus with other spec comps
Diab	E105	Insulin-dependent diabetes mellitus with periph circ comps
Diab	E102	Insulin-dependent diabetes mellitus with renal complication
Diab	E108	Insulin-dependent diabetes mellitus with unspec comps
Diab	E109	Insulin-dependent diabetes mellitus without complications
OtherL	Q631	Lobulated fused and horseshoe kidney
OtherL	Q615	Medullary cystic kidney
OtherH	C900	Multiple myeloma
Glom	N041	Nephrotic syndrome focal and segmental glomerular lesions
Diab	E116	Non-insulin-depend diabetes mellitus with other spec comp
Diab	E115	Non-insulin-depend diabetes mellitus with periph circ comp
Diab	E119	Non-insulin-depend diabetes mellitus without complication
Diab	E110	Non-insulin-dependent diabetes mellitus with coma
Diab	E111	Non-insulin-dependent diabetes mellitus with ketoacidosis
Diab	E117	Non-insulin-dependent diabetes mellitus with multiple comps
Diab	E114	Non-insulin-dependent diabetes mellitus with neuro comps
Diab	E113	Non-insulin-dependent diabetes mellitus with ophthalm comps
Diab	E112	Non-insulin-dependent diabetes mellitus with renal comps
Diab	E118	Non-insulin-dependent diabetes mellitus with unspec comps
Pyelo	N110	Nonobstructive reflux-associated chronic pyelonephritis
Pyelo	N139	Obstructive and reflux uropathy unspecified
Glom	M308	Other conditions related to polyarteritis nodosa
Pyelo	N138	Other obstructive and reflux uropathy
Polyc	Q612	Polycystic kidney adult type
Polyc	Q611	Polycystic kidney infantile type
Polyc	Q613	Polycystic kidney unspecified
Glom	N019	Rapidly progressive nephritic syndrome unspecified
RVD	I150	Renovascular hypertension
OtherH	M321	Systemic lupus erythematosus with organ or sys involv
Diab	E143	Unspecified diabetes mellitus with ophthalmic complications
Diab	E146	Unspecified diabetes mellitus with other specified comps
Diab	E145	Unspecified diabetes mellitus with periph circulatory comps
Diab	E142	Unspecified diabetes mellitus with renal complications
OtherH	M313	Wegener's granulomatosis

Appendix 5a: Grouping Algorithm for Clinical Classification Scheme ICD10 Reason for Admission into Renal Reason For Admission

Step 1: Grouping using ICD10 CCS group:

Abdominal Pain	Abdominal pain(251), Biliary tract disease(149), Diverticulosis and diverticulitis(146), Liver disease; alcohol-related(150), Appendicitis and other appendiceal co(142)
Access	Complication of device; implant or gr(237)
Biochemical Derangement	Other endocrine disorders(51), Other nutritional; endocrine; and met(58), Other liver diseases(151), Pancreatic disorders (not diabetes)(152), Poisoning by other medications and dr(242), Coagulation and hemorrhagic disorders(62), Sickle cell anemia(61), Diseases of white blood cells(63), Poisoning by psychotropic agents(241), Hepatitis(6), Poisoning by nonmedicinal substances(243), Other hematologic conditions(64), Fluid and electrolyte disorders(55)
Bronchitis	Acute bronchitis(125), Other upper respiratory disease(134), Other lower respiratory disease(133), Chronic obstructive pulmonary disease(127), Asthma(128), Viral infection(7), Other upper respiratory infections(126)
Cancer	Multiple myeloma(40), Cancer of bladder(32), Secondary malignancies(42), Cancer of bronchus; lung(19), Cancer of kidney and renal pelvis(33), Cancer of prostate(29), Non-Hodgkin`s lymphoma(38), Cancer of colon(14), Leukemias(39), Neoplasms of unspecified nature or un(44), Other non-epithelial cancer of skin(23), Cancer of rectum and anus(15), Cancer of breast(24), Cancer of head and neck(11), Cancer of ovary(27), Malignant neoplasm without specification(43), Cancer; other and unspecified primary(41), Cancer of other GI organs; peritoneum(18), Cancer of stomach(13), Cancer of esophagus(12), Cancer of liver and intrahepatic bile(16), Cancer of brain and nervous system(35), Cancer of pancreas(17), Cancer of uterus(25), Melanomas of skin(22), Cancer of bone and connective tissue(21), Cancer of cervix(26), Cancer of testis(30), Cancer of thyroid(36), Cancer of other urinary organs(34)
Urinary Procedures	Rehabilitation care; fitting of prost(254), Calculus of urinary tract(160), Hyperplasia of prostate(164)
CKD / Dialysis Care	Residual codes; unclassified(259), Acute and unspecified renal failure(157), Nephritis; nephrosis; renal sclerosis(156), Deficiency and other anemia(59), Other connective tissue disease(211), Genitourinary congenital anomalies(215), Other diseases of kidney and ureters(161), Diabetes mellitus without complicatio(49), Other diseases of bladder and urethra(162), Systemic lupus erythematosus and conn(210), Essential hypertension(98), Other male genital disorders(166), Other female genital disorders(175), Other congenital anomalies(217), Rheumatoid arthritis and related dise(202)
Chest Pain	Nonspecific chest pain(102), Other and ill-defined heart disease(104)
Cerebrovascular Accident	Acute cerebrovascular disease(109)
Fracture or Trauma	Fracture of neck of femur (hip)(226), Spondylosis; intervertebral disc diso(205), Other non-traumatic joint disorders(204), Superficial injury; contusion(239), Osteoarthritis(203), Fracture of lower limb(230), Other fractures(231), Fracture of upper limb(229), Crushing injury or internal

	injury(234), Open wounds of head; neck; and trunk(235), Pathological fracture(207), Open wounds of extremities(236), Other bone disease and musculoskeleta(212), Other injuries and conditions due to(244), Joint disorders and dislocations; tra(225), Sprains and strains(232), Skull and face fractures(228)
Gastroenteritis	Noninfectious gastroenteritis(154), Nausea and vomiting(250), Other gastrointestinal disorders(155), Intestinal infection(135), Gastritis and duodenitis(140), Regional enteritis and ulcerative col(144)
Gastrointestinal Bleed	Gastrointestinal hemorrhage(153), Gastroduodenal ulcer (except hemorrha(139)
Hernia	Abdominal hernia(143)
Ischaemic Heart Disease	Coronary atherosclerosis and other he(101), Other circulatory disease(117), Acute myocardial infarction(100), Peripheral and visceral atheroscleros(114), Chronic ulcer of skin(199), Gangrene(248), Aortic; peripheral; and visceral arte(115), Transient cerebral ischemia(112), Cardiac arrest and ventricular fibril(107), Pulmonary heart disease(103), Other and ill-defined cerebrovascular(111), Varicose veins of lower extremity(119)
Low Risk Sepsis	Skin and subcutaneous tissue infectio(197), Fever of unknown origin(246), Infective arthritis and osteomyelitis(201), Phlebitis; thrombophlebitis and throm(118), Bacterial infection; unspecified site(3), Other inflammatory condition of skin(198), Lymphadenitis(247), Other infections; including parasitic(8), Influenza(123)
Neurological Disease	Epilepsy; convulsions(83), Other psychoses(71), Other nervous system disorders(95), Headache; including migraine(84), Senility and organic mental disorders(68), Paralysis(82), Other hereditary and degenerative ner(81), Coma; stupor; and brain damage(85), Intracranial injury(233), Affective disorders(69), Other mental conditions(74), Alcohol-related mental disorders(66), Other CNS infection and poliomyelitis(78), Parkinson`s disease(79), Nervous system congenital anomalies(216)
Overload	Congestive heart failure; nonhyperten(108), Peri-; endo-; and myocarditis; cardio(97), Heart valve disorders(96)
Peritonitis	Peritonitis and intestinal abscess(148)
Pneumonia	Respiratory failure; insufficiency; a(131), Aspiration pneumonitis; food/vomitus(129)
High Risk Sepsis	Pneumonia (except that caused by tube(122), Septicemia (except in labor)(2), Pleurisy; pneumothorax; pulmonary col(130), Aortic and peripheral arterial emboli(116), Tuberculosis(1), Mycoses(4), HIV infection(5), Encephalitis (except that caused by t(77), Meningitis (except that caused by tub(76), Shock(249)
Syncope	Cardiac dysrhythmias(106), Syncope(245), Conditions associated with dizziness(93), Conduction disorders(105)
Urinary Tract Infection	Urinary tract infections(159), Genitourinary symptoms and ill-define(163), Inflammatory conditions of male genit(165)

Step 2. Group CCS groups of 50 (Diabetes Mellitus with complications), 99 (Hypertension with complications) and 158 (Chronic Kidney Disease)

Access	Vascular Access for Renal Replacement Therapy with CC (QZ13A), Vascular Access for Renal Replacement Therapy without CC (QZ13B), Therapeutic Endovascular Procedures with Intermediate CC (QZ15B), Miscellaneous Vascular Procedures with CC (QZ05A), Miscellaneous Vascular Procedures without CC (QZ05B), Therapeutic Endovascular Procedures without CC (QZ15C)
Urinary Procedures	Catheter 19 years and over (EA36A)
CKD NOS	Chronic Kidney Disease with length of stay 1 day or less associated with Renal Dialysis (LA08E), Chronic Kidney Disease with length of stay 2 days or more with Intermediate CC (LA08B), Chronic Kidney Disease with length of stay 2 days or more without CC (LA08C), Chronic Kidney Disease with length of stay 1 day or less not associated with Renal Dialysis (LA08F), Chronic Kidney Disease with length of stay 2 days or more with Major CC (LA08A), (WA14Z), Renal Replacement Peritoneal Dialysis Associated Procedures with CC (LA05A), Renal Replacement Peritoneal Dialysis Associated Procedures without CC (LA05B), Data invalid for grouping (UZ01Z), Hypertension without CC (EB04I), General Renal Disorders with length of stay 2 days or more with Intermediate CC (LA09F)
Hernia	Inguinal Umbilical or Femoral Hernia Repairs 19 years and over with Intermediate CC (FZ18B)
High Risk Sepsis	Unspecified Acute Lower Respiratory Infection with Major CC (DZ22A), Septicaemia with Major CC (WA03V)
Transplantation	Kidney Transplants (LA02A, LA03A, LA01A) and multiple organ transplants (GA12Z)

Step 3.

Remaining ungrouped admissions into Misc group

Appendix 6a: Improvements in model performance in predicting admissions in the first year of haemodialysis. Root mean square error and observed / expected centiles

Model performance for all centres with sequential adjustment for demography and comorbidity

Model	RMSE	Centile of Patient Observed over Expected				
		20%	50%	75%	90%	95%
Negative Binomial (12m)						
Age & Sex	2.650	0.000	0.692	1.442	2.549	3.504
+ Ethnicity, SES & Year	2.640	0.000	0.708	1.451	2.554	3.557
+ Comorbidity	2.606	0.000	0.734	1.468	2.523	3.423
Zero Inflated Negative Binomial (3/9m)						
Age & Sex	2.570	0.000	0.759	1.532	2.525	3.329
+ Ethnicity, SES & Year	2.558	0.000	0.759	1.517	2.526	3.329
+ Comorbidity	2.520	0.000	0.777	1.517	2.499	3.276
Zero Inflated Negative Binomial (12m)						
Age & Sex	2.590	0.000	0.761	1.549	2.642	3.582
+ Ethnicity, SES & Year	2.579	0.000	0.766	1.545	2.648	3.600
+ Comorbidity	2.541	0.000	0.784	1.556	2.611	3.488

Model performance following the addition of late referral and primary renal disease in appropriate renal centres

Model	RMSE	Centile of Patient Observed over Expected				
		20%	50%	75%	90%	95%
Negative Binomial (12m)						
+ Comorbidity	2.461	0.000	0.748	1.485	2.511	3.343
+ Late Referral	2.458	0.000	0.737	1.485	2.518	3.387
+ Primary Renal Disease	2.451	0.000	0.730	1.489	2.524	3.439
Zero Inflated Negative Binomial (3/9m)						
+ Comorbidity	2.384	0.000	0.786	1.528	2.510	3.276
+ Late Referral	2.380	0.000	0.776	1.529	2.520	3.281
+ Primary Renal Disease	2.373	0.000	0.768	1.522	2.503	3.281
Zero Inflated Negative binomial (12m)						
+ Comorbidity	2.401	0.000	0.791	1.556	2.588	3.433
+ Late Referral	2.398	0.000	0.782	1.559	2.593	3.453
+ Primary Renal Disease	2.390	0.000	0.777	1.560	2.615	3.445

Appendix 6b: Influence of demography and laboratory values on mortality according to dialysis day of the week.

		Overall	**HD1**	**Rest of Week**	**Ratio**
Age at 1st RRT	<40	5.5 (4.3 - 7.1)	8.4 (4.6 - 14)	5.1 (3.8 - 6.7)	1.65 (0.91 - 2.98)
	40 - 65	12 (11 - 13.1)	13.9 (11 - 17.2)	11.7 (10.6 - 12.9)	1.18 (0.93 - 1.5)
	> 65	23.8 (22.6 - 25.2)	28.2 (24.6 - 32.2)	23.2 (21.8 - 24.6)	1.22 (1.05 - 1.41)
Age at analysis week	<40	5.1 (3.8 - 6.8)	9.8 (5.2 - 16.7)	4.4 (3.1 - 6.1)	**2.23 (1.18 - 4.21)**
	40 - 65	10.6 (9.5 - 11.7)	13.4 (10.4 - 16.9)	10.1 (9 - 11.3)	1.32 (1.02 - 1.71)
	> 65	23 (21.9 - 24.3)	26.3 (23.1 - 29.9)	22.6 (21.3 - 23.9)	1.17 (1.01 - 1.34)
Ethnicity	White	18.8 (17.9 - 19.7)	22.9 (20.3 - 25.7)	18.2 (17.3 - 19.2)	**1.26 (1.11 - 1.43)**
	Black	9.8 (7.6 - 12.5)	8.3 (3.6 - 16.4)	10.1 (7.7 - 13)	0.83 (0.4 - 1.73)
	South Asian	10.4 (8.2 - 13)	8.6 (4 - 16.4)	10.7 (8.3 - 13.6)	0.81 (0.4 - 1.62)
	Other	9.1 (6.8 - 12.1)	10.3 (4.4 - 20.2)	9 (6.5 - 12.1)	1.14 (0.54 - 2.43)
Time on RRT	< 1 Year	17.7 (16.2 - 19.2)	19.7 (15.7 - 24.3)	17.4 (15.8 - 19.1)	1.13 (0.9 - 1.43)
	> 1 Year	17.1 (16.2 - 18)	20.8 (18.2 - 23.7)	16.5 (15.6 - 17.5)	1.26 (1.09 - 1.45)
Angina	Absent	15.8 (14.9 - 16.6)	19.3 (16.9 - 21.9)	15.2 (14.3 - 16.2)	1.27 (1.1 - 1.46)
	Present	23.8 (21.9 - 26)	26.3 (20.9 - 32.6)	23.5 (21.4 - 25.8)	1.12 (0.88 - 1.41)
Myocardial Infarct	Absent	14.4 (13.6 - 15.2)	17.3 (15 - 19.7)	13.9 (13.1 - 14.8)	1.24 (1.07 - 1.44)
	Present	30.7 (28.3 - 33.2)	35.7 (29.2 - 43.3)	30 (27.4 - 32.6)	1.19 (0.97 - 1.47)
Heart Failure	Absent	13.3 (12.6 - 14.1)	15.8 (13.6 - 18.2)	12.9 (12.1 - 13.8)	1.22 (1.04 - 1.42)
	Present	33.5 (31.1 - 36)	40 (33.3 - 47.7)	32.5 (30 - 35.2)	1.23 (1.02 - 1.49)
Stroke	Absent	14.8 (14 - 15.6)	18.1 (15.9 - 20.5)	14.3 (13.4 - 15.1)	1.27 (1.1 - 1.46)
	Present	34.5 (31.6 - 37.7)	37.8 (29.9 - 47.2)	34.1 (30.9 - 37.5)	1.11 (0.87 - 1.41)
Diabetes	Absent	15.7 (14.8 - 16.7)	17.4 (14.9 - 20.2)	15.5 (14.5 - 16.5)	1.13 (0.96 - 1.32)
	Present	20.7 (19.2 - 22.2)	26.9 (22.7 - 31.7)	19.7 (18.2 - 21.3)	1.37 (1.14 - 1.64)
COPD	Absent	15.8 (15 - 16.6)	18.9 (16.7 - 21.3)	15.3 (14.5 - 16.1)	1.23 (1.08 - 1.41)
	Present	35.8 (32 - 39.9)	41.2 (30.9 - 53.9)	35 (30.9 - 39.4)	1.18 (0.88 - 1.58)
Arrhythmia	Absent	16.8 (16 - 17.6)	20.2 (17.9 - 22.7)	16.2 (15.4 - 17.1)	1.24 (1.09 - 1.41)
	Present	26.1 (22.7 - 30)	27.8 (18.9 - 39.4)	26 (22.2 - 30.1)	1.07 (0.73 - 1.57)
All Patients		17.3 (16.5 - 18.1)	20.5 (18.3 - 22.9)	16.8 (16 - 17.6)	1.22 (1.08 - 1.38)

	Group	Overall	HD1	Rest of Week	Ratio
URR	<=65	22 (20 - 24.3)	24.2 (18.6 - 30.8)	21.8 (19.5 - 24.2)	1.11 (0.85 - 1.45)
67.1% Complete	65.1 - 70	17.4 (15.4 - 19.5)	20.7 (15.3 - 27.5)	16.8 (14.8 - 19.1)	1.23 (0.9 - 1.68)
	70.1 - 75	14.8 (13.2 - 16.6)	19.3 (14.6 - 25.2)	14.1 (12.4 - 16)	1.37 (1.02 - 1.84)
	>75	15.3 (13.7 - 17)	18.3 (13.9 - 23.7)	14.8 (13.2 - 16.7)	1.23 (0.93 - 1.64)
Potassium	<4.0	21.8 (17.2 - 27.2)	27.8 (15.2 - 46.6)	20.8 (16 - 26.7)	1.33 (0.75 - 2.38)
10.3% Complete	4.0 - 4.5	20.4 (15.3 - 26.5)	20.8 (9 - 40.9)	20.3 (14.9 - 27.1)	1.02 (0.48 - 2.16)
	4.6 - 5.2	17.9 (13.7 - 22.9)	23.9 (12.3 - 41.7)	16.9 (12.6 - 22.3)	1.41 (0.75 - 2.65)
	>5.2	12.4 (8.5 - 17.4)	18.5 (7.4 - 38)	11.4 (7.5 - 16.7)	1.62 (0.7 - 3.72)
Haemoglobin	<10.5	26.7 (24.8 - 28.7)	27.4 (22.5 - 32.9)	26.7 (24.7 - 28.8)	1.03 (0.84 - 1.25)
85.3% Complete	10.5 - 12.5	15.3 (14.2 - 16.5)	20.5 (17.1 - 24.3)	14.5 (13.3 - 15.8)	1.41 (1.16 - 1.7)
	> 12.5	10.2 (8.8 - 11.7)	12.2 (8.5 - 17.1)	9.9 (8.4 - 11.5)	1.24 (0.85 - 1.79)
Albumin	< 33	34.9 (32.7 - 37.2)	41.5 (35.3 - 48.5)	33.9 (31.6 - 36.4)	1.22 (1.03 - 1.45)
85.3% Complete	33 - 37	15 (13.6 - 16.6)	13.8 (10.3 - 18.1)	15.3 (13.7 - 17)	0.9 (0.68 - 1.21)
	37.1 - 40	10 (8.7 - 11.5)	14.2 (10.2 - 19.2)	9.3 (7.9 - 10.9)	1.52 (1.08 - 2.14)
	> 40	6 (4.9 - 7.2)	9.2 (6 - 13.5)	5.4 (4.4 - 6.7)	1.7 (1.1 - 2.62)
Bicarbonate	< 21	16.8 (15.2 - 18.6)	20.1 (15.5 - 25.7)	16.3 (14.6 - 18.3)	1.23 (0.94 - 1.61)
79.8% Complete	21 - 24	15.7 (14.4 - 17.2)	18.3 (14.6 - 22.7)	15.3 (13.9 - 16.9)	1.19 (0.94 - 1.51)
	24.1 - 26	17.8 (16 - 19.9)	23.4 (17.9 - 30)	17 (15 - 19.1)	1.38 (1.04 - 1.82)
	>26	21.9 (19.6 - 24.3)	24.7 (18.5 - 32.2)	21.5 (19 - 24.1)	1.15 (0.86 - 1.54)
Pre-HD Systolic BP	< 129	28.4 (26 - 30.8)	34.7 (28.1 - 42.4)	27.4 (24.9 - 30)	1.27 (1.02 - 1.58)
66.4% Complete	129 - 145	16 (14.2 - 17.9)	22.3 (17 - 28.7)	15 (13.1 - 17)	1.49 (1.12 - 1.98)
	146 - 165	12.7 (11.2 - 14.3)	13.8 (10 - 18.7)	12.5 (10.9 - 14.2)	1.11 (0.8 - 1.54)
	> 165	14.4 (12.6 - 16.5)	16.6 (11.5 - 23)	14.1 (12.1 - 16.3)	1.17 (0.82 - 1.69)
Post-HD Systolic BP	< 129	19.8 (18.3 - 21.4)	24.8 (20.4 - 29.8)	19.1 (17.5 - 20.8)	1.3 (1.06 - 1.59)
59.9% Complete	129 - 145	15.6 (13.7 - 17.7)	20.9 (15.3 - 27.8)	14.8 (12.8 - 17)	1.41 (1.02 - 1.94)
	146 - 165	14.4 (12.4 - 16.7)	16.5 (11.2 - 23.6)	14.1 (12 - 16.6)	1.17 (0.79 - 1.73)
	> 165	17.9 (14.8 - 21.4)	22.3 (13.8 - 34.1)	17.2 (13.9 - 21)	1.3 (0.81 - 2.08)
Overall		17.3 (16.5 - 18.1)	20.5 (18.3 - 22.9)	16.8 (16 - 17.6)	1.22 (1.08 - 1.38)

Appendix 7a: ICD 10 Codes for Organisms in patients experiencing peritoneal dialysis peritonitis

ICD10 Code	Organism Name	Organism Group
A280	Pasteurellosis	Gram Neg
A400	Septicaemia due to streptococcus, group A	Strep
A401	Septicaemia due to streptococcus, group B	Strep
A408	Other streptococcal septicaemia	Strep
A409	Streptococcal septicaemia, unspecified	Strep
A410	Septicaemia due to Staphylococcus aureus	Staph (other)
A411	Septicaemia due to other specified staphylococcus	Staph (other)
A412	Septicaemia due to unspecified staphylococcus	Staph (other)
A414	Septicaemia due to anaerobes	Other
A415	Septicaemia due to other Gram-negative organisms	Gram Neg
A490	Staphylococcal infection, unspecified	Staph (other)
A491	Streptococcal infection, unspecified	Strep
A492	Haemophilus influenzae infection, unspecified	Gram Neg
B377	Candidal septicaemia	Fungal
B378	Candidiasis of other sites	Fungal
B379	Candidiasis, unspecified	Fungal
B389	Coccidioidomycosis, unspecified	Fungal
B449	Aspergillosis, unspecified	Fungal
B909	Sequelae of respiratory and unspecified tuberculosis	Other
B950	Strept group A as cause of dis classified to other chapters	Strep
B951	Strept group B as cause of dis classified to other chapters	Strep
B952	Strept group D as cause of dis classified to other chapters	Strep
B953	Strep pneumoniae as cause of dis classif other chapters	Strep
B954	Other strep as cause of dis classified to other chapters	Strep
B955	Unspec strep as cause of dis classified to other chapters	Strep
B956	Staph aureus as cause of dis classified to other chapters	Staph Aureus
B957	Other staph as cause of dis classified to other chapters	Staph (other)
B958	Unspec staphy as cause of dis classif to other chapters	Staph (other)
B961	Klebsiella pneumoniae as cause dis class other chaps	Gram Neg
B962	Escherichia coli as cause of dis classified to other chaps	Gram Neg
B963	Haemophilus influenzae as cause of dis class oth chaps	Gram Neg
B964	Proteus (mirabilis)(morganii)cause of dis class oth chaps	Gram Neg
B965	P.(aerugin)(mallei)(pseudomallei)caus dis class oth chap	Gram Neg
B966	Bacillus fragilis as cause of dis classified to other chaps	Gram Neg
B967	Clostridium perfringens as cause of dis class to oth chaps	Fungal
B971	Enterovirus as cause diseases classified to other chapt	Other

Appendix 7b: Improvements in model performance in predicting admissions in the first year of peritoneal dialysis. Root mean square error and observed / expected centiles

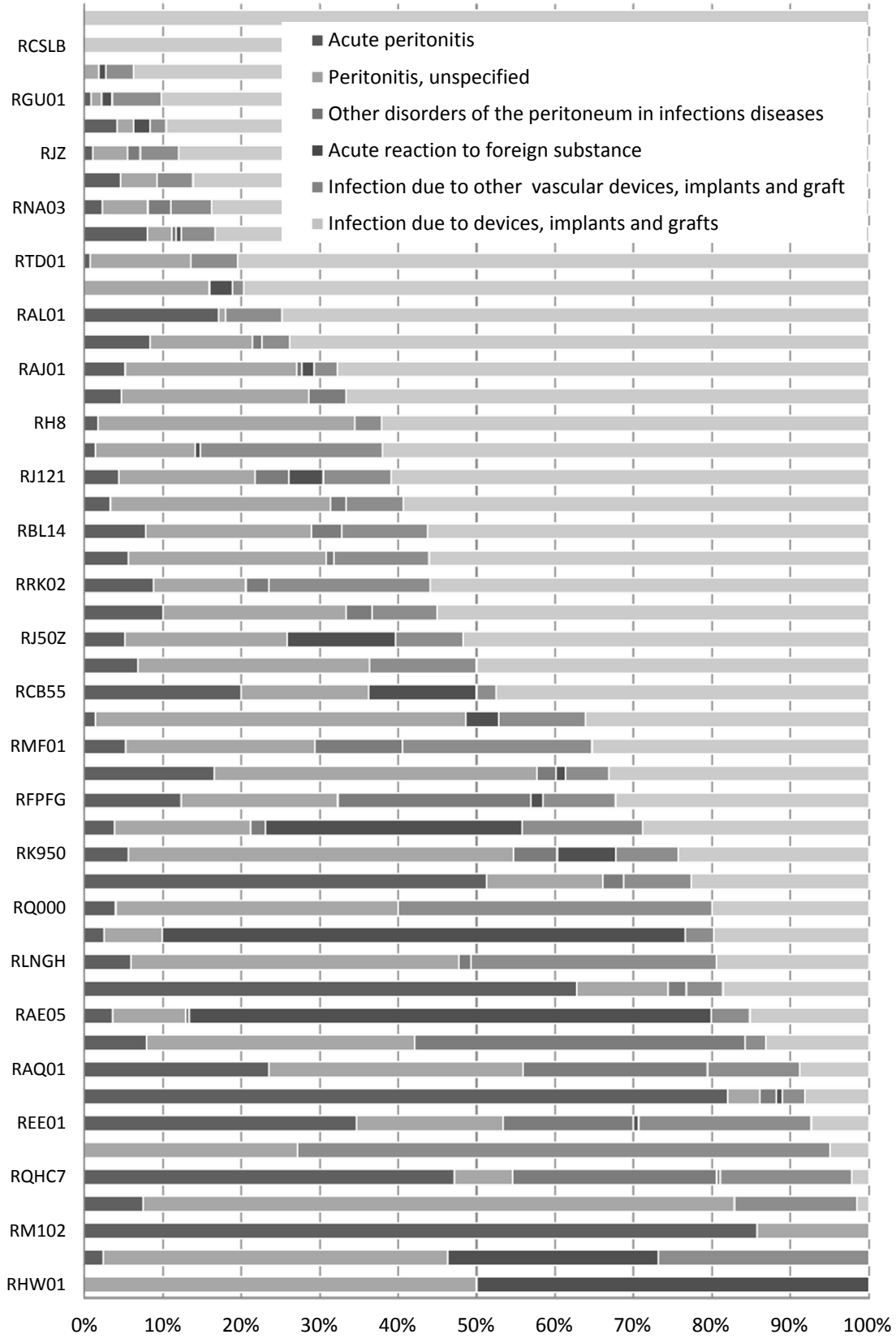
Model performance for all centres with sequential adjustment for demography and comorbidity

Model	RMSE	Centile of Patient Observed over Expected				
		20%	50%	75%	90%	95%
Negative Binomial (12m)						
Age & Sex	2.559	0.000	0.527	1.574	2.610	3.440
+ Ethnicity, SES & Year	2.556	0.000	0.568	1.481	2.552	3.454
+ Comorbidity	2.531	0.000	0.670	1.465	2.571	3.360
Zero Inflated (3/9m)						
Age & Sex	2.515	0.000	0.495	1.481	2.539	3.542
+ Ethnicity, SES & Year	2.511	0.000	0.536	1.423	2.596	3.526
+ Comorbidity	2.468	0.000	0.644	1.444	2.544	3.467
Zero Inflated Negative Binomial (12m)						
Age & Sex	2.526	0.000	0.527	1.575	2.647	3.566
+ Ethnicity, SES & Year	2.521	0.000	0.569	1.480	2.639	3.519
+ Comorbidity	2.479	0.000	0.667	1.492	2.611	3.444

Model performance following the addition of late referral and primary renal disease in appropriate renal centres

Model	RMSE	Centile of Patient Observed over Expected				
		20%	50%	75%	90%	95%
Negative Binomial (12m)						
+ Comorbidity	2.575	0.000	0.663	1.454	2.555	3.335
+ Late Referral	2.566	0.000	0.685	1.489	2.557	3.372
+ Primary Renal Disease	2.565	0.000	0.695	1.504	2.531	3.358
Zero Inflated Negative Binomial (3/9m)						
+ Comorbidity	2.510	0.000	0.638	1.452	2.532	3.462
+ Late Referral	2.501	0.000	0.665	1.472	2.549	3.412
+ Primary Renal Disease	2.498	0.000	0.666	1.478	2.546	3.425
Zero Inflated Negative Binomial (12m)						
+ Comorbidity	2.522	0.000	0.671	1.490	2.617	3.451
+ Late Referral	2.513	0.000	0.691	1.516	2.585	3.440
+ Primary Renal Disease	2.510	0.000	0.690	1.516	2.578	3.451

Appendix 7c: ICD 10 Codes employed by different centres to reflect an admission with PD peritonitis



Appendix 8a: Centre assignment for parent renal centre and NHS provider code

HES Procode	Trust Name	UKRR Centre	Centre Names	Centre City
RAE	Bradford Teaching Hospitals NHS Foundation Trust	RQ000	Leeds	Leeds
RCB	York Hospitals NHS Foundation Trust	RQ000	Leeds	Leeds
RCJ	South Tees Hospitals NHS Foundation Trust	RTD01	Freeman Hospital & Royal Victoria Infirmary	Newcastle-upon-Tyne
RCS	Nottingham University Hospitals NHS Trust	RCSLB	Nottingham City Hospital	Nottingham
RGM	Papworth Hospital NHS Foundation Trust	RGT01	Addenbrookes Hospital	Cambridge
RGT	Cambridge University Hospitals NHS Foundation Trust	RGT01	Addenbrookes Hospital	Cambridge
RHQ	Sheffield Teaching Hospitals NHS Foundation Trust	RK7CC	Northern General Hospital	Sheffield
RHU	Portsmouth Hospitals NHS Trust	RHU02	Queen Alexandra Hospital	Portsmouth
RJ1	Guy's And St Thomas' NHS Foundation Trust	RJ121	Guy's and St Thomas's Hospital	London
RJ5	Imperial College Healthcare NHS Trust	RJ50Z	London West	West London
RJ7	St George's Healthcare NHS Trust	RJ701	St George's Hospital	London
RJZ	King's College Hospital NHS Foundation Trust	RJ121	Guy's and St Thomas's Hospital	RAL01
RK9	Plymouth Hospitals NHS Trust	RK950	Derriford Hospital	Plymouth
RKB	University Hospitals Coventry And Warwickshire NHS Trust	RKB01	Walsgrave Hospital	Coventry
RM2	University Hospital Of South Manchester NHS Foundation Trust	RM574	Royal Infirmary Manchester	Manchester
RNJ	Barts And The London NHS Trust	RNJ00	Barts and the London Hospital	London
RNL	North Cumbria University Hospitals NHS Trust	RTD01	Freeman Hospital & Royal Victoria Infirmary	Newcastle-upon-Tyne
RQ6	Royal Liverpool And Broadgreen University Hospitals NHS Trus	RQ617	Royal Liverpool University Hospital	Liverpool
RQN	Imperial College Healthcare NHS Trust	RJ50Z	London West	West London
RR8	Leeds Teaching Hospitals NHS Trust	RQ000	Leeds	Leeds
RRK	X University Hospital Birmingham NHS Foundation Trust	RRK02	Queen Elizabeth Hospital	Birmingham
RTD	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	RTD01	Freeman Hospital & Royal Victoria Infirmary	Newcastle-upon-Tyne
RTH	Oxford Radcliffe Hospitals NHS Trust	RNX02	Oxford Radcliffe Hospital	Oxford
RTR	South Tees Hospitals NHS Foundation Trust	RTD01	Freeman Hospital & Royal Victoria Infirmary	Newcastle-upon-Tyne

HES Procode	Trust Name	UKRR Centre	Centre Names	Centre City
RVR	X Epsom And St Helier University Hospitals NHS Trust	RAZ	St Helier Hospital	Carshalton
RW3	X Central Manchester University Hospitals NHS Foundation Tru	RM574	Royal Infirmary Manchester	Manchester
RWA	Hull And East Yorkshire Hospitals NHS Trust	RQ000	Leeds	Leeds
RWE	University Hospitals Of Leicester NHS Trust	RFBAK	Leicester General Hospital	Leicester
RX1	Nottingham University Hospitals NHS Trust	RCSLB	Nottingham City Hospital	Nottingham
RYJ	Imperial College Healthcare NHS Trust	RJ50Z	London West	West London
RAL	Royal Free Hampstead NHS Trust	RAL01	Royal Free & Middlesex Hospital	London

Appendix 8b: ICD10 and OPCS codes for surgical complications

Description	Type	Group	OPCS / ICD10 (*)
Exploration of transplanted kidney	OPCS	Exploration	M084
Exploration of transplanted kidney	OPCS	Exploration	M084
Laparotomy approach NEC	OPCS	Exploration	Y502
Reopening of abdomen and re-exploration of intra-abdominal operation site and surgical arrest of postoperative bleeding	OPCS	Exploration	T301
Reopening of abdomen and re-exploration of intra-abdominal operation site NEC	OPCS	Exploration	T302
Reopening of abdomen NEC	OPCS	Exploration	T303
Unspecified opening of abdomen	OPCS	Exploration	T309
Excision of rejected transplanted kidney	OPCS	Nephrectomy	M026
Excision of rejected transplanted kidney	OPCS	Nephrectomy	M026
Nephrectomy NEC	OPCS	Nephrectomy	M025
Aspiration of haematoma of organ NOC	OPCS	NOS	Y221
Closure of colostomy	OPCS	NOS	H154
Closure of ileostomy	OPCS	NOS	G753
Drainage of kidney NEC	OPCS	NOS	M062
Emergency operations NOC	OPCS	NOS	Y701
Insertion of prosthesis into organ NOC	OPCS	NOS	Y022
Irrigation of organ NOC	OPCS	NOS	Y223
Other complications of procedures, not elsewhere classified	ICD10	NOS	T818 *
Other specified drainage of organ NOC	OPCS	NOS	Y228
Renewal of prosthesis in organ NOC	OPCS	NOS	Y032
Unspecified drainage of organ NOC	OPCS	NOS	Y229
Attention to nephrostomy tube NEC	OPCS	Ureteric	M064
Endoscopic insertion of tubal prosthesis into ureter NEC	OPCS	Ureteric	M292
Hydronephrosis with ureteral stricture NEC	ICD10	Ureteric	N131 *
Kinking and stricture of ureter without hydronephrosis	ICD10	Ureteric	N135 *
Mechanical complication of other urinary devices and implant	ICD10	Ureteric	T831 *
Nephroscopic insertion of tubal prosthesis into ureter	OPCS	Ureteric	M264
Nephrostomography	OPCS	Ureteric	M151
Other and unspecified hydronephrosis	ICD10	Ureteric	N133 *
Percutaneous insertion of nephrostomy tube	OPCS	Ureteric	M136
Percutaneous insertion of nephrostomy tube	OPCS	Ureteric	M136
Removal of nephrostomy tube	OPCS	Ureteric	M165
Unilateral replantation of ureter	OPCS	Ureteric	M202
Unspecified replantation of ureter	OPCS	Ureteric	M209

Description	Type	Group	OPCS / ICD10 (*)
Ischaemia and infarction of kidney	ICD10	Vasc	N280 *
Other specified transluminal operations on renal artery	OPCS	Vasc	L438
Percutaneous transluminal angioplasty of renal artery	OPCS	Vasc	L431
Percutaneous transluminal insertion of stent into renal artery	OPCS	Vasc	L435
Phlebitis/thrombophlebitis oth deep vessels low extremties	ICD10	VTE	I802 *
Pulmonary embolism without mention of acute cor pulmonale	ICD10	VTE	I269 *
Debridement of skin NEC	OPCS	Wound	S571
Disruption of operation wound, not elsewhere classified	ICD10	Wound	T813 *
Drainage of anterior abdominal wall	OPCS	Wound	T315
Dressing of skin using vacuum assisted closure device NEC	OPCS	Wound	S577
Excision of lymphocele	OPCS	Wound	T921
Open drainage of abdominal abscess NEC	OPCS	Wound	T343
Other specified drainage of lesion of lymph node	OPCS	Wound	T888
Other specified other operations on lymphatic tissue	OPCS	Wound	T928
Primary repair of incisional hernia using insert of prosthetic material	OPCS	Wound	T252
Repair of umbilical hernia using insert of prosthetic material	OPCS	Wound	T242
Repair of umbilical hernia using sutures	OPCS	Wound	T243
Unspecified primary repair of incisional hernia	OPCS	Wound	T259

Appendix 9: Research project outputs

Below are selected research outputs from this research project

Publications

Fotheringham J, Jacques R, Fogarty D, Tomson CRV, El Nahas M, Campbell M. Variation in centre-specific survival in patients starting renal replacement therapy in England is explained by enhanced comorbidity information from hospitalisation data. Nephrol. Dial. Transplant. (2013) doi: 10.1093/ndt/gft363

Fotheringham J, Fogarty D, Jacques R, El Nahas M and Campbell M. The linkage of incident renal replacement therapy patients in England (2002-2006) to hospital episodes and National Mortality Data: Improved demography and hospitalisation data in patients undergoing Renal Replacement Therapy. UKRR, 2011 Report/Nephron Clinical Practice

Presentations

Factors Influencing Hospital Admissions and Deaths over the two Day Gap in three times a week Hemodialysis. American Society of Nephrology Renal Week, Atlanta Nov 2013

Surgical complication rates in patients receiving kidney transplants in England; analysis by transplant centre using linked registry and hospitalisation data. British Transplant Society, Bournemouth – Awarded Medawar Medal March 2013

Length of stay and hospital admission rates in patients receiving kidney transplants in English centres using linked registry and hospitalisation data. Renal Association Meeting, Gateshead March 2013

Exploring hospitalisation events on RRT patients in the UK. Renal Association Meeting, Gateshead June 2012
Hospital associated mortality in incident renal replacement therapy patients in England 2002–2006: a performance indicator. Renal Association Meeting, Gateshead: Awarded Clinical Science Prize June 2012

Posters

Removing the two Day Gap in three times a week Hemodialysis: A Cost Effectiveness Model. American Society of Nephrology Renal Week, Atlanta Nov 2013

Hospitalisation for peritonitis in peritoneal dialysis patients starting Renal Replacement therapy in England between 2002 and 2006. Renal Association Meeting, Bournemouth – Awarded poster rosette March 2013

Using linked routine health data to improve survival and reduce hospitalisation in dialysis and kidney transplant patients. AMRC summer meeting, House of Commons

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