
Chapter 6

Comorbidities and Current Smoking Status amongst Patients starting Renal Replacement Therapy in England, Wales and Northern Ireland from 2003 to 2008: national and centre-specific analyses

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Key Words

Comorbidity · Diabetes · Dialysis · eGFR · Ethnicity · Haemoglobin · Mortality · Renal replacement therapy · Smoking · Transplant waiting list

Abstract

Introduction: The prevalence of comorbidities in incident renal replacement therapy (RRT) patients changes with age and varies between ethnic groups. This study describes these associations and the independent effect of comorbidities on outcomes. **Methods:** Adult patients starting RRT between 2003 and 2008 in centres reporting to the UK Renal Registry (UKRR) with data on comorbidity (n = 14,909) were included. The UKRR studied the association of comorbidity with patient demographics, treatment modality, haemoglobin, renal function at start of RRT and subsequent listing for kidney transplantation. The relationship between comorbidities and mortality at 90 days and one year after 90 days from start of RRT was explored

using Cox regression. **Results:** Completeness of comorbidity data was 40.0% compared with 54.3% in 2003. Of patients with data, 53.8% had one or more comorbidities. Diabetes mellitus and ischaemic heart disease were the most common conditions seen in 30.1% and 22.7% of patients respectively. Current smoking was recorded for 14.5% of incident RRT patients in the 6-year period. Comorbidities became more common with increasing age in all ethnic groups although the difference between the 65–74 and 75+ age groups was not significant. Within each age group, South Asians and Blacks had lower rates of comorbidity, despite higher rates of diabetes mellitus. In multivariate survival analysis, malignancy and ischaemic/neuropathic ulcers were the strongest independent predictors of poor survival at 1 year after 90 days from the start of RRT. **Conclusion:** Differences in prevalence of comorbid illnesses in incident RRT patients may reflect variation in access to health care or competing risk prior to commencing treatment. At the same time, smoking rates remained high in this 'at risk' population. Further work on this and ways to improve comorbidity reporting should be priorities for 2010–11.

Introduction

The importance of adjusting for comorbidity in centre [1, 2] and international survival comparisons [3] has long been recognised and evidence of its importance in anaemia [4], hospitalisation [5–7] healthcare costs [5] and quality of life [8] is emerging. As with all observational data, registry analyses for purposes of epidemiology, access to treatment or quality control, are open to a number of selection biases. Therefore, registry analyses can be significantly strengthened by adjustment for case mix, as differences in patient populations that exist across centres may affect process and outcome measures.

The aim of this chapter is to describe the prevalence of comorbid conditions and current smoking status in incident renal replacement therapy (RRT) patients reported to the UK Renal Registry (UKRR) and to examine the association between these comorbidities and early mortality.

The term established renal failure (ERF) used throughout this chapter is synonymous with the terms of end stage renal failure (ESRF) and end stage renal disease (ESRD), which are widely used internationally. Within the UK, patient groups have disliked the term ‘end stage’ due to its reference to the inevitable outcome of this disease.

Methods

Study population

Incident adult (≥ 18 years) RRT patients ($n = 32,356$) between 2003 and 2008 in the centres submitting data to the UKRR were considered. Of these, patients who had data on comorbidity were included ($n = 14,909$; 46.1%). Data on completeness of comorbidity returns from each centre and overall may differ from those in previous UKRR reports due to some centres retrospectively entering previously missing comorbidity data.

Centre exclusions

The nine centres in Scotland do not provide comorbidity data to the UKRR and are not included in these analyses. There was concern that data extraction in two centres (Stoke and Colchester) was inaccurate and these centres were excluded from this year’s analyses.

Definition of comorbidity and method of data collection

Clinical staff in each centre are responsible for recording (in yes/no format), on their renal information technology (IT) system, the presence or absence of 13 comorbid conditions and information on current tobacco smoking (table 6.1) for each patient at the time of starting RRT. Definitions of each of these conditions are given in appendix B. Patients were classified as

having complete comorbidity data if there was at least one entry (yes/no) for any one or more of the comorbid conditions. Comorbidities were grouped into broader categories for some analyses:

- ‘Ischaemic heart disease’ was defined as the presence of one or more of the following conditions: angina, myocardial infarction (MI) in the three months prior to starting RRT, MI more than three months prior to starting RRT or coronary artery bypass grafting (CABG)/angioplasty.
- ‘Peripheral vascular disease’ was defined as the presence of one or more of the following conditions: claudication, ischaemic or neuropathic ulcers, non-coronary angioplasty, vascular graft, aneurysm or amputation for peripheral vascular disease.
- ‘Non-coronary vascular disease’ was defined as the presence of cerebrovascular disease or any of the data items that comprise ‘peripheral vascular disease’.

Ethnicity data reporting

Some centres electronically upload ethnicity coding to their renal IT system from the hospital Patient Administration Systems (PAS) [9]. Ethnicity coding in PAS is based on self-reported ethnicity and uses a different system [10] to the remaining centres where ethnic coding is performed by clinical staff and recorded directly into the renal IT system (using a variety of coding systems). For all these analyses, data on ethnic origin were grouped into Whites, South Asians, Blacks and Others. Appendix G details the regrouping of the PAS codes into the above ethnic categories.

Statistical methods

The statistical methods for the four individual sections of this chapter are described separately. The number of patients with data

Table 6.1. Comorbid conditions listed in the UKRR dataset

Comorbidity
<ul style="list-style-type: none"> • Angina • Previous myocardial infarction (MI) within 3 months prior to start of RRT • Previous MI more than 3 months prior to start of RRT • Previous coronary artery bypass graft (CABG) or coronary angioplasty (in some analyses the above four variables are combined under the term ‘ischaemic heart disease’) • Cerebrovascular disease • Diabetes (when not listed as the primary renal disease) • Chronic obstructive pulmonary disease (COPD) • Liver disease • Claudication • Ischaemic or neuropathic ulcers • Non-coronary angioplasty, vascular graft, or aneurysm • Amputation for peripheral vascular disease (in some analyses these four variables are combined under the term ‘peripheral vascular disease’) • Smoking • Malignancy

on comorbidity and other variables included in the analyses are summarised in figure 6.1.

1) Patient demographics

The proportion of patients starting RRT with various comorbidities was examined by age group (18–34, 35–44, 45–54, 55–64, 65–74 and ≥ 75 years), primary renal disease, ethnic origin and first modality of RRT. Chi-squared, Fischer's exact and Kruskal Wallis tests were used as appropriate to test for significant differences between groups.

2) Late presentation (referral), haemoglobin (Hb) and renal function at start of RRT

Referral time was defined as the number of days between the date first seen by a nephrologist and the date of starting RRT. Referral times of more than 90 days and less than 90 days define early and late presentation, respectively. Data on referral time was incomplete and therefore only patients with data on comorbidity and referral time from centres with $>75\%$ data completeness for referral time were included in this analysis ($n = 6,714$; 20.8% of all patients starting RRT).

The association of various comorbidities with Hb concentration at start of RRT was studied amongst patients with comorbidity data and Hb data within 14 days before the start of RRT ($n = 9,447$; 29.2% of all patients starting RRT). Two-sample t-tests were used to compare the mean Hb at start of RRT amongst patients with each specific comorbidity with the mean for those with none of the comorbidities. As many tests were carried out, only p values <0.01 were considered statistically significant for these analyses.

The association of various comorbidities with estimated glomerular filtration rate (eGFR) at start of RRT was studied amongst patients with comorbidity data and eGFR data within 14 days before the start of RRT. The eGFR was calculated using the abbreviated 4 variable MDRD study equation [11]. For the purpose of eGFR calculation, patients who had missing ethnicity but a valid serum creatinine measurement were classed as White as the Black population only account for 6% of the total UK RRT population. The eGFR values were log transformed in order to normalise the data and then two-sample t-tests were used to compare the means of

the log eGFR of those patients with each specific comorbidity against those with none of the comorbidities present. As many statistical tests were carried out, only p values <0.01 were considered statistically significant for these analyses.

There is no defined eGFR at which patients should start RRT and a number of factors, including clinical presentation, symptoms, complications of uraemia and biochemistry, are used to determine dialysis initiation. However, there are defined eGFR thresholds for pre-emptive listing for a kidney transplant. The European Best Practice Guidelines (EBPG) recommend that patients with progressive irreversible deterioration in renal function and a creatinine clearance of $<15\text{ml/min/1.73 m}^2$ should be considered for pre-emptive transplantation; patients with ERF secondary to diabetes should be considered for early and pre-emptive transplantation when their eGFR decreases to $<20\text{ml/min/1.73 m}^2$ [12]. In the UK, the British Transplantation Society (www.bts.org.uk) endorse the EBPG and current UK Renal Association guidelines recommend that patients should be placed on the kidney transplant waiting list within six months of their anticipated dialysis start date [13]. There are no KDOQI guidelines for listing. It is therefore possible that patients could have started RRT with a transplant and an eGFR value as high as 20ml/min/1.73 m^2 .

For the eGFR analyses, 14,909 patients with comorbidity data were considered for inclusion. Patients with no eGFR data ($n = 2,632$) were excluded, as were those with no eGFR data in the 14 days preceding RRT ($n = 2,056$). Patients with an eGFR $>20\text{ml/min/1.73 m}^2$ ($n = 500$) were excluded from the eGFR analyses due to concerns about possible data extraction errors. Patients starting RRT between 2003 and 2005 from one centre (London West) were also excluded due to errors in the software data extraction process for this item ($n = 319$). This left 9,402 (29.1% of all patients starting RRT) eligible for analysis. Many UKRR analyses, including those presented here, rely on the accuracy of the date of start of RRT. A discussion of the issues around definition of the start date is included in chapter 13.

3) Activation on deceased donor kidney transplant waiting list

The association between comorbidity and activation on the

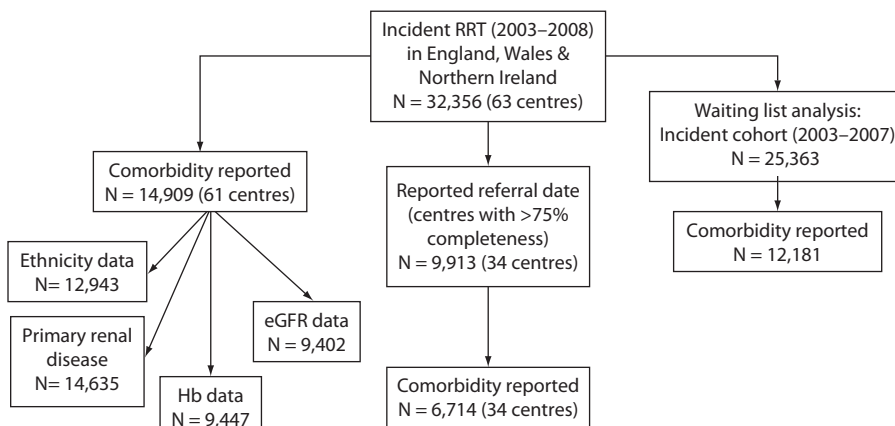


Fig. 6.1. Flow chart showing number of patients included in the various analyses

deceased donor kidney transplant waiting list within one year of starting treatment was examined ($n = 12,181$). In order to allow a year of follow up, incident patients in 2008 were not included. Date of first activation on the waiting list for all patients on the UKRR database starting RRT (HD or PD) between 2003 and 2007 were obtained from NHS Blood and Transplant, the organisation responsible for maintaining the national organ donor register. All patients were followed until 31st December 2008 to determine the date of activation on the waiting list. The prevalence of various comorbidities amongst patients activated on the waiting list within the first year of RRT was compared with those activated on the waiting list beyond the first year or not activated within the follow-up period. Patients who died within the first year and were not on the active waiting list at the time of death were included under the 'non-waitlisted' group.

4) Patient survival

The Registry collected data with a 'timeline' entry on all patients who had started RRT for ERF. Patients presenting acutely and initially classified as acute renal failure requiring dialysis who continued to require long-term dialysis, can be re-classified by clinicians as having had ERF from the date of their first RRT. The death rate is high in the first 90 days and variable between centres, due partly to individual clinical variation in the classification of patients with acute kidney injury who may be deemed from the start to be unlikely to recover renal function. To remove this centre variation and allow comparison with results from other national registries, the association of comorbid conditions and survival 1 year after 90 days from start of RRT was also analysed.

For each of the follow up periods, the association of baseline comorbidity with survival was studied using univariate and multivariate Cox regression models. For analyses of survival within the first 90 days, the cohort included patients starting RRT between 1st January 2003 and 30th September 2008 to allow a minimum of three months follow-up from the start of RRT. For the 1 year after 90 days survival analyses, the cohort included patients who survived at least 90 days on RRT and who started RRT between 1st January 2003 and 30th September 2007.

For each variable, the models were used to estimate the hazard ratio of death, comparing patients with a particular comorbidity with those who did not have the comorbidity. For both the univariate and multivariate Cox models, patients were first stratified by age group (<65 years and ≥ 65 years) to account for the increasing incidence of certain comorbidities with age, which may otherwise obscure the analyses. The multivariate models used an automatic selection procedure to identify the variables most strongly related to survival. The potential variables to be included were: age (per 10 year increase), angina, MI within 3 months prior to starting RRT, MI more than 3 months prior to starting RRT, coronary artery bypass grafting (CABG) or coronary angioplasty, cerebrovascular disease, diabetes mellitus (whether as a cause of primary renal disease or as a comorbidity), chronic obstructive pulmonary disease (COPD), liver disease, claudication, ischaemic/neuropathic ulcers, angioplasty/vascular graft, smoking and malignancy. The automatic procedure starts by including only the variable most strongly

related to survival. Then, with that variable included, it fits models adding each of the remaining variables in turn (singly) and chooses the variable that adds most to the model (in addition to the contribution made by the first variable included). The process continues in this way, adding variables that make a further significant contribution to the model, and removing any whose contribution becomes non-significant once other variables have been added. The final model only includes those variables selected by the process. These automatic methods have been used to give an indication of the variables most strongly related to survival but caution is needed in interpreting them because, amongst other things, when using correlated variables, a slight difference in the data (or in the algorithm chosen) could result in different variables being included in the final models. A better analysis would make a considered judgement of which variables should be included (rather than an automatic one) and would use interaction terms and/or adjustments other than age.

All statistical analyses were performed using SAS version 9.1.3.

Results

Completeness of comorbidity returns from each participating centre

Of the 6,107 patients commencing RRT in centres in England, Wales and Northern Ireland in 2008, comorbidity data were provided for 2,442 (40.0%) (tables 6.2 and 6.3). Table 6.2 highlights the continued wide variation in the completeness of data returns with 4 centres providing data on 100% of patients, but 19 centres providing data for less than 5% of their new patients in 2008.

Limiting the analysis to only the centres that reported in 2003, data completeness for comorbidity has fallen from 54.3% in 2003 to 43.8% in 2008. When centres with 0% completeness for comorbidity were excluded, the median percentage of comorbidity returns in 2008 was 52%.

Prevalence of multiple comorbidity

Including all incident patients from the years 2003–2008 ($n = 32,356$), comorbidity data were available for 14,909 (46.1%). More than half of these patients had one or more comorbidities (53.8%) (table 6.4) but in the subgroup of patients aged 65 years and over, 66.1% had one or more comorbidities (table 6.5).

Frequency of each comorbid condition

Table 6.5 lists the prevalence of specific comorbidities and the percentage this is of the total number of incident

Table 6.2. Completeness of comorbidity data returns on incident patients from individual centres (2003–2008)

Centre	2003		2004		2005		2006		2007		2008	
	N	% return	N	% return	N	% return	N	% return	N	% return	N	% return
Antrim					42	5	33	9	36	14	41	73
B Heart	103	0	102	0	116	1	115	0	101	1	108	0
B QEH			194	1	196	1	186	0	222	1	271	0
Bangor	33	48	36	64	40	55	42	60	36	64	42	57
Basldn	53	45	46	39	28	57	45	82	39	77	40	98
Belfast					130	15	112	14	89	28	68	46
Bradfd	74	85	62	92	66	95	50	100	87	99	59	92
Brightn			118	1	110	2	130	2	117	1	116	1
Bristol	163	87	163	80	175	81	176	97	154	84	181	62
Camb	94	1	107	1	110	1	156	1	125	0	102	1
Cardff	161	0	185	5	181	19	205	4	220	1	153	1
Carlis	31	29	29	79	32	94	27	93	26	92	31	97
Carsh	199	33	168	41	178	47	185	56	195	69	212	61
Chelms			49	47	37	49	48	83	51	55	33	79
Clwyd	11	0	14	0	27	4	18	0	23	4	13	0
Colchr											47	0
Covnt	75	1	76	0	83	0	102	2	110	0	113	0
Derby	60	75	67	82	71	92	70	89	61	98	92	91
Derry							3	67	7	43	6	67
Donc									18	94	25	28
Dorset	66	98	60	100	47	98	53	100	59	95	84	83
Dudley	41	0	54	0	38	0	44	2	39	0	49	0
Exeter	97	54	109	46	111	32	105	28	125	7	134	3
Glouc	53	87	54	89	60	97	73	88	58	95	45	91
Hull	80	90	108	86	126	98	100	96	99	98	117	83
Ipswi	37	43	45	47	58	31	42	62	39	49	38	34
Kent									172	5	132	29
L Barts			185	78	185	90	187	81	210	82	201	69
L Guys	93	3	100	4	128	6	132	3	162	6	169	1
L Kings	108	100	114	98	136	99	113	100	126	100	151	100
L Rfree					131	2	210	1	184	0	160	1
L St.G									89	64	89	57
L West	268	63	290	70	309	55	316	60	276	58	317	48
Leeds	185	86	178	82	161	71	172	73	125	74	155	65
Leic	167	96	162	94	226	64	242	66	244	72	215	73
Liv Ain			3	0	29	3	34	0	35	3	42	0
Liv RI	114	62	130	62	139	63	139	53	114	51	103	32
M Hope	143	33	111	42	112	35	130	12	107	8	112	1
M RI									155	23	136	34
Middlbr	103	99	101	91	84	90	109	70	99	55	93	81
Newc	109	5	114	1	101	2	85	1	107	2	101	2
Newry					28	14	13	23	15	27	20	100
Norwch			94	5	118	8	106	12	106	9	92	76
Nottm	115	98	107	95	145	99	137	98	128	94	117	44
Oxford	186	60	170	65	155	52	157	13	145	85	146	28
Plymth	64	28	62	44	58	47	91	63	76	74	70	31
Ports	140	64	117	68	151	62	174	63	157	64	169	34
Prestn	97	1	79	0	118	0	121	1	129	0	112	0
Redng	65	0	60	0	79	1	75	0	93	1	99	1
Sheff	159	65	167	59	157	41	168	58	166	55	180	45
Shrew			55	0	42	0	54	0	55	4	62	13
Stevng	123	7	83	7	92	9	121	7	88	22	101	39
Sthend	42	67	39	79	34	74	47	96	35	97	35	69

Table 6.2. Continued

Centre	2003		2004		2005		2006		2007		2008	
	N	% return	N	% return	N	% return	N	% return	N	% return	N	% return
Stoke									87	3	84	0
Sund	55	69	50	96	59	93	56	93	62	100	44	100
Swanse	134	97	95	93	98	97	115	97	128	98	120	86
Truro	53	83	67	81	32	88	50	78	46	91	39	36
Tyrone					23	30	30	50	22	41	25	52
Ulster					9	56	8	63	15	100	13	100
Wirral	52	13	66	14	59	7	53	0	53	0	41	5
Wolve	88	100	105	98	92	85	87	83	67	85	87	76
Wrexm	32	3	29	0	41	0	27	0	27	4	22	45
York	57	84	48	92	43	91	48	90	35	83	33	36
Totals	4,183		4,827		5,436		5,727		6,076		6,107	

Blank cells – no data returned to the UKRR for that year

Table 6.3. Summary of completeness of incident patient comorbidity returns (2003–2008)

	Years						Combined years
	2003	2004	2005	2006	2007	2008	
Number of renal centres included	43	50	56	57	62	63	
Total number of new patients	4,183	4,827	5,436	5,727	6,076	6,107	32,356
Number of patients with comorbid data entries	2,271	2,470	2,498	2,555	2,673	2,442	14,909
Percentage	54.3	51.2	46.0	44.6	44.0	40.0	46.1
Percentage restricted to centres reporting since 2003	54.3	55.6	51.6	50.0	51.4	43.8	51.0
Percentage with comorbidity returns							
Median percentage amongst only centres returning >0% comorbidity	63.7	67.5	52.3	62.5	56.6	52.0	60.2

patients for whom data was available for that item. Diabetes mellitus (either listed as cause of PRD or as a comorbidity) was present in 30.1% of all patients. Ischaemic heart disease, cerebrovascular disease and claudication were more prevalent in patients 65 years and over. Liver disease, ischaemic/neuropathic ulcers and prior amputation were more frequently observed in younger patients; actual percentages, nevertheless, were quite small (table 6.5). Smoking was also more common amongst patients under 65 years. This broad stratification is quite misleading however, as prevalence of comorbidities increased markedly from 18–65 years (figures 6.2 and 6.3).

Prevalence of comorbidity by age band

Figures 6.2 and 6.3 illustrate the increasing prevalence of comorbidity with increasing age up to the 65–74 year

age group in incident RRT patients. In those patients aged >75 years there was a levelling off or slight reduction of most reported comorbidities.

Prevalence of comorbidity by ethnic origin

Figure 6.4 illustrates the presence of comorbidity by ethnic origin, showing a higher prevalence of having at least one comorbidity amongst patients of White origin

Table 6.4. Number of reported comorbidities in patients starting RRT, as a percentage of those for whom comorbidity data were available (2003–2008)

Number of comorbidities	0	1	2	3	4	5+
Percentage	46.2	27.2	12.7	7.6	3.8	2.4

Table 6.5. Frequency with which each condition was reported in incident RRT patients 2003–2008

Comorbidity	Age <65 years		Age ≥65 years		p value*	% overall prevalence
	N	(%)	N	(%)		
Any comorbidity present	3,305	(42.5)	4,710	(66.1)	<0.0001	53.8
Angina	695	(9.0)	1,567	(22.2)	<0.0001	15.3
MI in past 3 months	127	(1.6)	264	(3.7)	<0.0001	2.6
MI > 3 months ago	506	(6.5)	1,125	(15.9)	<0.0001	11.0
CABG/angioplasty	408	(5.3)	694	(9.9)	<0.0001	7.5
Cerebrovascular disease	459	(5.9)	958	(13.5)	<0.0001	9.6
Diabetes (not listed as PRD)	387	(5.1)	791	(11.3)	<0.0001	8.1
Diabetes listed as PRD	1,955	(25.1)	1,321	(18.6)	<0.0001	22.0
COPD	312	(4.1)	689	(9.8)	<0.0001	6.8
Liver disease	252	(3.3)	130	(1.8)	<0.0001	2.6
Claudication	363	(4.7)	779	(11.0)	<0.0001	7.7
Ischaemic/neuropathic ulcers	282	(3.6)	190	(2.7)	0.0009	3.2
Angioplasty/vascular graft	140	(1.8)	362	(5.1)	<0.0001	3.4
Amputation	181	(2.3)	105	(1.5)	0.0002	1.9
Smoking	1,289	(17.0)	815	(11.9)	<0.0001	14.5
Malignancy	480	(6.2)	1,218	(17.2)	<0.0001	11.4

* p values from Chi-squared tests for differences between age groups in the percentage with the comorbidity

compared to the ethnic minority. At all ages, incident White RRT patients have more comorbidity than incident South Asian or Black patients (figure 6.5). This difference appears significant for Blacks at all ages above 18–34 (figure 6.5). This difference is attributable to lower rates of ischaemic heart disease, cerebrovascular disease, peripheral vascular disease and malignancy with lower rates of smoking but higher rates of diabetes mellitus (table 6.6). Despite rates of diabetes mellitus almost twice as high in South Asian patients (48.5%) compared to Whites (27.3%), ischaemic heart disease

rates are similar and cerebrovascular disease rates and peripheral vascular disease rates are slightly lower in South Asians (table 6.6).

Prevalence of comorbidity amongst patients with diabetes mellitus

Table 6.7 compares comorbidity amongst patients with and without diabetes (as either primary renal

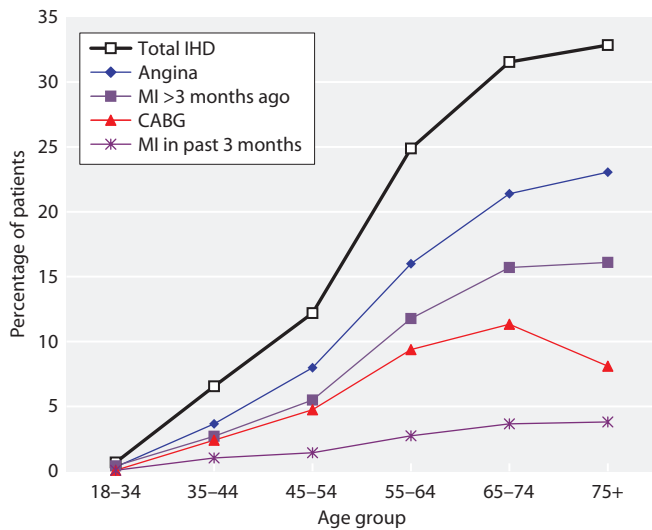


Fig. 6.2. Prevalence of ischaemic heart disease amongst incident patients 2003–2008 by age at start of RRT

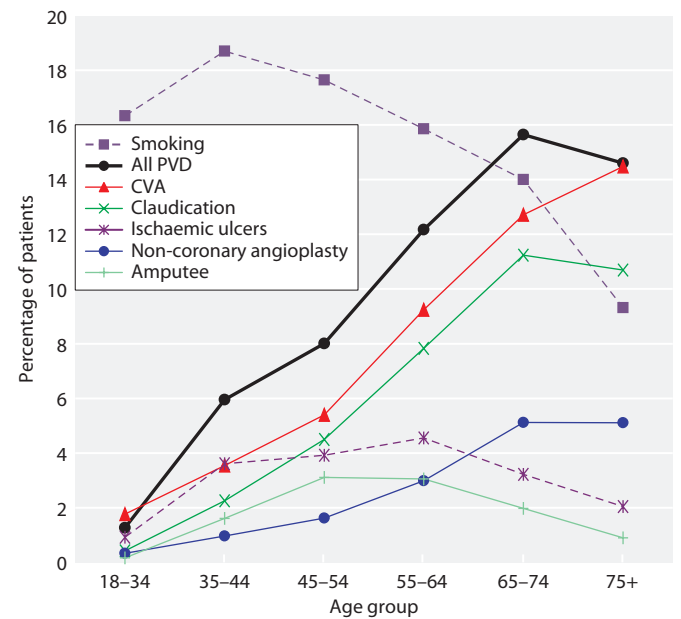


Fig. 6.3. Prevalence of non-coronary vascular disease amongst incident patients 2003–2008 by age at start of RRT

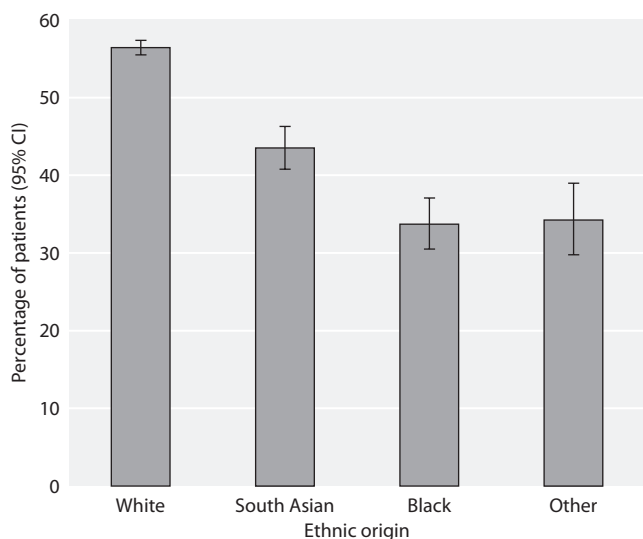


Fig. 6.4. Presence of comorbid conditions at the start of RRT by ethnic origin amongst patients starting RRT 2003–2008

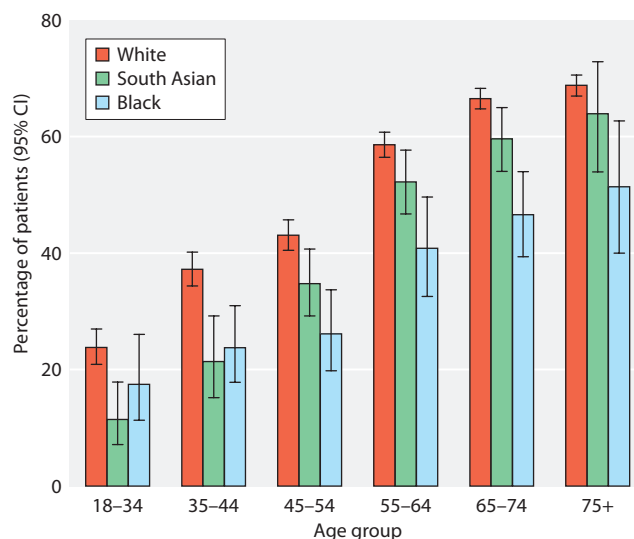


Fig. 6.5. Percentage of patients with comorbidity by ethnic origin in each age group at the start of RRT 2003–2008

Table 6.6. Prevalence of comorbidities amongst incident patients starting RRT 2003–2008 by ethnic group, as percentages of the total number of patients in that ethnic group for whom comorbidity data was available

	No. of patients (%) with comorbidity								
	White		South Asian		Black		Other		p value*
Ischaemic heart disease	2,453	(23.7)	307	(25.0)	77	(9.9)	46	(11.6)	
Cerebrovascular disease	1,029	(9.9)	106	(8.5)	67	(8.6)	25	(6.2)	0.03
Diabetes (not listed as PRD)	803	(7.8)	114	(9.4)	42	(5.4)	26	(6.5)	0.01
Diabetes listed as PRD	2,044	(19.5)	491	(39.1)	241	(30.5)	124	(30.5)	<0.0001
COPD	780	(7.5)	45	(3.7)	20	(2.6)	9	(2.3)	<0.0001
Liver disease	247	(2.4)	50	(4.0)	29	(3.7)	14	(3.5)	0.001
Peripheral vascular disease	1,298	(12.5)	97	(7.8)	38	(4.9)	28	(7.0)	<0.0001
Smoking	1,663	(16.3)	60	(5.0)	40	(5.2)	38	(10.0)	<0.0001
Malignancy	1,331	(12.7)	37	(3.0)	53	(6.8)	19	(4.7)	<0.0001

* p values from Chi-squared tests for differences between ethnic groups in the percentage with the comorbidities

Table 6.7. Number and percentage of patients with and without diabetes (either as primary diagnosis or comorbidity) who have other comorbid conditions

Comorbidity	Non-diabetic patients		Diabetic patients		p value*
	N	(%)	N	(%)	
Ischaemic heart disease	1,842	(18.3)	1,424	(32.4)	<0.0001
Cerebrovascular disease	795	(7.9)	591	(13.3)	<0.0001
COPD	697	(6.9)	283	(6.4)	0.3
Liver disease	240	(2.4)	130	(2.9)	0.1
Peripheral vascular disease	755	(7.5)	902	(20.4)	<0.0001
Smoking	1,438	(14.6)	610	(14.2)	0.5
Malignancy	1,320	(13.1)	317	(7.1)	<0.0001

* p values from Chi-squared tests for differences in the percentage with the comorbidities between diabetic patients and non-diabetic patients

Table 6.8. Percentage prevalence of specific comorbidities amongst patients presenting late (0–89 days) compared with those presenting early (>89 days)

Comorbidity	Late referral		Early referral		p value*
	N	(%)	N	(%)	
Ischaemic heart disease	371	(23.0)	1,235	(24.5)	0.2
Cerebrovascular disease	166	(10.2)	524	(10.3)	0.9
Diabetes (not listed as PRD)	132	(8.2)	438	(8.8)	0.5
COPD	112	(6.9)	341	(6.8)	0.8
Liver disease	47	(2.9)	116	(2.3)	0.2
Peripheral vascular disease	173	(10.7)	685	(13.5)	0.003
Malignancy	294	(18.1)	528	(10.4)	<0.0001
Smoking	265	(16.7)	768	(15.3)	0.2

* p values from Chi-squared tests for differences between referral groups in the percentage with the comorbidities

disease or comorbidity). As would be expected, patients with diabetes mellitus have higher rates of vascular disease (20.4% compared to 7.5% in non-diabetics). Similarly, ischaemic heart disease and cerebrovascular disease were more common in diabetics. Smoking at the time of initiation of RRT was similar for diabetics and non-diabetics (table 6.7).

Haemoglobin concentration at the time of starting RRT and comorbidity

The mean Hb prior to starting RRT in patients recorded as starting RRT without any comorbidity present was 10.3 g/dl compared to 10.2 g/dl for patients with one or more comorbidities. Of patients without any comorbidity, 57.1% achieved a Hb >10 g/dl compared to 53.4% with one or more comorbidities. Compared to those without any comorbidity, the mean Hb concentrations at the start of RRT were lower in patients with certain comorbidities, including malignancy (10.0 g/dl, $p = <0.0001$), a history of claudication (10.0 g/dl, $p = <0.0001$), ischaemic/neuropathic ulcers (9.8 g/dl, $p = <0.0001$) and amputation (9.8 g/dl, $p = 0.0002$). Although statistically significant, these Hb differences at initiation of RRT do not appear clinically significant.

Late presentation and comorbidity

Table 6.8 shows the referral time for patients with and without various comorbidities. Patients with peripheral vascular disease were more likely to be referred to a nephrologist early and patients with malignancy were more likely to be referred late. There was no association between time of presentation and any other comorbidity.

Renal function at the time of starting RRT and comorbidity

Table 6.9 shows the geometric mean eGFR prior to starting RRT in patients with each of the individual comorbidities. The (geometric) mean eGFR prior to starting RRT in patients who were recorded as starting without any comorbidity present was 7.6 ml/min/1.73 m². In each case, average eGFR was slightly higher amongst patients with comorbidity compared to patients without any comorbidity.

Age and comorbidity in patients by treatment modality at start of RRT

All comorbidities were more prevalent in patients receiving haemodialysis as their initial modality of treatment rather than peritoneal dialysis (table 6.10). This difference was statistically significant for all comorbid conditions other than previous CABG/coronary angioplasty. The median age of patients with comorbidity data starting RRT on HD was 66.0 years compared with 59.2 years for those starting PD (Kruskal Wallis test, $p < 0.0001$). For each of the comorbid conditions, the median age of patients on HD was higher than for patients on PD (table 6.10).

Comorbidity and subsequent activation on deceased donor transplant waiting list (TWL)

Table 6.11 shows that patients starting dialysis as their first RRT modality who were activated on the TWL within the first year, were younger and had significantly less comorbidity at the start of RRT than those who were not activated within the first year.

Table 6.9. eGFR within 2 weeks prior to the start of RRT by comorbidity 2003–2008

Comorbidity	eGFR geometric mean (ml/min/1.73 m ²)	eGFR 95% CI	p value*
No comorbidity present	7.6	7.5–7.7	Ref
Any comorbidity present	8.3	8.2–8.4	<0.0001
Angina	8.7	8.5–8.8	<0.0001
MI in past 3 months	8.8	8.4–9.2	<0.0001
MI >3 months ago	8.7	8.6–8.9	<0.0001
CABG/angioplasty	9.1	8.9–9.4	<0.0001
Cerebrovascular disease	8.6	8.4–8.8	<0.0001
Diabetes (not listed as PRD)	8.5	8.3–8.7	<0.0001
Diabetes listed as PRD	8.7	8.5–8.8	<0.0001
COPD	8.5	8.3–8.8	<0.0001
Liver disease	8.3	7.8–8.7	0.003
Claudication	8.8	8.5–9.0	<0.0001
Ischaemic/neuropathic ulcers	8.8	8.4–9.1	<0.0001
Angioplasty/vascular graft	8.6	8.3–9.0	<0.0001
Amputation	8.9	8.4–9.3	<0.0001
Smoking	8.2	8.0–8.4	<0.0001
Malignancy	7.9	7.7–8.1	0.002

* Two-sample t-tests compare log(eGFR) for each comorbidity against those without comorbidity

Comorbidity and survival within 90 days of starting RRT

On univariate analysis stratified for age, most comorbidity was associated with an increased risk of death in the first 90 days when compared with a patient in the same age group without that comorbidity. This was true amongst patients aged <65 years and those aged ≥65 years, the associations being more profound for those aged <65 years (data not shown). Multivariable

stepwise Cox regression analyses stratified by age group (<65 and ≥65) are shown in tables 6.12 and 6.13. As identified in the univariate models, comorbidities in younger patients were more indicative of early death than when present in older patients. Diabetes did not emerge as an independent predictor of death, probably due to its close association with ischaemic heart disease and peripheral vascular disease. Some comorbidities may appear not to be associated with an increased risk

Table 6.10. Number (and percentage) of incident patients with comorbid conditions starting PD and HD 2003–2008

Comorbidity	HD			PD			p value*
	N	(%)	Median age	N	(%)	Median age	
Angina	1,845	(16.9)	71.3	405	(11.6)	68.5	<0.0001
MI in past 3 months	339	(3.1)	70.7	51	(1.5)	69.1	<0.0001
MI >3 months ago	1,304	(11.9)	70.8	319	(9.1)	69.0	<0.0001
CABG/angioplasty	837	(7.7)	69.0	255	(7.3)	67.9	0.4
Cerebrovascular disease	1,177	(10.8)	71.1	230	(6.6)	66.4	<0.0001
Diabetes (not listed as PRD)	977	(9.1)	70.9	192	(5.5)	68.3	<0.0001
COPD	855	(7.9)	70.8	142	(4.1)	67.3	<0.0001
Liver disease	329	(3.0)	60.0	48	(1.4)	57.4	<0.0001
Claudication	957	(8.7)	70.6	180	(5.1)	67.5	<0.0001
Ischaemic/neuropathic ulcers	410	(3.7)	62.6	60	(1.7)	56.7	<0.0001
Angioplasty/vascular graft	411	(3.8)	71.4	90	(2.6)	70.1	0.001
Amputation	248	(2.3)	61.3	36	(1.0)	59.5	<0.0001
Smoking	1,629	(15.3)	61.2	441	(12.9)	55.3	0.001
Malignancy	1,457	(13.3)	72.0	232	(6.6)	70.1	<0.0001

* p values from Chi-squared tests for differences between modalities in the percentage with the comorbidities

Table 6.11. Number (and percentage) of incident dialysis patients with comorbid conditions who were activated on the transplant waiting list within one year of starting treatment compared to those patients who were not activated within one year of initiating RRT

Comorbidity	Not activated on waiting list in first year			Activated on waiting list in first year			p value*
	N	(%)	Median age	N	(%)	Median age	
Angina	1,849	(18.8)	71.3	86	(3.8)	57.9	<0.0001
MI in past 3 months	312	(3.2)	70.9	11	(0.5)	55.0	<0.0001
MI >3 months ago	1,287	(13.1)	71.0	48	(2.1)	58.9	<0.0001
CABG/angioplasty	818	(8.4)	69.3	57	(2.6)	58.4	<0.0001
Cerebrovascular disease	1,115	(11.3)	71.2	74	(3.3)	58.2	<0.0001
Diabetes (not cause of ERF)	895	(9.2)	71.1	65	(2.9)	54.6	<0.0001
COPD	773	(7.9)	71.1	51	(2.3)	57.9	<0.0001
Liver disease	270	(2.7)	60.1	37	(1.6)	54.6	0.002
Claudication	931	(9.4)	70.5	24	(1.1)	49.6	<0.0001
Ischaemic/neuropathic ulcers	373	(3.8)	63.4	24	(1.1)	45.1	<0.0001
Angioplasty/vascular graft	407	(4.1)	71.3	11	(0.5)	57.7	<0.0001
Amputation	218	(2.2)	61.3	13	(0.6)	52.0	<0.0001
Smoking	1,473	(15.4)	63.6	308	(13.8)	46.5	0.06
Malignancy	1,360	(13.8)	72.0	45	(2.0)	58.7	<0.0001

* p values from Chi-squared tests for differences between transplant waiting list groups in the percentage with the comorbidities

Table 6.12. Multivariate Cox proportional hazards model* for predictors of death within the first 90 days of starting RRT during 01/01/2003–30/09/2008: patients aged <65 years

Comorbidity	Hazard ratio	95% CI	p value
Malignancy	5.4	3.6–8.2	<0.0001
Liver disease	4.6	2.6–7.9	<0.0001
Amputation	4.4	2.3–8.3	<0.0001
Angina	2.1	1.3–3.3	0.001
Age (per 10 yrs)	1.5	1.2–1.9	<0.0001

* This is the result of a stepwise procedure. The variables considered in the model were: age (in 10 year units) and the 14 comorbidity variables except that 'diabetes (not listed as PRD)' and 'diabetes listed as PRD' were replaced by 'Diabetes of either category'.

Table 6.13. Multivariate Cox proportional hazards model* for predictors of death within the first 90 days of starting RRT during 01/01/2003–30/09/2008: patients aged ≥65 years

Comorbidity	Hazard ratio	95% CI	p value
Ischaemic/neuropathic ulcers	2.4	1.6–3.5	<0.0001
MI in past 3 months	2.1	1.5–2.9	<0.0001
COPD	1.6	1.2–2.0	0.001
Age (per 10 yrs)	1.6	1.3–1.8	<0.0001
Angina	1.4	1.2–1.8	0.001
MI >3 months ago	1.4	1.1–1.8	0.004
Malignancy	1.4	1.1–1.8	0.003

* This is the result of a stepwise procedure. The variables considered in the model were: age (in 10 year units) and the 14 comorbidity variables except that 'diabetes (not listed as PRD)' and 'diabetes listed as PRD' were replaced by 'Diabetes of either category'.

of death partly because of the low number of patients in these groups and partly because those who had severe disease and were thought likely not to survive 90 days, may not be started on RRT (for instance, liver disease in those aged ≥65 years).

Comorbidity and survival 1 year after 90 days of commencing RRT

Age and five comorbidities were independently associated with an increased hazard of death within the first year after 90 days for patients aged <65 years and 5 of these were among the 9 variables independently associated with mortality beyond day 90 in patients ≥65 years (tables 6.14 and 6.15). Although diabetes

Table 6.14. Multivariate Cox proportional hazards model* for predictors of death in the year after the first 90 days of starting RRT during 01/01/2003–30/09/2007: patients aged <65 years

Comorbidity	Hazard ratio	95% CI	p value
Malignancy	4.0	3.0–5.4	<0.0001
Ischaemic/neuropathic ulcers	2.5	1.7–3.7	<0.0001
Liver disease	2.2	1.4–3.4	0.0003
Diabetes of either category	1.8	1.4–2.3	<0.0001
Angina	1.4	1.0–1.9	0.03
Age (per 10 yrs)	1.3	1.2–1.5	<0.0001

* This is the result of a stepwise procedure. The variables considered in the model were: age (in 10 year units) and the 14 comorbidity variables except that 'diabetes (not listed as PRD)' and 'diabetes listed as PRD' were replaced by 'Diabetes of either category'.

Table 6.15. Multivariate Cox proportional hazards model* for predictors of death in the year after the first 90 days of starting RRT during 01/01/2003–30/09/2007: patients aged ≥ 65 years

Comorbidity	Hazard ratio	95% CI	p value
Liver disease	2.1	1.4–3.1	0.0003
Amputation	1.9	1.1–3.2	0.021
Malignancy	1.8	1.5–2.1	<0.0001
Age (per 10 yrs)	1.8	1.6–2.0	<0.0001
Ischaemic/neuropathic ulcers	1.6	1.1–2.4	0.011
Angina	1.5	1.3–1.7	<0.0001
COPD	1.3	1.1–1.7	0.008
Cerebrovascular disease	1.3	1.1–1.5	0.012
Smoking	1.2	1.0–1.5	0.048

* This is the result of a stepwise procedure. The variables considered in the model were: age (in 10 year units) and the 14 comorbidity variables except that ‘diabetes (not listed as PRD)’ and ‘diabetes listed as PRD’ were replaced by ‘Diabetes of either category’.

mellitus is independently associated with increased mortality in patients <65 years but not in those aged ≥ 65 years, the opposite was true for smoking (tables 6.14 and 6.15).

Discussion

Comorbidity data completeness has been a cause for concern since they were first reported by the UKRR in 1999 [14]. Worryingly, rates of completeness are decreasing not increasing and the current rate of 40% in the UK compares with rates of 85% in Canada, 95–100% in Australia and New Zealand and 100% in the USA. However for the latter, the USRDS has a ‘tick if present’ policy, therefore no tick is interpreted as no comorbidity but could also represent missing data. Some work has recently been undertaken to learn from experience in these countries [15]. Completeness should improve in the future through a combination of linkage with other secondary data sources (e.g. Hospital Episode Statistics Dataset), statistical imputation techniques and local governance pressures now that comorbidity items form part of the National Renal Dataset. Caution must be taken in interpreting the influence of comorbidity – in at least one study patients with comorbidity recorded have significantly better health outcomes than those with missing comorbidity [16] so the generalisation of findings from this selected group of patients cannot therefore be assumed.

There are two recent reports that highlight the relative contribution of comorbidity to survival analyses in renal replacement patients. Van Manen and colleagues studied

the role of comorbidity on survival in over 15,000 incident RRT patients from five European countries [17]. The addition of five comorbidities (diabetes mellitus, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease and malignancy) explained only an additional 1.9% of the variance in survival on top of the 14.4% explained by age, gender, PRD, treatment modality and country. In the DOPPS study, 45 comorbidities were systematically recorded for over 15,000 prevalent HD patients and their relative contribution to survival over 3 years explored [18]. Total R^2 increased from 0.13 to 0.17 upon the addition of the most significant 17 conditions, in addition to demographic (age, gender, race), clinical (systolic blood pressure, body mass index) and laboratory (Hb, albumin, phosphate) variables. These studies highlight that our routinely measured variables at present do not offer good prediction of survival. The need for more complete and perhaps novel comorbidity data goes beyond its role in survival analyses as comorbidity is clearly relevant to patients’ quality of life, the daily running of haemodialysis units and performance in other areas such as access to transplantation and achievement of permanent vascular access.

An alternative approach to case-mix adjustment for variations between centres in outcomes would be to use information on the levels of comorbidity or life expectancy in the general population served by a renal centre, given that most renal centres in the UK have relatively well-defined catchment areas. Such an approach has been suggested for analyses comparing different regions or countries [19, 20]. However, adjustment for general population mortality as well as individual patient comorbidity might risk over-adjustment and the catchment areas of many centres would not show uniform levels of general population life expectancy.

In the general population, the prevalence of cardiovascular disease increases exponentially with age, up to and beyond 75 years of age [21]. This appears at odds with the prevalence of cardiovascular disease in incident RRT patients, which increases only modestly beyond 65–74 years of age (figure 6.2). In early reports from the UKRR, the prevalence of cardiovascular disease was lower in incident RRT patients aged 75+ compared to those aged 65–74 [22]. One explanation for this paradox is competing risk: poorer cardiovascular outcomes are observed in patients with chronic kidney disease [23, 24], which may in part reflect lower use of medical therapies that are of proven benefit [25]. Alternatively, older patients with cardiovascular disease may be less

likely to be referred to a nephrologist for consideration of RRT [26, 27] (though this may have become less true in recent years [28]) or consider the benefits of dialysis over supportive care less convincing [29].

Another initially paradoxical observation is the lower (or equivalent) rate of vascular disease in South Asians and Blacks despite higher rates of diabetes mellitus. Rates of diabetes mellitus in ethnic groups commencing RRT in the UK are consistent with general population rates: in the English general population, compared to Whites, the age-adjusted risk ratios for diabetes mellitus range from 2.5 for Black Caribbean males to more than 5.0 for South Asians [30]. Considering the same general population health survey data, age-adjusted risk ratios of cardiovascular disease are only significantly higher for Pakistani and Bangladeshi males and females and Black Caribbean females (risk ratios 1.4–1.7) [30] and mortality from ischaemic heart disease has been observed to be lower for Blacks in the UK than Whites [31]. It is also important to remember that the UKRR diabetes mellitus and cardiovascular disease rates are not age-adjusted and the age profile of the Black and South Asian population in the UK also differs considerably from that of the White population. Sixteen percent of Whites are aged >65 compared with 6% of Blacks and 4% of South Asians [32], with incident non-White RRT patients being significantly younger than their White counterparts [33].

In these analyses, patients with comorbidity started RRT at a higher eGFR than patients with no reported comorbidity. This may suggest physicians advise patients with a higher comorbidity burden to start dialysis earlier or that these patients become symptomatic from their ERF earlier than patients with no comorbidity. Current evidence is conflicting as to whether starting dialysis at a higher eGFR is associated with better survival [34, 35] or poorer outcomes [36, 37]. It may be that improved survival associated with earlier start is just a reflection of lead time bias [38]. Further, this analysis is open to potential bias due to variability in the recording of 'RRT start date'.

The lower Hb concentrations at start of RRT associated with peripheral vascular disease and malignancies could be due to diminished erythropoietin (EPO) responsiveness or varying centre prescribing patterns for EPO amongst patients with these comorbidities. The lower Hb concentration associated with peripheral vascular disease does not seem to be explained by late referral or presentation, as these patients were referred earlier compared to those without this comorbidity.

Patients who started HD were older and had more comorbidity compared to those starting PD. These findings probably reflect a perception amongst UK healthcare practitioners and patients that PD is in general more suitable for younger and fitter patients. In addition, the presence of certain comorbid conditions such as cerebrovascular disease, liver disease and COPD can adversely affect the ability of patients to perform PD exchanges or to tolerate large volumes of dialysate in the peritoneum and hence influence the choice of HD in these patients. Some centres in the UK are starting to provide assisted PD (by a carer) which may alter the distribution of treatment modalities in the future.

The proportion of patients activated on the deceased donor transplant waiting list is much less amongst those with comorbidity compared to those without. Hence, when time taken to activate patients on the transplant waiting list is used as a marker of quality of care provided by the centres, adjustments for differences in comorbidity should be made for meaningful comparisons of the performance of each centre in listing patients for a transplant.

There are important and at times counter-intuitive associations between comorbidity and outcomes in RRT patients with differences between ethnic groups requiring further study. Individual comorbidity items are each associated with significant hazards of death and adjusting for this in centre (and international) comparisons must remain a priority.

Caution must also be taken when interpreting the results of the multivariate survival analyses in which smoking and diabetes are included alongside comorbidities which lie in the causal pathway (such as vascular disease); adjusting for the vascular disease that has been, in part, caused by the smoking or diabetes will attenuate the association between these variables and survival. The absence of an independent significant association between smoking and survival (for example) should not be interpreted as meaning that smoking does not increase a dialysis patient's risk of death. Indeed the observation that almost 15% of new RRT patients start dialysis as smokers is a major concern given the well recognised excess cardiovascular risk that dialysis patients have compared to those without CKD. Although this figure is slowly reducing perhaps it is time to better promote smoking cessation policies and guidance in CKD clinics and renal centres across the UK.

Conflict of interest: none

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