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Epidemiology of end-stage renal disease

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Definition

End-stage renal disease (ESRD) is the irreversible deterioration of renal function to an extent that is incompatible with life without renal replacement therapy (RRT), either by dialysis or transplantation. It is the end result of progressive chronic renal failure (CRF) (Table 1). The most valid measure of renal function is the glomerular filtration rate (GFR), but this can be measured only by complex clearance studies (eg inulin). The clearance of the muscle breakdown product creatinine can be used, but at low levels of GFR this overestimates GFR because of tubular secretion of creatinine and extrarenal secretion into the gut. In practice, ESRD is usually taken as a creatinine clearance of below 10 ml/min. Plasma creatinine above 500 μmol/l is a rough guide to ESRD. Several factors influence creatinine production and clearance such as age, sex, weight, ethnic origin and muscle mass.

A lower level of plasma creatinine will be compatible with ESRD in patients with low body weight (eg malnourished or small Indo-Asian women). Simple formulae (eg Cockroft and Gault[1]) use age, sex, weight and plasma creatinine to correct for this and to estimate GFR. These formulae are useful in clinical practice, but most epidemiological studies of CRF/ESRD have relied only on plasma creatinine. In clinical practice, the plot of serial reciprocal measures of plasma creatinine in an individual is a good indication of the rate of decline in GFR.

The epidemiology of ESRD is important as it determines the need for RRT, a complex, costly and lifelong package of care for which demand and provision have grown significantly in the last decade. One year of dialysis costs about £25,000, the first year of transplantation £15,000, with subsequent years over £5,000. It has been estimated that RRT costs consume 1.5–2% of the NHS budget, a figure that is predicted to rise to at least 3%[2].

Sources of information

The incidence of 'diagnosed' CRF in the population has been investigated using raised serum creatinine concentration results from chemical pathology laboratories. This is a specific, though insensitive, marker and is widely used in routine clinical practice. Such population studies of laboratory results are more likely to be representative than nephrology clinic studies where selection factors apply[4], although they exclude a proportion of people with CRF, for example those who are asymptomatic

Table 1. UK Registry definition of end-stage renal disease (ESRD).

A new patient with ESRD is defined as:

- one who is accepted for treatment and transplanted or dialysed for more than 90 days *or*
- one who is diagnosed as ESRD (ie accepted for dialysis in the anticipation that they will need RRT indefinitely), dialysed, and who dies within 90 days *or*
- one who is dialysed initially for ARF but who is subsequently diagnosed as having ESRD
- This excludes patients who were thought to have ESRD and started RRT in the expectation that this would continue indefinitely, but who subsequently recovered within 90 days and were therefore classified in retrospect as having had ARF

ARF = acute renal failure; RRT = renal replacement therapy.

and have not had a urea and electrolyte test, and high-risk groups such as diabetics who have not had regular blood tests[3]. Acceptance rates for RRT (ie new cases started per year per million population (pmp)) have been used as an indirect measure of the incidence of ESRD, but they are also influenced by levels of detection, referral and acceptance on to RRT. Mortality data are unreliable because of significant underascertainment of renal disease on death certificates[5]. Moreover, International Classification of Diseases coding does not reliably distinguish between acute and chronic forms of renal failure and lacks precision. Hospital episode statistics data are an invalid measure of incidence or prevalence because they relate only to known treated inpatient cases and because most RRT is delivered to outpatients or to patients at home.

Key Points

- Chronic renal failure (CRF) is not uncommon in the population
- The incidence of CRF rises with age and is commoner in men and in Indo-Asians and African Caribbeans
- End-stage renal disease (ESRD) is treated by renal replacement therapy (RRT), dialysis and transplantation
- Acceptance rates have risen fivefold in the last two decades, but population need is still not being met
- The main cause of ESRD is diabetic nephropathy, though many patients present late with small kidneys of uncertain cause
- Cardiovascular disease is a major cause of morbidity and mortality in patients with CRF and ESRD

KEY WORDS: CPD, chronic renal failure, dialysis, end-stage renal disease, epidemiology, incidence, late referral, prevalence, prognosis, renal replacement therapy

Population rates of end-stage renal disease/chronic renal failure

Three population incidence studies of 'diagnosed' CRF have been undertaken in the UK with differing levels of severity of renal disease (Table 2).

The prevalence of untreated ESRD is similar to the incidence because of poor survival. The incidence of ESRD in a population will vary depending on the population's age and sex distribution, ethnic composition and indicators of social deprivation. There have been prevalence studies in adults with milder levels of CRF. In the Framingham cohort study[9], at baseline 8% had mild renal impairment (men 136–265 μmol/l, women 120–265 μmol/l). Similar levels have been found in national dietary surveys in the UK[10,11].

Age and gender

All the studies have found that CRF is predominantly a disease of the elderly, rates rising steadily with age, and that there is a male excess of about 1.5. In the Southampton study[6] the median age was 77, while in Feest's ESRD study[8] rates were 58, 160, 282, 503 and 588 pmp in the age groups 20–49, 50–59, 60–69, 70–79 and 80+, respectively.

Ethnic minorities

People of African Caribbean and Indo-Asian (ie Indian, Pakistani, Bangladeshi and East African Asian) descent have higher rates of ESRD. In the USA, Black Americans have 4–5 times higher RRT acceptance rates than whites[12]. The 1993 National Renal Review in England[13] found threefold higher acceptance rates on to RRT in these populations compared with whites. This rate ratio increased with age, diabetic ESRD being the most common cause in both populations[14]. The two key drivers for the higher rates are hypertension and Type 2 diabetes:

- Hypertension is a major risk factor for progression of CRF. It has been studied more in African Caribbean populations who have a higher mortality from cerebrovascular and hypertensive disease[15] and a higher prevalence of hypertension than whites in the UK[16].
- People of Indo-Asian origin living in the UK have a higher prevalence and mortality from Type 2 diabetes[17].

In both ethnic groups there is evidence of more rapid progression of CRF to ESRD[18,19]. The reasons for these rates are a complex mix of genetic and environmental factors, and may partly reflect assimilation of a western lifestyle within a phenotype set for a lower availability of food[20]. The rising level of obesity is an important determinant of the Type 2 diabetes and hypertension seen in these populations.

Table 2. Population incidence studies of 'diagnosed' chronic renal failure (CRF).

Study	Ref	Year	Study length (years)	Location	Creatinine cut-off (μmol/l)	Annual rate (pmp)
Drey	6	1992–94	2	Southampton	>150*	1,700
Khan	7	1989–90	1	Grampian	>300 >500	450 130
Feest	8	1986–87	2	Devon, NW England	>500	148

* Termed mild CRF, yet 60–70% of renal function is lost before serum creatinine concentration rises above 150 μmol/l.
pmp = per million population.

End-stage renal disease and socio-economic status

The incidence of ESRD may be associated with socio-economic status. There is a strong inverse social class gradient in mortality from renal failure[21]. The rates of serum creatinine concentration over 150 μmol/l in the Southampton study were highest in the most deprived areas[6]. There is evidence for socio-economic gradients in underlying causes of ESRD such as Type 2 diabetes and hypertension[22]. Modelling studies of acceptances by area (ward level) deprivation show positive associations with deprivation[23,24]. However, area deprivation was not found to be a factor associated with acceptance on to RRT in two Scottish studies[25,26].

Causes of end-stage renal disease

A heterogeneous list of conditions can lead to ESRD including:

- primary renal diseases (eg glomerulonephritis, pyelonephritis, interstitial nephritis, polycystic kidney disease)
- multisystem disorders (eg diabetes, myeloma, systemic lupus erythematosus).

Their relative importance is difficult to ascertain from population studies because most patients in those studies were not referred to nephrologists and had not received any definitive diagnosis[6,7]. The main data come from studies of the causes of ESRD in patients accepted for RRT, a selected group which may under-represent certain causes (eg diabetes).

The commonest causes of ESRD in new patients presenting in 1999 in the units participating in the UK Registry are shown in Table 3 (excluding those with missing data). Patterns vary by age with, in particular, renovascular disease and an uncertain cause being commoner in the elderly. Registry data on type of diabetes are unreliable at present[27], though studies show that Type 2 predominates despite the greater risk of ESRD in Type 1 diabetics.

Hypertension is almost ubiquitous in patients with ESRD as it arises from chronic renal damage, particularly in African Caribbean patients. It is possible to assign it as a primary cause in only a minority of cases based on clinical criteria as many cases present with small shrunken kidneys and so do not have a renal biopsy[28]. However, in a biopsy study in the USA of non-diabetic, non-proteinuric hypertensive African Americans with CRF a very high proportion had changes consistent with hypertensive nephrosclerosis[29].

Time trends in end-stage renal disease incidence

There are no data on the incidence of ESRD over time. However, acceptance rates in the UK rose from 20 pmp to 92 pmp between the early 1980s and 1998[30]. This cannot be taken to mean that the incidence is rising because it could be explained, at least in part, by an increased ability to treat ESRD and by changing referral and acceptance rates. In fact, the type of patients being accepted has changed dramatically: in the late 1970s only 1–2% of new cases were over 65 or diabetic, but in 1998 these figures were 47% and 19%, respectively. Nevertheless, there are factors which will increase the incidence: there is an epidemic of Type 2 diabetes[31] and an ageing population[32].

Table 3. The commonest causes of end-stage renal disease (ESRD) in patients first presenting in 1999 and recorded in the UK Registry.

Cause of ESRD	% of patients
Diabetic ESRD	19
Glomerulonephritis	12
Renovascular disease	10
Pyelonephritis*	10
Polycystic kidney disease	7
Hypertension	5
Uncertain cause or glomerulonephritis unproven on biopsy	20

*including both prostatic hypertrophy and chronic pyelonephritis from childhood reflux nephropathy.

Renal replacement therapy

What is the population need for renal replacement therapy?

Population need is not being met, especially in the older age groups and in patients with associated comorbidity such as diabetes. Feest *et al* estimated that the overall incidence of ESRD suitable for RRT in those aged less than 80 was 78 pmp per year (95% CI 63–93)[8]. This was probably a minimum estimate of need for several reasons:

1 The areas included did not have large ethnic minority populations.
2 The over-80s should have been included because chronological age is not a bar to treatment – quality of life in elderly patients on dialysis, especially the mental health component, is comparable with an age-matched general population[33].
3 Clinical thresholds for acceptance vary: for example, acceptance rates were over 100 pmp in Wales and Scotland in 1998 and in several European countries with complete data[29,34], with a rate in Wales of 128 pmp (95% CI 115–140).
4 The population is ageing: population estimates predict increases of 15% in the 60–74 age group and 14% in over-75s between 1994 and 2011[32]. This is particularly so in ethnic minorities.

Prevalent rates of renal replacement

The prevalent rate of renal replacement will be the major driver of costs and resource use. Prevalent cases are those currently receiving RRT (termed the 'stock' of patients). These have risen from just under 400 pmp in 1993 to 523 pmp in 1998 (nearly 26,000 patients) in England. The modes of therapy have changed over the last decade, with an increasing proportion (30%) being treated by hospital haemodialysis (HD). Few patients are now being started on home HD, and the numbers on peritoneal dialysis have plateaued (20% of stock). Transplantation is the most cost-effective method of RRT, but supply outstrips demand. UK Transplant aims

to try to reverse the decline in organ availability by a series of measures, such as encouraging live donation, supporting non-heart beating donor schemes, and greater co-ordination of donation from intensive therapy units. There has been a growth in opening satellite units, largely nurse run, to provide more accessible HD, with over a third of HD patients now treated in such units[30].

Late referral for renal replacement therapy

A major problem is that up to 40% of patients requiring RRT are referred to the renal unit only when they are within a few months of needing treatment[35,36]. This reduces the opportunities:

- for interventions to reduce cardiovascular risk or the complications of CRF
- to establish permanent access for dialysis
- to assess suitability for dialysis
- to allow patient choice of treatment modality.

Patients presenting as uraemic emergencies almost always start with emergency HD and generally fare less well, having, for example, evidence of malnutrition (eg lower albumin), longer initial hospitalisation and a higher mortality[35]. Some of these are unavoidable (eg late presenters with no prior symptoms or signs of CRF, or irreversible acute renal failure), but about 50% are potentially avoidable having had documented rising creatinine levels for several years[37].

Survival on renal replacement therapy

Survival is influenced by a variety of types of factors:

- *fixed:* for example, age
- *factors not under the direct influence of renal units, depending on the degree of late referral:* for example, comorbidity, type of renal disease, albumin level (reflecting nutritional status)
- *those more directly related to the quality of subsequent care:* for example, dialysis adequacy.

Comparative audit of mortality within/between units and countries can be misleading as a method of assessing the quality of renal care without adjustment for case mix.

One-year survival on dialysis is currently 77%, but higher (88%) in those under 65 and lower (65%) in those over 65[27], while two-year survival is 67%. Primary renal diseases such as glomerulonephritis have a better prognosis than multisystem causes such as diabetes[38]. Comorbidity, especially cardiovascular, is common in patients starting RRT and is a major factor influencing survival. Comorbidity scores have been developed to take this into account[39,40].

The prognosis of CRF has been studied in the Southampton cohort of diagnosed CRF. Five-year survival was under 40%, the major cause of death being cardiovascular disease (CVD)[6], reflecting the complex interrelationship of renal failure and CVD risk[41]. Renal failure is associated with vascular disease even at mild degrees of impairment. It is not fully established whether renal impairment is a major risk factor for vascular disease or just a marker for organ damage, but it is associated with a range of known vascular risk factors. Renal impairment leads to secondary hypertension and abnormal lipid profiles. Serum cholesterol levels fall in ESRD, reflecting uraemic malnutrition, arterial wall damage and chronic inflammation – a case of reverse causation in which inverse relationships are found between mortality and cholesterol in RRT patients. Renal impairment also adversely alters other CVD risk factors (eg homocysteine and fibrinogen levels). Some factors such as smoking, and diseases such as diabetes, are important risk factors for both renal and cardiovascular disease.

Future demand for renal replacement therapy

Need and demand for RRT is likely to rise for the following reasons:

1 Demographic change, especially in ethnic minorities.
2 A Type 2 diabetes epidemic leading to increased ESRD rates[31,42].
3 Increased referral of patients to meet population need.
4 A steady state has not yet been reached at which input (acceptances per year and transfers in) is equal to the annual death rate and transfers out. Previous modelling suggests that this will not occur for over 20 years[43].
5 Improvements in the management of patients on RRT by implementation of Renal Association standards will improve survival, and hence increase the stock of patients on RRT.

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