A prospective national study of acute renal failure treated with RRT: incidence, aetiology and outcomes

Gordon J. Prescott1, Wendy Metcalfe2, Jyoti Baharani3, Izhar H. Khan4, Keith Simpson5, W. Cairns S. Smith6 and Alison M. MacLeod7

1Department of Public Health, University of Aberdeen, Polwarth Building, Aberdeen, AB25 2ZD, 2Renal Unit, Royal Infirmary, Edinburgh EH16 4SA, 3Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, 4Renal Unit, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, 5Chair of the Scottish Renal Registry; Glasgow Royal Infirmary, Glasgow, G4 0SF, 6Department of Public Health, University of Aberdeen, Polwarth Building, Aberdeen, AB25 2ZD and 7Department of Medicine and Therapeutics, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK

Abstract

Background. Acute renal failure (ARF) is a diverse condition with no standardized definition and is managed in several sub-specialty areas within hospitals. Its incidence and aetiology are unknown and studies show a wide range of incidences. ARF is becoming more common as the population ages leading to the hypothesis that the incidence is much higher than previous estimates.

Methods. This prospective population study investigated the incidence, aetiology and outcomes of ARF based on a standardized classification of ARF treated by renal replacement therapy (RRT) in all sub-specialty areas within hospitals where such treatment takes place. Data were collected prospectively on all patients starting RRT for ARF within three 12-week periods in 2002.

Results. Two hundred eighty-six adults per million population (pmp) per year received RRT for ARF. The incidence increased with age and pre-existing comorbid illness. Two hundred twelve adults pmp per year had no evidence of pre-existing chronic kidney disease (CKD) and the remainder had acute on CKD. The median age was 67 years. Fifty-one percent of the patients received their first RRT treatment in a critical care setting. Sepsis was the most common aetiological insult contributing to ARF in 48% of the patients. Mortality was high with 48% dying within 90 days of starting RRT. Age, comorbidity, sepsis and recent surgery were independent risk factors for death in those with no pre-existing CKD.

Discussion. This is the first national study to describe ARF treated with RRT in all hospital locations.

The hypothesis that ARF occurs more frequently than previously thought has been confirmed. This study provides data upon which to base effective decision making for prevention, patient care and resource planning for patients with ARF.

Keywords: acute renal failure; epidemiology and outcomes; mortality risk; renal replacement therapy; survival

Introduction

Acute renal failure (ARF) is a sudden sustained decline in glomerular filtration rate usually associated with uraemia and a fall in urine output [1]. It is associated with a high mortality rate; patients may present from the community with ARF, or more frequently ARF occurs in patients already hospitalized primarily for other reasons due to exposure to nephrotoxins, infection, surgery, trauma or haemorrhage [2]. Many patients require only a short period of renal replacement therapy (RRT) to support them through severe illness, but for others, particularly those with an acute deterioration of pre-existing chronic kidney disease (CKD), the need for RRT may be longer or even permanent.

Retrospective UK community-based studies of biochemistry laboratory results report the annual incidence of ARF and advanced ARF (serum creatinine ≥300 μmol/l and ≥500 μmol/l) as 620 and 140 pmp, respectively, with only 50 pmp patients with ARF and 22 with advanced ARF receiving RRT for ARF per year [3,4]. Patients with underlying CKD and those who failed to recover were excluded, as were those who received RRT with serum creatinine levels below the inclusion threshold.
However, a prospective study of ARF in hospital inpatients in East Kent [5], defining ARF as creatinine $\geq 300 \mu mol/l$ or urea $> 40 \text{mmol/l}$ (in patients with baseline creatinine $< 250 \mu mol/l$), found an incidence of ARF 545 pmp/year; 17% received RRT. A study in Greater Manchester identified 452 patients pmp with either serum creatinine $> 500 \mu mol/l$ or receiving RRT for ARF [6]. A Spanish prospective study of ARF (defined as creatinine $\geq 177 \mu mol/l$ or a doubling of serum creatinine in patients with baseline $< 264 \mu mol/l$) among all adult admissions to 13 tertiary-care hospitals only, close to Madrid, found an incidence of 209 (95% CI: 195–223) cases pmp; 36% received RRT [7]. Patients were excluded if serum creatinine had previously been $> 264 \mu mol/l$ or if there was evidence of renal cortical atrophy.

It is difficult to identify all patients with ARF receiving RRT because of the diversity of the condition, differences in definition and because it is managed in several sub-specialty areas within hospitals. There have been no comprehensive prospective population-based studies addressing the incidence and outcomes of ARF treated with RRT in all locations where such treatment takes place for patients living within a defined geographical area. Factors affecting the incidence and outcomes of ARF, treated with RRT, are unclear, and this has made it difficult to carry out and interpret interventional and cost-effectiveness studies. Making optimal decisions for patient care and for service planning are therefore hindered.

Using methodology developed from our pilot study [8], we aimed to establish the incidence of ARF treated with RRT, in adults resident in Scotland. We aimed to establish the demographic characteristics of such patients, their comorbid conditions, the causes of ARF treated with RRT, the location within hospitals that RRT took place and factors which influenced the survival and renal outcome in such patients.

**Subjects**

All adult patients (aged $\geq 15$ years) who received their first RRT in Scotland over 36 weeks were registered. All relevant Caldicott guardians were contacted regarding data protection; ethical permission was obtained from the Multi-centre and Local Research Ethics Committees. The pilot study [8] demonstrated that it was not logistically feasible to register patients over nine consecutive months, and therefore patients were registered between the dates of 21 January 2002 and 22 November 2002 in three separate periods of 12 weeks separated by 1 month between each period for completion of follow-up data.

**Methods**

All hospitals in Scotland were identified from the medical directory and contacted to establish those that provide RRT (intermittent and continuous) for ARF. Ten hospitals had an adult renal unit and an intensive care unit (ICU), of these four also provided RRT in a cardiac intensive care unit (CICU). A further 11 hospitals provided RRT for ARF in their ICU. Each hospital was contacted twice a week to identify those patients starting RRT for any reason. A research fellow or renal research nurse visited each location where RRT took place to confirm this information and register each patient. Patients beginning RRT for end-stage renal disease (ESRD), temporary visitors to Scotland and patients with renal transplants were excluded. Patients previously known to have CKD, but with a sudden deterioration in renal function resulting in RRT were included. Neighbouring hospitals outside Scotland were contacted regularly to identify if any Scottish residents received RRT for ARF there; none were identified. Data collected at baseline were demographics; home post code from which Carstairs deprivation index was derived [9] (see Appendix); time, location and mode of RRT; factors precipitating ARF and reasons stated for initiating RRT. Co-existing comorbidity was assessed and patients scored as high, medium or low Khan risk group using previously described methodology [10]. Follow-up data on mortality, renal outcome and hospitalization at 90 days after the initiation of the first RRT were collected. All data were entered on to the Scottish Renal Registry (SRR).

Patients with acute renal failure were defined as group A and those with acute on CKD were defined as group B. If there was no previously recorded creatinine, or the previously recorded creatinine was $< 150 \mu mol/l$ within 3 months of the date of first RRT patients were designated as group A. If imaging showed small kidneys or if previous CKD was recorded, they were assigned to group B. Patients with an elevated creatinine recorded within 4 weeks of their first RRT but not previously and who had normal-sized kidneys or no imaging available, were allocated to group A. Those with a diagnosis of vasculitis were also placed into group A (Figure 1).
Statistical analysis

For univariate analyses, chi-squared tests, *t*-tests or Mann–Whitney tests were used where appropriate. Direct standardization was used to relate the age and sex of the population in each NHS Board area to that of Scotland. Population statistics were obtained from the report of the Registrar General for Scotland. Multivariate Cox regression analyses were used to identify risk factors for death within 90 days and considered age, sex, Carstairs’ deprivation category, comorbidity (Khan risk) and causes of renal failure as risk factors. Khan risk group is defined using age, therefore, these cannot be considered as independent risk factors in a regression model. Logistic regression was used to examine risk factors for dependence on RRT at 90 days for survivors. A 5% significance level was used throughout. All statistical analyses were performed using SPSS version 12.0.

Results

Incidence

Over 36 weeks 809 patients with acute renal failure (group A) or acute on chronic kidney disease (group B) started RRT in Scotland (total population 5 054 800). This equates to an age standardized incidence of 286 per million of the adult population (pmp) per year (95% CI: 269–302). The incidence was 212 pmp (195–230) for group A and 74 pmp (64–85) for group B.

When starting RRT, the median values (range) of serum creatinine concentration and urea were 373 (49–2374) and 512 (68–1747) μmol/l and 26 (4–94) and 36 (9–110) mmol/l, for groups A and B, respectively. The first mode of RRT was recorded for 801 patients (continuous RRT for 61%, 60% group A and 72% group B). There was high background comorbidity (Table 2). No formal index of acute organ failure was recorded, but generally, at the time of the study, most patients in ICU required ventilation. The median age when starting RRT was 65.2 (group A, IQR 53.0–73.7) and 72.1 years (group B, IQR 62.9–77.8). A multivariate regression analysis showed that the odds of having ARF receiving RRT (groups A and B), increased with increasing age and was twice as high in men as women (odds ratio = 1.99 (1.73–2.30)) (Table 1).

There was wide, but not statistically significant, variation in the incidence of ARF treated by RRT observed among Health Board Areas. There was no relationship with Carstairs’ deprivation categories or any seasonal pattern in incidence.

Comorbidity

Eighty-six percent of the patients (83% group A, 97% group B) suffered from at least one comorbid illness at the time of first RRT. Twenty-two percent had one comorbid illness (27% group A, 9% group B) and 64% had two or more comorbid illnesses (55% group A, 88% group B). The most common comorbid illnesses were ischaemic heart disease (27%), chronic obstructive pulmonary disease (19%) and type II diabetes (18%). Using the Khan risk stratification based on age and comorbidity, 16% were in the low, 30% medium and 54% high Khan risk groups (18, 32, 50% group A; 11, 22, 67% group B).

More than one factor contributed to the development of ARF in 388 (48%) patients (Table 2). Sepsis was the most frequently recorded factor in both groups; of the 174 patients who had post-surgical ARF, 89 (51%) also had sepsis (56% of group A). High urea or creatinine concentration (53%), acidosis (45%) and fluid overload (34%) were the most common reasons for initiating RRT.
Outcomes

Just over half of the patients were alive at 90 days (Table 3). Mortality was higher in group A where 30% of patients had died within 10 days of starting RRT and 50% within 90 days of RRT; compared with 20 and 43%, respectively in group B.

Three-quarters of patients received <16 days of RRT. Of those dying within 90 days, the median duration of RRT was 3 days; the median length of hospital stay from the start of RRT was 6 days. Within groups A and B 53 and 40% of those who died within 90 days received RRT until the day of death.

The first RRT was in an ICU or CICU for 51.4% of patients, in a renal unit/ward for 44.6 and 4.0% in another ward/not recorded. Sixty percent of those in group A received their first RRT in an ICU or CICU compared with 24 and 37%, respectively in group B.

The majority of the remainder received their first RRT in renal units. Of those who had their first RRT session in an ICU (either general or cardiac) 62% died compared with 32% who were treated in other locations. Of 364 group A patients who started RRT in ICU and survived 90 days, only seven were still receiving RRT (Table 3).

A Cox regression analysis adjusting for confounders showed that patients in group B survived significantly longer than those in group A (log rank test, \(P=0.04\)) (Figure 2). Survival was significantly lower for those patients who had their first RRT in ICU probably reflecting the greater severity of their precipitating illness. Location of treatment is therefore likely to be acting as a marker for severity of illness, and thus it is not included as a risk factor.

A multivariate Cox regression model for group A patients showed that as age increased so did the risk of death (\(P=0.008\)); sepsis increased this risk by 40%. Another multivariate Cox regression model showed that patients classified as medium and high Khan risk group had hazard ratios (HR) for death of 50 and 70% higher than patients in the low Khan risk group (\(P=0.007\)) (Table 4, Figure 3). Presence of sepsis or being post-surgical increased the risk of death by 35 and 30%. However, in a multivariate analysis of group B patients, only the presence of sepsis (rather than age or comorbidity) was predictive of death (\(P=0.007\), HR = 1.76 (1.17–2.67)) increasing the risk of death by 76%.

RRT dependence (in those surviving 90 days)

Among patients who survived 90 days after first RRT, the presence of sepsis and being a post-surgical patient

Table 3. Patient survival, RRT dependence and length of stay (assessed after 90 days of starting RRT)

<table>
<thead>
<tr>
<th></th>
<th>Alive RRT independent</th>
<th>Alive RRT dependent</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients* n (%)</td>
<td>316 (39)</td>
<td>100 (12)</td>
<td>389 (48)</td>
<td>805 (100)</td>
</tr>
<tr>
<td>LOS median (IQR)</td>
<td>26 (15–42)</td>
<td>21 (9–39)</td>
<td>6 (2–17)</td>
<td>21 (11–40)</td>
</tr>
<tr>
<td>Days of RRT median (IQR)</td>
<td>5 (2–11)</td>
<td>90 (90–90)</td>
<td>3 (1–9)</td>
<td>5 (1–16)</td>
</tr>
<tr>
<td>Group A* n (%)</td>
<td>260 (44)</td>
<td>38 (6)</td>
<td>299 (50)</td>
<td>597 (100)</td>
</tr>
<tr>
<td>Non-ICU start of RRT n (%)</td>
<td>126 (54)</td>
<td>31 (13)</td>
<td>76 (33)</td>
<td>233 (100)</td>
</tr>
<tr>
<td>ICU start of RRT n (%)</td>
<td>134 (37)</td>
<td>7 (2)</td>
<td>223 (61)</td>
<td>364 (100)</td>
</tr>
<tr>
<td>LOS median (IQR)</td>
<td>26 (15–42)</td>
<td>27 (16–43)</td>
<td>5 (1–16)</td>
<td>21 (10–40)</td>
</tr>
<tr>
<td>Days of RRT median (IQR)</td>
<td>6 (2–11)</td>
<td>90 (90–90)</td>
<td>3 (1–9)</td>
<td>5 (1–12)</td>
</tr>
<tr>
<td>Group B* n (%)</td>
<td>56 (27)</td>
<td>62 (30)</td>
<td>90 (43)</td>
<td>208 (100)</td>
</tr>
<tr>
<td>Non-ICU start of RRT n (%)</td>
<td>44 (28)</td>
<td>57 (36)</td>
<td>57 (36)</td>
<td>158 (100)</td>
</tr>
<tr>
<td>ICU start of RRT n (%)</td>
<td>12 (24)</td>
<td>5 (10)</td>
<td>33 (66)</td>
<td>50 (100)</td>
</tr>
<tr>
<td>LOS median (IQR)</td>
<td>28 (12–46)</td>
<td>15 (7–34)</td>
<td>9 (2–23)</td>
<td>23 (11–39)</td>
</tr>
<tr>
<td>Days of RRT median (IQR)</td>
<td>2 (1–10)</td>
<td>90 (90–90)</td>
<td>5 (1–10)</td>
<td>8 (1–90)</td>
</tr>
</tbody>
</table>

LOS, length of stay (days) from start of RRT to discharge or death.
*For four patients (three, group A, one, group B) alive at 90 days RRT status could not be identified.
*Percentages are rounded to the nearest integer and so do not always sum to 100.
reduced the odds of being dependent on RRT at 90 days in both groups. Of 298 patients in group A who were alive at 90 days, 38 (13%) still received RRT. Twelve of these 38 had no previous creatinine value recorded so a degree of pre-existing renal impairment could not be excluded. The odds of a patient in group A receiving RRT at 90 days was reduced by 80% if he/she had had surgery or suffered from sepsis. A much higher proportion of patients in group B still received RRT at 90 days (62 (53%) of 118 alive at 90 days) and having sepsis or having had surgery significantly reduced the odds of being RRT dependent at 90 days by 68 and 82%, respectively.

Discussion

This national prospective study comprehensively characterizes patients with ARF receiving RRT. The annual incidence of ARF treated with RRT was 286 (95% CI: 266–306) per million of the adult Scottish population. Of these, 212 adults pmp had no evidence of pre-existing renal impairment, 74 pmp received RRT for acute on CKD. Sixty-one percent of the patients were male.

There was no protocol for initiation or withholding of RRT as this study was designed to assess what was happening in practice. There are no absolute contraindications for initiation of RRT. It was not the purpose of this study to consider all patients with ARF irrespective of treatment with RRT and, at the time of recruitment, a method of ensuring the capture of all subjects with ARF had not been established. Based on this research, a further study has been completed in all people in North East Scotland with ARF as defined by the ADQI criteria, irrespective of use of RRT [11].

The estimates of incidence of ARF treated by RRT ranged from approximately 22–110 pmp [3–5,7,12]. Even the largest estimate is around half of the incidence found in this study which confirms the hypothesis that the incidence of ARF treated with RRT is much higher than previous estimates including that of our own pilot [8]. This reflects the large population and the ability to study all patients within it. Many studies looked only at ARF within ICU. The reported incidence of ARF in critically ill patients treated in ICU ranges between 3–24% depending upon inclusion criteria [13,14]. A multinational study of over 29,000 ICU patients in 23 countries found 5.7% (95% CI: 5.5–6.0) to have ARF of whom the majority (72%) were treated by RRT [14]. We found that only 45% of patients received their first RRT for ARF in a renal ward or unit. Therefore, only by using comprehensive inclusion methodology is it possible to ensure all patients receiving RRT for ARF, wherever the location, are reported.

In some countries, ARF is usually treated in ICU. In Scotland, at the time of recruitment to this study, generally only those patients requiring ventilation would be admitted to ICU, where care would be managed by an anaesthetist usually in conjunction with a nephrologist. Those not requiring ventilation would be admitted to high dependency units or, if less severely ill, appropriate wards. It is likely that starting RRT in ICU was generally a surrogate for the need for ventilation, and hence severity of illness, but not necessarily severity of ARF.

All patients starting RRT with ESRD were excluded by cross referencing with the Scottish Renal Registry. Patients who have acute on CKD (group B in this study) comprise a grey area in epidemiological studies both of ESRD populations and of patients with ARF. When the renal function of such patients deteriorates such that they need RRT it is often difficult to predict whether recovery of renal function will occur. ESRD registries usually consider that those receiving RRT for more than 90 days have ESRD rather than ARF. A study using this 90 day rule found that 187 (95% CI: 170–203) pmp/year received <90 days of RRT [15].

Table 4. Factors affecting survival: multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Khan risk group (ref)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate Khan risk group</td>
<td>1.52</td>
<td>1.04</td>
<td>2.21</td>
<td>0.029</td>
</tr>
<tr>
<td>High Khan risk group</td>
<td>1.77</td>
<td>1.24</td>
<td>2.51</td>
<td>0.002</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.35</td>
<td>1.07</td>
<td>1.69</td>
<td>0.011</td>
</tr>
<tr>
<td>Post-surgical</td>
<td>1.30</td>
<td>1.01</td>
<td>1.68</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Low: Age <70 years and no comorbid illness; Medium: Age 70–80 or age <80 years with any one of the following: angina, previous myocardial infarction, cardiac failure, chronic obstructive airways disease, pulmonary fibrosis, or liver disease (cirrhosis, chronic hepatitis), (peripheral vascular and cerebrovascular disease) or <70 with diabetes mellitus, in addition to ARF; High: Age >80 or any age with two or more organ dysfunctions in addition to ESRD or any age with diabetes and cardiopulmonary disease, or any age with visceral malignancy in addition to ARF.

Fig. 3. Survival of patients in group A by comorbidity risk group.
We found that of those who survived for at least 90 days after the initiation of RRT, 13 and 53% of patients in groups A and B, respectively, received ongoing RRT at 90 days. The majority of patients in group A recovered function if they survived in contrast to those in group B, emphasizing the importance of analysing these groups separately. A study of ICUs reported long-term RRT-dependent renal failure in 1.6% of survivors of ARF and 33% of survivors of acute on CKD [16]. In contrast, Bagshaw et al. [12] report that of ICU patients with ARF treated with RRT, 29% of survivors at 90 days were still RRT dependent. A series of 1095 patients with ARF (serum creatinine $\geq$600 $\mu$mol/l or receiving RRT) reported that 16% received long-term RRT [17].

There did not appear to be any geographically based trend, nor a significant difference in the incident rates of ARF treated with RRT across Scottish Health Board areas. There was also no significant trend in the incidence of ARF, nor differences in renal outcomes according to Carstairs’ social deprivation categories.

Comorbidity was more common amongst this group of patients receiving RRT for ARF than is reported in the ESRD population [10]. We found that 16% of patients were in the low Khan comorbidity risk group, 30% medium and 54% in the high Khan risk group. Hegarty et al. [6] found similar percentages of 25, 29 and 46%, respectively, amongst patients with single-organ ARF. This high level of comorbidity in the population treated with RRT for ARF suggests that patients with pre-existing medical conditions are more pre-disposed to develop ARF.

In almost half (48%) the patients the aetiology of ARF was multi-factorial; the most common factor was sepsis (48% of patients). Two studies also report sepsis as the commonest causative factor of ARF (contributing to ARF in 48% of patients with ARF treated in ICU) [13,14]. The high incidence of post-surgical ARF at 34% in one of these reflects the entirely ICU based nature of the study [14]. ARF occurred in 16% of patients treated for sepsis in a surgical ICU [18]. In contrast, the aetiology of ARF acquired throughout the hospital is reported subsequent to renal hypoperfusion in 39% of cases, nephrotoxic medications in 16% of cases, 9% post-operative and only 6.5% due to sepsis in a further study [2]. The investigators attributed ARF to a single aetiological factor for each patient; our own experience has shown this is not usually the case.

Acute renal failure is universally reported to carry a bleak prognosis. Mortality rates like incidence rates, however, vary according to the definition of ARF used and locations studied. In-hospital mortality rates for ARF developing in hospital and receiving RRT is reported as 38 [2] and 44–45% among all cases of ARF presenting to hospitals [5,7]. In-hospital mortality is reported as 50% in CCU [19] and 58–64.2% in ICU patients [12–14,16]. In our study, 48% of patients had died by 90 days of starting RRT (groups A and B: 50 vs 43%, respectively). Many of the deaths were very early with 30 and 20% of patients in groups A and B dying within 10 days of starting RRT. By 90 days, mortality of patients starting RRT in the ICU was 62%, a similar rate to within-hospital mortality (60%) for ICU patients with ARF elsewhere [12,14].

Increasing age and comorbidity, the presence of sepsis and having had surgery were risk factors for death in patients in group A. For patients in group B the presence of sepsis increased the risk of death by 76%. The impact of sepsis both as an aetiological factor and poor indicator of prognosis is startling; it may be that with increased awareness and prompt therapeutic interventions this could be reduced. Those patients who had had surgery and survived sepsis rarely required long-term RRT. This indicated that those who had RRT initiated for sudden, catastrophic ill health and then survived are much more likely to regain renal function than those receiving RRT for ARF with a more insidious onset.

This national study, for the first time describes the incidence, aetiology and outcome of ARF receiving RRT in all hospital locations. 286 adults pmp received such treatment. The causes of ARF were multifactorial in the majority with sepsis playing a role in nearly half. Mortality is high with 48% of patients dying within 3 months; risk factors for death were age, comorbidity and sepsis. Of those who survived to 3 months, 13% with ARF and 53% with acute on CKD still received RRT.

Many patients with ARF are treated by more than one means of RRT, in more than one location within the hospital, by a variety of specialists during the course of their illness. It is only by a coordinated approach considering the disease process and treatment pathway as a whole, resulting in the inclusion of all appropriate patients, that useful relevant information can be derived to aid health care planning.

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Appendix: Details of the Carstairs Index

Carstairs Index

The Carstairs Index is designed to reflect material resources, which provide access to those goods, services, amenities and physical environment, which are customary in society. It is a summary measure applied to the population contained within a postcode sector and is derived by combining the following four Census variables to create a composite score:

(i) **Overcrowding**: the proportion of all persons living in private households with a density of more than one person per room

(ii) **Male unemployment**: the proportion of economically active males seeking or waiting to start work

(iii) **Low social class**: the proportion of all persons in private households with an economically active head of household in a semi-skilled or unskilled social class (class 4 or 5)

(iv) **No car**: the proportion of all persons in private households, which do not own a car

Scores range from 1 to 7. A score of 1 indicates the most affluent postcode sectors and a score of 7 indicates the most deprived postcode sectors.

References


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