The changing pattern of referral in acute kidney injury

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Summary

Background: Acute kidney injury (AKI) is not only managed by nephrologists, but also by several other subspecialists. The referral rate to nephrologists and the factors influencing it are unknown.

Aims: To determine the referral rate, factors affecting referral and outcomes across the spectrum of AKI in a population based study.

Methods: We identified all patients with serum creatinine concentrations ≥150 μmol/l (male) or ≥130 μmol/l (female) over a 6-month period. AKI was defined according to the RIFLE classification (risk, injury, failure, loss, end stage renal disease [ESRD]). Clinical information and outcomes were obtained from each patient’s case records.

Results: A total of 562 patients were identified as having AKI (incidence 2147 per million population/year [pmp/y]). One hundred and sixty-four patients (29%) were referred to nephrologists—referral rate 627 pmp/y. Forty-nine percent of patients whose serum creatinine rose to >300 μmol/l were referred compared with 22% in our previous study of 1997. Forty-eight patients required renal replacement therapy—incidence 184 pmp/y in comparison to 50 pmp/y in our previous study of 1997. Patients had higher odds of referral if they were male, of younger age and were in the F category of the RIFLE classification. Patients had lower odds of referral if they had multiple co-morbid conditions or if they were managed in a hospital without a nephrology service.

Conclusion: There has been a significant rise in the referral rate of patients with AKI to nephrologists but even during our period of study only one-third of such patients were being referred. With rising incidence and increased awareness, the referral rate will certainly rise putting a significant burden on the nephrology services.

Introduction

Acute kidney injury (AKI) is managed by a variety of specialities with or without the involvement of the renal services. The majority of patients with AKI, however, are not referred to nephrologists1,2 although the precise referral rate is not clear.

Recent studies have shown a much higher incidence of AKI than previously reported3,4 and there is evidence that the absolute incidence of AKI has risen in the past few decades.5 AKI is more common in the elderly6–8 and as patients with multiple co-morbid conditions survive longer due to advances in health-care, the incidence of AKI will continue to rise in keeping with the demographic trends. This will pose an increasing and significant burden on the health-care resources.

There are scant data on the burden of AKI on the nephrology services. A study from Manchester, UK has shown that that in a quarter of cases of AKI there
was a delay in a renal assessment resulting in potentially adverse effects on patients outcomes. The National Service Framework for Renal Services recommends that patients at risk of, or suffering from AKI should be identified promptly, with hospital services delivering high quality, clinically appropriate care in partnership with specialized renal teams. Our group reported a study in 1997 that showed that only 22% patients with AKI (serum creatinine of >300 \text{mol/l}) were referred to a nephrology service. Feest et al. some years earlier found that only 36% patients with severe AKI (serum creatinine of >500 \text{mol/}) were referred to nephrologists. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) whose purpose is to assist in maintaining and improving standards of medical and surgical care in the UK recently published a report on the process of care of patients with a primary diagnosis of AKI. This report has found significant deficiencies in the management of such patients during their hospital stay. The review reported that only one third of patients with AKI were referred to nephrologists and another 20% of patients should have been referred for advice. The incidence of referral in patients with AKI has not been well-studied in defined populations. The two population based studies which reported on referral rates have included only patients with severe AKI (serum creatinine of >500 \text{mol/l}) were referred to nephrologists. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) whose purpose is to assist in maintaining and improving standards of medical and surgical care in the UK recently published a report on the process of care of patients with a primary diagnosis of AKI. This report has found significant deficiencies in the management of such patients during their hospital stay. The review reported that only one third of patients with AKI were referred to nephrologists and another 20% of patients should have been referred for advice. The incidence of referral in patients with AKI has not been well-studied in defined populations. The two population based studies which reported on referral rates have included only patients with severe AKI. It is not clear which factors influence the referral to renal services and whether the outcomes are different in the two groups.

We aimed to determine the referral rate, factors affecting referral to nephrologists and outcome of AKI in a population based study. We also aimed to determine whether the referral rate in AKI changed over time.

### Subjects and Methods

We carried out a cohort study in a defined population (estimated as 523 390) of the Grampian region of Scotland. The key methods are summarized here and the methodology is described in detail elsewhere. We identified all adult patients who had a serum creatinine estimated during a 6-month period (1 January 2003 through 30 June 2003) in a defined population served exclusively by two biochemistry laboratories. Using the abbreviated modification of diet in renal disease (MDRD) equation, we estimated the GFR and applied the RIFLE classification (risk, injury, failure, loss, ESRD) (Table 1). We used the rise in serum creatinine concentration or fall in GFR (whichever was greater) to assign a category in the RIFLE classification; we did not use urine output as a criterion for classification, because it was not possible to obtain accurate records of urine output. Patients were classified as having AKI when serum creatinine rose from the baseline by a factor of 1.5 or more or the GFR was reduced from the baseline by 25% or more. When a baseline serum creatinine was not available but creatinine subsequently fell from the maximum creatinine by a factor of 1.5 or more, these patients were also defined as having AKI.

Patients were classified as having acute on chronic renal failure (ACRF) if they were known to have chronic kidney disease (CKD) in whom serum creatinine rose from the baseline by a factor of 1.5 or more or the GFR was reduced from the baseline by 25% or more. When a baseline serum creatinine was not available but creatinine subsequently fell from the maximum creatinine by a factor of 1.5 or more, these patients were also defined as having AKI.

Patients were excluded when baseline was not available and the patient died before renal recovery. They also were excluded when creatinine rise was less than a factor of 1.5 or rise was not sustained for 24 h.

We reviewed all the case notes of patients and also recorded information from the biochemistry and radiology databases which serve all hospitals in the Grampian region. Whether or not a patient was referred was identified from the entry in the case notes by the nephrologist or a note of any telephone discussion which took place with the nephrology team.

We applied the RIFLE classification and patients were placed in the first three categories as the last two categories are the outcome categories.

### Table 1 RIFLE classification

<table>
<thead>
<tr>
<th>Category</th>
<th>GFR criteria</th>
<th>Urine output (UO) criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk (R)</td>
<td>Increased creatinine × 1.5 or GFR ↓ by 25%</td>
<td>UO &lt; 0.5 ml/kg/h × 6 h</td>
</tr>
<tr>
<td>Injury (I)</td>
<td>Increased creatinine × 2 or GFR ↓ by 50%</td>
<td>UO &lt; 0.5 ml/kg/h × 12 h</td>
</tr>
<tr>
<td>Failure (F)</td>
<td>Increased creatinine × 3 or GFR ↓ by 75% or creatinine ≥350 \text{µmol/l}</td>
<td>UO &lt; 0.3 ml/kg/h × 24 h or anuria × 12 h</td>
</tr>
<tr>
<td>Loss (L)</td>
<td>Persistent AKI &gt; 4 weeks</td>
<td></td>
</tr>
<tr>
<td>ESRD (E)</td>
<td>End stage renal disease (&gt;3 months)</td>
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</tr>
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</table>
Patients were classified into low, medium, and high-risk categories using the Khan index\textsuperscript{13} (low risk: age <70 years and no co-morbid illness; medium risk: age >70 and ≤80 years, or age <70 years with one co-morbid illness, or age >70 years with diabetes; high risk: age >80 years, or any age with two or more co-morbidities, or any age with malignancy).

Patients who were referred to nephrologists and those factors which influenced the referral were identified from the case notes. The factors studied were age, gender, co-morbid conditions (ischaemic heart disease, hypertension, congestive cardiac failure, peripheral vascular disease, malignancy, chronic obstructive airways disease, connective tissue disease, diabetes, chronic liver disease and cerebrovascular disease), factors precipitating AKI (GI haemorrhage, pancreatitis, post-surgical, myocardial infarction, sepsis, nephrotoxins, myeloma, obstructive uropathy, hypotension, dehydration and rhabdomyolysis), RIFE classification and the Khan’s index. The outcomes of duration of hospital stay and mortality were recorded.

The data collected were analysed using SPSS software. For categorical variables, groups were compared using the χ²-test or Fisher exact test when expected values of <5 were obtained. Data are presented as frequency and percentage after cross tabulation. Continuous variables were described using means or medians and compared between groups using independent t-tests or Mann-Whitney tests as appropriate. Logistic regression was used to derive the odds ratio (OR) of being referred. An analysis including Khan’s index was adjusted only for sex, but not age or other co-morbidities (Khan’s index is itself derived from age and co-morbidities). The logistic regression analysis for referral including various co-morbid conditions was adjusted for the explanatory variables age, sex and maximum creatinine. A separate logistic regression analysis for referral considered all precipitating factors was adjusted for age and sex.

**Results**

A total of 474 patients were classified as having AKI, and 88 were classified as having ACRF giving an annual incidence of 2147 per million population/year (pmp/y). The annual incidence was 787 pmp/y and 299 pmp/y for those whose serum creatinine reached ≥300 µmol/l and >500 µmol/l, respectively. A total of 164 patients (29%) were referred to nephrologists giving an annual incidence of 627 pmp/y. 119 (25%) patients from the AKI group and 45 (51%) from the ACRF group were referred.

The data from patients with a serum creatinine of ≥300 µmol/l were also analysed for comparison with our previous study of 1997.\textsuperscript{2} We identified 206 such patients; 102 (49.5%) were referred to the nephrologists (390 pmp/y), which is significantly higher than the 22% referred in our previous study. There were 61 patients with a serum creatinine of >500 µmol/l and 36 (59%) of these were referred, equivalent to an annual referral rate of 137 pmp.

Forty-eight patients required renal replacement therapy (RRT) giving an annual incidence of 184 pmp/y in comparison to 50 pmp/y reported in our previous study of 1997.

Thirty-six percent of males and 21% female patients were referred (Table 2). The odds of being referred was lower in female patients (OR=0.593, P=0.018, 95% confidence interval (95% CI) = 0.385–0.914]. The mean age of the non-referred group was 76.5 and the referred group 69.5 years. Only 62 patients (19.6%) of those over 75 were referred. The odds of referral decreased significantly with increasing age (OR=0.963 for a 1-year increase in age, P<0.001, 95% CI=0.947–0.980) (Figure 1).

The OR relating referral to Khan’s index was adjusted for gender. A greater proportion of patients in the low-risk groups were referred (60.5%) than in the medium and high-risk groups (39.7% and 21.9%, respectively). The odds of being referred were significantly lower in the medium-risk group and the high-risk group when compared with the low-risk group (median vs. low OR=0.445, P=0.025 high vs. low OR=0.202, P<0.001) (Table 2).

Among the RIFE categories, 19.7% in R-category, 18.7% in L-category and 48% in F-category patients were referred to nephrologists. The OR of referral according to the RIFE classification was adjusted for age, gender and co-morbidities. Fewer patients in L-category were referred, compared with R-category (OR=0.887) however this finding was not statistically significant (P=0.691). The OR for referral was significantly higher in F- than R-category (OR=3.618, P<0.001, CI=2.044–6.404) (Table 2).

A baseline serum creatinine was available in 481 patients (85%) within 6 months prior to the date of development of AKI. A total of 149 (31%) such patients were referred. A baseline serum creatinine was not available in 81 patients, only 15 (18%) such patients were referred. Significantly, more patients were referred if a baseline serum creatinine was available (P=0.02).

Maximum creatinine value was significantly associated with the referral. The mean of the maximum serum creatinine values was 390 µmol/l in the
referred group and was 272 μmol/l in the non-referred group. The odds of referral increased as the maximum creatinine level increased (OR = 1.004 for a 1-μmol/l increase, \( P < 0.001 \), CI = 1.003, 1.005) adjusting for sex, age and other co-morbidities. This is equivalent to approximately a 50% increase in the odds of being referred for each 100-μmol/l increase in maximum creatinine.

There was evidence that patients with congestive cardiac failure (OR = 0.387, \( P = 0.010 \)), non-haematological malignancy (OR = 0.543, \( P = 0.040 \)) and dementia or cerebrovascular diseases (OR = 0.433, \( P = 0.011 \)) were referred less frequently. Other individual co-morbidities did not have a significant effect on the odds of referral (Table 3).

Certain precipitating factors were associated with higher odds of referral relative to those patients without these factors. Patients with AKI had significantly increased odds of referral with sepsis (OR 1.7, \( P = 0.032 \)), post-surgery (OR 3.3, \( P = 0.001 \)), nephrotoxins (OR 5.4, \( P < 0.001 \)), myeloma (OR = 5.5, \( P = 0.039 \)) or hypotension (OR = 2.9, \( P < 0.001 \)) (Table 4).

Renal imaging was performed in 294 (52%) patients; 142 (86%) patients in the referred group and 152 (38%) of the non-referred had a renal imaging done. This difference was statistically significant (\( P < 0.0001 \)).

A total of 72 (44%) patients in the referred group and 219 (55%) in the non-referred group died (\( P = 0.02 \)) at 6-months follow-up. The median duration of hospital stay was 18 days in the referred group and 16 days in the non-referred group, which was not statistically significant even after excluding those patients who had died (19 vs. 18 days, respectively).

As the patients with AKI were treated in a tertiary centre with a nephrology service or in a district general hospital with no nephrology service, we analysed the data to see whether this had any impact on the referral. Seventy patients had a postcode from the district general hospital area and 12 (17%) were referred whereas 152 of the 492 patients (31%) from the area with a renal service were referred (\( P = 0.01 \)).

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Table 2  Characteristics of AKI patients referred or not referred

<table>
<thead>
<tr>
<th></th>
<th>Referred</th>
<th>Not referred</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. (%)</td>
<td>164 (29.2)</td>
<td>398 (70.8)</td>
<td></td>
</tr>
<tr>
<td>Male no. (%)</td>
<td>110 (36.2)</td>
<td>194 (63.8)</td>
<td></td>
</tr>
<tr>
<td>Female no. (%)</td>
<td>54 (20.9)</td>
<td>204 (79.1)</td>
<td>0.018</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>69.5</td>
<td>76.5</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Renal imaging (%)</td>
<td>142 (86.6)</td>
<td>152 (38.2)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Khan’s index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>26 (60.5)</td>
<td>17 (39.5)</td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>54 (39.7)</td>
<td>82 (60.3)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>84 (21.9)</td>
<td>299 (78.1)</td>
<td></td>
</tr>
<tr>
<td>RIFLE classification</td>
<td></td>
<td></td>
<td>(&lt;0.001^b)</td>
</tr>
<tr>
<td>R (%)</td>
<td>23 (19.7)</td>
<td>94 (80.3)</td>
<td></td>
</tr>
<tr>
<td>I (%)</td>
<td>47 (18.7)</td>
<td>204 (81.3)</td>
<td></td>
</tr>
<tr>
<td>F (%)</td>
<td>94 (48.5)</td>
<td>100 (51.5)</td>
<td></td>
</tr>
<tr>
<td>Maximum creatinine (mean)</td>
<td>390³</td>
<td>272³</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>72 (44%)</td>
<td>219 (55%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median duration of stay</td>
<td>18</td>
<td>16</td>
<td>0.68</td>
</tr>
<tr>
<td>Mean creatinine at 6 month (AKI group)</td>
<td>123</td>
<td>133</td>
<td>0.52</td>
</tr>
<tr>
<td>Mean creatinine at 6 month (ACRF group)</td>
<td>257³</td>
<td>292³</td>
<td>0.64</td>
</tr>
</tbody>
</table>

³μmol/l.

\( ^a \)High vs. low.

\( ^b \)F-category vs. R-category.

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Figure 1. Referral rate and age.
In this study, less than a third of patients with AKI were referred to nephrologists. However, referral rate for those patients with serum creatinine >300 μmol/l has doubled in the last 10 years. The annual incidence of referral was 627 pmp/y. Patients had higher odds of referral if they were male, of younger age and had high-serum-creatinine values. Patients were less likely to be referred if they had multiple co-morbid conditions, malignancy, cardiovascular or cerebrovascular diseases.

Feest et al.\(^1\) reported an incidence of 140 pmp/y of AKI (creatinine of >500 μmol/l). Only 36% of patients were referred to a nephrologist which equates to an annual incidence of 51 pmp/y. Case notes review of these patients concluded that appropriate referral rate could have been 70 pmp/y. Khan et al.\(^2\) reported that only 22% of patients with AKI (creatinine of >300 μmol/l) were referred to a nephrologist from the same population area as in the present study. However, our study has shown that almost half of those with a serum creatinine of >300 μmol/l and some 60% with a creatinine of >500 μmol/l were referred. The annual referral rate in these groups is much higher than reported by Feest—patients with serum creatinine of >500 μmol/l (137 vs. 51 pmp/y), and by Khan—patients with serum creatinine of >300 μmol/l (390 vs. 138 pmp/y). We also noted that the incidence of RRT increased from 50 pmp/y reported in 1997 to 184 pmp/y reported in the present study. These findings show that there has been a significant increase in the incidence of AKI, referral rate to nephrologists and RRT. It is probably due to increase awareness and ability to treat these complex patients in advanced specialist units. It is likely that referral rate will rise in future which will pose an increasing burden on the nephrology services.

We have found that patients were significantly more likely to be referred if they were younger and male. Feest et al.\(^1\) also reported that age was a significant factor in referring patients and elderly patients were usually not referred. The reason for high male referral was not entirely clear, however we found that the median age in males was 73 years while in female patients median age was 80 years in the AKI group. It is thus possible that age played a role in making a decision for referral. Similarly, patients were less likely to be referred if they were in the high-risk category of Khan’s index. A previous study reported that 75% patients from the low risk category, 30% from medium and only 14% from the low-risk category were referred to nephrologists.\(^2\) The present study shows that referrals from the medium and high-risk groups are also increased from our previous study (40% vs. 30% and 22%
AKI is associated with prolonged duration of hospital stay.\textsuperscript{14–17} In the present study the duration of hospital stay was not different in the two groups. An American study has shown a progressive increase in mortality, length of stay and costs with increasing severity of AKI.\textsuperscript{18} Chertow et al. also found that larger increases in serum creatinine were associated with longer relative increases in hospital length of stay.\textsuperscript{14} This indicates the importance of preventing AKI as once it is established, the outcomes are worse.

The mortality in AKI remains very high.\textsuperscript{16,19–21} A recent meta-analysis confirmed adverse long-term outcomes in patients with AKI.\textsuperscript{22} In the present study mortality was around 50\% at 6 months (55\% patients in non-referred group and 44\% in the referred group died). However, many patients in the non-referred group had multiple co-morbid conditions and were in the high-risk group of Khan’s index which might have played a role in high mortality. We do not think that mortality was high just due to non-referral and a prospective study would probably give us more information on it.

There are few limitations of this study. It is a retrospective study and limited to one geographical area. As there was no nephrology service at one of the hospitals that could have introduced bias and could have some impact on referral. However, the number of patients was relatively small in the former group (70 vs. 492). Although our study has shown a much higher incidence of AKI than ever reported it is still an underestimate of the true incidence as patients were only included if serum creatinine had risen to a threshold of 150 $\mu$mol/l in male patients and to 130 $\mu$mol/l in females. We would have missed those patients who developed AKI but serum creatinine did not reach to the above threshold values. We also would have missed those patients who developed AKI in the community but due to lack of blood testing were missed. We also could have missed those patients who had AKI based on the urine criteria only: we did not use urine criterion due to lack of urine output records. Although after reviewing case notes we felt that more patients should have been referred but it was difficult to draw any conclusion due to retrospective nature of our study. Despite all limitations we have shown that referral rate has increased significantly, number of patients who require RRT rose sharply in 10-year period and more patients from the high risk category are being referred.

In conclusion, our study has shown that there has been a significant rise in the referral rate of patients with AKI to nephrologists but even during our period of study only one-third of such patients were being referred. With the rising incidence of AKI and
increasing awareness recently further stimulated by the NCEPOD report the referral rate will certainly rise putting a significant burden on the nephrology services. There is an urgent need for clear guidance for colleagues in all disciplines, particularly those in training, on when nephrology referral is appropriate.

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**Conflict of interest:** None declared.

**References**