# Unreferred Chronic Kidney Disease: A Longitudinal Study

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• ***Background:*** **Chronic kidney disease (CKD) is a major health problem. A better understanding of the epidemiological characteristics of the different stages of CKD and the associated adverse outcomes is needed to establish and implement appropriate management strategies.** ***Methods:*** **A serum creatinine (SCr) level of 2.03 mg/dL or greater (≥180 μmol/L) in men and 1.53 mg/dL or greater (≥135 μmol/L) in women was used to identify patients with moderate to severe CKD in a predominantly Caucasian area of the United Kingdom. Patients who were unknown to renal services were identified and followed up to establish survival, rate of referral, and change in glomerular filtration rate (GFR).** ***Results:*** **The prevalence of CKD defined by SCr cutoff values was 5,554 per million population (pmp). Median calculated GFR of the cohort was 28.5 mL/min/1.73 m² (range, 4.1 to 42.8 mL/min/1.73 m²), and median age was 83 years (range, 18 to 103 years). A total of 84.8% of patients were unknown to renal services. During a mean follow-up of 31.3 months, 8.1% of patients were referred. Median survival of the unreferred population was 28.1 months. Cardiovascular disease, cancer, and infection were the most common causes of death. Male sex, low GFR, and nonreferral were associated with poor outcome. The majority of unreferred patients had stable renal function. The incidence of new unreferred CKD during the first year of follow-up was 2,435 pmp, such that the prevalence remained stable at 4,910 pmp. Significant anemia (hemoglobin < 11 g/dL [<110 g/L]) was seen in 27.5% of the unreferred cohort.** ***Conclusion:*** **Referral of all patients with CKD is unrealistic and inappropriate. Management strategies aimed at improving adverse outcomes need to take account of this and be developed and implemented through collaboration between primary care and secondary care.** ***Am J Kidney Dis*** **43:825-835.**


**INDEX WORDS: Chronic kidney disease (CKD); prevalence; progression; unreferred.**

CHRONIC KIDNEY disease (CKD) is an escalating public health problem throughout the developed world. CKD carries with it not only a risk for progression to end-stage renal disease, but also increased morbidity and mortality, particularly from cardiovascular disease.[1-3] Despite a steady increase in renal services in the United Kingdom, additional expansion is needed during the next 20 years to meet population demand driven by an aging population and the epidemic of type 2 diabetes.[4] Early identification, entry into a CKD management program, and referral to renal services, when indicated, provide the keys to alleviating this health burden. All of these are currently suboptimal.

CKD is an insidious disease, and at-risk groups, such as patients with diabetes and hypertension, need to be assessed regularly and managed in line with established evidence-based guidelines.[5,6] The Kidney Early Evaluation Program screened more than 6,000 persons with hypertension or diabetes or a first-order relative with hypertension, diabetes, or CKD. It showed a high prevalence of CKD in these groups; 15.6% had a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m².[7] Despite this, in a study of primary care in the United Kingdom, only half the patients with diabetes or hypertension had had their serum creatinine (SCr) measured in the preceding 2 years. Furthermore, only 28% of those with an abnormal SCr level (>1.41 mg/dL [>125 μmol/L]) had been referred to a nephrologist.[8] There appears to be a general reluctance to refer patients with early CKD. In a French study of patients with CKD defined as an SCr level of 2.26 mg/dL or greater (≥200 μmol/L), 70% of those referred already had SCr levels of 3.39 mg/dL or greater (≥300 μmol/L),[9] levels at which the UK Renal Association advises urgent referral.[10] It is well established that 30% to 50% of patients start renal replacement therapy within a few months of referral, with detrimental consequences in terms of morbidity and mortality.[11-16] In half these cases, earlier referral may be possible with adequate screening of at-risk groups or recognition of the significance of an abnormal

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*Received August 18, 2003; accepted in revised form December 30, 2003.*

*Supported in part by a project grant from the National Kidney Research Fund (UK); The Alan Squirrel Artificial Kidney Fund; and the Renal Care and Research Group.*

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*0272-6386/04/4305-0008$30.00/0*

*doi:10.1053/j.ajkd.2003.12.046*

SCr level.[14,17] Even in advanced CKD (SCr > 5.66 mg/dL [>500 μmol/L]), only 35% to 50% of patients are referred.[18,19] Although this may be appropriate because of age and comorbidity, Feest et al[19] reported that 53% of unreferred patients younger than 80 years could have benefited from an opinion.[19]

Current guidelines and management practice need to be revised to facilitate both early referral of patients with progressive disease and appropriate management of CKD. Before strategies can be developed, it is essential to know epidemiological characteristics of the different stages of CKD in the population and accurately identify adverse outcomes of the disease. Aims of this study are to identify patients with significant CKD who had not been referred to renal service and describe their demographic characteristics, rate of disease progression, rate of referral to renal services, and survival.

## METHODS

### *Setting*

The study took place in East Kent, southeast England, which has a population of 688,193 (51.4% female), with less than 1.3% coming from an ethnic minority. Age and sex demographics are similar to those of England as a whole, except that East Kent has a greater percentage of elderly patients (13.8% of the East Kent population is >70 years compared with 11.5% in the general population).[20]

### *Patient Selection*

Biochemical samples were processed at 2 laboratories that use the same enzymatic method for measuring SCr; a Vitros analyzer (Ortho-Clinical Diagnostics, Rochester, NY). The day-to-day coefficient of variation is less than 2%. Normal range of SCr in both laboratories is 0.9 to 1.5 mg/dL (80 to 133 μmol/L) in men and 0.7 to 1.2 mg/dL (62 to 106 μmol/L) in women. SCr is always measured when requests are made for urea and electrolytes.

Since October 1, 2000, both chemical pathology databases have been analyzed on a monthly basis. All patients with an increased SCr level were identified, and demographic data were recorded (age, sex, and ethnicity). The threshold for inclusion was in line with The National Institutes of Health (NIH) referral criteria: an SCr of 2.03 mg/dL or greater (≥180 μmol/L) in men and 1.53 mg/dL or greater (≥135 μmol/L) in women.[21] Because SCr samples originated from both the hospital and primary care, measures were taken to exclude patients with transient elevations in SCr levels. Institutionalized patients with rapidly increasing or decreasing SCr levels were defined as having acute renal impairment and were excluded, together with those who had died without previous evidence of an increased SCr level. Analysis of increased SCr levels was made 3 months after initial identification to allow time for the clinician to recheck the SCr value and refer the patient. Patients were excluded if a repeated SCr level decreased to less than the selection threshold during this period. Patients with a single increased SCr level were excluded if they had a normal-range SCr result in the previous 6 months. A postcode analysis was performed to exclude patients living outside the geographic area.

Cross-reference was made with the renal database to identify patients already known to the renal service and patients subsequently referred. Patients on dialysis therapy or with a functioning renal transplant were excluded. Patients were defined as unreferred if no renal referral had been made within 3 months of the original abnormal SCr result.

The modified Modification of Diet in Renal Disease (MDRD) formula was used to give an estimate of GFR to aid comparison of results between the unreferred and known populations and determine the rate of progression[22-24]:

$$\text{GFR} = 186 \times (\text{SCr [mg/dL]})^{-1.154} \times \text{age (years)}^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

### *Patient Assessment*

The origin of the creatinine request was recorded according to specialty; Primary Care, General Medicine (including Diabetology and Cardiology), Elderly Medicine, Surgery (General, Vascular, Orthopaedic, Ophthalmology, and Ear, Nose, and Throat), Urology, Oncology, Hematology, Accident and Emergency Centre, and unknown.

When hemoglobin levels were available, the best result during the first year was recorded for each patient. The incidence of new unreferred CKD was identified by using the same method during the second year of the study.

All patients identified between October 2000 and September 2001 were followed up from the time of initial SCr measurement until July 31, 2003, to establish the rate of referral to renal services, mortality rate, and rate of progression of CKD in survivors.

### *Statistics*

Prevalence and incidence rates were calculated from the number of subjects identified and the population of East Kent obtained from the UK national census in 2001.[20]

The confidence interval (CI) of the sampling errors was assessed by calculating the SE of the proportion for the prevalence estimates and using the SE for rates, based on Poisson distribution for standard mortality rates (SMRs). SMRs were indirectly standardized to deaths rates for the year 2000 of the southeast England population.[20]

Comparisons between the known and unreferred populations were made by using a Mann-Whitney *U* test for nonparametric variables and chi-square for proportions. Kaplan-Meier survival curves were used to perform univariate analysis of survival. Multivariate analysis of survival was performed using Cox proportional hazards regression. Data are presented as median and range for nonparametric variables and mean ± SD for normally distributed variables. Data were analyzed using SPSS for Windows, version 11.0 (SSPS Inc, Chicago, IL).

**Table 1. Comparison of the Known and Unreferred Populations**

| | Known | Unreferred | *P* |
|---|---|---|---|
| Women (%) | 43.8 | 60.8 | <0.01 |
| Age (y) | | | |
| All | 70 (18-91) | 83 (18-103) | <0.01 |
| Men | 70 (20-91) | 82 (18-101) | <0.01 |
| Women | 70 (18-88) | 84 (18-103) | <0.01 |
| Prevalence (pmp) | | | |
| All | 846 ± 57.0 | 4708 ± 134.5 | <0.01 |
| Men | 988 ± 61.6 | 3842 ± 121.5 | <0.01 |
| Women | 713 ± 52.3 | 5512 ± 145.5 | <0.01 |
| Creatinine (mg/dL) | | | |
| Men | 2.74 (2.03-9.02) | 2.36 (2.03-9.85) | <0.01 |
| Women | 2.43 (1.53-9.33) | 1.79 (1.53-10.67) | <0.01 |
| GFR (mL/min/1.73 $m^2$) | | | |
| All | 23.4 (4.8-39.8) | 28.5 (4.1-42.8) | <0.01 |
| Men | 24.5 (6.0-39.8) | 28.2 (5.3-42.3) | <0.01 |
| Women | 20.6 (4.8-39.8) | 28.8 (3.6-42.8) | <0.01 |

NOTE. Values expressed as median (range) for age, creatinine, and calculated GFR. Prevalence rates of the population (pmp) are given with 95% CIs. To convert serum creatinine in mg/dL to $\mu$mol/L, multiply by 88.4.

## RESULTS

### *Overall Prevalence of CKD*

Between October 2000 and September 2001, a total of 13,658 patients were identified who fulfilled the NIH criteria. Of these, 8,827 patients were excluded because of an SCr level decreasing to less than the cutoff criteria, changes in SCr levels suggestive of acute renal failure, or an isolated increased SCr value with a normal SCr value in the previous 6 months. An additional 389 patients died without previous evidence of an increased SCr level, 342 patients lived outside the geographic area, and 278 patients were receiving renal replacement therapy. A total of 3,822 patients remained; 1,598 patients (41.8%) were men and 2,224 patients (58.2%) were women. Overall, the prevalence of diagnosed CKD was 5,554 per million population (pmp), median age was 82 years (range, 18 to 103 years), and median calculated GFR was 28.0 mL/min/1.73 $m^2$ (range, 3.6 to 42.8 mL/min/1.73 $m^2$).

Prevalences in the male and female populations were 4,830 and 6,225 pmp, respectively. The female population was significantly older (median, 82 years [range, 18 to 103 years] versus 80 years [range, 18 to 101 years]; $P < 0.01$), but levels of renal function in the female and male populations were the same (GFR, 28.4 mL/min/1.73 $m^2$ [range, 3.6 to 42.8 mL/min/1.73 $m^2$] versus 27.6 mL/min/1.73 $m^2$ [range, 5.3 to 42.3 mL/min/1.73 $m^2$]).

Only 15.2% of patients were known to the renal services. There was a strong male bias, with 20.4% of males known compared with only 11.4% of females. Table 1 shows a comparison between the unreferred population and patients known to the unit. The unreferred population was significantly older and had a greater proportion of women than the known population. Median SCr level was lower in the unreferred population, corresponding to a greater median GFR for both sexes and overall.

### *Unreferred Population: Demographic Characteristics*

Median age of the unreferred population was 83 years (range, 18 to 103 years), and 60.8% were women. Age distribution for patients for both sexes is listed in Table 2. There is a female predominance in most age ranges, particularly in patients 80 years or older. However, women account for 66.6% of the general population in this age group, for which the prevalence was actually greater in men than women (64,738 versus 55,994 pmp).

### *Unreferred Population: Level of Renal Function*

Median GFR (28.5 mL/min/1.73 $m^2$ [range, 3.6 to 42.8 mL/min/1.73 $m^2$]) did not differ

**Table 2. Distribution of Patients With Respect to Age in Both Sexes in the Unreferred Population**

| Age (y) | Men | Women | Total |
|---|---|---|---|
| <40 | 13 (48) | 14 (52) | 27 (0.8) |
| 40-49 | 11 (42.3) | 15 (57.7) | 26 (0.8) |
| 50-59 | 44 (55.7) | 35 (44.3) | 79 (2.4) |
| 60-69 | 106 (47.9) | 115 (52.1) | 221 (6.8) |
| 70-79 | 309 (41.8) | 430 (58.2) | 739 (22.8) |
| ≥80 | 788 (34.3) | 1,360 (65.7) | 2148 (66.4) |
| All | 1,271 (39.2) | 1,969 (60.8) | 3,240 (100) |

NOTE. Values expressed as number (percent).

between sexes in the age ranges listed in Table 2 and overall was slightly greater in the younger age group (30.5 mL/min/1.73 $m^2$ [range, 5.9 to 42.8 mL/min/1.73 $m^2$] in those <50 years) compared with those older than 80 years (27.9 mL/min/1.73 $m^2$ [range, 3.6 to 34.6 mL/min/1.73 $m^2$]; data not shown).

*Referral Patterns*

Table 3 lists age-related prevalences for the known and unreferred populations and the percentage that were known to the renal service. In both populations, there is a strong age-related prevalence, particularly in the unreferred population, increasing from 78.3 pmp in those younger than 40 years to 58,913 pmp in those 80 years or older. However, the prevalence of the known population reaches a peak in the 70- to 79-year age group. Age has an important part in referral to renal services. The percentage of patients referred decreases with increasing age, such that only 3.6% of those 80 years or older are known compared with approximately 50% in the younger age groups.

In Table 4, the percentage of patients known for different levels of renal function is listed. Only 9.6% of patients with moderately reduced GFR (stage 3 CKD, GFR of 30 to 42.8 mL/min/1.73 $m^2$) were known compared with 34.7% of those with end-stage renal failure (stage 5 CKD, GFR < 15 mL/min/1.73 $m^2$). A greater percentage of men were known at all levels of renal function. When patients older than 80 years were excluded (Table 5), there was a marked increase in patients with stage 5 CKD who were known (63.6%). However, 81% of patients with stage 3 CKD were unreferred. Again, there was underreferral of women relative to men.

*Origin of SCr Request*

The origin of the SCr request was identified to try to establish who might be responsible for nonreferral of patients (Fig 1). More than 77% of requests originated from Elderly and General Medicine and Primary Care. Small, but nevertheless significant, numbers were requested through Accident and Emergency and Surgery.

*Unreferred Population: Anemia*

Data for hemoglobin levels were available for 2,774 patients (85.6%). Figure 2 shows the distribution of hemoglobin levels in the patient cohort. Mean hemoglobin concentration was 12.1 ± 1.9 g/dL.

Current European guidelines recommend that workup for a diagnosis of anemia should be considered when hemoglobin level is less than 11 g/dL in premenopausal women and less than 12 g/dL in adult men and postmenopausal women.[25] In this study, 49.6% of men and 51.2% of women fulfilled these criteria. Furthermore, in 27.5% of patients identified, hemoglobin level was less than 11 g/dL, levels at which treatment with erythropoietin should be considered.[25]

**Table 3. Age-Related Prevalence in the Unreferred and Known Populations and Percentage of Patients Known to the Renal Services**

| Age (y) | Population (%) | Unreferred (pmp ± 95% CI) | Known (pmp ± 95% CI) | Known (%) |
|---|---|---|---|---|
| <40 | 50.1 | 78 ± 17 | 98.4 ± 19 | 52.7 |
| 40-49 | 12.7 | 295 ± 34 | 739 ± 53 | 68.4 |
| 50-59 | 13.4 | 858 ± 57 | 852 ± 57 | 44.4 |
| 60-69 | 10.0 | 3,072 ± 109 | 2,247 ± 93 | 37.3 |
| 70-79 | 8.5 | 12,648 ± 220 | 3,967 ± 123 | 22.6 |
| ≥80 | 5.3 | 58,913 ± 476 | 2,525 ± 99 | 3.6 |
| All | 100 | 4,708 ± 135 | 846 ± 57 | 15.2 |

**Table 4. Percentages of Patients of All Ages Known to the Renal Service by Level of Calculated GFR**

| GFR (mL/min/1.73 m$^2$) | Men (%) | Women (%) | All (%) |
|---|---|---|---|
| <15 | 42.6 | 29.0 | 34.7 |
| 15-30 | 21.3 | 12.1 | 16.2 |
| 30-42.8 | 13.7 | 7.0 | 9.6 |
| All | 20.4 | 11.4 | 15.2 |

**Table 5. Percentages of Patients Younger Than 80 Years Known to the Renal Service by Level of Calculated GFR**

| GFR (mL/min/1.73 m$^2$) | Men (%) | Women (%) | All (%) |
|---|---|---|---|
| <15 | 71.4 | 57.1 | 63.6 |
| 15-30 | 39.1 | 32.4 | 38.5 |
| 30-42.8 | 24.2 | 14.8 | 19.0 |
| All | 36.1 | 26.9 | 31.2 |

*Outcomes of the Unreferred Population*

All patients with a diagnosis of unreferred CKD in the first year were followed up for a mean of 31.3 months. Only 8.1% were referred to renal services. Median time from initial SCr measurement to referral was 8.1 months (range, 3.1 to 33 months). Median age of the referred population was 80 years (range, 18 to 102 years), 53.6% were men, and median GFR was 26.3 mL/min/1.73 m$^2$ (range, 3.6 to 42.3 mL/min/1.73 m$^2$). Outcomes of these patients (renal group) are considered separately from those of patients remaining unreferred (unreferred group).

At the end of follow-up, 38.6% of patients had died (26.6% of the renal group and 39.5% of the unreferred group). Median survival was 28.1 months and was better in the renal group than unreferred group (29.1 versus 27.4 months; $P < 0.001$). Univariate analysis showed that age, sex, initial GFR, and renal referral were associated with survival. Age was no longer significant on multivariate analysis using Cox proportional hazard, with male sex, lower GFR, and nonreferral of patients associated with worse survival (Table 6).

Overall, the most common cause of death was cardiovascular disease (39.7%), followed by infection (26.6%) and cancer (18.6%). Renal failure accounted for only 4.8% of deaths; 87.7% of these were in the unreferred group.

Mortality rates were indirectly standardized to an age- and sex-matched population from the southeast of England in 2001.[20]

SMRs were similar in the unreferred and renal groups (1.53; 95% CI, 1.44 to 1.62 versus 1.51; 95% CI, 1.13 to 1.89). In the unreferred group, SMR was greater for men compared with women (1.68; 95% CI, 1.53 to 1.83 versus 1.43; 95% CI, 1.31 to 1.54). The SMR in the unreferred group

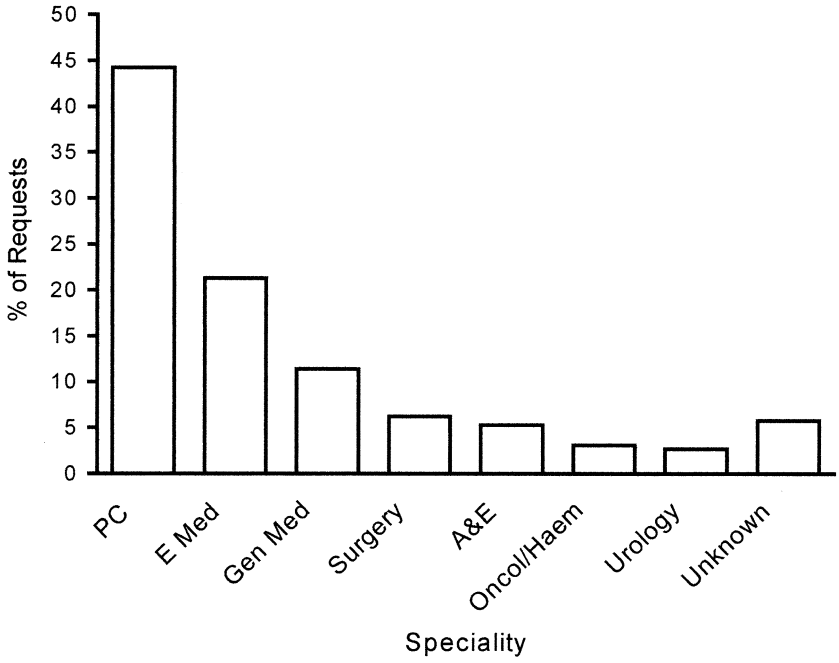


**Fig 1. Origin of creatinine request by specialty. Abbreviations: PC, Primary Care; E Med, Elderly Medicine; Gen Med, General Medicine; A&E, Accident and Emergency Centre; Oncol/Haem, Oncology and Haematology.**

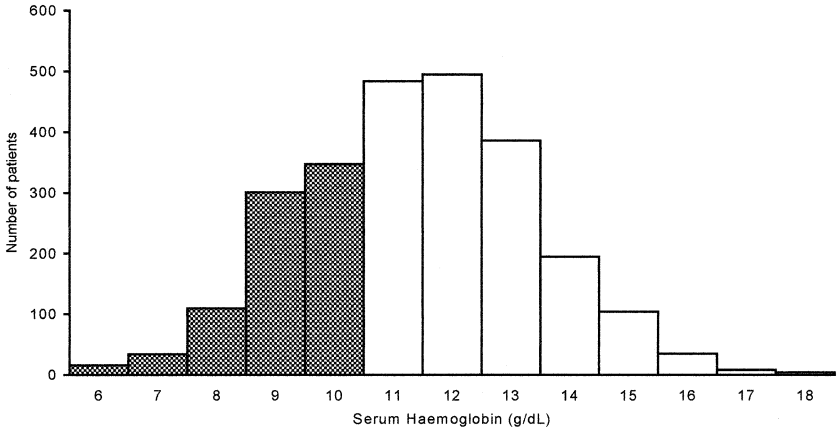


**Fig 2. Distribution of serum hemoglobin levels in 2,774 patients with unreferred CKD. Mean, 12.1 ± 1.9 g/dL; 27.5% had a serum hemoglobin level less than 11 g/dL (checkerboard). To convert hemoglobin in g/dL to g/L, multiply by 10.**

was greater in patients younger than 60 years (34.5; 95% CI, 22.54 to 46.8), but was still appreciable in older age groups (8.8; 95% CI, 6.7 to 11.0 in patients aged 60 to 70 years; 3.2; 95% CI, 2.8 to 3.6 in patients aged 70 to 80 years, and 1.2; 95% CI, 1.12 to 1.28 in patients ≥80 years).

For all patients, the SMR for cardiovascular deaths was 1.14 (95% CI, 1.03 to 1.25); the cardiovascular SMR was greatest in younger patients (<60 years; SMR, 10.8; 95% CI, 1.28 to 20.32) and lowest in patients 80 years and older (0.96; 95% CI, 0.86 to 1.06). No significant differences were seen between the renal and study groups.

Progression of renal disease was assessed in the unreferred group if a repeated SCr measurement had been requested. Patients who died in the first year were excluded from the analysis. Follow-up SCr results were available for 1,513 of 2,140 patients. Sixty-one percent of patients 80 years and older did not have a repeated SCr result compared with 13.3% of patients younger than 80 years. Table 7 lists percentages of patients with progressive CKD. The majority of patients had stable renal disease during the study, and there were no significant differences in rates of decline between men and women. The incidence of new unreferred patients during the first follow-up year was 2,435 pmp. Median age of this group was 81 years (range, 18 to 103 years),

**Table 6. Survival of Unreferred Patients With CKD**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Variable | Hazard Ratio | 95% CI | *P* | Hazard Ratio | 95% CI | *P* |
| Age (y) | | | | | | 0.113 |
| <50 | 1 | | | 1 | | |
| 51-60 | 2.40 | 1.23-4.70 | 0.011 | 2.43 | 1.24-4.76 | |
| 61-70 | 1.96 | 1.07-3.60 | 0.029 | 1.97 | 1.07-3.62 | |
| 71-80 | 2.05 | 1.15-3.65 | 0.015 | 1.92 | 1.08-3.43 | |
| ≥80 | 2.20 | 1.25-3.90 | 0.007 | 1.95 | 1.10-3.46 | |
| Sex | | | | | | <0.001 |
| Men | 1 | | | | | |
| Women | 0.75 | 0.67-0.84 | <0.001 | 0.73 | 0.65-0.82 | |
| GFR (mL/min/1.73 $m^2$) | | | | | | <0.001 |
| CKD stage 3 (30-42.8) | 1 | | | | | |
| CKD stage 4 (15-30) | 1.14 | 1.25-1.60 | <0.001 | 1.41 | 1.25-1.60 | |
| CKD stage 5 (<15) | 2.89 | 2.35-3.54 | <0.001 | 3.12 | 2.53-3.83 | |
| Group | | | | | | <0.001 |
| Renal | 1 | | | | | |
| Unreferred | 1.74 | 1.35-2.24 | <0.001 | 2.04 | 1.56-2.64 | |

**Table 7. Progression of CKD in the Unreferred Group by Age and Sex**

| | | Rate of Decline in GFR (mL/min/1.73 m²/y) | | | | |
|---|---|---|---|---|---|---|
| Age (y) | Sex | <2.0 | 2.0-2.9 | 3.0-3.9 | 4.0-4.9 | ≥5.0 |
| <70 | Men (%) | 81.7 | 2.4 | 4.8 | 4.8 | 6.3 |
| | Women (%) | 82.4 | 4.4 | 4.4 | 4.4 | 4.4 |
| | All (%) | 82.0 | 3.6 | 4.6 | 4.6 | 5.2 |
| 70-80 | Men (%) | 79.8 | 4.1 | 3.8 | 4.1 | 8.2 |
| | Women (%) | 82.9 | 5.1 | 3.8 | 2.4 | 5.8 |
| | All (%) | 81.7 | 4.7 | 3.7 | 3.1 | 6.8 |
| ≥80 | Men (%) | 76.7 | 4.8 | 2.8 | 4.2 | 11.5 |
| | Women (%) | 77.6 | 5.8 | 3.9 | 3.9 | 8.8 |
| | All (%) | 77.3 | 5.5 | 3.4 | 4.0 | 9.8 |
| All | Men (%) | 78.5 | 4.3 | 3.3 | 4.3 | 9.6 |
| | Women (%) | 79.6 | 5.5 | 3.9 | 3.5 | 7.5 |
| | All (%) | 79.3 | 5.0 | 3.7 | 3.7 | 8.3 |

NOTE. GFR calculated using the modified MDRD formula.

median calculated GFR was 29.3 mL/min/1.73 $m^2$ (range, 3.2 to 40.5 mL/min/1.73 $m^2$), and only 37.7% were men. After excluding patients from the original cohort who were either referred to the renal service or died in the first year, the prevalence of unreferred CKD remained constant at 4,910 pmp.

## DISCUSSION

To reduce the health burden that CKD poses, patients need to be identified, assessed, and entered into a management program early in the disease process. Understanding of the prevalence of CKD is needed to identify and implement these strategies and thus decrease adverse outcomes. The issue of which patients with CKD need to be referred to renal services and when this referral should occur is not easy to answer. This is reflected in a tendency for patients with CKD to be referred with advanced[26] or end-stage disease[16] or not be referred at all,[8,18,19,27] with detrimental consequences in terms of patient morbidity and mortality.[11-15]

The Kidney Disease Outcomes Quality Initiative (K/DOQI) CKD Workshop produced an action plan for the various stages of CKD.[28] It suggests that patients with stage 3 CKD (GFR, 30 to 59 mL/min/1.73 $m^2$) should be evaluated for complications and treated accordingly, and patients with stage 4 CKD (GFR, 15 to 29 mL/min/1.73 $m^2$) should be prepared for renal replacement therapy. In the United Kingdom, the Renal Association currently recommends referral of patients with progressive CKD when SCr level is 1.70 to 2.26 mg/dL or greater (≥150 to 200 $\mu$mol/L).[10] Currently, little information is available to advise whether seeing all patients with stages 3 to 4 CKD would be practical, cost-effective, or associated with a beneficial outcome. Previous estimates of the prevalence of CKD suggest that referral of all patients would overwhelm renal services. In the United States, data from the Third National Health and Nutrition Examination Survey (NHANES III) suggest that 4.3% of the general population have stage 3 CKD and 0.2% have stage 4 CKD.[29]

In this study, the prevalence of CKD identified by an SCr level of 2.03 mg/dL or greater (≥180 $\mu$mol/L) in men and 1.53 mg/dL or greater (≥135 $\mu$mol/L) in women[21] was 0.56% of the general population. These levels approximate to a significantly reduced GFR of 30 to 40 mL/min/1.73 $m^2$ or less,[30] and median GFR of the cohort was 28.5 mL/min/1.73 $m^2$.

The majority of patients identified were women, which is at odds with previous epidemiological studies[9,31] and the greater prevalence of male patients on dialysis therapy.[32] Jones et al[31] analyzed NHANES III data using an SCr level greater than 1.7 mg/dL (>150 $\mu$mol/L) to define chronic disease and found a prevalence rate of 2.49% in men and 0.71% in women. Jungers et al[9] reported a greater percentage of men (64%) than women with an SCr level greater than 2.26 mg/dL (>200 $\mu$mol/L). Both studies were biased against women because they used a single SCr

cutoff value. Culleton et al,[33] using different cutoff values for men (1.5 mg/dL [136 μmol/L]) and women (1.4 mg/dL [120 μmol/L]), reported a similar prevalence in both sexes; 8.9% in men and 8.0% in women. However, those SCr levels do not equate to similar GFRs (applying the MDRD formula to the SCr value used produces a GFR between 8 and 10 mL/min/1.73 $m^2$ greater in men than women of the same age). The SCr cutoff values used in our study approximate to the same level of calculated GFR and have shown a female predominance in the CKD population as a whole, but a male dominance in the population known to the renal service. Female patients may be denied early referral if attending clinicians use SCr level to guide referral, rather than calculated GFR.

The estimated prevalence may not reflect the true level of CKD for several reasons. First, SCr generally is accepted as an insensitive measure of early renal impairment. Levels vary depending on age, sex, muscle mass, and diet,[34] such that "normal" serum levels can significantly mask reduced renal function.[35] Duncan et al[36] reported that 14% of outpatients with an SCr level within the normal range had a calculated GFR less than 50 mL/min/1.73 $m^2$. Our study does not take account patients with a significantly reduced GFR for whom SCr level is less than the cutoff criteria. Use of a single random SCr measurement to define CKD, as used in the NHANES III analyses, also is an area of concern.[29,31,37] Within-person random errors caused by day-to-day variations in SCr levels will lead to misclassification of patients. The SCr of healthy individuals can vary during the day from a minimum of 0.97 mg/dL (86 μmol/L) at night to a maximum of 1.38 mg/dL (122 μmol/L) during the day.[38] Furthermore, systematic laboratory errors may give SCr measurements that differ from 0.1 to 0.2 mg/dL (8 to 17 μmol/L).[39] Such random and systematic errors will result in an overestimation of the number of patients with an SCr level greater than a certain cutoff value.[40] Although SCr levels were processed at 2 different laboratories in this study, both laboratories used the same standardized technique; thus, systematic errors should be kept to a minimum. We also reviewed individual SCr levels on a regular basis and excluded patients for whom SCr level subsequently decreased to less than the cutoff criteria and also those with a single increased SCr level if they had a normal-range SCr result within the previous 6 months. Therefore, any errors caused by random misclassification should be reduced.

Second, the population studied is predominantly Caucasian. Black and Asian people receive and have a greater need for renal replacement therapy, and this will not be reflected in the prevalence rate described.[41] Third, prevalence rate is based on the assumption that the entire population has had an SCr level measured; this clearly is not the case. Consequently, the true prevalence is likely to be greater; therefore, the number of patients known to the renal service will be less than the 15.2% described.

The unreferred population is older (81.3 ± 14.1 versus 66.3 ± 13.9 years), has a greater percentage of women (60.8% versus 43.8%), and has a greater median GFR (26.7 ± 6.3 versus 23.6 ± 6.3 mL/min/1.73 $m^2$) than the known population.

Sex, age, and level of GFR appear to influence referral patterns. Twenty percent of men were known to the renal services compared with only 11.4% of women.

The percentage of known patients declined with age from approximately 50% in the younger age group to only 3.6% in patients 80 years and older. Referral rates increased with declining GFR from 9.6% in patients with a GFR between 30 and 42.8 mL/min/1.73 $m^2$ to 16.2% in patients with stage 4 CKD (GFR, 15 to 29 mL/min/1.73 $m^2$) and 34.7% in patients with stage 5 CKD (GFR $<$ 15 mL/min/1.73 $m^2$). Excluding patients 80 years and older, the corresponding figures were 19.0%, 38.5%, and 63.6%. The latter compares with that reported by Feest et al,[19] in which 66% of patients with stage 5 CKD (SCr $>$ 500 μmol/L) younger than 80 years had been referred. Irrespective of age and sex, there clearly is underreferral of patients with stage 3 and 4 CKD; however, not all of this is inappropriate. The prevalence of unreferred CKD is 4,708 pmp, with an incidence of 2,435 pmp/y. In the United Kingdom, the Kidney Alliance suggested that 8 new patients could be seen in a clinic session (3.5 hours).[42] Seeing incident patients alone for initial assessment would require an extra 300 sessions/pmp/y and a significant increase in consultant numbers.

Age, comorbidity, cause of renal disease, and

rate of progression need to be considered in making a decision about whether patients should be referred to a nephrologist. Of great importance is the high mortality associated with unreferred CKD; 38.6% of patients had died by the end of the study. Although the lack of comorbid data at baseline limits any conclusions that may be drawn, nearly half the deaths were from cancer or infection. It is unlikely that these patients would have benefited from renal referral. The SMR is 34-fold in the younger age group (<60 years); however, the majority of unreferred patients are 80 years or older, for whom the SMR is only 1.2-fold. Furthermore, only 4.8% of deaths were caused by renal failure. The possible influence that renal referral can have on these outcomes needs to be questioned and investigated further. Not all causes of CKD need to be managed by a nephrologist. Obstructive uropathy, particularly when caused by prostatic outflow obstruction, is a disease preventable through adequate screening of renal function in men with untreated prostatism and closer follow-up of patients with CKD at the time of prostatectomy.[43] A nephrologist need become involved in the care of such patients only if there is evidence of progressive disease or complications of renal failure. At least 3% of patients in this study were under the care of urologists.

The age-related decline in renal function is approximately 1 mL/min/y[44] and has been reported to be slower in women,[45,46] although a recent study found no difference after adjusting for factors associated with progression.[47] In the MDRD study, 85% of patients showed a decline in GFR during a 2-year period, with an average rate of decline of 4 mL/min/y.[48] The majority of unreferred patients in this study had stable renal function; only 20% of patients showed a decline in GFR greater than 2 mL/min/1.73 $m^2$/y. There were no significant differences in decline in GFR observed between men and women. One reason for this may be that sex hormones may mediate effects on sex, and the majority of patients in this study are postmenopausal.[49] These patients with nonprogressive renal disease are unlikely to benefit from preparation for renal replacement therapy. However, there is increasing evidence that early CKD, irrespective of the risk for progression, serves as a marker of increased mortality, particularly from cardiovascular disease.[2,50] Patients with CKD should be considered at high risk for cardiovascular death and be managed appropriately irrespective of whether they are referred to a nephrologist. Overall, the SMR in those older than 80 years was 1.2, and the cardiovascular SMR was 0.96, suggesting that cardiovascular primary prevention in this age group may have little value. Other studies have not looked at this particular age group, and this clearly merits additional study.

Modification of cardiac risk in CKD involves not only the treatment of traditional risk factors, but attention to uremic risk factors and, in particular, anemia. Anemia develops early in the course of CKD,[51] and its correction is known to have beneficial effects on cardiac function.[52-54] The prevalence of anemia identified in the unreferred population is in keeping with other studies,[52,55] with 27.5% having a hemoglobin level less than 11 g/dL (110 g/L). Consequently, although all patients with CKD need to enter a management program, as outlined in the K/DOQI guidelines, renal referral should be reserved for patients with progressive disease or renal complications, such as anemia, and not based on level of GFR.

To be effective, the guidelines need to be properly targeted. Although the majority of SCr measurements in this study were requested through Primary and General Medical Care, significant numbers came from Surgery and the Accident and Emergency Centre and represent lost opportunities for assessment. Management programs need to take account of this.

In conclusion, this study identifies a large pool of patients with CKD that is currently unknown to renal services. Referral of all patients would overwhelm available renal resources; thus, guidelines are needed to aid the identification, assessment, and management of patients with the aim of modifying cardiovascular disease risk and pinpointing patients who would benefit from renal referral. The aims of referral would be to manage progressive disease, treat renal complications, and institute preparation for renal replacement therapy. Patients with stable disease without underlying complications could undergo regular monitoring in the community and general medical clinics. Protocols to facilitate this process need to be established and focused at a primary care level, as well as at hospital practitioners.

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