Outcomes in Patients with Chronic Kidney Disease Referred Late to Nephrologists: A Meta-analysis

Micah R. Chan MD, MPH

Department of Medicine, Division of General Internal Medicine, Milwaukee

Purpose

The study purpose was to compare differences in mortality and the duration of hospitalization in patients with chronic kidney disease who are referred early versus late to nephrologists.

Methods

We searched English-language literature from 1980 through December 2005, along with national conference proceedings, the Web of Science Citation Index, and reference lists of all included studies. Twenty-two studies with a total sample size of 12,749 met inclusion criteria.

Study Questions

We intended to answer the following questions: What is the risk of mortality in end-stage renal disease patients who are referred to nephrologists late versus those referred early? What is the difference in the duration of hospitalization, at the initiation of renal replacement therapy, between end-stage renal disease patients who are referred late and those referred early? In addition, we analyzed differences in the following laboratory parameters at the initiation of renal replacement therapy in subjects referred late versus those referred early: serum creatinine; creatinine clearance; albumin; hemoglobin; and hematocrit.

Literature Sources and Search Terms

We conducted a computerized search of the literature for clinical studies that addressed the issue of referral to nephrologists published during the period 1980 through December 2005 using MEDLINE, PREMEDLINE, and CINAHL. We used combinations of terms related to referral (referral, referral and consultation, timing, time factors), nephrology (chronic kidney disease, CKD, chronic kidney failure, end-stage renal disease, and ESRD), and dialysis (dialysis, renal dialysis, renal replacement therapy, and RRT). This strategy also combined 5 exploded Medical Subject Headings (referral and consultation, time factors, chronic kidney failure, dialysis, and renal replacement therapy).

Further, we hand searched journals that were indexed in the Web of Science-Science Citation Index from the years 1998 through 2005. We also examined the reference lists of all articles identified in the search as well as those of review articles. We reviewed the abstracts of the American Society of Nephrology, European Renal Association/European Dialysis Transplant Association, and National Kidney Foundation annual scientific meetings from 1995 through 2005. Whenever possible, we corresponded with the authors of the abstracts to clarify questions or obtain data.

Study Selection

Inclusion criteria were a measure of timing of referral to nephrology, defined as early or late, and an assessment of outcomes related to mortality or duration of hospitalization. It was decided, a priori, to exclude any of the following categories of articles: wrong topics, editorials, reviews, practice guidelines, patient education material, or pediatric studies.

From among 325 identified citations, we reviewed all relevant articles (Figure 1). Of those, 111 were abstracts or articles appropriate for detailed review. Two authors (MRC, ATD) independently reviewed each article from the initial search to determine if inclusion criteria were met. Disagreement was resolved by consensus and, when necessary, with arbitration from a third author (HT).

Discussion

Concerted efforts are needed to decrease the high morbidity and mortality of end-stage renal disease subjects. Because chronic kidney disease is a precursor, efforts have focused on better identification of these patients. The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (NKF/KDOQI) clinical practice guidelines for chronic kidney disease have published a staging system based on glomerular filtration rate.33 The abbreviated Modification of Diet in Renal Disease (MDRD) equation allows GFR estimation from demographic characteristics and a serum creatinine value . It has been suggested that laboratories routinely report GFR along with serum creatinine, the goal being better and earlier identification of chronic kidney disease. However, having been identified, the question arises whether such patients should be managed in the primary care setting or via referral to a specialist. There are multiple guidelines and recommendations from organizations such as the KDOQI, National Institutes of Health, British Renal Association, Canadian Society of Nephrology, among others that advocate timely referral. Unfortunately, there is a paucity of hard evidence that supports any specific guidelines.

It is unarguable that earlier referral allows more time to prepare subjects for dialysis. Patients have additional time to determine their preferred treatment modality and have earlier evaluation for transplantation.5 Our analysis suggests that chronic kidney disease

patients referred late to nephrologists have nearly a 2-fold risk of death as compared with earlier referred subjects (Figure 4). The excess mortality risk appears to extend at least up to 1 year after the initiation of renal replacement therapy. Further, patients referred early are hospitalized for much shorter duration at the time of initiation of dialysis (Figure 5). Whether such risks persist beyond these time periods needs further study.

Results

There was significantly increased overall mortality in the late referral group as compared with the early referral group (relative risk 1.99; 95% confidence interval [CI], 1.66 to 2.39, P <.0001). The duration of hospital stay, at the time of initiation of renal replacement therapy, was greater in the late referred group by an average of 12 days (95% CI, 8.0 to 16.1, P = .0007). Significant heterogeneity was detected for both outcomes.

The agreement between the 2 independent authors for citations eliminated, articles included, and those reviewed in detail was excellent (κ=0.85; 95% confidence interval [CI], 0.74 to 0.96). We identified 22 studies from 10 countries conducted between 1980 and 2002 that included 12,749 patients (Table 1, available online). Only 4 studies reported duration of follow-up for a mean of 2.2±0.7 years with a range of 0.8 to 4.9 years. The average age was 55.6 years (weighted by inverse variance), and 57.3% of subjects were men (weighted for sample size). Twenty studies, 1 prospective and 19 retrospective, evaluated mortality between early and late referrals. The average mortality across all studies was 16%±3%. The overall duration of hospitalization at the initiation of renal replacement therapy was 16.8±2.6 days.

Conclusion

Timing of referral emerged to be a significant factor impacting homogeneity in the mortality outcome. Our results suggest significantly higher mortality and increased early hospitalization of chronic kidney disease subjects referred late to nephrologists as compared with earlier referred subjects.

Our meta-analysis suggests that late referral of chronic kidney disease subjects is associated with significantly increased mortality and prolonged early hospitalization of end-stage renal disease patients along with greater abnormalities in important laboratory parameters. Although more research is needed in this arena, the data suggest that an emerging mandate should focus on increased education of primary care providers and patients on chronic kidney disease and the value of management and timely referral.