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CLINICAL RESEARCH STUDY

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

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## ABSTRACT

**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.

**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.

**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. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Chronic kidney disease; Dialysis; Hospitalization; Mortality; Referral; Timing

Chronic kidney disease is a continually growing problem worldwide. It has been estimated that 8 million people in the United States have a calculated glomerular filtration rate (GFR)  $< 60$  mL/min/1.73m<sup>2</sup> and another 12 million have microalbuminuria.<sup>1</sup> The prevalence of end-stage renal disease has increased over the past decade and continues to grow. The prevalence in the US was  $> 450,000$  in 2003 and is estimated to exceed 650,000 by 2010.<sup>1,2</sup> Subjects with end-stage renal disease have an exceedingly high morbidity and mortality as compared with the general population. The annual mortality rate has consistently exceeded 170 per 1000 patient-years-at risk.<sup>1</sup>

Along with the increase in end-stage renal disease prevalence, the costs of care have increased. In the year 2010,

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the projected direct health care costs borne by the Centers for Medicare and Medicaid is projected to increase to \$28.3 billion, more than double the Medicare cost in 1998.<sup>2,3</sup> Hospitalization is a significant component, constituting about 39.6% of direct costs in 2003. Hospital days per patient-year have consistently exceeded 13.6 from 1994 through 2004.<sup>1</sup> Probably prompted by these alarming figures, Healthy People 2010 includes among its goals improving the mortality of chronic kidney disease subjects and decreasing the economic costs. Defining contributing factors related to patient outcomes is paramount to improving these dismal statistics.

Over the past several years, interest has evolved in evaluating the timing of nephrology referral in the predialytic stage of chronic kidney disease as an important variable related to prognosis. Specifically, it is of interest whether early versus late referral of these subjects improves outcome. The definition of the time factor “late” is somewhat arbitrary and varies in the literature, ranging from  $< 1$  month

to 1 year before renal replacement therapy. In general, a patient is considered to have been referred late "when management could have been improved by earlier contact with renal services."<sup>4</sup>

Potential benefits of early referral include aggressive management of several dialysis-related and nondialysis issues.<sup>5</sup> These include control of blood pressure, treatment of anemia, attention to nutrition, and correction of metabolic abnormalities in the predialysis period. The underlying hypotheses are that these issues are better managed in the specialists' realm as opposed to the primary care setting, and that better management leads to improved outcome. Prior individual studies that have explored this issue consist of relatively small sample sizes and are predominantly retrospective. Further, results may be confounded by case-mix characteristics and regional differences in practice patterns. Therefore, the true benefit of early referral remains uncertain.

## METHODS

### 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).

### Data Abstraction

Of the 111 studies reviewed in detail, 36 were eliminated due to non-English studies, duplicate reports, case reports, simulation-based data, or reviews. Of the remaining 75 studies that assessed the timing of referral to nephrology, 53 were eliminated due to undefined or inestimable time factors, outcome of interest not available, or insufficient relevant data. Finally, 22 studies were retained for further analysis.

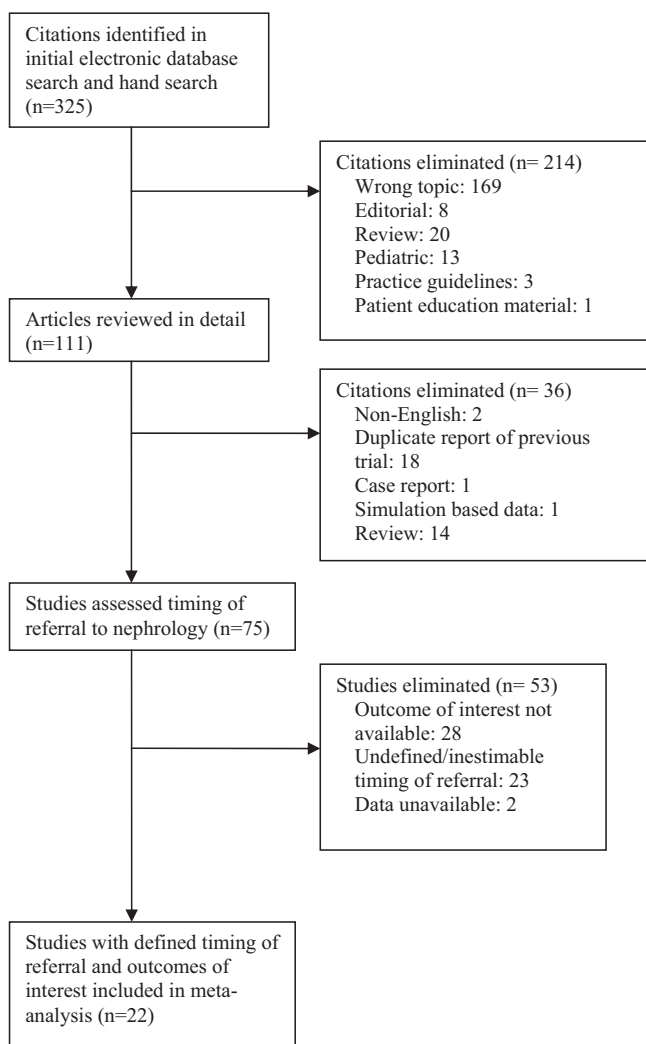
The data from each included article were abstracted by 2 authors (MRC, ATD). We used a standardized abstraction form that included patient number, demographics, control and study group information, study design, primary and secondary outcomes, and methodological concerns. Disagreements were resolved through consensus or by a third reviewer (HT). We were able to correspond with authors from 2 of the 4 studies for which we needed clarification.

### Statistical Analysis

The primary outcomes of interest were mortality and duration of hospitalization in the late versus early referred

## CLINICAL SIGNIFICANCE

- Early nephrology referral in the predialytic stage of chronic kidney disease improves outcomes in end-stage renal disease.
- In dialysis patients, prior early referral shortened hospital stays and decreased mortality by half, compared with late referral.
- Primary care physicians should receive increased training in diagnosis and evaluation of chronic kidney disease and the value of comanagement and timely referral.
- Specific guidelines for "early referral" have not yet been established.



**Figure 1** Literature search strategy.

groups of patients. Risk ratios of late versus early referred patients, as defined in individual studies, were calculated based on the mortality data reported in each study.<sup>6</sup> Similarly, differences in the duration of hospitalization between the late and early referred groups were calculated for each study. We employed Cochrane's Q tests to detect between-study heterogeneity. Random effects models based on moment methods, which detect within-study and between-study variation, were used to derive pooled risk ratios, difference in hospitalization days, and their variations. Estimates were computed using PROC MIXED in SAS v. 9.0 (SAS Institute Inc., Cary, NC). Subgroup analyses for 1-year mortality were done in a similar fashion.

In meta-regression models we evaluated timing (definition of early vs late referral) and design (prospective vs retrospective) as potential factors that might account for heterogeneity between studies. Exploratory meta-regressions were conducted using log-linear and linear models using PROC MIXED in SAS v.9.0. We considered a significance level of 0.1 in the univariate models for inclusion in multivariable meta-regression.

The secondary outcomes consisted of various laboratory parameters in the late versus early referred groups: albumin, hemoglobin, hematocrit, creatinine, and creatinine clearance. Meta regression, weighted by inverse variance, was used to assess the differences in the laboratory results.

Kappa statistics were used to assess the agreement between 2 independent reviewers. Rank correlation coefficients, Spearman's rho, and Kendall's tau were used to assess publication bias.<sup>7</sup>

## RESULTS

The agreement between the 2 independent authors for citations eliminated, articles included, and those reviewed in detail was excellent ( $\kappa = 0.85$ ; 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).<sup>8-29</sup> Only 4 studies reported duration of follow-up for a mean of  $2.2 \pm 0.7$  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  $16\% \pm 3\%$ . The overall duration of hospitalization at the initiation of renal replacement therapy was  $16.8 \pm 2.6$  days.

The definition of timing varied from study to study. Late referral defined as <3 months before initiation of renal replacement therapy had the highest cumulative frequency in the mortality studies, and the definition of <4 months in the studies that reported duration of hospitalization.

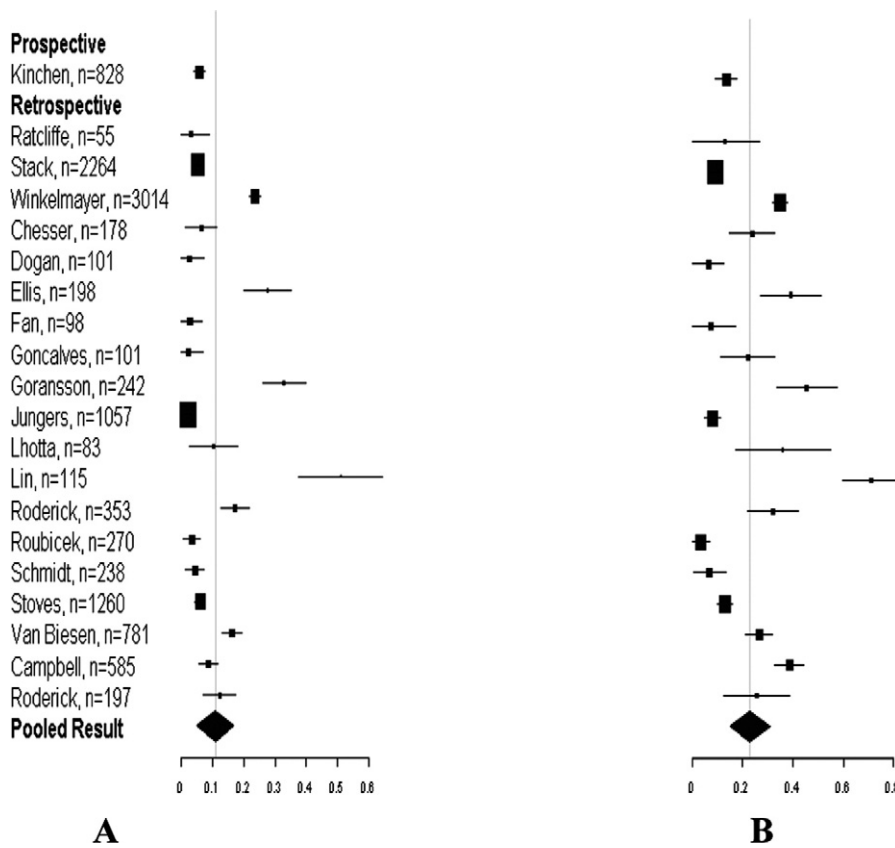
## Assessment of Study Quality

We defined studies as truly prospective only in instances in which the study was clearly planned at the time of collation of the study cohort, that is, a priori.<sup>30</sup> Only in such circumstances would study follow-up procedures be expected to be conducted for the purposes of the study question. Thus, post hoc analysis of a prospective study cohort was considered retrospective. Three study designs were prospective cohort trials and the rest were retrospective.

We assessed study quality by using a modification of the US Preventive Services Task Force criteria described by Fletcher et al.<sup>31,32</sup> These criteria assist in grading the internal validity of studies based on evidence-based guidelines. By these standards, properly designed randomized controlled trials constitute the highest tier evidence; well-designed nonrandomized trials, case-control, or cohort analytic studies provide second-tier evidence. All studies that were identified provided second-tier evidence (Table 2, available online).

## All-Cause Mortality

Our primary meta-analysis pooled results from 20 studies (total  $n = 12,018$ ) that presented mortality data in early and late referred groups of subjects. Using random effects models, pooled estimates of death in the late referral group was



**Figure 2** Mortality rate (percent/100) in the early (A) and late (B) referred groups of patients. Mean (black boxes) and 95% confidence bounds (horizontal lines).

23% ± 4%, compared with 11% ± 3% in the early referral group (Figure 2). Late nephrology referral of chronic kidney disease patients was associated with a significantly increased risk of death (relative risk [RR] 1.99; 95% CI, 1.66 to 2.39; *P* <.0001) (Table 3).

### Duration of Hospitalization at the Initiation of Renal Replacement Therapy

Eight studies assessed timing of referral and its impact on duration of hospital stay (total n = 3220). Late referred patients had a mean hospital stay of 25.3 ± 3.8 days at the time of initiation of renal replacement therapy, and early referred patients had a mean hospital stay of 13.5 ± 2.2 days (Figure 3). The prolonged duration of hospitalization in the late referred group, by an average of 12 days, was highly significant (95% CI, 8.0 to 16.1; *P* = .0007) (Table 3).

### Laboratory Parameters

The mean serum creatinine and creatinine clearance were not significantly different between the early and late referred groups. However, the late referred group had significantly lower albumin and hematocrit values at the initiation of renal replacement therapy (Table 4). There was a trend toward higher hemoglobin values in the early referred group, which, however, did not reach statistical significance.

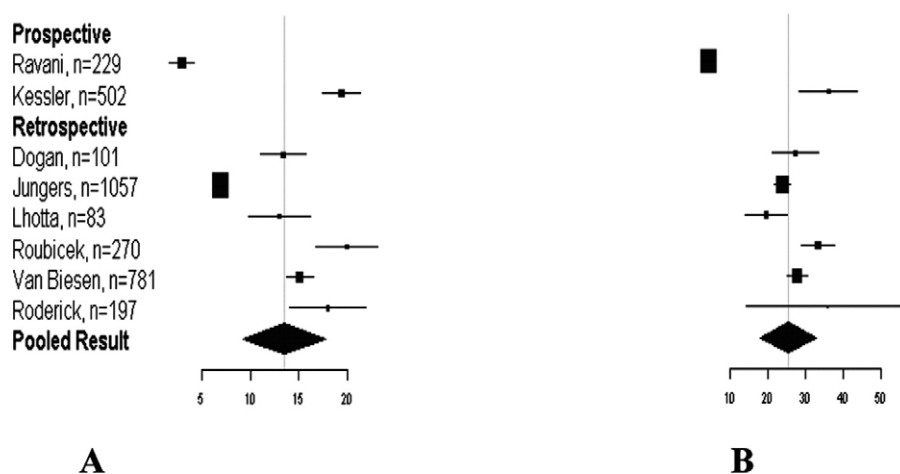
### Test of Homogeneity

There was significant heterogeneity across studies with respect to both the mortality (*I*<sup>2</sup> = 63%; *Q* = 53.2, *P* <.0001) and hospitalization duration (*I*<sup>2</sup> = 94%; *Q* = 149.6, *P* <.0001) outcomes. For the mortality outcome, meta-regression revealed that timing (definition of early and late) was a highly significant factor impacting homogeneity (*P* = .0005). The

**Table 3** Summary Outcome Based on Timing of Referral

Variable	Early Referrals Mean (SD)	Late Referrals Mean (SD)	Risk Ratio or Difference* (95% CI)	<i>P</i> -Value
Overall mortality (%) [n = 12,018]	11 (3)	23 (4)	1.99 (1.66-2.39)	<.0001
Duration of hospitalization at initiation of renal replacement therapy (days) [n = 3220]	13.5 (2.2)	25.3 (3.8)	12 (8-16.1)	.0007
1-year mortality (%) [n = 4777]	13 (4)	29 (5)	2.08 (1.31-3.31)	.028

\*Risk ratio for the mortality outcome, difference for the hospitalization outcome.



**Figure 3** Duration of hospitalization (days) at the time of renal replacement therapy in the early (A) and late (B) referred groups of patients. Mean (black boxes) and 95% confidence bounds (horizontal lines).

data did not permit adequate meta-regression analysis for the hospitalization outcome.

**Publication Bias**

There was no evidence of publication bias for either the mortality (Spearman’s rho 0.22, *P* = .34; Kendall’s tau = 0.16; *P* = .31) or hospitalization duration outcomes (Spearman’s rho 0.38, *P* = .35; Kendall’s tau = 0.29; *P* = .32).

**Subgroup Analyses**

A subgroup analysis of 1-year mortality depicted a conclusion similar to the primary results, a relative risk of death of 2.08 in the late referred group (95% CI, 1.31 to 3.31, *P* = .028) (Table 3). Further, there were no differences in the conclusions if the analysis incorporated weighting based on the frequency of the various timing definitions, for either the mortality or hospitalization duration outcomes (data not shown).

**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

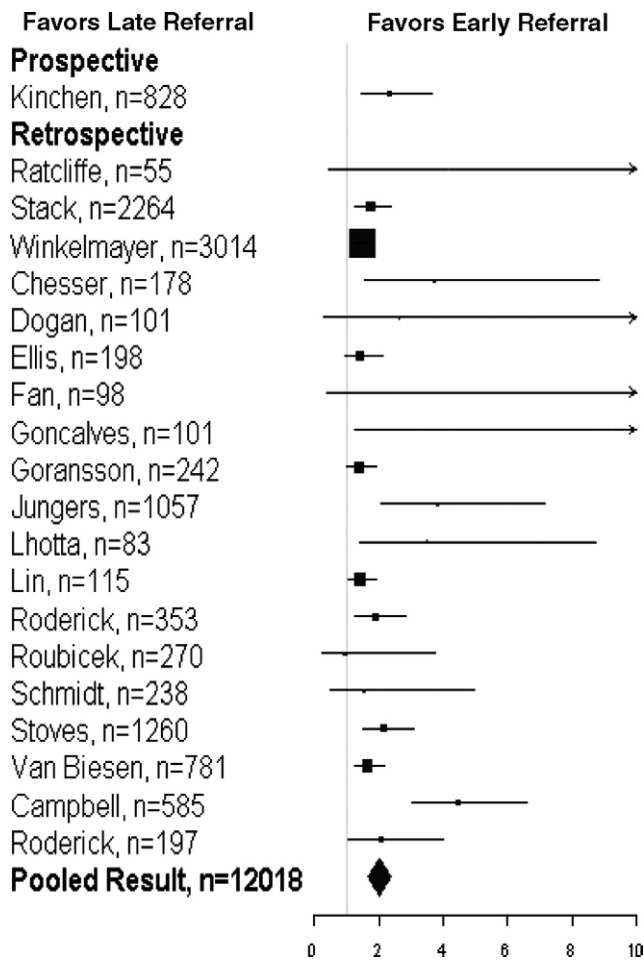
glomerular filtration rate.<sup>33</sup> The abbreviated Modification of Diet in Renal Disease (MDRD) equation allows GFR estimation from demographic characteristics and a serum creatinine value . It has been suggested that laboratories routinely report GFR along with serum creatinine, the goal being 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,<sup>33-36</sup> 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.<sup>5</sup> 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.

**Table 4** Reported Laboratory Values at Initiation of Renal Replacement Therapy

Laboratory Values	Early Referrals – Mean (SD)	Late Referrals – Mean (SD)	<i>P</i> -Value*
Serum albumin (g/dL)	3.62 (0.05)	3.40 (0.03)	.001
Hemoglobin (g/dL)	9.48 (0.36)	9.05 (0.31)	.07
Hematocrit (%)	30.54 (0.18)	29.71 (0.10)	.013
Serum creatinine (mg/dL)	8.33 (0.32)	8.96 (0.53)	.103
Creatinine Clearance (mL/min)	7.48 (0.69)	6.51 (0.86)	.47

\**P* values obtained by meta-regression weighted by inverse variance.



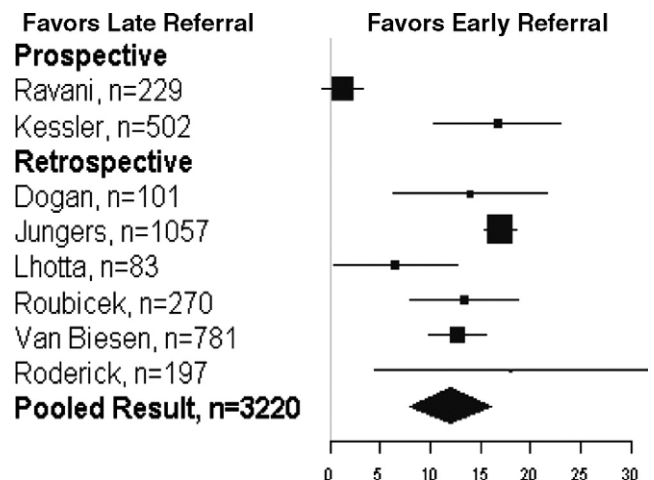
**Figure 4** Risk ratios of mortality in late/early referred groups. Mean (black boxes) and 95% confidence bounds (horizontal lines).

Therefore, the current body of evidence suggests there is need for improvement in the timing of referral for predialysis care. The opportunity for intervention begins with the primary care physician with proper identification and evaluation of chronic kidney disease. The NKF/KDOQI guidelines define a continuum of comanagement between specialist and primary care, referral or comanagement with a nephrologist at stage 3 chronic kidney disease (GFR 30 – 59 mL/min/1.73m<sup>2</sup>), and referral at stage 4 (GFR < 30 mL/min/1.73m<sup>2</sup>).<sup>33,37</sup>

Increased mortality of chronic kidney disease patients who are referred late and the issue of early nephrology referral have significant ramifications with regards to resource availability and utilization. Current data suggest that if the referral guidelines for chronic kidney disease subjects were universally followed, the health care system would be overwhelmed.<sup>38,39</sup> Further, a shortage of nephrologists is projected for handling the currently increasing patient burden, even if practice patterns, vis-à-vis referral, do not change.<sup>40</sup> Alternate approaches might be identification of the particular facets of care that are improved by early referral and implementation of strategies to improve universal care in these regards. We identified that earlier referred patients have

higher albumin and lesser degrees of anemia, both factors that are associated with better survival in end-stage renal disease subjects.<sup>41-43</sup> In a small series, patients referred to nephrologists early had better blood pressure control and were more frequently prescribed renoprotective agents such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.<sup>44</sup> Whether broad education strategies would enable delivery of optimal care in the primary care setting with equitable outcomes needs further study.

There are limitations of the present study. Firstly, we identified significant heterogeneity, implying a significant variation of effect (of early referral) across the studies. We recognized this as an inherent deficiency given the varying definitions of late referral (Table 1). We employed the random effects model that considers intrinsic random between-study variance of effect besides variance due to sampling error or within-study variance.<sup>7,45</sup> Moreover, differences between studies in key methodological issues such as, in the present case, due to variation in definition of late referral, can be expected to lead to differences in the observed effects. Statistical heterogeneity due to such methodological variation may not necessarily imply that the actual intervention effect differs.<sup>46</sup> Meta-regression demonstrated that the definition of “late” was a significant factor impacting homogeneity. Further, it must be pointed out that the sample population largely consists of subjects with advanced chronic kidney disease, close to requiring renal replacement therapy. It cannot be said with certainty that similar results would be obtained if referral-pattern-related outcomes were examined in the earlier stages, without additional study. Moreover, the majority of studies were retrospective with only 3 prospective cohort studies included. The predominance of retrospective studies may lead to confounding bias due to unrecognized differences between groups. Randomized controlled trials, to determine whether early referral of subjects leads to better outcome, would be fraught with unavoidable bias due to the inherent unblinded nature of



**Figure 5** Difference in the duration of early hospitalization (days) in late minus early referred groups. Mean (black boxes) and 95% confidence bounds (horizontal lines).

such a study, and may not be feasible due to ethical concerns. It is likely that such a trial will never occur.

## CONCLUSION

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 comanagement and timely referral.

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**Table 1** Summary of Included Studies

Source	Primary Location	Number of Patients	Study Design	Study Years	Mean Age (Years)	Male, Number (%)	Definition of Late Referral (Months)
Campbell et al, 1989 <sup>8</sup>	Missouri, US	585	Retrospective cohort	1982-1984	...	...	<1
Chesser and Baker, 1999 <sup>9</sup>	London, United Kingdom	178	Retrospective cohort	1993-1995	...	...	<3
Dogan et al, 2005 <sup>10</sup>	Van, Turkey	101	Retrospective cohort	1998-2002	44.8	54 (53)	<3
Ellis et al, 1998 <sup>11</sup>	London, United Kingdom	198	Retrospective cohort	1996-1997	59.8	116 (59)	<3
Fan et al, 2002 <sup>12</sup>	London, United Kingdom	98	Retrospective cohort	1998-1999	51.2	58 (59)	<1
Goncalves et al, 2004 <sup>13</sup>	São Paulo, Brazil	101	Retrospective cohort	1997-1999	51.3	62 (61)	<3
Goransson and Bergrem, 2001 <sup>14</sup>	Stavanger, Norway	242	Retrospective cohort	1984-1998	...	163 (67)	<3
Jungers et al, 2001 <sup>15</sup>	Paris, France	1057	Retrospective cohort	1989-1998	53.8	673 (64)	<6
Kessler et al, 2003 <sup>16</sup>	Nancy, France	502	Prospective cohort	1997-1999	62.8	298 (59)	<1
Kinchen et al, 2002 <sup>17</sup>	Massachusetts, US	828	Prospective cohort	1995-1998	...	457 (55)	<4
Lhotta et al, 2003 <sup>18*</sup>	Innsbruck, Austria	83	Retrospective cohort	1999-2000	56.9	...	<4
Lin et al, 2003 <sup>19</sup>	Taipei, Taiwan	115	Retrospective cohort	1988-2001	64.1	53 (46)	<6
Ratcliffe et al, 1984 <sup>20</sup>	Oxford, United Kingdom	55	Retrospective cohort	1981-1982	...	...	<1
Ravani et al, 2003 <sup>21</sup>	Cremona, Italy	229	Prospective cohort	1999-2002	66.4	142 (62)	<3
Roderick et al, 2002 <sup>22</sup>	Southampton, United Kingdom	197	Retrospective cohort	1997-1998	56.1	113 (57)	<4
Roderick et al, 2002 <sup>23</sup>	Southampton, United Kingdom	353	Retrospective cohort	1996-1997	...	206 (58)	<1
Roubicek et al, 2000 <sup>24</sup>	Marseille, France	270	Retrospective cohort	1989-1996	57.3	162 (60)	<4
Schmidt et al, 1998 <sup>25</sup>	West Virginia, US	238	Retrospective cohort	1990-1997	61	110 (46)	<1
Stack, 2003 <sup>26</sup>	Texas, US	2264	Retrospective cohort	1996-1997	58.1	1220 (54)	<4
Stoves et al, 2001 <sup>27</sup>	Leeds, United Kingdom	1260	Retrospective cohort	1980-1999	52.6	764 (61)	<3
Van Biesen et al, 1998 <sup>28†</sup>	Gent, Belgium	781	Retrospective cohort	1996-1997	61.1	445 (57)	<1
Winkelmayer et al, 2003 <sup>29</sup>	Massachusetts, US	3014	Retrospective cohort	1991-1996	...	1694 (56)	<3

\*Authors provided additional subjects' data that were incorporated into the analysis.

†Included patients from 7 European countries, specifics not provided.

**Table 2** Quality Indicators of Included Studies

Source	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Period of Follow-up Defined	Valid, Reliable Measurements	Timing Clearly Defined	Important Outcomes Considered	Statistical Analysis Performed
Campbell et al, 1989 <sup>8</sup>	Yes	Yes	No	Yes	No*	Yes	No
Chesser et al, 1999 <sup>9</sup>	Yes	Yes	No	Yes	Yes	Yes	No
Dogan et al, 2005 <sup>10</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Ellis et al, 1998 <sup>11</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Fan et al, 2002 <sup>12</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Goncalves et al, 2004 <sup>13</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Goransson and Bergrem, 2001 <sup>14</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Jungers et al, 2001 <sup>15</sup>	Yes	Yes	No	Yes	No†	Yes	Yes
Kessler et al, 2003 <sup>16</sup>	Yes	Yes	Yes‡	Yes	No§	Yes	Yes
Kinchen et al, 2002 <sup>17</sup>	Yes	Yes	Yes‡	Yes	No	Yes	Yes
Lhotta et al, 2003 <sup>18</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Lin et al, 2003 <sup>19</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ratcliffe et al, 1984 <sup>20</sup>	Yes	Yes	Yes‡	Yes	Yes	Yes	No
Ravani et al, 2003 <sup>21</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Roderick et al, 2002 <sup>22</sup>	Yes	Yes	No	Yes	No§	Yes	Yes
Roderick et al, 2002 <sup>23</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Roubicek et al, 2000 <sup>24</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schmidt et al, 1998 <sup>25</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Stack, 2003 <sup>26</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Stoves et al, 2001 <sup>27</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Van Biesen et al, 1998 <sup>28</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes
Winkelmayer et al, 2003 <sup>29</sup>	Yes	Yes	No	Yes	Yes	Yes	Yes

\*Timing based on late <1 mo, early 1-4 mo, >4 mo.

†Timing based on late <6 mo, early 6-35 mo, 36-71 mo, ≥72 mo.

‡Not included in follow-up analysis because no means or variability reported.

§Timing based on late <1 mo, early 1-4 mo, 4-12 mo, >12 mo.

||Timing based on late <4 mo, early 4-12 mo, >12 mo.