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A Propensity Analysis of Late *Versus* Early Nephrologist Referral and Mortality on Dialysis

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Abstract. Previous studies have analyzed the association between late *versus* early nephrologist referral (LR, ER) and poor clinical outcomes in patients with end-stage renal disease. We sought to determine whether these poor outcomes were causally related to LR, or whether LR was a proxy for poorer access to health care in general. An inception cohort of incident dialysis patients enrolled in the New Jersey Medicare or Medicaid programs was identified. Using a large number of demographic, clinical, and health care utilization covariates, propensity scores (PS) were then calculated to predict whether a given patient had been seen by a nephrologist at 90 d before first dialysis. Cox proportional hazards models were then built to test the association between timing of nephrologist referral and mortality during the first year of dialysis, using PS adjustment and matching to determine whether this association was confounded by other measures of reduced healthcare utilization. Neither adjustment for PS (HR = 1.31; 95% CI, 1.17 to 1.47) nor matching (HR = 1.40; 95% CI, 1.23 to 1.59) materially changed the initial 36% excess mortality in LR compared with ER patients (HR = 1.36; 95% CI, 1.22 to 1.51). Excess mortality among LR was limited to the first 3 mo of dialysis (HR = 1.75; 95% CI, 1.48 to 2.08) but not present thereafter (HR = 1.03; 95% CI, 0.84 to 1.25). Late nephrologist referral is an independent risk factor for early death on dialysis, even after controlling for other indicators of healthcare utilization. Further research is needed to identify patients at particular risk so that interventions to prevent early deaths on dialysis in LR patients can be developed and tested.

Several studies have examined the possible association between late referral to a nephrologist and mortality on maintenance dialysis in patients with chronic kidney disease (1–8). Other analyses have measured the effect of LR on outcomes such as timely vascular access creation (2,9–18), modality choice for renal replacement therapy (RRT), and technique survival (19,20) and health care costs (21). These analyses have made the implicit assumption that the association between outcomes and the timing of referral was direct, controlling for all other variables in the respective underlying multivariate models. Typically, the variables contained in such multivariate models were of demographic nature (age, race, gender, socioeconomic status) or related to comorbid conditions. It was implied, but not proven, that the favorable associations in patients referred early rather than late were a consequence of the nephrologist's contribution to their care. However, it is also possible that late nephrologist referral is merely a proxy for reduced access to adequate health care overall. If this were the case, some or all of the improved outcomes associated with early referral might instead simply be the result of better access to the healthcare system or an overall higher quality of care independent of nephrologist input.

Propensity scores are a tool that can correct for nonrandom exposure assignment and have been shown to reduce such potential bias in observational studies (22). The propensity score is the expected probability of receiving one treatment over another for a given patient, based on that patient's baseline characteristics. Typically, a logistic regression model of the actual treatment received is fit to the data, and the propensity score for each patient is then estimated. Numerous covariates as well as higher order terms and covariate interactions can thus be condensed into a single scalar variable, the propensity score (23,24). Several studies have demonstrated that propensity scores can reduce bias in observational studies to balance observed baseline covariates in two treatment groups. Once estimated, propensity scores can be used for analyses of outcomes as covariates in multivariate models, as matching factors, or to define strata for separate analyses. The use of propensity scores in analyzing the association between timing of first nephrologist referral and mortality during the first year of RRT offers a novel approach to compensate for potential differences in healthcare access and utilization among late referral *versus* early referral patients.

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Materials and Methods

The present analysis carried forward our previous findings of reduced survival on RRT in patients with delayed first referral to a nephrologist (8). We studied a large population of incident peritoneal and hemodialysis patients enrolled in the Medicaid, Medicare, or Pharmaceutical Assistance for the Aged and Disabled programs in the state of New Jersey who had progressed chronically rather than acutely to end-stage renal failure (ESRD) (n = 3014) and required chronic renal replacement therapy. To restrict the cohort in this fashion, we studied only patients who had been diagnosed with a renal disease >1 yr before first dialysis. We excluded patients who received only a single dialysis and survived >1 mo thereafter or who received a limited series of dialysis treatments and survived >2 mo. This approach defined an inception cohort of 3014 patients starting dialysis between 1991 and mid-1996. Timing of nephrologist referral was dichotomized; patients who saw a nephrologist >90 d before their first chronic dialysis were labeled as early referrals (ER), and all others were considered late referrals (LR). All traceable identifiers were removed before analysis to protect patient confidentiality. The study was approved by the institutional review board of our institution.

We calculated propensity scores using a logistic regression model, with timing of referral (LR *versus* ER) as the outcome studied. To build the propensity score model, we selected patient characteristics and healthcare utilization indicators in the 4 to 12 mo before the initiation of dialysis (Figure 1). We also included a number of higher order terms and covariate interactions (Tables 1 and 2). Model fit and predictive power were assessed using the c statistic. A c statistic of 1 indicates perfect prediction, whereas a value of 0.5 reflects random chance (25).

For the outcomes model we built a multivariate Cox proportional hazards model. Here, death was the outcome of interest; patients were censored at the earliest of 365 d after first dialysis, renal transplantation, loss to follow-up, and end of study period. The covariates that were entered into this outcomes model were assessed in the year before first dialysis (Figure 1). Those covariates were age (continuous), gender, race (White/Black/other), socioeconomic status, and a number of baseline comorbid conditions. The original models had adjusted for underlying renal disease or for a limited set of nonrenal comorbidities (hypertension, coronary artery disease, congestive heart failure, diabetes malignancy), but not for differences in healthcare utilization (8). The baseline model used here differs from the one published previously in that it contains a large number of comorbid conditions rather than renal diagnoses to control for confounding (8). Propensity scores were then used in two ways (23). First, we entered the propensity scores (in quintiles) into the same model for which the initial findings were first described. Second, we ran the same model within a population of 1039 pairs of patients from the late referral group and the early referral group who were matched by their propensity score. The propensity matching was conducted using the "greedy match" macro (26). We then sought to determine whether such control over the level of healthcare utilization changed the association between late referral and mortality in the first year of maintenance dialysis. For sensitivity analyses, we determined whether a patient had initiated dialysis on peritoneal dialysis or hemodialysis. Among those on hemodialysis, we created two variables indicating whether a peripheral vascular access procedure was performed (a) before first dialysis and (b) >14 d before onset of hemodialysis. The specific algorithms used to identify patients who started on peritoneal dialysis and who underwent surgery for peripheral vascular access before RRT among starters on hemodialysis have been published in detail previously (18).

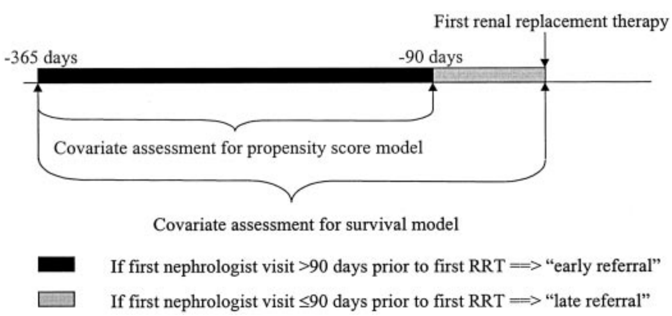

Figure 1. Periods of covariate ascertainment.

Results

Of the 3014 patients who comprised the cohort, 1429 patients died during the first year of dialysis. Twenty-one patients received a renal transplant during the first year and were censored. The remaining 1564 patients completed the 1-yr follow-up or were censored at the end of the database (June 30, 1996); no patient was lost for follow-up during the period of study. Table 3 shows the number of patients who died, were transplanted, or were censored by timing of referral and time period. The conventional model without inclusion of propensity scores indicated that patients who first saw a nephrologist ≤90 d before onset of dialysis had a 36% higher mortality rate compared with those who had their first nephrologist visit earlier (Hazards ratio [HR] = 1.36; 95% confidence interval [CI], 1.22 to 1.51) (8). Other characteristics that were associated with increased mortality were congestive heart failure (HR = 1.86; 95% CI 1.62 to 2.14), cancer (HR = 1.14; 95% CI, 1.01 to 1.29), cerebrovascular disease (HR = 1.15; 95% CI, 1.02 to 1.30), peripheral vascular disease (HR = 1.24; 95% CI, 1.09 to 1.41), liver disease (HR = 1.59; 95% CI, 1.20 to 2.10), chronic obstructive pulmonary disease (HR = 1.28; 95% CI, 1.14 to 1.43), and drug or alcohol abuse (HR = 1.50; 95% CI, 1.24 to 1.81). We then built the logistic regression model to estimate the likelihood of late referral (*i.e.*, the propensity score) for each patient, using all covariates listed in Table 1. The c statistic of the propensity score model indicated moderate prediction of late *versus* early referral (c = 0.683). When introducing quintiles of propensity scores into the otherwise identical Cox proportional hazards model, the effect estimate of LR *versus* ER on mortality was quite similar; patients referred late were now at a 31% higher risk of death compared with those referred >90 d before onset of chronic dialysis (HR = 1.31; 95% CI, 1.17 to 1.46). All other parameter estimates remained nearly identical.

Propensity scores were successfully matched on all 1039 LR patients to one patient each from the ER pool (n = 2078). A Kaplan-Meier plot of patient survival confirmed that patients who actually were referred late had a lower survival in the first year of maintenance dialysis compared with those who were referred to a nephrologist earlier, even in comparison with comparable patients who had the same expected likelihood of late referral based on their demographic characteristics and

Table 1. Covariates used to estimate propensity score for timing of nephrologist referral (≤90 d *versus* >90 d before first renal replacement therapy)

Demographic covariates	Comorbidities[b]
● age	● hypertension
● race (White/Black/other)	● diabetes
● gender	● coronary artery disease (CAD)
● socioeconomic status (SES)[a]	● congestive heart failure
	● cerebrovascular disease (CVD)
Renal underlying disease[b]	● peripheral vascular disease (PVD)
● acute (glomerulo) nephritis	● malignancy
● polycystic kidney disease	● gastrointestinal erosion/ulcer (without surgery
● diabetic nephropathy	
● hypertensive kidney disease	● severe liver disease
● chronic pyelonephritis	● obesity
● obstructive nephropathy	● chronic obstructive pulmonary disease
● renovascular disease	● HIV^{+}/AIDS
● miscellaneous	● dementia
● chronic renal disease not otherwise specified	● depression
	● alcohol or substance abuse
	● other mental disease
Healthcare utilization[b]	
● presence of primary care visits	Interaction/higher order terms
● presence of medical sub-specialist visits[c]	● age × gender, race (2 terms), SES
● presence of surgical consultations	● race × gender (2 terms), SES (2 terms)
● number of hospital days (0; 1 to 7; 8 to 28; 29^{+} days)	● diabetes × CVD, CAD, PVD
● presence of nursing home stay	● age^2, age^3
● year of first renal replacement therapy	

[a] Assessed using enrollment in Medicaid or the New Jersey Pharmaceutical Assistance for the Aged and Disabled program within the year prior to first renal replacement therapy as a proxy for lower socioeconomic status.
[b] All covariates were assessed between 365 and 91 d prior to first renal replacement therapy. Covariates were binary (absent/present) unless specifically noted otherwise.
[c] Cardiology, endocrinology-diabetology, gastroenterology-hepatology, hemato- oncology, infectious diseases, pulmonology, rheumatology.

clinical and healthcare utilization experience (Figure 2). Similarly, the corresponding Cox proportional hazards model revealed a 40% higher mortality rate during the first year among LR compared with ER (HR = 1.40; 95% CI, 1.23 to 1.59). Including the healthcare utilization covariates in the outcomes model as well did not change the results (see Table 4).

We next examined the time course of the observed mortality difference. On the basis of the Kaplan-Meier survival curve, the excess mortality rate among LR *versus* ER patients appeared limited to the first few months of RRT. We tested the validity of this impression by building two interval Cox models: one from onset of dialysis to 90 d of dialysis, the second one evaluating patients who survived 90 d of dialysis until 365 d after onset of maintenance dialysis. Indeed, the detrimental effect of late referral was limited to the first 3 mo, during which patients who were referred to a nephrologist late had a 75% excess mortality compared with those who were referred early (HR = 1.75; 95% CI, 1.48 to 2.08). After day 90 of maintenance dialysis, the death rate between those two groups was not different (HR = 1.03; 95% CI, 0.84 to 1.25).

We speculated whether the superior 90-d survival of patients who were referred early was attributable to modality choice or to vascular access creation among those starting on hemodialysis. A formal test of such a proposition is a significance test of an interaction between timing of referral and first treatment modality (peritoneal dialysis *versus* hemodialysis) in the full cohort, and between timing of referral and vascular access surgery before first dialysis among those initiating treatment on hemodialysis. Within the propensity-matched cohort, we found that baseline modality choice was not an effect modifier of the association between LR and 90-d mortality. The interaction term was nonsignificant ($P = 0.84$), and the main effect of LR was only slightly attenuated (HR = 1.66; 95% CI, 1.19 to 2.32). Similarly, we did not find a significant interaction between timing of referral and vascular access surgery before onset of dialysis on early mortality. While peripheral vascular access placement before first dialysis was associated with a survival benefit over the first 90 d of dialysis (HR = 0.66; 95% CI, 0.47 to 0.93), the test for effect modification remained nonsignificant ($P = 0.66$). Again, the effect estimate for the LR covariate remained materially unchanged. In a sensitivity analysis, we created a covariate that indicated whether a pe-

Table 2. Patient characteristics by timing of first nephrologist referral

Covariate[b]	Early Referrals[a] (n = 1975)		Late Referrals[a] (n = 1039)		P^c
	n	%	n	%	
Age (categorical)					
<45 yr	51	2.6	32	3.1	
45 to 54 yr	79	4.0	58	5.6	
55 to 64 yr	174	8.8	87	8.4	
65 to 74 yr	881	44.6	407	39.2	
75 to 84 yr	691	35.0	372	35.8	
>85 yr	99	5.0	83	8.0	0.002
Gender					
male	1,085	54.9	609	58.6	
female	890	45.1	430	41.4	0.05
Race					
White	1,484	75.1	756	72.8	
Black	391	19.8	195	18.8	
Other	100	5.1	88	8.5	0.66
Socioeconomic status					
lower	677	65.7	327	31.5	
higher	1,298	34.3	712	68.5	0.12
Hypertension	1,455	73.7	587	56.5	<0.0001
Diabetes	956	48.4	435	41.9	0.001
Coronary artery disease	1,299	65.8	594	57.2	<0.0001
Congestive heart failure	898	45.5	378	36.4	<0.0001
Peripheral vascular disease	268	13.6	109	10.5	0.015
Cerebrovascular disease	371	18.8	148	14.2	0.002
Malignancy	382	19.3	180	17.3	0.18
Upper GI erosion/ulcer (without surgery)	495	25.1	208	20.0	0.002
Severe liver disease	34	1.7	20	1.92	0.69
Massive obesity	28	1.4	9	0.9	0.19
Chronic obstructive pulmonary disease	372	18.8	168	16.2	0.07
HIV+/AIDS	18	0.9	8	0.8	0.69
Dementia	54	2.7	22	2.1	0.30
Depression	108	5.5	34	3.27	0.007
Alcohol or substance abuse	58	2.9	24	2.3	0.31
Other mental disease	215	10.9	72	6.9	0.0004
Nursing home admission	24	1.2	15	1.4	0.60
Hospital days					
none	781	39.5	581	55.9	
1 to 7 d	237	12.0	126	12.1	
8 to 28 d	568	28.8	225	21.7	
≥29 d	389	19.7	107	10.3	<0.0001
Family/primary care physician office visit					
none	536	27.1	339	32.6	
1 to 3	420	21.3	247	23.8	
4 to 10	565	28.6	270	26.0	
>10	454	23.0	183	17.6	<0.0001
Medical subspecialist office visit					
none	745	37.7	536	51.6	
1 to 3	462	23.4	207	19.9	
4 to 10	420	21.3	180	17.3	
>10	348	17.6	116	11.2	<0.0001
Surgical specialist office visit					
none	1023	51.8	699	67.3	
1	321	16.3	128	12.3	
2 to 3	345	17.5	111	10.7	
>3	286	14.5	101	9.7	<0.0001

[a] Late *versus* early referral was dichotomized at 90 d: patients who first saw a nephrologist >90 d prior to were "early referrals," otherwise they were "late referrals."
[b] Measured on or between 365 and 91 d before index date.
[c] From χ^2 test.

Table 3. Number of individuals at baseline, censored, and deaths by time interval and referral status

Time Interval	Referral	Deaths	Censored for Transplantation	Censored at End of Time Interval or on 6/30/96
Days 1 to 90	Early (*n* = 1975)	465	8	1502
	Late (*n* = 1039)	363	0	676
	Total (*n* = 3014)	828	8	2178
Days 91 to 365	Early (*n* = 1502)	411	11	1080
	Late (*n* = 676)	190	2	484
	Total (*n* = 2178)	601	13	1564

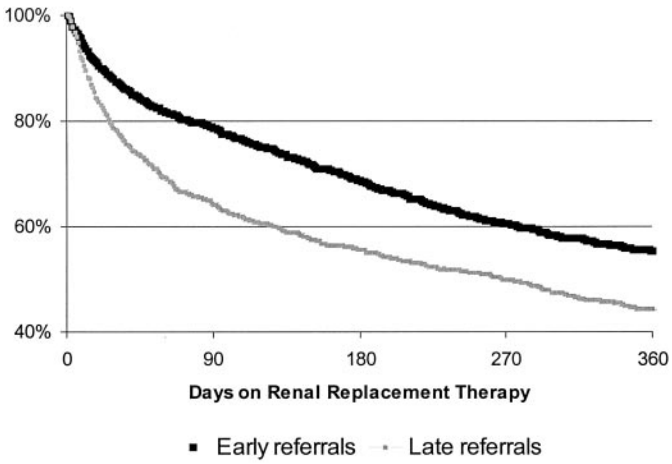

Figure 2. Kaplan-Meier plot of actuarial survival by timing of referral in propensity score matched population (*n* = 2078).

ripheral vascular access was created >14 d before first dialysis, thus making it more likely that the peripheral vascular access was used for the first dialysis. However, the results remained nearly identical to the ones described above.

Discussion

The purpose of this study was to test whether the first-year mortality benefit enjoyed by patients who first saw a nephrologist >90 d before dialysis might have been simply a surrogate for better healthcare access overall, rather than the benefit of subspecialist care. The introduction of propensity scores that included parameters of healthcare utilization did not materially change the estimate of this effect (HR = 1.36 → 1.31). Evaluating a cohort of pairs matched on propensity score also did not change the original finding materially (HR = 1.36 → 1.40). In all cases, late referral remained an important predictor of mortality in the first year of maintenance dialysis, even after such means of bias reduction (see Table 3).

These data indicate that late nephrologist referral is not simply a proxy for overall poor healthcare access/utilization, but that there is probably a specific and substantial contribution by nephrologists during preparation for dialysis that reduces early mortality.

A second finding is that the detrimental association of delayed nephrologist referral with mortality has its effect during the first 90 d of dialysis but not thereafter. This seeming disparity between the current finding and previous work is probably because the proportionality assumption was either not tested or not found to be significant (1–8). Of these studies, only the recent article by Jungers *et al.* (7) provides a Kaplan-Meier plot depicting survival by length of nephrologist care before RRT. Their plot also indicates that the effect of later referral on survival is most pronounced during the first months of RRT. This pattern of

Table 4. Effect estimates of the late *versus* early nephrologist referral association

Model[a]	Odds Ratio	95% Confidence Interval	*P*
Multivariate Cox proportional hazards model	1.36	1.22 to 1.51	<0.0001
additionally including quintiles of propensity score	1.31	1.17 to 1.47	<0.0001
in propensity score matched population (*n* = 2,078)	1.40	1.23 to 1.59	<0.0001
additionally including covariates of health care utilization in the Cox proportional hazards model[b]	1.39	1.22 to 1.58	<0.0001
Interval Cox model from onset of RRT to 90 d	1.75	1.48 to 2.08	<0.0001
Interval Cox model from 91 to 365 d	1.03	0.84 to 1.25	0.81

[a] All models controlled for age, gender, race (White, Black, other), socioeconomic status, hypertension, diabetes, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, malignancy, gastrointestinal erosion/ulcer, severe liver disease, obesity, chronic obstructive pulmonary disease, HIV^+/AIDS, dementia, depression, alcohol or substance abuse, other mental disease.

[b] Hospital days, primary care visits, surgical visits, medical subspecialist visits, nursing home stay.

early survival benefit after RRT can be explained by the concept of "depletion of susceptibles" (27), a form of survival bias. That is, those patients who are vulnerable to the effects of suboptimal preparation for RRT die at an excess rate, whereas those who are more robust are more likely to survive. Moreover, after depletion of those "susceptibles" the survival experience of the remaining subjects is indistinguishable from those who saw a nephrologist in a timely fashion. This concept would also suggest that associations between mortality and timing of first nephrologist referral or duration of nephrologist care are driven solely by the excess mortality of late referrals within the first few months of RRT.

We hypothesized that the benefits of early referral might be mediated through more educated decisions regarding modality choice and via timely creation of peripheral vascular access. When testing these hypotheses formally, we found that neither modality choice nor presence of a peripheral vascular access before onset of dialysis modified the association between LR and 90-d survival, indicating that other measures of care are instrumental in providing the survival benefit among ER. The current analysis does not permit us to define these other components of nephrology care that are probably associated with a reduction in medium or long-term mortality. However, on the basis of extrapolation from processes of care in prevalent ESRD patients, it is likely that interventions such as improved BP control, treatment of anemia, improved nutrition, managing derangements in divalent ion metabolism, etc. may contribute to this putative benefit (28).

Limitations of the present study include the use of claims data, which may be compromised by patient and data miscoding, missing data elements, and misclassification. An a priori assumption is made that these limitations occur in a random rather than systematic way, supporting the internal validity of the study. The overall similarity of our findings to those reported by others spanning a large period of time and multiple geographies suggest that these biases are not a major confounder. Similarly, it is likely that there is residual confounding arising from limited characterization of the severity of comorbid conditions. Additional clinical and laboratory information is unavailable that could enhance the robustness of our models and could serve as explanatory variables. For example, it would be of interest to have information on the rate of decline of residual renal function for inclusion into the propensity score model. Using such information, the predictive power of the model would likely be increased, which would lead to further bias reduction. The moderate prediction of the propensity score model ($c = 0.683$) indicates that several cofactors that contribute to the referral decision remained unobserved, thus leaving the possibility of residual confounding by such unobserved data.

Because this study captured information on patients who were older and/or indigent, further work will be needed to determine their generalizability to younger and less indigent populations or to populations in other geographic regions. Also, the results of this study do not apply to patients with acute renal failure or those patients who are not diagnosed with chronic kidney disease until shortly before the need for RRT.

These findings indicate that early referral to a nephrologist remains important in influencing the course of patients with chronic kidney disease progressing to ESRD, even after adjusting for other patterns of healthcare utilization during the predialysis phase. Furthermore, it seems that the deleterious effects of late referral occur within the first few months of RRT. These findings suggest important research and policy implications. If late patient referral does occur, extensive corrective interventions may have greater benefit if offered early after resuming RRT. Further research is needed to identify those at highest risk within the late referral population, and appropriate models of care delivery for the first months of RRT need to be developed and tested in this vulnerable population.

Acknowledgments

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