Association between Duration of Predialysis Care and Mortality after Dialysis Start

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Abstract

Background and objectives Early nephrology referral is recommended for people with CKD on the basis of observational studies showing that longer nephrology care before dialysis start (predialysis care) is associated with lower mortality after dialysis start. This association may be observed because predialysis care truly reduces mortality or because healthier people with an uncomplicated course of disease will have both longer predialysis care and lower risk for death. We examined whether the survival benefit of longer predialysis care exists after accounting for the potential confounding effect of disease course that may also be affected by predialysis care.

Design, setting, participants, & measurements We performed a retrospective cohort study and used data from 3152 adults with end stage kidney failure starting dialysis between 2004 and 2014 in five Canadian dialysis programs. We obtained duration of predialysis care from the earliest nephrology outpatient visit to dialysis start; markers of disease course, including inpatient or outpatient dialysis start and residual kidney function around dialysis start; and all-cause mortality after dialysis start.

Results The percentages of participants with 0, 1–119, 120–364, and ≥365 days of predialysis care were 23%, 8%, 10%, and 59%, respectively. When we ignored markers of disease course as in previous studies, longer predialysis care was associated with lower mortality (hazard ratio$_{120–364 \text{ versus } 0–119 \text{ days}}$, 0.60; 95% confidence interval, 0.46 to 0.78]; hazard ratio$_{\geq 365 \text{ versus } 0–119 \text{ days}}$, 0.60; 95% confidence interval, 0.51 to 0.71; standard Cox model adjusted for demographics and laboratory and clinical characteristics). When we additionally accounted for markers of disease course using the inverse probability of treatment weighted Cox model, this association was weaker and no longer significant (hazard ratio$_{120–364 \text{ versus } 0–119 \text{ days}}$, 0.84; 95% confidence interval, 0.60 to 1.18; hazard ratio$_{\geq 365 \text{ versus } 0–119 \text{ days}}$, 0.88; 95% confidence interval, 0.69 to 1.13).

Conclusions The association between longer predialysis care and lower mortality after dialysis start is weaker and imprecise after accounting for patients' course of disease.

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Introduction

CKD is a global health problem affecting approximately 10% of the adult population (1), and it is associated with increased risks of end stage kidney failure, cardiovascular disease, and mortality (2,3). Physicians must decide who to refer for specialty nephrology care and at what point during the disease course to refer them. Over the past three decades, >40 cohort studies have examined the association between duration of nephrology care before dialysis start (predialysis care) and patient outcomes after dialysis start (4–6). A systematic review found 40% lower mortality in people treated with dialysis for kidney failure who received at least 1 month of predialysis care (defined as "early referral") compared with those with shorter or no predialysis care (6). On the basis of these observational studies, guidelines (7–9) recommend referral to nephrology services for people with CKD who have an eGFR<30 ml/min per 1.73 m^2, a consistent finding of significant albuminuria, or signs of progressive disease (8). These guidelines have significant policy implications, because as many as five in 1000 people are potential candidates for referral to a nephrologist on the basis of eGFR alone (10)—far more patients than could be cared for given current resource constraints.

The evidence informing nephrology referral guidelines has been assessed as low to moderate quality (6). One concern is that previous studies looked back from the start of dialysis to define early or late referral and thus, the duration of predialysis care. This approach implies that dialysis start is predictable and that health care providers can both largely control the course of disease and determine the duration of predialysis care. Although predialysis care may slow CKD progression and reduce the risk of acute cardiovascular events or infections that may abruptly lower kidney function and require unplanned dialysis

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start, it is very difficult to predict whether and when a person with CKD will reach kidney failure (11). Acute unpredictable events may occur that shorten predialysis care or cause kidney failure quickly, making it impossible for patients to receive predialysis care (11). Because these events are associated with both the underlying patient health conditions and subsequent mortality, shorter predialysis care may be the result of a complicated course of disease, with rapid progression, in a sicker patient (Figure 1).

Given the current emphasis on early nephrology referral and the lack of evidence from randomized, controlled trials to support such recommendations (8), we aimed to examine the association between duration of predialysis care and mortality after dialysis start in a cohort of Canadian adults using two approaches. In the first approach, we used traditional methods that do not account for markers of disease course, because this approach assumes that predialysis care reduces the risk of acute events and thus, reduces mortality. As a result, markers of disease course are regarded as an intermediate variable and cannot be adjusted for in regression models. In the second approach, we used techniques that accounted for markers of disease course that may affect both the duration of predialysis care and mortality and that may be affected by predialysis care.

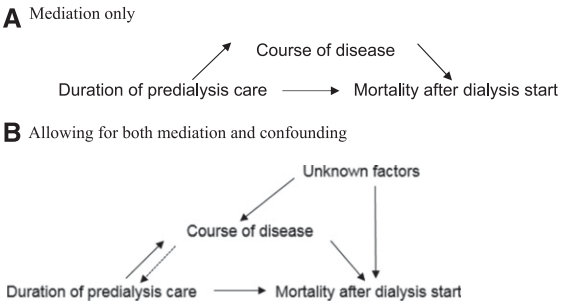

Figure 1. | The course of disease may mediate (top diagram) or confound (bottom diagram) the association between duration of predialysis care and mortality after dialysis start. Causal diagrams representing two possible scenarios of the influence of the course of disease on the association between duration of predialysis care and mortality after dialysis start. (A) The course of disease is an effect mediator on the causal pathway between duration of predialysis care and mortality after dialysis start. Under this assumption, the total effect of duration of predialysis care is estimated ignoring the influence of markers of disease course. (B) The course of disease may be both a mediator and a confounder of the relationship of interest. Conditioning the analysis on markers of disease course (adjustment by regression or stratification) in these situations could introduce collider bias (course of disease is a collider on the causal path: duration of predialysis care → course of disease ← unknown factors → mortality after dialysis start). Marginal methods have been proposed to control for this form of confounding and minimize collider bias (21).

Materials and Methods

Study Design and Participants

We did a retrospective cohort study using data from the Dialysis Measurement Analysis and Reporting (DMAR) system (12). The DMAR consecutively enrolled people who initiated dialysis for end stage kidney failure in the opinion of their attending nephrologist; received a single outpatient dialysis treatment; and presented with AKI or acute on chronic kidney injury and received 28 days of dialysis, regardless of whether they received an outpatient treatment. We identified people ages ≥18 years old who initiated dialysis between January 1, 2004 and August 31, 2014 at five Canadian sites (London Health Sciences Centre, the Ottawa Hospital, Sunnybrook Health Sciences Centre, the Manitoba Renal Program, and the Southern Alberta Renal Program–Calgary Zone). We excluded people who initiated dialysis after a failed kidney transplant.

Data Sources

The DMAR collects prospective, high-quality data for the purpose of quality improvement using an interactive, web-based data collection system. Data were entered by trained frontline staff using a standardized coding scheme. To ensure rigorous data quality, all data elements collected from medical records at the participating sites were double reviewed by the same two investigators (R.R.Q. and M.J.O.). Discrepancies identified during this review were communicated in real time to end users and were rectified before analysis. Data elements for this study included demographics, duration of predialysis care, height and weight, comorbidities, last available laboratory parameters before the start of dialysis, initial dialysis modality, setting of dialysis start, reasons for hospitalization at dialysis initiation (for inpatient starts), and follow-up information on outcome events. Ethics approvals were obtained at all participating sites. Patient consent was waived.

Exposure

The exposure of interest was the duration of predialysis care from the earliest recorded nephrology outpatient visit to the start of dialysis, which we categorized as 0, 1–119, 120–364, or ≥365 days as in previous studies (13–18) and on the basis of expert opinion (8).

Markers of Disease Course

We used the setting of dialysis start and eGFR on the basis of the last available serum creatinine measurement before dialysis start as markers of disease course that may reflect a change in the course of disease (11). For example, an unexpected decline in kidney function will be more likely lead to an inpatient (unplanned) dialysis start. In addition, eGFR measurements are artificially elevated in the setting of AKI, because serum creatinine measurements are not in equilibrium. As a consequence, a higher eGFR at the start of dialysis may reflect AKI or congestive heart failure with volume overload.

Outcome

The outcome of interest was all-cause mortality. Participants were followed from the time of dialysis start to the earliest of death, transplant, termination of dialysis due to recovery of kidney function, transfer out of the program, loss to follow-up, or end of the study (March 31, 2015).

Statistical Analyses

In outcome analyses, we first used Cox regression to examine the association between duration of predialysis care and mortality (Figure 1A). As in previous studies, we assumed that predialysis care influences the course of

disease, which mediates the effect of predialysis care on mortality. Markers of disease course are an intermediate variable on the causal path from duration of predialysis care to mortality in this scenario and cannot be controlled for (19). We, therefore, only adjusted this analysis for demographic characteristics, dialysis programs, serum albumin, and comorbidities. In the second approach, we used a Cox model with stabilized inverse probability of treatment weighting (IPTW) obtained using propensity score methodology (20–22) to account for the same covariates considered above and for markers of disease course (Figure 1B). This method first creates a pseudopopulation using IPTW, from which the covariate distribution becomes balanced across groups with different durations of predialysis care, and then estimates the exposure-outcome association in the weighted sample. Both setting of dialysis start and eGFR around dialysis start may be affected by predialysis care, and both may affect the duration of predialysis care and patient outcomes. These conditions motivated the use of weighted (marginal) outcome analysis to account for these complex relationships as opposed to standard regression methods. Methods for IPTW estimation and distributional checking (23) are in Supplemental Material.

In sensitivity analyses, we repeated the same analyses excluding people without predialysis care who may be sicker and more likely to start dialysis in an inpatient setting than people who received predialysis care. We also repeated all analyses on the basis of patientwise deletion for missing values (complete patient analysis) and by defining the duration of predialysis care as 0–119 or ≥120 days.

For all models, we verified the proportional hazards assumption using graphic methods. Details on model

Table 1. Participant characteristics by duration of predialysis care

Characteristic	Overall, *n*=3152	Predialysis Care		Any Predialysis Care, d		
		No, *n*=738	Any, *n*=2414	1–119, *n*=264	120–364, *n*=305	≥365, *n*=1845
Demographics						
Age, yr	64±15	63±16	65±15	63±16	64±16	65±15
Age ≥65 yr	1726 (55)	377 (51)	1349 (56)	140 (53)	153 (50)	1056 (57)
Men	1928 (61)	472 (64)	1456 (60)	152 (58)	195 (64)	1109 (60)
BMI, kg/m^2	28.4±7.2	28.3±7.7	28.4±7.0	27.7±7.4	27.5±6.4	28.6±7.1
Presence of comorbidities						
Diabetes	1656 (53)	292 (40)	1364 (57)	135 (51)	174 (57)	1055 (57)
Coronary artery disease	1067 (34)	251 (34)	816 (34)	77 (29)	95 (31)	644 (35)
Congestive heart failure	937 (30)	248 (34)	689 (29)	72 (27)	87 (29)	530 (29)
Other cardiac disease	907 (29)	273 (37)	634 (26)	58 (22)	85 (28)	491 (27)
Cerebrovascular disease	490 (16)	100 (14)	390 (16)	32 (12)	45 (15)	313 (17)
Peripheral vascular disease	532 (17)	121 (16)	411 (17)	42 (16)	49 (16)	320 (17)
Cancer	633 (20)	173 (23)	460 (19)	74 (28)	63 (21)	323 (18)
Chronic obstructive lung disease	215 (7)	60 (8)	155 (6)	15 (6)	14 (5)	126 (7)
Polycystic kidney disease	111 (4)	3 (0.4)	108 (4)	4 (2)	5 (2)	99 (5)
Gastrointestinal bleeding	299 (9)	91 (12)	208 (9)	20 (8)	20 (7)	168 (9)
Setting of dialysis starts						
Outpatient	1400 (44)	15 (2)[a]	1385 (57)	111 (42)	169 (55)	1105 (60)
Inpatient	1752 (56)	723 (98)	1029 (43)	153 (58)	136 (45)	740 (40)
Modality of dialysis initiation						
CRRT	228 (7)	182 (25)	46 (2)	5 (2)	5 (2)	36 (2)
HD	2302 (73)	543(74)	1759 (73)	234 (89)	237 (78)	1288 (70)
PD	622 (20)	13 (2)	609 (25)	25 (9)	63 (21)	521 (28)
Laboratory measurements						
eGFR, ml/min per 1.73 m^2	7.5 [5.6–10.2]	8.2 [5.2–14.7]	7.3 [5.7–9.6]	7.2 [5.5–9.7]	7.3 [5.6–9.6]	7.4 [5.7–9.6]
eGFR, ml/min per 1.73 m^2, category[b]						
<10	2310 (74)	430 (59)	1880 (78)	201 (76)	237 (78)	1442 (78)
10–15	532 (17)	121 (17)	411 (17)	41 (16)	47 (15)	323 (18)
>15	296 (9)	178 (24)	118 (5)	21 (8)	20 (7)	77 (4)
Missing	14	9	5	1	1	3
Serum albumin, g/dl	3.2±0.7	2.7±0.7	3.3±0.7	3.1±0.7	3.2±0.7	3.3±0.7
Serum albumin[b]						
<3.6 g/dl	2070 (67)	613 (88)	1457 (61)	181 (71)	197 (65)	1079 (59)
Missing	78	42	36	8	4	24
Hemoglobin, g/dl	9.7±1.6	9.3±1.7	9.8±1.6	9.3±1.7	9.7±1.6	9.9±1.5

Values for categorical variables are given as count (percentage); values for continuous variables are given as mean±SD or median [interquartile range]. BMI, body mass index; CRRT, continuous RRT; HD, hemodialysis; PD, peritoneal dialysis.
[a]These 15 patients had no outpatient nephrology care before starting dialysis, but they were seen by a nephrologist in an emergency department and stable enough to start dialysis in an outpatient setting without being admitted to hospital.
[b]Values do not sum up to subtotal due to missing data.

checking, power analysis, and methods for multiple imputation of missing values of serum albumin and creatinine are reported in Supplemental Material.

Results

We identified 3301 people who initiated dialysis at the five participating programs during the study period. We excluded 145 people who started dialysis after a failed kidney transplant, one person age <18 years old, and three people without age information. A total of 3152 people were included (median follow-up of 10.5 months).

Participant Characteristics by Duration of Predialysis Care

Participant characteristics according to the duration of predialysis care are described in Table 1. The percentages of participants with 0, 1–119, 120–364, and ≥365 days of predialysis care were 23%, 8%, 10%, and 59%, respectively. Compared with people who received predialysis care, those without predialysis care were younger and less likely to have diabetes and polycystic kidney disease, but they were more likely to have congestive heart failure, other cardiac disease, cancer, or gastrointestinal bleeding. The vast majority (98%) of people who did not receive predialysis care started dialysis in an inpatient setting, were more likely to receive an initial course of continuous RRT, and were less likely to have peritoneal dialysis as their initial treatment modality. This group tended to have higher eGFR and lower serum albumin and hemoglobin levels before starting dialysis than those with predialysis care.

Among people who received any predialysis care, those with longer predialysis care tended to be older; tended to have higher body mass index, serum albumin, and hemoglobin; were more likely to have polycystic kidney disease; and were more likely to use peritoneal dialysis as the initial modality. A smaller proportion of them had eGFR>15 ml/min per 1.7 $3m^2$ before starting dialysis or a history of cancer. Fifty-eight percent of people with 1–119 days of predialysis care initiated dialysis in an inpatient setting. This proportion decreased to 45% among those with 120–364 days of predialysis care, but it did not decrease considerably among those with ≥365 days of predialysis care (40%).

Among patients who started dialysis urgently in hospital, patients who received <120 days of predialysis care were more likely to be admitted for infection, malignancy, or elective surgery compared with those with longer predialysis care. CKD-related complications requiring urgent initiation of dialysis were more likely to occur in patients with longer predialysis care (Supplemental Table 1).

Mortality by Duration of Predialysis Care and Setting of Dialysis Start

Figure 2 shows that the trend toward lower mortality with longer predialysis care observed in the overall cohort was inconsistent and depended on whether a patient started dialysis in the hospital or not. The numbers of deaths for people with 0, 1–119, 120–364, and ≥365 days of predialysis care were 200, 76, 78, and 456, respectively. Overall, the mortality in people without predialysis care was substantially higher than in those with any predialysis care. People without predialysis care who started dialysis as an inpatient had the highest mortality. In those who received predialysis care, mortality tended to decrease with increasing duration of predialysis care but only after an outpatient dialysis start.

Association between Duration of Predialysis Care and Mortality

Figure 3A summarizes hazard ratios (HRs) and 95% confidence intervals (95% CIs) for mortality after dialysis start by duration of predialysis care. Compared with people with 0–119 days of predialysis care, people who received longer predialysis care had significantly lower mortality in standard Cox regression ($HR_{120–364\ days}$, 0.60; 95% CI, 0.46 to 0.78; $HR_{\geq 365\ days}$, 0.60; 95% CI, 0.51 to 0.71). In weighted Cox models, this association was weaker and nonsignificant ($HR_{120–364\ days}$, 0.84; 95% CI, 0.60 to 1.18; $HR_{\geq 365\ days}$, 0.88; 95% CI, 0.69 to 1.13).

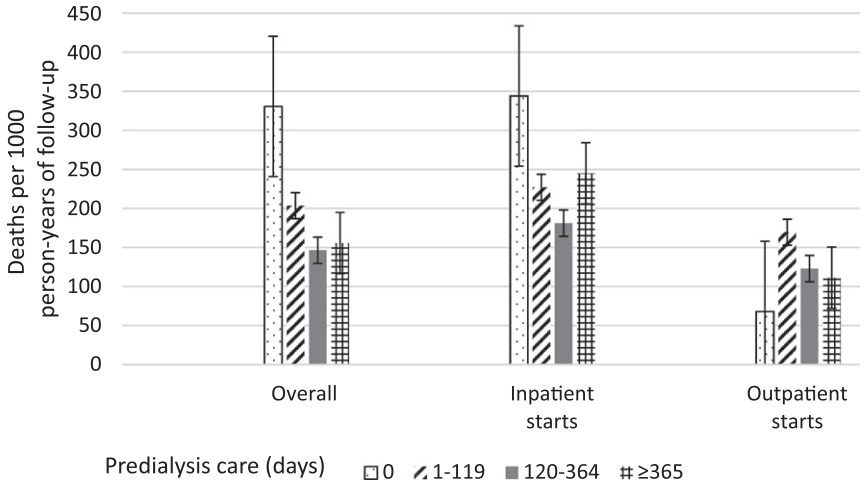

Figure 2. | The association between duration of predialysis care and mortality after dialysis start differed by setting of dialysis start. Unadjusted mortality by duration of predialysis care and setting of dialysis start. The numbers of deaths for people with 0, 1–119, 120–364, and ≥365 days of predialysis care were 200, 76, 78, and 456, respectively. Error bars represent SEM.

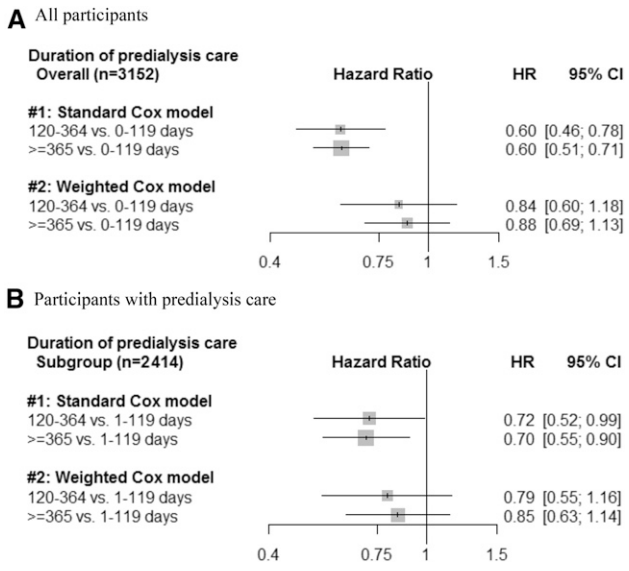

Figure 3. | The survival benefit associated with longer predialysis care was weaker and no longer significant after accounting for markers of disease course. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for mortality associated with duration of predialysis care. Models included all participants (A). Models included participants with predialysis care (B). (*1*) Standard Cox model adjusted for age at initiation of dialysis, sex, dialysis programs, the last available serum albumin before starting dialysis, and ten comorbidities (diabetes, congestive heart failure, cancer, other cardiac disease, cerebrovascular disease, coronary artery disease, peripheral vascular disease, chronic obstructive lung disease, polycystic kidney disease, and gastrointestinal bleeding). (*2*) Inverse probability of treatment weighted Cox model accounting for the same covariates as in the above Cox model and markers of disease course (inpatient or outpatient of dialysis start and the last available eGFR before starting dialysis). Analyses of inverse probabilities of treatment weighting are reported in Supplemental Figure 1 and Supplemental Tables 2 and 3.

Sensitivity Analyses

In analyses restricted to people who received predialysis care, longer duration was significantly associated with lower mortality in standard analyses (Figure 3B), although the association was weaker than in the analysis that included the full cohort. Conversely, estimates of association from the corresponding weighted Cox model were similar to those from the main analysis that included all participants. We found similar associations in analyses on the basis of patientwise deletion for missing values of serum albumin and creatinine (Supplemental Figure 2) or when predialysis care was defined as ≥120 versus 0–119 days (Supplemental Figure 3).

Discussion

In this cohort study of Canadian adults treated with dialysis, longer predialysis care was associated with lower mortality using traditional regression techniques that do not control for the effect of disease course. This approach assumes that predialysis care improves outcomes by reducing the risk of acute events. When we considered the possibility that acute events may affect both duration of predialysis care and mortality after dialysis start, this benefit was lessened and no longer significant. Although our study cannot distinguish between potentially preventable and nonpreventable acute events, this finding deserves careful examination considering the current recommendations regarding referral to nephrology care and the implications of these recommendations from a patient, care provider, and health system perspective.

Early nephrology referral has long been recommended to improve patient mortality (6–8). It may provide opportunities for early identification and management of modifiable risk factors for progression of CKD, cardiovascular disease, and CKD-related complications as well as for education, planning, and preparation for RRT or conservative management of kidney failure (8). Using an analytic approach that reflects this view, our data show that people with longer predialysis care had 40% lower mortality after dialysis start than people with shorter or no predialysis care. Our estimates of risk reduction mirror a recent meta-analysis of 40 cohort studies involving over 60,000 participants (6). However, when we allowed for the possibilities that the risk of acute events may be affected by predialysis care and that acute events may influence the course of disease and therefore, may affect both duration of predialysis care and mortality (19), we found that the benefit associated with longer predialysis care was weaker and no longer significant. This finding is consistent with that of a large study of older people initiating dialysis in the United States, which found no meaningful survival improvement, despite an increase (from 30% in 1996 to 49% in 2006) in the proportion of patients seen by a nephrologist for at least 1 year before initiation of dialysis (24).

Existing studies of the relationship between duration of predialysis care and survival in people treated with dialysis, including our study, have used a "look-back" approach to define early or late referral on the basis of the dialysis start date. However, previous studies have only assumed that predialysis care slows disease progression and prevents acute events (6). We also considered the possibility that unpredictable acute events may accelerate the progression to kidney failure, shorten predialysis care, and influence patient risk for death. Unmeasured patient factors, potentially associated with these acute events, may affect the relationship between duration of predialysis care and all-cause mortality. For example, referred patients who are healthier and have more stable CKD tend to be seen by a nephrologist for longer, are more likely to start dialysis electively in an outpatient setting, and are generally healthier. Acute complications of an underlying comorbid condition, such as a heart attack or an infection, are more common in people with more severe comorbidities, can be difficult to predict, and may be independent of the duration of predialysis care. These events can lead to a rapid loss of kidney function, necessitating an urgent dialysis start in an inpatient setting, and negatively affect a patient's prognosis (25). In our study, the proportion of inpatient dialysis start ranged from 58% in people with 1–119 days of predialysis care to 40% in people with at least 1 year of predialysis care, suggesting that acute events remain common in people with CKD, regardless of the duration of predialysis care.

Our study has limitations that are similar to those of previous studies. First, it is on the basis of a cohort of people who eventually started dialysis, and therefore, the effects of nephrology care among those who did not initiate

dialysis could not be assessed. Future studies should focus on populations of patients with CKD whose providers are faced with a decision about whether to refer for specialist nephrology care. Second, our study population had universal access to publicly funded predialysis care programs, and our findings may not be generalizable to other systems where different funding models are used. Third, we did not have data on whether predialysis care was provided by a single nephrologist or a multidisciplinary team. However, there are no data from clinical trials supporting the superiority of multidisciplinary predialysis care versus single-nephrologist practices. Fourth, we focused on mortality as our primary outcome, and there are a number of other potentially important outcomes to consider. Fifth, because of its retrospective design, our study could not control for potential residual confounding due to unequal distribution of unmeasured factors across groups.

Referral to specialist care is an intervention decision. People with CKD are referred to nephrology services to optimize the management of CKD and its complications, slow CKD progression, and prepare for renal replacement treatment or conservative care for kidney failure using pharmacologic and nonpharmacologic interventions (8). Whether predialysis care interventions improve outcomes has never been tested in a randomized, controlled trial (6). When guidelines promote interventions without sufficient evidence of benefits and risks, widespread inappropriate use of resources and services may occur. Ultimately, randomized, controlled trials are needed to clarify whether early nephrology referral for a given risk of progression to kidney failure will slow the progression of kidney disease, prevent adverse events, increase the duration of nephrology care before kidney failure, and improve outcomes as a result. High-quality data are also needed, for example, to clarify who should be referred, what referral criteria can best identify those at risk, and when they should be referred; to define what components of nephrology care before kidney failure may be responsible for the expected benefits, if any, and what interventions may more favorably influence patient outcomes; to determine the optimal care model to deliver these interventions (*e.g.*, specialty clinic versus primary care team or single-nephrologist practice versus multidisciplinary team); and to determine what outcomes are important in addition to mortality, including hospitalization and other measures of morbidity, patient-reported outcomes, and experience measures.

In conclusion, our study suggests that the survival benefit associated with longer predialysis care may have been overestimated in previous studies, because they may not have adequately addressed confounding by patient disease course. More data are required to address this important knowledge gap and explore where the real potential for improving CKD care is.

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Disclosures

None.

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