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ORIGINAL ARTICLE

Association of the frequency of pre-end-stage renal disease medical care with post-end-stage renal disease mortality and hospitalization

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ABSTRACT

Background. Previous studies have demonstrated that early pre-end-stage renal disease (ESRD) nephrology care could improve postdialysis prognosis. However, less is known about the specific types of interventions responsible for the improved outcomes. We hypothesized that more frequent predialysis laboratory testing is associated with better postdialysis outcomes in incident ESRD patients.

Methods. In all, 23 089 patients with available outpatient laboratory tests performed during the 2-year predialysis (i.e. prelude) period were identified from a total of 52 172 American veterans with chronic kidney disease (CKD) transitioning to dialysis between October 2007 and September 2011. The associations between the frequency of combined laboratory tests, including serum creatinine, serum potassium and hemoglobin (test trio), with postdialysis mortality and hospitalization were examined in multivariable adjusted Cox and logistic regression models.

Results. When entering the 2-year prelude period, the mean age (Standard Deviation) of the patients was 66.2 (SD 11.3) years and the mean estimated glomerular filtration rate was 46.8 (SD 23.9) mL/min/1.73 m^2. In all, 14% of patients had the test trio performed less than twice in 24 months and 8.9% had the trio measured more often than every other month. Over a 2.5-year median postdialysis follow-up period, 15 303 (66.3%) patients died (mortality rate 260/1000 patient-years). The adjusted hazard ratio of all-cause mortality and adjusted odds ratio of the composite of hospitalization or death associated with lab testing done >12/24 months compared with 2–≤4/24 months were 0.68 [95% confidence interval (CI) 0.65–0.73] and 0.70 (95% CI 0.62–0.79), respectively.

Conclusions. More frequent laboratory testing in patients with advanced CKD is associated with better clinical outcomes after dialysis. Further examination in clinical trials is needed before the implementation of more frequent laboratory testing in clinical practice.

Keywords: chronic kidney disease, end-stage renal disease, hospitalization, mortality, pre-ESRD laboratory testing

INTRODUCTION

The optimal way of managing chronic kidney disease (CKD) prior to renal replacement therapy (RRT) has been a focus of intense investigation [1]. CKD patients who have high morbidity require considerable health care attention, especially in later stages of their disease. With the increasing number of patients with CKD approaching end-stage renal disease (ESRD) and requiring RRT in recent years [2], optimized pre-ESRD care has become critical to slowing the progression of CKD, decreasing mortality and shortening hospitalizations. This should indirectly reduce the cost of health care and improve patient quality of life.

Many studies have demonstrated that pre-ESRD care involving nephrologists during the early stages of CKD could significantly improve post-ESRD prognosis [3, 4]. Less is known about what aspect of the care delivered by nephrologists would be responsible for the observed improved outcomes. It is unclear whether more frequent pre-ESRD routine lab testing could lead to better disease management or whether such routine tests could be administered and acted upon by general practitioners, without involving nephrologists. We designed

this study to examine the association between the frequency of laboratory testing prior to ESRD with post-ESRD all-cause mortality, cause-specific mortality and hospitalizations.

MATERIALS AND METHODS

Study population

As described previously [5, 6], we analyzed data from the Transition of Care in CKD (TC-CKD) study, which examines relationships between pre-ESRD factors and post-ESRD outcomes of CKD patients transitioning to RRT. Among 52 172 US veterans registered as incident ESRD patients in the US Renal Data System (USRDS) over the period of 1 October 2007–30 September 2011, we identified 23 089 patients with available outpatient laboratory tests performed during the last 2 years prior to the incident ESRD date (prelude).

Covariates

Patients' information related to demographics, socioeconomics and vital signs were obtained from the US Department of Veterans Affairs (VA) Corporate Data Warehouse (CDW) [7] and the USRDS Patient and Medical Evidence Form 2728. Information on race was cross-referenced with data obtained from Medicare through the VA-Medicare data merge project [8]. Blood pressure variability was defined as the SD of blood pressures in the 2-year prelude period. Patient's pre-ESRD laboratory results were extracted from CDW LabChem data files and the Decision Support System National Data Extracts Laboratory Results file [9]. Estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. Intra-individual changes of kidney function (eGFR slopes) in the 2-year prelude time were estimated from a mixed-effects model using all outpatient serum creatinine results. Information on prevalent comorbidities was extracted from the VA Inpatient and Outpatient Medical SAS Datasets [11] and from Centers for Medicare and Medicaid Services (CMS) datasets by using International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) [12] and Current Procedural Terminology (CPT) codes at the time of dialysis therapy initiation. Data related to medication exposure were obtained from CMS (Medicare Part D) and VA pharmacy dispensation records [13]. We used the proportion of days covered (PDC) medication possession ratio (MPR), and persistence [14] to assess patients' medication adherence. These were calculated for the following cardiovascular drugs: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, beta-blockers, alpha-blockers, direct vasodilators, diuretics (loop and thiazide), aspirin and statins in the last 2-year prelude period. The Charlson Comorbidity Index (CCI) score was calculated using the Deyo modification for administrative datasets [12], without including kidney disease. We also collected information related to pre-ESRD nephrology care based on CMS form 2728.

Exposure variable

The frequency of combined serum creatinine, serum potassium and blood hemoglobin measurements during the prelude period was the exposure variable. When patients had at least one measurement from each test performed in a month, we considered that as one pre-ESRD test trio; the number of test trios could thus range from a minimum of zero over the entire 2-year evaluation period to a maximum of 24 (one per month). The frequency of test trios was calculated from the total number of pre-ESRD test trios divided by 24 and then classified into 6 categories: 0 (without test trio), $>0–\leq 2/24$ months, $>2–\leq 4/24$ months, $>4–\leq 8/24$ months, $>8–\leq 12/24$ months and $>12/24$ months.

Outcomes

Information about post-ESRD all-cause mortality and censoring events along with the associated dates were obtained from VA and USRDS sources. Cause-specific mortality data were obtained from the USRDS. Information about post-ESRD hospitalizations was obtained from VA Inpatient Medical SAS Datasets [11]. We defined relevant post-ESRD hospitalization events based on the first or second inpatient diagnosis code of any admission related to cardiac or cerebrovascular disease, major infections and acute kidney injury within 6 months of dialysis initiation (Supplementary Appendix Table 6). The joint event of major hospitalizations or death was used as a composite outcome.

Statistical analyses

Descriptive analyses were performed using mean ± SD, median [interquartile range (IQR)] and proportions as appropriate. Cox proportional hazards models with adjustment for covariates were used for examining the association of the frequency of the pre-ESRD test trio with post-ESRD all-cause mortality and cause-specific mortality. Patients were followed in survival analyses from the ESRD date until death or other censoring events, including kidney transplantation, loss of follow-up or the last date of health care encounter before 27 December 2012 or before 6 October 2011 (for cause-specific mortality). The association between the frequency of test trios and the 6-month post-ESRD composite of hospitalization/death was analyzed in logistic regression models with adjustment for confounders.

The effect of potential confounders on outcomes was analyzed by multivariable adjustments including baseline age, race, gender, baseline blood pressure, blood pressure variability assessed during the 2-year prelude period, per capita income, marital status, VA service connection percentage, comorbid conditions assessed from ICD-9 codes recorded at inpatient and outpatient encounters during the entire available pre-ESRD period [cardiovascular (CV) disease, cerebrovascular disease, hypertension, congestive heart failure (CHF), dementia, rheumatologic disease, malignancy, depression, liver disease, chronic lung disease, diabetes, HIV and CCI] and, medication adherence measured during the 2-year prelude period (PDC, medication possession ratio and persistence), baseline eGFR (first outpatient eGFR at the beginning of the prelude period) and prelude eGFR slope.

In order to examine effect modification by age and by nephrology care received during the prelude, we estimated associations separately in patients categorized by age (≤65 and >65 years old) and by the presence/absence of pre-ESRD nephrology care based on information obtained from CMS form 2728 (a form used by US nephrologists to report initiation of chronic RRT) and by including interaction terms in the relevant multivariable models.

Statistical analyses were performed using Stata MP Version 14 (StataCorp, College Station, TX, USA). The study was approved by the institutional review boards at the Memphis and Long Beach VA Medical Centers.

RESULTS

The mean age of the cohort was 66.2 ± 11.3 years. A total of 98.2% ($n = 22\,680$) of patients were male, 72.1% ($n = 16\,624$) of them were white and 58.6% ($n = 13\,180$) were married. Nephrology care was provided to 62.0% ($n = 14\,316$) of cohort prior to ESRD. The mean eGFR was 46.8 ± 23.9 mL/min/1.73 m^2 at the beginning of the 2-year prelude period. Baseline characteristics of the cohort categorized by the frequency of the test trio are described in Table 1. In all, 14.0% of patients had the test trio performed less than twice in 24 months, 9.3% had no test trio measured during the prelude and 27.3% had the trio measured more than eight times in the 2-year prelude period. Patients with more frequent lab testing were significantly younger and had a higher median income and a higher percentage of VA service connection. They also had a lower prevalence of cardiac and cerebrovascular diseases. Patients with better medication adherence and diabetes were more likely to have frequent lab tests. Patients without nephrology care had lower median income, lower marriage rates and more baseline comorbidities, with the exception of diabetes and hypertension. However, they did have a higher baseline eGFR (Supplementary Appendix Table 1).

Mortality

A total of 15 303 (66.3%) patients died over a 2.5-year median follow-up period {mortality rate 260.2/1000 patient-years [95% confidence interval (CI) 256.1–264.4]}. More frequent lab testing was associated with lower post-ESRD mortality. Compared with the patients with at least two test trios, the adjusted hazard ratio (HR) for patients having lab tests more often than every other month was 0.68 (95% CI 0.64–0.73; $P < 0.001$) (Figure 1A, Table 2). The results remained

Table 1. Baseline characteristics of cohort by the frequency of test trio

	Frequency of test trio in 2-year prelude					
	No test trio ($n = 2145$)	≤1/year ($n = 3232$)	>1–≤2/year ($n = 7460$)	>2–≤4/year ($n = 3952$)	>4–≤6/year ($n = 4255$)	>6/year ($n = 2045$)
Age (years)	70 ± 11	69 ± 11	68 ± 11	64 ± 11	63 ± 11	63 ± 11
BMI (kg/m^2)	28.8 ± 5.9	28.7 ± 5.9	28.9 ± 6.5	29.8 ± 8.3	29.6 ± 9.3	29.2 ± 6.4
Median income (US$)	15 678	15 234	15 158	16 331	17 912	20 400
Covariates	(0–33 876)	(0–33 756)	(1722–33 276)	(7966–32 076)	(9588–33 120)	(10 624–33 876)
CCI	5 (3–7)	5 (3–7)	5 (3–7)	5 (3–7)	5 (3–7)	5 (4–7)
eGFR (mL/min/1.73 m^2)	44.8 ± 22.4	46.1 ± 23.9	47.0 ± 23.7	49.5 ± 24.5	47.0 ± 24.6	44.4 ± 23.4
eGFR slope (mL/min/1.73 m^2)	−5.7 ± 4.4	−5.6 ± 4.5	−6.0 ± 5.1	−7.4 ± 5.8	−7.4 ± 5.8	−6.9 ± 5.3
Prelude period	4.1 ± 1.3	4.2 ± 1.3	4.3 ± 1.2	4.4 ± 1.2	4.5 ± 1.2	4.6 ± 1.2
Service connected	67 ± 35	67 ± 35	67 ± 35	74 ± 33	77 ± 31	78 ± 31
Mean SBP (mmHg)	139 ± 18	141 ± 18	141 ± 16	143 ± 15	143 ± 14	142 ± 12
Mean DBP (mmHg)	72 ± 11	73 ± 11	73 ± 10	75 ± 10	74 ± 9	73 ± 9
SBP variability	15 ± 8	15 ± 8	16 ± 7	18 ± 6	19 ± 5	19 ± 5
DBP variability	8 ± 4	8 ± 5	9 ± 4	10 ± 3	10 ± 3	10 ± 4
Gender (males)	2115 (98.6)	3176 (98.3)	7325 (98.2)	3862 (97.7)	4156 (97.7)	2001 (97.8)
Race (white)	1745 (81.4)	2553 (79.0)	5707 (76.5)	2596 (65.7)	2670 (62.7)	1353 (66.2)
Married	1413 (65.2)	2053 (65.2)	4481 (62.0)	1947 (50.8)	2162 (52.3)	1124 (56.1)
CHF	1314 (61.3)	1962 (60.7)	4508 (60.4)	2224 (56.3)	2384 (56.0)	1145 (56.0)
Myocardial infarction	749 (34.9)	1149 (35.6)	2430 (32.6)	1054 (26.7)	1034 (24.3)	457 (22.3)
Cerebrovascular disease	772 (36.0)	1158 (35.8)	2695 (36.1)	1298 (32.8)	1381 (32.5)	634 (31.0)
Malignancies	85 (4.0)	118 (3.7)	219 (2.9)	88 (2.2)	93 (2.2)	72 (3.5)
Liver disease	32 (1.5)	50 (1.5)	120 (1.6)	94 (2.4)	106 (2.5)	66 (3.2)
Rheumatologic disease	109 (5.1)	162 (5.0)	341 (4.6)	169 (4.3)	178 (4.2)	99 (4.8)
Lung disease	1062 (49.5)	1575 (48.7)	3643 (48.8)	1853 (46.9)	1947 (45.8)	977 (47.8)
Diabetes	1024 (47.7)	1420 (43.9)	3650 (48.9)	2305 (58.3)	2621 (61.6)	1293 (63.2)
Hypertension	986 (46.0)	1491 (46.1)	3310 (44.4)	1425 (36.1)	1471 (34.6)	636 (31.1)
Hemiplegia	73 (3.4)	106 (3.3)	319 (4.3)	158 (4.0)	150 (3.5)	79 (3.9)
HIV/AIDS	21 (1.0)	25 (0.8)	48 (0.6)	46 (1.2)	82 (1.9)	29 (1.4)
Nonpersistence (30 days)	51 679 (78.3)	82 519 (77.9)	26 417 (86.0)	83 657 (92.5)	84 044 (95.0)	31 939 (94.8)
Nonpersistence (60 days)	1377 (64.2)	2103 (65.1)	5402 (72.4)	3261 (82.5)	3655 (85.9)	1763 (86.2)
PDC	882 ± 13	880 ± 13	881 ± 13	879 ± 12	880 ± 12	880 ± 12
MPR	92 ± 21	91 ± 29	92 ± 41	93 ± 26	94 ± 24	95 ± 19

Data are presented as mean ± SD, median (IQR) or *n* (% of total).
BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

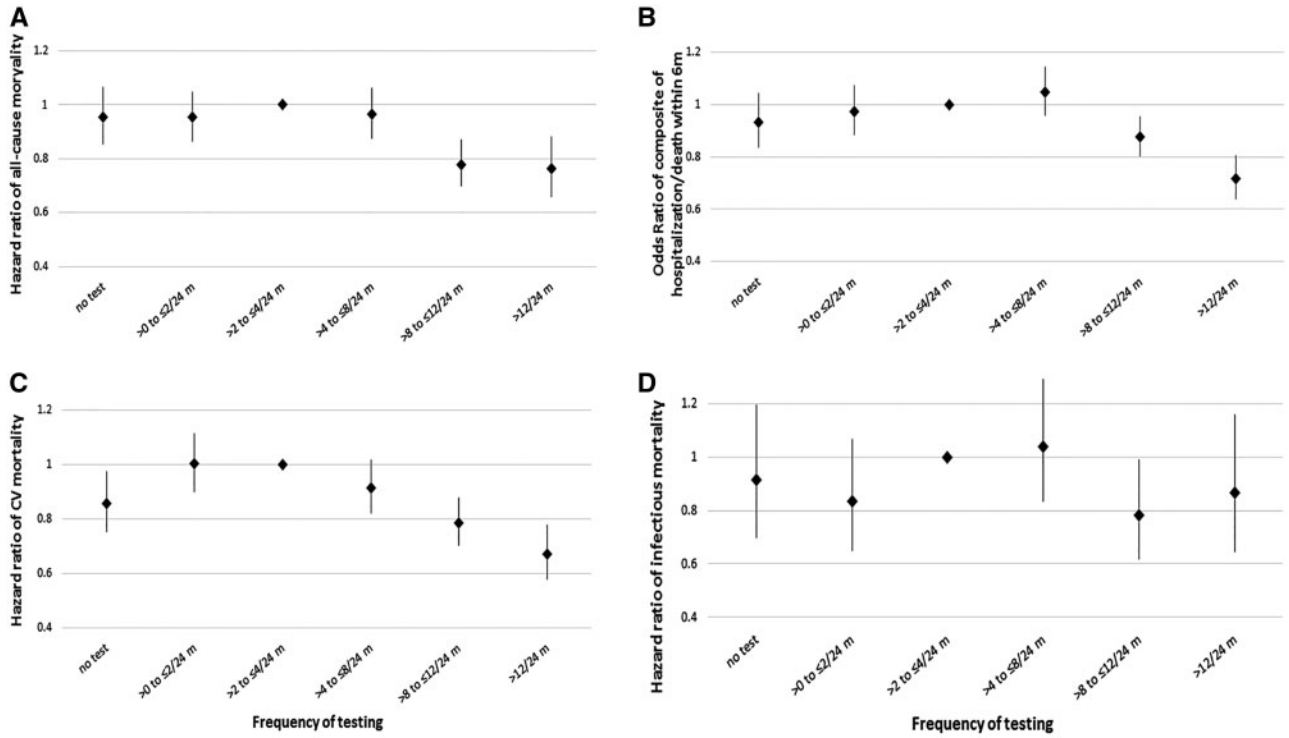

FIGURE 1: (**A**) Frequency of the test trio with all-cause mortality: multivariable adjusted HRs (95% CIs) of all-cause mortality associated with the frequency of the test trio in the 2-year RRT prelude time. **(B)** Frequency of the test trio with 6-month post-ESRD composite of hospitalizations/death: multivariable adjusted HR (95% CIs) of the major hospital admission within 6 months of RRT initiation associated with the frequency of the test trio in the 2-year RRT prelude time. **(C)** Frequency of the test trio with CV-specific mortality: multivariable adjusted HRs (95% CI) of CV mortality associated with the frequency of the test trio in the 2-year RRT prelude time. **(D)** Frequency of the test trio with infection-related mortality: multivariable adjusted HRs (95% CI) of infection mortality associated with the frequency of the test trio in the 2-year RRT prelude time.

Table 2. Hazard ratios for post-ESRD adverse outcomes by different frequency of the test trio

Frequency of test trio	All-cause mortality			CV mortality			Infection-related mortality			Composite of hospitalization/death		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	OR	95% CI	P-value
No trio tests	0.95	0.85–1.07	0.41	00.86	0.75–0.97	00.02	00.91	0.70–1.19	00.51	00.93	00.84–1.04	00.23
>0–≤2/24 m	0.95	0.86–1.05	0.33	10.00	0.90–1.11	00.98	00.83	0.65–1.07	00.15	00.97	00.89–1.07	00.60
>2–≤4/24 m	1.00			10.00			10.00			10.00		
>4–≤8/24 m	0.96	0.87–1.06	0.47	00.91	0.82–1.02	00.098	01.04	0.84–1.29	00.73	10.05	00.96–1.14	00.30
>8–≤12/24 m	0.78	0.70–0.87	0.001	00.79	0.70–0.88	<0.001	00.78	0.62–0.99	00.04	00.87	00.80–0.96	00.003
>12/24 m	0.76	0.66–0.88	<0.001	00.67	0.58–0.78	<0.001	00.86	0.65–1.16	00.33	00.72	00.64–0.80	<0.001

Patients who underwent testing with the trio of serum creatinine, potassium and hemoglobin measurement once every 6–12 months served as the referent.

significant for CV mortality [HR 0.68 (95% CI 0.58–0.79); P < 0.001] (Figure 1C) but not for infection-related mortality [HR 0.84 (95% CI 0.62–1.14); P = 0.26] (Figure 1D, Table 2). Associations in subgroups of patients with and without pre-ESRD nephrology care revealed a significant association with all-cause and CV mortality only in patients who received nephrology care (Figures 2A and 2C, Supplementary Appendix Tables 2 and 3). Associations between frequency of testing and infection-related mortality were not significant in either subgroup (Figure 2D, Supplementary Appendix Table 4). Age did not modify the observed associations (P for interaction = 0.66; Supplementary Appendix Table 7).

Composite outcome of major hospitalization events or death within 6 months of ESRD initiation

In the first 6 months after ESRD transition, 7137 (30.9%) patients experienced hospitalizations, 4100 patients died (17.8%) and 9405 (40.7%) patients reached the composite endpoint. The adjusted odds ratios (ORs) of the composite outcome associated with lab testing done >8–≤ 12/24 months or >12/24 months compared with >2–≤ 4/24 months were 0.88 (95% CI 0.81–0.97) and 0.70 (95% CI 0.62–0.79), respectively (Figure 1B, Table 2). The association was only significant in patients who received nephrology care and not in those who did not receive

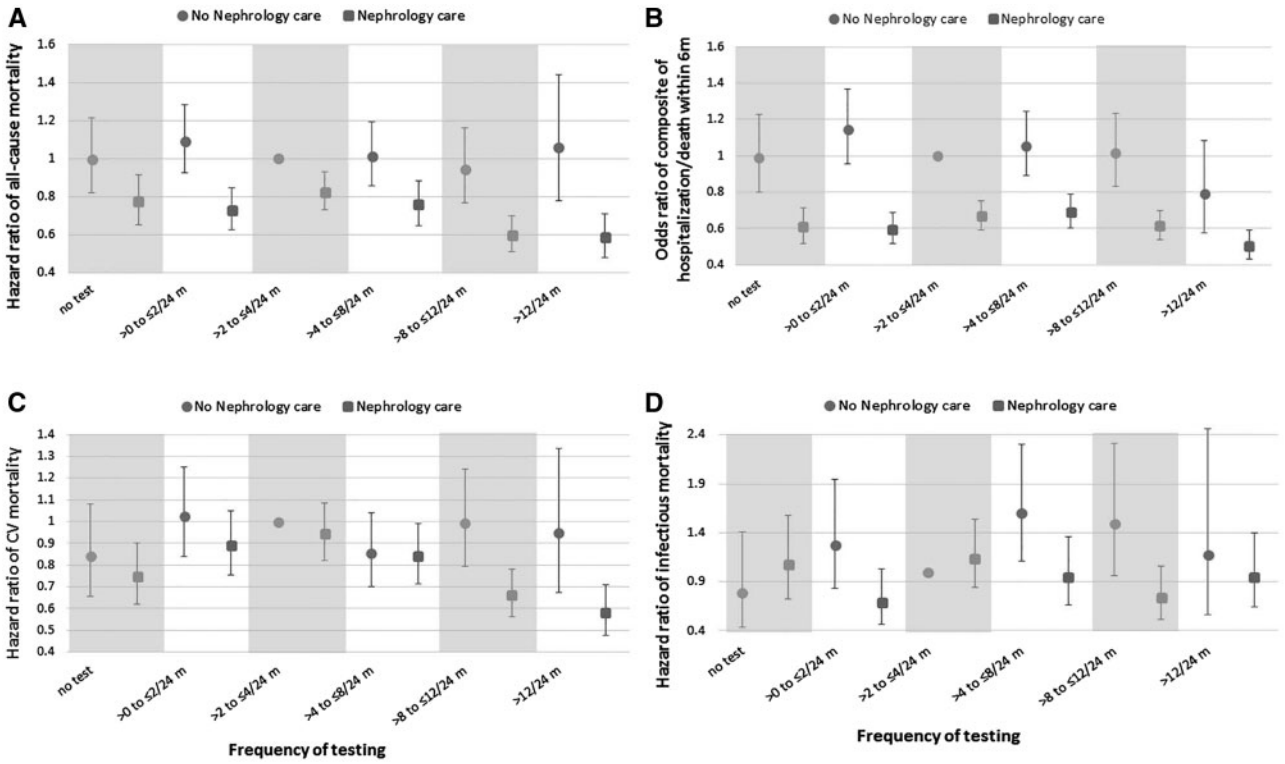

FIGURE 2: (**A**) Frequency of the test trio with all-cause mortality in subgroups: multivariable adjusted HRs (95% CI) of all-cause mortality associated with the frequency of the test trio in the 2-year RRT prelude time in subgroups. An interaction term for frequency of tests and nephrology care in the prelude time was used to compare subgroup differences. **(B)** Frequency of the test trio with 6-month post-ESRD composite of hospitalizations/death in subgroups: multivariable adjusted HRs (95% CI) of the major hospital admission within 6 months of RRT initiation associated with the frequency of the test trio in the 2-year RRT prelude time in subgroups. An interaction term for frequency of tests and nephrology care in the prelude time was used to compare subgroup difference. **(C)** Frequency of the test trio with CV-specific mortality in subgroups: multivariable adjusted HRs (95% CI) of CV mortality associated with the frequency of the test trio in the 2-year RRT prelude time in subgroups. An interaction term for frequency of tests and nephrology care in the prelude time was used to compare subgroup differences. **(D)** Frequency of the test trio with infection-related mortality in subgroups: multivariable adjusted HRs (95% CI) of infection-related mortality associated with the frequency of the test trio in the 2-year RRT prelude time in subgroups. An interaction term for frequency of tests and nephrology care in the prelude time was used to compare subgroup differences.

nephrology care (Figure 2B, Supplementary Appendix Table 5). Age did not modify the observed associations (P for interaction = 0.61; Supplementary Appendix Table 8).

DISCUSSION

We examined associations of frequency of pre-ESRD routine lab testing with post-ESRD mortality and the 6-month composite outcome of hospitalization or death. We found that a higher frequency of pre-ESRD lab testing was associated with lower post-ESRD all-cause and CV mortality and lower composite outcomes of hospitalization/death risk, but not with lower infection-related mortality. The beneficial associations of more frequent pre-ESRD laboratory testing were limited to patients who received nephrology care prior to dialysis and were not present in patients who did not receive such care.

Our results confirm and extend findings from prior studies showing that nephrology care [3, 15] or structured multidisciplinary care [16, 17] prior to ESRD is associated with improved post-ESRD clinical outcomes, including lower mortality and decreased hospital stays [16, 18]. Although some randomized clinical trials didn't show any significant difference in post-ESRD mortality between patients with or without pre-ESRD nephrology care [19, 20], there are still many observational studies [4, 21] and clinical trials [16] that have demonstrated that earlier and more frequent nephrology subspecialty pre-ESRD care significantly improves survival rate. Notwithstanding the importance of the aforementioned studies, their findings do not clarify what aspect of nephrology subspecialty care is responsible for the observed benefits. Subspecialty care involves the clinical management of complex metabolic abnormalities, the implementation and monitoring of renoprotective strategies, timely vascular access planning, patient education about impending ESRD and choice of renal replacement modality and the delivery of ancillary services such as renal nutritional care, case management or social work. In order to prospectively apply the most impactful interventions, it is important to determine if there are certain aspects of pre-ESRD clinical care that offer more downstream benefits. Our study suggests that more frequent monitoring of laboratory abnormalities could be one such intervention.

Routine laboratory testing is a simple procedure that can easily be applied even by non-nephrologists, such as general practitioners. Management of CKD by primary care physicians

has been successfully attempted [22, 23], with the UK even promoting nationwide primary care physician involvement in CKD care [24]. Although effects on post-ESRD outcomes have not been consistent, the motives behind such attempts are broader and involve the creation of a more cost-efficient, convenient and feasible choice of predialysis care in the face of increasing ESRD incidence [2] and a shortage of nephrologists [25]. Particularly, in certain US geographic areas, the increasing absence of nephrology pre-ESRD care has led to worse clinical outcomes in CKD patients [26]. In light of our finding that the benefits associated with more frequent laboratory testing were limited to patients who received nephrology specialty care during the pre-ESRD period, the potential long-term benefits of a non-nephrology-based pre-ESRD implementation, such as a general practitioner–based approach, is questionable. Intervention offered by subspecialists in response to certain laboratory abnormalities may be different, with nephrologists possibly providing more comprehensive evaluations and care compared with a general practitioner [23]. Nevertheless, benefits in other countries and in non-VA health care systems and shorter-term and/or non-medical benefits (e.g. economic advantages) from a non-nephrologist-based disease monitoring and intervention strategy cannot be ruled out.

The significant association between the more frequent application of the three routine laboratory tests examined in our study and improved post-ESRD outcomes could be attributed to better detection and management of the conditions that are monitored through these tests or other tests that might have been administered concomitantly. More frequent measurement of serum creatinine could help earlier detection of progression of CKD or episodes of acute kidney injury, which are associated with worse outcomes. In addition to the general effect on cardiac function [27, 28] and metabolic milieu [29], hypo- and hyperkalemia have been associated with poorer outcomes in patients with advanced CKD [30, 31]. It is possible that their more frequent measurement could result in earlier detection and ultimately improved outcomes. Moreover, lower hemoglobin has been associated with adverse outcomes in patients with CKD, such as higher mortality and progression to a higher incidence of ESRD [32]. While normalization of hemoglobin concentration using erythropoiesis-stimulating agents (ESAs) has resulted in no benefits or in harm [33, 34], it is possible that other interventions (e.g. ESA therapy using lower treatment targets or non-ESA-based therapies) triggered by the earlier detection of low hemoglobin could yield benefits in the post-ESRD period. Conversely, more frequent laboratory measurements could be surrogate measures of other aspects of care received in the context of laboratory monitoring, such as management of blood pressure, or other medical conditions.

Our study is notable as it is relatively large and represents a majority of US ESRD patients. Our study also has limitations. It was observational in nature and most patients' encounters were disease-driven and not for prevention. Therefore, frequent test trios could represent sicker patients. However, if more frequent testing was merely a surrogate of more severe illness, one would have expected to find worse, and not better, outcomes associated with it. Furthermore, the patients with more frequent test trios versus those without were much younger and had higher income. Therefore, we cannot determine the trigger(s) of increased frequency of testing and the results cannot be used to infer causality. Most of our patients were male US veterans; therefore the results may not apply to women, to the general US population or to patients outside of the USA.

CONCLUSION

More frequent laboratory testing during the 2-year ESRD prelude period is associated with lower post-ESRD, all-cause and CV mortality and also with lower hospitalization rates in the immediate post-ESRD period. However, due to the observational nature of our data, the practical implementation of a more frequent lab-based monitoring system for patients with advanced CKD and the use of such a system by nonnephrologists (independently or under supervision by a nephrologist) will need to be tested in prospective trials.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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AUTHORS' CONTRIBUTIONS

Study concept and design: J.L.L. and C.P.K.
Acquisition of data: C.P.K., J.L.L. and E.S.
Analysis and interpretation of data: J.L.L., C.P.K. and O.A.S.
Tables and figures: O.A.S., C.P.K. and J.L.L.
Drafting of the manuscript and approval of the final version: J.L.L., C.P.K., C.D.D. and K.K.Z.
Critical revision of the manuscript for important intellectual content and approval of the final version: J.L.L., C.P.K., M.Z.M., K.S. and K.K.Z.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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