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Association of thyroid status prior to transition to end-stage renal disease with early dialysis mortality

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ABSTRACT

Background. Advanced chronic kidney disease (CKD) patients, including those receiving dialysis, have a high prevalence of thyroid dysfunction. Although hypothyroidism is associated with higher death risk in end-stage renal disease (ESRD) patients, no studies have examined whether thyroid status in the pre-ESRD period impacts mortality after dialysis initiation.

Methods. Among US veterans with CKD identified from the national Veterans Affairs database that transitioned to dialysis over the period from October 2007 to September 2011, we examined the association of pre-ESRD serum thyrotropin (TSH) levels averaged over the 1-year pre-dialysis ('prelude') period with all-cause mortality in the first year following dialysis initiation.

Results. Among 15 335 patients in the 1-year prelude cohort, TSH levels >5.0 mIU/L were associated with higher mortality in expanded case-mix Cox models (reference: TSH 0.5–5.0 mIU/L): adjusted hazard ratio (aHR) [95% confidence interval (CI) 1.20 (1.07–1.33). Similar findings were observed for TSH >5.0 mIU/L and mortality in the 2- and 5-year cohorts: aHRs (95% CI) 1.11 (1.02–1.21) and 1.15 (1.07–1.24), respectively. Analyses of finer gradations of TSH in the 1-year prelude cohort demonstrated that incrementally higher levels >5.0 mIU/L were associated with increasingly higher mortality in expanded case-mix models (reference: TSH 0.5–3.0 mIU/L): aHRs (95% CI) 1.18 (1.04–1.33) and 1.28 (1.03–1.59) for TSH levels >5.0–10.0 mIU/L and >10.0 mIU/L, respectively. In the 2- and 5-year cohorts, mortality associations persisted most strongly for those with TSH >10.0 mIU/L, particularly after laboratory covariate adjustment.

Conclusions. Among new ESRD patients, there is a dose-dependent relationship between higher pre-ESRD TSH levels >5.0 mIU/L and post-ESRD mortality. Further studies are needed to determine the impact of TSH reduction with thyroid hormone supplementation in this population.

Keywords: incident ESRD, mortality, pre-ESRD prelude, thyroid, transition

INTRODUCTION

Thyroid dysfunction is a common yet underrecognized complication among end-stage renal disease (ESRD) patients requiring dialysis [1–9]. Comparatively greater emphasis has been placed upon other endocrine disorders in chronic kidney disease (CKD), such as diabetes and secondary hyperparathyroidism. However, multiple studies have shown that both hemodialysis and peritoneal dialysis patients have a disproportionately higher prevalence of hypothyroidism when compared with the general population (~11–23% versus 5%, respectively) [10–15]. Despite these data, hypothyroidism may be frequently overlooked in dialysis patients, possibly due to overlap of its accompanying signs and symptoms with those of uremia (e.g. fatigue, cold intolerance, depression, impaired cognition) [6, 7, 16]. Additionally, a majority of dialysis patients have subclinical hypothyroidism, defined by elevated serum thyrotropin (TSH) levels, ranging between 5 and 10.0 mIU/L with normal range serum free thyroxine (FT4) levels, and have been considered by some to be secondary to kidney dysfunction rather than primary thyroid disease that merits treatment [17].

Large population-based studies indicate that thyroid dysfunction manifests during even earlier stages of nondialysis-dependent CKD (NDD-CKD) [16, 18–23]. Indeed, multiple observational studies have shown that there is a graded association between the prevalence of hypothyroidism with increasingly impaired kidney function. In a study of 14 623 participants in

the Third National Health and Nutrition Examination Survey, there was an incrementally higher prevalence of hypothyroidism with increasing severity of kidney dysfunction: 5, 11, 20, 23 and 23% with estimated glomerular filtration rates (eGFRs) of ≥90, 60–89, 45–59, 30–44 and <30 mL/min/1.73 m^2, respectively [16]. Furthermore, in a study of 461 607 US veterans with Stages 3–5 NDD-CKD with concomitant thyroid functional tests and serum creatinine levels, each 10 mL/min/1.73 m^2 decrement in eGFR was associated with an 18% higher risk of hypothyroidism (defined as a serum TSH level >5.0 mIU/L or receipt of exogenous thyroid hormone replacement), independent of sociodemographics and comorbidities [21].

Although early studies hypothesized that thyroid hormone deficiency may be a physiologic adaptation among ESRD patients [24], contemporary studies in both hemodialysis and peritoneal patients have shown that hypothyroidism defined by serum TSH levels measured after commencement of dialysis is associated with higher mortality risk, even in the TSH ranges characterized as subclinical hypothyroidism [12–15]. More recently, a study strictly focused upon Stage 3 NDD-CKD patients also found that both high-normal (≥3.0 mIU/L) and lower (<0.5 mIU/L) TSH levels were associated with higher death risk, which may also approximate short-term associations of thyroid status with mortality [25]. However, there have not been prior studies on whether thyroid status prior to developing irreversible kidney failure influences long-term post-ESRD mortality among incident ESRD patients transitioning to dialysis. To address this knowledge gap, through linkage of pre-ESRD data from the national Veterans Affairs (VA) database with post-ESRD registries [e.g. United States Renal Data System (USRDS)] [26], we sought to examine the relationship between pre-ESRD thyroid status during the pre-dialysis transition period with post-ESRD mortality among US veterans with incident ESRD.

MATERIALS AND METHODS

Source cohort

We conducted a historical cohort study with longitudinal data from the Transition of Care in CKD (TC-CKD) study, a retrospective cohort study examining US veterans transitioning to renal replacement therapy over the period of 1 October 2007 through 30 September 2011 [26]. Our source population consisted of 52 172 patients who were identified from the national VA database linked to USRDS registry data. Patients were included in this study provided that they (i) were aged ≥18 years at the time of study entry, (ii) had plausible person-time follow-up (i.e. death/censoring events did not precede the exposure date) and (iii) underwent one or more TSH measurements during the exposure period (Supplementary data, Figure S1).

Patients were categorized into three analytic cohorts based on having pre-ESRD observation ('prelude') exposure intervals of 1, 2 or 5 years prior to transitioning to dialysis [26]. We *a priori* defined the 1-year prelude period cohort as our primary cohort. The study was approved by the Institutional Review Boards of the University of California Irvine Medical Center, VA Long Beach Healthcare System and Memphis VA Medical Center.

Exposure ascertainment

To determine the impact of pre-ESRD thyroid status upon post-ESRD mortality, we examined serial measures of TSH averaged over the prelude period. Our primary exposure was mean TSH level averaged over the 1-year prelude period, categorized according to the TSH reference range used in the general population: <0.5, 0.5 to <5.0 and ≥5.0 mIU/L (corresponding to hyperthyroid, euthyroid and hypothyroid TSH ranges, respectively) [13, 14, 27]. The strict classification of subclinical thyroid disease is based on a normal range serum FT4 concentration that was not available in sufficient numbers of our patients. In secondary analyses, we assessed thyroid status using finer gradations of TSH, defined according to the usual TSH ranges for these designations as overt hyperthyroid range (<0.1 mIU/L), subclinical hyperthyroid range (0.1 to <0.5 mIU/L), low-normal (0.5–3.0mIU/L), high-normal (>3.0 to <5.0 mIU/L), subclinical hypothyroid range (5.0 to <10.0 mIU/L) and overt hypothyroid range TSH levels (≥10.0 mIU/L) [13, 14]. In sensitivity analyses, in order to flexibly examine TSH as a continuous predictor of mortality, we examined restricted cubic splines with knots defined at the 33rd and 66th percentiles of observed TSH values (corresponding to TSH levels of 1.7 and 2.9 mIU/L, respectively). The median [interquartile range (IQR)] of TSH measurements per patient averaged over the 1-, 2- and 5-year prelude intervals were 1 (1–2), 2 (1–3) and 3 (1–5), respectively. The minimum–maximum range of TSH measurements per patient averaged over the 1-, 2- and 5-year prelude intervals were 1–22, 1–26 and 1–39, respectively.

Outcome ascertainment

The outcome of interest was all-cause mortality. At-risk time began the day after dialysis initiation. All-cause mortality data, censoring events and associated dates were obtained from VA, Center for Medicare and Medicaid Services (CMS) and USRDS data sources. Patients were censored for kidney transplantation, loss to follow-up or the last date of available follow-up data (27 December 2012), whichever occurred first.

Sociodemographic, comorbidity, medication and laboratory data

Data from the VA and USRDS patient and medical evidence files were used to determine patients' baseline sociodemographic information (e.g. age, sex, race, ethnicity) at the time of dialysis initiation. Data on cause of ESRD and initial dialysis modality were obtained from USRDS sources. Information about comorbidities at the time of dialysis initiation was extracted from the VA Inpatient and Outpatient Medical SAS datasets [28] and CMS datasets using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) diagnostic and procedure codes and current procedural terminology codes [29]. Charlson Comorbidity Index (CCI) scores were estimated using the Deyo modification for administrative datasets without including kidney disease [30]. Body mass index data were

Table 1. Baseline characteristics of 1-year prelude cohort according to thyroid status

	TSH (mIU/L)				
	Overall	<0.5	0.5–5.0	>5.0	P-value
n (%)	15 335	452 (3.0)	13 237 (86.3)	1646 (10.7)	N/A
Age at dialysis initiation (mean ± SD)	69.8 ± 11.4	70.1 ± 11.2	69.5 ± 11.4	71.4 ± 11.1	<0.001
Female (%)	2	2	2	2	0.85
Black race (%)	25	28	26	14	<0.001
Hispanic ethnicity (%)	7	3	7	9	<0.001
Cause of ESRD (%)					0.12
Diabetes	47	40	47	47	
Hypertension	28	31	28	29	
Glomerulonephritis	5	5	5	5	
Cystic disease	1	1	1	1	
Other urologic cause	1	1	1	1	
Other cause	11	15	11	11	
Unknown/missing	6	6	6	7	
Comorbidities					
CCI (mean ± SD)	4.2 ± 2.7	4.2 ± 2.8	4.2 ± 2.7	4.5 ± 2.8	0.002
Congestive heart failure (%)	42	41	42	48	<0.001
Coronary artery disease (%)	59	59	59	63	0.02
Cerebrovascular disease (%)	28	32	28	32	<0.001
Hypertension (%)	96	95	96	96	0.20
Hyperlipidemia (%)	83	81	83	84	0.20
Thyroid supplement use (%)	16	26	12	43	<0.001
Anti-thyroid agents (%)	<1	2	<1	<1	<0.001
Laboratory results, median (IQR)					
eGFR, 1-year averaged (mL/min/1.73 m^2)	26 (19–39)	27 (19–41)	26 (19–38)	27 (19–41)	0.02
Serum bicarbonate (mEq/L)	25 (22–27)	25 (23–27)	25 (22–27)	25 (23–27)	0.25

TSH, thyrotropin; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate.

obtained from the VA Vital Status file. Medication data were obtained from both CMS Part D and VA pharmacy dispensation records [31]. TSH levels and other laboratory data except serum creatinine were obtained from the VA Decision Support System-National Data Extracts Laboratory Results files [32]. VA Corporate Data Warehouse LabChem data files were used to extract data about pre-dialysis serum creatinine [33]. Using serum creatinine and demographic data, eGFR was calculated using the CKD Epidemiology Collaboration equation [34].

Statistical analysis

We estimated the association of pre-ESRD thyroid status with post-ESRD mortality using Cox proportional hazard models. Cox models were conducted using five hierarchical levels of covariate adjustment:

(i) minimally adjusted: adjusted for patient's calendar quarter of dialysis initiation to account for secular changes in care over time;
(ii) case-mix adjusted: adjusted for covariates in the minimally adjusted model, as well as age at dialysis initiation, sex, race and ethnicity;
(iii) expanded case-mix model: adjusted for covariates in the case-mix model, as well as cause of ESRD (e.g. diabetes, hypertension, glomerulonephritis, cystic disease, other urologic cause, other cause, unknown/missing), CCI score, congestive heart failure (CHF), cerebrovascular disease (CVD), coronary artery disease (CAD), hypertension and hyperlipidemia;
(iv) expanded case-mix + laboratory adjusted model: adjusted for covariates in the expanded case-mix model, as well as eGFR (i.e. proxy of residual kidney function), serum bicarbonate; and
(v) expanded case-mix + laboratory + medication adjusted model: adjusted for covariates in the expanded case-mix + laboratory test model, as well as use of thyroid hormone supplementation and use of anti-thyroid medications.

We *a priori* defined the expanded case-mix model as our preferred model, which included core sociodemographic measures and other confounders of the association between thyroid status and mortality. Candidate comorbidity, laboratory (i.e. markers of metabolic status [35], kidney function [16, 21, 23, 36] and underlying illness [4]) and medication covariates were selected as those covariates that were hypothesized to be associated with thyroid dysfunction and mortality based on published evidence but not thought to be on causal pathways linking thyroid status to death. For the 1- and 2-year prelude cohorts, comorbidity, laboratory and medication covariates were extracted over a time period spanning from the start of the prelude period to 1 year prior to commencement of the prelude period. For the 5-year prelude cohort, due to a high degree of missing laboratory and medication data in the 1 year prior to commencement of the 5-year prelude period (i.e. left truncation of data), only minimally adjusted, case-mix and expanded case-mix adjusted models were estimated.

In the 1-year prelude cohort, there were no missing values for age and sex; remaining covariates had <1% missing values, except CCI and comorbidities (each <5%), eGFR (15%) and

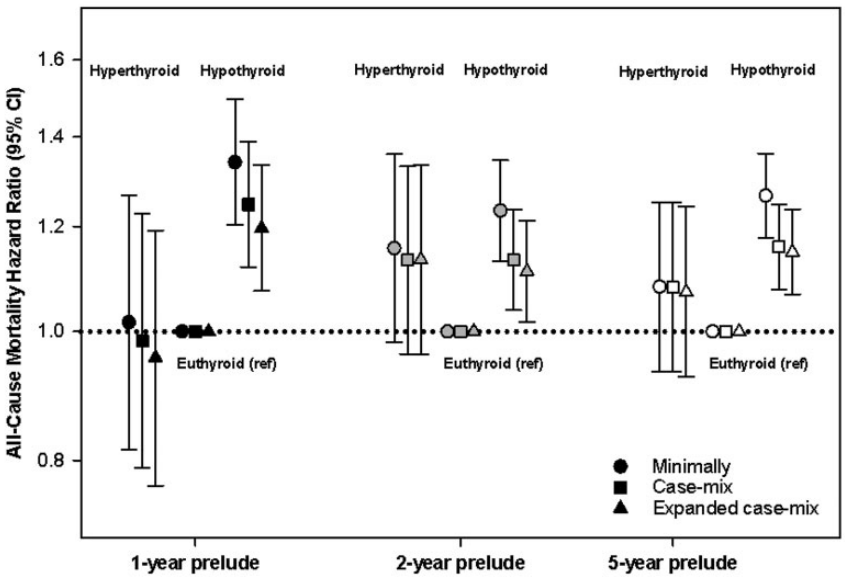

FIGURE 1: Association of thyroid status over the 1-year prelude period with post-ESRD all-cause mortality risk. Minimally adjusted models adjusted for patients' calendar quarter of dialysis initiation to account for secular changes in care over time. Case-mix models adjusted for covariates in the minimally adjusted model, as well as age at dialysis initiation, sex, race and ethnicity. Expanded case-mix model adjusted for covariates in the case-mix model, as well as cause of ESRD, CCI score, CHF, CVD, CAD, hypertension and hyperlipidemia.

serum bicarbonate (23%). Given the higher proportion of missing laboratory covariates, further adjustment for potential confounders in expanded case-mix + laboratory models were conducted as sensitivity analyses in which missing data were handled using multiple imputation. To explore whether receipt of thyroid-modulating therapy may be an intermediate in the association of thyroid status with mortality, we conducted sensitivity analyses in which we incrementally added receipt versus nonreceipt of thyroid-modulating therapy (e.g. thyroid hormone supplementation, anti-thyroid medication) as potential pathway intermediates in expanded case-mix + laboratory + medication models and observed for effect estimate attenuation. We also conducted subgroup analyses of thyroid status and mortality across clinically relevant subgroups. Proportional hazards assumptions were confirmed by graphical analysis. Analyses and figures were generated using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), Stata version 13.1 (Stata Corporation, College Station, TX, USA) and SigmaPlot Version 12.5 (Systat Software, San Jose, CA, USA).

RESULTS

Study population

Among 15 335 patients who met eligibility criteria for the 1-year prelude cohort, 3, 86 and 11% of patients had TSH levels <0.5 mIU/L (hyperthyroid range), 0.5–5.0 mIU/L (euthyroid range) and >5.0 mIU/L (hypothyroid range), respectively. The median (IQR), mean ± SD, and minimum–maximum values of TSH averaged over the 1-year prelude period were 2.2 (1.4–3.4), 3.2 ± 6.4 and 0.001–210.9 mIU/L, respectively. Compared with patients who were euthyroid, those with TSH levels >5.0 mIU/L tended to be older; were less likely to be African-American; were more likely to have CHF, CAD and CVD; and were more likely to be on thyroid hormone supplementation (Table 1). Compared with patients who were euthyroid, those with TSH levels <0.5 mIU/L were less likely to be Hispanic; were less likely to have diabetes as the cause of ESRD; were more likely to have CVD; and were more likely to be on anti-thyroid medications or thyroid hormone supplementation. Baseline characteristics stratified according to finer gradations of TSH are shown in Supplementary data, Table S1.

Thyroid status and mortality

In primary analyses of the 1-year prelude cohort, patients contributed a total of 12 702 patient-years of follow-up, during which time 2837 all-cause deaths occurred. Median (IQR) at-risk time was 12.0 (9.9–12.0) months. In minimally adjusted, case-mix and expanded case-mix models, we observed that pre-ESRD TSH levels >5.0 mIU/L over the 1-year prelude period were associated with higher mortality risk (reference: TSH 0.5–5.0 mIU/L): adjusted HRs (aHRs) [95% confidence interval (CI)] 1.34 (1.20–1.49), 1.25 (1.12–1.39) and 1.20 (1.07–1.33), respectively (Figure 1 and Supplementary data, Table S2). These associations persisted with incremental adjustment for laboratory covariates [aHR (95% CI) 1.18 (1.06–1.32)] and medications [aHR (95% CI) 1.19 (1.06–1.33)]. Across all levels of adjustment, we did not observe an association between TSH levels <0.5 mIU/L and mortality.

In sensitivity analyses, we also examined the thyroid status–mortality associations in the 2- and 5-year prelude cohorts (Figure 1 and Supplementary data, Table S2). Compared with pre-ESRD TSH levels of 0.5–5.0 mIU/L, TSH levels >5.0 mIU/L over the 2-year prelude period were associated with higher mortality risk in minimally adjusted, case-mix, expanded case-mix, expanded case-mix + laboratory and expanded case-mix + laboratory + medication models. Similar to the 1-year prelude cohort, we observed that pre-ESRD TSH levels >5.0 mIU/L over the 5-year prelude period were associated with

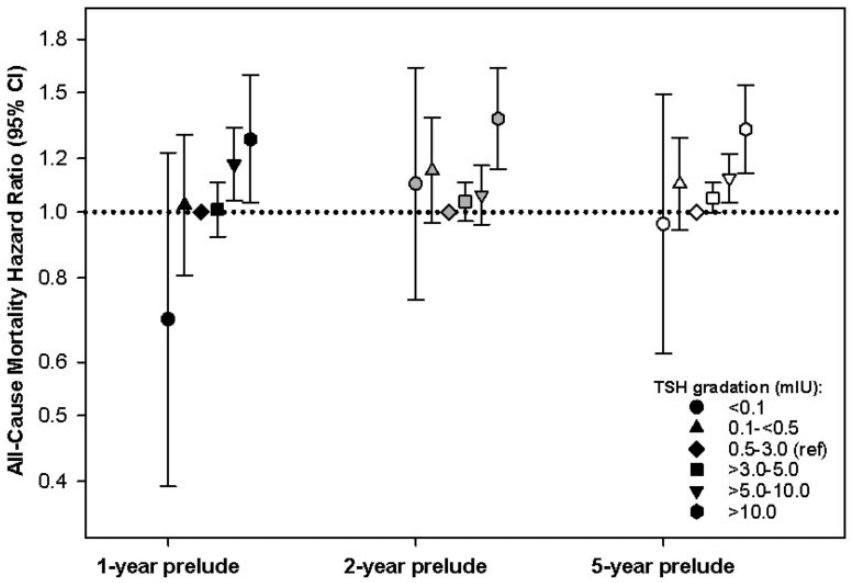

FIGURE 2: Association of TSH gradations over the 1-year prelude period with post-ESRD all-cause mortality risk. Analyses adjusted for expanded case-mix covariates, which included patients' calendar quarter of dialysis initiation, age at dialysis initiation, sex, race, ethnicity, cause of ESRD, CCI score, CHF, CVD, CAD, hypertension and hyperlipidemia.

higher mortality risk in minimally adjusted, case-mix and expanded case-mix models.

TSH gradations and mortality

In secondary analyses of finer TSH gradations, minimally adjusted analyses showed that TSH categories >3.0–5.0, >5.0–10.0 and >10.0 mIU/L were associated with incrementally higher death risk (reference: TSH 0.5–3.0 mIU/L): aHRs (95% CI) 1.10 (1.01–1.21), 1.35 (1.19–1.53) and 1.48 (1.19–1.83), respectively (Supplementary data, Table S3). However, upon adjustment for expanded case-mix covariates ('primary model'), only associations of TSH levels >5.0–10.0 mIU/L and >10.0 mIU/L with higher mortality persisted: aHRs (95% CI) 1.18 (1.04–1.33) and 1.28 (1.03–1.59), respectively (Figure 2 and Supplementary data, Table S3). In expanded case-mix-adjusted analyses of the 2-year prelude cohort, pre-ESRD TSH levels >5.0 mIU/L were numerically higher but did not achieve statistical significance, whereas there was a statistically significant association between TSH levels >10.0 mIU/L and mortality: aHRs (95% CI) 1.06 (0.96–1.17) and 1.37 (1.16–1.63), respectively.

In minimally adjusted analyses of continuous TSH examined as a restricted cubic spline, pre-ESRD TSH levels >3.0 mIU/L were monotonically associated with higher death risk (Figure 3A). However, in models adjusted for case-mix and expanded case-mix covariates, we observed a higher threshold of 5.0 mIU/L above which elevated TSH levels were associated with higher mortality risk (Figure 3B and C).

Thyroid status and mortality across clinically relevant subgroups

In expanded case-mix analyses, we did not detect effect modification on the basis of age, sex, race, ethnicity, CCI score, CHF, CVD, CAD, hypertension, hyperlipidemia, thyroid hormone supplement use or anti-thyroid medication use status: P-interaction = 0.54, 0.99, 0.52, 0.74, 0.79, 0.58, 0.91, 0.72, 0.45, 0.75, 0.33 and 0.50, respectively (Figure 4 and Supplementary data, Table S4). In all subgroups, the nominal HRs for TSH levels >5.0 mIU/L were >1 except among non-White patients and those without hypertension; nominal associations were statistically significant in the following subgroups: age ≥65 years, male, White, Non-Hispanic, CCI score ≥5, CHF present, CHF absent, CVD absent, CAD present, hypertension present, hyperlipidemia present, thyroid hormone supplement use, thyroid hormone supplement nonuse and anti-thyroid medication nonuse.

DISCUSSION

In a large national incident ESRD cohort of US veterans, we observed that approximately 11% of patients had TSH levels in the hypothyroid range (TSH >5.0 mIU/L) in the year preceding transition to dialysis. After accounting for confounders of sociodemographic and comorbidity status, we found that pre-ESRD TSH levels exceeding 5.0 mIU/L were incrementally associated with higher death risk in analyses examining TSH as both a categorical and continuous variable.

There is increasing recognition that aberrancies in thyroid status, particularly hypothyroidism, are associated with heightened death risk in the kidney disease population [6, 7, 12–15]. The first study of dialysis patients to examine thyroid status defined by serum TSH levels and mortality showed that, among a cohort of 2715 incident/prevalent dialysis from two tertiary care centers in Boston, hypothyroid range TSH levels (i.e. exceeding the assay reference ranges of >5.0 or >5.4 mIU/L) ascertained at baseline were independently associated with a 35% higher death risk versus euthyroidism [12]. Although a secondary analysis of 1000 incident/prevalent diabetic hemodialysis patients from the Deutsche Diabetes Dialyse Studie (4D)

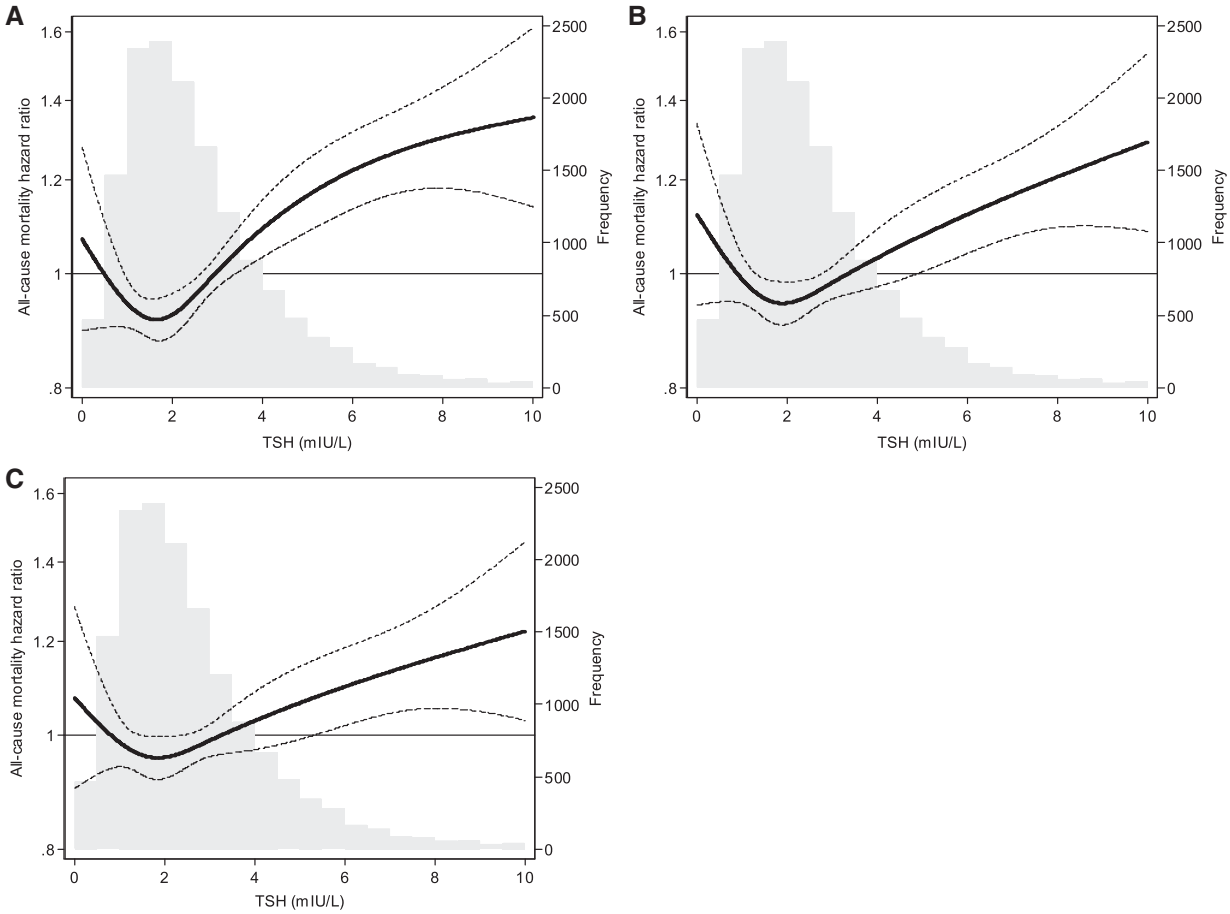

FIGURE 3: Association of continuous TSH levels over the 1-year prelude period with post-ESRD all-cause mortality risk using restricted cubic splines. Minimally adjusted models adjusted for patients' calendar quarter of dialysis initiation to account for secular changes in care over (Panel **A**). Case-mix models adjusted for covariates in the minimally adjusted model, as well as age at dialysis initiation, sex, race and ethnicity (Panel **B**). Expanded case-mix models adjusted for covariates in the case-mix models, as well as cause of ESRD, CCI score, CHF, CVD, CAD, hypertension and hyperlipidemia (Part **C**). Solid black lines present hazard ratios (dashed lines indicate 95% CIs) for TSH analyzed as a spline with knots at the 33rd and 66th percentiles of observed values (1.7 and 2.9, respectively). A histogram of observed TSH values and a hazard reference ratio of 1 (solid gray line) is overlaid. TSH levels >10 mIU/L were truncated (i.e. replaced by the value of 10 mIU/L) for the purposes of the spline analyses.

study did not observe that subclinical hypothyroidism examined alone nor in conjunction with overt disease was associated with higher mortality risk [37], subsequent studies have shown robust hypothyroidism–mortality associations. In an analysis of 8840 national incident hemodialysis patients from a large dialysis organization, hypothyroid-range TSH levels (>5.0 mIU/L) that were measured at dialysis initiation (i.e. baseline TSH levels as a proxy of long-term exposure–mortality associations) and over the study period (i.e. time-dependent TSH levels as proxy of short-term exposure–mortality associations) were independently associated with a 47 and 62% higher death risk, respectively, when compared with euthyroid range levels [13]. These findings were corroborated in a national study of 1484 incident/prevalent peritoneal dialysis patients among whom baseline and time-dependent TSH levels in the hypothyroid range (>5.0 mIU/L) were also associated with lower survival [14]. Similarly, in a prospective multicenter study of hemodialysis patients who underwent protocolized TSH measurement every 6 months, there was a 2.5-fold higher death risk observed with time-dependent TSH levels in the highest versus lowest tertiles [15]. More recently, in a study of 227 422 US veterans with Stage 3 CKD, it was observed that both high-normal (≥3.0 mIU/L) and lower (<0.5 mIU/L) TSH levels were associated with higher death risk, which may also approximate short-term associations of thyroid status with mortality [25]. Although the aforementioned studies have examined thyroid dysfunction and mortality in NDD-CKD patients who have not yet transitioned to ESRD, as well as studies in those with pre-existing ESRD that reflects short-term associations of thyroid status and mortality, there has been a paucity of data regarding the long-term sequelae of thyroid dysfunction among NDD-CKD patients who survive to ESRD.

To our knowledge, this is the first study that has examined the long-term impact of thyroid status during later stages of NDD-CKD upon the post-dialysis mortality risk of incident ESRD patients. We observed that hypothyroid-range TSH levels (>5.0 mIU/L) measured 1 year prior to dialysis initiation were associated with higher death risk across multiple secondary and sensitivity analyses. Several potential pathways have been suggested as underlying mechanisms of the

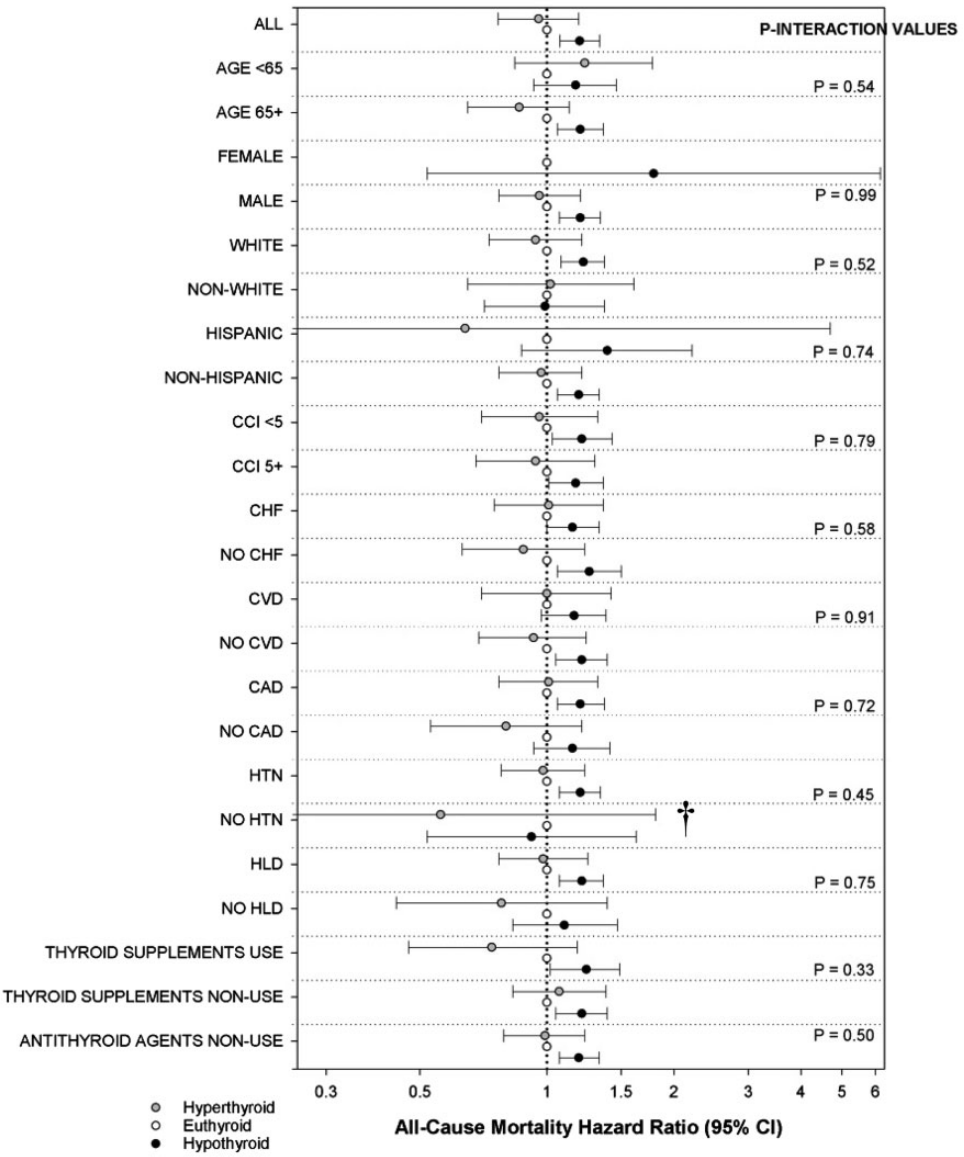

FIGURE 4: Subgroup analyses of the association of thyroid status over the 1-year prelude period with post-ESRD 1-year all-cause mortality. Analyses adjusted for expanded case-mix covariates, which included patients' calendar quarter of dialysis initiation, age at dialysis initiation, sex, race, ethnicity, cause of ESRD, CCI score, CHF, CVD, CAD, hypertension and hyperlipidemia. †Lower bound of 95% CI exceeds figure limits. HTN: hypertension; HLD: hyperlipidemia.

hypothyroidism–mortality association in dialysis patients. In the general population, hypothyroidism has been associated with adverse cardiovascular sequelae, including systolic and diastolic dysfunction due to genomic and nongenomic effects of thyroid hormone [38–40]; endothelial dysfunction and increased systemic vascular resistance that in conjunction with dyslipidemia may lead to accelerated atherosclerosis [38–41]; and changes in cardiac ion channel expression and prolongation of the QT interval, heightening the risk of malignant arrhythmias and sudden cardiac death [40]. As both hypothyroidism and cardiovascular disease are common in NDD-CKD patients, it is plausible that aberrant thyroid status during the pre-ESRD prelude period may have long-term implications upon cardiovascular outcomes in ESRD patients. Indeed, there is growing evidence that thyroid hormone deficiency is associated with cardiovascular complications (e.g. endothelial dysfunction, coronary calcification) in the dialysis population [2–4]. Emerging data also suggest that hypothyroidism may adversely impact dialysis patients via noncardiovascular pathways. In a prospective study of 450 hemodialysis patients across 17 outpatient dialysis centers, higher TSH levels were associated with worse physical function and energy/fatigue scores over time as ascertained by serial Short Form 36 surveys [42]. As thyroid hormones have direct action in skeletal muscle [43], the impact of hypothyroidism on impaired physical function may be an under-recognized yet important pathway to death in this population [42].

Another noteworthy finding in our study was the persistence of hypothyroid-range TSH level–mortality associations after adjustment for thyroid hormone-modulating therapy treatment versus nontreatment status. Examination of baseline characteristics of this cohort revealed that, among patients with

hypothyroid-range TSH levels in the 1-year pre-ESRD period, 43% were prescribed thyroid hormone supplementation, who may be representative of those with undertreated hypothyroidism. Although USRDS registry data have shown that levothyroxine is among the most commonly prescribed medications in NDD-CKD and ESRD patients who are Medicare Part D enrollees [44], it has yet to be determined whether thyroid hormone supplementation effectively corrects thyroid dysfunction in this population. In the general population, thyroid hormone supplementation in hypothyroid patients has been shown to reverse adverse cardiovascular surrogates (e.g. ventricular function, endothelial dysfunction, atherosclerosis [45–47]) and to improve certain aspects of physical function in the general population (e.g. strength, cardiopulmonary exercise performance [48]). Although data examining thyroid hormone supplementation use and outcomes in the kidney disease population are sparse, in a recent analysis of US veterans with Stage 3 CKD, it was shown that those with untreated and undertreated hypothyroidism had higher mortality risk compared with those who were spontaneously euthyroid, whereas those who were hypothyroid-treated-to-target had similar to slightly better survival [25]. In the present study, we were neither able to determine the indications for treatment versus nontreatment, intended TSH target, nor direct response to therapy across individual patients. However, our findings suggest that biochemical hypothyroidism is associated with worse survival irrespective of treatment status. At this time, prospective studies are needed to precisely determine whether correction of hypothyroidism with thyroid hormone supplementation improves cardiovascular endpoints, physical function and mortality in dialysis patients.

The strengths of our study include its examination of a large cohort of incident ESRD patients with both pre-ESRD and post-ESRD data; comprehensive availability of information on comorbidities, laboratory tests, medications and clinical events; and reduced confounding on the basis of differential healthcare access and nonuniform medical care by receiving care within the VA healthcare system. However, several limitations of our study bear mention. First, the indications for TSH testing in this cohort, a requirement for inclusion in the study, are unknown. However, this inclusion criterion was required of all patients irrespective of underlying thyroid status and thus should not impair the study's internal validity. Second, we defined thyroid status using serum TSH only, as the most sensitive and specific single metric of thyroid function in the general population, given its inverse logarithmic association with serum triiodothyronine (T3) and T4 levels, and its robust characteristics in the setting of nonthyroidal illness and uremia [6, 7, 27]. In contrast, the FT4 assay, used to classify subclinical versus overt functional thyroid disease, is an analog assay and dependent on normal hormone protein binding and may provide spurious results in conditions where serum protein levels are low (e.g. malnutrition) or circulating substances impair hormone protein binding (e.g. uremia) [6, 7, 49]. In addition, the vast majority of circulating T3 is derived from the peripheral conversion of T4-to-T3, which is highly sensitive to inflammation, malnutrition and mild illness independent of thyroid functional status [6, 7, 50]. Third, our examination of pre-ESRD TSH levels and post-ESRD mortality neither assesses the relationship between thyroid status and short-term death risk, nor did our analyses include those who maintained stable kidney function, experienced death or underwent kidney transplantation prior to dialysis initiation, or those who declined dialysis. However, as prior data have confirmed an association between thyroid status and short-term mortality risk in dialysis patients [13–15], our intention was to specifically examine the long-term impact of thyroid aberrancies in the pre-ESRD period upon post-ESRD mortality. Fourth, as the study cohort was predominantly male, our findings may have limited generalizability to populations with differing sociodemographic composition. Lastly, as with all observational studies, residual confounding cannot be excluded, and our findings do not confirm a causal association between thyroid status and mortality risk.

In summary, our study shows that incident ESRD patients with TSH levels in the hypothyroid range during the pre-ESRD prelude period have higher post-ESRD mortality, and this risk is increasingly stronger with incrementally higher TSH levels. At this time, future studies are needed to precisely define the underlying mechanistic pathways linking hypothyroidism with mortality. There is a disproportionately high prevalence of abnormally elevated serum TSH levels and hypothyroidism in dialysis patients, and a growing body of evidence demonstrating its adverse associations with survival. Rigorous studies, including randomized clinical trials, are needed to determine the impact of longitudinal thyroid hormone treatment on mortality and other clinically relevant endpoints (i.e. cardiovascular and patient-centered outcomes) in this population.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

A.S.Y. and C.M.R. designed the study; C.P.K. and K.K.-Z. obtained the data resources; A.S.Y. analyzed the data; A.S.Y. created the figures; A.S.Y. and C.M.R. drafted the paper; C.M.R. and K.K.-Z. provided oversight of the study; A.S.Y., J.J.S., C.P.K., E.S., D.V.N., G.A.B., K.K.-Z. and C.M.R. contributed to interpretation of results and revision of the manuscript; all authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

None of the authors have relevant conflicts of interest to report. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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