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Thyroid Status and Mortality in a Prospective Hemodialysis Cohort

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Context and Objective:
Compared to the general population, hemodialysis patients have a substantially higher risk of hypothyroidism, as defined by an elevated serum thyrotropin (TSH) level, and cardiovascular mortality. Whereas an elevated serum TSH is associated with cardiovascular disease and death in the general population, these associations among dialysis patients have been inconsistent.

Design, Setting, Participants, and Main Outcome:
We examined 541 hemodialysis patients from 17 Southern California dialysis centers in the prospective *Hypothyroidism, Cardiovascular Health, and Survival (HyCARDS)* study who underwent protocolized measurement of repeated serum TSH levels every six months from May 2013 to August 2015. Associations between TSH tertiles (<1.28, 1.28-<2.14, and 2.14-86.7 mIU/L) and mortality were estimated using time-dependent Cox models with four adjustment levels. In sensitivity analyses, we excluded patients receiving thyroid hormone supplementation.

Results:
Compared with the lowest TSH tertile, the highest TSH tertile was associated with a 2.2-to-2.5-fold higher mortality risk in unadjusted, case-mix, expanded case-mix+laboratory, and expanded case-mix+laboratory+thyroid medication models: HRs (95%CI) 2.54 (1.32-4.89), 2.53 (1.30-4.93), 2.19 (1.11-4.32), and 2.28 (1.45-3.58), respectively. We observed a consistent trend between higher TSH tertiles and numerically higher mortality risk across all four models. Similar findings were observed in analyses that excluded patients receiving thyroid hormone supplementation.

Conclusion:
In time-dependent analyses, repeated measures of serum TSH levels in the high-normal to high range are independently associated with higher death risk in hemodialysis patients. Further studies are indicated to determine whether normalization of TSH levels with thyroid hormone supplementation improves survival in this population.

PRECIS: In a prospective cohort of hemodialysis patients who underwent protocolized measurement of repeated serum thyrotropin (TSH) levels, higher TSH levels were associated with higher death risk.

Introduction

Disorders of thyroid function are an exceedingly common endocrine complication of chronic kidney disease (CKD) patients, including those receiving dialysis.[1-7] Data from the Third National Health and Nutrition Examination Survey (NHANES III) have shown an increasing burden of hypothyroidism with incrementally impaired kidney function, such that participants with an estimated glomerular filtration rate (eGFR) of <45ml/min/1.73m^2 had a nearly five-fold higher prevalence compared to those with an eGFR ≥90ml/min/1.73m^2 (~23% vs. ~5%, respectively).[2] In a study of 461,607 US veterans with stages 3 to 5 CKD, it was also shown that a 10ml/min/1.73m^2 lower eGFR was associated with an 18% higher risk of hypothyroidism, defined by elevated serum thyrotropin (TSH) levels and/or receipt of thyroid hormone supplementation, independent of socio-demographic and comorbidity characteristics.[4] While varying prevalence estimates have been reported in dialysis studies,[3,5-7] a greater burden of hypothyroidism has also been observed in these patients vs. the general population (i.e., ~13-25% vs. ~5%, respectively).[8]

In the general population, hypothyroidism has been identified as a risk factor for adverse cardiovascular sequelae via multiple pathways (e.g., systolic and diastolic dysfunction, endothelial dysfunction, dyslipidemia, accelerated atherosclerosis).[9-12] While large population-based studies of hypothyroidism and mortality have shown mixed findings, it has been suggested that these associations may depend upon underlying cardiovascular risk. For example, there has been a tendency towards positive associations in high cardiovascular risk populations (i.e., recent cardiac events or atherosclerotic risk factors),[13-15] and NHANES III data have shown that hypothyroidism is associated with higher death risk in participants with congestive heart failure but not in those without.[16] Given the exceedingly high prevalence of structural heart disease and cardiovascular mortality of dialysis patients (40% of deaths), thyroid status may have important implications upon the cardiovascular health and survival of this population.[17-19]

Indeed, an increasing number of studies have examined thyroid status, defined by serum TSH levels,[20] as a novel risk factor for mortality in dialysis patients.[3,5,6,21] Among these, three retrospective studies using US regional clinical data and/or large national dialysis organization records (i.e., in which thyroid testing was conducted at the discretion of medical providers) have demonstrated a significant association between higher serum TSH levels (i.e., hyperthyotropinemia) and death risk in hemodialysis and peritoneal dialysis patients.[3,5,6] However, in a secondary analysis of diabetic hemodialysis patients from the *Die Deutsche Diabetes Dialyse Studie* (4D Trial) (i.e., in which thyroid testing was conducted amongst all patients), thyroid functional disease assessed at baseline was not associated with mortality.[21] Thus, to better inform the field, we designed the prospective, multi-center "Hypothyroidism, Cardiovascular Health, and Survival in Kidney Disease" (HyCARDS) study which recruited a well-characterized cohort of hemodialysis patients who underwent protocolized thyroid functional tests every six months, as well as rigorous collection of socio-demographic, comorbidity, other laboratory, medication, and outcomes data. In this study, we examined the association of baseline and repeated (longitudinal) measures of serum TSH with mortality in hemodialysis patients across Southern California.

Materials and Methods

Source Cohort

The *HyCARDS* study is an ongoing prospective, multi-center observational study of incident/prevalent hemodialysis patients enrolled from 17 outpatient dialysis units in the South Bay-Los Angeles area undergoing protocolized assessment of various thyroid functional markers, cardiovascular measures, and outcomes. The study population was recruited from a subcohort of patients from the *Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease* (MADRAD) cohort (Clinicaltrials.gov# NCT01415570) examining racial and ethnic differences in dietary factors and nutritional status in hemodialysis patients who had serum TSH measurement over the period of May 2013 to August 2015.[22] Patients were included provided that they were age 18 to 85 years old, received thrice-weekly in-center hemodialysis for at least four consecutive weeks and signed a local institutional review board approved consent form. Patients were excluded if they were actively receiving peritoneal dialysis, had a life expectancy of less than six months (e.g., stage IV cancer), or were unable to provide consent without a proxy (e.g., dementia). The study was approved by the institutional review board of the University of California Irvine Medical Center.

Exposure Ascertainment

The exposure of interest was thyroid status defined by serum TSH level. Serum TSH was measured from fresh serum samples that were obtained pre-dialysis during weekday hemodialysis treatments at the time of study entry and that chronologically coincided with routine blood tests conducted at outpatient dialysis facilities. Patients' TSH levels were tested at the time of serum collection. Serum TSH was measured using second generation chemiluminescent immunoassay tests (Beckman Coulter, Chaska, MN; reference range 0.5-5.0mIU/L) in the Clinical Pathology Laboratory of the University of California Irvine Medical Center. The coefficient of variation for inter-assay precision was 3.7%.

In primary analyses, we sought to examine the association between *time-dependent thyroid function* and all-cause mortality, in which thyroid status was time-updated with repeated TSH measures in order (1) ascertain the *short-term* association of thyroid function with death risk, and (2) to account for changes in thyroid function over time.[23] Using this approach, patients who were found to have a change in TSH testing immediately crossed over to the new exposure category, with the reasoning that change in thyroid function had occurred during the prior exposure period; the minimum-maximum number of TSH measurements contributed by each patient ranged from one to five. In secondary analyses, we examined the association between *baseline thyroid function* and all-cause mortality in order to ascertain the *long-term* association of thyroid function with death risk. As the "normal" reference range for TSH in dialysis patients remains undefined, we elected to categorize TSH levels into tertiles of observed baseline values: Tertile 1, 2, and 3 corresponded to TSH levels of <1.28, 1.28-<2.14, and 2.14-86.7mIU/L, respectively.

Outcome Ascertainment

The primary outcome of interest was all-cause mortality. At-risk time began the day after serum TSH measurement, and patients were censored for kidney transplantation, transfer to a non-affiliated outpatient dialysis unit or peritoneal dialysis, or at end of the study (September 15, 2015). Each semester, information regarding mortality, censoring events, and associated dates from the preceding six months was collected from event forms completed by the

HyCARDS/MADRAD research coordinators and reviewed by two HyCARDS/MADRAD study nephrologists (CMR and KKZ).

Socio-Demographic, Comorbidity, Medication, Laboratory, and Body Anthropometry Data

Information on socio-demographics, comorbid conditions, medications, and dialysis treatment characteristics (vascular access type) were collected at study entry and every semester thereafter by HyCARDS/MADRAD research coordinators. Dialysis vintage was defined as the time between the date of study entry and the date of hemodialysis initiation. Routine dialysis laboratory measurements were performed by the outpatient dialysis laboratories on a monthly or quarterly basis using automated methods. Serum lipid tests (total cholesterol, triglycerides, low density lipoprotein cholesterol, and high density lipoprotein cholesterol) were conducted every semester in the University of California Irvine Medical Center Clinical Pathology Laboratory.

At study entry and every semester thereafter, measurements of body composition surrogates were conducted while patients underwent routine hemodialysis treatments, which included body mass index, subcutaneous fat (determined from biceps and triceps skinfold), visceral fat (determined from waist circumference), lean muscle mass (determined from mid-arm circumference [MAC] and mid-arm muscle circumference [MAMC]), and body fat percentage (measured by near-infrared [NIR] interactance). MAMC (centimeters) was estimated using the following formula: MAMC = MAC – 3.142 * triceps skinfold.[24,25] NIR interactance body fat (percent) was measured by placing a Futrex NIR interactance sensor (portable 6100; Futrex Inc.) on the non–vascular access upper arm for several seconds, after inputting the required data (date of birth, sex, weight, and height) for each patient, and has been shown to be highly correlated with other body fat and nutritional metrics in hemodialysis patients.[26-28]

Statistical Analyses

Baseline characteristics between exposure groups were compared using chi-squared, analysis of variance, and Kruskal-Wallis tests according to variable type. We first examined the relationship of relevant clinical characteristics with high serum TSH level at study entry (defined as the highest TSH tertile) using logistic regression. We then estimated the association between time-dependent and baseline TSH tertiles with all-cause mortality using time-dependent and fixed covariate Cox regression, respectively. In the time-dependent analytic approach, the follow-up time for each patient was divided into different time windows (i.e., approximately six-month intervals) defined by their serial TSH measurements over time. For each time window, a separate Cox regression was carried out using the specific value of TSH at the start of the specific time window, and a weighted average of all time window-specific results was calculated. The weighted average of a series of relatively short-term effects was presented as one hazard ratio as the result of the analysis.[23] Logistic regression and Cox regression models were analyzed using three incremental levels of covariate adjustment:

(1) Unadjusted model: Included serum TSH level as the primary exposure of interest;
(2) Case-mix analyses: Adjusted for covariates in the unadjusted model, as well as age, sex, race, ethnicity, and diabetes;
(3) Expanded case-mix+laboratory adjusted analyses: Adjusted for covariates in the case-mix model, as well as vintage, vascular access, body mass index, and serum albumin levels ascertained at study entry.

To account for thyroid hormone replacement, we also conducted sensitivity analyses in which we (1) incrementally adjusted for use of thyroid hormone supplementation use in expanded case-mix+laboratory+medication adjusted analyses (adjusted for covariates in the expanded case-mix+laboratory model, as well as baseline thyroid hormone supplementation use), and (2) excluded patients receiving thyroid hormone supplementation at study entry (N=37).

Given the wide range of TSH values of the highest TSH tertile, we also conducted sensitivity analyses in which we excluded outlier TSH levels above the ~99.5[th] percentile of observed values (TSH >16.0mIU/L).

The proportional hazards assumption was checked graphically. Effect modification of TSH—mortality associations on the basis of age, sex, race, ethnicity, diabetes, vintage, vascular access, body mass index, and serum albumin level was explored through the addition of two-way interaction terms with TSH (separately) using likelihood ratio testing. Missing data were handled using multiple imputation (with ten imputed datasets). There were no missing values for age, sex, race, ethnicity, and diabetes. The remaining covariates ascertained at baseline had ≤1% missing values, except for vascular access (26%), body mass index (16%), and serum albumin (20%). Analyses and figures were generated using SAS version 9.4 (SAS Institute Inc., Cary, NC), Stata version 13.1 (Stata Corporation, College Station, TX), and SigmaPlot Version 12.5 (Systat Software, San Jose, CA).

Results

Study Population

Among 541 patients meeting eligibility criteria (Supplemental Figure 1), the mean ± SD, median (IQR), and minimum-maximum baseline TSH values were 2.21 ± 4.19, 1.60 (1.08, 2.45), and 0.01-86.7 mIU/L, respectively (Supplemental Figure 2). Based upon TSH levels and thyroid medication status ascertained at study entry, 3.3% (N=18), 86.1% (N=466), and 10.5% (N=57) of patients were considered to be hyperthyroid (defined as TSH <0.5mIU/L), euthyroid (defined as TSH 0.5-5.0mIU/L), and hypothyroid (defined as TSH >5.0mIU/L and/or thyroid hormone supplementation use), respectively. Since serum thyroxine (T4) and triiodothyronine (T3) measurements were not available, the hyperthyroid category included patients with subclinical hyperthyroidism (low serum TSH and normal T4 and T3) and overt hyperthyroidism (low serum TSH and elevated T4 and T3). The hypothyroid category included patients with subclinical hypothyroidism (elevated serum TSH and normal T4) and overt hypothyroidism (elevated serum TSH and low T4).

Compared with patients in the lowest TSH tertile, those in the highest tertile were less likely to be Black and more likely to be Hispanic (Table 1). In contrast, patients were similar in terms of sex, prevalence of diabetes, body mass index, vintage, vascular access type, serum albumin levels, and use of thyroid hormone supplementation (6-7% of patients across each tertile). Notably, no patients were receiving anti-thyroid medications at study entry.

Clinical Characteristics Associated with Thyrotropin Level

In unadjusted, case-mix, and expanded case-mix+laboratory adjusted logistic regression analyses, patients of Hispanic ethnicity and longer dialysis vintage had a higher risk of having a high serum TSH level (defined as the highest TSH tertile) at study entry (Table 2). In unadjusted analyses, patients of Black race were less likely to have a high TSH level, but these associations were somewhat attenuated with adjustment for case-mix and expanded case-mix+laboratory covariates. In case-mix and expanded case-mix+laboratory adjusted analyses, higher serum albumin level was inversely associated with risk of having a high serum TSH level.

Serum Thyrotropin Level and All-Cause Mortality

Patients contributed a total of 817 patient-years of follow up, during which time 71 all-cause deaths occurred. The median (IQR) at-risk time was 1.60 (1.08, 2.09) years. In time-dependent analyses, the highest TSH tertile was associated with higher mortality risk in comparison to the lowest TSH tertile in unadjusted models (Figure 1 and Supplemental Table 1):

HR (95% CI): 2.54 (1.32-4.89), p=0.005. The association between the highest TSH tertile and higher mortality remained statistically significant with incremental adjustment for case-mix and expanded case-mix+laboratory covariates. The middle TSH tertile was associated with numerically higher risk but did not reach statistical significance in unadjusted, case-mix, and expanded case-mix+laboratory models. In expanded case-mix+laboratory+medication analyses that incrementally adjusted for thyroid hormone supplementation use, we observed a robust relationship between the highest TSH tertile and higher mortality risk: adjusted HR (aHR) 2.28 (1.45-3.58), p<0.001.

In secondary analyses of baseline TSH, compared to the lowest TSH tertile, the middle and highest TSH tertiles were associated with numerically higher risk but did not reach statistical significance in unadjusted, case-mix, expanded case-mix+laboratory, and expanded case-mix+laboratory+medication models (reference: lowest TSH tertile; Supplemental Table 1).

Sensitivity Analyses Excluding Patients on Thyroid Hormone Supplementation Use and Outlier Thyrotropin Levels

In sensitivity analyses that excluded patients on thyroid hormone supplementation, we observed a persistent association between the highest time-dependent TSH tertile and higher mortality risk in unadjusted, case-mix, and expanded case-mix+laboratory adjusted models (Figure 2A and Supplemental Table 2). In analyses that excluded outlier TSH values, we similarly observed a persistent association between the highest time-dependent TSH tertile and higher death risk across all three multivariable models (Figure 2B and Supplemental Table 3). We did not observe a significant association between baseline TSH tertile and mortality risk in sensitivity analyses that excluded patients on thyroid hormone supplementation (Supplemental Table 2) or outlier TSH values (Supplemental Table 3).

Subgroup Analyses

We did not detect effect modification on the basis of age, sex, race, ethnicity, underlying diabetes, dialysis vintage, vascular access type, body mass index, or serum albumin level: p-interaction = 0.76, 0.08, 0.22, 0.14, 0.59, 0.50, 0.86, 0.93, and 0.44, respectively (Figure 3 and Supplemental Table 4). In all subgroups, the nominal HR for the highest TSH tertile was >1 except among Hispanic patients; nominal associations were statistically significant in the following subgroups: age ≤65 years, male, non-Black, non-Hispanic, diabetic, vintage <24 months, and those with serum albumin <4g/dl.

Discussion

In this prospective, multi-center cohort of 541 hemodialysis patients who underwent protocolized serum TSH testing every six months, we found that time-dependent TSH levels in the highest tertile were associated with a more than two-fold higher mortality risk independent of case-mix and laboratory covariates. This strong association between the highest serum TSH tertile and death risk was robust across multiple sensitivity analyses that accounted for thyroid medication use and excluded patients with outlier TSH values.

An increasing body of evidence has demonstrated that underlying thyroid status is associated with survival in dialysis patients.[3,5,6] Among 2715 prevalent dialysis patients who underwent TSH testing within two tertiary care centers in Boston, those with hypothyroidism at baseline (12.9% of the cohort) had a higher mortality risk compared to euthyroid patients independent of socio-demographic and comorbidity status.[3] In a subsequent study of 8840 incident hemodialysis patients receiving care from a large national dialysis organization in the US, time-dependent and baseline hypothyroidism were each associated with higher death risk in case-mix adjusted

analyses.[5] Most recently, in a study of 1484 national peritoneal dialysis patients who underwent repeated TSH measures over time, time-dependent TSH levels in the subclinical and overt hypothyroid range were associated with 1.63- and 3.11-fold higher death risk, respectively.[6]

To our knowledge, this is the first prospective study that has examined the association between time-dependent thyroid status defined by repeated TSH measures and mortality risk in hemodialysis patients. It should be noted that the aforementioned studies examined data collected for clinical purposes, in which thyroid functional testing was conducted at the discretion of medical providers, with potential implications upon generalizability. As an important distinction, in the present study we collected repeated serum TSH measures at protocolized, uniform (i.e., every six months) intervals in all patients. There has been one previous study that uniformly examined thyroid function, defined by serum TSH, T4, and T3 levels, in 1000 diabetic hemodialysis patients from the 4D Trial, albeit at a single-point-in-time (i.e., baseline) only.[21] While adjusted analyses did not demonstrate a significant association between subclinical hypo- nor hyperthyroidism (assessed separately or in conjunction with the corresponding overt thyroid disorder) with adverse cardiovascular events, sudden cardiac death, or all-cause mortality, when follow up time was parsed into short- vs. longer-term (>1-4 years) intervals, there was a trend towards an association between subclinical hyperthyroidism and sudden cardiac death over short-term follow up only (≤1 year). In our study, we similarly observed a significant relationship between thyroid status and mortality over short-term follow-up (i.e., time-dependent TSH analyses) with mortality, whereas a null association was observed over long-term follow up (i.e., baseline TSH analyses). While our findings suggest that higher serum TSH levels carry short-term risk,[23] the lack of an observed association in baseline analyses may have been due to an attenuation in thyroid status as a risk factor over longer-term follow up, change in thyroid function over time, and/or limited sample size to detect significant associations.

Another notable finding of our study was the observation that both high-normal and high TSH levels in the highest TSH tertile (defined as TSH ≥2.14mIU/L) predict higher death risk in hemodialysis patients. In the general population, some expert groups have recommended that the upper limit of normal of the euthyroid reference range should be reduced from 4.0-5.0mIU/L to 2.5–3.0mIU/L, while others have advised using reference ranges based upon age and race/ethnicity.[29-32] While the optimal TSH range in dialysis patients remains uncertain, our observations corroborate findings from a national study of hemodialysis patients showing that higher TSH levels within the normal range (>3.0mIU/L) were incrementally associated with higher death risk.[5] Although our multivariable-adjusted analyses showed that elevated TSH levels were associated with adverse outcomes independent of age, it is important to note there is a shift towards higher TSH concentrations with increasing age in the general population.[33] Thus, it is possible that a sizeable proportion of our hemodialysis patients with TSH levels in the highest tertile may be considered euthyroid based upon general population thresholds. At this time, future studies are needed to confirm the "normal" TSH range in hemodialysis patients, and whether treatment of high-normal and hypothyroid TSH levels to a low-normal target (<2.5-3.0mIU/L) improves survival in this population.

We elected to focus upon TSH-based ascertainment of thyroid function as a more sensitive and specific metric of thyroid functional status.[20] While T3 and T4 levels may be used to distinguish severity of thyroid disease (i.e., subclinical vs. overt thyroid functional disease) and other etiologies of thyroid functional test abnormalities (i.e., non-thyroidal illness), in patients with end-stage renal disease 1) T3 levels may be confounded by underlying illness (i.e., the

peripheral conversion of T4-to-T3 is highly sensitive to mild illness, malnutrition, and inflammation),[19,34,35] and 2) routinely-used free T4 assays measuring the minute fraction of bioactive T4 (e.g., free T4 analog assay or free T4 index) are hormone-protein binding dependent and may not be accurate in dialysis patients (i.e., in conditions where circulating substances such as uremic toxins impair hormone-protein binding, routinely-used free T4 assays may result in spurious levels).[19,35,36]

While TSH levels are a comparatively more robust marker of thyroid functional status, we are unable to confirm a causal relationship between TSH levels and mortality in this study given its observational nature. For example, some TSH aberrations have been reported in kidney disease, such as impaired glycosylation and function, blunted response to thyrotropin releasing hormone, altered clearance, decreased pulsatility, and increased half-life,[19,35] and we cannot exclude confounding of the TSH—mortality association on this basis. TSH levels may also be altered in illness states. However, while TSH levels are suppressed in the setting of severe illness,[34,37] our study population was restricted to ambulatory hemodialysis patients presenting for their routine thrice-weekly dialysis treatments, rendering the inclusion of patients with severe illness states to be low.

Our study has a number of strengths including its prospective examination of a well-defined hemodialysis cohort with detailed collection of longitudinal data on socio-demographics, laboratory tests, and medications; rigorous outcome adjudication procedures; protocoled measurement of serum TSH samples among all patients in the outpatient setting that were uniformly tested in a single laboratory; comprehensive adjustment for confounders of the thyroid status—mortality association; and robust findings across multiple sensitivity analyses accounting for thyroid medication use and outlier TSH levels. However, several limitations of our study bear mention. First, while the "normal" TSH reference in dialysis patients remained undefined, categorization of TSH levels into tertiles may have combined patients with heterogenous etiologies of TSH aberrations (i.e., the lowest TSH tertile may have included patients with non-thyroidal illness as well as those with hyperthyroidism and euthyroidism based on general population thresholds). Second, our study was not specifically designed to examine the relationship between hyperthyroidism (subclinical and overall) and outcomes in the general population. As recent data in the general population suggest that subclinical hyperthyroidism may have important implications upon cardiovascular health and survival,[9,38] future studies examining this relationship in kidney disease patients are needed. Third, our study had a modest sample size which may have resulted in limited power to detect significant associations, particularly in the baseline and subgroup analyses. Fourth, we lacked information on cause-specific mortality in order to gain greater insight into mechanistic pathways by which thyroid status impacts mortality in hemodialysis patients. Fifth, while we had reliable information regarding the patients' thyroid medication status at the time of study entry, we were not able to accurately determine patients' longitudinal receipt of thyroid-modulating therapy over time. Lastly, it is possible that our findings may not be generalizable to geographic regions with distinct socio-demographic distributions and practice patterns.

In summary, our study shows that TSH levels in the high-normal to high range are associated with short-term mortality risk in a prospective cohort of hemodialysis patients. Future studies are needed to confirm findings, determine the optimal target TSH range in dialysis patients, and define the underlying mechanisms by which high-normal and high TSH levels negatively impact survival in this population.

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Disclosure Summary:
None of the authors declare conflicts of interest.

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Figure 1. Association of time-dependent thyrotropin (TSH) tertiles with all-cause mortality. Case-mix analyses adjusted for age, sex, race, ethnicity, and diabetes. Expanded case-mix +laboratory analyses adjusted for covariates in case-mix model, plus vintage, vascular access, body mass index, and serum albumin. Expanded case-mix+laboratory+medication analyses adjusted for covariates in the expanded case-mix+laboratory model, plus thyroid hormone supplementation use. TSH tertiles 1, 2, and 3 correspond to TSH levels of <1.28, 1.28-<2.14, and 2.14-86.7mIU/L, respectively.

Figure 2. Sensitivity analyses of the association between time-dependent (TSH) and all-cause mortality with medication exclusion (N=504) (Panel A) and with removal of TSH outliers* (N=538) (Panel B). Case-mix analyses adjusted for age, sex, race, ethnicity, and diabetes. Expanded case-mix +laboratory analyses adjusted for covariates in case-mix model, plus vintage, vascular access, body mass index, and serum albumin. Expanded case-mix+laboratory+medication analyses adjusted for covariates in the expanded case-mix+laboratory model, plus thyroid hormone supplementation use (Panel B only). TSH tertiles 1, 2, and 3 correspond to TSH levels of <1.28, 1.28-<2.14, and 2.14-31.3mIU/L, respectively (Panel A). TSH tertiles 1, 2, and 3 correspond to TSH levels of <1.27, 1.27-<2.13, and 2.13-15.2mIU/L, respectively. **Outliers defined as TSH values greater than the ~99.5[th] percentile of observed values (TSH >16.0mIU/L).*

Figure 3. Subgroup analyses of the association between time-dependent thyrotropin (TSH) tertiles with all-cause mortality adjusted for expanded case-mix+laboratory covariates. Expanded case-mix +laboratory analyses adjusted for age, sex, race, ethnicity, diabetes, vintage, vascular access, body mass index, and serum albumin. TSH tertiles 1, 2, and 3 correspond to TSH levels of <1.28, 1.28-<2.14, and 2.14-86.7mIU/L, respectively.

Table 1. Baseline characteristics according to baseline serum thyrotropin (TSH) level categorized as tertiles.

	SERUM TSH CATEGORIES				
	Overall (N=541)	Tertile 1 (N=181)	Tertile 2 (N=179)	Tertile 3 (N=181)	P-value
Age (years)					
Mean ± SD	54 ± 15	54 ± 13	54 ± 15	55 ± 15	0.84
Female (%)	45	44	43	48	0.60
Black (%)	30	40	28	23	0.001
Hispanic (%)	51	44	48	61	0.004
Diabetes (%)	55	53	56	54	0.81
Body Mass Index (kg/m^2)					
Mean ± SD	28 ± 7	28 ± 6	28 ± 7	28 ± 7	0.70
Dialysis Characteristics					
Vintage (months)					
Mean ± SD	53 ± 46	51 ± 46	50 ± 44	59 ± 49	0.08
Vascular Access (%)					
AVF/AVG	80	79	81	81	0.93
Catheter	20	21	19	19	
Laboratory Tests					
Mean TSH (mIU/L)					
Mean ± SD	2.21 ± 4.19	0.83 ± 0.30	1.64 ± 0.25	4.16 ± 6.82	N/A
Serum Albumin (g/dl)					
Median (IQR)	4.0 (3.8, 4.2)	4.0 (3.8, 4.2)	4.0 (3.8, 4.2)	4.0 (3.7, 4.2)	0.57
Medications					
Thyroid Hormone Supplementation Use (%)	7	7	6	7	0.90

TSH tertiles 1, 2, and 3 correspond to TSH levels of <1.28, 1.28-<2.14, and 2.14-86.7mIU/L, respectively.
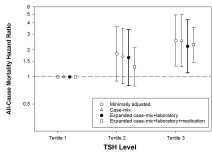*Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft.*

Table 2. Clinical characteristics associated with the highest thyrotropin (TSH) tertile using logistic regression with three levels of adjustment (vs. lowest and middle tertiles combined).
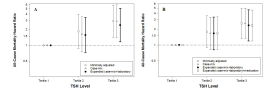
	Minimally adjusted	Case-mix adjusted	Expanded case-mix+ laboratory adjusted
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (Δ10 years)	1.04 (0.92, 1.17)	1.09 (0.95, 1.25)	1.07 (0.93, 1.22)
Female	1.20 (0.84, 1.71)	1.24 (0.86, 1.78)	1.13 (0.78, 1.65)
Black (vs. Non-Black)	**0.57 (0.38, 0.86)**	0.86 (0.46, 1.31)	0.67 (0.39, 1.15)
Hispanic (vs. Non-Hispanic)	**1.81 (1.26, 2.60)**	**1.69 (1.06, 2.70)**	**1.62 (1.00, 2.61)**
Diabetes	0.98 (0.68, 1.40)	0.83 (0.56, 1.23)	0.84 (0.55, 1.28)
Body Mass Index (Δ5 kg/m^2)	1.07 (0.92, 1.23)	1.09 (0.94, 1.27)	1.07 (0.92, 1.26)
Vintage (Δ6 months)	**1.03 (1.00, 1.05)**	**1.03 (1.00, 1.05)**	**1.03 (1.01, 1.06)**
Vascular Access	0.76 (0.27, 2.10)	0.51 (0.17, 1.51)	1.02 (0.41, 2.52)
AVF/AVG (vs. Catheter)	1.32 (0.48, 3.68)	1.96 (0.66, 5.79)	0.98 (0.40, 2.42)
Thyroid Hormone Supplementation Use	1.08 (0.54, 2.18)	1.05 (0.51, 2.16)	1.03 (0.50, 2.14)
Laboratory Tests			
Serum Albumin (Δ0.5g/dl)	0.77 (0.59, 1.01)	**0.75 (0.56, 1.00)**	**0.74 (0.56, 1.00)**
nPCR (Δ0.2g/kg/day)	1.00 (0.87, 1.15)	0.94 (0.81, 1.09)	0.94 (0.81, 1.10)
Serum Creatinine (Δ1mg/dL)	0.98 (0.91, 1.04)	1.01 (0.93, 1.09)	1.01 (0.93, 1.10)
spKt/V (Δ0.2)	1.06 (0.94, 1.19)	0.98 (0.86, 1.12)	0.98 (0.86, 1.13)
Calcium (Δ1mg/dL)	1.09 (0.80, 1.48)	1.06 (0.77, 1.47)	1.04 (0.75, 1.44)
Phosphate (Δ1mg/dL)	0.96 (0.86, 1.09)	0.96 (0.84, 1.09)	0.97 (0.85, 1.10)
PTH (Δ25pg/mL)	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)
Hemoglobin (Δ1g/dL)	0.92 (0.76, 1.11)	0.91 (0.75, 1.11)	0.93 (0.76, 1.13)
Ferritin (Δ25ng/mL)	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)
Iron saturation (Δ5%)	1.06 (0.98, 1.15)	1.05 (0.97, 1.14)	1.07 (0.98, 1.16)
Platelet Count (Δ50 x10^9/L)	0.90 (0.78, 1.04)	0.91 (0.79, 1.06)	0.92 (0.80, 1.07)
Mean Platelet Volume (Δ1 fL)	1.11 (0.91, 1.36)	1.14 (0.92, 1.40)	1.15 (0.93, 1.43)
WBC Count (x10^9/L)	0.95 (0.86, 1.05)	0.95 (0.86, 1.05)	0.95 (0.86, 1.06)
Total Cholesterol (Δ50 mg/dl)	0.94 (0.75, 1.17)	0.90 (0.72, 1.13)	0.94 (0.75, 1.19)
HDL (Δ10 mg/dl)	1.08 (0.97, 1.20)	1.08 (0.96, 1.21)	1.11 (0.98, 1.25)
LDL (Δ25 mg/dl)	0.92 (0.80, 1.07)	0.90 (0.77, 1.04)	0.91 (0.78, 1.06)
Triglycerides (Δ50 mg/dl)	0.99 (0.92, 1.07)	0.98 (0.90, 1.06)	0.99 (0.91, 1.07)
Body Anthropometry			
Waist Circumference (Δ5 cm)	1.02 (0.93, 1.11)	1.03 (0.93, 1.13)	0.99 (0.85, 1.14)
Biceps Skinfold (Δ10 mm)	1.12 (0.86, 1.46)	1.10 (0.83, 1.47)	0.88 (0.61, 1.25)
Triceps Skinfold (Δ10 mm)	1.11 (0.87, 1.40)	1.10 (0.85, 1.43)	0.91 (0.66, 1.26)
Near Infra-Red Body Fat (Δ10 mm)	**1.35 (1.04, 1.75)**	**1.57 (1.09, 2.27)**	1.78 (0.93, 3.41)

Case-mix analyses adjusted for age, sex, race, ethnicity, and diabetes. Expanded case-mix +laboratory adjusted analyses adjusted for covariates in case-mix model, plus vintage, vascular access, body mass index, and serum albumin.

TSH tertiles 1, 2, and 3 correspond to TSH levels of <1.28, 1.28-<2.14, and 2.14-86.7mIU/L, respectively.
Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; WBC, white blood cell; HDL, high-density lipoprotein; LDL, low-density lipoprotein.