



Assessment of mortality associated with thyroid status in a cohort of euthyroid older adults from a geriatric outpatient clinic at a university hospital

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Abstract

Objective: To assess the associations between the mean thyrotropin (TSH) and mean free thyroxine (FT4), detected during follow-up, and mortality in a group of older euthyroid patients according to age-specific reference range (as-RR) for TSH. **Method:** Retrospective survival analysis cohort including euthyroid elderly patients who were being monitored at the outpatient clinic of a university hospital from 2010 to 2013. All participants had been assessed for the risk of functional disability as a criterion for admission to this outpatient clinic. Mean TSH and FT4 values were calculated using hormone dosages obtained during the follow-up period. Each as-RR for TSH was divided into four equal parts, considering the lower levels as the main exposure variable (≤ 1.75 mIU/L for < 80 , and ≤ 2.0 mIU/L for ≥ 80 years). FT4 levels were explored according to two categories ($< e \geq 1.37$ ng/dL). The outcome was time to death. We used Cox proportional hazard regression to estimate the hazard ratio (HR) and 95% confidence interval (CI). **Results:** 285 participants (73% females, mean age = 80.4 years) followed by a median of 5.7 years (IQR = 3.7–6.4; maximum = 7), of which 114 died. After the adjusted final model, mortality was associated with the lowest mean TSH (HR=1.7; CI=1.1–2.7; $p=0.016$) and with the upper mean of FT4 (HR=2.0; CI=1.0–3.8; $p=0.052$). **Conclusions:** Higher FT4 and lower TSH mean levels were associated with risk of death in a cohort of euthyroid older adults using an as-RR of TSH.

Keywords: Thyroid hormones. Geriatric assessment. Mortality.

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INTRODUCTION

The relationship between thyroid hormone levels and mortality depends on several conditions, but primarily on the age of the studied group. Since the publication of the first study¹ in 2004, which demonstrated differences in the association between mortality and subclinical hypothyroidism (SCH) according to the age of the population, several researchers have been interested in studying why and how this association differs in older adults. Longitudinal studies have demonstrated that elevated thyroid-stimulating hormone (TSH) (also known as thyrotropin) levels and decreased free thyroxine (FT4) are associated with a lower risk of mortality²⁻⁴ and other adverse outcomes, such as functional decline^{5,6} and sarcopenia⁷.

These studies differ in their methodology, as some assess thyroid status based on the presence or absence of SCH^{1,5}, while others examine various spectrums of thyroid function, even including individuals with serum TSH within the normal range¹⁻⁴, by studying variations in serum levels of TSH or FT4. A recent review of longitudinal studies involving euthyroid adults identified that low concentrations of TSH were associated with a higher risk of cardiovascular disease and mortality regardless of age, while upper-normal levels of FT4 were associated with increased risk only in individuals over 70 years old⁸.

It is well documented that TSH levels increase progressively with age, even when excluding individuals with biochemical evidence of thyroid disease. This phenomenon does not correspond to chronic thyroid dysfunction but is likely a normal consequence of the aging process⁹, including without evidence of benefit from levothyroxine replacement¹⁰. Therefore, it has become necessary to redefine what constitutes normal TSH values in older populations, as current reference values tend to overestimate the diagnosis of subclinical hypothyroidism in this population^{11,12}.

Age-adjusted TSH reference ranges have not been applied in previous studies assessing the associations between thyroid function in older individuals and mortality. This may explain the results suggesting better outcomes in older patients with SCH. One

hypothesis is that these older adults may represent a group of individuals who exhibit physiologically expected elevations in serum TSH and do not necessarily have a diagnosis of SCH. In this manner, this group of older adults with higher serum TSH levels likely exhibit better overall health than those with lower TSH levels. Moreover, and of greater significance, this group could receive a thyroid disease diagnosis that would not exist if appropriate age-specific references were applied for serum TSH levels^{11,12}.

As of the present date, scientific data are insufficient to assert that associations between TSH levels and outcomes in older adults are in concordance with variations in serum FT4. A meta-analysis has indicated that serum FT4 likely exhibits greater association power with clinical outcomes than TSH¹³. However, it is important to note that we cannot place individuals with different characteristics and health conditions, which are related to different impacts on deiodinase function, into the same analysis group. Considering that certain specific populations, such as older adults and those with chronic diseases, may have impaired deiodinase function, it would be expected and justified that TSH may not reflect a good parameter of thyroid function in this patient group.

No previous study has assessed the associations between thyroid status and mortality in older adults considering the mean values of thyroid hormones obtained over time rather than solely relying on baseline measures. Furthermore, no study has applied age-specific reference range (as-RR) for TSH to define euthyroidism. Therefore, the aim of the present study was to evaluate the associations between mean TSH and FT4 levels with mortality in a group of euthyroid older adult patients, using as-RR for TSH to define normal thyroid function.

METHOD

This is a retrospective cohort study of survival analysis, which included patients aged ≥ 65 years followed by the geriatrics outpatient clinic of a tertiary university hospital. Participants had previously been screened for functional disability

risk¹⁴, as the presence of higher risk was a criterion for admission to this outpatient clinic. Annual functional, cognitive, and laboratory assessments are routine in the geriatrics outpatient clinic. All patients who regularly attended the clinic between March 2010 and December 2013 were considered for inclusion in the study. Data were collected from medical records at baseline, and at the third and sixth years of follow-up.

Only patients who maintained serum TSH within the age-adjusted reference interval¹¹ (0.4–5.8 mIU/L for individuals <80 years and 0.4–6.7 mIU/L for those ≥80 years) throughout the entire cohort period were included in the statistical analyses.

Exclusion criteria included a history of thyroid disease, use of levothyroxine or drugs affecting thyroid function (such as lithium, amiodarone, interferon, and radioiodine), recent hospitalization (≤2 months before the geriatric assessment scales and hormonal assays). These criteria were assessed at the beginning of the cohort and sought in medical record records at the third and sixth years after the initial assessment.

To assess the impact of specific hormonal profiles on the studied outcome, we determined the means of serum TSH and FT4 levels obtained during the follow-up period. Serum levels of TSH and FT4 were assessed using immunometric assays with a third-generation automated chemiluminescence system (Immulite 2000, Diagnostic Products Corporation, Gwynedd, United Kingdom). The reference range (RR) for TSH recommended by the manufacturer was 0.4 to 4.0 mIU/L. However, instead of adopting the manufacturer's recommended RR, we utilized the age-specific reference range (as-RR) for TSH previously determined for our population¹¹ (0.4–5.8 mIU/L for individuals <80 years and 0.4–6.7 mIU/L for those ≥80 years). The mean TSH was divided into four equal parts of the as-RR for individuals <80 years (0.4–1.75; 1.76–3.10; 3.11–4.46; 4.47–5.8) and for individuals aged 80 years or older (0.4–2.00; 2.01–3.60; 3.61–5.20; 5.21–6.7). The lower limit (0.4–1.75 mIU/L for individuals <80 years and 0.4–2.0 mIU/L for those ≥80 years) was considered the main exposure variable.

The RR for FT4 recommended by the manufacturer was 0.8–1.9 ng/dL, and the mean FT4 levels were divided into two categories: values in the upper half (1.37–1.9 ng/dL) or in the lower half (0.8–1.36 ng/dL) of the RR.

All participants underwent a comprehensive geriatric assessment, which included cognitive evaluation using the Mini-Mental State Examination (MMSE)¹⁵, assessment of basic activities of daily living (ADL) using the Katz Index¹⁶, instrumental activities of daily living (IADL) using the Health Assessment Questionnaire (HAQ)¹⁷, and depression using either the Geriatric Depression Scale (GDS)¹⁸ or the Cornell Scale for Depression in Dementia (CSDD)¹⁹. All scales used were validated for the Brazilian population and administered by trained physicians in the hospital's geriatrics department.

The cutoff value for cognitive impairment was adjusted according to specific educational levels for the Brazilian population¹⁵ (MMSE <25 for participants with formal education and MMSE <19 for those without formal education). An GDS score >5 (in patients with MMSE scores ≥13) or a CSDD score ≥10 (MMSE scores <13) defined the occurrence of depressive symptoms. The CSDD has been recommended as a better instrument for assessing depressive symptoms in patients with decreased cognition¹⁹. Patients who scored maximum on both scales (6 on the Katz Index and 3 on the HAQ) were considered to have total functional dependence.

We defined "polypharmacy" as the use of five or more medications²⁰. The occurrence of the fall syndrome was determined by the report of ≥2 falls in the previous year²¹. We defined "underweight" as patients with a body mass index (BMI) ≤21 kg/m²²². Smoking was defined as current or former smoking cessation within the last 10 years. The presence of medical comorbidities was assessed using the Charlson Comorbidity Index, which takes into account the patient's age and the presence of common medical conditions²³.

The outcome was time until death. Death was initially sought through information in medical records and telephone calls. In cases where medical

records showed no record of outpatient consultation for more than 6 months, no record of death, and unsuccessful telephone contact, the mortality outcome was accessed through probabilistic linkage processes with the mortality database of the State of Rio de Janeiro, Brazil, access to which was authorized by the Rio de Janeiro State Health Department (SES/RJ), subject to ethical approval. The linkage process followed best practice guidelines to ensure data security and privacy. Thus, there was no loss of follow-up for the outcome analysis (death). We considered participants as survivors until the end of the study as censoring.

The research complies with Resolution number 466/2012 and Resolution number 510/2016. The Research Ethics Committee of the Hospital Universitário Clementino Fraga Filho of the Universidade Federal do Rio de Janeiro (UFRJ) approved the study under opinion number 2,465,187, on January 11, 2018, with a waiver of the requirement for Informed Consent Form.

In the statistical analysis, we employed the Kaplan-Meier method and the log-rank test to calculate survival time and compare survival time between different groups of patients. The Cox regression model was used for both simple and multiple analyses. We calculated hazard ratios (HR) and corresponding 95% confidence intervals (CI) while adjusting for all available covariates. All covariates significant in the crude model at the $p < 0.20$ level was included in the multivariable Cox regression model. The proportional hazards assumption was assessed for all covariates, and none of them violated the assumption. We performed adjustment of the multivariable model and used the p -values from the Wald tests of individual variables to identify variables that could be excluded from the model to remove a residual effect. This procedure resulted in the removal of the total functional dependence and baseline cognitive impairment covariates from the final model. We included gender, which we considered to be an important demographic variable.

DATA AVAILABILITY

The data availability is not publicly accessible due to the presence of information compromising the privacy of research participants. The data file for this study includes information derived from a probabilistic linkage process, which precludes its public sharing due to the commitment to disclose only aggregated data.

RESULTS

Initially, a total of 427 patients were considered potentially eligible. After applying the exclusion criteria, the study group consisted of 285 participants, as shown in Figure 1.

The population had a mean age of 80.4 years and exhibited a high prevalence of cognitive impairment (62.8%), with 4.2% showing total functional dependence. The studied population consisted of 73% women, presented with over 70% polypharmacy, and a high Charlson Comorbidity Index. The maximum follow-up period for a participant was 7 years. The median duration was 5.7 years (IQR=3.7–6.4).

Table 1 displays the participants' characteristics and compares these features between those who died ($n=114$) and those who did not ($n=171$) during the follow-up period.

The overall survival was 4.9 years (CI=4.7–5.1; $p < 0.001$), while among participants with mean TSH maintained at the lower limit, it was 4.4 years (CI=3.8–4.9; $p=0.011$), and among those with FT4 in the upper half, it was 3.8 years (CI=2.6–5.0; $p=0.041$).

Kaplan-Meier survival curves were generated for different variables that could be associated. The lowest survival rates were observed in euthyroid individuals with mean FT4 in the upper half and in those with mean TSH at the lower limit of normality. The respective curves are presented in Figures 2 and 3.

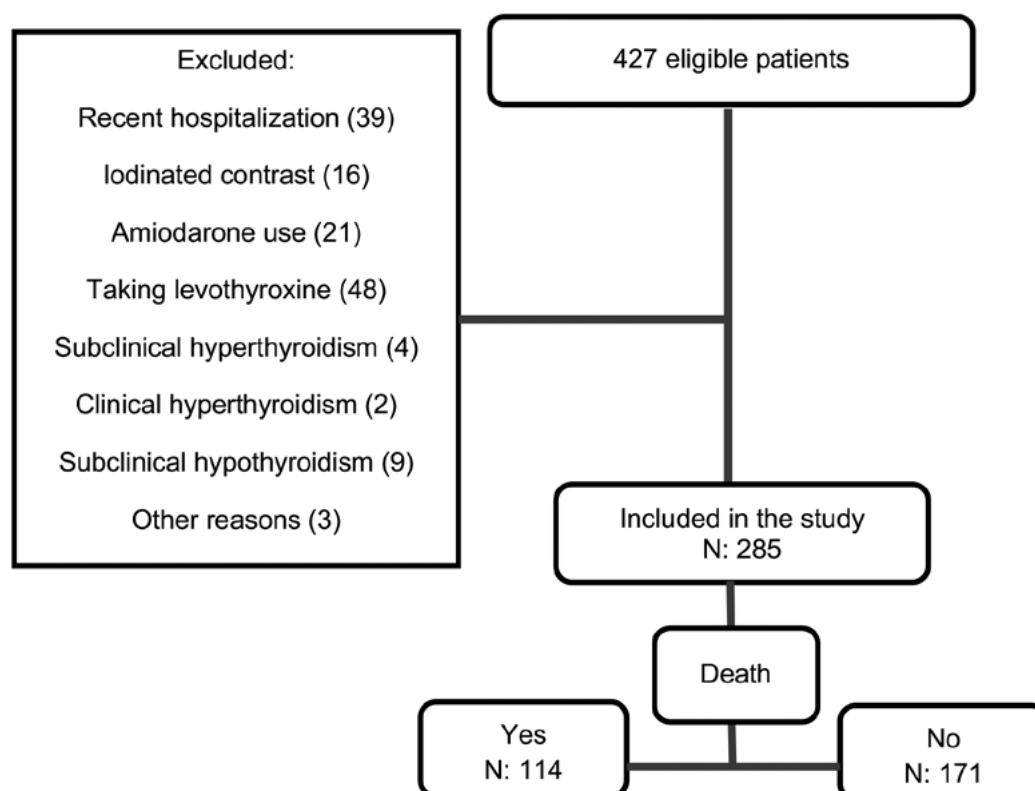


Figure 1. Flowchart of selection of study participants. Rio de Janeiro, RJ, Brazil, 2010/2013 and 2016/2018.

Table 1. Participants characteristics and comparison between those who died and those who did not die during the follow-up period. Rio de Janeiro, RJ, Brazil, 2010/2013 and 2016/2018.

Characteristics	Total sample (285)	Death		p-values
		Yes (n =114)	No (n= 171)	
Mean Age (SD) years	80.4 (\pm 6.9)	82.6 (\pm 6.6)	78.9 (\pm 6.6)	<0.001
Female:Male	208:77	72:42	136:35	-----
Females. No. (%)	208 (73%)	72 (63.2%)	136 (79.5%)	0.002
Total Functional Dependence. No. (%)	12 (4.2%)	10 (8.8%)	2 (1.2%)	0.002
Cognitive Impairment. No. (%)	179 (62.8%)	90 (78.9%)	89 (52%)	<0.001
Depressive Symptoms. No. (%)	102 (35.8%)	42 (39.3%)	60 (36.4%)	0.631
Polypharmacy. No. (%)	210 (73.7%)	86 (75.4%)	124 (72.5%)	0.583
Fall Syndrome. No. (%)	63 (22.1%)	25 (21.9%)	38 (22.2%)	0.954
Underweight. No. (%)	22 (7.7%)	14 (12.4%)	8 (4.7%)	0.015
Charlson Comorbidity Index. median (IQR)	5.0 (4.0 – 6.0)	6.0 (5.0 – 7.0)	5.0 (4.0 – 5.0)	<0.001
Smoking. No. (%)	106 (37.2%)	44 (38.6%)	62 (36.5%)	0.717
Lower limit of the mean TSH. No. (%)	54 (18.9%)	32 (28.1%)	22 (12.9%)	0.002
Upper half of the mean FT4. No. (%)	14 (4.9%)	10 (9.3%)	4 (2.4%)	0.022
Follow-up Time in years. median (IQR)	5.7 (3.7 – 6.4)	3.2 (2.0 – 4.4)	6.3 (5.8 – 6.7)	<0.001

SD: standard deviation; IQR: interquartile range; TSH: thyroid-stimulating hormone; FT4: free thyroxine.

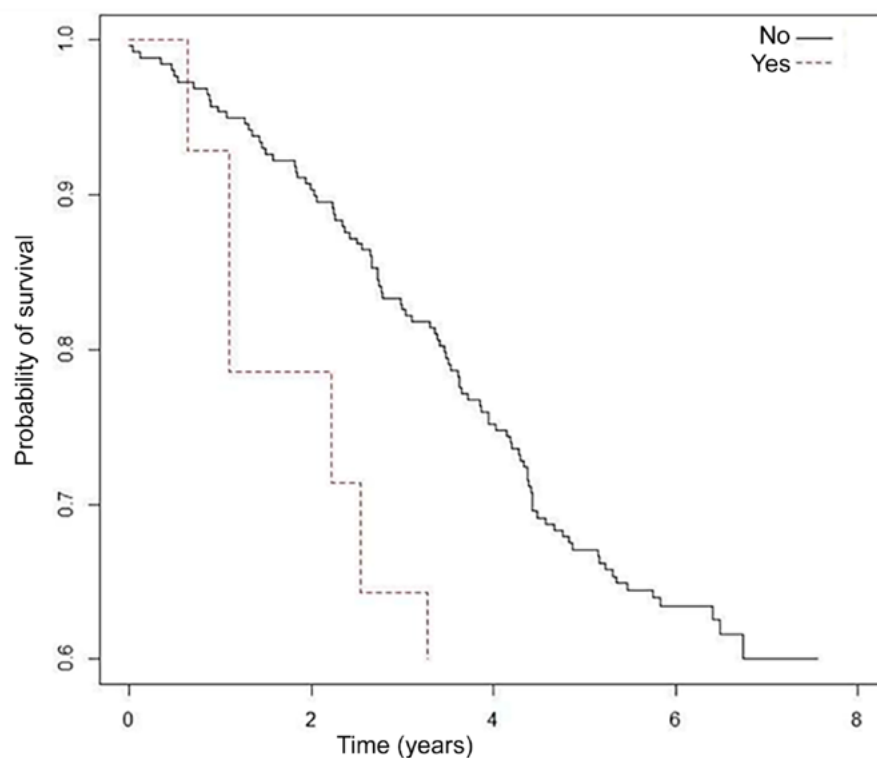


Figure 2. Kaplan-Meier survival curve for individuals with mean FT4 levels in the upper half of normality. Rio de Janeiro, RJ, Brazil, 2010/2018.

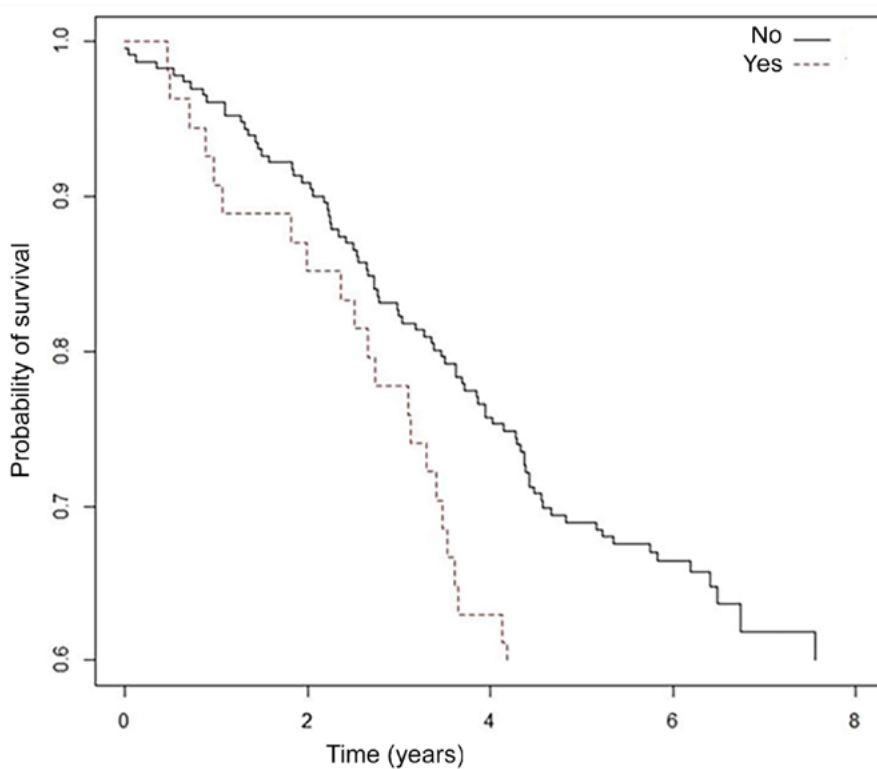


Figure 3. Kaplan-Meier survival curve for individuals with mean TSH at the lower limit of normality. Rio de Janeiro, RJ, Brazil, 2010/2018.

Table 2 shows crude and multivariate Cox regression model for all covariates estimating overall mortality in patients between 2010 and 2018. The risk of death in the crude model was associated with age (HR=1.07; CI=1.04–1.09; $p<0.001$), female sex (HR=0.5; CI=0.4–0.8; $p=0.001$), total functional dependence (HR=4.6; CI=2.3–8.8; $p<0.001$), cognitive impairment (HR=2.6; CI=1.7–4.1; $p<0.001$), underweight (HR=2.5; CI=1.4–4.4; $p=0.002$), Charlson index (HR=1.3; CI=1.2–1.4; $p<0.001$), mean TSH at the lower limit (HR=2.0; CI=1.3–3.0; $p=0.001$), and mean T4L in the upper half (HR=2.6; CI=1.5–5.0; $p=0.004$). All

significant covariates in the univariate model at the $p<0.20$ level was included for the multivariate Cox regression model. Total functional dependence and cognitive impairment were excluded from the model to remove a residual effect (Wald test). After the final adjusted model, mortality remained associated with age (HR=1.06; CI=1.02–1.09; $p=0.02$), low weight (HR=2.2; CI=1.2–4.1; $p=0.012$), Charlson index (HR=1.2; CI=1.1–1.3; $p=0.005$), mean TSH at the lower limit of normality (HR=1.7; CI=1.1–2.7; $p=0.016$), and tended to be associated with mean T4L in the upper half (HR=2.0; CI=1.0–3.8; $p=0.052$).

Table 2. Crude and multivariate Cox regression model for all covariates estimating overall mortality. Rio de Janeiro, RJ, Brazil, 2010/2018.

Characteristics	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Baseline age. Years	1.07 (1.04;1.09)	< 0.001*	1.06 (1.02;1.09)	0.002
sex (female)	0.5 (0.4; 0.8)	0.001*	0.73 (0.47;1.1)	0.160
Total functional dependence (yes)	4.6 (2.3;8.8)	< 0.001*	NS	NS
Cognitive impairment (yes)	2.6 (1.7;4.1)	< 0.001*	NS	NS
Depressive symptoms (yes)	0.9 (0.6;1.4)	0.720	-	-
Polypharmacy (yes)	1.1 (0.8;1.8)	0.530	-	-
Falls syndrome (yes)	1.0 (0.6;1.5)	0.940	-	-
Underweight (yes)	2.5 (1.4;4.4)	0.002*	2.2 (1.2;4.1)	0.012
Charlson comorbidity index	1.3 (1.2;1.4)	< 0.001*	1.2 (1.1;1.3)	0.005
Smoking (yes)	1.1 (0.7-1.6)	0.740	-	-
Lower limit of the mean TSH (yes)	2.0 (1.3;3.0)	0.001*	1.7 (1.1;2.7)	0.016
Upper half of the mean FT4 (yes)	2.6 (1.5;5.0)	0.004*	2.0 (1.0;3.8)	0.052

HR. Hazard ratio; CI. Confidence interval; NS. Not significant* Variables with p-value < 0.20 were included in the multiple Cox regression.

DISCUSSION

This study is the first to assess the associations between values obtained through the means of TSH and FT4 levels, conducted during a cohort, and mortality in a group of euthyroid older patients. It is noteworthy that the definition of normal thyroid function was established based on age-specific reference range for TSH. Several longitudinal studies have evaluated the association between thyroid hormone levels within the reference range and mortality^{1-5, 8, 24-31}, but none of them used mean

values obtained during follow-up, nor applied age-specific reference ranges when defining what would be considered normal serum TSH levels.

This cohort showed an association between overall mortality and age, underweight, and high comorbidity index; however, it did not find an association with depressive disorder, contrary to what was identified in a recent study conducted on Brazilian community-dwelling older adults³². The risk of death was also associated with the mean TSH at the lower limit of normality (≤ 1.75 mIU/L for

<80 years and ≤ 2.0 mIU/L for ≥ 80 years), which remained statistically significant after multivariate analysis models. These findings are consistent with previous studies that demonstrated that baseline TSH levels at the lower limit of normality are positively associated with mortality^{8,24-26}. It should be noted that only one of these studies obtained more than one TSH measurement throughout the cohort⁴. Other studies found an association between TSH and mortality only among women^{2,27} and not among euthyroid participants in general. Our group is mainly composed of women, but the association remained even after controlling for gender.

The association between the mean levels of FT4 in the upper half of the normal range (≥ 1.37 ng/dL) and the risk of death maintained borderline significance in the multivariate analysis in our study. These results are in line with the majority of previous longitudinal studies^{1,3,8,28,29} that assessed thyroid function and the risk of all-cause mortality and cardiovascular mortality. Some studies demonstrated association only in men^{2,5,30}. In a few studies^{4,24,25} with older populations, the risk of death was associated with higher levels of FT4 and lower levels of TSH simultaneously, which is consistent with our findings.

An important differentiating factor of the present study is the characteristics of the evaluated population, which consisted of older adults with a mean age of 80.4 years, with a high prevalence of cognitive impairment and functional dependence. Many studies assessing mortality and thyroid status have included younger populations than ours, even middle-aged individuals^{8,27,29,31}, with only a few including people over 80 years old^{1-3,28}. Most mortality studies in euthyroid patients were conducted in robust older community-dwelling groups, except for two^{2,3} that included frail older adults and demonstrated that lower FT4 levels were associated with lower mortality rates. However, these studies did not include cognitive assessment, functional status, or the Charlson Comorbidity Index in any stage of their analyses. These covariates were considered in the present study, although in the final adjusted model, cognitive impairment and total functional dependence variables were not included to remove their residual effect.

The cohort size was a limitation of the study, which was justified by the strict exclusion criteria and some peculiarities of the population, such as a high comorbidity index and advanced age. Additionally, it is a group of older adults selected with a high risk of functional decline, as this is an admission criterion in this geriatrics outpatient clinic. Our results cannot be generalized to robust older adults with few comorbidities. The association found between thyroid status and mortality also cannot be considered valid for older individuals with recent hospitalization or who started levothyroxine treatment, as they were excluded from the study.

Another possible limitation of the study was using the mean hormone levels without considering the analysis of the individual correlation of this variable over time through specific tests. However, considering that the vast majority of studies that evaluated the association between mortality and thyroid status used only a single baseline hormonal measurement, the fact that this cohort had multiple hormonal measurements evaluated can be considered a positive differentiator.

Although not the focus of this study, the absence of measurements of free triiodothyronine (FT3) and reverse triiodothyronine (rT3) can also be considered a limitation. While there is ample evidence of the association of FT4 with the risk of death^{1,3,5,13}, the results of research that evaluated the association between T3 and mortality are conflicting. A recent longitudinal study with middle-aged adults showed that higher levels of FT3 were associated with higher mortality in women but not in men²⁸. Conversely, a retrospective cohort demonstrated that a higher FT3/FT4 ratio was linked to decreased all-cause and cardiovascular mortality³¹. Another longitudinal study that evaluated overall mortality in euthyroid adults identified a U-shaped association with the FT3/FT4 ratio³³. In groups of older individuals, rT3 concentrations are associated with lower physical function⁵. A study that assessed mortality in nonagenarians showed that higher FT3/FT4 ratios, higher T3L levels, and lower FT4 levels were associated with a lower mortality rate independent of family longevity status³. These findings suggest that better conversion of T4 to T3 is associated with

lower mortality. However, the reduction in this conversion may be a consequence of comorbidities leading to decreased deiodinase action, which in turn is also associated with higher mortality; thus, it is not possible to establish a direct causal relationship between survival and the T3/T4 ratio.

CONCLUSION

The results of our study identify a positive association between mean FT4 values maintained at the upper limit, as well as mean TSH at the lower limit, with mortality in euthyroid older adults, using an age-specific reference range for TSH to define normal thyroid function.

These findings suggest that slightly reduced thyroid function may be associated with better survival in older patients with similar characteristics to the evaluated population, namely advanced age, a high comorbidity index, and risk of functional impairment. Thus, the present study reinforces the need to avoid overdiagnosis of hypothyroidism in older adults, particularly in the presence of minimal elevations in TSH. Such an approach could lead to overtreatment and iatrogenesis. Additionally, it may be inferred that therapeutic targets for TSH in older patients receiving levothyroxine treatment should possibly be differentiated; however, further studies are needed to validate this conclusion.

REFERENCES

1. Gussekloo J, Van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA* 2004; 292(21):2591–2599. doi:10.1001/jama.292.21.2591
2. Ogliari G, Smit RA, Van Der Spoel E, Mari D, Torresani E, Felicetta I et al. Thyroid status and mortality risk in older adults with normal thyrotropin: sex differences in the Milan geriatrics 75+ cohort study. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2017; 72(4), 554-559. doi: 10.1093/gerona/glw113.
3. Van Vliet NA, van der Spoel E, Beekman M, Slagboom PE, Blauw GJ, Gussekloo J et al. Thyroid status and mortality in nonagenarians from long-lived families and the general population. *Aging (Albany NY)* 2017; 9(10):2223. doi: 10.18632/aging.101310.
4. Cappola AR, Arnold AM, Wolczyn K, Carlson M, Robbins J, Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. *J Clin Endocrinol Metab* 2015; 100(3):1088–1096. doi: 10.1210/jc.2014-3586.
5. Van den Beld AW, Visser TJ, Feelders RA, Grobbee DE, Lamberts SW. Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. *J Clin Endocrinol Metab* 2005; 90(12):6403–6409. doi: 10.1210/jc.2005-0872.

AUTHORSHIP

- Aline Saraiva da Silva Correia – conception and design of the research, collection, analysis and interpretation of data, writing of the article.
- Natália Santana Paiva – statistical analysis, creation of graphs, interpretation of collected data.
- Cláudia Medina Coeli - critical review of the article and approval of the version to be published.
- Mário Vaisman – conception and design of the research, critical review of the article and approval of the version to be published.
- Patrícia de Fátima dos Santos Teixeira – conception and design of the research, interpretation of data, critical review of the article and approval of the version to be published.

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6. Correia ASDS, Nascimento ML, Teixeira LBDM, Silva SO, Vaisman M, Teixeira PF. Free thyroxine but not TSH levels are associated with decline in functional status in a cohort of geriatric outpatients. *European Geriatric Medicine* 2022; 13(1): 147-154. doi: 10.1007/s41999-021-00589-y.
7. Szlejf C, Suemoto CK, Janovsky CC, Barreto SM, Diniz MdFH, Lotufo PA et al. Thyroid function and sarcopenia: results from the ELSA-Brasil study. *J Am Geriatr Soc* 2020; 68(7):1545–1553. doi: 10.1111/jgs.16416.
8. Xu Y, Derakhshan A, Hysaj O, Wildisen L, Ittermann T, Pingitore A et al. The optimal healthy ranges of thyroid function defined by the risk of cardiovascular disease and mortality: systematic review and individual participant data meta-analysis. *Lancet Diabetes and Endocrinology* 2023; 11 (10):743 - 754. doi: 10.1016/S2213-8587(23)00227-9.
9. Cappola A R, Auchus R J, El-Hajj Fuleihan G , Handelsman D J, Kalyani R R, McClung M et al. Hormones and Aging: An Endocrine Society Scientific Statement. *The Journal of Clinical Endocrinology & Metabolism* 2023;108(8):1835-1874. doi: 10.1210/clinem/dgad225
10. Mooijaart SP, Du Puy RS, Stott DJ, Kearney PM., Rodondi N, Westendorp RG et al. Association between levothyroxine treatment and thyroid-related symptoms among adults aged 80 years and older with subclinical hypothyroidism. *JAMA* 2019; 322(20): 1977-1986. doi: 10.1001/jama.2019.17274.
11. Fontes R, Coeli CR, Aguiar F, Vaisman M. Reference interval of thyroid stimulating hormone and free thyroxine in a reference population over 60 years old and in very old subjects (over 80 years): comparison to young subjects. *Thyroid Res* 2013; 6(1):13. doi: 10.1186/1756-6614-6-13.
12. Yamada S, Horiguchi K, Akuzawa M, Sakamaki K, Yamada E, Ozawa A et al. The Impact of Age- and Sex-Specific Reference Ranges for Serum Thyrotropin and Free Thyroxine on the Diagnosis of Subclinical Thyroid Dysfunction: A Multicenter Study from Japan. *Thyroid* 2023; 33(4), 428-439. doi: 10.1089/thy.2022.0567
13. Fitzgerald SP, Bean NG, Falhammar H, Tuke J. Clinical parameters are more likely to be associated with thyroid hormone levels than with TSH levels: a systematic review and meta-analysis. *Thyroid* 2020; 30(12):1695–1709. doi: 10.1089/thy.2019.0535.
14. Lachs MS, Feinstein AR, Cooney LM Jr, Drickamer MA, Marottoli RA, Pannill FC et al. A simple procedure for general screening for functional disability in elderly patients. *Ann Intern Med* 1990; 112(9):699–706. doi: 10.7326/0003-4819-112-9-699.
15. Lourenco RA, Veras RP. Mini-mental state examination: psychometric characteristics in elderly outpatients. *Rev Saude Publica* 2006; 40:712–719. doi: 10.1590/s0034-89102006000500023.
16. Lino V, Pereira S, Camacho L, Ribeiro SF, Buksman S (2008) Cross-cultural adaptation of the independence in activities of daily living index (Katz Index). *Cad Saude Publica* 2008; 24(1):103–112. doi: 10.1590/s0102-311x2008000100010.
17. Ferraz M, Oliveira LM, Araujo P, Atra E, Tugwell P. Crosscultural reliability of the physical ability dimension of the health assessment questionnaire. *J Rheumatol* 1990; 17(6):813
18. Paradelo EMP, Lourenco RA, Veras RP. Validation of geriatric depression scale in a general outpatient clinic. *Rev Saude Publica* 2005; 39:918–923. doi: 10.1590/s0034-89102005000600008.
19. Carthery-Goulart MT, Areza-Fegyveres R, Schultz RR, Okamoto I, Caramelli P, Bertolucci PHF et al. Versao brasileira da Escala Cornell de depressao em demencia (Cornell depression scale in dementia). *Arq Neuropsiquiatr* 2007; 65(3B):912–915. doi: 10.1590/s0004-282x2007000500037
20. Pazan F, Wehling, M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. *European geriatric medicine* 2021; 12: 443-452. doi: 10.1007/s41999-021-00479-3.
21. Montero-Odasso M, van der Velde N, Martin F C, Petrovic M, Tan M P, Ryg J et al. World guidelines for falls prevention and management for older adults: a global initiative. *Age and ageing* 2022; 51(9): 1- 36. doi: 10.1093/ageing/afac205.
22. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr* 2019; 38(1):10–47. doi: 10.1016/j.clnu.2018.05.024.
23. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; 47(11):1245–1251. doi: 10.1016/0895-4356(94)90129-5.
24. Ceresini G, Marina M, Lauretani F, Maggio M, Bandinelli S, Ceda G P, Ferrucci L. Relationship Between Circulating Thyroid-Stimulating Hormone, Free Thyroxine, and Free Triiodothyronine Concentrations and 9-Year Mortality in Euthyroid Elderly Adults. *Journal of the American Geriatrics Society* 2016; 64(3), 553-560. doi: 10.1111/jgs.14029.
25. Bano A, Chaker L, Mattace-Raso FUS, Terzikhan N, Kavousi M, Ikram MA, et al. Thyroid function and life expectancy with and without noncommunicable diseases: A populationbased study. *PLoS Med* 2019; 16(10): e1002957. doi: 10.1371/journal.pmed.1002957.

26. Zhu P, Lao G, Chen C, Luo L, Gu J, Ran J. TSH levels within the normal range and risk of cardiovascular and all-cause mortality among individuals with diabetes. *Cardiovascular Diabetology* 2022; 21(1): 254. doi:10.1186/s12933-022-01698-z
27. Altay S, Onat A, Can G, Tusun E, Şimşek B, Kaya A. High-normal thyroid-stimulating hormone in euthyroid subjects is associated with risk of mortality and composite disease endpoint only in women. *Archives of Medical Science* 2018; 14(6): 1394-1403. doi: 10.5114/aoms.2016.63264.
28. Van de Ven A C, Netea-Maier R T, De Vegt, F, Ross H A, Sweep F C, Kiemeny L A, et al. Associations between thyroid function and mortality: the influence of age. *European journal of endocrinology* 2014; 171(2): 183-191. doi: 10.1530/EJE-13-1070.
29. Groothof D, Flores-Guerrero J L, Nolte I M, Bouma H R, Gruppen E G, Bano A, et al. Thyroid function and risk of all-cause and cardiovascular mortality: a prospective population-based cohort study. *Endocrine* 2021; 71, 385-396. doi: 10.1007/s12020-020-02397-z.
30. Yeap BB, Alfonso H, Hankey GJ, Flicker L, Golledge J, Norman PE et al. Higher free thyroxine levels are associated with all-cause mortality in euthyroid older men: the Health In Men Study. *Eur J Endocrinol* 2013; 169(4):401–408. doi: 10.1530/EJE-13-0306
31. Lang X, Li Y, Zhang D, Zhang Y, Wu N, Zhang Y. FT3/FT4 ratio is correlated with all-cause mortality, cardiovascular mortality, and cardiovascular disease risk: NHANES 2007-2012. *Front. Endocrinol* 2022; 13:964822. doi:10.3389/fendo.2022.964822
32. Nascimento PPP do, Aprahamian I, Yassuda MS, Neri AL, Batistoni SST. Fragilidade, depressão e mortalidade em uma coorte de pessoas idosas residentes na comunidade. *Rev bras geriatr gerontol* [Internet]. 2022;25(5):e210225. doi:10.1590/1981-22562022025.210225.pt
33. Yu G, Liu S, Song C, Ma Q, Chen X, Jiang Y et al. Association of sensitivity to thyroid hormones with all-cause mortality in euthyroid US adults: a nationwide cohort study. *European Thyroid Journal* 2024;13(1), e230130. doi:10.1530/ETJ-23-0130