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How Reliable Are Thyroid Hormone Levels For Predicting Mortality Before Amputation?

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ABSTRACT

The aim of this study was to investigate the correlation between thyroid hormone (TH) levels before amputation and mortality.

The 30-day and 1-year mortality rates of 194 patients (84 females and 110 males) who underwent lower extremity amputations in our clinic were retrospectively analyzed. To evaluate the relationship between TH levels and mortality, archival records were used to obtain necessary information such as age, gender, and TH levels. Patients were divided into six groups according to TH levels: control, overt hyperthyroidism, subclinical hyperthyroidism, euthyroid sick syndrome (ESS), subclinical hypothyroidism, and overt hypothyroidism.

The 30-day and 1-year mortality rates were 22.7% (44/194) and 52.6% (102/194), respectively. The log-rank test of the Kaplan–Meier curves revealed statistically significant differences in 30-day and 1-year survival rates between patients with different thyroid status. Univariate analysis showed that thyroid status was significantly associated with both 30-day mortality and 1-year mortality rates. In terms of 1-year mortality, ESS, overt hypothyroidism, subclinical hypothyroidism, overt hyperthyroidism, and subclinical hyperthyroidism were associated with an increased risk of death compared to patients with normal thyroid function in the control group.

The current study found that impaired TH levels were associated with 30-day and 1-year mortality after amputation in a geriatric population. Increasing age and overt hyperthyroidism were associated with a higher rate of postoperative complications.

Keywords: thyroid, lower extremity amputation, mortality

Introduction

The mortality rates after lower limb amputation (LLA) are high because the patient population is elderly and medically frail. Some of the known risk factors for morbidity and mortality include the presence and number of medical comorbidities, age, body mass index, and various biomarkers such as parathyroid hormone, cardiac troponin I, serum albumin, tumor necrosis factor-a, and interleukin 6 and 10 (1-4). Advanced age, proximal amputation levels, renal disease, and multimorbidity are associated with a higher mortality rate after amputation (5-8).

Thyroid hormone (TH) has numerous biological functions that affect many organ systems, including the musculoskeletal system, where it plays a role in bone remodeling and articular cartilage health (9,10). Specific TH levels are critical for the development of different tissues and for the regulation of metabolic processes in life (11).

Thyroid hormones (THs) are associated with acute physiology and chronic health evaluations, a model for end-stage liver disease, Child-Turcotte-Pugh, and sequential organ failure assessment scores and have a predictive value for mortality (12). The Charlson Comorbidity Index has been used to predict mortality in intensive care units, but it does not address comorbid factors such as thyroid disease (13,14).

Hypothyroidism is known to have many effects on the bone maturation and the cardiovascular system, including endothelial dysfunction, atherogenic lipid profiles and insulin resistance (15-19). Hypothyroidism is associated with an increased risk of mortality (20). It is also thought to have an indirect effect on mortality as a consequence of many events, such as malnutrition as well as acute and chronic diseases (21).

Hyperthyroidism has been associated with increased oxidative stress and a dysregulated inflammatory response in adult patients (22). It is also associated with cardiovascular diseases (23),

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thyrotoxic stroke, osteoporosis, reproductive system abnormalities, and neurodegenerative diseases (24).

The aim of this study was to investigate the correlation between TH levels before amputation and mortality. To the best of our knowledge, there are no studies in the literature investigating the relationship between TH levels and mortality in patients undergoing LLA.

Material and Methods

Study Design and Patient Selection: Patients who underwent lower extremity amputation between 2017 and 2022 in the orthopedics and traumatology clinic of Health Sciences University Trabzon Kanuni Training and Research Hospital were included in the study. A data file was created for each patient by reviewing the patient's file. The data file contained information related to the patient's gender, age, date of surgery, blood test values, and date of death (if the patient died). The study was approved by the ethics committee of Health Sciences University Trabzon Kanuni Training and Research Hospital on 24.08.2022 with the decision number 2022-05.

Patients were divided into six groups:

1: Control group (patients with normal TH levels)

2: Overt hyperthyroidism (low thyroid-stimulating hormone [TSH] levels and above-normal free thyroxine [fT4] levels)

3: Subclinical hyperthyroidism (low TSH levels and above-normal fT4 levels)

4: Euthyroid Sick Syndrome (ESS) (normal or low TSH levels and below-normal free triiodothyronine fT3 levels)

5: Subclinical hypothyroidism (high TSH levels and normal fT4 levels)

6: Overt hypothyroidism (high TSH levels and below-normal fT4 levels)

The primary dependent variable was the time to death. For the primary endpoint of 1-year all-cause mortality, hospital records, family physicians' records, and the National Population Registration System were used. The data included the date of birth, gender, and vital status.

Age and gender were considered independent variables. Amputations due to trauma, cancer, or congenital causes were excluded from the study.

Statistical Analysis: Continuous data are summarised as mean ± SD and categorical variables are presented as the frequency (percentage).Independent samples t-tests were used for the comparison of continuous variables between survivors and non-survivors. The relationships between the mortality and the categorical variables were assessed with Pearson's chi-square test or Fisher's exact test, where appropriate. Univariable Cox proportional hazard models were fitted to estimate the effect of eachfactor on 30-days and 1-year mortalities. Furthermore, multivariable Cox regression analysis was conducted to identify the independent risk factors of mortality. In the multivariable analysis, age and gender were included as independent variables in the model. Hazard ratios (HR) along with their 95% confidence intervals were calculated. Survival was also estimated using the Kaplan–Meier curves and the differences between thyroid groups were assessed using the log-rank test. The analyses were performed using the Statistical Package for Social Sciences 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The results were assessed within a 95% reliance and at a level of $p < 0.05$ significance.

Results

A total of 194 patients (84 female, 110 male) were included in the study. The baseline characteristics of the study population are summarised in Table 1. The mean age of participants was 78.2±16.1 years.

The mortality rates at 30 days and 1 year were 22.7% (44/194) and 52.6% (102/194), respectively. In Table 2, comparison of patients' characteristics between survivors and non-survivors based on 30 days and 1-year mortality were presented. The univariate analysis showed that thyroid status were statistically significantly associated with both 30-days mortality (p=0.003) and 1 year mortality (p=0.001). Furthermore, the patients who did not survive at the end of 1-year follow up were significantly older compared to the patients who survived (81.3±12.3 vs. 75.0±15.2, p=0.002).

For 30-days mortality, both univariable and multivariable Cox proportional hazard models revealed that subclinical hyperthyroidism was associated with an increased hazard of death relative to the control group (Univariate HR: 4.776, 95%CI: 2.001-11.401, p<0.001; Adjusted HR: 4.892, 95%CI: 2.039-11.737, p<0.001) (Table 3). Moreover, univariable analysis indicated a borderline significance for overt hyperthyroidism implying that, patients with overt hyperthyroidism are 2.6 times more likely to die at the end of 30

Table 1. Baseline Characteristics of 194 Patients

Characteristics	Value
Age, mean±sd	78.2±16.1
Gender, n (%)	
Female	84 (43.3)
Male	110 (56.7)
Thyroid Status, n (%)	
Control Group	100 (51.5)
Euthyroid Sick Syndrome	48 (24.7)
Overt Hypothyroidism	4 (2.1)
Subclinical Hypothyroidism	10 (5.2)
Overt Hyperthyroidism	18 (9.3)
Subclinical Hyperthyroidism	14 (7.2)

Table 2. Univariate Comparisons of Patient Characteristics Between Survivors and Non-Survivors Based On 30-Days Mortality and 1-Year Mortality

	30 days mortality			1 year mortality		
Variables	Survived (n=150)	Died (n=44)	p	Survived (n=92)	Died (n=102)	p
Age, mean±sd	77.7±14.1	80.2±13.9	0.295	75.0±15.2	81.3±12.3	0.002
Gender, n (%)			0.308			0.090
Female	62 (41.3)	22 (50.0)		34 (37.0)	50 (49.0)	
Male	88 (58.7)	22 (50.0)		58 (63.0)	52 (51.0)	
Thyroid Status, n (%)			0.003			0.001
Control Group	86 (57.3)	14 (31.8)		62 (67.4)	38 (37.3)	
Euthyroid Sick Syndrome	36 (24.0)	12 (27.3)		16 (17.4)	32 (31.4)	
Overt Hypothyroidism	4 (2.7)	0 (0)		0 (0)	4 (3.9)	
Subclinical Hypothyroidism	6 (4.0)	4 (9.1)		2 (2.2)	8 (7.8)	
Overt Hyperthyroidism	12 (8.0)	6 (13.6)		6 (6.5)	12 (11.8)	
Subclinical Hyperthyroidism	6 (4.0)	8 (18.2)		6 (6.5)	8 (7.8)	

For categorical variables Pearson's chi-square or Fisher's exact tests are used. Continuous variables were analysed with independent samples t-test. Bold p-values indicate statistical significance at $\alpha<0.05$

days follow-up compared to the control group (HR: 2.559, 95%CI:0.983-6.660, p=0.054).

With respect to 1-year mortality, ESS (HR: 2.212, 95%CI: 1.380-3.545, p=0.001), overt hypothyroidism (HR: 3.579, 95%CI: 1.267-10.108, p=0.016), subclinical hypothyroidism (HR: 2.534, 95%CI: 1.070-6.000, p=0.035), overt hyperthyroidism (HR: 2.590 , 95%CI: 1.350-4.970, p=0.004) and subclinical hyperthyroidism (HR: 2.224, 95%CI: 1.036-4.774, p=0.040) were associated with an increased hazard of death compared to the control group patients with normal thyroid function (Table 4). When the analysis was adjusted for age and gender, overt hypothyroidism and subclinical hypothyroidism were no longer associated with 1-year mortality, however ESS (HR: 1.998, 95%CI: 1.230-3.245, p=0.005), overt hyperthyroidism (HR: 2.498, 95%CI: 1.294-4.820, p=0.006) and subclinical hyperthyroidism (HR: 2.215, 95%CI: 1.029-4.767, p=0.042) significantly increased the hazard of death at the end of 1-year follow up (Table 4). Age was also found as a significant predictor for 1-year mortality in both univariable and multivariable analysis (Univariate HR: 1.027, 95%CI: 1.010-1.043, p=0.001; Adjusted HR: 1.021, 95%CI:1.002-1.040, p=0.032).

The log-rank test of the Kaplan–Meier curves implied statistically significant differences in 30-day and 1-year survivals between patients with different thyroid status (p=0.003 and p=0.001, respectively) (Figure 1 and 2).

Table 3. Univariable and Multivariable Cox Proportional Hazard Models For The Risk Factors Associated With 30-Days Mortality

Variables	Univariate HR (95% CI)	p	Adjusted HR (95% CI)	p
Age	1.019 (0.994-1.044)	0.134	1.019 (0.989-1.050)	0.220
Gender				
Female	reference	-	Reference	-
Male	0.816 (0.445-1.495)	0.511	0.848 (0.433-1.66)	0.631
Thyroid Status				
Control Group	reference	-	Reference	-
Euthyroid Sick Syndrome	1.918 (0.887-4.148)	0.098	1.805 (0.822-3.965)	0.141
Overt Hypothyroidism	NAa	NAa	NAa	NAa
Subclinical Hypothyroidism	1.843 (0.419-8.113)	0.419	1.402 (0.308-6.389)	0.662
Overt Hyperthyroidism	2.559 (0.983-6.660)	0.054	2.389 (0.904-6.315)	0.079
Subclinical Hyperthyroidism	4.776 (2.001-11.401)	<0.001	4.892 (2.039-11.737)	<0.001

HR: Hazard ratio, CI: Confidence interval. [a] HRs were not computed as no events were observed in that category. Bold p-values indicate statistical significance at $\alpha<0.05$

Table 4. Univariable and Multivariable Cox Proportional Hazard Models For The Risk Factors Associated With 1-Year Mortality

Variables	Univariate HR (95% CI)	p	Adjusted HR (95% CI)	p
Age	1.027 (1.010-1.043)	0.001	1.021 (1.002-1.040)	0.032
Gender				
Female	reference	-	Reference	-
Male	0.766 (0.517-1.134)	0.182	0.877 (0.565-1.362)	0.558
Thyroid Status				
Control Group	reference	-	Reference	-
Euthyroid Sick Syndrome	2.212 (1.380-3.545)	0.001	1.998 (1.230-3.245)	0.005
Overt Hypothyroidism	3.579 (1.267-10.108)	0.016	2.686 (0.926-7.790)	0.069
Subclinical Hypothyroidism	2.534 (1.070-6.000)	0.035	1.969 (0.811-4.782)	0.134
Overt Hyperthyroidism	2.590 (1.350-4.970)	0.004	2.498 (1.294-4.820)	0.006
Subclinical Hyperthyroidism	2.224 (1.036-4.774)	0.040	2.215 (1.029-4.767)	0.042

HR: Hazard ratio, CI: Confidence interval. [a] HRs were not computed as no events were observed in that category. Bold p-values indicate statistical significance at $\alpha<0.05$

Discussion

Irregularities in thyroid function tests are common in the elderly, and current literature has conflicting results on their clinical significance (25). In the present study was to investigate thyroid function in terms of its association with major medical comorbidities and to better predict postoperative complications in amputation patients before surgery. If the TH has a significant predictive value, it can be used to reduce possible postoperative complications and, consequently, post-amputation mortality. Understanding the timing and causes of post-amputation mortality in different patient subgroups may also help in the identification of specific risk factors and the development of preoperative and postoperative care strategies. The results showed that TH is a significant risk factor for postoperative medical and surgical complications and is associated with increased mortality following LLA.

Buller et al.(26) found that hypothyroidism was a significant risk factor for postoperative medical and surgical complications and was associated with an episode of increased care costs following primary total knee arthroplasty. They attributed this to the fact that patients with hypothyroidism as an underlying cause had significantly higher odds of thromboembolic disease, including deep vein thrombosis (odds ratio [OR], 1.252) and pulmonary embolism (OR, 1.206), than matched controls. In addition, these patients required more blood transfusions (OR, 1.428) due to higher acute postoperative anemia (OR, 1.326). These findings may be explained by direct and indirect effects of TH on platelet maturation and function,

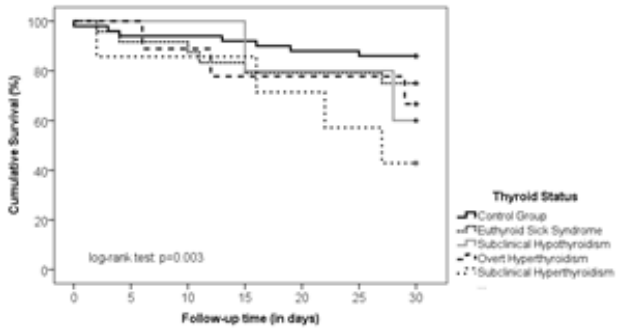

Fig. 1. Kaplan–Meier Survival Analyses For 30-Days Mortality According To Tyhroid Status

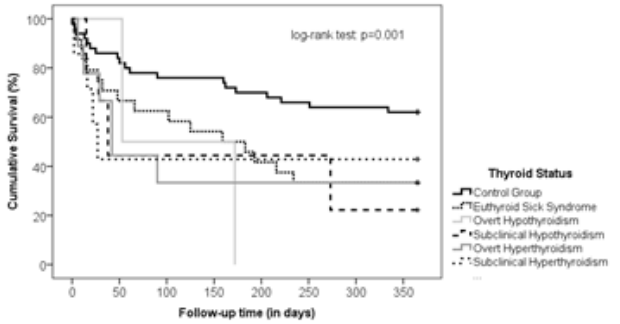

Fig. 2. Kaplan–Meier Survival Analyses For 1-Year Mortality According To Tyhroid Status

synthesis and action of coagulation factors, and maintenance of blood viscosity (27).

Kalra et al. reported that hypothyroidism or hyperthyroidism did not affect 1-year mortality in patients operated for hip fracture (25). Ling et al. reported a 4-fold increased risk of at least one medical or surgical complication in the first 30 days after hip fracture surgery in patients with hyperthyroidism, but they did not find any increase in 30-day mortality (4).

After adjusting for various comorbidities affecting mortality, Sohn et al.(20) found an increase in mortality (adjusted hazard ratio, 1.14; 95% confidence interval, 1.12–1.16) in patients with hypothyroidism compared to the control group. In the present study, it was found that hyperthyroidism was more associated with an increased risk of death compared to patients in decreasing short-term mortality rates. In the literature, a significant risk association was observed between hyperthyroidism and mortality after adjusting for the effect of anti-thyroid treatment. This observation is supported by the fact that hyperthyroidism has been associated with increased oxidative stress and a dysregulated inflammatory response in adult patients (22). Hyperthyroidism should therefore be considered an independent risk factor for amputation.

In a meta-analysis focusing on the elderly population, a significant association was reported between all-cause mortality and overt hypothyroidism, but no such association was found between subclinical hypothyroidism and mortality (28). In the present study, subclinical hypothyroidism was significantly associated with 1-year mortality but not with 30-day mortality.

Studies have reported increased morbidity and mortality due to an increased risk of infection in hypothyroidism owing to the role of TH in modulating cell-mediated immunity and cellular metabolism (26,29-31). It is also hypothesized that during severe disease, alterations in thyroid function occur to prevent excessive tissue catabolism (32,33). Thyroid dysfunction is associated with increased postoperative mortality because of an increased risk of complications, particularly cardiac events.

In a study examining patients with partial foot amputation, mortality rates 1 year after amputation were as low as 22% (34). If studies focus only on transtibial and proximal levels, 1-year mortality rates can reach 52% (35,36). In the present study, the 30-day mortality rate was 22.7% and the 1-year mortality rate was 52.6%.

Despite the obvious high risk of death after LLA, reported rates vary greatly. These differences are largely explained by differences in inclusion criteria. Additional factors such as the inclusion of patients undergoing first amputation or subsequent amputations, different causes of amputation, and the source used for death registration affect these rates. Unfortunately, this information is not always clear, which limits our ability to make valid comparisons across studies (37).

The present study has some limitations. Other potential confounding factors, such as initial injury severity scores, pre-illness quality of life indices, and nursing home residents, were excluded from the study because they could not be controlled. The results may have been insufficient to capture other secondary outcomes, such as complication rates, or to detect small differences in mortality.

Another limitation of the study is that smoking is an external factor affecting the inflammatory process in the body. However, smokers among the patients were not excluded in this study. Since it is a retrospective study, detailed analysis could not be performed. Different results can be obtained with a prospective study.

The results obtained in the present study showed that impaired TH levels were associated with 30-day and 1-year mortality rates after amputation in

a geriatric population. These results support our hypothesis that increasing age and overt hyperthyroidism are associated with higher postoperative complication rates. The results also showed that the correlative abilities of TH affect mortality on a monthly basis and are effective beyond 1 year. This information is vital, especially in an aging population, and accurate identification can lead to increased access to health services and a reduction in mortality through close follow-up of high-risk patients.

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