Thyroid Hormones as Predictors of Short- and Long-term Mortality in Very Old Hospitalized Patients

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Background. Although extensively investigated, the prognostic role of thyroid hormone abnormalities in older participants remains uncertain. We investigated the relationship between thyroid hormones and mortality during hospitalization and in a prolonged follow-up in frail older patients.

Methods. A nonconcurrent cohort study was conducted by enrolling 450 participants hospitalized for an acute disease, who were classified into four groups (euthyroidism, hypothyroidism, hyperthyroidism, and low triiodothyronine [T₃] syndrome), according to clinical and laboratory data. Multidimensional geriatric assessment variables were considered in order to identify short- and long-term predictors of death.

Results. Participants were very old (mean age: 84 years) and frail, as indicated by severely impaired functional status, extensive comorbidity, high prevalence of dementia, and hospital mortality (8%). Prevalence of any thyroid dysfunction was 40.7%; 32% of participants had low T₃ syndrome, which was associated with an excess hospital mortality risk (odds ratio: 2.7, 95% confidence interval [CI]: 1.1–6.5; p = .025), adjusted for demographic, clinical, functional, and laboratory data. Conversely, long-term mortality was unrelated to low T₃ syndrome. In euthyroid participants, increasing levels of free thyroxine (FT₄) were associated with a slightly greater mortality (hazard ratio, CI: 2.12, 0.99–4.54; p = .053) in adjusted Cox regression models.

Conclusions. This observational study on a cohort of very old, frail hospitalized patients gives support to the independent prognostic short-term, but not long-term, role of low T₃ syndrome. Moreover, in older euthyroid participants, increasing levels of FT₄ are a weak marker of poorer long-term survival. Thyroid hormones may help monitor changes in general health status and predict short- and long-term clinical outcomes in very old, frail patients.

Key Words: Thyroid hormones—Elderly—Mortality.

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Changes in thyroid function during the aging process have been extensively investigated over the past 20 years, but only recently a few studies focused on the possible role of the hypothalamus–pituitary–thyroid axis in longevity (1–8). Some evidence has been provided that decreased thyroid hormone and increased thyroid-stimulating hormone (TSH) levels may be associated with prolonged survival (3,6,9) in representative samples of independently living older participants, and a heritable phenotype characterized by increased serum TSH levels was shown to be associated with extreme longevity, at least in Ashkenazi Jewish individuals (10). However, causation remains an unproven speculation in this association, as results of studies on the relationship between mortality and isolated baseline measurements of thyroid hormones in elderly populations are conflicting.

Besides the biologic implications of the studies mentioned, the prognostic role of thyroid hormone abnormalities have been also investigated in older patients hospitalized for acute conditions (11–13). Thyroid dysfunction, indeed, is observed with increasing frequency with advancing age (12) in hospital settings. In particular, low triiodothyronine (T₃) syndrome is found in 32%–62% of hospitalized older patients and it has been recognized as a powerful independent predictor of short-term survival (11–13). Nevertheless, the prognosis of hospitalized older patients depends on a variety of other factors (eg, acute derangements vs chronic illnesses, or use of medications), which, in turn, may interfere with thyroid function, and, therefore, this issue is still highly controversial. Moreover, it is unknown whether low T₃ syndrome detected during acute hospitalization may still influence long-term prognosis, after clinical stabilization and discharge.
In the present study, we considered a large cohort of very old patients hospitalized for acute diseases, in order to evaluate whether alterations in thyroid function—in particular, low $T_3$ syndrome—detected on admission are related with mortality in the index hospitalization, in addition to conducting a prolonged follow-up. Moreover, we also aimed to assess whether levels of free thyroxine or $T_3$ ($FT_3$) in the absence of definite thyroid dysfunction predict long-term mortality.

**METHODS**

A nonconcurrent cohort study was conducted, and the protocol was approved by the Local Ethics Committee of the Grosseto Local Health Unit.

**Patients**

All patients aged 65 and older admitted between 2004 and 2005 to the geriatrics unit of our community hospital were enrolled, regardless of the cause of hospitalization. In general, patients are admitted to the unit directly from the emergency department or from other hospital units; in the latter case, admission is justified by the need for intensive rehabilitation, in the presence of persisting clinical instability.

**Data Collection**

Demographics, social condition (education, marital status, and living arrangement), clinical history, and physical examination data were collected on admission, whereas laboratory tests were conducted the subsequent morning, after overnight fasting; among these, thyroid function tests were routinely conducted in all patients admitted. Length of stay, disposition, discharge diagnoses, and procedures, coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM)*, were abstracted from the discharge summaries.

**Comprehensive Geriatric Assessment**

Global functional status was evaluated with a modified version of Barthel Index (BI), which provides a reliable and accurate description of autonomy in daily living activities and is sensitive even to small changes in functional capacity (14). Items in the BI relate to self-care (feeding, grooming, bathing, dressing, bowel and bladder continence, and toilet use) and mobility (ambulation, transferring, and climbing stairs). The scale ranges from 0, representing a totally dependent, bedridden state, to 100, indicating full independence, with a minimum change of 5 points per item. BI has been previously shown to allow highly correlated self- and informant ratings (15). Preadmission BI (BIpre) was recorded by asking patients or caregivers (for patients who were unable to respond, such as those with dementia) about the patient’s functional status 15 days prior to hospital admission, whereas direct, observational functional assessment was conducted by study physicians with the same instrument on admission and the day before discharge.

**Comorbidity Evaluation**

Comorbidity was assessed at discharge, based on both the number of diseases listed in the discharge summary and the Geriatric Index of Comorbidity (GIC), which takes into account the number of diseases as well as the occurrence of very severe diseases, assuming that both are determinants of health (16). Assessment of disease severity in the GIC is based on Greenfield’s Index of Disease Severity (IDS) (17), which assigns a score from 0 to 4 ($0 = $ disease absent; $1 = $ asymptomatic disease; $2 = $ symptoms controlled by treatment; $3 = $ symptoms not controlled by treatment; $4 = $ life-threatening or the worst possible severity of the disease; IDS) to each of 15 somatic conditions. GIC groups patients into four classes of more severe comorbidity; for example, Class I includes patients with IDS $= 1$ or lower, Class II patients with one or more conditions with IDS $= 2$, Class III patients with at most one condition with an IDS $= 3$, and Class IV patients with two or more conditions with IDS $= 3$ or one or more conditions with IDS $= 4$. GIC has been shown to predict 1-year mortality in hospitalized older patients (16) and in older community dwellers (18).

Because GIC does not include a diagnosis of dementia, this condition was considered a separate diagnosis. To this purpose, an accurate evaluation of mental status was systematically performed, based on the criteria of the *Diagnostic and Statistical Manual for Mental Disorders—Fourth edition* (19).

**Criteria for Diagnosis of Thyroid Dysfunction**

The study sample was divided into the following four groups, according to clinical and laboratory data: Group 1 = euthyroidism, Group 2 = overt or subclinical hypothyroidism, Group 3 = overt or subclinical hyperthyroidism, and Group 4 = low $T_3$ syndrome. Hypothyroidism was diagnosed when patients were (a) taking replacement therapy, (b) in the presence of low $T_3$ and/or $T_4$ levels ($FT_3$, $FT_4$) and high TSH levels (overt hypothyroidism), or (c) high TSH levels with normal $FT_4$ (subclinical hypothyroidism). Similarly, a diagnosis of hyperthyroidism was made in the presence of (a) thyrostatic treatment on admission, independent of actual hormone levels, (b) high $FT_3$ and/or $FT_4$ with suppressed TSH levels (overt hyperthyroidism), or (c) low TSH levels with normal $FT_3$ and $FT_4$ (subclinical hyperthyroidism). Low $T_3$ syndrome was recognized when serum $FT_3$ was low and TSH level was normal or inappropriately low. Normal ranges of thyroid hormones and TSH in our laboratory are as follows: $FT_3 = 1.45–3.48$ ng/dL; $FT_4 = 0.71–1.85$ ng/dL; and TSH = $0.49–4.67$ mU/L.
Participants receiving drugs that may interfere with thyroid function (ie, glucocorticoids, amiodarone, phenobarbital, carbamazepine, phenytoin, bromocriptine, levodopa, lithium, dopamine, rifampicin, 5-fluorouracil, salicylates in high dose, propranolol) were not excluded, and use of these agents was considered as a potential confounder in analytic models.

Long-term Outcome

Survival after discharge through December 2010 was assessed from administrative archives, maintained by the Local Health Unit.

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 statistical software package (SPSS Inc., Chicago, IL). Continuous variables are expressed as means ± SEM, categorical variables as percentages. ANOVA was used to compare continuous normally distributed variables, and the chi-square test was used for categorical or dichotomous variables. When a statistically significant difference was observed in the omnibus test, the significance of the differences between Groups 2, 3, and 4 versus Group 1 was tested with binary simple contrast general linear models and logistic regression models for continuous and dichotomous variables, respectively.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Hospital Mortality</th>
<th>Long-term Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>136</td>
<td>15%</td>
<td>No. deceased: 3</td>
</tr>
<tr>
<td>2</td>
<td>132</td>
<td>30%</td>
<td>No. deceased: 8</td>
</tr>
<tr>
<td>3</td>
<td>134</td>
<td>45%</td>
<td>No. deceased: 16</td>
</tr>
<tr>
<td>4</td>
<td>133</td>
<td>60%</td>
<td>No. deceased: 20</td>
</tr>
</tbody>
</table>

The effect of low T₃ syndrome on hospital mortality, independent of other prognosticators, was investigated in multivariable logistic regression models: According to a hierarchical approach, a diagnosis of low T₃ syndrome was entered first, followed by demographics and clinical variables (age, gender, BIpre, diagnosis of dementia, and comorbidity) and finally by laboratory variables (albumin, total cholesterol, lymphocyte count, blood urea nitrogen, and serum creatinine). Redundant variables were backward removed at each step with a p value for deletion of .1.

In euthyroid participants, separate Cox models were built to identify factors predicting long-term mortality, always controlling for age and gender. In particular, thyroid hormones were either entered as continuous variables or categorized into tertiles, to take into account a possibly non-normal distribution. From these preliminary models, variables resulting as possible predictors (p < .1) were entered into a final multivariable model.

Results

Clinical Features

The study initially recruited 463 patients, of whom 13 were excluded because of missing data on survival status, leaving a final sample of 450. As shown in Table 1, the sample assembled was definitively old (more than two out of five participants were aged 85 and older) and in poor general health, as documented by low BIpre, severe GIC classification, a great number of coexistent diseases, frequent occurrence of dementia, and high hospital mortality. The prevalence of any thyroid dysfunction was very high (40.7%) and increased significantly with advancing age (younger than 75 years: 21.2%; 75–84 years: 34.1%; 85 years and older: 51.5%; p < .001). In particular, 267 participants had euthyroidism (Group 1), 13 had clinical or subclinical hypothyroidism (Group 2), 27 had clinical or subclinical hyperthyroidism (Group 3), and almost one third (n = 143) had low T₃ syndrome (Group 4). Four out of the 13 patients in Group 2 and 3 out of the 27 in Group 3 were newly diagnosed, in the absence of previous pharmacological treatment.

Thyroid hormones showed the differences expected on the basis of classification criteria (Table 1): Participants in Group 2 had FT₄ and TSH values significantly lower and higher, respectively, than those in Group 1; TSH tended to be lower and FT₄ and FT₃ higher in Group 3 than in Group 1, in agreement with the prevalent condition of treated hyperthyroidism; FT₄ and FT₃ values were lower in Group 4 than in Group 1. Most of the other clinical variables were differently distributed according to thyroid status (Table 1). Participants in the groups with abnormal thyroid function were, on average, significantly older than those with normal thyroid status. In particular, participants with low T₃ syndrome were frailer, as suggested by the greater number of diseases, worse GIC classification, slightly higher prevalence of dementia, lower functional status before admission and at discharge, low cholesterol and albumin levels, low lymphocyte count, and higher levels of creatinine and blood urea nitrogen. Length of stay was significantly longer in patients diagnosed with hyperthyroidism (Group 3). Hospital mortality was more than threefold greater in participants with this condition than in those with normal thyroid status.

Hospital Mortality

To confirm the short-term prognostic value of low T₃ syndrome, logistic regression models were built, where only participants in Groups 1 and 4 were compared and possible confounding variables were progressively added. Taken alone, the diagnosis of low T₃ syndrome was associated with a significant 3.9 odds ratio (OR) of death (Table 2, Model 1). The strength of this association increased slightly when demographics, functional status (BIpre), and comorbidity (number of ICD9-CM coded diseases) were added in Model 2, where only BIpre was retained as strong contributor to prognosis and a diagnosis of dementia appeared to reduce the risk of death nonsignificantly; age and gender were backward deleted from the model. The substitution of GIC classification (Class III–IV versus I–II) did not change these findings (data not shown). After inclusion of laboratory variables (Model 3), the association between
### Table 1. Clinical and Laboratory Data of the Study Population, Grouped According to Thyroid Function.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 450)</th>
<th>Group 1 (euthyroidism) (n = 267)</th>
<th>Group 2 (hypothyroidism) (n = 13)</th>
<th>Group 3 (hyperthyroidism) (n = 27)</th>
<th>Group 4 (low T₃) (n = 143)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>83.8 ± 0.3</td>
<td>82.6 ± 0.4</td>
<td>86.4 ± 1.3*</td>
<td>85.5 ± 1.1*</td>
<td>85.4 ± 0.5†</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>65–74</td>
<td>7.3</td>
<td>9.7</td>
<td>0</td>
<td>3.7</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>75–84</td>
<td>49.6</td>
<td>55.1</td>
<td>30.8</td>
<td>48.1</td>
<td>41.3</td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td>43.1</td>
<td>35.2</td>
<td>69.2</td>
<td>48.1</td>
<td>54.5</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>66.4</td>
<td>64.4</td>
<td>76.9</td>
<td>77.8</td>
<td>67.1</td>
<td>.437</td>
</tr>
<tr>
<td>ICD9-CM coded diseases, n</td>
<td>4.7 ± 0.1</td>
<td>4.5 ± 0.1</td>
<td>5.0 ± 0.3</td>
<td>5.4 ± 0.2</td>
<td>4.9 ± 0.1†</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>GIC class III–IV</td>
<td>62.7</td>
<td>58.1</td>
<td>69.2</td>
<td>51.9</td>
<td>72.7†</td>
<td>.017</td>
</tr>
<tr>
<td>Dementia</td>
<td>26.4</td>
<td>21.7</td>
<td>61.5†</td>
<td>25.9</td>
<td>32.2*</td>
<td>.003</td>
</tr>
<tr>
<td>Barthel preadmission</td>
<td>66.6 ± 1.5</td>
<td>69.2 ± 1.9</td>
<td>50.8 ± 9.3*</td>
<td>75.2 ± 4.0</td>
<td>61.7 ± 2.7*</td>
<td>.012</td>
</tr>
<tr>
<td>Barthel discharge–preadmission</td>
<td>−17.2 ± 1.3</td>
<td>−13.5 ± 1.7</td>
<td>−2.1 ± 4.7</td>
<td>−22.0 ± 4.6</td>
<td>−18.8 ± 2.5*</td>
<td>.048</td>
</tr>
<tr>
<td>Barthel discharge–admission</td>
<td>20.5 ± 1.0</td>
<td>19.6 ± 1.3</td>
<td>32.5 ± 6.2</td>
<td>27.7 ± 4.1*</td>
<td>19.7 ± 1.8</td>
<td>.048</td>
</tr>
<tr>
<td>Participants taking drugs that interfere with thyroid function</td>
<td>16.2</td>
<td>18.7</td>
<td>23.1</td>
<td>11.1</td>
<td>11.9</td>
<td>.243</td>
</tr>
<tr>
<td>Drugs at discharge, n</td>
<td>4.5 ± 0.1</td>
<td>4.4 ± 0.1</td>
<td>5.3 ± 0.4</td>
<td>4.7 ± 0.4</td>
<td>4.6 ± 0.2</td>
<td>.370</td>
</tr>
<tr>
<td>FT₃, ng/dL</td>
<td>1.12 ± 0.01</td>
<td>1.15 ± 0.01</td>
<td>1.01 ± 0.05</td>
<td>1.18 ± 0.07</td>
<td>1.05 ± 0.03†</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>TSH, mU/L</td>
<td>1.33 ± 0.08</td>
<td>1.16 ± 0.05</td>
<td>7.31 ± 1.68†</td>
<td>0.66 ± 0.24</td>
<td>1.23 ± 0.07</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cholesterol, mg/dL‡</td>
<td>171 ± 2</td>
<td>182 ± 3</td>
<td>171 ± 12</td>
<td>168 ± 8</td>
<td>151 ± 4†</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Albumin, mg/dL‡</td>
<td>2.96 ± 0.03</td>
<td>3.13 ± 0.03</td>
<td>2.99 ± 0.11</td>
<td>2.86 ± 0.10‡</td>
<td>2.67 ± 0.05‡</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Lymphocyte count, /μL‡</td>
<td>1.593 ± 44</td>
<td>1.747 ± 59</td>
<td>1.502 ± 250</td>
<td>1.698 ± 190</td>
<td>1.298 ± 63†</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Creatinine, mg/dL‡</td>
<td>1.20 ± 0.03</td>
<td>1.16 ± 0.04</td>
<td>1.44 ± 0.31</td>
<td>0.97 ± 0.07</td>
<td>1.31 ± 0.07‡</td>
<td>.022</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>57.8 ± 1.7</td>
<td>53.5 ± 1.9</td>
<td>71.2 ± 12.4</td>
<td>49 ± 6.0</td>
<td>66.2 ± 3.6‡</td>
<td>.002</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>17.4 ± 0.5</td>
<td>16.1 ± 0.7</td>
<td>20.6 ± 4.0</td>
<td>22.2 ± 2.1†</td>
<td>18.6 ± 1.0</td>
<td>.012</td>
</tr>
<tr>
<td>In-hospital deaths, %</td>
<td>7.8</td>
<td>4.5</td>
<td>7.7</td>
<td>0.0</td>
<td>15.4†</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Survival, months</td>
<td>37.9 ± 1.4</td>
<td>41.1 ± 1.8</td>
<td>28.2 ± 8.3</td>
<td>33.8 ± 5.2</td>
<td>32.8 ± 2.7†</td>
<td>.035</td>
</tr>
<tr>
<td>Alive at the end of follow-up</td>
<td>30.4</td>
<td>31.4</td>
<td>16.7</td>
<td>25.9</td>
<td>30.6</td>
<td>.700</td>
</tr>
</tbody>
</table>

Notes: Data are mean ± SEM or percentage. GIC = Geriatric Index of Comorbidity; ICD9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

* p < .05 and † p < .01 versus Group 1.

**Data were missing in 16, 10, 6, 3, and 1 cases, respectively.

§Three cases with chronic lymphatic leukemia not included in these figures.

† Calculated in the 415 participants discharged alive.

Low T₃ syndrome and hospital mortality diminished slightly but remained statistically significant, confirming that this clinical condition was an independent predictor of hospital mortality; the risk of death was again, strongly reduced with increasing BIpere, whereas it increased with blood urea nitrogen level and decreased, though nonsignificantly, with albumin level. The presence of drugs potentially interfering with thyroid function (amiodarone: 20 cases, including one also taking phenobarbital and one aspirin at a daily dosage of 250 mg or more; high-dose aspirin only: 17 cases; carbamazepine: 1 case; levodopa: 24 cases; and phenobarbital only: 11 cases), entered as a summary dummy variable or in terms of individual agents, did not change the strength of the association between low T₃ syndrome and hospital mortality (data not shown).

### Long-term Mortality

Of the 415 participants discharged alive, 255 were in Group 1, 12 in Group 2, 27 in Group 3, and 121 in Group 4. As shown in Table 1, the proportion of long-term survivors was independent of thyroid status, although length of survival of discharged patients was slightly different across the study groups, with participants in Group 4 surviving approximately 8 months less than those in Group 1 (< .001 in paired contrast). When long-term mortality was compared between Groups 1 and 4 in a Cox regression model adjusted for age, gender, BIpere, comorbidity, diagnosis of dementia, levels of total cholesterol, albumin, and creatinine, and lymphocyte count on admission, the presence of low T₃ syndrome was associated with only a nonsignificant 20% greater risk of death (hazard ratio [HR] = 1.2; 95% confidence interval [CI] = 0.9–1.6; p = .138). Advanced age (per year: HR = 1.03; 95% CI = 1.01–1.05; p = .004), male gender (HR = 1.8; 95% CI = 1.3–2.3; p < .001), and low BIpere (per point: HR = 0.991, 95% CI = 0.987–0.995; p < .001) were the only long-term predictors of death.

Long-term effects of thyroid hormones and other predictors on survival were evaluated in euthyroid participants using Cox regression. Each individual predictor was initially entered in a separate Cox model, always adjusting for age and gender: as shown in Table 3, increasing levels of FT₃ entered as a continuous variable, were associated with greater mortality, whereas the other hormones did not.
Table 2. Multivariable Prediction of In-hospital Death.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Low T&lt;sub&gt;3&lt;/sub&gt; syndrome</td>
<td>3.9 (1.5–8.0)</td>
<td>.003</td>
<td>4.1 (1.8–9.2)</td>
</tr>
<tr>
<td>Barthel preadmission</td>
<td>—</td>
<td>—</td>
<td>0.97 (0.96–0.99)</td>
</tr>
<tr>
<td>Dementia (yes vs no)</td>
<td>—</td>
<td>0.4 (0.2–1.0)</td>
<td>0.5 (0.2–1.3)</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>—</td>
<td>—</td>
<td>0.5 (0.3–1.1)</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>—</td>
<td>—</td>
<td>1.01 (1.00–1.02)</td>
</tr>
</tbody>
</table>

Notes: Only low T<sub>3</sub> syndrome was entered in Model 1, whereas demographics and clinical variables (age, gender, preadmission Barthel index, diagnosis of dementia, and comorbidity) were entered in Model 2 and laboratory variables (albumin, total cholesterol, blood urea nitrogen, creatinine levels, and lymphocyte count) were entered in Model 3. Backward deletion of redundant variables was applied in Models 2 and 3 (p value for deletion = .1). CI = confidence interval; OR = odds ratio.

Table 3. Predictors of Long-term Mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT&lt;sub&gt;4&lt;/sub&gt;, ng/dL</td>
<td>2.4 (1.2–5.1)</td>
<td>.016</td>
</tr>
<tr>
<td>FT&lt;sub&gt;3&lt;/sub&gt;, ng/dL</td>
<td>1.1 (0.9–1.4)</td>
<td>.247</td>
</tr>
<tr>
<td>TSH, mU/L</td>
<td>0.9 (0.8–1.1)</td>
<td>.485</td>
</tr>
<tr>
<td>Barthel preadmission</td>
<td>0.992 (0.988–0.997)</td>
<td>.003</td>
</tr>
<tr>
<td>Barthel discharge–preadmission</td>
<td>0.994 (0.988–1.000)</td>
<td>.054</td>
</tr>
<tr>
<td>Barthel discharge–admission</td>
<td>0.990 (0.983–0.997)</td>
<td>.008</td>
</tr>
<tr>
<td>ICD9-CM coded diseases, n</td>
<td>1.1 (0.9–1.2)</td>
<td>.369</td>
</tr>
<tr>
<td>GIC Class (III–IV vs I–II)</td>
<td>1.38 (1.02–1.87)</td>
<td>.035</td>
</tr>
<tr>
<td>Dementia (yes vs no)</td>
<td>1.4 (1.0–2.0)</td>
<td>.050</td>
</tr>
<tr>
<td>Drugs at discharge, n</td>
<td>1.1 (1.0–1.2)</td>
<td>.096</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>1.0 (0.7–1.3)</td>
<td>.821</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>1.001 (0.997–1.004)</td>
<td>.619</td>
</tr>
<tr>
<td>Lymphocyte count, /μL</td>
<td>1.000 (1.000–1.000)</td>
<td>.865</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.03 (0.79–1.34)</td>
<td>.832</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>1.003 (0.998–1.008)</td>
<td>.292</td>
</tr>
</tbody>
</table>

Notes: Each predictor was separately entered in a Cox regression model, adjusted for age and gender. GIC = Geriatric Index of Comorbidity; ICD9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; CI = confidence interval; HR = hazard ratio.

Table 4. Multivariable Prediction of Long-term Mortality in 255 Euthyroid Patients Discharged Alive From Hospital.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT&lt;sub&gt;4&lt;/sub&gt;, ng/dL</td>
<td>2.12 (0.99–4.54)</td>
<td>.053</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.05 (1.02–1.07)</td>
<td>.001</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.5 (1.1–2.1)</td>
<td>.008</td>
</tr>
<tr>
<td>Dementia (yes vs no)</td>
<td>1.5 (1.1–2.2)</td>
<td>.016</td>
</tr>
<tr>
<td>Drugs at discharge, n</td>
<td>1.09 (1.00–1.20)</td>
<td>.058</td>
</tr>
</tbody>
</table>

Notes: Preadmission Barthel index, discharge–admission Barthel index, GIC classification (III–IV versus I–II), and use of drugs interfering with thyroid function were entered and backward deleted as redundant variables (p value for deletion = .1). CI = confidence interval; HR = hazard ratio.

Discussion

In this observational study on a cohort of very old, severely ill, hospitalized patients, low T<sub>3</sub> syndrome contributed significantly to predict hospital, but not long-term, mortality, independent of other strong prognosticators. Moreover, in participants with normal thyroid function at baseline, increasing FT<sub>4</sub> levels tended to predict long-term mortality.

Attention has been recently devoted to thyroid hormones as factors modulating health in acute diseases and in old age. As this and other studies (12) show, thyroid dysfunction is very frequent in hospitalized elderly patients and is apparently associated with increased mortality. However, ascertainment of a definite, independent prognostic role of thyroid hormones in older patients is complex because hormonal levels may be frequently altered in the presence of nonthyroidal illness, use of drugs interfering with thyroid function, and nutritional deficiencies in advanced age. Acutely ill older patients typically present with low circulating T<sub>3</sub> and increased reverse T<sub>3</sub> levels. Moreover, when illness is prolonged and severe, pulsatile TSH secretion and circulating T<sub>4</sub> levels are low. This constellation of changes is referred to as the low T<sub>3</sub> syndrome and comprises both peripheral and central alterations in the thyroid axis (20). Low T<sub>3</sub> syndrome has been found in 32%–62% of older hospital patients, in whom it might predict poor short-term survival (11–13). Our findings confirm previous studies on the prevalence and short-term prognostic role of low T<sub>3</sub> syndrome (13), whose presence was associated with a more-than-twofold greater hospital mortality. The association was robust, as it was confirmed after controlling for several variables with proven prognostic value, such as comorbidity, functional status, presence of dementia, renal function, and nutritional status (as represented by albumin level and lymphocyte count). To our knowledge, these covariates had
never been considered in previous studies on low T<sub>1</sub>
syndrome in older hospitalized patients. Our results suggest
that detection of low T<sub>1</sub> syndrome may allow simple, low-
cost, routine identification of subjects at an increased risk of
death among very old hospital patients with complex health
problems, whose prognostic assessment remains challeng-
ing in the setting of acute care internal medicine and
geriatrics departments (21,22). Interestingly, in our models,
hospital mortality was independent of age and gender, vari-
ables that are usually incorporated in most prognostic tools.
This finding contributes to satisfying the need, emphasized
in a recent article (23), for accurate estimation of prog-
nosis in older patients, not based on simple demographic
information.

In contrast with the acute phase, low T<sub>1</sub> syndrome did not
predict mortality in a prolonged follow-up after discharge,
an issue that again, to our knowledge, had never been investi-
gated before. This might represent true inability of the
low T<sub>1</sub> syndrome, detected on admission, to maintain any
prognostic ability in the long term. Alternatively, it could
be hypothesized that such a hormonal alteration in the acute
phase might revert to normal along with recovery from ill-
ness: In this case, derangements observed on admission
cannot be taken as representative of subsequent hormonal
status and of its possible, persisting prognostic value. How
closely thyroid hormone patterns follow the clinical course
of an acute illness is unknown and, therefore, this specula-
tion deserves further investigation.

Data on changes in thyroid function in healthy aging
are extremely contradictory. According to some authors,
TSH concentration decreases in the latest stage of life
(24), whereas it mildly increased in other studies (25). At
any age, TSH secretion is modulated by T<sub>3</sub> levels, but the
responsiveness of the thyroid–pituitary axis in advanced
age is probably different from that in adulthood (26–29); on
the other hand, TSH levels also depend on renal and hepatic
metabolism, which changes with aging. In addition, blunted
circadian secretion pattern and lower peak nocturnal lev-
els may actually contribute to diminished TSH levels in the
elderly (24). TSH increase has been documented both in
a healthy aged population (25) and in ethnic groups with
exceptional longevity (a finding suggesting some underly-
ing genetic factors) (10), whereas TSH levels have been
found to be either elevated or normal in offspring of cen-
tenarians (3,4,6,7). From a clinical standpoint, although a
mildly increased TSH level cannot be assumed as a defi-
nite predictor of prolonged survival (5), it does not per se
represent a diagnostic clue for subclinical hypothyroidism
deserving substitutive treatment that, in fact, does not pro-
vide any real benefit (9,29,30–32).

Secretion of T<sub>4</sub> and T<sub>3</sub> is reduced in healthy aging (24).
Studies of heterogeneous populations suggest that T<sub>3</sub>
levels decline with aging, and FT<sub>3</sub> was found to be lower in
nonagenarians and centenarians (4,6,7), although this has
not been confirmed in other samples (33–35). In spite of
its blunted secretion, serum concentrations of total and
free T<sub>3</sub> remain relatively unchanged (2) or decrease only
minimally with aging (4), perhaps because T<sub>3</sub> degradation
also is reduced in late life (24). Descendants of centenar-
ians and nonagenarians have been shown to have lower FT<sub>3</sub>
levels (4,6,7), which were found to be associated with bet-
ter 4-year survival (2) and physical performance in longitudi-
ナル studies of independently living elderly men (2,36).
Thus, this thyroid hormone pattern might be a marker of
longevity and healthy aging. For each unit increase in FT<sub>3</sub>,
we observed a more-than-twofold greater risk of death in an
average 3-year follow-up duration: Although not fully
statistically significant and obtained in patients recovering
after hospitalization, this finding is consistent with the
hypothesis, mainly derived from population-based studies,
that lower levels of FT<sub>3</sub> are associated with improved
survival in late life. The pathophysiological mechanisms
underlying this association are to be fully elucidated, but
it might be suggested that lower thyroid hormone levels
decrease energy production and requirements, hence free
radical production, thus decreasing oxidative stress and
preventing catabolism (37). Thus, blunted thyroid activity
might represent a biologic component of resilience, ie, the
ability to adapt and self-manage even in the face of inter-
nal and external challenges, which permit oldest, extremely
vulnerable participants to perform, live, function, and reach
a satisfactory level of well-being even without full physical
recovery and comfort (38–39).

This study reports the experience of a single community
hospital in a rural area of Tuscany: As such, it has limitations
that should be recognized. We acknowledge that data were
obtained retrospectively from medical charts and adminis-
trative databases and not from a rigorous, prospective, ad-
hoc data collection. Low T<sub>3</sub> syndrome was detected only on
the basis of TSH and T<sub>3</sub> values, because reverse T<sub>3</sub> data were
not available: This diagnostic approach creates a potential
misclassification between low T<sub>3</sub> syndrome and pituitary
hypothyroidism, a condition that is nevertheless extremely
rare in the elderly. Besides reverse T<sub>3</sub>, other potentially
important clinical data, including body mass index, were
missing in a substantial share of the sample and could
not, therefore, be included in our analyses. As previously
acknowledged, hormonal data were available in the whole
sample only on hospital admission and were not systemati-
cally repeated in the following course. Finally, our findings
may be poorly generalizable to other social contexts.

In conclusion, this study gives support to the independ-
ent prognostic short-term, but not long-term, role of low T<sub>3</sub>
syndrome in very old patients, admitted to hospital because
of an acute condition. Further studies need to be conducted
to understand whether low T<sub>3</sub> syndrome follows the clinical
course of the disease and, therefore, can be used to monitor
changing general health status. Finally, in older euthyroid
participants, FT<sub>3</sub> seems to be a weak marker of poorer long-
term survival.
REFERENCES