Low T3 syndrome upon admission and response to nutritional support in malnourished medical inpatients

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Abstract

Introduction: During illness, deiodination of thyroxine (T4) to triiodothyronine (T3) is down regulated. This is called “low T3 syndrome”, an adaptive metabolic mechanism to reduce energy expenditure and prevent catabolism. We investigated the prognostic role of low T3 syndrome in patients at nutritional risk regarding mortality, clinical outcomes and response to nutritional support.

Methods: This is a secondary analysis of the *Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial* (EFFORT), a randomized-controlled Swiss multicenter trial comparing effects of individualized nutritional support with usual care in adult medical inpatients at nutritional risk. The primary endpoint was all-cause mortality over 30-,180-days and 5-years.

Results: We had complete data including fT3 concentration of 801/2028 (39.5%) patients from the initial trial. Of these 492 (61.4%) had low T3 syndrome (fT3 <3.2 pmol/l). Low T3 syndrome was associated with higher mortality over 30 days (adjusted hazard ratio 1.97 [95%CI 1.17 to 3.31], p 0.011) and other adverse clinical outcomes. Nutritional support only lowered mortality in the group of patients with but not in those without low T3 syndrome (adjusted odds ratio of nutritional support of 0.82 [95%CI 0.47 to 1.41] vs. 1.47 [95%CI 0.55 to 3.94]). This finding, however, was not significant in interaction analysis (p for interaction = 0.401).

Conclusions: Our secondary analysis of a randomized trial suggests that medical inpatients at nutritional risk with low T3 syndrome have a substantial increase in mortality and may show a more pronounced beneficial response to nutritional support interventions.

Introduction

Low T3 syndrome, also known as “Euthyroid sick syndrome” or “Non thyroidal illness syndrome”, is an adaptive metabolic reaction to acute and chronic illness, fasting and starvation intending to reduce energy expenditure and thus prevent catabolism (1-4). This syndrome is defined as an isolated decrease of triiodothyronine (T3) below the lower laboratory reference value, in the absence of a preexisting thyroid disease, whilst thyroid-stimulating-hormone (TSH) and thyroxine (T4) remain within the normal reference range (or decrease also in case of persistence of critically illness over a longer time) (5,6). Several mechanisms contribute to the lowering of T3 during illness including changes in thyrotropin-releasing-hormone (TRH) secretion, in thyroid hormone binding protein and transporter concentrations, in thyroid hormone deiodinases activity and expression, and in thyroid hormone receptor expression (5). While there is extensive research looking at intensive care patients and patients with infections (3,7,8), with cardiovascular disease (9-12) and chronic kidney disease patients (13-16), there is little clinical investigation looking at the role of the low T3 syndrome in malnourished patients receiving nutritional support.

Disease-related malnutrition (DRM) is a growing health concern especially in but not limited to elderly polymorbid patients leading to protein catabolism and negative impact on clinical outcome and mortality (17). Recent data have shown that individualized nutritional support is an effective and cost-efficient intervention to lower the risk of adverse clinical outcome including mortality among medical patients at nutritional risk (18,19). However, there is data suggesting that not all DRM patients show the same treatment response. For example, patients with high metabolic stress and high inflammation did not show a strong response to nutritional support (20,21), while patients with advanced kidney failure (22) and impaired muscle strength (23) showed a more favorable response. A better understanding of a patients DRM phenotype thus may allow an individualized and personalized approach.

Herein, we investigated the prevalence of prognostic implications of the low T3 syndrome regarding mortality rate, clinical outcomes and response to nutritional support among malnourished medical inpatients included in a previous randomized-controlled nutritional trial (18).

Material and Methods

Study design and Setting

This is a secondary analysis of the *"Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients"-Trial (EFFORT)*, a pragmatic, investor-initiated, open-label and randomized controlled trial conducted in eight Swiss medical centers (18,24). In the original trial, the effect of individualized nutritional support was compared to usual care in adult medical inpatients at nutritional risk regarding the incidence of adverse clinical outcomes after 30 days and other clinical endpoints. The protocol and the main results as well as long-term-follow-up of different secondary analyses have been published previously (18-30). The Ethics Committee of Northwest/Central Switzerland approved the study protocol in January 2014 (EKNZ; 2014_001). Additional information about coinvestigators of the initial trial, and outcome definitions are presented in the **supplemental material** (31).

Patient population

For this secondary analysis, we included all patients of the original trial with available free serum triiodothyronine (fT3) measurement at time of admission to hospital care. Inclusion criteria were age older than 18 years, risk for malnutrition defined by three or more points in the Nutritional Risk Screening 2002 (NRS-2002) score, expected length of hospital stay of more than four days and informed consent within 48h after admission. Patients were excluded, if they were initially admitted to the intensive care unit or to surgical units, unable to ingest oral nutrition, already were under nutritional support, had a terminal condition, suffered from anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis or stem-cell transplantation, had a gastric bypass

surgery, and if they had contraindications for nutritional support or were previously included into the trial (18).

Assessment of nutritional status and nutritional intervention

To identify patients at nutritional risk, the NRS-2002 score, a validated tool to determine risk of malnutrition, was used (32). The NRS-2002 score is composed of nutritional status (based on weight loss, body mass index (BMI), and food intake; scoring 0-3 points); disease severity (0-3 points) and age over 70 years, scoring one extra point; a higher score indicating a higher risk for malnutrition. A score ≥ 3 points classifies patients as “nutritionally at risk” or “malnourished”. After providing informed consent, patients were randomized (1:1) either into the intervention or the control group. The intervention group received personalized nutritional support, supervised by a trained dietitian with an individual nutritional plan composed after individually calculated energy and protein intake goals, within 48 hours after hospital admission. To reach at least 75% in protein and energy goals was the aim of the individual nutritional support. Energy goals were predicted using weight-adjusted Harris-Benedict equation. The protein intake goal to be reached was defined as 1.2 – 1.5 grams per kilogram of bodyweight (g/kg) per day, with lower targets for patients with acute renal failure (0.8 g/kg). The individual plan based on oral nutrition and oral supplements. If less than 75% of the daily energy and protein target goals were achieved after 5 days of nutritional support, the nutritional support was escalated to enteral or parenteral feeding. The control group received standard hospital food without any nutritional support.

Definition of low T3 syndrome

The definition of low T3 syndrome was based on admission fT3 concentration because we did not have information on other thyroid hormone concentration. Specifically, during the initial trial, one study center systematically collected blood samples for measurement of additional blood markers including fT3, but not TSH or fT4. Based on the admission serum fT3 concentration, we

stratified patients into two population, i.e., patients with and without low T3 syndrome using the recommended cut off of 3.2 pmol/l (lower laboratory reference limit of the used immunoassay kit [Siemens, Cat# K6416, RRID:AB_2924986]). There was no patient with an fT3 concentration higher than the upper reference laboratory level. As our definition of low T3 syndrome was based on fT3 concentration only, we also performed a sensitivity analysis excluding any patient with intake of medicaments possibly affecting thyroid hormones (e.g., levothyroxine, amiodarone, lithium, or thyreostatic agents), and patients with possible or proved thyroid disease in the past medical history.

Outcomes

The primary endpoint was mortality over 30 days, 180 days and 5 years. Secondary outcomes were adverse clinical outcomes, length of hospital stay (LOS), loss of function (defined by 10% decrease in Barthel index; scale range from 0-100 with a higher score indicating more ability with self-care and mobility), nutritional outcomes, and handgrip strength (HGS). More detailed definitions of outcomes are presented in the **supplemental material** (31)**.** Blinded study nurses performed the outcome assessment through a structured telephone interview at day 30, 180 and 5 years after trial inclusion of the patient.

Statistical Analysis

Continuous variables are expressed as mean and standard deviation or median and interquartile range, binary and categorical variables as number or count and percentages. To compare the baseline characteristics between the intervention and the control group two-sample-t-test was used for the continuous variables, while for binary and categorical variables Pearson's Chi-squared-test was performed. To investigate the association of low T3 syndrome and patient baseline characteristics, we calculated uni- and multivariate linear regression models; results are reported as coefficient (95% confidence interval [95% CI]). For laboratory

and anthropometric parameters, we calculated the spearman correlation coefficient and visualized its association with fT3 concentration in a scatterplot. Hazard ratio (HR) was calculated for all (30- and 180-day and 5-year) mortality endpoints. To assess the association between low T3 syndrome and the secondary clinical outcomes, we calculated logistic and linear regression models, reported as odds ratio (OR), and coefficient, respectively. Data was adjusted for age, sex, nutritional status (NRS-2002 score), metabolic diagnosis, comorbidities (cancer, renal insufficiency, congestive heart failure, diabetes mellitus, coronary disease and chronic obstructive pulmonary disease [COPD]), intervention, and study center. Kaplan-Meier estimates was used for the graphical display of the probability of all-cause of mortality within 5 years. Finally, we investigated the effect of nutritional support on 30-, 180-day and 5-year mortality and all secondary outcomes stratifying by low T3 syndrome. We used the intention-to-treat principle in all our analyses.

STATA 15.0 (StataCorp) was used to perform all statistical analysis. P-values < 0.05 were considered to indicate statistical significance.

Results

Patient population

We included 801 of 2028 (39.5%) patients with full data from the original trial. A total of 61.4% (492/801) patients met the definition of low T3 syndrome (**Figure 1**).

Baseline characteristics, stratified by low T3 syndrome are shown in **Table 1**. Overall, the mean age was 73.3 (± 13.0) years, and 46.7% were female. Infectious diseases were the most common admission diagnosis (26.8%), followed by cancer (23.2%), and cardiovascular disease (11.9%).

In patients with and without low T3 syndrome, mean (± SD) serum fT3 was 2.4 (± 0.5) and 3.9 (± 0.8) pmol/l. There were also differences in the two groups regarding age, nutritional risk,

handgrip strength and admission laboratory parameters, including CRP and albumin concentrations and glomerular filtration rate (GFR).

Association of baseline characteristics with fT3 concentration

In a second step, we investigated the association of different baseline characteristics with fT3 concentration in uni- and multivariate linear regression models, respectively (**Table 2**). Several admission diagnoses and comorbidities (e.g., infectious disease, renal disease) were associated with lower admission serum fT3 concentration. Higher CRP was also associated with lower serum fT3. In addition, loss of appetite was associated with low fT3 concentration too. Correlation of fT3 concentration with CRP, GFR, and albumin as well as anthropometric parameters are visualized in (**Supplemental Figure 1 and 2**) (31).

Association of low T3 syndrome with clinical outcomes

In a third step, we assessed the association of low T3 syndrome with mortality rates and other clinical outcomes (**Table 3**). Patients with low T3 syndrome had an almost twofold higher probability to die within 30-days compared to those with normal fT3 (adjusted HR 1.97 [1.17 to 3.31]; p = 0.011). Results were consistent also for longer-term mortality at 180 days and 5 years (adjusted HR 1.39 [1.04 to 1.85]; p=0.025 and 1.26 [1.03 to 1.53]; p=0.023, respectively). **Figure 2** visualizes the survival probability over 5 years among the two populations.

Additionally, the low T3 syndrome was associated with some other secondary outcomes including decline in functional capacity measured by a 10% decrease of Barthel Index (17.3% vs. 10.4%, adjusted OR 1.66 [1.06 to 2.60], p = 0.028), and lower handgrip strength (HGS), (22.4 vs. 24.9 kg, adjusted coefficient -2.42 [-3.66 to -1.19] kg; p-value < 0.001). Regarding nutritional outcomes, patients with low T3 syndrome had both, a lower mean caloric intake (1225.3 [± 606.9] vs. 1309.4 [± 650.9] kcal, adjusted coefficient -77.54 (-166.69 to 11.60) kcal; p

= 0.088) and a lower mean protein intake (49.9 [± 24.2] vs. 53.8 [± 25.8] g, adjusted coefficient -3.79 (-7.41 to -0.18) g; p = 0.04) per day.

Association of low T3 syndrome with response to nutritional support

Finally, we compared the effect of nutritional support on mortality and other outcomes among patients with and without the low T3 syndrome (**Figure 3**). Overall, compared to patients without low T3 syndrome, the effect of nutritional treatment on 30-day mortality was more pronounced in patients with low T3 syndrome (adjusted OR 1.47 [95%CI 0.55 to 3.94] vs. 0.82 [95%CI 0.47 to 1.41]), without a significant result in the interaction analysis (p for interaction 0.401) (**Figure 3**). In the subgroup analysis we found that gender as well as CRP concentration importantly influenced the association of low T3 syndrome and mortality.

We also repeated the analysis for other endpoints including adverse clinical outcome and decline in functional status, where similar results were found (**Supplemental Table 2 and Supplemental Figure 3**) (31).

Sensitivity analysis

In a sensitivity analysis, we repeated the above analyses in the population after excluding any patient with intake of medicaments possibly affecting thyroid hormones or preexisting thyroid disease (**Supplemental Figure 4**) (31). Thereby, results were robust for the most part, particularly when regarding the prognostic value of low T3 syndrome, clinical outcomes, and treatment response to nutritional intervention (**Supplemental Tables 3 to 6**) (31).

Discussion

This secondary analysis of a large multicenter nutritional trial has three key findings: First, we found the low T3 syndrome to be very prevalent in medical inpatients at nutritional risk outside of the critically ill setting. Second, low T3 syndrome was associated with short- and long-term

mortality with a twofold increase in the risk of dying compared to patients without low T3 syndrome. Third, nutritional support tended to lower mortality only in the group of patients with a low T3 syndrome but not in patients with normal fT3 concentration. Latter trend, however, was not significant in interaction analysis.

In our cohort of patients at nutritional risk, the prevalence of low T3 syndrome was 61% which is consistent to other observational studies looking at patients in the ICU setting (33), but higher to patients in non-ICU settings, where prevalences around 40% were previously reported (34). However, to our knowledge, this is the first large-scale study looking specifically at the population of patients at nutritional risk where low T3 syndrome may play an important pathophysiological role. In fact, from a pathophysiological view, it is interesting that even though low T3 syndrome is supposed to be a natural mechanism to protect the body against catabolism, fT3 concentration was not significantly associated with the degree of malnutrition as assessed by NRS in our dataset. However, we did not have a control group without malnutrition risk in our cohort. Previous research looking at acute heart failure patients in the ICU found lower fT3 concentration to be associated with degree of malnutrition assessed by the prognostic nutritional index (PNI) (11).

It is well known that low thyroid hormone concentration is associated with mortality and other clinical outcomes among different patient populations (1,7,8,34,35). This association may not be explained by direct effect of low T3 hormone only but rather be confounded by severity of illness and high comorbidity burden. Also, in our analysis we found a significant association between presence of low T3 syndrome upon admission and mortality at short- and long-term. Indeed, patients with a low T3 syndrome had an almost twofold higher 30-day mortality risk. However, adjustment for important confounders such as age, sex, nutritional risk, main diagnosis, and comorbidities did not alter these association significantly. Consequently, our data confirms a

strong and independent prognostic value of low T3 syndrome at time of admission to predict short- and long-term mortality risk, and thus measurement of fT3 concentration may help to detect a population of patients that is particularly vulnerable and at risk for worse clinical outcomes and thus needs further attention.

Importantly, to our knowledge, this is the first study looking at the prognostic value of low T3 syndrome regarding treatment response in malnourished patients. Here, our secondary analysis of a randomized trial suggested that medical inpatients at nutritional risk with low T3 syndrome had a more pronounced beneficial response to nutritional support with odds ratios regarding mortality ranging from 0.82 in patients with low T3 syndrome and 1.47 in patients without low T3 syndrome. However, interaction analysis did not prove a significant result which may be due to the smaller sample size as only a part of the patients from the initial trial were included in this analysis. This finding is interesting for several reasons. First, low T3 syndrome was also associated with lower appetite and lower caloric and protein intake, and nutritional support may particularly help this specific group of patients. Second, low T3 syndrome may be a biological mechanism for prevention of catabolism in illness through a reduction of energy expenditure, and reduction in resting energy turnover rate. This leads to a reduction in energy and protein requirements and thus even small increases in intake may help to reach nutritional goals. Third, fT3 concentration correlated inversely with CRP concentration and previous research found highly inflamed patients (CRP >100mg/l) to have less benefit of nutritional support compared to patients with lower levels of inflammation (20). In line with this, our subgroup analysis showed a pronounced mortality benefit of low T3 syndrome patients particularly in those with CRP below 100 mg/l. Additionally, a previous study found that patients with reduced kidney function had a more pronounced benefit from nutritional support (22). Our subgroup analysis was in line with this result and found no difference in the response to nutritional support intervention for the low T3 syndrome in patients according to the kidney function. Also, albumin was not associated with

treatment response in a previous study (26). Interestingly, the predictive value of the low T3 syndrome in our study was most pronounced in patients with albumin values >30 g/l. Regarding albumin as a negative acute phase protein, with lower values indicating a higher burden of inflammation, this result is in line with the more pronounced effect of nutritional support in patients with lower CRP concentration and thus suggesting that inflammation is an important factor to influence the response to nutritional support.

This report has strengths and limitations. Herein we present the first study to investigate the effect of low admission serum fT3 concentration in a heterogenous medical inpatient population being at nutritional risk. Furthermore, until now, there has been no data from a large randomized controlled trial on the role of low T3 syndrome on nutritional treatment response. However, we only included a subgroup from the initial trial from mainly one center with available fT3 concentration, lowering the power of our analysis and reducing external validity. In comparison to the original trial, in our cohort mean age was slightly higher and more patients were severely malnourished. However, in our subgroup analyses, there was no signal for different response to nutritional support according to age and degree of malnutrition. Additionally, the main analysis of this work was based on isolated serum fT3 concentration without considering the remaining thyroid hormones or the presences of any known thyroid diseases nor any medication interfering with thyroid hormone metabolism. Therefore, we conducted the sensitivity analysis, which showed similar results as the main analysis of this work, however due to the small sample size, results presented no longer to be statistically significant.

Conclusion

Our secondary analysis of a randomized trial suggests that medical inpatients at nutritional risk with low T3 syndrome have an important increase in mortality and adverse outcomes, and may show a more pronounced beneficial response to nutritional support intervention.

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Data availability

Our analyzed data will be available to others with the publication of this manuscript on receipt of a letter of intention detailing the study hypothesis and statistical analysis plan, as already outlined in the primary EFFORT publication. Signing a data access agreement is asked from all applicants. Please send any request to the principal investigator of this trial.

Declaration of interests

The following Drs. received grants outside of this submitted trial and outside of the original EFFORT trial: Dr. Schuetz reports grants from Nestlé Health Science and Abbott Nutrition, Dr. Stanga reports grants from Nestlé Health Science and Abbott Nutrition and personal fees from Nestlé Health Science and Fresenius Kabi. All other authors declare no conflicts of interest.

Contributors / Coauthors

Natasha Anouschka Müller, Nina Kaegi-Braun, and Philipp Schuetz were responsible for the design, statistical data analysis and interpretation of results as well as drafting the final manuscript and implementing critical revisions into the manuscript. Further, Beat Mueller, Zeno Stanga, Pascal Tribolet, Carla Gressies and Mirsada Durmisi were involved in the design and concept of this analysis. All authors read and approved the final version of the manuscript. Drs. Schuetz, Stanga, and Mueller obtained the funding for the study. All authors approved the final version of this manuscript and confirmed, that they had full access to all the data in this secondary analysis. All authors accept responsibility for the decision to submit for publication.

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Legends

Legend for Figure 1:

Figure 1 Study Flow Chart

Abbreviation: IC, informed consent, fT3, free triiodothyronine; T3, triiodothyronine

[a] Reasons for exclusion: 145 surgical patients, 268 unable to ingest oral nutrition, 158 terminal condition, 719 already receiving nutritional therapy upon admission, 31 anorexia nervosa, 161 acute pancreatitis, 81 acute liver failure, 6 cystic fibrosis, 11 stem-cell transplantation, 27 malnutrition after gastric bypass operation, 43 contraindication against nutritional support, 228 earlier inclusion in the trial

Legend for Figure 2:

Figure 2 Survival probability over 5 years stratified by patients with and without low T3 syndrome

Abbreviation: Low-T3S, low T3 syndrome; HR; hazard ratio; 95% CI, 95% confidence interval

* adjusted for age, sex, NRS, metabolic diagnosis, comorbidities, intervention and centre

Legend for Figure 3:

Figure 3 Response to nutritional support on 30-day mortality overall, stratified by patients with and without low T3 syndrome and divided into various subgroups; data is presented in a logarithmic scale.

Abbreviations: Low-T3S, low T3 syndrome; OR, odds ratio; 95% CI, 95% confidence interval; NRS, nutritional risk scale 2002 score; CRP, C-reactive proteine; GFR, Glomerular Filtration Rate

[a] adjusted for age, sex, NRS, metabolic diagnosis, 6 comorbidities, intervention and centre

Legend for Table 1:

The two-sample-t-test was used to compare the baseline characteristics between patients with and without low T3 syndrome for the continuous variables and Pearson's Chi-squared-test for binary and categorical variables. Data are expressed as number (%) unless otherwise indicated.

Abbreviations: fT3, free triiodothyronine; Low-T3S, low T3 syndrome; n, number; BMI, Body Mass Index; NRS 2002 score, Nutritional Risk Screening 2002 score; CRP, C-reactive proteine; GFR, Glomerular Filtration Rate

[a] Metabolic disease included, but was not limited to, ketoacidosis, hypo- and hyperglycemia and electrolyte disturbances including hypo- and hypernatriaemia, as well as hypo- and hyperkaliemia.

[b] Type 1 or type 2

Legend for Table 2:

Univariate and multivariate linear regression analysis to identify predictors of low fT3 concentration upon admission to hospital care. Values are mean (SD), and regression coefficients (95% CI) in pmol/l. The coefficient indicates the decrease or increase of fT3 concentration in patients presenting with the characteristic compared to patients without the characteristic.

Abbreviations: fT3, free triiodothyronine; SD, standard deviation; 95% CI, 95% confidence interval; NRS 2002 score, Nutritional Risk Screening 2002 score

[a] Metabolic disease included, but was not limited to, ketoacidosis, hypo- and hyperglycemia and electrolyte disturbances including hypo- and hypernatriaemia, as well as hypo- and hyperkaliemia.

Legend for Table 3:

Multivariable logistic regression models reporting hazard or odds ratios according to presence of low T3 syndrome. Continuous variables were assessed through linear regression models, results are expressed as coefficients (marked with *).

Abbreviations: Low-T3S, low T3 syndrome; n, number: SD, standard deviation; 95% CI, 95 confidence interval; HR, hazard ratio; OR, odds ratio; kg, kilograms; kcal/d, calories per day; g/d, grams per day

[a] adjusted for age, sex, NRS, metabolic diagnosis, comorbidities, intervention and centre

[b] Loss of function defined as 10% decrease in Barthel index

[c] until day 10 of hospitalization

1 **Tables**

Table 1 Baseline characteristics overall and stratified by low T3 syndrome

	overall	without Low-T3S	with Low-T3S	p-value
n (%)	801	309 (38.6)	492 (61.4)	
Sociodemographic factors				
Age, mean (SD), years	73.3 (13.0)	71.5 (14.1)	74.5 (12.2)	**0.001**
Male sex	427 (53.3)	149 (48.2)	278 (56.5)	**0.022**
Nutritional assessment				
BMI, mean (SD), kg/m^2	24.8 (5.2)	25.1 (5.3)	24.7 (5.1)	0.33
Weight, mean (SD), kg	71.2 (16.0)	72.2 (17.0)	70.6 (15.2)	0.22
Height, mean (SD), cm	167.7 (9.1)	167.8 (9.4)	167.7 (8.9)	0.86
Handgrip strength, mean (SD), kg	23.4 (10.7)	24.9 (11.4)	22.4 (10.2)	**0.003**
NRS 2002 score				
3 points	221 (27.6)	95 (30.7)	126 (25.6)	**0.031**
4 points	308 (38.5)	126 (40.8)	182 (37.0)	
≥ 5 points	272 (34.0)	88 (28.5)	184 (37.4)	
Admission main diagnosis				
Infectious disease	215 (26.8)	66 (21.4)	149 (30.3)	**0.006**
Cancer disease	186 (23.2)	78 (25.2)	108 (22.0)	0.28
Cardiovascular disease	95 (11.9)	50 (16.2)	45 (9.1)	**0.003**
Frailty	57 (7.1)	29 (9.4)	28 (5.7)	**0.048**
Gastrointestinal disease	61 (7.6)	15 (4.9)	46 (9.3)	**0.02**
Metabolic disease [a]	32 (4.0)	13 (4.2)	19 (3.9)	0.81
Comorbidities				
Hypertension	478 (59.7)	182 (58.9)	296 (60.2)	0.72
Malignant disease	298 (37.2)	111 (35.9)	187 (38.0)	0.55
Chronic kidney disease	288 (36.0)	94 (30.4)	194 (39.4)	**0.01**
Coronary heart disease	192 (24.0)	69 (22.3)	123 (25.0)	0.39
Diabetes mellitus [b]	190 (23.7)	63 (20.4)	127 (25.8)	0.079
Congestive heart failure	150 (18.7)	58 (18.8)	92 (18.7)	0.98
Chronic obstructive pulmonary disease	106 (13.2)	41 (13.3)	65 (13.2)	0.98
Peripheral arterial disease	81 (10.1)	23 (7.4)	58 (11.8)	**0.047**
Laboratory parameter at admission				
fT3, mean (SD), pmol/l	3.0 (1.0)	3.9 (0.8)	2.4 (0.5)	**<0.001**
CRP, mean (SD), mg/l	74.2 (78.9)	52.6 (63.2)	87.8 (84.6)	**<0.001**
GFR, mean (SD), ml/min	35.5 (16.2)	39.7 (15.1)	33.4 (16.4)	**<0.001**
Albumin, mean (SD), g/l	27.7 (5.7)	30.2 (5.2)	26.1 (5.5)	**<0.001**

The two-sample-t-test was used to compare the baseline characteristics between patients with and without low T3 syndrome for the continuous variables and Pearson's Chi-squared-test for binary and categorical variables. Data are expressed as number (%) unless otherwise indicated.

Abbreviations: fT3, free triiodothyronine; Low-T3S, low T3 syndrome; n, number; BMI, Body Mass Index; NRS 2002 score, Nutritional Risk Screening 2002 score; CRP, C-reactive proteine; GFR, Glomerular Filtration Rate

[a] Metabolic disease included, but was not limited to, ketoacidosis, hypo- and hyperglycemia and electrolyte disturbances including hypo- and hypernatriaemia, as well as hypo- and hyperkaliemia.

[b] Type 1 or type 2

Table 2 Association of different baseline characteristics with fT3 concentration

Baseline characteristic	Patients without characteristic fT3, mean (SD)	Patients with characteristic fT3, mean (SD)	univariate Coefficient (95% CI)	p-value	multivariate Coefficient (95% CI)	p-value
Sociodemographic factors						
Age ≥ 75 years	3.07 (1.00)	2.92 (0.96)	-0.16 (-0.29 to -0.02)	**0.026**	-0.12 (-0.27 to 0.02)	0.093
Male (vs. Female)	3.06 (0.97)	2.93 (0.99)	-0.13 (-0.26 to 0.01)	0.071	-0.13 (-0.26 to 0.01)	0.067
Nutritional status						
NRS 2002 Score						
3 points	-	3.04 (0.88)	Reference	-	Reference	-
4 points	-	3.05 (1.01)	0.01 (-0.16 to 0.18)	0.917	0.02 (-0.15 to 0.19)	0.825
≥ 5 points	-	2.89 (1.03)	-0.15 (-0.32 to 0.02)	0.093	-0.10 (-0.28 to 0.08)	0.272
Loss of appetite	3.24 (1.03)	2.96 (0.97)	-0.28 (-0.50 to -0.07)	**0.01**	-0.24 (-0.45 to -0.02)	**0.031**
Main diagnosis						
Cancer disease	2.97 (1.00)	3.05 (0.91)	0.08 (-0.08 to 0.25)	0.307	0.03 (-0.21 to 0.27)	0.808
Cardiovascular disease	2.96 (0.98)	3.20 (0.96)	0.24 (0.03 to 0.45)	**0.027**	0.21 (-0.04 to 0.46)	0.103
Infectious disease	3.06 (1.03)	2.80 (0.81)	-0.26 (-0.41 to -0.10)	**0.001**	-0.22 (-0.42 to -0.02)	**0.033**
Frailty	2.97 (0.99)	3.19 (0.83)	0.21 (-0.05 to 0.48)	0.118	0.11 (-0.18 to 0.41)	0.459
Gastrointestinal disease	3.00 (0.96)	2.85 (1.21)	-0.15 (-0.41 to 0.10)	0.244	-0.24 (-0.53 to 0.04)	0.096
Metabolic disease [a]	2.99 (0.98)	2.94 (0.96)	-0.05 (-0.40 to 0.30)	0.784	-0.05 (-0.42 to 0.32)	0.802
Main Comorbidities						
Hypertension	3.06 (0.99)	2.94 (0.98)	-0.11 (-0.25 to 0.03)	0.117	-0.07 (-0.21 to 0.08)	0.361
Malignant disease	3.01 (1.02)	2.95 (0.92)	-0.06 (-0.20 to 0.08)	0.391	-0.10 (-0.27 to 0.07)	0.248
Chronic renal disease	3.06 (0.98)	2.87 (0.98)	-0.19 (-0.33 to -0.05)	**0.008**	-0.15 (-0.31 to -0.004)	**0.044**

Univariate and multivariate linear regression analysis to identify predictors of low fT3 concentration upon admission to hospital care. Values are mean (SD), and regression coefficients (95% CI) in pmol/l. The coefficient indicates the decrease or increase of fT3 concentration in patients presenting with the characteristic compared to patients without the characteristic.

Abbreviations: fT3, free triiodothyronine; SD, standard deviation; 95% CI, 95% confidence interval; NRS 2002 score, Nutritional Risk Screening 2002 score

[a] Metabolic disease included, but was not limited to, ketoacidosis, hypo- and hyperglycemia and electrolyte disturbances including hypo- and hypernatriaemia, as well as hypo- and hyperkaliemia.

Table 3 Prognostic value of low T3 syndrome on mortality rate and other secondary clinical and nutritional outcomes

Short- and long-term mortality					
	n (%)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
30-day mortality					
without Low-T3S	19/309 (6.2)	reference		reference	
with Low-T3S	64/492 (13.0)	2.21 (1.32 to 3.68)	**0.002**	1.97 (1.17 to 3.31)	**0.011**
180-day mortality					
without Low-T3S	69/309 (22.3)	reference		reference	
with Low-T3S	154/492 (31.3)	1.52 (1.15 to 2.02)	**0.004**	1.39 (1.04 to 1.85)	**0.025**
5-year mortality					
without Low-T3S	156/291 (53.6)	reference		reference	
with Low-T3S	296/469 (63.1)	1.36 (1.12 to 1.65)	**0.002**	1.26 (1.03 to 1.53)	**0.023**
Secondary clinical outcomes	**n (%) or mean (SD)**	**OR / Coefficient* (95% CI)**	**p-value**	**OR / Coefficient* (95% CI)**	**p-value**
Adverse clinical outcomes					
without Low-T3S	73/309 (23.6)	reference		reference	
with Low-T3S	144/492 (29.3)	1.34 (0.97 to 1.85)	0.081	1.27 (0.91 to 1.78)	0.164
Length of hospital stay, days					
without Low-T3S	9.0 (6.3)	reference		reference	
with Low-T3S	9.7 (6.7)	0.74* (-0.19 to 1.67)	0.118	0.54* (-0.41 to 1.49)	0.262
Loss of function [b]					
without Low-T3S	32/309 (10.4)	reference		reference	
with Low-T3S	85/492 (17.3)	1.81 (1.17 to 2.79)	**0.008**	1.66 (1.06 to 2.60)	**0.028**
Handgrip strength, kg					
without Low-T3S	25.6 (11.3)	reference		reference	
with Low-T3S	22.3 (9.8)	-3.26* (-6.13 to -0.38)	**0.027**	-3.47* (-5.6 to -1.33)	**0.002**
Secondary nutritional outcomes	**n (%) or mean (SD)**	**OR / Coefficient* (95% CI)**	**p-value**	**OR / Coefficient* (95% CI)**	**p-value**
Mean caloric intake per day, kcal/d [c]					
without Low-T3S	1309.4 (650.9)	reference		reference	
with Low-T3S	1225.3 (606.9)	-84.12* (-175.63 to 7.38)	0.072	-77.54* (-166.69 to 11.60)	0.088
Mean protein intake per day, g/d [c]					
without Low-T3S	53.8 (25.8)	reference		reference	
with Low-T3S	49.9 (24.2)	-3.89* (-7.61 to -0.18)	**0.04**	-3.79* (-7.41 to -0.18)	**0.04**
Reaching caloric-intake goals					
without Low-T3S	201/266 (75.6)	reference		reference	
with Low-T3S	290/412 (70.4)	0.77 (0.54 to 1.09)	0.141	0.73 (0.50 to 1.08)	0.117
Reaching protein-intake goals					
without Low-T3S	187/243 (77.0)	reference		reference	
with Low-T3S	310/396 (78.3)	1.08 (0.74 to 1.58)	0.695	1.01 (0.66 to 1.52)	0.979

Multivariable logistic regression models reporting hazard or odds ratios according to presence of low T3 syndrome. Continuous variables were assessed
through linear regression models, results are expressed as coefficient (marked with *).
Abbreviations: Low-T3S, low T3 syndrome; n, number: SD, standard deviation; 95% CI, 95% confidence interval; HR, hazard ratio; OR, odds ratio;
kg, kilograms; kcal/d, calories per day; g/d, grams per day
[a] adjusted for age, sex, NRS, metabolic diagnosis, comorbidities, intervention and centre
[b] Loss of function definded as 10% decrease in Barthel index
[c] until day 10 of hospitalisation

1

2

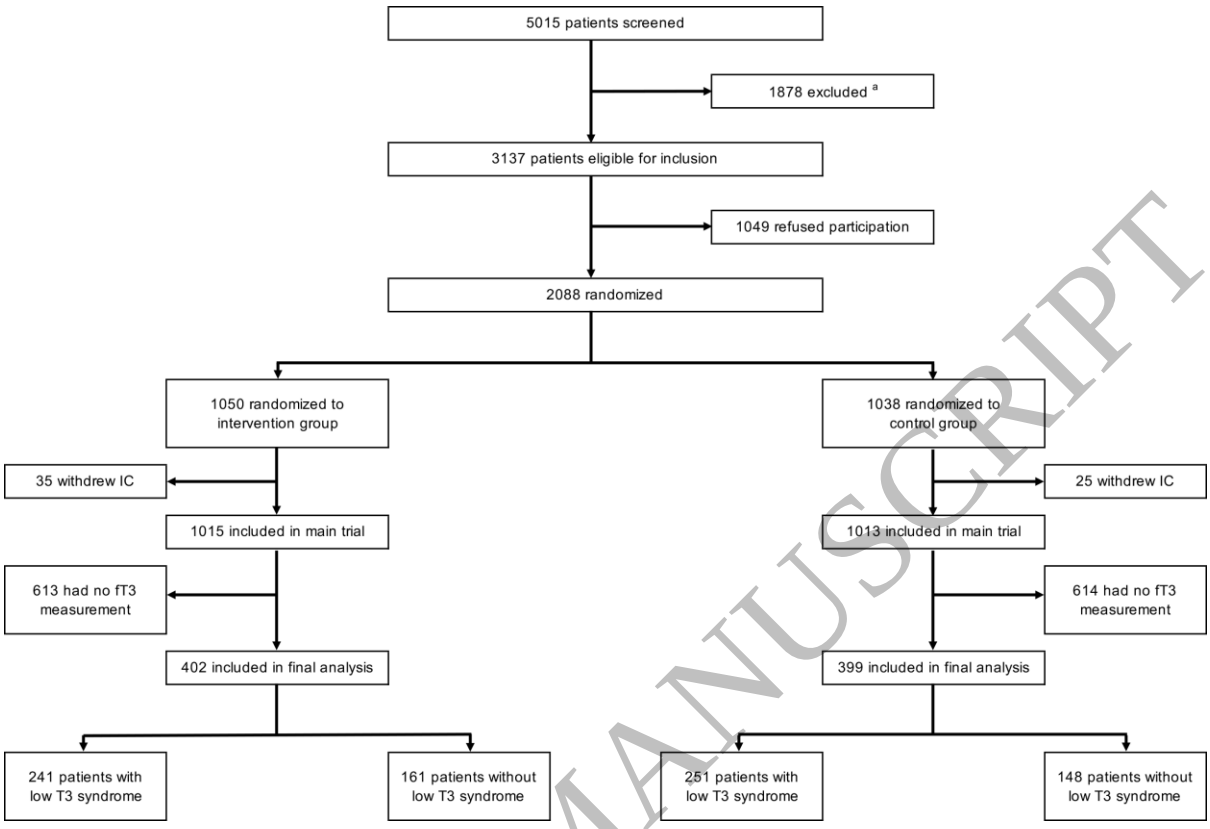

Figure 1
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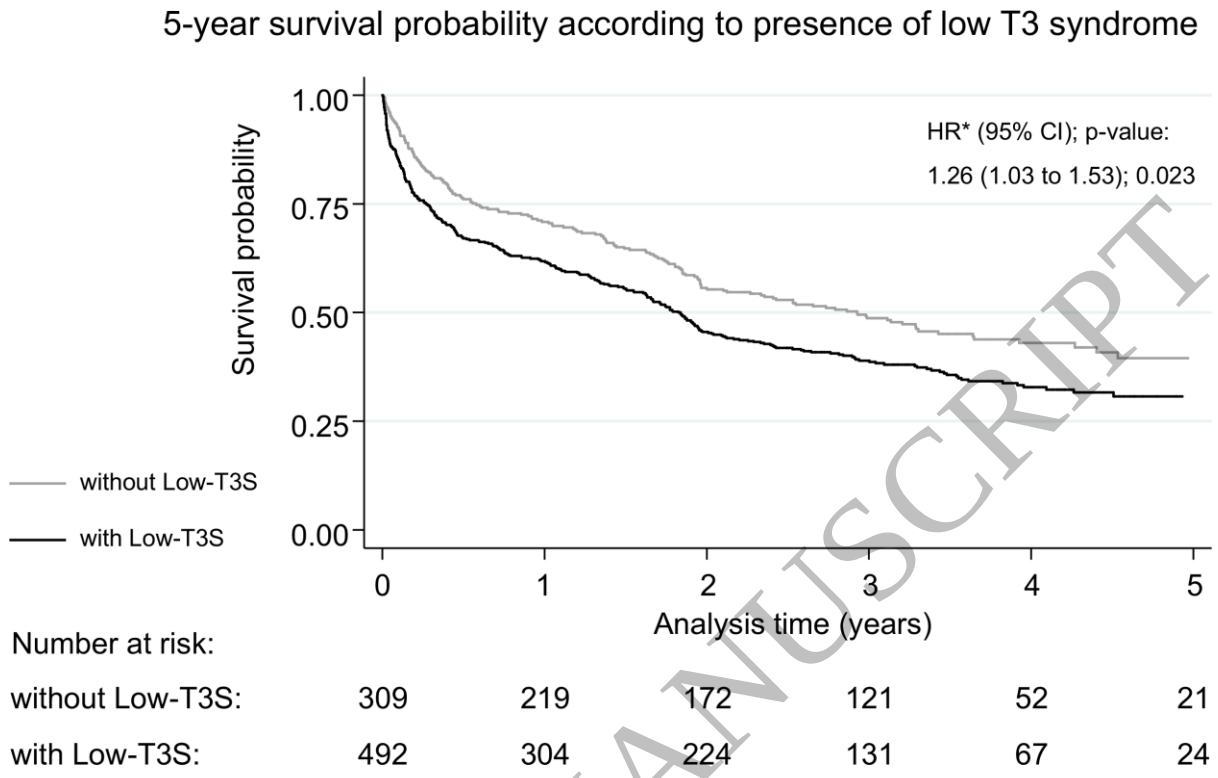

Figure 2
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30-DAY MORTALITY	No nutritional support events (%)	Nutritional support events (%)	adjusted [a] OR (95% CI)	p-value	p for interaction
overall effect	44/399 (11.0)	39/402 (9.7)	0.91 (0.57 to 1.44)	0.678	
without Low-T3S	8/148 (5.4)	11/161 (6.8)	1.47 (0.55 to 3.94)	0.447	0.401
with Low-T3S	36/251 (14.3)	28/241 (11.6)	0.82 (0.47 to 1.41)	0.465	
Sociodemographic factors					
Age					
< 75 years					
without Low-T3S	5/75 (6.7)	5/87 (5.8)	1.18 (0.24 to 5.76)	0.84	
with Low-T3S	12/103 (11.7)	11/104 (10.6)	0.93 (0.37 to 2.34)	0.879	0.867
≥ 75 years					
without Low-T3S	3/73 (4.1)	6/74 (8.1)	2.90 (0.62 to 13.65)	0.178	
with Low-T3S	24/148 (16.2)	17/137 (12.4)	0.71 (0.36 to 1.43)	0.343	0.235
Gender					
Female					
without Low-T3S	2/76 (2.6)	7/84 (8.3)	6.58 (0.97 to 44.77)	0.054	
with Low-T3S	12/109 (11.0)	7/105 (6.7)	0.37 (0.12 to 1.12)	0.079	**0.019**
Male					
without Low-T3S	6/72 (8.3)	4/77 (5.2)	0.75 (0.15 to 3.79)	0.727	
with Low-T3S	24/142 (16.9)	21/136 (15.4)	0.93 (0.48 to 1.82)	0.837	0.456
Nutritional Status					
NRS 2002 score					
3 or 4 points					
without Low-T3S	6/104 (5.8)	7/117 (6)	1.10 (0.34 to 3.54)	0.874	
with Low-T3S	19/148 (12.8)	16/160 (10)	0.83 (0.39 to 1.74)	0.622	0.644
≥ 5 points					
without Low-T3S	2/44 (4.6)	4/44 (9.1)	2.92 (0.41 to 20.72)	0.283	
with Low-T3S	17/103 (16.5)	12/81 (14.8)	1.02 (0.42 to 2.92)	0.967	0.493
Labaratory parameters					
CRP					
< 100 mg/l					
without Low-T3S	5/115 (4.4)	8/127 (6.3)	1.67 (0.50 to 5.60)	0.409	
with Low-T3S	20/148 (13.5)	10/158 (6.3)	0.39 (0.17 to 0.89)	**0.026**	0.061
≥ 100 mg/l					
without Low-T3S	3/33 (9.1)	3/34 (8.8)	2.31 (0.24 to 22.48)	0.47	
with Low-T3S	16/103 (15.3)	18/82 (22.0)	1.33 (0.58 to 3.05)	0.503	0.993
Albumin					
< 30 g/l					
without Low-T3S	6/65 (9.2)	5/79 (6.3)	1.18 (0.28 to 4.93)	0.825	
with Low-T3S	27/187 (14.4)	23/182 (12.6)	0.87 (0.47 to 1.60)	0.648	0.733
≥ 30 g/l					
without Low-T3S	2/76 (2.6)	6/72 (8.3)	4.69 (0.77 to 28.56)	0.094	
with Low-T3S	8/56 (14.3)	3/48 (6.3)	0.25 (0.04 to 1.38)	0.112	**0.021**
GFR					
< 30 ml/min/m²					
without Low-T3S	1/17 (5.9)	2/19 (10.5)	0.39 (0.00 to 55.68)	0.708	
with Low-T3S	13/63 (20.6)	8/69 (11.6)	0.33 (0.11 to 0.98)	0.053	0.186
≥ 30 ml/min/m²					
without Low-T3S	4/44 (9.1)	3/53 (5.7)	0.95 (0.16 to 5.60)	0.952	
with Low-T3S	10/77 (13)	3/64 (4.7)	0.35 (0.08 to 1.50)	0.156	0.331

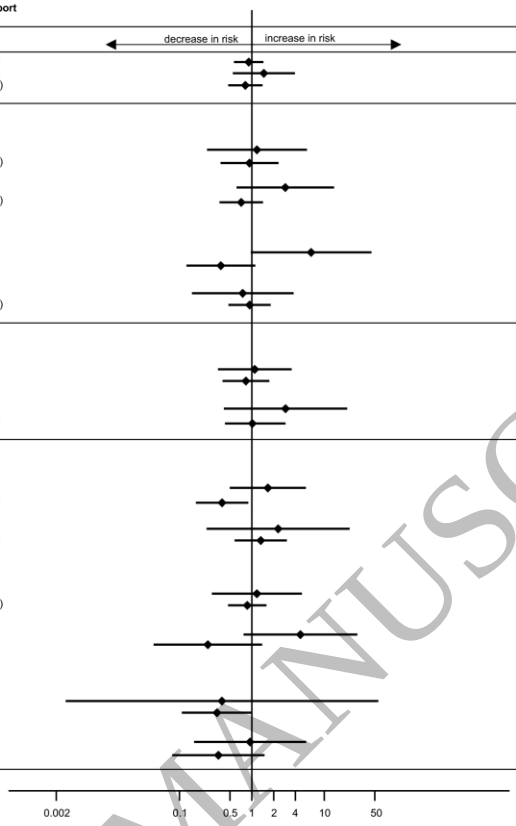

Figure 3
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