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Research Paper

Low triiodothyronine is associated with high risk of malnutrition and poor functional status in subacute stroke patients

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ABSTRACT

Background and aims: Stroke patients may exhibit low thyroid hormone (TH) levels and disease-related malnutrition, both potentially affecting clinical status; their relationships remain unexplored. This study aimed to evaluate TH concentrations in subacute stroke patients and investigate the relationships between TH levels, nutritional risk, and functional status.

Methods and results: Early subacute stroke patients admitted to a rehabilitation unit were assessed using various nutritional screening tools (Geriatric Nutritional Risk Index-GNRI, Prognostic Nutritional Index-PNI, and Controlling Nutritional Status-CONUT score) and with the Global Leadership Initiative on Malnutrition (GLIM) criteria.

Thyroid-Stimulating Hormone (TSH), free Tetraiodothyronine-Thyroxine (fT4) and free Triiodothyronine (fT3) levels were determined. Functional and cognitive status was evaluated using different scales. Associations between altered THs and nutritional status were examined through univariate/multivariate analyses and ROC analyses.

Among 264 patients (age 72.0 ± 10.5 yrs), significant correlations emerged between fT3 and nutritional risk and functional tests (mostly $p < 0.001$). The prevalence of high nutritional risk determined by GNRI, PNI and CONUT increased from higher to lower fT3 tertiles. Lower fT3 levels were observed in patients at high nutritional risk and with GLIM-based malnutrition. fT3 exhibited reasonable predictive power for high nutritional risk (particularly PNI: AUC 0.769, 95%CI 0.702–0.836, $p < 0.001$). Multivariate logistic regression identified nutritional risk ($p < 0.001$) and time from stroke onset as predictors of low fT3 values.

Conclusion: Altered fT3 levels in early subacute stroke patients correlate with high nutritional risk and poor functional status. Low fT3 values upon admission for stroke rehabilitation may serve as a further parameter to be considered in patients at high nutritional risk.

1. Introduction

Thyroid hormones (THs) exert complex effects on body tissues related to control of cell functions and macronutrient metabolism, with triiodothyronine (T3) being much more effective than tetraiodothyronine-thyroxin (T4) [1]; free or unbound hormones (mostly, free T3 = fT3) in the circulation are directly responsible for the actions on target tissues. THs explicate their functions mainly by binding nuclear receptors and modulating gene expression, while cellular deiodinases affect tissue levels of THs in different pathophysiological conditions [2].

The "low T3 syndrome" is characterized by an isolated reduction in T3 below normal range, with normal levels of thyroid-stimulating hormone (TSH) and T4 [3]. A limited number of studies have indicated high prevalence of low T3 syndrome in intensive care unit patients [4], non-critically ill patients [5], patients with acute heart failure [6] and malnourished inpatients [7], with significant associations with major clinical outcomes [5–7]. Limited evidence has demonstrated that low T3

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syndrome affects a large proportion of acute stroke patients (few data available in the subacute ones [8]), being associated with higher risk of functional [9,10] and cognitive impairment [11], and also infections [12] and mortality [1]. Overall, a reduction in T3 levels is a well-known adaptive response to prevent catabolism in acute and chronic illness, as well as during fasting/starvation [7,13,14].

Stroke is one of the primary cause of death [15] frequently resulting in either temporary or chronic disability [16,17]. A substantial prevalence of disease-related malnutrition has been found in those patients, which increases in the subacute compared to the acute phase of disease [17], due to factors such as comorbidities, dysphagia and reduced level of consciousness [11,18]. Malnutrition negatively impacts quality of life and clinical outcomes, for instance mortality rate, impaired functional recovery, susceptibility to infections, and hospital stay [19,20].

Nutritional screening, which is the preliminary step in the nutrition care process [21,22], aims to identify patients at risk to be malnourished, who can be submitted to a more comprehensive evaluation of nutritional status, but also those who are at risk to become malnourished (even if overweight/obese). Different screening tools have been used in stroke patients, with different nutritional risk in the different clinical settings [20]. The Geriatric Nutritional Risk Index (GNRI), the Prognostic Nutritional Index (PNI) and the Controlling Nutritional Status (CONUT) score have become widely used due to the simplicity of accessing information regarding body weight and laboratory test [20].

Thus, taken as a whole, stroke patients may exhibit low THs and disease-related malnutrition, both possibly affecting clinical status and outcomes. Considering this background and the lack of specific information, this study aimed to evaluate THs levels in early subacute stroke patients and to investigate the mutual relationships between THs levels and nutritional risk. As further aims, the association between THs and functional status was also assessed.

2. Methods

This retrospective study was performed at a rehabilitation care (S. Maria del Pozzo Hospital, Somma Vesuviana, Naples, Italy), between January 2021 and October 2023 to evaluate consecutive early subacute stroke patients (>15 days and <3 months after stroke [23]). Patients aged ≥50 years, with stroke diagnosed with computed tomography or magnetic resonance imaging, and admitted to a rehabilitation unit after hospital discharge, were included. Both ischemic and haemorrhagic stroke (including subarachnoid haemorrhage) were considered. Patients on treatment for hypothyroidism, given antithyroid drugs or with a history of recent thyroid disease were excluded.

Participants signed the informed consent prior to enrolment. The study respected the ethical principles of the Declaration of Helsinki and received the approval Ethical Committee of Campania Sud (Italy) (no. 147/2023). Clinical data and the assessments/measurements were collected within 48 h following admission. The assessments were conducted by well-trained staff members observing good clinical practice guidelines.

2.1. Clinical assessment

Demographic, anamnestic and clinical data were recorded, according to the hospital reports or provided by the patients or their family members. Dysphagia was evaluated with the Food Intake Level Scale [24]. Pressure ulcers were defined by the European Pressure Ulcer Advisory Panel guidelines [25]. Routine variables concerning nutritional status and inflammation were considered; in particular, C-reactive protein (CRP) levels >5 mg/L were considered indicative of inflammation [21]. The reference normal ranges for THs were: TSH = 0.35–4.94 μUI/mL, fT4 = 0.70–1.50 ng/dL, and fT3 = 1.58–3.91 pg/mL.

2.2. Anthropometry and body composition

Following standard procedures [26], body weight was measured to the nearest 0.1 kg in duplicate with a chair weighing scale (7708 Soehnle Industrial Solutions GmbH, Backnang, Germany). Stature was measured to the nearest 0.1 cm in triplicate with patients lying in bed, with a portable stadiometer (Seca 213; Seca Hamburg, Germany). Body mass index (BMI) was calculated as weight in kilograms divided by squared stature in meters.

Bioelectrical impedance analysis (Human IM Touch, DS Medica, Milan, Italy) was performed on the non-affected side according to standardized procedures for determining impedance, resistance, reactance and phase angle at the frequency of 50 kHz [27]. Fat-free mass (FFM) was estimated using predictive equations [28] and fat-free mass index (FFMI) was calculated as FFM divided by squared stature.

2.3. Nutritional status

As previously reported [29], the nutritional risk of patients was determined using three different screening tools. GNRI was obtained using the following equation: 14.89 × serum albumin (g/dL)+41.7 × (body weight[kg]/ideal body weight [kg]) [20]. The Lorentz formula was used to determine the ideal body weight. The body weight/ideal body weight ratio was truncated at 1 when actual body weight exceeded ideal body weight [30]. Nutritional risk was defined as normal (GNRI ≥98), mild (97-92), moderate (91-82) or severe (<82).

PNI was obtained from: 10 × serum albumin (g/dL)+0.005 × total lymphocyte count (n/mm^3) [20]. A normal, moderate and severe nutritional risk was defined according to a PNI score >38, 35–38 and < 35 indicates, correspondingly.

Finally, CONUT score [20] was derived from the sum of scores regarding albumin, lymphocyte count, and total cholesterol, separately. As mentioned elsewhere [29], participants were categorized into levels of nutritional risk: normal (score 0–1), light (2–4), moderate (5–8) and severe (9–12).

Overall, high (moderate or severe) nutritional risk was identified as: GNRI <92, PNI ≤38 and CONUT score ≥5.

Malnutrition was identified according to the Global Leadership Initiative on Malnutrition (GLIM) criteria [31] (at least one phenotypic and one etiologic criterion needed). Phenotypic indicators were: unintentional weight loss, low BMI or low FFMI. The etiologic criterion chosen was stroke + inflammation (CRP >5 mg/L) [21].

2.4. Functional status

As reported elsewhere [29], functional status was assessed using different scales. The Barthel Index (BI) determines independence in activity of daily living (score from 0 = full dependence to 100 = full independence) [32]. The modified Rankin Scale (mRS) defines the level of disability (score from 0 = no symptoms to 6 = death) [33]. The Trunk Control Test (TCT) evaluates rolling, sitting and balance maintenance (score from 0 to 100; higher scores indicate better performance) [34]. The Sitting Balance Scale (SBS) assesses sitting balance (scores from 4 = no physical assistance needed to 1 = unable to maintain a static position) [35]. Finally, cognitive status was evaluated with the Short Portable Mental Status Questionnaire (SPMSQ), with scores ranging from 0 to 10, indicating increasing severity [36].

2.5. Statistical analysis

Statistical analysis was carried out using SPSS Statistics (version 28.0, SPSS Inc, Chicago IL, United States). Results were reported as mean ± standard deviation, median and interquartile range/distance, or number and % of patients, were appropriate. A p-value<0.05 was considered significant for all tests (2-tailed). A post-hoc analysis indicated that statistical power was 0.80 for a correlation coefficient of 0.20

and an alpha level = 0.05 (194 participants).

The Kolmogorov–Smirnov normality test was used as test of normality. Comparisons between groups were assessed using the Student's t-test and the one-way analysis of variance (ANOVA) with post-hoc Tukey's test for parametric variables, while the Mann-Whitney *U* test and the Wilcoxon-Rank Sum test were applied for non-parametric variables. The chi-squared test was used for testing differences between categorical variables.

Correlation analysis was carried out with the Spearman's rank coefficient to examine the relationship of THs with variables of interest. Logistic regression analyses were performed to determine independent risk factors of low fT3; the potential predictors were age, male sex, GNRI, PNI, CONUT score, GLIM, atrial fibrillation, hypertension, diabetes mellitus, coronary heart disease, hyperlipemia, previous stroke, dysphagia, pressure ulcers and time from stroke onset. No information was available for nutrient intakes.

The receiver operating characteristic (ROC) method was used to assess the predictive power of fT3 for high nutritional risk and malnutrition. The optimal cut-off value of each index was determined by identifying the greatest Youden's index.

3. Results

Two hundred and eighty-one subacute stroke patients participated in the study. Twelve were ruled out from the analysis because of lacking data and 5 declined to participate. Thus, 264 subacute stroke patients (46 % women), with ischemic stroke (81 % of total sample), haemorrhagic stroke (17 %) or subarachnoid haemorrhage (2 %), were selected. No patients were treated with amiodarone and only a low percentage (<5 %) was given corticosteroids.

Table 1 shows the characteristics of the patients in terms of demographic and clinical features, clinical data, and anthropometric measurements. On the whole, 6 % of the participants were underweight (BMI <18.5 kg/m^2), 25 % normal weight (18.5–24.99), 51 % overweight (25–29.99) and 19 % had obesity (≥30). The prevalence of high nutritional risk was greater for GNRI than PNI or CONUT score while GLIM-based malnutrition was found in around 10 % of patients.

Compared to the normal reference ranges, 9.4 % of participants had high TSH, 8.7 % low fT3, and 0.8 % low fT4 levels. As for functional status, women exhibited poorer scores than men for BI, TCT, SBS and SPMSQ but not for mRS (Table 1).

As reported in Table 2, there were several relationships between variables of interest and fT3 (but not TSH or fT4); results are thereafter

Table 1
General characteristics of the stroke patients.

	Total		Men		Women		*p-value*
	n = 264		n = 142		n = 122		
Age, years	72.0	±10.5	70.0	±9.9	73.3	±11.1	0.066
Weight, kg	70.9	±13.6	76.4	±12.1	68.9	±14.2	**<0.001**
Stature, cm	163.8	±9.5	169.1	±7.6	157.8	±7.8	**<0.001**
BMI, kg/m^2	26.8	±3.9	26.4	±3.0	27.4	±4.6	**0.035**
FFM, kg	48.5	±8.17	54.0	±6.21	42.0	±6.78	**<0.001**
FFMI, kg	17.9	±2.07	18.9	±1.45	16.8	±2.16	**<0.001**
Atrial fibrillation	46	(17.4)	18	(12.7)	28	(23.0)	**0.021**
Hypertension	204	(77.3)	105	(73.9)	99	(81.1)	0.106
Diabetes mellitus	91	(34.5)	48	(33.8)	43	(35.2)	0.453
Coronary heart disease	94	(35.6)	54	(38.0)	40	(32.8)	0.082
Hyperlipemia	108	(40.9)	53	(40.8)	54	(44.3)	0.184
Previous stroke	44	(16.7)	26	(18.3)	18	(14.8)	0.273
Dysphagia	96	(36.4)	45	(31.7)	51	(41.8)	0.158
Pressure ulcers	52	(19.8)	24	(16.9)	28	(23.3)	0.215
High nutritional risk with GNRI	160	(60.6)	78	(54.9)	82	(67.2)	**0.028**
High nutritional risk with PNI	106	(40.2)	48	(33.8)	58	(57.5)	**0.016**
High nutritional risk with CONUT score	128	(48.5)	67	(47.2)	61	(50)	0.370
GLIM based malnutrition	26	(9.8)	10	(7)	16	(13.1)	0.074
BI	5	[5–15]	10	[5–20]	5	[0–15]	**<0.01**
mRS	4	[4,5]	4	[4,5]	4	[4,5]	0.116
TCT	24	[0–48]	36	[12–48]	12	[0–36]	**<0.001**
SBS	2	[1–3]	2	[2,3]	2	[1–3]	**<0.001**
SPMSQ	6	[4–10]	5	[2–8]	7	[5–10]	**<0.001**
Albumin, g/dL	3.23	±0.58	3.30	±0.50	3.15	±0.60	**0.027**
Cholesterol, mg/dL	144.3	±41.7	139.5	±40.3	156.5	±42.1	**<0.001**
Lymphocyte count/mL	1400	[1000–1900]	1400	[1100–1900]	1400	[1000–1900]	0.566
Neutrophil count/mL	5500	[4100–7150]	5500	[4275–6900]	5400	[3975–7200]	0.495
Haemoglobin, g/dL	12.9	±1.93	13.4	±1.91	12.4	±1.97	**<0.001**
Platelet count/mL × 1000	246	[203–309]	240	[192–304]	254	[210–310]	0.205
C-reactive protein, mg/L	13.0	[4.6–38.1]	11.5	[4.1–35.8]	15.4	[4.5–43.1]	0.305
Fibrinogen, mg/dL	511	[424–620]	519	[432–627]	493	[400–601]	0.760
D-dimer, μg/mL	0.96	[0.46–2.20]	0.81	[0.41–1.80]	0.49	[1.08–3.02]	0.191
TSH, μUI/mL	1.20	[0.68–2.00]	1.13	[0.63–1.51]	1.55	[0.71–2.52]	**<0.01**
fT4, ng/dL	1.14	[1.03–1.32]	1.12	[1.02–1.28]	1.17	[1.04–1.34]	0.538
fT3, pg/mL	2.23	±0.45	2.30	±0.50	2.15	±0.36	**0.015**

Variables were expressed as mean ± SD, median [interquartile range] or frequencies (percentages).
BMI=Body Mass Index; FFM=Fat-Free Mass; FFMI=Fat-Free Mass Index; GNRI=Geriatric Nutritional Risk Index; PNI=Prognostic Nutritional Index; CONUT=Controlling Nutritional Status Score; GLIM = Global Leadership Initiative On Malnutrition Criteria; BI=Barthel Index; mRS = modified Rankin Scale; TCT = Trunk Control Test; SBS=Sitting Balance Scale; SPMSQ=Short Portable Mental Status Questionnaire; TSH=Thyroid-Stimulating Hormone; fT4 = Free Tetraiodothyronine-Thyroxine; fT3 = Free Triiodothyronine.
None of the patients who tolls statins had low cholesterol levels. 67 % of patients displayed low serum albumin (<3.5 g/dL), 71 % high CRP (>5 mg/L), 64 % high fibrinogen (>450 mg/dL) and 67 % high D-dimer levels (>0.5 μg/mL).
In 36 % of participants high nutritional risk was detected by all the screening tools, in 11 % by two tools, in 20 % by one (no nutritional risk at all in 33 %). High nutritional risk = moderate + severe.

Table 2
Spearman's correlation between thyroid hormones and body composition, nutritional risk, biochemical variables and functional status in the stroke patients.

	TSH		fT4		fT3	
	r	*p-value*	r	*p-value*	r	*p-value*
Weight	0.154	0.225	0.006	0.962	0.118	0.354
BMI	0.050	0.482	−0.026	0.710	0.147	**0.036**
FFM	0.033	0.640	0.004	0.954	0.021	0.762
FFMI	0.061	0.385	0.027	0.706	0.065	0.357
GNRI	0.101	0.151	0.055	0.433	0.313	**<0.001**
PNI	0.127	0.071	0.092	0.192	0.344	**<0.001**
CONUT score	−0.111	0.115	−0.051	0.469	−0.353	**<0.001**
Albumin	0.930	0.186	0.062	0.382	0.304	**<0.001**
Cholesterol	−0.019	0.786	−0.028	0.692	0.060	0.397
Lymphocyte count	0.102	0.148	0.084	0.230	0.189	**0.007**
Neutrophil count	0.116	0.097	0.066	0.349	−0.195	**0.005**
Haemoglobin	0.099	0.159	0.129	0.066	0.225	**<0.001**
Platelet count	0.063	0.368	−0.058	0.411	0.012	0.868
C-reactive protein	0.007	0.922	0.082	0.245	−0.376	**<0.001**
BI	0.006	0.938	0.003	0.971	0.113	0.113
mRS	−0.109	0.132	0.003	0.967	−0.225	**0.002**
TCT	0.121	0.102	−0.076	0.310	0.222	**0.003**
SBS	0.138	0.067	−0.130	0.085	0.168	**0.026**
SPMSQ	−0.065	0.416	−0.018	0.827	−0.103	0.200

TSH=Thyroid-Stimulating Hormone; fT4 = Free Tetraiodothyronine-Thyroxine; fT3 = Free Triiodothyronine; BMI=Body Mass Index; FFM=Fat-Free Mass; FFMI=Fat-Free Mass Index; GNRI=Geriatric Nutritional Risk Index; PNI=-Prognostic Nutritional Index; CONUT=Controlling Nutritional Status score; BI=Barthel Index; mRS = modified Rankin Scale; TCT = Trunk Control Test; SBS=Sitting Balance Scale; SPMSQ=Short Portable Mental Status Questionnaire.

reported almost always only for fT3. fT3 was significantly associated with albumin, haemoglobin, and lymphocyte count (but not with total cholesterol) and also with GNRI, PNI or CONUT score. Specifically, fT3 values were lower ($p < 0.001$) in patients at high nutritional risk compared to those at low nutritional risk (2.09 ± 0.37 vs. 2.46 ± 0.46 pg/mL for GNRI, 2.00 ± 0.37 vs. 2.39 ± 0.42 for PNI and 2.07 ± 0.41 vs. 2.38 ± 0.43 for CONUT score). fT3 was also lower in patients with GLIM-based malnutrition than in those who were well-nourished (2.07 ± 0.39 vs. 2.25 ± 0.45 pg/mL, $p = 0.070$). Additionally, weaker relationships were also observed between the fT3/fT4 ratio and nutritional risk ($p < 0.01$): $r = 0.167$ for GNRI, $r = 0.179$ for PNI and $r = -0.215$ for CONUT score.

For statistical analysis, stroke patients were subdivided into tertiles of fT3. The prevalence of high nutritional risk increased along the tertiles (Fig. 1), and significant differences were also found in terms of median values (Table 3). Patients at high nutritional risk according to all the tools were 64 % in the 1st, 30 % in the 2nd and only 18 % in the 3rd tertile. Similarly, malnutrition was found in 16 % of stroke patients in the 1st, 7.2 % in the 2nd and 8.8 % in the 3rd tertile. When fT3 values were below the lower normal limit (<1.60 pg/mL), a very high proportion of patients (89 % for GNRI, 83.3 % for PNI and 83.3 % for CONUT score) exhibited high nutritional risk, with 11 % who were malnourished according to GLIM criteria. The combination of high nutritional risk and inflammation was 52 % using GNRI, 35 % for PNI and 42 % for CONUT score, becoming less prevalent from the 1st to the 3rd tertile.

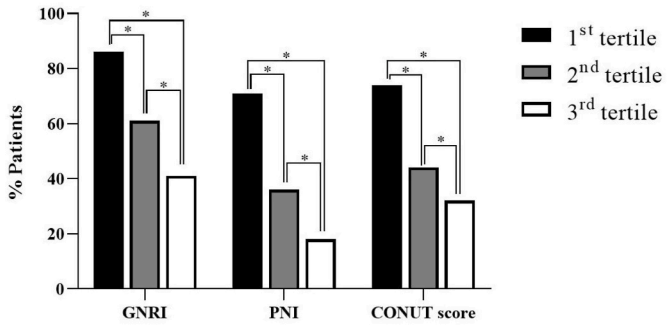

Fig. 1. Prevalence of high nutritional risk according to fT3 tertiles in 264 stroke patients.
Legend: GNRI = geriatric nutritional risk index; PNI = prognostic nutritional index; CONUT = controlling nutritional status score. * = $p < 0.05$.

A ROC analysis was performed considering fT3 as a predictor of high nutritional risk. As shown in Fig. 2, the highest predictive power was observed with PNI followed by GNRI and CONUT score. According to the Youden's index, the optimal cut-off values were 2.16 for both GNRI (sensitivity 83 % and specificity 59 %) and PNI (77 % and 71 %) and slightly lower (2.09 pg/mL) for CONUT score (80 % and 56 %). Conversely, fT3 did not emerge as a consistent predictor of GLIM-based malnutrition ($p = 0.078$). The cut-off value of fT3 for identifying patients with high nutritional risk and inflammation was around 2.10 pg/mL for all the three tools (Fig. S1).

As for functional status, significative associations were found between fT3 and mRS, TCT or SBS (Table 2). Similar relationships were also observed between the fT3/fT4 ratio and mRS, TCT and SBS (data not shown). In addition, all the functional tests differed comparing the 2nd vs. the 3rd and the 1st vs. the 3rd tertile of fT3 (Table 3).

Finally, as shown in Table 4, univariate logistic analysis indicated that age≥75 years, dysphagia, pressure ulcers and time from stroke onset as well as GNRI, PNI and CONUT score were associated with having low serum fT3 level (i.e. 1st tertile <2.03 pg/mL). In multivariate logistic analysis, the nutritional screening tools ($p < 0.001$), considered one at a time, remained significant predictors of low fT3 values along with time from stroke onset (Table 4).

Table 3
Nutritional risk, biochemical variables and functional status analyzed considering tertiles of fT3 in stroke patients.

	1st tertile (n = 88, males 48 %)	2nd tertile (n = 88, males 48 %)	3rd tertile (n = 88, males 63 %)
GNRI	84 (11)	90 (11)[a]	92 (8)[c]
PNI	35 (7)	41 (11)[a]	43 (6)[c]
CONUT score	6 (4)	4 (4)[a]	3 (3)[c]
Albumin, g/dL	2.87 (0.74)	3.27 (0.76)[a]	3.40 (0.54)[c]
Cholesterol, mg/dL	136 (52)	159 (69)[a]	137 (56)[b]
Lymphocyte count/mL	1200 (800)	1500 (900)[a]	1600 (700)[c]
Neutrophil count/mL	5800 (2650)	5050 (3600)	4800 (2100)[c]
Haemoglobin, g/dL	12.60 (2.05)	12.80 (1.88)	13.40 (1.90)[c]
Platelet count/mL × 1000	245 (120)	244 (113)	253 (95)
C-reactive protein, mg/L	33.6 (82.3)	11.6 (24.9)[a]	8.5 (19.6)[c]
BI	5 (12)	5 (11)	5 (10)[b,c]
mRS	5 (1)	5 (1)	4 (1)[b,c]
TCT	12 (36)	24 (48)	36 (36)[b,c]
SBS	2 (4)	2 (2)	3 (1)[b,c]
SPMSQ	7 (6)	6 (6)	5 (6)[b,c]

fT3 = Free Triiodothyronine; 1st tertile = 1.10–2.02 pg/mL; 2nd tertile = 2.03–2.37 pg/mL; 3rd tertile = 2.38–3.87 pg/mL.
GNRI=Geriatric Nutritional Risk Index; PNI=Prognostic Nutritional Index; CONUT=Controlling Nutritional Status score; BI=Barthel Index; mRS = modified rankin scale; TCT = Trunk control test; SBS = sitting balance scale; SPMSQ = short portable mental status questionnaire.
[a] = $p < 0.05$ vs. 1st tertile.
[b] = $p < 0.05$ vs. 2nd tertile.
[c] = $p < 0.05$ vs. 1st tertile.

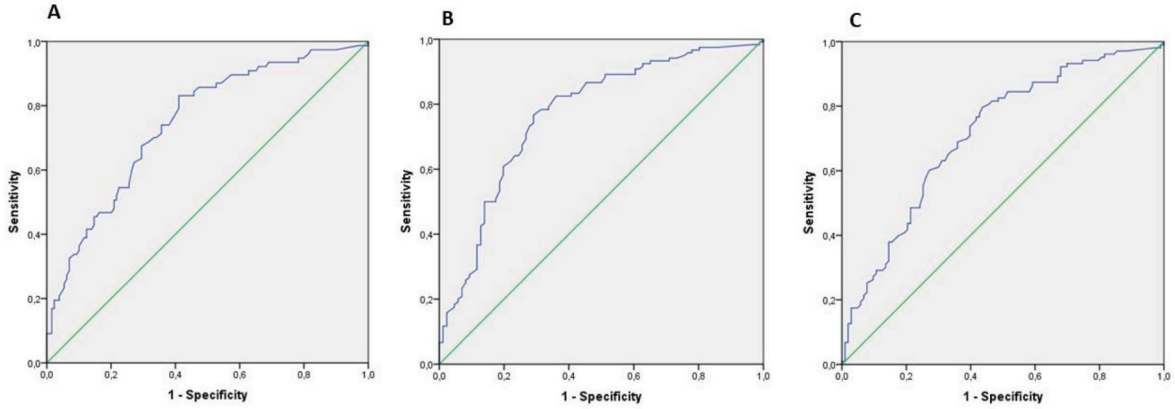

Fig. 2. Receiver operating characteristic (ROC) curves of fT3 for high nutritional risk with GNRI (A), PNI (B), and CONUT score (C).
Legend: GNRI = geriatric nutritional risk index; PNI = prognostic nutritional index; CONUT = controlling nutritional status score.
PNI (AUC 0.769, 95 % CI: 0.702–0.836, p < 0.001); GNRI (AUC 0.747, 95 % CI: 0.679–0.816 p < 0.001); CONUT score (AUC, 0.713, 95 % CI: 0.642–0.783 p < 0.001).

Table 4
Logistic regression analyses: potential predictors of having a low fT3 value (within the 1st tertile).

	Univariate coefficients		Multivariate coefficients including GNRI		Multivariate coefficients including PNI		Multivariate coefficients including CONUT score		Multivariate coefficients including GNRI, PNI and CONUT score	
	Odds ratio (95 % CI)	*p*	Odds ratio (95 % CI)	*p*	Odds ratio (95 % CI)	*p*	Odds ratio (95 % CI)	*p*	Odds ratio (95 % CI)	*p*
Age≥75 years	2.12 (1.18–3.82)	**0.012**	1.03 (0.99–1.06)	0.104	1.02 (0.98–1.05)	0.246	1.01 (0.98–1.05)	0.538	1-01 (0.98–1.05)	0.434
Men (vs women)	0.72 (0.40–1.28)	0.257								
Atrial fibrillation	1.50 (0.73–3.06)	0.270								
Hypertension	0.97 (0.48–1.95)	0.925								
Diabetes mellitus	1.40 (0.78–2.54)	0.274								
Coronary heart disease	2.79 (0.99–7.83)	0.052								
Hyperlipemia	1.19 (0.66–2.14)	0.572								
Previous stroke	1.21 (0.57–2.59)	0.616								
Dysphagia	1.83 (1.31–2.56)	**<0.001**	1.35 (0.85–2.14)	0.201	1.37 (0.86–2.18)	0.181	1.51 (0.95–2.42)	0.083	1.45 (0.90–2.34)	0.126
Pressure ulcers	2.38 (1.22–4.65)	**0.011**	1.60 (0.63–4.00)	0.315	1.44 (0.58–3.58)	0.433	1.84 (0.73–4.65)	0.197	1.65 (0.64–4.24)	0.298
Time from stroke onset	0.96 (0.93–0.99)	**0.002**	0.94 (0.91–0.98)	**0.002**	0.95 (0.91–0.98)	**0.003**	0.94 (0.90–0.97)	**<0.001**	**0.94 (0.90 to 0.98)**	**0.002**
GLIM	2.17 (0.89–5.30)	0.088								
GNRI	0.91 (0.87–0.95)	**<0.001**	0.90 (0.86–0.94)	**<0.001**					0.99 (1.04–1.70)	0.873
PNI	0.87 (0.82–0.92)	**<0.001**			0.87 (0.82–0.93)	**<0.001**			0.95 (0.85–1.07)	0.417
CONUT score	1.48 (1.27–1.72)	**<0.001**					1.50 (1.27–1.76)	**<0.001**	**1.33 (1.04 to 1.70)**	**0.023**

fT3 = Free Triiodothyronine; 1st tertile of fT3 = 1.10–2.02 pg/mL; CI = confidence interval; GLIM = Global Leadership Initiative On Malnutrition Criteria; GNRI=Geriatric Nutritional Risk Index; PNI=Prognostic Nutritional Index; CONUT=Controlling Nutritional Status score.

4. Discussion

To our knowledge, this is the first study to explore the relationships between THs and nutritional status in stroke patients. fT3 (but not TSH nor fT4) showed an inverse association with nutritional risk. High nutritional risk progressively increased as fT3 levels decreased. Furthermore, fT3 levels were associated with some functional tests commonly used in stroke patients.

The research described in this paper was motivated by the fact that T3 levels in stroke patients have been related to major clinical outcomes [1] but not to nutritional status. Data on free or unbound hormones in the circulation, responsible for the actions of THs on target tissue, were available and therefore considered for statistical analysis. Since no significant findings emerged for T4, the discussion is focused on data concerning T3.

A significant prevalence of low T3 syndrome [1] has been found in

stroke patients with few data in the subacute phase of disease [1,8]. Low T3 levels have been related to severity of disease, complications, higher mortality rates and a greater risk of poor functional outcomes [1] in agreement with previous evidence in other types of patients [4,5,7].

In this study, the proportion of stroke patients with low fT3 was smaller than the one observed in the acute phase of disease [1]; indeed, 30 % of the participants exhibited fT3 levels <2 pg/mL. It could be argued that THs are influenced by patient's clinical status before stroke onset, stroke impact and hospitalization; in particular, fT3 was found to be negatively associated with longer time from stroke onset.

The major aim of the study was to explore the relationships between THs and nutritional risk. Previous limited studies have showed that fT3 levels were not associated with NRS-2002 in medical inpatients [7], but they were related to PNI in acute heart failure patients [6]. More specifically, keeping in mind that nutritional status tends to worsen during hospitalization due to reduced food intake, inflammation, complications and comorbidities [16,17,20,37], nutritional screening has been indeed related to various clinical outcomes in the acute as well as (even if less frequently) in the subacute phase of stroke [20,29]. Nutritional screening is used for identifying patients at risk to be malnourished but also identifies subjects who are not but can become malnourished; these latter cannot be identified as suffering from undernutrition by specific criteria (for instance those proposed by GLIM) because of the high prevalence of high BMI. GNRI, PNI and CONUT score were here selected as screening tools because of ease of application, consistency and increasing use [20]. As already reported in a paper by our group in a slightly smaller group of patients [29] and in other papers [38,39], high prevalence of nutritional risk emerged in the study sample. Given that inflammation is a major determinant of disease-related malnutrition [31], the findings of the present study show that the combination of high nutritional risk and inflammation also occurred in a large proportion of patients. Looking at the components of the three screening tools, there was a substantial association of albumin and lymphocyte count with fT3 but no association with body weight or total cholesterol; it is worth noting that the relationship was stronger for screening scores than their single components.

GNRI, PNI and CONUT score significantly differed between tertiles of fT3, with the prevalence of high nutritional risk being two-to four-fold higher in the lowest tertile. On the opposite, high nutritional risk was very uncommon when fT3 levels were >2.4 pg/mL (i.e., 3rd tertile). Similar results emerged also for the combination of nutritional risk and inflammation. In addition, when ROC analyses were performed, fT3 came out as a significant but fair predictor of high nutritional risk with cut-off values around 2.10 pg/mL. Nutritional risk remained a significant predictor of fT3 also in multivariate analysis, along with time from stroke onset, with CONUT score being possibly more effective than GNRI or PNI (Table 4). Interestingly, a much weaker association emerged between fT3 and GLIM-derived malnutrition.

Overall, these findings may be ascribed to the complex interrelationships between T3 and nutritional status. Low T3 might reflect a reduction in energy intake during the acute phase of disease, due to dysphagia and/or cognitive impairment, or may be a biological response to reduced catabolism in critical illnesses, possibly also inversely related to inflammation. In this view, the assessment of T3 may help improve the multidimensional evaluation of subacute stroke patients also in terms of response to nutritional treatment [7].

Of note, the assessment of muscle function and independence in the activities of daily living is commonly included in the comprehensive evaluation of stroke patients. It must also be considered that the association of low T3 levels with muscle strength, function and sarcopenia has recently been reported in older males [40] and stroke patients [41]. Actually, preliminary findings in this study showed only a weak relationship between fT3 and functional tests, suggesting that the role of T3 in improving recovery in patients with T3 syndrome should be further evaluated possibly with intervention studies.

To our knowledge, this is the first study providing consistent data on the relationships between THs and nutritional risk using different screening tools in a cohort of subacute stroke patients. Functional status was assessed using standard scoring systems and major biochemical prognostic factors were selected. Indeed, some limitations need to be addressed. Firstly, this is a single centre study, which limits the generalizability of results. Secondly, given the limited number of patients with haemorrhagic stroke, conducting a thorough analysis specifically for this subgroup was not possible. No detailed information regarding the pharmacological treatment of patients during prior hospital stay is available. Additional biochemical parameters or tools to assess functional status, not available for this study, may also be related to altered THs. Further data of interest might be added by considering reverse triiodothyronine, and also thyroxine-binding globulin, total triiodothyronine, and total thyroxine.

In conclusion this study contributes novel insights to the comprehensive evaluation of subacute stroke patients in rehabilitation, highlighting a significant association between fT3 and nutritional risk as assessed using different screening tools. Patients in the lowest fT3 tertile had a much higher nutritional risk compared to higher tertiles. Additionally, those with high nutritional risk had significantly lower fT3 values in comparison to those with no/low nutritional risk (also when other predictors were included in multivariate analysis). As reported in a very recent review [42], low T3 after severe illnesses seems to be an adaptive response to conserve energy. In this regard, previous studies showed that subclinical hypothyroidism does not need treatment; and this is true also in stroke patients. Indeed, further studies are needed to examine the relationships of THs with dietary patterns and additional outcomes, such as quality of life, and to evaluate THs and nutritional risk changes after rehabilitation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2024.09.008.

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