Annals of Hematology (2023) 102:851–862
https://doi.org/10.1007/s00277-023-05117-5

ORIGINAL ARTICLE

Low T3 syndrome as a predictor of poor outcomes in patients with follicular lymphoma

Lian-Guo Xue[1,2,3,4] · Hao-Rui Shen[1,2,3] · Rui Gao[5] · Kai-Xin Du[1,2,3] · Tong-Yao Xing[1,2,3] · Wei-Ting Wang[1,2,3] · Li Wang[1,2,3] · Jian-Yong Li[1,2,3] · Jin-Hua Liang[1,2,3] · Wei Xu[1,2,3]

Received: 10 July 2022 / Accepted: 27 January 2023 / Published online: 3 February 2023

Abstract

The aim of this study was to investigate the prognostic value of low T3 syndrome in follicular lymphoma (FL). A total of 221 FL patients with detailed serum thyroid hormone levels and other complete clinical data were enrolled. Baseline features associated with low T3 syndrome were analyzed and balanced by propensity score matching. Univariate and multivariate regression analyses were performed to determine independent risk factors for progression-free survival (PFS) and overall survival (OS). A receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was calculated to assess the predictive accuracy of FL international prognostic index FLIPI-1/FLIPI-2 and low T3 syndrome. A total of 22 patients (10.0%) had low T3 syndrome at diagnosis, which was associated with poor PFS and OS in the rituximab era. It is an independent prognostic factor for PFS and OS. Low T3 syndrome and FLIPI-1/FLIPI-2 significantly increased the AUC of PFS and OS compared to FLIPI-1/FLIPI-2 alone. Low T3 is a risk factor for POD24. In conclusion, low T3 syndrome may be a good candidate for predicting the prognosis of CLL in future clinical practice. Our study demonstrates that low T3 syndrome is associated with poorer survival outcomes in FL patients.

Keywords Low T3 syndrome · Follicular lymphoma · Prognosis

Introduction

Follicular lymphoma (FL) is the second most common indolent non-Hodgkin's lymphoma (NHL), with highly heterogeneous clinical features and outcomes [1]. The incidence of FL in the USA and Western European countries is the highest, accounting for 22–35% of non-Hodgkin lymphoma (NHL) patients, while the proportion in China is lower than that in western countries, accounting for 8.1–23.5% of NHL patients, and the incidence is increasing year by year [2]. FL is currently uncurable, with frequent recurrence despite a high treatment response rate [3], and median overall survival (OS) of more than 10 years, but some patients may experience early progression and 15% of patients die of FL within 2 years of diagnosis [4]. Prevention of early recurrence is particularly important for high-risk patients. If patients develop disease progression within 24 months of starting first-line immunochemotherapy (POD24), the risk of death is significantly increased. Early identification of patients at high risk for FL minimizes the risk of death, malignancy (histological transformation), and duration of treatment

Lian-Guo Xue, Hao-Rui Shen, and Rui Gao contributed equally to this work.

✉ Jin-Hua Liang
1151525490@qq.com

✉ Wei Xu
xuwei10000@hotmail.com

1 Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing 210029, China

2 Key Laboratory of Hematology of Nanjing Medical University, Nanjing 210029, China

3 Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing 210029, China

4 Department of Hematology, Lianyungang Clinical College of Nanjing Medical University, Lianyungang 222002, China

5 Department of Endocrinology and Metabolism, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu, China

response to reduce pain and morbidity from this disease [5]. FL international prognostic index FLIPI-1 and FLIPI-2 are widely used prognostic indicators of FL baseline characteristics, especially the latter, which remains the current clinical prognostic standard in the rituximab era [6, 7], but of limited value. How to identify patients more effectively with early recurrence and more accurately implement first-line stratified treatment are still urgent problems to be solved.

Low triiodothyronine (T3) syndrome, also known as euthyroid disease syndrome (ESS) or non-thyroid disease syndrome (NTIS), is characterized by decreased peripheral T3 concentration and normal thyroid stimulating hormone (TSH), on behalf of the thyroid hormone metabolism changes [8], common in severe patients, as well as some acute and chronic disease patients. Low T3 syndrome is generally associated with cardiovascular disease (CVD) and increased risk of death [8], which is often observed in acute myocardial infarction, is associated with myocardial injury and poor prognosis [9–11], and is also associated with high mortality in hospitalized patients with heart failure [12]. More and more evidence indicates that low T3 syndrome is a predictor of poor prognosis in patients with community acquired pneumonia [13], suppurative liver abscess [14], hemodialysis (HD) [15], autoimmune encephalitis (AE) [16], and brain tumor surgery [17] and is also associated with hemorrhagic transformation in patients with acute ischemic stroke [18]. According to a recent study, low T3 syndrome has also been observed in patients with COVID-19 [19]. Low free T3 (FT3) values are also associated with clinical and radiological scores of disease severity and can be considered as a prognostic marker of COVID-19 [20]. In addition, low T3 syndrome has been considered as a predictor of poor prognosis in Hodgkin lymphoma (HL) [21], chronic lymphocytic leukemia (CLL) [22] and diffuse large B-cell lymphoma [23].

However, to our knowledge, no studies to date have focused on FL patients with low T3 syndrome. The aim of our study was to investigate the association between low T3 syndrome and FL, and the prognostic value of low T3 syndrome in identifying patients at high risk for FL.

Materials and methods

Patients' selection and data collection

A total of 221 patients with FL who were admitted to the First Affiliated Hospital of Nanjing Medical University from August 2009 to October 2019 were included in this study. All patients were diagnosed according to WHO 2016 tumor and hematopoietic lymphoid tissue classification for pathology [24, 25]. Confirmed with detailed serum thyroid hormone levels and other complete clinical data. Exclusion criteria: (1) history of thyroid disease (hypothyroidism, hyperthyroidism, thyroiditis, or central hypothyroidism due to hypothalamic or pituitary disease/condition). (2) Complications with other malignant tumors, severe infection, severe cardiovascular disease, severe liver disease, and renal failure that can lead to low T3. (3) Patients who died due to other medical conditions not related to FL. (4) Incomplete clinical data. The flow chart of patient enrollment is shown in Fig. 1. After admission, blood samples, bone marrow and bone marrow biopsy specimens were collected for examination, and various clinical baseline characteristics and data were evaluated, including age, gender, physical performance score, B symptoms, pathological grade, number of lymph node involvement sites, bulky lesions, location and number of external involvement, bone marrow involvement (BMI), Ann Arbor stage, and blood count, serum lactate dehydrogenase (LDH) and serum β2 microglobulin (β2-MG), albumin (ALB), and other laboratory data. FLIPI-1 and FLIPI-2 were used for prognostic stratification. Treated according to the National Comprehensive Cancer Network (NCCN) recommended regimen. Of these 221 patients,156 patients received chemotherapy with or without rituximab during induction chemotherapy, including 143 patients (91.67%) in euthyroid group, 13 patients (8.3%) with low T3 syndrome. 25 patients received rituximab monotherapy, including 23 patients (92%) in euthyroid group, and 2 patients (8%) with low T3 syndrome. 16 cases received reduced intensity chemotherapy, including 9 cases (56.3%) in euthyroid group, 7 cases (43.8%) with low T3 syndrome. The remaining 3 patients received radiotherapy only. 21 patients had no indication for treatment and were watch and wait, and all of them had normal thyroid function. The treatment intensity of normal thyroid function group was significantly higher than that of patients with low T3 syndrome. After 1:1 matching, there was no statistically significant difference between the two groups (Table 1).

Ethics

The study was agreed and approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. All aspects of this study, including the measurement of thyroid hormone levels such as serum FT3, free T4 (FT4) and thyroid-stimulating hormone (TSH), and other clinical and laboratory tests, were performed in accordance with the principles of the Declaration of Helsinki (2013 No. 64).

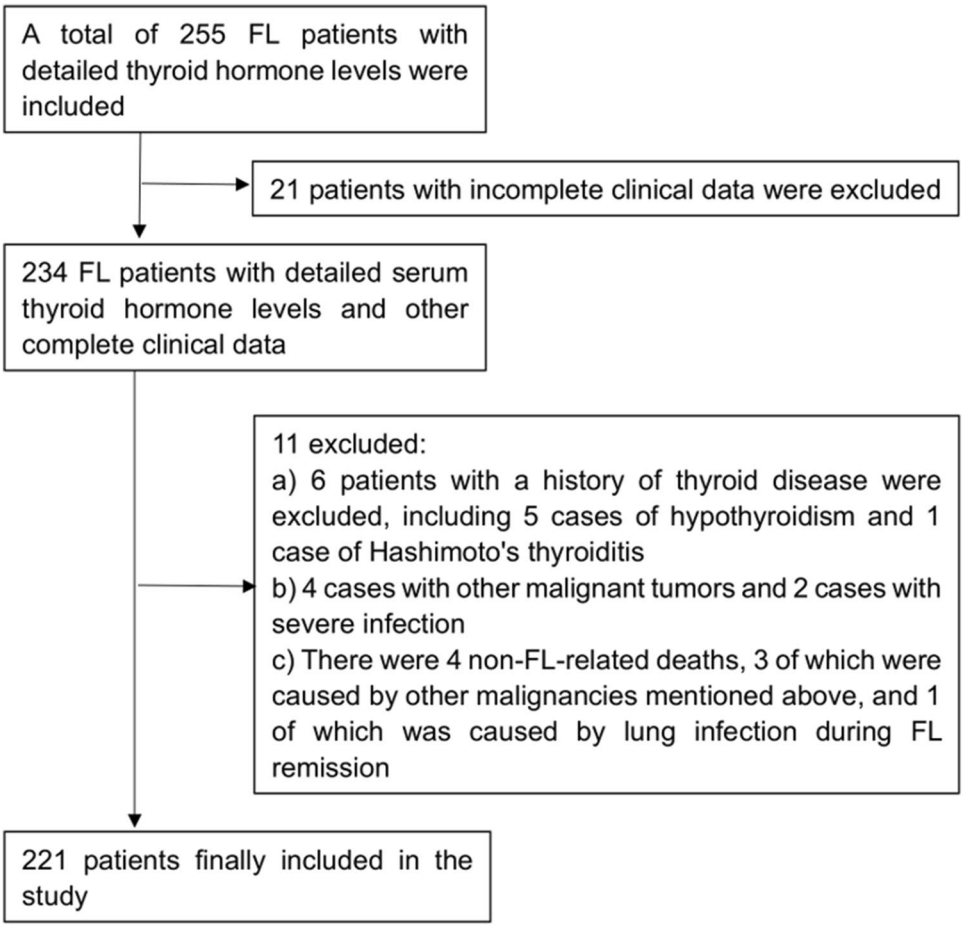

Fig. 1 Consort diagram of enrolled patients. Abbreviations: FL, follicular lymphoma

Thyroid hormone function test

Serum thyroid hormone levels were detected by chemiluminescence immunoassay (AutoBio 12 Co., Ltd., Zhengzhou, China) for all patients after the first admission. Combined with the manufacturer's standard values, our laboratory's reference ranges are 0.270−4.200 mIU/L for TSH, 3.10−6.80 pmol/L for FT3, 1.30−3.10 nmol/l for TT3, and 12.00−22.00 pmol/l for FT4, respectively, TT4 was 66.00–181.00 nmol/l. Low T3 syndrome was defined as low serum FT3 levels,low or normal serum FT4 and normal TSH levels.

Outcome and follow-up

All follow-up data came from the following three channels: visiting patients by telephone, viewing the patient's inpatient records, and our hospital's outpatient visit records. OS was defined as the time from diagnosis to the last follow-up until October 2021 or death from any cause. PFS is defined as the time from diagnosis to recurrence or progression. POD24 was defined as the first documented disease progression within 24 months of starting first-line therapy (immunotherapy or radiation therapy).

Statistical analysis

Statistical analysis of data was performed using SPSS statistical software (version26.0), MedCalc statistical software (version 20.1.0) and GraphPad Prism (version 9.0). Categorical variables were expressed as percentage (%) and compared by chi-square test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation or median (interquartile range). We used the Mann–Whitney *U* test for nonnormally distributed data and the *t*-test for normally distributed data. Survival curves were drawn using the Kaplan–Meier method, and differences in survival were compared using the log-rank test. Univariate and multivariate Cox regression analyses were used for independent risk factors for PFS and OS. To reduce the effects of data bias and confounding variables, propensity score matching (PSM) analysis was used to reassess to ensure a better balance. The prediction accuracy of FLIPI and low T3 syndrome and low T3 in predicting POD24 was assessed by constructing receiver

Table 1 Main clinical characteristics of 221 FL patients with or without low T3 syndrome before and after propensity matching

Variables		Unmatched (complete) dataset				Propensity score-matched (1:1) dataset			
		Total	Without low T3 syndrome ($n=199$)	Low T3 syndrome ($n=22$)	p value	Total	Without low T3 syndrome ($n=22$)	Low T3 syndrome ($n=22$)	p value
Gender	Male	104	94 (90.38%)	10 (9.62%)	0.874	19	9 (47.37%)	10 (52.63%)	0.761
	Female	117	105 (89.74%)	12 (10.26%)		25	13 (52.00%)	12 (48.00%)	
Age	< 60 years	155	141 (90.97%)	14 (9.03%)	0.483	31	17 (54.84%)	14 (45.16%)	0.322
	≥ 60 years	66	58 (87.88%)	8 (12.12%)		13	5 (38.46%)	8 (61.54%)	
ECOG PS	0−1	208	194 (93.27%)	14 (6.73%)	< 0.001	33	19 (57.58%)	14 (42.42%)	0.082
	≥ 2	13	5 (38.46%)	8 (61.54%)		11	3 (27.27%)	8 (72.73%)	
Symptoms status	A symptoms	158	152 (96.20%)	6 (3.80%)	< 0.001	20	14 (70.00%)	6 (30.00%)	0.015
	B symptoms	63	47 (74.60%)	16 (25.40%)		24	8 (33.33%)	16 (66.67%)	
Ann Arbor Stage	I/II	38	36 (94.74%)	2 (5.26%)	0.288	8	6 (75.00%)	2 (25.00%)	0.118
	III/IV	183	163 (89.07%)	20 (10.93%)		36	16 (44.44%)	20 (55.56%)	
Histological grade	1−2	190	174 (91.58%)	16 (8.42%)	0.059	36	20 (55.56%)	16 (44.44%)	0.118
	3	31	25 (80.65%)	6 (19.35%)		8	2 (25.00%)	6 (75.00%)	
LDH	≤ ULN	174	164 (94.25%)	10 (5.75%)	< 0.001	23	13 (56.52%)	10 (43.48%)	0.365
	> ULN	47	35 (74.47%)	12 (25.535%)		21	9 (42.86%)	12 (57.14%)	
β2-MG	≤ ULN	122	117 (95.90%)	5 (4.10%)	0.001	19	14 (73.68%)	5 (26.32%)	0.006
	> ULN	99	82 (82.83%)	17 (17.17%)		25	8 (32.00%)	17 (68.00%)	
HB	≥ 120	159	150 (94.34%)	9 (5.66%)	0.001	19	10 (52.63%)	9 (47.37%)	0.761
	< 120	62	49 (79.03%)	13 (20.97%)		25	12 (48.00%)	13 (52.00%)	
PLT	≥ 100	202	187 (92.57%)	15 (7.43%)	< 0.001	34	19 (55.89%)	15 (44.12%)	0.150
	< 100	19	12 (63.16%)	7 (36.84%)		10	3 (30.00%)	7 (70.00%)	
FLIPI1	0−1	42	41 (97.62%)	1 (2.38%)	0.001	6	5 (83.33%)	1 (16.67%)	0.164
	2	83	80 (96.39%)	3 (3.61%)		7	4 (57.14%)	3 (42.86%)	
	≥ 3	96	78 (81.25%)	18 (18.75%)		31	13 (41.94%)	18 (58.06%)	
FLIPI2	0−1	109	105 (96.33%)	4 (3.67%)	< 0.001	14	10 (71.43%)	4 (28.57%)	0.046
	2	49	45 (91.84%)	4 (8.16%)		10	6 (60.00%)	4 (40.00%)	
	≥ 3	63	49 (77.78%)	14 (22.22%)		20	6 (30.00%)	14 (70.00%)	
Number of nodal sites	< 5	56	56 (100.00%)	0	0.004	6	6 (100.00%)	0	0.008
	≥ 5	165	143 (86.67%)	22 (13.33%)		38	16 (42.11%)	22 (57.89%)	
Bulky lesion	≤ 6 cm	164	155 (94.51%)	9 (5.49%)	< 0.001	24	15 (62.50%)	9 (37.50%)	0.069
	> 6 cm	57	44 (77.19%)	13 (22.81%)		20	7 (35.00%)	13 (65.000	
Bone marrow	Uninvolved	133	123 (92.48%)	10 (7.52%)	0.137	27	17 (62.96%)	10 (37.04%)	0.030
	Involved	88	76 (86.36%)	12 (13.64%)		17	5 (29.41%)	12 (70.59%)	
Extranodal site (s)	≤ 2	191	175 (91.62%)	16 (8.38%)	0.048	35	19 (54.29%)	16 (45.71%)	0.262
	> 2	30	24 (80.00%)	6 (20.00%)		9	3 (33.33%)	6 (66.67%)	
ALB	≥ 40 g/L	146	141 (96.58%)	5 (3.42%)	< 0.001	18	13 (72.22%)	5 (27.78%)	0.014
	< 40/L	75	58 (77.33%)	17 (22.67%)		26	9 (34.62%)	17 (65.38%)	
ESR	men ≤ 15 mm/h women ≤ 20 mm/h	176	160 (90.9%)	16 (9.09%)	0.396	33	17 (51.52%)	16 (48.482%)	0.728
	Men > 15 mm/h Women > 20 mm/h	45	39 (86.67%)	6 (13.33%)		11	5 (45.45%)	6 (54.55%)	
CRP	≤ 10 mg/L	183	172 (93.99%)	11 (6.01%)	< 0.001	28	17 (60.71%)	11 (39.29%)	0.060
	> 10 mg/L	38	27 (71.05%)	11 (28.95%)		16	5 (31.25%)	11 (68.75%)	
The spleen involved	Uninvolved	202	183 (90.59%)	19 (9.41%)	0.374	40	21 (52.50%)	19 (47.50%)	0.294
	Involved	19	16 (84.21%)	3 (15.79%)		4	1 (25.00%)	3 (75.00%)	

Table 1 (continued)

Variables		Unmatched (complete) dataset				Propensity score-matched (1:1) dataset			
		Total	Without low T3 syndrome ($n=199$)	Low T3 syndrome ($n=22$)	p value	Total	Without low T3 syndrome ($n=22$)	Low T3 syndrome ($n=22$)	p value
Pleural and abdominal effusion	Absence	213	193 (90.61%)	20 (9.39%)	0.148	39	19 (48.72%)	20 (51.28%)	0.635
	Presence	8	6 (75.00%)	2 (25.00%)		5	3 (60.00%)	2 (40.00%)	
Treatment	chemotherapy ± Rituximab	156	143 (91.67%)	13 (8.3%)	< 0.001	29	16 (55.17%)	13 (44.83%)	0.236
	Rituximab monotherapy immunotherapy	25	23 (92.0%)	2 (8.0%)		3	1 (33.33%)	2 (66.67%)	
	Other reduced-intensity chemotherapy	16	9 (56.3%)	7 (43.8%)		10	3 (30.0%)	7 (70.0%)	
	Radiation therapy	3	3 (100.0%)	0		0	0	0	
	observed and waited	21	21 (100.0%)	0		2	2 (100.0%)	0	

ALB, serum albumin; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *ECOG*, eastern cooperative oncology group; *FL*,follicular lymphoma; *FLIPI-1* the Follicular Lymphoma International Prognostic Index 1;*FLIPI-2* the Follicular Lymphoma International Prognostic Index2; *Hb*, hemoglobin; *LDH*, lactate dehydrogenase; *PLT*, platelet; *ULN*, upper limit of normal; *β-2MG*, β2-microglobulin. *P* value < 0.05 in italic font is statistically significant. The tests used in Table 1 were the $\chi 2$ test or the Fisher's exact test

operating characteristic (ROC) curves and corresponding area under the curve (AUC). A two-sided *P* value of < 0.05 was considered statistically significant.

Result

Clinical features

A total of 221 FL patients with detailed thyroid hormone records were analyzed, and the baseline clinical characteristics are shown in Table 1. Among them, 104 (47.1%) were male and 117 (52.9%) were female, with a median age of 54 years (range 22−89 years). Two hundred and eight patients (94.1%) had an ECOG score of 0−1, and 63 patients (28.5%) were accompanied by symptom B. There were 183 (82.8%) patients with Ann Arbor stage III/IV, 190 patients (86.0%) had histological grades 1−2, 31 cases (14.0%) were grade 3, and 165 (74.7%) with more than 5 involved lymph node regions. Fifty-seven cases (25.8%) had the largest lymph node with a maximum diameter of > 6 cm. There were 30 patients (13.6%) with more than 2 extra-nodal sites involved, 88 patients (39.8%) with bone marrow involved, 19 patients (8.6%) with spleen involved, 8 patients (3.9%) with pleural and abdominal effusion, and 96 patients (43.4%) with FLIPI-1 score 3−5, while 63 patients (28.1%) had a FLIPI-2 score 3−5.

Twenty-two (10.0%) patients had low T3 syndrome at the time of diagnosis. The demographics, clinical parameters, and laboratory tests of the euthyroid group and patients with low T3 syndrome are shown in Table 1. Compared with patients of normal thyroid function, patients with low T3 syndrome were more likely to have B symptom, higher ECOG score ($P < 0.001$), more extensive lymph node involvement, and higher incidence of large mass ($P < 0.001$). More than 2 extranodal sites were more likely to be involved ($P = 0.048$). Laboratory results showed that decreased hemoglobin (Hb), platelet (PLT), and ALB, as well as increased LDH, β2-MG and CRP were significantly associated with low T3 syndrome, with a *P* value of about 0.001. In addition, patients with a score 3−5 of FLIPI-1 or FLIPI-2 were more likely to develop a low T3 syndrome.

PFS and OS curves for the entire queue

The median PFS for all 221 patients was 48 months, and the overall PFS was 85.97% (95% CI 80.77−89.94%) at 2 years, 75.11% (95% CI 69.01−80.35%) at 5 years, and 45.17% (95% CI 38.82−51.84%) at 10 years. The median OS was 54 months and overall survival was 92.76% (95% CI 88.56−95.49%) at 2 years, 87.76% (95% CI 82.81−91.46%) at 5 years, and 71.81% (95% CI 65.69−77.46%) at 10 years (Fig. 2A, B).

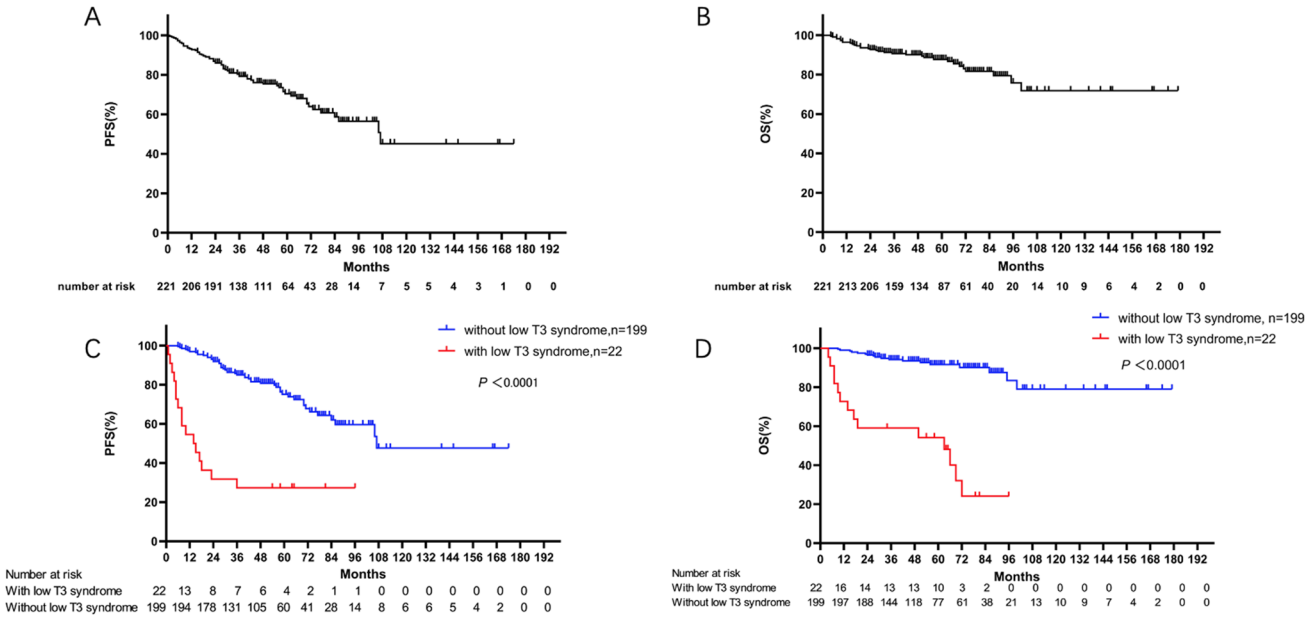

Fig. 2 **A**. The PFS and OS curves (**A** and **B**) for the whole cohort. Kaplan–Meier curves of PFS (**C**) and OS (**D**) stratified by low T3 syndrome before propensity matching. Abbreviations: PFS, progression-free survival; OS, overall survival; T3, triiodothyronine

Prognostic value of low T3 syndrome in FL

Two hundred and twenty-one patients with FL were finally followed up to October 31, 2021, with a median follow-up of 54 months (range 4−179 months). 200 patients (90.5%) were treated, and 21 patients (9.5%) were not treated during follow-up management. Disease progression occurred in 68 patients (30.8%), including 32 patients (14.5%) who progressed within 24 months (POD24), and 34 (15.4%) who developed progression after 24 months. By the end of follow-up, 32 patients (14.5%) had died. As shown in Fig. 2 C and D, patients with low T3 syndrome had significantly shorter median PFS than those without low T3 syndrome (14.5 months vs 49 months, $P<0.0001$). For OS, the median survival was 52 months for patients with low T3 syndrome while non-low T3 syndrome patients did not achieve median survival ($P<0.0001$).

We performed univariate and multivariate COX regression analysis of PFS and OS to study the adverse prognostic factors of FL, as shown in Table 2. Bone marrow infiltration (HR = 5.334; 95% CI: 1.836−15.498; $P=0.002$), FLIPI-2(3−5) score (HR = 0.090; 95% CI: 0.019−0.420; $P=0.002$), low T3 syndrome (HR = 0.182; 95% CI: 0.061−0.546; $P=0.002$) were independent prognostic factors for OS; β2-MG (HR = 0.365; 95% CI: 0.176−0.761; $P=0.007$), ECOG ≥ 2 (HR = 0.301; 95% CI: 0.119−0.763; $P=0.011$), low T3 syndrome (HR = 0.271; 95% CI: 0.124−0.592; $P=0.001$) were independent prognostic factors of PFS. Therefore, low T3 syndrome is an independent prognostic factor for PFS and OS.

Subgroup analysis of low T3 syndrome in FL

In the subgroup analysis, patients were divided into two groups according to age, ECOG score, symptoms status, large mass, FLIPI score, β2-MG and LDH level. We found that low T3 syndrome showed worse OS in patients with ECOG score 0−1 ($P<0.001$) and no significant difference in patients with ECOG score ≥ 2 ($P=0.0586$), but there were significant differences in PFS between the two groups. For PFS, there was no significant difference among patients with A symptoms and Bulky lesion > 6 cm ($P=0.0586$, $P=0.0648$). These results suggest that low T3 syndrome is more effective as a predictor of poor prognosis in patients with low ECOG score. For PFS, low T3 syndrome with B symptoms and Bulky lesion ≤ 6 cm performed worse. However, regardless of age, FLIPI score, β2-MG, and LDH level, low T3 syndrome was a prognostic factor for poor FL (supplement Fig. 1).

Propensity score matching analysis

To minimize confounding bias in non-randomized controlled studies and further confirm the results observed in the entire cohort, we performed a PSM analysis. Given the imbalance of baseline features between patients with low T3 syndrome and those without low T3 syndrome in FL, we used a 1:1 match. In this study, the differences in clinical and laboratory distribution characteristics between the low T3 syndrome group and the non-low T3 syndrome group were significantly improved by PSM, which improved the reliability of subsequent analysis and research conclusions. After 1:1 matching, there were 22 patients

Table 2 Univariate and multivariate Cox regression analyses of PFS and OS before and after propensity matching

		Unmatched (complete) dataset				Propensity score-matched (1:1) dataset			
		Univariate analyses		Multivariate analyses		Univariate analyses		Multivariate analyses	
	Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
OS	age ≥ 60 years	0.420 (0.210–0.841)	**0.014**	1.712 (0.638–4.598)	**0.286**	0.526 (0.211–1.310)	**0.167**	1.706 (0.378–7.706)	**0.487**
	Hb < 120 g/L	0.316 (0.158–0.633)	**0.001**	2.315 (0.808–6.633)	**0.118**	0.648 (0.254–1.654)	**0.365**	11.019 (1.542–78.759)	**0.017**
	LDH > ULN (271 U/l)	0.199 (0.099–0.400)	**< 0.001**	0.477 (0.159–1.431)	**0.187**	0.269 (0.096–0.748)	**0.012**	0.241 (0.023–2.560)	**0.238**
	Ann Arbor Stage III/IV	0.480 (0.146–1.576)	**0.226**	1.366 (0.296–6.302)	**0.690**	0.743 (0.216–2.558)	**0.638**	2.337 (0.161–34.004)	**0.534**
	Involved nodal sites ≥ 5	0.390 (0.137–1.111)	**0.078**	3.330 (0.748–14.835)	**0.114**	0.236 (0.031–1.782)	**0.161**	2.759 (0.098–78.058)	**0.552**
	β2-MG > ULN (2.53 mg/L)	0.109 (0.038–0.312)	**< 0.001**	0.276 (0.068–1.115)	**0.071**	0.227 (0.071–0.693)	**0.009**	0.413 (0.014–12.052)	**0.607**
	Bone marrow involvement	0.625 (0.311–1.255)	**0.186**	5.334 (1.836–15.498)	**0.002**	0.497 (0.200–1.236)	**0.133**	66.900 (5.125–873.334)	**0.001**
	Bulky lesion > 6 cm	0.143 (0.069–0.297)	**< 0.001**	0.523 (0.201–1.357)	**0.183**	0.085 (0.024–0.297)	**< 0.001**	0.243 (0.033–1.789)	**0.165**
	B symptoms	0.241 (0.119–0.489)	**< 0.001**	0.463 (0.176–1.220)	**0.119**	0.219 (0.071–0.675)	**0.008**	0.049 (0.005–0.501)	**0.011**
	ECOG grade ≥ 2	0.090 (0.043–0.187)	**< 0.001**	0.347 (0.101–1.185)	**0.091**	0.197 (0.080–0.488)	**< 0.001**	0.939 (0.187–4.722)	**0.939**
	tissue grade: III	0.547 (0.236–1.266)	**0.159**	1.791 (0.711–4.515)	**0.217**	0.594 (0.214–1.653)	**0.319**	1.538 (0.426–5.552)	**0.511**
	FLIPI–I (high vs. low/int.)	0.171 (0.070–0.417)	**< 0.001**	0.778 (0.163–3.712)	**0.753**	0.347 (0.101–1.198)	**0.094**	28.797 (0.418–1981.742)	**0.120**
	FLIPI–2 (high vs. low/int.)	0.124 (0.057–0.268)	**< 0.001**	0.090 (0.019–0.420)	**0.002**	0.161 (0.057–0.457)	**0.001**	0.003 (0.000–0.196)	**0.007**
	Low T3 syndrome	0.098 (0.048–0.200)	**< 0.001**	0.182 (0.061–0.546)	**0.002**	0.188 (0.061–0.579)	**0.004**	0.052 (0.006–0.436)	**0.006**
PFS	age ≥ 60 years	0.556 (0.340–0.908)	**0.002**	0.933 (0.453–1.921)	**0.851**	0.479 (0.213–1.080)	**0.076**	1.782 (0.412–7.715)	**0.440**
	Hb < 120 g/L	0.456 (0.279–0.746)	**0.002**	0.812 (0.404–1.632)	**0.559**	0.612 (0.266–1.405)	**0.247**	1.534 (0.363–6.477)	**0.560**
	LDH > ULN (271 U/l)	0.401 (0.242–0.662)	**< 0.001**	0.948 (0.451–1.993)	**0.888**	0.356 (0.150–0.846)	**0.019**	0.932 (0.178–4.879)	**0.934**
	Ann Arbor Stage III/IV	0.501 (0.228–1.097)	**0.084**	0.956 (0.359–2.546)	**0.929**	0.951 (0.353–2.556)	**0.920**	9.218 (0.868–97.891)	**0.065**
	Involved nodal sites ≥ 5	0.499 (0.261–0.955)	**0.036**	1.219 (0.524–2.837)	**0.646**	0.347 (0.080–1.503)	**0.157**	0.411 (0.028–6.093)	**0.518**
	β2-MG > ULN (2.53 mg/L)	0.248 (0.144–0.428)	**< 0.001**	0.365 (0.176–0.761)	**0.007**	0.179 (0.065–0.492)	**0.001**	0.161 (0.019–1.372)	**0.095**
	Bone marrow involvement	0.604 (0.373–0.980)	**0.041**	1.437 (0.730–2.826)	**0.294**	0.692 (0.307–1.558)	**0.374**	35.681 (5.360–237.519)	**0.000**
	Bulky lesion > 6 cm	0.330 (0.202–0.540)	**< 0.001**	0.553 (0.302–1.010)	**0.054**	0.169 (0.067–0.422)	**0.000**	0.268 (0.054–1.329)	**0.107**
	B symptoms	0.426 (0.261–0.695)	**0.001**	0.889 (0.485–1.630)	**0.704**	0.227 (0.083–0.617)	**0.004**	0.207 (0.042–1.026)	**0.054**
	ECOG grade ≥ 2	0.172 (0.089–0.331)	**< 0.001**	0.301 (0.119–0.763)	**0.011**	0.269 (0.117–0.617)	**0.002**	0.579 (0.103–3.261)	**0.535**
	tissue grade: III	0.807 (0.412–1.583)	**0.533**	1.502 (0.715–3.154)	**0.282**	0.734 (0.274–1.970)	**0.540**	1.574 (0.449–5.515)	**0.478**
	FLIPI–I (high vs. low/int.)	0.344 (0.207–0.571)	**< 0.001**	0.993 (0.405–2.434)	**0.988**	0.312 (0.106–0.922)	**0.035**	1.621 (0.074–35.620)	**0.759**
	FLIPI–2 (high vs. low/int.)	0.268 (0.165–0.436)	**< 0.001**	0.609 (0.245–1.513)	**0.286**	0.214 (0.090–0.511)	**0.001**	0.039 (0.002–0.652)	**0.024**
	Low T3 syndrome	0.170 (0.096–0.301)	**< 0.001**	0.271 (0.124–0.592)	**0.001**	0.246 (0.099–0.611)	**0.003**	0.136 (0.029–0.629)	**0.011**

95% CI, 95% confidence interval; *ECOG*, eastern cooperative oncology group; *Hb*, hemoglobin; *HR*, hazard ratio; *IGHV*, immunoglobulin heavy chain variable region; *LDH*, lactate dehydrogenase; *PLT*, platelet; *PS*, performance status; *T3*, triiodothyronine; *β2-MG*, β2-microglobulin

in each group. As shown in Kaplan–Meier survival curves after matching (Fig. 3), the differences in OS between the two groups were statistically significant, but PFS showed no obvious significant difference. Furthermore, multivariate analysis showed that low T3 syndrome remains an independent prognostic factor for PFS (HR = 0.136; 95% CI: 0.029–0.629; *P* = 0.011) and OS (HR = 0.052; 95% CI: 0.006–0.436; *P* = 0.006) (Table 2).

Correlation between FT3, FT4, and low T3 syndrome and short-term survival

According to the time of disease progression, there were 32 patients (14.5%) with POD24, 34 patients (15.4%) with progression of disease (POD) greater than 24 months, and the remaining 155 patients had no POD. The level of FT3

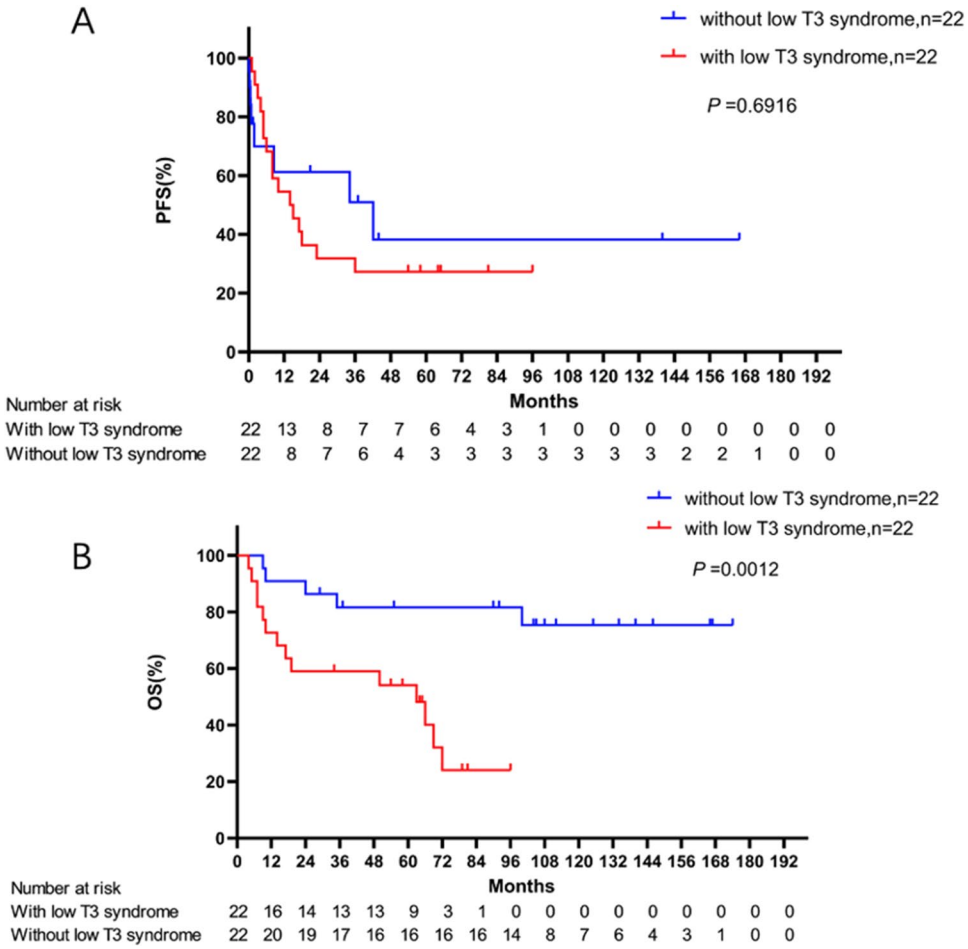

Fig. 3 Kaplan–Meier curves of PFS (**A**) and OS (**B**) stratified by low T3 syndrome after propensity matching. Abbreviations: T3, triiodothyronine; PFS, progression-free survival; OS, overall survival

of POD24 patients (3.34 ± 1.14 pmol/L) was the lowest, and the level of FT3 (4.40 ± 0.72 pmol/L) was the highest in patients without POD, and the difference was significant ($P < 0.001$). The patients with POD24 had the highest incidence of low T3 syndrome among the three subgroups (46.9%) ($P = 0.001$), with significant differences between the subgroups. Regarding the OS group, 189 patients (85.5%) were alive, and among the 32 patients who died, 16 (7.2%) died within 2 years of diagnosis, and the other 16 (7.2%) were non-surviving patients with OS > 2 years. FL patients with OS ≤ 2 years had the lowest level of FT3 (3.31 ± 1.38 pmol/L) and FT4 (16.04 ± 4.09 pmol/L), but there was no significant difference in the prevalence of low T3 syndrome among the three groups ($P = 0.554$) (Table 3). Low T3 syndrome is not associated with short-term OS status. To further evaluate the value of FT3 in predicting POD24, we plotted the ROC curve for FT3 in the entire cohort. The sensitivity and specificity of FT3 in predicting POD24 in FL patients were 94.62% and 60.71%, (AUC = 0.7817) (Fig. 4).

Low T3 syndrome improves the risk stratification of FLIPI

In multivariate analysis, low T3 syndrome was an independent prognostic predictor of PFS and OS. Since the incidence of low T3 syndrome is highest in patients with PFS or OS less than 24 months, we introduced PFS and OS at 24 months to better analyze the impact of low T3 syndrome on short-term progression and disease-related death. Currently, the prognosis of FL patients is predicted by FLIPI standard, including FLIPI-1 and FLIPI-2. We included FLIPI-1/FLIPI-2 and low T3 syndrome to generate a new prognostic index FLPI-1/FLPI-2, respectively, and compared its predictive power with FLIPI-1/FLIPI-2 alone for PFS, OS, 24-month PFS, and 24-month OS. The results showed that the new FLPI-1 significantly increased the AUC of PFS and OS compared with FLIPI-1 alone (PFS 0.699 vs 0.686, $P = 0.0078$; OS 0.806 vs 0.780, $P = 0.0109$) (Fig. 5A–B). Similarly for 24-month PFS and 24-month OS, FLPI-1 also show statistically higher accuracy than FLIPI-1 alone (for 24-month PFS, AUC: 0.791 vs 0.758, P = 0.0023,

Table 3 FT3, FT4 levels and incidence of low T3 syndrome according to POD and OS status

Status of POD and OS		Total	FT3 (pmol/l)	*P* value	FT4 (pmol/l)	*P* value	Low T3 syndrome ($n=22$) (%)	*P* value
POD	POD24	32	3.34 ± 1.14	< 0.001	17.17 ± 4.06	0.013	15 (46.88%)	0.001
	POD > 24 months	34	4.30 ± 0.68		18.65 ± 3.27		1 (2.94%)	
	Non-POD	155	4.40 ± 0.72		17.21 ± 2.64		6 (3.87%)	
OS	Non-survivor with OS ≤ 2 years	16	3.31 ± 1.38	< 0.001	16.04 ± 4.09	0.009	8 (50.00%)	0.554
	Non-survivor with OS > 2 years	16	3.61 ± 1.01		18.81 ± 4.08		5 (32.25%)	
	Survivor	189	4.36 ± 0.72		17.42 ± 2.76		9 (4.76%)	

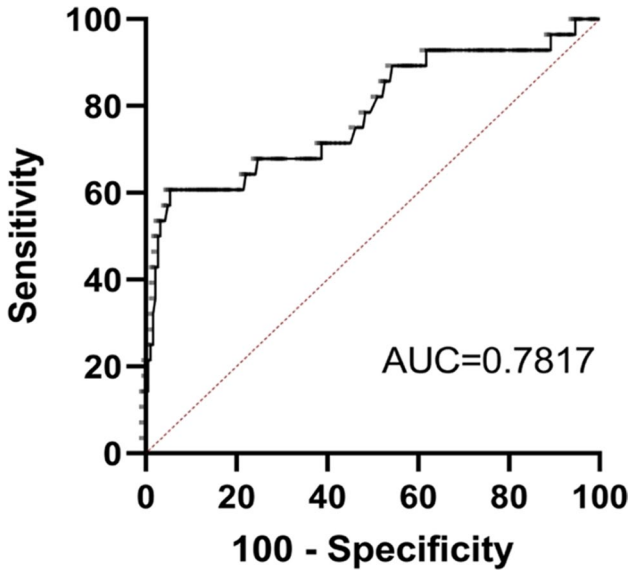

Fig. 4 Receiver operating characteristic (ROC) curve of the ability of FT3 to predict POD24 in patients with FL. The area under curve (AUC) for FT3 was 0.7817, with 94.62% sensitivity and 60.71% specificity

while for 24-month OS, AUC: 0.793 vs 0.757, P = 0.0204) (Fig. 5C–D). Similarly, our new FLPI-2, a combination of FLIPI-2 and low T3 syndrome, was a better prognostic indicator for PFS and OS (PFS, AUC: 0.744 vs 0.732, $P=0.0078$; OS, AUC: 0.854 vs 0.830, $P=0.0030$), especially for 24-month PFS (AUC: 0.884 vs 0.807, $P=0.0056$) and 24-month OS (AUC: 0.871 vs 0.834, $P=0.0042$). Therefore, our new FLPI, the combination of FLIPI and low T3 syndrome, is a better prognostic indicator for PFS and OS, as well as 24 months of PFS and 24 months of OS.

Discussion

Low T3 syndrome refers to abnormal thyroid function caused by non-thyroid diseases. In recent years, studies have found that low T3 syndrome (ESS or NTIS) is associated with poor prognosis of cancer [17]. Our study shows that low T3 syndrome can be an independent adverse prognostic factor for FL, even after adjusting for possible confounders.

Thyroid hormone plays an important role in various clinical non-thyroid diseases, such as acute myocardial infarction, respiratory failure, severe infection [26], and even Crohn's disease [27]. In these acute severe and chronic wasting diseases, the occurrence of low T3 syndrome was generally considered to be a self-protective adaptive response when the body was traumatized in the past [28]. However, there is increasing evidence that the severity of low T3 levels is associated with disease progression [29] and is a poor prognostic factor for these diseases. In addition, low T3 also reached 31.9% in elderly patients hospitalized for acute diseases [30, 31]. Low FT3 is considered as a possible marker of frailty in the elderly [32]. As for the occurrence of low T3 syndrome in malignant tumors, Yasar et al. reported that it accounts for 42.25% in non-small cell lung cancer and 44.90% in small cell lung cancer [33]. The prevalence of low T3 syndrome in breast cancer patients diagnosed for the first time (16.5%) was also higher than that in benign breast lesions (7.3%) [34]. Our study found that the incidence of low T3 syndrome in FL was 10%, lower than the results of the above study and also lower than the results of our team's previous studies in DLBCL (12.77%) [23] and CLL (14.34%) [22], considering that FL is an indolent non-Hodgkin's lymphoma (NHL),usually with favorable outcomes [35].

By analyzing the baseline characteristics of FL, we found that patients with low T3 syndrome often have B symptoms, worse physical status, extensive involvement of lymph nodes, and frequent large mass and extranodal organs, which all showed that the occurrence of low T3 syndrome is positively correlated with the severity of various parameters in FL patients. This has also been confirmed in other disease studies. Pingitore et al. found that T3 measurement contributes to the risk stratification of patients with heart failure [36]. Low T3 level is not only a prognostic marker, but also directly related to the progression of heart failure. In laboratory data, low T3 is positively correlated with anemia and ALB levels, while negatively correlated with CRP, which is consistent with the report of Fan et al. [37], suggesting that

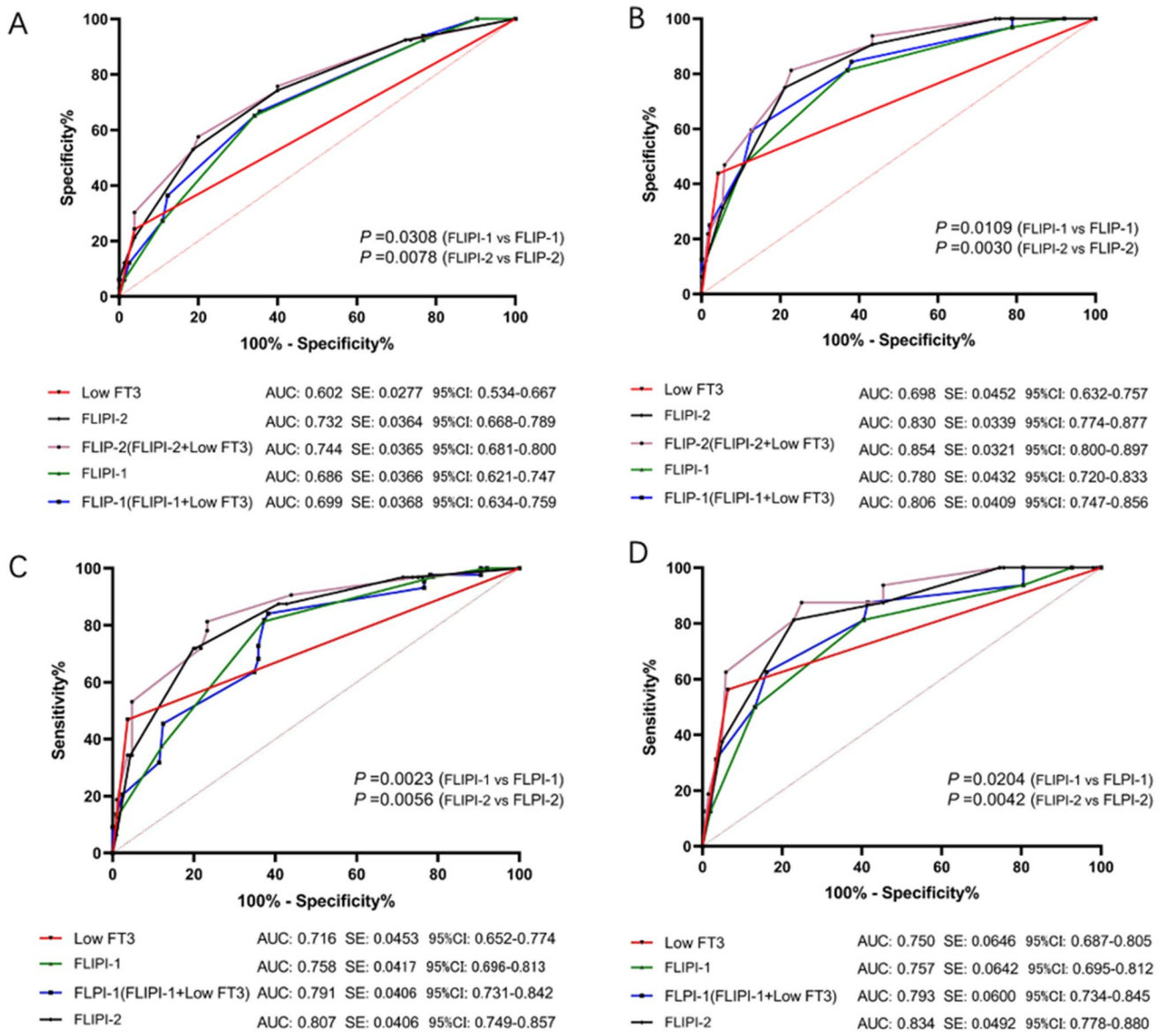

Fig. 5 FLIPI together with low T3 syndrome is a better prognostic index for PFS and OS (**A** and **B**), and FLIPI together with low T3 syndrome is a better prognostic index for 24-month PFS (**A**) and 24-month OS (**B**) in FL Abbreviations: PFS, progression-free survival; OS, overall survival; FLIPI, FL International Prognostic Index; FLPI, FL Prognostic Index (FLIPI + low T3); AUC, area under the curve; SE, standard error; 95% CI, 95% confidence interval

the occurrence of low T3 syndrome may be related to anemia, chronic wasting malnutrition and inflammation.

However, the mechanism of low T3 syndrome has not yet been fully elucidated. Combined with our research results, it is believed that it may be related to the following factors: (1) the activity of 5' deiodinase caused by anemia is inhibited [38], which in turn converts T4 to T3. (2) The involvement of a variety of cytokines [39], especially in critically ill patients with hematological tumors, often complicated with infection, and then the high expression of a series of cytokines, such as interleukin-6 (IL-6), interferon γ (IFNγ), tumor necrosis factor α (TNFα), inhibits the synthesis of thyroid hormones; Glasgowscoring system (GPS) has been used to assess inflammation and nutritional status of cancer patients, suggesting systemic inflammatory response and nutritional deterioration in cancer patients with high CRP level and low ALB level [40]. In this study, patients with low T3 syndrome also showed higher CRP level and lower serum ALB level. Considering the long-term wasting tumor like FL, the body will have negative nitrogen balance, decreased ALB and thyroglobulin levels, and accelerated T4 clearance rate, which aggravate the decrease of T3 and T4 levels [41].

Our study found that FL patients with low T3 syndrome exhibited worse PFS ($P<0.0001$) and OS ($P<0.0001$) and were independent prognostic predictors of PFS ($P=0.001$) and

OS ($P=0.002$). This is consistent with our previous observations in CLL [22] and DLBCL [23]. POD24 as a risk factor for poor prognosis in FL has been confirmed by many studies, especially Casulo et al. conducted a prospective multicenter study of more than 5000 patients from 13 randomized trials, proving that POD24 was an early clinical endpoint of poor survival in FL patients [42]. Our study found that low T3 syndrome is closely related to POD24, which has a certain predictive value. In addition, FLIPI-1 and FLIPI-2 are currently recognized as effective prognostic scoring models for FL, but their ability to discriminate high-risk patients is limited. We introduced new prognostic models FLPI-1 and FLPI-2 constructed after low T3 syndrome into both prognostic models, which significantly improved the accuracy of FLIPI in predicting PFS and OS.

In conclusion, low T3 syndrome is associated with worse prognosis in FL and is an independent prognostic predictor of PFS and OS in FL patients. FLIPI combined with low T3 syndrome improved the ability to predict PFS and OS, and low T3 is a risk factor for POD24.Thyroid function test is simple and reproducible, which can be used as a routine measurement parameter and may be a good candidate for predicting FL prognosis in the future. However, this study was a single-center retrospective study with a limited sample size and inevitable confounding factors. Further prospective studies in a larger sample size and multi-center population are needed to verify our findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-023-05117-5.

Acknowledgements This study was supported by National Natural Science Foundation of China (81720108002), Jiangsu Province's Medical Elite Programme (ZDRCA2016022), Project of National Key Clinical Specialty, Jiangsu Provincial Special Program of Medical Science (BE2017751), National Science and Technology Major Project (2018ZX09734007).

Author contribution Lian-Guo Xue, Hao-Rui Shen, and Rui Gao: conceptualization, methodology, data curation, formal analysis, writing-original draft, and visualization. Kai-Xin Du, Tong-Yao Xing, and Wei-Ting Wang: data curation, formal analysis, and visualization. Li Wang and Jin-Hua Liang: conceptualization, writing-review & editing, and supervision. Wei Xu and Jian-Yong Li: conceptualization, methodology, funding acquisition, supervision, writing-review & editing.

Data Availability The date that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Freedman A, Jacobsen E (2020) Follicular lymphoma: 2020 update on diagnosis and management. Am J Hematol J Artic; Rev 95(3):316–27
2. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R et al (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood J Artic; Rev; Res Support, N.I.H., Extramural; Res Support, Non-U S Gov't] 127(20):2375–90
3. Kridel R, Sehn LH, Gascoyne RD (2012) Pathogenesis of follicular lymphoma. J Clin Invest J Artic; Res Support, Non-U S Gov't; Rev 122(10):3424–31
4. Kumagai S, Tashima M, Fujikawa J, Iwasaki M, Iwamoto Y, Sueki Y et al (2014) Ratio of peripheral blood absolute lymphocyte count to absolute monocyte count at diagnosis is associated with progression-free survival in follicular lymphoma. Int J Hematol J Artic 99(6):737–42
5. Casulo C (2021) Upfront identification of high-risk follicular lymphoma. Hematol Oncol J Artic; Rev 39 Suppl 1(1):88–93
6. Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R et al (2004) Follicular lymphoma international prognostic index. Blood J Artic; Res Support, Non-U S Gov't 104(5):1258–65
7. Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U et al (2009) Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol J Artic; Res Support, Non-U S Gov't 27(27):4555–62
8. Gilani N, Wang K, Muncan A, Peter J, An S, Bhatti S et al (2021) Triiodothyronine maintains cardiac transverse-tubule structure and function. J Mol Cell Cardiol J Artic; Res Support, N I H, Extramural 160:1–14
9. Pingitore A, Mastorci F, Piaggi P, Aquaro GD, Molinaro S, Ravani M et al (2019) Usefulness of triiodothyronine replacement therapy in patients with ST elevation myocardial infarction and borderline/reduced triiodothyronine levels (from the THIRST Study). Am J Cardiol J Artic; Randomized Control Trial 123(6):905–12
10. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I et al (2018) Thyroid hormones and cardiovascular function and diseases. J Am Coll Cardiol J Artic; Rev 71(16):1781–96
11. Su W, Zhao XQ, Wang M, Chen H, Li HW (2018) Low T3 syndrome improves risk prediction of in-hospital cardiovascular death in patients with acute myocardial infarction. J Cardiol Eval Study; J Artic; Res Support, Non-U S Gov't] 72(3):215–9
12. Sato Y, Yoshihisa A, Kimishima Y, Kiko T, Kanno Y, Yokokawa T et al (2019) Low T3 syndrome is associated with high mortality in hospitalized patients with heart failure. J Card Fail 25(3):195–203
13. Liu J, Wu X, Lu F, Zhao L, Shi L, Xu F (2016) Low T3 syndrome is a strong predictor of poor outcomes in patients with community-acquired pneumonia. Sci Rep 6(1):22271
14. Xu J, Wang L (2019) Low T3 syndrome as a predictor of poor prognosis in patients with pyogenic liver abscess. Front Endocrinol 10:541
15. Inaba M, Mori K, Tsujimoto Y, Yamada S, Yamazaki Y, Emoto M et al (2021) Association of reduced free T3 to free T4 ratio with lower serum creatinine in Japanese hemodialysis patients. Nutrients 13(12):4537
16. Qiao S, Zhang SC, Zhang RR, Wang L, Wang ZH, Jiang J et al (2022) Thyroid function and low free triiodothyronine in Chinese patients with autoimmune encephalitis. Front Immunol J Artic; Res Support, Non-U S Gov't 13:821746
17. Bunevicius A, Deltuva V, Tamasauskas S, Tamasauskas A, Laws EJ, Bunevicius R (2013) Low triiodothyronine syndrome as a predictor of poor outcomes in patients undergoing brain tumor surgery: a pilot study: clinical article. J Neurosurg J Artic; Res Support, Non-U S Gov't 118(6):1279–87
18. Huang G, Zeng Y, Cheng Q, Cheng H, Ruan Y, Yuan C et al (2019) Low triiodothyronine syndrome is associated with

hemorrhagic transformation in patients with acute ischaemic stroke. Aging (Albany, NY) 11(16):6385–97
19. Chen M, Zhou W, Xu W (2021) Thyroid function analysis in 50 patients with COVID-19: a retrospective study. Thyroid J Article; Res Support, Non-U S Gov't 31(1):8–11
20. Sciacchitano S, De Vitis C, D'Ascanio M, Giovagnoli S, De Dominicis C, Laghi A et al (2021) Gene signature and immune cell profiling by high-dimensional, single-cell analysis in COVID-19 patients, presenting Low T3 syndrome and coexistent hematological malignancies. J Transl Med J Artic; Res Support, Non-U S Gov't 19(1):139
21. Mohn A, Di Marzio A, Cerruto M, Angrilli F, Fioritoni C, Chiarelli F (2001) Euthyroid sick syndrome in children with Hodgkin disease. Pediatr Hematol Oncol J Artic 18(3):211–5
22. Gao R, Chen RZ, Xia Y, Liang JH, Wang L, Zhu HY et al (2018) Low T3 syndrome as a predictor of poor prognosis in chronic lymphocytic leukemia. Int J Cancer J Artic; Res Support, Non-U S Gov't 143(3):466–77
23. Gao R, Liang J, Wang L, Zhu H, Wu W, Wu J et al (2017) Low T3 syndrome is a strong prognostic predictor in diffuse large B cell lymphoma. Brit J Haematol 177(1):95–105
24. Meignan M, Cottereau AS, Versari A, Chartier L, Dupuis J, Boussetta S et al (2016) Baseline metabolic tumor volume predicts outcome in high-tumor-burden follicular lymphoma: a pooled analysis of three multicenter studies. J Clin Oncol J Artic 34(30):3618–26
25. Sabattini E, Bacci F, Sagramoso C, Pileri SA (2010) WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview. Pathologica Editorial 102(3):83–7
26. Plikat K, Langgartner J, Buettner R, Bollheimer LC, Woenckhaus U, Scholmerich J et al (2007) Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. Metab Clin Trial; J Artic 56(2):239–44
27. Liu S, Ren J, Zhao Y, Han G, Hong Z, Yan D et al (2013) Nonthyroidal illness syndrome: is it far away from Crohn's disease? J Clin Gastrolenterol Comp Study; J Artic; Res Support, Non-U S Gov't 47(2):153–9
28. Utiger RD (1995) Altered thyroid function in nonthyroidal illness and surgery. To treat or not to treat? N Engl J Med Comment; Editorial 333(23):1562–3
29. Iltumur K, Olmez G, Ariturk Z, Taskesen T, Toprak N (2005) Clinical investigation: thyroid function test abnormalities in cardiac arrest associated with acute coronary syndrome. Crit Care Compa Study; Control Clin Trial; J Artic 9(4):R416-24
30. Boelaert K (2013) Thyroid dysfunction in the elderly. Nat Rev Endocrinol J Artic; Rev 9(4):194–204
31. Tognini S, Marchini F, Dardano A, Polini A, Ferdeghini M, Castiglioni M et al (2010) Non-thyroidal illness syndrome and short-term survival in a hospitalised older population. Age Ageing J Artic; Res Support, Non-U S Gov't] 39(1):46–50
32. Bertoli A, Valentini A, Cianfarani MA, Gasbarra E, Tarantino U, Federici M (2017) Low FT3: a possible marker of frailty in the elderly. Clin Interv Aging J Arti; Observational Study 12:335–41
33. Yasar ZA, Kirakli C, Yilmaz U, Ucar ZZ, Talay F (2014) Can non-thyroid illness syndrome predict mortality in lung cancer patients? A prospective cohort study. Horm Cancer J Artic 5(4):240–6
34. Huang J, Jin L, Ji G, Xing L, Xu C, Xiong X et al (2013) Implication from thyroid function decreasing during chemotherapy in breast cancer patients: chemosensitization role of triiodothyronine. BMC Cancer J Artic 13:334
35. Sarkozy C, Maurer MJ, Link BK, Ghesquieres H, Nicolas E, Thompson CA et al (2019) Cause of death in follicular lymphoma in the first decade of the rituximab era: a pooled analysis of French and US cohorts. J Clin Oncol J Arti; Res Support, N I H, Extramural 37(2):144–52
36. Pingitore A, Landi P, Taddei MC, Ripoli A, L Abbate A, Iervasi G (2005) Triiodothyronine levels for risk stratification of patients with chronic heart failure. Am J Med 118(2):132–6
37. Fan J, Yan P, Wang Y, Shen B, Ding F, Liu Y (2016) Prevalence and clinical significance of low T3 syndrome in non-dialysis patients with chronic kidney disease. Med Sci Monit J Artic; Res Support, Non-U S Gov't 22:1171–9
38. Galli E, Pingitore A, Iervasi G (2010) The role of thyroid hormone in the pathophysiology of heart failure: clinical evidence. Heart Fail Rev J Artic; Rev 15(2):155–69
39. Wajner SM, Goemann IM, Bueno AL, Larsen PR, Maia AL (2011) IL-6 promotes nonthyroidal illness syndrome by blocking thyroxine activation while promoting thyroid hormone inactivation in human cells. J Clin Invest J Artic; Res Support, N I H, Extramural; Res Support, Non-U S Gov't 121(5):1834–45
40. McMillan DC (2009) Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care J Artic; R Support, Non-U S Gov't; Rev 12(3):223–6
41. Bello G, Pennisi MA, Montini L, Silva S, Maviglia R, Cavallaro F et al (2009) Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. Chest J Art 135(6):1448–54
42. Casulo C, Dixon JG, Le-Rademacher J, Hoster E, Hochster HS, Hiddemann W et al (2022) Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. Blood J Artic; Res Support, Non-U S Gov't 139(11):1684–93