Thyroid-stimulating hormone suppression in low-risk papillary thyroid cancer: a large-scale retrospective analysis of real-world data

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Summary

Background Over 500,000 new cases are diagnosed with papillary thyroid cancer (PTC) globally per year, of whom the vast majority are in the low-risk stratification. Although thyroid-stimulating hormone (TSH) suppression is traditionally recommended for all postoperative PTCs in current guidelines, its necessity remains highly controversial in low-risk patients. Since relevant recommendations in current guidelines are still empirical, we aim to provide a direct, large-scale, real-world evidence.

Methods This large-scale real-world retrospective study included 11,140 low-risk PTC patients from two Chinese large-volume centers (Fudan University Shanghai Cancer Center [FUSCC] and Cancer Hospital of Chinese Academy of Medical Sciences [CH-CAMS]) treated from January 1, 2000 to June 30, 2022. The mean TSH level was calculated based on postoperative serum TSH values during follow-up. The primary outcome was the association between postoperative TSH level and structural recurrence assessed by Kaplan–Meier, log-rank, multivariate Cox regression analyses and equivalence testing by Two One-Sided Tests (TOST) procedure. Propensity score matching (PSM) was used to adjust for confounders among groups.

Findings A total of 11,140 patients with low-risk PTC were included with a median follow-up of 70 months. Based on the mean TSH level, we classified these patients into ≤0.5 (n = 1,504, 13.5%), (0.5–1] (n = 4,336, 38.9%), (1–2] (n = 4,285, 38.5%), (2–3] (n = 704, 6.3%) and >3 (n = 311, 2.8%) mU/L groups. After PSM adjusting for age, sex, T and N stage, 8991 patients were included in further analysis, for whom the log-rank analyses showed no significant differences between any two groups (all $P > 0.05$) in recurrence-free survival (RFS), locoregional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS), and suppressed TSH was not associated with tumor recurrence in the multivariate Cox analysis (TSH > 2 group vs TSH ≤ 2 group: HR = 1.30, 95% CI = 0.85–2.01, $P = 0.23$). Furthermore, the TOST equivalence tests showed that tumor recurrence status of any two TSH groups were statistically comparable (all Bonferroni-corrected P values < 0.005). Subgroup multivariate analyses showed that TSH level did not impact tumor recurrence regardless of age, tumor size, lymph node metastasis, multifocality, surgical extent, biochemical evidence.

Interpretation Our results suggested that postoperative TSH level was not associated with tumor recurrence in patients with low-risk PTC, for whom deliberate TSH suppression may be exempted to avoid potential secondary complications. Maintaining a TSH level within the normal range may be safe for these patients.

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Research in context

Evidence before this study

We searched PubMed for studies published between January 1, 2014 and January 1, 2024, using the terms ("thyroid-stimulating hormone" OR "TSH" OR "thyrotropin") AND ("suppressive therapy" OR "suppression therapy" OR "suppression") AND ("papillary thyroid cancer" OR "PTC") AND ("low-risk"). The search was restricted to all kinds of studies with no language restrictions. Our search yields 14 studies, all of which are retrospective studies with small sample size. Most studies focused on PTC patients after thyroid lobectomy, but there is no previous research focusing on prognostic effect of postoperative TSH level in low-risk PTC, especially for those undergoing total thyroidectomy.

Added value of this study

To the best of our knowledge, this study is the first large-scale real-world study to report the impact of postoperative TSH level on tumor recurrence of the low-risk PTC population. Using a retrospective cohort of 11,140 patients, we report a negative prognostic effect of postoperative TSH in low-risk PTC.

Implications of all the available evidence

Our results suggest that postoperative TSH level is not associated with tumor recurrence in patients with low-risk PTC, for whom deliberate TSH suppression may be exempted to avoid potential secondary complications. Maintaining a TSH level within the normal range may be safe for these patients, further real-world multicenter prospective studies are necessary.

Introduction

Thyroid cancer is the most common endocrine malignancy with a very fast-growing incidence worldwide, with approximately 600,000 cases newly diagnosed per year, among whom over 500,000 (>95%) are papillary thyroid cancer (PTC).[1,2] In 2009, the American Thyroid Association (ATA) guidelines proposed a widely-used risk stratification system for differentiated thyroid cancer to predict the risk of disease recurrence and/or persistence, which was further modified in the 2015 updated version.[3,4] With the widespread use of ultrasonography, the vast majority of newly diagnosed thyroid cancer cases are actually low-risk PTC, especially papillary thyroid microcarcinoma (PTMC, refers to PTC ≤ 1 cm in diameter).[5] Therefore, the management of low-risk PTC concerns millions of survivors and is therefore of great clinical importance.

Experimental and clinical data have demonstrated that thyroid follicular cell proliferation is dependent on thyroid-stimulating hormone (TSH, or thyrotropin), thereby providing the rationale of TSH suppression in the management of PTC.[6] Traditionally, TSH suppression is recommended for all PTC patients following surgery with the goal varying from different guidelines. The 2015 ATA guidelines recommended that low-risk patients should be maintained with a low-normal TSH level between 0.5 and 2.0 mU/L, and the European Society of Medical Oncology (ESMO) guidelines held the same view.[3,7] On the other hand, the National Comprehensive Cancer Network (NCCN) guidelines had a different opinion, they recommended a TSH level of 0.1–0.5 mU/L for low-risk patients with biochemical evidence (Tg-positive), while a normal range is allowed for Tg-negative low-risk patients.[8] However, relevant recommendations of all these guidelines are based on historical, small-size, and indirect evidence, making TSH suppression highly empirical and controversial in these patients. It is well recognized that TSH suppression may cause harms related with iatrogenic hyperthyroidism, including cardiovascular disease, osteoporosis, anxiety, depression and even poor sleep function.[9] Therefore, the use of TSH suppressive therapy in low-risk PTC must be weighed against pros and cons.

Currently, there is still a lack of direct large-scale research evaluating the prognostic impact of TSH suppression in low-risk PTC. Here, we established a large retrospective cohort of PTC patients with high-quality follow-up in two Chinese large-volume hospitals. Based on this resource, we aim to provide a convincing evidence for this clinical controversy with real-world data of more than 10,000 patients.

Methods

Study population and selection criteria

This retrospective cohort study included consecutive PTC patients at two Chinese large-volume centers (Fudan University Shanghai Cancer Center [FUSCC] and Cancer Hospital of Chinese Academy of Medical Sciences [CH-CAMS]) initially treated from January 2000 to June 2022. We excluded patients who were (1) younger than 18 years old; (2) aggressive pathologic subtypes including tall-cell, columnar-cell, diffuse

sclerosing or insular variants, (3) all scenarios of intermediate-risk or high-risk stratifications according to the 2015 ATA guidelines[3]; (4) absent of clinicopathologic information; (5) We also excluded those with fewer than three postoperative serum TSH values. Finally, a total of 11,140 patients were included in our study. The selection process was shown in Fig. 1.

Variables

Variables obtained from medical records include demographics (age at initial surgery, sex), tumor characteristics (T stage, N stage, American Joint Committee on Cancer [AJCC] staging, tumor size, pathologic type, multifocality), serological biomarker (preoperative and postoperative serum TSH level, postoperative serum Tg level), type of primary thyroid surgery (hemithyroidectomy or total thyroidectomy) and whether it is very low-risk disease. Hemithyroidectomy represents lobectomy with or without isthmusectomy, while total thyroidectomy indicates complete removal of the thyroid gland. Very low-risk PTC means unifocal PTMC without lymph node metastasis and extrathyroidal extension, according to the 2015 ATA guidelines.[3] As some patients did not receive TSH measurement before surgery, there are missing values in the variable "preoperative TSH level". These missing data were not specifically handled (such as data imputation), but were instead simply labeled as "NULL" in our raw data matrix, because this variable was used only as a stratification label for subgroup analyses, but not as a confounding covariate in multivariate analyses.

In both contributing hospitals, prophylactic central neck dissection was routinely performed for patients with preoperatively suspicious thyroid cancer, while lateral neck dissection was performed for patients with clinically N1b disease. Radioactive iodine (RAI) therapy confers no prognostic benefit and is not recommended for low-risk PTC patients in current guidelines,[3,10] very few patients underwent postoperative RAI, therefore this factor was not included in the baseline characteristics.

Physical examination, blood test of thyroid function, neck ultrasonography, and computed tomography or chest radiography were performed regularly every 3–6 months within the first 5 years and every 12 months thereafter. The normal reference range of serum TSH is 0.35–4.94 mU/L and 0.56–5.91 mU/L in FUSCC and CH-CAMS, respectively, while the normal reference range of serum Tg is 3.50–77.00 ng/mL and 1.59–50.03 ng/mL in FUSCC and CH-CAMS, respectively. The mean TSH level was calculated based on the average serum TSH value during follow-up with a minimum time of three months between measurements, while the data in the first month after surgery was excluded, as it was always unstable at this time. As the ATA guidelines recommended 2 mU/L as the upper threshold of TSH suppression, we used this cutoff value to differentiate patients into TSH suppressive and non-suppressive groups. For patients treated with total thyroidectomy, Tg-positive was determined as a detectable serum Tg level in any blood test during the follow-up period (>0.04 ng/mL in the two contributing hospitals), which was regarded as an indication for a lower TSH suppression target in the NCCN guidelines.[3,8]

Outcomes

This primary endpoint of our study was structural recurrence. Locoregional recurrence was determined by

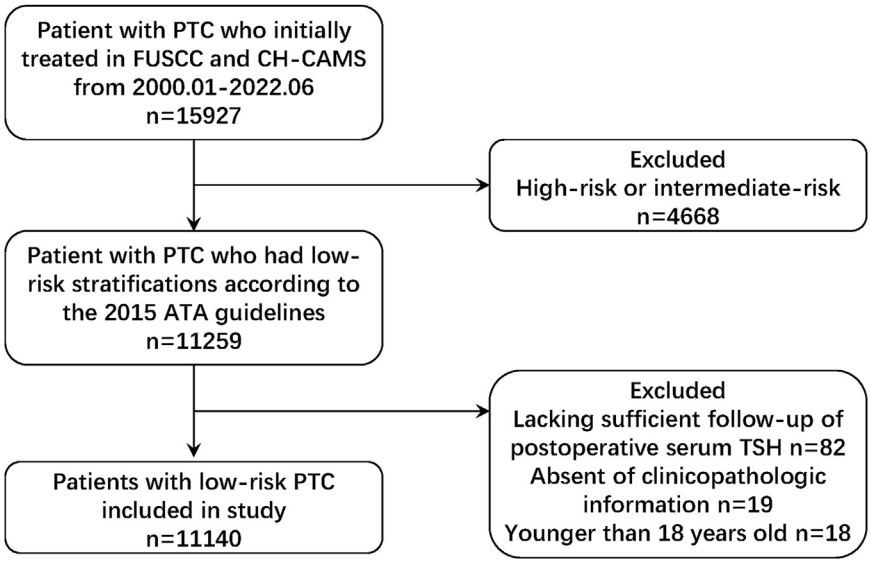

Fig. 1: Selection process of the study cohort.

pathology of second surgery or cytology of fine-needle aspiration, while distant metastasis was determined by imaging examinations including chest computed tomography, abdominal ultrasonography, RAI scan or positron emission tomography-computed tomography. Recurrence-free survival (RFS), locoregional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS) were defined as the duration from initial surgery to the first structural recurrence of all, locoregional and distant sites, respectively.

Statistics

In order to control potential confounders and selection bias between the TSH suppressive and non-suppressive groups, we performed a sensitivity analysis using generalized propensity score matching (PSM) by caliper matching with the R package "Matching" (version 4.10–14). The overall cohort of 11,140 patients were matched with age (dichotomized based on the cutoff of 55 years old), sex (male and female), T stage and N stage. Student's t-test was used to compare continuous variables, while Pearson's chi-square test was employed to evaluate the difference of categorical variables between groups. After PSM, RFS, LRRFS, DMFS between the TSH suppressive and non-suppressive groups in the matched population were compared using Kaplan–Meier analysis with the log-rank test. Furthermore, univariate and multivariate Cox proportional hazards regression model was used to calculate hazards ratio (HR) and 95% confidence interval (CI) of prognostic factors for structural recurrence. The proportional hazards assumption of the multivariable Cox model was tested using Schoenfeld residuals test *via* the cox.zph() function. Equivalence testing was conducted using the Two One-sided Tests (TOST) procedure for each pair of groups, utilizing the R package TOSTER version 0.8.3, with the parameters set as follows: eqb = 0.05, α (after Bonferroni correction) = 0.05/10.

All analyses were conducted using IBM SPSS Statistics 22.0 software (SPSS Inc, Chicago, IL, USA) and R version 4.1.0 (www.r-project.org). A two-tailed P value < 0.05 was considered to be statistically significant.

Ethics

Written informed consent was obtained at the time of initial surgery from all patients. This study was approved by the Ethics Review Board of Fudan University Shanghai Cancer Center (Reference number: 2108240-18) and Cancer Hospital of Chinese Academy of Medical Sciences (Reference number: NCC2024C-347).

Role of funding source

The funding source had no role in the study design, data collection, data analysis, interpretation of data, or writing of the report.

Results

Baseline characteristics before and after propensity score matching

A total of 11,140 patients were included in the study cohort with a median follow-up period of 70 months (range: 6–211 months) and a mean postoperative TSH measurements of 8.34 times (range: 3–48 times). The median age at diagnosis was 42 years (range: 18–84 years) with a female-to-male ratio of ∼ 3: 1 (76.3% vs 23.7%). Very low-risk PTMC accounted for 47.2% (n = 5261), and 83.1% of patients (n = 9262) received hemithyroidectomy as their initial surgery. During the follow-up period, structural recurrence was observed in 316 patients (2.8%), of whom 312 and 5 patients had locoregional and distant metastases, respectively. Based on the mean postoperative TSH level, we classified patients into ≤0.5 (n = 1,504, 13.5%), (0.5–1] (n = 4,336, 38.9%), (1–2] (n = 4,285, 38.5%), (2–3] (n = 704, 6.3%) and >3 (n = 311, 2.8%, mean: 4.52) mU/L groups. The five TSH-stratified groups were significantly different in sex (P < 0.0001), N stage (P = 0.0079), surgery type (P < 0.0001), multifocality (P < 0.0001), preoperative TSH level (P < 0.0001) and follow-up duration (P = 0.00020) (Table 1).

As these groups differed in multiple baseline characteristics, we then performed PSM adjusting for age, sex, T and N stage in a ratio of 4: 15: 15: 2: 1 (the closest integer ratio) in the ≤0.5, (0.5–1], (1–2], (2–3] and >3 groups. After PSM, 8991 patients were available for further analysis, and none of these baseline characteristics had significant differences among groups. Moreover, the proportion of structural recurrence events were similar among the five groups (3.7%, 2.4%, 2.6%, 2.7%, and 4.1% for the ≤0.5, (0.5–1], (1–2], (2–3] and >3 groups, respectively, P = 0.11) (Supplementary Table S1).

Survival analysis for structural recurrence of different TSH suppressive groups

We then conducted survival analysis of different TSH suppressive groups. Kaplan–Meier analysis revealed that the 5-year RFS rate was 97.4%, 98.4%, 98.2%, 98.1% and 97.5%, respectively, and the 10-year RFS rate was 92.8%, 95.1%, 94.3%, 95.0% and 92.3% for the ≤0.5, (0.5–1], (1–2], (2–3] and >3 groups, respectively. Log-rank analyses showed there were no significant differences in RFS (log-rank P = 0.062), LRRFS (log-rank P = 0.072) and DMFS (log-rank P = 0.83) among these groups (Fig. 2). Furthermore, the TOST equivalence tests showed that tumor recurrence status of any two TSH groups were statistically comparable (all Bonferroni-corrected P values < 0.005) (Supplementary Table S2).

To facilitate the Cox regression analysis, we dichotomized the patients into TSH-suppressive (≤2) and non-suppressive (>2) groups using a mean TSH level of 2 mU/L as the cutoff value, consistent with the

Characteristics	Total	TSH≤0.5	TSH in (0.5,1]	TSH in (1,2]	TSH in (2,3]	TSH >3	P value
	N = 11,140 (%)	N = 1504 (%)	N = 4336 (%)	N = 4285 (%)	N = 704 (%)	N = 311 (%)	
Sex							<0.0001
Male	2636 (23.7)	222 (14.8)	920 (21.2)	1201 (28.0)	192 (27.3)	101 (32.5)	
Female	8504 (76.3)	1282 (85.2)	3416 (78.8)	3084 (72.0)	512 (72.7)	210 (67.5)	
Age at initial surgery							0.21
<55	9417 (84.5)	1277 (84.9)	3637 (83.9)	3659 (85.4)	582 (82.7)	262 (84.2)	
≥55	1723 (15.5)	227 (15.1)	699 (16.1)	626 (14.6)	122 (17.3)	49 (15.8)	
T stage							0.085
T1a	8381 (75.2)	1155 (76.8)	3275 (75.5)	3210 (74.9)	521 (74.0)	220 (70.7)	
T1b	2358 (21.2)	287 (19.1)	922 (21.3)	924 (21.6)	151 (21.4)	74 (23.8)	
T2	401 (3.6)	62 (4.1)	139 (3.2)	151 (3.5)	32 (4.5)	17 (5.5)	
N stage							0.0079
N0	7694 (69.1)	992 (66.0)	2961 (68.3)	3027 (70.6)	494 (70.2)	220 (70.7)	
N1	3446 (30.9)	512 (34.0)	1375 (31.7)	1258 (29.4)	210 (29.8)	91 (29.3)	
AJCC staging							0.41
I	10,720 (96.2)	1443 (95.9)	4181 (96.4)	4129 (96.4)	669 (95.0)	298 (95.8)	
II	420 (3.8)	61 (4.1)	155 (3.6)	156 (3.6)	35 (5.0)	13 (4.2)	
Very low risk							0.00018
No	5879 (52.8)	862 (57.3)	2250 (51.9)	2199 (51.3)	388 (55.1)	180 (57.9)	
Yes	5261 (47.2)	642 (42.7)	2086 (48.1)	2086 (48.7)	316 (44.9)	131 (42.1)	
Surgery							<0.0001
Hemithyroidectomy	9262 (83.1)	1011 (67.2)	3827 (88.3)	3702 (86.4)	524 (74.4)	198 (63.7)	
Total thyroidectomy	1878 (16.9)	493 (32.8)	509 (11.7)	583 (13.6)	180 (25.6)	113 (36.3)	
Multifocality							<0.0001
No	9208 (82.7)	1112 (73.9)	3727 (86.0)	3621 (84.5)	522 (74.1)	226 (72.7)	
Yes	1932 (17.3)	392 (26.1)	609 (14.0)	664 (15.5)	182 (25.9)	85 (27.3)	
Tumor size							0.078
≤1 cm	8381 (75.2)	1156 (76.9)	3275 (75.5)	3209 (74.9)	521 (74.0)	220 (70.7)	
1–2 cm	2358 (21.2)	286 (19.0)	922 (21.3)	925 (21.6)	151 (21.4)	74 (23.8)	
2–4 cm	401 (3.6)	62 (4.1)	139 (3.2)	151 (3.5)	32 (4.5)	17 (5.5)	
Preoperative TSH[a]							<0.0001
≤2	5377 (54.3)	760 (64.8)	2487 (62.7)	1851 (46.9)	192 (32.1)	87 (40.5)	
2-3	2541 (25.7)	240 (20.5)	909 (22.9)	1162 (29.5)	178 (29.7)	52 (24.2)	
>3	1980 (20.0)	172 (14.7)	573 (14.4)	930 (23.6)	229 (38.2)	76 (35.3)	
Recurrence							0.0062
No	10,824 (97.2)	1444 (96.0)	4228 (97.5)	4176 (97.5)	678 (96.3)	298 (95.8)	
Yes	316 (2.8)	60 (4.0)	108 (2.5)	109 (2.5)	26 (3.7)	13 (4.2)	
Follow up period							0.00020
≤5 years	4625 (41.5)	639 (42.5)	1669 (38.5)	1857 (43.3)	319 (45.3)	141 (45.3)	
5–10 years	5216 (46.8)	697 (46.3)	2126 (49.0)	1955 (45.6)	306 (43.5)	132 (42.4)	
>10 years	1299 (11.7)	168 (11.2)	541 (12.5)	473 (11.0)	79 (11.2)	38 (12.2)	

[a]Preoperative TSH was evaluated in 9898 patients whose preoperative TSH results were available.

Table 1: **Patient characteristics for the overall 11,140 low-risk PTC patients before propensity score matching.**

recommendation of TSH suppressive target for low-risk patients in the ATA guidelines.[3] In the univariate Cox regression analysis, age, sex, T stage, N stage and surgery type were statistically significant and were further included in the multivariate analysis. Schoenfeld residuals tests showed that these covariates had a constant hazard effect over time ($P < 0.05$ for both global model and individual features), which means the major assumptions in Cox regression were not violated (Supplementary Fig. S1A). After adjusting for these confounders, multivariate Cox regression analysis demonstrated that TSH suppression was not an independent prognostic factor for structural recurrence (TSH ≤2 group as reference, HR 1.30, 95% CI 0.85–2.01, $P = 0.23$ for the TSH >2 group) (Table 2).

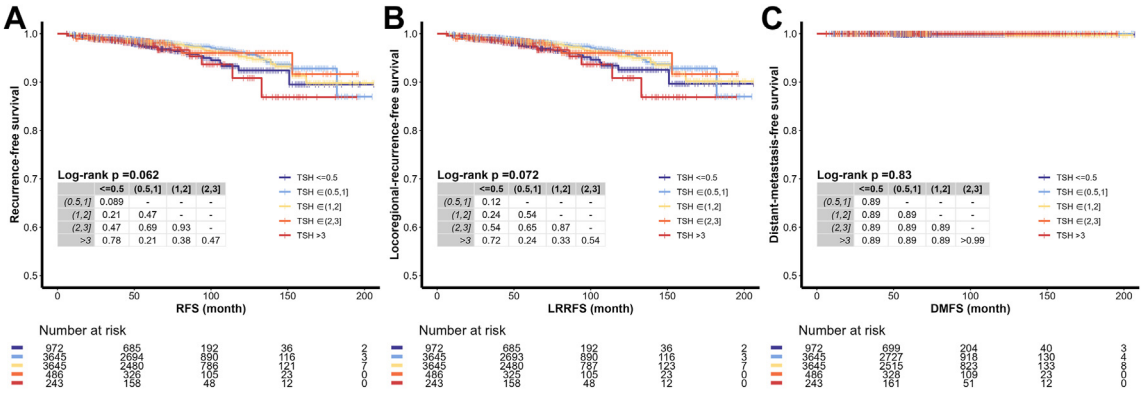

Fig. 2: Survival plots of **(A)** RFS, **(B)** LRRFS and **(C)** DMFS for the TSH ≤ 0.5, (0.5–1], (1–2], (2–3] and >3 groups in the overall post-PSM cohort (n = 8991). Abbreviations: RFS, recurrence-free survival; LRRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival; TSH, thyroid-stimulating hormone.

Prognostic impact of TSH suppression on structural recurrence in subgroup analyses stratified by clinicopathologic factors

Next, we performed subgroup analyses of the post-PSM cohort to investigate the prognostic impact of TSH suppressive therapy according to different clinicopathologic factors. After adjusting for significant factors in the univariate Cox analysis (data not shown), the multivariate Cox analyses did not reveal prognostic difference for structural recurrence between the TSH suppressive (≤2) and non-suppressive (>2) groups regardless of age, sex, surgery type, multifocality, T stage, N stage and preoperative TSH level. The results of subgroup multivariate analyses were summarized in a forest plot (Fig. 3).

Characteristic	Structural Recurrence of All Sites			
	Univariate		Multivariate	
	HR (95%CI)	P	HR (95%CI)	P
Sex				
Male	1 [Reference]		1 [Reference]	
Female	0.66 (0.49–0.88)	0.0053	0.84 (0.63–1.14)	0.27
Age				
<55	1 [Reference]		1 [Reference]	
≥55	0.64 (0.42–0.97)	0.030	0.84 (0.55–1.28)	0.39
T stage				
T1a	1 [Reference]		1 [Reference]	
T1b	1.55 (1.17–2.05)	0.0024	1.19 (0.89–1.58)	0.25
T2	3.48 (2.16–5.61)	<0.0001	2.36 (1.45–3.84)	0.00056
N stage				
N0	1 [Reference]		1 [Reference]	
N1	3.10 (2.40–4.00)	<0.0001	2.79 (2.13–3.65)	<0.0001
Surgery				
Hemithyroidectomy	1 [Reference]		1 [Reference]	
Total thyroidectomy	0.42 (0.26–0.67)	0.00027	0.41 (0.26–0.66)	0.00025
Multifocality				
No	1 [Reference]		1 [Reference]	
Yes	1.10 (0.76–1.50)	0.76	NA	NA
Postoperative TSH				
≤2	1 [Reference]		1 [Reference]	
>2	1.24 (0.81–1.91)	0.33	1.30 (0.85–2.01)	0.23

HR, hazard ratio. CI, confidence interval.

Table 2: **Prognostic factors for structural recurrence of all sites in the overall matched cohort using univariate and multivariate Cox regression models.**

Prognostic impact of TSH suppression on structural recurrence in Tg-positive patients undergoing total thyroidectomy

As the NCCN guidelines suggest a lower TSH suppressive target for Tg-positive low-risk patients (0.1–0.5 mU/L),[8] we next focused on the prognostic effect of TSH suppression in this subset of patients. In our post-PSM cohort, 1417 patients were initially treated with total thyroidectomy, of whom 1204 (85.0%) had positive serum Tg (>0.04 ng/mL, see **Methods**) during the follow-up period. Similarly, Kaplan–Meier analysis revealed that the survival curves of the TSH ≤2 and >2 groups were virtually overlapping (5-year RFS rate of TSH ≤2 and >2 groups: 98.8% vs 99.3%; 10-year RFS rate: 97.3% vs 96.8%; log-rank P = 0.88) (Fig. 4A), After the Schoenfeld residuals tests validated the appropriateness of Cox proportional hazards model (Supplementary Fig. S1B), multivariate Cox analyses also revealed that TSH suppression was not an independent prognostic factor for structural recurrence (TSH ≤2 group as reference, HR 0.95, 95% CI 0.28–3.30, P = 0.94 for the TSH >2 group) (Supplementary Table S3).

Similarly, when we used 0.5 mU/L as the cutoff value based on the recommendation of the NCCN guidelines, we failed to observe prognostic benefit of lower TSH level in Kaplan–Meier analyses (5-year RFS rate of the TSH ≤0.5 and >0.5 groups: 97.8% vs 99.1%; 10-year RFS rate: 97.3% vs 97.1%; log-rank P = 0.32) (Fig. 4B). After the Schoenfeld residuals tests validated

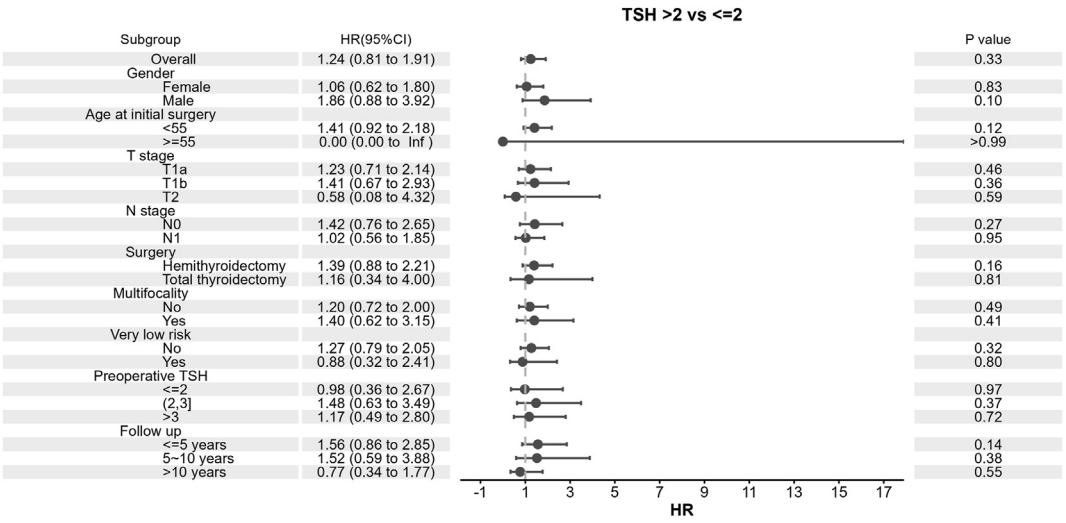

Fig. 3: Forest plot summarizing the HRs and 95% CIs of subgroup analyses investigating the prognostic effect on RFS between the TSH ≤ 2 and >2 groups. Abbreviations: HR, hazard ratio; CI, confidence interval; RFS, recurrence-free survival; TSH, thyroid-stimulating hormone.

the appropriateness of Cox proportional hazards model (Supplementary Fig. S1C), multivariate Cox analyses revealed a comparable prognosis between the TSH ≤0.5 and TSH >0.5 groups (TSH ≤0.5 group as reference, HR 0.56, 95% CI 0.20–1.60, P = 0.26 for the TSH >0.5 group) (Fig. 4B and Supplementary Table S4).

Discussion

Low-risk PTC is the most common type of thyroid cancer with millions of survivors worldwide, which makes postoperative care essential at a population-based level. Despite variations in target level, most mainstream guidelines still recommended postoperative TSH suppression in all or a subset of low-risk PTC patients.[3,7,8] However, these guidelines do not provide direct evidence that TSH suppression can lead to an improved clinical outcome. In the 2015 ATA guidelines, the goal of TSH suppression is below 2 mU/L, and this cutoff value is based on an old retrospective study of 366 patients, where the authors found patients with TSH ≥2.0 mU/L had significantly higher risk of recurrence, approximately 30% vs 10%.[11] However, this study enrolled patients of all risk groups, and its conclusion

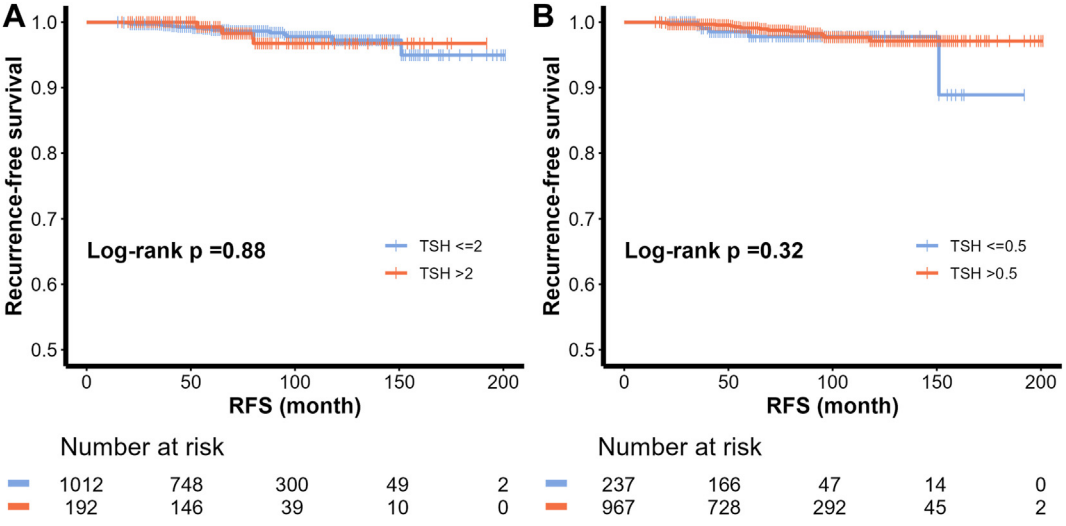

Fig. 4: Survival plots of RFS for the **(A)** TSH ≤ 2 and >2 groups, and **(B)** TSH ≤0.5 and >0.5 groups in Tg-positive low-risk PTC patients treated with total thyroidectomy of the post-PSM cohort (n = 1204). Abbreviations: RFS, recurrence-free survival; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; PTC, papillary thyroid cancer; PSM, propensity score matching.

might be largely biased by the high proportion of high-risk patients.[9] More critically, the NCCN guidelines do not give reference for their recommendations on TSH suppression targets of 0.1–0.5 mU/L for Tg-positive low-risk PTC.[8] Therefore, additional studies are needed to fill in this gap of knowledge.

Despite the controversy over its benefits, many physicians still favor routine TSH suppression for low-risk thyroid cancer in accordance with existing guidelines. In a physician survey study of 448 endocrinologists and surgeons, the authors found that 80.8% of physicians were likely/extremely likely to recommend TSH suppression for intermediate-risk PTC, while the rate was still 48.8% and 29.7% for low-risk and very low-risk patients, respectively, which was inversely related to hospital volume.[12] And in China, with our observations in clinical practice, the vast majority of physicians recommend different degrees of TSH suppression for low-risk or very low-risk patients to avoid potential medical conflicts if structural recurrence occurs. In this "less is more" era with the pendulum swinging toward less intensive treatment of low-risk patients, more high-quality studies are warranted to guide physician behavior regarding TSH suppression.

In fact, several recent data have denied the protective benefit of TSH suppression against recurrence for postlobectomy patients. In a propensity score-matched study of 446 low-risk patients treated with lobectomy, Park et al. found a negative correlation between levothyroxine administration and tumor recurrence,[13] while Xu et al. reported a negative correlation not only in low-risk, but also in intermediate-to high-risk postlobectomy PTC patients.[14] More evidence is awaited from a South Korean randomized controlled trial to study the role of TSH suppression in low-to intermediate-risk PTC treated by lobectomy.[15] However, most of these studies are small-size relative to the high incidence of PTC, and there are currently no studies of TSH suppression in low-risk patients after total thyroidectomy.

In the present study, we supply evidence to support the negative correlation between postoperative TSH suppression and structural recurrence, not only in the whole cohort, but also in patients presenting with well-recognized risk factors, including positive lymph node metastasis, larger tumor size and multifocal disease. Notably, regardless of total thyroidectomy or hemithyroidectomy, lower TSH level failed to bring a more favorable prognosis, suggesting that the dose of L-T4 administration is enough if postoperative hypothyroidism is corrected, while deliberate overdose of levothyroxine to suppress TSH to a specific value is unnecessary.

Biochemical response may also concern. Although thyroglobulin is a commonly used serum biomarker to monitor disease recurrence of PTC patients treated with total thyroidectomy and following RAI remnant ablation, lobectomy or total thyroidectomy alone without RAI is more widely adopted for low-risk patients in the current "less is more" era, making the predictive value of Tg monitoring rather controversial.[9,16] Nevertheless, the NCCN guidelines still recommended a low TSH target level of 0.1–0.5 mU/L for Tg-positive low-risk PTC in the absence of direct evidence.[8] In our study, we did not observe a positive correlation of serum TSH level and recurrence in patients with postoperative positive serum Tg, no matter if the patient had total thyroidectomy or lobectomy. Therefore, we do not advocate TSH suppressive therapy even for low-risk patients with detectable Tg after surgery.

This study has some limitations. First, despite a very large cohort size, our study is still limited by its retrospective nature, which may bring some inevitable bias, even though propensity score matching was applied to reduce these bias. Second, a well-designed prospective study can minimize the selection bias. However, low-risk PTC generally has an excellent prognosis with a recurrence rate <5%, such a low rate of endpoint requires a very large sample size for a prospective trial. Moreover, a prospective study requires patient's serum TSH level to be maintained at the target value for a long period of time per protocol, requiring an extremely high level of patient compliance. The extremely high demand for patient volume and compliance makes a high-quality prospective trial very difficult for this study subject. Therefore, this large-scale real-world study already represents a very strong evidence. Third, as the main side effects of TSH suppressive therapy, thyrotoxicosis-related comorbidities were not routinely documented in the medical records, thus their association with TSH suppression was not demonstrated in our study. Fourth, female patients may experience a physiologically variation (often lower) in TSH values during pregnancy, but the gestational status during follow-up was not routinely documented, thus the effect of pregnancy on postoperative TSH level was not demonstrated in this study. Fifth, although the overall cohort has a median follow-up of 70 months, a longer follow-up period would be desirable considering the time to recurrence of PTC.

In conclusion, using the largest cohort to date of over 10,000 patients, this study suggests that TSH suppression may not bring prognostic benefits in low-risk PTC, even for those having potential risk factors such as positive lymph node metastasis, larger tumor size, multifocal disease and postoperative biochemical evidence. Future multicenter prospective analyses are needed to determine if TSH suppressive therapy may be exempted for low-risk PTC patients to avoid secondary complications, while L-T4 replacement is only needed to correct hypothyroidism by maintaining the TSH level at a normal range.

Contributors

YW, JL and QHJ conceived and designed the study. XS, HTT, TTZ and YJW were responsible for study methodology. XS, HTT, TTZ, YJW, CKS, YZ, YXD, WJW, ZML, CQL, XQM, SYL, QHJ, JL and YW recruited patients and collected data. XS, HTT, TTZ and YJW were responsible for formal analysis. XS, HTT, TTZ, YJW, CKS, YZ, YXD,

WJW, ZML and CQL were responsible for data visualization. XS, HTT, TTZ and YJW wrote the original draft. XS, HTT, TTZ and YJW edited the manuscript. MH, QHJ, JL and YW were responsible for the project administration. XS and JW was responsible for project supervision and funding acquisition. XS, HTT and YW verified the underlying data. All authors reviewed and approved the final version of the manuscript. All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit for publication.

Data sharing statement

De-identified patient data will be available upon reasonable request to the corresponding author (*via* email) after institutional approval and with a signed data access agreement, with no time limits after publication, and with the permission of Fudan University Shanghai Cancer Center and Cancer Hospital of Chinese Academy of Medical Sciences.

Declaration of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Funding sources were not involved in the study design, data collection, analysis and interpretation, writing of the report, or decision to submit the article for publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102912.

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