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Research article

The necessity of thyroid-stimulating hormone suppression therapy for low-risk differentiated thyroid carcinoma following hemithyroidectomy: A systematic review and meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

Background and objective: Thyroidectomy, followed by postoperative thyroid-stimulating hormone (TSH) suppression therapy, is the established therapeutic approach for low-risk differentiated thyroid carcinoma (DTC). Recently, there has been a growing body of research dedicated to postoperative TSH suppression therapy in low-risk DTC. This study aims to conduct a comprehensive literature review concerning the necessity of TSH suppression therapy in DTC after hemithyroidectomy.
Methods: A systematic search of publicly available literature on postoperative TSH suppression therapy in DTC was conducted by querying databases such as PubMed, Embase, Cochrane, and Web of Science. Patients were stratified into two groups: the experimental group (patients who received TSH suppression therapy) and the control group (patients who did not receive TSH suppression therapy). Concurrently, the five selected studies were categorized into two groups based on the average follow-up period (5–8.6 years).
Results: A total of five eligible studies, involving 2964 participants, were included in the analysis. The analysis of these five studies indicated low heterogeneity ($I^2 = 40$ %). During the follow-up period, patients who received TSH suppression therapy had similar recurrence rate ($P = 0.13$) compared to those who did not. In both average follow-up period less than 6 years group ($P = 0.85$) and more than or equal to 6 years group ($P = 0.07$), postoperative TSH suppression therapy did not affect the recurrence of DTC after hemithyroidectomy.
Conclusion: This study demonstrates that postoperative TSH suppression therapy does not reduce the recurrence rate of low-risk DTC patients after hemithyroidectomy.

1. Introduction

Thyroid cancer has become the most prevalent malignant tumor within the head and neck cancer domain. In recent years, the incidence rate of thyroid cancer has demonstrated a notable surge on a global scale, rendering thyroid carcinoma the most rapidly

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escalating neoplasm in terms of prevalence in select regions, especially in regions characterized by iodine deficiency [1]. Differentiated thyroid carcinoma (DTC) is the most prevalent histological subtype of thyroid cancer, accounting for approximately 90 % of all thyroid cancer cases [2,3].

In comparison to other malignancies, DTC demonstrates one of the most favorable prognoses, leading to growing concerns about the issues of overdiagnosis and overtreatment. Two principal factors are believed to contribute to the increase incidence of thyroid carcinoma. The first factor relates to an intrinsic elevation in the neoplasm's incidence rate, while the second one is attributed to advancements in screening and diagnostic technologies [4]. In terms of treatment, appropriate surgical resection is the most effective therapeutic approach for DTC. For low-risk DTC, hemithyroidectomy, which contains removal of one lobe and the isthmus of the thyroid gland with selective central neck dissection is the most suitable surgical option [5–7].

In previous studies, the structural recurrence rate of postoperative DTC patients ranges from 15 % to 30 % [8,9]. Postoperative interventions such as radioiodine remnant ablation therapy and TSH suppression therapy, which can inhibit the proliferation of thyroid carcinoma cells, have been employed to prevent structural recurrence [10–13]. In accordance with the most recent guidelines established by the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN), DTC patients are categorized into distinct risk groups based on various surgical and pathological characteristics. The categorization largely determines the initial degree of postoperative TSH suppression therapy. For patients categorized as high-risk or intermediate-risk DTC cases, guidelines strongly advocate to suppress TSH levels to below 0.1 mU/L and within the range of 0.1–0.5 mU/L respectively. Nevertheless, controversy persists regarding the degree of TSH suppression and the necessity of thyroid hormone therapy for low-risk patients who have undergone hemithyroidectomy [14]. Recent investigations have indicated that TSH suppression therapy may lead to adverse effects in DTC patients, including an increased risk of cardiovascular events and osteoporosis in postmenopausal women [15,16].

In view of these considerations, we conducted a thorough systematic review and meta-analysis to evaluate the effects of thyroid hormone therapy on patients with DTC who have undergone hemithyroidectomy. The primary objective of this study is to evaluate the necessity of postoperative TSH suppression therapy in preventing recurrency in low-risk DTC patients following hemithyroidectomy.

2. Materials and methods

2.1. Search strategy and selection criteria

We conducted a systematic review and meta-analysis to elucidate the necessity of TSH suppression therapy in treating low-risk DTC following hemithyroidectomy. Our systematic search encompassed 4 databases, namely PubMed, Embase, Cochrane and Web of Science, from January 1, 2010 to August 1, 2023 with the terms "differentiated thyroid carcinoma" and "thyrotropin". We employed controlled vocabulary to identify pertinent topic terms and explored synonyms associated with these topic terms to expand the scope of keyword selection. Based on these identified terms, we formulated a comprehensive search strategy and integrated all relevant terminologies into the search process. To ensure comprehensive literature retrieval, meticulous attention was devoted to the keywords utilized, and a manual examination of relevant reviews and articles was performed to preclude the omission of pertinent publications.

The inclusion criteria for this study centered on the examination of the impact of postoperative TSH suppression therapy on recurrence rates after hemithyroidectomy in low-risk DTC patients, guided by the PICO (Participants, Interventions, Comparisons, Outcomes) framework. The selection criteria of this study included: (1) articles published between January 1, 2010, and August 1, 2023; (2) articles exclusively focused on low-risk DTC patients following hemithyroidectomy in their analysis and (3) articles precisely reported the number of patients treated with or without thyroid hormone following hemithyroidectomy, as well as the number of structural recurrences in each group. The exclusion criteria of this study included: (1) absence of experimental data or results; (2) experimental outcomes conflicting with the objectives of this article and (3) the surgical procedure deviating from hemithyroidectomy. Ultimately, five articles were deemed suitable for systematic evaluation and inclusion in the meta-analysis.

The comprehensive analysis process adhered to the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Any discrepancies encountered during the literature inclusion process throughout the systematic review and meta-analysis were resolved through collaborative discussion and consensus between two researchers. Subsequently, the extracted data underwent analysis using Review Manager 5.4 (Cochrane, London, UK).

2.2. Quality assessment and data Extraction

To comprehensively assess the quality of the five retrospective cohort studies, we employed Newcastle-Ottawa Scale (NOS) to evaluate their risk-of-bias. The bigger number evaluated, the better the quality. Generally, at least five or more than that can be included in the meta-analysis.

All patients included in the eligible literature were divided into two groups. The experimental group included patients who received postoperative TSH suppression therapy, while the control group included patients who did not receive such therapy. Analysis was conducted to compare the recurrence rate between the two groups during the follow-up period, as well as the hazard ratio for recurrence rate. Furthermore, eligible studies were subdivided into two subgroups based on the duration of follow-up, with follow-up periods of less than 6 years (<6 years) and greater than or equal to 6 years (≥6 years). The impact of the follow-up period on recurrence in both groups was analyzed.

The recurrence rate was defined as number of patients experienced structural recurrence divided by number of all patients, as documented in the published literature. Data including author, publication year, trial type, follow-up years, number of total patients, number of patients with or without TSH suppression therapy, number of patients experienced structural recurrence and relevant clinical characteristics was extracted. Engauge Digitizer was also employed to extract data.

2.3. Outcome

According to the prespecified protocol, the primary outcome of this study is the overall recurrence rate of each group. Although not presented here, we also intended to discuss the appropriate serum TSH level following hemithyroidectomy for low-risk DTC and the incidence of side effects after TSH suppression therapy.

2.4. Statistical analysis

Two researchers conducted statistical analysis using Review Manager 5.4 (Cochrane, London, UK). For the meta-analysis of the total number of recurrent patients, we applied a fixed-effects model with logit transformation. The primary outcome is the recurrence rate. We calculated 95 % confidence intervals (CIs) along with the recurrence rate using a fixed-effects model with logit transformation. The treatment-related recurrence rate profile was analyzed by summing the number of recurrent patients as the numerator and the number of total patients as the denominator.

Post-hoc analysis was conducted to assess the treatment-related recurrence profile. The effect size was evaluated using an odds ratio (95 % CI), and a fixed-effects model was employed for the pooled analysis of the odds ratio. Review Manager was used to assess nominal differences in recurrence rates between the two groups.

We employed statistics I^2 to assess the heterogeneity across different studies, categorizing them as having low, moderate, or high heterogeneity based on I^2 values within the ranges of 25–50 %, 50–75 % and over 75 %, respectively. Specifically, we considered categorical variables, such as whether patients underwent TSH suppression therapy following hemithyroidectomy. Publication bias was assessed using a classic funnel plot. Meanwhile, in order to better delve into the sources of heterogeneity and conduct sensitivity analysis, we also used "one by one elimination method" to reassessment the heterogeneity and the sensitivity of the study. The results showed that, besides Lee, M. C.'s study ($P = 0.04$) [17], after removing any one of the other four articles included, the conclusion remained the same ($P < 0.05$). We can tell that the heterogeneity of this Meta-analysis is relatively positive. As for that inconsistency, the large sample size may be the reason for that result, which means that article plays an important role in this Meta-analysis and can significantly improve the stability of the article.

3. Results

After independent review by two researchers, five studies were included in the study. Table 1 presents a list of included studies, their respective research data and the clinical characteristics of the enrolled patients [18–22].

The inclusion process is depicted in Fig. 1. A total of 2964 patients were extracted from five studies. The experimental group contained a total of 1742 individuals, who received postoperative TSH suppression therapy leading to serum TSH value lower than the normal range. The control group contained a total of 1222 individuals, who did not receive postoperative TSH suppression therapy. A summary chart presenting the risk-of-bias assessment outcomes is depicted in Fig. 2.

The five selected studies underwent follow-up for an average duration of 6.8 (5–8.6) years. During the follow-up period, 61 patients experienced recurrence. Among the 1742 patients in the experimental group 27 patients had recurrence, the 6.8-year recurrence rate was 1.55 %. The control group consisted of 1222 patients, and 34 patients had recurrence, with a 6.8-year recurrence rate of 2.78 %. Compared to the control group, the odds ratio of the experimental group was 0.65 (odds ratio [OR] 0.65; 95 % confidence interval [CI] 0.38–1.13, P = 0.13) (presented in Figs. 3 and 4). The analysis indicated a heterogeneity index (I^2) of 40 %, indicating low heterogeneity.

Furthermore, an analysis within the subgroups based on average follow-up years showed that within the group with an average follow-up period of less than 6 years, the OR was 0.93 (odds ratio [OR] 0.93; 95 % confidence interval [CI] 0.41–2.09, $P = 0.85$). Within the other group with an average follow-up period of more than or equal to 6 years, the OR was 0.49 (odds ratio [OR] 0.49; 95 % confidence interval [CI] 0.23–1.07, $P = 0.07$).

4. Discussion

Thyroid cancer has emerged as the most prevalent endocrine neoplasm, with its incidence displaying a notable upward trend in recent years. Despite advancements in treatment, the concern of tumor recurrence remains a prominent issue, prompting an increasing focus on individual risk assessments to tailor treatment strategies for patients [23]. In this context, the 2015 ATA guidelines introduced a risk stratification system to estimate the likelihood of thyroid cancer recurrence, although it lacks clinical validation [24]. The risk of thyroid cancer recurrence is categorized into three levels. While this risk stratification is widely recognized and applied by clinicians, it has not been clinically validated [25].

For DTC, traditional approaches typically involve surgical interventions such as total thyroidectomy or hemithyroidectomy combined with postoperative TSH suppression therapy to mitigate the risk of recurrence. TSH suppression therapy has been the cornerstone of thyroid cancer management for the past several decades [26]. However, recent investigations have revealed a range of side effects and adverse outcomes associated with postoperative TSH suppression therapy, including an increased risk of osteoporosis in postmenopausal women and a potential link to cardiovascular and cerebrovascular events [27,28]. Notably, studies have shown that

Table 1
The selected studies with respective research data and the clinical characteristics of the enrolled patients.

Author & Year	Number of Patients	Average Duration of Follow-up (year)	Study Design	Participant (Number of Patients)				Average Age	Gender(Male/Female)		
				Experimental Group	Recurrence of Experimental group	Control Group	Recurrence of Control group		Experimental Group	Control Group	Total
Ahn et al. 2020	401	6.5	Retrospective Cohort Study	154	3	247	16	47.35	16/138	46/201	62/339
Kang et al. 2019	200	5.0	Retrospective Cohort Study	100	2	100	5	44.11 ± 9.33	13/87	14/86	27/173
Bae et al. 2022	369	6.0	Retrospective Cohort Study	168	0	201	4	49	NA	NA	89/280
Lee et al. 2019	1528	5.6	Retrospective Cohort Study	1087	16	441	5	47	NA	NA	177/1345
Park et al. 2017	466	8.6	Retrospective Cohort Study	233	6	233	4	47.42 ± 10.12	39/194	31/202	70/396

Experimental Group: The DTC patients with TSH suppression therapy after hemithyroidectomy.
Control Group: The DTC patients without TSH suppression therapy after hemithyroidectomy.

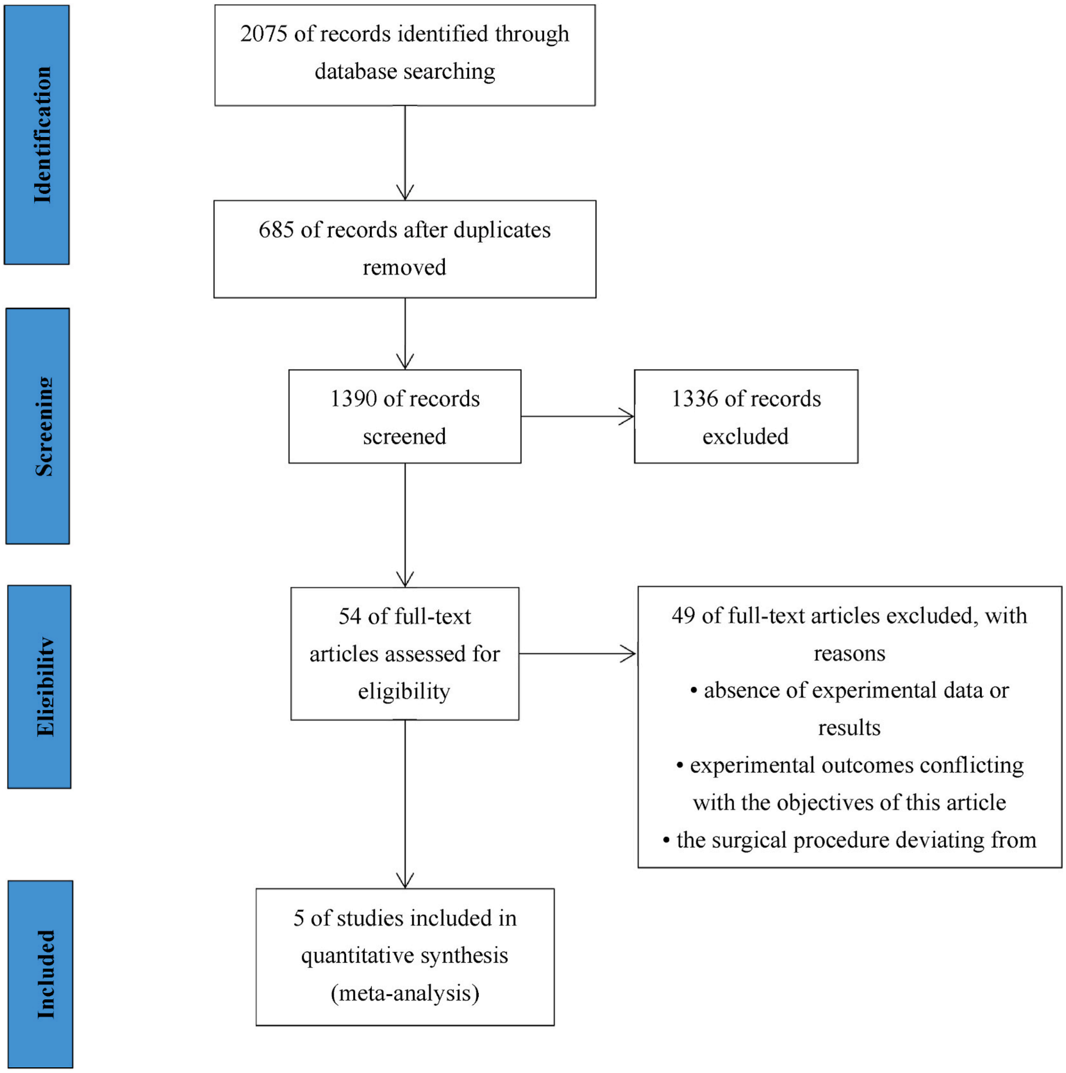

Fig. 1. Prisma literature retrieval Flowchart.

Author & Year	Selection				Comparability Control for Important Factor	Exposure			Scores
	Adequate Definition of Cases	Representativeness of The Cases	Selection of Controls	Definition of Controls		Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non-response Rate	
Ahn et al. 2020	●	●	-	●	●	●	●	●	7
Kang et al. 2019	●	●	-	●	●	●	●	●	7
Bae et al. 2022	●	●	-	●	●	●	●	●	7
Lee et al. 2019	●	●	●	●	●	●	●	●	8
Park et al. 2017	●	●	●	●	●●	●	●	●	9

Fig. 2. Quality evaluation and risk bias evaluation of NOS scale.
●,one score; -, no score.

women undergoing TSH suppression therapy are 4.3 times more likely to develop osteoporosis than those not receiving such therapy [29]. Consequently, emerging evidence suggests that postoperative TSH suppression therapy may be unnecessary for DTC patients following hemithyroidectomy, with limited impact on recurrence rates.

Numerous studies have presented compelling evidence challenging the necessity of TSH suppression therapy in low-risk DTC

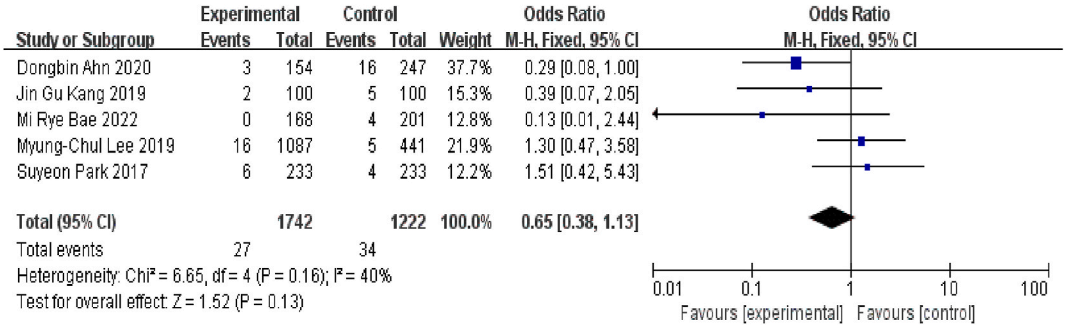

Fig. 3. Forest Plot showing odds ratios of the recurrence rate of patients who received TSH suppression therapy compared to the patients who did not receive TSH suppression therapy. Black squares and horizontal lines represent a odds ratio (OR) and a 95 % confidence interval (CI) for each study; Experimental group: patients who received TSH suppression therapy; Control group: patients who did not receive TSH suppression therapy.

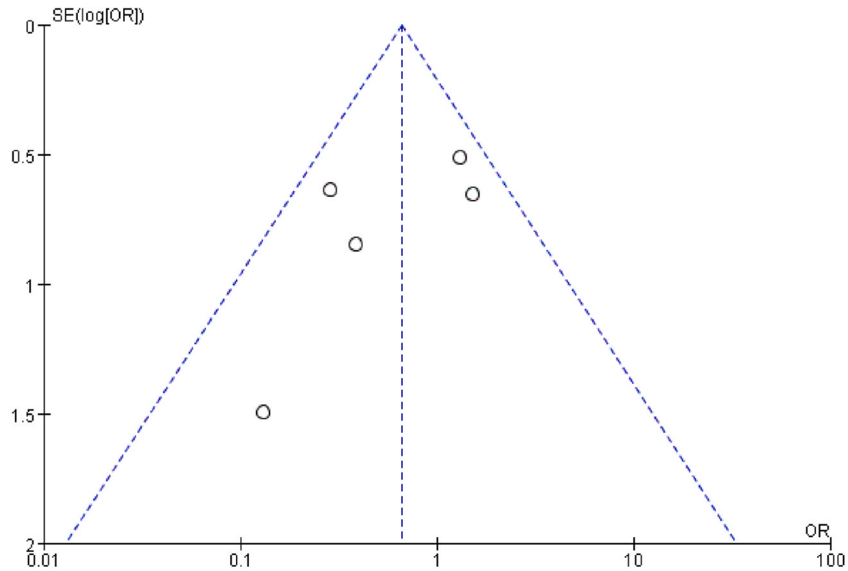

Fig. 4. Funnel plot.
Every dot represents an included study, OR odds ratio, SE standard error.

patients following surgery. For instance, Wang, L. Y. indicates that TSH suppression therapy significantly elevates the risk of post-operative osteoporosis in patients with medium to low-risk DTC but exerts no discernible influence on tumor recurrence [29]. Similarly, Park, S. suggests that TSH suppression therapy does not eliminate recurrence rates and provides no clinical benefits for low-risk DTC patients undergoing hemithyroidectomy [21]. Additionally, Lamartina, L. suggests that TSH suppression therapy has no impact on the incidence of structural diseases at one year and three years after treatment [30]. Furthermore, a randomized controlled trial in 2010 demonstrated that the majority of patients undergoing hemithyroidectomy for DTC can enjoy a normal lifespan without medication, advocating against postoperative TSH suppression therapy for low-risk DTC [31].

Moreover, multiple studies over the past decade have indicated that postoperative TSH suppression therapy has minimal bearing on tumor recurrence. Currently, thyroid hemithyroidectomy typically serves as the initial treatment for low-risk DTC. Nevertheless, there remains a paucity of evidence regarding the necessity of postoperative TSH suppression therapy, and the established target range for postoperative serum TSH concentration remains elusive, necessitating further research for elucidation.

Our study signifies a lack of statistical significance ultimately, which means there is no need using TSH suppression therapy for DTC after hemithyroidectomy. Considering that the length of follow-up may have an impact on the research result, we divided the five studies into two subgroups, and comparisons within subgroups indicates no statistical significance neither. It suggests that the length of follow-up does not profoundly influence the results. We tried our best to minimize the influence. But simultaneously, although we artificially divided the five researches into two subgroups based on the average follow-up period. The specific follow-up periods are different and we are unable to standardize them. So it will still have an impact on our analysis results. Larger data analysis will be needed to eliminate this influence in future research.

Regarding serum TSH levels, data from Ahn, D. et al., encompassing 19 cases of recurrence and 382 cases of non-recurrence, revealed average TSH values of 4.1 mIU/L and 3.78 mIU/L respectively, with a p-value of 0.56 [19]. In a separate study, which was not integrated into the analysis due to incomplete data, the disease-free survival rate at 10 years after surgery was examined. This study indicated that postoperative TSH suppression therapy only affected the disease-free survival rate of high-risk patients, while exerting no impact on recurrence in medium to low-risk patients, mean serum TSH levels are not associated with recurrence, a normal TSH reference range is suggested [32]. Additionally, findings by Kim, S. Y. et al. suggested that the need for levothyroxine replacement therapy in postoperative thyroid cancer patients with hypothyroidism is intricately linked to preoperative serum TSH levels and the presence or absence of thyroiditis [33]. Therefore, further prospective randomized controlled trials with larger sample sizes are essential to explore and substantiate the necessity of postoperative TSH suppression therapy for low-risk DTC patients, as well as to determine the optimal range of maintained TSH values when employing thyroid hormone replacement therapy.

This study has some limitations. Firstly, due to the type of the five studies are all retrospective cohort studies instead of randomized controlled trials, the allocation and selection of the experimental and control groups lacked randomness. Secondly, significant variations in clinical characteristics among patients, like the average follow-up years, both within and between groups, posed challenges for ensuring consistent patient selection. Thirdly, the inclusion of only five experiments in this systematic review and meta-analysis resulted in a limited number of trials and reduced randomness, which could potentially affect the persuasiveness of the findings. Lastly, the varying degrees and numerical definitions of TSH inhibition across these five experiments resulted in a lack of uniformity.

Moreover, there are still many influencing factors that have not been analyzed regarding the study itself. For instance, the lymph node metastasis in DTC patients can have an impact on the prognosis. Usually, we decide whether to perform lymph node dissection and the extent based on the actual condition of the tumor. Some studies suggest that the neck dissection may influence the recurrence rate of DTC [34,35]. Also, sometimes a comprehensive neck dissection may identify several small metastatic lymph nodes which may reclassify it into intermediate risk. Then it will not be suitable to be included, which need a deeper study in future. Additionally, after statistical analysis, a 40 % level of heterogeneity was observed in this systematic review and meta-analysis, highlighting the need for the inclusion of more prospective randomized controlled trials in future analyses.

5. Conclusion

The systematic review and meta-analysis encompassed an examination and synthesis of findings from a total of five studies. The potential influence of the follow-up period was considered and found to be non-significant. When focusing solely on the recurrence rate, the administration of TSH suppression therapy does not appear imperative for low-risk DTC. When making treatment decisions for patients following hemithyroidectomy, we recommend exercising caution in assessing its necessity and being attentive to potential adverse effects associated with TSH suppression therapy. It is also recommended to explore further research endeavors aimed at elucidating the necessity of postoperative TSH suppression therapy for low-risk DTC following hemithyroidectomy.

CRediT authorship contribution statement

Xinyu Wang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yuqian Ye:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mizaniya Amdulla:** Writing – review & editing, Formal analysis, Conceptualization. **Chenglong Ren:** Writing – review & editing, Formal analysis, Conceptualization. **Yunhe Liu:** Formal analysis, Conceptualization. **Song Ni:** Writing – review & editing, Supervision, Formal analysis, Conceptualization, Hui Huang, Writing – review & editing, Supervision, Conceptualization.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All data accessed and analyzed in this study are available in the article.

Ethics approval

Not applicable.

Ethics statement

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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