

SYSTEMATIC REVIEW

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Thyroidectomy versus antithyroid drugs in Graves' disease: a meta-analysis of randomized controlled trials

XiaoGang Zheng¹, Yi Zhu², Ming Gao Chen³, Yong Cheng Su⁴ and Xiao Ming Wu^{3*}

Abstract

Objective This meta-analysis was developed to compare the clinical outcomes associated with thyroidectomy and antithyroid drug treatment in Graves' disease patients, with a focus on outcomes including ophthalmopathy onset or progress, the hyperthyroid cure rate, and the incidence of adverse events.

Methods A systematic search of the PubMed, Web of Science, Embase, National Knowledge Infrastructure, China, and SinoMed databases was performed to identify randomized controlled trials (RCTs) comparing thyroidectomy and antithyroid drugs as treatments for Graves' disease. Study quality was measured with the Cochrane risk of bias tool. Review Manager 5.4 and Stata 14.0 were employed to analyze the pooled data from these studies. The resultant data were reported as 95% confidence interval (CI) values and weighted mean differences. Fixed- or random-effects models were selected for pooled estimates based on the degree of heterogeneity among studies.

Results Following a review of the literature, 7 RCTs enrolling 715 patients were incorporated into this meta-analysis. Thyroidectomy was associated with a significantly better hyperthyroid cure rate as compared to antithyroid drugs (OR 3.03, 95% CI: 1.05 to 8.97, $P=0.04$), while also being associated with a lower rate of recurrence. Ophthalmopathy onset/worsening and adverse event incidence were comparable in both groups.

Conclusion As compared to antithyroid drug administration, thyroidectomy can achieve higher hyperthyroid cure rates and a lower risk of recurrence in Graves' disease patients without any concomitant rise in ophthalmopathy risk or adverse event incidence. In cases where antithyroid drug treatment is not optimal, thyroidectomy can thus be recommended as a more promising approach to treating Graves' disease.

Keywords Graves' disease, Meta-analysis, Thyroidectomy, Antithyroid drugs

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Introduction

As a common autoimmune disease, Graves' disease affects an estimated 14 in 100,000 individuals [1]. Females bear the largest burden of Graves' disease, as do people who reside in iodine-sufficient areas [2, 3]. The most common approaches to treating this disease include radioiodine treatment, prednisone administration, anti-thyroid drug (ATD) treatment, and total thyroidectomy (TTx). In many cases, the initial course of treatment recommended to patients consists of ATD administration [3].

The occurrence or recurrence of Graves' ophthalmopathy may be related to surgical treatment, because the process of reducing thyroid tissue through total thyroidectomy (TTx) may deplete autoreactive T lymphocytes, which may be beneficial to the clinical course of Graves' ophthalmopathy (GO). Therefore, in patients already experiencing overt symptoms of Graves' ophthalmopathy, ablating the thyroid may not be sufficient to counteract autoimmune disease progression. In these cases, ATD treatment may be a more viable clinical option. Data pertaining to the relative advantages of these strategies, however, are limited [4]. The most optimal means of treating patients suffering from moderate-to-severe Graves' ophthalmopathy thus remains uncertain. Many factors can affect the degree to which patients respond to particular treatments including age, sex, race, smoking, elevated serum TSH-receptor antibody (TRAb) levels, and severe thyrotoxicosis. The key goals of disease management for affected patients include the cessation of smoking and euthyroid restoration [5, 6].

ATD treatment has been reportedly not associated with the onset or worsening of eye disease [6], but it can lead to hyperthyroidism recurrence at rates of 20–70% after treatment has been discontinued. To address the relative benefits of ATD versus thyroidectomy as an approach to Graves' disease management, this study was devised as a meta-analysis of randomized controlled trials (RCTs) related to this topic [7–11].

Methods and materials

Search strategy

The PubMed, Embase, National Knowledge Infrastructure China, Web of Science, and SinoMed (Chinese BioMedical Literature Service System, China) databases were independently searched for relevant RCTs by two investigators using the following approach: ("thyroidectom*" [Title/Abstract] OR "hemithyroidectom*" [Title/Abstract] OR "thyroid" [Title/Abstract] OR "Thyroid Gland" [MeSH Terms] OR "Thyroidectomy" [MeSH Terms]) AND ("Propylthiouracil" [Title/Abstract] OR "Propylthiouracil" [MeSH Terms] OR "Methimazole" [Supplementary Concept] OR

"Methimazole" [All Fields] OR "thiamazole" [All Fields] OR "Methimazole" [MeSH Terms] OR "thiamazole" [All Fields] OR "Methimazole" [MeSH Terms]) OR ("Carbimazole" [Title/Abstract] OR "Carbimazole" [MeSH Terms]) OR ("antithyroid agent" [Title/Abstract] OR "antithyroid drug" [Title/Abstract] OR "Anti-thyroid Agents" [MeSH Terms])) AND ("Graves disease" [MeSH Terms] OR ("graves" [All Fields] AND "disease" [All Fields]) OR "Graves disease" [All Fields] OR ("graves" [All Fields] AND "disease" [All Fields]) OR "Graves disease" [All Fields]) AND ("randomized controlled trial" [Publication Type] OR "randomized" [Title/Abstract] OR "placebo" [Title/Abstract]). The language of selected studies was not restricted, but the search was specifically limited to human subjects. The references of relevant RCTs were also searched to identify other relevant articles. The ClinicalTrials.gov registry (<https://clinicaltrials.gov/>) was also searched for other RCTs in English that have not yet been published. The PROSPERO guidelines (CRD42024550029) were used to conduct this search process. For further details regarding the specific search strategies employed, see Supplementary Table S2. Overall, both the FS and control groups contained 715 participants. Patients were randomized to two groups, one-to-one randomization rules were obeyed. The experimental group received thyroid surgery, while the placebo control group received antithyroid drug treatment. The demographic characteristics and patient details are presented in Table 1.

Study selection

To be eligible for inclusion, articles had to: [1] be RCTs [2], focus on Graves' disease patients [3], compare patients who underwent ATD treatment to those patients who underwent thyroidectomy [4], measure outcomes including ophthalmopathy, hyperthyroid cure rate, hypothyroidism incidence, recurrence, and adverse event incidence [5], include more than 50 patients, and [6] employed a follow-up duration exceeding 12 months.

Patients, methods and outcomes

Individuals with moderate to severe GO who met the following conditions were included in the study:

- 1 Graves' orbitopathy (GO) and hyperthyroidism emerged within the recent six-month period.
- 2 Thyroid volume ≥ 15 ml.
- 3 No previous treatment except local interventions for GO.
- 4 GO activity was characterized by a clinical activity score (CAS) of ≥ 3 , along with at least one of the following conditions: proptosis measuring ≥ 21 mm in one eye, a difference of ≥ 2 mm in Hertel measurements between both eyes, occurrence of

Table 1 The demographic characteristics and patient details

Study	Treatment regimen	Number of patients	Year	Female/ male (n)	Study type	Age (mean $\pm$ SD) (years)	Race	Follow-up (years)
Tallstedt et al.	Antithyroid drug plus thyroxine/ subtotal thyroidectomy followed by thyroxine 64	65/64	1992	107/22	RCT	Young adults: 28 ± 4 old adults: 45 ± 6	Sweden	2
Trgring et al.	Antithyroid drugs plus T4/subtotal thyroidectomy followed by T4	71/67	1996	113/25	RCT	Young adults: 29 ± 4 old adults: 45 ± 6	Sweden	2
Ljunggren et al.	Antithyroid drug plus thyroxine/subtotal thyroidectomy followed by thyroxine	68/76	1998	NR	RCT	NR	Sweden	2
Abraham Nordlin et al.	Antithyroid drugs plus/subtotal thyroidectomy followed by thyroxine thyroxine	55/56	2005	NR	RCT	NR	Sweden	1.5
P Laurberg et al.	Antithyroid drugs plus L-thyroxine/ subtotal thyroidectomy followed by L-T4	48/47	2008	NR	RCT	NR	Sweden	2
Ta et al.	Anti-thyroid drugs/subtotal thyroidectomy	28/28	2010	12/72	RCT	35.83 ± 12.01	China	1
Erdoğan et al.	Antithyroid drug /total thyroidectomy	18/24	2016	Total thyroidectomy: 7/11 antithyroid drug: 12/12	RCT	Total thyroidectomy: 44 ± 8.7 antithyroid drug: 35 ± 12.9	Britain	3

diplopia, or lid aperture measuring ≥ 9 mm. Diplopia was identified as persistent, occurring in the primary position and during gaze movements. All patients exhibited moderate to severe activity levels. (i.e. CAS ≥ 3). Thyroid ultrasonography was utilized to evaluate thyroid volume and nodularity. Biopsies of the nodules were conducted as required. The assessment of activity was carried out using the CAS, which comprises seven components (eyelid swelling, eyelid redness, conjunctival irritation, chemosis, caruncle swelling, spontaneous eye pain, and pain during eye movements). Exophthalmos was assessed using a Hertel exophthalmometer, along with lid gap and double vision. These evaluations were conducted by the same skilled endocrinologist. Patients were only sent to an ophthalmologist when required. TSH, free T4, TRAb, anti-TPO, and anti-Tg levels were measured in 3-month to 6-month intervals during follow-up [12].

Data collection

Independent data extraction was performed by two researchers (ZXG, SYC), who extracted the following: publication year, first author, patient numbers (control, intervention), follow-up duration, study design, hyperthyroid cure rate, recurrence rate, adverse events, and any other data pertaining to clinical outcomes. Data were extracted using an Excel® (Microsoft, WA, USA) spreadsheet that had been standardized. If a given population was included in multiple publications, only the most complete study was used for this meta-analysis. Discussion and consensus were employed to resolve any disagreements among researchers.

Quality analyses

The Cochrane Collaboration tool was employed to evaluate the risk of bias and methodological quality for the included studies, with a focus on blinding, follow-up, randomization, outcomes, allocation concealment, and intention-to-treat protocols [13].

Statistical analyses

To control for potential heterogeneity across studies included in these analyses, fixed-effects models were not employed, with random-effects models instead having been utilized [12]. The 95% confidence intervals (CIs) were used when comparing the means for dichotomous and continuous variables. Heterogeneity, as measured with the I^2 statistic and Cochrane's Q test, was considered significant with an $I^2 > 50\%$ and a $P < 0.1$ [14]. All other analyses were deemed significant if $P < 0.05$. Publication bias and possible sources of heterogeneity were detected with funnel plots [1]. Review Manager 5.4.1 was employed for all analyses, which were conducted as per the guidelines from the Cochrane Collaboration and the PRISMA statement [15].

Results

Study selection

An initial review of 1,508 identified studies led to the exclusion of 1,021 articles through title and abstract review. Of the remaining 159 articles, 152 were excluded as they were not RCTs ($n = 54$), included a control group that did not meet the established criteria ($n = 71$), lacked outcomes of interest ($n = 11$), were duplicates ($n = 15$), were reviews or meta-analyses ($n = 5$), or could not be used for data extraction ($n = 3$). The remaining 7 RCTs

were used to conduct this meta-analysis. For further details, see Fig. 1.

The Cochrane risk of bias tool was next employed to evaluate these 7 RCTs [16], evaluating them in terms of potential sources of bias (each rated as being low, high, or unclear), including allocation concealment, outcome assessment blinding, participant and personnel blinding, random sequence generation, and selective reporting (Fig. 2). With respect to study quality, 3 RCTs [17–19] did not exhibit allocation concealment, while 1 [20] did not blind patients or personnel. Randomization methods were detailed for all RCTs [11, 13, 21, 22], and 3 exhibited good outcome assessor blinding and selective reporting bias.

Hyperthyroid cure rates

Hyperthyroid cure rate-related data were reported in all 7 RCTs. When a random-effects model was used for the pooled analysis of these results, thyroidectomy was found to be associated with a significantly better hyperthyroid cure rate as compared to ATD treatment OR 3.03, 95% CI: 1.05 to 8.97, $P=0.04$ (Fig. 3). Significant heterogeneity was observed ($P=0.0002$, $I^2=77\%$).

Four studies compared the risk of new ophthalmopathy between the thyroidectomy and ATD treatment groups (Fig. 4), revealing no significant differences in new ophthalmopathy risk between these two populations of Graves' disease patients ($I^2=0\%$, 95% CI 0.63 to 1.77, $P=0.84$).

Adverse events

Adverse events including joint pain, fever, rashes, and convulsions were described in four of the included RCTs. studies reported data on adverse events, including rashes, joint pain, fever, and convulsions. Pooled results using a random-effects model showed no significant difference in the incidence of adverse reactions between the thyroid surgery and antithyroid drug groups (OR 0.54, 95%CI: 0.05, 5.50; $P=0.61$) (Fig. 5). The test for heterogeneity was significant (heterogeneity $P=0.02$, $I^2=68\%$).

The 95% CI is represented by the two vertical axes, while the overall HR is denoted by the horizontal axis. The pooled OR is represented by the circles when omitting the indicated study, while the bars denote the 95% CI. CI: confidence interval, HR: hazards ratio, OR: odds ratio.

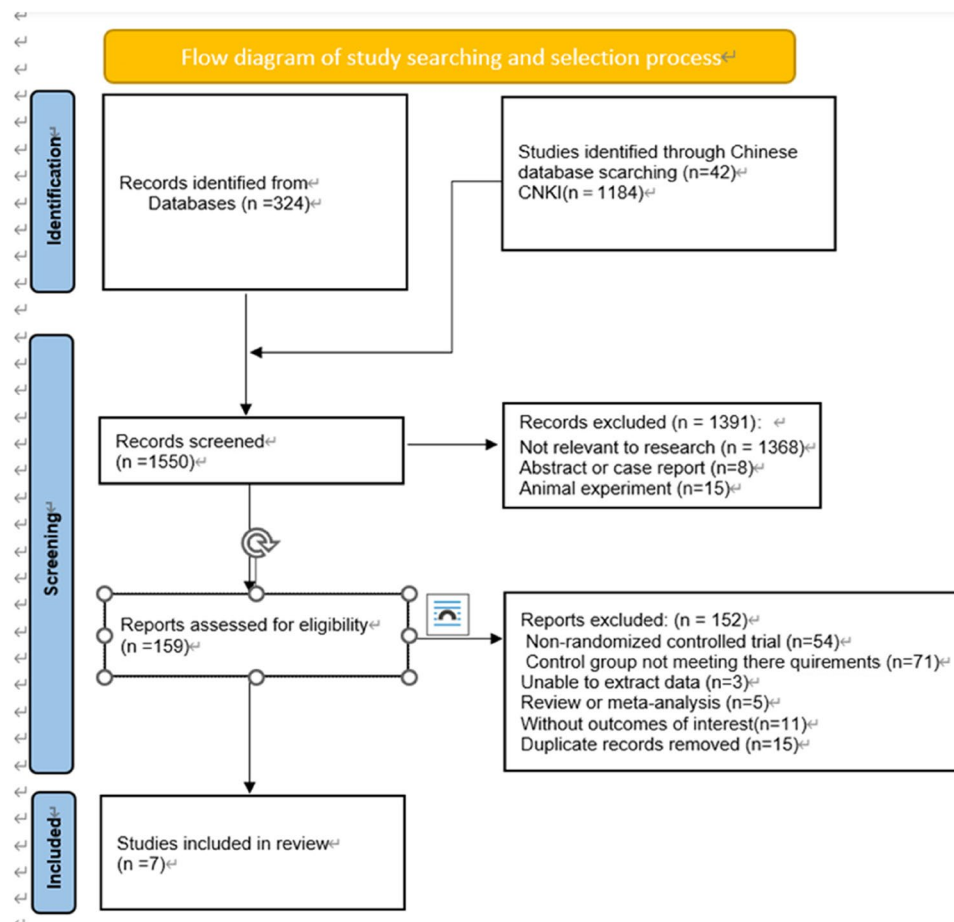


Fig. 1 Flow diagram of study searching and selection process

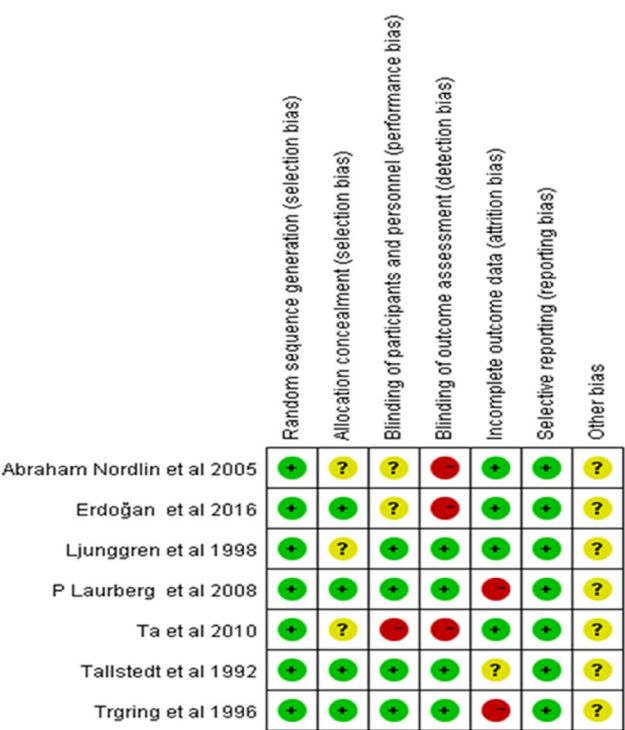


Fig. 2 Risk of bias summary

Sensitivity analyses of these seven RCTs were next performed. Given that this meta-analysis was conducted

using varying sample sizes, we carried out a sensitivity analysis to determine if the result was affected by this factor. Upon excluding two studies with moderate sample sizes, we observed no substantial difference in the hyperthyroidism cure rate between the two groups, confirming the stability of the final results of this analysis (as shown in Fig. 6).

Publication bias

When assessing the hyperthyroid cure rate data, funnel plots did not exhibit any apparent asymmetry (Fig. 7), consistent with a lack of publication bias.

Discussion

The most appropriate treatment strategy for the management of Graves’ disease remains a matter of some controversy. Administering radioiodine can trigger the worsening of the disease course in Graves’ disease patients, and thyroidectomy or long-term ATD treatment for at least 18–24 months are the most commonly employed therapeutic strategies. Data clarifying the relative superiority of these two strategies, however, is not available in sufficient quantities [13].

The present meta-analysis compared the efficacy of ATD and thyroidectomy as treatments for Graves’ disease, focusing solely on results published in RCTs. These pooled analyses should thus have superior power as a

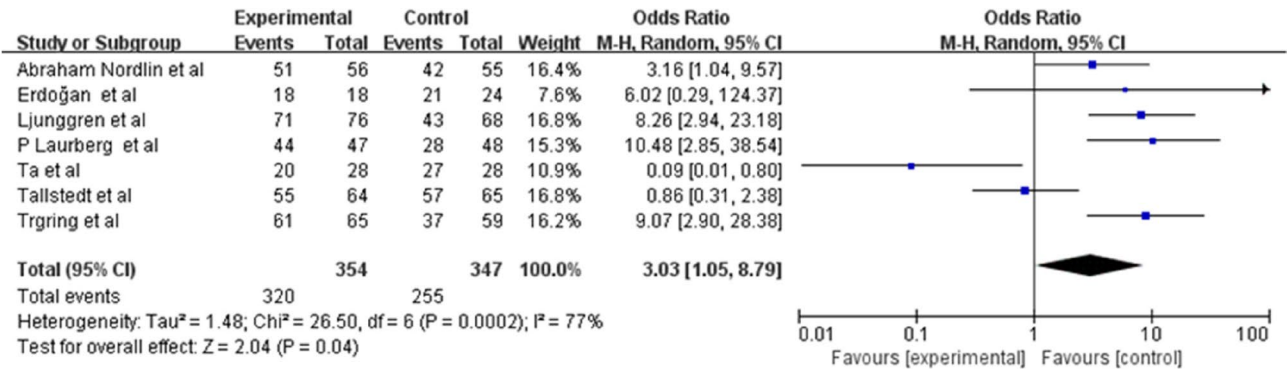


Fig. 3 Comparison of hyperthyroid cure rate between thyroidectomy and antithyroid drugs for patients with Graves’ disease.CI, confidence interval; OR, odds ratio. The experimental group: thyroidectomy; the placebo control group: antithyroid drugs

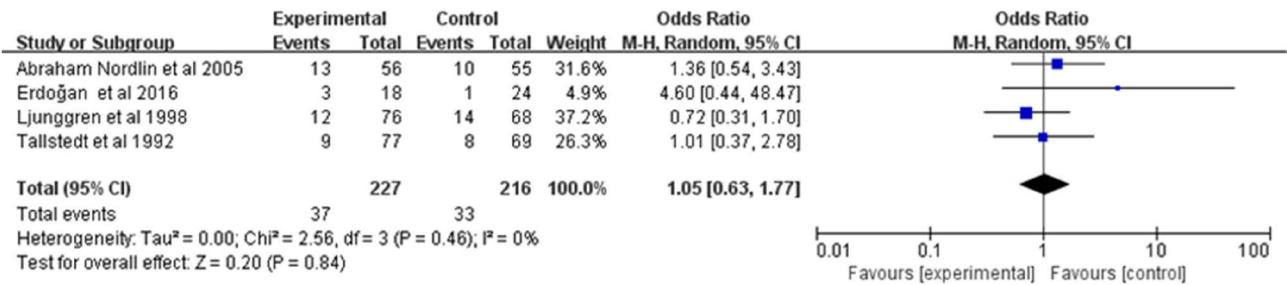


Fig. 4 Comparison of new ophthalmopathy between thyroidectomy and antithyroid drugs for patients with Graves’ disease.CI, confidence interval; OR, odds ratio. The experimental group: thyroidectomy; the placebo control group: antithyroid drugs

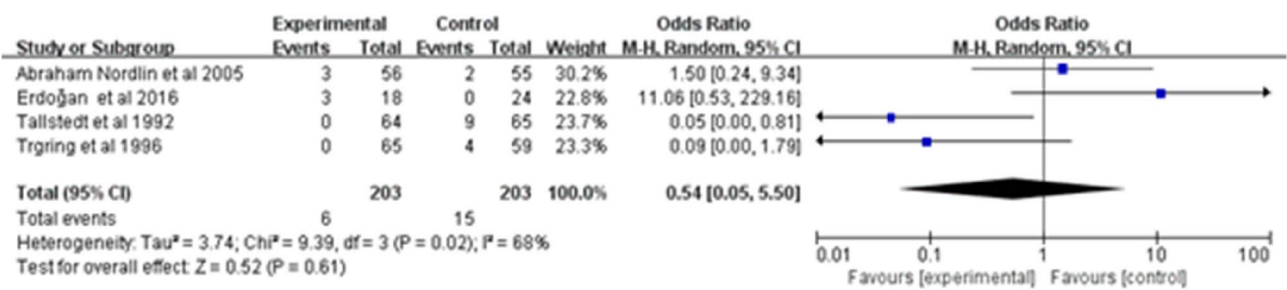


Fig. 5 Comparison of adverse events between thyroidectomy and antithyroid drugs for patients with Graves’ disease.CI, confidence interval; OR, odds ratio. The experimental group: thyroidectomy; the placebo control group: antithyroid drugs

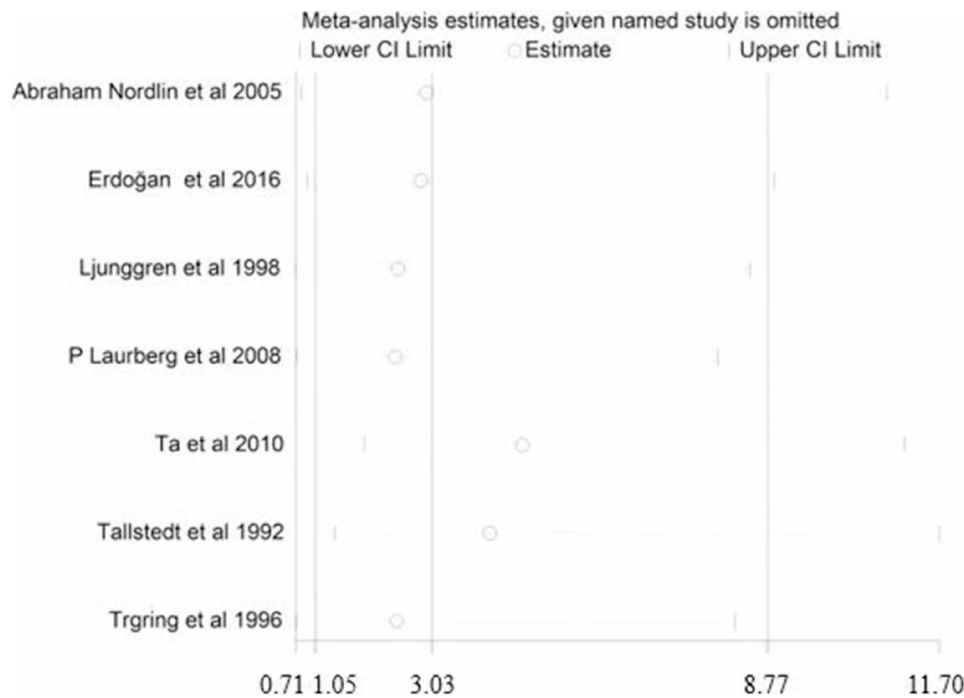


Fig. 6 Sensitivity analyses of the included studies regarding hyperthyroid cure rate. The two vertical axes represent the 95% CI, and the horizontal axis represents the overall HR. In the current review, the pooled OR was represented by a hollow, round shape and was excluded from the remaining studies. The two ends of each broken line represent the corresponding 95% CI. CI: confidence interval, HR: hazards ratio, OR: odds ratio

means of assessing the relative advantages of these two therapeutic strategies. Ultimately, these analyses indicated that thyroidectomy was not related to any greater risk of new-onset or worsening ophthalmopathy in treated patients, nor did it entail any greater risk of other adverse events. Hyperthyroid cure rates were higher for patients who underwent thyroidectomy as compared to those patients who underwent ATD treatment. In addition, we assessed the effects of these two therapies on other clinical outcomes, such as adverse events. Given that surgical intervention and medication represent fundamentally distinct treatment approaches, each with its own set of risks, physicians should carefully consider these findings prior to implementing them in clinical practice. Considerable heterogeneity was observed among the selected RCTs, the quality of the evidence

is limited, reflected the uncertainties brought about by these findings. When performing thyroidectomy, different surgical methods such as total thyroidectomy or subtotal thyroidectomy may lead to a certain degree of bias, resulting in significant heterogeneity ultimately detected in these studies. Mu L et al. [23] investigated that near-total thyroidectomy for Graves’ disease was superior to total thyroidectomy in terms of permanent hypoparathyroidism, but there was no significant difference in preventing recurrent hyperthyroidism and other postoperative complications. Total thyroidectomy is more effective than subtotal thyroidectomy (both bilateral subtotal thyroidectomy and the Dunhill procedure) at preventing recurrent hyperthyroidism in Graves’ disease. Liu ZW et al. [24] investigated that total thyroidectomy is more effective than subtotal thyroidectomy (both bilateral

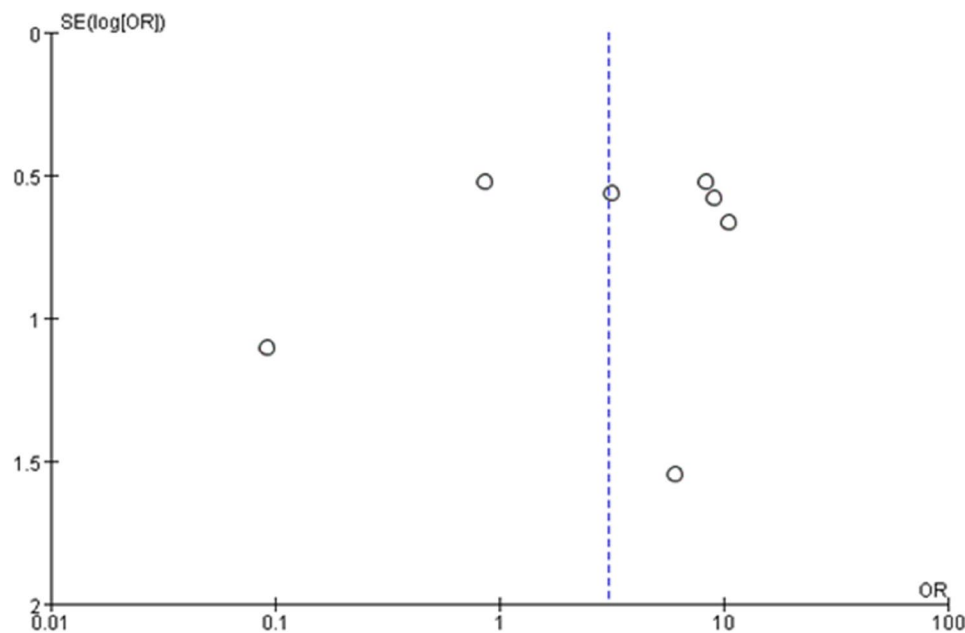


Fig. 7 Funnel plot analysis of publication bias related to hyperthyroid cure rate

subtotal thyroidectomy and the Dunhill procedure) at preventing recurrent hyperthyroidism in Graves' disease. We adopted the random effects model to mitigate this impact, but caution is still needed when evaluating these results.

Patients who undergo surgical or pharmacological treatment generally exhibit gradual declines in serum TRAb levels, with 50–60% of these individuals having entered into a state of remission after 1 year as defined by the absence of serum TRAbs and the consequent cessation of autoimmunity directed against the TSH receptor. The mechanistic basis for this treatment-related remission has not been elucidated in detail. As noted in a past report [25], hyperthyroidism may play some role in provoking or exacerbating autoimmune responses. When patients achieve a euthyroid state following treatment, most will thus enter into remission, although a minority of patients fail to do so. Even in cases when patients exhibit good responses to surgery or pharmacological treatment, gradual reductions in serum TRAb levels tend to be observed over extended periods. While successful thyroidectomy procedures in Graves' disease patients can immediately abrogate the hyperthyroid state, autoimmune abnormalities will require more time to return to normal levels.

While TRAb levels decline similarly after surgery or in response to pharmacological treatment, a rebound in serum TRAb levels may occur in some patients after the cessation of medical treatment that coincides with recurrent hyperthyroidism. This potential for new-onset hyperthyroidism is a more significant threat in patients who remain TRAb-positive when they complete

treatment, and prolonged medical treatment may help mitigate this risk [26–29]. However, this therapeutic strategy needs to be carefully weighed against the side effects associated with drug use [30]. Further research will be vital to establish optimal approaches to pharmacologically managing Graves' hyperthyroidism, and the advent of novel ATDs with fewer side effects may improve the palatability of long-term treatment [31].

Multiple limitations to this study warrant discussion. For one, as this meta-analysis only included 7 RCTs and some enrolled relatively limited numbers of patients, this may have led to some degree of overestimation of the efficacy of treatment relative to studies with larger patient populations, this may have potential publication bias. Secondly, these studies exhibited a high degree of heterogeneity, enrolling patients with different genders, ages, thyroid function levels, and hyperthyroidism durations. These differences may have had an impact on the overall study results. Details regarding thyroid gland size, hyperthyroidism severity, and other specific factors such as thyroid surgery extent or ATD doses were not available, which precluded any comprehensive subgroup analyses. Third, adverse event-related analyses were based on data from just four RCTs, with many articles failing to describe complications following thyroid surgery. Fourthly, in the included studies, we found that the scope of thyroid surgery (total thyroidectomy and near-total thyroidectomy) was not explicitly mentioned. Since the extent of resection will affect the cure rate and the risk of complications. However, these data cannot be obtained from the included randomized controlled trials, which is a limitation. Lastly, one of these studies was conducted in

China. Differences in regional demographics and clinical practices and the variability of surgical techniques (the scope of thyroidectomy) may necessitate caution when generalizing these results across patient populations. Caution is thus important when interpreting or applying these study results.

In conclusion, the present results suggest that thyroidectomy procedures can achieve hyperthyroid cure rates higher than those associated with ATD treatment together with lower rates of recurrence. Importantly, no differences in ophthalmopathy or hypothyroidism risk were observed when comparing these two therapeutic strategies. In Graves' disease patients, ATD treatment often fails to adequately control, and hyperthyroidism often recurs when treatment is discontinued. Thyroidectomy may thus be a better treatment option for Graves' disease patients in cases when ATD therapy fails to yield ideal outcomes. However, considerable heterogeneity was observed among the selected RCTs, the quality of the evidence is limited, reflected the uncertainties brought about by these findings.

Abbreviations

CI	Confidence intervals
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
SD	Standard deviation
ATD	Antithyroid drugs
TTx	Total thyroidectomy
GO	Graves' ophthalmopathy

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12893-025-03081-7>.

Supplementary Material 1

Acknowledgements

DeclarationsEthical approvalThis study was approved by the local institutional review board, and the requirement for informed consent was waived because of the retrospective nature of this study. Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) were completely observed by the authors.**Consent for publication**Not applicable.**Competing interests**The authors declare no competing interests.**Author contributions**ZXG and CMG wrote the main manuscript text, SYC prepared figures, WXM and WMZ provided financial support.**Data availability**No datasets were generated or analysed during the current study.**Funding**This study didn't receive any funding.**List of Abbreviations**CI Confidence intervalsPRISMA Preferred Reporting Items for Systematic Reviews and Meta-AnalysesRCTs randomized controlled trialsSD standard deviationATD Antithyroid drugsTTx total thyroidectomyGO Graves' ophthalmopathy**Acknowledgment**The authors thank the participants included in our study for theirContributions.

Author contributions

Author contributionsZXG and CMG wrote the main manuscript text, SYC prepared figures, ZY and WXM provided financial support.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study was approved by the local institutional review board, and the requirement for informed consent was waived because of the retrospective nature of this study. Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) were completely observed by the authors.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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