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Risk Factors and Rates for Hypocalcemia After Pediatric Thyroidectomy: A Systematic Review and Meta-analysis

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Abstract

Objective. Postoperative hypocalcemia after total thyroidectomy (TT) affects pediatric patients at higher rates than adult patients, yet its rate remains poorly defined. This study aims to determine the rates of transient, permanent, and any hypocalcemia after TT in pediatric patients and analyze potential risk factors.

Data Sources. PubMed, EMBASE, Scopus, and Cochrane.

Review Methods. A database search was conducted through March 2024 according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Data concerning postoperative hypocalcemia, risk factors, and clinical context were collected and analyzed. Transient hypocalcemia was defined as lasting less than 6 months and permanent as lasting greater than 6 months after surgery.

Results. In total, 67 studies with 7331 pediatric patients met the inclusion criteria. Surgical indications for TT in this cohort included malignant conditions (54.75%), benign conditions (19.70%), Graves' disease (18.59%), genetic syndromes (MEN2A/2B, RET mutation) (6.04%), and Hashimoto's thyroiditis (0.92%). The pooled incidence rates were 25.2% (95% CI 0.20-0.31) for transient, 7.4% (95% CI 0.05-0.10) for permanent, and 32.1% (95% CI 0.26-0.39) for any hypocalcemia. Fifteen of the included studies also examined risk factors for postoperative hypocalcemia. Patients undergoing TT for malignancy (odds ratio [OR] 2.82, 95% CI [1.18-6.73]; $P = .02$) or Graves' disease (OR 6.12, 95% CI [3.10-12.01]; $P < .0001$), as well as those undergoing any lymph node dissection (OR 3.71, 95% CI [1.95-7.06]; $P < .0001$) were at higher risk for postoperative hypocalcemia.

Conclusion. Hypocalcemia is a common postoperative complication of TT in pediatric patients. Risk factors include malignant surgical indication, Graves' disease, and any lymph node dissection.

Keywords

pediatric malignancy, pediatric thyroidectomy, postoperative hypocalcemia, thyroid

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Total thyroidectomy (TT) is a standard treatment for various benign and malignant pediatric conditions. One of the most common postoperative complications of TT is hypocalcemia secondary to hypoparathyroidism, which can be transient or permanent in nature.[1] Hypocalcemia after TT is often caused by inadvertent removal of the parathyroid glands or compromise to their vasculature in surgery, a complication that is more pervasive in the pediatric population compared to adults.[1-4] Postoperative hypocalcemia may be asymptomatic when calcium levels are mildly reduced but can lead to muscle spasms, paresthesia, arrhythmia, seizures, and other neuromuscular and neurological complications if untreated and/or not recognized.[1,5] Additionally, hypocalcemia following pediatric TT has been associated with prolonged

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hospital stays, increased monitoring requirements, and greater morbidity.[6,7] Although there is extensive literature on thyroidectomy outcomes in adults, reports focusing on pediatric populations are often small retrospective case series, making it hard to draw definitive conclusions. Despite the relatively meager amount of data regarding outcomes in pediatric patients compared to adult patients, evidence points to a higher incidence of postoperative complications in children.[8-11]

Rates of postthyroidectomy hypocalcemia vary widely in the pediatric population literature, ranging from less than 10% to greater than 60%.[7,9] A 2021 systematic review evaluating hypocalcemia prevention and management in postthyroidectomy pediatric patients reported a pooled incidence of 35.5% for transient hypocalcemia and 4.2% for permanent hypocalcemia, based on 15 studies. In their evaluation of management options, most studies used treatment algorithms requiring admission for intravenous calcium therapy.[12] Despite these findings, there is no consensus or established estimate regarding the likelihood of postoperative hypocalcemia following TT, which complicates counseling patients and their families about expectations for the immediate postoperative period and potential lifelong sequelae. Additionally, little is known about the risk factors and predictors of postoperative hypocalcemia in pediatric patients. These outcomes have primarily been reported in single-institution case series, which have identified factors such as neck dissection, age at surgery, Graves' disease (GD), and malignancy as potential predictors of postoperative hypocalcemia.[7,13-15] However, to the best of our knowledge, no study has conducted a formal analysis of these predictors or synthesized outcomes across multiple studies in the pediatric population.

In this study, we conduct a systematic review and meta-analysis to assess the rates of postoperative transient, permanent, and any hypocalcemia in the pediatric population following TT. Additionally, we analyze potential risk factors for postoperative hypocalcemia, as identified by the existing literature.

Methods

Study Design and Search Strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[16] An extensive literature search was initially conducted in August 2022 and repeated in March 2024. Multiple electronic databases including PubMed, EMBASE, Scopus, and Cochrane were queried to identify studies that examined postoperative hypocalcemia in pediatric patients after TT. The search terms included: "thyroidectomy" or "total thyroidectomy" or "thyroid resection" or "thyroid surgery" and "pediatric" or "children" or "adolescent" and "hypocalcemia" or "low calcium" or "postoperative hypocalcemia" and "risk factors" or "predictors" or "associated factors" or "influencing factors."

All databases were searched back to their inception, and no date limits were applied. Titles and abstracts were searched using the PRISMA methodology. Covidence systematic review software (Veritas Health Innovation), a web-based software used to assist research in screening references and extracting data, was used to collect, organize, and manage all studies.

Eligibility Criteria and Study Selection

This review was limited to English language studies focusing on pediatric patients, aged ≤21 years. Animal studies, systematic reviews and meta-analyses, letters, abstracts, commentaries, and editorials were excluded. Studies were included only if the surgery performed was a TT and postoperative hypocalcemia was reported as an outcome. Studies including mixed surgical cohorts (eg, TT, sub-TT, and partial thyroidectomy) were included if hypocalcemia outcomes specific to the TT cohort could be isolated. Studies were included only if they explicitly reported on postoperative hypocalcemia; studies that examined postoperative hypoparathyroidism without explicit information on hypocalcemia were excluded. Two authors (M.A. and C.F.) independently screened articles on title, abstract, and full text for eligibility, with uncertain cases reviewed by an independent third reviewer (R.H.B.).

Data Extraction

Two authors (M.A. and C.F.) abstracted relevant data from the included articles in accordance with a prepared standardized form. The following data points were collected: author(s), year of publication, country of study, study design, number of patients undergoing TT, number of total patients, patient demographics, surgical indication, outcomes of transient and permanent hypocalcemia, and overall hypocalcemia outcomes. For the studies that included a risk factor analysis, the risk factor data collected included age, GD, lymph node dissection (LND), and malignant surgical indication.

Given that there is no internationally accepted definition of hypocalcemia, studies were included irrespective of the definitions used. The most common definition of hypocalcemia observed in the studies was biochemical hypocalcemia, defined as a serum calcium level of less than 8 mg/dL or an ionized calcium level of less than 1 mmol/L. Some studies further explored symptomatic versus asymptomatic hypocalcemia, but this was not uniformly reported throughout. Based on most of the studies' definitions of transient versus permanent hypocalcemia, transient for this article was defined as occurring immediately postsurgery and lasting less than

6 months, whereas permanent was defined as occurring for 6 months or longer postsurgery. Any or overall hypocalcemia was defined as the total rate of hypocalcemia reported in the study, including both transient and permanent. In addition, if a study did not specify transient or permanent hypocalcemia, then the outcome was reported as any hypocalcemia.

Quality Assessment

Two investigators (M.A. and D.R.S.H.) independently evaluated the quality of the included studies using the Joanna Briggs Institute (JBI) critical appraisal tool.[17] The JBI tool is used to assess individual studies' risk for bias by evaluating the aims, selection criteria, study design, data collection methods, and statistical analyses. The JBI assessment describes a study as high quality, moderate quality, low quality, or critically low quality based on how well it meets the criteria specified.[17]

Statistical Analyses

All the statistical analyses were performed using R software. A meta-analysis to determine the aggregate rate of hypocalcemia was performed when two or more studies reported data on transient, permanent, or any hypocalcemia. The pooled incidence for the hypocalcemia rates was presented as proportions with 95% confidence intervals (CIs). All of the studies were reviewed, and a subgroup that explicitly reported data about risk factors for postoperative hypocalcemia was identified. To be included in the meta-analysis, each study needed to explicitly report the outcomes of hypocalcemia in the two comparator groups, that is, malignant versus benign. These data were then synthesized in a meta-analysis and presented as odds ratios (ORs) with 95% CIs to demonstrate the risk factors for postoperative hypocalcemia. A P-value < .05 was considered statistically significant. The OR estimates are presented in forest plots. Heterogeneity was assessed using the Q-test and the I^2 statistic. Due to significant between-study heterogeneity observed in all analyses ($P \leq .1$ and $I^2 \geq 50\%$), a random-effects model was applied for all meta-analyses to account for variability in study designs and populations. The Spearman's rank-order correlation coefficient was used to measure the association between study publication year and rate of overall hypocalcemia.

Results

The literature search identified 4258 studies, of which 2055 duplicates were removed. The remaining 2195 studies were screened for title and abstract, of which 297 met the criteria for full-text review. After applying exclusion criteria, 67 studies were included in this meta-analysis, representing a total of 7331 pediatric patients who underwent TT, with 15 studies also examining risk factors for postoperative hypocalcemia (**Figure 1**). These studies originated from 24 different countries, with the United States (40.3%), Canada (7.6%), and Italy (7.6%) being the most common. The included studies were predominantly cohort (58.2%) and case series (23.9%) designs. Surgical indications for TT were as follows: malignant condition (54.75%), benign condition excluding GD (19.70%), GD (18.59%), genetic syndromes (MEN2A/2B, RET mutation) (6.04%), and Hashimoto's thyroiditis (0.92%). Complete information about the 67 included studies is found in Supplemental Table S1, available online.

Rates of Hypocalcemia

The results of the meta-analysis showed a wide range of transient, permanent, and any hypocalcemia rates across the included studies. Among the 54 studies reporting transient hypocalcemia, the pooled incidence was 25.2% (95% CI 0.20-0.31; $I^2 = 94.0\%$, $P < .0001$), with a range of 0% to 93.7% (**Figure 2**). For the 55 studies reporting permanent hypocalcemia, the pooled incidence was 7.4% (95% CI 0.05-0.10; $I^2 = 85.0\%$, $P < .0001$), ranging from 0% to 55.2% (**Figure 3**). The overall incidence of any hypocalcemia across the 55 studies reporting it was 32.1% (95% CI 0.26-0.39; $I^2 = 93.9\%$, $P < .0001$), ranging from 4.5% to 96.8% (**Figure 4**). Pediatric patients underwent TT at children's hospitals in 22 studies, at non-children's designated hospitals in 23 studies, and at both types of hospitals in 5 studies. No significant correlation was observed between year of study publication and rate of postoperative hypocalcemia ($\rho = 0.028$, $P = .8409$).

Risk Factors of Postoperative Hypocalcemia

Malignant Surgical Indication

Six studies explored malignant surgical indication as a risk factor for postoperative hypocalcemia, comparing outcomes for malignant versus benign conditions.[7,14,15,18-20] A random-effects model showed that malignant surgical indication was associated with a higher risk of postoperative hypocalcemia after TT (OR 2.82, 95% CI [1.18-6.73]; $P = .02$; $I^2 = 77.4\%$, $P = .0005$) (**Figure 5**).

Graves' Disease

GD as a surgical indication was explored as a risk factor in three studies, comparing it to other benign surgical indications, excluding GD.[7,15,18] A random-effects model indicated that GD was associated with an increased risk of postoperative hypocalcemia (OR 6.12, 95% CI [3.10-12.01]; $P < .0001$; $I^2 = 0.0\%$, $P = .6694$) (**Figure 6**).

Lymph Node Dissection

Any LND, including central LND, lateral LND, and bilateral central LND, was identified as a risk factor in nine studies.[7,13,14,18-23] A random-effects model showed that any LND in addition to a TT was associated with an

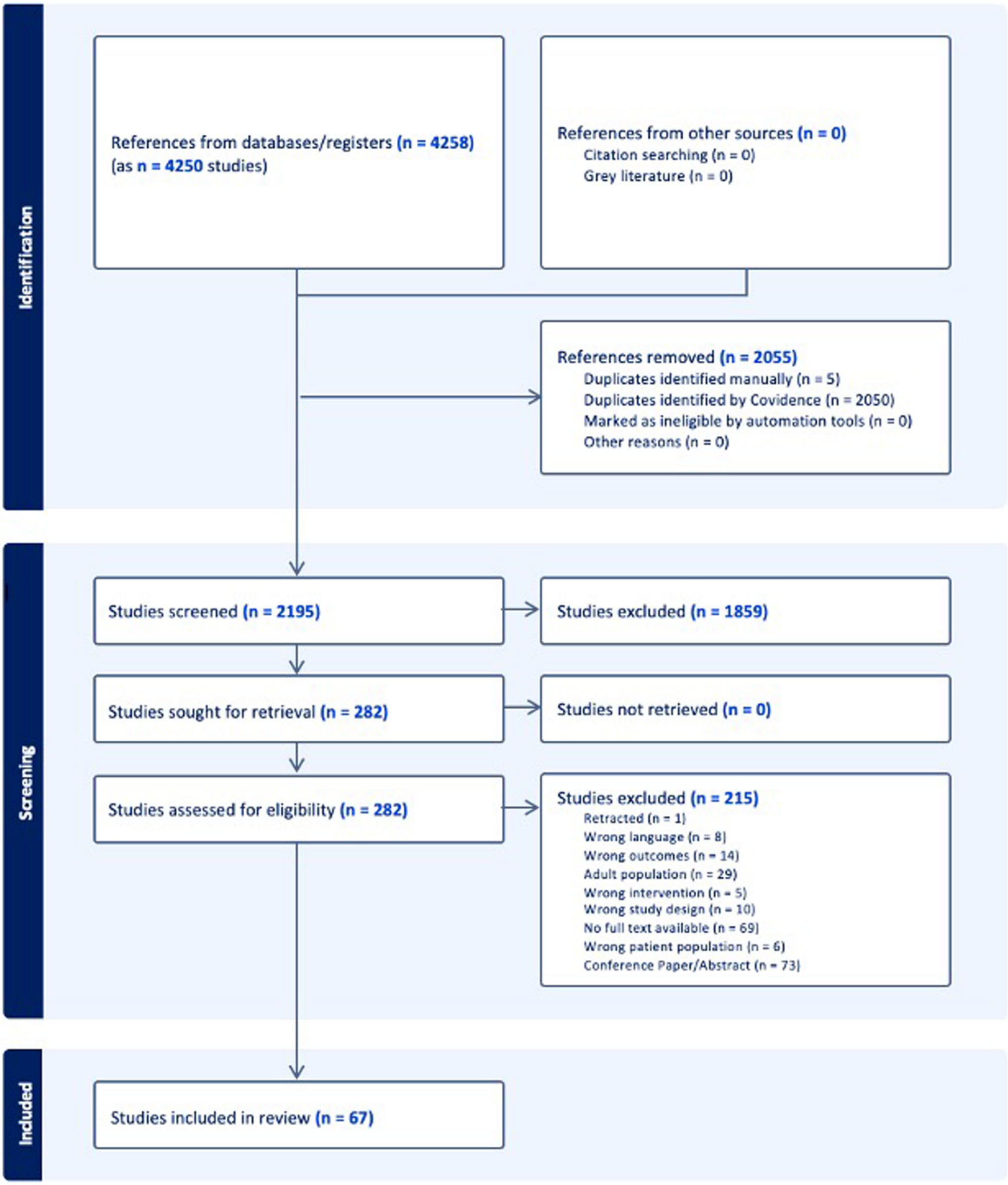

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram.

increased risk of postoperative hypocalcemia as compared to no LND (OR 3.71, 95% CI [1.95-7.06]; $P < .0001$; $I^2 = 66.9\%$, $P = .0021$) (**Figure 7**).

Quality Assessment

Overall, there was a medium- to high-quality global rating across the 67 studies included in this review. These studies demonstrated strong adherence to the key criteria, with some limitations in areas such as sample size, risk of bias, and reporting of confounding factors. Despite these limitations, the studies were deemed sufficiently rigorous to be included in the meta-analysis.

Discussion

In this systematic review and meta-analysis, we found significant variations in rates of postoperative hypocalcemia following TT in the pediatric population. Our study aimed to quantify the rates of transient, permanent, and overall hypocalcemia, outcomes that are not well-defined in the pediatric population but have substantial implications on postoperative management. We found pooled incidences of 25.2% (95% CI 0.20-0.31) for transient hypocalcemia, 7.4% (95% CI 0.05-0.10) for permanent hypocalcemia, and 32.1% (95% CI 0.26-0.39) for any hypocalcemia. Additionally, we identified malignant surgical indication, GD, and any LND

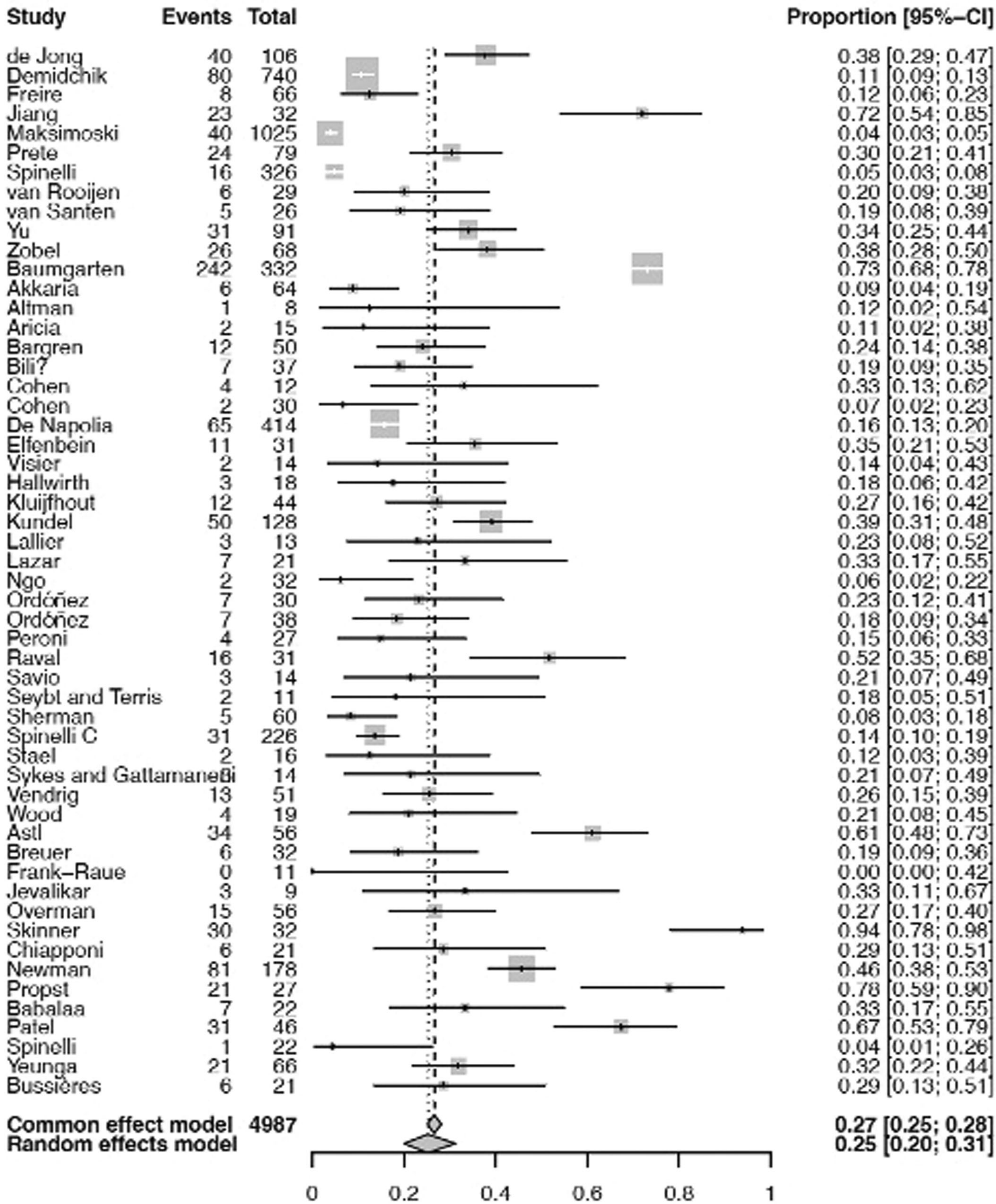

Figure 2. Meta-analysis of the incidence of transient hypocalcemia.

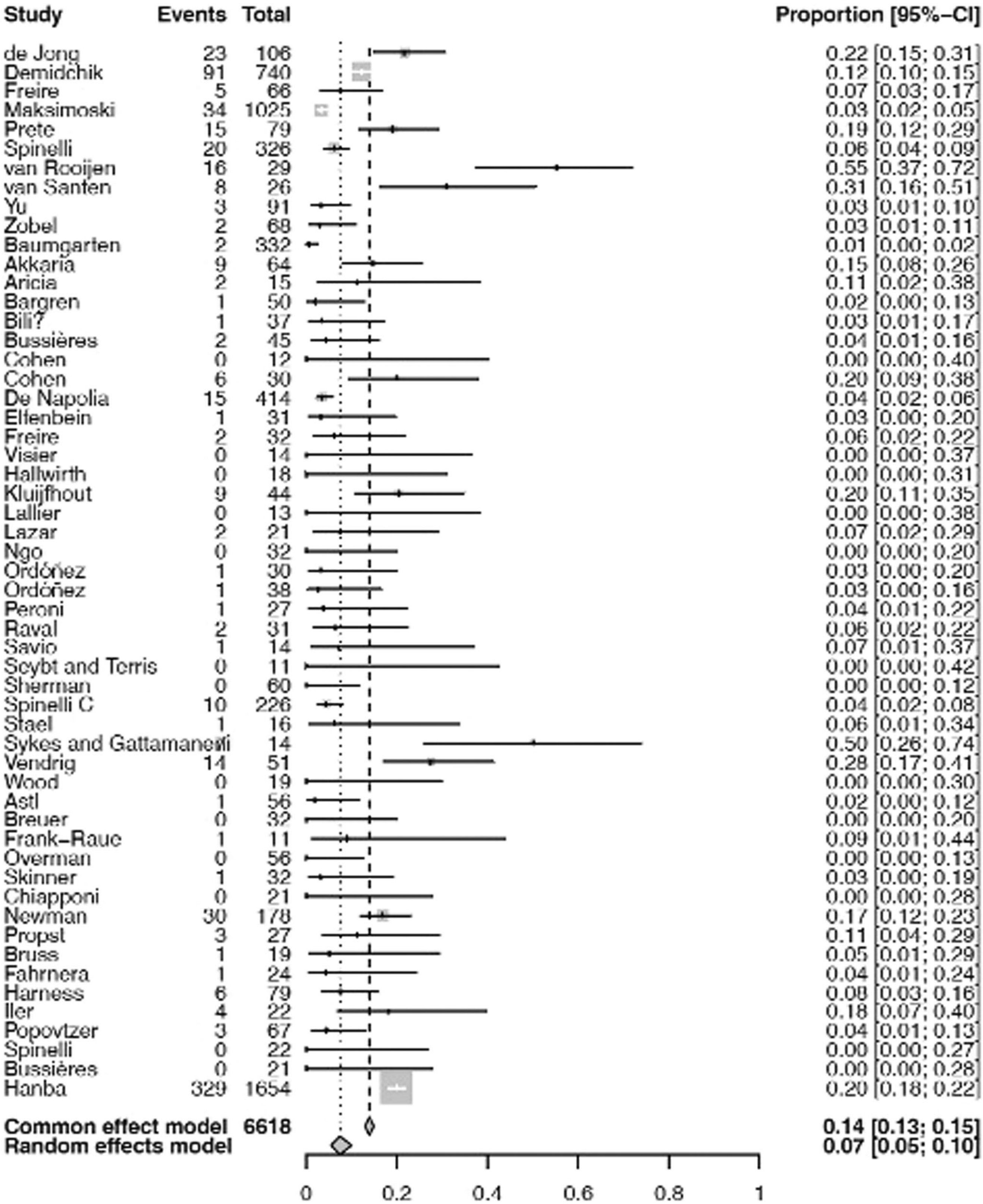

Figure 3. Meta-analysis of the incidence of permanent hypocalcemia.

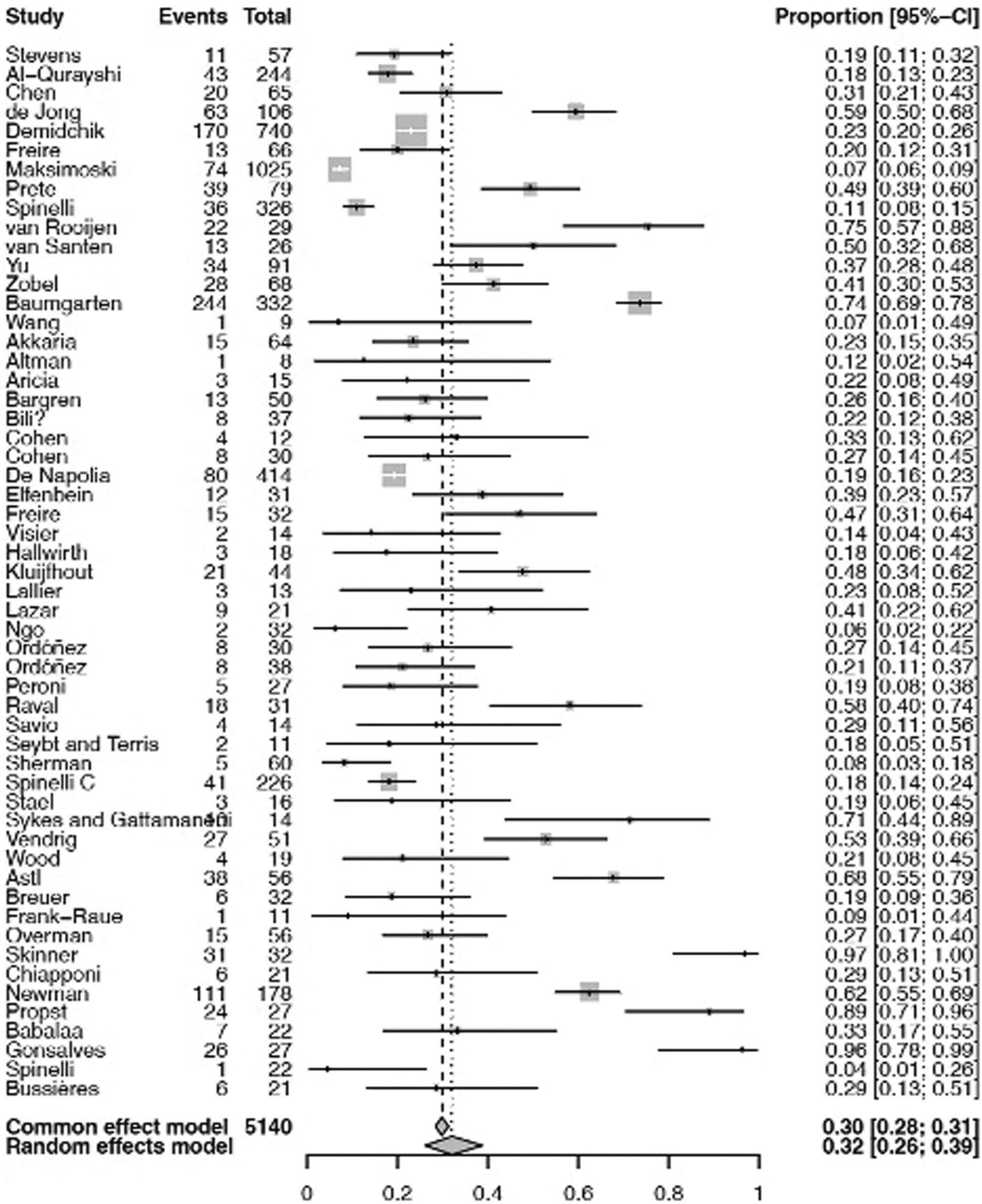

Figure 4. Meta-analysis of the incidence of overall hypocalcemia.

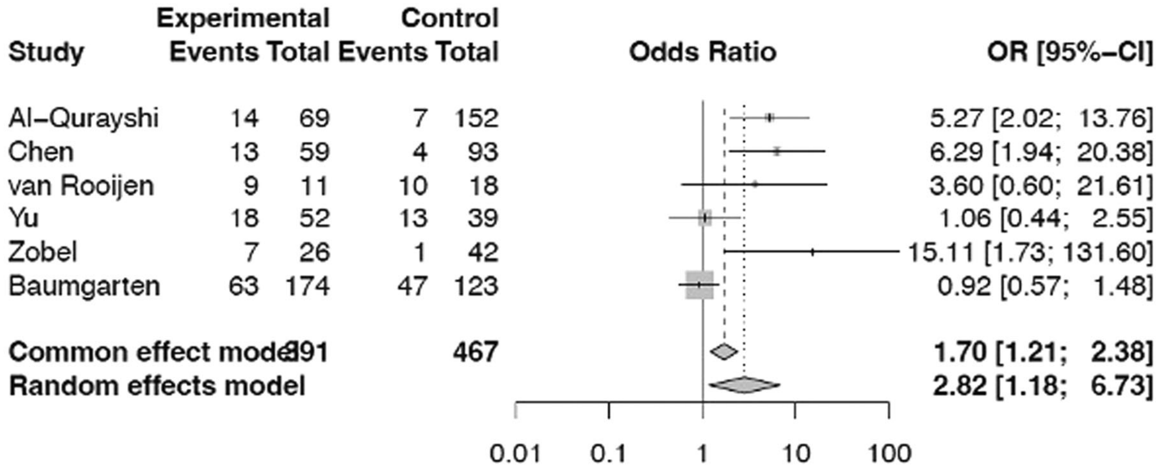

Figure 5. Meta-analysis of malignant surgical indication versus benign surgical indication. OR, odds ratio.

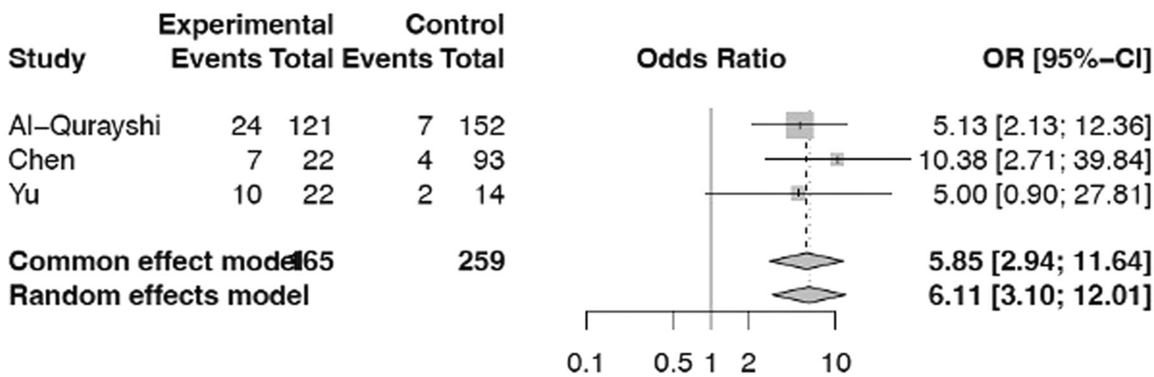

Figure 6. Meta-analysis of Graves' disease versus other benign indications. OR, odds ratio.

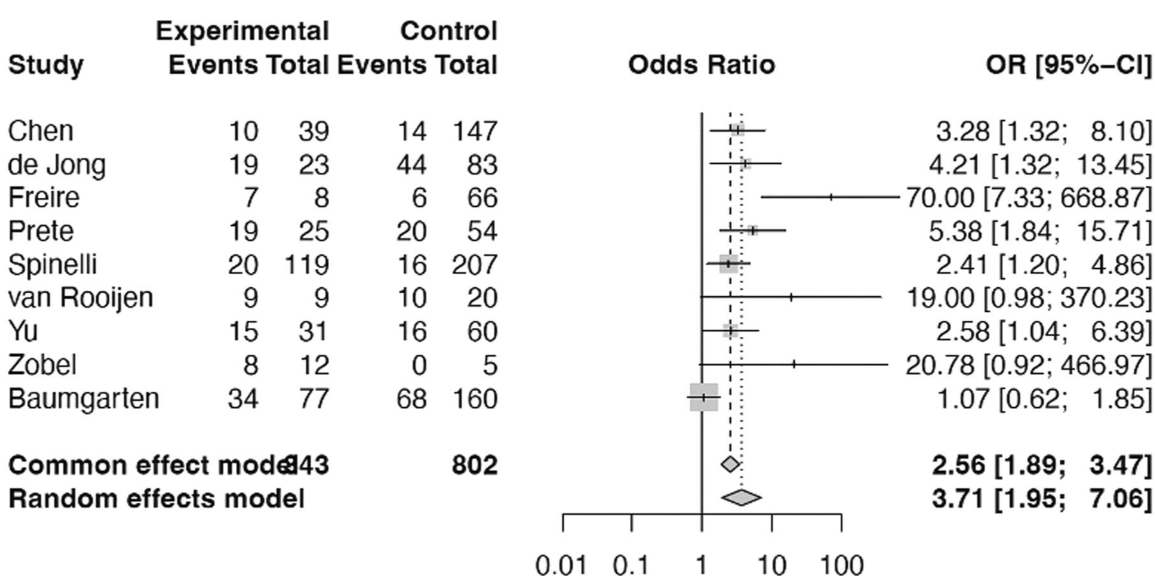

Figure 7. Meta-analysis of lymph node dissection versus no lymph node dissection. OR, odds ratio.

as significant risk factors for postoperative hypocalcemia. This is one of the largest reports to date on postoperative hypocalcemia in pediatric patients after TT. Although some findings have been previously identified, this study's strengths include a larger patient cohort and updated data, further expanding on prior research.

The rates of postoperative hypocalcemia observed in our study are consistent with previous reports in the pediatric population. A systematic review investigating the prevention and management of hypocalcemia after thyroidectomy in 1552 pediatric patients reported a pooled incidence of 35.5% and 4.2% for transient and permanent hypocalcemia, respectively.[12] There were several studies included in this review with hypocalcemia rates considerably different from the pooled incidence. One study from 1997 evaluated the efficacy of heterotopic parathyroid autotransplantation for the prevention of permanent hypocalcemia in patients receiving prophylactic TT for MEN 2A/2B syndromes. This study reported a transient hypocalcemia rate of 93.7% and a permanent hypocalcemia rate of 3.1%.[24] Notably, the high transient hypocalcemia rate is an outlier and may be attributed to the surgical indication (prophylaxis for malignancy), small sample size, study year, and the specific intervention under investigation. In contrast, another study reported an overall hypocalcemia rate of 4.5% in patients undergoing minimally invasive endoscopic TT for predominantly benign conditions.[25] The comparatively lower hypocalcemia rate in this study likely reflects differences in surgical indication and extent of intervention.

The significant variation in hypocalcemia rates across studies likely reflects differences in surgical indications, patient populations, and specific risk factors. Although the lack of a standardized definition of hypocalcemia across studies poses a challenge, this study aimed to address this by only including studies that explicitly reported hypocalcemia as an outcome, most of which defined it as biochemical hypocalcemia. Studies using parathyroid hormone (PTH) levels, presence of symptoms of hypocalcemia, or calcium/vitamin D supplementation as sole measures of hypocalcemia were excluded. Additionally, the use of a random-effects model in the meta-analyses accounted for both within- and between-study variability, enhancing the generalizability of the findings. Despite the diversity of included studies, this meta-analysis provides valuable insights by synthesizing findings and examining risk factors, particularly in the underinvestigated pediatric population.

Our meta-analysis identified malignant surgical indication, GD, and any LND as independent predictors of postoperative hypocalcemia. A limitation of these findings is the relatively small sample size, as only 15 studies explicitly investigated and reported risk factors for hypocalcemia, whereas the remaining studies solely provided rates of hypocalcemia. It is important to note that although our meta-analysis did not directly control for additional variables such as age and surgical indication, the individual studies included in this analysis accounted for these factors within their respective methodologies. Each study conducted its own risk factor analysis, adjusting for relevant covariates. To maintain comparability, we exclusively included studies that used similar comparators, such as malignant versus benign indications, and used a random-effects model. The objective of this meta-analysis was to aggregate and synthesize the findings from these studies, providing a more comprehensive summary based on a larger sample size.

The risk factor analysis findings are consistent with those reported in adult populations. In a systematic review and meta-analysis of outcomes in adults undergoing thyroidectomy, the incidences of transient and permanent hypocalcemia were 27% (range, 19-38) and 1% (range, 0-3), respectively. GD and female gender were identified as independent risk factors.[3] Similar to our study, the adult analysis included various surgical indications, allowing for a large sample size. Wang et al reported that in adults undergoing TT, age, gender, LND, and operation type were significant risk factors for postoperative hypocalcemia.[26] Roh et al found that central LND significantly increased postoperative hypocalcemia rates compared to TT alone.[27] This may be due to vascular damage or inadvertent parathyroidectomy during LND.[28] Our findings, which show slightly higher rates of hypocalcemia postoperatively compared to these adult studies, underscore the necessity of studying pediatric populations independently.

Pediatric patients are believed to be at higher risk for postoperative hypocalcemia after TT because of the smaller size of the parathyroid glands, possible decreased vascularity of the glands, and their positioning within a shorter neck.[4,29] Particularly in infants and younger children, the parathyroid glands are small, translucent, and difficult to distinguish from the surrounding soft tissue, thymus, and central neck nodes.[30,31] An additional challenge in operative exposure is the presence of the thymus, which may reach the size of the normal thyroid gland in infants and young children.[32] A study by de Jong et al reported the number of parathyroid glands preserved in situ to be the only factor associated with hypocalcemia after TT in children. The authors found that in almost half of their cohort, at least one parathyroid gland was either detached from its blood supply during surgical resection or found in the specimen by the pathologist.[13] This rate is substantially higher than the rate of inadvertent parathyroidectomy reported in the literature for adult series, which is estimated at 20%.[33] Therefore, another potential contributing factor to the higher incidence of postoperative hypocalcemia in pediatric patients is the increased incidence of inadvertent parathyroidectomy.

In the adult literature, several studies have investigated interventions to prevent postoperative hypocalcemia. Recent randomized control trials have shown that administering vitamin D and calcium preoperatively, in addition to postoperative supplementation, reduces the risk of both symptomatic and biochemical hypocalcemia compared to postoperative hypocalcemia alone.[34,35] Similarly, in the pediatric population, a retrospective cohort study found that perioperative supplementation with calcium and calcitriol was associated with a reduced risk of postoperative hypocalcemia and a shorter hospital stay in total or completion thyroidectomy patients with or without concomitant neck dissection.[36] These findings highlight the need for future prospective studies to determine whether incorporating calcium and calcitriol interventions could further reduce postoperative hypocalcemia rates in pediatric patients.

There are several limitations to this systematic review and meta-analysis. The 7331 patients in this analysis are derived from multiple studies, many with relatively small numbers of study participants. The study by Hanba et al represents the largest study cohort, with 1654 pediatric patients undergoing TT.[9] The overall quality of the studies was medium to high, with the majority being single-center studies and case series. Additionally, the 67 studies included had heterogeneous definitions of hypocalcemia, surgical indications, and outcome measures. However, we addressed this limitation by using specific inclusion criteria for definitions of hypocalcemia and outcome measures. Our review is strengthened by its inclusion of TT patients only, rather than subtotal or partial, as the rate of postoperative hypocalcemia depends on the surgical extent. Additionally, our meta-analysis of specific risk factors was limited by the number of studies available for each factor. To mitigate this, we concentrated on risk factors that were evaluated in two or more studies. Despite these limitations, our study contributes to the limited knowledge of postoperative hypocalcemia following TT in pediatric patients and identifies risk factors of interest for future research.

Conclusion

In this systematic review and meta-analysis, we identified 67 studies describing the prevalence of transient, permanent, or any hypocalcemia following TT in pediatric populations. Our review demonstrated that approximately one in three children will experience postthyroidectomy hypocalcemia, particularly in high-risk groups such as those with malignancy or GD as surgical indications. Further investigation, including high-quality, multicenter prospective studies and randomized trials, would benefit the understanding of why this patient population experiences these hypocalcemia rates more often than the adult population.

Author Contributions

Marina Aweeda, design, writing and drafting manuscript, editing, data collection, analysis; **Carly Fassler**, data analysis, data collection, editing; **Daniel R. S. Habib**, data collection, editing of manuscript; **Alexis B. Miller**, data collection, editing of manuscript; **Carlos Ortega**, design, data collection, editing of manuscript; **Kavita Prasad**, data collection, editing of manuscript; **Chiu-Lan Chen**, data analysis, editing of manuscript; **Sara H. Duffus**, design, editing of final manuscript; **Ryan H. Belcher**, design, concept development, analysis, major editing of final manuscript.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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