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Review Article

Predictors of postoperative complications following thyroidectomy: A systematic review

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ABSTRACT

Introduction: Thyroidectomy is considered a relatively safe procedure with a low risk of postoperative complications, making it challenging to identify predictors of complications to improve shared decision making. Recent advancements in clinical bioinformatics and surgical decision-making tools have the potential to improve patient outcomes. This systematic review aimed to assess the current understanding of factors predicting such complications following thyroidectomy.

Methods: We searched PubMed/MEDLINE, Web of Science, and EMBASE for studies published between 2010 and October 2023, investigating predictors of postoperative complications after thyroidectomy. Studies were included if they investigated predictors of hypocalcemia, hypoparathyroidism, vocal cord paresis (VCP), hematoma, or other postoperative complications. Studies solely reliant on univariate and ROC analyses were excluded. Independent predictors of each postoperative complication were evaluated and categorized as biochemical, surgical, and patient/disease specific.

Results: Forty-five studies were included. Biochemical hypocalcemia and transient hypoparathyroidism were the most investigated complications, with reported rates ranging from 15.7 % to 76.7 % and 12.9 % to 53.8 %, respectively. The majority of studies (n = 35, 77 %) focused on these complications. Biochemical markers (e.g., serum calcium, parathyroid hormone) were the most frequent predictors identified for these complications. Surgical factors (inadvertent parathyroidectomy) were frequently studied for all complications. Age, gender, and thyroid pathology were common patient/disease-specific predictors.

Conclusion: This review highlights the disparity in research on complication predictors. Most studies focused on hypocalcemia and hypoparathyroidism, with fewer examining VCP, hematoma, and mortality. Notably, a lack of high-quality evidence exists due to the scarcity of prospective and randomized controlled trials. Future research should explore incorporating a wider range of independent predictors, especially surgical factors, into comprehensive predictive models. This review can serve as a foundation for developing such models to improve risk prediction for a broader spectrum of thyroidectomy complications.

Introduction

Thyroid surgery is one of the most common head and neck operations with curative or therapeutic intent for benign or malignant thyroid diseases. Although thyroidectomy is considered a safe surgery with a low risk of complications, the few complications that may arise from these operations can be life limiting [1-3]. The causes of these complications are complex and span the spectrum of patients' clinical experience, ranging from patient sociodemographic factors, disease entity and stage, surgeon volume, and even hospital-specific factors [4-7].

With the emergence of predictive modeling, it is ever more important for endocrinologists, endocrine surgeons, and other providers involved in the care of patients with thyroid disease to have a thorough understanding of the predictors of thyroid surgery complications to better educate patients. The widespread use of clinical bioinformatics to create large administrative databases, such as American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), National Inpatient Sample, or Vizient Clinical Data Base®, has improved our

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ability to identify a broader range of predictors for rare post-thyroidectomy complications across a variety of hospital systems [1,8,9]. A contemporary systematic review of predictors of thyroid surgery morbidity is necessary to incorporate the advancements in clinical bioinformatic analyses and use of large administrative databases, both of which enhance the detection of predictors of complications with low incidence through the power of increased patient volume.

The last decade has seen a tremendous change in the management and evaluation of postoperative morbidity following thyroid surgery, such as improvements in patient education and recognition of high-risk populations, increased use of intraoperative techniques and technologies in hopes of decreasing postoperative morbidity, and a more representative and large-scale data with the implementation of clinical bioinformatic tools to analyze statewide and national data. The aim of this study is to examine contemporary literature regarding the predictors of postoperative complications following thyroid surgery, in hopes to provide a more modern analysis and generation of a predictive modeling to guide clinicians when educating patients regarding postoperative risk.

Methods

Protocol and search

This systematic review of the literature adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [10]. An exhaustive search was conducted on PubMed/-MEDLINE, EMBASE and Web of Science in October 2023 for articles published between 2010 and October 2023. The search strategy encompassed a combination of subject heading and keywords, including but not limited to "thyroid surgery", "postoperative complications", and "predictors", along with their synonyms and relevant terms. The defined search strategy is available in Supplemental Table 1.

Eligibility and study selection

Articles were deemed eligible using the following criteria: (1) underwent thyroid surgery (thyroid lobectomy, total thyroidectomy, or thyroidectomy with nodal dissection); (2) observational studies, cohort studies and randomized clinical trials; (3) outcomes with vocal cord paralysis (VCP), hypoparathyroidism, hypocalcemia, hematoma, morbidity, mortality, readmission, or surgical site infection (SSI); and (4) published during or after the year 2010. The potential studies were independently screened by two different individuals. Articles were considered ineligible based on the following criteria: (1) pediatric population, (< 18 years); (2) systematic reviews, meta-analysis, opinion pieces, and commentaries; (3) interventions beyond the specified thyroid surgeries, including intentional parathyroidectomy; (4) outcomes unrelated to the predetermined list; (5) studies with only univariate predictive analysis or receiver operating characteristic; (6) duplicate studies. The stringent criteria were designed to uphold the relevance of the systematic review.

Quality of evidence assessment

This systematic review was conducted without including a quality of evidence analysis given the paucity of randomized control trials that predict post-thyroidectomy complications. We recognize the limitation, high risk of bias, and heterogeneity in patient selection.

Data extraction

Covidence software (Veritas Health Innovation Melbourne, Australia) was utilized to facilitate the screening process. Two authors were independently involved in reviewing the literature. To ensure systematic and consistent data extraction, the reviewers utilized a standardized form to collect information on three key areas: study characteristics, outcomes, and predictors. This was performed for the following complications: hypocalcemia, hypoparathyroidism, vocal cord paralysis, hematoma, and "other". "Other" included readmission, surgical site infection (SSI), postoperative morbidity (i.e., wound complication, venous thromboembolism, acute kidney injury, shock, pulmonary disease, stroke, and cardiac disease) and postoperative mortality. Although hypocalcemia is often used as a proxy for hypoparathyroidism, hypocalcemia and hypoparathyroidism were considered two distinct complications in this systematic review. Studies that were exclusively included in the hypocalcemia cohort did not perform bivariate or multivariate regression on predictors of hypoparathyroidism, and vice versa. Given that the purpose of this systematic review is to identify predictors of specific post-thyroidectomy complications that can then be used for predictive modeling, the specific postoperative complication examined using multivariate regression and their associated predictors are shown in the systematic review. The following information were extracted: (1) Study Characteristics - author, year, study period, study design, sample size, and extent of thyroidectomy (type of surgery performed); (2) Outcomes – type of outcome, subtype of outcome, definition of outcome, and incidence of outcome; (3) Predictors - methods of statistical analysis and statistically significant predictors. After devising extraction tables, predictors were grouped based on whether they represented biochemical data, defined by preoperative, intraoperative, or postoperative laboratory analysis; surgical data, defined by surgical procedures and surgeon/hospital case volume; and patient and disease-specific data, such as patient sociodemographic characteristics, clinical comorbidities, and thyroid pathology.

Results

The literature search from PubMed/MEDLINE, Web of Science, and EMBASE databases yielded 392 studies. Amongst 392 studies, 99 duplicates were removed, and 293 studies were screened against the title and abstract. After the initial search, 182 studies were excluded, and 111 studies were assessed for full-text eligibility. Amongst them, 66 studies were excluded due to absence of description of postoperative complications, absence of independent predictors, a non-thyroidectomy intervention, or unavailability of the full text. Finally, 45 studies were included in the systematic review (Fig. 1). These 45 studies were then evaluated for postoperative complications after thyroidectomy.

Hypocalcemia

Twenty-one studies that described postoperative hypocalcemia were identified (Table 1). Of the identified studies, 7 studies were prospective, 14 studies were retrospective, and 0 studies were randomized controlled trials (RCT). Definitions of hypocalcemia were not consistent across studies, with the most common being biochemical, symptomatic, transient and permanent. General hypocalcemia rates were described in tree studies as 6.2 %, 8.8 % and 27.1 %, [2,4,5] biochemical hypocalcemia ranged from 15.7 % to 76.7 %, [11-22] transient hypocalcemia ranged from 7 % to 28.2 %, [18,23-27] symptomatic hypocalcemia ranged from 2.1 % to 33.8 %, [11,15-22,28] and permanent hypocalcemia ranged from 0.6 % to 15.5 % [12-14,18,20,23-27]. Definitions of general, biochemical, transient, symptomatic, and permanent hypocalcemia varied considerably between studies, ranging from the International Classification of Diseases (ICD) diagnosis to inclusion of laboratory and clinical parameters. Independent predictors of hypocalcemia were identified as being biochemical in 8 studies, surgical in 14 studies, and patient and disease-specific in 10 studies.

Biochemical analysis of parathyroid hormone (PTH), serum calcium, and 25-hydroxy vitamin D (25-OHD) were the most common predictors of hypocalcemia. Four-hour postoperative PTH level and the percent decline in PTH, when comparing preoperative to postoperative PTH, were the most common predictors of postoperative hypocalcemia. One

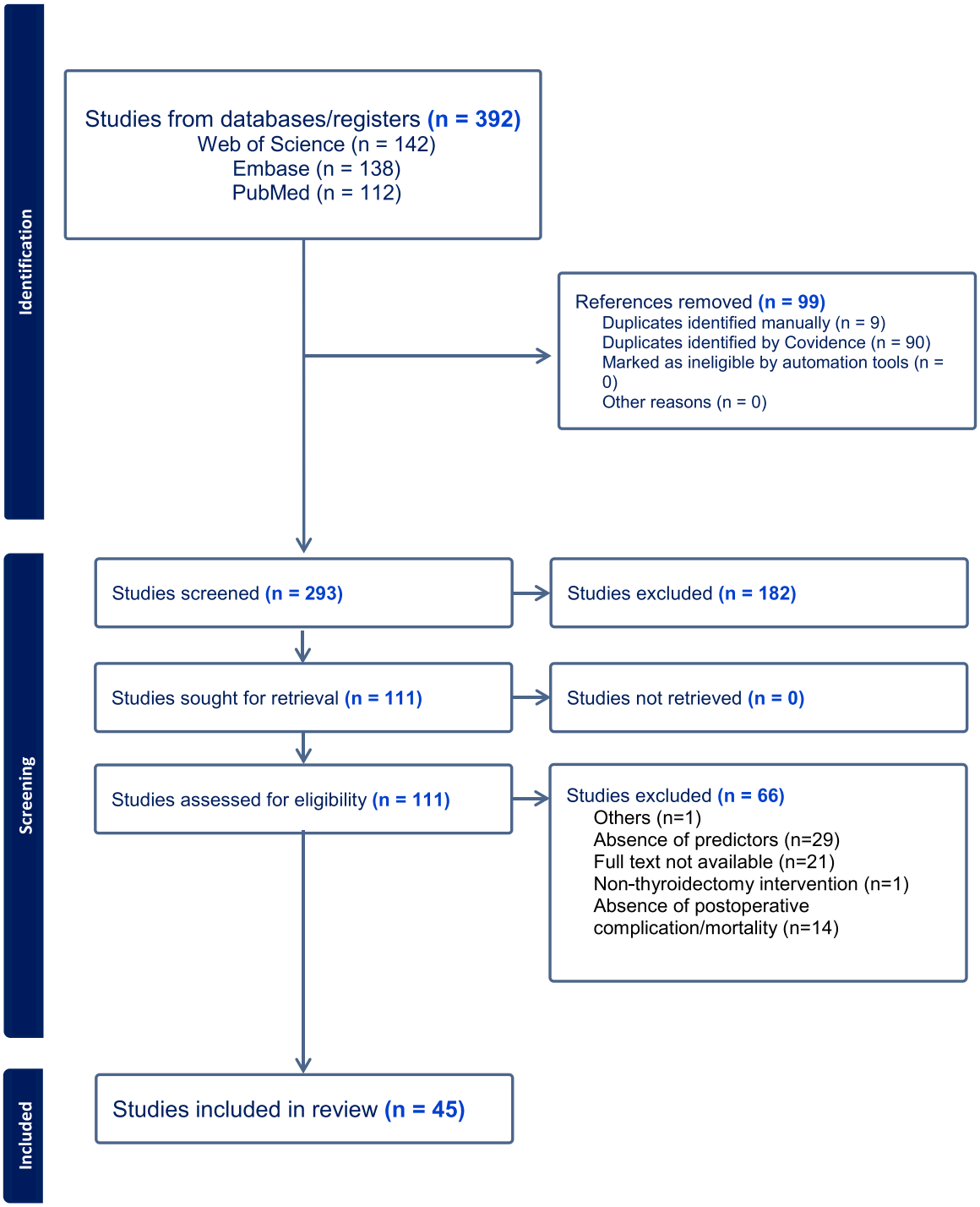

Fig. 1. PRISMA Flowchart of literature from Pubmed/MEDLINE, EMBASE and Web of Science.

study treated the PTH level 20 minutes after total thyroidectomy as a continuous variable and found that higher 20-minute postoperative PTH is associated with decreased rates of hypocalcemia [17]. The authors then perform a Youden's index to identify a 20-minute PTH cutoff of 9 pg/mL to be the most sensitive and specific value to predict post-operative hypocalcemia. Preoperative levels of calcium and 25-OHD have also been implicated in predicting hypocalcemia. Two studies examined the predictive potential of preoperative 25-OHD and found that a level <25 ng/mL increased the risk of hypocalcemia by 7.3-fold and 14-fold [19,20].

Intraoperative elements and surgeon/hospital case volume were common predictors of hypocalcemia. Seven studies found that identification of all parathyroid glands and preservation of parathyroid glands were associated with decreased risk of hypocalcemia, while inadvertent parathyroidectomy was associated with increased risk of hypocalcemia [11,14,15,21,25,26,28]. Four studies found that the presence of matted central neck lymph nodes and central neck dissection were associated with increased risk of hypocalcemia [12,18,23,24]. Three studies examined the extent of thyroidectomy on hypocalcemia and, unsurprisingly, found total thyroidectomy to be associated with increased risk of hypocalcemia due to risk of hypoparathyroidism [2,13,25]. Furthermore, two studies found that low hospital case volume (<50 cases per year) and medium hospital bed size was associated with increased rates of hypocalcemia [2,5].

Table 1
Results of the systematic review for hypocalcemia.

Authors, Year	N	Extent of Thyroidectomy (n, %)	Type of Hypocalcemia	Definition of Hypocalcemia	Rate of Hypocalcemia, n (%)	Statistically Significant Predictors
Riordan, F, et al. [14]	551	TT (551, 100 %)	Biochemical Symptomatic	Biochemical: <2.0 mmol/L on either day 1 or day 2 after surgery Symptomatic: presence of any paresthesias, numbness or muscle cramps during the hospital stay	Biochemical 169 (30.7 %) Symptomatic: 81 (14.7 %)	Biochemical: - Malignancy: OR 1.7, 95 % CI 1.1–2.8 - Graves disease: OR 1.8, 95 % CI 1.1–2.7 - Identification of 3–4 PG: OR 1.7, 95 % CI 1.0–2.9 Symptomatic: - Identification of 2–4 PG: OR 5.9, 95 % CI 1.5–23.1 - Identification of 3–4 PG: OR 3.0, 95 % CI 1.0–9.1
Priya, SR, et al. [24]	41	TT (37, 90 %), Completion Thyroidectomy (4, 10 %); Bilateral CND 24 (59 %), Ipsilateral CND 17 (42 %)	Transient Temporary Permanent	Transient: Serum total calcium < 7.5 mg/dl below 14 days and NOT dependent on calcium Temporary: Serum total calcium < 7.5 mg/dl between 14 days and 12 months Permanent: Serum total calcium < 7.5 mg/dl beyond 12 months and dependent on oral/intravenous calcium	Transient: 10 (24.4 %) Temporary: 6 (14.6 %) Permanent: 2 (4.9 %)	All Hypocalcemia: - Presence of Matted Central Nodes: $p = 0.021$
Roh, JL, et al. [26]	45	Recurrent/Persistent Disease (16, 36 %), CND (45, 100 %)	Transient Biochemical Permanent Biochemical	Transient Biochemical: Total calcium concentration <8.0 mg/dl during hospital stay or at any time after discharge < 6 months from surgery Permanent Biochemical: Total calcium concentration <8.0 mg/dl during hospital stay or at any time after discharge > 6 months from surgery	Transient Biochemical: 19 (46.3 %) Permanent Biochemical: 2 (4.9 %)	Transient and Permanent Biochemical: - Bilateral CND: OR 7.523, 95 % CI 1.72–80.0 - Low iPTH level on Day 1 (<12 pg/mL): OR 22.37, 95 % CI 5.83–253
Al-Adhami, et al. [25]	149	TT (53, 35.6 %), Subtotal Thyroidectomy (73, 49.0 %), Dunhill procedure (23, 15.4 %)	Transient Biochemical Permanent Biochemical	Transient Biochemical: serum calcium <2.2 mmol/l, no definition of temporality provided Permanent Biochemical: serum calcium <2.2 mmol/l, no definition of temporality provided	Transient Biochemical: 87 (58 %) Permanent Biochemical: 6 (4 %)	Transient Biochemical: - TT vs Subtotal Thyroidectomy or Dunhill Procedure: RR 1.94, 95 % CI 1.51–2.50
Lale, A, et al. [23]	818	TT (755, 92.5 %), Lobectomy (63, 7.7 %); CND (34, 64.2 %)	Transient Permanent	Transient: serum calcium <8 mg/dl at 24 and 72 h after thyroidectomy with hypocalcemic symptoms and/or medical therapy for <1y Permanent: Requiring exogenous calcium and vitamin D for >1y	Transient: 218 (26.7 %); Permanent: 14 (1.7 %)	Transient: - Female: OR 2.78, 95 % CI 1.47–5.27, $p = 0.002$ - Substernal Thyroid: OR 2.73, 95 % CI 1.39–5.39, $p = 0.004$ - CND: OR 8.77, 95 % CI 3.05–25.17, $p < 0.001$
Vibhatavata, P, et al. [31]	43	TT (39, 91 %), Completion Thyroidectomy (4, 9 %); CND (10, 23 %)	Biochemical Significant Biochemical Symptomatic	Biochemical: albumin-adjusted calcium level <8.6 mg/dL Significant Biochemical: albumin-adjusted calcium level <7.5 mg/dL Symptomatic: albumin-adjusted calcium level <8.6 mg/dL in addition to the presence of any symptoms or signs	Symptomatic: 11 (26 %)	Significant Biochemical Hypocalcemia: - Preservation of PG: OR 0.69, 95 % CI 0.52–0.90, $p = 0.007$ Symptomatic Hypocalcemia: - Preservation of PG: OR 0.81, 95 % CI 0.69–0.97, $p = 0.02$
Iflazoglu, N, et al. [33]	2381	TT (1721, 72 %), Subtotal Thyroidectomy (228, 10 %)	Transient Permanent	Transient: serum calcium level < 8.5 mg/dL with clinical symptoms or serum calcium level <8.0 mg/dL without clinical symptoms Permanent: serum calcium level <8.0 mg/dL, PTH < 13 pg/mL or clinical symptoms with prescribed calcium 6 months postoperatively	Transient: 316 (16.1 %) Permanent: 105 (5.1 %)	Transient: - Incidental Parathyroidectomy: OR 1.767, OR 1.23–5.54, $p = 0.002$ - TT vs SubtotalThyroidectomy: OR 3.017, 95 % CI 1.76–5.17, $p < 0.001$ Permanent: - Age: OR 0.981, 95 % CI 0.7–0.996, $p = 0.017$ - Female: OR 3.60, 95 % CI 1.47–9.27, $p = 0.005$ - Hyperthyroidism: OR 0.377, 95 % CI 0.16–0.87, $p = 0.023$ - TT vs Subtotal Thyroidectomy: OR 4.27, 95 % CI 1.33–13.67, $p = 0.014$ - Hashimoto Thyroiditis: OR 1.74, 95 % CI 1.15–2.64, $p =$

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Table 1 (*continued*)

Authors, Year	N	Extent of Thyroidectomy (n, %)	Type of Hypocalcemia	Definition of Hypocalcemia	Rate of Hypocalcemia, n (%)	Statistically Significant Predictors
						0.009 - Thyroid Volume: OR 1.002, 95 % CI 1.001–1.003, $p = 0.003$ - Incidental Parathyroidectomy: OR 2.235, 95 % CI 1.311–3.81, $p = 0.003$
Edafe, O, et al. [12]	238	TT (206, 86.6 %), Completion Thyroidectomy (27, 11.3 %), Other (5, 2.1 %); CND (51, 21.1 %)	Biochemical Permanent	Biochemical: Corrected serum calcium <2.10 mmol/l on POD1 Permanent: Need for calcium and/or vitamin D supplements to maintain normocalcemia at 6 months or more after date of surgery	Biochemical: 69 (29.0 %) Permanent 12 (5.5 %)	Biochemical: - Preoperative Corrected Calcium: Test statistic 10.7, $p = 0.001$ - PG autotransplantation: Test statistic 6.2, $p = 0.013$
Wang, X, et al. [16]	237	TT + Unilateral CND (97, 41 %), TT + Bilateral CND (140, 59 %)	Biochemical Symptomatic	Biochemical: adjusted serum calcium <2.0 mmol/L in postoperative period Symptomatic: presence of any clinical symptoms or signs of hypocalcemia concomitant with the postoperative serum calcium <2.0 mmol/L	Biochemical: 124 (52.3 %) Symptomatic: 80 (33.8 %)	Biochemical: - Postoperative PTH <1.60 pmol/L: HR 14.37, 95 % CI 6.07–34.0, $p < 0.001$ Symptomatic - PG autotransplantation: HR 2.02, 95 % CI 1.04–3.91, $p = 0.038$ - Postoperative PTH <1.60 pmol/L: HR 7.47, 95 % CI 3.84–14.5, $p < 0.001$
Rubio, GA, et al. [9]	215,068	TT (215,068, 100 %)	NA	International Classification of Diseases, 9th Revision code for hypocalcemia	Hypocalcemia: 8.8 %	Hypocalcemia: - Thyroid Cancer: aOR 1.42, 95 % CI 1.37–1.47, $p < 0.01$ - Graves' Disease: aOR 1.65, 95 % CI 1.54–1.77, $p < 0.01$
Cho, JN, et al. [22]	1030	TT + Unilateral CND (383, 53.7 %), TT + Bilateral CND (157, 22.0 %)	Transient Permanent	Transient: received calcium replacement and who had serum iPTH < 13 pg/mL Permanent: PTH level < 13 pg/mL and need for calcium or vitamin D supplements >6 months after surgery	Transient: 291 (28.2 %) Permanent: 27 (2.6 %)	Transient: - Female: OR 2.285, 95 % CI 1.391–3.751, $p = 0.001$ - Bilateral CND: OR 1.556, 95 % CI 1.094–2.212, $p = 0.014$ - Inadvertent Parathyroidectomy: OR 1.509, 95 % CI 1.030–2.212, $p = 0.035$
Eismontas, V, et al. [15]	400	TT + Unilateral CND (56, 14 %); TT + Bilateral CND (10, 2.5 %)	Biochemical Symptomatic	Biochemical: serum calcium level <2.10 mmol/L without symptoms Symptomatic: Presence of clinical symptoms in patients with serum calcium level <2.10 mmol/L	Biochemical: 197 (76.7 %) Symptomatic: 60 (15 %)	Biochemical Hypocalcemia: - Age: OR 1.05, 95 % CI 1.01–1.09, $p = 0.029$ - Female: OR 5.94, 95 % CI 1.13–31.26, $p = 0.035$
Reddy AC, et al. [17]	100	TT (91, 91 %), Completion Thyroidectomy (9, 9 %)	Biochemical Symptomatic	Biochemical: Serum calcium of <8.0 mg/dL without symptoms of hypocalcemia Symptomatic: clinical signs or symptoms of hypocalcemia with or without a serum calcium <8.0 mg/dL	Biochemical: 52 (52 %) Symptomatic: 23 (23 %)	Biochemical Hypocalcemia: - Intraoperative PTH 20 min after TT: OR 0.63, 95 % CI 0.47–0.83, $p = 0.001$
Docimo, G, et al. [20]	328	TT (328, 100 %); TT + CND (36, 10.9 %)	Biochemical Transient Symptomatic Permanent	Biochemical: Serum total calcium <8.0 mg/dL Transient: No definition Symptomatic: presence of clinical signs or symptoms of hypocalcemia Permanent: No definition	Biochemical: 92 (28 %) Transient: 48 (14.6 %) Symptomatic: 26 (7.9 %) Permanent: 2 (0.6 %)	Transient: - Malignant Pathology: OR 4.0, 95 % CI 0.192–0.564, $p < 0.001$ - CND: OR 2.484, 95 % CI 0.182–0.484, $p = 0.013$ Symptomatic: - Malignant Pathology: OR 7.18, 95 % CI 0.279–0.490, $p < 0.000$ - CND: OR 2.843, 95 % CI 0.284–0.932, $p < 0.005$
Al-Khatib T, et al. [18]	213	TT or Completion Thyroidectomy (213, 100 %)	Biochemical Symptomatic	Biochemical: Any single corrected postoperative calcium level of 2 mmol/L or less Symptomatic: Presence of clinical signs and symptoms of hypocalcemia	Biochemical: 42 (19.2 %) Symptomatic: 38 (17.8 %)	Biochemical: - POD0 PTH: OR 0.6, 95 % CI 0.5–0.8, $p = 0.002$ - Preoperative 25(OH)$D < 25$ nmol/L: OR 7.3, 95 % CI 2.3–22.9, $p = 0.001$
Vashishta, R, et al. [4]	59,478	TT (31,862, 53.6 %), Lobectomy (19,725, 33.2 %)	NA	International Classification of Diseases, 9th Revision, Volume 3 (ICD-9), Hypocalcemia (275.41)	3352 (6.18 %)	Female: OR 1.31, 95 %CI 1.02–1.68, $p = 0.0001$ Malignancy: OR 1.94, 95 % CI 1.56–2.42, $p < 0.0001$ Thyrotoxicosis: OR 2.09, 95 % CI 1.63–2.68, $p < 0.0001$ Acquired Hypothyroidism: OR 1.92, 95 % CI 1.49–2.49, $p < 0.0001$

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Table 1 (*continued*)

Authors, Year	N	Extent of Thyroidectomy (n, %)	Type of Hypocalcemia	Definition of Hypocalcemia	Rate of Hypocalcemia, n (%)	Statistically Significant Predictors
						TT: OR 2.80, 95 % CI 2.00–3.92, $p < 0.0001$, Cardiac Dysrhythmias: OR 1.73, 95 % CI 1.26–2.39, $p < 0.0001$ Hospital bed size: $p = 0.0054$ -Medium vs Large: OR 1.58, 95 % CI 1.19–2.09 -Small vs Large: OR 0.92, 95 % CI 0.62–1.35
Remer, LF, et al. [32]	1135	TT (1135, 100 %)	Transient Permanent	Transient: Serum calcium <8 mg/dL within 6-mo time period Permanent: serum calcium <8 mg/dL that did not return to normal within 6 months without calcium supplementation	Transient: 81 (7 %) on POD0, 104 (9 %) on POD1 Permanent: 1 (0.08 %)	Transient: - Overweight (POD0): OR 0.52, 95 % CI 0.29–0.92, $p = 0.03$ - Age (POD0): OR 0.98, 95 % CI 0.96–0.99, $p = 0.001$ - Overweight (POD1): OR 0.53, 95 % CI 0.32–0.89, $p = 0.02$ - Obese (POD1): OR 0.60, 95 % CI 0.37–0.97, $p = 0.04$
Bove, A, et al. [21]	117	TT (117, 100 %)	Biochemical/ Asymptomatic Symptomatic Permanent	Biochemical/Asymptomatic: Serum calcium level <8.0 mg/dL or 1.10 mmol/L Symptomatic: No definition Permanent: No definition	Biochemical/ Asymptomatic: 35 (19.8 %) Symptomatic: 28 (15.8 %) Permanent: 3 (2 %)	Biochemical: - Preoperative 25-OHD <25 ng/mL: OR 14.82, 95 % CI 1.59–59.70, $p = 0.013$ Symptomatic: - 25-OHD < 25 ng/mL: OR 18.1 %, $p = 0.045$
Lee, GH, et al. [29]	134	- TT + CND (134, 100 %)	Biochemical Symptomatic	Biochemical: Total calcium concentration <8.0 mg/dL Symptomatic: Subjective or objective symptoms of hypocalcemia with biochemical hypocalcemia	Biochemical: 57 (43 %) Symptomatic: 25 (19 %)	Symptomatic: - Incidental parathyroidectomy: OR 2.95, 95 % CI 1.08–8.03, $p < 0.05$
Rubin, SJ, et al. [30]	517	TT (517, 100 %)	Biochemical Symptomatic	Biochemical: Corrected serum calcium <8.0 mg/dL Symptomatic: No definition	Biochemical: 81 (15.7 %) Symptomatic: 11 (2.1 %)	Biochemical: - 25-OHD <30 ng/mL: OR 1.9, 95 % CI 1.0–3.3, $p = 0.04$
Mintziras, I, et al. [8]	7911	TT (7911, 100 %)	Hypocalcemia	Hypocalcemia: Requiring calcium supplementation (oral or IV) after surgery	2142 (27.1 %)	Age <57: OR 0.725, 95 % CI 0.648–0.811, $p < 0.001$ Male: OR 0.681, 95 % CI 0.597–0.77, $p < 0.001$ Reoperative Surgery: OR 1.395, 95 % CI 1.054–1.845, $p = 0.02$ Hyperthyroidism: OR 1.275, 95 % CI 1.111–1.462, $p = 0.001$ Hospital Volume (vs ≥385 cases/year) - ≤50: OR 2.074, 95 % CI 1.496–2.877, $p < 0.001$ 51–384: OR 1.725, 95 % CI 1.541–1.931, $p < 0.001$

NA - Not Available; TT - Total Thyroidectomy; Sub-TT - Subtotal Thyroidectomy; Near-TT - Near Total Thyroidectomy; CND - Central Neck Dissection; ICD-9 - International Classification of Diseases, 9th Revision code; POD - Postoperative Day; IV - Intravenous; (i)PTH - parathyroid hormone; OR - Odds Ratio; aO - adjusted Odds Ratio; CI - Confidence Interval; NPV - Negative Predictive Value; PPV - Positive Predictive Value; PG - Parathyroid Gland; HR - Hazard Ratio; 25-OHD - 25-Hydroxy Vitamin D; ROC - Receiver Operating Curve; AUC - Area Under the Curve.
*Hypocalcemic symptoms - Perioral or acral parasthesias or muscle cramps in the extremities that improved with calcium supplementation.

Patient and disease-specific factors associated with hypocalcemia include gender, age, thyroid pathology, and extent of thyroid disease. Six studies found that women are more likely to experience postoperative hypocalcemia [2,5,16,24-26]. Increased age was associated with decreased risk of hypocalcemia in two studies and increased risk of hypocalcemia in two studies [5,16]. Thyroid malignancy, Graves' disease, and Hashimoto's thyroiditis were associated with increased risk of postoperative hypocalcemia [2,4,5,11,18,25].

The majority of the studies ($n = 17$, 81 %) were single institution studies with the number of patients ranging from 41 to 2381 patients. Two studies were multi-institutional studies, one including data from the prospective thyroid surgery registry for the German Society of General and Visceral Surgery and the other from two university medical centers in Lithuania [5,16]. Rubio et al. and Vashishta et al. included data from the National Inpatient Sample with the number of patients at 215,068 and 59,478, respectively [2,4].

Hypoparathyroidism

Fourteen studies that described postoperative hypoparathyroidism were identified (Table 2). Of the identified studies, 1 study was prospective, 13 studies were retrospective, and 0 studies were RCT. Definitions of hypoparathyroidism were not consistent across studies, with the most common being transient and permanent. One study reported an overall hypoparathyroidism rate of 0.8 % based on the ICD-9 code for hypoparathyroidism [9]. Transient hypoparathyroidism rates ranged from 12.9 % to 53.8 % [29-39] while permanent rates ranged from 0.56 % to 14.5 % [29-40]. Independent predictors of hypoparathyroidism were identified as being biochemical in 9 studies, surgical in 10 studies, and patient and disease-specific in 8 studies.

Table 2
Results of the systematic review for hypoparathyroidism.

Authors, Year	N	Extent of Thyroidectomy (n,%)	Type of Hypoparathyroidism	Definition of Hypoparathyroidism	Rate of Hypoparathyroidism, n (%)	Statistically Significant Predictors
Mazotas IG, et al. [29]	591	TT (568, 96 %); Completion Thyroidectomy (23, 4 %)	Transient Permanent	Transient: recovery of PTH level (>10 pg/mL) or normal serum calcium levels in absence of hypocalcemic symptoms and no calcium supplementation by 6 months postoperatively Permanent: PTH level <10pg/mL associated with hypocalcemic symptoms and the need for ongoing calcium supplementation >1200 mg/day with or without calcitriol supplementation for > 6 months postoperatively	Transient: 76 (12.9 %) Permanent: 15 (3 %)	Transient: - Inadvertent Parathyroidectomy: OR 3.17, 95 % CI 1.21–5.11, $p < 0.001$ - Malignancy: OR 1.60, 95 % CI 1.05–2.44, $p = 0.028$ - Thyroiditis: OR 1.84, 95 % CI 1.21–2.80, $p = 0.004$ - Preoperative 25OHD >20: OR 2.02, 95 % CI 1.19–3.44, $p = 0.009$
Manzini G, et al. [30]	361	TT (214, 59.3 %), Hartley-Dunhill (71, 19.7 %), Completion Thyroidectomy (19, 5.3 %); CND (76, 21.0 %)	Transient Permanent	Transient: Total calcium level <2.1 mmol/L, a PTH level < 10 pg/mL or typical clinical symptoms despite normal PTH or calcium level Permanent: ongoing necessity of calcium or vitamin D supplementation due to decreased PTH or calcium levels at 6 months	Transient: 111 (30.7 %) Permanent: 13 (3.6 %)	Transient: - Female: $p = 0.0006$ - PG Autotransplantation: $p < 0.0001$ - POD1 PTH <10 pg/mL: $p < 0.0001$
Karamanakos SN, et al. [31]	2043	TT (1149, 47.81 %), Near-TT (777, 32.33 %), Sub-TT (117, 4.9 %)	Transient Permanent	Transient: NA Permanent: requirement of calcium supplementation and/or vitamin D to maintain eucalcemia 6 months postoperatively	Transient: 568 (27.8 %) Permanent: 98 (4.8 %)	Transient: - Extent of surgical resection: OR 2.2, $p < 0.001$ - Graves' disease: OR 2.1, $p < 0.001$ - Recurrent goiter: OR 1.7, $p = 0.006$ - Specimen weight > 45 gm: OR 1.6, $p = 0.02$ Permanent: - Extent of surgical resection: OR 2.7, $p < 0.001$ - Graves' disease: OR 1.8, $p = 0.003$ - Recurrent goiter: OR 1.5, $p = 0.01$ - Malignant disease: OR 1.5, $p = 0.008$
Moten, AS, et al. [9]	110,889	Substernal Thyroidectomy (5525, 5.0 %); Nonsubsternal Thyroidectomy (105,364, 95 %)	Hypoparathyroidism	International Classification of Diseases, 9th Revision code for hypoparathyroidism	904 (0.8 %)	Substernal Thyroidectomy: OR 1.49, 95 % CI 1.11–2.00)
Sieniawski, K, et al. [41]	142	TT (142, 100 %)	Hypoparathyroidism	NA	NA	Preoperative PTH: OR 0.39, 95 % CI 0.20–0.78, $p = 0.007$ 1 hour Percent Change in PTH: OR 1.15, 95 % CI 1.08–1.22, $p < 0.001$ Preoperative Calcium: OR 0.32, 95 % CI 0.13–0.78, $p = 0.012$
Zheng J, et al. [32]	546	TT (230, 42.1 %), TT + CND (316, 57.9 %)	Transient Biochemical Transient Clinical Permanent	Transient Biochemical: iPTH level below 15 pg/mL accompanied by biochemical hypocalcemia Transient Clinical: biochemical hypoparathyroidism accompanied by symptoms and/or signs of hypocalcemia Permanent: need for calcium and/or vitamin D supplementation at 6 months postoperatively to maintain normal blood calcium concentration and with PTH <15 pg/mL	Transient Biochemical: 90 (16.4 %) Permanent: 22 (4.0 %)	Permanent: - Low POD1 Calcium: OR 2.584, 95 % CI 1.017–6.567, $p = 0.046$ - Low POD1 PTH: OR 2.932, 95 % CI 1.129–7.616, $p = 0.027$
Loncar, I, et al. [40]	749	TT (470, 62.8 %), Completion Thyroidectomy (279, 37.2 %); CND (153, 20.4 %)	Permanent	Permanent: Use of prescribed vitamin D analogues with or without supplements 12 months after surgery and unable to wean off supplementation	53 (7.9 %)	Persistent: - Postoperative Calcium: OR 0.004, 95 % CI 0.000–0.054, $p = 0.000$ - PG Autotransplantation: OR 2.851, 95 % CI 1.057–7.687, $p = 0.038$

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Table 2 (*continued*)

Authors, Year	N	Extent of Thyroidectomy (n,%)	Type of Hypoparathyroidism	Definition of Hypoparathyroidism	Rate of Hypoparathyroidism, n (%)	Statistically Significant Predictors
						- Surgical Complication: OR 2.410, 95 % CI 1.032–5.629, $p = 0.042$
Díez, JJ, et al. [33]	1792	TT (1054, 58.8 %), TT + CND (738, 41.2 %)	Transient Permanent	Transient: Hypoparathyroidism at discharge from surgery, but absence of need for calcium and calcitriol therapy at visit 3–6 months after surgery Permanent: Need for treatment with calcium or calcitriol at the last visit of the follow-up	Transient: 455 (25.4 %) Permanent: 260 (14.5 %)	Transient: - Hospital Volume: OR 0.996, 95 % CI 0.994–0.998, $p = 0.000$ - Lymph Node Dissection: OR 2.39, 95 % CI 1.77–3.22, $p = 0.000$ - 2-stage thyroidectomy: OR 0.36, 95 % CI 0.23–0.56, $p = 0.000$ - PG Autotransplantation: OR 1.83, 95 % CI 1.04–3.22, $p = 0.035$ - Inadvertent Parathyroidectomy: OR 1.88, 95 % CI 1.38–2.55, $p = 0.000$ - Malignancy: OR 0.61, 95 % CI 0.43–0.88, $p = 0.007$ - Preoperative Ca: OR 0.63, 95 % CI 0.49–0.80, $p = 0.000$ Permanent - Specialized Surgical Team: OR 0.53, 95 % CI 0.30–0.94, $p = 0.029$ - Lymph Node Dissection: OR 2.07, 95 % CI 1.29–3.32, $p = 0.002$ - 2-Stage Thyroidectomy: OR 2.16, 95 % CI 1.20–3.88, $p = 0.01$ - Inadvertent Parathyroidectomy: OR 1.84, 95 % CI 1.24–2.74, $p = 0.003$ - Malignancy: OR 0.42, 95 % CI 0.25–0.71, $p = 0.001$ - Postoperative Calcium: OR 0.22, 95 % CI 0.17–0.28, $p = 0.000$
Sonne-Holm, E, et al. [34]	582	TT (582, 100 %); CND (214, 36.8 %)	Transient Persistent Permanent	Hypoparathyroidism: Serum level of PTH <1.6 pmol/L and/or postoperative decline in serum level of PTH of >50 % of preoperative value OR patients with mild hypocalcemic symptoms and low serum calcium but normal PTH Transient: Not defined Persistent: Hypoparathyroidism at 3 months Permanent: Hypoparathyroidism after 1 year	Transient: 275 (47.8 %) Persistent: 99 (17.0 %) Permanent: 62 (10.7 %)	Transient - Age: $p = 0.049$ - PG Autotransplantation: $p = 0.000$ - Duration of Surgery: $p = 0.033$ Persistent: - Malignancy: $p = 0.021$ - PG Autotransplantation: $p = 0.015$ - Duration of Surgery: $p = 0.019$
Privitera, F, et al. [35]	189	TT (183, 96.8 %), Lobectomy (6, 3.2 %)	Transient Permanent	Transient: PTH level < 12pg/mL Permanent: PTH < 12 pg/mL or clinical symptoms of permanent hypocalcemia at 6 months follow-up	Transient: 59 (31.1 %) Permanent: 5 (8 %)	Transient: - Lymph Node Dissection: OR 2.56, 95 % CI 1.36–4.82, $p = 0.004$ - Incidental Parathyroidectomy: OR 2.44, 95 % CI 1.22–4.88, $p = 0.017$ Permanent: - Postoperative PTH < 5 pg/mL: OR 24.5, 95 % CI 2.83–212.51, $p < 0.0001$
Yazıcıoğlu MÖ, et al. [36]	352	TT (321, 91.2 %); CND (31, 8.8 %)	Transient Permanent	Transient: Resolution of postoperative hypoparathyroidism (PTH <15 at 4–6 h postoperatively) Permanent: Not defined	Transient: 58 (16.5 %) Permanent: 14 (4.0 %)	Permanent: - 4hr Postoperative PTH <5.95 pg/mL: OR 134.842, 95 % CI 17.254–1053.820, $p = 0.000$

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Table 2 (*continued*)

Authors, Year	N	Extent of Thyroidectomy (n,%)	Type of Hypoparathyroidism	Definition of Hypoparathyroidism	Rate of Hypoparathyroidism, n (%)	Statistically Significant Predictors
Xing, ZC, et al. [37]	1424	TT + Bilateral CND (1434, 100 %)	Transient Permanent	Transient: PTH < 14 pg/mL occurring for less than 6 months after surgery Permanent: PTH < 14 pg/mL beyond 6 months after surgery	Transient: 766 (53.8 %) Permanent: 21 (1.5 %)	Transient: - PG Autotransplantation: OR 2.047, 95 % CI 1.557–2.764, $p < 0.001$ - Incidental Parathyroidectomy: OR 2.379, 95 % CI 1.480–3.824, $p < 0.001$ - Hashimoto's Thyroiditis: OR 1.436, 95 % CI 1.113–1.852, $p = 0.005$
Fields, T, et al. [38]	352	TT (352, 100 %)	Transient Permanent	Transient: PTH < 12 pg/mL with resolution by 6 months after surgery Permanent: PTH < 12 pg/mL longer than 6 months after surgery	Transient: 65 (18.4 %) Permanent: 2 (0.56 %)	Postoperative PTH: - BMI: Coefficient: 0.528, 95 % CI 0.19–0.87, $p = 0.003$ - Preoperative PTH: Coefficient 0.238, 95 % CI 0.16–0.30, $p < 0.001$ - Non-white race: Coefficient 4.942, 95 % CI 0.47 9.42, $p = 0.03$
Xue, SH, et al. [39]	93	TT + Unilateral CND (43,46.2 %), TT + Bilateral CND (50, 53.7 %)	Biochemical Permanent	Biochemical: Corrected calcium below 1.9 mmol/L or between 1.9 and 2.0 mmol/L with hypocalcemia Permanent: patients who need to take calcium and vitamin supplements 6 months from surgery	Biochemical: 49 (49.5 %) Permanent: 2 (2.2 %)	Biochemical: - Perithyroidal Extension: OR 19.30, 95 % CI 2.67–139.67, $p = 0.003$ - Bilateral Central Neck Dissection: OR 1.86, 95 % CI 1.38–9.06, $p = 0.044$

NA - Not Available; TT - Total Thyroidectomy; Sub-TT - Subtotal Thyroidectomy; Near-TT - Near Total Thyroidectomy; CND - Central Neck Dissection; ICD-9 - International Classification of Diseases, 9th Revision code; POD - Postoperative Day; IV - Intravenous; (i)PTH - parathyroid hormone; OR - Odds Ratio; aO - adjusted Odds Ratio; CI - Confidence Interval; NPV - Negative Predictive Value; PPV - Positive Predictive Value; PG - Parathyroid Gland; HR - Hazard Ratio; 25-OHD - 25-Hydroxy Vitamin D; ROC - Receiver Operating Curve.
*Hypocalcemic symptoms - Perioral or acral parasthesias or muscle cramps in the extremities that improved with calcium supplementation.

Biochemical analysis of PTH, serum calcium, and 25-OHD were the most common predictors of hypoparathyroidism. Postoperative serum calcium [32,33,40] and PTH [30,32,35,36,41] were the most common predictors of postoperative transient and permanent hypoparathyroidism. Zheng et al. reports that low postoperative day 1 calcium and PTH were associated with a higher risk of permanent hypoparathyroidism, although explicit cut-off values were not provided [32]. Higher preoperative PTH [38,41] and serum calcium [41] were associated with decreased risk of postoperative hypoparathyroidism, while preoperative 25-OHD >20 was associated with increased risk of postoperative hypoparathyroidism [29].

Devascularization of the parathyroid gland and extent of surgery were common predictors of hypoparathyroidism. Seven studies found that incidental parathyroidectomy and/or parathyroid autotransplantation were associated with an increased risk of hypoparathyroidism.[29,30,33–35,37,40] Five studies found that extent of surgery (i.e. two-stage thyroidectomy, substernal thyroidectomy, and central neck dissection) were associated with an increased risk of hypoparathyroidism [9,31,33,35,39].

Patient and disease-specific factors associated with hypocalcemia include thyroid pathology and sociodemographic patient characteristics. Four studies found that malignancy was associated with hypoparathyroidism, with three studies showing malignancy increased the risk of hypoparathyroidism [29,31,34] and one study showing malignancy decreased the risk of hypoparathyroidism [33]. Thyroiditis (in the form of hyperthyroidism, Graves' disease or Hashimoto's) was associated with an increased risk of hypoparathyroidism in three studies [29,31,37].

Of the 12 studies examining predictors of hypoparathyroidism, only 1 study used a large administrative database, the National Inpatient Sample, to identify 110,889 patients who underwent thyroidectomy and found that substernal thyroidectomy was associated with an increased risk of hypoparathyroidism [9]. Two studies were multicenter, nationwide studies, [33,40] while the remaining studies identified in this cohort of studies were single institution studies.

Vocal cord paresis and paralysis

Six studies that described VCP were identified (Table 3). All six studies were retrospective cohort analyses. Types of VCP included transient, permanent, partial, and complete. Three of the six studies neither described the type of VCP nor provided definitions for VCP. Two studies noted that VCP was assessed via postoperative laryngoscopy, [5,6] while the remaining studies did not discuss assessment. Three studies discussed the use of intraoperative nerve monitoring which were used in 61.7 % to 99.5 % of thyroidectomies [5,6,42]. Three studies described general rates of VCP ranging from 0.9 % to 5.9 % [2,4,42]. Transient VCP was reported as 1.6 % and 3 %, [5,31] while permanent VCP was reported as 0.6 %, 0.9 %, and 2.1 % [5,6,31]. Independent predictors of VCP were identified as being biochemical in 1 study, surgical in 5 studies, and patient and disease-specific in 5 studies.

Biochemical predictors of VCP were found to be albumin < 3.5 g/dL and hematocrit <30 % [42]. Surgical predictors of VCP include extent of resection, reoperation, and hospital volume. Extent of resection was included in three studies that found that more extensive surgeries (i.e. substernal involvement, lymph node dissection, and increased operative time) were associated with increased risk of VCP [6,31,42]. Three studies examined hospital or surgical case volume as predictors of VCP with two studies finding decreased hospital volume was associated with increased risk of VCP [5,6]. Another study showed that small hospital bed size was associated with reduced risk of VCP, [2] although the latter study was potentially being confounded by the use of ambulatory surgery centers by high volume surgeons. Reoperation was associated with increased risk of VCP in two studies [5,6]. One study examined the use of

Table 3
Results of the systematic review for vocal cord paralysis.

Authors, Year	N	Extent of Thyroidectomy (n,%)	Type of Vocal Cord Paralysis	Definition of Vocal Cord Paralysis	Assessment of Vocal Cord Paralysis	Use of IONM	Incidence of VCP	Statistically Significant Predictors
Karamanakos, S.N, et al., [31]	2043	TT (1149, 56.2 %), Near-TT (777, 38.0 %), Sub-TT (117, 5.7 %)	Transient Permanent	Transient: Not defined Permanent: Sustained immobility of vocal cords 6 months after surgery	NA	No	Transient: 34 (1.6 %) Permanent: 19 (0.9 %)	Transient: - Extent of Resection: OR 1.6, $p = 0.03$ - Graves' Disease: OR 2.7, $p < 0.001$ - Recurrent Goiter: OR 2.3, $p < 0.001$ - Malignancy: OR 1.7, $p = 0.01$ - Thyroiditis: OR 2.1, $p < 0.001$ Permanent: - Graves' Disease: OR 2.2, $p < 0.001$ - Recurrent Goiter: OR 1.7, $p = 0.03$
Mintziras, I, et al. [5]	7911	TT (7911, 100 %)	Transient Permanent	Transient: Vocal cord palsy persisting less than 6 months after surgery Permanent: Vocal cord palsy when persistent longer than 6 months after surgery	Postoperative laryngoscopy	7872 (99.5 %), 1855 (23.4 %) with continuous IONM	Transient: 480/15,822 nerves at risk (3.03 %) Permanent: 99/15,822 (0.63 %)	Transient: - ASA>II: OR 1.47, 95 % CI 1.14–1.89, $p = 0.003$ - Reoperative Surgery: OR 1.63, 95 % CI 1.11–2.41, $p = 0.013$ - Thyroid Tissue Weight >100 g: OR 1.46, 95 % CI 1.11–1.93, $p = 0.007$ - Hospital Volume (vs ≥350 cases/yr) –<50 cases/yr: OR 2.38, 95 % CI1.47–3.85, $p < 0.001$
Rubio, GA, et al. [4]	215,068	TT (215,068, 100 %)	NA	International Classification of Diseases, 9th Revision code for vocal cord paralysis	NA	NA	3441 (1.6 %)	- Malignancy: aOR 2.85, 95 % CI 2.63–3.10, $p < 0.01$ - Graves' Disease: aOR 1.36, 95 % CI 1.08–1.69, $p = 0.01$
Mahoney, RC, et al. [42]	11,522	TT or Sub-TT (7290, 63.1 %), Neck Dissection (3267, 28.3 %)	NA	NA	NA	7130 (61.7 %)	682 (5.9 %)	- Age > 65: aOR 1.57, 95 % CI 1.32–1.87, $p < 0.0001$ - Black Race: aOR 1.83, 95 % CI 1.48–2.26, $p < 0.0001$ - Malignancy: aOR 1.19, 95 % CI 1.00–1.41, $p = 0.0484$ - Extent of Surgery - TT or SubTT: aOR 1.32, 95 % CI 1.10–1.59, $p = 0.0038$ - Concurrent Neck Surgery: aOR 1.57, 95 % CI 1.28–1.92, $p < 0.0001$ - Use of IONM: aOR 0.76, 95 % CI 0.65–0.90, $p = 0.0018$ - Operative Time > 104min: aOR 1.61, 95 % CI 1.25–1.93, $p < 0.0001$ - Albumin <3.5 g/dL: aOR 1.58, 95 % CI 1.03–2.34, $p = 0.0288$ - Hematocrit <30 %: aOR 1.81, 95 % CI 1.04–2.03, $p = 0.0286$
Godballe C, et al. [6]	6859	TT (1501, 22 %), Sub-TT (164, 2 %), Lobectomy (4365, 63	Transient Permanent	Unilateral Permanent: unilateral vocal cord palsy (partial or	Postoperative Laryngoscopy	5487 (80 %)	Unilateral Permanent: 142 (2.1 %)	Permanent Palsy (Unilateral or Bilateral):

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Table 3 (*continued*)

Authors, Year	N	Extent of Thyroidectomy (n,%)	Type of Vocal Cord Paralysis	Definition of Vocal Cord Paralysis	Assessment of Vocal Cord Paralysis	Use of IONM	Incidence of VCP	Statistically Significant Predictors
		%), Resection of Isthmus (228, 5 %)		complete) present at last follow-up Bilateral Permanent: bilateral vocal cord palsy (partial or complete) present at last follow-up			Bilateral Permanent: 5 (0.1 %)	- Neck Dissection: RR 5.8, 95 % CI 4.0–8.3, $p < 0.001$ - Malignancy: RR 5.4, 95 % CI 3.8–7.6, $p < 0.0001$ - Extent of Surgery - TT: RR 2.4, 95 % CI 1.3–2.7, $p < 0.0001$ - Substernal Involvement: RR 1.8, 95 % CI 1.5–3.2, $p = 0.0016$ - Age > 50: RR 1.7, 95 % CI 1.3–2.3, $p = 0.0003$ - Low Case Volume (<150/yr): RR 1.6, 95 % CI 1.2–2.1, $p = 0.002$ - Previous Thyroid Surgery: RR 1.6, 95 % CI 1.1–2.3, $p = 0.0228$
Vashishta, R, et al. [2]	59,478	TT (31,862, 53.6 %), Lobectomy (19,725, 33.2 %)	NA	International Classification of Diseases, 9th Revision, Volume 3 (ICD-9), VCP (478.30, 478.31, 478.32, 478.33 and 478.34)	NA	NA	535 (0.9 %)	Female: OR 0.52, 95 % CI 0.33–82, $p = 0.0001$ Nontoxic Nodular Goiter: OR 0.52, 95 % CI 0.27–0.99, $p < 0.0001$ Malignancy: OR 2.69, 95 % CI 1.66–4.35, $p < 0.0001$ Acquired Hypothyroidism: OR 1.94, 95 % CI 1.04–3.63, $p < 0.0001$ Cardiac Arrhythmias: OR 3.53, 95 % CI 2.11–5.91, $p < 0.0001$ Small vs. Large Hospital Bed Size: OR 0.34, 95 % CI 0.13–0.88, $p = 0.0054$

VCP - Vocal Cord Paresis/Paralysis; TT - Total Thyroidectomy; Sub-TT - Subtotal Thyroidectomy; NA - Not Applicable; ICD-9 - International Classification of Diseases, 9th Revision code; IONM - Intraoperative Nerve Monitoring; OR - Odds Ratio; RR - Relative Risk; CI - Confidence Interval; NPV - Negative Predictive Value; PPV - Positive Predictive Value.

intraoperative nerve monitoring and found it to be associated with a decreased risk of VCP [42]. Patient and disease-specific factors associated with VCP most commonly included malignancy and age. Four studies found that thyroidectomy for malignant neoplasms was associated with increased risk of VCP [2,6,31,42]. Two studies found that increased age (specifically age >50 and >65) were associated with increased risk of VCP [6,42].

Of the 6 studies in the VCP cohort, only 1 study was a single institution study. Three studies were from large national databases, such as the National Inpatient Sample [2,4] and ACS-NSQIP, [42] with patient numbers ranging from 59,478 to 215,068. The remaining two studies were from multi-institutional national databases with patient numbers of 6859 and 7911 [5,6]. This is not surprising given the low rate of VCP and the large number of patients needed to be studied in order to identify predictors of a complication with such low incidence.

Hematoma

Six studies that described hematoma were identified (Table 4). All six studies were retrospective cohort analyses. No study provided a clear definition of hematoma, yet described rates of hematoma ranging from 1.2 % to 1.9 % [4,5,43,44]. One study that reported a hematoma rate of 1.9 % noted that only 0.4 % of all patients (21 % of patients who developed hematoma) required reoperation for hematoma evacuation [4]. Independent predictors of hematoma were identified as being biochemical in 1 study, surgical in 6 studies, and patient and disease-specific in 5 studies.

The surgical predictors of hematoma most examined included hospital/surgeon case volume and extent of resection. Decreased hospital/surgeon case volume was found to be associated with increased risk of hematoma in three studies [5,7,43]. Extent of resection was included in three studies that found that substernal resection, partial thyroidectomy, and total thyroidectomy were associated with increased risk of hematoma [7,9,43]. Interestingly, only one study reported on the use of hemostatic energy devices and found that they decreased the risk of hematoma [44]. Patient and disease-specific factors associated with hematoma most commonly included age and gender. Two studies showed that older patients had an increased risk of developing hematoma, [5,43] while three studies also showed that male gender was associated with increased risk of hematoma [7,43,44]. Hyperthyroidism (i.e. Graves' disease, inflammatory thyroid conditions) was associated with increased risk of hematoma in two studies [4,7] and bleeding

Table 4
Results of the systematic review for hematoma.

Authors, Years	N	Extent of Thyroidectomy (n,%)	Incidence of Hematoma	Statistically Significant Predictors
Moten, AS, et al. [9]	110,889	Substernal thyroidectomy (5525, 4.98 %), Nonsubsternal thyroidectomy (105,364, 95.02 %)	NA	Substernal thyroidectomy: OR 1.34; 95 % CI 1.09 - 2.65
Mintziras, I, et al. [5]	7911	TT (7911, 100 %)	74 (0.9 %)	Age >57 years: OR 1.963, 95 % CI 1.079–3.569, p=0.027 Hospital volume (vs ≥350 cases/yr) - < 50: OR 3.924, 95 % CI 1.330–11.580, p=0.013
Doran, H. E, et al. [43]	52,838	TT (19,548, 37 %), Lobectomy (33,290, 63 %)	666 (1.2 %)	Male: OR 1.76, 95 % CI 1.44 - 2.16, $p < 0.001$ Age: OR 1.01, 95 % CI 1.00–1.02, $p = 0.001$ Retrosternal goiter: OR 1.41, 95 % CI 1.13 - 1.77 $p = 0.003$ Redo surgery: OR 1.59 95 % CI 1.17 - 2.17 $p = 0.003$ Total thyroidectomy: OR 1.88, 95 % CI 1.52 - 2.33 $p < 0.001$ Surgeon monthly rate: OR 0.96, 95 % CI 0.93 - 0.99, $p = 0.015$ Primary surgeon being a consultant: OR 0.77, 95 % CI 0.60 - 0.99, $p = 0.042$
Rubio, GA, et al. [4]	215,068	TT (215,068, 100 %)	Hematoma: 4086 (1.9 %) Reoperation for Hematoma: 860 (0.4 %)	Malignancy: aOR 0.84, 95 % CI 0.78–0.91, $p < 0.01$ Graves' disease: aOR 1.89, 95 % CI 1.65–2.17, $p < 0.01$
Mahoney, RC, et al. [44]	11,552	TT (11,552, 100 %)	195 (1.69 %)	Male: OR 1.71, 95 % CI 1.25–2.32, $p = 0.0007$. Black Race: OR 1.89, 95 % CI 1.27–2.77, $p = 0.0014$, Other Race: OR 1.76, 95 % CI 1.23–2.50, $p = 0.001$ Hypertension: OR 1.68, 95 % CI 1.20–2.35, $p = 0.0026$, Diabetes: OR 1.45, 95 % CI 1.00–2.06, $p = 0.0460$, Bleeding disorders: OR 3.63, 95 % CI 1.61–7.28, $p = 0.0007$, Energy Device Use: OR 0.63, 95 % CI 0.46–0.87, $p = 0.0041$ Dyspnea: OR 1.57, 95 % CI 0.99–2.39, $p = 0.0435$, Hematocrit < 30 %: OR 2.41, 95 % CI 0.98–5.08, $p = 0.0338$,
Weiss, A, et al. [7]	150,012	TT (64,996, 43.3 %) Lobectomy (57,695, 38.5 %), Partial thyroidectomy (29,484,19.7 %)	1870 (1.25 %)	Black race: OR 1.37, 95 % CI 1.17–1.16 Native American race: OR 1.84, 95 % CI 1.04–3.26 Partial thyroidectomy: OR 1.69, 95 % CI 1.2–2.37 Inflammatory thyroid conditions, OR 1.59 95 % CI, 1.23–2.06 Chronic Kidney Disease: OR 1.8 95 % CI 1.08–3.03 Bleeding Disorder; OR 3.38 95 % CI 1.76–6.5 Female: OR 0.61, 95 % CI 0.54–0.69 High volume institution: OR 0.71, 95 % CI 0.6–0.83

NA – Not applicable; TT - Total Thyroidectomy; OR - Odds Ratio; aOR - adjusted Odds Ratio; CI - Confidence Interval.

disorders was associated with increased risk of hematoma in two studies [7,44].

All studies in the hematoma cohort included either national registries or large administrative databases. Three studies were from the National Inpatient Sample, [4,7,9] while one study analyzed patients from ACS-NSQIP [44]. Two studies used national registries, one from the United Kingdom [43] and another from Germany [5]. The number of patients analyzed ranged from 7911 to 215,068.

Other

Four studies that described general postoperative morbidity (i.e., wound complication, venous thromboembolism, acute kidney injury, shock, pulmonary disease, stroke, cardiac disease), 3 studies that described postoperative mortality, 3 studies that described surgical site infections (SSI) and 2 studies that described readmission were identified (Table 5). All 13 studies were retrospective cohort analyses. Readmission rates ranged from 1.7 % for total thyroidectomy and 1.2 % for lobectomy to 4.7 % (for all thyroidectomies) [43,45]. General

Table 5
Results of the systematic review for other complications.

Authors, Year	N	Extent of Thyroidectomy (n, %)	Outcome Measure	Definition of Outcome Measure	Incidence of Outcome Measure, n(%)	Statistically Significant Predictors
Doran, HE, et al. [43]	52,838	TT (19,548, 37 %), Lobectomy (33,290, 63 %)	Readmission	Return to hospital for inpatient care related to thyroidectomy after discharge	TT: 599 (1.7 %) Lobectomy: 261 (1.2 %)	Male sex: OR 1.24, 95 % CI 1.01–1.51, $p = 0.036$ TT: OR 1.30, 95 % CI 1.05–1.61, $p = 0.017$ Retrosternal Goiter: OR 1.30, 95 % CI 1.06–1.50, $p = 0.012$ Reoperation for Bleeding: OR 4.13, 95 % CI 2.85–5.98, $p < 0.001$ Hypocalcemia on POD1: OR 4.64, 95 % CI 3.80–5.67, $p < 0.001$
Attia, AS, et al. [45]	181,007	Thyroidectomy: 181,007 (100 %)	Readmission	30-day	8468 (4.7 %)	Age: HR 1.14, 95 % CI 1.05–1.24, $P = 0.002$ Presence of psychiatric comorbidities: HR 1.18, 95 % CI 1.03–1.18, $P = 0.047$ High CCI: HR 1.48, 95 % CI 1.36–1.62, $P < 0.001$ Postoperative complications: HR 9.28, 95 % CI 8.69–9.91, $P < 0.001$ Female: HR 0.85, 95 % CI 0.7–0.92, $P < 0.001$ High-income patients: HR 0.89, 95 % CI 0.82–0.97, $P < 0.001$ Anxiety disorder: HR 1.08, 95 % CI 1.02–1.20, $P = 0.042$ Mood disorder: HR 1.39, 95 % CI 1.11–1.72, $P = 0.003$ Manic depression disorder: HR 1.37, 95 % CI 1.07–1.74, $P = 0.011$ Psychosis: HR 1.51, 95 % CI 1.07–2.13, $P = 0.019$ Drug abuse: HR 1.31, 95 % CI 1.03–1.73, $P = 0.046$
Abraham, CR, et al. [1]	38,577	TT (22,482, 58.3 %) Partial thyroidectomy (14,826, 38.4 %) Substernal thyroidectomy (1269, 3.3 %)	Morbidity	Complications in 6 categories: Pulmonary, Infectious, Neurologic, Renal, Cardiovascular and Other (bleeding, deep venous thrombosis)	575 (1.49 %)	Hypertension: OR 1.35, 95 % CI 1.1–1.6, $p = 0.002$ Diabetes: OR 1.36, 95 % CI 1.1–1.7, $p = 0.008$ Age > 70: OR 2.08, 95 % CI 1.7–2.6, $p < 0.001$ COPD: OR 3.52, 95 % CI 2.6–4.8, $p < 0.002$ Use of Steroids: OR 2.84, 95 % CI 2.0–4.1, $p < 0.001$ Dialysis Use: OR 4.6, 95 % CI 2.5–8.6, $p < 0.001$ Malignancy: OR 1.31, 95 % CI 1.1–1.6, $p = 0.003$ TT: OR 1.33, 95 % CI 1.12–1.60, $p = 0.002$
Vashishta, R, et al. [2]	59,478	TT (31,862, 53.6 %) Lobectomy (19,725, 33.2 %)	Morbidity	Based on ICD-9 code for complications of surgical procedures or medical care (Clinical Classification Software code 238)	3432 (5.8 %)	Female: OR 0.74, 95 % CI 0.61–0.90, $p < 0.0001$ Nontoxic nodular goiter: OR 0.65, 95 % CI 0.51–0.82, $p < 0.0001$ Malignancy: OR 0.65, 95 % CI 0.51–0.82, $p < 0.0001$ Benign neoplasm: OR 0.32, 95 % CI 0.22–0.47, $p < 0.0001$ Thyrotoxicosis: OR 0.70, 95 % CI 0.49–0.99, $p < 0.0001$ Acquired Hypothyroidism: OR 1.75, 95 % CI 1.33–2.30, $p < 0.0001$ TT: OR 0.85, 95 % CI 0.66–1.11 Coronary atherosclerosis: OR 1.84, 95 % CI 1.41–2.39, $p < 0.0001$ Cardiac dysrhythmias: OR 3.17,

(*continued on next page*)

Table 5 (*continued*)

Authors, Year	N	Extent of Thyroidectomy (n, %)	Outcome Measure	Definition of Outcome Measure	Incidence of Outcome Measure, n(%)	Statistically Significant Predictors
						95 % CI 2.44–4.13, $p <$ 0.0001Diabetes Mellitus: OR 1.29, 95 % CI 1.05–1.58 Urban Teaching Nonteaching vs Urban Teaching: OR 0.73, 95 % CI 0.59–0.90, $p = 0.006$
Kandil, E, et al. [46]	46,261	TT (46,261, 100 %)	Morbidity	Inpatient vocal cord paralysis or hoarseness, hypoparathyroidism, hypocalcemia, or tetany, tracheomalacia, neck seroma or hematoma, or wound complications	3127 (14.5 %)	Low Surgeon Volume - Graves Disease vs Benign Disease: OR 1.39, 95 % CI 1.08–1.79; $p = 0.01$ - Malignancy vs Benign Disease: OR 0.74, 95 % CI 0.57–0.97, $p = 0.03$ Intermediate Surgeon Volume: - Graves Disease vs Benign Disease: OR 1.34, 95 % CI 1.06–1.69, $p = 0.02$
Sahli ZT, et al. [47]	75,141	TT (29,946, 39.1 %) Lobectomy (2821, 37.4 %)	Morbidity	International Classification of Diseases, 9th Revision	2750 (3.7 %)	Age > 80: OR 1.610, 95 % CI 1.296–2.0, $p < 0.001$
Moten, AS, et al. [9]	110,889	Substernal Thyroidectomy (5525, 5.0 %); Nonsubsternal Thyroidectomy (105,364, 95 %)	Mortality	Overall	NA	Substernal Thyroidectomy: OR 1.73, 95 % CI 1.03–2.92
Doran, HE, et al. [43]	52,838	TT (19,548, 36.99 %), Lobectomy (33,290, 63 %)	Mortality	Overall	23 (0.04 %)	Age: OR 1.08, 95 % CI 1.05 - 1.12, $p < 0.001$ Lymph Node Dissection: OR 6.26, 95 % CI 2.44 - 16.05, $p <$ 0.001
Weiss, A, et al. [7]	150,012	TT (64,996, 43.3 %) Lobectomy (57,695, 38.5 %), Partial thyroidectomy (29,484,19.7 %)	Mortality	Overall	484 (0.3 %)	Hematoma: OR 2.94, 95 % CI 1.76–4.9
Rubio, GA, et al. [4]	215,068	TT (215,068, 100 %)	SSI	NA	645 (0.3 %)	Malignancy: aOR 1.47, 95 % CI 1.20–1.81, $p < 0.01$ Graves' Disease: aOR 0.28, 95 % CI 0.12–0.65, $p < 0.01$
De Palma M, et al. [48]	2926	TT or Near-TT (2630, 89.9 %) Lobectomy: (296, 10.1 %)	SSI	NA	28 (1 %)	Belonging to Center A: OR 7.611, 95 % CI 3.04–19.06, $p < 0.001$
Mintziras, I, et al. [5]	7911	TT (7911, 100 %)	SSI	Superficial Deep	Superficial SSI: 111 (1.4 %) Deep SSI: 35 (0.4 %)	SSI (Superficial + Deep): Male: OR 1.96, 95 % CI 1.384–2.776, $p < 0.001$ Age >57: OR 1.477, 95 % CI 1.037–2.102, $p = 0.031$ Thyroid Tissue Weight >100 g: OR 1.861, 95 % CI 1.203–2.880, $p = 0.005$

TT - Total Thyroidectomy; POD1 – Postoperative Day 1; CCI – Charlson Comorbidity Index; COPD – Chronic Obstructive Pulmonary Disease SSI - Surgical Site Infection; OR - Odds Ratio; CI - Confidence Interval; HR - Hazard Ratio; aOR - adjusted Odds Ratio.

postoperative morbidity ranged from 3.7 % to 14.5 % [1,2,46,47]. Importantly, the definition for general postoperative morbidity varied greatly. Vashishta et al. and Sahli et al. used the ICD-9 codes for complications of surgical procedures or medical care (CCSC 238) [2,47]. Abraham et al. looked specifically at pulmonary, infectious, neurologic, renal, cardiovascular and other complications, which included SSI [1]. Furthermore, Kandel et al. included all thyroid-specific complications and SSI in the definition of morbidity. Mortality rates were exceedingly low, ranging from 0.04 to 0.06 % [7,43]. SSI rates ranged from 0.3 % to 1.4 % [4,5,48]. Independent predictors of other complications were identified as being biochemical in 1 study, surgical in 8 studies, and patient and disease-specific in 8 studies.

The surgical predictors of other complications most commonly involved extent of resection and reoperation for bleeding. General morbidity and mortality were more common in patients who underwent substernal thyroidectomy and lymph node dissection, as reported in two studies [9,43]. Studies were conflicting regarding total thyroidectomy compared to partial thyroidectomy, with one study showing an increased risk of morbidity and another showing decreased risk of morbidity [1,2]. Reoperation for bleeding or development of a hematoma were associated with an increased risk of readmission and overall mortality [7,43]. Patient and disease-specific factors associated with other complications were most commonly age and gender. Two studies showed that SSI was more common with increasing age [8,53]. Readmission, general morbidity, and mortality were more common with increasing age as well as in men as show in five studies [1,2,43,45,47].

Given the low incidence of readmission, morbidity, mortality and SSI, the studies included in this cohort of complications obtained their data from either large administrative databases or multi-institutional registries. Three studies obtained data from multi-institutional registries in the United Kingdom, Italy and Germany [5,43,48]. The remaining studies obtained data from the National Inpatient Sample, National Readmissions Database, ACS-NSQIP or other large administrative databases [1,2,4,9,45-47].

Discussion

This review has systematically appraised and summarized the literature over the past 13 years on predictors of postoperative complications following thyroidectomy. Of all the complications discussed in this review, biochemical hypocalcemia and transient hypoparathyroidism are the most common complications, ranging from 15.7 % to 76.7 %, [11-22] and 12.9 % to 53.8 %, [29-39] respectively. As such, it is no surprise that the majority (77 %) of publications identified in this systematic review addressed hypocalcemia and hypoparathyroidism. In each study, we assessed independent predictors of postoperative complications to identify targetable elements of patient care that can be used to improve outcomes. We divided the predictors into biochemical, surgical, and patient and disease-specific predictors. Unsurprisingly, nearly 50 % of predictors for hypocalcemia and hypoparathyroidism were biochemical, while the majority of predictors for VCP, hematoma and other complications were surgical and patient and disease specific.

Predictors are similar for hypocalcemia and hypoparathyroidism as they are often a proxy for each other. Nevertheless, we divided the two complications to be as granular as possible and provide the specific predictors for each complication identified by the specific studies. Biochemical predictors of hypocalcemia and hypoparathyroidism remain the most common predictors due to the ease with which they can be obtained preoperatively, intraoperatively, and postoperatively. In addition, the most common surgical predictor of hypocalcemia and hypoparathyroidism was inadvertent parathyroidectomy and/or parathyroid autotransplantation which was found in 52 % of studies assessing surgical predictors. Within the last 5 years, the use of near infrared-induced autofluorescence (NIRAF) was found to provide real-time objective images of normal and pathologic parathyroid glands and has been found to help improve early postoperative hypocalcemia rates by decreasing inadvertent parathyroidectomy [49-51]. Unfortunately, the search terms utilized in this systematic review did not identify studies which examined the role of NIRAF as a potential predictor of decreased hypocalcemia or hypoparathyroidism. The robust amount of literature examining predictors of hypocalcemia and hypoparathyroidism lends itself to devising predictive models to aid clinicians in identifying patients most at risk for these postoperative complications. Several groups have devised predictive models for hypocalcemia and hypoparathyroidism, [52-54] including a combination of biochemical, surgical, and patient and disease-specific predictors, but none of these have incorporated inadvertent parathyroidectomy. Furthermore, no studies have shown that use of these predictive models have led to improved outcomes.

Permanent vocal cord paresis and paralysis and hematoma, which we find are exceedingly low after thyroidectomy at approximately 3 %, [4-7,31,43,44] are the least likely complications following thyroidectomy yet are perhaps the most life-altering. These complications, however, appear to be highly understudied. Each complication was discussed in only 10 % of the studies included in this systematic review. This may be because one of the exclusion criteria was performance of only univariate analysis, which many smaller studies are limited by for VCP and hematoma assessment due to the low number of events. The few studies that were included show a lack of consensus on the definition and assessment of VCP and no definition of hematoma. The few studies that were large enough to perform multivariate analyses found that decreased hospital/surgeon case volume and more extensive resections (i.e. substernal thyroidectomy, total thyroidectomy, lymph node dissection) were associated with increased risk of hematoma and VCP [2,5-7,42,43]. Although use of intraoperative nerve monitoring and energy devices are commonly used elements by high volume thyroid surgeons, only one study examined intraoperative nerve monitoring use in predicting VCP and one study examined energy device use in predicting hematoma. The former showed contradictory results, [42,44] suggesting that more large-scale studies are needed to examine these as predictors.

Due to the low incidence of VCP and hematoma, many investigators have utilized large administrative databases, such as the National Inpatient Sample or the ACS-NSQIP databases, to capitalize on the large number of patients from thousands of institutions across the United States. Five studies in this systematic review accessed the National Inpatient Sample, identifying between 59,000 and 220,000 patients to study, while two studies used the ACS-NSQIP database with access to over 100,000 patients. Not surprisingly, the majority of studies that identified predictors of VCP and hematoma included data from large administrative databases or multi-institutional national registries in order to provide enough patient data to overcome the low incidence of VCP and hematoma. This is in contrast to the studies identifying predictors of hypocalcemia and hypoparathyroidism, which have incidence rates largely above 10 %. Both hypocalcemia and hypoparathyroidism only included 2 and 1 study, respectively from large administrative databases. This could be due to lack of granularity in the definition of hypocalcemia and hypoparathyroidism from these databases, which largely obtained each diagnosis based on ICD code, rather than discrete biochemical or clinical criteria.

Numerous factors, as seen above, are associated with post-thyroidectomy complications with varying ways to assess these risk factors. To overcome these variables, predictive modeling using machine learning techniques has aided in other fields to predict post-operative complications, sometimes outperforming clinician based predictive models [55-57]. To better inform patients about their risk-factors and improve shared decision-making, development of predictive models may become paramount in driving these discussions and informed consent [58,59].

This systematic review has limitations. While broad search terms like 'thyroid surgery,' 'postoperative complications,' and 'predictors' were used to identify studies on predictors of postoperative complications after thyroidectomy, the search strategy may have missed relevant studies, such as those examining NIRAF for predicting hypocalcemia. Thus, studies utilizing innovative and advanced approaches might not be a part of our search. nother major limitation of this review includes heterogeneity of the data presented with variability in definitions and assessment of predictors and outcomes. This is most notable in the types of hypocalcemia and their associated definitions, which can be seen in Table 1. Quality of evidence analysis was not able to be done due to the lack of randomized controlled trials in post-thyroidectomy complications also provide limitations in reducing bias and accurate assessment. However, our analysis excluded all studies with analysis only including univariate and ROC to only assess independent variables within our study.

Conclusion

This review has revealed a research gap in predicting postoperative complications after thyroidectomy, with most studies concentrating on relatively common hypocalcemia and hypoparathyroidism, while fewer address the more severe issues such as VCP and hematoma. There is a sheer lack of prospective or randomized controlled trials examining postoperative complications of thyroidectomy, highlighting the current limitation of high-quality evidence in this surgical population. Although some centers are delving into predictive modeling of thyroidectomy postoperative complications, it is the hope that this systematic review serves as a primer for more comprehensive predictive modeling efforts. Future models should incorporate a wider range of factors, including biochemical, surgical, and patient and disease-specific predictors, to improve risk prediction for all thyroidectomy complications.

CRediT authorship contribution statement

Philip KW Hong: Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Aman Pathak:** Conceptualization, Data curation, Formal analysis,

Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **Aditya S Shirali:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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Supplementary materials

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