

Thyroid and parathyroid surgery: new and emerging concepts

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Thyroid and parathyroid surgery: new and emerging concepts

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Editorial: Thyroid and parathyroid surgery: new and emerging concepts

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KEYWORDS

thyroid cancer, parathyroid carcinoma, hyperparathyroidism, minimally invasive thyroid surgery, minimally invasive parathyroid surgery

Editorial on the Research Topic

Thyroid and parathyroid surgery: new and emerging concepts

The diagnosis of and surgical approach to thyroid and parathyroid diseases have completely changed in recent decades due to the development of new technologies and increase in knowledge.

The number of detected thyroid nodules has increased significantly thanks to the ultrasound accuracy. In addition, the management of hyperparathyroidism has similarly evolved with an increase in endocrine diseases. Prompt recognition and treatment of thyroid and parathyroid disorders could have a beneficial impact on health outcomes and could reduce the economic and social burden associated with the treatment of advanced disease.

Treatment and management of thyroid disease has seen many advances over the past decade, with most developments related to technologies focusing on the reduction of complications. Devices developed for surgical dissection with improved hemostasis and reduced heat transfer (and hence collateral tissue damage) is of particular interest in thyroid surgery. Laryngeal nerve injury and parathyroid gland dysfunction are complications of surgery with potentially devastating consequences and hence have been an area of focus for recent technological developments.

Conventional thyroidectomy and parathyroidectomy are still considered the standard of care, but other innovative and minimally invasive techniques have been pioneered such as the gasless endoscopic transaxillary approach, bilateral axillary-breast approach (BABA), behind-the-ear (RA) facelift approach, transoral endoscopic thyroidectomy via vestibular approach (TOETVA), Minimally Invasive Video-Assisted Thyroidectomy (MIVAT), or parathyroidectomy (MIVAP). The role of multidisciplinary teams with an endocrine surgeon, endocrinologist, oncologist, nuclear radiologist, and radiotherapist is essential to correctly manage these patients.

The aim of this special issue was to focus on new and emerging concepts about Thyroid and Parathyroid Surgery, including surgical techniques with possible complications, referral center experience, oncological outcomes, and multidisciplinary approaches. The contributions from leading experts in this field have reached this objective, especially

with state of the art reviews on minimally invasive surgery or novel approaches to thyroid and parathyroid cancer.

This topic about Endocrine Surgery achieved excellent results, with 11 manuscripts accepted of high quality and scientific level. The authors belong to referral centers for thyroid and parathyroid disease from different countries.

All the accepted manuscripts contribute to the improvement of literature in this field.

[Pacilli et al.](#) reported the importance of the surgical approach in cases of lymph node disease for recurrence differentiated thyroid carcinoma (DTC) and demonstrated the safety and effectiveness of the ultrasound-guided approach. The aim of this method is to identify all pathological nodes and to facilitate exact localization; the best outcome is to perform a curative surgery.

[Sang et al.](#) considered an innovative approach in parathyroidectomy by using artificial intelligence (AI) to recognize the parathyroid glands (PGs). This technique can be very useful for young inexperienced surgeons. The authors provided a retrospective study based on a new AI model to detect PGs, which demonstrated improved performance with superior accuracy and precision over other models.

[Cianci et al.](#) underlined the safety of the fine-needle aspiration cytology (FNAC) technique, performed with 25 G caliber needles. In fact, FNAC plays a crucial role in the diagnosis of thyroid nodules and is an easy and cost-effective method. The proposed technique by the authors is less painful for patients, with low complication rates.

[Staibano et al.](#) provided a systematic review and network meta-analysis of diagnostic test accuracy to identify the intraoperative parathyroid hormone (iPTH) criteria and post-gland excision timepoint. The main aim was to predict surgical cures for hyperparathyroidism and unify the existing iPTH monitoring criteria to address the lack of standardization in the timing of post-parathyroid gland excision.

[He et al.](#) conducted a comprehensive systematic review and meta-analysis on the application of carbon nanoparticles in thyroid surgery in order to detect intraoperative and/or metastatic lymph nodes and improve surgical skills while protecting the integrity and function of the parathyroid glands. The authors demonstrated that the application of carbon nanoparticles can effectively improve the effects of surgical treatment, reducing post-operative complications such as hypocalcemia and minimizing the need for repeat surgery for undetected intraoperative and metastatic nodes.

[Ünlü et al.](#) reported a non-randomized prospective clinical study on the comparison between the severity of surgical trauma in TOETVA vs. Conventional open thyroidectomy (COT), using the inflammatory surgical stress markers interleukine-6 (IL-6), C- reactive protein (CRP), and white blood cells (WBC). The secondary objective was the evaluation of operative time, post-operative pain, and hospital stay. The results suggested that the higher postoperative CRP level and VAS score were in the TOETVA group balanced by a postoperative aesthetic satisfaction.

[Jin et al.](#) documented a very interesting clinical case on a non-recurrent laryngeal nerve (NRLN), well-known as a rare variation of the recurrent laryngeal nerve, with an overall incidence of 0.7%. This variation can lead to intraoperative nerve injury. The authors detected the NRLN during an areola approach for radical thyroidectomy after an accurate intraoperative search of the nerve.

[Wang et al.](#) reported a systematic review and meta-analysis on the global prevalence of secondary hyperparathyroidism (SHPT) due to chronic kidney disease (CKD). This review demonstrated a high prevalence of SHPT in patients with CKD, highlighting the importance of the therapeutic approach for primary care.

[Yamashita et al.](#) reported a prospective cohort study about the treatment of hypocalcemia after total thyroidectomy. This condition represents a comprehensive post-operative complication. The use of 1,25-dihydroxyvitamin D can act as a sudden therapy option for burden hypocalcemia.

[Zhao et al.](#) considered, with an accurate Mendelian randomization, the genetic connection between immune cell traits and Hashimoto's Thyroiditis. Their findings provide guidance and direction for future treatment and clinical research.

[Laforgia et al.](#) described a retrospective observational study about parathyroid carcinoma (PC), which represents less than 1% of malignant neoplasms among endocrinological diseases. PC is still considered a great challenge in terms of preoperative diagnosis, management, and treatment. A surgical approach represents the best option for PC in referral endocrine surgery units.

Author contributions

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Non-recurrent right laryngeal nerve identified during endoscopic thyroidectomy via areolar approach: a case report

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Background: Nonrecurrent laryngeal nerve (NRLN) is a rare but significant anatomical variation in thyroid surgery, and lack of awareness of NRLN may lead to intraoperative injury. Here, we report a clinical case of NRLN discovered during endoscopic thyroid surgery via total areola approach in a 23-year-old female patient.

Case presentation: A 23-year-old female patient presented with bilateral thyroid nodules for three years. She underwent bilateral thyroid nodule fine-needle aspiration biopsy and BRAF gene testing at our hospital, with results indicating bilateral papillary thyroid carcinoma and positive BRAF gene V600E mutation. Neck-enhanced CT revealed bilateral thyroid nodules and the right subclavian artery branching from the aortic arch on the distal side of the left subclavian artery. The patient underwent endoscopic thyroidectomy via total areola approach for radical resection of bilateral thyroid cancer. Intraoperatively, NRLN was found on the right side and RLN on the left side. The surgery was successful, and no postoperative complications were observed. Postoperative pathology confirmed bilateral papillary thyroid carcinoma.

Conclusions: Although NRLN is a rare occurrence, clinicians should not overlook its presence to prevent serious complications. Preoperative imaging confirmation of the presence or absence of an abnormal subclavian artery course is crucial in preventing the sudden discovery of NRLN during surgery. Endoscopic thyroid surgery via total areola approach is a safe and effective technique but requires a high level of professional skills and an understanding of anatomical variations to prevent nerve injury.

KEYWORDS

nonrecurrent laryngeal nerve, recurrent laryngeal nerve, endoscopy, thyroidectomy, case report

Introduction

NRLN is a rare variation of the recurrent laryngeal nerve, with the estimated incidence rate of NRLN on the right side being relatively low (0.2%–1.5%), and even lower on the left side (0.04%). The overall incidence rate is only 0.7% (1–3). The formation of NRLN is mainly related to abnormal arterial development during embryonic development, such as the maldevelopment of the aortic arch or the brachiocephalic trunk. This may explain why NRLN is more common on the right side and often associated with subclavian or lusoria artery anomalies. During thyroid surgery, the laryngeal recurrent nerve is of

Abbreviations

NRLN, Nonrecurrent laryngeal nerve; RLN, recurrent laryngeal nerve; Sca, Subclavian artery; Ep, Esophagus; Tr, Trachea; A, Aorta; IONM, Intraoperative neural monitoring.

considerable importance to the surgeon, so much so that surgical strategies are continuously being optimized to avoid complications such as hoarseness or dysphagia (4). NRLN originates directly from the vagus nerve and does not recur into the mediastinum, which increases the difficulty and risk of complications during surgery. Therefore, accurately identifying the course of NRLN and protecting it is crucial during surgery.

Case presentation

In March 2023, a 23-year-old female patient presented to our hospital's thyroid surgery department with a history of bilateral thyroid nodules detected during a routine physical examination for 3 years. She had no known medical history or chronic diseases and no hoarseness or compression symptoms. Thyroid function, anti-peroxidase antibody, and calcitonin levels were all within normal limits. Ultrasound showed a solitary solid nodule measuring 2.5×2.0 mm with unclear margins and a regular shape in the left thyroid lobe, with a longitudinal-to-transverse ratio greater than 1. A solitary solid nodule measuring 5.5×3.5 mm with unclear margins and a regular shape, with punctate calcification inside, was found in the right thyroid lobe. No abnormal lymph nodes were found in the neck. The patient underwent bilateral thyroid nodule fine-needle aspiration biopsy and BRAF gene testing, with results indicating bilateral papillary thyroid carcinoma and positive BRAF gene V600E mutation. Neck-enhanced CT revealed bilateral thyroid nodules and the right subclavian artery branching from the aortic arch on the distal side of the left subclavian artery (Figure 1). Due to the patient's young age and aversion to a midline neck incision, she underwent endoscopic thyroid surgery via total areola approach for radical resection of bilateral thyroid cancer, including total thyroidectomy and ipsilateral and contralateral central compartment VI lymph node dissection. During the surgery, a small nerve was discovered that wrapped around the inferior thyroid artery and passed upward along the tracheoesophageal groove on the right side. Further dissection revealed a cord-like grayish-white structure emanating from the neck sheath and extending horizontally to the posterior aspect of the thyroid

gland. Careful dissection along this cord-like structure revealed a nerve running horizontally inward to the thyroid cartilage below the inferior horn, which was identified as NRLN (Figure 2). The postoperative period was uneventful, with no changes in the patient's voice and no numbness in the extremities. According to the postoperative pathological examination, the patient was found to have bilateral micro-papillary thyroid carcinoma.

Discussion

NRLN is a rare developmental anomaly that was first discovered during a cadaver dissection by Stedman in 1823 (5). NRLN on the right side is usually associated with an abnormal subclavian artery, which is often referred to as the right vagus below the clavicle artery or "arteria lusoria", and is usually due to the regression of the fourth pharyngeal arch during embryonic development. NRLN on the left side is often associated with complete visceral situs inversus (6). NRLN can be classified into different types based on its course, with the Toniato classification (7) system being commonly used. Type I NRLN originates directly from the vagus nerve trunk in the neck, accompanying the superior thyroid artery and descending into the larynx. Type IIA NRLN arises from the recurrent laryngeal nerve trunk at the level of the inferior thyroid artery and runs parallel to the inferior thyroid artery into the larynx. Type IIB NRLN arises from the recurrent laryngeal nerve trunk at the level of the inferior thyroid artery and runs parallel to the inferior thyroid artery into the larynx, passing between the inferior thyroid artery and its branches before entering the larynx. Our case does not fit into either Type I or Type IIA, but rather appears to be a combination of Type I and Type IIA NRLN. To date, only Mohammed AA (8) has reported a case in which 2 ipsilateral NRLN (double nerves) were found to cross over and parallel to the inferior thyroid artery at the time of a routine right thyroid lobectomy. The presence of NRLN increases the risk of nerve injury during thyroidectomy. However, NRLN is not visible on any imaging examinations. Therefore, NRLN is often "accidentally" discovered during surgery and may sometimes be overlooked or inadvertently injured. Accurate prediction of NRLN before surgery is crucial for avoiding nerve injury during surgery.

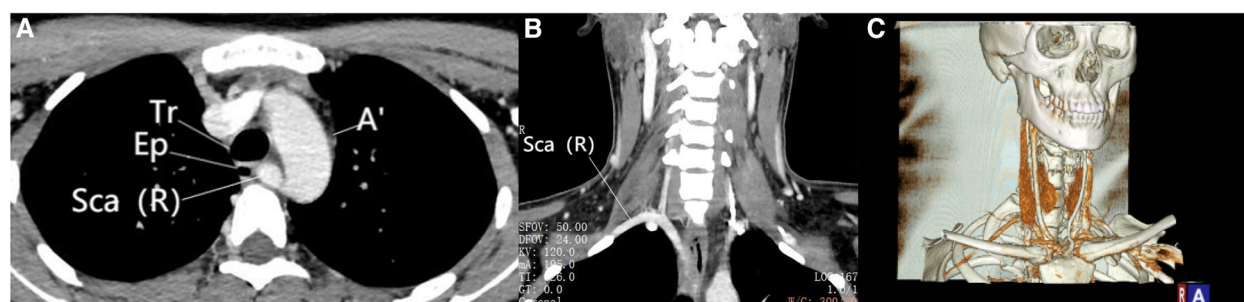


FIGURE 1
Enhanced CT scan. (A) Viewed in axial view, the right subclavian artery originates from the aortic arch and courses between the vertebrae and the esophagus. (B) Viewed in coronal view, the ectopic course of the right subclavian artery can be observed. (C) The blood vessels under three-dimensional reconstruction can be observed. Sca (R), Right subclavian artery; Ep, Esophagus; Tr, Trachea; A, Aorta.

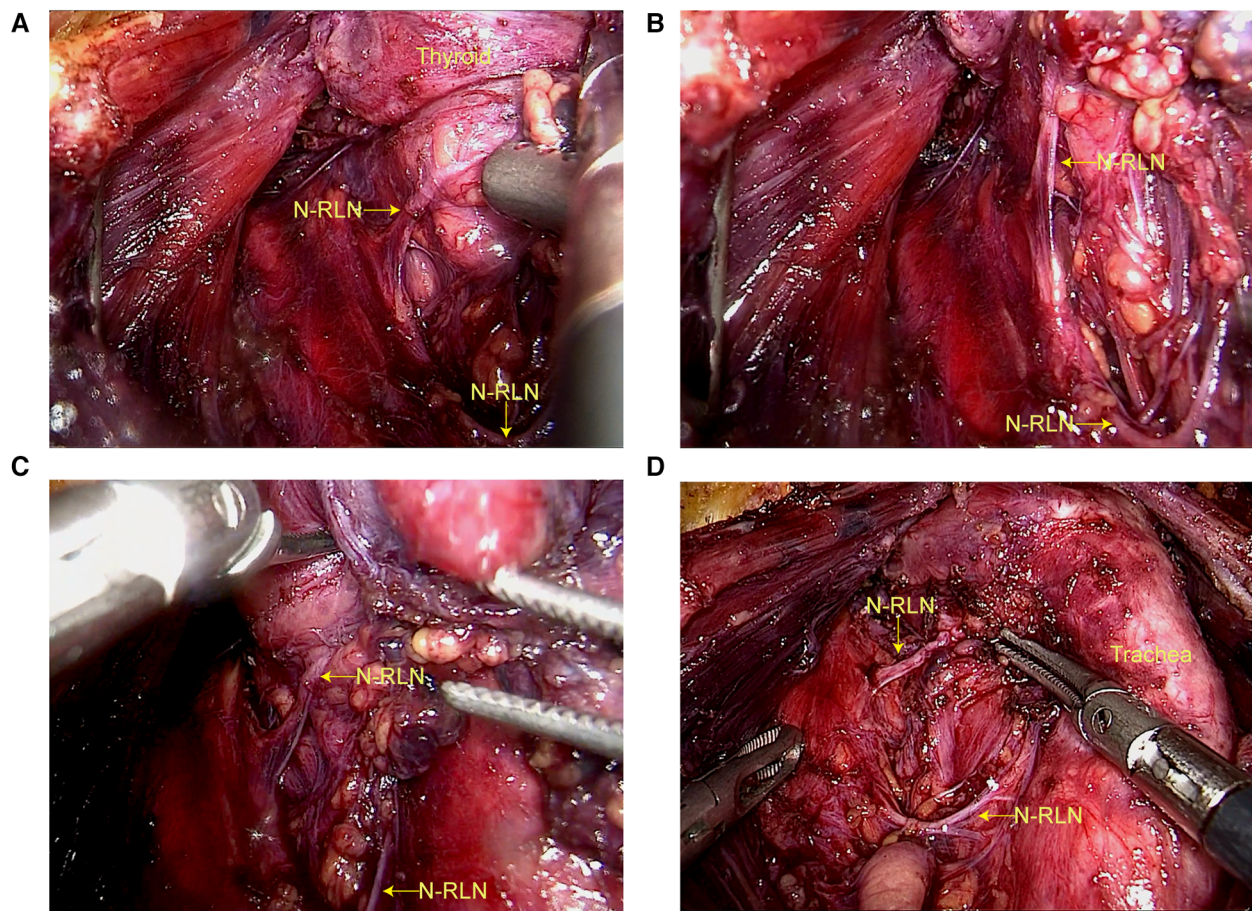


FIGURE 2

Right nonrecurrent laryngeal nerve during endoscopic thyroidectomy via areolar approach. (A) Mistakenly identified as the superior thyroid artery, the NRLN. (B) Due to preoperative confirmation of anomalous course of the subclavian artery, the NRLN, which was mistakenly identified as the superior thyroid artery, was carefully dissected along its course instead of being transected. (C) Found to course through the thyroid gland and into the larynx. (D) Ultimately confirmed to be the NRLN.

Esophageal barium meal examination may reveal the compression of the esophagus by the abnormal right subclavian artery, which can create a circular notch on the left edge of the esophagus. However, this is not a routine preoperative examination for patients with thyroid disease, so it has certain limitations in diagnosing NRLN. Ultrasound is the preferred preoperative auxiliary examination for patients with thyroid disease and can also be used to diagnose NRLN by evaluating the presence of vascular malformations. Normally, the right common carotid artery and right subclavian artery originate from the brachiocephalic trunk. Under ultrasound, this structure is called the “Y sign”. When both the right common carotid artery and right subclavian artery originate separately from the aortic arch, the “Y” sign disappears under ultrasound, indicating the absence of the brachiocephalic trunk and the possible presence of NRLN (9). However, sometimes ultrasound cannot detect the branching of the brachiocephalic artery due to the pseudo-image of thyroid nodules and the clavicle, which is a limitation of ultrasound in identifying NRLN. Preoperative CT has a high detection rate for NRLN (10). CT can not only understand the anatomical relationship between the thyroid and surrounding tissues and the presence of lymph node metastasis in the neck but also discover the

absence of the brachiocephalic trunk. Three-dimensional reconstruction technology can also improve the detection rate of NRLN. If the three-dimensional reconstruction shows that the right subclavian artery originates from the distal aortic arch of the left subclavian artery and crosses the midline behind the esophagus to the anterior cervical vertebrae on the right side, then the presence of right NRLN should be considered. Therefore, CT and ultrasound images can be used for preoperative diagnosis of NRLN. As in our case, neck-enhanced CT identified the abnormal position of the right subclavian artery, suggesting the presence of right NRLN. Knowing the presence of anatomical variation before surgery and the possibility that the RLN nerve may not be located in the tracheoesophageal groove before surgery, the discovery of NRLN during surgery is not surprising.

Intraoperative neural monitoring (IONM) has been widely used for identifying and monitoring the recurrent laryngeal nerve (RLN) during thyroid and parathyroid surgery. The use of IONM is beneficial for preventing RLN and NRLN injury. Demet Sengul et al. (11) reported a case of sutureless total thyroidectomy with intermittent intraoperative neuromonitoring (I-IONM) and energy-based instrumentation without sternotomy

for the treatment of retrosternal goiter with chronic lymphocytic thyroiditis, demonstrating that IONM provides a strong barrier for complex thyroid surgery. Using IONM during surgery resulted in a lower incidence of nerve paralysis, especially in cases involving NRLN (12). In this case, it was fortunate that the NRLN could be identified despite the absence of an IONM, which was also attributed to the preoperative CT identification of the aberrant right subclavian artery as well as the magnified field of endoscopic thyroidectomy. Whether thyroidectomy (13), endoscopic thyroidectomy (14) or robotic thyroidectomy (15), the IONM can be used to guide the precise dissection of the NRLN as well as improve safety. As technology has evolved, new methods of neuromonitoring have also emerged. Iyad Hassan et al. (16) used and confirmed a new neural monitoring method, Abu Dhabi Neural Mapping (ADNM), for early identification of NRLN issues and preservation of its function during minimally invasive thyroidectomy.

Despite the help of IONM, (abnormal) anatomical knowledge should also be a core component of medical students and surgical interns' skills (17). A comprehensive understanding of the normal and abnormal anatomical structures of RLN is still crucial for the optimal results of thyroid surgery. Boyan Fu et al. (18) reported a novel "hands-as-feet" teaching method that can more effectively help medical students and young medical workers understand complex anatomical relationships and variations, making the teaching process more visualized.

Conclusion

We report a case of a 23-year-old lady who underwent endoscopic thyroid surgery via total areola approach for radical resection of bilateral thyroid cancer and a NRLN was encountered intraoperatively. Although the incidence of NRLN is low, the risk of iatrogenic injury is high if this anatomical anomaly is not taken seriously. This case highlights this anatomical variant. If no RLN is found after meticulous dissection in the usual location, combined with preoperative radiologic analysis (CT, ultrasound), NRLN should be highly suspected.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

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Ethics statement

The studies involving humans were approved by the Ethics Committee of the Second Affiliated Hospital of Nantong University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. The manuscript presents research on animals that do not require ethical approval for their study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XJ: Writing – original draft, Writing – review & editing. RY: Project administration, Supervision, Validation, Writing – review & editing.

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Management and surgical treatment of parathyroid carcinoma: a 6-year experience of a single centre of endocrine surgery unit

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Background: Parathyroid carcinoma (PC) affects 0.1-0.3% of the general population and represents the rarest malignant neoplasms among endocrinological diseases, comprising less than 1%. The best therapeutic treatment and management methods are still debated in the literature. The aim of this study is to evaluate the management and surgical treatment of parathyroid carcinoma after 6 years of enrolment with the Endocrine Surgery Unit of the University Hospital of Bari.

Materials and methods: A retrospective observational study was carried out using a prospectively maintained database of patients affected by primary hyperparathyroidism between January 2017 and September 2022. Consecutive patients over 18 years old with a final histopathological finding of PC were included in the study. Patients with secondary or tertiary hyperparathyroidism, parathyroid hyperplasia, and parathyroid adenoma were excluded. All patients underwent follow-up every 6 months for the first 2 years, and annually thereafter.

Results: In this study, 9 out of 40 patients affected by hyperparathyroidism were included; 6 (66.6%) were female and 3 (33.3%) were male patients, with a median age of 59 years (IQR 46-62). None had a family history of PC. No mortality was recorded while the incidence of recurrence was 22.2%, with a disease-free survival of 8 and 10 months. Parathyroidectomy was performed in five patients, while four patients underwent parathyroidectomy with concurrent thyroidectomy for thyroid goitre. No intraoperative complications were recorded. Open parathyroidectomy was performed with a mini-cervicotomy in seven patients, while two patients underwent robotic surgery. All patients were discharged on the second postoperative day.

Conclusion: PC represents a great challenge in terms of preoperative diagnosis, management and treatment. A surgical approach represents the first best option for PC in referral endocrine surgery units. The early identification of risky patients should be the dominant goal to plan an appropriate therapy and to perform adequate en bloc surgery.

KEYWORDS

parathyroid carcinoma, endocrine surgery, parathyroidectomy, hyperparathyroidism, PTH - parathyroid hormone

1 Introduction

Parathyroid carcinoma (PC) affects 0.1-0.3% of the general population and represents the rarest malignant neoplasms among endocrinological diseases, comprising less than 1% (1). A histological examination is used to detect PC in the majority of cases, because a preoperative diagnosis is difficult due to the absence of specific criteria and fine-needle aspiration is impossible as the violation of the parathyroid capsule could determine subsequent tumour seeding (2–5).

The aetiology of PC is still unknown (6). PC may occur in sporadic cases, especially in those with a single-gland disease, or may be associated with hereditary endocrinopathies such as Multiple Endocrine Neoplasia type 1 (MEN1) or type 2A (MEN 2A), HPT-jaw tumour syndrome (HPT-JT), or familial isolated hyperparathyroidism (FIHP) (7–9).

The increase in parathyroid hormone (PTH) and serum calcium represents clear signs of hyperparathyroidism along with subsequent signs and symptoms. Patients (pts) can be affected by gastrointestinal, neurological, cardiological, bone and kidney diseases, and in some cases, a palpable neck mass. Unfortunately, metastatic disease could affect 10-30% of pts at the time of the diagnosis, where patients present with lung, liver and bone invasion (10).

Differential diagnosis from parathyroid hyperplasia and adenomas could be complex, but the suspicion of cancer increases in cases of certain findings, such as higher levels of serum PTH and calcium, parathyrotoxicosis, and a palpable neck mass. PTH reaches high levels that are 3 to 10 times higher than the normal serum value in cases of PC. In total, 98% of cancers are functioning tumours associated with more frequent bone and kidney disease, while only 2% are characterized by normal serum levels of PTH and calcium along with the evidence of a palpable and invasive mass (11, 12).

Prognosis is poor for PC because of mortality due to uncontrollable levels of hypercalcemia and subsequent diseases. The overall survival rate at 5 years is 78-85%, and at 10 years it is 49-70% (4).

Differential diagnosis from malignant to benign disease is challenging, and the best therapeutic treatment and management methods are still being debated in the literature (13). Several studies have revealed the inefficacy of chemo- and radiotherapy, and

further options such as immunotherapy and targeted therapies have been proposed in several studies (11). Concerning surgical treatment, it is mandatory to reach the best oncological result and to also evaluate the gland's hyperfunction in order to verify whether all pathological tissues were removed or not. In order to predict the eradication of the disease, intraoperative PTH testing is considered as a reliable method, as is the application of two preoperative scores, especially in case of impossibility to verify intraoperative PTH. The CaPTHUS score, described by Kebebew et al. in 2006 (14), and the Wisconsin index (Win score), described by Mazeh et al. (15) in 2013, were applied for predicting single-gland disease with primary hyperparathyroidism by De Pasquale et al. (16).

The aim of this study is to evaluate the management and surgical treatment of parathyroid carcinoma after 6 years of enrolment with the Endocrine Surgery Unit of the University Hospital of Bari. The secondary aim is to compare the results with those from existing studies. PC remains a difficult disease to preoperatively detect and prevent. The early identification of at-risk patients should be the dominant goal to plan an appropriate therapy and to perform adequate en bloc surgery.

2 Materials and methods

A retrospective observational study was carried out using a prospectively maintained database of patients affected by primary hyperparathyroidism with suspected PC who, according to the guidelines for the management of primary hyperparathyroidism from the American Association of Endocrine Surgeons (17), underwent surgery in the Endocrine Surgery Unit between January 2017 and September 2022. Consecutive patients over 18 years old with a final histopathological finding of PC were included in the study. Patients with secondary or tertiary hyperparathyroidism, parathyroid hyperplasia, and parathyroid adenoma were excluded.

All patients underwent a physical examination, cervical ultrasound, computer tomography and 99m Tc sestamibi scintigraphy as part of their diagnostic work-up to locate the lesion; F-fluorodeoxyglucose pet/ct was performed only in selected cases.

Gender, age, clinical symptoms at admission and family history, as well as serum PTH, calcium, phosphate, creatinine, and 24-hour

urinary calcium and phosphate levels, were recorded preoperatively. Calcium was recorded in mg/dL (normal range 8.4–10.2 mg/dL), PTH in pg/mL (normal range 8.7–79.6 pg/mL), phosphate in mg/dL (range 2.5–4.5 mg/dL), creatinine in mg/dL (range 0.84–1.21), 24-hour calciuria in mg/kg/24 h (normal value < 4 mg/kg/24 h) and 24-hour phosphaturia in g/L/24h (normal value < 1.35 g/L/24h). The postoperative parameters registered included serum PTH, calcium, and possible surgical complications. All patients underwent follow-up every 6 months for the first 2 years, and annually thereafter. Postoperative hypocalcaemia was considered as a serum calcium value lower than 8.4 mg/dL with a normal PTH value. Postoperative hypoparathyroidism was considered as a serum PTH value lower than 8.7 pg/mL with a calcium value lower than 8.4 mg/dL. Both complications were considered transient if lasting less than six months and definitive if lasting longer. Informed consent was obtained from all patients before enrolment. All investigations complied with the principles of the Declaration of Helsinki.

2.1 Statistical analysis

Continuous parameters were reported as medians and IQRs. The categorical variables were recorded as numbers and percentages. Statistical analysis was carried out using RStudio (R version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

3 Results

In this study, 9 out of 40 patients affected by hyperparathyroidism were included; 6 (66.6%) were female and 3 (33.3%) were male patients, with a median age of 59 years (IQR 46–62). At admission, two (22.2%) patients had nephrolithiasis, four (44.4%) had bone disease, four (44.4%) had chronic kidney failure (where two of them were waiting for kidney transplantation), one had Berger's disease and three patients (33%) were asymptomatic. None had a family history of PC.

In the preoperative work-up, all patients had a high level of PTH (median 432 pg/mL, IQR 296.5 – 877) and hypercalcaemia (median value 11.20 mg/dL, IQR 11–14.30) except for one female patient with a value of 8.8 mg/dL, whose PC was discovered during a total thyroidectomy for a thyroid goitre. Calciuria and phosphaturia were recorded in only two patients. Parathyroidectomy was performed in five patients, while four patients underwent parathyroidectomy with concurrent thyroidectomy for a thyroid goitre. No intraoperative complications were recorded. Open parathyroidectomy was performed with a mini-cervicotomy in seven patients, while two pts underwent robotic surgery. All patients were discharged on the second postoperative day. Postoperative complications included five patients (55.5%) who had transient postoperative hypocalcaemia, which was treated with oral calcium supplementation, and three (33.3%) patients who developed

definitive postoperative hypoparathyroidism. Two patients had high postoperative PTH values of 180 and 249 pg/mL, while seven patients were in the normal range. Histopathological examination revealed that all patients had PC with a Ki67 always $\geq$ 4% (median value 4%, IQR 4–7), while three (33%) patients were chromogranin-positive, and two (22.2%) patients were synaptophysin-positive.

After a median follow-up of 36 months (IQR 12–48), no mortality was recorded while the incidence of recurrence was 22.2% (2 patients) with a disease-free survival of 8 and 10 months. Follow-up included endocrinological, surgical and dental evaluations, a renal US scan, and a biochemical blood test. Two patients had the highest postoperative PTH values of the series, and both underwent parathyroidectomy with uneventful recovery and were discharged on the second postoperative day.

The clinical data of patients with PC are summarized in [Table 1](#).

4 Discussion

The best therapeutic option to cure pts affected by PC is a pre- or intraoperative diagnosis and a complete resection of the tumour during the first initial surgical approach.

In this study, nine cases of PC were detected in 6 years, according to the evident percentage in the literature¹. The prevalence of female patients is relevant (66.6%), and this result can be important in cases where there is suspicion of PC, considering that there is the same prevalence in primary hyperparathyroidism (18). The median age of patients in this study was 59 years (IQR 46–62), while Machado et al. reported a tendency for a younger age of about 50 years at the time of the diagnosis (11, 18). A certain diagnosis of PC was evident after the histological examination in all cases. All patients presented high serum levels of PTH and calcium.

The first surgical approach was parathyroidectomy in five patients, with a subsequent secondary surgical step according to a multidisciplinary evaluation; in four cases, thyroidectomy was performed because of a compressive goitre. The same experienced endocrine surgeon performed all procedures, respecting all principles of en bloc surgery: complete exploration, a bloodless field, minimal manipulation of the tumour, evaluation of nodal involvement and exploration of the ipsilateral laryngeal nerve. In all cases, no nodal or nerve involvement was evident. The suspicion of PC could be also intraoperative because the tumour presents with a hard consistency, a fibrous capsule, and a white or grey hue, and it is adherent to nearby structures ([Figures 1, 2](#)). Adenomas can appear softer and have a reddish colour with well-defined limits (11, 19).

Two cases of recurrence (22.2%) are still not treated because of a clinical condition not suitable for surgery. According to Cetani et al., 3 years represents the mean time to diagnose recurrence, although some studies reported recurrences after 20 years (2, 6). In cases of recurrences, surgery still represents the best therapeutic option with the main aim of relieving symptoms and eradicating the residual disease.

TABLE 1 Clinicopathologic features of parathyroid carcinoma patients.

Gender	Age	Clinical Symptoms	Calcium (mg/dL)	PTH (pg/mL)	Phosphate (mg/dL)	Creatinine (mg/dL)	Phosphaturia (mg/dL)	Calciuria (mg/dL)	Sugery	Calcium Post (mg/dL)	PTH Post (pg/mL)	Definitive hypo-parathyroidism
F	46	nephrolithiasis, osteopenia, osteoporosis	11.2	1800	1.9	0.96	38.1	7.3	TT + PrT	10.1	28	Yes
M	65	nephrolithiasis, osteopenia, osteoporosis	9.7	180	45	1.65	0	0	Inferior right PrT	10.2	180	No
F	43	CKF	8.8	/	/	14.3	0	0	TT+ PrT	6.3	<6	Yes
F	59	None	14.3	/	/	1.06	0	0	TT+ PrT	6.5	<6	Yes
F	61	osteopenia, osteoporosis, fatigue, dyspesia	11.1	238	3	0.63	546	323	inferior right PrT	7.4	37	No
M	37	osteopenia, osteoporosis CKF, hyperuricemia	17.6	355	/	1.51	0	0	inferior left PrT	8.5	249	No
F	62	CKF, Berger's disease	14.3	1156	7	12.3	0	0	superior, inferior right and inferior left PrT + TT	5.5	8	Yes
F	57	None	14.1	598	2.1	0.9	0	0	inferior right PrT	9.3	13	Yes
M	63	CKF	11	432	7.5	9.46	0	0	inferior left PrT	6.7	78	No

TT, total thyroidectomy; PrT, parathyroidectomy; PTH, parathyroid hormone; CKF, chronic kidney failure.
/, not available.

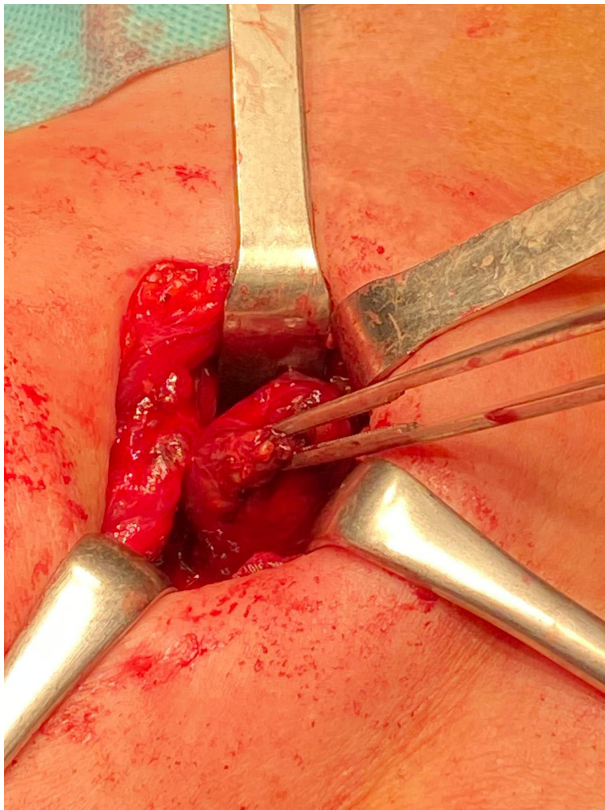


FIGURE 1
Intraoperative visualization of parathyroid gland.

Several studies have contributed to understanding the natural history, diagnosis, genetics and treatment of PC. Unfortunately, the rarity of this disease, the existing results coming from the few cases that have been reported and a lack of complete clinical data represent the main reason for the absence of adequate guidelines. Moreover, follow-up information is not usually available.

The prevention of PC is difficult and the best expectation is to develop a specific genetic analysis and preoperative diagnosis method. In 2017, Silva-Figueroa et al. (20) proposed a prognostic scoring system to detect PC. The score was based on three risk groups (low, moderate and high) according to three main variables and the recurrence-free survival rate. Although this score is still not validated, it could be associated with clinical, genetic and

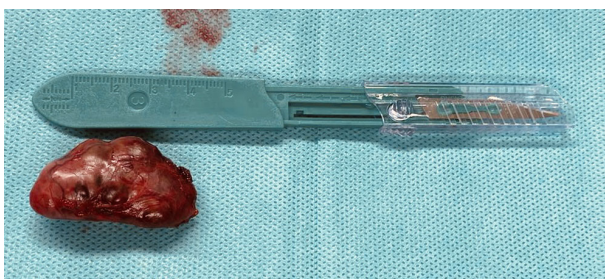


FIGURE 2
Parathyroidectomy.

histological markers in order to realise a preoperative PC diagnosis. In 2021, Shulte et al. (21) distinguished the main histological and clinical features between parathyromatosis, atypical parathyroid adenomas and PC. This study included a strict number of cases and revealed a higher level of cellular necrosis in PC and in adenomas without a clear distinction.

According to the existing results in the literature, the suspicion of PC should be based on severe PTH high levels, hypercalcemia, bone and kidney diseases, and an evident neck mass. The best therapeutic option is still surgery due to the en bloc surgery concepts carried out in referral endocrine surgery units (19, 22–24). Gurrado et al. (25) also suggested that the suspicion of PC should be considered in cases of high values of PTH, hypercalcemia and a mass with an ultrasound diameter that is more than 3 cm.

The role of immunotherapy could be useful to decrease tumour size in isolated cases, as demonstrated by Betea et al. (26). According to Wei and Harari, two cases of inoperable metastatic PC underwent experimental immunotherapy with satisfying results (3).

Genetic and epigenetic investigations are in progress, aiming to identify specific factors and characterize biological molecules and the genetic network of PC cells in order to subsequently develop targeted therapies (12).

5 Conclusion

PC represents a great challenge in terms of preoperative diagnosis, management and treatment. Its rarity is not helpful in acquiring clear genetic, clinical and histological features. A surgical approach represents the first best option for PC in referral endocrine surgery units. In this context, in order to offer the best treatment that can optimize clinical management and surveillance, a multidisciplinary team should play a key role. Further multicentric trials are necessary to improve preoperative diagnoses and outcomes, to prevent recurrences, and to recognize at-risk patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Azienda Ospedaliero Consorziiale Policlinico di Bari. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RL: Conceptualization, Writing – original draft. GT: Writing – review & editing. FC: Data curation, Writing – original draft. MS: Software, Writing – original draft. AS: Data curation, Writing – original draft. FA: Validation, Writing – original draft. PL: Validation, Writing – review & editing. RM: Supervision, Validation, Writing – review & editing. APA: Validation, Writing – original draft. APe: Conceptualization, Writing – review & editing.

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Comparison of transoral endoscopic thyroidectomy vestibular approach and open conventional thyroidectomy regarding inflammatory responses, pain, and patient satisfaction: a prospective study

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Introduction: The application of transoral endoscopic thyroidectomy vestibular approach (TOETVA) is becoming widespread throughout the world. We primarily aimed to evaluate the severity of surgical trauma in TOETVA and conventional open thyroidectomy (COT) regarding the inflammatory response including the comparison of surgical stress markers [interleukin-6 (IL-6), C-reactive protein (CRP), white blood cell (WBC)].

Material and method: This non-randomized prospective study enrolled two groups with 20 patients each: COT group and TOETVA group. Patients aged 18–65 years with benign thyroid disease; with fine needle aspiration biopsy results of Bethesda III, IV or Bethesda V, VI (<1 cm nodule); thyroid volume <50 cm³; nodule diameter <4 cm; female gender without a previous neck, chin, and/or oral surgery; without vocal cord paralysis preoperatively; and patients in euthyroid state were enrolled to the study. Preoperative, postoperative second hour, first day, and second day CRP, WBC, and IL-6 levels were evaluated. Pain intensity was evaluated with the visual analog scale (VAS) score on the 2nd and 12th hour, 1st and 2nd days postoperatively.

Results: All the patients were female and mean age was significantly higher in the COT group. The operative time was significantly longer in the TOETVA group. No significant difference was found between the two groups regarding IL-6 levels. In the TOETVA group, postoperative second hour WBC value ($p = 0.044$) and first ($p = 0.002$) and second day ($p = 0.005$) CRP values were significantly higher. In the TOETVA group, the lower lip and lower chin VAS scores were significantly higher at 2nd and 12th hour, on the first and second days. The anterior neck VAS score was significantly higher in the TOETVA group at the second hour ($p = 0.025$). General and cosmetic satisfactions were similar at the 15th and 30th days in both groups.

Conclusion: The longer operative time and higher postoperative CRP level and VAS score in the chin and lower lip in the TOETVA group suggested that the method is not a minimally invasive technique compared to COT. However, the presence of similar total complication rates and early postoperative general and esthetic satisfaction that improves over time in both groups suggests that the clinical effect of increased magnitude of systemic inflammatory response in TOETVA might be temporary and acceptable.

KEYWORDS

open thyroidectomy, TOETVA, postoperative pain, cosmesis, complications, comparison

Introduction

Thyroidectomy is the most common endocrine surgical procedure and the standard approach is open thyroidectomy via cervical incision (1). Conventional open thyroidectomy (COT) leaving an incision scar of 5–10 cm in the neck has an esthetically negative effect on the patient population consisting of mostly young females, which may lead to psychological trauma and reduce the quality of life (2). Minimally invasive surgery can be defined as the novel traditional surgical procedure, which can be performed in new ways that would leave the surgical field with minimal trauma (3).

Minimally invasive surgery, which started with the first laparoscopic cholecystectomy approximately 30 years ago, has replaced many conventional surgeries today and is among the standard treatment approaches. Techniques defined as minimally invasive, such as total endoscopic thyroidectomy and minimally invasive video-assisted thyroidectomy, were introduced in thyroid surgery in the 1990s. However, these techniques also leave a visible incision scar on the neck, albeit small (2).

In the past two decades, remote access endoscopic or robotic thyroidectomy methods such as transaxillary approach and axillo-breast approach have been popular (4). These techniques do not cause a scar in the neck, but the incisions are moved to the areas that can be covered with clothing to eliminate the need for a smaller incision. These methods are not minimally invasive as a wide dissection of the chest and neck is required to reach the thyroid (2, 5, 6). After transoral thyroidectomy, a natural orifice transluminal endoscopic surgical technique was developed by Witzel et al. in 2008, and different transoral thyroidectomy techniques were tried (7). In 2016, after Anuwong reported that the transoral endoscopic thyroidectomy vestibular approach (TOETVA) is a safe and feasible technique, it became popular. The application of the TOETVA technique is becoming widespread throughout the world (8). TOETVA is a minimally invasive procedure compared to other remote access thyroidectomies because it requires less flap dissection to reach the thyroid gland and is a true scarless technique (9).

However, it is not clear whether TOETVA is a real minimally invasive technique compared to COT, requiring three incisions in the vestibulum, and more subplatysmal flap dissection to reach the thyroid gland than COT requires. All minor and major surgeries cause systemic inflammatory response (SIR) due to operative injuries in the body. In clinical practice, cortisol, interleukin-6 (IL-6) (a proinflammatory cytokine), white blood

cell (WBC), and C-reactive protein (CRP) are the most commonly used parameters to evaluate the magnitude of the SIR. SIR severity after elective surgery is related to the extent of operative injury and invasiveness of the operation (10). In addition to SIR, pain score, operative time, postoperative drainage volume, and length of the postoperative hospital stay can be used to evaluate the level of surgical trauma (11, 12).

Despite the significant differences in the surgical site, localization and length of incision, and tissue retracting between COT and TOETVA, surgical stress markers (IL-6, CRP, and WBC) can be used to compare the magnitude of SIR as a quantifiable method to evaluate the surgical stress.

During the planning period of the present study, there has been no study in the literature evaluating the surgical stress markers related to the severity of surgical trauma in TOETVA. The research question of this study is whether the severity of surgical stress in TOETVA is less than COT or not.

In the present study, as a primary end-point, we aimed to evaluate the severity of surgical trauma in TOETVA and COT regarding the inflammatory response including the comparison of surgical stress markers (IL-6, CRP, and WBC). We also evaluated the postoperative pain, operative time, and hospital stay as secondary end-points.

Material and methods

Study design and patients

This non-randomized prospective clinical study was performed in our clinic between September 2019 and January 2020 with the approval of the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (Ethics committee date: 19/03/2019, number: 2313). In addition, support was received from the Health Science University, scientific research projects coordinator with project no 2019/067.

The sample size was calculated with G*Power 3.1.9.3. Since there has been no study in the literature comparing TOETVA and COT regarding the inflammatory response related to the severity of the surgical stress, the sample size was found as a total of 34 patients (17 for each group) considering the alpha margin of error as 0.05, power (1-Beta): 0.80, effect size: 1, N1/N2 = 1/1 for calculating the sample size. The sample size was decided as 40 patients with 20 per group.

Inclusion criteria

Patients aged 18–65 years with benign thyroid disease; with fine needle aspiration biopsy (FNAB) results of Bethesda III, IV or Bethesda V, VI (below 1 cm nodule); thyroid volume less than 50 cm³; nodule diameter less than 4 cm; female gender without a previous neck, chin, and/or oral surgery; without vocal cord paralysis (VCP) preoperatively; clinically euthyroid and laboratory results in the euthyroid state; and who agreed to participate in the study were enrolled in the study. Female gender was preferred because male patients may have more difficult passage from the chin to the neck due to the more robust tissue. Male gender's thyroid cartilage is larger and protruding, preventing the endoscopic vision and manipulation of the instruments, which might prolong the operation time and affect the severity of traumatic injury.

Exclusion criteria

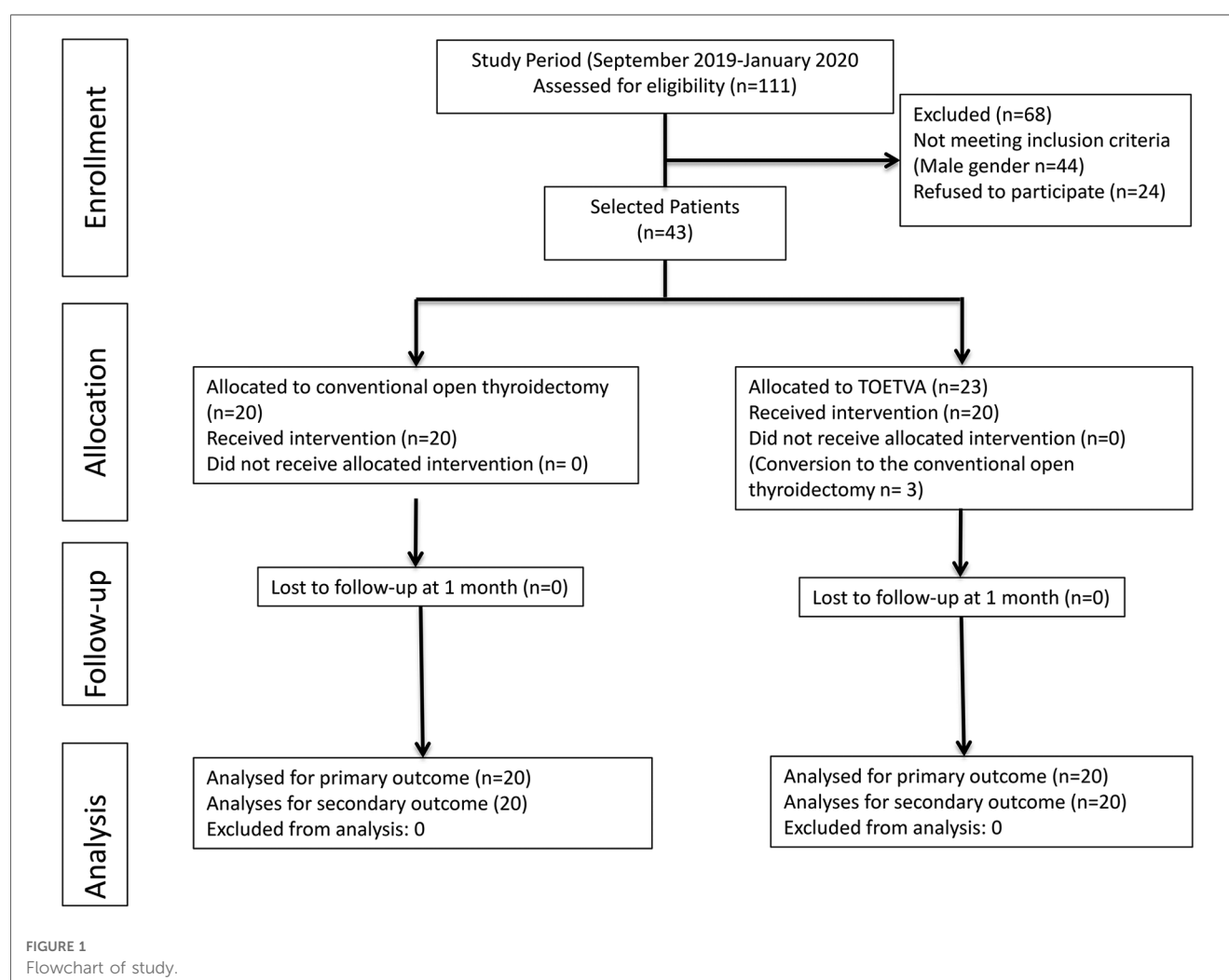
Patients with an FNAB result of Bethesda V, VI over 1 cm nodule in size, planning of central and/or lateral neck dissection due to thyroid cancer, thyroid volume greater than 50 cm³,

secondary intervention cases, patients with accompanying hyperparathyroidism, patients with preoperative VCP, and patients with ASA score of III and IV were not included. Patients with conversion from TOETVA to the conventional method intraoperatively were also excluded from the study.

Creating groups

The study enrolled two groups including 20 patients in each: COT group (Group 1) and TOETVA group (Group 2). All patients who agreed to participate in the study were informed about both surgical techniques and complications, and written consent was obtained. Patients took part in Group 1 or Group 2 according to their own preferences.

As presented in the flowchart (Figure 1), during this period, 111 patients underwent thyroidectomy. Patients who did not comply with the study criteria were excluded from the study. About 67 female patients were selected out of those who were eligible for the study. Of these patients, 24 did not agree to participate in the study. Three patients whose surgical procedures were converted to open surgery were excluded from the study, and a total of 40 patients were included in the study.



Surgical technique

All surgeries were performed by an experienced endocrine surgeon (MU).

Intraoperative neuromonitorization technique

The NIM 3.0 Nerve Monitoring System (Medtronic Xomed, Jacksonville, FL, USA) including endotracheal surface electrodes was used to check the nerve intraoperatively. General anesthesia was administered to each patient with a low-dose short-acting neuromuscular blockade (rocuronium 0.3 mg/kg) and intubated with a Medtronic Xomed Nerve Integrity Monitor Standard Reinforced Electromyography Endotracheal Tube (size 6.0, 7.0, or 8.0). Standard intraoperative neural monitoring (IONM) technique was performed as a four-step procedure (V1, R1, R2, and V2). The IONM setup, applications, and data interpretation were applied in compliance with International Neural Monitoring Guidelines (13, 14). Vocal cord examination was performed preoperatively and between postoperative 24th–48th hours for all patients.

Conventional open thyroidectomy

After neck extension with a thyroid pillow and patient positioning, thyroidectomy and/or central neck dissection was performed using a 4 to 6 cm collar transverse incision. Subplatysmal flap dissection was limited to the sternal notch inferiorly and the thyroid cartilage superiorly, and through the midline of the strap muscles, the thyroid gland was reached. After receiving a positive signal from the vagus nerve, upper pole dissection was performed under the guidance of IONM. Identification and monitoring of recurrent laryngeal nerves (RLNs) and external branch of the superior laryngeal nerves (EBSLNs) were carried out systematically, as described previously (15, 16). The upper pole vessels were divided on the thyroid capsule with Ultracision® or bipolar cautery. With lateral approach, RLN was identified in the region where it crosses the inferior thyroid artery (ITA). Then, RLN was exposed till its laryngeal entry under the cricopharyngeal muscle (CPM). Preserving parathyroids, ITA branches were divided from the capsule. R2 and V2 signals were obtained after bleeding control. Surgicel® was placed in the surgical field and strap muscles were reapproximated with 3/0 polyglactin. The subcutaneous tissue was sutured separately with polyglactin. The skin was reapproximated subcutaneously with polyglactin.

Transoral endoscopic thyroidectomy vestibular approach

All patients received preoperative chlorhexidine mouthwash and preoperative intravenous amoxicillin/clavulanic acid was administered for prophylaxis. Orotracheal intubation was performed. A slight extension posture was given to the neck with a

pillow placed under the shoulder, and the patients were placed in 15° in the Trendelenburg position. Skin and oral cavity were wiped with povidone iodine. A central 1.5–2 cm transverse incision was performed in the middle of the distance between the first vermilion inner edge and the inferior labial frenulum in the oral vestibule. Through the peripheral fibers of the submucosa and orbicularis oris muscle, the jaw tip was reached with monopolar electrocautery between the two mentalis muscles deep in the subdermal layer. Through this incision, 50 cc of 1/500,000 adrenaline-saline solution was applied to the anterior neck with a Veress needle. A surgical field was created through this incision toward the thyroid cartilage via dissection with Kelly forceps. The surgical field was formed by blunt dissection using a blunt-type tunnel probe in the subplatysmal area, limited to anterior edges of sternocleidomastoid muscles (SCMs) laterally and to the sternal notch inferiorly. A 10-mm blunt-tipped port was entered through the central incision to insert the 30° camera and operation was performed under 6 mmHg CO₂ pressure with a 15 L/min CO₂ flow rate. In addition, with three or four silk sutures placed on the front neck, the skin is mechanically hung and an optimal working area is provided. Two vertical 5 mm incisions were made at the level of canine tooth and on the edges of vermilion at both sides, and two working ports were placed parallel to the 10 mm port. The subplatysmal workspace was opened completely with hook cautery and harmonic scalpel. Strap muscles were opened in the midline and dissected over the thyroid gland. The strap muscles were retracted by a transcutaneous 2/0 silk sutures. Thyroid isthmus is divided. The upper pole was dissected, the EBSLN was checked with the monitoring probe, and the thyroid vessels were divided from the thyroid capsule with Ultracision. The superior parathyroid gland was identified and dissected carefully. The RLN was identified at the laryngeal entry and mapped proximally. The Berry fibers were divided on the thyroid capsule to protect the RLN. The inferior parathyroid gland was identified and protected. The thyroid gland was separated from the trachea and placed in the endobag inserted through the 10 mm port and then it was extracted. The same surgical procedures were applied to the opposite lobe in total thyroidectomy. Following bleeding control, RLN (R2) and vagus (V2) signals were obtained using the IONM probe and recorded. A Surgicel was placed into the surgical field. The SCMs were approximated with 3/0 polyglactin sutures. No drain was used in any patient. Intraoral incisions were sutured with 4/0 polyglactin. A 24-h pressure dressing was applied over the chin.

Inflammatory response

Preoperative, postoperative second hour, first day, and second day CRP (normal range: <5 mg/L), WBC (normal range: 4.5–10.5 × 10⁹/L), and IL-6 (normal range: <7 ng/L) levels were measured to evaluate the inflammatory response in all patients. To measure IL-6, blood samples were collected from patients, centrifuged, and stored at –80°C. After all the serums were collected, they were evaluated using the Human IL-6 ELISA kit. To evaluate postoperative hypoparathyroidism, postoperative first day calcium, phosphorus, and parathormone values were

checked. Hypocalcemic patients were controlled weekly and evaluated both clinically and with laboratory values.

Postoperative pain and analgesia

Routinely, in terms of pain palliation, all patients received $4 \times 1,500$ mg paracetamol intravenously and $3 \times 1,100$ mg tramadol HCL on the first day; and $3 \times 1,500$ mg paracetamol intravenously on the second day in the postoperative period.

Pain intensity of the patients was evaluated with the visual analog scale (VAS) score (0–10) on the second and 12th hour, first, and second days postoperatively. Lower lip, lower chin, and anterior neck area pain were evaluated separately using the VAS scale. VAS scores were determined by patients marking the intensity of pain on the ruler, demonstrating 0 for the absence of pain and 10 for the most severe pain sensation (17). No patient was given extra analgesic.

Patient satisfaction was evaluated on postoperative 15th and 30th days in both groups. Patients were asked to evaluate and score the operation in general and in terms of cosmesis (1: bad and 4: very good).

Vocal cord examination with fiber optic laryngoscopy was performed to all patients in the preoperative period and within the first two days postoperatively by an independent otorhinolaryngologist. Control examinations were planned for

patients with VCP at the 15th day, 1st, 2nd, 4th, and 6th months postoperatively.

Intraoperative and postoperative complications of patients were recorded.

Statistical analysis

Data analysis was performed with IBM SPSS Statistics Version 25. Non-parametric tests were preferred in all comparisons, since the number of cases in groups was less than 30. Mann–Whitney U test, Chi-squared test, Wilcoxon signed-rank test, and McNemar tests were used in comparisons between groups. $P < 0.05$ was considered statistically significant. Subgroup analyses of each groups (Group 1 and Group 2) were calculated with Kruskal–Wallis one-way ANOVA test, pair-wise comparisons were calculated with independent-samples Kruskal–Wallis test, significance values have been adjusted by the Bonferroni correction for multiple tests.

Results

All the patients in the present study were female and the mean age was significantly higher in the COT than in the TOETVA group (50.3 ± 6.2 years vs. 42.9 ± 9.7 years, respectively, $p = 0.008$) (Table 1). There was no significant difference between the two

TABLE 1 General characteristics of two groups, duration of surgery and hospital stay.

		TOETVA	COT	<i>p</i>
Age	Mean $\pm$ SD Min–max	42.9 ± 9.7 18–57	50.3 ± 6.2 34–59	0.008
BMI	Mean $\pm$ SD Min–max	26.6 ± 4.6 20.2–36.6	27.9 ± 4.2 19.7–37.2	0.267
Preoperative diagnosis (<i>n</i>)				
	MNG	9	13	0.349
	Basedow Graves	5	2	
	Bethesda III and IV	6	5	
Postoperative diagnosis (<i>n</i>)				
	Adenomatous Hyperplasia	13	13	0.856
	Lymphocytic Thyroiditis	3	2	
	Malignity	4	5	
Thyroid volume (cm ³)	Mean $\pm$ SD Min–max	17.8 ± 10.6 2.9–46.9	24.6 ± 12.0 5.2–49.5	0.479
Largest nodule diameter (mm)	Mean $\pm$ SD Min–max	18.8 ± 12.2 6–46	27.4 ± 16.2 10–50	0.116
Surgery type				0.736
	Lobectomy	7	6	
	Total thyroidectomy	13	14	
Operated lobe				
	Right	19	19	0.889
	Left	14	15	
Operation time (min)				
Total thyroidectomy	Mean $\pm$ SD Min–max	195 ± 51.4 105–300	99.6 ± 29.8 60–140	<0.001
Lobectomy	Mean $\pm$ SD Min–max	112.9 ± 34 80–170	49.2 ± 17.7 30–70	0.003
Duration of hospital stay (days)		2.5 ± 1.8 2–10	2 ± 0 2–2	0.076

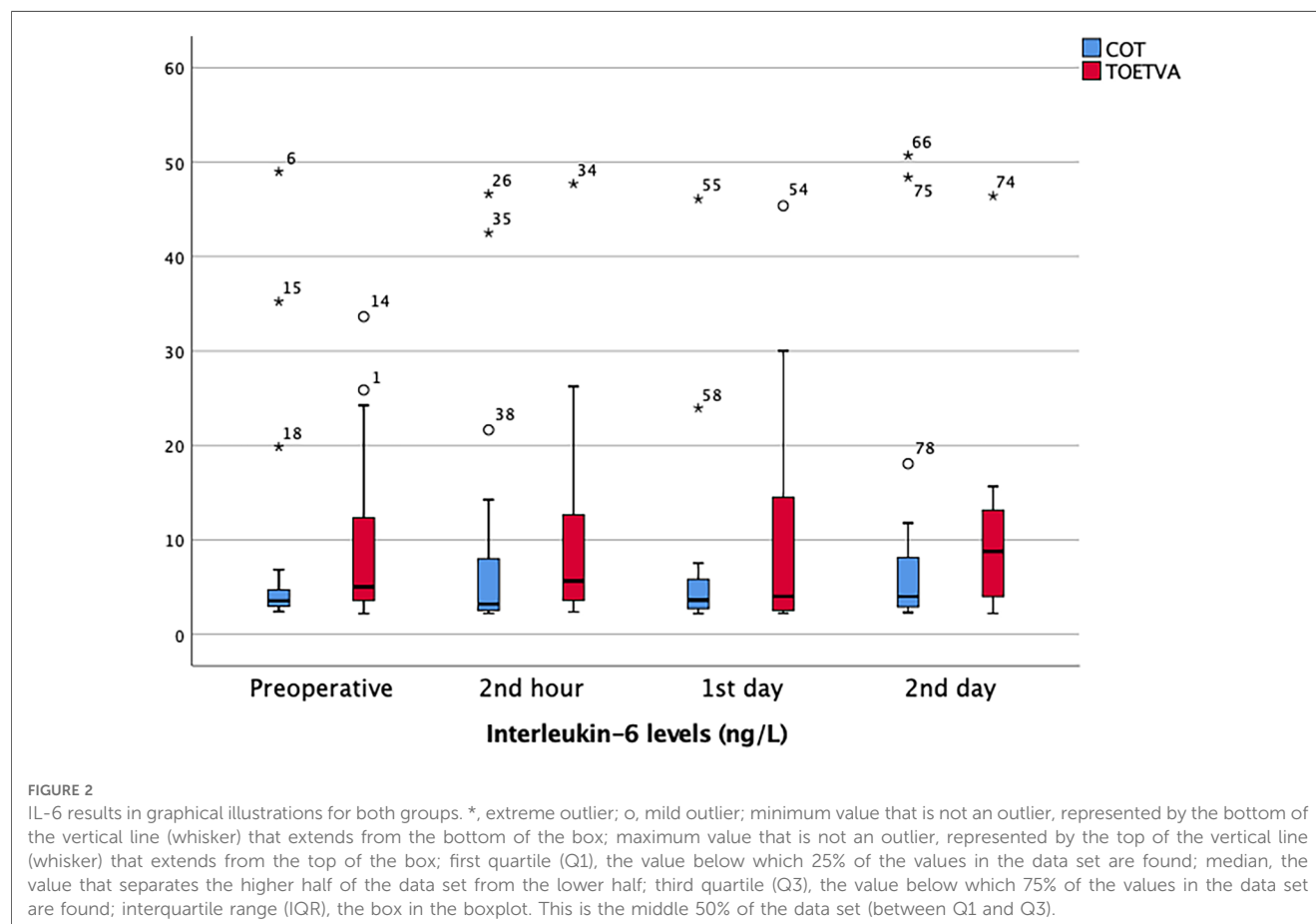
Min, minimum; Max, maximum; SD, standard deviation; *n*, number; MNG, multinodular goiter.

TABLE 2 IL-6, CRP, and WBC levels.

	Time	TOETVA	COT	<i>p</i>
IL-6 (ng/L) Mean ± SD Min–max	Preoperative	8.3 ± 12.4 2.4–49	9.5 ± 9.2 2.18–33.64	0.168
	Second hour	9.2 ± 13.1 2.2–46.6	9.9 ± 10.8 2.4–47.7	0.091
	First day	7 ± 10.3 2.2–46.1	9.4 ± 11.2 2.2–45.4	0.607
	Second day	9.8 ± 14.1 2.3–50.7	10.2 ± 9.6 2.2–46.4	0.130
WBC (10 ⁹ /L) Mean ± SD Min–max	Preoperative	6.8 ± 2 ^a 3.8–11.6	7.2 ± 1.6 ^e 4.1–10.6	0.425
	Second hour	13.1 ± 4.8 ^b 4.4–21.6	10.2 ± 4 ^f 5.2–19.3	0.044
	First day	10.7 ± 2.5 ^c 6.2–14.8	10 ± 3 ^g 5.4–15.3	0.449
	Second day	8.8 ± 1.9 ^d 4.8–12.9	9.2 ± 2.7 ^h 4.2–14.6	0.607
CRP (mg/L) Mean ± SD Min–max	Preoperative	2.9 ± 2.5 ^{a1} 0.4–9.4	3.2 ± 4 ^{e1} 0.5–18	0.935
	Second hour	4.1 ± 5 ^{b1} 0.6–21.6	4.1 ± 4.9 ^{f1} 0.6–18.1	0.957
	First day	54.3 ± 36 ^{c1} 6.1–157.6	32.6 ± 37.9 ^{g1} 5.7–146.3	0.002
	Second day	79.4 ± 54.6 ^{d1} 21.1–199.4	44.1 ± 39.9 ^{h1} 12.7–181.3	0.005

Min, minimum; Max, maximum; SD, standard deviation.

Group 1 WBC ($p < 0.001$, Kruskal–Wallis test) adjusted by Bonferroni correction for multiple tests: a vs. b: $p < 0.001$, a vs. c: $p < 0.001$, b vs. d: $p = 0.022$; group 2 WBC ($p = 0.011$, Kruskal–Wallis test) adjusted by Bonferroni correction for multiple tests: e vs. f: $p = 0.044$, e vs. g: $p = 0.017$; group 1 CRP ($p < 0.001$, Kruskal–Wallis test) adjusted by Bonferroni correction for multiple tests: a1 vs. c1: $p < 0.001$, a1 vs. d1: $p < 0.001$, b1 vs. c1: $p < 0.001$, b1 vs. d1: $p < 0.001$; group 2 CRP ($p < 0.001$, Kruskal–Wallis test) adjusted by Bonferroni correction for multiple tests: e1 vs. g1: $p < 0.001$, e1 vs. h1: $p < 0.001$, f1 vs. g1: $p < 0.001$, f1 vs. h1: $p < 0.001$.



groups in terms of height, weight, body mass index (BMI), thyroid volume, largest nodule diameter, type of surgery, number of operated lobes, and duration of hospital stay (Table 1).

The operation time in the TOETVA group was significantly longer in patients undergoing both lobectomy (113 ± 34 vs. 49 min, $p = 0.003$) and total thyroidectomy (195 ± 51 vs. 100 ± 30 , $p < 0.001$) (Table 1).

Systemic inflammatory response (traumatic inflammatory response)

IL-6 (<7 ng/L): Preoperative, postoperative second hour, first, and second day IL-6 levels were similar, and no significant difference was found between the two groups (Table 2) (Figure 2).

WBC ($4.5\text{--}10.5 \times 10^9/\text{L}$): Preoperative WBC values were similar and postoperative second hour WBC value was significantly higher in the TOETVA group (13.1 ± 4.8 vs. 10.2 ± 4 , $p = 0.044$). There was no difference between the two groups regarding WBC values on postoperative day 1 and day 2 (Table 2) (Figure 3). In both groups (COT and TOETVA), WBC values at second hour ($p < 0.001$, $p = 0.044$, respectively) and day 1 ($p < 0.001$, $p = 0.017$, respectively) were significantly higher than preoperative WBC values. Day 2 values were

similar to preoperative values ($p = 0.147$, $p = 0.122$, respectively).

CRP (<5 mg/L): Preoperative and postoperative second hour CRP values were similar between the two groups. CRP values were significantly higher on the postoperative day 1 (54.3 ± 36 vs. 32.6 ± 37.9 , $p = 0.002$) and day 2 (79.4 ± 54.6 vs. 44.1 ± 39.9 , $p = 0.005$) in the TOETVA compared to the COT group (Table 2) (Figure 4). An increase in CRP over time was noted in both groups, and CRP values were higher in the TOETVA group. In COT, CRP values were found to be significantly higher on day 1 ($p < 0.001$, $p < 0.001$, respectively) and day 2 ($p < 0.001$, $p < 0.001$, respectively) compared to preoperative and postoperative second hour CRP values. Similarly, in the TOETVA group, day 1 ($p < 0.001$, $p < 0.001$, respectively) and day 2 CRP values ($p < 0.001$, $p < 0.001$, respectively) were significantly higher than those of preoperative and postoperative second hour.

Evaluation of postoperative pain

Lower lip

Lower lip VAS scores were significantly higher in the TOETVA than in the COT group at postoperative second hour ($p < 0.001$),

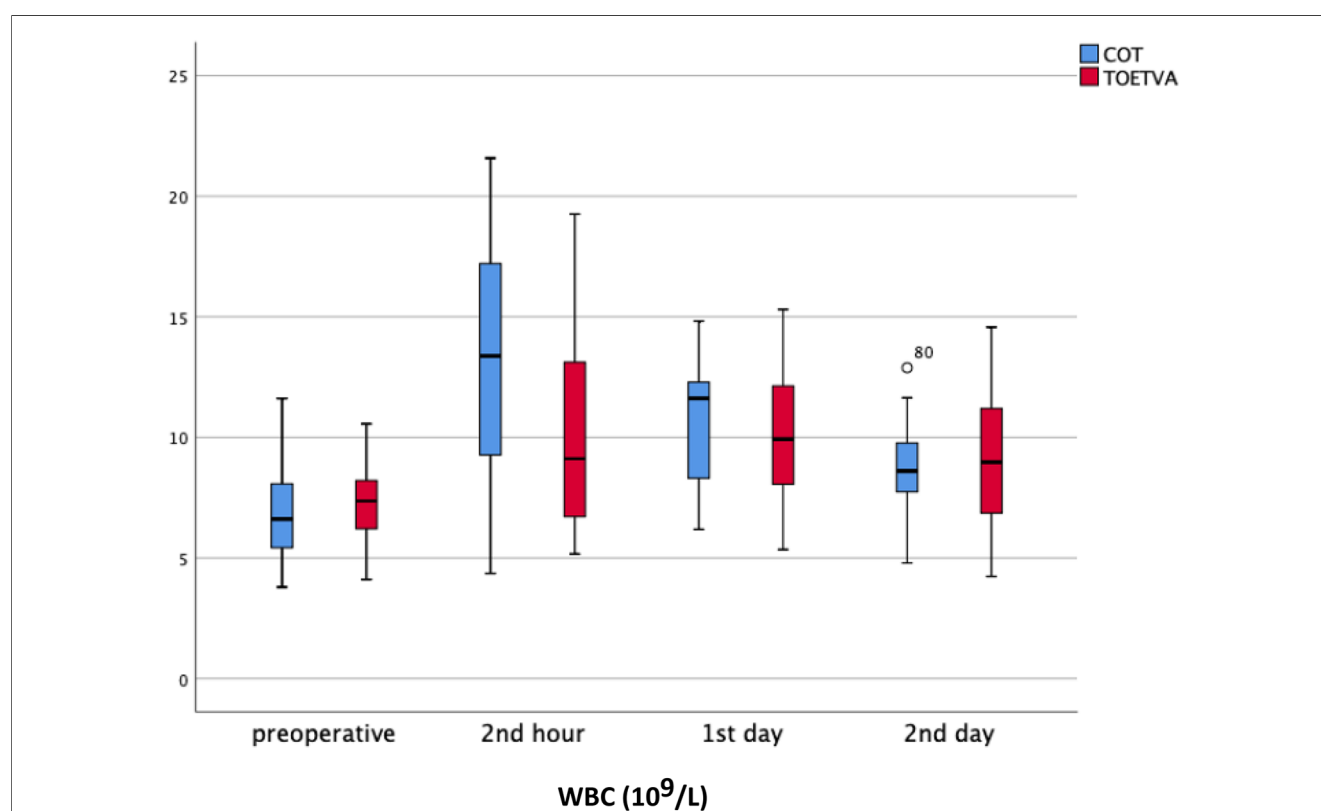
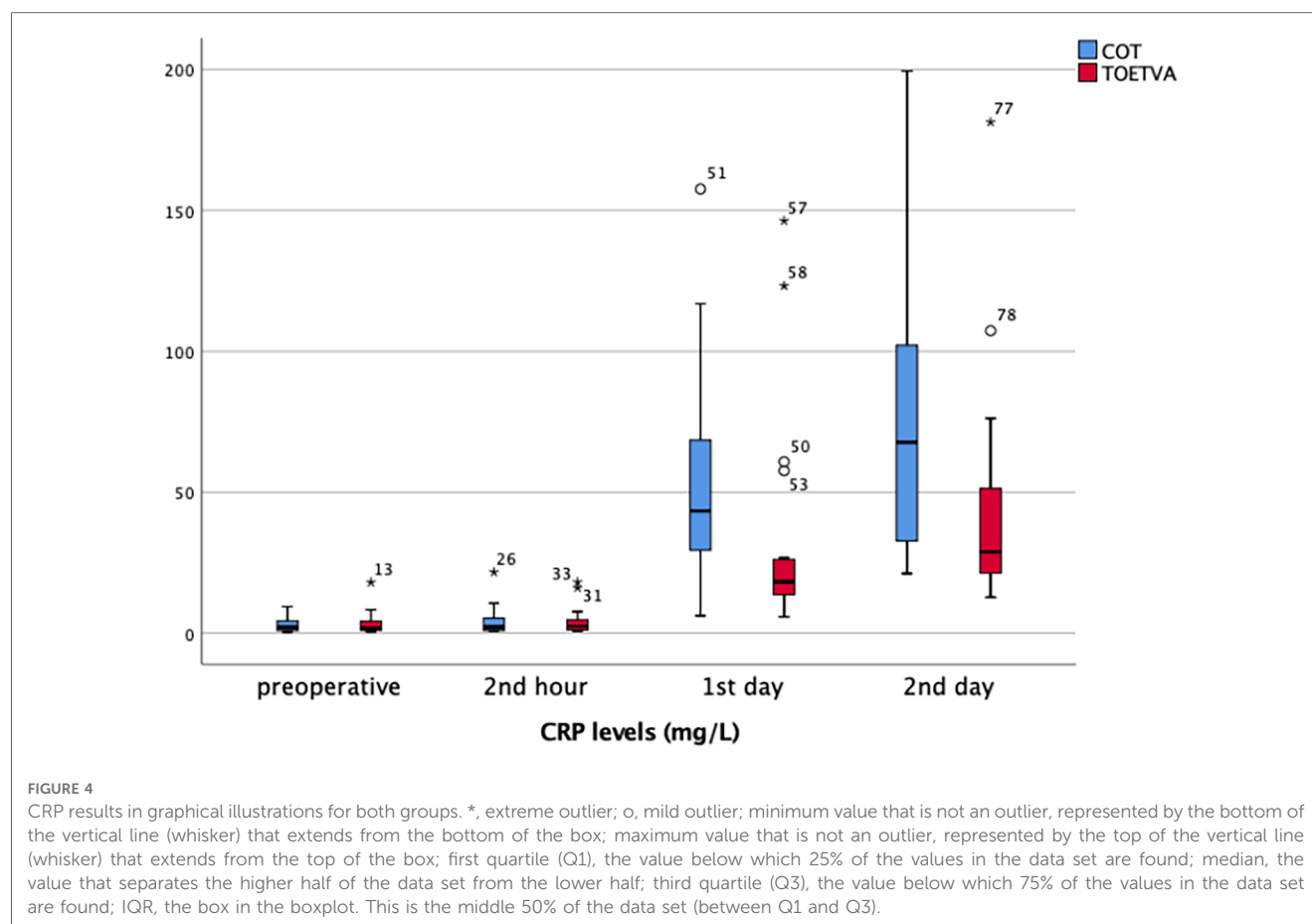


FIGURE 3

WBC results in graphical illustrations for both groups. o, mild outlier; minimum value that is not an outlier, represented by the bottom of the vertical line (whisker) that extends from the bottom of the box; maximum value that is not an outlier, represented by the top of the vertical line (whisker) that extends from the top of the box; first quartile (Q1), the value below which 25% of the values in the data set are found; median, the value that separates the higher half of the data set from the lower half; third quartile (Q3), the value below which 75% of the values in the data set are found; IQR, the box in the boxplot. This is the middle 50% of the data set (between Q1 and Q3).



12th hour ($p = 0.016$), and second day ($p = 0.030$). Although the lower lip VAS score was higher in the TOETVA on the postoperative first day, the difference was not statistically significant (1.7 ± 2.8 vs. 0.1 ± 0.3 , $p = 0.075$) (Table 3) (Figure 5).

Lower chin

Lower chin VAS pain score was significantly higher in the TOETVA compared to the COT group at the second hour ($p < 0.001$), 12th hour ($p < 0.001$), and on the first ($p < 0.001$), and second days ($p = 0.001$) (Table 3) (Figure 6).

Anterior neck VAS pain score

Neck VAS score was significantly higher in the TOETVA group at the postoperative second hour ($p = 0.025$). There was no significant difference regarding the VAS scores between two groups at postoperative 12th hour and on the first and second days (Table 3) (Figure 7). However, it is noteworthy that there was a significant decrease in pain over time in both the COT group and the TOETVA group ($p = 0.001$, $p < 0.001$, respectively).

Complications

In the TOETVA group, three (13%) patients were excluded because of conversion to open thyroidectomy. In the TOETVA group, three of 20 patients had a skin burn while making the

incision for the camera port. In the TOETVA group, loss of sensation on the lower chin or lower lip was detected in 10 patients (50%) in the early postoperative period and decreased over time. Loss of sensation on the chin and lower lip persisted on the 15th day in seven patients and on the 30th day in one patient (Table 4).

In the TOETVA group, one patient had tracheal perforation that was recognized preoperatively and repaired by primary suturing. Secondary pneumomediastinum and bilateral pneumothorax were observed postoperatively, and treated with a unilateral thorax tube. Wound infection was detected in the thyroid region of one patient on postoperative sixth day in the TOETVA group, and the collection was percutaneously drained by ultrasound guidance and treated with antibiotherapy. Transient RLN paralysis and hypoparathyroidism rates were similar between the two groups. No permanent RLN paralysis and hypoparathyroidism were detected (Table 4).

There was no significant difference between TOETVA and COT in terms of visual (cosmetic) satisfaction (Table 5). The cosmetic satisfaction score was significantly higher in both TOETVA and COT on the 30th day compared to the 15th day ($p = 0.003$, $p = 0.003$, respectively) (Table 5). There was no significant difference between TOETVA and COT in terms of general satisfaction. General satisfaction scores in both TOETVA and COT were significantly higher on the 30th day compared to the 15th day ($p = 0.001$, $p = 0.002$, respectively) (Table 5).

TABLE 3 Postoperative lower lip, lower chin and anterior neck pain VAS scores.

	Time	TOETVA	COT	<i>p</i>
Lower lip VAS score Mean ± SD Min–max	Postop second hour	3.9 ± 3.4 0–9	0.2 ± 0.9 0–4	<0.001
	Postop 12th hour	2.9 ± 3 0–8	0.7 ± 1.5 0–6	0.016
	Postop first day	1.7 ± 2.8 0–8	0.1 ± 0.3 0–1	0.075
	Postop second day	2 ± 3.2 0–8	0.2 ± 0.7 0–3	0.030
Lower chin VAS score Mean ± SD Min–max	Postop second hour	5.1 ± 3.4 0–9	0.7 ± 1.8 0–6	<0.001
	Postop 12th hour	4.6 ± 2.4 0–8	0.8 ± 1.6 0–6	<0.001
	Postop first day	4.2 ± 2.9 0–8	0 ± 0 0–6	<0.001
	Postop second day	3.5 ± 3.1 0–8	0.6 ± 2 0–8	0.001
Anterior neck VAS Score Mean ± SD Min–max	Postop second hour	7.7 ± 2.1 2–10	6 ± 2.7 0–10	0.025
	Postop 12th hour	6.8 ± 2.7 0–10	6.3 ± 2 0–9	0.150
	Postop first day	5 ± 3.4 0–10	4 ± 1.6 2–7	0.195
	Postop second day	3.9 ± 3.2 0–10	2.7 ± 1.9 0–8	0.299

Min, minimum; Max, maximum; SD, standard deviation; postop, postoperative. Group 1 anterior neck VAS ($p = 0.001$, Kruskal–Wallis test) adjusted by Bonferroni correction for multiple tests: a vs. d: $p = 0.001$, a vs. c: $p = 0.047$, b vs. d: $p = 0.023$; group 2 anterior neck VAS ($p < 0.001$, Kruskal–Wallis test) adjusted by Bonferroni correction for multiple tests: e vs. g: $p = 0.044$, e vs. h: $p < 0.001$, f vs. g: $p = 0.011$, f vs. h: $p < 0.001$.

Discussion

The application of TOETVA is becoming widespread and accepted as an alternative to traditional thyroidectomy, as a remote access and scarless method in selected cases (18). Although some studies have claimed that TOETVA is a minimally invasive method, discussions are still ongoing whether it is a true minimally invasive method compared to COT or not (9, 11, 19).

Cortisol, IL-6, WBC, and CRP values increase and peak due to SIR after all elective laparoscopic and open surgeries (10). The magnitude of operative injury and invasiveness of surgery after all elective surgeries are associated with only IL-6 and CRP concentrations. Unlike IL-6 and CRP, WBC value is variable, and its relationship with the magnitude of operative injury and invasiveness of the procedure is unclear (10). Therefore, Watt et al. reported that CRP and IL-6 may be used as markers for evaluating and monitoring the magnitude of SIR after elective operations (10).

To the best of our knowledge, the present study is the first prospective one comparing TOETVA with COT in terms of postoperative SIR. WBC, IL-6, and CRP values were monitored to evaluate SIR. In our study, no significant difference was found between preoperative and postoperative IL-6 levels between both groups. Although the postoperative second hour WBC value was significantly higher in the TOETVA group, similar results were obtained on the first and second postoperative days. CRP values

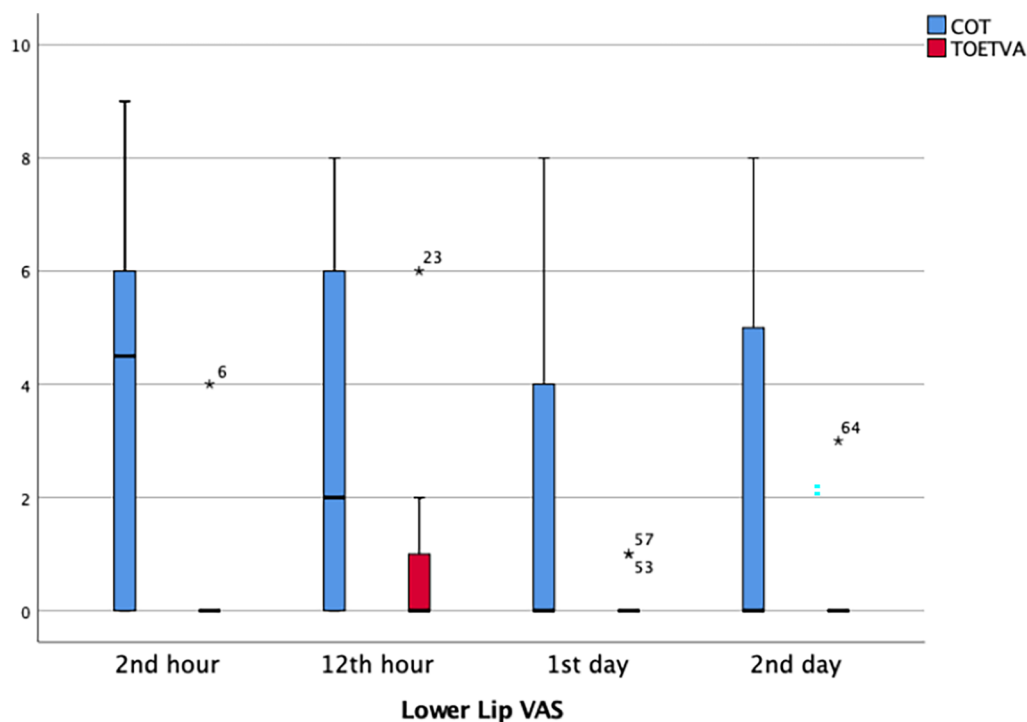


FIGURE 5

Lower Lip VAS score results in graphical illustrations for both groups. *, extreme outlier; minimum value that is not an outlier, represented by the bottom of the vertical line (whisker) that extends from the bottom of the box; maximum value that is not an outlier, represented by the top of the vertical line (whisker) that extends from the top of the box; first quartile (Q1), the value below which 25% of the values in the data set are found; median, the value that separates the higher half of the data set from the lower half; third quartile (Q3), the value below which 75% of the values in the data set are found; interquartile range (IQR), the box in the boxplot. This is the middle 50% of the data set (between Q1 and Q3).

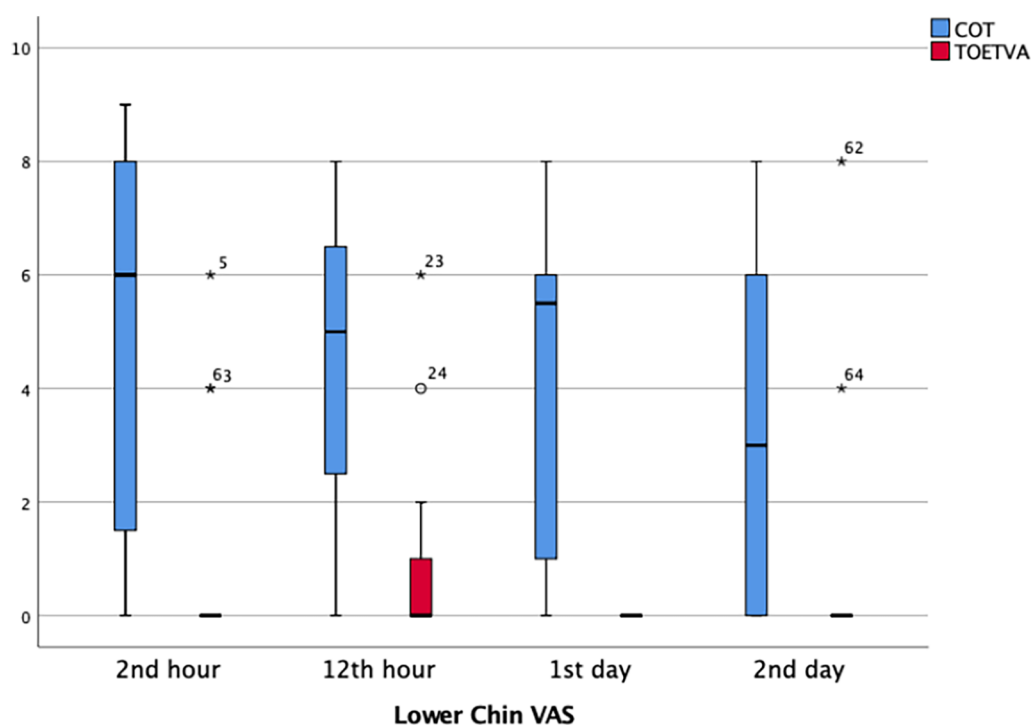


FIGURE 6

Lower chin VAS score results in graphical illustrations for both groups. *, extreme outlier; o, mild outlier; minimum value that is not an outlier, represented by the bottom of the vertical line (whisker) that extends from the bottom of the box; maximum value that is not an outlier, represented by the top of the vertical line (whisker) that extends from the top of the box; first quartile (Q1), the value below which 25% of the values in the data set are found; median, the value that separates the higher half of the data set from the lower half; third quartile (Q3), the value below which 75% of the values in the data set are found; IQR, the box in the boxplot. This is the middle 50% of the data set (between Q1 and Q3).

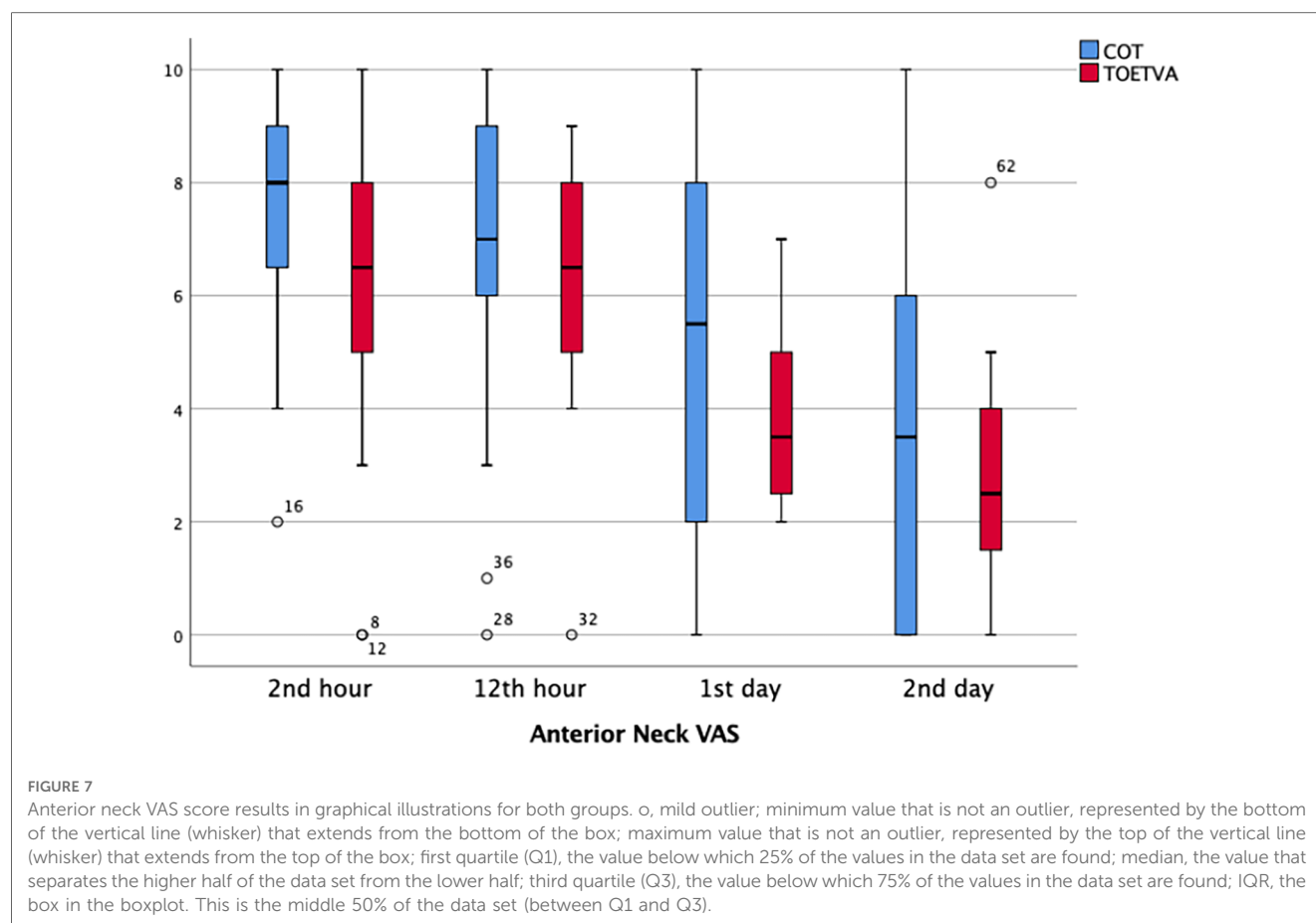
were found to be similar preoperatively and at postoperative second hour. At first and second days, although there was a significant increase of CRP in both of the groups, the rate of increase was found to be significantly higher in the TOETVA group. In our study, no drain was used in any patient and no patient required drainage due to seroma. According to our results, the TOETVA operation generates a stronger inflammatory response and is not a minimally invasive method compared to COT. This situation may be related to the fact that more flap dissection is required to reach the surgical site and longer operative time is needed in TOETVA compared to COT.

Sun et al. retrospectively evaluated TOETVA, endoscopic thyroidectomy via areola (ETA), and open conventional thyroidectomy in the treatment of papillary thyroid cancer in terms of SIR. The researchers found that the TOETVA had a higher postoperative CRP and WBC levels than that of the ETA group and the COT group. In addition, the operation time and drainage volume were found to be higher in both TOETVA and ETA groups compared to the COT group. They concluded that although TOETVA and ETA are thought to be more traumatic, these are effective and safe options for the treatment of papillary thyroid cancer (11). In a randomized study comparing the complete endoscopic thyroidectomy via transoral vestibular and areolar approaches, the VAS score on the postoperative first day was lower in the transoral group; however, VAS score on the postoperative third day, CRP, and WBC values were similar (12).

When evaluating the inflammatory response due to operative trauma, potential confounding factors such as age, obesity, comorbid disease, emergency presentation, inflammatory status, and postoperative complications that may affect SIR should also be considered (10). In the last meta-analysis, surgical site infection rate was found higher in TOETVA compared to that in open method (20).

In our study, it can be thought that the postoperative complications such as secondary pneumomediastinum and bilateral pneumothorax caused by intraoperative tracheal perforation in a patient in the TOETVA, and wound infection of another patient may affect the CRP values. When the inflammatory response via CRP is evaluated excluding these two patients, the result did not change, so the data of these patients were not excluded from the study. Although postoperative complications may affect SIR, CRP values on the postoperative second day were similarly increased in the group with and without complications, and CRP values on the postoperative second day were found to be similar (21, 22).

Minimally invasive surgery is generally associated with lower postoperative pain, especially in the abdomen and thorax, compared to open surgery. TOETVA may cause pain complaints in different regions, due to its dissection area, compared to open thyroidectomy. Therefore, regional assessment of pain scores in different regions such as anterior neck, posterior neck, lower lip, chin, and while brushing teeth may be more appropriate (22).



We also evaluated the pain symptom separately in the anterior neck region where the incision exists in open thyroidectomy and in the lower chin and lower lip which are the access areas of TOETVA. The same preoperative and postoperative analgesia protocols were applied to both groups of patients. As expected, the VAS score in the lower lip and chin was significantly higher in the TOETVA group compared to open thyroidectomy, and was progressively decreasing in both regions; this is associated with the incision sites and port entry areas. This expected situation is tolerable and has minimal clinical significance. Pain

in the neck region was highest at the second postoperative hour and progressively decreased in both groups. Although VAS scores in the TOETVA group was significantly higher only at the postoperative second hour, the difference was not significant in other comparisons. It is noteworthy that neck pain decreased significantly over time in both groups. In another recent study, VAS score was higher in the TOETVA group in the lower lip and chin, and in addition when brushing teeth in the early postoperative period. In the first 24 h postoperatively, contrary to our findings, they found the VAS score lower in the anterior neck and while swallowing in the TOETVA group. It was claimed that less pain was due to more pain receptors in the skin than in the mucosa and less pain receptors in the

TABLE 4 Postoperative complications of the two groups.

	TOETVA	COT	<i>p</i>
Hypoparathyroidism (<i>n</i> , %)	6 (30%)	5 (25%)	1
Vocal cord paralysis (Number of nerves)			1
Absent	30	31	
Present	3 (9.1%)	3 (8.8%)	
Loss of sensation on the chin			
Postop second day	10	0	<0.001
Postop 15th day	7	0	0.008
Postop first month	1	0	1
Skin burn	3	0	0.231
Wound infection	1	0	1
Tracheal perforation	1	0	1

n, number; postop, postoperative.

TABLE 5 Patient satisfaction.

		TOETVA	COT	
Cosmetic satisfaction Mean ± SD Min-max	15th day	3.1 ± 0.8 ^a 2-4	2.9 ± 0.7 ^c 2-4	0.385
	30th day	3.5 ± 0.7 ^b 2-4	3.3 ± 0.5 ^d 3-4	0.160
General satisfaction Mean ± SD Min-max	15th day	3.1 ± 1.1 ^e 1-5	3.7 ± 0.8 ^g 2-5	0.122
	30th day	3.8 ± 1 ^f 2-5	4.2 ± 0.7 ^h 3-5	0.312

Postop, postoperative.

a vs. b: *p* = 0.003, c vs. d: *p* = 0.003, e vs. f: *p* = 0.001, g vs. h: *p* = 0.002.

subplatysmal area in that study. In addition, it has been suggested that due to the different mobility characteristics of the incision sites, patients can better control pain by fixing the inferior vestibular region more easily in TOETVA. They attributed less pain in the posterior neck to less extension in TOETVA than in open surgery (23).

RLN paralysis, hypoparathyroidism, and other rare complications related to thyroidectomy were similar between the two groups. However, TOETVA has revealed new complications such as skin injuries and mental nerve injury. Although Anuwong et al. reported 0.7% transient mental nerve injury, this complication is not uncommon (24). In our study, there was numbness in the access site of the 10 mm port, on the chin or lower lip in the early period, and it decreased over time; it was present in seven patients on the 15th day and in only one patient on the 30th day. This may be related to the temporary loss of function in the sensorial branch of mental nerve branches due to compression at the entry of the midline port and the edema caused by the manipulation of the port during surgery. In a multicentric study involving four centers, numbness was detected in the total lower lip with a rate of 33.6% or of 38.5% in the lower chin, and the incidence ranged between 0% and 100% in different centers. Permanent loss of sensation was detected in only one patient (0.7%), and the mean healing time was 9.2 weeks for the lower lip and 8.1 weeks for the chin tip in that multicentric study (25). Permanent main mental nerve injury can be prevented by applying 5 mm port on both sides of vermillion edge and lateral to the canine tooth and 10 mm port on the middle of the lower lip (9).

Another complication of TOETVA technique is skin puncture and burn marks. In our study, three patients had a burn mark in the mentum developed while entering the camera port. Full-thickness perforations, abrasions, and burns that may develop on the skin can also be the result of hydrodissection with the Veress needle, during port entry or subplatysmal dissection with cautery, or due to energy devices used during thyroidectomy (26).

General and cosmetic patient satisfaction was similar on the 15th and 30th days. In both groups, general and cosmetic satisfaction on the 30th day was significantly higher than that on the 15th day. Surgery-related satisfaction increased over time. The fact that the satisfaction results of the two groups are similar suggests that the performed surgery meets the general and cosmetic expectations of each patient, as they decided on the type of surgery themselves.

The main limitation of the study was the lower mean age in the TOETVA group (42.9 ± 9.7 vs. 50.3 ± 6.2 ; $p = 0.008$), since it was non-randomized and the surgery type was preferred by the patient. This situation might be considered a limitation in terms of cosmetic evaluation. In addition, the positive and negative aspects of both methods were explained to the patients, and the groups were organized according to the patients' will in an unbiased manner. Another limitation is that the highest power value has been calculated as 0.623 for the CRP value in the *post-hoc* analysis, which might suggest that the sample size of this study can be considered relatively small. However, prospective studies with larger number of patients are needed.

Conclusion

In conclusion; the longer operative time, higher postoperative CRP level, and VAS score in the chin and lower lip in the TOETVA group suggest that the method is not a minimally invasive technique compared to COT. However, the presence of similar total complication rates and early postoperative general and esthetic satisfaction, which improves over time in both of the groups, suggest that the clinical effect of increased magnitude of SIR in TOETVA might be temporary and acceptable.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (Ethics committee date: 19/03/2019, number: 2313). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MÜ: Conceptualization, Data curation, Formal analysis, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. NA: Conceptualization, Methodology, Supervision, Writing – review & editing. ES: Data curation, Formal analysis, Methodology, Writing – original draft. MU: Conceptualization, Formal analysis, Investigation, Supervision, Writing – review & editing, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Intraoperative parathyroid hormone monitoring in parathyroidectomy for hyperparathyroidism: a protocol for a network meta-analysis of diagnostic test accuracy

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Intraoperative parathyroid hormone (iPTH) monitoring is standard-of-care in the surgical management of hyperparathyroidism. It involves real-time determination of circulating PTH levels to guide parathyroid gland excision. There exists several iPTH monitoring criteria, such as the Miami criteria, and a lack of standardization in the timing of post-parathyroid gland excision samples. We present a protocol of a systematic review and network meta-analysis of diagnostic test accuracy to identify the iPTH criteria and post-gland excision timepoint that best predicts surgical cure in hyperparathyroidism. The database search strategy will be developed in conjunction with a librarian specialist. We will perform a search of Medline (Ovid), EMBASE (Ovid), CINAHL, Cochrane Collaboration, and Web of Science from 1990–present. Studies will be eligible if they include adult patients diagnosed with hyperparathyroidism who undergo parathyroidectomy with iPTH monitoring. We will only include studies that report diagnostic test properties for iPTH criteria and/or post-excision sampling timepoints. All screening, full-text review, data extraction, and critical appraisal will be performed in duplicate. Critical appraisal will be performed using QUADAS-2 instrument. A descriptive analysis will present study and critical appraisal characteristics. We will perform evaluation of between-study heterogeneity using I^2 and Cochrane Q and where applicable, we will perform sensitivity analysis. Our network meta-analysis will include Bayesian hierarchical framework with random effects using multiple models. Ethics approval is not required. This proposed systematic review will utilize a novel Bayesian network meta-analysis model to help standardize iPTH monitoring in hyperparathyroidism, thereby optimizing patient outcomes and healthcare expenditures.

KEYWORDS

parathyroid, hyperparathyroidism, network meta-analysis, surgery, intraoperative parathyroid hormone (PTH) assay

Introduction

Hyperparathyroidism is characterized by the abnormal circulating levels of parathyroid hormone (PTH) and calcium that can lead to osteoporosis, renal calculi, and cognitive deficits (1). Primary hyperparathyroidism is often caused by a single hyperfunctioning parathyroid adenoma, but in 10%–15% of cases can be caused by double adenoma and/or parathyroid hyperplasia. Secondary and tertiary hyperparathyroidism, which are associated with chronic kidney disease are often secondary to parathyroid hyperplasia (2). In all cases, however, definitive cure requires surgical extirpation of the affected parathyroid gland(s). Advances in imaging continue to improve our ability to detect parathyroid lesions and therefore guide minimally invasive surgical approaches, but current imaging modalities remain inaccurate in detecting parathyroid hyperplasia (3, 4). Patients with discordant or negative imaging, in addition to those with suspected parathyroid hyperplasia, still often require bilateral neck exploration (5).

Intraoperative PTH (iPTH), which involves the real-time sampling of circulating PTH levels to guide parathyroidectomy, improves surgical outcomes and is standard-of-care for managing primary hyperparathyroidism (6, 7). Moreover, iPTH monitoring has high sensitivity in predicting surgical cure within renal hyperparathyroidism and may assist in identifying parathyroid carcinoma (8, 9). Several iPTH criteria exist to assist surgeons in standardizing changes in circulating parathyroid level during surgery, including the Miami criteria, which defines operative success as >50% decrease in iPTH from baseline value for all hyperfunctioning glands (10).

The primary goal of this systematic review and diagnostic test accuracy network meta-analysis will be to determine the optimal iPTH criteria and post-parathyroid gland excision sampling timepoint that best predict surgical cure in primary and renal hyperparathyroidism.

Methods

Protocol and registration

We will conduct a diagnostic test network meta-analysis to determine the iPTH criteria and post-parathyroid gland excision sampling timepoints most predictive of surgical cure. We registered the protocol with the Open Science Framework register of systematic reviews (OSF Registration; DOI: 10.17605/OSF.IO/4WEMJ). This protocol will be published under the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols (PRISMA-P) (11). Any notable protocol amendments will be reported and published alongside the final review, which will be reported in accordance with the PRISMA statement (12).

Study eligibility criteria

Population

We will include studies that investigate adult patients (≥ 18 years old) diagnosed with primary, secondary, and/or tertiary

hyperparathyroidism who have undergone primary or revision parathyroidectomy via traditional midline neck incision or minimally invasive approach. There will be no further restrictions on the patient population.

Comparator (index test)

Our index test is the iPTH assay using any validated laboratory instrument. We will be evaluating any of the published iPTH criteria (e.g., Miami, Vienna, Rome, or Halle criteria) and/or the post-parathyroid gland excision sampling time points (e.g., 5-, 10-, 15-, 20-, and 25-min post-parathyroid gland ligation).

Reference standard

Our reference standard will be surgical cure following parathyroidectomy. We will define surgical cure as the resolution of hyperparathyroidism (i.e., resolution of hypercalcemia and/or hyperparathyroidism) within 3–6 months of parathyroidectomy.

Outcome

Our primary outcome will be centred around diagnostic test properties for all index tests as compared to the reference standard (e.g., pooled sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios). We will also determine diagnostic odds ratio, post-test probabilities, and superiority index.

Study designs

We will consider studies eligible if they are randomized or non-randomized trials, cross-sectional, case-control, cohort studies, or case series with more than five patients. All studies must report study outcomes in a way that permits analysis of diagnostic test properties. There will be no restrictions on length of follow-up for longitudinal studies.

Language

Google Translate may be utilized for eligible articles published in non-English languages. This software, however, may not be appropriate for all languages, and so translators may be considered depending on the number of articles retrieved, in addition to the time and costs associated with each translation.

Study exclusions

We will exclude articles that study pediatric populations and those that do not report data in manner that permits extraction of diagnostic test properties.

Information sources

We will perform a database search of PubMed (Ovid), EMBASE (Ovid), Cochrane Central Register of Controlled Trials, and Web of Science from January 1, 1990, to July 20, 2023. We will include studies published after 1990 since operative use of PTH was first described in 1991 (13). We will include human studies and will not place any language restrictions. We will also perform a search of reference lists of relevant systematic reviews, narrative reviews, and meta-analyses. We will not perform a search of the grey literature.

Search strategy

We will include relevant search terms and MeSH headlines. All terms will be exploded when appropriate. We did evaluate the quality of the search by determining its ability to capture three pre-selected candidate articles. We will include the following example terms: primary, secondary, renal, and tertiary hyperparathyroidism, intraoperative parathyroid hormone monitoring, and iPTH criteria (e.g., Miami, Rome, Halle, etc.). The Medline search algorithm is presented in [Appendix A](#).

Data management

A single reviewer will implement the search strategy with the help of librarian specialist and manage all citations. These combined citations will be exported into an article management software, Covidence (Melbourne, Australia), which removes duplicate articles. All extracted data will be managed in a piloted, customized Excel (Redmond, Washington, USA) spreadsheet.

Selection process

We will begin screening with a pilot screening aid to assess agreement between two reviewers using 10% of the articles. We will define good agreement as a two-reviewer consensus rate of 75% based on the inclusion and exclusion decisions of reviewers. If this pilot identifies discrepancies of >75%, then we will consider modifying the inclusion criteria and report these protocol deviations in the final review.

Data extraction

We will pilot a tailored extraction form by evaluating five articles to assess agreement between the reviewers. This extraction pilot will be evaluated by third reviewer and if deemed congruent between reviewers, then extraction for all full-text articles will proceed. We will evaluate study characteristics (e.g., name of first author, year of publication, country, gold standard, index tests), patient characteristics (e.g., gender, mean age, sample, method, cut-off level, type of disease, type of surgery, details of preoperative workup), and outcomes (i.e., true positive, false positive, true negative, false negative). All final extraction information will be performed by two reviewers and evaluated by a third reviewer. We have included the extraction form in [Appendix B](#).

Critical appraisal of individual articles (risk of bias)

Two reviewers will critically appraise the selected studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument (14). All disagreements will be solved by consensus review between the two reviewers and/or by a third reviewer. The methodological quality of individual studies will be reported in the final text and tables.

Data synthesis and analysis

Descriptive synthesis

A descriptive synthesis will present the characteristics of included studies, critical appraisal results, and descriptions of the main findings. Where applicable, the descriptive synthesis will be summarized according to each iPTH criteria and/or post-gland excision sampling timepoint.

Network meta-analysis

We will perform our network meta-analysis of diagnostic test accuracy using a Bayesian hierarchical framework with random effects using multiple models (15, 16). We will implement our analysis through a Markov Chain Monte Carlo simulation in WinBUGS, OpenBUGS, and R. Within our network diagram, the size of nodes will be proportional to the number of participants and the line connecting nodes will be proportional to the number of direct comparisons.

Pairwise meta-analysis

We will perform pairwise pooled analysis of diagnostic test characteristics, including sensitivity, specificity, likelihood ratios, diagnostic odds ratio, superiority index, and the area under the receiver operating curve. We will evaluate between-study heterogeneity using Cochran Q and the inconsistency index (whereby $I^2 = 25\%$, 50% , and 75% will be indicative of low, moderate, and high statistical heterogeneity, respectively).

Indirect comparison and ranking of competing index tests

Our reference standard will be the resolution of hyperparathyroidism, as measured by circulating intact PTH level and/or corrected calcium level, at 3–6 months following surgery. Against this reference standard, we will be comparing the relative diagnostic outcomes for each index test. There remains controversy in the ideal pooled statistic for which to compare diagnostic test (17). Diagnostic odds ratio has been used to rank diagnostic tests, but its utility is hampered by its inability to weigh sensitivity and specificity independently and its lack of clinical applicability (18). An alternative statistic for ranking is the superiority index, which applies greater weight to index tests that perform well with both diagnostic test measures and lesser weight to those tests that perform well in one measure but poorly in another or perform poorly in both (19). Subgroup analysis may be challenging in the context of the chosen Bayesian network, but we will plan to perform sensitivity analyses, where applicable.

Publication bias analysis

If there are at least ten studies of the index test are included in the meta-analysis, then we will perform a Deeks' test of asymmetry and funnel plot analysis to evaluate for publication bias (20).

Results reporting and presentation

We will report findings within the final publication in accordance with the PRISMA statement for diagnostic test accuracy meta-analysis (PRISMA-DTA) (21). A PRISMA flow diagram will be used for reporting the screening and article selection process, including the number of citations at each stage and the reasons for exclusion (i.e., full-text stage only). The discussion will include a summary of the major findings, the methodological limitations, and the application of these findings to clinical practice. The findings will be published in a peer-reviewed scientific journal and presented at national and/or international meetings. The published findings from the review will be disseminated to existing endocrine and otolaryngology-head and neck surgery networks.

Discussion

This proposed meta-analysis has been registered in OSF and this protocol was developed to adhere to the PRISMA-P guidelines. Our proposed study will utilize pooled network analyses to determine the iPTH protocol and post-gland excision sampling timepoints most predictive of surgical cure in hyperparathyroidism. A network meta-analytic approach will permit direct and indirect comparisons and will facilitate ranking of iPTH criteria and, where applicable, post-excision sampling timepoints. These results will help to standardize the application of iPTH assays, optimize the use of these assays, and streamline healthcare expenditures in the management of hyperparathyroidism. Standardization of iPTH protocols may facilitate application in surgery for atypical parathyroid tumours and parathyroid carcinoma (22). In terms of possible final study limitations, there is the potential for inconsistent quality and selection bias in the reporting of included observational studies. We will employ a novel Bayesian statistical model to perform this network meta-analysis and provide a ranking of multiple diagnostic tests. Though hierarchical Bayesian models have been suggested for network meta-analysis, methodological challenges remain and so, development of our model will facilitate reproduction in future studies (23).

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Ethics statement

This study is exempt from institutional research board approval.

Author contributions

PS: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. KU: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. SY: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. MB: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. MG: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. MA: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. JY: Conceptualization, Writing – original draft, Writing – review & editing. Resources. HZ: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Medline (Ovid) search strategy.

Search terms	No. citations
1. exp hyperparathyroidism.sh	13,671
2. exp hyperparathyroidism, primary.sh	3,842
3. exp hyperparathyroidism, secondary.sh	5,890
4. exp parathyroid hormone.sh	30,003
5. exp parathyroid neoplasms.sh	8,487
6. exp multiple endocrine neoplasia.sh	2,185
7. exp multiple endocrine neoplasia, type 1.sh	2,004
8. exp multiple endocrine neoplasia, type 2a.sh	1,421
9. exp hypoparathyroidism.sh	4,999
10. hyperparathyroid*.tw. or primary hyperparathyroid*.tw. or secondary hyperparathyroid*.tw. or tertiary hyperparathyroid*.tw. or parathyroid adenoma*.tw. or parathyroid hyperplas*.tw. or parathyroid multi-gland.tw. or (MEN 2 or multiple endocrine neoplasia type 2 or MEN type 2 or multiple endocrine neoplasia 2).tw. or (MEN 2a or multiple endocrine neoplasia type 2a or MEN type 2a or multiple endocrine neoplasia 2a).tw. or (MEN 1 or multiple endocrine neoplasia type 1 or MEN type 1 or multiple endocrine neoplasia 1).tw.	34,650
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	63,808
12. limit 11 to (humans and yr = "1990 -Current")	36,345
13. (Charleston criteria or Charleston protocol or (Vienna criteria or Vienna protocol) or (Rotterdam criteria or Rotterdam protocol) or parathyroid hormone monitor* or intraop* parathyroid hormone or intraop* PTH or pth monitor* or ioPTH or iPTH or Miami criteria or (Mayo criteria or Mayo protocol) or (Halle criteria or Halle protocol) or (Rome criteria or Rome protocol)).tw.	5,167
14. limited 13 to (humans and yr = "1990 -Current")	3,989
15. 12 and 14	2,351

Appendix B. Data extraction form.

Study characteristics	
Study number	
First Author	
Year of publication	
Journal	
Location of study	
Study design	
Single or multi-centre	
Tertiary care centre (Y/N/NR)	
Patient characteristics	
Diagnosis (1 = PHPT, 2 = SHPT, 3 = THPT)	
No. patients enrolled	
No. patients analyzed	
No females (%)	
Relevant past medical history	
Length of follow up period	
Preoperative imaging	
Preoperative imaging performed (Y/N)	
Type of preoperative imaging (e.g., NM, US, NM + US, CT, None)	
Concordance between preoperative imaging modalities (Y/N) AND/OR preop localizing CT scan (Y/N)	
Preoperative imaging results	
Preoperative bloodwork	
Preoperative Ca (nadir or most recent value)	
Preoperative Cr (nadir or most recent value)	
Preoperative PTH (nadir or most recent value)	
Surgical details	
Primary vs. revision surgery	
Surgery technique (midline neck incision, video-assisted, minimally invasive)	
Central lab vs. point of care test for iPTH	
Central vs. peripheral blood sampling	
Baseline iPTH (pre-incision)	
Baseline iPTH (pre-ligation)	

Reference standard			
Index test (iPTH criteria)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (iPTH criteria)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (iPTH criteria)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (iPTH criteria)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (iPTH criteria)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (iPTH criteria)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (Post-excision timepoint)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (Post-excision timepoint)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (Post-excision timepoint)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			
Reference standard			
Index test (Post-excision timepoint)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			

Reference standard			
Index test (Post-excision timepoint)	Reference standard +	Reference standard –	Total
Name:			
Index test +	TP	FP	
Index test –	FN	TN	
Total			

TP, true positive; FP, false positive; FN, false negative; TN, true negative.



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Application of carbon nanoparticles in endoscopic thyroid cancer surgery: a systematic review and meta-analysis

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Background: There has been a substantial increase in incidence of thyroid cancer globally over the past three decades, emphasizing the necessity for efficient surgical management. Surgical intervention requires meticulous lymphatic dissection; however, it is challenging to both accurately identify lymph nodes and preserve the surrounding structures. We investigated the role of carbon nanoparticles in endoscopic thyroid cancer surgery to improve surgical effects and reduce postoperative complications.

Methods: Chinese and English literature databases from inception to May 2023 were searched based on inclusion criteria, and data were extracted independently by two investigators. STATA software was used for data analysis.

Results: A comprehensive systematic review and meta-analysis were conducted with 13 publications (9 randomized and 4 non-randomized controlled trials). The results demonstrated that the application of carbon nanoparticles in thyroid surgery led to an increase in the number of retrieved lymph nodes and identification of metastatic lymph nodes. Furthermore, it considerably reduced the rate of improper parathyroidectomy and the incidence of postoperative hypocalcemia.

Conclusion: The application of carbon nanoparticles can effectively improve the effects of surgical treatment, can enhance the identification of intraoperative lymph nodes, reduce postoperative complications, and protect the integrity and function of the parathyroid gland.

Systematic Review Registration: www.crd.york.ac.uk/PROSPERO, identifier, CRD42023420504.

KEYWORDS

carbon nanoparticles, endoscopy, meta-analysis, systematic review, thyroid cancer

Abbreviations

CI, confidence interval; NRCT, non-randomized controlled trials; OR, odds ratio; RCT, randomized controlled trial; WMD, weighted mean difference.

1 Introduction

Over the past three decades, the global incidence of thyroid cancer has increased by 240% (1, 2), making it one of the most prevalent endocrine tumors (1). While most thyroid cancers are less aggressive, with a 90% chance of a 10-year survival rate (3), the risk of lymph node metastasis exists even in early-stage thyroid cancer. Between 20% and 90% of individuals undergoing therapy for thyroid carcinoma develop cervical lymph node metastases (4). Cervical lymph node metastasis is an important factor affecting the outcome of papillary thyroid cancer and is also a potential risk factor for disease recurrence (5). Therefore, thorough intraoperative lymphatic dissection plays a crucial role in the outcome and prognosis of the disease.

The continuous development of endoscopy technology has led to the widespread utilization of minimally invasive endoscopic surgery, greatly contributing to thyroid cancer management. Owing to the increasing prevalence of young patients seeking to improve cosmetic outcomes without visible scarring, endoscopic surgery has emerged as the optimal choice considering both treatment efficacy and aesthetic results. Thyroid cancer surgery entails a meticulous dissection of the affected lymph nodes while preserving the adjacent structures, such as nerves and blood vessels; thus, precise identification of lymph nodes is a prerequisite for this. Previously, the surgeon's expertise was required to accurately identify the tissues of lymph and non-lymph nodes, which made it difficult to provide consistent and reliable results. Moreover, considerable anatomical variations in the tissue surrounding the thyroid gland increase the risk of damaging the parathyroid gland and recurrent laryngeal nerve, leading to post-surgical complications such as hypocalcemia, hoarseness, and dysphagia (6). The use of carbon nanoparticle tracers in thyroid cancer endoscopic surgeries is associated with substantial improvements in accurate tumor diagnosis and resection, while reducing postoperative complications.

Carbon nanoparticles are specially treated smooth spherical particles with a diameter of 150 nm, possessing several advantages such as precise targeting, ease of use, and stability (7). They enable enhanced visualization of the thyroid tissue and its associated lymph nodes, creating a distinct contrast with the surrounding tissues, thereby tracing lymph nodes and protecting the surrounding tissue structures. Accurate identification of the lymph node and thyroid structure in the drainage area and increased lymph node clearance reduce postoperative complications caused by parathyroid miscut and laryngeal nerve injury. Thus, after being approved, carbon nanoparticle tracers have been widely employed in clinical thyroid cancer surgery.

Here, we aimed to systematically analyze and evaluate the effects of carbon nanoparticles in endoscopic thyroid cancer surgery and provide more conclusive evidence for the clinical application of carbon nanoparticle tracers.

2 Methods

The protocol of this systematic review (register number: CRD42023420504) was registered at PROSPERO (www.crd.york.ac.uk/PROSPERO).

2.1 Search strategy

Investigators searched PubMed, ClinicalTrials.gov, EMBASE, the Cochrane Database of Systematic Reviews, the China Biology Medicine Database, CNKI, the WANFANG database, and CqVIP, and compared all available literature on the use of carbon nanoparticles in endoscopic thyroid cancer surgery. The keywords “carbon nanoparticles, thyroid cancer, and endoscopy” were used to search literature in English, and those that met the criteria were included in this study.

Taking PubMed as an example, the specific search strategy: “((Endoscopy) OR (Endoscopic)) AND (((((((Nano carbon) OR (CN)) OR (CNs)) OR (CNPS)) OR (carbon nanoparticles)) OR (nano-carbon)) OR (Nanocarbon)) AND (((((((((((Thyroid Neoplasms) OR (Neoplasm, Thyroid)) OR (Thyroid Neoplasm)) OR (Neoplasms, Thyroid)) OR (Neoplasms, Thyroid)) OR (Carcinoma, Thyroid)) OR (Carcinomas, Thyroid)) OR (Thyroid Carcinomas)) OR (Cancer of Thyroid)) OR (Thyroid Cancers)) OR (Thyroid Cancer)) OR (Cancer, Thyroid)) OR (Cancers, Thyroid)) OR (Cancer of the Thyroid)) OR (Thyroid Adenoma)) OR (Adenoma, Thyroid)) OR (Adenomas, Thyroid)) OR (Thyroid Adenomas)),” was employed. We also used the “snowball” approach to trace the references included in the study.

2.2 Inclusion criteria

The following criteria were used to determine the choice of our reviewed studies. (1) Patients: patients who were diagnosed with thyroid cancer using preoperative puncture pathology and underwent thyroid cancer surgery for the first time. (2) Intervention: the intervention for the test group was a carbon nanoparticle tracer, while that for the control group was a blank without any tracer. (3) Outcome: the observed indicators comprised the average number of lymph nodes dissected, the average number of positive lymph nodes dissected, the average number of metastatic lymph nodes dissected, parathyroid resection, recurrent laryngeal nerve injury, and postoperative hypocalcemia. (4) Study type: randomized controlled trials, non-randomized controlled trial, and retrospective studies were used. (5) The language was Chinese or English only.

2.3 Exclusion criteria

We excluded research or literature pertaining to the following factors from our review: (1) open thyroid cancer surgery; (2) experimental groups combined with other study variables; (3) case reports, reviews, and meta-analysis; and (4) experiments in which animals or cells were used as research objects. Low-quality literature (Jadad scale score <4) was also excluded.

2.4 Data extraction and quality assessment

Two researchers were independently involved in the screening process, and relevant experimental data were extracted, including

time of publication, first author, journal of publication, number of experimental and control groups, patients' sex, mean age, study methods, study index data, and outcomes. The obtained data were combined and analyzed. When there was a discrepancy in the literature extracted by the two researchers, we involved a third researcher for data extraction and screening. The extracted information and data were analyzed.

2.5 Statistical analysis

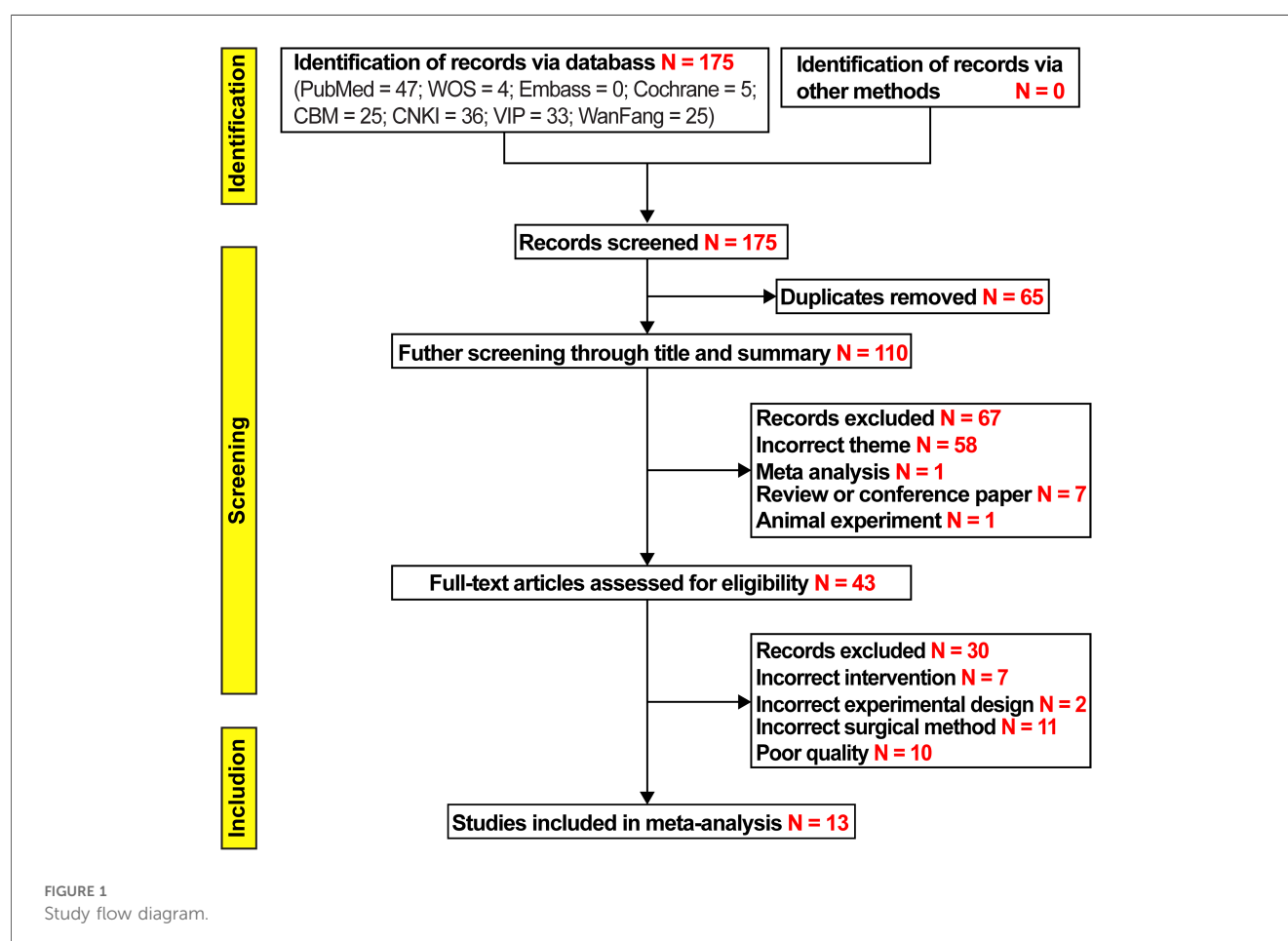
STATA SE 18 software (<https://www.stata.com/>) was used for all data analyses in this review. While continuous outcome variables were compared using the weighted mean difference (WMD), dichotomous outcome variables were compared using the odds ratio (OR). We calculated the 95% confidence interval (CI) for both WMD and OR. The statistical results were processed to determine the effect model. When $P \geq 0.1$ and $I^2 \leq 50\%$, a fixed-effects model was used for meta-analysis. When $P < 0.1$ and $I^2 > 50\%$, sensitivity analysis was performed on the data to evaluate the effect of each group of data on the heterogeneity of the results. If there were data with large effects, they were excluded, and then the fixed-effect analysis was performed. If there was no significant shadow heterogeneity in the data, a random-effects model was used to conduct a meta-

analysis. The results were considered statistically different when $P < 0.05$. Forest plots were also drawn per the statistical results. When the number of included literatures was >10 , funnel plots were drawn, and the symmetry of the funnel plots was evaluated further to analyze the publication bias of the included data.

3 Results

3.1 Study selection

The researchers completed literature screening per the established screening process and conditions. The flow chart of the literature screening is shown in Figure 1. Initially, 175 articles were screened based on the keywords. Based on the titles and abstract, we removed 65 duplicates, 58 non-conforming articles, 1 meta-analysis, 7 systematic reviews, and 1 animal analysis per the exclusion criteria. Based on the full-text review of the 43 articles, we further excluded 7 reports of studies with inconsistent interventions, 2 with inconsistent experimental design, 11 with inconsistent surgical methods, and 10 with poor literature quality. In total, 13 (8–20) studies were considered eligible for inclusion in this meta-analysis, comprising 4 studies reported in English and 9 studies reported in Chinese, involving a total of 1,463 patients.



3.2 Study characteristics

Information on the characteristics of the studies analyzed in the meta-study is included in Table 1. We used the Jadad scale (21) for nine randomized controlled trials included in this study. Four aspects of literature quality were evaluated: random sequence production (0–2), allocation concealment (0–2), blinding method (0–2), and withdrawal (0–1). While literature with a composite score of 1–3 was considered low quality, that with a score of 4–7 was considered high quality. An overview of the evaluation findings is presented in Table 2. Furthermore, we used the Newcastle–Ottawa Scale (22) for evaluating the quality of four non-randomized controlled trials, based on three evaluation aspects: selection (0–4), comparability (0–2), and exposure (0–3). Studies with a comprehensive score exceeding 5 points were considered eligible for inclusion in the meta-analysis. The evaluation results are presented in Table 3.

3.3 Average number of retrieved lymph nodes

We evaluated 13 studies in this review to assess the number of retrieved lymph nodes. Strong heterogeneity among the studies was noted, following a heterogeneity test, where $I^2 = 89.0\%$ and $P = 0.000$ (Q-test). The sensitivity analysis indicated that no study had a substantial impact on the overall research results (Figure 2). For the meta-analysis, we selected random-effects modeling. The combined effect size (WMD = 3.033, 95% CI: 2.100–3.967, $P = 0.000$) demonstrated that the use of carbon nanoparticle tracers resulted in an average increase of 3.033 lymph nodes compared with that in the control group. Thus, carbon nanoparticle tracers had a notable effect on lymph node staining and could improve lymph node dissection efficiency (Figure 3). To investigate potential publication biases among the 13 literature sources, we drew a funnel diagram (Figure 4). The statistical analysis yielded a P value of 0.468, indicating the absence of publication bias in the included literature.

3.4 Average number of retrieved positive lymph nodes

In this study, four studies were assessed for heterogeneity. The analysis revealed a high level of heterogeneity among the included studies with $I^2 = 96.5\%$ and a significant Q-test result ($P = 0.000$). The sensitivity analysis identified the study by Liu et al. (8) as the source of heterogeneity (Figure 5). Upon the exclusion of this study, no heterogeneity was observed among the remaining studies, with $I^2 = 0.00\%$ and $P = 0.462$ for Q-test. Consequently, the fixed-effects model was employed. The effect size after meta-merger (WMD = 0.457, 95% CI: 0.224–0.726, $P = 0.000$) indicated that the application of carbon nanoparticle tracers resulted in the removal of 0.457 additional positive lymph nodes during surgery compared with that in the control group. This finding suggests that the use of carbon nanoparticle tracers before surgery can assist surgeons in achieving a more thorough removal of positive lymph nodes, thereby reducing the risk of thyroid cancer recurrence to a certain extent. A visual representation of the obtained results is presented in Figure 6.

3.5 Average number of metastatic lymph nodes

A comprehensive review yielded a total of five relevant studies that were subsequently incorporated into this analysis. After testing for heterogeneity, $I^2 = 38.7\%$ and $P = 0.163$ for Q-test, we did not record any significant heterogeneity among the studies analyzed for the average number of metastatic lymph nodes, and the fixed-effects were selected for the combined effect size. The combined effect size (WMD = 0.304, 95% CI: 0.132–0.477, $P = 0.001$) indicated that the use of carbon nanoparticle tracers led to the identification of approximately 0.304 additional metastatic lymph nodes compared to conventional methods alone (Figure 7). These findings suggest that the implementation of carbon nanoparticles as a diagnostic tool may enhance the detection accuracy, ultimately improving overall surgical outcomes in treating thyroid cancer.

TABLE 1 Characteristics of the 13 studies included in the meta-analysis.

Year	Author	N		Sex (male/female)		Average age (years)		Study design	Concealment of allocation	Blinding	Indices
		Experimental	Control	Experimental	Experimental	Experimental	Control				
2022	Liu et al. (8)	160	134	32/128	33/101	40.64 ± 10.70	40.25 ± 10.02	NRCT	Unclear	Unblinding	①②
2020	Cheng et al. (9)	50	52	–	–	–	–	NRCT	Unclear	Unblinding	①④
2017	Chen et al. (10)	33	32	5/28	7/25	30.45 ± 6.72	32.71 ± 5.9	NRCT	Unclear	Unblinding	①②④⑥
2018	Wu et al. (11)	13	13	5/8	7/25	43.15 ± 8.97	44.08 ± 7.62	RCT	Unclear	Unclear	①④⑥
2016	Ye et al. (12)	45	40	9/36	8/32	46.89 ± 9.08	46.32 ± 9.10	RCT	Unclear	Unblinding	①③④
2013	Yang et al. (13)	21	22	1/20	1/21	32.48 ± 4.69	32.32 ± 5.35	RCT	Unclear	Unclear	①③④
2022	Cao et al. (14)	58	40	–	–	–	–	NRCT	Unclear	Unclear	①②⑤⑥
2018	You et al. (15)	60	60	18/42	20/40	35.42 ± 3.61	34.38 ± 3.52	RCT	Unclear	Unclear	①⑥
2018	Rao et al. (16)	32	40	–	–	–	–	RCT	Unclear	Unblinding	①④⑤
2020	Ma et al. (17)	51	42	8/43	5/37	31.8 ± 7.3	30.2 ± 9.2	RCT	Unclear	Unclear	①②
2021	Rao et al. (18)	50	58	9/41	16/42	46.8 ± 11.9	44.0 ± 10.2	RCT	Unclear	Unclear	①④⑤
2020	Zhang et al. (19)	152	150	9/143	13/137	33.32 ± 9.32	33.57 ± 9.62	RCT	Unclear	Unblinding	①③⑤
2015	Wang et al. (20)	28	27	1/28	2/27	30.25 ± 6.04	29.44 ± 6.27	RCT	Unclear	Unblinding	①③④

① Average number of retrieved lymph nodes; ② average number of retrieved positive lymph nodes; ③ average number of metastatic lymph nodes; ④ number of accidental parathyroid removal; ⑤ number of recurrent laryngeal nerve injuries; ⑥ number of hypocalcemia.

RCT, randomized controlled trial; NRCT, non-randomized controlled trials.

TABLE 2 Details of the quality assessment of randomized controlled trials.

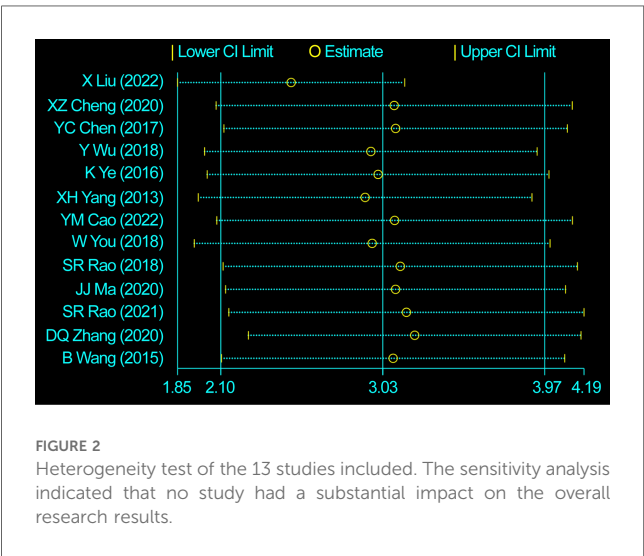
Year	Author	Randomization	Concealment of allocation	Blinding	Loss to follow-up, %	Quality assessment
2018	Wu et al. (11)	No mentioned description	Only mentioned randomized	Unclear	0	4
2016	Ye et al. (12)	No mentioned description	Only mentioned randomized	Unblinding	0	3
2013	Yang et al. (13)	No mentioned description	Only mentioned randomized	Unclear	0	4
2018	You et al. (15)	No mentioned description	Only mentioned randomized	Unclear	0	4
2018	Rao et al. (16)	Random-number table	Only mentioned randomized	Unblinding	0	4
2020	Ma et al. (17)	No mentioned description	Only mentioned randomized	Unclear	0	4
2021	Rao et al. (18)	Random-number table	Only mentioned randomized	Unclear	0	5
2020	Zhang et al. (19)	Computer-generated randomization chart	Only mentioned randomized	Unblinding	0	4
2015	Wang et al. (20)	Computer-generated randomization chart	Only mentioned randomized	Unblinding	0	4

Quality assessment based on the Jadad scale.

TABLE 3 Details of the quality assessment of nonrandomized controlled trails.

Year	Author	Study design	Selection	Comparability	Exposure	Quality assessment
2022	Liu et al. (8)	Concurrent retrospective chart review	4	2	2	8
2020	Cheng et al. (9)	Concurrent retrospective chart review	4	2	2	8
2017	Chen et al. (10)	Concurrent retrospective chart review	4	2	2	8
2022	Cao et al. (14)	Prospective controlled study	4	2	2	8

Quality assessment based on the Newcastle–Ottawa Scale.



3.6 Number of accidental parathyroid removals

We evaluated eight studies focusing on the number of accidental parathyroid removals. After testing for heterogeneity, no significant heterogeneity was found among the studies, indicated by the I^2 value of 6.3% and non-significant Q-test result ($P = 0.382$). Consequently, the fixed-effects model was employed for estimating the pooled effect sizes. The analysis revealed a fixed-effects combined effect size ($OR = 0.146$, 95% CI: 0.084–0.256, $P = 0.000$), indicating that the use of carbon nanoparticle tracers considerably contributed to the identification of parathyroid glands. The preoperative application of carbon nanoparticles resulted in a 14.6% reduction in the rate of parathyroid miscutting compared with that in the control group

(Figure 8). These findings demonstrate the effectiveness of carbon nanoparticles in reducing the occurrence of parathyroid miscutting and the subsequent complications.

3.7 Number of hypocalcemia cases

We analyzed four studies focusing on the number of hypocalcemia cases. With $I^2 = 0.00\%$ and $P = 0.449$ for the Q-test, the heterogeneity test did not reveal any notable heterogeneity among the studies. Therefore, we chose the fixed-effects methodology for calculating the combined effect sizes. The combined effect size using the fixed-effects analysis ($OR = 0.440$, 95% CI: 0.206–0.940, $P = 0.034$) demonstrated that the utilization of carbon nanoparticle tracers in thyroid surgery reduced the probability of postoperative hypocalcemia by 44% compared with that in the control group (Figure 9). These findings suggest that the application of carbon nanoparticles in thyroid surgery can effectively prevent postoperative hypocalcemia, reduce its incidence, and improve the safety of thyroid surgery.

3.8 Number of recurrent laryngeal nerve injury cases

The analysis included four studies focusing on the number of recurrent laryngeal nerve injuries. After testing for heterogeneity, we observed no considerable variation among the studies, with $I^2 = 30.4\%$ and $P = 0.230$ for the Q-test. Consequently, the fixed-effects model was chosen to estimate the combined effect sizes ($OR = 0.440$, 95% CI: 0.524–1.925, $P = 0.990$) (Figure 10). Importantly, no significant difference was observed in the mean scores between the experimental and control groups, suggesting

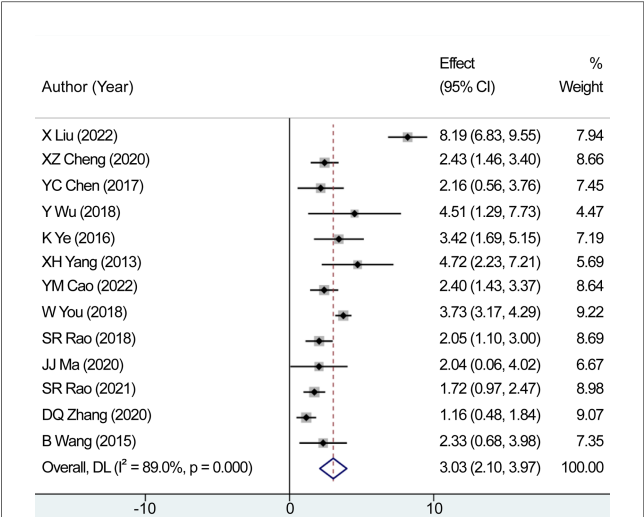


FIGURE 3
Combined effect size of the average number of retrieved lymph nodes. The carbon nanoparticle tracers had a notable effect on lymph node staining and could improve lymph node dissection efficiency.

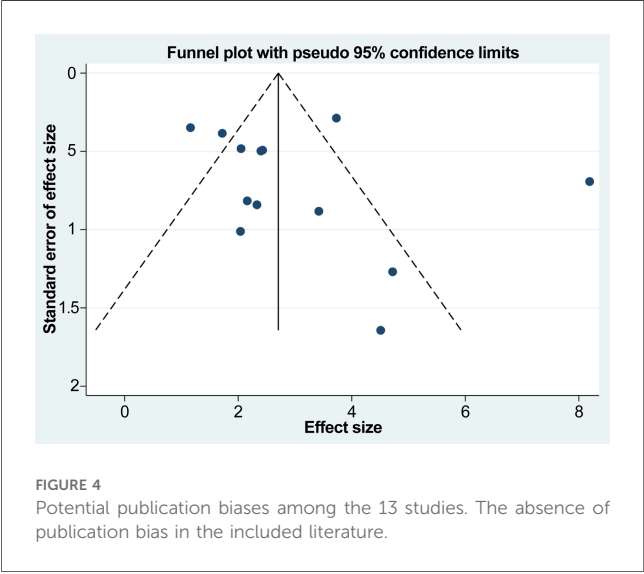


FIGURE 4
Potential publication biases among the 13 studies. The absence of publication bias in the included literature.

that the use of carbon nanoparticle tracers may protect from recurrent laryngeal nerve injuries. However, the preventive effect did not exhibit substantial distinction compared with that of the control group.

4 Discussion

This study showed that preoperative applications of nanocarbon in endoscopic thyroid cancer surgery can increase the number of cleared lymph nodes. As a result, it indirectly improves the clearance rate of positive and metastatic lymph nodes, protects the parathyroid glands, reduces the rate of

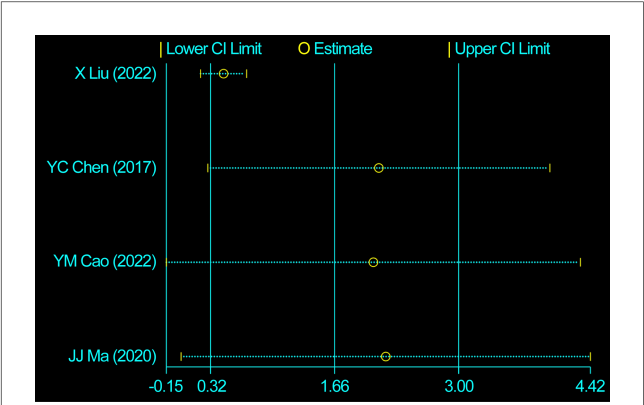


FIGURE 5
Heterogeneity test of four studies. The sensitivity analysis identified the study by Liu et al. as the source of heterogeneity.

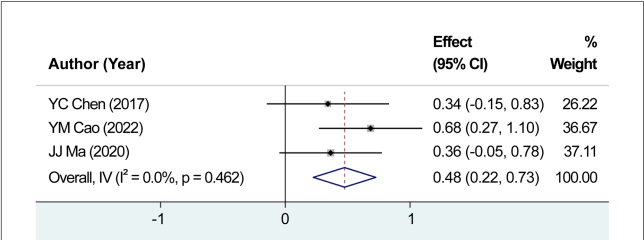


FIGURE 6
Combined effect size of the average number of retrieved positive lymph nodes. The effect size after meta-merger indicated that the application of carbon nanoparticle tracers resulted in the removal of 0.457 additional positive lymph nodes during surgery compared with that in the control group.

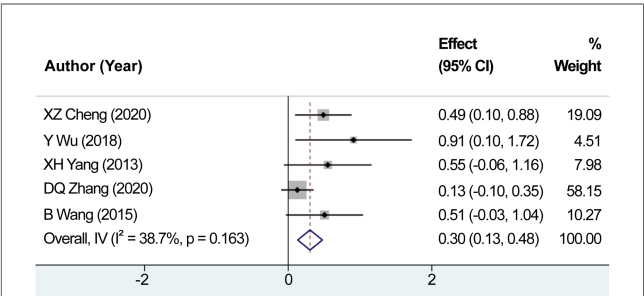


FIGURE 7
Combined effect size of the average number of metastatic lymph nodes. The combined effect size indicated that the use of carbon nanoparticle tracers led to the identification of approximately 0.304 additional metastatic lymph nodes compared to conventional methods alone.

parathyroid miscutting, and lowers the incidence of postoperative hypocalcemia.

In recent years, the global incidence of thyroid carcinoma has considerably increased, making it one of the most widespread endocrine malignancies (1). While most thyroid cancers have a favorable prognosis, studies have revealed that even microscopic

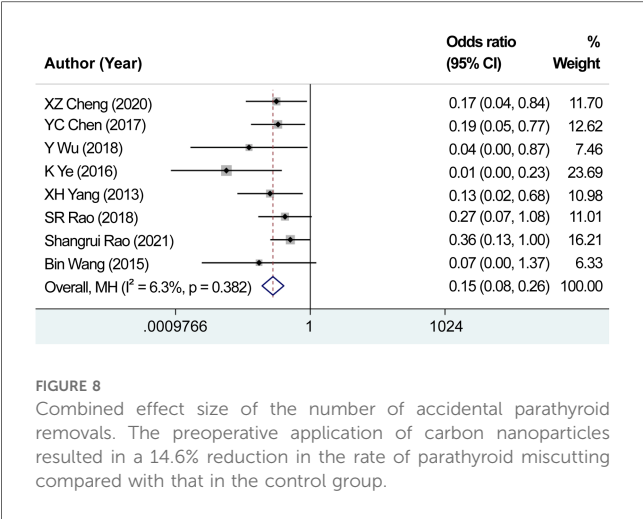


FIGURE 8
Combined effect size of the number of accidental parathyroid removals. The preoperative application of carbon nanoparticles resulted in a 14.6% reduction in the rate of parathyroid miscutting compared with that in the control group.

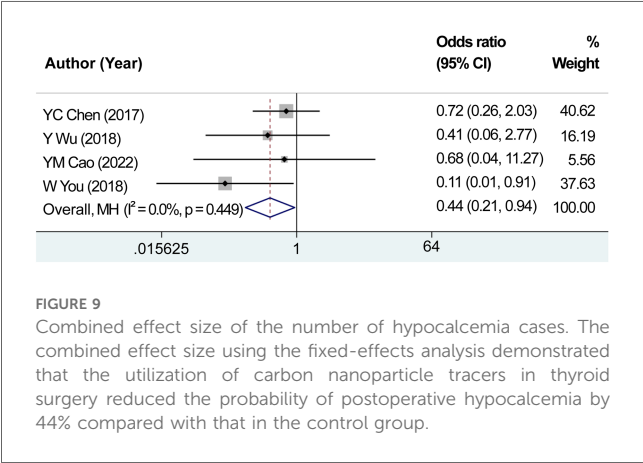


FIGURE 9
Combined effect size of the number of hypocalcemia cases. The combined effect size using the fixed-effects analysis demonstrated that the utilization of carbon nanoparticle tracers in thyroid surgery reduced the probability of postoperative hypocalcemia by 44% compared with that in the control group.

thyroid cancers carry a potential risk of lymph node metastasis. Extensive research has consistently demonstrated the significance of cervical lymph node metastasis in evaluating the prognosis of thyroid cancer. Moreover, its occurrence may lead to higher chances of disease recurrence, serve as an indicator for clinical staging, and guide subsequent management strategies. In clinical

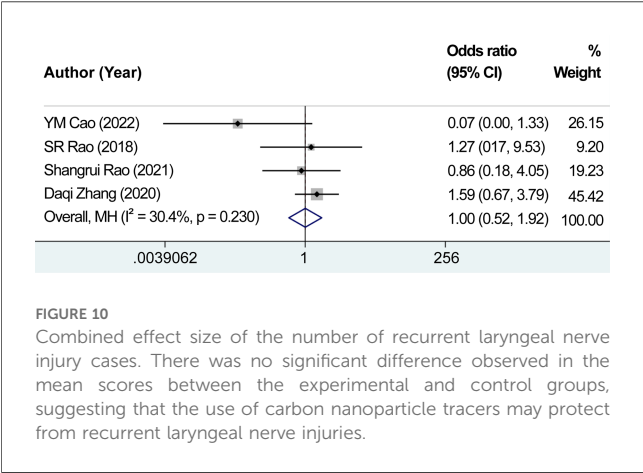


FIGURE 10
Combined effect size of the number of recurrent laryngeal nerve injury cases. There was no significant difference observed in the mean scores between the experimental and control groups, suggesting that the use of carbon nanoparticle tracers may protect from recurrent laryngeal nerve injuries.

practice, central and lateral cervical lymph nodes are the most common areas of thyroid cancer lymphatic metastasis (23). Therefore, selecting appropriate surgical methods for thorough lymph dissection plays a crucial role in the treatment effect and prognosis of the disease.

With the continuous progress made in endoscopic surgery technology, endoscopic minimally invasive surgery has also been widely used to treat thyroid cancer. It can ensure the efficacy and safety of surgery and considerably reduce the postoperative scar discomfort and stigma caused by open surgery. Therefore, endoscopic thyroidectomy with ipsilateral lymph node dissection is gradually becoming the mainstream operation for thyroid cancer. Both endoscopic and traditional open surgeries to manage thyroid carcinomas emphasize comprehensive cervical lymphadenectomy, concurrently preserving adjacent structures. Studies have shown that the degree of thorough cervical lymph node dissection directly affects the therapeutic effect of surgery. Therefore, a thorough dissection of the lymph nodes in the thyroid drainage area during surgery is essential. A prerequisite for thorough cervical lymph node dissection would be accurate identification of the lymph nodes. In the past, the distinction between lymph node tissue and non-lymph node tissue usually relied on the surgeon's experience; nonetheless, it might be difficult to provide thorough and accurate assessments just by visual inspection. In addition, the anatomical structure of the tissue around the thyroid varies considerably between individuals, and the parathyroid glands are closely attached to the back of the thyroid gland, making it difficult to accurately distinguish the difference between the two with the naked eye. Hence, the problem of parathyroid miscutting is prone to occur. Unintentional parathyroidectomy during thyroid procedures may result in a range of postoperative complications, including postoperative hypocalcemia, which presents itself through symptoms such as muscle twitches, facial numbness, and cardiac dysfunction, necessitating prolonged pharmacological supplementation, thus markedly affecting individuals' post-surgical quality of life. Studies have found a 5%–25% chance of parathyroid miscutting during thyroid cancer surgery resulting in complications (24). During thyroid cancer surgery, recurrent laryngeal nerve injury could be caused by unclear identification of the recurrent laryngeal nerve, resulting in further complications—postoperative hypocalcemia, hoarseness, and dysphagia.

Carbon nanoparticle technology in thyroid cancer surgery holds immense promise for addressing the previously outlined issues. Currently, the carbon nanoparticles commonly used in clinical practice have the advantages of good targeting, simplicity, and stable properties. Carbon nanoparticles are specially treated smooth spherical particles with 150-nm diameter. After being phagocytosed by macrophages, these nanoparticles can quickly enter the thyroid lymphatic capillaries with a relatively open cell space and accumulate in the lymph nodes in the drainage area, thus staining the lymph nodes and thyroid in the drainage area black. As the gap between endothelial cells of thyroid lymphatic capillaries is smaller than the diameter of carbon nanoparticles, carbon nanoparticle tracers cannot enter the blood, resulting in staining of the parathyroid gland and other peripheral tissues. Applying carbon nanoparticles can help surgeons accurately

identify the lymph nodes and thyroid structure in the drainage area in order to increase the number of cleared lymph nodes and avoid postoperative complications caused by the miscutting of the parathyroid gland and recurrent laryngeal nerve injury. Therefore, after approval, carbon nanoparticle tracers have been widely used in clinical thyroid cancer surgery. Adverse effects of carbon nanoparticle injection are relatively rare, and it has a positive effect on the recognition of cervical lymph nodes and protection of parathyroid glands.

In this meta-analysis, we included 13 studies involving 1,463 patients to assess the application effect of carbon nanoparticle tracers in endoscopic thyroid cancer surgery. The analysis focused on six observational indicators, and the discussion is divided into three aspects: the impact of the carbon nanoparticle tracer technique in tracing lymph nodes, protection of parathyroid glands against hypocalcemia, and protective effect on the laryngeal recurrent nerve.

4.1 Dissection of traced lymph nodes

According to the meta-analysis, the average quantity of the excised lymph nodes was approximately 3.033 greater within the experimental cohort than the control group following the administration of carbon nanoparticles. As the carbon nanoparticles enter the lymphatic capillary, all lymph nodes in the drainage area of the thyroid gland can be stained. The staining efficiency of carbon nanoparticles was found to be higher than visual inspection alone as it enabled the identification of lymph nodes that were not visually apparent. The analysis revealed that carbon nanoparticle tracers exerted a significant beneficial effect by reducing adverse effects during surgery, thereby facilitating enhanced lymphadenectomy efficiency. However, the ability of carbon nanoparticles to increase the number of lymph nodes retrieved is not always absolute. This is because the clearance of positive lymph nodes can be influenced by the patency of lymphatic capillaries. Additionally, tumor growth can result in a partial blockage of lymphatic capillaries, preventing the desired labeling effect. In the experimental group, 0.457 more positive lymph nodes were cleared and 0.304 more metastatic lymph nodes were identified than those in the control group. However, this effect of carbon nanoparticles on positive lymph nodes and metastatic lymph nodes was not significant probably because the carbon nanoparticles had no significant diagnostic effect on cleared lymph nodes but only marked lymph nodes in the drainage area along the lymphatic capillaries. The use of carbon nanoparticle tracers resulted in a greater number of cleared lymph nodes than traditional methods using visual inspection alone. Additionally, the method led to a slight increase in detecting cancerous and metastasized lymph nodes compared with that in the control group. The present study results corroborate those of Koimtzis et al. (25), suggesting that the utilization of carbon nanoparticles might aid in identifying minute suspect lymph nodes, which will need to be subsequently proven by further studies.

4.2 Protecting the parathyroid glands to prevent postoperative hypocalcemia

The results showed that carbon nanoparticles played a major role in the identification of parathyroid glands, and the application of carbon nanoparticle tracers before surgery reduced the parathyroid miscutting rate by 14.6% compared with that in the blank control group. Furthermore, incorporating carbon nanoparticle tracers can markedly decrease the incidence of accidental parathyroidectomy and potentially mitigate the associated postoperative complications. Meanwhile, the probability of postoperative hypocalcemia in the experimental group was reduced by 44% compared with that in blank the group and suggested that the application of carbon nanoparticles in endoscopic thyroid surgery could effectively prevent the occurrence of postoperative hypocalcemia and reduce its incidence, thus improving the safety of surgery. Distinguishing the parathyroid glands from the thyroid tissue is challenging owing to the anatomical structure, which may result in accidental intraoperative parathyroidectomy. The preoperative application of carbon nanoparticles can stain the thyroid gland and lymph nodes in the drainage area. The carbon nanoparticles cannot enter due to the dense interstitial space of the vascular cells. Therefore, without lymphatic capillary drainage, the tissue around the thyroid gland cannot be stained black, resulting in a contrasting black-stained tissue around the gland, thereby reducing the probability of miscutting of the parathyroid glands and the postoperative complications caused by the miscutting of the parathyroid glands. The results of this study were similar to those of Li et al. (26).

4.3 Protection of the recurrent laryngeal nerve

In this analysis, the protective effect of carbon nanoparticle tracers on the recurrent laryngeal nerve was not obvious. There was no significant difference in the recurrent laryngeal nerve injury rate between the experimental and control groups. Apart from the included study of Zhang et al. (19), other studies have reported a higher incidence of recurrent laryngeal nerve injury following carbon nanoparticle usage, indicating that these particles offered a degree of neuroprotection. Owing to the limited literature on this issue, more studies on protecting the recurrent laryngeal nerves by carbon nanoparticles should be included for further analysis.

This study has a few limitations. One potential drawback is that it involved a small number of studies, none of which employed blinding methods, affecting how representative the reported findings are. In the future, more randomized, controlled, multi-center, high-quality original studies using blinding methods should be added. Second, the languages of literature searched were only Chinese and English, and there is a lack of original studies reported in other languages and studies on other ethnicities, which might have led to language bias. In addition, the literature included in this study did not focus on the effects of carbon nanoparticles on the recurrence

rates and prognosis of thyroid cancer; thus, further research is needed to provide evidence.

5 Conclusions

The integration of carbon nanoparticles during endoscopic procedures for thyroid cancer aids in the efficient removal of lymph nodes within the thyroid drainage region. This approach also enhances the identification of pathological lymph nodes and metastases, potentially improving long-term disease outcome and overall patient survival. Application of carbon nanoparticles can also protect the parathyroid glands and reduce postoperative hypocalcemia occurrence and various complications caused by parathyroid miscutting of the parathyroid gland after surgery. These findings suggest that the incorporation of carbon nanotechnology in thyroid surgery holds promise for optimizing therapeutic efficacy and ultimately ensuring more favorable clinical outcomes. However, additional rigorous investigations involving large populations and randomized controlled designs are required in order to confirm these preliminary benefits and fully elucidate the actual impact of carbon nanoparticle technology in this context. The application of carbon nanoparticles can enhance the clearance rate of lymph nodes and protect the tissue around the thyroid.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

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A novel deep learning method to segment parathyroid glands on intraoperative videos of thyroid surgery

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Introduction: The utilization of artificial intelligence (AI) augments intraoperative safety and surgical training. The recognition of parathyroid glands (PGs) is difficult for inexperienced surgeons. The aim of this study was to find out whether deep learning could be used to auxiliary identification of PGs on intraoperative videos in patients undergoing thyroid surgery.

Methods: In this retrospective study, 50 patients undergoing thyroid surgery between 2021 and 2023 were randomly assigned (7:3 ratio) to a training cohort ($n = 35$) and a validation cohort ($n = 15$). The combined datasets included 98 videos with 9,944 annotated frames. An independent test cohort included 15 videos (1,500 frames) from an additional 15 patients. We developed a deep-learning model Video-Trans-U-HRNet to segment parathyroid glands in surgical videos, comparing it with three advanced medical AI methods on the internal validation cohort. Additionally, we assessed its performance against four surgeons (2 senior surgeons and 2 junior surgeons) on the independent test cohort, calculating precision and recall metrics for the model.

Results: Our model demonstrated superior performance compared to other AI models on the internal validation cohort. The DICE and accuracy achieved by our model were 0.760 and 74.7% respectively, surpassing Video-TransUnet (0.710, 70.1%), Video-SwinUnet (0.754, 73.6%), and TransUnet (0.705, 69.4%). For the external test, our method got 89.5% precision 77.3% recall and 70.8% accuracy. In the statistical analysis, our model demonstrated results comparable to those of senior surgeons (senior surgeon 1: $\chi^2 = 0.989$, $p = 0.320$; senior surgeon 2: $\chi^2 = 1.373$, $p = 0.241$) and outperformed 2 junior surgeons (junior surgeon 1: $\chi^2 = 3.889$, $p = 0.048$; junior surgeon 2: $\chi^2 = 4.763$, $p = 0.029$).

Discussion: We introduce an innovative intraoperative video method for identifying PGs, highlighting the potential advancements of AI in the surgical domain. The segmentation method employed for parathyroid glands in intraoperative videos offer surgeons supplementary guidance in locating real PGs. The method developed may have utility in facilitating training and decreasing the learning curve associated with the use of this technology.

KEYWORDS

artificial intelligence, deep learning, parathyroid glands, intraoperative videos, localization, segmentation

1 Introduction

The parathyroid gland (PG) is the smallest endocrine organ in the human body and plays an important role in maintaining the balance of calcium metabolism. Identifying and safeguarding PGs constitute a pivotal aspect of thyroid surgery. Given their small size and close anatomical proximity to lymph nodes or adipose tissues, there exists a risk of PG damage and compromised blood supply during thyroid surgery. Unfamiliarity with the morphology and anatomy of PGs heightens the susceptibility to damage, resulting in hypocalcemia that adversely affects the patient's quality of life. The injury of PGs can easily lead to postoperative hypocalcemia and other complications. One of the most common complications after total thyroidectomy is hypoparathyroidism. According to existing research, the incidence rate is about 30%–60% (1–3). It has been reported that the incidence of accidental parathyroid removal is up to 12%–28% (4). The symptoms of PG injury mainly include hand and foot twitching, limb sensory abnormalities, muscle spasms, and even life-threatening conditions.

Distinguishing PGs from similar tissues like thyroid, lymph nodes, or brown adipose tissues poses a significant challenge. Although all surgeons learn to differentiate PGs from other tissues, the length of this learning curve may be different for each surgeon, depending on experience. Even experienced surgeons cannot guarantee that all PGs will be recognized and protected in every thyroid surgery. At present, there are some methods to recognize PGs, such as carbon nanoparticles negative development, parathyroid hormone (PTH) in fine-needle aspiration (FNA) washout fluids, pathology validation, or near-infrared autofluorescence (NIRAF) (5–7). However, these methods have some limitations, such as longer periods of detection, high costs, false-positive results. Therefore, the existing recognition skills of PGs still rely on experienced surgeons. Nevertheless, early recognition of PGs before dissection is very helpful to guide dissection. In this case, a visual algorithm that recognizes the shapes and localization of a PG in the surgical field based on deep learning would be useful to shorten the learning curve and guide dissection.

To address those issues, we proposed the Video-Trans-U-HRNet model. At present, video AI technology has developed rapidly and is widely used in the medical field, such as robot surgery (8). Our task is to locate and segment the PG during thyroidectomy. To our knowledge, the application of AI methods to the localization and segmentation of PGs has mainly been limited to static images. However, thyroid surgery is a dynamic process that requires the full attention of the surgeon, and intraoperative videos can better reflect the real situation of the PG during surgery. Furthermore, the position and shape of PGs can undergo deformation and displacement due to the surgeon's manipulation, emphasizing the need for automatic localization and segmentation during the procedure. This not only enhances precision but also helps prevent accidental injury to PGs by the surgeon. In thyroid surgery, the PGs exhibit similarities to many other tissues, creating a challenge for existing AI models employed in medical segmentation and detection tasks to accurately recognize them. The objective of our study is to test a new AI-based method for recognizing PG and compare its performance to both junior and senior surgeons, with the ultimate aim of enhancing patient safety.

2 Methodology

2.1 Developing the AI model

The entire method is illustrated in Figure 1, comprising four parts: (A) The overall data flow of our method. (B) The detailed structure of our AI model, consisting of the Temporal Contextual Module (TCM), Encoder part, and Decoder part. (C) The dataset employed in this study. (D) The legends used in this figure. Zeng et al.'s work demonstrated the applicability of classical semantic segmentation models in medical segmentation. Drawing inspiration from their Video-TransUNet, we devised a deep-learning segmentation method tailored for the specific task of PGs video segmentation (9). The TransUnet model demonstrates robust performance in organ segmentation tasks, achieving outstanding results across diverse public datasets (10). Building upon TransUnet, we introduced a TCM to establish links between contextual information across frames for video segmentation (11). As depicted in Figure 1B, the TCM module comprises three parallel frames processing modules, all sharing a softmax layer. This module adeptly captures information from both preceding and succeeding frames, skillfully integrating it for feature extraction of the current key frame.

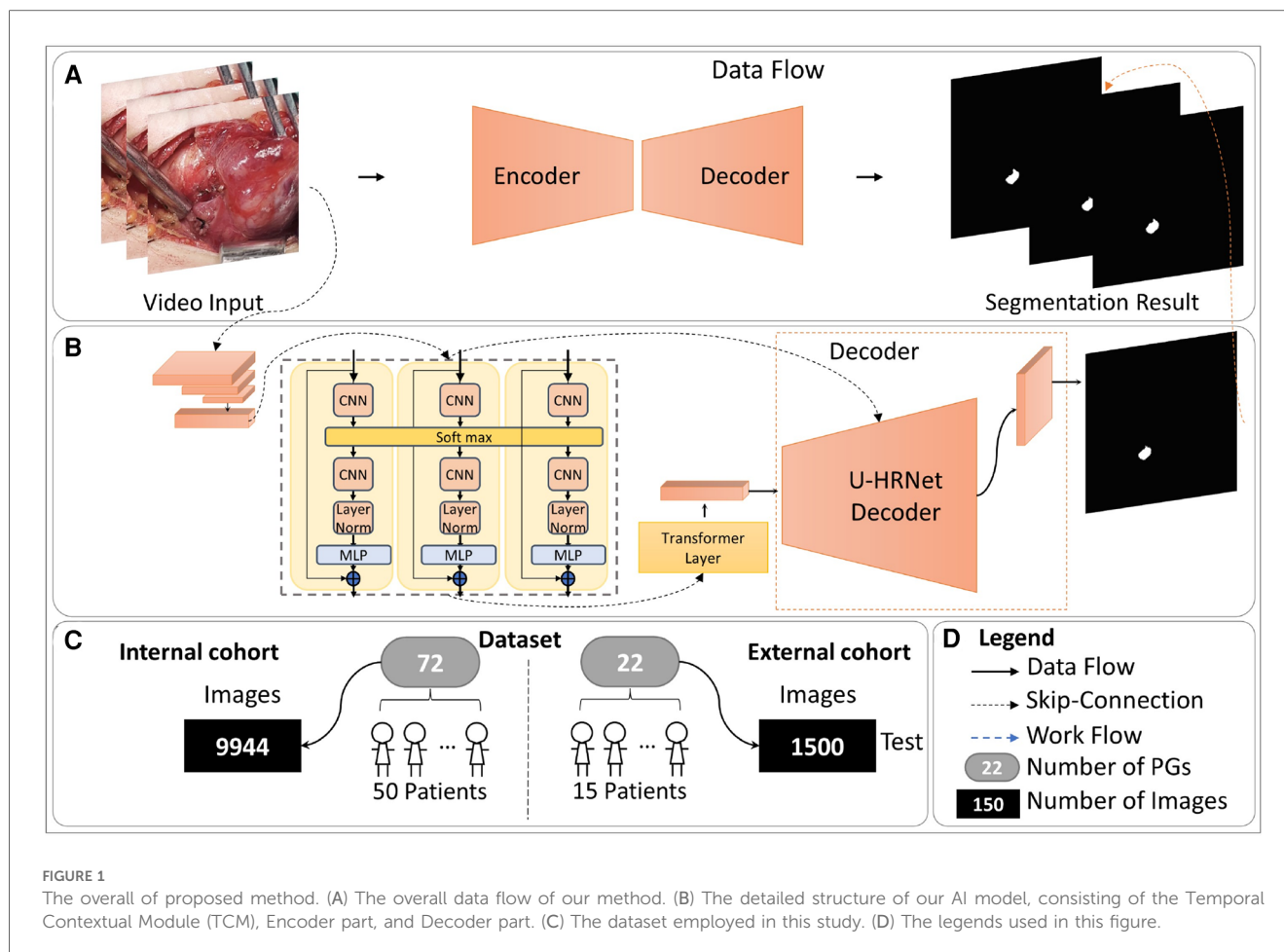
Skip-connections in U-shape net are crucial in multi-scale features transfer and fusion, we added a dynamic region-aware convolution (DRConv) module into skip-connection for preliminary extraction of multi-scale features (12). The specific module structure and our implementation details are shown in Figure 2.

To improve the communication of high-level semantic information and enhance the integration of low-level features, we modified the decoder structure based on Wang's work, as illustrated in Figure 3 (13). In contrast to the TransUnet decoder, the U-HRNet Decoder is more intricate, featuring additional feature transfer paths between adjacent layers and more fusion components. This redesign is geared towards achieving more accurate segmentation results. To align with reality, we implemented a post-processing method that excludes prediction results smaller than 50×50 pixels in size.

2.2 Patients and surgical technique

A prospective analysis was conducted on a total of 65 patients undergoing thyroid surgery at Shanghai Sixth People's Hospital from August 24, 2021, to June 17, 2023. Approval for this study was obtained from the Institutional Ethics Review Board and the Ethics Committee of Shanghai Sixth People's Hospital [Approval no. 2022-KY-178 (K)].

During surgery, a high-resolution camera was used to take videos of the wound surface, with the lens placed 15 cm away from the surgical field. Each patient underwent the recording of 1–2 videos. Each PG in videos was validated by the immune colloidal gold technique (ICGT) (5). A total of 116 videos, comprising 11,444 frames, were collected. Each video spanned 5–10 s, containing 50–100 frames. Within the internal cohort, 101 videos with 9,944 frames were meticulously labeled based on pathological results. In contrast, the external cohort consisted of



15 videos with 1,500 frames, serving solely for evaluation purposes and lacking specific segmentation labeling. Specific patient characteristics were shown in [Table 1](#).

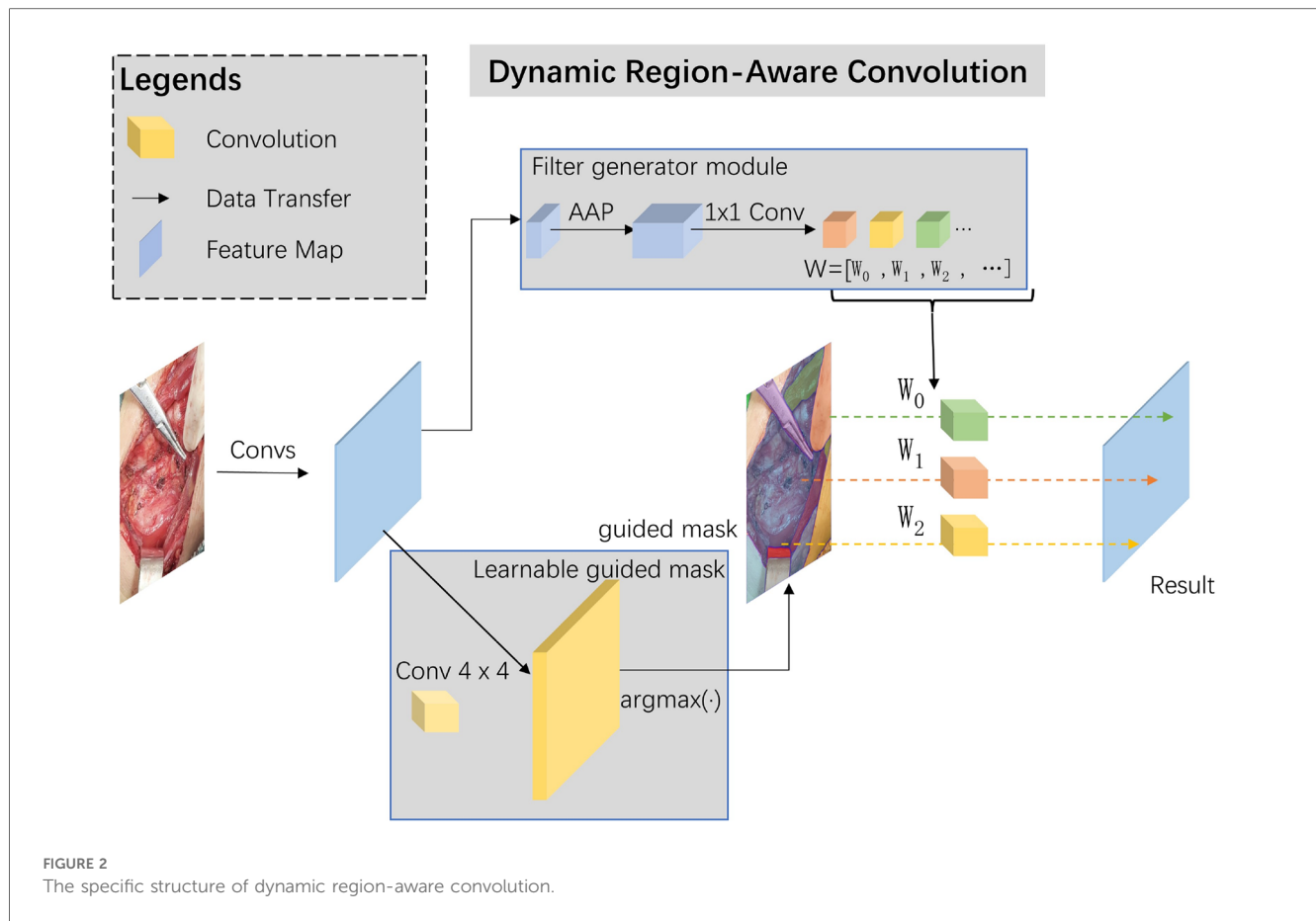
2.3 Dataset and comparison method

During this process, a senior surgeon with over 20 years of experience labeled all the PGs in videos using labelme software, including the location and contour of the PGs. The video data from 50 patients were allocated for internal training and validation sets, whereas the remaining data from 15 patients constituted the independent external validation cohort. The intersection over union (IoU) threshold selected for comparing prediction results with ground truth was set at 0.5. Performance evaluation of the deep learning model was based on the overlap in prediction masks generated by the model and those manually placed by the research team on each frame. Precision and recall were calculated for the study. Precision of deep learning models is similar to “positive predictive value,” and attempts to answer what proportion of positive classifications was actually correct. The specific calculations were placed in [Section 2.4](#). On the other hand, recall measures the model’s ability to detect positive samples, similar to “sensitivity,” and was calculated as the ratio between the number of positive samples correctly classified as positive to the total

number of positive samples. Two levels of surgeons evaluated the videos in the external validation cohort. Two levels of surgeons include 2 surgeons with more than 10 years of clinical experience in thyroidectomy and 2 surgeons with less than 10 years of clinical experience. They represented senior surgeons and junior surgeons respectively. All surgeons participating in the study had received specialist training in thyroid surgery. Our participating surgeons—both junior and senior—perform an average of 600 thyroid and parathyroid surgeries annually. This also includes the necessary training and assessments relevant to these procedures. Surgeons figured out the possible location of PGs in the video. Precision, recall, and accuracy were calculated. We compared the performance of the AI model and 2 levels of surgeons.

2.4 Evaluation metrics

For the evaluation of the AI model, we employed AI evaluation metrics. In this section, we introduced an evaluation metric specifically designed for PGs identification. Positive samples were calculated based on samples with an IoU threshold greater than 50% with the Ground Truth. Given that parathyroid glands are instances, segmentation results with an IoU of more than 50% were considered reasonable in the medical field. During the inference process, our method was evaluated in both the internal validation set and the



external test cohort. Precision, recall, and accuracy were abbreviated as PRE, REC, and ACC, respectively. True positive, false positive, false negative, and true negative were abbreviated as TP, FP, FN, and TN, respectively. Specific computations are shown below.

$$\text{Precision} = \text{TP} / (\text{TP} + \text{FP})$$

$$\text{Recall} = \text{TP} / (\text{TP} + \text{FN})$$

$$\text{Accuracy} = (\text{TP} + \text{TN}) / (\text{TP} + \text{FN} + \text{FP} + \text{TN})$$

Dice coefficient and Jaccard coefficient is the most commonly used evaluation metric in medical segmentation field, and the formulas are as follows. While X represents the area of the Ground Truth, Y represents the area of Prediction results. Both Dice and Jaccard may evaluate how well the prediction results cover the Ground Truth. Jaccard is abbreviated as JAC.

$$\text{Dice} = 2 \times (|X \cap Y|) / (|X| + |Y|)$$

$$\text{Jaccard} = (|X \cap Y|) / (|X| + |Y| - |X \cap Y|)$$

For evaluation of video, we proposed a new coefficient for frame loss performance. Loss Frames represented the number of frames with no target. Total Frames represented the total number of frames. The

formula is as follows.

$$\text{FLR} = (\text{Loss Frames}) / (\text{Total Frames})$$

A χ^2 test was used to compare the PG recognition rate between the AI model and different groups of surgeons. Comparisons between groups were statistically processed by SPSS 26.0, and statistical significance was assigned for p values < 0.05 .

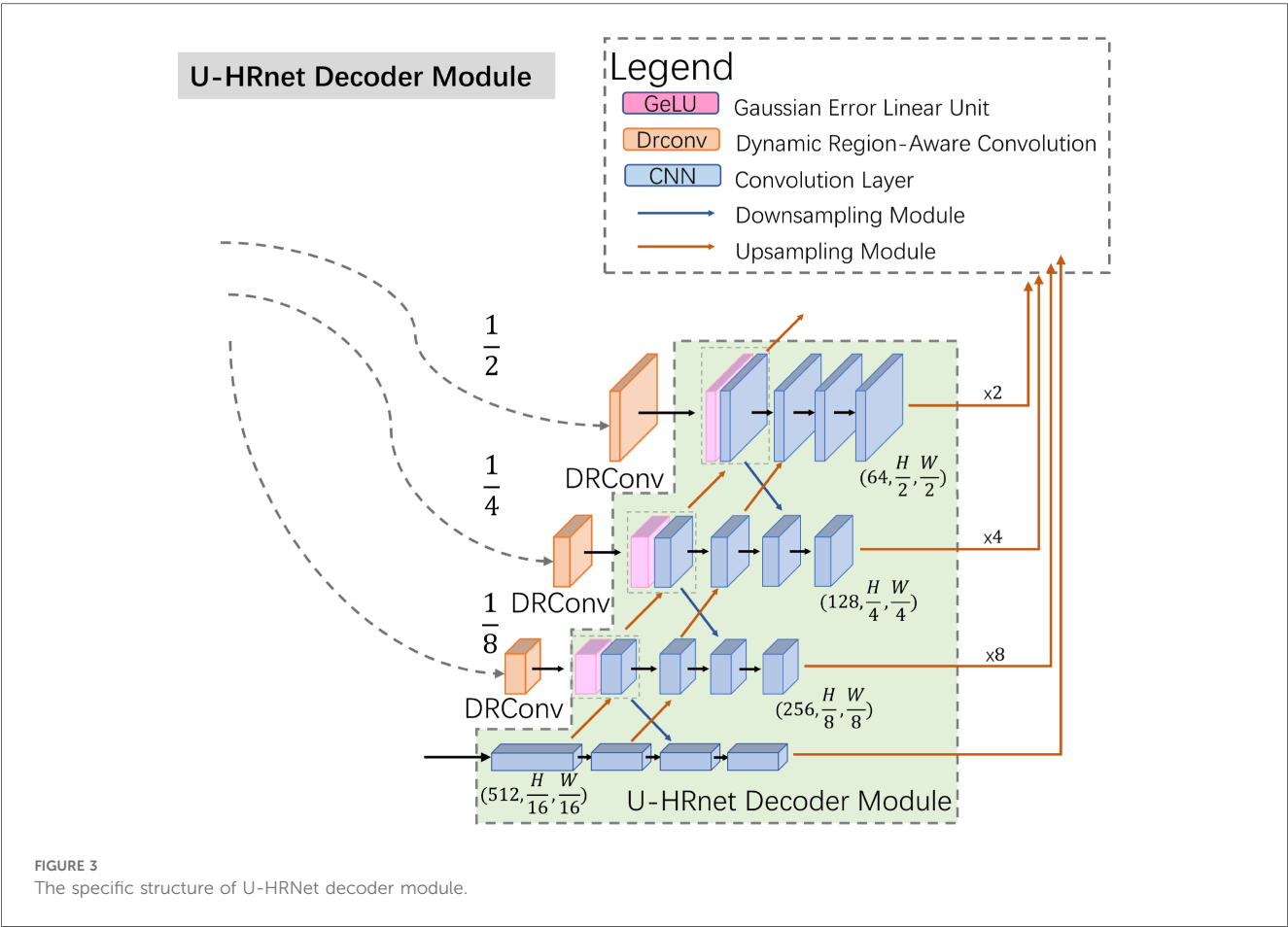
3 Results

3.1 Internal validation results

We conducted a comparative analysis of our method against three advanced deep-learning methods applied in the relevant medical field using our validation dataset. The results are presented in Table 2. As shown in Table 2, our proposed method outperformed the others in the validation dataset, indicating its superior performance. In internal validation cohort, we got 84.9% Precision and 81.3% Recall.

3.2 Comparison with surgeons

For external validation, our method was compared with two different levels of surgeons, junior surgeons and senior surgeons.



As the external cohort lacked specific labels, frames in the external validation dataset only had coarse labels, making accuracy evaluation metrics impractical for this cohort. Detailed

comparison results are presented in Table 3. In this comparison, our method achieved a precision of 89.5% and an accuracy of 70.8% in identifying PGs, outperforming all other surgeons. In comparison to all surgeons, our method achieved higher precision results as it tends to provide more accurate outcomes, while surgeons leaned towards offering more candidates to avoid missing PGs. Despite surgeons having more prior information, such as potential PG locations and their numbers, both the accuracy and precision of our method surpassed those of the surgeons. Comparison with senior surgeons revealed that surgeons with extensive experience identified more accurate PGs. The results suggest that the AI model can assist in providing more accurate PG results, thereby reducing the time and effort required for surgeons to identify PGs. Additionally, our method, based on a video recognition algorithm, demonstrates the ability to track PGs throughout the entire process of thyroidectomy, as depicted in Figure 4.

In addition, we compared the differences between our model and two levels of surgeons in the external cohort. Our AI model demonstrated results comparable to those of senior surgeons, with no significant difference (senior surgeon 1: $\chi^2 = 0.989$, $p = 0.320$; senior surgeon 2: $\chi^2 = 1.373$, $p = 0.241$). And our model was superior to two junior surgeons, with a statistically significant difference (junior surgeon 1: $\chi^2 = 3.889$, $p = 0.048$; junior surgeon 2: $\chi^2 = 4.763$, $p = 0.029$).

TABLE 1 Patient characteristics.

Parameter	Value
Age, year, median (IQR)	47 (21.5)
Sex, n (%)	
Female	47 (72.3)
Male	18 (27.7)
Diagnosis, n (%)	
Thyroid cancer	48 (73.8)
Thyroid nodule	12 (18.5)
Graves' disease	5 (7.7)
Procedure, n (%)	
Total thyroidectomy	28 (43.1)
Thyroid lobectomy	37 (42.1)
Hospital duration, day, median (IQR)	5 (3.5)
Operation time, min, median (IQR)	70 (35)
Parathyroid Glands	
Training	52
Internal Validation Cohort	20
Independent Test Cohort	22

Parathyroid glands represent the number of parathyroids used for model training.

TABLE 2 Result of proposed method.

Model	DICE	ACC	PRE	REC	hd_95	JAC	FLR
Our method	0.760	74.7%	80.2%	82.4%	28.44	0.769	11%
Video-TransUnet	0.710	70.1%	76.2%	71.4%	18.49	0.677	15%
Video-SwinUnet	0.754	73.6%	84.8%	80.4%	19.22	0.714	12%
TransUnet	0.705	69.4%	76.2%	74.3%	19.98	0.650	20%

TABLE 3 Result of proposed method.

Model	PRE	REC	ACC
Our method	89.5%	77.3%	70.8%
Junior surgeon 1	75.0%	81.8%	64.3%
Junior surgeon 2	80.0%	72.7%	64.0%
Senior surgeon 1	70.0%	63.6%	50.0%
Senior surgeon 2	84.6%	84.6%	45.8%

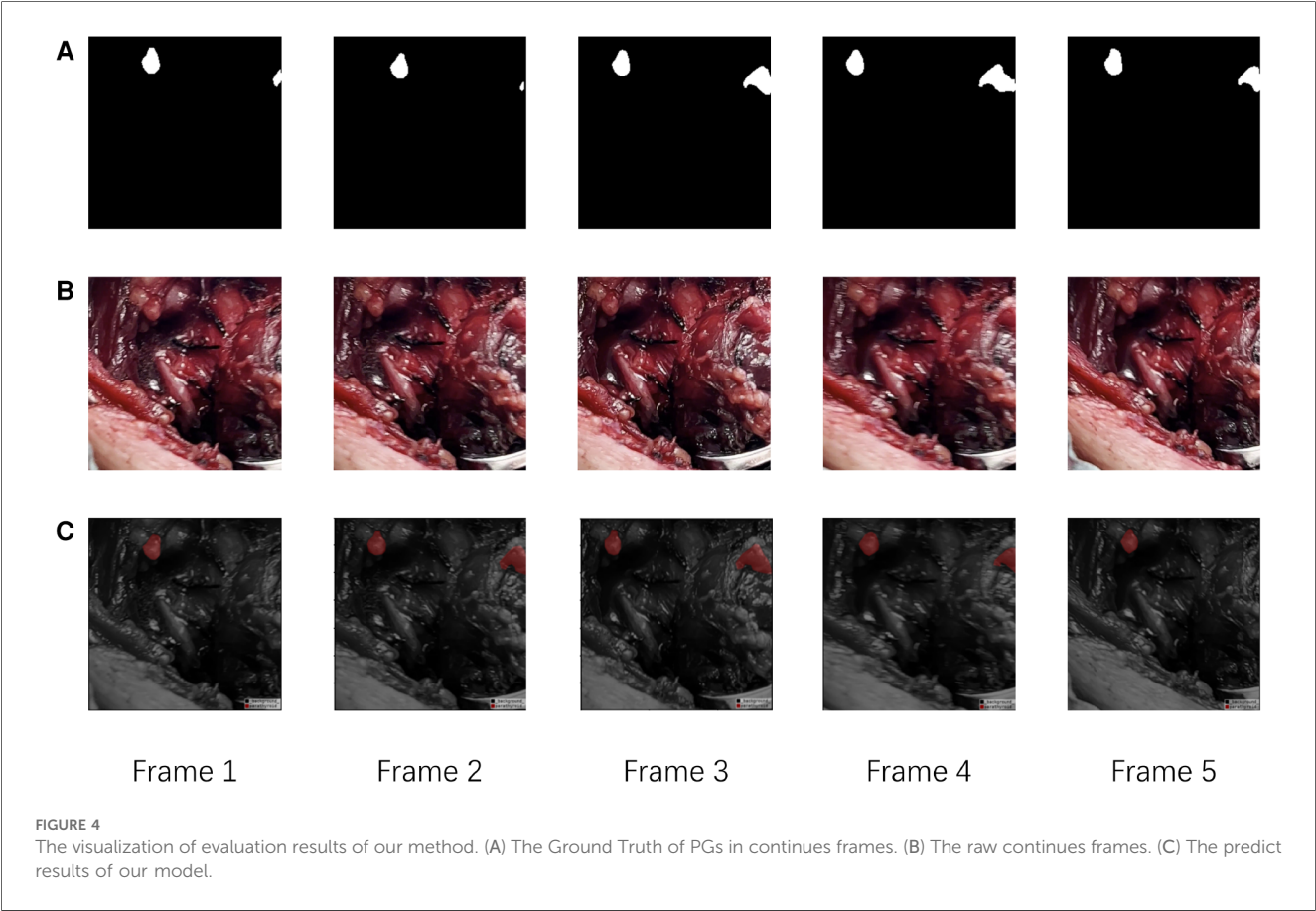
4 Discussion

In our retrospective study, we evidenced the proficiency of the proposed AI model in the recognition of PG in intraoperative videos. This model achieved a performance level demonstrating equivalence to that of two senior surgeons. A comparative analysis with multiple surgeons further solidified the potential of our presented method, indicating its application could bolster intraoperative recognition of PG. Ultimately, the implementation of this methodology could

precipitate a meaningful advancement in surgical accuracy, thereby substantially augmenting patient safety measures. To the best of our knowledge, this marks the inaugural instance of an AI model predicting the location and masks of PGs through the analysis of intraoperative videos in patients undergoing thyroidectomy.

AI in medicine holds the potential for expedited and standardized training. Kitaguchi et al. demonstrated the application of convolutional neural networks for automatic surgical skill assessment in laparoscopic colorectal surgery (14). Similarly, Wang and Fey described a deep learning framework for skill assessment in robotic surgery (15). As surgical procedures undergo increased digitalization, coupled with advancements in the automatic and real-time recognition of objects and tasks, the operating room stands as a focal point for progress. The newly developed tools have the capacity to enhance the performance and capabilities of surgical teams.

In the current medical landscape, video plays a crucial role in diagnostic solutions, spanning various applications such as



ultrasound, robotic surgery, and endoscopy (16). In contrast to static images, videos offer an effective means to comprehensively depict the entire process and intricacies of diagnosis or surgery. Doctors can grasp the situation and characteristics of lesions or surgical areas in multiple dimensions through time series data. Consequently, the study of video data in the medical field holds considerable significance. In 2022, Zeng et al. proposed Video-Transunet for assisted swallowing therapy in ultrasound video data. Based on this, Zeng's team proposed that Video-SwinUnet could also be applied to assist in swallowing therapy diagnosis in ultrasound videos (17). In the field of ultrasound diagnosis, Yeh et al. applied real-time object detection models to assess the recovery of the median nerve in ultrasound videos (18). Yu et al. also applied the U-Net network to the segmentation of surgical instruments in surgical video data for robotic surgery (19). The above research reflects that existing AI models can effectively assist in the automatic localization and segmentation of special targets in ultrasound videos or surgical videos.

Our proposed AI model demonstrated improved performance relative to several other advanced AI models. In evaluation of external cohort, our model equaled the performance of two experienced, senior surgeons with no significant difference ($p = 0.320$, $p = 0.241$; t -test). Notably, our model exhibited superior accuracy and precision, albeit with a reduced recall rate. Nevertheless, there are two primary limitations to our model. Firstly, due to the disparities in judgment between the AI model and the surgeons' recognition of PGs, our model might generate more false negatives than surgeons. This observation is evident from the comparison of recall rates between surgeons and our method. Secondly, as videos were recorded subsequent to the initial surgeon's PG identification, there exists the potential for false negatives or overlooked PGs. To mitigate these risks, an experienced surgeon, with over 20 years in the field, validated the PGs in the videos, with additional validation supplied by ICGT. These measures seek to minimize the likelihood of false negatives or missed PGs.

In practical application scenarios, due to the fixed number of PGs, incorrect judgment can easily lead to damage to the correct PG during surgery. Due to our method being more stable in determining the correct PG, it can provide surgeons with a certain degree of judgment advice. Moving forward, our ambition is to apply this method for real-time recognition of PG during surgical procedures. Concurrently, it shall function as an assistive tool for less experienced, junior surgeons in PG recognition, thereby minimizing the incidence of postoperative hypoparathyroidism. We anticipate that these efforts will play an instrumental role in enhancing patient prognosis.

In this retrospective study, we introduced a novel AI-based method to detect the shapes and localization of PGs in thyroid surgery, providing assistance to surgeons in PG detection. Comparative results with surgeons reveal that our method surpasses junior doctors in identifying PGs in intraoperative videos of thyroid surgery and performs at a level equivalent to that of senior surgeons. This provides valuable assistance for surgeons during thyroid surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Institutional Ethics Review Board and the Ethics Committee of Shanghai Sixth People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TS: Conceptualization, Formal Analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. FY: Data curation, Formal Analysis, Visualization, Writing – review & editing, Writing – original draft. JZ: Data curation, Supervision, Writing – review & editing. BW: Conceptualization, Funding acquisition, Project administration, Validation, Writing – review & editing. XD: Methodology, Project administration, Supervision, Writing – review & editing. CS: Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Significant role of 1,25-dihydroxyvitamin D on serum calcium levels after total thyroidectomy: a prospective cohort study

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Introduction: Although active vitamin D (VD) has been used both preoperatively and postoperatively to prevent hypocalcemia risk in patients undergoing total thyroidectomy, the role of 1,25-dihydroxyvitamin D (1,25(OH)₂D) has not been examined. This study comprehensively investigated the effects of 1,25(OH)₂D on calcium (Ca) concentrations after total thyroidectomy.

Methods: Serum Ca, parathyroid hormone (PTH), and 1,25(OH)₂D levels were measured in 82 patients with thyroid disease before and after surgery.

Results: Serum Ca, PTH, and 1,25(OH)₂D levels decreased significantly on the morning of the first postoperative day. Notably, the decrease in 1,25(OH)₂D concentration was significantly lower than that of PTH concentration ($10.5 \pm 33.4\%$ vs. $52.1 \pm 30.1\%$, $p < 0.0001$), with 28% of patients showing increases in 1,25(OH)₂D. The only factor predicting a postoperative 1,25(OH)₂D decrease was a high preoperative 1,25(OH)₂D concentration. Postoperative 1,25(OH)₂D concentrations, as well as the magnitude and rate of decrease from preoperative levels, showed strong positive correlations with preoperative 1,25(OH)₂D concentrations ($p < 0.0001$ for all three variables) but not with PTH concentrations. These findings suggest that 1,25(OH)₂D concentrations after thyroidectomy were more strongly dependent on preoperative concentrations than on the effect of PTH decrease and were relatively preserved, possibly preventing sudden severe postoperative hypocalcemia. A high 1,25(OH)₂D level was the most important preoperative factor for hypocalcemia (< 2 mmol/L; $p < 0.05$) on the first postoperative day; however, only PTH decrease was statistically significant ($p < 0.001$) when intraoperative factors were added. In the PTH > 10 pg/mL group, the decrease in 1,25(OH)₂D levels was significantly associated with postoperative hypocalcemia ($p < 0.05$). Similarly, in the PTH levels > 15 pg/mL group, a decrease in 1,25(OH)₂D concentration was a significant factor, and the amount of PTH decrease was no longer significant.

Conclusion: 1,25(OH)₂D plays an important role in preventing sudden, severe hypocalcemia due to decreased PTH levels after total thyroidectomy, whereas high preoperative 1,25(OH)₂D levels are a significant risk factor for postoperative

hypocalcemia. Optimizing preoperative protocols to adjust Ca, PTH, and 1,25(OH)₂D levels to improve the management of patients undergoing total thyroidectomy and to prevent extreme intraoperative PTH decreases may reduce the risk of hypocalcemia.

KEYWORDS

hypocalcemia, total thyroidectomy, 1, 25-dihydroxyvitamin D, Graves' disease, thyroid cancer

1 Introduction

Hypoparathyroidism and hypocalcemia are well-documented consequences of thyroidectomy. The symptoms of hypoparathyroidism range from no symptoms to mild numbness and tingling, muscle spasms, tetany, seizures, life-threatening laryngospasm, and cardiac arrhythmias (1, 2). These symptoms not only prolong the hospital stay but also lead to increased costs for additional testing and treatment (2, 3). Various factors contribute to the risk of post-thyroidectomy hypocalcemia, including perioperative parathyroid hormone (PTH) levels, preoperative vitamin D (VD) deficiency, and potential parathyroid gland damage or removal during surgery (3). Recently, the introduction of new intraoperative modalities aimed at preserving intraoperative parathyroid function has been reported (4, 5). The literature also discusses using preoperative VD or calcium (Ca) supplementation (1, 3, 6), as well as various postoperative Ca management strategies (7, 8), to address this issue. However, evidence supporting these interventions, including those involving natural and active VD (calcitriol or alfacalcidol), remains inconclusive (9).

Our previous investigations focused on elucidating the mechanisms underlying postoperative tetany after subtotal thyroidectomy in patients with Graves' disease (10–14). These findings attributed the tetany to secondary hyperparathyroidism (SHPT), a consequence of preoperative Ca and VD deficiency (a preoperative risk factor), and acute parathyroid dysfunction related to surgery (an intraoperative risk factor) (11). With our newly established thyroid hospital, total thyroidectomy has become the preferred surgical approach for patients with Graves' disease and approximately half of those with thyroid cancer. Total thyroidectomy has a more significant impact on parathyroid function than other types of thyroidectomies (15, 16).

PTH is crucial in regulating Ca concentrations, both directly and indirectly, by producing 1,25-dihydroxyvitamin D (1,25(OH)₂D). However, the difference in the half-life of PTH and 1,25(OH)₂D (3–5 min for the former and 5–20 h for the latter) (17–19) suggests that 1,25(OH)₂D is not completely subordinate to PTH in influencing Ca metabolism. While both PTH and 1,25(OH)₂D are vital for managing Ca concentration after thyroidectomy, research on the role of 1,25(OH)₂D is very limited. Consequently, our study

comprehensively investigated the effects of 1,25(OH)₂D on Ca levels after total thyroidectomy.

2 Materials and methods

2.1 Ethical considerations

The study protocol was approved by the Ethics Committee of Yamashita Thyroid Hospital (No. 2022-12). Written informed consent was obtained from all participants. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

2.2 Study population and procedures

Eighty-two consecutive patients with Graves' disease (n = 31), thyroid cancer (n = 42), or benign nodules (n = 9) who underwent total thyroidectomy at our hospital between June 2022 and October 2022 were included in the present study. Two patients with thyroid cancer also had Graves' disease. One patient each with undifferentiated carcinoma, coexisting hyperparathyroidism, and completion thyroidectomy, who underwent total thyroidectomy during the same period, was excluded from the study. None of the participants had severely impaired hepatic or renal function that could have affected VD metabolism.

All surgeries were performed by five endocrine surgeons using standardized procedures. Post-surgery, the patients fasted in the following morning and received a Ca-free maintenance fluid infusion.

Serum levels of Ca, magnesium (Mg), PTH, and 1,25(OH)₂D were measured in 82 patients before surgery, and all variables were measured again the morning after surgery. The time between thyroidectomy and postoperative blood sampling was 17.1 ± 2.0 h (range: 12.8–21.0 h). The same variables were measured 3 days and 4 weeks after surgery in patients not receiving postoperative alfacalcidol supplementation. Serum 25-hydroxyvitamin D (25(OH)D) levels were measured in all patients before surgery and 4 weeks after. Ca-related variables of all other patients were measured

as needed. Ca data from the postoperative day were excluded from the analyses because two patients presented with symptoms of tetany and received intravenous Ca glucuronide before postoperative blood sampling. Postoperative hypocalcemia was defined as a corrected Ca level of < 2 mmol/L.

2.3 Laboratory tests

Serum levels of alkaline phosphatase (ALP; normal range, 38–113 IU/L), total Ca (2.20–2.53 mmol/L), Mg (1.6–2.6 mg/dL), albumin (34–48 g/L), and inorganic phosphate (0.87–1.49 mmol/L) were measured using routine automated procedures. The Ca level (mmol/L) was calculated using the formula: $[\text{Ca concentration (mg/dL)} + 0.8 \times (4 - \text{albumin (g/dL)})] \times 0.250$. Free thyroxine (T₄, 0.9–1.7 ng/dL), free triiodothyronine (T₃, 2.3–4.3 pg/mL), thyroid-stimulating hormone (TSH, 0.50–5.0 mIU/L), PTH (15–65 pg/mL), anti-TSH receptor antibody (< 2 IU/L), and 25(OH)D levels were determined using an electrochemiluminescence immunoassay (COBAS 8000 e801 analyzer, Roche Diagnostics, Indianapolis, IN, USA). Serum 1, 25(OH)₂D levels (20–60 pg/mL) were measured by radioimmunoassay (RIA) using an 125I-labelled 1,25(OH)₂D derivative tracer and Sac-cell separation. The inter- and intra-assay coefficients of variation were 9.8 and 13%. VD deficiency was defined as a 25(OH)D concentration below 20 ng/mL, whereas VD insufficiency was described as a concentration between 20 and 30 ng/mL (20, 21).

2.4 Statistical analyses

Data are expressed as mean $\pm$ standard deviation. Statistical differences between the two study groups were assessed using the Mann–Whitney U test for continuous variables. Biochemical changes before and after surgery were analyzed using Wilcoxon signed-rank test. Cross-tabulated data were analyzed using Fisher's exact probability test or Pearson's method. Correlations were tested using Spearman's rank correlation coefficients. Factors defining Ca and 1,25(OH)₂D were tested using univariate and multivariate analyses before logistic regression analysis. Logistic regression analysis used the above significant factors to identify factors associated with hypocalcemia. All statistical analyses were performed using JMP software (version 17.0; SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant at $p < 0.05$.

3 Results

3.1 Overall analysis

The baseline demographic and clinical characteristics of the patients are presented in Table 1. The most common surgical indication for patients with Graves' disease was the unwanted effects of antithyroid drugs ($n = 14$), followed by marked thyroid

TABLE 1 Baseline characteristics of the study population.

Patient variables	Value (n=82)
Sex	
Male	20
Female	62
Age at surgery (years), mean (s.d.)	48.0 (16.0)
BMI (kg/m ²), mean (range)	23.2 (16.0–39.0)
Indication for surgery	
Graves' disease	31
Malignancy	42*
Benign	9
Type of lymph node dissection	
None	40
Central lymph node dissection	21
Central and lateral neck node dissection (unilateral/bilateral)	21 (17/4)
Parathyroid transplantation	
None	24
Yes (number of transplantations: 1/2/3)	58 (34/23/1)
Operation time (min), mean (s.d.)	130 (50)
Blood loss (g), mean (s.d.)	24 (25)
Excised thyroid gland tissue (g), mean (s.d.)	56 (46)

BMI, body mass index; s.d., standard deviation.

*Two patients also had Graves' disease.

gland enlargement ($n = 10$). A preoperative cytological diagnosis of malignancy was made in 48 cases, with two additional suspected cases, all of which underwent central lymph node dissection. The suspected malignancy cases were identified as follicular carcinoma and malignant lymphoma. The preoperative diagnosis of the nine benign tumors was adenomatous goiter, and thyroid function was normal, except for TSH suppression in one case.

Table 2 summarizes the pre-operative and postoperative biochemical and operative data of the 82 patients. Before surgery, serum 1,25(OH)₂D levels showed a significant positive correlation with PTH levels ($r^2 = 0.155$, $p < 0.001$) and a negative correlation with Ca levels ($r^2 = 0.05$, $p < 0.05$), but not with 25(OH)D levels ($r^2 = 0.005$, $p = 0.526$). Serum levels of Ca, Mg, PTH, and 1,25(OH)₂D all significantly decreased the following day compared with their preoperative values ($p < 0.001$ for all four items). However, the rate of 1,25(OH)₂D decrease was significantly lower than that of PTH ($10.3\% \pm 32.4\%$ vs. $52.0\% \pm 28.8\%$, $p < 0.001$), with a 28% (23/82) elevation.

The morning after surgery, 1,25(OH)₂D concentrations, as well as the amount and rate of decrease from preoperative levels, were strongly positively correlated with preoperative 1,25(OH)₂D concentrations ($p < 0.0001$ for all three items) (Figure 1). This was not observed for PTH concentrations. These results were consistent when patients with Graves' disease and those with tumors were separately analyzed.

Table 3 shows the comparison of clinical and biochemical data between the groups with decreased ($n = 59$) and increased ($n = 23$)

TABLE 2 Changes in biochemical data of patients after total thyroidectomy.

Parameter	Preoperative values	Postoperative Values	Decrease amount	Decrease rate (%)	P value*
Serum calcium (mmol/L)	2.30 ± 0.07	2.05 ± 0.14	0.25 ± 0.15	10.9 ± 6.5	<0.001
Serum phosphate (mmol/L)	1.10 ± 0.17	1.37 ± 0.23	-0.27 ± 0.23	-26.1 ± 24.0	<0.001
Serum magnesium (mg/dL)	2.04 ± 0.15	1.76 ± 0.15	0.27 ± 0.18	13.2 ± 8.2	<0.001
PTH (pg/mL)	54.1 ± 23.3	26.5 ± 21.7	27.6 ± 19.2	52.0 ± 28.8	<0.001
1,25(OH) ₂ D (pg/mL)	81.2 ± 30.6	68.0 ± 23.5	13.2 ± 28.8	10.3 ± 32.4	<0.001

1,25(OH)₂D, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone.

*Comparisons of serum concentrations before surgery (preoperative) and the morning after surgery (postoperative).

1,25(OH)₂D levels. 1,25(OH)₂D-related variables and postoperative Mg levels were significantly different; the 25(OH)D levels also differed between the two groups but without reaching statistical significance ($p = 0.064$).

Table 4 summarizes the results of the univariate and multivariate analyses of the pre-operative factors defining the Ca concentration in the morning after thyroidectomy. Among the variables considered clinically important, 1,25(OH)₂D and SHPT were significant in the univariate analysis; however, only 1,25(OH)₂D (the higher the value, the lower the Ca concentration) was significant in the multivariate analysis (Table 4). Logistics regression analysis with the two significant factors defining Ca concentration showed that only 1,25(OH)₂D levels were a predictor of hypocalcemia (< 2 mmol/L) on the morning after surgery (odds ratio: 1.22, 95% confidence interval: 1.04–1.44, $p < 0.01$).

Given the strong influence of a PTH decrease on Ca concentrations and an extreme PTH decrease on the morning after surgery masking the effect of 1,25(OH)₂D, the factors defining morning Ca concentrations (Table 5) and hypocalcemia (< 2 mmol/L) (Table 6) were analyzed for all enrolled patients in addition to the groups with PTH levels >10 pg/mL or >15 pg/mL. We identified 31 cases (37.8%) of hypocalcemia on the morning after surgery in the group with all 82 patients, 19 of 61 patients (31%) in the group with PTH >10 pg/mL, and 10 of 50 patients (20%) in the group with PTH >15 pg/mL. In all cases, univariate and multivariate analyses of all factors, including intraoperative

factors that might determine the Ca concentration on the morning following surgery and hypocalcemia, showed that the amount of PTH decrease was a significant parameter in multivariate analysis. In the group with PTH >10 pg/mL, the decrease in 1,25(OH)₂D was a significant factor for Ca concentrations and hypocalcemia. Similarly, in the group with PTH levels above 15 pg/mL, the decrease in 1,25(OH)₂D concentration was a significant factor for the two items. However, the decrease in the amount of PTH was no longer a significant factor for either.

Regarding the VD status of the 82 patients, 66 had VD deficiency (80.5%), 14 had insufficiency (17.1%), and only 2 had sufficient VD levels (2.4%). Four weeks post-surgery, 25(OH)D concentrations significantly decreased from 16.4 ± 5.7 ng/mL to 14.9 ± 6.5 ng/mL compared with preoperative levels ($p < 0.0001$). The rate of 25(OH)D reduction and the pre-operative 25(OH)D concentration were negatively and significantly correlated ($p < 0.05$), indicating that the greater the pre-operative VD deficiency, the greater the reduction in postoperative 25(OH)D concentration.

Postoperative bleeding occurred in two patients, and recurrent nerve palsy occurred in four patients (three transient, one resected, and one nerve reconstructed due to cancer invasion). In 47 patients, alfacalcidol and Ca therapy were initiated in the morning following surgery. Of these patients, 7 (8.5%) were prescribed low doses of alfacalcidol (0.5–1.0 μ g) without Ca supplementation at the last postoperative visit. Of these seven patients, three had Graves' disease, and four had thyroid cancer. The Ca and PTH levels of

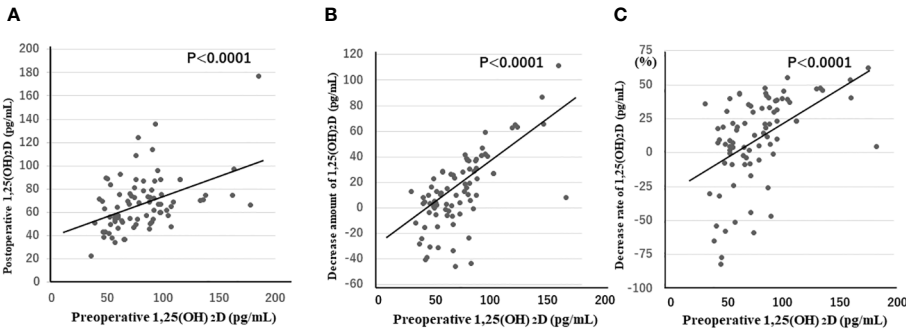


FIGURE 1 1,25(OH)₂D concentrations (A), as well as the amount (B) and rate (C) of decrease from preoperative levels in the morning after surgery, are strongly positively correlated with preoperative 1,25(OH)₂D concentrations ($p < 0.0001$ for all three items). 1,25(OH)₂D, 1,25-dihydroxyvitamin D.

TABLE 3 Comparison of clinical and biochemical data between patient groups with decreased and increased 1,25(OH)₂D Levels.

Variables	Decreased levels (n=59)	Increased levels (n=23)	p value*
Age	46.7 ± 13.0	48.4 ± 17.2	0.668
Sex (M/F)	16/46	7/13	0.426
BMI (kg/m ²)	22.7 ± 4.3	24.4 ± 5.1	0.145
Graves' disease (%)	21/59 (35.6%)	12/23 (52.2%)	0.169
SHPT (PTH>65 pg/mL)	13/59 (22.0%)	4/23 (17.4%)	0.641
Preoperative laboratory findings			
Free T4 (ng/dL)	1.24 ± 0.35	1.29 ± 0.69	0.476
TSH (μU/mL)	1.49 ± 1.39	1.19 ± 0.30	0.233
PTH (pg/mL)	55.2 ± 25.6	51.5 ± 16.6	0.865
Calcium (mmol/L)	2.29 ± 0.07	2.30 ± 0.09	0.598
Phosphate (mmol/L)	1.08 ± 0.16	1.15 ± 0.17	0.116
Magnesium (mg/dL)	2.06 ± 0.15	2.00 ± 0.10	0.112
ALP (IU/L)	92.1 ± 56.6	86.4 ± 35.9	0.765
Creatinine (mg/dL)	0.65 ± 0.19	0.64 ± 0.16	0.808
1,25(OH) ₂ D (pg/mL)	87.6 ± 32.5	64.9 ± 16.4	0.002 [#]
25(OH)D (ng/mL)	15.7 ± 4.6	18.3 ± 7.7	0.345
Postoperative laboratory findings			
PTH (pg/mL)	25.6 ± 22.6	28.9 ± 19.3	0.317
PTH decrease (pg/mL)	29.6 ± 19.3	22.6 ± 18.1	0.160
Calcium (mmol/L)	2.03 ± 0.14	2.08 ± 0.16	0.403
Phosphate (mmol/L)	1.37 ± 0.24	1.34 ± 0.20	0.350
Magnesium (mg/dL)	1.74 ± 0.14	1.83 ± 0.14	0.015 [#]
1,25(OH) ₂ D (pg/mL)	62.0 ± 21.6	83.4 ± 21.6	0.001 [#]
1,25(OH) ₂ D decrease (pg/mL)	25.6 ± 22.7	-18.5 ± 15.3	0.001 [#]

1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase.
BMI, body mass index; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism; T4, thyroxine; TSH, thyroid-stimulating hormone.
Values are presented as mean ± SD or number (percentage).
*Comparison between the groups with decreased and increased 1,25(OH)₂D levels.
[#]Significantly different at p<0.05.

these nine patients were 2.12 ± 0.03 (2.00–2.23) mmol/L and 29.6 ± 5.8 (23.5–39.5) pg/mL, respectively.

3.2 Sub-group analysis

Changes in Ca, PTH, and 1,25(OH)₂D levels were analyzed separately in the group (n = 28) that did not receive alfacalcidol or Ca postoperatively. **Figure 2** shows the percent changes in patients' Ca, PTH, and 1,25(OH)₂D levels from preoperative to postoperative

TABLE 4 Univariate and multivariate analysis of preoperative factors determining the calcium concentration on the morning following the thyroidectomy.

Variable	Univariate p value	Multivariate p value
Age	0.412	
Sex	0.325	
BMI	0.580	
Graves' disease	0.060	
TSH	0.525	
Free T4	0.189	
PTH	0.173	
SHPT (PTH >65 pg/mL)	0.035*	0.225
Calcium	0.155	
Phosphate	0.419	
Magnesium	0.494	
ALP	0.405	
Creatinine	0.902	
25(OH)D	0.260	
1,25(OH) ₂ D	0.015*	0.035*

1,25(OH)₂, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase.
BMI, body mass index; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism; T4, thyroxine; TSH, thyroid-stimulating hormone.
*Significant at p<0.05.

week 4. PTH and Ca concentrations were significantly lower on the first and third days after surgery than preoperatively; however, 1,25 (OH)₂D concentrations were not significantly different. PTH concentrations at 3 days and 4 weeks postoperatively were 10–20% lower than those preoperatively; however, 1,25(OH)₂D was approximately 20% higher.

Four weeks after surgery, 25(OH)D concentrations decreased significantly from the pre-operative level of 14.7 ± 4.0 ng/mL to 13.1 ± 5.7 ng/mL (p < 0.005). Similar to the analysis of all study participants, both the amount and rate of 25(OH)D reduction 4 weeks post-surgery were significantly negatively correlated with preoperative 25(OH)D concentration (p < 0.05 and p < 0.01, respectively).

4 Discussion

In the current study, we investigated Ca metabolism after thyroid surgery, focusing on SHPT induced by Ca and VD deficiency (11). SHPT is generally associated with normal-to-low serum Ca levels, elevated PTH levels, decreased 25(OH)D levels, and increased 1,25(OH)₂D levels (11). The production of 1,25(OH)₂D is achieved by 1α-hydroxylation of 25(OH)D catalyzed by the enzyme CYP27B1, which is upregulated by PTH (22). Therefore, extremely low 25(OH)D levels could result in lower 1,25(OH)₂D levels; however, such cases are rarely seen, even in Japan, where VD

TABLE 5 Univariate and multivariate analysis of pre- and intraoperative factors determining the calcium concentration on the morning following the thyroidectomy.

Variable	Univariate p value	Multivariate* p value
Total (n=82)		
Postoperative PTH	0.008 [#]	
PTH decrease amount	<0.001 [#]	<0.001 [#]
PTH decrease rate	<0.001 [#]	
Preoperative 1,25(OH) ₂ D	0.015 [#]	
Postoperative 1,25(OH) ₂ D	0.429	
1,25(OH) ₂ D decrease amount	0.001 [#]	0.119
1,25(OH) ₂ D decrease rate	0.006 [#]	
Postoperative magnesium	0.022 [#]	0.130
Lymph node dissection	0.08	
Group with PTH >10 pg/mL (n=61)		
Postoperative PTH	0.101	
PTH decrease amount	<0.001 [#]	<0.001 [#]
PTH decrease rate	0.005 [#]	
Preoperative 1,25(OH) ₂ D	0.002 [#]	
Postoperative 1,25(OH) ₂ D	0.7632	
1,25(OH) ₂ D decrease amount	0.001 [#]	0.011 [#]
1,25(OH) ₂ D decrease rate	0.003 [#]	
Postoperative magnesium	0.081	
Lymph node dissection	0.206	
Group with PTH >15 pg/mL (n=50)		
Postoperative PTH	0.781	
PTH decrease amount	0.004	0.176
PTH decrease rate	0.064	
Preoperative 1,25(OH) ₂ D	0.001 [#]	0.003 [#]
Postoperative 1,25(OH) ₂ D	0.844	
1,25(OH) ₂ D decrease amount	<0.001 [#]	
1,25(OH) ₂ D decrease rate	0.003	
Postoperative magnesium	0.702	
Lymph node dissection	0.129	

1,25(OH)₂D, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone.
*To prevent the nullification of effects among relevant variables, the multivariate analysis concentrated on the reduction in the levels of PTH and 1,25(OH)₂D among those variables that exhibited significance in the univariate analysis.
[#]Significant at p<0.05.

deficiency is widespread (23). Similar to PTH, 1,25(OH)₂D plays a key role in correcting hypocalcemia by promoting Ca release from the bones, renal Ca reabsorption, and intestinal Ca absorption. With a longer half-life (5–16 h) than that of PTH (3–5 min) (17–19), 1,25(OH)₂D may have important bioprotective properties against rapid decreases in Ca levels that accompany a

TABLE 6 Logistic analysis of pre- and intraoperative factors determining hypocalcemia (< 2mmol/L) on the morning following the thyroidectomy.

Variable	Univariate p value	Multivariate* OR (95% CI), p value
Total (n=82)		
Postoperative PTH	0.002 [#]	
PTH decrease amount	<0.001 [#]	1.901 (1.32–2.72), <0.001 [#]
PTH decrease rate	<0.001 [#]	
Preoperative 1,25(OH) ₂ D	0.020 [#]	
Postoperative 1,25(OH) ₂ D	0.635	
1,25(OH) ₂ D decrease amount	0.006 [#]	1.16 (0.93–1.45), 0.164
1,25(OH) ₂ D decrease rate	0.032 [#]	
Postoperative magnesium	0.026 [#]	0.74 (0.51–1.06), 0.098
Lymph node dissection	0.378	
Group with PTH >10 pg/mL (n=61)		
Postoperative PTH	0.012	
PTH decrease amount	0.001 [#]	2.19 (1.30–3.67), <0.001 [#]
PTH decrease rate	<0.001 [#]	
Preoperative 1,25(OH) ₂ D	0.013 [#]	
Postoperative 1,25(OH) ₂ D	0.729	
1,25(OH) ₂ D decrease amount	0.005 [#]	1.49 (1.01–2.01), 0.021 [#]
1,25(OH) ₂ D decrease rate	0.014 [#]	
Postoperative magnesium	0.021 [#]	0.72 (0.46–1.13), 0.150
Lymph node dissection	0.592	
Group with PTH >15 pg/mL (n=50)		
Postoperative PTH	0.342	
PTH decrease amount	0.009 [#]	1.65 (0.82–3.32), 0.151
PTH decrease rate	0.012 [#]	
Preoperative 1,25(OH) ₂ D	0.008 [#]	
Postoperative 1,25(OH) ₂ D	0.692	
1,25(OH) ₂ D decrease amount	0.005 [#]	1.86 (1.11–3.14), 0.001 [#]
1,25(OH) ₂ D decrease rate	0.010 [#]	
Postoperative magnesium	0.362	
Lymph node dissection	0.669	

1,25(OH)₂D, 1,25-dihydroxyvitamin D; CI, confidence interval; OR, odds ratio (calculated per 10 pg/mL change); PTH, parathyroid hormone.
*To prevent the nullification of effects among relevant variables, the multivariate analysis concentrated on the reduction in the levels of PTH and 1,25(OH)₂D among those variables that exhibited significance in the univariate analysis.
[#]Significant at p<0.05.

decrease in PTH. To the best of our knowledge, no comprehensive study has been conducted on postoperative hypocalcemia concerning 1,25(OH)₂D levels. The lack of previous research on 1,25(OH)₂D is probably due to its shorter half-life compared with

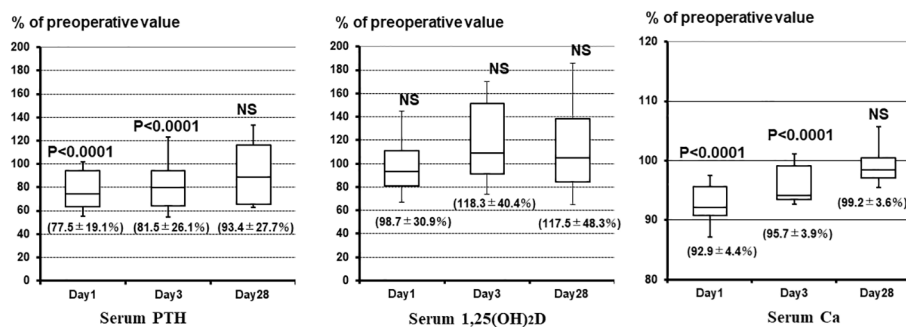


FIGURE 2

Percent changes in Ca, PTH, and 1,25(OH)₂D concentrations from before surgery to postoperative week 4. PTH and Ca concentrations are significantly lower on the first and third days postoperatively than preoperatively; however, 1,25(OH)₂D concentrations are not significantly different. PTH concentrations at 3 days and 4 weeks postoperatively are 10–20% lower than preoperatively, but the 1,25(OH)₂D concentration is approximately 20% higher. 1,25(OH)₂D, 1,25-dihydroxyvitamin D; Ca, calcium; PTH, parathyroid hormone; NS, not significant.

25(OH)D and its tendency to increase in cases of VD deficiency, making it an inadequate indicator of VD insufficiency (24, 25). In addition, its presence in serum only in trace amounts makes its measurement financially burdensome. The results of this study shed light on the complex interplay between VD metabolism, PTH regulation, and post-thyroidectomy hypocalcemia. Understanding these dynamics is critical for refining perioperative management strategies and potentially reducing the risk of hypocalcemia in patients undergoing total thyroidectomy.

Our study revealed two important implications of 1,25(OH)₂D after total thyroidectomy. First, 1,25(OH)₂D significantly prevents sudden, severe postoperative hypocalcemia due to decreased PTH levels. The half-life of 1,25(OH)₂D is considerably longer than that of PTH, suggesting that even if 1,25(OH)₂D production is suppressed by PTH decreases, the decrease in 1,25(OH)₂D is milder than that of PTH. Therefore, the Ca-raising effect of 1,25(OH)₂D remained, to some extent, even when the PTH levels decreased. Furthermore, the postoperative PTH concentrations were considerably lower than preoperative levels in most cases. In contrast, the 1,25(OH)₂D concentration decreased to a lesser degree and even increased in approximately 30% of cases. The exact mechanism is unknown; however, the activity of 1 α -hydroxylase from 25(OH)D persisted to some extent even as PTH decreased, suggesting that the production of 1,25(OH)₂D may have exceeded its catabolism in these patients. The 1,25(OH)₂D level is thought to be primarily determined by the amount of 1,25(OH)₂D produced from 25(OH)D by 1 α -hydroxylation and its metabolism via 24-hydroxylation by the enzyme CYP24A1 (Figure 3) (22). Based on the results of PTH and 1,25(OH)₂D concentrations up to 3 weeks post-surgery, the 1,25(OH)₂D levels increased to compensate for the inadequate recovery of PTH levels. The increase in the levels of 1,25(OH)₂D, which has a longer-lasting Ca-elevating effect than PTH does, may be a consistent physiological adaptation. Moreover, extrarenal 1,25(OH)₂D production may be involved, but the mechanism needs further investigation (26).

Second, a high preoperative 1,25(OH)₂D level was a significant risk factor for postoperative hypocalcemia. Furthermore, higher levels of 1,25(OH)₂D increase the formation of 1,24,25-trihydroxyvitamin D through catabolism by 24-hydroxylase (22, 27, 28). Given that the

higher the pre-operative 1,25(OH)₂D concentration, the higher the amount and rate of decrease in 1,25(OH)₂D concentration, the postoperative reduction in 1,25(OH)₂D levels is likely attributed to the metabolic effects of high preoperative 1,25(OH)₂D concentrations rather than to the reduced 1,25(OH)₂D production due to postoperative PTH decrease. This finding prompts the reevaluation of active preoperative VD supplementation protocols because it could induce CYP24A1, increasing 1,25(OH)₂D catabolism, which may lead to postoperative hypocalcemia. Optimizing preoperative Ca, PTH, and 1,25(OH)₂D levels may be crucial for reducing the incidence of hypocalcemia after thyroidectomy.

The risk of hypocalcemia after total thyroidectomy was also studied by grouping patients according to their PTH levels. The clinical significance of 1,25(OH)₂D cannot be properly determined at PTH-deficient concentrations. The results showed that a decrease in 1,25(OH)₂D concentration in the group with PTH levels above 15 pg/mL was the only significant factor for next-morning Ca concentration and hypocalcemia. Preoperative control of risk factors and improvement of surgical techniques to prevent

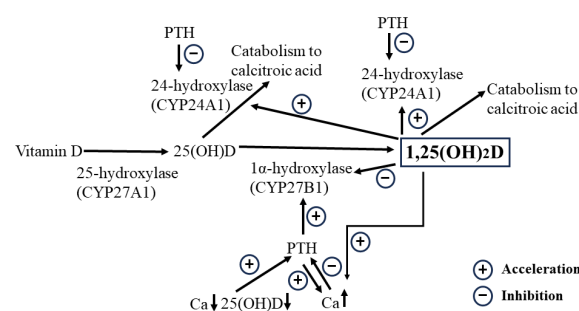


FIGURE 3

Schematic representation of the relationships among 1,25(OH)₂D, Ca, and 25(OH)D concentrations. Increased 1,25(OH)₂D due to the activation of 25(OH)D by 1 α -hydroxylation facilitates Ca increases but downregulates the Ca concentration in situations where PTH depletion is likely to occur after total thyroidectomy, as it promotes catabolism through activation of the 24-hydroxylase. 1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; Ca, calcium; PTH, parathyroid hormone.

intraoperative PTH decreases represent the two main approaches to preventing hypocalcemia after total thyroidectomy. Such decreases can be controlled to some extent by advances in surgical techniques and adjunctive technologies. PTH is not a significant risk factor for hypocalcemia when the PTH level is 15 pg/mL or higher on the day after surgery (20% of patients in this group had hypocalcemia in the present results), suggesting that improving the $1,25(\text{OH})_2\text{D}$ levels before surgery will reduce the incidence of hypocalcemia.

The findings of this study provide new insights into various hypocalcemic etiologies. First, we discuss the “hungry bone syndrome” in postoperative patients with Graves’ disease and hyperparathyroidism who have hyperdynamic bone disease. It is often observed that prescribing high doses of active VD and Ca in these patients does not result in the expected increase in serum Ca (29, 30). It is thought that the high preoperative PTH and $1,25(\text{OH})_2\text{D}$ levels lead to a hypercatabolic state of $1,25(\text{OH})_2\text{D}$, which is further aggravated by the postoperative PTH decrease (PTH is known to inhibit 24-hydroxylase activity) (Figure 3) (31), while the Ca-elevating effect of $1,25(\text{OH})_2\text{D}$ is severely suppressed. Prescribing high doses of active VD for such a condition may further activate $1,25(\text{OH})_2\text{D}$ catabolism-promoting 24-hydroxylase; therefore, it would be appropriate to provide intravenous Ca infusion therapy during this period and then wait for PTH recovery and a decrease in bone hypermetabolism. Second, in clinical practice, the timing of hypocalcemia onset varies among patients, even when PTH levels are similarly reduced, and $1,25(\text{OH})_2\text{D}$ may also be involved. In other words, although a decrease in PTH concentration lowers the $1,25(\text{OH})_2\text{D}$ levels, the rate of decline depends not only on the PTH decrease but also on the pre-operative $1,25(\text{OH})_2\text{D}$ concentration. A slower rate of decline in $1,25(\text{OH})_2\text{D}$ may delay the onset of hypocalcemia. Finally, some differences in active VD requirements for postoperative hypocalcemia at similar levels of PTH reduction may be partly explained by the rate of $1,25(\text{OH})_2\text{D}$ metabolism. It has been noted that VD deficiency increases $1,25(\text{OH})_2\text{D}$ metabolism (22, 27, 28), and thus, the prescription requirements would be expected to be higher than those in VD-sufficient patients. As discussed below, many patients require an active VD prescription even if their postoperative PTH is normal. Many of these patients may not only have low levels of 25(OH)D, the substrate for 1 α -hydroxylase, but may also have hypermetabolism of $1,25(\text{OH})_2\text{D}$.

The American Thyroid Association guidelines strongly recommend preoperative assessment of Ca and 25(OH)D levels, repletion if necessary, or prophylactic administration (32). Low serum 25(OH)D concentration is the most important diagnostic marker of VD deficiency (33, 34). In the present study, VD deficiency was also found to be common in Japanese patients, with only 2 of 82 patients meeting the criteria. The mean 25(OH)D concentration in this study was 16.4 ng/mL, which is the same as the 16.4 ng/mL reported in our previous study in 2000 (12). $1,25(\text{OH})_2\text{D}$ values are elevated in VD deficiency, but there was no negative correlation between serum 25(OH)D and $1,25(\text{OH})_2\text{D}$ values in the present study. Since $1,25(\text{OH})_2\text{D}$ has a significant positive correlation with PTH, we speculate that in Japan, where 25(OH)D and Ca deficiency is prevalent, $1,25(\text{OH})_2\text{D}$ may rely more on PTH than on 25(OH)D as a substrate. The Japanese Ministry of Health, Labour

and Welfare recommends a daily Ca intake of at least 700 mg for men and 650 mg for women, but in a preliminary survey of our inpatients, less than 10% of patients met this recommendation (data not shown). Japanese food is known to have a good balance of nutrients, and Ca is efficiently absorbed, but Japanese are gradually moving away from Japanese food, and there are few foods fortified with Ca and VD. Additionally, Japanese people, especially women, tend to avoid ultraviolet rays for cosmetic reasons, and few people take VD supplements.

The 25(OH)D concentration at 4 weeks postoperatively was significantly lower than that preoperatively. It is also noteworthy that the rate of decline was higher in patients with lower 25(OH)D. Factors that might be related to 25(OH)D concentrations after surgery, such as postoperative $1,25(\text{OH})_2\text{D}$ concentrations and the presence or absence of active VD and/or medications, were examined; however, no significant associations were found between these variables and the decrease in 25(OH)D. As the patients were 4 weeks postoperatively, lower UV production due to seasonal variations in UV radiation was unlikely, and it is possible that they were less active outdoors after surgery. Seven patients were taking alfacalcidol at the last postoperative visit, although their PTH levels were normal, and it is possible that 25(OH)D, the substrate for 1 α -hydroxylation, is not sufficient in these patients. Under the Japanese National Health Insurance system, 25(OH)D measurement is not allowed only for suspected VD deficiency, and natural-type VD is not covered by insurance. Due to these problems, it is necessary to educate patients about VD deficiency measures and lobby the government for insurance coverage of 25(OH)D testing and natural-type VD.

The results of this study can be used to discuss preventive measures against hypocalcemia in patients undergoing total thyroidectomy. The adequacy of VD and Ca differs with the country and region and must be addressed according to these circumstances (35). In general, serum 25(OH)D is lower at higher latitudes and with darker skin types, and its prevalence ranges from 24% in the United States to 90% in the Middle East (35). In Japan, the frequency of SHPT caused by VD and Ca deficiency is high, and it is imperative to improve the SHPT status. Ideally, only natural VD and adequate Ca supplementation are desired; however, improvements are expected to take time. The amount and duration of VD and Ca needed to improve SHPT status should be considered. Active VD (calcitriol or alfacalcidol) and Ca would raise serum Ca to the upper limit of the normal range in a short period and lower PTH levels, both of which benefit postoperative hypocalcemia. However, preoperative active VD administration may adversely affect postoperative Ca concentrations by increasing the preoperative $1,25(\text{OH})_2\text{D}$ level and 24-hydroxylase activity (Figure 3). The duration of 24-hydroxylase induction by operational VD administration, which promotes catabolism, remains unknown. Therefore, the appropriate dose and duration of active VD and Ca administration should be considered.

Although this study provides valuable insights into the effects of $1,25(\text{OH})_2\text{D}$ on Ca metabolism in patients with Graves’ disease and thyroid tumors undergoing total thyroidectomy, it has some limitations. The frequency of SHPT due to inadequate VD and Ca intake is high in Japan, and its sufficiency varies in different

countries and regions; therefore, the results of this study may not apply to all countries. Nevertheless, our findings will be helpful in countries and regions where SHPT is less frequent. In such areas, preoperative identification of patients with SHPT and targeting these patients for treatment to improve SHPT would be more efficient than treating all patients uniformly. Patients with Graves' disease differ significantly from those with other thyroid diseases in terms of preoperative thyroid hormone status and the bone- and Ca-related effects of thyroid hormones and thyroid-stimulating antibodies (3, 10, 11). Most surgical indications for our patients with tumors were peritracheal or lateral neck malignancies requiring lymph node dissection, which tend to have decreased postoperative PTH levels compared with Graves' disease. The greater the number of cases and the greater the variability in PTH decrease after thyroidectomy, the better the understanding of the role of $1,25(\text{OH})_2\text{D}$. Furthermore, the most important finding of this study was that $1,25(\text{OH})_2\text{D}$ levels on the morning of the first postoperative day were dependent on preoperative $1,25(\text{OH})_2\text{D}$ levels, which was confirmed when patients with Graves' disease and tumors were analyzed separately.

In conclusion, we demonstrated the important role of $1,25(\text{OH})_2\text{D}$ in preventing sudden, severe hypocalcemia due to decreased PTH levels after total thyroidectomy. High preoperative $1,25(\text{OH})_2\text{D}$ levels were significant risk factors for hypocalcemia. This study provides a basis for reviewing current clinical practice and developing more effective strategies for managing patients undergoing total thyroidectomy, with the aim of reducing the burden of hypocalcemia and improving patient outcomes. Further studies are warranted to validate these findings and refine perioperative protocols to improve patient care.

Data availability statement

The datasets presented in this article are not readily available because The datasets generated or analyzed during the current study are not publicly available because of the institution's policy but are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to Hiroyuki Yamashita, yamaftc@kojosen.com.

Ethics statement

The studies involving humans were approved by Ethics Committee of Yamashita Thyroid Hospital. The studies were

conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HY: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Data curation, Methodology. YM: Conceptualization, Data curation, Writing – review & editing, Formal analysis, Validation, Project administration. SS: Conceptualization, Data curation, Writing – review & editing, Validation. HS: Data curation, Writing – review & editing, Investigation, Validation. KY: Data curation, Writing – review & editing, Investigation. ST: Data curation, Writing – review & editing. TF: Data curation, Writing – review & editing. HT: Writing – review & editing, Conceptualization, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Causal role of immune cells in Hashimoto's thyroiditis: Mendelian randomization study

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Objectives: Hashimoto's thyroiditis (HT) is a common autoimmune disease whose etiology involves a complex interplay between genetics and environment. Previous studies have demonstrated an association between immune cells and HT. However, the casual relationship was not clear. We aimed to explore the causal associations between signatures of immune cells and HT.

Methods: In this study, bidirectional two-sample Mendelian randomization (MR) analysis was conducted to investigate the potential causal relationship between 731 immune cell signatures and HT by using genome-wide association study (GWAS) data. Heterogeneity and horizontal pleiotropy were detected through extensive sensitivity analyses.

Results: The increased levels of six immune phenotypes were observed to be causally associated with increased risk of HT $P < 0.01$, which were CD3 on CM CD8br, CD3 on CD39+ secreting Treg, HLA DR on CD33dim HLA DR+ CD11b-, CD3 on CD4 Treg, CD62L- plasmacytoid DC %DC, and CD3 on CD45RA+ CD4+. In addition, the levels of FSC-A on HLA DR+ T cell and CD62L on monocyte were associated with disease risk of HT $P < 0.01$. In addition, HT also had causal effects on CD3 on CM CD8br, CCR2 on monocyte, CD25 on CD39+ resting Treg, and CCR2 on CD62L+ myeloid DC $P < 0.05$.

Conclusions: In this study, we demonstrated the genetic connection between immune cell traits and HT, thereby providing guidance and direction for future treatment and clinical research.

KEYWORDS

immunity, Hashimoto's thyroiditis, Mendelian randomization, causal inference, thyroid

1 Introduction

As one of the most common autoimmune disorders in the world, Hashimoto's thyroiditis (HT) is characterized by lymphocyte infiltration and thyroid autoantibodies such as against thyroid peroxidase (anti-TPO) or thyroglobulin (anti-TG), which eventually leads to thyroid fibrosis and hypothyroidism (1, 2). According to statistics, there are 0.3–1.5 cases of HT per 1,000 people worldwide, with a male-to-female ratio of 1:7–10 (3). HT is the most common cause of hypothyroidism in iodine-sufficient areas (4). In the current state of science, there are few, if any, effective treatments available for people with HT in addition to thyroid hormone replacement (5). Thus, a better understanding of pathogenesis of HT is vital for the development of more effective treatments.

A growing number of studies have revealed the complex relationships between immune system and HT (6). Laboratory studies demonstrated that Treg cell deficiency was associated with infiltration of the thyroid gland, which could lead to thyroid cell apoptosis and hypothyroidism (7, 8). In addition, Breg cells appears to be involved in HT progression, although its mechanism of action is not yet fully understood (9, 10). In addition, several polymorphisms of cytokine genes, such as IL1 and IL17, were reported to be associated with the production of anti-TPO, which suggests that these cytokines participated in HT progression (11, 12). Although the close relationship between HT and immune system was identified by numerous observation studies, whether this association was causal still remains unknown.

Because genetic variants are randomly allocated at conception, the two-sample Mendelian randomization (MR) method can be used to evaluate the potential causal effect between an exposure and an outcome based on genetic variants, which reduces the effect of confounding factors and conquers reverse causality (13, 14). To further explore the causal relationship between immune cell signature and HT, a bidirectional two-sample MR analysis was conducted to examine the influence of immune cells on HT.

2 Methods

2.1 Study design

Two-sample bidirectional MR analysis was performed to evaluate the causal association between 731 immune cell signatures (seven groups) and HT. In MR analysis, single-nucleotide polymorphisms (SNPs) are used as instrumental variables to estimate the causal impact of exposure variables. Thus, it is essential that the valid instrumental variables (IVs) meet the following three core assumptions (1): IVs are highly associated with exposure (2); IVs must be unrelated to confounders (3); the IVs influence the outcome only via the exposure.

2.2 Exposure and outcome data sources

For each immune trait, full genome-wide association study (GWAS) summary statistics are publicly available through the GWAS Catalog server at <https://www.ebi.ac.uk/gwas/home> (accession

number from GCST90001391 to GCST90002121) (15). These GWAS data involve 3,757 subjects of Europeans, which reports the influence of 22 million variants on 731 immune cell signatures.

GWAS summary statistics for HT were acquired from study of Sakaue et al. (16). The data consist 395,640 cases and 379,986 controls of European ancestry. It was not necessary to obtain ethical approval for this study that used publicly available GWAS summary statistics.

2.3 Selection of instrumental variables

The threshold of significance of IVs for each immunotype was set to 1×10^{-5} according to recent research (15, 17). A threshold value of 0.001 was applied to the linkage disequilibrium parameter (R^2) in order to select the relevant SNPs. To ensure independence and eliminate the effect of linkage of disequilibrium on the results, a genetic distance of 10,000 kb was set. All of the above operations were performed by using R package "TwoSampleMR". Furthermore, we conducted a reverse-direction-MR analysis to examine the possibility of reverse-direction causal relationships. For immune cell traits, the significance level was adjusted to 5×10^{-8} .

2.4 Statistical analysis

All analyses were conducted in R (version 4.0.3).

We estimated the causal relationship between immune cell traits and HT using an inverse variance weighted (IVW-random), MR-Egger, and weighted median method and MR pleiotropy residual sum and outlier (MR-PRESSO) test. Among these, the IVW method is the primary approach.

For IVW ratio method MR, the Wald estimator was used to generate MR estimates for each SNP and exposure and outcome associations were both estimated with standard errors based on the Delta method (18). Cochran's Q statistics were conducted to examine the heterogeneity among estimates between each SNP, and if there is statistical heterogeneity among the findings ($P < 0.05$), we will select a random-effects model, and otherwise, a fixed-effects model will be used (19). Second, $P > 0.05$ indicated that there was no horizontal pleiotropy by using the intercept test of MR-Egger (20). In addition, we used the weighted median estimator, which allows the use of invalid instruments when at least half of the instruments are valid in the MR analysis (21). As an additional measure of robustness to the presence of heterogeneity among SNP effects, MR-PRESSO was employed in order to produce an MR estimate (22). As a visual inspection of symmetry and effect estimates, funnel plots and scatter plots were analyzed.

3 Result

3.1 Exploration of the causal effect of immunophenotypes on HT onset

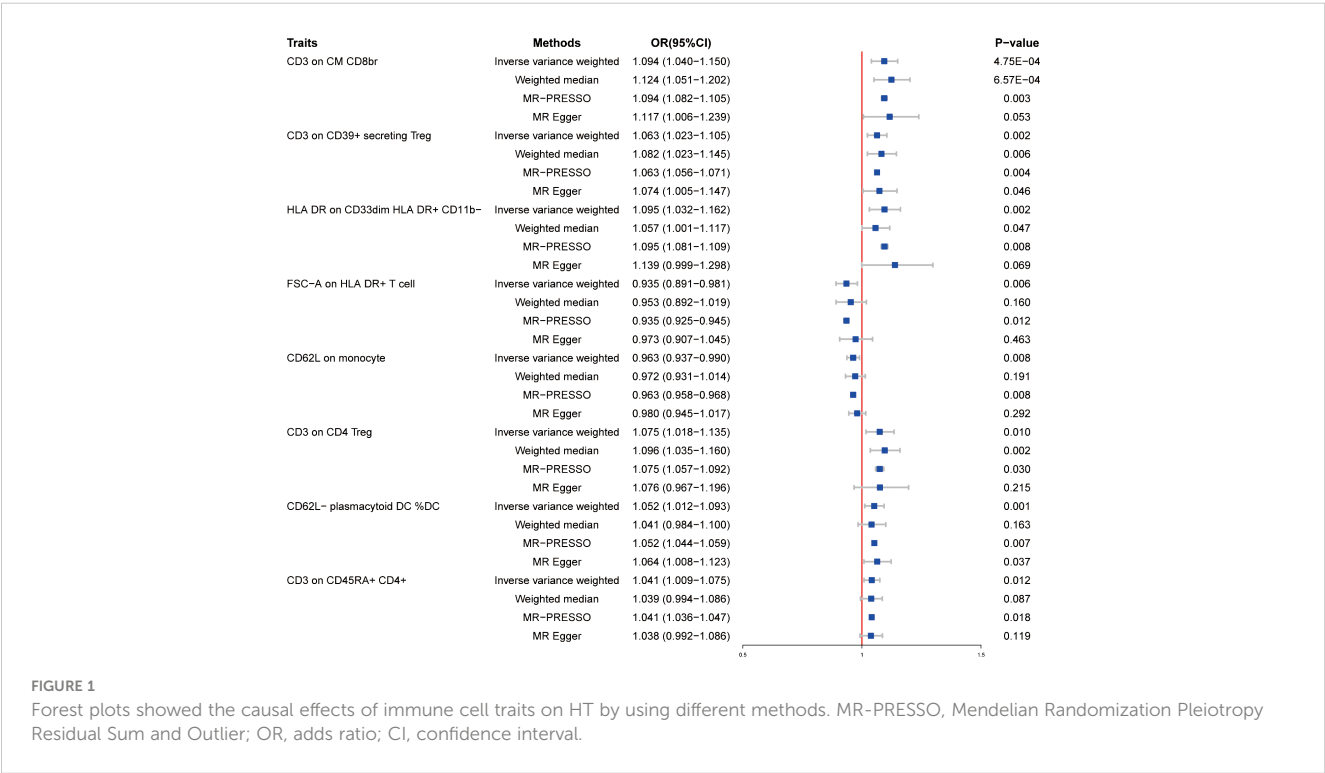
We examined the causal effect of immune cells on HT by using the two-sample MR analysis. When the P-value was set at $P < 0.05$,

a total of 34 immunophenotypes were identified. Of those, top 8 of them are shown in [Figure 1](#). As shown in [Figure 1](#), the level of CD3 on CD39+ secreting Treg was related to increased susceptibility of HT [odds ratio (OR) = 1.063, 95% confidence interval (CI) = 1.023–1.1015, P = 0.002]. In addition, the level of CD3 on CM CD8br increased the risk of HT (OR = 1.094, 95% CI = 1.040–1.150, P = 0.00048). HLA DR on CD33dim HLA DR+ CD11b– was also observed to be positively associated with the risk of HT (OR = 1.095, 95% CI = 1.032–1.162, P = 0.002). For CD3 on CD4 Treg, a positive association was observed (OR = 1.075, 95% CI = 1.018–1.135, P = 0.01), which was consistent with weight median (OR = 1.096, 95% CI = 1.035–1.160, P = 0.002). The causal effect of CD62L– plasmacytoid DC %DC on HT was estimated to be 1.052 (95% CI = 1.012–1.093, P = 0.001). This association was, however, not supported by the weighted median approach (OR = 1.041, 95% CI = 0.984–1.100, P = 0.163). Additionally, CD3 on CD45RA+ CD4 + was also found to be positively related to the increased risk of HT onset (OR = 1.041, 95% CI = 1.009–1.075, P = 0.012), but the association was not supported by weighted median (OR = 1.039, 95% CI = 0.994–1.086, P = 0.087) and MR Egger (OR = 1.038, 95% CI = 0.992–1.086, P = 0.119). However, the levels of FSC-A on HLA DR+ T cell (OR = 0.935, 95% CI = 0.891–0.981, P = 0.006) and CD62L on monocyte (OR = 0.963, 95% CI = 0.937–0.990, P = 0.008) were associated with disease risk of HT, which suggests the protective role of FSC-A on HLA DR+ T cell and CD62L on monocyte in HT. Details of the MR results and results of heterogeneity and pleiotropy are provided in [Supplementary Table S1](#). Detailed information about SNP exceeding the threshold level is listed in [Supplementary Table S2](#). We also provided the scatter plots and funnel plots for better

demonstration of causality and identification of heterogeneity ([Supplementary Figure 1](#)).

3.2 Exploration of the causal effect of HT on immunophenotypes

To determine whether the results could be explained by reverse causality, we performed MR analysis in the reverse direction. Four immunophenotypes were detected at P < 0.05: CD3 on CM CD8br (maturation stages of the T-cell panel), CCR2 on monocyte (monocyte panel), CD25 on CD39+ resting Treg (Treg panel), and CCR2 on CD62L+ myeloid DC (cDC panel) ([Figure 2](#)). Specifically, the OR of HT on CD3 on CM CD8br risk was estimated to be 0.853 (95% CI = 0.758–0.961, P = 0.009) by using the IVW method. A similar result was observed by performing the MR-PRESSO approach (OR = 0.853, 95% CI = 0.816–0.890, P = 0.026). In addition, results from the IVW method revealed that HT onset could decrease the level of CCR2 on monocyte (OR = 0.875, 95% CI = 0.773–0.990, P = 0.035), which was consistent with MR Egger (OR = 0.875, 95% CI = 0.893–0.911, P = 0.046). We also found that the risk of HT was negatively associated with the level of CD25 on CD39+ resting Treg (OR = 0.891, 95% CI = 0.798–0.996, P = 0.042) under the IVW model. A similar association was found for CCR2 on CD62L+ myeloid DC (OR = 0.864, 95% CI = 0.748–0.999, P = 0.049). Detailed results of reverse MR analysis as well as results of heterogeneity and pleiotropy test are shown in [Supplementary Table S3](#). Information of SNPs used for these four immune cell traits is listed in [Supplementary Table S4](#). Scatter plots and funnel plots also indicated the stability of the results ([Supplementary Figure 2](#)).



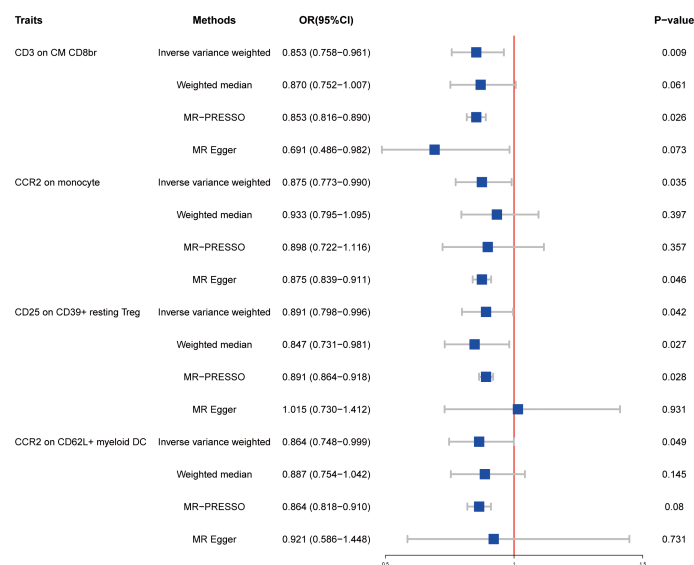


FIGURE 2

Forest plots showed the causal effects of HT on immunotypes. MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier; OR, odds ratio; CI, confidence interval.

4 Discussion

The lymphocytic infiltration in the thyroid gland represented the principal feature of HT; in this way, the thyroid gland can be invaded by lymphocytic cells, which leads to follicular atrophy hyperemia accompanied by oncocyctic metaplasia of follicular cells and eventually hypothyroidism (23, 24). Multiple lines of evidence have suggested that immune cells exert function in developments of HT. In a cross-sectional study, the investigators extracted peripheral blood mononuclear cells from both HT patients and healthy controls and the results showed that the percentage of Treg cells was significantly lower in HT patients (8). Another study identified an upregulation of Breg cells but a downregulation of their regulatory activity in HT patients (9, 10). However, whether there is a cause-and-effect relationship is still unclear.

For the first time, we used the GWAS summary data to analyze the causality between the 731 immune cell traits and HT. To the best of our knowledge, this is the first MR study to explore the causal associations between immunotypes and HT. In this study, among 731 immunotypes, 8 immunotypes had significant causal effects on HT ($P < 0.01$) and HT was found to have causal effects on four immunotypes ($P < 0.05$).

As mentioned above, T cells play an essential role in all stages of the development of HT. The CD3 molecule is identified as the T-cell-specific marker which is involved in T-cell development and signaling (25). It is well known that T cells can be divided into two distinct functional subtypes: the CD4+ T helper cells (Th) and the CD8+ cytotoxic T lymphocytes (CTL) (26). According to the difference of surface molecular and endogenous cytokines, CD4+ T cells could be classified into several subsets including Th1, Th2, Th9, Th17, Th22, and Tregs (27). Many lines of evidence suggest

that the balance between Th17 and Treg cells play a crucial role in progression of HT (28–30). The ratio of Th17/Treg increases as HT progresses, which is consistent with our research findings that the susceptibility of HT was negatively correlated with the level of CD25 on CD39+ resting Treg (31). However, the role of Tregs in occurrence of HT is still less defined. In our study, levels of three types of Tregs (CD3 on CD39+ secreting Treg, CD3 on CD4 Treg, and CD3 on CD45RA+ CD4+) were identified to be positively associated with the risk of HT. Foxp3 is the specific marker of Treg cells (32). It has been shown that genetic polymorphisms of Foxp3 increased the susceptibility of HT in Caucasian women, which could partly explain our results (33). In addition, we found that onset of HT was associated with greater proportions of CD3 on CM CD8br. CD3 on CM CD8br is a type of maturation stage of T cell that derived from bone marrow (34). There is evidence showing that CCR7 mediated the recruitment of mature T cells into the thyroid gland and hence promoted the formation of tertiary structures, which play an important role in HT (35). In addition, our findings reveal that the occurrence of HT decrease the level of CD3 on CM CD8br. This may be attributed to the persistent antigen stimulation leading to T-cell exhaustion in HT (36).

Macrophages are heterogeneous and can differentiate toward various phenotypes under different stimulations (37). Phenotype M1 is pro-inflammatory and can clear necrotic cell debris through releasing pro-inflammatory factors, whereas M2 is an anti-inflammatory phenotype which can facilitate tissue repair and remodeling in the reparative stage of inflammation (38). IL4 is a well-known cytokine that polarizes macrophages to M2 type (39). An animal experiment showed that the ectopic expression of IL4 in thyroid cells increased the incidence of HT and aggravated the severity of HT. Compared with the wild type, mice overexpressing

IL4 in the thyroid exhibited more infiltrations of macrophages (40). From this, we speculated that IL4 promoted progression of HT through motivating M2 macrophage polarization. However, our results could not prove that macrophages have a causal relationship with HT, and more studies are needed to prove these aspects.

The dendritic cell (DC) is one of the antigen-presenting cells which could coordinate adaptive immunity and innate immunity (41). Depending on developmental origin, surface marker, and committing transcription factors, DCs can be divided into classical DCs (cDCs), plasmacytoid DCs (pDCs), and monocyte-derived DCs (moDCs) (42). In our study, we found that the risk of HT increased with an increase in the proportion of CD62L⁺-plasmacytoid DC %DC. It was discovered that the density of plasmacytoid dendritic cells was significantly increased in patients with HT compared with controls and the density of plasmacytoid dendritic cells was positively associated with the progression of HT (43). These previous findings are consistent with the result of our present study, indicating that plasmacytoid cells play a critical role in the pathogenesis of HT. Notably, the presence of HT was found to be associated with decreased CCR2 on monocyte and CCR2 on CD62L⁺ myeloid DC. CCR2 are structurally chemokine receptors which can exert either proinflammatory or anti-inflammatory effects depending on the cellular context (44, 45). To date, there has been limited research on the role of CCR2 in HT. There are reports proving that the concentration of serum CCR2 ligands was higher in healthy controls compared with patients with autoimmune disorders such as multiple sclerosis (46, 47). These findings combined with our results let us to speculate that CCR2 may play an anti-inflammatory role in HT.

HLA DR, an MHC class II cell surface receptor, is encoded by the human leukocyte antigen complex on chromosome 6 region 6P21 (48). Several studies have shown that HLA DR⁺ thyroid epithelial cells exerted an *in situ* stimulation effect on the immune system within the thyroid gland of patients with HT (49, 50). In our study, we found that HLA DR on CD33dim HLA DR⁺ CD11b⁺ in the myeloid cell panel was associated with increased HT risk, which suggesting HLA DR⁺ myeloid cell may play a causative role for HT. However, the effect of FSC-A on the HLA DR⁺ T cell is opposite to the effect of HLA DR on CD33dim HLA DR⁺ CD11b⁺ in our study. FSC-A is a morphological parameter; thus, the result suggests that the immune cells morphology might affect their function.

Previous study has identified hub genes with high diagnostic accuracy in HT by the bioinformatic method, and immune profiling revealed that the infiltration of monocyte was inversely associated with the expression of hub genes. This is in agreement with our finding that the risk of HT decreases as the level of CD62L on monocyte increase (51).

TPO is a key enzyme for synthesizing the thyroid hormone (52). It is demonstrated by *in vitro* experiments that anti-TPO could injure thyroid follicular cells through the antibody-dependent cytotoxic mechanism (53). TG is a type of glycoprotein mainly in the thyroid follicular epithelium. A large amount of TG is released when thyroid tissue damage occurs, and the level of anti-TG also increases (54). However, the immunological mechanism underlying

the effects of anti-TG in HT is unclear therefore further research is still required.

We have to admit that our research has limitations. First of all, the single population from the Europeans may limit the generalization of our results to other populations. Secondly, due to the lack of individual data such as age or gender, we were unable to perform stratified analysis in this study. Finally, the substantial causal relationship between immune features and HT needs to be further explained due to lack of direct biological evidence.

5 Conclusion

In conclusion, this MR study offers genetic evidence for a potential association between immune cell traits and HT. In future studies, animal experiments and large-scale clinical randomized controlled trials are needed to elucidate the underlying mechanism linking these immune cell traits and HT.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#). Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

ZZ: Conceptualization, Writing – original draft, Writing – review & editing. YG: Writing – review & editing. XP: Data curation, Writing – review & editing. WW: Data curation, Writing – review & editing. HZ: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1352616/full#supplementary-material>

SUPPLEMENTARY TABLE 1

MR results as well as heterogeneity and pleiotropy results of the causal effect of immune cells on HT ($P < 0.05$).

SUPPLEMENTARY TABLE 2

Detailed information about SNPs associated with immune cell traits whose $P < 0.05$.

SUPPLEMENTARY TABLE 3

Results of MR and results of heterogeneity and pleiotropy of causal relationship between HT and immunotypes.

SUPPLEMENTARY TABLE 4

Detailed information about SNPs of immunotypes which are causally affected by HT.

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Estimating the global prevalence of secondary hyperparathyroidism in patients with chronic kidney disease

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Background: Chronic kidney disease (CKD)-related secondary hyperparathyroidism (SHPT) is associated with higher morbidity and death. The goal of this study was to mine the SHPT data already available to do a meta-analysis on the global prevalence of SHPT caused by CKD.

Methods: Embase, Medline, Web of Science, Cochrane Central Databases, and Google Scholar were searched to identify studies on the prevalence of SHPT due to CKD from inception to November 2023. Pooled prevalence was calculated using the DerSimonian-Laird random effects model with a logit transformation.

Results: Twenty-one eligible studies involving 110977 patients were included. Our results revealed that the estimated global prevalence of SHPT due to CKD was 49.5% (95% CI 30.20–68.18), regardless of the diagnostic criteria. For subgroup analysis, Southern Asia (84.36%, 95% CI 79.35–88.34) had a significantly higher SHPT prevalence than other geographic regions. SHPT due to CKD was most prevalent in China (85.14%, 95% CI 81.74–88.00).

Conclusions: SHPT due to CKD is highly prevalent. This necessitates awareness and therapeutic approaches from primary care physicians, medical professionals, and health strategy authorities.

Systematic Review Registration: <https://www.crd.york.ac.uk/PROSPERO>, identifier CRD42024514007.

KEYWORDS

secondary hyperparathyroidism, prevalence, chronic kidney disease, meta-analysis, meta

1 Introduction

Hyperparathyroidism (HPT) is classified as primary, secondary, and tertiary. The causes of secondary hyperparathyroidism (SHPT) include chronic kidney disease (CKD), deficiencies of vitamin D, rickets, and other factors (1, 2). CKD, considered an abnormality of kidney structure or function, is widely recognized as the leading cause of SHPT. It is evident that the prevalence of CKD in the general population is rapidly growing. SHPT, as one of the common comorbidities associated with advanced CKD, has become almost universal in CKD patients (2). SHPT, characterized by elevated parathyroid hormone (PTH), hypocalcemia, and hyperphosphatemia, affects cardiovascular, nervous, skeletal, blood, and other systems. As a result, SHPT may contribute to the development of bone demineralization, high bone turnover, and extraskelatal calcification (3). Patients with SHPT may suffer from severe cardiovascular calcification, renal osteopathy, fractures, erythropoietin resistance, and other adverse clinical events (3). Increasing evidence suggests that SHPT patients are more likely to suffer from worse quality of life, increased cardiovascular morbidity, and mortality (4, 5). Alarming, SHPT has become a major public health issue associated with the enormous consumption of economic and social resources (6, 7).

It has been demonstrated that the prevalence of SHPT resulting from CKD varies widely, ranging from 31% to 85% (6, 8, 9). A systematic review has documented that the prevalence of SHPT due to CKD ranges from 30% to 54% in Europe, Australia, and the Americas, but this rate reaches as low as 11.5%–28% in Asia (10). However, to date, there is a paucity of meta-analysis that assesses SHPT prevalence in CKD patients. To address this issue, we conducted a systematic review and meta-analysis to evaluate the global prevalence of SHPT due to CKD by exploring the existing epidemiologic data on SHPT due to CKD.

2 Materials and methods

This study was conducted entirely in compliance with the PRISMA declaration, and this protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews of the University of York (CRD42024514007).

2.1 Systematic literature search

Embase, Medline, Web of Science, Cochrane Central Databases, and Google Scholar were searched systematically for all articles published in the English language up until November 2023. The following terms were used: “secondary hyperparathyroidism,” “chronic kidney disease,” “epidemiology,” and “prevalence” (the full search strategies are provided in the [Supplementary Methods](#)). To locate pertinent research, reference lists of earlier papers were also found. Only human studies with full-text descriptions that were published in English were considered. When two independent reviewers could not agree on whether or not an article should be included, a third reviewer was chosen to make the final decision.

2.2 Inclusion and exclusion criteria

Two reviewers independently screened and identified the search findings for eligible studies. Inclusion criteria were as follows: (1) studies identified SHPT; (2) patients with CKD; (2) studies reported clear documentation of the prevalence of SHPT; (3) study period from January 1990 to November 2023. Studies were excluded from the analysis based on the following: (1) case reports, abstracts, reviews, correspondence, letters, editorials, and expert opinions; (2) studies with no clear data for authors to calculate the aggregated prevalence; and (3) studies that were not reported in English.

2.3 Data extraction and quality assessment

Data were extracted by three independent reviewers from eligible studies using standardized forms, with 10% of studies randomly checked by another author. When similar studies were published by the same institution or authors, either the largest sample size or the most recent publication was included in the analysis. The recorded data included: year of publication, study year, first author, country or region, level of country development, sex, mean age, diagnostic criteria, prevalence of disease, number of patients, study design, and study source. The quality of the included study was assessed using the Newcastle Ottawa scale (NOS) by examining three factors: patient selection, comparability of the two groups, and assessment of outcome (11). Studies valued at six or more stars were considered to be of higher quality. Based on the quality score, studies were not excluded for improving transparency and ensuring available data were reported.

2.4 Statistical analysis

Meta-analysis was performed using the “Meta” and “Metafor” modules in the R-4.0.0 statistical software package. A 95% confidence interval (CI) was calculated using the Wilson score method, and pooled prevalence was analyzed using the DerSimonian-Laird random-effects model with logit transformation. Heterogeneity was measured using the Cochran Q statistics and I^2 statistics. Pooled prevalence was calculated using a random-effects model because global evidence was expected to be heterogeneous. Additionally, sensitivity analyses were undertaken by leave-one-out diagnostic tests, and findings were verified by a built-in function. Subgroup analyses were also undertaken to evaluate potential heterogeneity. *P* values were used for the evaluation of the difference between subgroup analyses. *P* values <0.05 indicated a significant difference.

3 Results

3.1 Study characteristics

The search generated 680 records after removing duplicates. Initial screening of titles and abstracts resulted in the exclusion of 388 records. The full text of 292 articles was selected for further investigation.

Finally, 21 studies (6, 8, 9, 12–29) matched our inclusion criteria and were included in the analysis (Figure 1). The general characteristics of the included studies in the meta-analysis are shown in Table 1. The quality assessment scores for the included studies are given in Table 2. The quality scores of all studies ranged from 6 to 8. As a result, the majority of the included studies had a cross-sectional design. The mean or median age of participants ranged from 44.47 years to 65.40 years. The percentages of women ranged from 18.75% to 53.30%.

3.2 SHPT prevalence

Overall, 21 studies from five countries or regions (three European countries, five African countries, seven Northern American countries, five Asian countries and regions, and one

South American country) involved a total of 110,977 individuals who reported SHPT prevalence in patients with chronic kidney disease. A total of 10,233 participants were diagnosed with SHPT. The overall pooled estimated prevalence was 49.5% (95% CI 30.20 – 68.18, $I^2 = 100\%$, Figures 2, 3A), regardless of the diagnostic criteria. By performing sensitivity analysis and leave-one-out analysis, we failed to identify outliers. (Supplementary Tables 1, 2; Supplementary Figure 1). After conducting subgroup analysis, varied prevalences of SHPT were observed across different geographic regions ($P < 0.05$). The highest SHPT prevalence was found in Southern Asia with an estimated rate of 84.36% (95% CI 79.35–88.34, Figure 3B), followed by Western Europe (67.24%, 95% CI 62.54–71.61), Eastern Asia (60.48%, 95% CI 10.26–95.35), Eastern Europe (56.52%, 95% CI 47.34–65.27), Western Africa (53.29%, 95% CI 40.88–65.31), Western Asia (45.00%, 95% CI

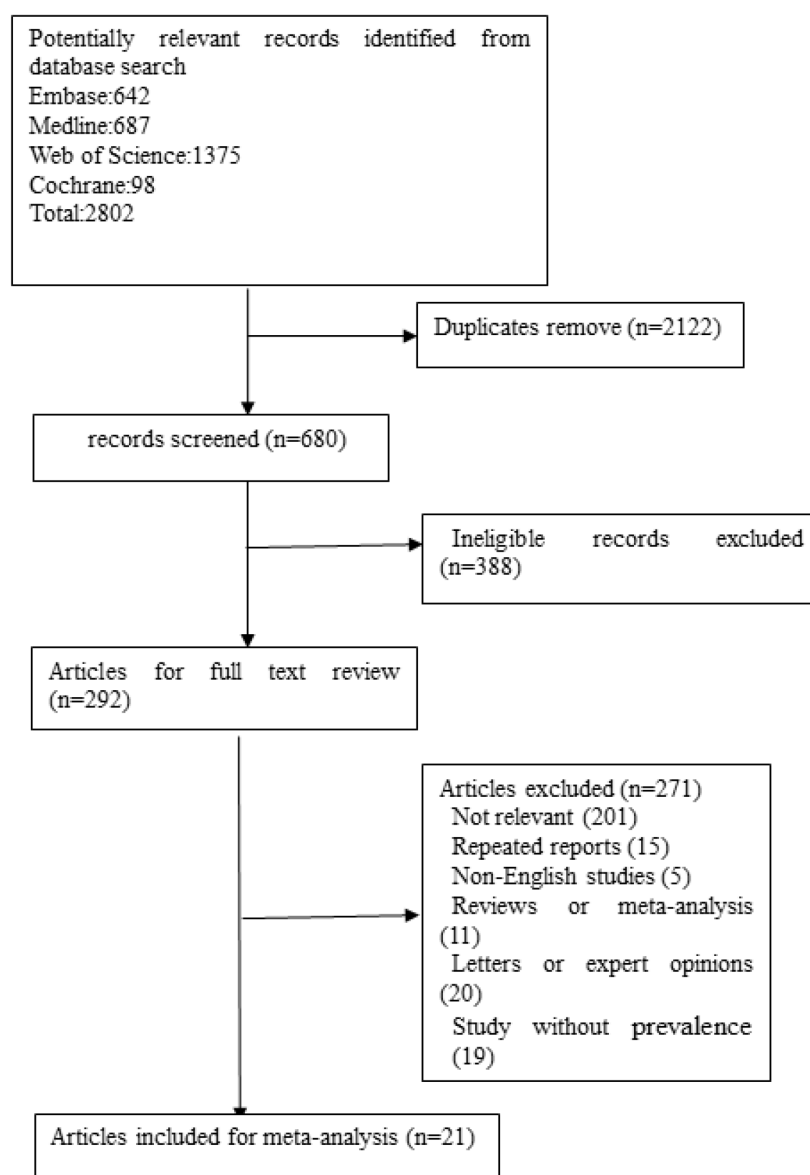


FIGURE 1
Flow diagram depicting the study selection.

TABLE 1 Characteristics of the studies included in the meta-analysis.

Study	Country	Year	Study time	Design	Sample source	Diagnostic criteria	Age	CKD stage	SHPT	Individuals
Xu Y (6)	Sweden	2021	2006–2011	Cross-sectional	School	iPTH > 65 pg/mL	65.4 ±14.5	stage 1–5	784	2,556
Okoye JU (8)	Nigeria	2015	2010–2011	Cross-sectional	Hospital	iPTH > 65 pg/mL	Not specified	Not specified	72	85
Owda A (9)	USA	2016	2013	Cross-sectional	Hemodialysis center	iPTH > 200 pg/mL	58 ± 14	Not specified	95	122
Arévalo-Lorido JC (12)	Spain	2016	2013	Cross-sectional	Community	iPTH ≥ 70 pg/mL	Not specified	stage 3 and 4	275	409
Gimba ZM (13)	Nigeria	2018	2011–2012	Cross-sectional	Hospital	iPTH ≥ 65 pg/mL	44.17 ± 15.60	stage 2–5	127	230
Abdu A (14)	Nigeria	2019	2011–2012	Cross-sectional	Hospital	iPTH > 400 pg/mL	45.96 ± 13.7	Not specified	15	48
Sutton W (15)	USA	2022	2008–2020	Prospective	Hospital	iPTH ≥ 70 pg/mL	53.1 ± 13.7	Not specified	524	849
Seck SM (16)	Senegal	2012	2011	Cross-sectional	Dialysis center	Patients with high turn-over osteopathy	Not specified	Not specified	57	118
Gutiérrez OM (17)	USA	2008	2004	Cross-sectional	SEEK	iPTH > 65 pg/mL	Not specified	Not specified	103	1,860
Căpușă C (18)	Romania	2016	Not specified	Cross-sectional	Tertiary care center	iPTH > 73 pg/mL	Not specified	stage 2–5	65	115
Salem MM (19)	USA	1997	2012–2013	Cross-sectional	Outpatient dialysis units	iPTH > 195 pg/mL	56 ± 15	Not specified	305	612
Ghosh B (20)	India	2012	2008–2010	Cross-sectional	Hospital	iPTH > 69 pg/mL	45.67 ± 16.96	stage 4 and 5	131	150
Vikrant S1	India	2016	2011–2014	Cross-sectional	Community	iPTH > 65 pg/mL	56.8 ± 13.1	stage 3 and 5	382	462
Rahimian M (22)	Iran	2008	2009–2010	Cross-sectional	Hospital	Not specified	Not specified	Not specified	36	80
Bhan I (23)	USA	2010	2002–2007	Retrospective	MGPC network	iPTH > 60 pg/mL	Not specified	stage 3 and 4	688	1,252
Chua CC (24)	Philippine	2010	2000–2009	Cross-sectional	Community	Not specified	64 ± 11	Not specified	41	142
Schumock GT (25)	USA	2008	2000–2004	Retrospective	PharMetrics Patient-centric database	based on at least one medical or facility claim indicative of the diagnosis, ICD-9 code 588.8x	Not specified	Not specified	667	66,019
Jovanovich A (26)	USA	2012	2001–2003	prospective	Medical centers	iPTH > 65 pg/mL	Not specified	Not specified	1,285	1,497
Lou I (27)	Nigeria	2015	2004–2012	Cross-sectional	Hospital	iPTH > 72 pg/mL	51.5 ± 0.51	Not specified	694	1,609
Oliveira RB (28)	Brazil	2011	2010–2011	Cross-sectional	Dialysis units	iPTH > 1,000 pg/mL	Not specified	Not specified	3,463	32,264
Wei Y (29)	China	2016	2008–2012	Cross-sectional	School	iPTH > 88 pg/mL	49.45 ± 16.33	Not specified	424	498

iPTH, intact parathyroid hormone; SHPT, secondary hyperparathyroidism; CKD, chronic kidney disease; MGPC, Massachusetts general hospital primary care; and ICD, international classification of diseases.

TABLE 2 Newcastle-Ottawa scoring for including studies.

	Year	Representative (0–1)	Present outcome at the beginning of study (0,1)	Sample size (0, 1)	Diagnostic tool (0–2)	Comparability of study population (0 or 2)	Outcome assessment (0–1)	Statistical test (0–1)	Score
Xu Y (6)	2021	1	1	1	1	2	1	1	8
Okoye JU (8)	2015	1	0	1	1	2	1	1	7
Owda A (9)	2016	1	1	1	1	2	1	1	8
Arévalo-Lorido JC (12)	2016	1	1	1	1	2	1	1	8
Gimba ZM (13)	2018	1	0	1	1	1	1	1	6
Abdu A (14)	2019	1	1	1	1	2	1	1	8
Sutton W (15)	2022	1	1	1	1	2	1	1	8
Seck SM (16)	20127	1	0	1	1	1	1	1	6
Gutiérrez OM (17)	2008	1	1	1	1	2	0	1	7
Căpușă C (18)	2016	1	1	1	1	2	1	1	8
Salem MM (19)	1997	1	1	1	1	1	1	1	7
Ghosh B (20)	2012	1	1	1	1	1	1	1	7
Vikrant S (21)	2016	1	0	1	1	1	1	1	6
Rahimian M (22)	2008	1	1	1	1	2	1	1	8
Bhan I (23)	2010	1	0	1	1	2	1	1	7
Chua CC (24)	2010	1	0	1	0	2	1	1	6
Schumock GT (25)	2008	1	0	1	1	2	0	1	6
Jovanovich A (26)	2012	1	1	1	1	2	0	1	7
Lou I (27)	2015	1	1	1	1	2	1	1	8
Oliveira RB (28)	2011	1	1	1	1	1	1	1	7
Wei Y (29)	2016	1	0	1	1	2	1	1	7

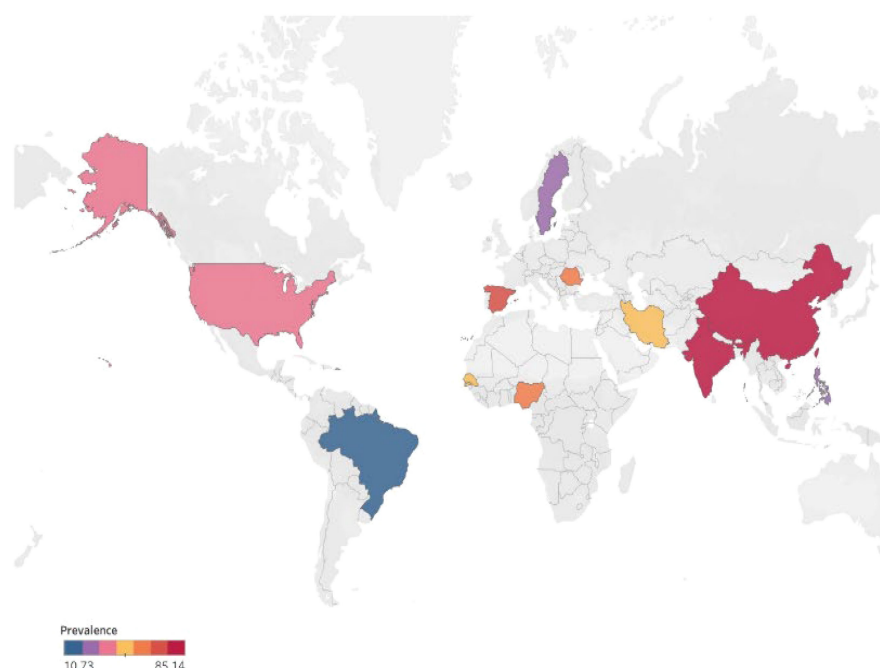


FIGURE 2

Global prevalence of secondary hyperparathyroidism in patients with chronic kidney disease.

34.50–55.97), Northern America (37.08%, 95% CI 6.31–83.76), Northern Europe (30.67%, 95% CI 28.911–32.49), and South America (10.73%, 95% CI 10.40–11.08). By stratifying data according to countries and regions, SHPT prevalence varied from 10.73% (Brazil, 95% CI 10.40–11.08, **Figure 3C**) to 85.14% (Chin, 95% CI 81.74–88.00, **Figure 3C**) ($P < 0.05$). Considering the country income, SHPT prevalence was higher in lower-middle-income countries (58.63%, 95% CI 43.44–72.34, **Figure 3D**) than in high-income countries (39.59%, 95% CI 11.49–76.80, **Figure 3D**) or upper-middle-income countries (49.03%, 95% CI 5.67–93.90, **Figure 3D**), although without a significant difference. The SHPT prevalence was 56.29% (95% CI, 33.05–53.3%, **Figure 3E**) and 39.59% (95% CI, 11.49–76.80%, **Figure 3E**) in developing and developed countries, respectively. Moreover, SHPT prevalence for the quality scores of studies valued above or below 8 points was 52.13% (95% CI 40.28–63.74, **Figure 3F**) and 47.27% (95% CI 22.06–73.95, **Figure 3F**), respectively. When stratifying data by sex, the SHPT prevalence was 39.88% (95% CI 19.14–65.01, **Figure 3G**) in men and 38.47% (95% CI 17.35–65.07, **Figure 3G**) in women.

4 Discussion

To the best of our knowledge, this is the first comprehensive meta-analysis aimed at estimating the global prevalence of SHPT due to CKD. In our meta-analysis, we estimated the global prevalence of SHPT due to CKD through existing epidemiology data. We found that the overall prevalence of SHPT due to CKD is 49.5% (95% CI 30.20–68.18), regardless of the diagnostic criteria.

More importantly, our results revealed significant differences among geographic regions and countries, with Southern Asia and China having the highest prevalence rates (84.36%, 95% CI 79.35–88.34) and (85.14%, 95% CI 81.74–88.00), respectively.

There has been one systematic review showing that SHPT prevalence among dialysis populations is highly variable based on geographic regions. In Europe and Australia, SHPT prevalence varied from 30% to 49% (10). SHPT prevalence in the Americas was estimated at 54%, while that in Asia (India and Japan) was 28% and 11.5%, respectively (10). In contrast, we observed that Southern Asia led with the highest prevalence (84.36%), followed by Western Europe (67.24%). SHPT prevalence was lowest in South America (10.73%). This discrepancy might be attributed to differences in cutoff values for diagnostic criteria, cultural traditions, population selection, and duration of dialysis (29). In addition, underdiagnosis in lower-middle-income geographic regions may be a factor contributing to the discrepancy.

It is evident that sex is considered one of the risk factors for SHPT, though the effect of sex remains debated. A previous study documented that the female sex is associated with the development of SHPT in CKD patients (13). However, Xu et al. reported that the male sex is correlated with a higher risk of SHPT due to CKD (6). Unexpectedly, in the current study, we observed a comparable prevalence of SHPT between men and women. Further prospective trials with larger sample sizes are needed to confirm the effects of sex on SHPT.

It has been demonstrated that various factors are correlated with the development of SHPT. Hyperphosphatemia, hypocalcemia, and elevated alkaline phosphatase levels are identified as risk factors for SHPT (13). Additionally, a low estimated glomerular filtration rate, young age, male sex, and diabetes are strong risk factors for SHPT

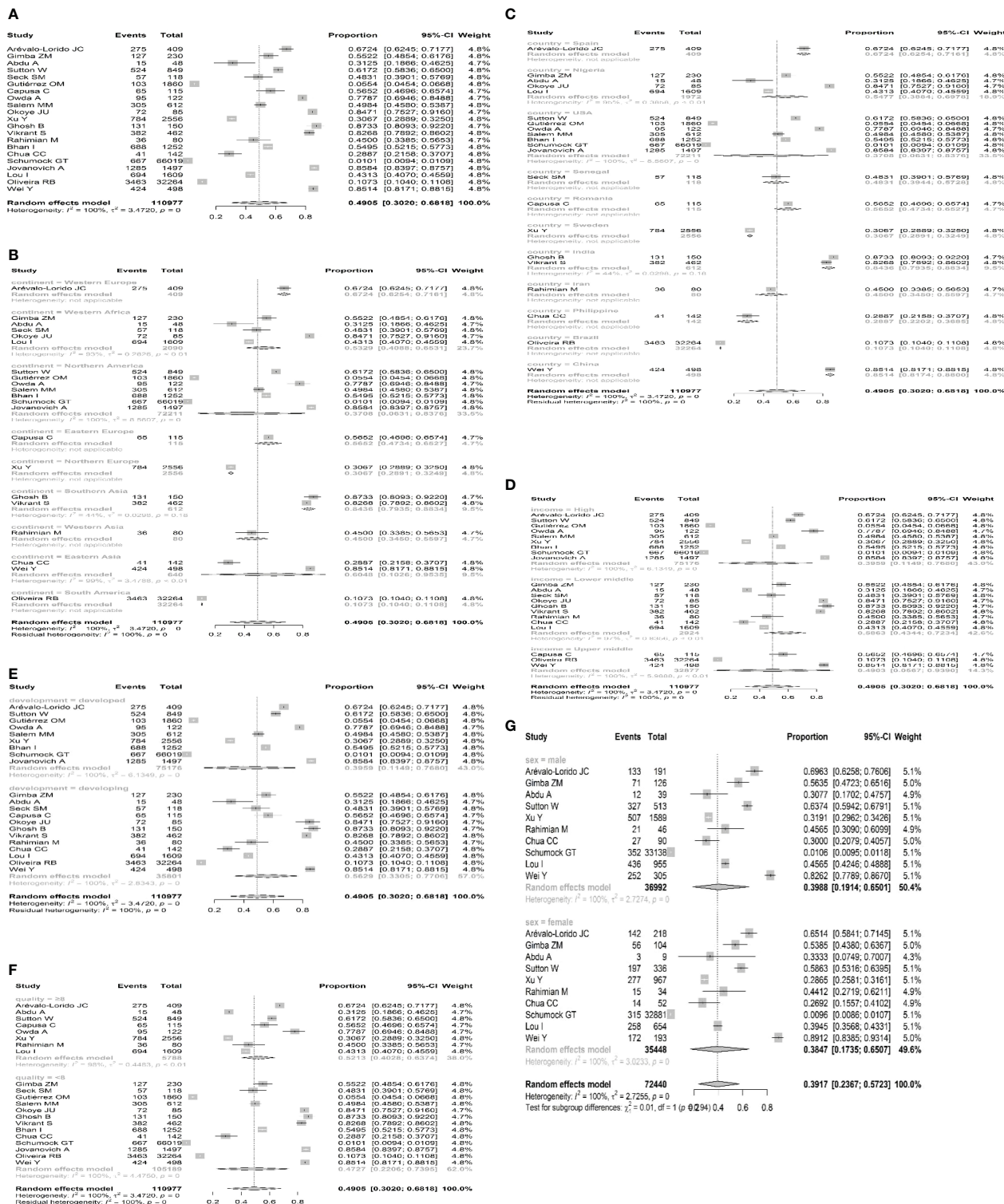


FIGURE 3

(A) Forest plots displaying prevalence in CKD patients. SHPT, secondary hyperparathyroidism; CKD, chronic kidney disease; and CI, confidence intervals. (B) Forest plots displaying the prevalence of SHPT stratified by continents. SHPT, secondary hyperparathyroidism; CKD, chronic kidney disease; and CI, confidence intervals. (C) Forest plots displaying the prevalence of SHPT stratified by countries and regions. SHPT, secondary hyperparathyroidism; CKD, chronic kidney disease; and CI, confidence intervals. (D) Forest plots displaying the prevalence of SHPT stratified by country income. SHPT, secondary hyperparathyroidism; CKD, chronic kidney disease; and CI, confidence intervals. (E) Forest plots displaying the prevalence of SHPT stratified by the development of countries. SHPT, secondary hyperparathyroidism; CKD, chronic kidney disease; and CI, confidence intervals. (F) Forest plots displaying the prevalence of SHPT stratified by study quality. SHPT, secondary hyperparathyroidism; CKD, chronic kidney disease; and CI, confidence intervals. (G) Forest plots displaying the prevalence of SHPT stratified by sex. SHPT, secondary hyperparathyroidism; CKD, chronic kidney disease; and CI, confidence intervals.

development (6). Previous studies have also highlighted that serum creatinine and phosphorus are independently associated with SHPT (29). Unfortunately, we cannot calculate pooled estimates of the risk factors associated with SHPT prevalence due to the limited number of studies.

Nevertheless, the current study has several limitations. First, a relatively small number of studies were included in the meta-analysis. Second, limited data from Western Europe, Eastern Europe, Northern Europe, Western Asia, and South America made it challenging to accurately estimate SHPT prevalence in these continents. Third, the different cutoff values for diagnostic criteria could result in publication bias. Additionally, this study failed to pool and estimate some stratified data due to the limited number of studies on CKD stage, dialysis vintage, co-morbidities such as diabetics, hypertension, and race.

5 Conclusion

In summary, this systematic review demonstrates a high prevalence of SHPT in patients with CKD. The significant threat to public health and growing burden on SHPT patients are more worrisome. Our findings call for increased attention and management for SHPT in CKD patients from primary care physicians, medical professionals, and health strategy authorities. More emphasis should also be placed on improving the diagnosis of SHPT. However, there is a need for further adequately powered, well-designed prospective studies to clarify the global epidemiology of SHPT in CKD patients.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

Author contributions

ZL: Resources, Project administration, Writing – review & editing, Visualization, Validation, Supervision, Methodology,

Conceptualization. YW: Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. JL: Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. YF: Writing – original draft, Validation, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. SZ: Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization. XL: Writing – review & editing, Visualization, Validation, Supervision, Methodology, Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1400891/full#supplementary-material>

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Ultrasound-guided approach to surgery for nodal recurrence following lateral neck dissection for differentiated thyroid carcinoma. A single institution experience

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Introduction: Total thyroidectomy (TT) and central neck dissection (CND) had a significant effect on the reduction of local recurrence compared with TT alone. Lateral Neck Dissection (LND) was performed in all the cases with therapeutic intent. The suspicion of nodal recurrence is provided by the appearance of one or more enlarged nodes in the central and/or laterocervical compartment during the follow up period.

Methods: From January 2018 to November 2023, 16 patients at the University General Surgery unit of the Polyclinic of Foggia underwent reoperation due to nodal recurrence after previously undergoing total thyroidectomy with central and lateral cervical dissection.

Results: All surgical interventions were approached with intraoperative ultrasound performed by the operating surgeon. In all cases, ultrasound identification of the suspicious lymph node led to histological confirmation of malignancy. In only two cases it was necessary to carry out an extemporaneous intraoperative histological examination. No complications were recorded during the operations.

Conclusions: Surgical reintervention in patients with nodal recurrence is challenging and requires an assessment by members of the interdisciplinary team. The ideal method should be economically convenient, easy to practice, with a quick learning curve, easily reproducible, and safe for patients. Intraoperative, ultrasound-guided, is a safe and effective technique. It facilitates tumor localization and removal, especially in patients requiring re-operative neck surgery.

KEYWORDS

thyroid carcinoma, nodal recurrences, intraoperative ultrasound, lateral neck dissection, neck surgery

Introduction

Differentiated thyroid carcinoma (DTC) is a gradually increasing tumor with an excellent prognosis and a 10-year survival rate above 90% (1). Data from 2006 to 2012 indicate that the annual incidence of thyroid cancer is approximately 5.4% in men and 6.5% in women. In addition, thyroid cancer is the fifth most common malignant tumor in women and the most common cancer in women under the age of 25, with an average annual incidence

rate of 6.2% (2, 3). Surgery is certainly still the cornerstone in treatment and implicates the removal of the thyroid with associated removal of the involved cervical lymph nodes.

Nodal involvement may include the central compartment (CC) or the lateral cervical compartment (LC), and the lateral neck dissection (LND) is considered an important surgical procedure and is executed merely with therapeutic intent when node involvement is confirmed (preoperatively or intraoperatively) and not for prophylactic purpose as in the case of central neck dissection (CND) (4). However, nodal recurrent disease (defined as clinically detectable disease in the central and/or lateral compartment lymph nodes) (5), it is the most frequent site of disease recurrence, although it is by no means a very frequent event, especially in cases in which a lymph node dissection has already been performed (6).

Surgery for lateral neck lymph node recurrence following LND represents a challenging event for both patients and surgeons due to the difficulties of reoperation, including an increasing risk of postoperative morbidities.

The aim of this study is to demonstrate how in our center, the use of intraoperative ultrasound can allow surgery to be conducted in a safe and effective manner.

Methods

Between January 2018 and November 2023, nearly 400 thyroid surgeries were performed at the University General Surgery unit of the Polyclinic of Foggia, addressing both benign and malignant conditions, including central and lateral neck dissections.

This study included patients who had previously undergone total thyroidectomy with central neck dissection (CND) and lateral neck dissection (LND) and who experienced nodal recurrence during the follow-up period, presenting a significant surgical challenge. Patients without evidence of nodal recurrence or those with locoregional or distant recurrence were excluded from the study.

Postoperative follow-up was conducted for all patients, involving consistent hormonal suppressive treatment. Patients underwent an ultrasound neck evaluation initially six months post-surgery, followed by annual assessments, including the evaluation of thyroglobulin (Tg) levels. Radioactive iodine (RAI) therapy was considered based on the stage and associated risk factors. In cases of suspected nodal recurrence, fine-needle aspiration cytology (FNAC) and scintigraphic studies were performed for further evaluation.

Results

Overall 16 patients were included in this study: 5 male and 11 female and a mean age of 55.25 ± 11.44 years. All preoperative patients' characteristics are reported in Table 1.

All patients previously underwent total thyroidectomy + CND + LND. The postoperative histological examination showed a prevalence of pT3/T4 cases, multifocality and extracapsular

TABLE 1 Preoperative patients' characteristics.

N patients	16
Age (years)	
Range	38–72
Mean	55.25
Median	55.5
M:F	11:5
pT stage	
T1/T2	6
T3/T4	10
Multifocality Yes/No	12/4
Extracapsular invasion	14/2
No. of removed lateral neck nodes	
Range	22–46
Mean	35.93
Median	34.5
No. of metastatic lateral neck nodes	
Range	4–8
Mean	5.81
Median	6
Lymph node ratio	
Range	0.17–0.22
Mean	0.18
Median	0.2
Bilateral lateral neck dissection Yes/No	4/12
Comprehensive LND (levels II–V)/Limited LND	11/5
First surgery outside our Institution Yes/No	9/7

invasion. The average number of lymph nodes removed was 35.93, with an average lymph node ratio of 0.18. Bilateral lymphadenectomy was performed in 4 patients, and 7 operations were conducted at a center other than ours.

All patients examined in this study developed nodal recurrence (Table 2). Nodal recurrence was diagnosed during the follow-up period, with an average time of 6.21 years. The patients underwent a complete neck ultrasound, followed by FNAC or scintigraphic examination. In all cases, lateral neck lymph node recurrence was shown on the ultrasound and confirmed with FNAC, except for one case where the position and relationship

TABLE 2 Data regarding nodal recurrence.

Nodal recurrence	16/16
Time of recurrence (years)	
Range	2–8.2
Mean	6.21
Median	6.20
DS	± 1.29
Diagnostic tools	
- FNAC Yes/No	15/1
- Scintigraphy Yes/No	14/2
Previous RAI treatment	16/16
Ultrasound-guided surgical approach	16/16
Correspondence with preoperative ultrasound Yes/No	11/5
Need for extemporaneous histological examination Yes/No	2/14
Postoperative complication	//
Postoperative hospital stay (days)	
Range	1–2
Mean	1.19
Median	1.00



FIGURE 1

(A) Intraoperative ultrasound detection of suspicion node; (B) intraoperative ultrasound control after node's removal (C) pathological node.

of the suspicious lymph node with the large vessels of the neck made the procedure impractical and unsafe.

In all cases, preoperative and intraoperative ultrasounds were performed by the surgical team. Knowing the exact location of the suspected lymphadenopathy is crucial for ensuring the surgical intervention is quick, effective, and safe. Therefore, in all cases of reoperation, a new ultrasound is performed with the patient already positioned on the operating bed, in addition to analyzing the preoperative ultrasound. The entire operation is conducted with the aid of an intraoperative ultrasound to ensure the correct identification and subsequent removal of the previously described lesion (Figure 1).

The value of intraoperative ultrasound is highlighted by the inconsistencies we observed between the ultrasound descriptions during follow-up and the actual findings in some cases.

Furthermore, in two cases, a frozen section examination was necessary before concluding the operation due to discrepancies between the preoperative and intraoperative ultrasound evaluations. In both instances, the diagnosis of thyroid cancer metastasis was confirmed. No postoperative complications were recorded, and the average postoperative hospital stay was 1.19 days.

Discussion

Recurrence of DTC commonly occurs in the lymph nodes of the neck after initial treatment (7). However, extensive extension beyond the thyroid observed during surgery is also a significant factor for recurrence in the thyroid bed. When small, suspicious sub-centimeter lymph nodes are detected on ultrasound, a watch-and-wait approach can be adopted to monitor for any progression. A recent retrospective study (8) observed a 51-month progression-free survival (PFS) rate of 35% in 14 out of 40 patients who had metastatic lymph nodes measuring less than 2 cm in their largest diameter. According to the guidelines provided by the ATA, central compartment lesions larger than 5 mm (in the smallest diameter) and lateral neck lesions larger

than 8 mm (in the smallest diameter) may be recommended for fine-needle aspiration (FNA) biopsy, along with Tg levels determination through aspiration if necessary, but only if a specific treatment plan is in place (9, 10).

There are some alternative treatments to surgery, such as or limited lesions (less than 2 cm) that show RAI uptake, 131I can serve as an alternative treatment, or other treatments that have been used for cases of isolated metastasis include ethanol injection and US-guided percutaneous ablation (radiofrequency, laser, microwave, or cryotherapy), but surgery remains the first choice in all cases of resectable disease (11, 12).

If a previous LND has not been performed, compartmental dissection of the target level is indicated. However, if the recurrence occurs on a neck in which lymph node dissection has already been performed, the operation may be more challenging selective excision of the lymph nodes can be made (13).

Utilizing an ultrasound-guided approach to surgery for lymph node recurrence enables targeted surgery, focused on removing a small lesion within an already manipulated surgical field. Without ultrasound guidance, there is a risk of failing to identify the suspicious lymph node, necessitating larger skin incisions to expose the surgical field adequately. This could result in longer operating times and increased morbidity for the patients.

The ultrasound performed by the operating surgeon, with the patient already positioned on the operating bed, allows the identification of ultrasound landmarks, which act as a guide for surgery and can be reproduced during surgery with intraoperative ultrasound. Further tips and tricks include measuring the size of the suspected lymph node, the distance from the skin margin, studying its shape, margins and relationships with the closest anatomical structures. If these ultrasound parameters were confirmed during surgery then identification is easier and more effective.

It's essential to acknowledge significant limitations in this study. Firstly, it's a retrospective, single-institution study. We recognize that the number of patients included is insufficient for drawing conclusions with high scientific certainty. However, the

limited case count is attributed to the rarity of nodal recurrence in patients who have undergone both CND and LND. The primary goal of the study is to share our experiences and highlight the challenges encountered during reoperation for identifying suspicious lymph nodes. We propose that intraoperative ultrasound can serve as a valid, safe, effective, and cost-efficient tool in such cases.

A notable strength of this study is its novelty; there are currently no other studies in the literature describing this technique and approach. Therefore, this work represents the outcomes of a treatment method consistently applied at a single institution by the same surgical team.

Conclusions

The most prevalent form of recurrence in DTC is the reappearance or persistent presence of lymph node disease. Managing patients with suspected recurrent or persistent nodal DTC is challenging and relies on ultrasound imaging, Tg levels, a comprehensive whole-body iodine scan, and final decisions made by an interdisciplinary team.

When clear evidence of a structural abnormality is present, surgical intervention is the optimal treatment for nodal recurrence. The goal of surgery should be curative, and the approach should be economically and logistically feasible, relatively easy to perform with a quick learning curve, and should ensure minimal interobserver variation in identifying pathological nodes, all while being safe for patients.

The intraoperative, ultrasound-guided technique is a safe and effective method. It facilitates the localization and removal of tumors, especially in patients who have already undergone neck surgery, allowing reoperation to be performed safely and effectively.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

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Needle size for thyroid fine needle aspiration cytology. A single institution experience

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Background: Fine needle aspiration cytology (FNAC) is an invasive diagnostic technique which is widely used for the cytological diagnosis of thyroid nodules. This procedure is generally widely tolerated by patients, albeit often accompanied by local pain and discomfort. Despite various proposals of execution methods, no approach is universally accepted, especially regarding the size of the needle to be used for sampling. Needle gauge preferences vary across regions, with 25-gauge needles more common in Western countries and 22-gauge needles favored in Asian countries. Complications associated with larger needles have been studied but remain inconclusive.

Materials and methods: Over one year, we conducted 300 FNAC procedures under ultrasound guidance, employing both 22-gauge and 25-gauge needles. In no patient was local anesthesia performed before starting the procedure, which in all was performed by the same operator. Similarly the cytological examination of the material taken was performed by a single operator. Patients, 105 males and 195 females, were divided into two groups of 150 each based on the needle size used.

Results: Patients treated with 22-gauge needles reported higher levels of pain during the procedure and increased discomfort afterward. Similarly, a greater incidence of hematomas and vasovagal reactions was noted in this group. However, the cell sample obtained and diagnostic response rates were consistent across both groups.

Conclusion: On the basis of our observations we concluded that the size of the needle used is irrelevant for the purposes of the diagnostic result, as long as the procedure is performed by expert personnel. However, the 25-gauge needle is preferable because it's more tolerated and accepted by patients. Our results do not represent a single and conclusive verdict, but they could represent the starting point for further research.

KEYWORDS

thyroid gland, fine needle aspiration, thyroid nodules, cytology, interventional ultrasonography

Abbreviations

FNAC, fine needle aspiration cytology; BMI, body mass index; VAS, visual analogue scale; G, gauge.

1 Introduction

Thyroid fine needle aspiration cytology (FNAC) is a procedure first described in 1948 (1) that allows the collection of biological material through a very fine needle. This material is then subjected to cytological examination to determine whether it is benign or malignant in nature (2). This method represents the gold standard for the preoperative diagnosis of thyroid nodules because the cytological results obtained allow the identification of nodules with malignant features, which require surgical intervention, and those with benign features, which should be subjected to surveillance, thus reducing the number of thyroidectomies in patients with benign pathologies (3). Thyroid nodules are common, with a clinical prevalence estimated at around 3%–7% of the general population. They are more prevalent in females (4), and their incidence increases with age. The extensive use of ultrasound as a screening tool has demonstrated that many individuals harbor non-palpable nodules (5). In the presence of a thyroid nodule, clinical examination alone does not allow the distinction between benign and malignant nodules (6), and international guidelines suggest that further diagnostic procedures should be initiated in such patients. Bethesda System for Reporting Thyroid Cytopathology is currently the most used, in Italy in addition to this international classification there is another reporting system “The Italian thyroid cytology classification system” which was recently updated by the United Italian Society of Endocrine Surgery. The Italian classification system is more detailed regarding the percentage of malignancy risk (7, 8). In this context, ultrasound-guided FNAC is recognized as the most reliable diagnostic technique due to its high precision, safety, ease of execution, and cost-effectiveness (9). Over time, efforts have been made to improve both the methodology and the instrumentation used in FNAC. It is undeniable that the procedure, like all techniques, requires a learning curve for the operator, and its accuracy may differ among different operators based on different operational planning (5). Ideally, it is useful to seek ergonomics in the workplace, with the correct positioning of the patient and instruments, and finding the most suitable position for the assistant to achieve comfort in movements and avoid awkward crosses. To these subjective parameters, variables related to the equipment are added, such as the type of ultrasound column, the ultrasound probe, and the type and size of the needle. In particular, the needle size has been taken as a parameter for comparison to assess whether using needles of different gauges can improve the performance of the procedure. As for the needle size, in Western countries, needles of 25 or 27 G are primarily used, while in Eastern countries, the use of 21–22 G needles is common (3).

Few studies have compared the results obtained using needles of different gauges, and in most cases, the results are controversial, as other factors likely contribute to the determination of outcomes (10). Building on these premises, we wanted to initiate a study in our group where the results obtained using two different gauges of fine needles for the procedure were compared: needles with a gauge of 22 G and needles of 25 G.

2 Materials and methods

From June 2022 to June 2023, in our Department, we performed 300 ultrasound-guided FNAC for thyroid nodules. We used, alternatively for each patient, a 22-gauge or 25-gauge needle, until reaching a sample of 150 for each group. Ultrasound was performed using the TOSHIBA NEMIO SSA-550A unit with a linear probe PLM-703AT (Toshiba Medical Systems Corporation, Otawara-Shi, Tochigi-Ken, Japan). By choice, no local anesthetic was administered before the procedure, for aspiration we used a 5 ml syringe and we gave ourselves a limit of 3 attempts per patient. Following the indications of our pathologists, the aspirated materials were smeared and pressed onto the surface of 2 glass slides. After this application, the remaining part of the sample was processed by ThinPrep® 2000. Of the 300 patients observed, we treated 105 males (35%) and 195 females (65%) with a mean age of 54.01 years (range 16–81). The characteristics of the patients are shown in Table 1. We conducted our observations prospectively, assigning patients to one of the two groups with a 1 to 1 ratio. All procedures were performed by a single operator and a single cytopathologist, this to minimize biases due to the technique.

2.1 Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Science, IBM SPSS Statistics, Version 28; IBM Corp., Armonk, NY, USA). Data are presented as number and percentage, with mean value and standard deviation, median and range. For bivariate two-sided comparisons between the Group 22G and the Group 25G, Chi-squared test or Fisher's exact test were used for categorical variables, whereas the Mann–Whitney U test was applied for continuous variables. Differences were considered significant at p -values <0.05 .

TABLE 1 Demographic data.

	Group 22G (<i>n</i> = 150)	Group 25G (<i>n</i> = 150)	<i>p</i> - value
Gender (<i>n</i> , %)			0.628
Male	55 (36.7)	50 (33.3)	
Female	95 (63.3)	100 (66.7)	
Age (year)			0.660
Mean (SD)	54.25 (13.85)	53.76 (13.64)	
Median	42.5	49	
Range	16–81	18–80	
BMI (kg/m ²)			0.912
Mean (SD)	20 (4.28)	21.5 (4.54)	
Median	20	19	
Range	18–22	18–20	
Nodule size (mm)			0.764
Mean (SD)	25.29 (10.26)	23.92 (8.87)	
Median	22	22	
Range	11–55	10–56	

3 Results

Of the 300 total patients, 150 were assigned to Group 22G and the same number to Group 25G. The assignment was conducted prospectively and with random alternation with a 1 to 1 ratio. As highlighted in Table 1, the demographic data (gender, age, BMI, nodule size) showed no differences in the 2 study groups. For complications related to the procedural technique, we have included both the most frequent variables and the less common events in Table 2. The differences found concerned the pain reported by the patients and the finding of hematoma. To detect pain, the VAS scale was used which for ease of calculation was divided into 2 levels (L1 0–5, L2 6–10). 98.7% of patients belonging to Group 25G reported L1 pain compared to 90% of Group 22G, on the other hand major pain (L2) was observed in 10% of cases of the latter group (*p*-value 0.002), denoting therefore a difference between the 2 samples in favor of Group 25G. The finding of hematoma (extrathyroidal, intrathyroidal) also highlighted differences in favor of the 25G Group (0.7%) compared to 4.6% of the other Group (*p*-value 0.037). Regarding the other minor complications, no differences were highlighted (Site infection, Vasovagal reaction, Vocal cord injury, Tracheal puncture, Dysphagia, Paresthesia). In Table 3 we have included the results obtained from the performed procedures. The mean value of the procedure time was the same (*p*-value 0.150), as well as the comparison of the samples obtained (*p*-value 0.906) and the cytology results divided into Bethesda categories (*p*-value 0.679) showed no differences. Our observations indicate that the only differences found were in patient-reported pain and the occurrence of postprocedural hematoma, and that the 25G needle offers fewer complications.

4 Discussion

FNAC is a simple procedure to perform, with a low cost-benefit ratio, characterized by high diagnostic accuracy, making it the gold standard for the preoperative diagnosis of thyroid

nodules (3). However, it is essential to be aware that adverse events may occur during the procedure, and one should be prepared for the possible onset of complications. FNAC is generally well-accepted by patients, although in some particularly sensitive individuals, the sight of the ultrasound column, syringe with a needle, and ultrasound probe may induce anxiety, which can persist even after the procedure. Most patients report pain at the time of needle insertion, but no intervention is necessary for its intensity or duration (11). Quantifying the pain intensity using the VAS Scale, the subjective perception of discomfort varies widely, from a sensation of tenderness to actual pain, albeit transient. The severity of painful symptoms has been related to various factors: the needle diameter (12), the number of “punctures,” the time taken for the procedure, the location of the nodules (13), and, not least, the operator’s experience and the patient’s character (14). However, isolating a characteristic element is difficult, and there is no consensus in the literature, which is discordant and certainly inconclusive (10). In our experience, we observed differences in the two groups, as reported by others (12, 15). The group treated with a 22 G needle reported higher pain intensity during the procedure and a discomfort sensation that persisted beyond 24 h after the procedure. We did not find differences in the two groups regarding the time taken, and concerning the amount of biological material collected, the needle caliber used did not affect the adequacy of the sample for cytological examination (16–20). Microscopic evaluation was performed at the Pathological Anatomy Institute of the Hospital without any information regarding the caliber of the needle used for the sample aspiration, and we never received reports of insufficient material. Cytological evaluation was then performed based on the Bethesda System for Reporting Thyroid Cytopathology on these samples. No

TABLE 2 Procedural complications.

	Group 22G (n = 150)	Group 25G (n = 150)	<i>p</i> -value
Pain (VAS scale) (n, %)			0.002
0–5	135 (90)	148 (98.7)	
6–10	15 (10)	2 (1.3)	
Hematoma (n, %)			0.037
Extrathyroidal	2 (1.3)	1 (0.7)	
Intrathyroidal	5 (3.3)	0 (0)	
Site infection (n, %)	1 (0.7)	1 (0.7)	1
Vasovagal reaction (n, %)	5 (3.3)	2 (1.3)	0.448
Vocal cord injury (n, %)	0	0	1
Tracheal puncture (n, %)	0	0	1
Dysphagia (n, %)	1 (0.7)	0	1
Paresthesia (n, %)	1 (0.7)	1 (0.7)	1

TABLE 3 Results of thyroid aspiration cytology using 22- and 25-gauge needles.

	Group 22G (n = 150)	Group 25G (n = 150)	<i>p</i> -value
Time of procedure (min.)			0.150
Mean (SD)	6.84 (1.73)	6.58 (1.56)	
Median	7	6	
Range	4–10	4–10	
Sample obtained (n, %)			0.906
1	90 (60)	88 (58.7)	
2–3	60 (40)	62 (41.3)	
Bethesda categories (n, %, Italian classification system)			0.679
I. Non diagnostic	10 (6.7) (Tir 1)	9 (6)	
II. Benign	115 (76.7) (Tir 2)	120 (80)	
III. Atypia of undetermined significance	15 (10) (Tir 3A)	16 (10.7)	
IV. Follicular neoplasm	0 (Tir 3B)	0	
V. Suspicious for malignancy	8 (5.3) (Tir 4)	5 (3.3)	
VI. Malignant	2 (1.3) (Tir 5)	0	

serious complications occurred during the procedure in both groups. We reported the occurrence of a hematomas (9) at the puncture site with a slight prevalence in the group treated with a 22 G needle. In this respect, the decision to interrupt the intake of anticoagulants or antiplatelet agents before performing FNAC is under discussion. Recent experiences show no statistical significance between patient groups in whom the procedure was performed without suspending the intake of anticoagulant or antiplatelet drugs and groups where drug intake was suspended. The final decision is left to the individual operator, who should decide based on the individual characteristics of patients due to the low risk of bleeding events after FNAC of thyroid nodules (21–24). Cases of rare but sometimes fatal thyroid bleeding after FNAC requiring intubation or surgical intervention have been reported. Bonsignore et al. (25) reported the case of a 78-year-old woman who died due to a hematoma causing tracheal compression, and they conducted a literature review of 12 cases of severe thyroid bleeding, mostly managed with surgical interventions or conservative measures (25, 26). Vasovagal reactions are rare (27, 28). In our experience, they were more frequent in the 22G group, but mild and transient. Only one patient had a severe syncopal episode, requiring Trendelenburg positioning and prompt saline infusion. No structures adjacent to the puncture site were affected in either group. Only one patient in the 22G group reported dysphagia, while paresthesia at the puncture site and a mild infection at the puncture site were reported by four patients, two in each group. No patient experienced vocal cord injury or tracheal puncture. Dysphonia has been reported in some studies (22, 29). Possible mechanisms of recurrent laryngeal nerve palsy after FNAC have been attributed to rapid stretching of the nerve caused by a thyroid hematoma or direct nerve injury with the needle (30). This study certainly has a limitation, we only used 2 gauges for the needles during the procedures, leaving out those of 21, 23 and 27 gauge (15, 31, 32). The high costs and the difficulty in finding them influenced our choices, however in the near future it is our intention use them to have a broader and more conclusive comparison.

5 Conclusion

Based on our experience, as well as literature reports (12), it can be stated that FNAC is a safe technique with a low and not particularly relevant complication rate, not discouraging the execution of the procedure in the preoperative diagnosis of thyroid nodules. Especially concerning individual tolerance, we observed that the procedure performed with 25 G caliber needles is more accepted by patients, especially regarding subjective pain sensitivity. Like all procedures, however, it must be performed with caution, adopting all precautions to minimize adverse events that, although minimal, are always bothersome for patients (7). Our results represent only a single experience and certainly cannot be considered conclusive, but they could represent the starting point for further research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Head of the Department of Surgery and Traumatology. ASL BAT. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PC: Conceptualization, Writing – original draft. RT: Writing – review & editing. IC: Data curation, Writing – original draft. DT: Software, Writing – original draft. GT: Data curation, Writing – original draft. GL: Validation, Writing – original draft. VL: Writing – original draft, Data curation, Formal Analysis. MC: Writing – original draft, Data curation, Investigation. MM: Writing – original draft, Data curation, Investigation. FC: Writing – original draft, Data curation, Formal Analysis. ER: Validation, Writing – review & editing.

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Conflict of interest

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