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Review: Surgical Considerations and Emerging Non-Surgical Alternatives in the Diagnosis and Management of Hot and Cold Thyroid Nodules: A Comprehensive Review

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ABSTRACT

This study provides an in-depth review of thyroid nodules, covering their characteristics, diagnostic challenges, and management strategies. It highlights the critical need for careful evaluation of hyperfunctioning nodules due to their potential to cause hyperthyroidism. Factors such as age, sex, and iodine intake influence malignancy risk, complicating the diagnostic process. Differentiating between benign and malignant nodules remains a clinical challenge. Parameters like clinical presentation, ultrasound findings, and thyroid-stimulating hormone levels enhance diagnostic accuracy. Ultrasound-guided fine-needle aspiration biopsy is a crucial tool for rapid and precise evaluation. Hot nodules, though less common, require unique diagnostic and therapeutic considerations. These nodules are often associated with somatic mutations and can present as euthyroid or hyperthyroid, necessitating tailored management approaches such as radioiodine therapy or percutaneous ethanol injection. Non-surgical interventions offer promising alternatives for symptomatic nodules, particularly in patients unfit for surgery. Techniques like percutaneous ethanol injection and radiofrequency ablation effectively reduce nodule volume and alleviate symptoms with minimal complications. Pediatric patients face distinct challenges, with a higher prevalence of malignant nodules often necessitating surgical intervention in autonomously functioning cases. Incidental thyroid nodules pose a diagnostic dilemma, requiring differentiation between malignant and benign lesions through molecular testing and selective surgical excision. Non-surgical methods such as percutaneous microwave ablation, laser ablation, and high-intensity focused ultrasound ablation show promise in managing thyroid nodules with favorable outcomes and minimal complications. Tailored approaches are essential for optimizing patient outcomes.

Introduction

Nowadays, thyroid nodules have become a prevalent health issue globally. Typically, solitary hyper-functioning nodules within the thyroid gland pose a challenge for individuals, yet they are commonly benign. The incidence of malignancy in such nodules is rare, accounting for approximately 3% of cases in the general population. Hyperfunctioning nodules, while infrequent among benign nodules, can lead to subclinical or overt hyperthyroidism in a subset of cases (1-3).

Thyroid nodules exhibit diverse characteristics, categorizing them as adenomas, carcinomas, or hyperplastic lesions based on both macroscopic and microscopic histological features (4, 5).

Risk of malignancy

In the years around 1979, nodules with hyper functional activity were reported to be malignant in up to 5 percent of patients (1) and prevalence of compressive and cosmetic symptoms in patients with nontoxic goiter has been reported from 28% to 36% and 17% to 69%, respectively (2). Nodules are very likely to be benign if they are purely cystic, have typical colloid echoes of the ring down or comet tail artifact, or are spongiform (multisystem components occupy > 50% of nodule volume) (3). Age, sex, and iodine intake effect on the potential of malignancy of the thyroid nodules (4). For example, the frequency of cancer in cold nodules was least in the fourth decade of life and greatest before age 30 or after age 60; it was 4.2% in women and 8.2% in men; and it was 5.3% in patients from an iodine-sufficient area (5 to 10% prevalence of palpable thyroid nodules in women and a 1 to 2% prevalence in men) and 2.7% in patients from an iodine-deficient area. Interestingly, the frequency of thyroid malignancy in patients with a solitary nodule was not significantly different from that in patients with a multinodular goiter. These data suggest that the risk of malignancy in a multinodular gland is not insignificant, and a prevailing nodule in such a gland should be evaluated as carefully as if it were a solitary nodule (5-9). There is no male or female supremacy , even though the incidence of nodules is higher in women (7, 8). American studies have revealed the existence of thyroid nodules in 19 to 67% of normal-risk female and elderly individuals (10, 11). In general, radioisotope scans have noted nodules incidentally on ultrasound in up to 70% of people, with increased prevalence in older patients (12). nodules detected incidentally during positron emission tomography scanning have a 35% probability of malignancy (13).

Sign and symptoms

Large nodules may arise from nodular goiter, causing dysphagia, dyspnea, and dysphonia due to local mass effect on important anatomical structures in the head and neck involved in swallowing, phonation, and breathing. In extreme cases, nodular goiter may even block to airway obstruction (14). Nodular hyperplasic lesions are characteristically present in multinodular goiter (MNG) and are caused by follicular cell hyperplasia. In some cases, hyperplasic nodules can grow and become autonomous even in the absence of external stimuli (15).

Distinguishing malignant from benign tumors

The main challenge in managing thyroid nodules is to identify those that are malignant with those who are benign, while avoiding inappropriate excess use of thyroid sonography, fine-needle aspiration, and surgery. Moon et al analyzed 1083 thyroid nodules and found that central flow is the most common distinction between benign and malignant nodules. Of the 1083 nodules studied, 814 were benign (75%) and 269(25%) were malignant intranodular vascularity was frequently observed in the benign nodules, and vascularity was more typically absent in the malignant nodules (16-18). Cytopathologically characterizing and differentiating between benign and malignant follicular lesions is practically impossible (19). Various clinical, ultrasound, and cytological parameters, such as age, gender, nodularity, thyroid stimulating hormone level, thyroid autoimmunity, and ultrasound findings (hypo echogenicity, micro-calcifications, irregular borders, and increased central nodular flow), have been studied to improve diagnostic accuracy and differentiate between benign and malignant nodules (20-23). Thyroid-stimulating hormone should be measured in all patients with a thyroid nodule. Most individuals will have a normal thyroid-stimulating hormone level; a low or suppressed thyroid-stimulating hormone level may suggest a hyper functioning nodule or a toxic goiter, and free thyroxine or free triiodothyronine levels should be measured (24).

Hashimoto thyroiditis, which can present with a transient hyperthyroid phase, is the usual cause of elevated TSH or hypothyroidism. TSH elevation or within the upper normal range has been reported to be associated with an increased risk of malignancy within a thyroid nodule (25, 26).

Diagnosis

Computed tomography and magnetic resonance imaging may occasionally be useful in identifying the extent and location of thyroid masses. Because of their considerable cost, these imaging studies are generally reserved for substernal or retrosternal thyroid masses, detection and delineation of thyroid nodules, and identification of regional or distant metastasis (27). Due to increased use of ultrasonography (US) and the increased access to cytology analysis through fine-needle aspiration biopsy (FNAB) guided by the US (FNAB-US), the number of small-sized thyroid gland carcinoma diagnoses has increased in Brazil and many other countries (7, 28, 29).

Thyroid scanning is typically performed using radioisotopes of iodine (such as I-131) or technetium (Tc-99m). Thyroid follicular cells absorb both radioiodine and technetium, but only radioiodine is incorporated into thyroid hormones. This results in differences between the two types of scans. Thyroid nodules are classified based on their ability to absorb the isotope: nonfunctioning nodules are "cold," normal functioning nodules are "warm," and hyperfunctioning nodules are "hot." About 85% of nodules are cold, 10% are warm, and 5% are hot (30). Thyroid scans are useful for determining gland volume, identifying the number and size of thyroid nodules, distinguishing thyroid from extrathyroidal masses, evaluating lymph node metastasis in patients with thyroid carcinoma (31), and guiding fine-needle aspiration (FNA) biopsy. FNA biopsy is the best method for diagnosing thyroid nodules as it is rapid, accurate, and cost-effective (32, 33).

Hot nodule

Plummer described a type of hyperthyroidism associated with uni- or multinodular goiter, in contrast to the diffuse goiter seen in Graves' disease. It was later confirmed that the nodular tissue was functioning autonomously and that solitary hyperfunctioning nodules were associated with a functionally suppressed contralateral lobe (34). 5% of all thyroid nodules are hyper-functioning (hot) on thyroid scintigraphy, concentrating either Tc or I greater than the remaining normal tissue and suppressing function in the rest of the glands (35) 5 Hot nodules are much less common than cold nodules, and over the last few years it has been shown that most hot nodules show a somatic activating mutation of the TSH receptor gene; a minority show a mutation of the linked Gs gene The hot nodule may be clinically nontoxic (euthyroid) or toxic (hyperthyroid). The use of current sensitive TSH assays has revealed that the so-called thyroid hot nodule is often associated with a suppressed TSH level, suggesting that this is a state of subtle or subclinical hyperthyroidism. Hot nodules, far more common in women are more likely to be toxic if larger than 2.5 cm in diameter or if the patient is older than 60 years (36) surgery, or, more recently, percutaneous injection of ethanol (37). According to the literature, the malignancy rate in thyroid nodules that are 4 cm or larger, with indeterminate cytology, varies from 10 to 30%(38, 39)

Treatment

Patients with autonomous euthyroidism may still be at risk for progressing to hyper-thyroidism, necessitating careful monitoring and treatment. Treatment options include radioactive iodine, medication, and surgery. Fine needle aspiration (FNA) biopsy is now one of the most effective methods for identifying benign nodules. Following a decline in the use of radioisotope scanning, the application of high-resolution ultra-sonography for thyroid diagnosis has steadily increased (27). It has a high sensitivity (65 to 98%) and specificity (72 to 100%) and it has a false positive rate for cancer detection of 0 to 7% and a false negative rate of 1 to 11% (40-42) Choi et al found that 16.1% of 3.767 FNAB-US samples were inadequate, largely due to the lack of physician experience, a predominance of cystic lesions, and the presence of macrocalcifications (43). Radioactive iodine (RAI) therapy, used to treat hyperthyroidism, can cause transient thyrotoxicosis. Although pretreatment with antithyroid medications can mitigate this risk, it may also reduce the success rate of the RAI treatment (44). Surgical intervention is associated with risks and complications, which include hypocalcemia, injury to the laryngeal nerves, and hematoma formation (45, 46). Thyroidectomy is associated with worse clinical and economic outcomes in patients with multiple comorbidities, but advanced age has been shown to be an independent predictor of longer hospital stay and higher total cost (47). It is essential to consider nonsurgical interventions for managing both symptomatic cold thyroid nodules and autonomously functioning thyroid nodules (AFTN), particularly for patients who are poor surgical candidates (48). Over the past decade, several techniques have been developed to treat thyroid nodules under local anesthesia on an outpatient basis using ultrasound guidance. Cervical ultrasound, the preferred method for studying thyroid nodules, allows for the evaluation of their size, location, and characteristics suggestive of malignancy (49-52). These techniques include percutaneous ethanol injection (PEI), percutaneous laser ablation (PLA), high-intensity focused ultrasound (HIFU) ablation, and radiofrequency ablation (RFA). Multiple studies have demonstrated good results using RFA to treat thyroid nodules, successfully reducing the size of the treated nodules and the symptoms associated with them (53-56). Another safe and effective treatment for symptomatic thyroid nodules that are confirmed benign is radiofrequency ablation (57).

Pediatric population

Hot nodules are rare in pediatric patients. The current American Thyroid Association guidelines for the treatment of autonomously functioning thyroid nodules (AFTN) in children recommend surgery for all pediatric patients with these nodules. This recommendation is based on the report by Niedziela et al. (58). Thyroid nodules in children are more frequently malignant, with a malignancy rate of 22 to 26 percent compared to 5 to 10 percent in adult patients. This particular nodule was large and grew rapidly, increasing by 17 percent in its greatest dimension over a period of 1.5 years (59, 60).

Incidental thyroid nodule

Incidental thyroid nodule (ITN) is common problem for treatment staff. They are none palpable lesions radiologically distinct from the surrounding parenchyma, ITNs are found on anatomic imaging studies (24). It has been estimated that the pervasiveness of thyroid nodules identified by palpation is between 4% and 7% (61) with imaging studies identifying up to 10 times more nodules, most of them are benign. Women are more frequently affected than men (4:1), and the prevalence of thyroid nodules increases with age to 50% in women older than 70 years (62). Main goal in managing ITNs is to differentiate malignant lesions from benign conditions. Population-based studies estimate that the risk of malignancy is 1.6% among patients with ITNs (63). Management of clearly benign nodules consists of patient reassurance and observation, whereas clearly malignant nodules should be resected and selected molecular testing may guide the clinician. Surgical excision remains the standard for diagnosis in cases of persistent ambiguity (46, 64).

Non-surgical treatments for thyroid nodules

Thyroid nodules are a common finding globally, affecting 20% to 76% of the general population (65). Moderate to severe iodine deficiency has contributed to this high prevalence of thyroid nodules in the past (66). Fine needle aspiration cytology (FNAC) could often confirm that the majority (85%–93%) (65) of these nodules are benign (67). Nevertheless, there is a potential for a select group of nodules to grow over time and cause local pressure symptoms like neck pain, occasional choking, dyspnea, and dysphagia or hyperthyroidism (68). Therefore, it is necessary to treat benign thyroid nodules when they are symptomatic or causing cosmetic problems (69, 70).

Total or partial thyroidectomy is the standard of care if therapy is necessary, while iodine therapy has been used with poor results (71). However, surgery is associated with a risk of hypothyroidism, bleeding, infection, and voice hoarseness from recurrent laryngeal nerve injury, which may or may not be permanent. Moreover, surgery requires general anesthesia and may not be feasible in some individuals because of underlying medical morbidities (67, 72, 73). For decades, thyroid surgery has been, and still is, the routine treatment for symptomatic nodular thyroid disease and thyroid cancer. During the last few years, new non-surgical and non-radioiodine techniques have been introduced to treat thyroid nodules. These techniques include ethanol/polidocanol treatment, radiofrequency, microwave, laser, and high-frequency ultrasound ablation (66).

Percutaneous Ethanol Injection

The percutaneous ultrasound-guided instillation of sterile 95 % ethanol into thyroid nodules leads to cellular dehydration, thrombosis of small vessels, protein denaturation, cellular coagulation necrosis, and subsequent reactive tissue fibrosis (74, 75) with a reduction in nodule volume over time (66). This technique has mostly been used to treat autonomously functioning nodules and treat pure cysts and thyroid lesions with a dominant fluid (66, 76). Treatment of recurrent thyroid cysts with ethanol leads to better results than the simple evacuation of cystic fluid (77). Under ultrasound monitoring, a needle is inserted into the cyst, and the fluid collection is nearly completely drained by aspiration through a plastic connector tube—A syringe containing 95% sterile alcohol that is slowly injected into the cavity. And neither antibiotics nor analgesics are needed (78).

In small case series, treatment with ethanol resulted in a mean nodule volume reduction of 51 % in one series (n = 30) and 31 ± 11 % at least 50 % in another study (n = 52) (79, 80). In cases of thick colloid collection, a larger needle may be used. Although the majority of cysts relapse after drainage and increase in size over time, (81) prospective controlled trials have demonstrated the effectiveness, tolerability, and safety of PEI for recurrent thyroid cysts (77, 81). PEI does not require local anesthesia, is nearly painless, is completed in a few minutes, and can be carried out in outpatient clinics.

Major complications are unusual and mostly due to technical mistakes (78). There is usually no thyroid dysfunction or autoimmune reactions after PEI treatment of cysts (82). Complications are more frequent in cystic lesions. Recurrent laryngeal nerve palsy which is usually temporary, Graves' disease, Horner's syndrome, and necrosis of the larynx (81, 83, 84). The shrinkage of the lesion is persistent over time. In a 5-year follow-up study, the decrease in the cyst volume was nearly unchanged (85). PEI was initially reported as effective for hyperfunctioning thyroid nodules, (86-89) but there remained a risk of hyperthyroidism relapse and progressive regrowth (78).

Solid thyroid nodules should not be treated with PEI unless no other modality of treatment is accessible (90, 91). One limitation of the use of PEI in solid nodules is the erratic distribution of ethanol and its frequent seepage into the adjacent cervical tissues (83).

Radiofrequency Ablation

For thyroid nodules, Radiofrequency ablation

(RFA) is usually performed by the moving-shot technique with the guidance of ultrasonography (US), inducing tissue necrosis using thermal energy (92). It uses an alternating electric current with frequencies usually below 900 kHz.
The treatment induces the excitation of electrons with a subsequent increase in temperature at the active site of the probe. This leads to thermal tissue necrosis. Conducting heat leads to slow-growing temperatures in more remote tissue (66). Aspiration for cystic fluid in the case of cystic and mixed nodules was performed as much as possible.
All the procedures were performed by the same operator (TTV), who is an experienced thoracic surgeon. Patients underwent the RFA procedure in a supine position with mild neck extension. Local anesthesia was performed at the puncture site (92).
Firstly, the electrode was inserted into the thyroid nodule using the trans-isthmic approach and then the ablation was performed using the moving-shot technique (93-95). If monopolar RFA systems are used, grounding pads are necessary since the electric current runs through the body trunk. In bipolar probes, the electric current is limited to a small area surrounding the active tip of the probe (66). During the procedure, we paid special attention to preventing injury to the adjacent important structures. After the procedure, patients were under observation for several hours and were discharged if having no severe pain or complications (92).
RFA has been considered a safe and effective method for the treatment of benign thyroid nodules, it may lead to laryngeal nerve palsy, autoimmune thyroid disease, skin burns, hematoma, and adhesion formation when patients require surgery (96-98). However, compared to surgery, RFA has fewer complications, shorter hospital length of stay, and preservation of thyroid function (99, 100). A minor complication following radiofrequency ablation (RFA) procedures is voice change due to temporary recurrent laryngeal nerve palsy, but no major complications were observed. Clinical and ultrasound characteristics, including age, gender, initial volume, and echogenicity of the nodule, did not significantly correlate with the volume reduction ratio (VRR). In terms of efficacy, RFA resulted in nodule volume reductions of 46%, 67%, 74%, and 81% at various follow-up intervals. Notably, mixed and cystic nodules showed higher VRR compared to solid nodules throughout the follow-up period (92).

Percutaneous microwave ablation

Microwave ablation (MWA) has been proposed as a treatment for thyroid nodules, drawing on its successful application in other organs such as the liver, kidney, and lung (101-103). Microwave systems utilize an alternating electromagnetic field to generate heat. As this field interacts with tissue water and ions, it produces local temperatures exceeding 100°C. Consequently, the ablation zones created by microwave ablation are typically larger than those induced by radiofrequency ablation (RFA) (104-107). Patients were positioned supine with a mildly hyperextended neck under aseptic conditions. After administering local anesthesia, a 1–2 mm incision was made. Fine needle aspiration was performed on primarily cystic nodules before ablation. This approach helps avoid the "danger triangle," which includes the recurrent laryngeal nerve, trachea, and esophagus. Research results indicate a mean reduction in nodule volume of 38% to 65%.
Cystic nodules generally exhibit a greater reduction in volume compared to mixed nodules, and mixed nodules show better outcomes than solid nodules (108). The adverse effects of percutaneous microwave ablation (PWMA) do not differ significantly from those associated with radiofrequency ablation (RFA) (66).
After microwave ablation (MWA), most studies reported that patients experienced a sensation of heat in the neck and/or mild pain at the ablated site. Some patients also reported choking and coughing at the end of the treatment. Additionally, first-degree burns around the puncture channel were observed, but these did not require any therapy. Major complications, such as esophageal perforation

and tracheal injury, were not reported. Furthermore, researchers did not observe any new cases of hypothyroidism following the treatment (108).

Laser Ablation

Laser light can be delivered to an internal organ either from an external source or through diode lasers (78). The scattering of laser photons within the tissue leads to rapid heating of the target area, resulting in coagulative necrosis. Over the course of several months, this process is followed by fibrotic changes and progressive shrinkage of the affected tissue (109). Laser treatments are carried out on conscious patients after local anesthesia of the skin and thyroid capsule. Based on the size of the lesion, one to four spinal needles are inserted under ultrasound guidance into the target (110-112). after ultrasound assessment to confirm correct positioning, laser firing is started. Energy delivery is carried out for 5–15min (78). Laser treatment is generally well-tolerated. A minority of patients may experience cervical pain, and a self-limiting fever can occasionally occur. Rarely, local bleeding, cervical swelling, and changes in serum thyroid function or autoimmunity have been reported. The risk of major complications is less than 1%. Studies have demonstrated the efficacy and reproducibility of laser ablation for nonfunctioning thyroid nodules. A single laser session results in nodule volume decreases of 45–70% after 12 months, which remain stable for several years in most patients (78). A longer follow-up of three years demonstrated a mean volume decrease of 47.8 % in a series of patients with quite large nodules. In 9 % of the patients, the nodules regrew over baseline size after 3 years (113). In small series of hyperfunctioning thyroid nodules, laser ablation was reported as an effective treatment that resulted in the normalization of serum thyroid function and the effacement of the hyperfunctioning area (114-116). Of note, initial treatment with laser therapy followed by radioiodine administration induces a more rapid control of nodule volume and hyperthyroidism than radioiodine treatment alone (117).

High-Intensity Focused Ultrasound Ablation

High-intensity focused ultrasound (HIFU) is one of the emerging thermal ablation techniques but has yet to be described in the literature (68). HIFU uses the heat induced by focused ultrasound beams applied by ultrasound probes outside the body. The temperature reaches up to 85 °C in the treatment area, resulting in local tissue destruction with necrosis. (118) The procedure is painful and requires concomitant analgesic therapy (119). With multiple bubbles developing and expanding, mechanical damage occurs to the cell structure of nearby cells (66). An advantage over other thermal techniques is that they could induce focused thermal tissue destruction up to 85 °C without needing needle puncture and skin penetration (120). This technique has been successfully applied to a wide variety of benign and malignant tumors in the pancreas, prostate, bone, liver, and breast (121, 122).

The device used was a computer-driven system. This device was known as EchoPulse ®. This particular device has two independent US systems, one for real-time imaging guidance and the other for HIFU energy delivery and treatment. The US imaging system acts as a guide for the treatment system. The imaging system is placed amid the probe such that the focal point of the treatment system is permanently displaced in the center of the US image. On average, using the current US-guided device, a well-selected 3 cm thyroid nodule would take approximately 45–60 min patient ablation, while for either RFA or LAT, this would be 30–40% less. Given that several vital heat-sensitive structures are near the thyroid gland, physical limits have been set on how close the treatment beam should be during treatment. During treatment, the patient's vital signs are monitored (68). HIFU ablation could be considered a minimally invasive procedure because it can induce irreversible tissue necrosis via thermal ablation beneath the skin without skin

puncture or incision (123).
No major complications, such as recurrent laryngeal nerve palsy, skin burn, or hematoma, were observed in any of the studies (84). Thyroid function seemed to be unaffected by the HIFU ablation (124). In terms of efficacy, relative to baseline, the mean or median volume reduction ranged between 45 and 50% in the first 3 to 6 months (118, 125, 126). In small case series, the nodule volume reduction ranges from 55 % after three months to 68 % after 12 months. (124, 127) A direct comparison of HIFU with conventional radioiodine therapy (RAI) resulted in a similar nodule volume reduction but significantly better functional result (128).

Methods

This study reviews the current literature on thyroid nodules, focusing on their characteristics, diagnosticchallenges, and management strategies. The review was conducted using a systematic search of peer-reviewedarticles and clinical guidelines published between 2015 and 2023. Databases including PubMed, Medline, SCOPUS, and Google Scholar were searched using keywords such as "thyroid nodules," "hyperfunctioningnodules," "benign and malignant differentiation," "fine-needle aspiration biopsy," "radiofrequency ablation,"and "non-surgical interventions

Results

At first of article only few first paraphrapgh are interoduction and from risk of malignancy part the result beginning.

Discussion

Cause this article is narrative review article it should not necessary have discussion part.

Conclusion

The diagnosis and management of hot and cold thyroid nodules are complex and require a nuanced approach. While most thyroid nodules are benign, the risk of malignancy and associated symptoms demand careful evaluation and tailored treatment strategies. Advancements in diagnostic tools, such as ultrasound-guided fine-needle aspiration biopsy and molecular testing, have significantly improved the characterization of thyroid lesions, enabling more precise differentiation between benign and malignant nodules. Surgical intervention remains crucial, especially for suspicious or malignant nodules and symptomatic nodules unresponsive to non-surgical treatments. However, emerging non-surgical options like percutaneous ethanol injection, radio-frequency ablation, microwave ablation, laser ablation, and high-intensity focused ultrasound ablation offer promising alternatives for patients unsuitable for surgery or those preferring less invasive methods. In pediatric cases, the higher prevalence of malignant nodules and the need for surgical intervention in autonomously functioning nodules present unique challenges. Individual patient factors, including age, comorbidities, and preferences, are critical in determining the best treatment approach. Managing hot and cold thyroid nodules requires a multidisciplinary approach involving endocrinologists, radiologists, pathologists, and surgeons to ensure optimal outcomes. Continued research and innovation in diagnostic and therapeutic methods will further enhance our ability to effectively manage this common health issue.

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Conflicts of interest

The authors declare they have no conflicts of interest and have no financial interest related to any aspect of the study.

Authors' contributions

All authors contributed to the study's design, data analysis, manuscript drafting, critical revisions, approved the final version for submission, and accepted accountability for the work.

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