World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

Check for updates

Predictors of malignancy in STN vs MNG thyroid: Metanalysis

J. A. JAYALAL, S. YUVARAJ and VIGNESH B *

Department of General Surgery, Kanyakumari Govt. Medical college, Asaripallam, TN, India.

World Journal of Advanced Research and Reviews, 2024, 23(02), 1473–1484

Publication history: Received on 06 July 2024; revised on 13 August 2024; accepted on 16 August 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.23.2.2474

Abstract

Background: The incidence of thyroid cancer is different between solitarynodular (SN) thyroid and multinodular goiter (MNG). Therefore, a meta-analysis is performed to evaluate the existing literature on the comparative incidence of thyroid cancer in SN versus MNG.

Methods: Papers were identified using a systematic search of PubMed/MEDLINE, Cochrane Central, ScienceDirect, GoogleScholar, International Clinical Trials Registry and reference lists of included articles. There are no restrictions on time, study design, language or country of publication. Two independent reviewers screened the most relevant articles according to PRISMA guidelines.

Results: Twenty-two studies were included in this analysis and included 50, 321 patients, of which 44.2% were in the STN subgroup and 55.37% were in the

MNG subgroup. MNG was significantly associated with a lower risk of thyroid cancer compared to STN (OR=0.76; 95% CI 0.61-0.96). Papillary carcinoma was the most common carcinoma in both groups, followed by follicular and medullary carcinoma. Subgroup analysis was performed to evaluate the effectiveness of the two most commonly used diagnostic tools, surgery and fine needle aspiration cytology (FNAC), but yielded non-significant results, indicating comparable utility between the two. Another subgroup analysis based on participants' assumed iodine status also yielded non-significant results.

Conclusion: The incidence of thyroid cancer is higher in patients with STN, but since the available evidence on this topic is of low quality, it is important to carry out larger studies that confirm the association with precision.

Keywords: Thyroid nodule; Thyroid cancer; Thyroid carcinoma; Single thyroid nodule; Single nodule; Multi-nodular goiter; Nodular goiter

1. Introduction

Thyroid nodules are discrete lesions of the thyroid parenchyma with a relatively low but still significant potential for malignancy. They are common clinical findings, usually discovered incidentally, with a prevalence of 2–6% for clinically recognizable nodules and 19–35% for ultrasound detected nodules. The incidence is even higher during surgery.

The risk of malignancy in thyroid nodules is estimated to be 7-15% , which is high enough to warrant appropriate diagnostic measures when carcinoma is suspected. Various factors are known to predict the risk of malignancy. Female gender and exposure to radiation appear to increase the likelihood of developing cancerous nodules. While the older literature suggests a bimodal distribution of the risk of progression to carcinoma, i.e., both the young and the elderly are associated with a higher risk of cancer progression, the more recent literature assumes that overall thyroid

* Corresponding author: VIGNESH

malignancy decreases. Recent advances in the understanding of thyroid nodules also implicate their place as an independent predictor of malignancy risk, with the central lobe, upper poles, and lateral nodules most likely to progress to carcinoma. It should also be noted that cold nodules have a much higher risk of malignancy compared to hot nodules.

The term goiter refers to abnormal growth or enlargement of the thyroid gland, caused by a single nodule or multiple nodules. Multi-nodular goiter (MNG) has historically been considered as a benign disease with a low risk of malignancy, but this notion has been challenged because numerous studies have reported an incidence of MNG carcinoma approaching that of a solitary thyroid nodule (STN) and sometimes even exceeds it with. The conflicting results of different studies investigating the comparative risk of carcinoma in STN and MNG require a meta-analysis to answer this question. Because the risk of malignancy determines the diagnostic evaluation and management of thyroid nodules, assessing the risk of carcinoma has significant clinical value. It also excluded studies that included important populations, such as children, and therefore lacks the complete picture that a meta-analysis allows.

2. Material and method

2.1. Study types

Study designs accepted for the systematic review were observational studies (cross-sectional, cohort, case comparison) and randomized controlled trials (RCTs). However, we found no RCT evidence relevant to our topic. No language or location restrictions apply. Databases were searched from conception to present and non-English articles were translated for relevant information.

2.2. Types of participants

Studies in which patients were diagnosed with MNG or STN either by needle aspiration biopsy (FNAC) or histopathology involved in a surgical procedure. Studies in which the diagnosis of cancer was made clinically, ultrasound, or studies that reported the incidence of cancer in patients with toxic nodules.

- Types of comparisons: In the analysis, we compared the risk of thyroid cancer MNG and STN side by side.
- Types of outcomes: Our main outcome was the incidence of thyroid cancer patients with MNG and STN.

2.3. Data Sources and search strategy

Electronic databases: MEDLINE (via PubMed), Cochrane Database of Systematic Reviews (CDSR), Science Direct.

A combination of keywords and MeSH terms like “Multi-nodular goiter”, “Goiter, Nodular’’, “Thyroid Neoplasms” was used to search the databases. The complete search strategy of MEDLINE is provided in the supplementary file. The same search strategy was followed for the other databases. No filter of language, time and study design was used in order to retrieve the maximum literature. We also manually sieved the reference lists of retrieved articles and previous reviews to identify any missed studies, and contacted authors of the respective articles for any missing information vital to our review.

Eligibility criteria were included. Two reviewers independently extracted the following information from each study: type of study, country where the study was conducted, study sample size, total number of patients, age, sex, type of nodular goiter (MNG vs STN), duration of follow-up prevalence of thyroid cancer, cancer diagnosis (by surgery or FNAC), type of thyroid cancer, reason for surgery, family history of thyroid cancer, radiation exposure and histo- pathological findings. Any disagreements between the two reviewers were resolved by mutual discussion. The PRISMA flowchart is designed to illustrate the research selection process.

2.3.1. Risk of bias in individual

Two authors independently assessed the methodological quality of our included studies using the Newcast Ottawa Scale (NOS) in cohort studies. The study received a star based on three aspects: selection of study groups; comparability of groups; and identifying the outcome of interest. The modified NOS scale was used to assess the quality of the selected cross-sectional studies. A third reviewer resolved any disputes that arose between the two reviewers regarding the quality assessment.

2.4. Study selection and data extraction

All literature search results were uploaded to Mendeley, and after duplicate articles were removed, titles and abstracts were independently reviewed by two reviewers. Other articles underwent full-text screening and only studies that met the above

2.5. Assessment of heterogeneity

We assessed heterogeneity among the studies included in our analysis using the Chi-square test. Values were interpreted according to the Cochrane

Handbook for Systematic Reviews of Interventions, Sect. 10.10. Significance level was set at p value less than 0.10. Inconsistency was quantified using the I2 index. I2>50 percent constitutes a major inconsistency.

2.6. Assesment of reporting biases

Our meta-analysis consisted of more than 10 studies, so we created a funnel plot and performed a visual inspection of it to assess the presence of reporting bias. However, the asymmetry may also be due to other reasons, such as factual heterogeneity or publication bias.

2.7. Statistical analysis

We performed meta-analyses using Review Manager (RevMan) (version 5.4. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We used the DerSimonian and Laird random -effect model for conducting our meta-analysis. Prevalence of thyroid cancer in patients with MNG was compared to the prevalence of thyroid cancer in patients with STN. Pooled odds ratio with 95 percent confidence interval was calculated.

2.8. Additional analyses

We aimed to perform subgroup analyses based on the type of diagnostic method (surgery vs FNAC), history of thyroid cancer in family, history of radiation exposure and iodine status of the locale where the study was conducted. WHO data on iodine status of different locales worldwide was used to run this subgroup analysis.

2.9. Confidence in Cumulative Evidence

The strength of the evidence was assessed using the assessment tool GRADE (Grade for Recommendations on Assessment, Development and Evaluation). The GRADE approach characterizes the quality of the evidence in one of four categories: high (the true effect is close to the estimated effect), moderate (the true effect is probably close to the estimated effect, but it is possible that it is significantly different), low (the true effect may significantly differ from the estimated effect), very low (the true effect is likely to differ significantly from the estimated effect). The quality of evidence was rated lower in our pooled assessment due to study design or implementation limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision and publication bias (Appendix 2).

3. Result

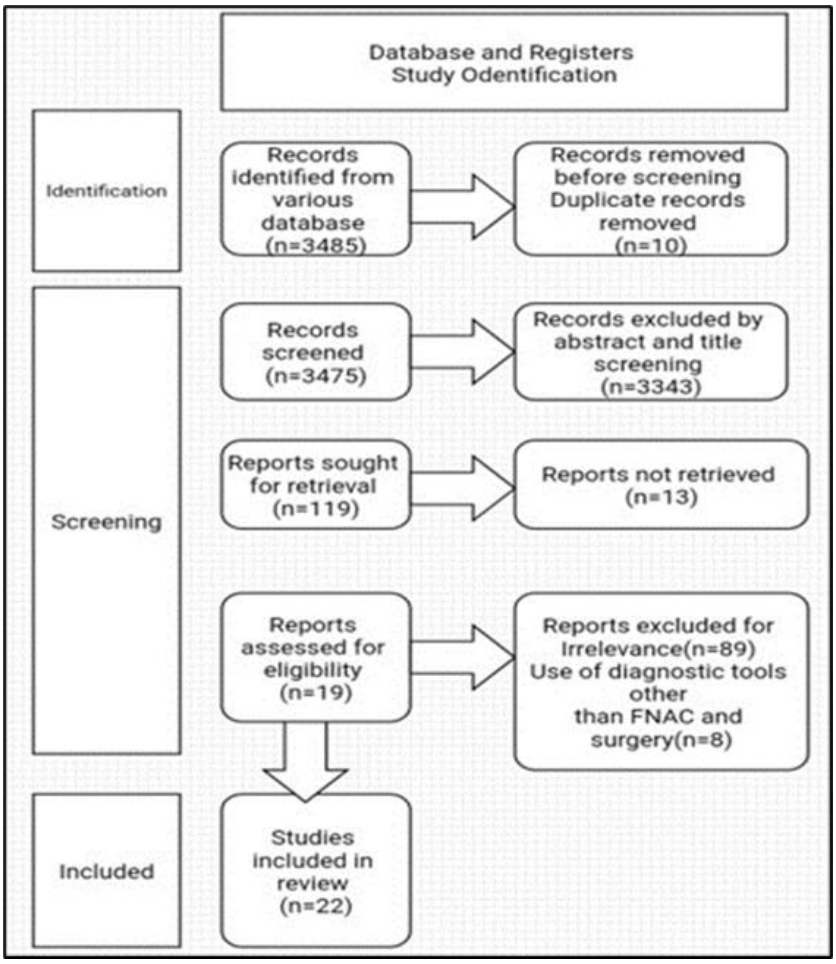


Figure 1 Prisma Flow Diagram

3.1. Study selection

We identified 3485 records through a comprehensive database search. After removal of duplicates (n=10), 3475 records were screened on the basis of titles and abstracts. 3343 records were excluded through screening of title and abstract according to the eligibility criteria. 13 records were excluded as their full texts could not be retrieved. The remaining 119 articles were assessed for full text eligibility. 89 studies were found to be irrelevant, and were thus excluded. 8 articles were excluded because they used diagnostic criteria other than FNAC and surgery. The remaining 22 studies were included in this systematic review.

3.2. Studies and patient characteristics

22 studies were included in our meta- analysis after a comprehensive literature review. 50,321 patients participated in the study.22, 352/50,321 (44.42%) patients were included in the STN subgroup and 27,864/50,321 (55.37%) were included in the MNG group. The most common type of cancer was found to be papillary thyroid cancer, followed by follicular and medullary thyroid cancer. Almost half of the studies included in the meta- analysis used surgical procedures for diagnostic purposes, and the remainder used FNAC. Most studies performed thyroidectomy. The most studies from one country (6/22) were from Italy, followed by Turkey, Saudi Arabia and the United States

3.2.1. Quality assessment

Newcastle Ottowa Scale (NOS) was used to assess risk of bias in 13 cohort studies. 4/13 (30.8%) were prospective cohorts and 9/13 (69.2%) studies were retrospective cohorts. Out of 13 included cohort studies, 2/13(15.4%) had a low risk of bias and 11/13 (84.6%) had moderate risk. 11/13(84.6%) cohort studies didn't assess comparability which contributed to an increased risk of bias. We used modified NOS to find out the risk of bias in 9 cross-sectional studies

included in our meta-analysis. 3/10 (30%) cross- sectional studies reported low risk of bias and 7/10 (30%) had moderate risk. Only 3 cross-sectional studies performed comparability analysis. All included studies had representative samples, ascertainment of exposure and negligible non-respondent numbers.

3.2.2. Risk of thyroid cancer in patients with Multi-nodular goiter (MNG) vs. Solitary thyroid nodule (STN):

We constructed a forest plot using a random effects model for meta-analysis. MNG was found to have a significantly lower risk of thyroid cancer than STN. The pooled OR was calculated as 0.76(CI: 0.61- 0.96), with significant disparity between studies [I2=76%].

3.2.3. Subgroup analyses

Table 1 Characteristics of studies

AUTHOR	STUDY DESIGN	IODINE DEFICIENCY	MEAN AGE	GENDER DISTRIBUTION
Taneri et al	Cross-sectional	Yes	47.2 y	81% F, 19% M
Sippel et al	Retrospective cohort	No	47 y	81.5% F, 18.5% M
Sachmechi et al	Retrospective cohort	No	52 y	92.5% F, 7.5% M
Rios et al	Prospective cohort	No	51.9 +/- 16.7 y	86% F, 14%M
Rago et al	Cross-sectional	Yes	M, 50 +/- 17 Y F, 48 +/- 23 y	81% F, 19% M
Provenzale et al	Retrospective cohort	Yes	50.1 +/- 13.8 y	70% F, 30% F
Papini et al	Cross-sectional	Yes	47.8 +/- 13.3 y	87% F, 13% M
Papendieck et al	Prospective cohort	-	< 19 y	-
Nobrega et al	Retrospective cohort	No	47.9 +/- 15.2 y	92% F, 8%M
Miccoli, Paola et al	Prospective cohort	Yes	49.5 y	70%F, 30% M
Matesa et al	Retrospective cohort	No	-	93%F, 7%M
Marqusse et al	Cross-sectional	No	46.3 y	91%F, 9%M
Khairi et al	Cross-sectional	No	-	-
Kaliszewski, Krzsztof et al	Retrospective cohort	Yes	53.0+/- 16.4 y	-
Frates et al	Retrospective cohort	No	46.2+/- 0.9 y	87.8% F, 12.2% M
Franklyn JA et al	Prospective cohort	-	-	-
Edino ST et al	Cross-sectional	No	38.8 y	-
Dirikoc A et al	Cross-sectional	Yes	49.09+/- 11.93y	80%F, 20% M
Deandrea et al	Retrospective cohort	Yes	51y	96.7%F, 3.3%M
Belfiore, Antonio et al	Cross-sectional	Yes	-	89%F, 11%M
Ajarma, Khalid Y et al	Cross-sectional	No	44.3+/- 14.5y	77.8%F, 22.2%M
Abhu Eshy, SA et al	Retrospective cohort	No	STN, 34.7 +/- 14.2 y MNG, 37.7 +/- 14.3y	84.5% F, 15.5%M

We performed subgroup analyses on the basis of diagnostic method and the iodine status in the locale to explore the causes of heterogeneity. 11/22 (50%) of our included studies used surgical resection as the diagnostic method while the other 11/22 (50%) diagnosed thyroid cancer via FNAC. On running the subgroup analysis, no significant differences between the two groups were observed. Similarly, subgroup analysis on the basis of iodine status in the locale reported an insignificant difference between the two groups. Insufficient data was available to perform subgroup analysis on the basis of history of thyroid cancer in the family and history of radiation exposure .Assessment of reporting bias: A

funnel plot for these 22 studies was subjected to visual inspection. Minor asymmetry was observed which confirmed insignificant publication bias.

Table 2 Diagnostic findings of studies

AUTHOR	TOTAL PATIENTS	DIAGNOSTIC METHOD	DIAGNOSIS	THYROID CARCINOMA
Taneri et al	370	Surgery	STN: 133(25.6), MNG:237(45.7%)	STN:24/133(18.04%), MNG:35/237(14.64%)
Sippel et al	295	FNAC	STN: 132(45%), MNG:163(55%)	STN:37/132(28%), MNG27/163(16.6%)
Sachmechi et al	142	FNAC	STN: 50(35.2%), MNG:92(64.8%)	STN:4/50(8%), MNG:9/92(9.78%)
Rlos et al	221	Surgery	STN: 169(76.5%), MNG:52(23.5%)	STN:29/169(17.12%), MNG:3/52(5.7%)
Rago et al	33472	FNAC	STN: 13549(40.5%), MNG:19923(59.5%)	STN:531/13549(3.9%), MNG:471/19923(2.4%)
Provenzale et al	665	Surgery	STN: 259(39%), MNG:406(61%)	STN:59/259(22.8%), MNG:100/406(24.6%)
Papini et al	402	FNAC	STN: 195(48.5%), MNG:207(51.5%)	STN:18/195(9.2%), MNG:13/207(6.3%)
Papendieck et al	62	Surgery	STN: 45(72.6%), MNG:17(27.4%)	STN:7/45(15.6%), MNG:7/17(41.2%)
Nobrega et al	220	Surgery	STN:72(32.7%), MNG:148(67.3%)	STN:27/72(37.5%), MNG:47/148(31.8%)
Miccoli, Paola et al	510	Surgery	STN: 69(13.5%), MNG:441(86.5%)	STN:1/69(1.4%), MNG:63/441(14.3%)
Matesa et al	406	FNAC	STN: 117(29%), MNG:289(71%)	STN:6/117(5.1%), MNG:15/289(5.2%)
Marqusee et al	150	FNAC	STN: 60(40%), MNG:90(60%)	STN:4/60(6.7%), MNG:8/90%(8.9%)
Khairy et al	296	Surgery	STN: 172(58%), MNG:124(42%)	STN:24/172(14%), MNG:16/124(12.9%)
Kaliszewski, Krzysztoff et al	1645	Surgery	STN: 493(30%), MNG:1152(70%)	STN:98/493(19.9%), MNG:68/1152(5.9%)
Frates et al	1985	FNAC	STN: 1181(59.5%), MNG:804(40.5%)	STN:175/1181(14.8%), MNG:120/804(14.9%)
Feanklyn JA et al	393	FNAC	STN: 321(81.%), MNG:72(18.3%)	STN:19/321(5.9%), MNG:1/72(1.4%)
Edino ST et al	173	Surgery, FNAC	STN: 13(7.5%), MNG:160(92.5%)	STN:1/13(7.6%), MNG:24/160(15%)
Dirikoc, A et al	1719	Surgery	STN: 227(13.2%), MNG:1492(86.8%)	STN:105/227(46.3%), MNG:618/1492(41.4%)
Deandrea et al	420	FNAC	STN: 246(58.5%), MNG:174(41.5%)	STN:15/246(6.1%), MNG:12/174(6.9%)
Belfiore, Antonino et al	5637	FNAC	STN:4485(79.5%), MNG:1152(20.5%)	STN:212/4485(4.7%), MNG:47/1152(4.7%)
Ajarma, Khalid Y et al	567	Surgery	STN: 224(39.5%), MNG:343(60.5%)	STN:92/224(41.1%), MNG:100/343(29.2%)
Abu Eshy, SA et al	277	Surgery	STN: 105(38%), MNG:172(62%)	STN:16/105(15.2%), MNG:14/172(8%)

Figure 3 Forest Plot of risk of malignancy in STN vs MNG

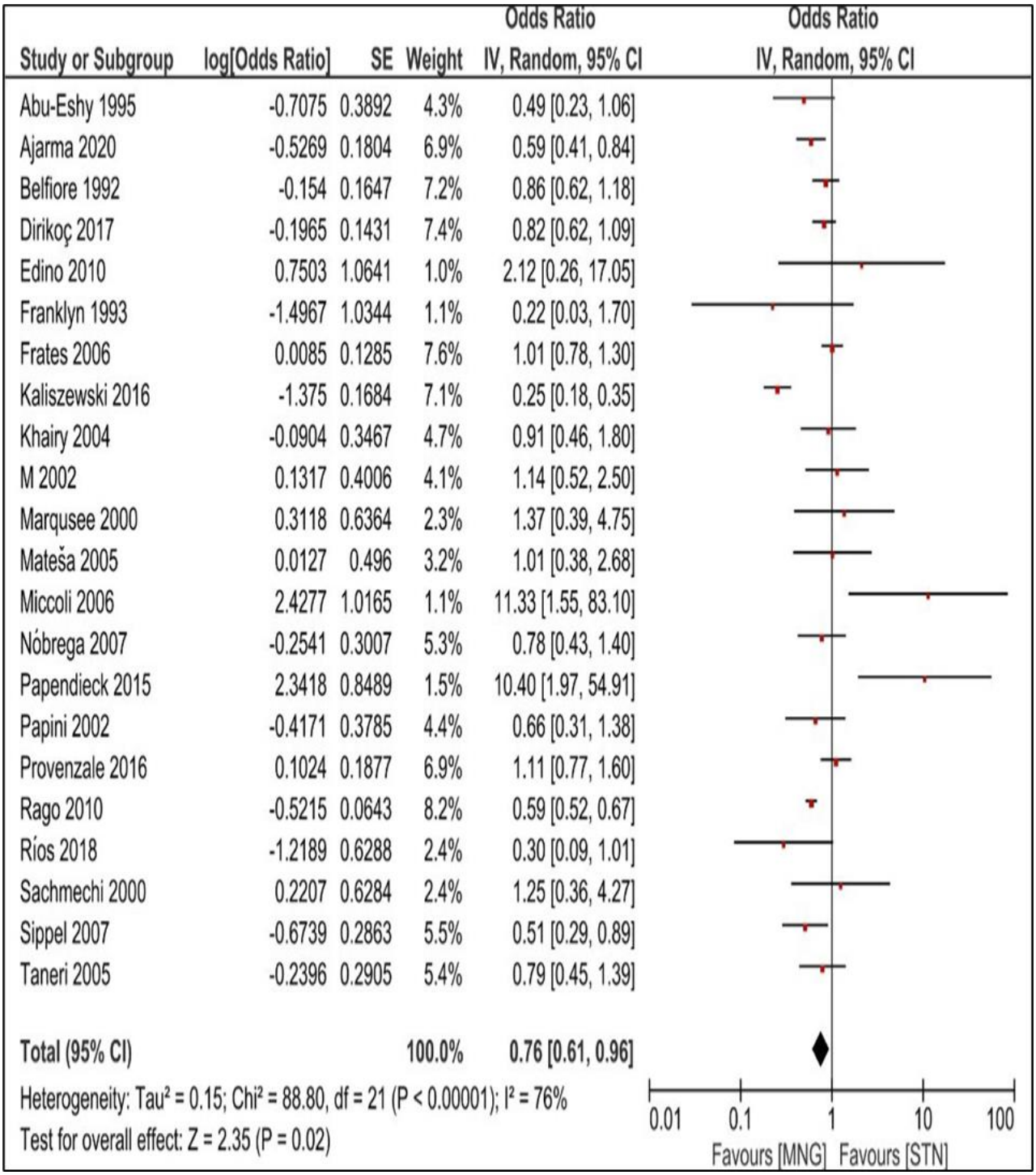


Figure 4 Subgroup analysis of bias of diagnostic methods

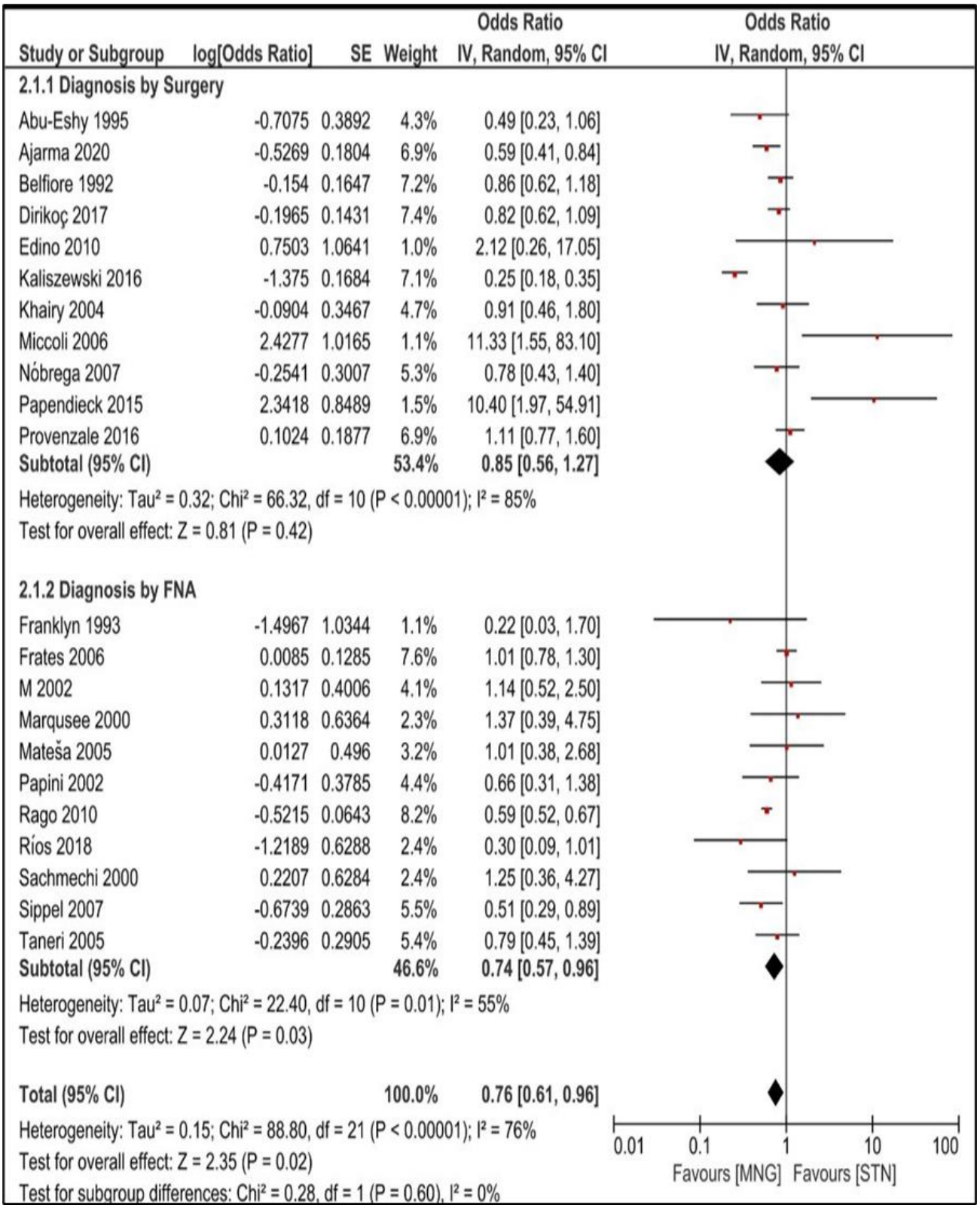
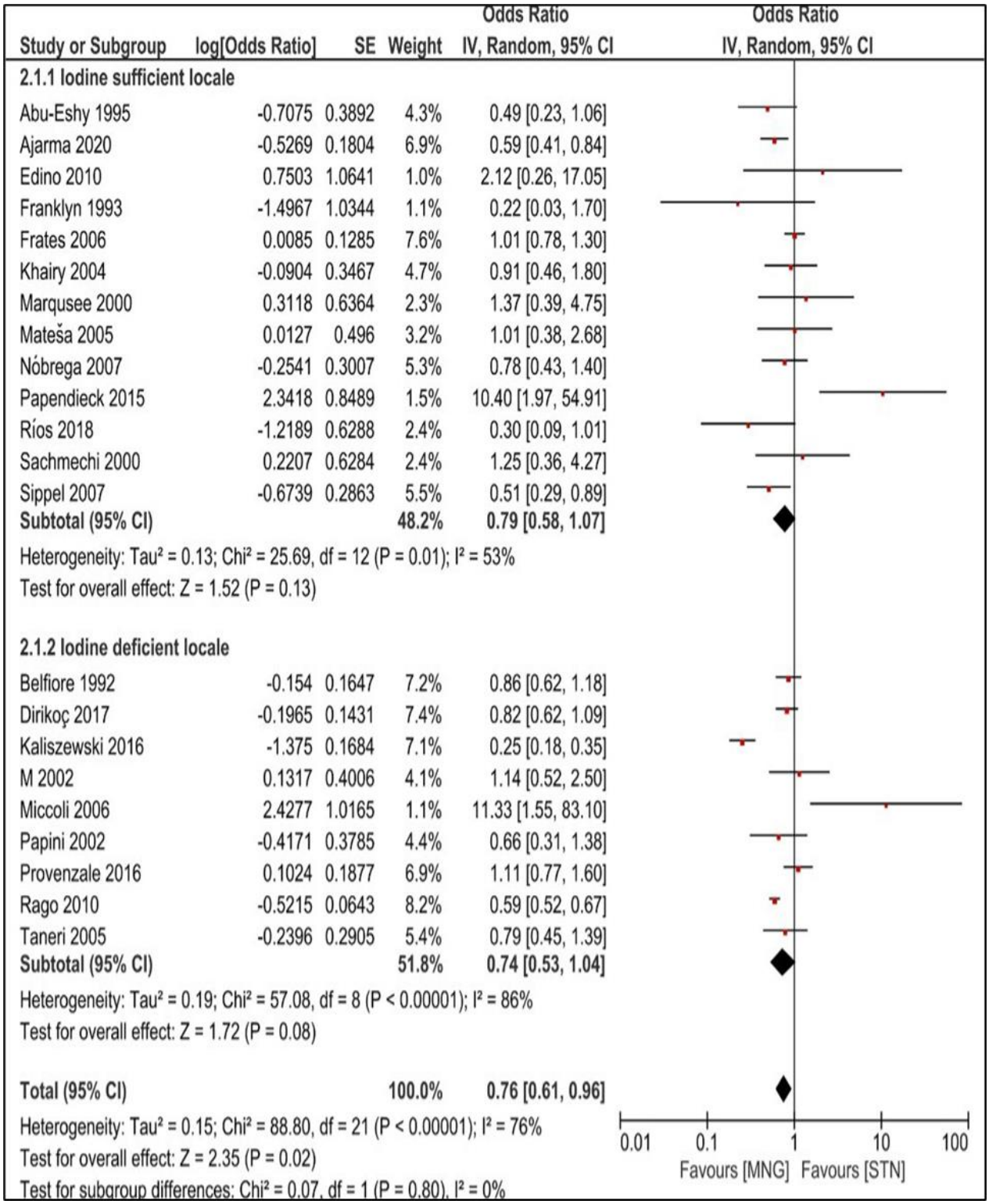


Figure 5 Subgroup Analysis of bias of Iodine status in locale



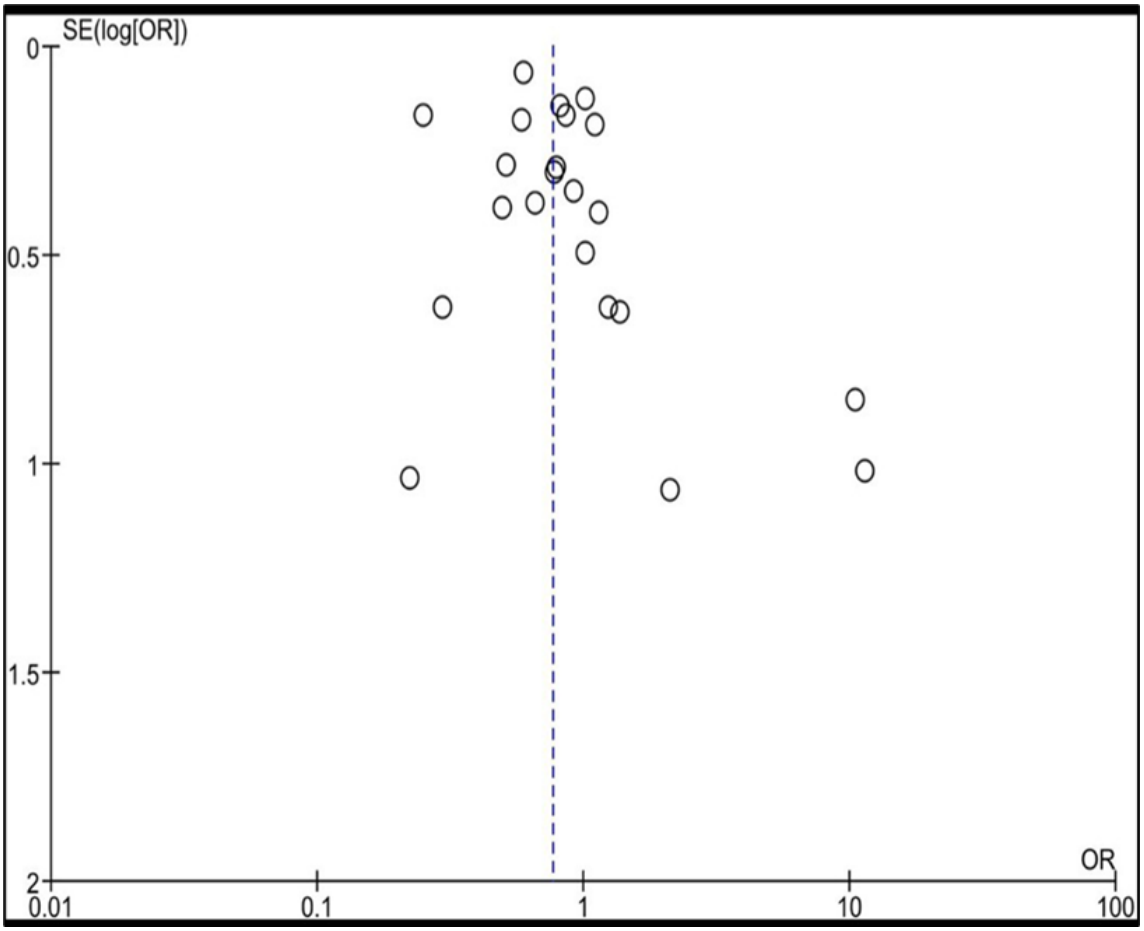


Figure 2 Funnel Plot for assessment of Reporting bias

4. Discussion

Solitary thyroid nodules (STN) and multinodular goiters (MNG) may appear as a single nodule on palpation. This is because a large MNG nodule can make it difficult to see other smaller nodules. However, a more significant problem arises when the results of cytological evaluation are inconclusive and doctors are left with surgery as the only option to definitively diagnose malignant tumors. However, since surgical evaluation of all cases of indeterminate thyroid nodules is neither clinically feasible nor recommended, it is necessary to define variables such as nodules as risk factors for malignancy to better clinically assess the cancer risk of an individual patient. It is estimated that if surgery is performed on all indeterminate FNAC cases, thyroid cancer will be detected in only 10-40% of cases, making the remaining operations unnecessary and futile. Therefore, there is a need to predict the carcinoma risk of patients based on their clinical characteristics and examination findings, especially nodularity.

Our analysis confirmed the previously accepted view that isolated thyroid nodules are associated with a higher risk of thyroid cancer than multi- nodular goiter, and therefore can be considered as an independent risk factor used in carcinoma risk stratification.Therefore, the goal of thyroid nodule evaluation is to identify both potentially malignant nodules and non malignant nodules. Such risk stratification allows avoiding unnecessary and invasive histological evaluation for indeterminate thyroid nodules. However, considering that some more recent studies have shown an equal or even higher risk of carcinoma in MNG, our results may be related to multiple factors or limitations. First, it was estimated that 23% of clinically diagnosed isolated nodules are actually MNG-dominant nodules, considering what would greatly increase not only the prevalence of MNG, but also the associated risk of thyroid cancer in MNG. Thyroid cancer detection has increased with the development of better diagnostic tools, so carcinoma rates should increase compared to MNG. In addition, MNG has traditionallybiopsied only the dominant noduleuntil recent guideline updates, which limits this study and future meta-analysis. Frates et al found that biopsy of only the largest nodule carries a 15% risk of missing thyroid cancer. Although the dominant nodule in MNG has a relatively higher risk of developing thyroid cancer, the other nodules have sufficient risk and to be treated separately as single nodules. There is also increasing

evidence that although the risk of cancer per noduleis reduced in multi-nodular goitre, the cumulative risk in terms of number of nodules is equal to that of a single nodule.

However, probably the most important finding in this regard is that of Kaliszewski et al. FNAC was found to be three times more likely to give false- negative results in MNG compared to STN, mainly due to biopsy of a specific nodule only in MNG or collection of non-diagnostic specimens.

This is part of the reason why MNG is associated with higher reoperation than patients with STN. Because FNAC is the most commonly used tool in the diagnosis of malignancy, it becomes an important underlying factor contributing to the lower than expected incidence of cancer in MNG. Subgroup analysis was performed by diagnosis. Methods to compare histological diagnosis (surgery) and cytological diagnosis (FNAC). Although surgery has long been considered the gold standard for the diagnosis of thyroid malignancies, the results have shown no statistically significant difference between the two effectiveness. However, the significantly higher incidence of nodules at autopsy is a problem because visualization of a greater number of nodules automatically increases the probability of diagnosing carcinoma at surgery. Therefore, the lack of results was probably due to the fact that FNAC was performed only on those nodules that already had malignant features on ultrasound. This phenomenon is called "FNAC enrichment". In addition, another subgroup analysis based on the state of iodine intake of participants gave statistically insignificant results, indicating that the effect of iodine consumption on carcinoma progression was minimal. This differs from a previous meta-analysis suggesting that the difference in cancer risk between MNG and STN in different populations may be due to differences in iodine intake in different areas. Although further studies, especially prospective studies, are crucial. To determine nodularity as a reliable predictor of malignancy, the impact of this meta- analysis on understanding the Thyroid Nodule Imaging and Reporting System (TI-RADS) should certainly be considered. , a parallel malignancy risk stratification system based entirely on ultrasound Patients with a lower risk of malignancy, as determined clinically by clinicians based on available nodular evidence, may require ultrasound alone, reducing the need for invasive procedures such as FNAC or surgery while improving accuracy and sensitivity. This may even make nodulation more important in predicting the risk of malignancy.

Strengths and Limitations

The strengths of this study are the comprehensive literature search, inclusion of all demographics including children excluded from previous literature, rigorous quality assessment, and low reporting bias. Due to the paucity of literature on the subject, this meta-analysis not only provides the largest body of information on the subject to date, but also points to gaps in the existing literature. The limitations of this meta-analysis are mainly due to the limited data available that determine treatment. Most studies on this topic are observational and therefore ill-equipped to detect correlation. In addition, most of the included studies are retrospective, which is an important source of potential selection bias, i.e., isolated nodules are more likely to be referred for FNAC than MNG. This can further contaminate the results, increasing the risk of cancer in individual nodes. Second, important demographic data such as age and gender were reported inconsistently, and the difference in findings between sporadic and sporadic micro carcinomas precluded any attempt to perform a subgroup analysis and establish a trend based on these.

5. Conclusion

Conclusions: Solitary thyroid nodules have been found to have an increased risk of thyroid cancer compared with multinodular goiter, but the validity and strength of this association is questionable because the literature on the subject is weak.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical committee approval not needed for Metanalysis research work.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors

Availability of data and materials

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

References

[1] Pemayun TGD. Current Diagnosis and Management of Thyroid Nodules. Acta Med Indones. 2016;48(3):11.

[2] Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clin Endocrinol Metab. 2008;22(6):901–11.

[3] Ajarma KY, Al-Faouri AF, Al Ruhaibeh MK, Almbaidien FA, Nserat RT, AlShawabkeh AO, et al. The risk of thyroid carcinoma in multinodular goiter compared to solitary thyroid nodules: A retrospective analysis of 600 patients. Med J Armed Forces India. 2020;76(1):23–9.

[4] Liu Y, Su L, Xiao H. Review of factors related to the thyroid cancer epidemic. Int J Endocrinol. 2017;7(2017): e5308635.

[5] Wasikowa R, Iwanicka Z, Zak T, Lukieńczuk T, Sawicz-Birkowska K. Nodular goiter and thyroid carcinoma in children and adolescents in a moderate endemic area (lower Silesia-Sudeten endemia) in the last twelve years. J Pediatr Endocrinol Metab JPEM. 1999;12(5):645–52.

[6] Schlinkert RT, Heerden JAV, Goellner JR, Gharib H, Smith SL, Rosales RF, et al. Factors that predict malignant thyroid lesions when fneneedle aspiration is "suspicious for follicular neoplasm." Mayo Clin Proc. 1997;72(10):913–6.

[7] Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of "follicular neoplasm": a gray zone in thyroid fne-needle aspiration cytology. Diagn Cytopathol. 2002;26(1):41–4.

[8] Grani G, Brenta G, Trimboli P, Falcone R, Ramundo V, Maranghi M, et al. Sonographic risk stratifcation systems for thyroid nodules as rule-out tests in older adults. Cancers (Basel). 2020;12(9):2458.

[9] Di Fermo F, Sforza N, Rosmarin M, MorosanAllo Y, Parisi C, Santamaria J, et al. Comparison of diferent systems of ultrasound (US) risk stratifcation for malignancy in elderly patients with thyroid nodules. Real world experience Endocrine. 2020;69(2):331–8.

[10] Zhang F, Russell YX, Guber HA. Transverse and Longitudinal Ultrasound Location of Thyroid Nodules and Risk of Thyroid Cancer. Endocr Pract Of J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2021;27(7):682–90.

[11] Ramundo V, Lamartina L, Falcone R, Ciotti L, Lomonaco C, Bifoni M, et al. Is thyroid nodule location associated with malignancy risk? Ultrason (Seoul, Korea). 2019;38(3):231–5.

[12] Belfore A, La Rosa GL, La Porta GA, Giufrida D, Milazzo G, Lupo L, et al. Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity. Am J Med. 1992;93(4):363–9.

[13] Gandolf PP, Frisina A, Rafa M, Renda F, Rocchetti O, Ruggeri C, et al. The incidence of thyroid carcinoma in multinodular goiter: retrospective analysis. Acta Bio-Medica Atenei Parm. 2004;75(2):114–7.

[14] Tollin SR, Mery GM, Jelveh N, Fallon EF, Mikhail M, Blumenfeld W, et al. The use of fne-needle aspiration biopsy under ultrasound guidance to assess the risk of malignancy in patients with a multinodular goiter. Thyroid. 2000;10(3):235–41.

[15] Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, Cibas ES, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab. 2006;91(9):3411–7