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Risk Factors for Large-Volume Lymph Node Metastasis in Papillary Thyroid Carcinoma: A Meta-Analysis

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Abstract

Background We defined large-volume lymph node metastasis (L-VLNM) as more than five lymph node metastases (LNMs) or any lymph node with a diameter of 2 mm or greater in any case of papillary thyroid cancer (PTC). This study investigated risk factors for the development of L-VLNM in PTC with meta-analysis.

Methods Articles published until July 2021 on clinicopathological factors of L-VLNM in PTC were searched in electronic databases (PubMed, Web of Science (WOS), Embase, Cochrane, Wanfang Data and Chinese National Knowledge Infrastructure (CNKI)) to identify studies based on predefined criteria. Statistical analysis was performed using STATA 14.0. The outcomes were clinical and pathologic factors for L-VLNM, and the individual and pooled odds ratios (ORs) with 95% confidence intervals (CIs) of each outcome were analysed by fixed-/random-effects models. Egger's test was used to assess publication bias in the publications. This study is registered with PROSPERO (CRD 42020213831).

Results Twelve studies included 10806 patients in total. Meta-analysis revealed that an increased risk of L-VLNM was associated with male sex (*OR=2.20, 95% CI=1.63–2.97, P<0.001*), age<45 years (*OR=2.34, 95% CI=1.36–4.02, P<0.001*), tumour diameter>1 cm (*OR=3.99, 95% CI=3.45–4.62, P<0.001*), extrathyroidal extension (*OR=2.42, 95% CI=1.90–2.82, P<0.001*), capsule invasion (*OR=3.62, 95% CI=1.44–9.06, P<0.001*) and multifocality (*OR=2.02, 95% CI=1.47–2.77, P<0.001*). Hashimoto's thyroiditis (HT; *OR=0.82, 95% CI=0.60–1.11, P=0.03*) was not associated with L-VLNM.

Conclusions Male sex, age <45 years, tumour diameter >1 cm, extrathyroidal extension, capsule invasion and multifocality were risk factors for L-VLNM, HT was not a risk factor.

Introduction

Thyroid cancer is the most common malignant endocrine tumour, and its global incidence has rapidly increased in recent years. In 2018, the number of newly diagnosed thyroid cancer patients worldwide exceeded 567,000, ranking 9th among all cancers[1]. Papillary thyroid cancer (PTC) is the most common pathological type of thyroid cancer, accounting for approximately 89.9%[2]. Although PTC has a good overall prognosis, it is prone to lymph node metastasis (LNM); 24%-63% of patients have LNM at the time of PTC diagnosis, and LNM is closely related to postoperative recurrence and poor prognosis[3].

In the 2015 American Thyroid Association (ATA) guidelines, the risk stratification system classifies PTC as high, intermediate or low risk. In clinical practice, the majority of PTC cases have a low to intermediate risk of recurrence. In recurrence risk stratification, the presence of > 5 LNMs is regarded as an intermediate-risk factor, and a metastatic lymph node diameter > 3 cm is regarded as a high-risk factor[4]. Studies have shown that the risk of recurrence when the metastatic lymph node diameter is 2 mm or greater is significantly greater than the risk of pathologically confirmed micrometastasis[5]. In this study, any PTC patient confirmed by postoperative pathology to have > 5 LNMs or a maximum metastatic lymph node diameter ≥ 2 mm was considered to have a large-volume LNM (L-VLNM)[6]. It is one of the most important indicators to distinguish a low and an intermediate risk of recurrence and is also an important predictor of the risk of recurrence.

Different clinical treatments and management methods were used to treat PTC patients with various risk stratifications. A more conservative unilateral lobectomy is recommended for low-risk patients, and even active surveillance can be used for low-risk patients in certain circumstances. In contrast, therapeutic lymph node dissection or even ^{131}I therapy is recommended for intermediate-risk patients. It is therefore particularly important to differentiate between a low and an intermediate risk of recurrence. This study explores high-risk clinical factors for L-VLNM by performing the meta-analysis of included observational studies, attempts to distinguish the presence of L-VLNM based on preoperative high-risk factors, and provides a reliable basis for differentiating most prevalent low- and intermediate-risk PTCs in clinical practice.

Methods

Search strategy and study identification

PubMed, Web of Science (WOS), Embase, Cochrane Library, the Wanfang Data and Chinese National Knowledge Infrastructure (CNKI) database searches were performed to retrieve papers linking PTC and L-VLNM that were available by September 2020 without language restrictions. We used the following search terms: ((papillary thyroid) AND ((((cancer) OR (tumour)) OR (carcinoma)) OR (neoplasm))) AND ((((((large volume lymph node metastasis) OR (high volume lymph node metastasis)) OR (large volume lymph node metastases)) OR (high volume lymph node metastases)) OR (macrometastasis)) OR (non small volume lymph node metastasis)). Our study strictly followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.

Inclusion and exclusion criteria

Inclusion criteria: (1) Retrospective or prospective cohort studies without language restrictions. (2) Postoperative pathologically confirmed PTC. (3) A postoperative diagnosis of L-VLNM: >5 LNMs or a maximum LNM diameter ≥ 2 mm. (4) Data available on the risk factors for L-VLNM that could be used to calculate the combined odds ratio (OR) value.

Exclusion criteria: (1) The research centre or time frame overlapped with other studies. (2) The original data were incomplete or complete original data were not obtained after contact. (3) Reviews, case reports, and conference reviews.

Data extraction

All data were independently retrieved by two researchers (*F. Wu and T.H. Zhou*) and extracted from the literature: first author, publication year, research centre, research type, number of cases and controls, number of L-VLNM cases, and related risk factors (sex, age, tumour diameters, Hashimoto's thyroiditis (HT), multifocal, extrathyroidal extension, etc.). For the uncertain parts of the literature, the results were discussed with a supervisor (D.C. Luo).

Risk of bias assessment

The quality of the included literature was independently assessed by two reviewers (*F. Wu and T.H. Zhou*) based on the Newcastle-Ottawa Scale (NOS). The NOS consists of eight items containing the following three items: the selection of study groups, ascertainment of exposure and outcomes, and comparability of groups. The NOS has a 9-star maximum rating and a total scale score of 9. A score of ≥ 7 was considered high-quality literature, 5–6 was considered moderate-quality literature, and < 5 was considered poor-quality literature.

Statistical analysis

Statistical analysis was performed using STATA 14.0 for the meta-analysis of data extracted from the collected and collated literature. The level of heterogeneity of the included literature was assessed by I^2. A fixed-effects model or a random-effects model was chosen according to the heterogeneity of the literature. When $P > 0.05$ and $I^2 < 50\%$, a fixed-effects model was used; otherwise, a random-effects model was used. The combined OR and its 95% confidence interval (CI) were calculated with STATA 14.0, and the results obtained by meta-analysis were plotted on a forest plot.

Publication bias

If over 10 studies were included for a certain outcome indicator, a funnel chart was used to evaluate publication bias. Egger's test and Begg's test were used to assess publication bias, and $P > 0.05$ was considered statistically significant. A funnel chart was generated to evaluate the relationship between the content of the literature data sample and the degree of dispersion.

Certainty of evidence and strength of recommendations

The GRADEpro system of the Cochrane collaboration network was used to evaluate the quality of the evidence for each outcome. The evaluation levels were divided into four levels: high, moderate, low, and very low[7]. In the GRADE approach, randomized controlled trials (RCTs) were considered high-certainty evidence, while observational studies were considered low-certainty evidence. Then, we assessed five reasons to possibly decrease the rating of the certainty of the evidence (the risk of bias, imprecision, inconsistency of results, indirectness of evidence and publication bias) and three (including a large magnitude of an effect and dose-response gradient) to possibly increase the certainty rating. If there were reasons to increase the rating (for example, smoking as a causal exposure in lung cancer), the certainty of the evidence from observational studies could be adjusted to moderate- or even high-certainty evidence. We provided a summary of the findings in tables and formed the final recommendation combined with the clinical situation.

Results

Based on the above search strategy, a total of 845 articles in English and Chinese were retrieved from the major databases listed above (PubMed, 79 papers; WOS, 86 papers; Embase, 568 papers; Cochrane, 7 papers; CNKI, 32 papers; and the Wanfang Data: 83 papers. After reading the titles and abstracts of the articles, 732 articles were excluded, and the full texts of 123 articles were carefully reviewed. According to the established inclusion and exclusion criteria, a total of 12 articles were included after a strict literature quality assessment and screening, 9 in the English literature[8–16], and 3 in the Chinese literature [17–19]. There were 11 retrospective studies and 1 prospective study. The literature review process is shown in Fig. 1. The total number of cases in the 12 studies included in the study was 10806, and 1408 cases of L-VLNM accounted for 13.03% of all patients. The included literature was scored using the NOS scoring system, and the scores were all over 7 points, indicating that the quality of the literature was relatively high. The basic characteristics of the included studies are shown in Table 1.

Table 1
Characteristics of included studies.

Author	Year	Countries	Design	No.of L-VLNM	toal	Risk Factor	Quality assement
Min	2008	Korea	Case-control	51	198	□□□	7
Ahn	2015	Korea	Case-control	166	255	□□□□□□	8
Lee	2016	Korea	Case-control	119	411	□□□□□□	8
Oh	2017	Korea	Case-control	472	2329	□□□□	8
Kim	2017	Korea	Case-control	62	242	□□□□	7
wang	2019	China	Case-control	67	611	□□□□□□□	8
Dong	2019	China	Case-control	605	4265	□□□□□	8
Wu	2019	China	Case-control	21	512	□□□□	8
Zhao	2019	China	Case-control	68	372	□□□□	7
Shen	2020	China	Case-control	84	947	□□□□□	8
Gao	2020	China	prospective cohort	31	138	□□□□	8
Huang	2021	China	Case-control	40	364	□□□□□□□□	8

L-VLNM: large -volume lymph node metastasis.Risk Factor:□gender □Age □Tumor diameter:1cm □ Tumor diameter:0.5cm □ Hashimoto thyroidies □Extrathyroid extension □ Capsule invasion □Multifocality

Sex

This study included 11 articles and a total of 10244 cases, including 1357 L-VLNMs and 9251 non-L-VLNMs. Males accounted for 34.19% and 9.66% of the L-VLNMs and the non-L-VLNMs, respectively. The random-effects model used in this study showed that male sex was a high-risk factor for L-VLNM (OR = 2.20, 95% CI = 1.63–2.97, P < 0.001, Fig. 3a). The heterogeneity in this study was high (I^2 = 71.6%, P-heterogeneity < 0.001). Heterogeneity was significantly lower (I^2 = 10.9%, P-heterogeneity = 0.343) after excluding the studies by Oh.

Age

Five studies were included; however, there were multiple age grouping methods in the previous literature. The method used in the study with the largest sample size was age < 45 years vs. ≥ 45 years. Meanwhile, we found that age less than 45 years, that is, younger age, was a risk factor for L-VLNM (OR = 2.34, 95% CI = 1.36–4.02, P < 0.001, Fig. 3b). High heterogeneity was found in this study (I^2 = 83.1%, P-heterogeneity < 0.001). Heterogeneity was significantly lower (I^2 = 0%, P-heterogeneity = 0.640) after excluding the studies by Kim.

Tumour diameters

There were 10 studies containing data on tumour diameters, of which 6 articles were related to PTMC (tumour diameter ≤ 1 cm), and 4 articles mentioned PTC (no tumour diameter limitation). This study used a fixed-effects model for analysis. Tumour diameter > 1 cm was a risk factor for L-VLNM in PTCs (OR = 3.99, 95% CI = 3.45–4.62, P < 0.001, Fig. 3c). The heterogeneity in this study was low (I^2 = 36.5%, P-heterogeneity = 0.163, I^2 = 47.6%). However, tumour diameter > 0.5 cm was not a risk factor for PTMCs to develop into L-VLNM (OR = 2.00, 95% CI = 0.89–4.49, P < 0.001, Fig. 3d).

HT

We found 7 articles containing data related to HT and L-VLNM, which included a total of 9616 patients, 2453 Hashimoto patients, 7163 non-Hashimoto patients, 1166 L-VLNMs, and 8510 non-L-VLNMs. Unfortunately, the results of this study did not show significant differences. The random-effects model used in this study showed OR = 0.82, 95% CI = 0.60–1.11, P = 0.031 (Fig. 3e), and high heterogeneity was found (I^2 = 54.7%, P-heterogeneity = 0.03).

Extrathyroidal extension

A total of 9 studies described the extrathyroidal extension of PTC. There were 704 L-VLNMs and 5156 non-L-VLNMs. The fixed-effects model was used to compare extrathyroidal extension and intrathyroid invasion, and the results showed significant differences (OR = 2.42, 95% CI = 1.90–2.82, P < 0.001, Fig. 3f). There was no obvious heterogeneity (I^2 = 23.2%, P-heterogeneity = 0.24).

Capsule invasion

A total of 3 studies involved capsule invasion in PTC. There were 811 L-VLNMs and 4073 non-L-VLNMs. A random-effects model was applied, and the results showed that tumour infiltration of the capsule was a highly significant risk factor for L-VLNM (OR = 3.61, 95% CI = 1.44–9.06, P < 0.001, Fig. 3g). Unfortunately, the heterogeneity of the current study was high (I^2 = 91.1%, P-heterogeneity < 0.001). Heterogeneity was significantly lower after excluding research by Ahn (I^2 = 0%, P-heterogeneity = 0.465).

Multifocality

A total of 10496 cases from 11 studies were included, with L-VLNM accounting for 18.22% and 10.43% of multifocal and solitary lesions, respectively. Multifocality was a significant risk factor for L-VLNM (OR = 2.02, 95% CI = 1.47–2.77, P < 0.001, Fig. 3h) and possessed comparatively low heterogeneity (I^2 = 42.7%, P-heterogeneity = 0.121).

Heterogeneity test and sensitivity analysis

The results of each of the above studies were tested for heterogeneity according to the P-value and I^2, and the results of the tests are shown in Table 2. The heterogeneity ranged from 23.1–91.1%. Among the outcome variables, sex, age, tumour diameter, HT and capsule invasion were heterogeneous (I^2 > 50%), and the random-effects model was used to merge the OR values. We performed sensitivity analysis by omitting each study sequentially with STATA. The analysis results were robust, without obvious deviation (data not shown).

Table 2
Meta-analysis result

Risk Factors	Studies	Toal	P	I^2	OR	95%CI	Z	*P*
gender(male vs female)	11	10608	0.001	71.6%	2.20	1.63–2.97	5.14	< 0.001
age(45 VS ≥ 45)	5	1874	0.001	77.4%	2.34	1.36–4.02	3.06	0.009
Tumor diameter(>1cmVS ≤ 1cm)	6	6223	0.163	36.5%	3.99	3.45–4.62	18.51	< 0.001
Tumor diameter(>0.5cmVS ≤ 0.5cm)	4	1889	0.029	66.6%	2.00	0.89–4.49	1.69	< 0.001
Hashimoto's thyroiditis(yes VS no)	7	9616	0.03	54.7%	0.82	0.60–1.11	1.29	0.031
Extrathyroid extension(yes VS no)	9	5860	0.24	23.1%	2.42	1.90–2.82	7.88	< 0.001
Capsule invasion(yes VS no)	3	4884	0.001	91.1%	3.62	1.44–9.06	2.74	0.006
Multifocality(yes VS no)	11	10496	0.093	38.5%	2.02	1.47–2.77	4.36	< 0.001

Publication bias

The Begger test funnel plot showed symmetry; therefore, there was no significant publication bias for L-VLNM (Fig. 2). A linear regression analysis using Egger's test showed symmetrical funnel plots with a p-value of 0.650 (p > 0.05), which indicated no significant publication bias.

Certainty of evidence and strength of recommendation

We assessed the certainty of the evidence for each risk factor with the GRADEpro system. The results showed that extrathyroidal extension and multifocality grade had moderate certainty, and the strength of the recommendation was strong. The certainty of the evidence for sex, age, tumour diameter > 1 cm, and capsule invasion was low, and the strength of the recommendation was strong. The certainty of the evidence for tumour diameter > 0.5 cm and HT was very low, and the strength of the recommendation was weak (Table 3).

Table 3
GRADE summary of findings

Risk Factor	No. of studies	Certainty of evidence assessment							No. of cases		Effe size
		Design	Risk of Bias	Inconsist-ency	Indirectness	Imprecision	Publication bias	Uplifting factors	L-VLNM	Non L-VLNM	
Gender (male vs female)	11	observational study	Not serious	Serious[b]	Not serious	Not serious	Not serious	Large effect[a]	463/1357 (33.12%)	1855/9251 (20.05%)	OR 2.2((1.6 2.9
Age (≤ 45 vs > 45)	5	observational study	Not serious	Serious[b]	Not serious	Not serious	Not serious	Large effect[a]	261/454 (57.49%)	689/1420 (48.52%)	OR 2.3 (1.3 4.0
Tumor diameter (> 1.0cm vs ≤ 1.0cm)	6	observational study	Not serious	Not serious	Not serious	Not serious	Not serious	Large effect[a]	637/1056 (60.32%)	1375/5167 (26.61%)	OR 3.9 (3.4 4.6
Tumor diameter (> 0.5cm vs ≤ 0.5cm)	4	observational study	Not serious	Serious[b]	Not serious	Not serious	Not serious	Large effect[a]	143/178 (80.34%)	1147/1711 (67.04%)	OR 2.0((0.8 4.4
Hashimoto thyrodities	8	observational study	Not serious	Serious[b]	Not serious	Not serious	Not serious	none	219/1106 (19.80%)	2234/8510 (26.25%)	OR 0.8 (0.6 1.1
Extrathyroid extension	7	observational study	Not serious	Not serious	Not serious	Not serious	Not serious	Large effect[a]	400/704 (56.82%)	1801/5156 (34.93%)	OR 2.4 (1.9 2.8
Capsule invasion	3	observational study	Not serious	Serious[b]	Not serious	Not serious	Not serious	Large effect[a]	492/811 (60.67%)	1538/4073 (37.76%)	OR 3.6 (1.4 9.0
Multifocality	10	observational study	Not serious	Not serious	Not serious	Not serious	Not serious	Large effect[a]	664/1379 (48.15%)	2980/9117 (43.65%)	OR 2.0 (1.6 2.1

CI: Confidence Interval; OR: Odds Ratio; RR: Risk Ratio

Explanations:

a. RR > 2.0 based on consistent evidence from at least 2 studies, with no plausible confounders.

b. High Heterogeneity

Discussion

According to the 2018 GLOBOCAN report, the global incidence of thyroid cancer is approximately 14.42/100000, and its mortality rate is 0.46/100000; however, the incidence of thyroid cancer in this country is approximately 14.6/100000, and the mortality rate is 0.48/100000, both of which are higher than the global level[1]. Although the vast majority of thyroid cancer is low risk and the prognosis is better[4, 20], CLNM is significantly related to recurrence and poor prognosis[21, 22]. Studies have found that as the number of metastatic lymph nodes increases, the recurrence rate of PTC also increases[23]. Leboulleux[22] reported that the risk of recurrence in patients with > 10 LNMs (21%) was significantly higher than that of patients with 6–10 LNMs (7%) or patients with < 5

LNMs (3%). In addition, in a follow-up study of 621 N1b patients, a metastatic lymph node diameter greater than 3 cm and more than 5 metastatic lymph nodes independently affected patient's disease-free survival time[24]. In the study, when CLNM occurred, ≥ 3 LNMs and the maximum diameter of a metastasis ≥ 0.2 cm were associated with recurrence-free survival ($P < 0.05$)[6]. Patients with more than 5 LNMs had a significantly higher recurrence rate than those with 5 or fewer LNMs[25]. Based on a large number of clinical studies, the more recognized studies define L-VLNMs as > 5 LNMs in a patient or a maximum diameter of any metastatic lymph node ≥ 2 mm.

Among the 6 risk factors included in this study, sex, age, tumour diameter, extrathyroidal extension and multifocal invasion were high-risk factors for L-VLNM in PTC patients, while HT was not significantly related to L-VLNM. A long-term epidemiological survey of thyroid cancer found that the incidence of PTC in female patients was significantly higher than that in males. Although the incidence was lower in men, male patients often had more tumour invasion characteristics and a higher risk of LNM[9]. In previous studies, male sex was considered an independent risk factor for L-VLNM[11]. In this study, male sex was a risk factors that affected L-VLNM. It is still unclear how sex affects the development of L-VLNM in PTC patients. Therefore, male patients should undergo careful risk assessment before and after surgery.

Studies have shown that L-VLNM is more likely to occur in younger patients[11], and younger age is considered to be related to PTC aggressiveness, such as vascular invasion and LNM. This study further verified that age < 45 years affects L-VLNM in PTC patients. However, in the 12 articles included in this study, there were multiple age categories. In the eighth edition of the American Joint Committee on Cancer (AJCC) guidelines from 2018, the recommended age cut-off point was 55 years old. The study with the largest sample size included in this paper used 45 years as the cut-off point for the study, further validating age < 45 years as a risk factor for L-VLNM in patients with PTC. However, there is currently relatively little data in the literature due to the relatively recent introduction of this classification. Sex and age, as some of the most readily available clinical information, are worthy of further inclusion in studies with larger samples.

Tumour diameter is an important parameter for T staging. Large diameters are frequently associated with higher aggressiveness and a greater the risk of LNM. Compared with patients with smaller tumours, those with larger tumours have a higher possibility of postoperative recurrence, invasion and lymph node metastasis[26]. Ahn, Lee, Zhang, Dong, Wang, Zhao, and Gao proposed that a tumour diameter > 1 cm in non-PTMC patients is a significant risk factor for L-VLNM (*OR = 3.99, 95% CI = 3.45–4.62)* (Fig. 3c). This is an indication that more treatment may be needed to achieve effective eradication, such as prophylactic lymph node dissection, and should be recommended for patients who require surgery. There are currently different management strategies for PTMC. A meta-analysis of studies involving PTMC by Min, Ahn, Oh, Wu, Shen and Huang showed that a tumour diameter > 0.5 cm was not a risk factor for the development of L-VLNM in PTMC (*OR = 2.14, 95% CI = 1.59–2.88)* (3d). However, as an increasing number of PTMCs are now being detected through early screening, the demand for precise treatment for PTMC is increasing. However, given the smallest sample size included in this study and because tumour diameter is one of the most intuitive clinical factors with radiography, identifying the right cut-off value and including more cases is the emphasis of current research.

Tumour invasion of the capsule is considered to be an early stage of extrathyroidal extension and often indicates a greater susceptibility for invasion and recurrence as manifestations of the aggressiveness of PTC[27]. Tumour capsule invasion was also found to be an important risk factor for L-VLNM in this study (*OR = 3.62, 95% CI = 1.44–9.06).* We found that the study by Ahn was the main source of heterogeneity; after the relevant data were removed, the heterogeneity was significantly reduced and the confidence intervals were more reliable (*OR = 2.09, 95% CI = 1.77–2.48).* Adequate preoperative neck imaging can be useful for assessing the size of the lesion and the distance between the lesion and the capsule.

After reviewing these cases, we suggest that if the PTMC tumour is < 1 cm and is not located close to the capsule and there are no obvious suspected metastatic lymph nodes in the neck, a relatively conservative treatment approach can be adopted. For example, active monitoring with regular outpatient follow-up accompanied by neck ultrasound is effective in reducing overtreatment.

Extrathyroidal extension is closely associated with CLNM and is an important factor in the prognosis and recurrence of patients with PTC. A meta-analysis showed that extrathyroidal extension is a risk factor for CLNM in patients with cN0 stage PTC[28]. Extrathyroidal extension is an independent prognostic factor that affects the disease-free survival of patients and the survival of specific diseases[29]; it significantly elevates the risk of recurrence (23%-40%) and has become a major predictor of poorer prognosis in PTC. The results of this study show that extrathyroidal extension significantly increases the risk of L-VLNM in PTC (*OR = 2.31, 95% CI = 1.90–2.82).* Preoperative or intraoperative extrathyroidal extension with a small number of positive LNMs or a small maximum diameter of metastatic lymph nodes may be considered an indication to expand the cervical lymph node biopsy as appropriate. If postoperative pathology confirms the presence of extrathyroidal extension but the absence of L-VLNM, patients should be advised to under go more intensive follow-up with strict follow-up and regular review or even ^{131}I radioiodine therapy.

Multifocality is an important biological characteristic of PTC. After analysing the 10 included articles and studying 10132 patients, we found that the risk of L-VLNM was higher for patients with multiple foci than for those with a single focus. However, it is interesting that Wang[13] and Shen[14] found that multifocality was not significantly associated with the occurrence of L-VLNM in PTC at the cN_0 stage in a univariate analysis. Numerous studies[30, 31] have also supported this association. In this study, a comprehensive meta-analysis revealed (n = 5132) that multifocality was an important risk factor for L-VLNM in patients with stage cN_0 PTC *(OR = 2.07, 95% CI = 1.42–3.01)* (Fig. 3i), and we believe that the inclusion of multicentre,, large sample data will help to refine the results. This means that prophylactic central lymph node dissection and appropriately relaxing the indications for lateral cervical lymph node dissection are recommended when multiple lesions combined with cN_0 disease are identified preoperatively by imaging.

HT is easily diagnosed by medical history, physical examination, elevated thyroid autoantibodies in serum and characteristic ultrasound findings. However, whether HT is related to LNM is still controversial. Previous studies have shown no significant association between PTC combined with HT and LNM[32]. A related meta-analysis of 9369 PTC patients showed that PTC combined with HT was not associated with LNM[33]. It has also been reported that PTC

combined with HT has a better prognosis and can prevent LNM in the central and lateral cervical compartments[34]. Moon et al.[35] performed a meta-analysis that included 71 published studies enrolling 44034 participants and concluded that patients with PTC combined with HT showed better clinicopathological characteristics and a better prognosis than patients with PTC without HT. The results of this study (n = 9616) showed that HT was not associated with L-VLNM (Fig. 3e). After excluding the study by Oh, lower heterogeneity and relatively narrow CIs suggested that the results were relatively reliable. The reason for this finding is considered to be related to the fact that HT patients experience long-term, chronic inflammation, which tends to cause the enlargement of the cervical lymph nodes but does not promote L-VLNM. We should therefore be cautious when considering HT as a high-risk factor for cervical lymph node dissection.

Conclusion

The findings of this meta-analysis suggest that male sex, age < 45 years, tumour diameter > 1 cm, extrathyroidal extension, invasion of the capsule and multifocality are risk factors for L-VLNM in patients with PTC. The presence of these risk factors suggests that clinicians need to be more aggressive in the treatment of this condition. First, fine-needle aspiration is one of the most important examinations for PTC, with BRAF mutations being the most common mutated gene in PTC. However, most of the included studies did not examine this, and therefore, follow-up with an in-depth exploration of the association between BRAF gene mutations and L-VLNM is warranted. Second, few reports have investigated whether L-VLNM is associated with areas of LNM, such as in the central or lateral cervical regions, and it is believed that this is a hot topic for future research on the diagnosis and treatment of PTC. Third, most of the included studies were retrospective analyses, and some had small sample sizes, so there is a possibility of selective bias. The above reasons resulted in low GRADE evidence levels for some of the outcome indicators and reduced the strength of the recommendations; therefore, further multicentre, larger sample size and higher quality prospective studies are urgently needed to further explore the risk factors affecting L-VLNM in patients with PTC.

Abbreviations

L-VLNM
large-volume lymph node metastasis, LNMs:lymph node metastases, PTC:papillary thyroid cancer, WOS:Web of Science, CNKI:Chinese National Knowledge Infrastructure, CI:confidence intervals, OR:Odds Ratio, HT:Hashimoto's thyroiditis, ATA:American Thyroid Association, GRADE:Grading of Recommendations Assessment Development and Evaluation.

Declarations

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Authors' contributions

Study conception and design: F W and T Z. Material preparation, data retrieval, and analysis: P T, K L, and Y N. Interpretation of the results: L Z and K J. Paper writing: F W and D L. All authors read and approved the final manuscript.

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Availability of data and materials

All data are available from the corresponding author.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figures

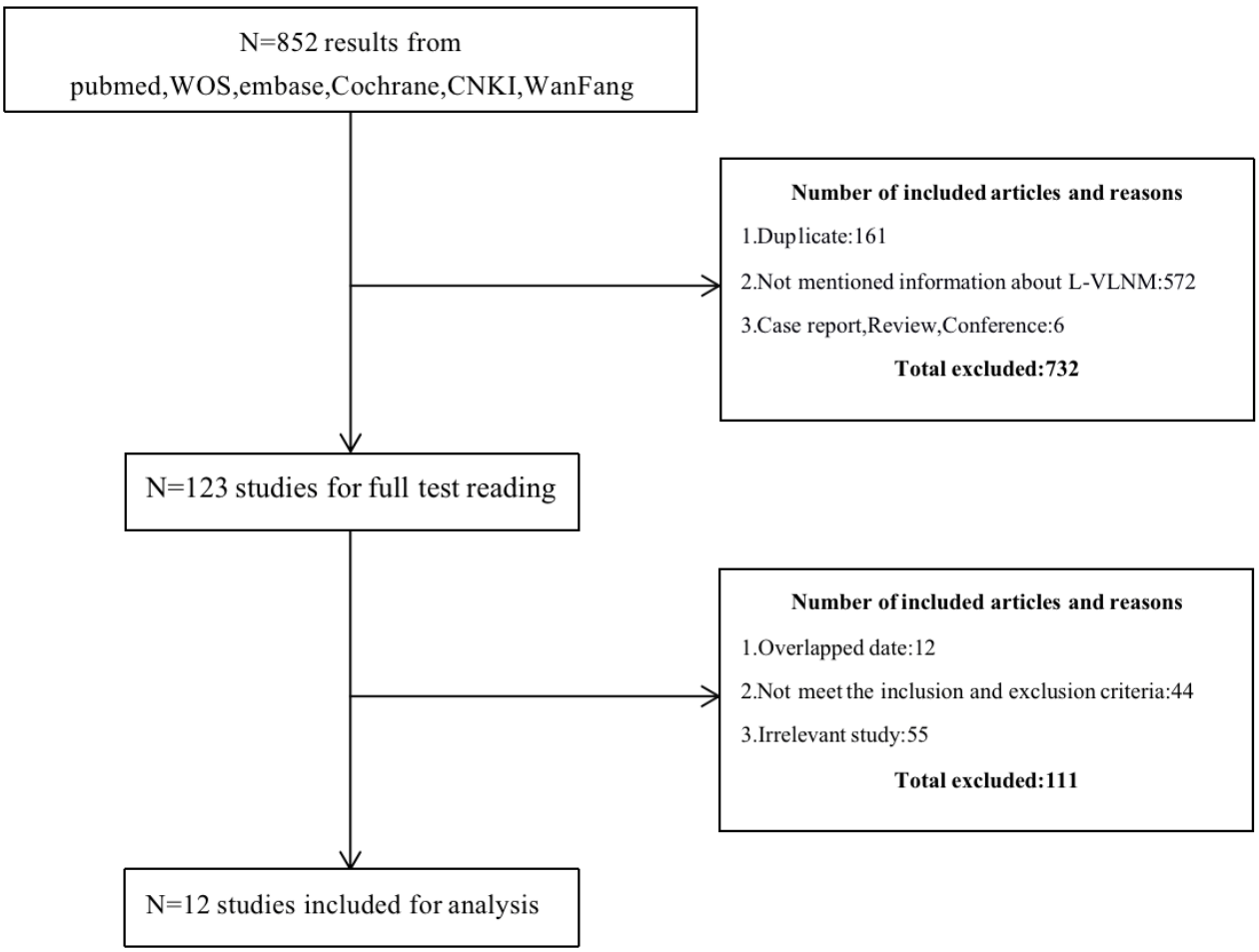

Figure 1

Flow chart of the study selection process

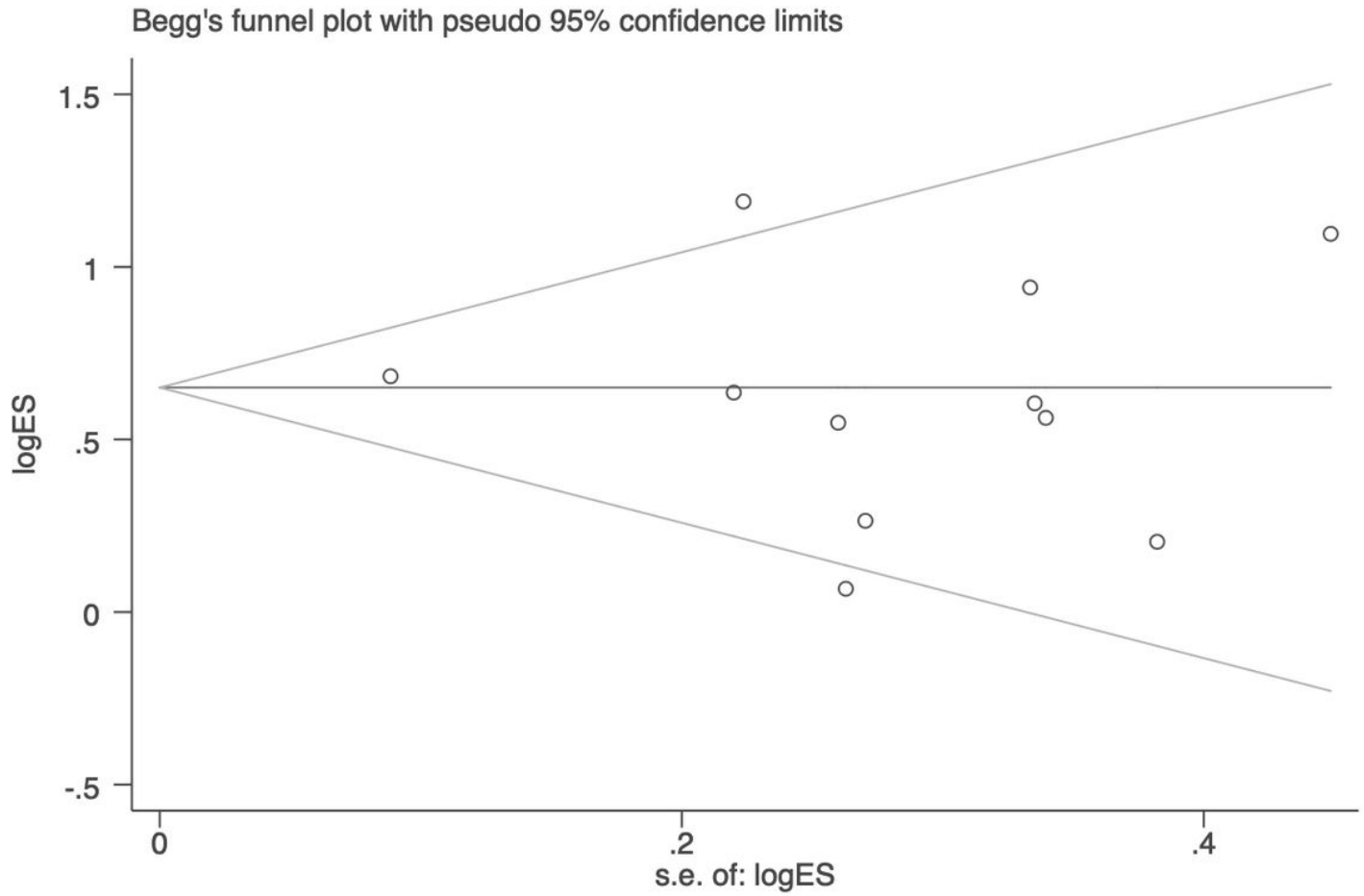

Figure 2

Funnel plot for testing the publication bias of the association between gender and the risk of L-VLNM.

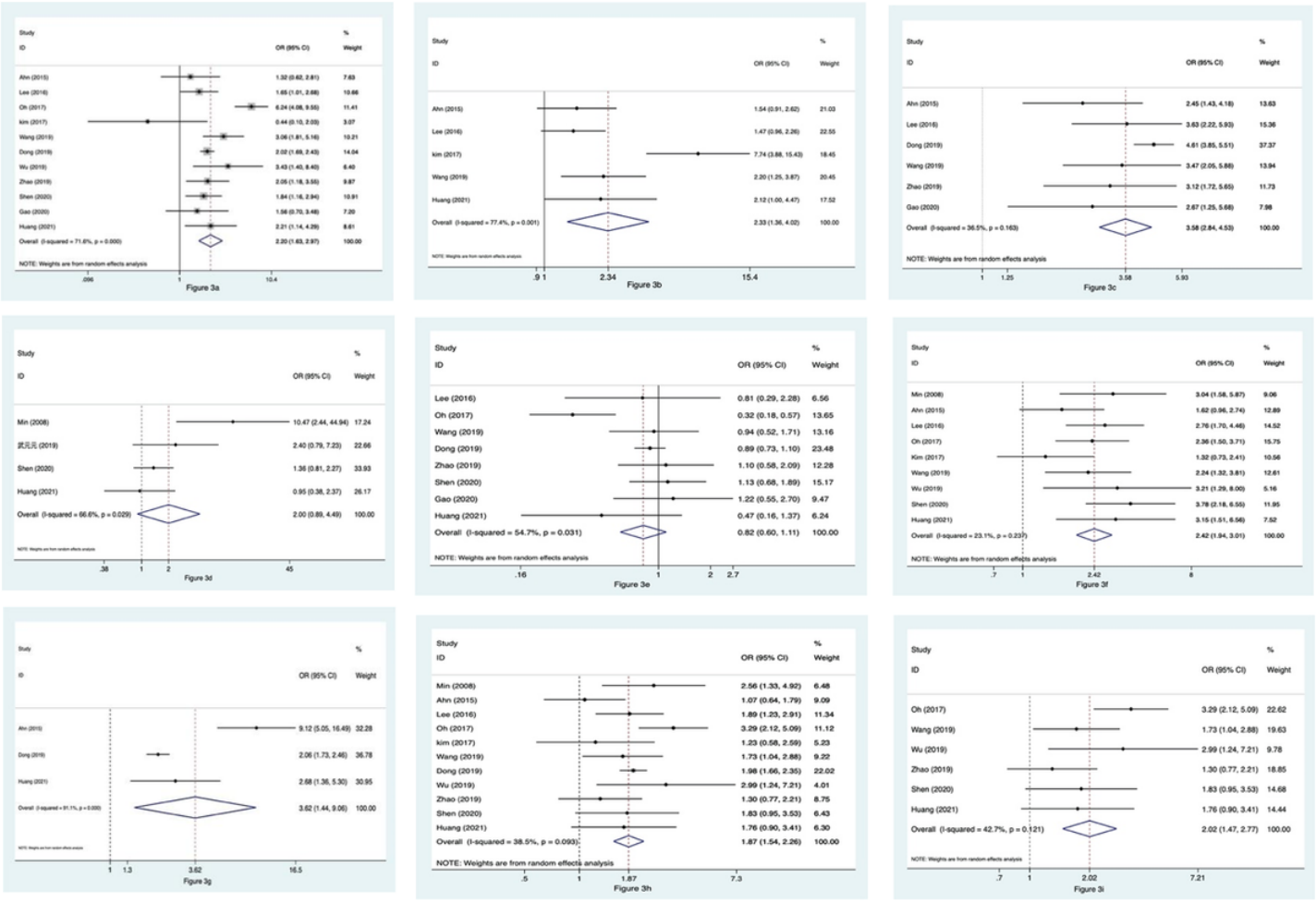

Figure 3

3a Forest plot of the association between male and L-VLNM. Figure 3b Forest plot of the association between age≥45 and L-VLNM. Figure 3c Forest plot of the association between tumor diameter >1.0cm and L-VLNM in papillary thyroid carcinoma. Figure 3d Forest plot of the association between tumor diameter >0.5cm and L-VLNM in papillary thyroid microcarcinoma. Figure 3e Forest plot of the association between Hashimoto thyroiditis and L-VLNM. Figure 3f Forest plot of the association between Extrathyroidal extension and L-VLNM. Figure 3g Forest plot of the association between capsule invasion and L-VLNM. Figure 3h Forest plot of the association between multifocality and L-VLNM. Figure 3i Forest plot of the association between multifocality and L-VLNM in CN0 PTC patients.

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