

Review

The Prognostic Role of Lymphatic Vessel Density in Papillary Thyroid Carcinoma: A Systematic Review and Meta-analysis

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Abstract

Background/Aim: Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer accounting for 75-85% of cases. Despite its favorable prognosis, 30-50% of patients develop regional lymph node metastases. Lymphatic vessel density (LVD) is a potential predictor of tumor progression, metastasis, and patient survival in PTC. This systematic review and meta-analysis evaluate the prognostic significance of LVD in PTC, focusing on intratumoral and peritumoral LVD and their association with nodal metastasis.

Materials and Methods: A systematic review and meta-analysis were conducted following PRISMA guidelines and the Cochrane Handbook. Eligible studies included patients with PTC who underwent tumor resection and had LVD assessed via immunohistochemistry (D2-40, LYVE-1). Literature search was performed in MEDLINE, Cochrane Library, and PubMed. Two independent reviewers screened studies and extracted data, including survival outcomes and LVD measurements. Hazard ratios (HRs) and mean differences were calculated using fixed-effects or random-effects models, with heterogeneity assessed via I^2 statistics.

continued



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Results: A total of 21 studies were identified, with nine meeting eligibility criteria. Meta-analysis demonstrated a significant association between high overall LVD and increased nodal metastasis (summary mean difference: 2.64; 95%CI=1.45, 3.82; $p<0.001$, $I^2=30.6\%$). No statistically significant association was observed for intratumoral (summary HR=1.33; 95%CI=0.88-2.02; $p=0.176$, $I^2=74.3\%$) or peritumoral LVD (summary HR=1.58; 95%CI=0.51-4.89; $p=0.429$, $I^2=74.7\%$). Heterogeneity across studies suggested potential variability in LVD measurement techniques and patient populations.

Conclusion: This meta-analysis highlights the prognostic role of overall LVD in predicting nodal metastasis in PTC. However, intratumoral and peritumoral LVD did not show a significant correlation, indicating the need for further research. Standardization of LVD assessment and integration with molecular markers could enhance risk stratification and personalized treatment approaches in PTC management.

Keywords: Papillary thyroid cancer, lymphatic vessel density, lymph node metastasis, D2-40, review.

Introduction

Thyroid cancer is the most common type of endocrine cancer, presenting a substantial rise in incidence among younger patients (1). Papillary subtype represents 75-85% of all thyroid malignancies and poses significant global public health concerns (2). Although papillary thyroid cancer (PTC) is known to have a good prognosis with a the 5-year survival rate of about 98.6%, 30-50% of patients present regional lymph nodes metastases and 5-20% local recurrence (3-6). The risk of recurrence has been associated with patient age, extra thyroid extension and nodal metastasis at presentation, regardless of lateral neck dissection and high dose iodine therapy (7, 8). The route for metastasis and loco regional invasion of PTC preferentially occurs by lymphatic vessels, contrary to the other thyroid tumors (9). Recent studies suggest lymphangiogenesis as an underrated emerging predictor of tumor enlargement, lymph node metastasis tendency and patient survival (10). For this reason, the assessment of lymphatic vessel density (LVD) is supposed to represent both a prognostic parameter and a potential therapeutic target, underscoring the need for improved risk stratification, personalized treatment options and maintenance of patient quality of life.

Lymphangiogenesis is the formation of new lymphatic vessels, which are required for the growth of the tumor and its spread to surrounding tissues. The development of molecular and immunohistochemical techniques has

identified D2-40, a monoclonal antibody developed against the lymphatic endothelium marker podoplanin, as a valuable tool for assessing lymphatic vascular density (LVD) in several tumors, including PTC (11, 12). Using D2-40 staining, increased LVD has been found to be closely related to lymph node metastasis and may, therefore, be implemented for detection of more aggressive disease subtypes (13-15). The expression of D2-40 in intratumoral and peritumoral locations has been further found to contribute to differentiating PTCs that may have important implications for diagnosis and prognosis (16, 17).

The aim of this systematic review and meta-analysis was firstly to present the given knowledge and data regarding the impact of LVD on patient prognosis and secondly to statistically analyze the relationship between LVD, evaluated by D2-40 intratumorally and peritumorally, its importance as an indicator of lymph node metastasis and thus as a determinant factor for management decisions of PTCs.

Materials and Methods

This systematic review was conducted in accordance with the methodologies outlined in the Cochrane Handbook for Systematic Reviews (18) and the PRISMA guidelines (19).

Study eligibility criteria. The population targeted were patients with PTC who had undergone tumor resection. The

inclusion criteria generated to filter the studies included in the present meta-analysis were: 1. full research paper that evaluated tumor LVD, 2. results referred to overall survival (OS) and/or disease/recurrence-free survival (DFS), 3. immunohistochemistry using antibodies against podoplanin (D2-40, AngioBio, Del Mar, CA, USA) or lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), employed to assess LVD, 4. HR and 95%CI mentioned or indirectly calculated through given data. Both prospective and retrospective studies were eligible. Studies examining specimens' LVD using VEGF as a marker of LVD were excluded, as well as those carried on animals. VEGF was not considered specific for the identification of lymphatic endothelial cells because it showed reactivity with blood vessel endothelium, myoepithelial cells, and cells of certain non-endothelial tumours (20, 21). The majority of the studies used the D2-40 antibody against podoplanin and LYVE-1 was used in only one study (17, 22, 23). Although LYVE-1 may not be considered specific for the identification of lymphatic endothelial cells because it is absent in some tumor-associated lymphatics, its use did not affect the statistical homogeneity of the present review (20). No case reports were included. Reviews and meta-analyses were also excluded, but their bibliographies were searched for potential eligibility.

Information sources. The electronic databases MEDLINE, Cochrane Library, and PubMed were used and studies from the past 25 years were selected through a search conducted up to January 31, 2025.

Search strategy. The search strategy included the terms “papillary thyroid cancer AND lymphatics”, “papillary AND LVD” and “thyroid cancer AND LVD”. Only studies written in English language were included.

Selection process-data items - data collection - bias assessment. Two authors (DV & AM) performed the full text screening and independently extracted the data from all eligible studies including first author's name, publication year, geographic location, sample size, sex, method of immunohistochemistry (antibodies, hot-spots, magnification field), LVD (peritumoral

and intratumoral), follow up period and survival/recurrence data. For any missing or unclear information, the authors were contacted. All extracted information was stored in an Excel file (Microsoft) and was checked for accuracy by one more author (GD).

Quantitative synthesis and analysis. Summary hazard ratios (HRs) were calculated to assess nodal metastasis across the groups under investigation. Additionally, when available, the extent of nodal metastasis was also evaluated using summary mean differences in the number of lymphatics per field, along with their corresponding 95% confidence intervals (CIs). Comparisons were conducted for nodal metastasis between participants with high *versus* low LVD, high *versus* low intratumoral LVD, and high *versus* low peritumoral LVD.

HRs and summary mean differences were derived by pooling study-specific estimates using either fixed-effects or random-effects models (24), depending on the degree of heterogeneity observed. Heterogeneity was assessed using Cochran's Q statistic and quantified with the I² statistic (25). All statistical analyses were performed using Stata (version 14; StataCorp, College Station, TX, USA).

Results

Study selection and population characteristics. The systematic search of the electronic databases (Medline, PubMed) identified a total of 21 studies, 17 of which were selected for full text screening. Nine studies were considered eligible for data extraction and meta-analysis according to our eligibility criteria. Figure 1 shows the flow chart of the study selection process. Table I provides an overview of the key characteristics of the studies included.

Study outcomes. Adequate data for quantitative synthesis were available for nodal metastasis in participants with high *versus* low LVD, high *versus* low intratumoral LVD, and high *versus* low peritumoral LVD.

Four studies reported nodal metastasis as the number of lymphatics per field in participants with high *versus* low

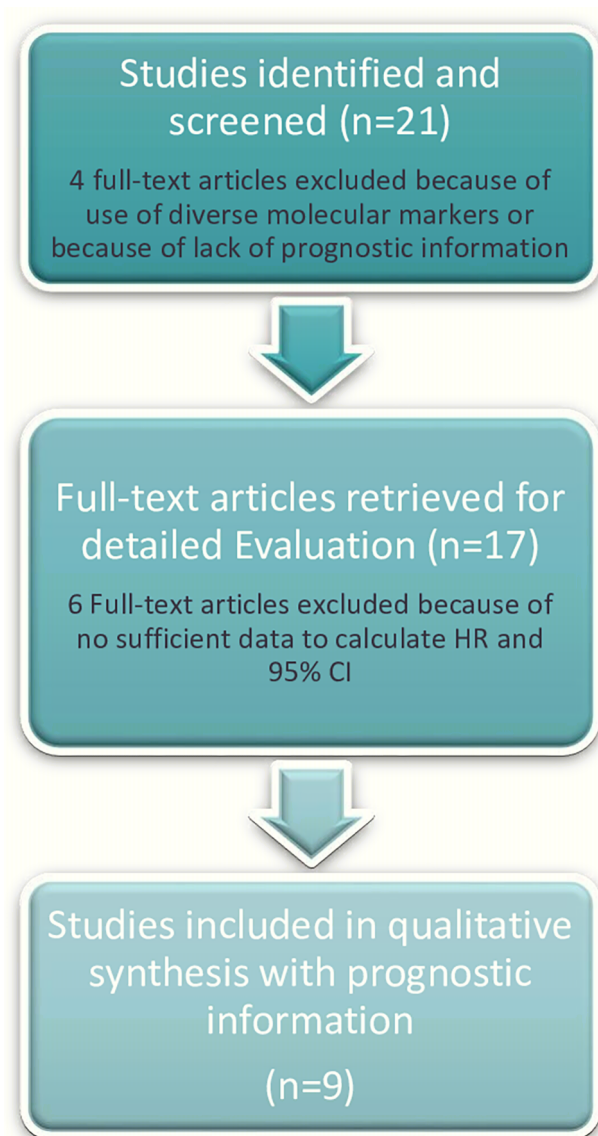


Figure 1. Flowchart of the study selection process.

LVD. A statistically significant difference was observed between the two groups, with higher nodal metastasis in participants with high LVD (summary mean difference: 2.64; 95%CI=1.45-3.82; $p<0.001$; Figure 2), and moderate heterogeneity ($I^2=30.6\%$).

Three studies reported nodal metastasis in participants with high *versus* low intratumoral LVD. No statistically significant difference was observed between

the two groups (summary HR=1.33; 95%CI=0.88-2.02; $p=0.176$; Figure 3), with considerable heterogeneity ($I^2=74.3\%$). Additionally, two studies assessed nodal metastasis in participants with high *versus* low intratumoral LVD, using the number of lymphatics per field as a measure. No statistically significant difference was observed in this analysis either (summary mean difference: 1.15; 95%CI=-0.71-3.01; $p=0.224$; Figure 4), with no heterogeneity detected ($I^2=0\%$).

Finally, two studies reported nodal metastasis in participants with high *versus* low peritumoral LVD. No statistically significant difference was observed between the two groups (summary HR=1.58; 95%CI=0.51-4.89; $p=0.429$; Figure 5), with considerable heterogeneity ($I^2=74.7\%$).

Discussion

This systematic review and meta-analysis provide insights into the role of LVD in nodal metastasis among patients with PTC. By exclusively including studies that utilized the D2-40 and LYVE-1 markers for LVD assessment, we ensured statistical homogeneity and specificity in evaluating lymphatic endothelial cells. Our findings contribute to the ongoing discussion on the prognostic significance of LVD in PTC and its potential implications for clinical decision-making.

The primary outcome of this meta-analysis demonstrated a statistically significant association between high LVD and increased nodal metastasis. Specifically, studies that quantified nodal metastasis as the number of lymphatics per field, found a significantly higher metastatic burden in patients with high LVD compared to those with low LVD (summary mean difference: 2.64; 95%CI=1.45-3.82; $p<0.001$). This finding aligns with the biological premise that a denser lymphatic network could facilitate tumor cell dissemination, emphasizing the potential utility of LVD as a prognostic biomarker.

In an attempt to establish a reliable prognostic scoring system in PTC, numerous studies have primarily considered clinical factors such as age, sex, tumor size, and

Table I. Characteristics of the studies included in the meta-analysis.

First author	Year	Country	Number of patients	Antibody type	Hotspots selected	Magnification field	Cut-off value	Reference
Gong	2012	China	38	D2-40	5	X200	NR	(14)
Lee	2012	Korea	72	D2-40	3	X200	NR	(3)
Lei	2022	China	73	D2-40	5	X200	NR	(34)
Khalil	2023	Egypt	50	Podoplanin	5	NR	NR	(4)
Choi	2012	Korea	126	D2-40	NR	X200	NR	(12)
Eloy	2011	Portugal	32	D2-40	10	X200	NR	(13)
Hall	2003	Canada	109	LYVE-1	3	X250	NR	(16)
Hakala	2014	Finland	40	D2-40	NR	X200	NR	(28)
Chung	2011	Korea	60	D2-40	NR	X200	PLVD:8, ILVD: 0.6	(15)

ILVD: Intratumoral lymphatic vessel density; PLVD: peritumoral lymphatic vessel density.

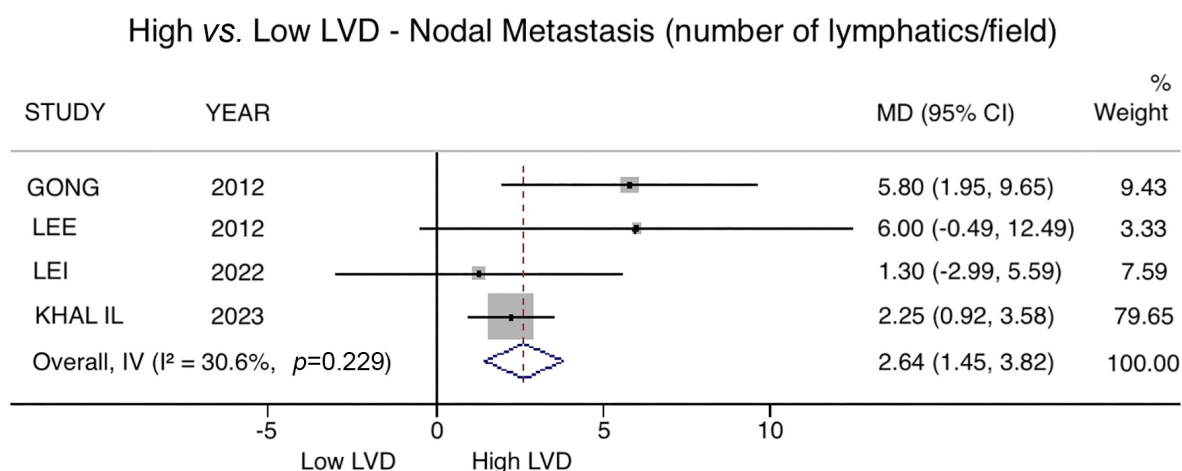
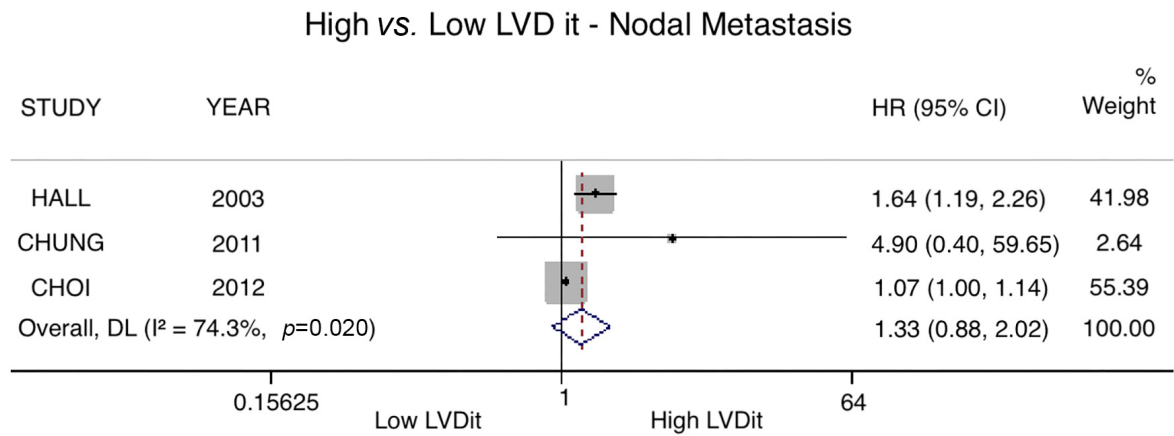


Figure 2. Forest plot of the meta-analysis for nodal metastasis, measured as the number of lymphatics per field, in participants with high versus low lymphatic vessel density (LVD).

extra thyroidal extensions. Nevertheless, neither clear conclusion has been obtained nor the key indicators predicting poor prognosis in PTC have been determined. Since PTCs mainly metastasize via the lymphatic channels to regional cervical lymph nodes (26), nodal metastasis plays a critical role in the determination of staging, treatment options and prognosis of PTC. Malignant tumors can spread to lymph nodes through preexisting lymphatic vessels or newly formed, producing various growth factors. Increased LVD is commonly associated with more aggressive behavior of this tumor, which escape from the primary site preferentially through lymphatic vessels due to its structural features lacking cohesive pericytes and thin

endothelial wall (27, 28). Although immunohistochemistry has been widely recognized as an effective adjunct tool for the detection of lymphatic vessels, there has been controversy over the prognostic value of peritumoral or intratumoral LVD (15). Here, we conducted the first review and meta-analysis on the clinical usefulness of LVD in both tumor tissue and surrounding tissue, assessed with immunohistochemical staining, for the prediction of lymph node metastasis in PTC.

Interestingly, analyses focusing on intratumoral and peritumoral LVD yielded inconsistent results. PTC seems to have a constant stimulus for lymphatic vasculature promoting factors, the effects of which are found



NOTE: Weights are from random-effects model

Figure 3. Forest plot of the meta-analysis for nodal metastasis for participants with high versus low intratumoral (it) lymphatic vessel density (LVD).

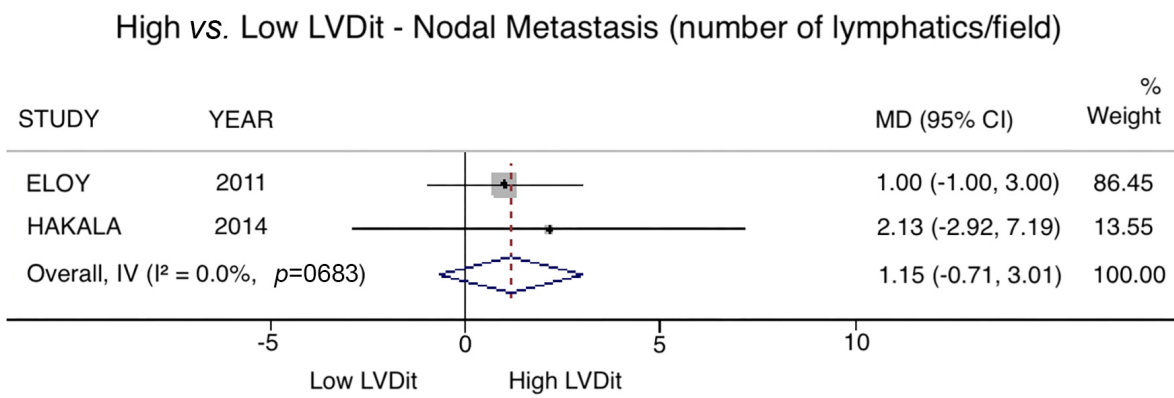


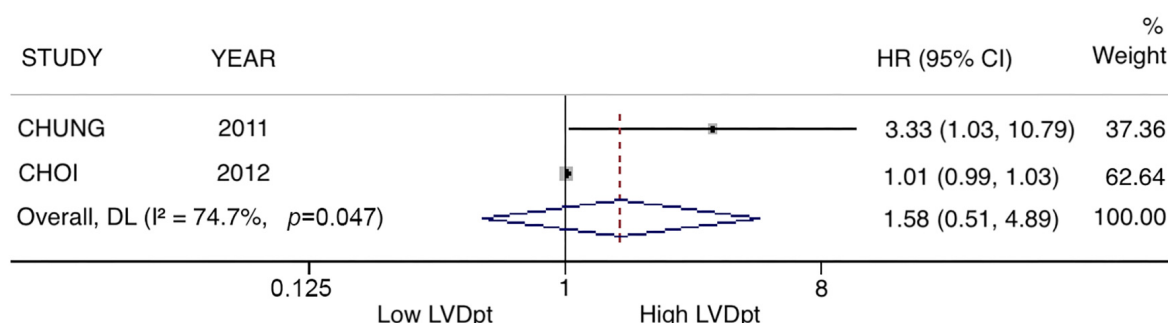
Figure 4. Forest plot of the meta-analysis for nodal metastasis, measured as the number of lymphatics per field, for participants with high versus low intratumoral (it) lymphatic vessel density (LVD).

pronounced in peritumoral areas (29). Indeed, an abundant network of well-defined and large vessels has been depicted in the peritumoral area of PTC (22). Several studies underscore the prognostic role of peritumoral LVD regarding nodal metastasis (16). However, the results remain inconsistent as peritumoral LVD could not be associated with LNM in other series, which could be in accordance with the good prognoses imputed for thyroid cancer in general (23, 30). In line with that, high peritumoral LVD was also not significantly associated with nodal metastasis (summary HR=1.58; 95%CI=0.51-4.89; $p=0.429$). Notably, the substantial heterogeneity observed

($I^2=74.7\%$) may indicate some variability in measurement techniques, patient populations, or sample processing methods across studies. Nevertheless, this lack of association may reflect tumor microenvironment heterogeneity or differential functional roles of intratumoral and peritumoral lymphatics in metastasis (31).

On the other hand, the until-recently ignored intratumoral lymphatics gained attention as D2-40 facilitated their detection. Hall *et al.* examined the role of intratumoral LVD, consenting to its predicting value for LNM but not for tumor recurrence among PTC patients (17). Moreover, previous studies found that intratumoral, but not

High vs. Low LVDpt - Nodal Metastasis



NOTE: Weights are from random-effects model

Figure 5. Forest plot of the meta-analysis for nodal metastasis for participants with high versus low peritumoral (pt) lymphatic vessel density (LVD).

peritumoral, LVD can predict cervical lymph node metastasis (LNM), expressing tumor aggressiveness and affecting patient survival (13, 14, 32). Nevertheless, conflicting data presented lack of association between intratumoral LVD and LNM prediction, not only in thyroid tumors but also in breast cancer (30, 33). In line with the above, no statistically significant difference was observed between high and low intratumoral LVD groups regarding nodal metastasis (summary HR=1.33; 95%CI=0.88-2.02; $p=0.176$). Similarly, the assessment of intratumoral LVD based on the number of lymphatics per field showed no significant difference (summary mean difference: 1.15; 95%CI=-0.71-3.01; $p=0.224$). Eloy *et al.* tried to explain these contradictory findings suggesting that intratumoral D2-40 negative vessels may constitute less efficient pathways for PTC dissemination, implying that intratumoral D2-40 positive vessels may be in fact peritumoral tissues, including peritumoral D2-40 positive lymph vessels, which invade the bulk of the tumor. In this scenario, a well-preserved tumor capsule may result in an almost complete absence of D2-40 positive intratumoral lymph vessels, despite the tumor's spread to regional lymph nodes (14). It has also been reported that intratumoral lymphatic vessels, although occasionally large, are often weak, distorted, and newly formed; they may collapse easily and thus be incapable of supporting the spread of malignant cells (34).

Overall, the results regarding the association between PTC peritumoral and intratumoral LVD and the occurrence of LNM are conflicting (23). Since intratumoral lymph vessels are defined within the tumor area, whereas peritumoral lymph vessels include vessels in both the capsule and in the remaining non tumoral thyroid tissue, their demarcation has been proven problematic. The above has led to a more holistic approach that combines information from intra and peritumoral LVD, supporting the prognostic value of LVD, not referring to peritumoral or intratumoral lymphatics (3, 4, 35). In line with the aforementioned findings, Lei *et al.* have found that LNM is correlated with LVD but not with the traditional risk factors such as sex, bilateral involvement, lymphovascular tumor thrombus, tumor diameter and Hashimoto's thyroiditis (35). The results of the present meta-analysis are in agreement with the above, suggesting that LVD measured by D2-40 staining is a critical indicator of LNM in PTC. The heterogeneity observed in several comparisons emphasizes the complexity of LVD as a prognostic marker. Variability in immunohistochemical protocols, differences in patient demographics, and variations in tumor biology may all contribute to inconsistencies across studies. Additionally, the relatively small number of eligible studies limits the statistical power of our subgroup analyses.

Recently, the importance of LNM for disease progression, local recurrence and worse prognosis in PTC has been questioned and the ability of the tumor itself to invade lymphatic vessels emerges as a more important prognostic LNM factor than lymphatic vessel generation (22, 36). Indeed, a recent review highlights the role of certain circulating miRNAs in nodal metastasis prediction of PTC (37). Additionally, published data signify that the tendency of the PTC to spread to regional lymph nodes may alter treatment options (38, 39). More specifically, surgery can be followed by radioactive iodine treatment (RAI), but the extent of surgery has been frequently debated, with no clear consensus-particularly regarding the role of prophylactic lymph node dissection (40, 41). It is also important that the rate of LN metastasis remains high even after the use of radioactive iodine ablation. Consequently, there is an urgent clinical need for novel prognostic indicators of LN metastases in PTC (42). This discrepancy has led to the development of new tools to assess not only the risk of LNM via LVD but also to use LVD as a predictor for the response to adjuvant treatment options (43, 44).

Despite these limitations, our study underscores the potential relevance of LVD in PTC, particularly regarding nodal metastasis. Future research should aim to standardize LVD measurement methodologies, explore the interplay between LVD and molecular markers, and investigate its predictive value in guiding therapeutic strategies. Prospective studies with larger cohorts and standardized immunohistochemical approaches will be essential in validating LVD as a prognostic tool in PTC.

Conclusion

In conclusion, this meta-analysis highlights a significant association between high LVD and LNM in PTC, supporting its potential role as a prognostic indicator. Our meta-analysis is the first to correlate LVD with LNM in PTC. In the era of personalized medicine, LVD can be used in distinguishing between indolent PTC cases and those with a propensity for more aggressive behavior. We underscore the critical role of LVD in guiding tailored clinical management protocols and

in helping to avoid aggressive therapeutic approaches in PTC. However, no significant associations were observed for intratumoral and peritumoral LVD, emphasizing the need for further research to elucidate the mechanistic underpinnings and clinical implications of LVD in thyroid cancer progression.

Conflicts of Interest

Aikaterini Marini, Theocharis Chatzoglou, Georgios Ntritsos, Roubini Zakopoulou, Kalliopi Iliou, Georgios Papanikolaou, Panagiotis Kitsoulis, Asimakis Asimakopoulos, Dimitrios Varvarousis have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

Authors' Contributions

AM: Conceptualization (equal); investigation (lead); methodology (equal), writing- original draft; visualization (equal); writing- review and editing (equal). TC: Investigation. GN: Data curation; formal analysis. RZ: Writing-review and editing (equal), visualization (equal). KI: Methodology, validation. GP: Investigation. PK: Conceptualization (equal); supervision (equal). AA: Supervision (equal). DV: Conceptualization (equal); writing-review and editing (equal), supervision (equal).

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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