

Microvessel density in differentiated thyroid carcinoma: A systematic review and meta-analysis

Konstantinos Perivoliotis, Athina A Samara, Prodromos Koutoukoglou, Panagiotis Ntellas, Katerina Dadouli, Sotirios Sotiriou, Maria Ioannou, Konstantinos Tepetes

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Konstantinos Perivoliotis, Athina A Samara, Konstantinos Tepetes, Department of Surgery, University Hospital of Larissa, Larissa 41110, Greece

Prodromos Koutoukoglou, Katerina Dadouli, Postgraduate Programme Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics, University of Thessaly, Larissa 41110, Greece

Panagiotis Ntellas, Maria Ioannou, Department of Pathology, University of Thessaly, Larissa 41100, Greece

Sotirios Sotiriou, Department of Embryology, University of Thessaly, Larissa 41100, Greece

Corresponding author: Athina A Samara, MD, MSc, Surgeon, Department of Surgery, University Hospital of Larissa, Mezourlo Hill, Larissa 41110, Greece. at.samara93@gmail.com

Abstract

BACKGROUND

Microvessel density (MVD) has been proposed as a direct quantification method of tumor neovascularization. However, the current literature regarding the role of MVD in differentiated thyroid carcinoma (DTC) remains inconclusive.

AIM

To appraise the effect of tumoral MVD on the survival of patients with DTC.

METHODS

This meta-analysis was based on the PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. The electronic databases Medline, Web of Science, and Scopus were systematically screened. A fixed-effects or random-effects model was used, according to the Cochran Q test. The data were then extracted and assessed on the basis of the *Reference Citation Analysis* (<https://www.referencecitationanalysis.com/>).

RESULTS

A total of nine studies were included in the present study. Superiority of low MVD tumors in terms of 10-year disease free survival (OR: 0.21, 95%CI: 0.08-0.53) was recorded. Lowly vascularized thyroid cancers had a lower recurrence rate (OR: 13.66, 95%CI: 3.03-61.48). Moreover, relapsing tumors [weighed mean difference (WMD): 11.92, 95%CI: 6.32-17.52] or malignancies with regional lymph

node involvement (WMD: 8.53, 95%CI: 0.04–17.02) presented with higher tumoral MVD values.

CONCLUSION

MVD significantly correlates with the survival outcomes of thyroid cancer patients. However, considering several study limitations, further prospective studies of higher methodological and quality level are required.

Key Words: Cancer; Density; Microvessel; Thyroid; Vascularization

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Core Tip: This systematic review is the first meta-analysis investigating the effect of tumoral vascularity, through microvessel density (MVD) assessment, on the survival of patients with differentiated thyroid carcinoma. Higher intratumoral MVD values were associated with inferior disease-free survival outcomes.

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INTRODUCTION

Thyroid cancer is the most common endocrine tumor and includes several subtypes with different histologic, epidemiologic, and prognostic characteristics. Although they display a stable mortality rate, thyroid carcinomas are characterized by a rising trend of overall incidence of nearly 5.5% annually[1-3]. The above-mentioned increase is primarily attributed to a steady increment of new papillary thyroid cancer cases[1-3]. This is translated to an average of 56000 new cases and 2000 deaths per year in the United States alone[4]. Therefore, an attempt to identify survival-prognostic indicators for thyroid cancer has been implemented[5,6]. More specifically, extrathyroidal infiltration, aggressive histological pattern, vascular invasion, lymph node involvement, distant metastases, and BRAF mutations have been linked to a poorer survival outcome[7,8]. Various other serological, genetic, molecular, and immunohistochemical markers have also been considered[5,6,9-11].

Angiogenesis represents a pivotal part of tumor expansion and metastasis development. It includes a cascade of processes such as degradation of the basal membrane, remodeling of the extracellular matrix, migration of the endothelial cells, and maturation of the newly formed capillaries, which are regulated by several angiogenic and angioinhibitory factors[12-14]. Activation of the “angiogenic switch” due to alterations in the concentration of agents, such as vascular endothelial growth factor (VEGF) and thrombospondin-1 (TSP-1), as well as the subsequent upregulation of the *de novo* formation of blood vessels, has been associated with survival outcomes in thyroid cancer[15,16]. Microvessel density (MVD) as described by Weidner *et al*[17] has been proposed as a direct quantification method of tumor neovascularization. The methodology of MVD assessment involves the immunohistochemical staining for endothelium specific markers, such as von Willebrand factor (vWF), cluster of differentiation (CD)31, and CD34, for the labeling of microvessels[18]. The correlation between survival outcome and vascularity of a solid tumor has been extensively validated[19-22].

The current literature regarding the role of MVD in differentiated thyroid carcinoma (DTC) remains inconclusive. Initial studies reported that MVD displayed negative prognostic value in terms of survival, and was reversibly associated with the differentiation status of thyroid carcinomas[9,23,24]. However, subsequent trials did not confirm the prognostic role of MVD value or even document a positive correlation with survival endpoints[25,26]. Taking into consideration the above-mentioned evidence, a systematic literature review and meta-analysis was designed and conducted to clarify the effect of tumoral vascularity - through MVD assessment - on the survival of patients with DTC.

MATERIALS AND METHODS

Study protocol

This review was performed by applying the guidelines proposed in the PRISMA Statement and the Cochrane Handbook for Systematic Reviews of Interventions[27].

Endpoints

The primary endpoint of the present meta-analysis was the pooled odds ratio (OR) of disease-free survival (DFS) between high and low MVD measurements in patients with DTC[28,29]. Secondary endpoints included the hazard ratio (HR) of DFS and the OR of overall survival (OS) and DFS at specific time endpoints (5 and 10 years). Moreover, the effect of MVD on certain disease outcomes was examined, such as lymph node involvement, extrathyroidal infiltration, and recurrence rates.

Eligibility criteria

All prospective or retrospective studies that included a trial population diagnosed with DTC, reported outcomes of interest in English, and could be retrieved were considered as eligible. The MVD assessment of the primary tumor should have been introduced in the study design. The exclusion criteria for this meta-analysis were studies: (1) Written in a language other than English; (2) With no outcome of interest; (3) With insufficient data; (4) With no human subjects; (5) Including a pediatric study population; (6) Including undifferentiated or medullary thyroid cancer; or (7) In the form of editorials, letters, conference abstracts, or expert opinions.

Literature search

A systematic literature search was performed in the electronic scholar databases Medline, Scopus, and Web of Science. The last search date was August 31, 2021. The following keywords were used: "Thyroid", "thyroid cancer", "thyroid carcinoma", "papillary", "follicular", "Hurthle cell", "well differentiated", "MVD", "microvessel density", "microvascular density", and "vessel density".

Study selection and data collection

The first step of our review was removal of duplicate entries, followed by screening of titles and abstracts for consistency with the eligibility criteria. The remaining articles were submitted to a full text review. Searching of electronic databases, study selection, data extraction, and methodological assessment of the studies were performed blindly and in duplicate by two independent investigators (Perivoliotis K, Koutoukoglou P). If disagreement arose between the two investigators, a mutual revision and discussion process followed. If consensus was not achieved, the opinion of a third researcher was considered (Ntellas P). The methodological and quality evaluation was performed on the basis of the Newcastle-Ottawa Scale (NOS)[30]. This evaluation tool ranks non-RCT trials based on different domains, such as selection and comparability of the study groups and confirmation of the exposure. All eligible studies were rated with a score ranging from 0 to 9. Interrater agreement was estimated based on Cohens *k* statistic.

Statistical analysis

The statistical software used for the analyses included the Cochrane Collaboration RevMan version 5.3 and IBM SPSS version 23. All results are presented with the corresponding 95%CI. If the trials included did not directly provide data concerning the HR and OR endpoints, they were then estimated through the implementation of the algorithm proposed by Parmar *et al*[31] and Tierney *et al*[32]. By utilizing digitizing software, an accurate reconstruction of the primary data from the Kaplan-Meier (KM) curves was performed[33,34]. Furthermore, if the mean and standard deviation (SD) of the continuous variables were not reported, they were estimated from the respective median, range, or interquartile range (IQR)[35,36].

The statistical methods applied were the Maentel-Haenszel (MH) and inverse variance (IV), for OR and HR, respectively. If a statistically significant heterogeneity was present (Cochran *Q* test $P < 0.1$), a random-effects (RE) model was used. Otherwise, the pooled result estimation was based on a fixed-effects (FE) model. Overall heterogeneity was also quantified through the calculation of I^2 . Statistical significance was considered at the level of $P < 0.05$.

Risk of bias across studies

Visual inspection of the primary outcome funnel plot was applied, to identify possible outliers. Moreover, Egger's statistical test was calculated.

RESULTS

Study selection

Application of the search algorithm resulted in the retrieval of 2208 citations (Figure 1). More specifically, the number of studies identified through Medline, Scopus, and Web of Science were 992, 517, and 699, respectively. After removal of 507 duplicate records, 1701 titles and abstracts were reviewed. In this phase of literature screening, 1626 studies (125 non-human studies, 130 reviews or meta-analyses, and 1371 irrelevant trials) were excluded. Full text review was applied to 75 articles to assess consistency with the inclusion criteria. After the exclusion of 50 irrelevant records and 16 studies

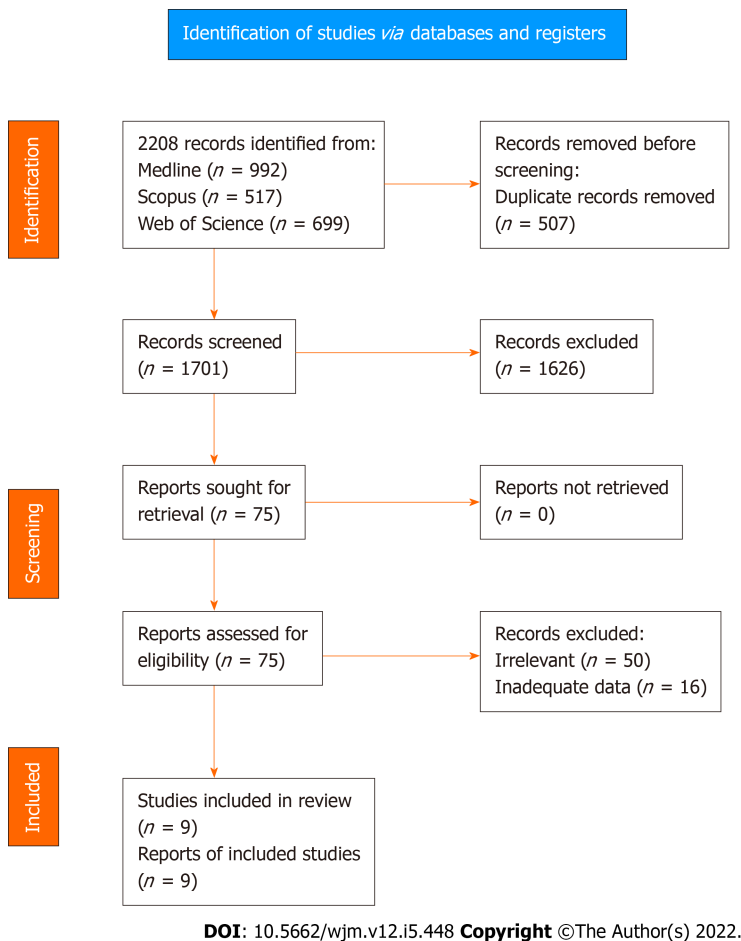


Figure 1 Study flow diagram.

with inadequate survival data, a total of nine trials[23,25,37-43] were introduced in the qualitative and quantitative synthesis of the present systematic review.

Study characteristics

Table 1 summarizes the characteristics of studies included in the systematic review. Concerning the study design, all trials were retrospective and single centered, with publication years ranging from 1998 to 2017. In total, 738 patients were included in this meta-analysis. Mean age and gender allocation are also presented in Table 1. Mean follow up extended from 61.7 mo to 180 mo.

Supplementary Table 1 provides information regarding the tumor characteristics. The most frequent malignancy was papillary thyroid carcinoma (PTC) (708 cases), followed by follicular thyroid carcinoma (FTC) (27 cases). Although data regarding the tumor stage and the TNM classification were scarce and inconsistent, the respective allocations are also displayed.

Regarding MVD assessment method (Supplementary Table 2), in the majority of the articles[23,25,37,39,40], the technique proposed by Weidner *et al*[17] was implemented. In the remaining studies[38,41-43], variations of the hot spot method, such as the methodology described by Bono *et al*[44], were applied. The antibodies used for the immunohistochemical staining of the microvessels included the anti-CD34[35-39], anti-CD31[42,43], and anti-VIII antibodies[23,25]. The initial magnification applied spanned from 4 × to 40 ×, whereas the final magnification included values ranging from 200 × to 400 ×. The number of pathologists and hot spots examined varied among studies, thereby increasing the methodological heterogeneity. Blinding of the MVD estimator was applied in four trials[23,37,40,43]. Assessment of both intra- and peri-tumoral vessels was performed in only two studies[25,40]. Furthermore, the MVD cut off values are included in Supplementary Table 2. Overall, 324 total or subtotal thyroidectomies and 71 lobectomies were performed (Supplementary Table 3). Lymph node dissection was reported in 574 cases. Data regarding the adjuvant chemotherapy or radiotherapy mode were not systematically provided.

Risk of bias within studies

Supplementary Table 4 provides a detailed report on the quality and methodological evaluation of the included trials. Although the number of stars awarded ranged from 3[39] to 7[42], the majority of trials

Table 1 Study characteristics

Ref.	Type of study	Year	Country	Center	Sample (patients)	Age	Gender (male/female)	Follow-up
Lee <i>et al</i> [36]	Retrospective	2017	Korea	Single center	202	43.4 (13.6)	43/159	NA
Liu <i>et al</i> [37]	Retrospective	2017	China	Single center	42	49.1 (13.5)	9/33	NA
Hakala <i>et al</i> [40]	Retrospective	2014	Finland	Single center	51	52	19/32	NA
Lee <i>et al</i> [41]	Retrospective	2012	Korea	Single center	47	> 45: 24	11/36	NA
Yasuoka <i>et al</i> [38]	Retrospective	2005	Japan	Single center	49	48.8 (15)	7/42	NA
Kilicarslan <i>et al</i> [39]	Retrospective	2003	Turkey	Single center	48	39.8	21/27	61.7 (29.7)
Akslen <i>et al</i> [25]	Retrospective	2000	Norway	Single center	128	45.1	36/89	145 (35.8)
Dhar <i>et al</i> [35]	Retrospective	1998	Japan	Single center	71	50 (9.8)	11/60	180 mo
Ishiwata <i>et al</i> [23]	Retrospective	1998	Japan	Single center	100	48 (9.6)	5/95	101 mo

NA: Not available.

received a 5 star grade. A satisfying rate of interrater agreement was identified (Cohen's k : 72.1%, $P < 0.001$).

Primary endpoint

Data regarding the primary outcome were extracted from three studies (Figure 2). Pooled analysis of these data showed a statistically significant OR ($P < 0.001$) for DFS between high and low MVD groups (OR: 0.21, 95%CI: 0.08–0.53). Heterogeneity levels were not significant (Q test $P = 0.12$, $I^2=53\%$) and as a result, a FE model was applied. Due to the small number of studies reporting on the primary outcome and the moderate heterogeneity, further sub-analyses included only sensitivity analysis Supplementary Figure 1).

Secondary endpoints

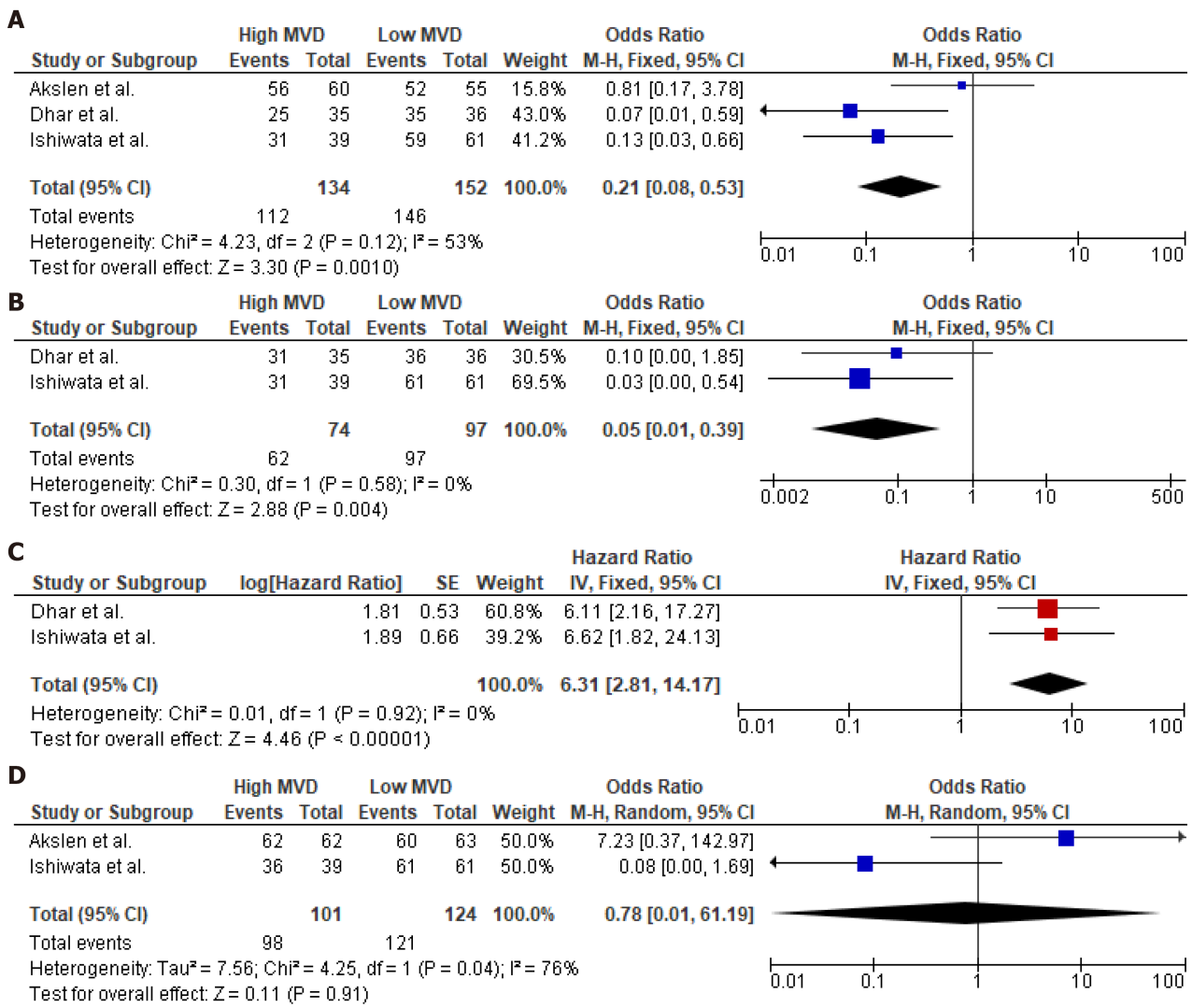
In accordance with the primary outcome, a statistically significant OR for DFS at 5 years (Figure 1) was identified ($P = 0.004$). Therefore, overall HR ($P < 0.001$) for DFS was in favor of the low vascularity group (HR: 6.31, 95%CI: 2.81–14.17). However, meta-analysis of the raw data at 10 years postoperatively did not show a significant difference in survival terms (10-year OS: OR: 0.78, 95%CI: 0.01–61.19, $P = 0.91$). In total, five studies (Figure 3) provided data regarding mean MVD measurements between tumors with positive and negative lymph nodes. Although heterogeneity was high (Q test $P < 0.001$, $I^2 = 93\%$), tumors that involved lymph nodes had higher mean MVD measurements (weighed mean difference [WMD]: 8.53, 95%CI: 0.04–17.02, $P = 0.05$) when compared to DTCs with negative nodes. Despite this, extrathyroidal infiltration was not associated with tumoral vascularity (OR: 1.86, 95%CI: 0.56–6.15, $P = 0.31$). Finally, recurrence rates in DTCs were significantly higher in the highly vascularized tumors (OR: 13.66, 95%CI: 3.03–61.48, $P = 0.0007$). Besides this, the thyroid malignancies that relapsed had significantly higher mean vascularization values (WMD: 11.92, 95%CI: 6.32–17.52, $P < 0.001$) than those that did not recur.

Risk of bias across studies

Concerning the funnel plot of the primary outcome (Supplementary Figure 2), eligible trials were symmetrically distributed on both sides of the combined effect size line. Moreover, Egger's test did not confirm the presence of a significant publication bias ($P = 0.585$).

DISCUSSION

Our study validated a negative linkage between the intratumoral vascularity and the survival outcomes in DTC. Specifically, higher MVD values translated to a lower HR of DFS. In a similar manner, the DFS probabilities at 5 and 10 years after diagnosis increased when the DTC was hypovascularized. Furthermore, lymph node metastases were associated with a denser microvessel plexus in the primary tumor. In terms of recurrence, higher MVD measurements were correlated to superior relapse rates and *vice versa*. The rate of extrathyroidal invasion, however, did not appear to be affected by the tumor vascularization pattern. The effect of microvessel quantity in thyroid carcinoma is still a matter of controversy[16]. In 1994, Herrmann and his colleagues reported that reduced vascularization was found in less differentiated tumors[9]. Similarly, according to Kavantzias *et al*[45], FTCs and medullary thyroid



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Figure 2 Survival endpoints. A: 10 year disease free survival (DFS) odds ratio (OR); B: 5 year DFS OR; C: DFS hazard ratio; D: 10 year overall survival OR.

cancers (MTCs) were characterized by different mean MVD values. Diversity in the neovascularization pattern was also found among the differentiated carcinomas. Giatromanolaki *et al*[46] showed that FTCs displayed a higher vascular density, whereas subsequent research by Gulubova *et al*[26] suggested higher CD31 MVD in PTCs. However, several successive studies which applied either a CD34 or CD31 immunohistochemical marker for staining of the endothelium, could not identify a correlation between MVD and histology[10,11].

The fact that most of our quantitative comparisons were statistically significant suggests a possibly strong overall correlation between MVD and prognosis in DTCs. In a retrospective analysis of 71 DTCs, Dhar *et al*[37] correlated a lower recurrence free survival rate with a hypervascularized tumor. Correspondingly, using VIII-related immunohistochemical stain, Ishiwata *et al*[23] identified mean microvessel count as an independent prognostic factor for DFS. A denser angiogenetic pattern was also reported in tumors with a higher metastatic potential[47]. Additionally, MVD has been found significantly higher in malignancies with high risk characteristics, such as extrathyroidal and vascular invasion[48].

In contrast to the above-mentioned statements, a considerable number of studies do not recognize the prognostic character of MVD in thyroid carcinomas. Goldenberg *et al*[11] showed that although mean vessel density in the tumor was higher when compared to the healthy surrounding tissues, MVD lacked a significant correlation with histology or recurrence rates. Furthermore, in the study by Gulubova *et al* [26], postoperative survival rates in PTC patients were not associated with MVD values. Lee *et al*[43] also suggested that lymph node status was not linked to the MVD value of the primary malignancy. Moreover, in a study by Akslen *et al*[25], higher MVD was associated with improved OS rates in PTC patients.

The process of angiogenesis and the corresponding modulators have been extensively studied and related to MVD in thyroid carcinoma. VEGF was directly linked to the number of microvessels, and was characterized as a negative prognostic index for lymph node metastasis as well as local and distant

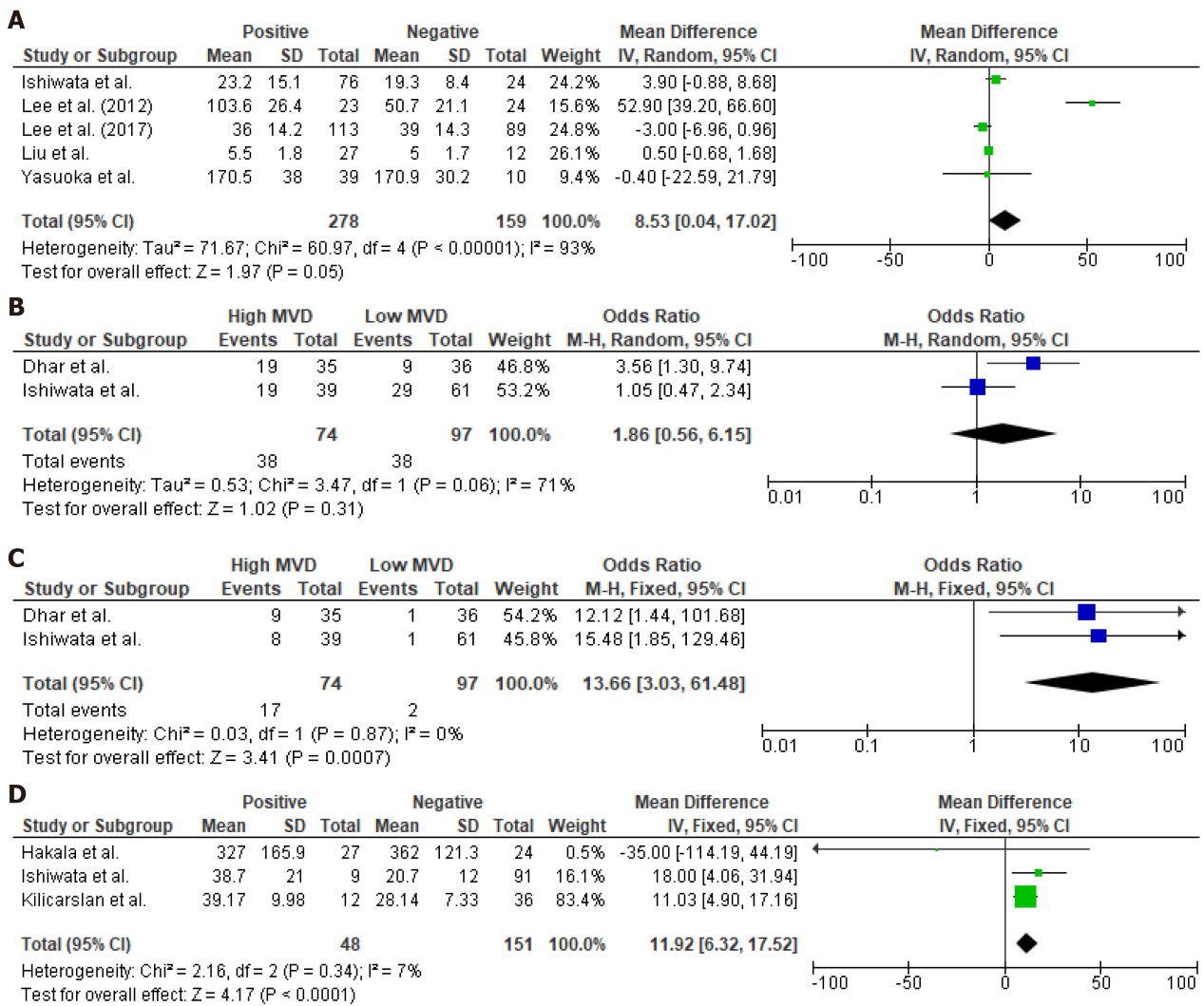


Figure 3 Secondary endpoints. A: Lymph node involvement; B: Extrathyroidal involvement; C: Recurrence rate; D: Recurrence microvessel density value.

recurrence[26,40,41,43]. A higher rate of immunoreactive cells for metalloproteinase-9, an enzyme necessary for collagen degradation and subsequent angiogenesis, were present in advanced stages of FTCs[14]. Increased values of circulating and tumoral angiopoietins (Ang) have also been linked to poorer outcomes in thyroid cancer[49-51]. Based on the work of Tanaka *et al.*, the levels of TSP-1 have been inversely correlated with the infiltration status of the tumor and MVD[52]. As a result, ratios representing the balance of angiogenic and inhibitory factors VEGF/TSP-1, VEGF-C/TSP-1, and Ang-2/TSP-1 have been significantly associated with the number of microvessels[52].

In addition to prognosis, tumor vascularization has also been proposed as a diagnostic tool in thyroid carcinomas. Using color flow Doppler sonographic analysis with a cut off value at 70% of microvessels, differential diagnosis between PTCs and adenomas or adenomatous nodules demonstrated a sensitivity of 92% and specificity of 89%[53]. The administration of contrast agents further validated the correlation of tumoral MVD and ultrasonographic assessment of vascularity, and increased the accuracy of PTC detection at the level of 95.9%[54,55]. In addition, the application of a shear elastography model by Gu *et al.*[56] linked tumor stiffness with MVD values. Therefore, subsequent studies examined the role of the relationship between ultrasound estimation of vascularity and MVD, as a potential prognostic and risk assessment factor[38,39].

Before assessing the results of our meta-analysis, several limitations should be appraised. First, only a limited number of studies with a small sample size were introduced in each comparison, thus compromising the validity of our estimations. Moreover, all eligible studies had a retrospective study design, with a moderate-to-low methodological evaluation. Although significant heterogeneity was identified in only two endpoints, bias could be introduced from the non-homogeneous stratification of factors such as the histopathological subtype, the stage, and the TNM status. Another source of potential bias could be the heterogeneous allocation in operative and adjuvant treatment modules. Inconsistency was further identified in technical characteristics of the MVD assessment process. Finally, the estimation of survival endpoints required the reconstruction of raw information from the KM curves; therefore, a

small amount of bias was inherent in our data extraction methodology, although this process has been reported and applied in several studies[31,32,57].

The present systematic review and meta-analysis is the first study that attempts to provide a pooled correlation between MVD and survival endpoints in DTC. Higher intratumoral MVD values were associated with inferior DFS outcomes. Moreover, the thyroid malignancies presenting with lymph node infiltration displayed a higher vascularization pattern. Similarly, relapsing thyroid cancers when compared to non-recurring tumors were characterized by a denser microvascular plexus. Our study concludes that there are significant primary indications of a negative relationship between intratumoral MVD and survival outcomes. However, to clarify the exact effect of MVD on thyroid cancer and due to several study limitations, further prospective studies with a larger sample size as well as a higher methodological and quality level are required.

CONCLUSION

MVD significantly correlates with the survival outcomes of thyroid cancer patients. However, considering several study limitations, further prospective studies of higher methodological and quality level are required.

ARTICLE HIGHLIGHTS

Research background

An attempt to identify survival-prognostic indicators for thyroid cancer has been implemented

Research motivation

Microvessel density (MVD) has been used as a direct quantification method of tumor neovascularization

Research objectives

This meta-analysis attempted to clarify the effect of tumoral vascularity - through MVD assessment - on the survival of patients with differentiated thyroid carcinoma (DTC).

Research methods

The present meta-analysis was based on the PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.

Research results

Lowly vascularized thyroid cancers had a lower recurrence rate. Moreover, relapsing tumors or malignancies with regional lymph node involvement presented with higher tumoral MVD values.

Research conclusions

MVD significantly correlates with the survival outcomes of DTC patients

Research perspectives

Further prospective studies and randomized controlled trials have to be conducted in order to elucidate the correlation between MVD and prognosis in DTC.

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FOOTNOTES

Author contributions: Perivoliotis K, Ntellas P, and Samara AA performed study conception and design; Dadouli K and Koutoukoglou P acquired the data; Perivoliotis K and Ntellas P analyzed and interpreted the data; Perivoliotis K, Ntellas P, and Samara AA drafted the manuscript; Ioannou M, Tepetes K, and Sotiriou S critically revised the manuscript; all authors have approved the final version of the present manuscript.

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Country/Territory of origin: Greece

ORCID number: Konstantinos Perivoliotis 0000-0002-6622-5734; Athina A Samara 0000-0002-6177-7281; Prodromos Koutoukoglou 0000-0002-7083-0718; Panagiotis Ntellas 0000-0003-1708-3861; Katerina Dadouli 0000-0002-8821-0795; Sotirios Sotiriou 0000-0002-9466-6086; Maria Ioannou 0000-0003-2154-9310; Konstantinos Tepetes 0000-0001-9435-6849.

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