

The diagnostic and prognostic values of Ki-67/MIB-1 expression in thyroid cancer: a meta-analysis with 6,051 cases

Deng-hua Pan¹
 Dong-yue Wen¹
 Yi-huan Luo²
 Gang Chen³
 Hong Yang¹
 Jun-qiang Chen²
 Yun He¹

¹Department of Ultrasonography,
²Department of Gastrointestinal
 Surgery, ³Department of Pathology,
 First Affiliated Hospital of Guangxi
 Medical University, Nanning, Guangxi
 Zhuang Autonomous Region, People's
 Republic of China

Background: Growing evidence has demonstrated that Ki-67/MIB-1 has an effect on the clinical progression and prognosis in cancers. However, the diagnostic and prognostic values of Ki-67/MIB-1 in thyroid cancer remain unclear.

Materials and methods: The meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies were retrieved from PubMed, EBSCO, EMBASE, ISI Web of Science, China National Knowledge Infrastructure, WanFang and Chinese VIP databases. MetaDiSc and STATA12.0 were used to analyze the meta-analysis. Fixed-effect analysis and random-effect analysis were applied to pool the relative ratio based on heterogeneity in this meta-analysis.

Results: In the meta-analysis, 51 eligible studies were included. The pooled sensitivity of Ki-67/MIB-1 was 0.61 (95% confidence interval [CI]: 0.59–0.63) and specificity was 0.75 (95% CI: 0.74–0.77) in thyroid cancer. The pooled positive likelihood ratio was 3.19 (95% CI: 2.30–4.42) and negative likelihood ratio was 0.43 (95% CI: 0.35–0.54). In the diagnosis of thyroid cancer, the pooled diagnostic odds ratio of Ki-67/MIB-1 was 8.54 (95% CI: 5.03–14.49). The area under the symmetric receiver operating characteristic curve was 0.804 (standard error = 0.031). Our results showed that there were statistical associations between Ki-67/MIB-1 and age (odds ratio [OR] = 1.71, 95% CI: 1.14–2.57, $P=0.010$), tumor size (OR = 1.86, 95% CI: 1.17–2.96, $P=0.008$), lymph node metastasis (OR = 2.49, 95% CI: 1.42–4.39, $P=0.002$), metastasis status (OR = 6.96, 95% CI: 2.46–19.69, $P<0.001$), tumor node metastasis stage (OR = 6.56, 95% CI: 3.80–11.34, $P<0.001$) and extrathyroid extension (OR = 1.91, 95% CI: 1.27–2.87, $P=0.002$). Furthermore, thyroid cancer patients with a high level of Ki-67/MIB-1 had a worse disease-free survival as compared to patients with a low level of Ki-67/MIB-1 (hazard ratio = 5.19, 95% CI: 3.18–8.46, $P<0.001$). Also, Ki-67/MIB-1 was found to be associated with increased risk of mortality (hazard ratio = 3.56, 95% CI: 1.17–10.83, $P=0.025$).

Conclusion: Our results demonstrated that Ki-67/MIB-1 might act as a potential factor in diagnosing thyroid cancer in Chinese. Also, the meta-analysis indicated that Ki-67/MIB-1 might have an effect on prognosis in non-Chinese thyroid cancer patients.

Keywords: thyroid cancer, Ki-67/MIB-1, diagnosis, progression, prognosis, meta-analysis

Introduction

Thyroid carcinoma, accounting for nearly 1% of all the cancers, is the most common malignancy in the endocrine organs.¹ Traditionally, thyroid carcinomas are classified into papillary thyroid cancer (PTC), follicular thyroid cancer, medullary thyroid cancer, poorly differentiated thyroid cancer and anaplastic thyroid cancer, based on histopathology.² In China, it has been reported that 90 per 100,000 people were

Correspondence: Yun He
 Department of Ultrasonography, First
 Affiliated Hospital of Guangxi Medical
 University, 6 Shuangyong Road, Nanning,
 Guangxi Zhuang Autonomous Region
 530021, People's Republic of China
 Email 228388072@qq.com

diagnosed with thyroid cancer and 6.8 people died among these patients.³ In USA, it has been estimated that 1,980 people died of the disease in 2016⁴ and there will be 64,300 new patients of thyroid cancer. The diagnosis of thyroid cancer is often based on magnetic resonance imaging, ultrasound, computed tomography, fine needle aspiration and radionuclide imaging. Although various methods are well applied in clinics, patients often have poor outcome. Reports have shown that the patients' age when being diagnosed, sex, tumor size, lymph node, distant metastases and pathologic differentiation of the cancer are the risk factors of prognosis in thyroid cancer.⁵⁻⁸

However, no studies showed the markers had prognostic value in thyroid cancer. Cell proliferative activity is an important factor in cancer biologic behavior. Ki-67, considered as a nuclear antigen, is expressed in all cell nuclei, except those in the G0 phase. Further, MIB-1 acts as a monoclonal antibody which increases against Ki-67. In recent years, Ki-67 has been studied in many cancers, including cervical cancer,⁹ lung cancer,¹⁰ breast cancer¹¹ and thyroid cancer.¹² It has been reported that Ki-67 is an independent prognostic factor in thyroid cancer patients.¹³ A study predicted that patients with Ki-67 labeling index (LI) >3% would show a worse cause-specific survival than those with Ki-67 LI <3%.¹² However, Gnemmi et al¹⁴ reported that Ki-67 LI ($\geq 4\%$) is an independent factor and predictor of cause-specific survival.

Though many studies have demonstrated Ki-67/MIB-1 is expressed in thyroid cancer, there is no systematic literature assessing the relationship between Ki-67/MIB-1 expression and clinical factors in thyroid cancer patients. So, the significance of Ki-67/MIB-1 for prognostication of thyroid cancer remains uncertain. Thus, a literature-based meta-analysis study was performed to evaluate the diagnostic and prognostic values of Ki-67/MIB-1 in thyroid cancer.

Materials and methods

Studies selection

Studies were selected to demonstrate the diagnostic and prognostic values of Ki-67/MIB-1 for thyroid cancer. Electronic literatures were searched in PubMed, EBSCO, EMBASE, ISI Web of Science, WanFang, China National Knowledge Infrastructure and Chinese VIP databases from April 1, 1989 to July 31, 2016. The following keywords were used to identify the related publications: "thyroid cancer", "Ki-67", "MIB-1", "proliferative marker", "proliferative index", "diagnosis", "prognostic", "survival". The eligible studies were selected in accordance with the following criteria: 1) studies should be

published in full assays; 2) the goal of the publication was to illustrate the clinical significance of Ki-67/MIB-1 in primary thyroid cancer; 3) sufficient data were used to determine the connection between Ki-67/MIB-1 and clinicopathologic parameters; 4) when the same patient cohort was reported in different publications, only the most complete and recent study was selected in the meta-analysis.

Also, we screened the references from the reviews and identified articles.

Data extraction and assessment of study quality

Three authors (Deng-hua Pan, Dong-yue Wen and Yi-huan Luo) read the studies carefully and independently. The information of the publications was collected from each study: first author's name, publication date, the number of patients, patient age, country, follow-up time, antibody of testing Ki-67/MIB-1, the method of detecting Ki-67/MIB-1 expression and threshold used for assessing Ki-67/MIB-1 expression positively. True positive, true negative, false positive and false negative were extracted to construct a diagnostic contingency table. Disease-free survival (DFS) or mortality or distant recurrences-free survival was used to measure the effect of Ki-67/MIB-1 expression on survival in thyroid cancer patients. The following clinical parameters were extracted to evaluate the connection between Ki-67/MIB-1 and thyroid cancer aggressiveness: age, tumor size, lymph node metastasis, metastasis status, extrathyroid extension, tumor node metastasis stage. Minimal size of patients and minimal follow-up time are not defined in this meta-analysis. Studies that met the following criteria were excluded: 1) reviews, conference papers, case reports, expertise public opinion, letters, zoopery were not included; 2) studies without sufficient information to calculate the impact of diagnosis, survival and prognosis of Ki-67/MIB-1 in primary thyroid cancer were excluded; 3) studies with duplicated data from similar or the same population were excluded. QUADAS-2 was used to assess the quality of the studies for diagnosis.¹⁵ Newcastle–Ottawa scale (NOS) was used to assess the quality of the studies for prognosis.¹⁶ The study with NOS scores ≥ 6 was identified as a high-quality study and the study with NOS scores <6 was considered as a low-quality study.

Statistical methods

According to the cut-off values, Ki-67/MIB-1 expression was divided into positive and negative groups. The pooled

sensitivity and specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), diagnostic odds ratio (DOR) and the area under the symmetric receiver operating characteristic curve were used to measure the diagnosis of Ki-67/MIB-1 in thyroid cancer. The odds ratio (OR) and 95% confidence intervals (CIs) were used to estimate the relationship between Ki-67/MIB-1 and clinicopathologic parameters in thyroid cancer patients. When the OR was >1 , it indicated that high Ki-67/MIB-1 was a risk factor in thyroid cancer. Hazard ratio (HR) and 95% CI were calculated to measure the effect of Ki-67/MIB-1 on prognosis. Also, when the HR was >1 , it indicated that high level of Ki-67/MIB-1 was related to worse survival in thyroid cancer patients.

Further, Cochran's Q -test was performed to measure heterogeneity. Also, I^2 was calculated to assess the inconsistency of the studies. When I^2 was over 50% or chi-squared P -value was >0.1 , fixed-effect meta-analysis was performed; otherwise, random-effect meta-analysis was used when there

was less or no heterogeneity (when I^2 was less than 50% or chi-squared P -value was <0.1). MetaDiSc was used to measure the diagnosis of Ki-67/MIB-1 in thyroid cancer. STATA12.0 was used to calculate the progression and prognosis of Ki-67/MIB-1 in thyroid cancer. The potential publication bias was investigated through funnel plot and by computation of Begg's test. When the P -value was <0.05 , it was considered significant.

Results

Description of studies

The flow chart of search process is presented in Figure 1. One thousand one hundred and sixty-two relevant studies were identified. After reviewing the abstracts and full text, only 51 studies^{1,12,14,17-64} were found to be eligible and were included in the meta-analysis. The characteristics of these articles are summarized in Tables 1–3. Table 1 gives the main information of the studies included in diagnosis. Thirty-seven studies

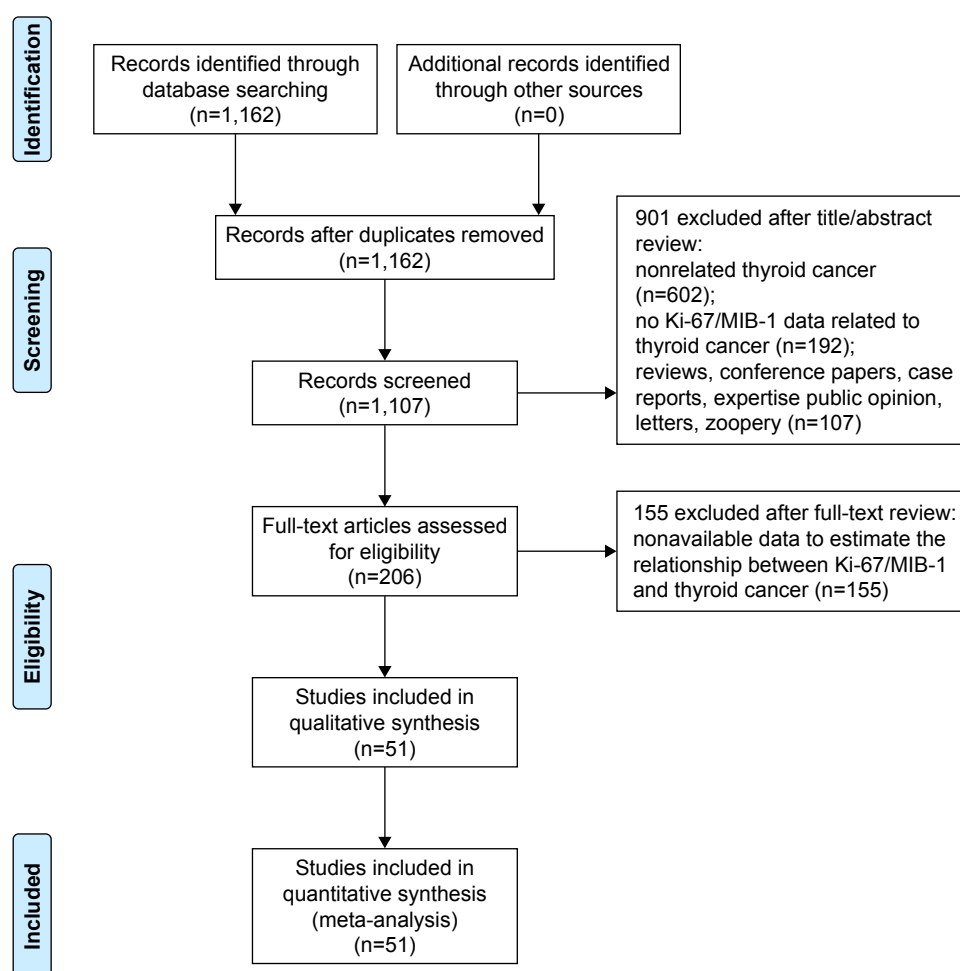


Figure 1 Flow diagram of reviewing and selecting studies.

Table 1 Characteristics of studies included in diagnosis

First author	Country	Patients	Type of cancer	Type of control	Antibody	Test method	Threshold, %	TP	FP	FN	TN
Horii et al ²⁹	Japan	50	PTC, FTC, ATC	Adenomatous goiter, FA	Ki-67 monoclonal antibody	IHC	20	276	2	6	15
Huang et al ³⁴	China	160	PTC	FA, goiter	Mouse monoclonal antibody	IHC	5	103	9	0	128
Chou et al ³⁰	Taiwan	46	PTC, FVPTC	NG, normal tissue	Mouse monoclonal antibody anti-Ki-67	IHC	10	16	2	13	15
Nie et al ³⁵	China	26	PTC	TA, NG, toxic goiter	Anti-Ki-67	IHC	25	9	2	5	10
Liang et al ³⁶	China	200	PTC	NG, TA	Ki-67	IHC	25	93	1	7	99
Gan et al ³⁷	China	135	PTC	Adjacent tissue of thyroid carcinoma, normal tissue, NG, FA	Mouse monoclonal antibody	IHC	10	38	26	7	64
Wang et al ³⁸	China	94	PTC, FTC, MTC, ATC	NG, TA	Ki-67	IHC	10	20	0	45	29
Shang et al ³⁹	China	100	PTC, FTC, OCTC	PTA, FTA, OCTA	Anti-Ki-67	IHC	1.50	42	29	8	21
Cui et al ⁴³	China	87	PTC, FTC	TA, normal tissue	Mouse monoclonal antibody	IHC	10	35	3	19	20
Feng et al ⁴⁰	China	199	PTC, FTC, MTC	NG, FA, adjacent tissue of thyroid carcinoma	Ki-67	IHC	5	58	16	18	107
Jin et al ⁴⁴	China	79	PTC, FTC, MTC, ATC	TA, normal thyroid gland tissue beside adenoma	Mouse monoclonal antibody	IHC	25	39	3	17	20
Huang et al ⁴²	China	70	PTC	Thyroid hyperplasia, TA	Anti-Ki-67	IHC	10	20	9	10	31
Li and Du ⁴³	China	136	PTC	NG, NG with adenoma hyperplasia, NGWPH	Anti-Ki-67	IHC	10	55	27	0	54
Hao ⁴⁴	China	236	PTC	NG, TA	Ki-67	IHC	ND	17	2	101	116
Song et al ²⁷	China	592	PTC	NG, nonmalignant follicular adenoma	Mouse monoclonal antibody	IHC	10	179	56	262	95
Tan et al ³¹	Turkey	39	PTC, FTC	FA	Ki-67	IHC	5	8	10	16	5
Zeng et al ⁴⁵	China	108	TC	Normal tissue	Mouse monoclonal antibody	IHC	5	46	11	22	29
Qin et al ⁴⁶	China	120	PTC	NG, normal tissue	Anti-Ki-67	IHC	10	25	78	15	1
Zhao et al ⁴⁷	China	129	PTC	Multinodular goiters, follicular adenomas, Hashimoto's thyroiditis	Ki-67	IHC	ND	34	22	9	64
Jiang et al ⁴⁸	China	63	PTC	TA	Mouse monoclonal antibody	IHC	10	23	2	12	26
Yao et al ⁴⁹	China	103	PTC, FTC, MTC, ATC	Normal tissue, NG, FA	Mouse monoclonal antibody	IHC	25	60	10	8	25
Yang et al ⁵⁰	China	55	FTC	FA	Mouse monoclonal antibody	IHC	5	15	6	17	17
Lj ⁵¹	China	246	PTC	Normal tissue, NG, NGWPH	Mouse monoclonal antibody	IHC	10	68	22	8	68
Shi et al ⁵²	China	130	TC	TA, NG, normal thyroid gland tissue	Rabbit monoclonal antibody	IHC	10	42	10	8	70
Zhang et al ²⁸	China	146	PTC	Multinodular goiter	Ki-67	IHC	1.65	57	9	19	61
Maruta et al ²³	Japan	108	FC	FA	Anti-Ki-67	IHC	50	47	35	21	5
Guo et al ⁵³	China	117	PTC, FTC, ATC	TA, normal thyroid tissues	Anti-Ki-67	IHC	10	62	2	87	30
Wang et al ⁵⁴	China	33	PTC	Hyalinizing trabecular tumor	MIB-1	IHC	10	20	10	0	3
Zhou et al ⁵⁵	China	120	PTMC	TA, NG, Hashimoto's thyroiditis	Anti-Ki-67	IHC	25	34	6	46	34
Li et al ⁵⁶	China	370	PTC	Benign thyroid nodule	Mouse monoclonal antibody	IHC	1.00	112	48	68	142
Xu et al ⁵⁷	China	62	PTC	Thyroid benign tumor	Ki-67	IHC	5	32	3	14	13
Wang et al ⁵⁸	China	95	PTC	NGWPH	Ki-67	IHC	10	26	44	19	6
Zhou et al ⁵⁴	China	158	PTMC	NG, TA, Hashimoto's thyroiditis	Mouse monoclonal antibody	IHC	25.00	50	7	58	43
Zhu et al ⁵⁹	China	96	PTC	Thyroid hyperplasia	Anti-Ki-67	IHC	5	40	10	24	22
Li and Pu ⁶⁰	China	150	PTC	Follicular adenoma, normal tissue	Ki-67	IHC	5	18	9	32	91
Li and Zhang ⁶¹	China	120	PTC	TA, NG, normal tissue	Mouse monoclonal antibody	IHC	10	25	8	5	82
Feng and Wang ⁶²	China	60	MTC	Adjacent tissue of thyroid carcinoma	Mouse monoclonal antibody	IHC	1	36	0	6	18

Abbreviations: ATC, anaplastic thyroid cancer; FA, follicular adenoma; FN, false negative; FP, false positive; FTA, follicular thyroid carcinoma; FVPTC, follicular variant of papillary thyroid carcinoma; IHC, immunohistochemistry; MTC, medullary thyroid carcinoma; ND, no data; NG, nodular goiter; NGWPH, nodular goiter with papillary hyperplasia; PTA, papillary thyroid adenoma; OCTA, oxyphilic cell thyroid adenoma; OCTC, oxyphilic cell thyroid carcinoma; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; TA, thyroid adenoma; TP, true positive; TN, true negative.

Table 2 The relationships between Ki-67/MIB-1 expression and clinicopathologic parameters

Clinicopathologic parameters	Studies (n)	Test group		Control group		Heterogeneity		Meta-analysis model	OR (95% CI)	P-value
		Events	Total	Events	Total	I ² , %	P-value			
Age (45 years)	10	124	303	91	239	0.00	0.806	Fixed-effect analysis	1.71 (1.14–2.57)	0.01
Tumor size (4 cm)	5	35	165	76	730	2.00	0.395	Fixed-effect analysis	1.86 (1.17–2.96)	0.008
Lymph node metastasis	15	233	345	226	509	50.20	0.014	Random-effect analysis	2.49 (1.42–4.39)	0.002
Metastasis status	7	75	133	121	920	59.80	0.021	Random-effect analysis	6.96 (2.46–19.69)	<0.001
TNM stage	7	113	146	103	247	0.00	0.96	Fixed-effect analysis	6.56 (3.80–11.34)	<0.001
Extrathyroid extension	4	64	225	79	413	31.30	0.224	Fixed-effect analysis	1.91 (1.27–2.87)	0.002

Abbreviations: CI, confidence interval; OR, odds ratio; TNM, tumor node metastasis.

Table 3 The features of the studies relating Ki-67/MIB-1 to patients' prognosis

Type of survival	First author	Country	Year	Patients	Age	Median FU	Test method	Antibody	Threshold, %	HR (95% CI)	P-value
DFS	Kjellman et al ¹	Sweden	2003	30	62	146 months	IHC	MIB-1	1.85	4.93 (1.91–12.77)	0.001
	Ito et al ¹²	Japan	2010	371	49	125 months	IHC	Anti Ki-67 antibody	1	4.13 (2.19–7.75)	<0.001
Mortality	Miyauchi et al ²²	Japan	2013	390	50.8	88 months	IHC	Anti Ki-67 antibody (clone MIB-1)	>10	15.33 (4.13–56.96)	<0.001
	Wang et al ³³	Sweden	1996	21	53	10.5 years	IHC	Ki-67	5	0.514 (0.086–3.089)	0.467
	Tisell et al ²⁶	Sweden	2003	36	45	20 years	IHC	Anti-Ki67	1	2.12 (0.862–5.233)	0.102
	Ito et al ¹²	Japan	2010	371	49	125 months	IHC	Anti Ki-67 antibody	3	25.64 (2.49–250)	0.006
	Chen et al ²⁰	USA	2011	9	64.8	32.5 months	IHC	MIB-1	5	0.088 (0.008–1.026)	0.052
	Miyauchi et al ²²	Japan	2013	390	50.8	88 months	IHC	Anti Ki-67 antibody (clone MIB-1)	>10	34.08 (3.81–305.16)	0.002
	Gnemmi et al ¹⁴	France	2014	82	ND	68 months	IHC	MIB-1	4	6.126 (1.662–22.574)	0.007
	Jovanovic et al ³²	Macedonia	2015	20	51.2	73 months	IHC	MIB-1	6.50	24.25 (3.63–161.99)	0.001
	Feng and Wang ⁶²	China	2014	42	53.2	7.8 years	IHC	MIB-1	1	2.28 (0.61–8.55)	0.228
	Gnemmi et al ¹⁴	France	2014	82	ND	68 months	IHC	MIB-1	4	7.322 (3.141–17.07)	<0.001

Abbreviations: CI, confidence interval; DFS, disease-free survival; DRFS, distant recurrences-free survival; FU, follow-up; HR, hazard ratio; IHC, immunohistochemistry; ND, no data.

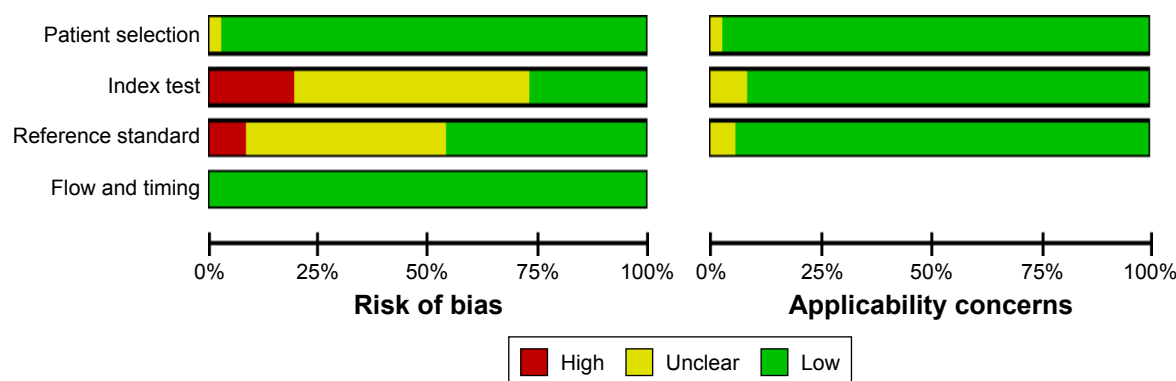


Figure 2 Risk of bias of studies included in diagnosis with QUADAS-2 tool.

detecting the diagnostic value of Ki-67/MIB-1 in thyroid cancer were included in our analysis, including 4,818 samples (2,601 cases and 2,217 controls). The quality assessment of the included studies in diagnosis is shown in Figure 2. The risks of bias in “index test” and “reference standard” were unclear in this meta-analysis. Table 2 shows the correlation between clinicopathologic parameters and Ki-67/MIB-1, including 4,375 samples (1,317 cases and 3,058 controls). As shown in Table 3, a total of 10 studies reporting the relation between Ki-67/MIB-1 and thyroid cancer patient survival were included, of which three studies had data on DFS, seven on mortality and only one on distant recurrences-free survival (DRFS). The studies included in survival analysis had 1,083 samples. The age of patients ranged from 45 to 64.8 years, and the median follow-up time ranged from 68 months to 20 years. Immunohistochemistry (IHC) was used to detect the expression of Ki-67/MIB-1 in all the included studies. The cut-off value ranged from 1% to 10%. The quality assessment of the studies included in prognosis is shown in Table 4.

Effect of Ki-67/MIB-1 on diagnosis

Due to heterogeneity, random-effect model was used to calculate the overall performance of Ki-67/MIB-1 in thyroid tissues in diagnosing thyroid cancer. Ki-67/MIB-1 was found to be a valuable diagnostic factor for thyroid cancer. The pooled sensitivity was 0.61 (95% CI: 0.59–0.63; Figure 3A) and specificity was 0.75 (95% CI: 0.74–0.77; Figure 3B). The pooled LR+ was 3.19 (95% CI: 2.30–4.42; Figure 3C) and the pooled LR– was 0.43 (95% CI: 0.35–0.54; Figure 3D). The pooled DOR of Ki-67/MIB-1 was 8.54 (95% CI: 5.03–14.49; Figure 4). The area under the symmetric receiver operating characteristic curve was 0.804 (standard error = 0.031; Figure 5). For Ki-67/MIB-1, the summary indexes of 37 studies are displayed in forest plots. High heterogeneity was found in sensitivity ($I^2=94.5\%$, $P<0.001$) and specificity ($I^2=94.7\%$,

$P<0.001$). Also, subgroup analysis was performed to identify the possible reasons for heterogeneity. There were 12 studies with Ki-67/MIB-1 cut-off value $\leq 5\%$, which revealed a pooled sensitivity of 0.70 (95% CI: 0.67–0.73), specificity of 0.80 (95% CI: 0.77–0.83) and DOR of 7.49 (95% CI: 3.61–15.52). Fifteen studies had Ki-67/MIB-1 cut-off value of 10%, a pooled sensitivity of 0.56 (95% CI: 0.53–0.59), specificity of 0.67 (95% CI: 0.63–0.70) and DOR of 7.73 (95% CI: 2.68–22.30). There were eight studies with a cut-off value $>10\%$, and the pooled sensitivity, specificity and DOR were 0.78 (95% CI: 0.75–0.81), 0.79 (95% CI: 0.74–0.84) and 15.40 (95% CI: 3.41–69.62), respectively. In the subgroup analysis of PTC, the results showed that the pooled sensitivity, specificity and DOR were 0.63 (95% CI: 0.60–0.65), 0.74 (95% CI: 0.72–0.76) and 8.22 (95% CI: 4.08–16.56), respectively. In the subgroup analysis of

Table 4 Quality assessment of included studies according to NOS

Studies	First author	Year	Selection					Comparability			Outcome			Total score
			A	B	C	D	E	F	G	H				
Kjellman et al ¹	Kjellman	2003	*	*	*				*	*	*			6
Feng and Wang ⁶²	Feng and Wang	2015	*	*	*				*	*	*			6
Ito et al ¹²	Ito et al	2010	*	*	*				*	*	*			6
Jovanovic et al ³²	Jovanovic et al	2015	*	*	*				*	*	*			6
Gnemmi et al ¹⁴	Gnemmi et al	2014	*	*	*		*		*	*	*			7
Miyauchi et al ²²	Miyauchi et al	2013	*	*	*				*	*				5
Chen et al ²⁰	Chen et al	2011	*	*	*				*	*	*			6
Wang et al ³³	Wang et al	1996	*	*	*				*	*	*			6
Tisell et al ²⁶	Tisell et al	2003	*	*	*				*	*	*			6

Notes: A: representative of the exposed cohort; B: selection of the nonexposed cohort; C: ascertainment of exposure; D: demonstration that outcome of interest was not present at the start of study; E: comparability of cohorts on the basis of the design or analysis; F: assessment of outcome; G: adequacy of follow-up for outcomes to occur (≥ 2 years or outcomes occurred in all patients); H: adequacy of follow-up of cohorts (follow-up rate $\geq 75\%$).

Abbreviation: NOS, Newcastle–Ottawa scale.

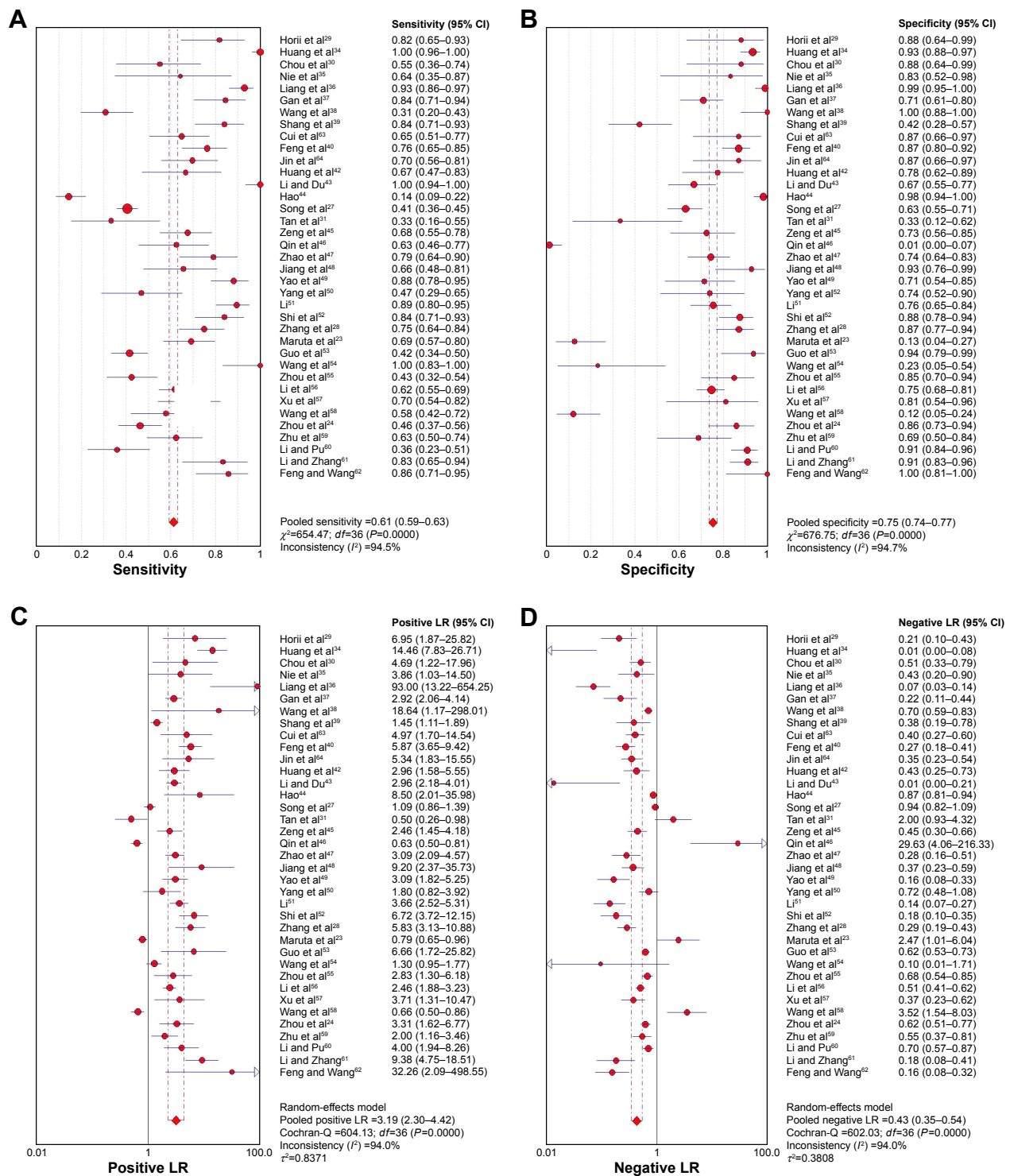


Figure 3 Forest plots for the accuracy of Ki-67/MIB-1 for the diagnosis of thyroid cancer.

Notes: (A) Sensitivity; (B) specificity; (C) positive LR (LR+); (D) negative LR (LR–).

Abbreviations: CI, confidence interval; df , degrees of freedom; LR, likelihood ratio.

papillary thyroid microcarcinoma (PTMC), the results showed that the pooled sensitivity, specificity and DOR were 0.45 (95% CI: 0.37–0.52), 0.86 (95% CI: 0.77–0.92) and 4.76 (95% CI: 2.48–9.17), respectively (Table S1).

Associations of Ki-67/MIB-1 with clinicopathologic parameters

Table 2 shows the main results of the effects value of Ki-67/MIB-1 on clinicopathologic parameters in thyroid cancer

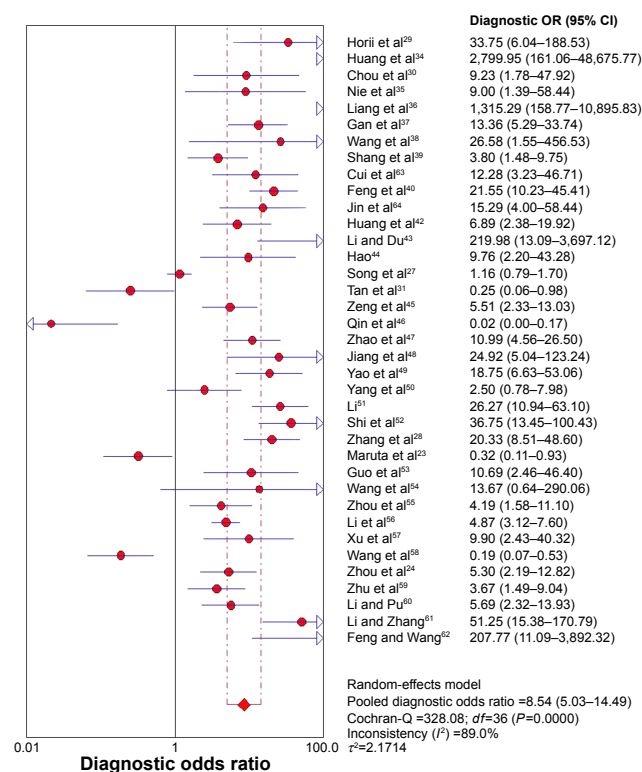


Figure 4 Forest plot of DOR of Ki-67/MIB-1 for the diagnosis of thyroid cancer.
Note: The pooled DOR of Ki-67/MIB-1 for the diagnosis of thyroid cancer was 8.54 (95% CI: 5.03–14.49).
Abbreviations: CI, confidence interval; df, degrees of freedom; DOR, diagnostic odds ratio; OR, odds ratio.

patients. The results suggested that older patients (>45 years old) had high level of Ki-67/MIB-1 with a pooled OR of 1.71 (95% CI: 1.14–2.57, $P=0.010$; $I^2=0.00\%$, $P=0.806$; Figure 6A). The level of Ki-67/MIB-1 was higher in large tumor size (>4 cm) than in small-sized tumor (<4 cm; pooled OR = 1.86, 95% CI: 1.17–2.96, $P=0.008$; $I^2=2.00\%$, $P=0.395$; Figure 6B). Overall, 15 studies had data to estimate the relationship between Ki-67/MIB-1 and lymph node metastasis. The pooled OR estimated from 15 studies indicated that Ki-67/MIB-1 was lower in negative lymph node metastasis than in positive lymph node metastasis (pooled OR = 2.49, 95% CI: 1.42–4.39, $P=0.002$; $I^2=50.20\%$, $P=0.014$; Figure 6C). Also, the association between Ki-67/MIB-1 and metastasis status was calculated and the combined OR was 6.96 (95% CI: 2.46–19.69, $P<0.001$; Figure 6D). The combined OR for tumor node metastasis stage was 6.56 (95% CI: 3.80–11.33, $P<0.001$; $I^2=0.00\%$, $P=0.960$), suggesting that overexpression of Ki-67/MIB-1 was significantly correlated with advanced stage (Figure 6E). In addition, four studies provided insufficient information to estimate the effect of extrathyroid extension. The pooled OR was 1.91 (95% CI: 1.27–2.87, $P=0.002$; Figure 6F).

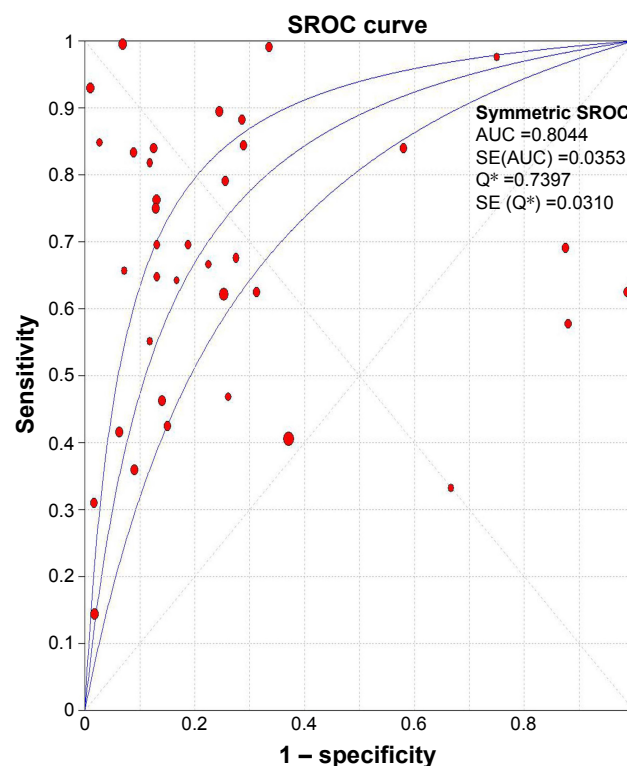


Figure 5 SROC curve for the accuracy of Ki-67/MIB-1 in the diagnosis of thyroid cancer.

Notes: The area under the SROC curve was 0.804 (SE = 0.031). Q^* represents the index to judge the accuracy of the diagnostic experiment.

Abbreviations: AUC, area under the curve; SE, standard error; SROC, symmetric receiver operating characteristic.

Impact of Ki-67/MIB-1 expression on survival in thyroid cancer

Furthermore, three studies assessing the association of Ki-67/MIB-1 expression on DFS were identified in this meta-analysis. The combined HR was 5.19. It was demonstrated that overexpression of Ki-67/MIB-1 was associated with worse DFS in thyroid cancer by fixed-effect model (95% CI: 3.18–8.46, $P<0.001$; $I^2=36.1\%$, $P=0.209$; Figure 7). The meta-analysis showed overexpression of Ki-67/MIB-1 had effect on mortality (HR = 3.56, 95% CI: 1.17–10.83, $P=0.025$) in eight studies, with heterogeneity ($I^2=73.5\%$, $P<0.001$; Figure 8). Worsened mortality was found among patients with Ki-67/MIB-1 cut-off value >10% (HR = 34.08, 95% CI: 3.81–305.00, $P=0.002$) by subgroup analysis. Nevertheless, when Ki-67/MIB-1 was more than 5%, the patients were afflicted with poor mortality (HR = 28.06, 95% CI: 6.68–117.87, $P<0.001$) in thyroid cancer. No connection was found between Ki-67/MIB-1 and thyroid cancer when Ki-67/MIB-1 was less than 5% (HR = 1.98, 95% CI: 0.65–6.06, $P=0.230$). In subgroup analysis, no significant association was found between medullary thyroid cancer and mortality (HR = 0.96, 95% CI: 0.24–2.16). In addition,

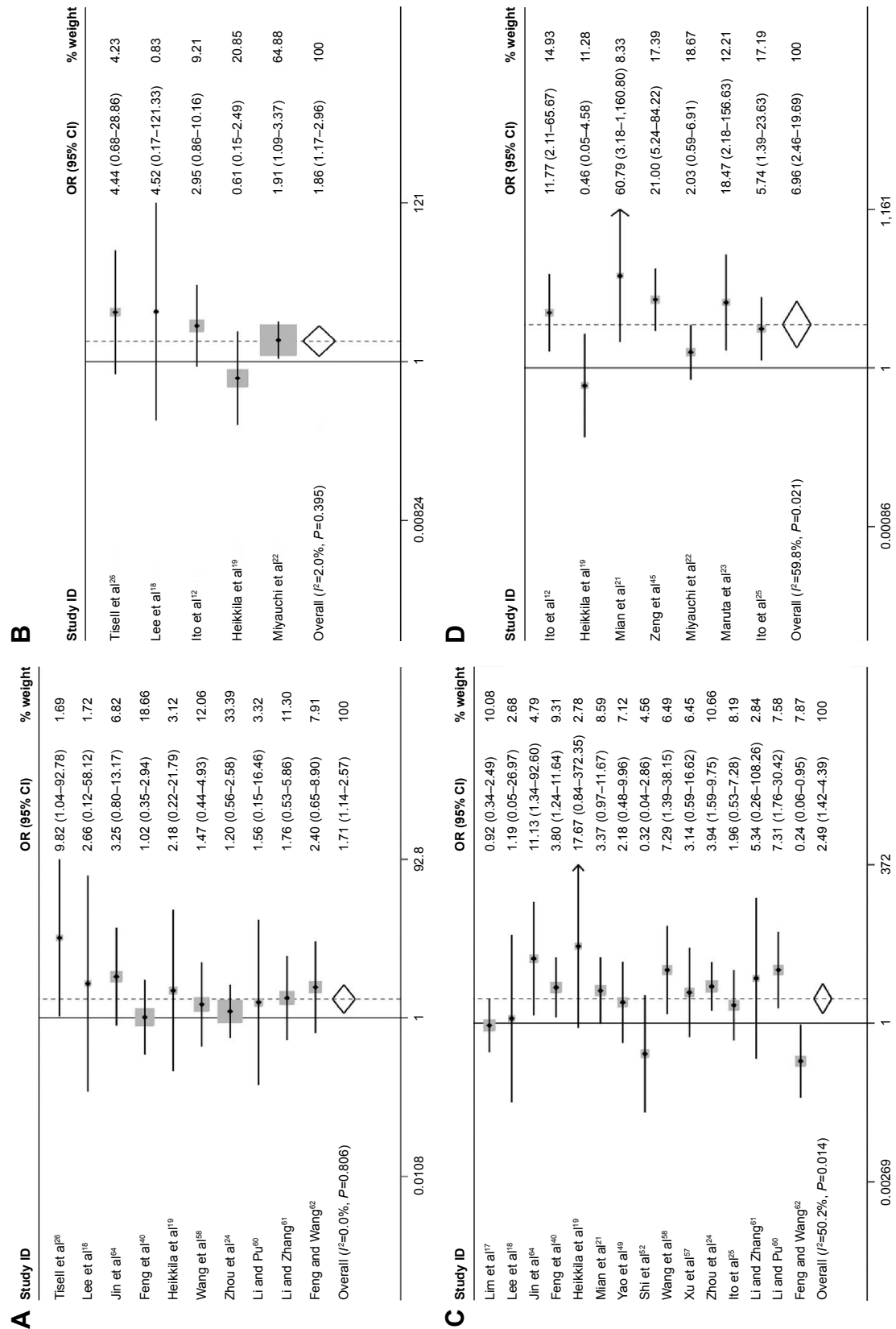


Figure 6 (Continued)

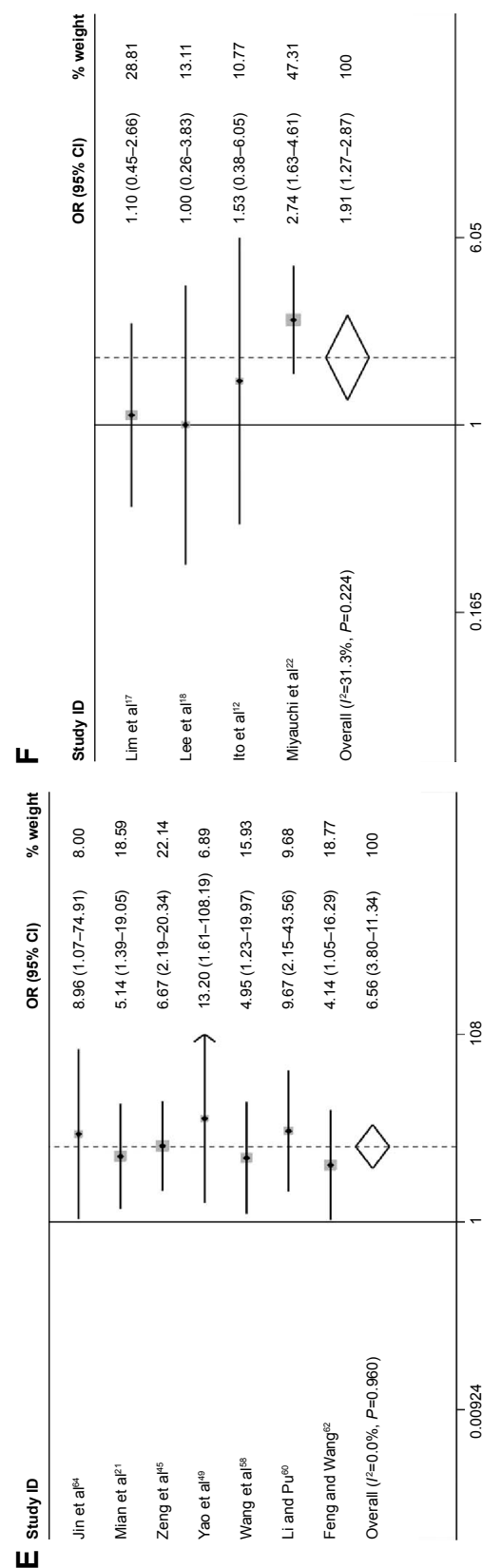


Figure 6 Forest plots of Ki-67/MIB-1 and clinicopathologic parameters in thyroid cancer patients. **Notes:** (A) Age; (B) tumor size; (C) lymph node metastasis; (D) metastasis status; (E) TNM stage; (F) extrathyroid extension. Weights are from random-effects analysis. **Abbreviations:** CI, confidence interval; OR, odds ratio; TNM, tumor node metastasis.

no significant relationship was observed between PTC and mortality (HR =1.47, 95% CI: 2.23–5.18; Table S2).

Publication bias

The Begg's test and funnel plot showed that there was no evidence of publication bias present among all the analyses in our meta-analysis (all $P>0.05$; Figures 9 and 10).

Discussion

Cell proliferative activity is regarded as an important factor for evaluating the biologic behavior of cancer cells. It is a key process in the development of tumors when the balance between cell death and proliferation is destroyed. We used IHC to detect cell cycle-specific antigens and this method can assess the proliferative activity of cells. Ki-67/MIB-1 is the most widely used marker for assessing the proliferative capacity of tumor cells. Increased expression of Ki-67/MIB-1 has been linked to increased invasiveness in many cancers.^{10,65–67} Many meta-analyses have shown that high expression of Ki-67/MIB-1 contributed to poor survival in many tumors.^{68–72} However, there is no consensus on the association between high level of Ki-67/MIB-1 and thyroid cancer at present. Meta-analysis is a systematical method applied widely to evaluate the prognostic indicators in different trials. Thus, in this meta-analysis, we explored the diagnosis and prognosis of Ki-67/MIB-1 expression in thyroid cancer.

In our study, we found the valuable predicting effect of Ki-67/MIB-1 for the diagnosis of thyroid cancer with a high accuracy for Chinese. In clinical practice, detecting Ki-67/MIB-1 expression may contribute to diagnosing thyroid cancer when combined with clinical symptoms, laboratory examinations and other radiologic imaging. Our analysis demonstrated that patients with overexpression of Ki-67/MIB-1 seemed to have a poor survival in thyroid cancer. Also, Ki-67/MIB-1 was found to be associated with tumor size, lymph node metastasis, metastasis status, extrathyroid extension and other clinicopathologic parameters. However, the mechanism of Ki-67/MIB-1 in thyroid cancer is still unclear. Ki-67/MIB-1 as a cellular marker has a positive effect on cell proliferation. Ki-67/MIB-1 expression detected by IHC can evaluate tumor cell proliferation. A previous study confirmed that Sp1 plays an important role in regulation of Ki-67/MIB-1 gene expression.⁷³ Another study pointed out that E2F2 transcription factor was positively correlated with Ki-67/MIB-1 expression in human glioblastoma⁷⁴ and E2F1–3 factors are the transcriptional activator in tumor progression and the retinoblastoma tumor suppressor

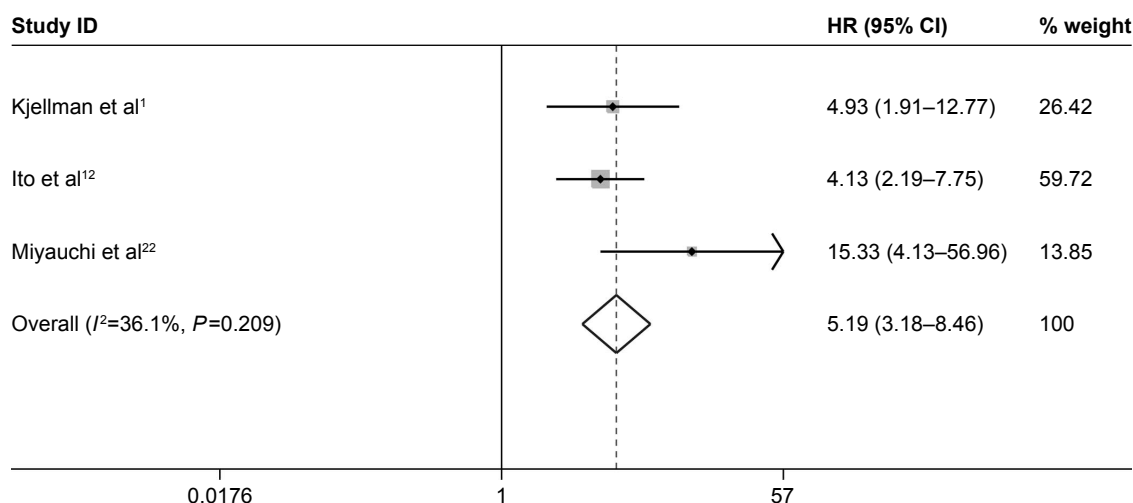


Figure 7 Meta-analysis evaluating the association between Ki-67/MIB-1 and DFS (fixed-effect analysis).

Note: The combined fixed-effect HR was 5.19 (95% CI: 3.18–8.46, $P<0.001$), indicating that high level of Ki-67/MIB-1 was associated with worse DFS.

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio.

pathway regulates E2F1–3 factors which could control cellular proliferation.⁷⁵

In this meta-analysis, heterogeneity existed among the studies. Heterogeneity was still a potential problem which affected the meta-analysis results, though random-effect models were used to analyze the data. Meanwhile, in order to reduce heterogeneity, only the studies with the method of IHC to detect Ki-67/MIB-1 were included in this meta-analysis. However, evaluation standards, study location, number of patients, sex and age of patients were different,

which contributed to the heterogeneity. Also, various cut-off values were used to define thyroid cancer with Ki-67/MIB-1 positive expression by different investigators, which potentially contributed to the heterogeneity. So, it is difficult to apply a standard critical value in clinical practice. Spyrtos et al⁷⁶ found that few tumors with low proliferation rate were under misclassification when the cut-off value of Ki-67/MIB-1 was 10%, and it is acceptable to identify a highly proliferative tumor with a Ki-67/MIB-1 cut-off value of 25%. In this meta-analysis, the cut-off values of Ki-67/MIB-1 ranged from 0.5%

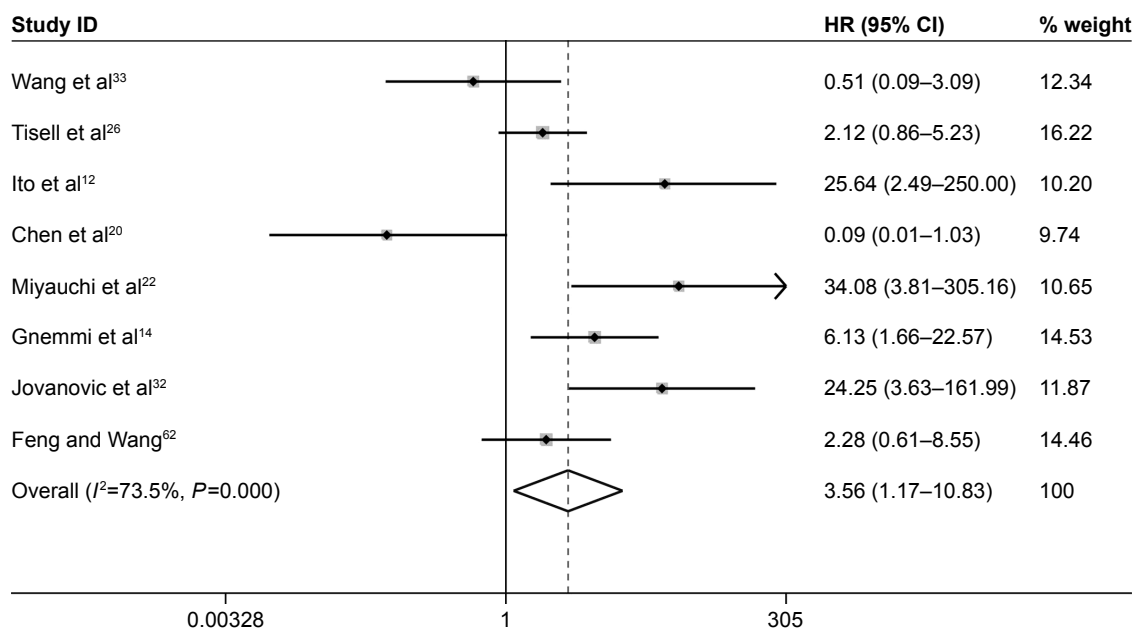


Figure 8 Meta-analysis evaluating the association between Ki-67/MIB-1 and mortality (random-effect analysis).

Notes: The pooled fixed-effect HR was 3.56 (95% CI: 1.17–10.83, $P=0.025$), indicating that high level of Ki-67/MIB-1 was associated with increased of risk of mortality. Weights are from random-effect analysis.

Abbreviations: CI, confidence interval; HR, hazard ratio.

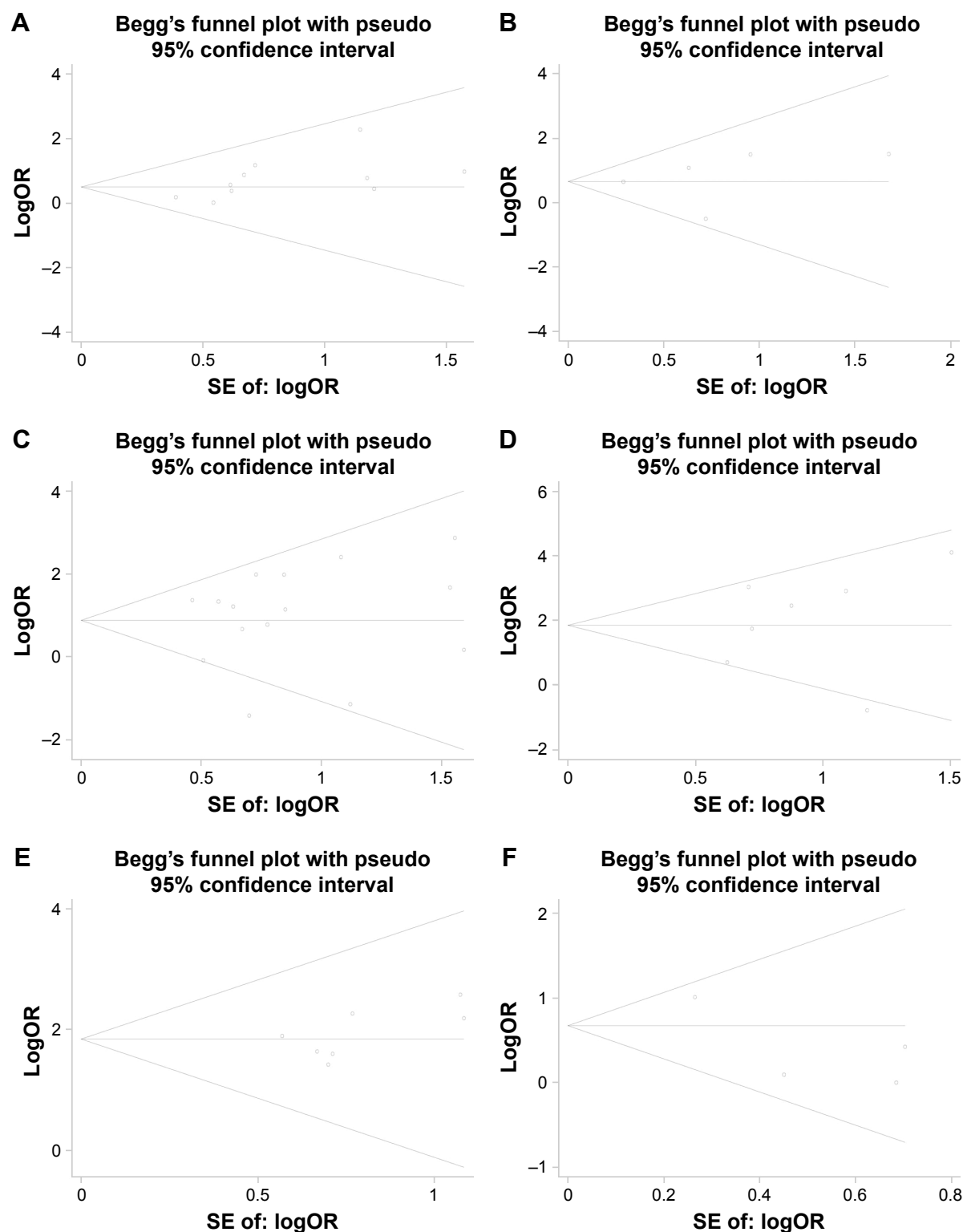


Figure 9 Assessment of publication bias for clinicopathologic parameters.

Notes: (A) Age; (B) tumor size; (C) lymph node metastasis; (D) metastasis status; (E) TNM stage; (F) extrathyroid extension.

Abbreviations: OR, odds ratio; SE, standard error; TNM, tumor node metastasis.

to 25%. Therefore, different Ki-67/MIB-1 cut-offs may cause heterogeneity. Higher sensitivity, specificity and DOR were found in patients with cut-off value >10% by diagnostic subgroup analysis. Furthermore, those patients may have

worse mortality. Given the small size of studies included in mortality analysis, further research with larger sample size would be needed to explore the impact of KI-67/MIB-1 on mortality. Besides, HRs were extracted from survival curves

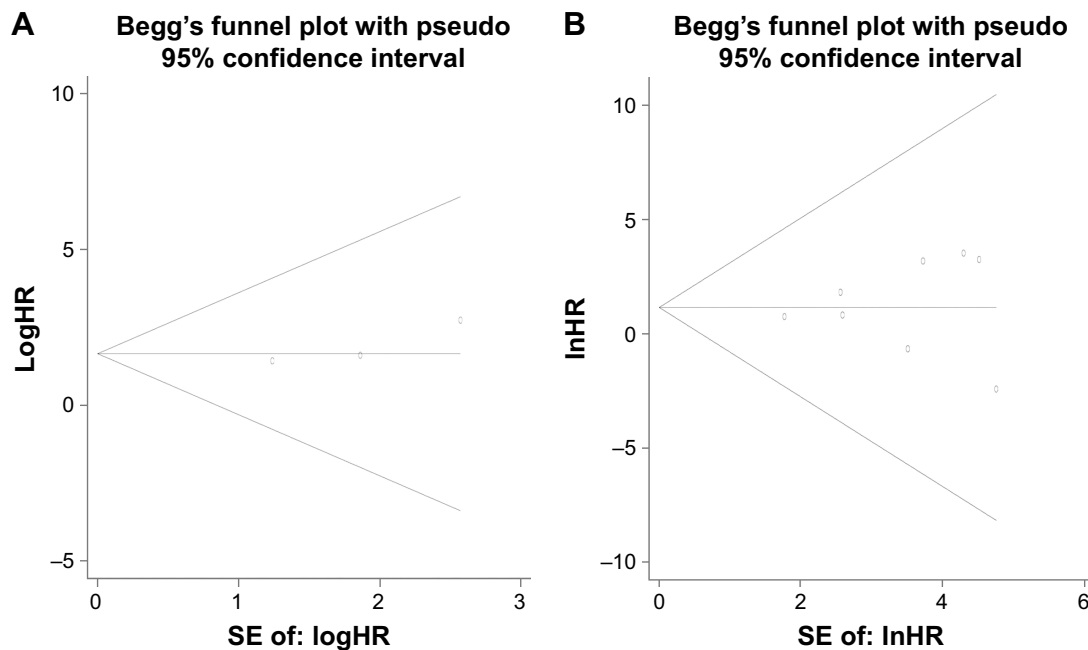


Figure 10 Assessment of publication bias for DFS and mortality.

Notes: (A) DFS; (B) mortality.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; SE, standard error.

or calculated from data which might be less than another variance. Most of the studies included in diagnosis were from China; however, most of the studies related to DFS and mortality were from outside of China. We found that Ki-67/MIB-1 had a diagnostic value in Chinese. However, we did not have enough data to calculate the relationship between Ki-67/MIB-1 and mortality for Chinese. So, regional variation may become a score of heterogeneity. Besides, due to several types of thyroid cancer dealt with in the same study, we conducted subgroup analysis in this meta-analysis. Ki-67/MIB-1 had diagnostic effect on different thyroid cancer types. We did not find significant association between Ki-67/MIB-1 and different thyroid cancer types.

Despite the above limitations, the current meta-analysis proves the associations between high Ki-67/MIB-1 and tumor deterioration, poor DFS and increased mortality in patients with thyroid cancer. In conclusion, we showed that high expression of Ki-67/MIB-1 was significantly connected with tumor size, lymph metastasis, metastasis status, extrathyroid extension and poor prognosis of thyroid cancer in this study.

Conclusion

Our meta-analysis shows that Ki-67/MIB-1 may be a biomarker for clinical deterioration in Chinese and has an effect on prognosis in thyroid cancer among non-Chinese. Therefore, detection of Ki-67/MIB-1 in the clinic will be beneficial to the treatment and prognostic assessment for

thyroid cancer patients. However, well-designed prospective studies are necessary to further confirm our results.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Subgroup analysis evaluating the diagnostic value of Ki-67/MIB-I in thyroid cancer

Groups	No of studies	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	DOR (95% CI)
Cut-off, %				
≤5	12	0.70 (0.67–0.73)	0.80 (0.77–0.83)	7.49 (3.61–15.52)
10	15	0.56 (0.53–0.59)	0.67 (0.63–0.70)	7.73 (2.68–22.30)
>10	8	0.78 (0.75–0.81)	0.79 (0.74–0.84)	15.40 (3.41–69.62)
Types				
PTC	21	0.63 (0.60–0.65)	0.74 (0.72–0.76)	8.22 (4.08–16.56)
PTMC	2	0.45 (0.37–0.52)	0.86 (0.77–0.92)	4.76 (2.48–9.17)

Abbreviations: CI, confidence interval; DOR, diagnostic odds ratio; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma.

Table S2 Subgroup analysis evaluating the prognostic value of Ki-67/MIB-I for mortality in thyroid cancer

Groups	Pooled HR	95% CI	Heterogeneity test		Statistical method
			I ² , %	P-value	
Univariate cut-off, %					
≤5	1.98	0.65–6.06	68.80	0.007	Random
>5	28.06	6.68–117.87	0.00	0.818	Random
<10	2.73	0.89–8.38	72.20	0.001	Random
Types					
PTC	1.47	2.23–5.18	87.10	<0.001	Random
MTC	0.96	0.24–2.16	65.50	0.035	Random

Abbreviations: CI, confidence interval; HR, hazard ratio; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

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