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Original Article

Diagnostic accuracy of CK-19, Galectin-3 and HBME-1 on papillary thyroid carcinoma: a meta-analysis

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Abstract: The study aimed at evaluating the diagnostic accuracy of cytokeratin 19 (CK-19), Galectin-3 and hector battifora mesothelial antigen-1 (HBME-1) for papillary thyroid carcinoma (PTC). The eligible studies were searched in relevant databases with predefined key searching terms and inclusion criteria. Then, the quality assessment was performed by using Diagnostic Accuracy Studies scoring tool. Following the heterogeneity test, a meta-analysis of pooled several effect size including sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) with their 95% confidence intervals (CIs) were conducted by Meta-DiSc software. Next, the summary receiver operating characteristic ROC (SROC) curve was drawn. Total 29 studies with high quality were included in this meta-analysis. The pooled result of CK-19 showed that sensitivity, specificity, PLR, NLR and DOR were 0.816 (95% CI: 0.799-0.832), 0.872 (95% CI: 0.855-0.888), 5.900 (95% CI: 5.193-6.703), 0.205 (95% CI: 0.185-0.228), respectively. For Galectin-3, the pooled sensitivity, specificity, PLR, NLR and DOR were 0.842 (95% CI: 0.825-0.858), 0.833 (95% CI: 0.814-0.851), 5.057 (95% CI: 4.494-5.690), 0.176 (95% CI: 0.154-0.200) and 33.312 (95% CI: 26.403-42.029). For HBME-1, the pooled sensitivity, specificity, PLR, NLR and DOR were 0.928 (95% CI: 0.913-0.941), 0.864 (95% CI: 0.847-0.880), 6.204 (95% CI: 5.498-7.002), 0.082 (95% CI: 0.067-0.102), 57.107 (95% CI: 43.421-75.107), respectively. The area under curve (AUC) value in SROC curve of CK-19, Galectin-3 and HBME-1 were 0.9134 (95% CI: 0.877-0.950), 0.8452 (95% CI: 0.809-0.882) and 0.9047 (95% CI: 0.868-0.941), respectively. Compared with CK-19 and Galectin-3, HBME-1 was a more accurate maker and might be used independently for PTC diagnosis. CK-19 and Galectin-3 might as second-line detection for PTC diagnosis.

Keywords: Papillary thyroid carcinoma, cytokeratin 19, Galectin-3, hector battiforamesothelial antigen-1, diagnostic accuracy

Introduction

Thyroid cancer is one of most common malignant disease, and papillary thyroid carcinoma (PTC) comprises more than half of thyroid cancer [1]. PTC is the seventh most common cancer in women among the world, and the incidence rate of PTC has increased sharply [2]. Several risk factors have been demonstrated to be related with the increased PTC incidence, such as radiation, thyroid-stimulating hormone levels and iodine intake, body weight, insulin resistance, diet, environmental pollutants, as well as family inheritance [3, 4]. Although the survival rate for PTC is up 90% [5], early diagnosis and treatment of PTC are still important for better prognosis and higher survival rates.

The growth of thyroid nodule is a prominently clinical feature of PTC, and the fine-needle aspiration biopsy (FNAB) is a frequently used method for diagnosing PTC [6]. However, papillary cancers misdiagnosed as benign nodules in the early stage of PTC happens occasionally by using FNAB, and FNAB has limitations for decision making in cellular atypia and suspicious cytology of PTC [7, 8]. In the recent years, the application of molecular diagnosis offers an accurate tool for early diagnosis and heterogeneous group of lesions in PTC [9]. Cytokeratin

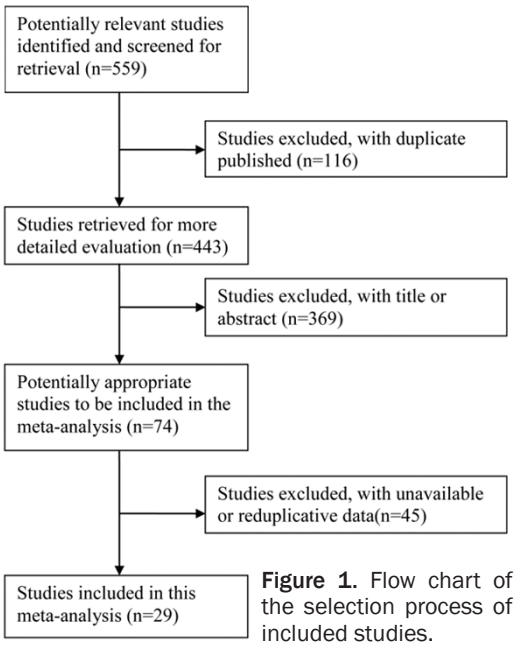

Figure 1. Flow chart of the selection process of included studies.

(CK)-19 is a member of the keratin family and is strongly up-regulated in PTC than in non-thyroid tissue, the positive rate of CK-19 in PTC is 83.3% which may function as an crucial role in the diagnosis of PTC [10]. Galectin-3 is a carbohydrate binding protein of the galectin family with an antiapoptotic activity in PTC cells [11], also is a well-recognized indictor for improving cytological diagnosis of PTC [12]. battifora mesothelial antigen-1 (HBME-1) is a kind of antigen composition of mesothelial cells, and is routinely considered as a useful marker for mesothelioma cells [13]. So far, HBME-1 has been reported to be overexpressed in PTC and may act as a potential marker in PTC diagnosis [14].

Despite most studies have been indicated that CK-19, Galectin-3 and HBME-1 may provide a useful diagnosis for PTC, the roles of those molecule markers are still controversial, and the diagnostic accuracy of CK-19, Galectin-3 and HBME-1 for PTC are unclear. Thus, in this meta-analysis, we analyzed the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and summary receiver operating characteristic ROC (SROC) curve of CK-19, Galectin-3 and HBME-1, and aimed to comprehensively evaluate their accuracy for the PTC diagnosis.

Materials and methods

Data resources

Eligible studies published in the databases such as Embase (http://www.embase.com) and Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) up to November, 2016 were searched. The key searching terms were "papillary thyroid carcinoma" OR "thyroid papillary carcinoma" OR "papillary carcinoma of the thyroid" OR "papillary thyroid cancer" OR "papillary adenocarcinoma of thyroid gla" AND Galectin-3 ("Galectin-3" OR "Galectin 3") AND HBME-1 ("Hector Battifora mesothelial-1" OR "Hector Battiforamesothelial cell-1") AND CK-19 (Cytokeratin-19). Clinical studies published only in English language were considered.

Inclusion and exclusion criteria

The inclusion criteria were strictly established as follows: (1) The studies were those that evaluated the diagnostic test of CK-19, Galectin-3 or HBME-1 for patients with PTC; (2) The number of binned true positive (TP), false positive (FP), false negative (FN) and true negative (TN) were provided or might be obtained or calculated from other known indicators; (3) In the articles, - or less than 5% were used to indicate negative expression, while +, ++, +++, and ++++ or more than 5% were used for positive expression.

The exclusion criteria for the study were: (1) The study was a review, abstractor report or not a case-control study; (2) The study had the different emphasis in spite of the same research field.

Data extraction and quality assessment

Two investigators independently extracted the data from the included studies, including first author's name, publication time, research region and time, case numbers of TP, FP, TN and FN on using CK-19, Galectin-3 and HBME-1 for diagnosing PTC. In addition, a quality assessment was performed by using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [15]. The tool contains a series of 14 questions which may be scored with Yes (the information match this item), No (the information does not meet this item) and Unclear (the item is not reported in the study). If there existed divergences during the process of data

Table 1. Characteristics of the included studies

First author	Year	Country	Total number	Galectin-3				HBME-1				CK-19			
				PTC		Non-PTC		PTC		Non-PTC		PTC		Non-PTC	
				+	-	+	-	+	-	+	-	+	-	+	-
Abd-El Raouf SM	2014	Egypt	50	26	2	2	20	25	3	5	17	NA	NA	NA	NA
Atik E	2014	Turkey	45	29	7	3	5	31	4	3	5	33	4	2	5
Casey MB	2003	USA	60	30	0	12	18	30	0	1	29	30	0	12	18
Ceyran AB	2015	Turkey	181	66	35	5	75	57	44	17	63	85	16	51	29
Cheung CC	2001	Canada	213	NA	NA	NA	NA	76	9	0	60	91	9	15	60
Chui MH	2013	Canada	240	45	58	0	137	83	20	4	133	82	21	35	102
Chung SY	2013	South Korea	258	172	24	6	56	169	27	10	52	166	30	10	52
Cui W	2012	China	150	68	4	18	54	68	4	8	64	68	4	24	48
Davidov T	2014	USA	79	21	5	39	14	NA	NA	NA	NA	NA	NA	NA	NA
Dencic TI	2012	USA	318	NA	NA	NA	NA	NA	NA	NA	NA	119	46	3	150
Hong Z	2010	China	32	19	1	4	8	18	2	0	12	20	0	2	10
Ma H	2014	China	77	41	2	7	27	37	6	2	32	43	0	25	9
Ohta M	2015	Japan	49	NA	NA	NA	NA	29	2	2	16	NA	NA	NA	NA
Prasad ML	2005	USA	169	63	4	17	85	57	10	1	101	48	19	13	89
Sapio MR	2008	Italy	47	17	7	6	17	NA	NA	NA	NA	NA	NA	NA	NA
Schmitt AC	2010	USA	52	NA	NA	NA	NA	25	7	1	19	24	8	1	19
Scognamiglio T	2016	USA	127	73	5	9	40	68	10	2	47	75	3	7	42
Song Q	2011	China	592	427	14	77	74	NA	NA	NA	NA	425	16	39	112
Torregrossa L	2010	Italy	100	28	22	0	50	47	3	3	47	NA	NA	NA	NA
Wu G	2013	China	995	271	60	51	613	262	69	14	650	307	24	72	592
Htwe TT	2010	Malaysia	142	107	1	31	3	NA	NA	NA	NA	NA	NA	NA	NA
Nasr MR	2006	USA	108	NA	NA	NA	NA	49	2	4	53	51	0	39	18
Selemetjev SA	2015	Serbia	99	55	14	12	18	NA	NA	NA	NA	NA	NA	NA	NA
Gong L	2012	China	50	37	1	2	10	38	0	1	11	NA	NA	NA	NA
Lavra L	2011	Italy	29	22	2	2	3	NA	NA	NA	NA	NA	NA	NA	NA
Barut F	2010	Turkey	85	52	3	10	20	54	1	13	17	55	0	15	15
Trimboli P	2015	Italy	19	2	2	1	14	4	0	1	14	4	0	5	10
Cameron BR	2003	Canada	68	NA	NA	NA	NA	NA	NA	NA	NA	32	2	21	13
Mai KT	2001	Canada	21	NA	NA	NA	NA	7	5	4	5	9	3	7	2

Notes: +: positive expression; -: negative expression; PTC: papillary thyroid carcinoma; CK-19: cytokeratin 19; HBME-1: hector battiforamesothelial antigen-1.

abstraction and quality evaluation, disagreements were resolved by discussion with a third assessor to reach a final agreement.

Statistical analysis

We used the Meta-DiSc software (version 1.4) to conduct the diagnostic meta-analysis, and the sensitivity, specificity, PLR, NLR and DOR with their 95% confidence intervals (CIs) were used to measure the effect size. Besides, threshold effect was one of main causes for producing heterogeneity in the diagnostic test, and it was calculated by the spearman correlation coefficient (CC) between specificity and-logit sensitivity, and P<0.05 was considered as the cut-off for significance.

Additionally, SROC curve analysis was conducted to evaluate the overall diagnostic effect. Heterogeneity was examined by Q statistic and I^2 test based on chi-square test [16]. If there exist obviously heterogeneity between the studies (P<0.05 or $I^2 \geq 50\%$), the DerSimonian-Laird random effects model was utilized to calculate the pooled effect size. Otherwise, the Mantel-Haenszel fixed effects model was used to calculate the pooled effect size with no significant

Table 2. Quality assessment of the included studies

Studies	Year	QUADAS list item													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Abd-El Raouf SM	2014	+	+	-	-	+	-	+	+	+	+	0	+	-	+
Atik E	2014	+	0	+	0	+	+	-	+	-	+	+	+	+	+
Casey MB	2003	+	+	-	+	+	+	+	+	0	+	+	+	+	+
Ceyran AB	2015	0	+	+	+	-	+	0	+	+	0	+	0	+	0
Cheung CC	2001	+	-	+	+	-	+	-	+	+	-	+	-	-	+
Chui MH	2013	0	+	+	-	+	+	+	-	+	+	+	+	+	+
Chung SY	2013	+	+	+	+	+	+	-	+	-	+	+	-	+	+
Cui W	2012	+	0	+	+	0	+	+	+	+	+	-	+	+	+
Davidov T	2014	+	0	-	+	0	+	+	+	-	+	+	+	-	+
Dencic TI	2012	0	+	0	+	+	+	-	+	+	-	+	0	+	+
Hong Z	2010	0	-	+	0	+	0	+	0	-	0	-	-	0	0
Ma H	2014	+	+	+	+	+	0	+	+	+	+	+	0	+	-
Ohta M	2015	0	+	0	0	-	+	0	+	+	+	-	+	-	+
Prasad ML	2005	+	+	0	0	+	+	+	-	+	0	+	+	+	0
Sapio MR	2008	+	+	+	+	-	+	+	-	+	-	-	+	+	+
Schmitt AC	2010	0	+	+	+	-	+	0	+	+	0	+	0	+	0
Scognamiglio T	2016	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Song Q	2011	0	+	-	+	+	-	+	-	+	+	+	+	+	+
Torregrossa L	2010	+	+	+	-	+	+	+	+	+	-	-	+	-	+
Wu G	2013	+	0	+	+	0	+	+	+	+	+	+	+	+	+
Htwe TT	2010	+	-	0	+	0	+	+	-	+	+	+	+	-	+
Nasr MR	2006	0	+	0	+	+	+	+	0	0	0	+	0	0	0
Selemetjev SA	2015	0	-	+	+	+	-	+	+	+	+	0	-	0	+
Gong L	2012	+	+	+	+	+	0	+	+	+	0	+	0	+	0
Lavra L	2011	0	+	+	+	+	+	+	-	+	+	+	+	+	+
Barut F	2010	+	+	+	-	+	+	-	+	+	+	-	+	+	+
Trimboli P	2015	+	0	+	+	-	+	+	+	+	+	0	+	+	+
Cameron BR	2003	+	-	0	+	-	+	+	+	0	+	-	+	0	+
Mai KT	2001	+	0	+	+	0	+	+	+	+	+	+	+	+	+

Notes: QUADAS: Quality Assessment of Diagnostic Accuracy Studies. +: YES; -: NO; 0: Not clear. 1. Was the spectrum of patients representative of the patients who will receive the test in practice? 2. Were selection criteria clearly described? 3. Is the reference standard likely to correctly classify the target condition? 4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? 5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis? 6. Did patients receive the same reference standard regardless of the index test result? 7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? 8. Was the execution of the index test described in sufficient detail to permit replication of the test? 9. Was the execution of the reference standard described in sufficient detail to permit its replication? 10. Were the index test results interpreted without knowledge of the results of the reference standard? 11. Were the reference standard results interpreted without knowledge of the results of the index test? 12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? 13. Were uninterpretable/intermediate test results reported? 14. Were withdrawals from the study explained?

heterogeneity between the studies (P>0.05 or I^2<50%) [17].

Results

Eligible studies and their characteristics

Based on the searching strategies, total 559 studies (PubMed: 176; Embase: 383) were searching after the preliminary selection from both PubMed and Embase databases. Then, 116 repetitive articles were found and eliminated, and 369 irrelevant studies were removed via reading the titles and abstracts. Following further selection, another 45 studies without concrete data or with the repeated study sites were excluded. Finally, a total of 29 studies conformed to all the inclusion criteria were obtained [18-46] (**Figure 1**).

As shown in **Table 1**, the published data of the included articles were from 2001 to 2016, and the studies were from different countries such as USA, Japan, Turkey, Canada, South Korea, Italy, Egypt, Malaysia and China. Moreover, a total of 4455 participants were included in this meta-analysis.

Quality assessment of the selected studies

The QUADAS scoring system was performed to assess the quality of the 29 selected studies. As shown in **Table 2**, a majority of studies were conformed to larger than nine of the 14 described criteria, showing that the quality of studies were relatively high. Summary scores were not calculated, since the interpretation can be problematic and potentially misleading.

Quantitative data pooling

In this meta-analysis, based on the Meta-DiSc software, the pooled effect size of sensitivity, specificity, PLR, NLR and DOR of diagnostic indicators of CK-19,

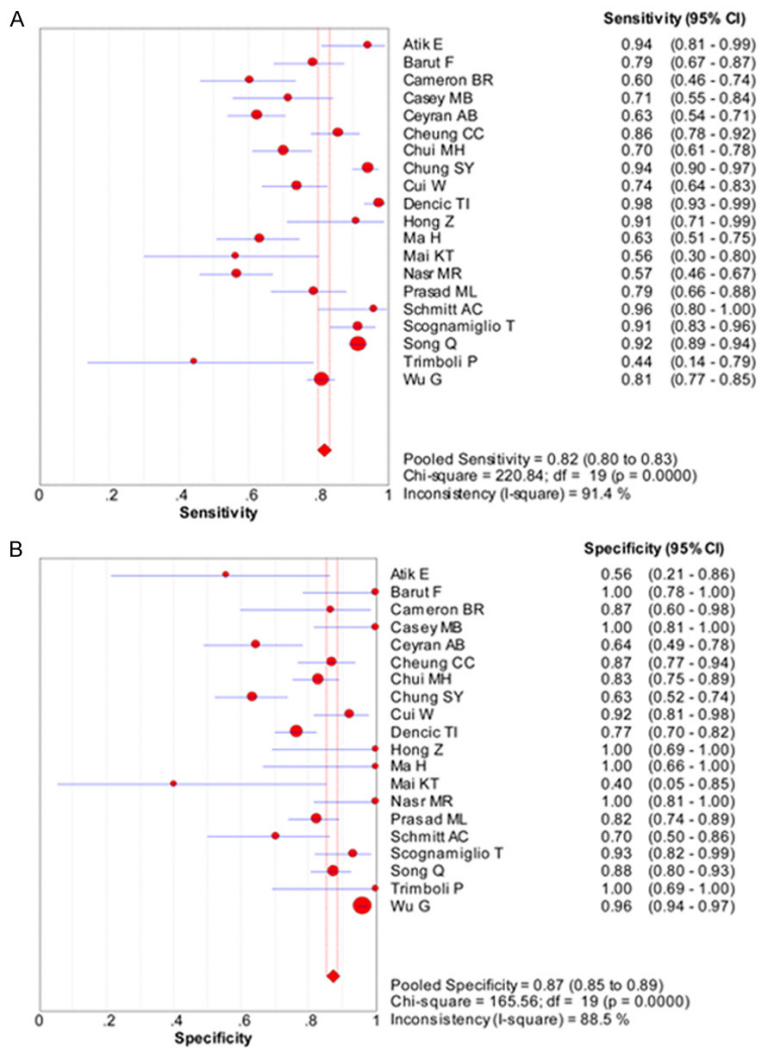

Figure 2. Diagnostic analysis of papillary thyroid carcinoma using cytokeratin 19. A: Sensitivity; B: Specificity.

Galectin-3 and HBME-1 were conducted to synthetically evaluate the diagnosis effect for PCT.

CK-19

A total of 20 included studies were related to the diagnosis value of CK-19 for PCT [19-27, 31, 33-35, 37, 39, 40, 42, 44-46], and remarkably heterogeneity were detected between the studies (sensitivity: P<0.01, I^2=91.4%; specificity: P<0.01, I^2=88.5%; PLR: P<0.01, I^2=87.7%; NLR: P<0.01, I^2=90.7%; DOR: P<0.01, I^2=-83.5%). Thus, the DerSimonian-Laird random effects model was chosen to combine the pooled effect value of sensitivity, specificity, PLR, NLR and DOR. As a result, the pooled sensitivity was 0.816 (95% CI: 0.799-0.832, **Figure 2A**), the overall specificity was 0.872 (95% CI: 0.855-0.888, **Figure 2B**), the pooled PLR was 5.900 (95% CI: 5.193-6.703), NLR was 0.205 (95% CI: 0.185-0.228) and DOR was 30.024 (95% CI: 25.861-39.655), respectively.

The SROC method estimated the diagnostic reporting pairs of specificity and sensitivity. The outcome of the threshold effect indicated that no significant difference (P=0.8591) was detected between the CC value of the logit sensitivity and specificity and "0", suggesting that the SROC curve was symmetrical. Then, the Mantel-Haenszel fixed effects model was used for the statistical analysis. As shown in **Figure 3**, the area under curve (AUC) was 0.9134 (95% CI: 0.877-0.950) and the Q index was 0.8459 (95% CI: 0.805-0.887).

Galectin-3

Among the 29 included studies, 22 studies investigated the diagnosis value of Galectin-3 for PCT [18-20, 22, 23, 25-30, 32, 33, 37, 38, 40-46]. A DerSimonian-Laird random effects model was selected to pool the effect value of sensitivity, specificity, PLR, NLR and DOR between above studies due to the significant heterogeneity (sensitivity: P<0.01, I^2=86.8%; specificity: P<0.01, I^2=85.5%; PLR: P<0.01, I^2=85.5%; NLR: P<0.01, I^2=84.4%; DOR: P<0.01, I^2=70.7%). The pooled value of sensitivity was 0.842 (95% CI: 0.825-0.858, **Figure 4A**), specificity was 0.833 (95% CI: 0.814-0.851, **Figure 4B**), PLR was 5.057 (95% CI: 4.494-5.690), NLR was 0.176 (95% CI: 0.154-0.200) and DOR was 33.312 (95% CI: 26.403-42.029), respectively.

In addition, there was no statistical significance for the threshold effect (P=0.7606), and SROC curve showed symmetrical. Therefore, a Man-

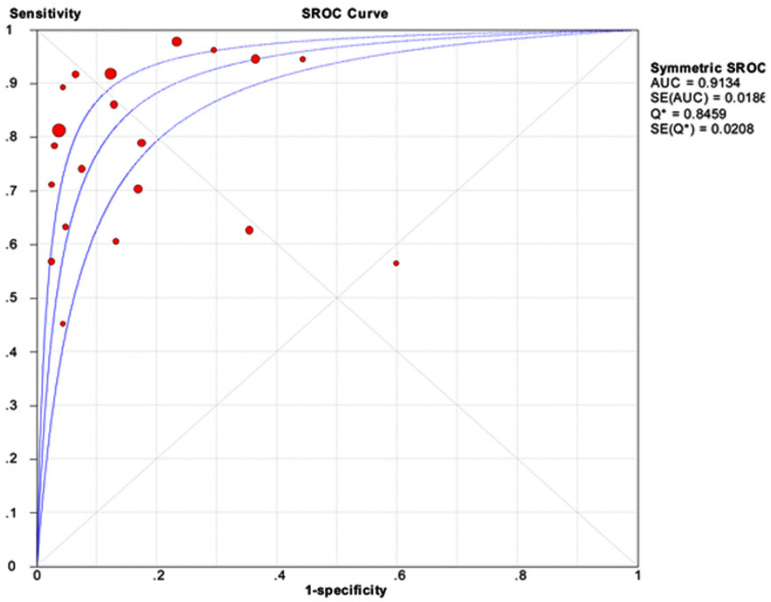

Figure 3. SROC curve for papillary thyroid carcinoma using cytokeratin 19. SROC: Summary receiver operating characteristic; AUC: Area under curve.

tel-Haenszel fixed effects model was used for the statistical analysis. The pooled AUC was 0.9128 (95% CI: 0.880-0.946) and the Q index was 0.8452 (95% CI: 0.809-0.882, **Figure 5**).

HBME-1

Twenty-one studies were involved in assessing the diagnostic value of HBME-1 for RTC [18-20, 22-27, 29, 33-37, 39, 40, 43-46], and the obviously heterogeneity were detected between those studies for each effect size including sensitivity, specificity, PLR, NLR and DOR. Thus, we selected the DerSimonian-Laird random effects model to calculate those pooled effect size. The result showed that pooled sensitivity was 0.928 (95% CI: 0.913-0.941; P<0.01, I^2= 71.1%; **Figure 6A**), specificity was 0.864 (95% CI: 0.847-0.880; P<0.01, I^2=84.7%; **Figure 6B**), PLR was 6.204 (95% CI: 5.498-7.002; P<0.01, I^2=88.5%)), NLR was 0.082 (95% CI: 0.067-0.102; P<0.01, I^2=79.7%) and DOR was 57.107 (95% CI: 43.421-75.107; P<0.01, I^2=82.8%), respectively. Additionally, through performing the threshold effect test between the studies, no striking significance were examined (P=0.7682), and the Mantel-Haenszel fixed effects model was chosen for the statistical analysis. As a result, the summary AUC was 0.9601 (95% CI: 0.935-0.985) and the Q index was 0.9047 (95% CI: 0.868-0.941, **Figure 7**).

Discussion

In the present study, total 29 studies were used to evaluate the diagnostic accuracy of CK-19, Galectin-3 and HBME-1 for PTC. According to the criterion, PLR>10 or NLR<0.1 of the molecular marker can be considered as an independent diagnostic indicator, and DOR>25 is considered as moderately accurate and >100 is considered as highly accurate [47]. Our results showed that the moderate PLR (5.900), moderate NLR (0.205) and moderate DOR (30.024) of CK-19, and moderate PLR (5.057), moderate NLR (0.176) and moderate DOR (33.312) of Galectin-3 did not meet the criterion to be as independent diagnostic indicators for PTC. However, CK-19 and Galectin-3 might act as second-line detection due to their value of sensitivity, specificity, AUC and Q index of CK-19 and Galectin-3 were both high with more than 0.810, suggesting a high accuracy of CK-19 and Galectin-3 in diagnosis of PTC. Notably, HBME-1 might act as independent diagnostic maker with the NLR value (0.082) was less than 0.1. Additionally, the pooled value of PLR (6.204), sensitivity (0.928), specificity (0.864), DOR (57.107), AUC (0.9601) and Q index (0.9047) of HBME-1 were the maximum among those three makers.

Although our results showed that CK-19 and Galectin-3 could not be independently used to detect PTC from benign nodes, they also had certain diagnostic value for PLR. Reportedly, CK-19 is positive expression in papillary carcinomas, but not high expression or negative expression in papillary hyperplasia [48]. In addition, it has been proved that CK-19 can distinguish the follicular variant of papillary carcinoma from other follicular thyroid tumor [49]. Htwe *et al* have provided that an obviously overexpressed level of Galectin-3 is detected in PTC cells versus the neighboring normal matrix

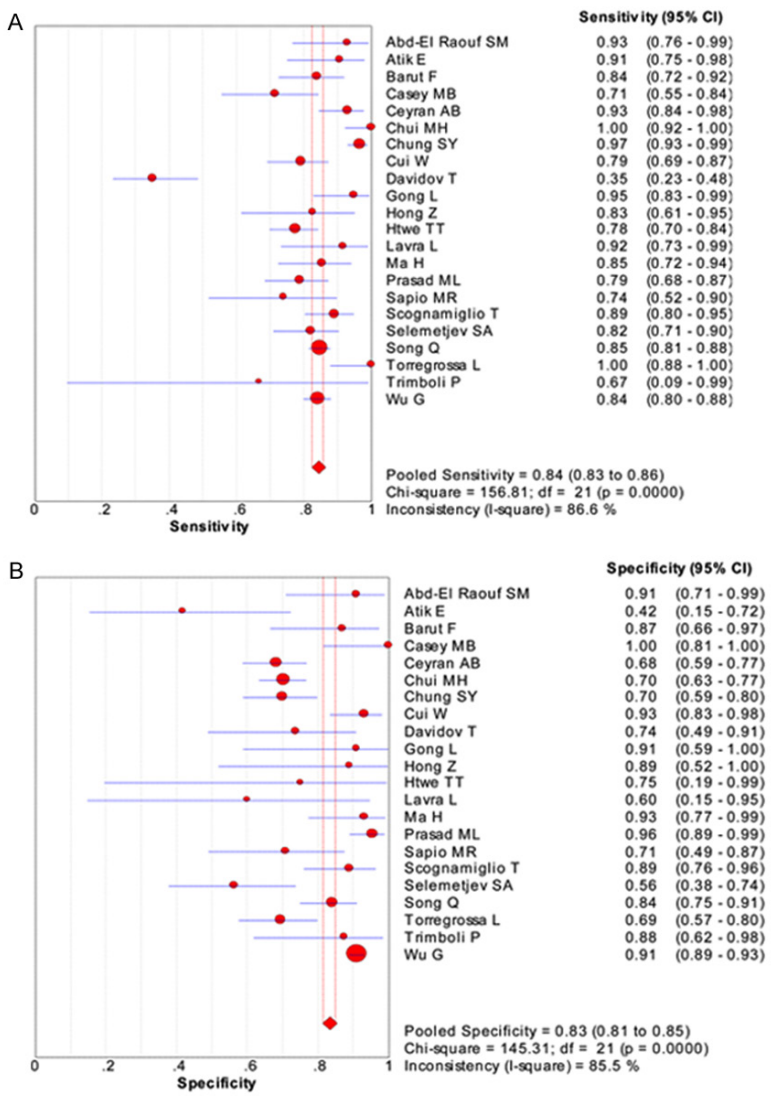

Figure 4. Diagnostic analysis of papillary thyroid carcinoma using Galectin-3. A: Sensitivity; B: Specificity.

cells, suggesting that Galectin-3 is involved with the tumor progression and metastasis [30]. Moreover, serum Galectin 3 is high expression in the early stage of PTC and may be considered as an early circulating tumor marker for PTC, but failed to discriminate different PTC stages [50]. Similarly, a meta-analysis by Tang has indicated that the positive expression rate of Galectin-3 in PTC is 64.86% (275/424), and Galectin-3 has a small amount of expression in other types of thyroid lesions (58/424, 13.68%) [51]. Furthermore, CK-19 and Galectin-3 might improve the diagnose accuracy for PTC by combing other markers [52].

Additionally, our result showed that HBME-1 could be independently used for diagnosing PTC with high sensitivity, AUC and low NLR. In addition, HBME-1 immunostaining is beneficial for differentiating PTC tissues from benign thyroid tissues [53]. Similarly, Dencic et al have observed that diffuse, Tall cell and solid PTC variants are respectively presented 100%, 66.67% and 56.52% as HBME-1 positive immunoreaction, and they recommend using HBME-1 to enhance the diagnostic rate of most PTC variants [54]. Besides, it has been reported that HBME-1 has high sensitivity (94.5%) and moderate specificity (77.08%) for diagnosing PTC [14]. Interesting, the sensitivity, specificity and positive predictive value arerespectively 100%, 92.9% and 0.9 by only using HBME-1 as single discriminator between PTC and goitrous nodules, and uniting HBME-1 and CK-19 is up to 100%, 100% and 1 [55].

Among CK-19, Galectin-3 and HBME-1, HBME-1 was the best choice. It was consistent with another study which has evaluated the thyroid tumor markers of CK-19, Galectin-3 and HBME-1, they have indicated HBME-1 is most accurate to act as a single maker for PTC, but they also have proposed that Galectin-3 may be served as a single maker for PTC [56]. The sample size might be the cause for this difference, and our sample size was larger. In addition, there were several limitations in the present study. At first, there were significant heterogeneities in each effect size which might be caused by different sampling conditions and detection methods. However, we failed to perform subgroup analyses by these factors, since the data were insufficient. Second, the popula-

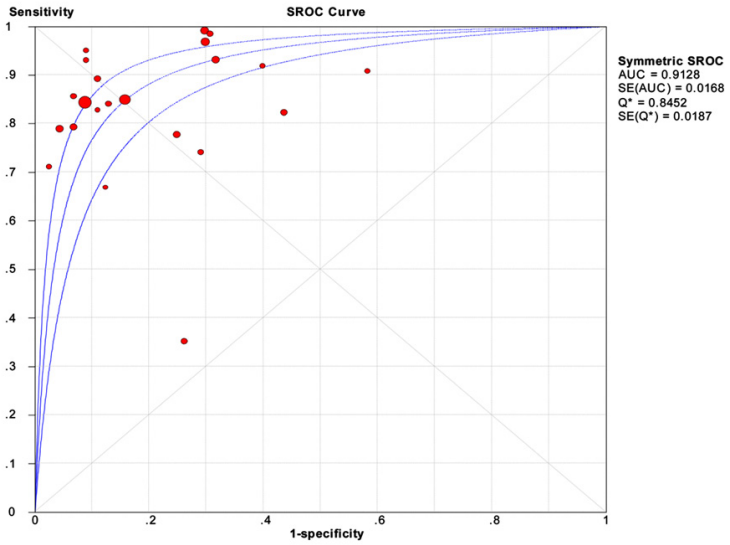

Figure 5. SROC curve for papillary thyroid carcinoma using Galectin-3. SROC: Summary receiver operating characteristic; AUC: Area under curve.

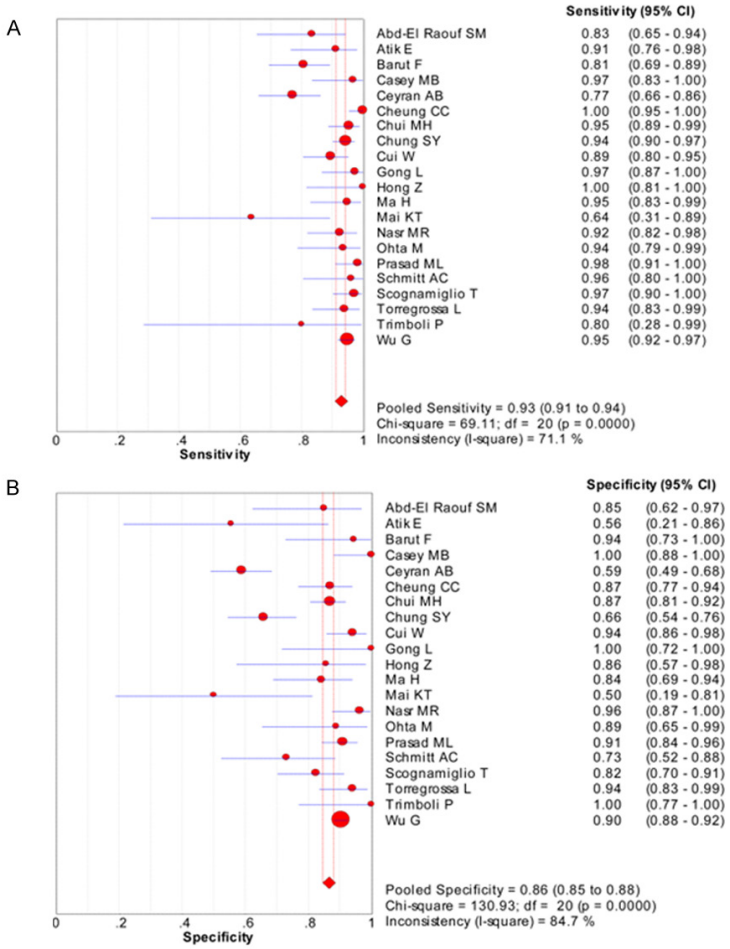

Figure 6. Diagnostic analysis of papillary thyroid carcinoma using hector battiforamesothelial antigen-1 (HBME-1). A: Sensitivity; B: Specificity.

tions of the included studies were not unified, and they were from different countries including China, Egypt, South Korea, Turkey, Canada, American, Malay-sia, Japan, Italy and Serbia, which might lead to bias. Third, the sample size were still needed to add to attenuate the statistical difference and improve the reliability of the results. Therefore, more studies involving large samples and detailed demographic information may be needed to provide potent evidence. However, our study was still of great value, since our included samples were at most in the same type of research to systematically evaluate the diagnostic accuracy of CK-19, Galectin-3 and HBME-1.

HBME-1 might be used as single discriminator for PCT diagnosis, and CK-19 and Galectin-3 might also have important diagnostic value for PCT.

Disclosure of conflict of interest

None.

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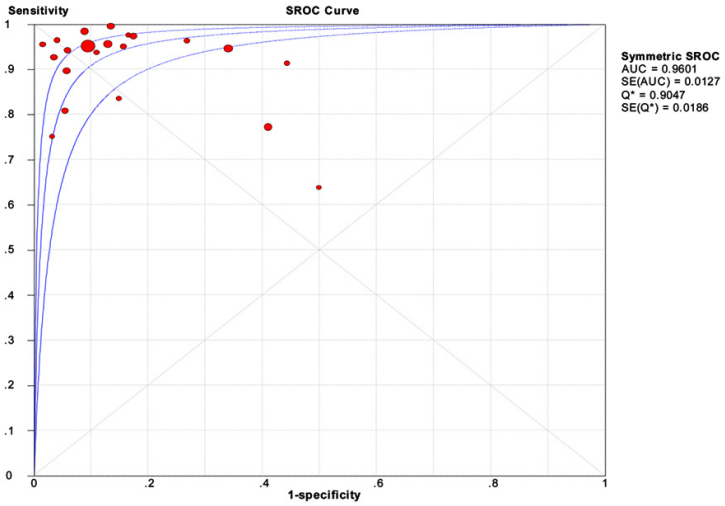

Figure 7. SROC curve for papillary thyroid carcinoma using hector battiforamesothelial antigen-1 (HBME-1). SROC: Summary receiver operating characteristic; AUC: Area under curve.

quent in anaplastic thyroid carcinoma compared to papillary thyroid carcinoma and is related to adverse clinical outcome. J Clin Pathol 2013; 67: 125-133.

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