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Review Article

Serum Tg level used as predictor of radioiodine remnant ablation success in patients with differentiated thyroid cancer: a diagnosis meta-analysis

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Abstract: Thyroidectomy followed by radioiodine remnant ablation (RRA) treatment is the standard initial treatment for most patients with differentiated thyroid carcinoma (DTC). Thyroglobulin (Tg) has been widely practiced to detect recurrence of DTC after surgery. We try to evaluate the predictive of Tg for RRA treatment success. Databases (Web of Science, PubMed, EMBASE, OVID, Elsevier Science Direct, and ProQuest) were searched to get the related articles. Basic information of research, clinical information, laboratory evaluation and diagnosis analysis information were extracted from recruited studies, and analyzed by diagnostic meta-analysis. Deeks' funnel plot asymmetry analysis was done to identify the publication bias. A total of 2716 DTC patients were recruited in these 10 retrospective studies. The pooled estimates of Tg level in the predicting of success of ablation were divided into three parts based on the cut-off value. The Diagnostic Odds Ratio and AUROC values of Tg were 9.213 [6.704, 12.662] and 0.82 [0.79, 0.85] (cut-off value < 10 ng/ml), 12.362 [8.253, 18.516] and 0.83 [0.80, 0.86] (cut-off value > 10 ng/ml), 9.903 [7.527, 13.029] and 0.82 [0.79, 0.85] (given best cut-off value), respectively. Compared with the fixed probability (20%) in preliminary experiments, the positive likelihood ratio (PLR) increased to about 40%, and the negative likelihood ratio (NLR) reduced to about 6%. No publication bias was found by Deeks' test. In conclusion, Tg levels before ablation can be used as a moderate predictor for radioiodine remnant ablation success.

Keywords: Differentiated thyroid carcinoma (DTC), thyroglobulin (Tg), radioiodine remnant ablation (RRA), diagnostic meta-analysis

Introduction

As the most common malignancy of the endocrine system, thyroid cancer owed about 2.1% of the diagnosed cancer worldwide [1]. According to its origin, thyroid cancer can be further subdivided into differentiated thyroid cancer (DTC), medullary thyroid cancer and anaplastic thyroid cancer [2, 3]. DTC is the most common form of thyroid cancer, accounts for over 90% of all thyroid cancers [4, 5]. It includes papillary (80%) and follicular (15%) subtypes, as well as a small proportion of mixed tumors [6]. The tri-combination therapy of surgery, radioactive iodine, and thyroxine replacement treatment is widely used for patients with DTC [7-10]. Radioiodine remnant ablation (RRA) treatment can ablate remaining thyroid tissue after surgery, eliminate any suspected micrometastases, or decrease the recurrence of DTC [11, 12]. However, the variables related with successful RRA are not well defined.

Thyroglobulin (Tg) is an iodide glycoprotein comprising two 330 kDa protein chains [13, 14]. Generally, Tg is only synthesized in follicular epithelial cells, stored and utilized entirely within thyroid gland, minuscule amounts of Tg can be released into blood circulation [15, 16]. Barely any Tg can be detected after total or subtotal thyroidectomy, which allows Tg as a biomarker when thyroid cell exists because of persistent DTC, distant metastasis, or recurrence of DTC [7, 17]. Studies [17-23] indicated that the success rate of RRA was closely related with Tg level, and a high Tg level could be a prognostic marker for predicting the persistence, recurrence, or metastasis of a tumor.

Table 1. The research and clinical information of the included studies

Study	Country	Study type	Research period	Sample number	Cancer type	Treatment	Successful ablation rate
Marin Prpic (2017)	Croatia	Retrospective	2005-2014	740	DTC	After primary surgical treatment, all patients received adjuvant ^{131}I therapy	81.22%
Hyukjin Yoon (2015)	Korea	Retrospective	2011-2012	143	DTC	First prepared radioiodine therapy by the thyroid hormone withdrawal	63.64%
Seunggyun Ha (2015)	Korea	Retrospective	2006-2015	780	DTC	Underwent total thyroidectomy and treated with 1.1 GBq of radioiodine for remnant thyroid ablation	47.09%
Nosheen Fatima (2014)	Pakistan	Retrospective	2012-2014	64	DTC	After primary surgical treatment, all patients received adjuvant ^{131}I therapy	57.81%
Syed Zubair Hussain (2014)	Pakistan	Retrospective	2003-2013	75	DTC	Underwent total thyroidectomy and treated radioiodine for remnant thyroid ablation	60.00%
Ilhan Lim (2012)	Korea	Retrospective	2001-2004	173	DTC	Total thyroidectomy followed by ^{131}I ablation therapy	56.07%
Daniel B. Kendler (2012)	Brazil	Retrospective	1998-2007	96	DTC	First administration of ^{131}I after surgical resection	54.44%
Michael Tamilia (2011)	Cananda	Prospectively	1998-2007	157	PTC	Levothyroxine therapy postoperatively for approximately 4 weeks and then switched to liothyronine for 3 weeks	87.90%
Hyo Jin Lee (2007)	Korea	Retrospective	2001-2004	81	DTC	Total thyroidectomy followed by ^{131}I ablation therapy	82.72%
Marie-Odile Bernier (2005)	France	Retrospective	1995-2002	407	DTC	Radioiodine therapy after thyroidectomy	87.47%

DTC: Differentiated thyroid cancer.

In this article, we tried to figure out the value of Tg in prediction of radioiodine remnant ablation successful rate and provide a reference on treatment of DTC through diagnostic meta-analysis.

Methods

Search strategy

Both medical subject headings (MeSH) search and text word search were used in article retrieval. Keywords including ("thyroid neoplasms" OR "thyroid cancer" OR "thyroid carcinoma" OR "carcinoma of thyroid"), "ablation", "thyroglobulin", (success OR failure OR successful), and (predict OR prediction OR sensitive OR "area under the curve, AUC" OR Specificity) were searched in PubMed, Web of Science, and Embase data base. Secondary literature search was added to improve the call rate. All researches were completed in January 5st 2017.

Titles, abstracts and full texts of the searched articles were screened by two independent researchers. The third person would join the discussion if there was a disagreement. The studies were strictly selected according to the pre-set inclusion and exclusion criteria.

Inclusion criteria: (1) Thyroid cancer related articles written in English; (2) Tg level was detected before radioiodine therapy; (3) Exact success rate of radioactive iodine and cut-off value; (4) The success of radioactive iodine therapy was clearly defined; (5) The recent published data or the most detailed data was included when there is duplicate publication.

Exclusion criteria: (1) Reviews, case reports, comments, guides or letters; (2) Researches focused on cell experiments, animal experiments or simulations experiments; (3) Unable to extract exact data; (4) Tg level was detective during or after radioiodine therapy; (5) No golden standard of radiation-point ablation success.

Data abstraction

Two researchers extracted the data and discussed with the third person to solve the dis-

Table 2. The laboratory evaluation and diagnosis analysis information of the included studies

Study	Detection target	Detection time	Detection method	Analytical sensitivity	Successful ablation	Cut-off Value
Marin Prpic (2017)	Serum Tg levels	Before ablation	-	-	Absence of remnant thyroid tissue (no visible accumulation of I-131) in the thyroid bed and cervical region on WBS	N1a 2.4 ng/ml N1b 14.9 ng/ml
Hyukjin Yoon (2015)	Serum Tg levels	Before ablation	-	-	Negative FuWBS, stimulated serum Tg < 2 ng/ml and no pathologic evidence of residual tumor	1.8 ng/ml
Seunggyun Ha (2015)	Serum Tg levels	Before ablation	Immunoradiometric assay (Cisbio Bioassays, Codolet, France)	-	An absence of visible radioiodine uptake on a subsequent scan or undetectable serum Tg	1 ng/ml and 10 ng/ml
Nosheen Fatima (2014)	Serum Tg levels	Before ablation	Chemiluminescent assays	0.2 ng/mL	STg < 2 ng/ml with negative anti-Tg-ab and no evidence of tumor on DWBIS and neck ultrasound 7-12 months after RRA	14.5 ng/ml
Syed Zubair Hussain (2014)	Serum Tg levels	Before ablation	Chemiluminescent assays	0.2 ng/mL	STg < 2 ng/mL with negative Anti-Tg antibodies, no evidence of tumor on diagnostic WBIS as well as on neck ultrasound 6-12 months afer RRA	18 ng/ml
Ilhan Lim (2012)	Serum Tg levels	Before ablation	Immunoradiometric assay (Tg-s IRMA CT; Radim, Pomezia, Italy)	0.1 ng/mL	A negative WBS and undetectable thyroglobulin levels with TSH stimulation (Tg/1 ng/ml, TSH [30 IU/ml)	5 ng/ml
Daniel B. Kendler (2012)	Serum Tg levels	Before ablation	Chemiluminescence assays (IMMULITE 1000; Siemens, United Kingdom)	0.2 ng/mL	An undetectable level of Tg at 6 to 12 months after ablation therapy	18 ng/ml
Michael Tamilia (2011)	Serum Tg levels	Before ablation	-	-	Tg of less than 1 ng/ml	6 ng/ml
Hyo Jin Lee (2007)	Serum Tg levels	Before ablation	Immunoradiometric assay (BRAHMS Tg-pluS RIA; BRAHMS Aktienge- sellschaft, Hennigsdorf, Germany)	0.2 ng/mL	A negative WBS with a stimulated Tg after THW G2 ng/mL, 6 to 12 months after ablation	1, 2, 5, 10, 20 ng/ml
Marie-Odile Bernier (2005)	Serum Tg levels	Before ablation	Radioimmunoassay (Cis Bio International, France)	0.2 ng/mL	Tg level < 2 ng/ml	5 ng/ml

Table 3. Diagnosis results

Test	No. of study	Author	Year	Cut-off value (ng/ml)	TP	FN	FP	TN
Test 1	1	Hyo Jin Lee	2007	1	48	19	2	12
	2	Seunggyun Ha	2015	1	67	14	26	67
	3	Hyukjin Yoon	2015	1.8	70	21	22	30
	4	Hyo Jin Lee	2007	2	58	9	2	12
	5	Marin Prpic	2017	2.4	20	1	27	29
	6	Hyo Jin Lee	2007	5	58	9	5	9
	7	Ilhan Lim	2012	5	72	21	21	59
	8	Marie-Odile Bernier	2005	5	231	125	7	44
	9	Michael Tamilia	2011	6	116	22	9	10
Test 2	1	Michael Tamilia	2011	10	123	15	9	10
	2	Hyo Jin Lee	2007	10	62	5	8	6
	3	Seunggyun Ha	2015	10	72	9	29	64
	4	Nosheen Fatima	2014	14.5	25	12	3	24
	5	Marin Prpic	2017	14.9	38	3	3	10
	6	Daniel B. Kendler	2012	18	35	14	14	33
	7	Syed Zubair Hussain	2014	18	34	11	7	23
	8	Hyo Jin Lee	2007	20	63	4	9	5
Test 3	1	Daniel B. Kendler	2012	18	35	14	14	33
	2	Hyo Jin Lee	2007	10	62	5	8	6
	3	Hyukjin Yoon	2015	1.8	70	21	22	30
	4	Ilhan Lim	2012	5	72	21	21	59
	5	Marie-Odile Bernier	2005	5	231	125	7	44
	6	Marin Prpic	2017	2.4	20	1	27	29
	7	Marin Prpic	2017	14.9	38	3	3	10
	8	Michael Tamilia	2011	6	116	22	9	10
	9	Nosheen Fatima	2014	14.5	25	12	3	24
	10	Seunggyun Ha	2015	1	67	14	26	67
	11	Seunggyun Ha	2015	10	72	9	29	64
	12	Syed Zubair Hussain	2014	18	34	11	7	23

TP: the group of true positive; FN: the group of false negative; FP: the group of false positive; TN: the group of true negative.

agreement. **Tables 1** and **2** showed the basic information of research, clinical information, laboratory evaluation and diagnosis analysis information extracted from recruited studies. The extracted data include research information, clinical information, laboratory evaluation and diagnosis analysis results. The cut-off values and the numbers of people under or above the cut-off value were extracted separately (**Table 3**). When the dose of successful ablation under the cutoff value, people were classified into the group of true positive (TP) when they got successful ablation, otherwise, false positive (FP) was defined. When the dose of successful ablation under the cutoff value, people were classified into the group of true negative (TN) when they got successful ablation, otherwise, false negative (FN) was defined.

Statistics analysis

The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), diagnostic score, and area under the summary receiver operating curve (AUSROC) with the corresponding 95% confidence interval (CI) were obtained by a bivariate binomial mixed model. The sensitivity, specificity, DOR, and AUSROC were considered as the major outcomes in this study.

A Cochrane-*Q* test of heterogeneity was performed using inconsistency index, I^2, as a measure to illustrate the percentage of the total variability in effect estimates among trials that was caused by heterogeneity instead of chance. A value of I^2 more than 50% was defined as heterogeneity and the random model was chosen. Fixed model was used when I^2 value less than 50%. A two-sided *p* value < 0.05 indicated statistical significance.

Since the cut-off values were different among the included studies, diagnostic threshold effects were inspected. The summary receiver operating curve (SROC) was visually evaluated at first. A Spearman correlation analysis was used to assess the heterogeneity derived from diagnostic threshold effects. Deeks's funnel plot asymmetry analysis was performed to identify the publication bias. Fagan's Nomogram Analysis was done to analyze the pre-test and post-test probability, and the likelihood ratio of having the disease. Bivariate Box Plot was used to assess the distributional proper-

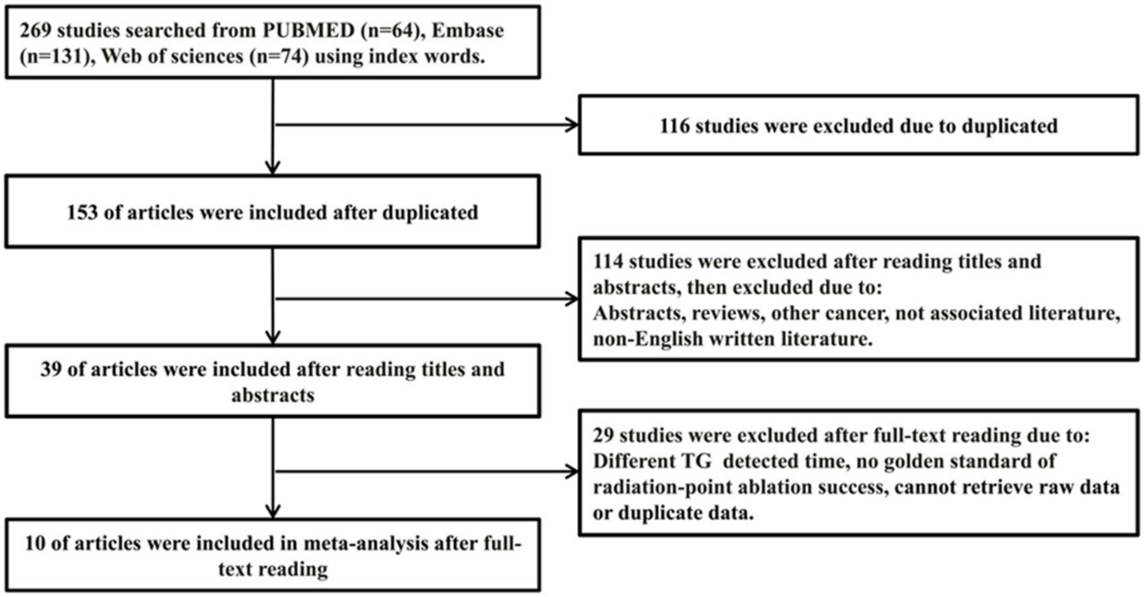

Figure 1. The process of study selection for the meta-analysis.

Table 4. Summary of the pooled estimates of Tg level in the Predicting of success of ablation

	Cut-off value < 10 ng/ml estimates (95% CI)	Cut-off value > 10 ng/ml estimates (95% CI)	Best cut-off value estimates (95% CI)
No. of study	9	8	9
Sensitivity	0.802 [0.744, 0.849]	0.859 [0.784, 0.911]	0.814 [0.754, 0.862]
Specificity	0.695 [0.604, 0.773]	0.671 [0.562, 0.764]	0.694 [0.619, 0.76]
Positive likelihood ratio	2.627 [2.064, 3.346]	2.606 [1.994, 3.406]	2.657 [2.191, 3.221]
Negative likelihood ratio	0.285 [0.231, 0.352]	0.211 [0.147, 0.302]	0.268 [0.213, 0.338]
Diagnostic score	2.221 [1.903, 2.539]	2.515 [2.111, 2.919]	2.293 [2.018, 2.567]
Diagnostic odds ratio	9.213 [6.704, 12.662]	12.362 [8.253, 18.516]	9.903 [7.527, 13.029]
NPV	0.70 [0.65, 0.74]	0.70 [0.66, 0.74]	0.70 [0.66, 0.74]
PPV	0.65 [0.61, 0.69]	0.66 [0.62, 0.70]	0.66 [0.62, 0.70]
ROC area, AUROC	0.82 [0.79-0.85]	0.83 [0.80-0.86]	0.82 [0.79-0.85]

NPV: negative p predictive value; PPV: positive predictive value; ROC: receiver operating curve; AUROC: area under the summary receiver operating curve.

ties of sensitivity against specificity and investigate possible outliers. Goodness-of-fit, bivariate normality analysis, influence analysis, and outlier detection were run to evaluate sensitivity of meta-analysis. All data synthesis and most statistical analysis were undertaken by STATA software version 12.0 (College Station, TX, USA).

Results

Literature research

As shown in **Figure 1**, a total of 269 articles were collected after researching with the keywords from database of PubMed (n = 64), Embase (n = 131), Web of sciences (n = 74). 116 articles were excluded due to duplicated after pre-screen. Then titles and abstracts were screened, 114 articles were excluded due to reviews, other cancers, not associated or non-English written. The remained articles were further full-text screened and 29 articles were excluded because of different Tg detected time, no golden standard of radiation-point ablation success, cannot retrieve raw data or duplicate data. Finally, 10 articles [20, 21, 24-31] were included in this meta-analysis. A total of 2716 differentiated thyroid carcinoma (DTC) patients were recruited in these 10 retrospective studies. Characteristics of the included studies and patients' baseline demographics were described in **Tables 1** and **2**.

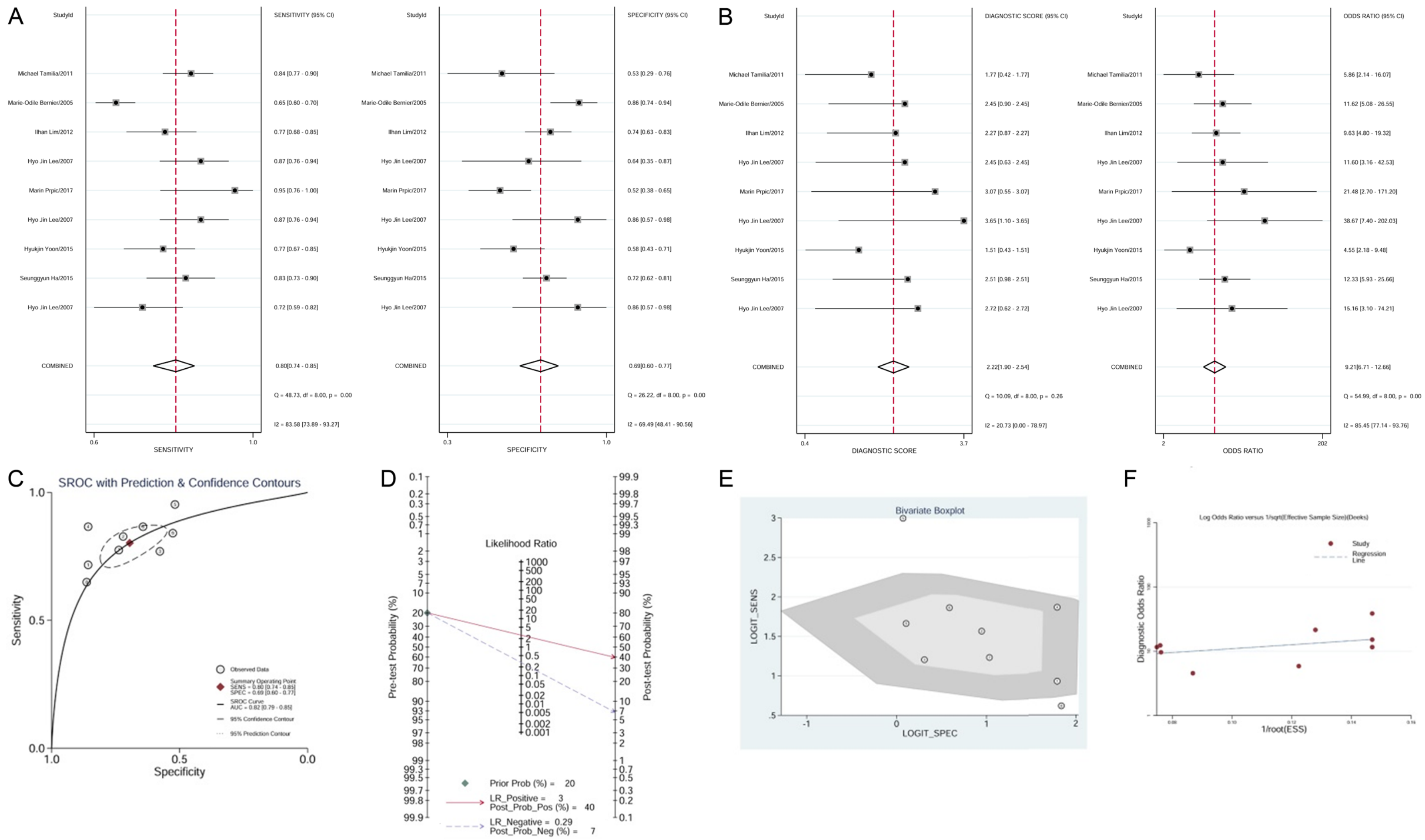

Figure 2. The sensitivity and specificity (A) and the diagnostic odds ratio (B) of Tg to predict radioactive iodine remnant ablation success when cut-off value < 10 ng/ml; Summary ROC curve with confidence and prediction regions (C) and fagan plot analysis to evaluate the predictive of Tg (D) when cut-off value < 10 ng/ml; Bivariate box plot result (E) and Deeks' funnel plot asymmetry analysis (F) when cut-off value < 10 ng/ml.

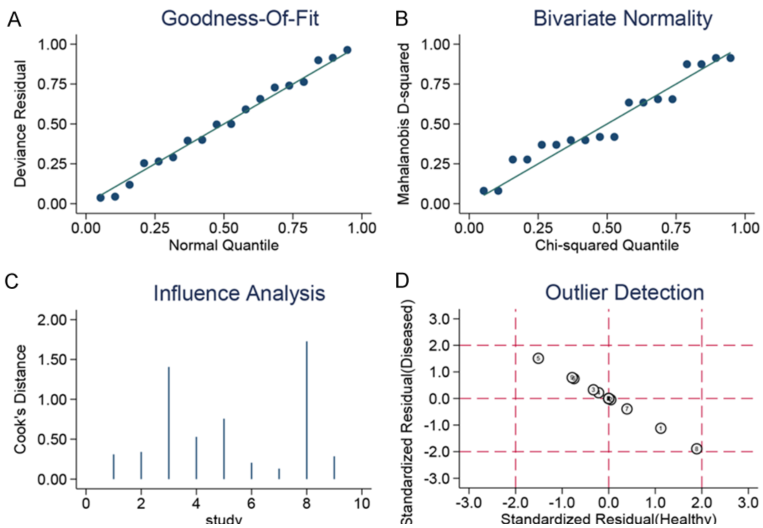

Figure 3. Sensitivity analyses of meta-analysis when cut-off < 10 ng/ml. The quantile plot of residual-based goodness-of fit (A) and Chi-squared probability plot of squared Mahalanobis distances for assessment of the bivariate normality assumption (B) were done to analyze the stability. The spike plot for checking for particularly influential observations using Cook's distance (C) and scatter plot for checking for outliers using standardized predicted random effects (standardized level-2 residual > s) (D) were done to analyze the outlier.

Diagnostic accuracy assessment

All the serum Tg levels in the 10 studies were detected before ablation. A total of seventeen cut-off values extracted from these included studies were analyzed in this systematic research. Using a two-variable model, Tg level was used to predict the success rate of DTC radioactive ablation. The pooled estimates of Tg level in the predicting of success of ablation were divided into three parts based on cut-off value: cut-off value < 10 ng/ml estimates, cut-off value > 10 ng/ml estimates, and given best cut-off value estimates (**Table 4**).

Cut-off value < 10 ng/ml

The sensitivity, specificity and DOR values were 0.802 [0.744, 0.849] (**Figure 2A**), 0.695 [0.604, 0.773] (**Figure 2A**), and 9.213 [6.704, 12.662] (**Figure 2B**) when cut-off value < 10 ng/ml. AUROC value was 0.82 [0.79-0.85] (**Figure 2C**). The Spearman correlation coefficient = -1 and the proportion of heterogeneity likely due to threshold effect = 1.00 suggested that there was no threshold effect. As shown in **Table 4**, the results of Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) were 2.627 [2.064, 3.346] and 0.285 [0.231, 0.352], the results of Diagnostic Score and Diagnostic Odds Ratio (DOR) were 2.221 [1.903, 2.539] and 9.213 [6.704, 12.662]. The Fagan' s nomogram analysis result was shown in **Figure 2D** that compared with the fixed pre-test probability 20%, the post-test probability raised to 40% after PLR test and dropped to 7%.

In order to assess the distribution properties of sensitivity and specificity and determine the possible outliers of the diagnosis, we used Bivariate Box Plot as the analysis method. Though the data from Marin Prpic (2017) and Marie-Odile Bernier (2005) were shown as abnormal values, the whole shape Binary box plot was symmetrical (**Figure 2E**), which indicated that data within the normal distribution was compact. Deeks' funnel plot was used to assess the publication bias. **Figure 2F** showed that the scatter distribution was symmetrical funnel, $p = 0.312$, which indicated that no publication bias existed in this analysis. High stability was shown during the sensitivity analysis and no outlier was found (**Figure 3**).

All these results suggested that Tg level could be used to predict the success rate of DTC radioactive ablation when the cut-off value < 10 ng/ml.

Cut-off value > 10 ng/ml

The sensitivity, specificity and DOR values were 0.859 [0.784, 0.911] (**Figure 4A**), 0.671 [0.562, 0.764] (**Figure 4A**), and 12.362 [8.253, 18.516] (**Figure 4B**) when cut-off value > 10 ng/ml. AUROC value was 0.83 [0.80, 0.86] (**Figure 4C**). The Spearman correlation coefficient = -1 and the proportion of heterogeneity likely due to threshold effect = 1.00 suggested that there was no threshold effect. As shown in **Table 4**, the results of Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) were 2.606 [1.994, 3.406] and 0.211 [0.147, 0.302], the results of Diagnostic Score and Diagnostic Odds Ratio (DOR) were 2.515 [2.111,

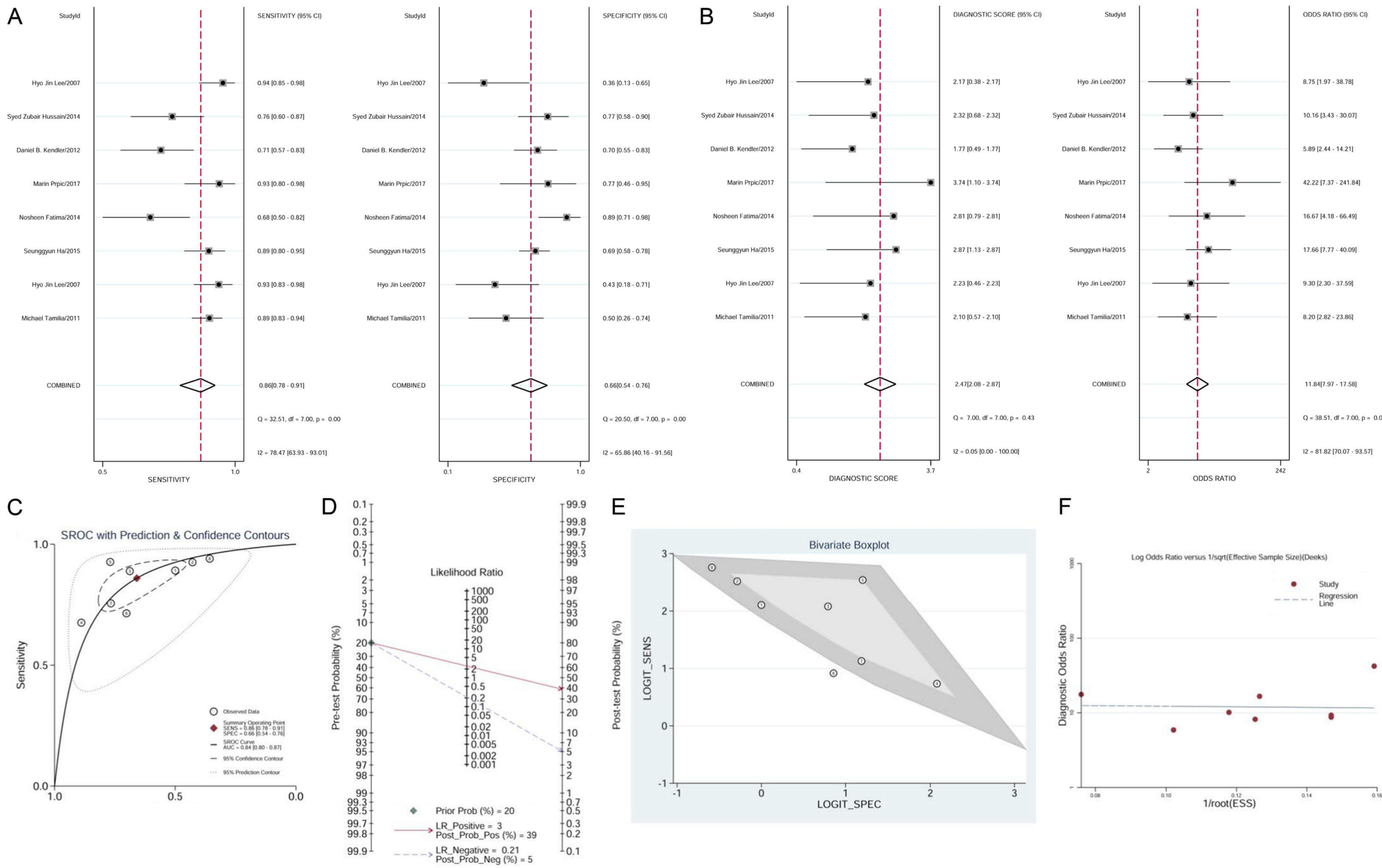

Figure 4. The sensitivity and specificity (A) and the diagnostic odds ratio (B) of Tg to predict radioactive iodine remnant ablation success when cut-off value > 10 ng/ml; Summary ROC curve with confidence and prediction regions (C) and fagan plot analysis to evaluate the predictive of Tg (D) when cut-off value > 10 ng/ml; Bivariate box plot result (E) and Deeks' funnel plot asymmetry analysis (F) when cut-off value > 10 ng/ml.

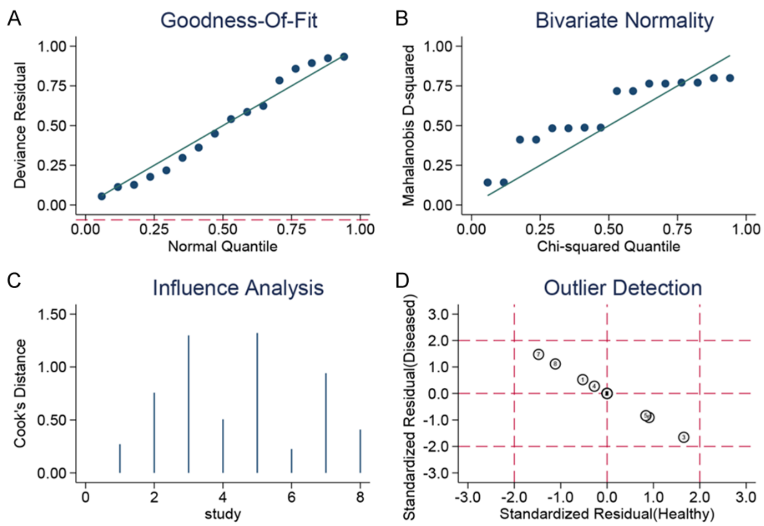

Figure 5. Sensitivity analyses of meta-analysis when cut-off > 10 ng/ml. The quantile plot of residual-based goodness-of fit (A) and Chi-squared probability plot of squared Mahalanobis distances for assessment of the bivariate normality assumption (B) were done to analyze the stability. The spike plot for checking for particularly influential observations using Cook's distance (C) and scatter plot for checking for outliers using standardized predicted random effects (standardized level-2 residual > s) (D) were done to analyze the outlier.

2.919] and 12.362 [8.253, 18.516]. The Fagan' s nomogram analysis result was showed in **Figure 4D** that compared with the fixed pre-test probability 20%, the post-test probability raised to 39% after PLR test and dropped to 5%.

In order to assess the distribution properties of sensitivity and specificity and determine the possible outliers of the diagnosis, we used Bivariate Box Plot as the analysis method. Though the data from Daniel B. Kendler (2012) were shown as abnormal values, the whole shape Binary box plot was symmetrical (**Figure 4E**), which indicated that data within the normal distribution was compact. Deeks' funnel plot was used to assess the publication bias. **Figure 4F** showed that the scatter distribution was symmetrical funnel, $p = 0.912$, which indicated that no publication bias existed in this analysis. The sensitivity analysis results showed high stability and no outlier was found (**Figure 5**).

These results suggested that Tg level could be used to predict the success rate of DTC radioactive ablation when the cut-off value > 10 ng/ml.

Given best cut-off value

The sensitivity, specificity and DOR values were 0.814 [0.754, 0.862] (**Figure 6A**), 0.694 [0.619, 0.76] (**Figure 6A**), and 9.903 [7.527, 13.029] (**Figure 6B**) when use the given best cut-off value. AUROC value was 0.82 [0.79, 0.85] (**Figure 6C**). The Spearman correlation coefficient = -1 and the proportion of heterogeneity likely due to threshold effect = 1.00 suggested that there was no threshold effect.

As shown in **Table 4**, the results of Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) were 2.657 [2.191, 3.221] and 0.268 [0.213, 0.338], the results of Diagnostic Score and Diagnostic Odds Ratio (DOR) were 2.293 [2.018, 2.567] and 9.903 [7.527, 13.029]. The Fagan' s nomogram analysis result was showed in **Figure 6D** that compared with the fixed pre-test probability 20%, the post-test probability raised to 40% after PLR test and dropped to 6%.

In order to assess the distribution properties of sensitivity and specificity and determine the possible outliers of the diagnosis, we used Bivariate Box Plot as the analysis method. Though the data from Nosheen Fatima (2014), Marie-Odile Bernier (2005) were shown as abnormal values, the whole shape Binary box plot was symmetrical (**Figure 6E**), which indicated that data within the normal distribution was compact. Deeks' funnel plot was used to assess the publication bias. **Figure 6F** showed that the scatter distribution was symmetrical funnel, $p = 0.598$, which indicated that no publication bias existed in this analysis. A good stability could be concluded through the sensitivity analysis, goodness-of-fit and bivariate normality analyses (**Figure 7A** and **7B**) showed that the bivariate model was moderately robust and only one outlier was identified by influence analysis and outlier detection (**Figure 7C** and **7D**).

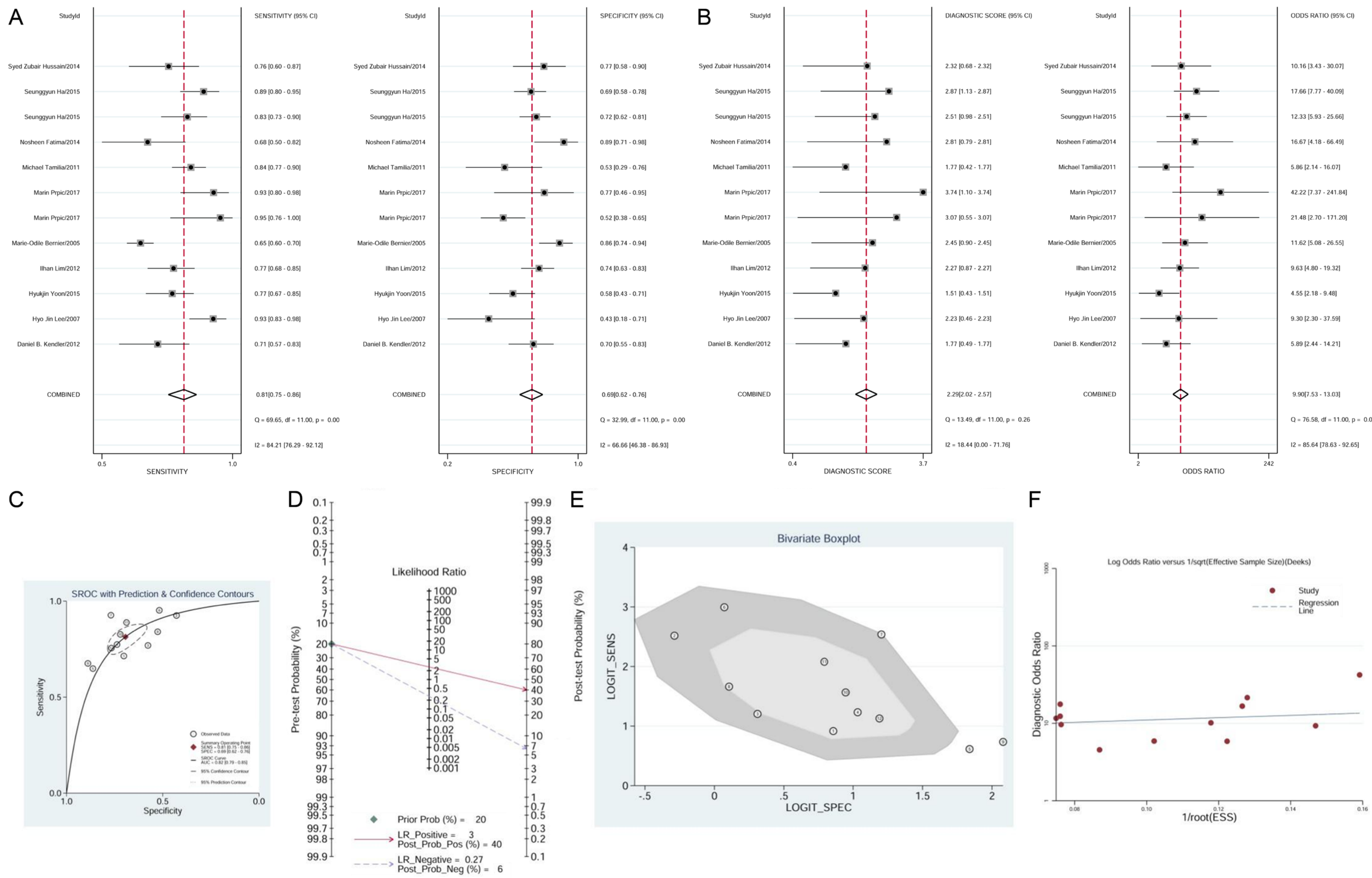

Figure 6. The sensitivity and specificity (A) and the diagnostic odds ratio (B) of Tg to predict radioactive iodine remnant ablation success when cut-off value is Best Cut-off value; Summary ROC curve with confidence and prediction regions (C) and fagan plot analysis to evaluate the predictive of Tg (D) when cut-off value is Best Cut-off value; Bivariate box plot result (E) and Deeks' funnel plot asymmetry analysis (F) when cut-off value is Best Cut-off value.

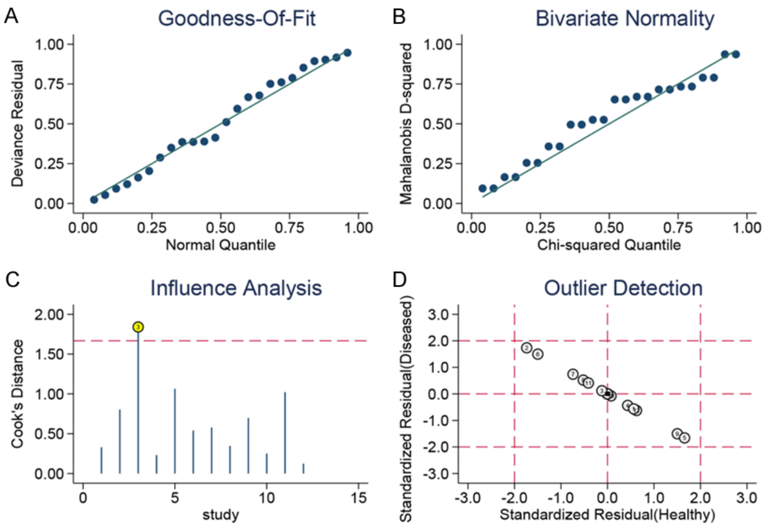

Figure 7. Sensitivity analyses of meta-analysis when cut-off is Best Cut-off value. The quantile plot of residual-based goodness-of fit (A) and Chi-squared probability plot of squared Mahalanobis distances for assessment of the bivariate normality assumption (B) were done to analyze the stability. The spike plot for checking for particularly influential observations using Cook's distance (C) and scatter plot for checking for outliers using standardized predicted random effects (standardized level-2 residual > s) (D) were done to analyze the outlier.

These results suggested that Tg level could be used to predict the success rate of DTC radioiodine remnant ablation under the given best cut-off value.

Discussion

Total or subtotal thyroidectomy followed by RRA treatment is the standard initial treatment for most patients with DTC [23, 32]. ^{131}I in systemic circulation is absorbed and stored in DTC cells. Then the radiation damage to the DTC cells and limited injury caused by β-ray released from ^{131}I will induce cell lysis and apoptosis. Through RRA treatment, the residual tissues after operation or unresectable DTC metastases can be eliminated and dissolved. Simultaneously, the high-energy γ-ray released from ^{131}I can pass through flesh and detected by corresponding apparatus. Successful RRA treatment can decrease the DTC recurrence and mortality rate by eliminating microscopic residual post-operative tumor foci [21, 33-35]. Furthermore, a highly sensitive post-therapy whole body scans (WBS) can be used due to the radioactivity that may reveal previously undetected tumor foci outside of the thyroid bed [36]. However, 20%-30% patients [37, 38] might still get ablation failure after higher ablative doses of ^{131}I, and be exposed with higher recurrence or metastasis rate, and repeat ablation treatments. Although the efficacy and safety of RRA treatment on DTC has been fully recognized, the serious side effects cannot be ignored, especially for the patients who receive repeat RRA treatment. Because of the impact of RRA on nonthyroid tissue like recurrent laryngeal nerve, salivary gland or lacrimal system, patients may have hoarse voice, sialadenitis, xerostomia, sialolithiasis, epiphora, xerophthalmia, and recurrent or chronic conjunctivitis [39-44]. The hither-does of ^{131}I therapy patients received, the more and worse adverse effects would show up. Therefore, selection of patients with high success rate of RRA is necessary before the treatment.

Recent studies focused on the discovery of predictors for RRA success, including serum Tg level, pattern in WBS, lymph node stage and so on. It was reported that serum thyroglobulin (Tg) and ^{131}I WBS were used to assess the possible persistence or recurrence of thyroid tissues in the follow-up of DTC patients with RRA treatment [9, 45-49]. However, proper predictors of successful RRA in DTC patients after operation for treatment selection after thyroidectomy have not been previously fully investigated simultaneously. Thyroglobulin (Tg), serving as a precursor of the thyroid hormones [50], has been widely practiced to detect recurrence of DTC after surgery [51, 52]. Tg was reported to be associated with disease recurrence and progression [18]. Menendez *et al.* [22, 53] reported that the follow-up Tg levels after RRA might predict earlier recurrent or persistent disease. Based on the source of serum Tg, synthesized and released by residual thyroid tissue and DTC after operation, and the aim of ablation, it's reasonable that the serum Tg level before RRA could be a predictor for RRA success.

In our study, a series diagnosis meta-analysis was accomplished to increase the sample size and analyze the sensitivity and specificity of Tg level as a predictor of successful RRA treatment. Despise the different cut-off value groups, higher than 10 ng/ml, lower than 10 ng/ml, or the given best cut-off value, the sensitivity and specificity values of serum Tg level from those three groups in the predicting of success of ablation were in a similar level, and the pooled AUCs were in the range of 0.7-0.9. These results of our analysis indicated that regardless of cut-off value, serum Tg level before RRA had a stable and remarkable correlation with RRA treatment success and showed moderate predictive ability, in consistent with other researches. Serum Tg level after thyroidectomy can be a reliable predictor for RRA treatment guidance. In addition, compared with the fixed probability (20%) in preliminary experiments, the positive likelihood ratio (PLR) of serum Tg level significantly increased to about 40%, and the negative likelihood ratio (NLR) reduced to about 6% among all three conditions. While, there are still problems (various cut-off values, unfixed detecting time) need to be solved before using serum Tg level to predict the RRA treatment success, more researches are needed.

In conclusion, our work meta-analyzed the association between serum Tg levels and radioiodine remnant ablation successful rate after total or subtotal thyroidectomy. The diagnosed meta-analysis showed strong evidence that the serum Tg levels before ablation can be used as a moderate predictor for radioiodine remnant ablation success.

Disclosure of conflict of interest

None.

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References

[1] Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer 2013; Available from: http://globocan.iarc.fr, accessed on 25/06/2017.

[2] Burns WR and Zeiger MA. Differentiated thyroid cancer. Semin Oncol 2010; 37: 557-566.

[3] Conzo G, Avenia N, Bellastella G, Candela G, de Bellis A, Esposito K, Pasquali D, Polistena A, Santini L and Sinisi AA. The role of surgery in the current management of differentiated thyroid cancer. Endocrine 2014; 47: 380-388.

[4] Cabanillas ME, McFadden DG and Durante C. Thyroid cancer. Lancet 2016; 388: 2783-2795.

[5] Davies L and Welch HG. Increasing incidence of thyroid cancer in the united states, 1973-2002. JAMA 2006; 295: 2164-2167.

[6] Parker WA, Edafe O and Balasubramanian SP. Long-term treatment-related morbidity in differentiated thyroid cancer: a systematic review of the literature. Pragmat Obs Res 2017; 8: 57-67.

[7] Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SI, Cooper DS, Braunstein GD, Lee S, Davies TF, Arafah BM, Ladenson PW and Pinchera A. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003; 88: 1433-1441.

[8] Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee RF, Rosai J, Shah JP, Fremgen AM, Stewart AK and Hölzer S. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the united states during 1996. U.S. and German thyroid cancer study group. An American college of surgeons commission on cancer patient care evaluation study. Cancer 2000; 89: 202-217.

[9] American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL and Tuttle RM. Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19: 1167-1214.

[10] Hölzer S, Reiners C, Mann K, Bamberg M, Rothmund M, Dudeck J, Stewart AK and Hundahl SA. Patterns of care for patients with primary differentiated carcinoma of the thyroid gland treated in Germany during 1996. U.S. and German thyroid cancer group. Cancer 2000; 89: 192-201.

[11] Worden F. Treatment strategies for radioactive iodine-refractory differentiated thyroid cancer. Ther Adv Med Oncol 2014; 6: 267-279.

[12] Fang Y, Ding Y, Guo Q, Xing J, Long Y and Zong Z. Radioiodine therapy for patients with differentiated thyroid cancer after thyroidectomy: direct comparison and network meta-analyses. J Endocrinol Invest 2013; 36: 896-902.

[13] van de Graaf SA, Ris-Stalpers C, Pauws E, Mendive FM, Targovnik HM and de Vijlder JJ. Up to date with human thyroglobulin. J Endocrinol 2001; 170: 307-321.

[14] Torréns JI and Burch HB. Serum thyroglobulin measurement. Utility in clinical practice. Endocrinol Metab Clin North Am 2001; 30: 429-467.

[15] Evans C, Tennant S and Perros P. Thyroglobulin in differentiated thyroid cancer. Clin Chim Acta 2015; 444: 310-317.

[16] Giovanella L, Treglia G, Sadeghi R, Trimboli P, Ceriani L and Verburg FA. Unstimulated highly sensitive thyroglobulin in follow-up of differentiated thyroid cancer patients: a meta-analysis. J Clin Endocrinol Metab 2014; 99: 440-447.

[17] Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J and Burch HB. The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: a meta-analysis involving 3947 patients. J Clin Endocrinol Metab 2012; 97: 2754-2763.

[18] Cailleux AF, Baudin E, Travagli JP, Ricard M and Schlumberger M. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? J Clin Endocrinol Metab 2000; 85: 175-178.

[19] Hall FT, Beasley NJ, Eski SJ, Witterick IJ, Walfish PG and Freeman JL. Predictive value of serum thyroglobulin after surgery for thyroid carcinoma. Laryngoscope 2003; 113: 77-81.

[20] Tamilia M, Al-Kahtani N, Rochon L, Hier MP, Payne RJ, Holcroft CA and Black MJ. Serum thyroglobulin predicts thyroid remnant ablation failure with 30 mCi iodine-131 treatment in patients with papillary thyroid carcinoma. Nucl Med Commun 2011; 32: 212-220.

[21] Lim I, Kim SK, Hwang SS, Kim SW, Chung KW, Kang HS and Lee ES. Prognostic implication of thyroglobulin and quantified whole body scan after initial radioiodine therapy on early prediction of ablation and clinical response for the patients with differentiated thyroid cancer. Ann Nucl Med 2012; 26: 777-786.

[22] Kim TY, Kim WB, Kim ES, Ryu JS, Yeo JS, Kim SC, Hong SJ and Shong YK. Serum thyroglobulin levels at the time of 131I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2005; 90: 1440-1445.

[23] Toubeau M, Touzery C, Arveux P, Chaplain G, Vaillant G, Berriolo A, Riedinger JM, Boichot C, Cochet A and Brunotte F. Predictive value for disease progression of serum thyroglobulin levels measured in the postoperative period and after (131) I ablation therapy in patients with differentiated thyroid cancer. J Nucl Med 2004; 45: 988-994.

[24] Kendler DB, Vaisman F, Corbo R, Martins R and Vaisman M. Preablation stimulated thyroglobulin is a good predictor of successful ablation in patients with differentiated thyroid cancer. Clin Nucl Med 2012; 37: 545-549.

[25] Bernier MO, Morel O, Rodien P, Muratet JP, Giraud P, Rohmer V, Jeanguillaume C, Bigorgne JC and Jallet P. Prognostic value of an increase in the serum thyroglobulin level at the time of the first ablative radioiodine treatment in patients with differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2005; 32: 1418-1421.

[26] Fatima N, uz Zaman M, Ikram M, Akhtar J, Islam N, Masood Q, Zaman U and Zaman A. Baseline stimulated thyroglobulin level as a good predictor of successful ablation after adjuvant radioiodine treatment for differentiated thyroid cancers. Asian Pac J Cancer Prev 2014; 15: 6443-6447.

[27] Ha S, Oh SW, Kim YK, Koo do H, Jung YH, Yi KH and Chung JK. Clinical outcome of remnant thyroid ablation with low dose radioiodine in korean patients with low to intermediate-risk thyroid cancer. J Korean Med Sci 2015; 30: 876-881.

[28] Lee HJ, Rha SY, Jo YS, Kim SM, Ku BJ, Shong M, Kim YK and Ro HK. Predictive value of the preablation serum thyroglobulin level after thyroidectomy is combined with postablation 131I whole body scintigraphy for successful ablation in patients with differentiated thyroid carcinoma. Am J Clin Oncol 2007; 30: 63-68.

[29] Prpic M, Kust D, Kruljac I, Kirigin LS, Jukic T, Dabelic N, Bolanca A and Kusic Z. Prediction of radioactive iodine remnant ablation failure in patients with differentiated thyroid cancer: a cohort study of 740 patients. Head Neck 2017; 39: 109-115.

[30] Yoon H, Kim SH, O JH, Seo YY, Lee Y, Kim H and Ryu J. Correlation of consecutive serum thyroglobulin levels during hormone withdrawal and failure of initial radioiodine ablation in thyroid cancer patients. Nucl Med Mol Imaging 2015; 49: 276-283.

[31] Zubair Hussain S, Zaman MU, Malik S, Ram N, Asghar A, Rabbani U, Aftab N and Islam N. Preablation stimulated thyroglobulin/TSH ratio as a predictor of successful I(131)remnant ablation in patients with differentiated thyroid cancer following total thyroidectomy. J Thyroid Res 2014; 2014: 610273.

[32] Mazzaferri EL and Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001; 86: 1447-1463.

[33] Van Nostrand D and Wartofsky L. Radioiodine in the treatment of thyroid cancer. Endocrinol Metab Clin North Am 2007; 36: 807-822, vii-viii.
[34] Sawka AM, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A, Straus S and Goldstein DP. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin North Am 2008; 37: 457-480, x.
[35] Verburg FA, de Keizer B, Lips CJ, Zelissen PM and de Klerk JM. Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. Eur J Endocrinol 2005; 152: 33-37.
[36] Pacini F, Schlumberger M, Harmer C, Berg GG, Cohen O, Duntas L, Jamar F, Jarzab B, Limbert E, Lind P, Reiners C, Sanchez Franco F, Smit J and Wiersinga W. Post-surgical use of radioiodine (131I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. Eur J Endocrinol 2005; 153: 651-659.
[37] Karam M, Gianoukakis A, Feustel PJ, Cheema A, Postal ES and Cooper JA. Influence of diagnostic and therapeutic doses on thyroid remnant ablation rates. Nucl Med Commun 2003; 24: 489-495.
[38] Kogai T, Taki K and Brent GA. Enhancement of sodium/iodide symporter expression in thyroid and breast cancer. Endocr Relat Cancer 2006; 13: 797-826.
[39] Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, Baek SM, Kim YS, Shin JH, Park JS, Kim DW, Kim JH, Kim EK, Jung SL, Na DG; Korean Society of Thyroid Radiology. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology 2012; 262: 335-342.
[40] Jonklaas J. Nasal symptoms after radioiodine therapy: a rarely described side effect with similar frequency to lacrimal dysfunction. Thyroid 2014; 24: 1806-1814.
[41] Solans R, Bosch JA, Galofré P, Porta F, Roselló J, Selva-O'Callagan A and Vilardell M. Salivary and lacrimal gland dysfunction (sicca syndrome) after radioiodine therapy. J Nucl Med 2001; 42: 738-743.
[42] Mandel SJ and Mandel L. Radioactive iodine and the salivary glands. Thyroid 2003; 13: 265-271.
[43] Brockmann H, Wilhelm K, Joe A, Palmedo H and Biersack HJ. Nasolacrimal drainage obstruction after radioiodine therapy: case report and a review of the literature. Clin Nucl Med 2005; 30: 543-545.
[44] Kloos RT, Duvuuri V, Jhiang SM, Cahill KV, Foster JA and Burns JA. Nasolacrimal drainage system obstruction from radioactive iodine therapy for thyroid carcinoma. J Clin Endocrinol Metab 2002; 87: 5817-5820.
[45] Mazzaferri EL and Kloos RT. Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? J Clin Endocrinol Metab 2002; 87: 1490-1498.
[46] Baloch Z1, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruf J, Smyth PP, Spencer CA, Stockigt JR; Guidelines Committee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003; 13: 3-126.
[47] Giovanella L, Clark PM, Chiovato L, Duntas L, Elisei R, Feldt-Rasmussen U, Leenhardt L, Luster M, Schalin-Jäntti C, Schott M, Seregni E, Rimmele H, Smit J and Verburg FA. Thyroglobulin measurement using highly sensitive assays in patients with differentiated thyroid cancer: a clinical position paper. Eur J Endocrinol 2014; 171: R33-46.
[48] Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W; European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154: 787-803.
[49] Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR; British Thyroid Association. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) 2014; 81 Suppl 1: 1-122.
[50] Wong J, Lu Z, Doery J and Fuller P. Lessons from a review of thyroglobulin assays in the management of thyroid cancer. Intern Med J 2008; 38: 441-444.
[51] Ringel MD and Nabhan F. Approach to follow-up of the patient with differentiated thyroid cancer and positive anti-thyroglobulin antibodies. J Clin Endocrinol Metab 2013; 98: 3104-3110.
[52] Indrasena BS. Use of thyroglobulin as a tumour marker. World J Biol Chem 2017; 8: 81-85.
[53] Menéndez Torre E, López Carballo MT, Rodríguez Erdozáin RM, Forga Llenas L, Goñi Iriarte MJ and Barbería Layana JJ. Prognostic value of thyroglobulin serum levels and 131I whole-body scan after initial treatment of low-risk differentiated thyroid cancer. Thyroid 2004; 14: 301-306.