Systematic Review

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Threshold Effect of Serum Thyroglobulin Levels on the Detection Rate of Recurrent Differentiated Thyroid Carcinoma by ^{18}F-FDG PET/CT: A Systematic Review and Meta-Analysis

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Background: The optimal serum thyroglobulin (Tg) threshold for performing ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in patients with recurrent differentiated thyroid carcinoma (DTC) and negative radioiodine scintigraphy (TENIS syndrome) remains controversial. This study aimed to systematically evaluate the relationship between Tg levels and PET/CT detection rates and to determine if a clinically meaningful threshold exists.

Methods: A systematic literature search was conducted in Web of Science, PubMed, and Cochrane Library up to January 2026 following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies reporting Tg-stratified PET/CT detection rates in adult patients with suspected recurrent DTC were included. The primary outcome was the per-patient detection rate, which was pooled using a random-effects model. Risk of bias was assessed using QUADAS-2.

Results: Eight studies met the inclusion criteria, with six contributing to the quantitative synthesis. The overall pooled detection rate was 0.54 (95% CI 0.29–0.78), with significant heterogeneity across studies (I^2 = 93.4%). A pronounced threshold effect was observed: detection rates were negligible in low-Tg strata ($<$5 ng/mL), increased substantially in intermediate strata (5–10 ng/mL), and were consistently high in high-Tg strata ($>$10 ng/mL). Specifically, the pooled detection rate was 0.71 (95% CI 0.00–1.00) for patients with Tg $>$10 ng/mL and increased to 0.97 (95% CI 0.90–0.99) in the subgroup with Tg $\geq$18 ng/mL, although this estimate was based on a limited number of studies.

Conclusion: ^{18}F-FDG PET/CT diagnostic yield demonstrates a monotonic increase with rising serum Tg levels. A Tg threshold in the range of approximately 10–18 ng/mL appears promising for identifying structural disease, although the upper bound of this threshold warrants further validation in larger cohorts. These findings support a Tg-guided, risk-stratified approach to selecting candidates for ^{18}F-FDG PET/CT.

Keywords: differentiated thyroid carcinoma; thyroglobulin; ^{18}F-FDG PET/CT; recurrence; meta-analysis

Introduction

Thyroid cancer ranks among the most common endocrine malignancies globally. According to GLOBOCAN 2022, an estimated 821,214 new cases and 47,507 deaths occurred worldwide, with age-standardized incidence rates approximately three times higher in women than in men [1]. Differentiated thyroid carcinoma (DTC), encompassing papillary and follicular histological subtypes, accounts for over 90% of all thyroid malignancies and generally carries an excellent prognosis [2]. The 5-year relative survival rate exceeds 98% for localized disease [3]. Standard treatment includes total thyroidectomy followed by radioactive iodine (RAI) ablation in selected patients, with subsequent lifelong surveillance for disease recurrence [4].

Serum thyroglobulin (Tg) serves as the cornerstone biomarker for postoperative monitoring of DTC. Produced exclusively by thyroid follicular cells, Tg becomes undetectable in athyrotic patients following successful treatment [5]. Elevated or rising Tg levels during follow-up signal persistent or recurrent disease, prompting further diagnostic evaluation [6]. However, the presence of thyroglobulin antibodies (TgAb) may interfere with Tg measurement and also exhibits independent prognostic significance [7]. The 2015 American Thyroid Association (ATA) guidelines recommend Tg measurement in conjunction with neck ultrasonography as the primary surveillance strategy [4]. Stimulated Tg testing, achieved through thyroid hormone withdrawal or recombinant human TSH administration, improves risk stratification and detection of disease [8].

A subset of DTC patients presents with a challenging clinical scenario characterized by elevated serum Tg levels with negative whole-body RAI scintigraphy. This condition, termed Thyroglobulin Elevated Negative Iodine Scintigraphy (TENIS) syndrome, affects approximately 10–25% of patients during follow-up [9,10] and indicates loss of iodine-concentrating ability due to tumor dedifferentiation [10,11]. The phenomenon reflects tumor dedifferentiation, a process associated with more aggressive biological behavior and poorer prognosis [11]. Management of TENIS syndrome remains difficult, as conventional RAI imaging fails to localize disease, limiting therapeutic options [12].

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has emerged as a valuable diagnostic tool for patients with suspected RAI-refractory DTC [13,14]. The "flip-flop" phenomenon describes the inverse relationship between RAI and FDG uptake that dedifferentiated thyroid cancer cells lose the ability to concentrate iodine while demonstrating increased glucose metabolism [15]. Current guidelines recommend ^{18}F-FDG PET/CT for high-risk patients with elevated or rising Tg levels and negative RAI imaging [4,16]. A recent study reported a pooled sensitivity and specificity of 0.87 and 0.76, respectively, for ^{18}F-FDG PET/CT in detecting recurrent disease in TENIS syndrome [10].

The optimal Tg threshold for ordering ^{18}F-FDG PET/CT remains controversial. Published cutoff values vary considerably across studies, ranging from 2.5 to 28.5 ng/mL, as reported in single-center studies by Choi *et al.* [17], Albano *et al.* [18], and Trybek *et al.* [19]. This heterogeneity reflects differences in patient populations, TSH stimulation protocols, assay methodologies, and verification standards. At low Tg concentrations, ^{18}F-FDG PET/CT detection rates approach zero, rendering the examination clinically uninformative [20]. Detection rates increase substantially at higher Tg levels, suggesting a threshold effect, and FDG PET/CT also achieves good performance in patients with elevated anti-Tg antibodies despite unreliable Tg measurements [21,22]. Identifying this threshold is of significant clinical importance, as premature imaging wastes resources and exposes patients to unnecessary radiation, whereas delayed imaging may miss treatable disease.

Several single-center studies have explored the relationship between Tg levels and ^{18}F-FDG PET/CT diagnostic yield. Albano *et al.* [18] identified a Tg cutoff of 18 ng/mL, above which detection rates was 97%. Schlüter *et al.* [23] reported that FDG PET proved most informative at Tg levels exceeding 10 µg/L. Trybek *et al.* [19] proposed 28.5 ng/mL as the optimal threshold using receiver operating characteristic analysis. These disparate findings highlight the need for systematic evidence synthesis. Recent investigations have also explored Tg kinetics, demonstrating that Tg doubling time may predict PET/CT results more accurately than absolute Tg values [24], while others have emphasized the prognostic significance of Tg dynamics in recurrent DTC [25].

No previous meta-analysis has systematically evaluated the threshold effect of serum Tg levels on ^{18}F-FDG PET/CT detection rates in recurrent DTC. Prior systematic reviews focused primarily on overall diagnostic accuracy rather than Tg-stratified performance [26]. The absence of pooled estimates across Tg categories limits evidence-based guidance for clinical decision-making. Determining whether a Tg threshold exists and quantifying detection rates above and below this threshold would inform individualized imaging strategies.

This systematic review and meta-analysis aimed to address this knowledge gap. We sought to evaluate the relationship between serum Tg levels and ^{18}F-FDG PET/CT detection rates in patients with recurrent or persistent DTC and negative RAI scintigraphy. We aimed to pool per-patient detection rates across included studies, analyze detection rates stratified by Tg categories, and explore whether a clinically meaningful Tg threshold exists above which the diagnostic yield of ^{18}F-FDG PET/CT increases substantially. We hypothesized that detection rates would increase monotonically with rising Tg levels, thereby supporting a threshold-based approach to imaging selection.

Methods

Protocol and Reporting Standards

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [27]. The completed PRISMA 2020 checklist is available in **Supplementary File 1**. The protocol outlining the research question, eligibility criteria, and analytic plan was defined a priori. All methodological decisions followed established guidance for diagnostic test accuracy reviews.

Research Question

The study aimed to evaluate whether serum Tg levels are associated with the diagnostic yield of ^{18}F-FDG PET/CT in detecting recurrent or persistent differentiated thyroid carcinoma (DTC). We examined whether a Tg threshold exists above which PET/CT detection rate increases substantially.

The PICO framework was applied as follows:

- Population: Adults ($\geq$18 years) with previously treated DTC (papillary or follicular) undergoing surveillance for suspected recurrence or persistent disease.
- Index Test: ^{18}F-FDG PET/CT performed for evaluation of suspected recurrent DTC.
- Comparator: Categories of serum Tg level (stimulated or suppressed), defined by each study.
- Outcome: PET/CT detection rate (proportion of patients with PET-positive findings).

Literature Search Strategy

Three electronic databases, PubMed, Web of Science Core Collection and Cochrane Library, were systematically searched. The final search was performed on 28 November 2025 for PubMed, 1 December 2025 for Web of Science, and 6 January 2026 for Cochrane Library.

The PubMed search strategy combined Medical Subject Headings (MeSH) and free-text terms related to Tg, differentiated thyroid carcinoma, PET/CT, and recurrent disease:

> ("Thyroglobulin"[Mesh] OR thyroglobulin[tiab] OR Tg[tiab])

> AND

> ("Thyroid Neoplasms"[Mesh] OR "Differentiated thyroid carcinoma"[tiab] OR papillary thyroid carcinoma[tiab] OR follicular thyroid carcinoma[tiab] OR PTC[tiab] OR FTC[tiab])

> AND

> ("Positron-Emission Tomography"[Mesh] OR PET[tiab] OR PET/CT[tiab] OR FDG PET[tiab] OR ^{18}F-FDG[tiab])

> AND

> (recurrence[tiab] OR recurrent[tiab] OR persistent[tiab] OR metastasis[tiab])

The Web of Science and Cochrane Library strategy used comparable keywords. No language restriction was applied. Reference lists of included studies were manually screened to identify additional eligible publications.

We acknowledge that restricting the search to three databases represents a potential limitation. The Embase database was not searched, which may have resulted in the omission of some relevant studies, particularly those published in non-indexed journals or regional publications. However, PubMed, Web of Science and Cochrane Library together provide comprehensive coverage of the biomedical and nuclear medicine literature, and manual screening of reference lists was performed to minimize the risk of missing eligible studies. This limitation is further addressed in the Discussion section.

Eligibility Criteria

Inclusion Criteria

Studies were eligible if they met the following criteria:

1. Adult patients ($\geq$18 years) with confirmed DTC.

2. ^{18}F-FDG PET/CT performed for suspected recurrent or persistent disease.

3. Serum Tg measured proximal to PET/CT (stimulated or suppressed).

4. PET/CT detection rate reported by Tg strata or sufficient data for derivation.

5. Observational cohort studies, cross-sectional studies, or clinical trials.

6. Full-text articles published in peer-reviewed journals.

Exclusion Criteria

Studies were excluded if they were:

1. Case reports or case series with $<$10 patients, reviews, editorials, letters, or conference abstracts.

2. Studies without Tg data or without Tg-stratified PET/CT results.

3. Non-DTC thyroid malignancies without separable DTC-specific data.

4. Duplicate publications or overlapping patient cohorts.

5. Studies lacking extractable numerical data for detection rate.

Study Selection Process

All records were imported into a reference manager (EndNote 20; Clarivate, Philadelphia, PA, USA), and duplicates were removed. Screening for title and abstract was performed by two independent reviewers. For potentially eligible articles, full texts were assessed using prespecified criteria. Disagreements were resolved through discussion. The PRISMA flow diagram summarizes the process of the study selection and is shown in Fig. 1.

Data Extraction

Two reviewers independently extracted the following data elements using a standardized form:

- Study identifiers (authors, year, country, design).
- Patient characteristics and inclusion criteria.
- PET/CT parameters and interpretation criteria.
- Serum Tg levels (stimulated or suppressed) and Tg stratification.
- PET/CT detection rate per Tg category.
- Reference standard definitions.
- Risk-of-bias judgments.

Where necessary, proportions were recalculated from raw numerators and denominators.

Risk of Bias Assessment

Study quality was evaluated using the QUADAS-2 tool, covering four domains: patient selection, index test, reference standard, and flow and timing. Each domain was rated as low, unclear, or high risk of bias. Applicability concerns were also assessed. Two reviewers completed QUADAS-2 independently.

Statistical Analysis

The primary outcome was the per-patient PET/CT detection rate, defined as the proportion of patients with PET-positive findings within each Tg stratum. Detection rates were pooled using a random-effects model given anticipated heterogeneity among studies.

Statistical heterogeneity was evaluated using:

- I^2 statistic.
- τ^2 (between-study variance).

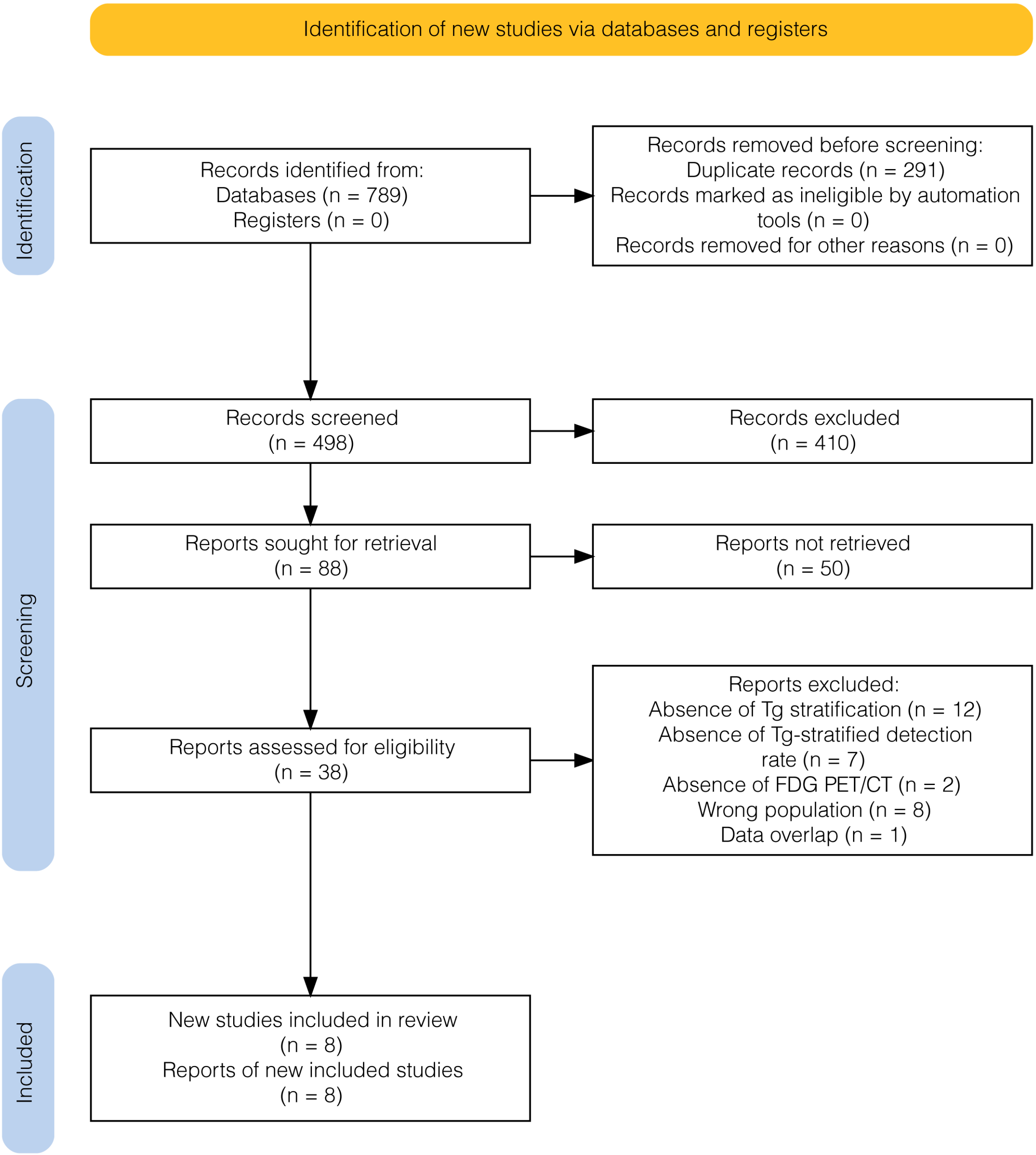

Fig. 1. PRISMA 2020 flow diagram summarizing the study selection process for inclusion. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- Cochran Q test.

Tg-stratified analyses were performed according to study-defined categories, with high-Tg subgroups (e.g., $>$10 ng/mL, $\geq$18 ng/mL) analyzed separately. In addition, a subgroup reporting only stimulated Tg was evaluated to reflect clinical scenarios where TSH stimulation guides decision-making.

Sensitivity analyses included:

1. Excluding studies with unclear TSH stimulation status.
2. Excluding studies at higher risk of selection or verification bias.
3. Excluding combinations of studies to test robustness.

Publication bias was not assessed due to fewer than ten studies, as recommended for diagnostic meta-analyses. All analyses used established meta-analytic frameworks for proportions. Results are presented as pooled detection rates with 95% confidence intervals.

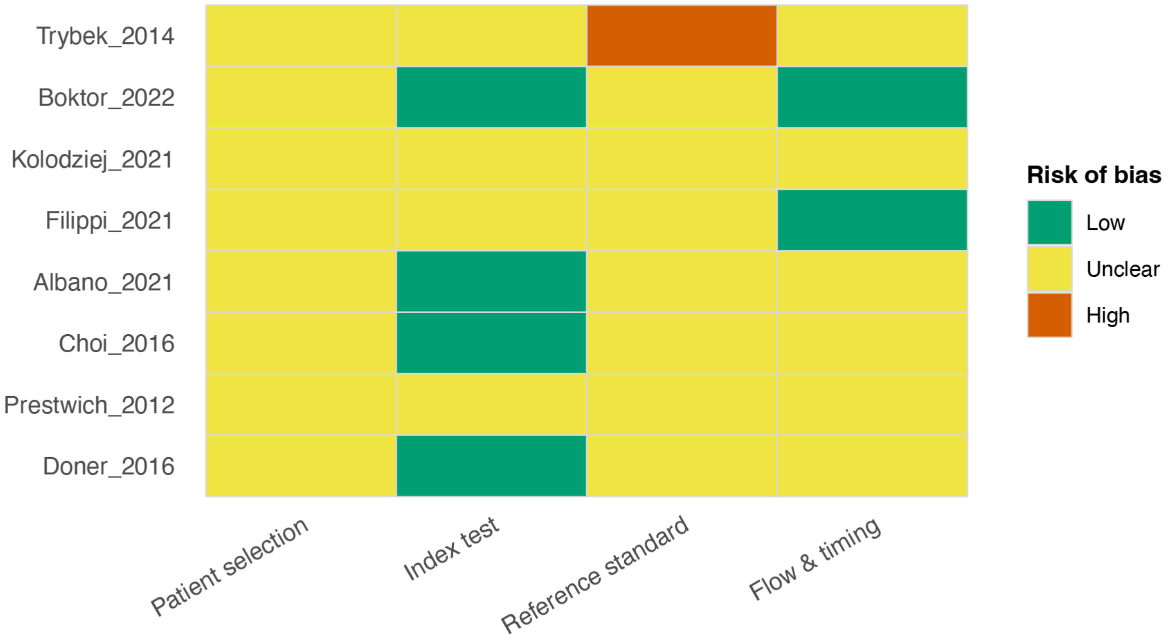

Fig. 2. QUADAS-2 per-study heatmap illustrating risk-of-bias assessments across four domains in each included study. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2.

Software and Implementation

All statistical analyses were performed using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). The meta-analysis of proportions was conducted using the "meta" package (version 7.0-0; Guido Schwarzer, University of Medical Center Freiburg, Freiburg, Germany), with pooled detection rates calculated using the inverse variance method and the Freeman-Tukey double arcsine transformation to stabilize variances. Forest plots were generated using the "forest" function within the same package. Heterogeneity statistics (I^2, τ^2, and Cochran's Q) were computed automatically.

Definition and Exploration of Threshold Effect

The threshold effect of serum Tg levels on PET/CT detection rate was explored descriptively rather than through formal meta-regression due to the limited number of included studies. We defined a threshold effect as a consistent pattern in which PET/CT detection rates increase substantially above a certain Tg concentration compared with rates below that level. To explore this effect, we extracted Tg-stratified detection rates from each study using study-defined cutoffs (e.g., <5, 5–10, >10 ng/mL; or <18, ≥ 18 ng/mL), plotted detection rates across ordered Tg strata to visually assess monotonic trends, conducted subgroup meta-analyses at clinically relevant Tg thresholds (>10 ng/mL and ≥ 18 ng/mL) to quantify detection rates above these cutoffs, and compared pooled detection rates between low-Tg and high-Tg subgroups to determine clinical significance. This prespecified descriptive threshold analysis aimed to inform clinical decision-making regarding the optimal Tg level for ordering ^{18}F-FDG PET/CT.

Results

Study Selection

As shown in Fig. 1, the database search yielded 789 records (PubMed n = 320; Web of Science n = 461; Cochrane Library n = 8). After removing duplicates, 498 unique records were screened, of which 410 were excluded based on titles and abstracts. The full texts of 88 articles were assessed for eligibility, and 80 were excluded for prespecified reasons, most commonly lack of available full text (n = 50), absence of thyroglobulin (Tg) stratification (n = 12), or absence of Tg-stratified detection rate (n = 7). Finally, eight studies were included in the qualitative synthesis, and six contributed to the quantitative meta-analysis.

Characteristics of Included Studies

The eight included studies were published between 2012 and 2022, with sample sizes ranging from 19 to 139 patients. The included studies were predominantly retrospective cohort studies. All studies evaluated ^{18}F-FDG PET/CT for suspected recurrent or persistent differentiated thyroid carcinoma (DTC), and each provided stratified detection rates according to serum Tg levels (stimulated or suppressed). A detailed summary of study characteristics is provided in Table 1 (Ref. [14,17–19,21,22,28,29]).

Methodological Quality Assessment

Risk-of-bias assessment using QUADAS-2 is illustrated in Fig. 2 (per-study heatmap) and Fig. 3 (domain-summary plot). Across studies, an unclear risk-of-bias was the most frequent assessment, especially in the domains of

Table 1. Study characteristics.

Study ID	Country/Center	Design	Unit	Population (key inclusion)	Tg type at/around PET	WBS status	N	PET+ (x)	Notes
Trybek_2014 *et al.* [19]	Poland (single center)	NR observational case series	Patient	Suspected recurrence/metastasis; elevated Tg; conventional imaging negative	Stimulated Tg (rhTSH or withdrawal)	Negative	19	6	ROC cut-off 28.5 ng/mL; Tg >28.5 ng/mL: 6/6 PET+; Tg ≤28.5 ng/mL: 0/13 PET+
Boktor_2022 *et al.* [14]	Australia (single center)	NR observational	Patient	DTC; negative 131I WBS; elevated stimulated Tg; anti-Tg Ab <10 kU/L	Stimulated Tg (pmol/L)	Negative	67	30	Tg groups <5/5–10/>10 pmol/L; TP/TN/FP/FN by group
Kolodziej_2021 *et al.* [28]	Poland (single center)	Retrospective	Scan	DTC; diagnostic WBS negative; sTg >1 ng/mL; US negative	natTg & sTg reported	Negative	37	16	natPET 6/15; sPET 10/22; multiple ROC cut-offs; possible repeat patients
Filippi_2021 *et al.* [21]	Italy (3 centers)	Retrospective observational	Patient	DTC after RAI; PET/CT under TSH stimulation; anti-Tg Ab elevated excluded	Stimulated Tg	Negative	66	51	Setting 1 Tg >10 ng/mL (n = 40); Setting 2 Tg ≤10 ng/mL + suspicious imaging (n = 26)
Albano_2021 *et al.* [18]	Italy (single center)	Retrospective	Patient	Detectable Tg; negative 131I scan; anti-Tg Ab negative	Stimulated Tg (within 2 months)	Negative	139	115	ROC cut-off 18 ng/mL; Tg <18 ng/mL: 31/52 PET+; Tg ≥18 ng/mL: 84/87 PET+
Choi_2016 *et al.* (Tg+) [17]	Korea (2 hospitals)	Retrospective	Patient	PTC; negative diagnostic scan; Tg-positive group defined by stimulated Tg >2 ng/mL	Stimulated Tg (ETS)	Negative	75	21	Use Tg-positive cohort only; Tg 2–10 ng/mL: 2/39 PET+; Tg >10 ng/mL: 19/36 PET+
Prestwich_2012 *et al.* [29]	UK (single center)	Retrospective	Scan	DTC; rTSH-stimulated PET/CT (mixed indications)	Unstimulated Tg groupings; some stimulated Tg available	Mixed	58	25	Unstimulated Tg <10 ng/mL: 11/35 PET+; >10 ng/mL: 13/18 PET+; repeat patients
Döner _2016 [22]	Turkey (single center)	Retrospective	Patient	DTC; negative 131I scan; high Tg; normal anti-Tg	Tg elevated; stimulation not explicit	Negative	104	54	ROC cut-off 10.4 ng/mL; group sizes <10.4 ng/mL n = 40; ≥10.4 ng/mL n = 64; PET+ by group NR

NR, Not Reported; Tg, thyroglobulin; PET, positron emission tomography; WBS, Whole-Body Scan; rhTSH, recombinant human Thyroid-Stimulating Hormone; ROC, Receiver Operating Characteristic; DTC, differentiated thyroid carcinoma; TN, True Negative; FP, False Positive; FN, False Negative; PTC, papillary thyroid carcinoma; ETS, Endogenous TSH Stimulation.

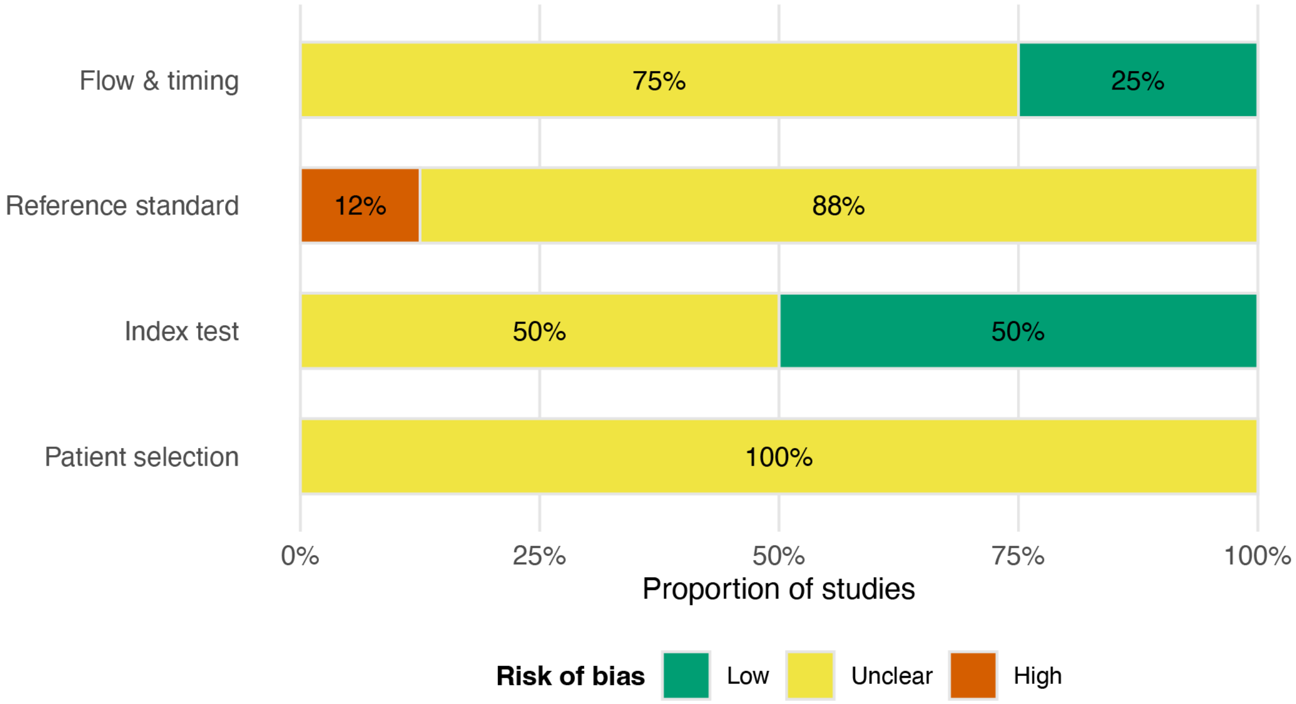

Fig. 3. Summary plot of risk-of-bias assessments across all included studies, showing proportions rated as low, unclear, or high risk in each QUADAS-2 domain.

patient selection, reference standard, and flow/timing, reflecting the incomplete reporting typical of retrospective imaging research. The exact QUADAS-2 assessment was shown in **Supplementary Table 1**.

Pooled Per-Patient Detection Rate of ^{18}F-FDG PET/CT

Six studies provided per-patient PET/CT detection rates suitable for quantitative synthesis. Under a random-effects model, the pooled detection rate of ^{18}F-FDG PET/CT was 0.54 (95% CI 0.29–0.78), with considerable heterogeneity (I^2 = 93.4%). Individual study estimates ranged from 0.28 to 0.83, consistent with substantial clinical heterogeneity related to Tg levels, TSH stimulation, imaging protocols, and verification pathways across studies. The meta-analysis is presented in Fig. 4.

PET/CT Detection Rate Across Study-Defined Tg Strata: Evidence of a Threshold Effect

Across 11 Tg-defined strata reported in the included studies, PET/CT detection rates increased monotonically with rising Tg levels. The detection rates were near zero in multiple cohorts within the Low Tg strata (<2–5 ng/mL). In the Intermediate Tg strata (5–10 ng/mL), detection rates markedly increased, ranging from 20 to 65% across studies; in the High Tg strata (>10 ng/mL), the rates were consistently elevated at 60–97%. This trend demonstrates a clear threshold effect, indicating that ^{18}F-FDG PET/CT becomes markedly more informative once Tg reaches a moderate-to-high concentration. The pooled analysis of Tg-stratified detection rates is shown in Fig. 5 and **Supplementary Table 2**, providing central evidence supporting the Tg threshold hypothesis.

High-Tg Subgroup Analysis: Tg >10 ng/mL and Tg ≥18 ng/mL

Two clinically relevant Tg thresholds were examined. In the group of Tg >10 ng/mL, two studies contributed to this subgroup (Fig. 6A). The pooled PET/CT detection rate was 0.71 (95% CI 0.00–1.00; I^2 = 88.3%). In the group of Tg ≥18 ng/mL, only one study (Albano *et al.* [18]) reported a significantly high detection rate of 0.97 (95% CI 0.90–0.99) (Fig. 6B). These findings suggest that PET/CT is a high-yield diagnostic test when Tg exceeds approximately 10–18 ng/mL.

Stimulated Tg–Only Analysis

In studies explicitly reporting TSH-stimulated Tg, the pooled PET/CT detection rate remained high at 0.60 (**Supplementary Fig. 1**). This subgroup aligns more closely with clinical decision-making scenarios where stimulated Tg is used to guide further imaging.

Sensitivity Analyses

To assess the robustness of pooled estimates, three prespecified sensitivity analyses were performed. After excluding Doner 2016 (**Supplementary Fig. 2A**) and Trybek 2014 (**Supplementary Fig. 2B**), the pooled detection rate

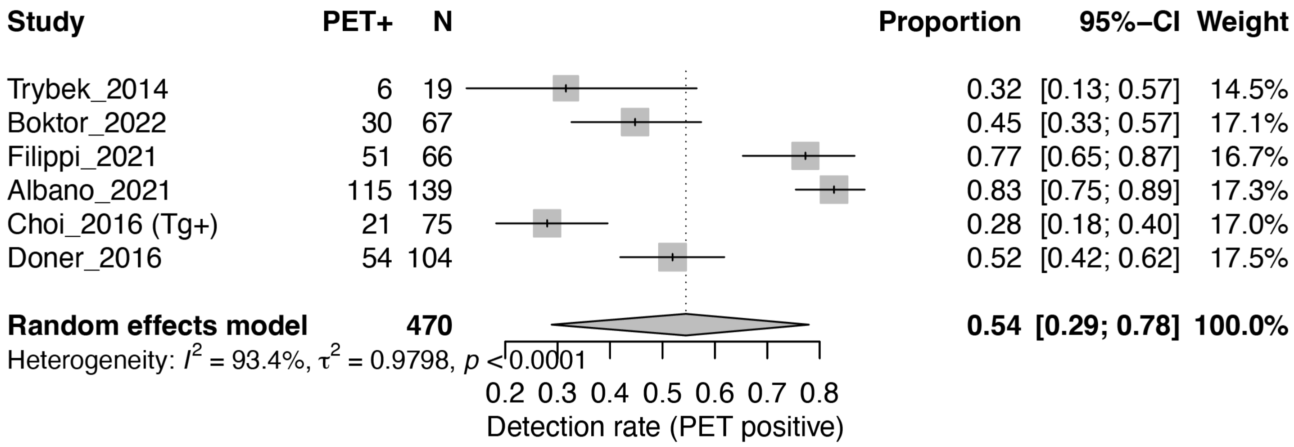

Fig. 4. Forest plot of per-patient ^{18}F-FDG PET/CT detection rates across included studies (random-effects model). Considerable heterogeneity was observed (I^2 = 93.4%). ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

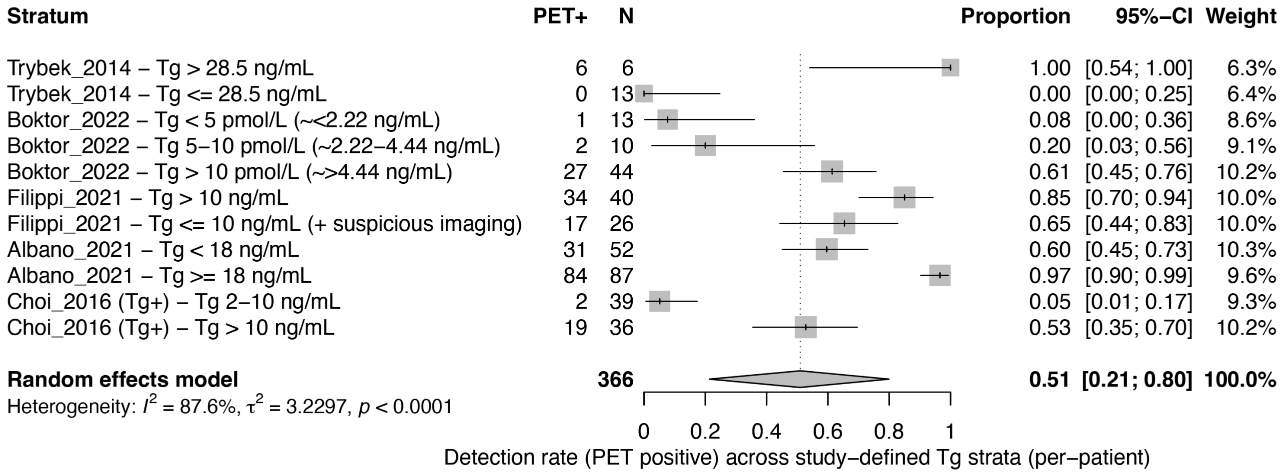

Fig. 5. Forest plot of per-patient PET/CT detection rates across study-defined Tg strata, demonstrating a consistent upward trend in diagnostic yield with increasing thyroglobulin levels. Note: Some studies contributed data to multiple Tg strata (e.g., a single cohort stratified into <5, 5–10, and >10 ng/mL groups). Therefore, these subgroups are displayed separately to illustrate the threshold effect, but they represent partitions of the same original patient cohorts. Tg, thyroglobulin.

was 0.55 and 0.58, respectively. Furthermore, after excluding both Doner 2016 and Trybek 2014 (**Supplementary Fig. 2C**), the pooled detection rate was 0.60. Despite persistent heterogeneity, the pooled effect remained highly stable across scenarios, indicating that findings were not driven by any single study.

Discussion

This systematic review and meta-analysis provided the first pooled evidence examining the threshold effect of serum thyroglobulin (Tg) levels on ^{18}F-FDG PET/CT detection rates in recurrent differentiated thyroid carcinoma (DTC) with negative radioactive iodine (RAI) scintigraphy. The pooled per-patient detection rate of 0.54 demonstrates moderate diagnostic yield across the included studies. A clear threshold effect emerged from the Tg-stratified analysis: detection rates approached zero in low-Tg strata (<5 ng/mL), increased substantially in intermediate-Tg strata (5–10 ng/mL), and reached consistently high values (60–97%) in high-Tg strata (>10 ng/mL). At Tg $\geq$18 ng/mL, detection rates reached 97%, suggesting that ^{18}F-FDG PET/CT becomes a high-yield diagnostic test above this threshold.

Our findings align with and extend previous meta-analyses in this field. Bang *et al.* [30] reported a pooled sensitivity of 0.87 and specificity of 0.84 for ^{18}F-FDG PET/CT in detecting recurrent disease in TENIS syndrome. Gelardi *et al.* [10] conducted a comprehensive systematic review of nuclear imaging modalities in TENIS syndrome, demonstrating comparable diagnostic performance across 22 studies. These prior investigations focused primarily on overall

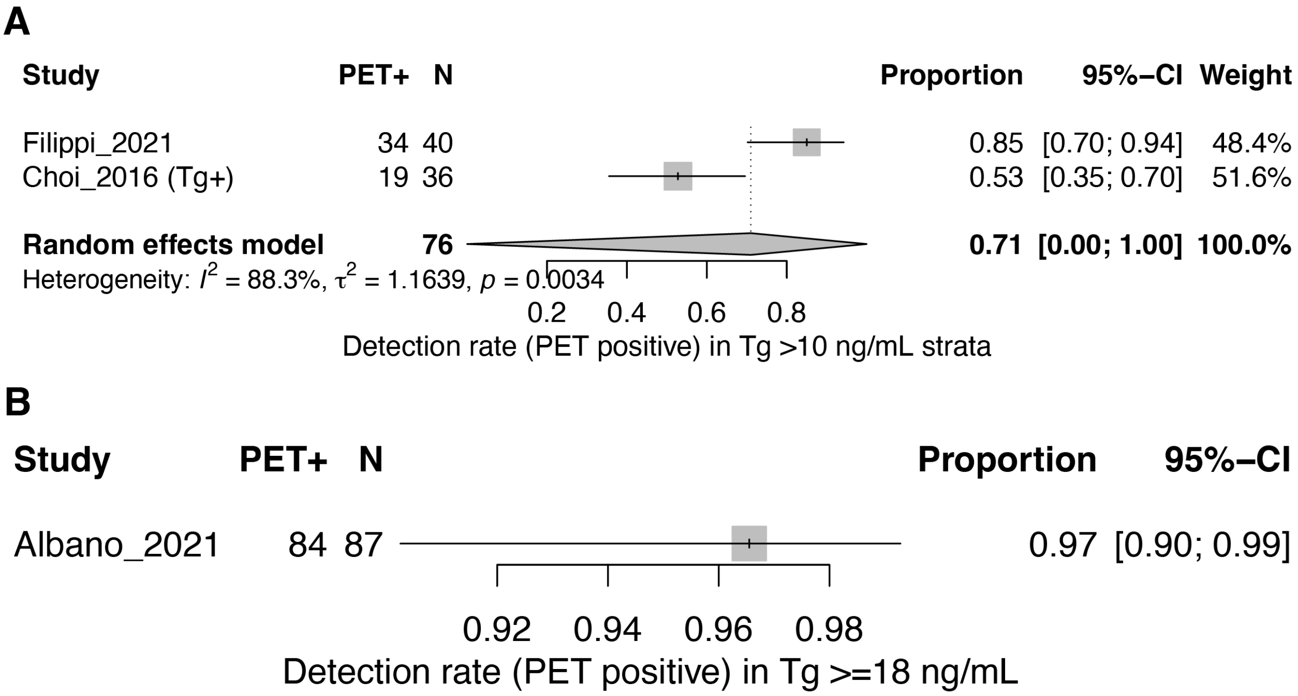

Fig. 6. Forest plots demonstrating PET/CT detection rates in high-Tg subgroups. (A) Tg >10 ng/mL subgroup. (B) Tg ≥18 ng/mL subgroup. These analyses highlight a pronounced threshold effect.

diagnostic accuracy rather than Tg-stratified performance. The present study fills this knowledge gap by quantifying the relationship between Tg concentration and detection rates. Our observed pooled detection rate of 0.54 reflects the heterogeneous in Tg distributions across the included studies, with lower rates observed in cohorts that enrolled patients with relatively low Tg levels.

The threshold effect observed in this meta-analysis has a clear biological basis. The phenomenon of tumor dedifferentiation in DTC leads to simultaneous loss of iodine-concentrating ability and an increase in glucose metabolism, commonly termed the “flip-flop” phenomenon [31,32]. Poorly differentiated thyroid cancer cells demonstrate reduced sodium-iodide symporter (NIS) expression and enhanced related transporter activity, creating reciprocal patterns of radioiodine and FDG uptake [33]. Petranović Ovčariček *et al.* [31] emphasized that ^{18}F-FDG PET/CT serves as the imaging modality of choice for RAI-refractory disease precisely because of this metabolic reprogramming. The higher Tg levels observed in our high-detection subgroups likely reflect greater tumor burden and more advanced dedifferentiation, both of which correlate with increased FDG avidity [34].

Tumor histology represents another potential variable influencing the Tg threshold. Follicular thyroid carcinoma (FTC) is generally associated with a higher risk of distant metastases and may exhibit different glucose metabolic patterns compared to papillary thyroid carcinoma (PTC). Ideally, a stratified analysis by histological subtype would define specific thresholds for PTC and FTC. However, the majority of included studies reported only aggregate detection rates, without providing detailed data linking Tg levels to PET/CT outcomes specifically for each histological subtype.

The clinical implications of these findings are substantial. Current guidelines recommend considering ^{18}F-FDG PET/CT in patients with high Tg levels and negative RAI imaging [4,35]. Our meta-analysis provides quantitative support for this recommendation. At Tg levels below 5 ng/mL, detection rates were near zero across multiple cohorts, suggesting that routine ^{18}F-FDG PET/CT offers minimal diagnostic benefit in this population. Boktor *et al.* [14] demonstrated that the detection rate increased significantly when stimulated Tg exceeded 10 pmol/L, with 92.9% of positive PET findings occurring in patients with Tg above this threshold. Albano *et al.* [18,24] identified 18 ng/mL as an optimal cutoff, above which detection rates reached 97%. These converging findings suggest that a Tg threshold between 10 and 18 ng/mL may represent the optimal range for initiating ^{18}F-FDG PET/CT evaluation. It should be noted that the high detection rate (97%) observed at Tg ≥18 ng/mL is primarily driven by the data from Albano *et al.* [18]. Although this finding is compelling, reliance on a single-center dataset introduces the potential for sampling error and center-specific bias. Therefore, this specific numeric threshold should be interpreted with caution until validated by multi-center studies.

Recent evidence suggests that Tg kinetics may complement or even supersede absolute Tg values in predicting ^{18}F-FDG PET/CT results. Giovanella *et al.* [36] demonstrated in a meta-analysis that Tg doubling time (Tg-DT) values significantly predict PET/CT positivity, with a sensitivity of 0.84 and a specificity of 0.71. Albano *et al.* [24] further showed that Tg-DT offers a better threshold (no more than 2.5 years) than absolute Tg level for selecting optimal candidates for ^{18}F-FDG PET/CT in non-iodine avid DTC. In patients with Tg-DT of less than 1 year, the survival risk ratio was 2.09, indicating a poor prognosis [36]. These findings suggest that rapidly rising Tg levels warrant earlier imaging regardless of absolute values. Araz *et al.* [37] confirmed the relationship between Tg-DT and FDG PET metabolic parameters, reinforcing the prognostic significance of Tg kinetics. Future studies should incorporate Tg-DT into predictive algorithms alongside absolute Tg thresholds.

Beyond its diagnostic utility, ^{18}F-FDG PET/CT positivity carries significant prognostic implications. Manohar *et al.* [38] reported five-year overall survival of only approximately 30% and median survival of 3–4 years following diagnosis of metastatic RAI-refractory disease. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) derived from FDG PET/CT predict survival in this population [38,39]. Nervo *et al.* [32] emphasized that FDG-avid lesions correlate with more aggressive disease biology and poorer clinical outcomes. The prospective study by Phuong *et al.* [39] demonstrated that clinico-pathological factors combined with FDG PET/CT metabolic parameters effectively predict progression-free survival in RAI-refractory DTC. These observations underscore the significance of ^{18}F-FDG PET/CT not only for lesion detection but also for risk stratification and treatment planning.

The management of patients with TENIS syndrome remains challenging. Yuan *et al.* [9] demonstrated that empirical RAI therapy improves progression-free survival and Tg normalization rates in TENIS syndrome without structural disease. Basu *et al.* [12] proposed a step-care algorithm incorporating ^{18}F-FDG PET/CT for localizing disease and guiding subsequent surgical or systemic therapy. Identification of FDG-avid lesions enables targeted interventions, including surgical resection, external beam radiotherapy, and tyrosine kinase inhibitor therapy [40,41]. Kim *et al.* [41] evaluated the efficacy of empirical RAI therapy in patients with both well-differentiated thyroid carcinoma and TENIS syndrome, providing additional management guidance. The threshold effect identified in our meta-analysis directly informs this decision algorithm by clarifying when ^{18}F-FDG PET/CT is most likely to yield actionable findings.

Substantial heterogeneity was observed across the included studies ($I^2 = 93.4\%$), warranting cautious interpretation of the pooled results. This heterogeneity likely reflects differences in patient populations, Tg assay methodologies, TSH stimulation protocols, and verification standards. Van de Berg *et al.* [42] highlighted the absence of a consistent definition of recurrence in DTC literature, which may contribute to outcome heterogeneity. Despite this heterogeneity, the monotonic association between Tg levels and detection rates was consistent across studies, strengthening confidence in the threshold effect. Sensitivity analyses demonstrated robustness of the pooled estimates, with detection rates remaining stable (0.55–0.60) after sequential exclusion of individual studies.

A significant challenge in synthesizing the available evidence is the variability in Tg stratification thresholds across included studies. Cutoff values for defining "high" Tg ranged widely, from $>$10 ng/mL to $>$28.5 ng/mL. This heterogeneity precluded a formal meta-regression analysis to determine a mathematically unified optimal threshold. The impact of these differing thresholds on our pooled results must be considered with caution. Specifically, the "High-Tg" category in our meta-analysis aggregates patients with moderately elevated Tg levels (e.g., 10–18 ng/mL) and those with very high levels. This aggregation likely yields a conservative estimate of the detection rate in the highest Tg subgroups. Despite this limitation, the monotonic trend remains robust: regardless of the specific cutoff used, all studies consistently reported negligible detection rates at the lower end of their respective scales and substantially higher rates at the upper end. The data consistently support a clinical decision zone between 10 and 18 ng/mL, where the diagnostic yield of ^{18}F-FDG PET/CT transitions from low to clinically actionable.

Several limitations should be acknowledged. First, the literature search was restricted to PubMed and Web of Science, potentially missing relevant studies indexed in other databases. Second, most included studies were retrospective, introducing inherent risks of selection and verification biases. Third, Tg stratification thresholds varied across studies, precluding meta-regression analysis of specific cutoff values. Fourth, the reference standard for determining true disease status was heterogeneous, ranging from histopathological confirmation to clinical follow-up. Additionally, anti-thyroglobulin antibody interference was not systematically addressed in all studies, which may affect Tg reliability in some patients. Publication bias assessment was not performed due to the limited number of included studies. Furthermore, the pooled estimate for the highest Tg stratum ($\geq$18 ng/mL) was based on a limited sample size, which restricts the generalizability of this specific cutoff value. Finally, we were unable to perform subgroup analyses based on histological subtypes (papillary vs. follicular) because the primary studies did not consistently report Tg-stratified detection rates separately for each subtype. Future research should aim to report diagnostic yields distinctively for PTC and FTC to refine subtype-specific thresholds.

Future research should address several priorities. Prospective multicenter studies with standardized Tg thresholds and uniform reference standards are needed to validate the threshold effect identified in this meta-analysis. Integration of Tg-DT alongside absolute Tg values may refine patient selection algorithms. Emerging imaging modalities, including 68Ga-FAPI PET/CT and 68Ga-DOTA-RGD2 PET/CT warrant comparative evaluation against ^{18}F-FDG PET/CT in this population. Cost-effectiveness analyses should evaluate the impact of Tg threshold-guided imaging strategies on healthcare resource utilization and patient outcomes.

Conclusion

This systematic review and meta-analysis demonstrated a threshold effect of serum Tg levels on ^{18}F-FDG PET/CT detection rates in recurrent DTC with negative RAI scintigraphy. Detection rates increased monotonically with rising Tg concentrations, approaching near-complete sensitivity at Tg levels $\geq$18 ng/mL. These findings provide quantitative evidence supporting current guideline recommendations and offer a framework for individualized imaging decisions based on Tg concentration. A Tg threshold of approximately 10–18 ng/mL appears to optimize ^{18}F-FDG PET/CT diagnostic yield while avoiding unnecessary imaging in low-risk patients.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

WPL and RZL designed the research study. YXZC and QGG performed the research. JJZ analyzed the data. WPL drafted the article. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638206.77.

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