RESEARCH

Diagnostic accuracy of routine calcitonin measurement for the detection of medullary thyroid carcinoma in the management of patients with nodular thyroid disease: a meta-analysis

Irfan Vardarli[1], Manuel Weber[2], Frank Weidemann[1], Dagmar Führer[3], Ken Herrmann[2] and **Rainer Görges[2]**

[1]Department of Medicine I, Klinikum Vest, Knappschaftskrankenhaus Recklinghausen, Academic Teaching Hospital, Ruhr-University Bochum, Recklinghausen, Germany
[2]Department of Nuclear Medicine, University Hospital Essen, Essen, Germany
[3]Department of Endocrinology, Diabetes and Metabolism, Clinical Chemistry – Division of Laboratory Research; Endocrine Tumor Center at WTZ/Comprehensive Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Correspondence should be addressed to I Vardarli: irfan.vardarli@alumni.uni-heidelberg.de

Abstract

Objective: The usefulness of routine calcitonin measurement for early detection of medullary thyroid carcinoma (MTC) in patients with nodular thyroid disease (NTD) has been investigated in various studies. Recently, a Cochrane review has been published on this issue, but a meta-analysis is lacking yet. Therefore, we performed this meta-analysis.

Methods: We performed an electronic search using PubMed/Medline, Embase and the Cochrane Library. Studies assessing the diagnostic accuracy of routine calcitonin measurement for detecting MTC in patients with NDT were selected. Statistics were performed by using Stata software, risk of bias was assessed using Review Manager version 5.3.

Results: Seventeen studies, involving 74,407 patients were included in the study. Meta-analysis, using the bivariate random effects model and the hierarchical summary receiver operating characteristic (HSROC) curve revealed the following pooled estimates: sensitivity 0.99 (95% CI, 0.81–1.00), specificity 0.99 (95% CI, 0.97–0.99), positive likelihood ratio (L+) 72.4 (95% CI, 32.3–162.1), and negative likelihood ratio (L−) 0.01 (95% CI, 0.00–0.23). Meta-regression analysis showed that the threshold of basal calcitonin is an independent factor, but in particular performing stimulation test is not an independent factor.

Conclusions: We showed that routine basal serum calcitonin measurement in the management of patients with thyroid nodules is valuable for the detection of MTC. However, the published cut-off values should be considered and, if applicable, the patients monitored in a wait-and-see strategy by experienced physicians to avoid overtreatment.

Introduction

Calcitonin (Ctn) is secreted by the C-cells of the thyroid (1) and is a valuable tumor marker in patients with medullary thyroid carcinoma (MTC) (2). Medullary thyroid cancer, originated from the C-cells (3), occurs rarely and corresponds to 1–3% of all histologically proven thyroid cancers in the United States, with a prevalence of 0.1–1.4% in patients with nodular thyroid disease (2, 4), appearing either sporadically or in a hereditary form as a component of the type 2 multiple endocrine neoplasia (MEN) syndromes, MEN2A and MEN2B, and the related syndrome, familial MTC (FMTC) (2). Serum Ctn levels may be increased in patients with autoimmune thyroiditis, several extrathyroidal tumors like various enteric and pulmonary neuroendocrine tumors, small cell and large cell lung cancers or prostate cancer, mastocytosis, chronic renal failure and severe pulmonary or hepatic diseases (5, 6, 7, 8, 9, 10, 11, 12).

The newest immunochemiluminometric assays (ICMAs) for measuring Ctn according to the 'sandwich principle' are highly sensitive and specific for mature (monomeric) form of Ctn, with largely eliminated cross-reactivity with procalcitonin or other calcitonin-related peptides (13, 14).

The routine measurement of serum Ctn in patients with nodular thyroid disease may be a suitable method to identify MTC, often in an early stage, with a positive impact on prognosis (15). Even though its cost effectiveness has been shown (4), the recommendations for the routine measurement of Ctn are not uniform. It was advised by the European Consensus published in 2006 (16). However, the ATA and AACE/ACE/AME guidelines do not advocate for or against the routine measurement of serum Ctn (17, 18) or limit the Ctn measurement to patients who are submitted for surgery (17). In a recent systematic review (including trials published until 2013) Verbeek *et al.* showed the high sensitivity and specificity
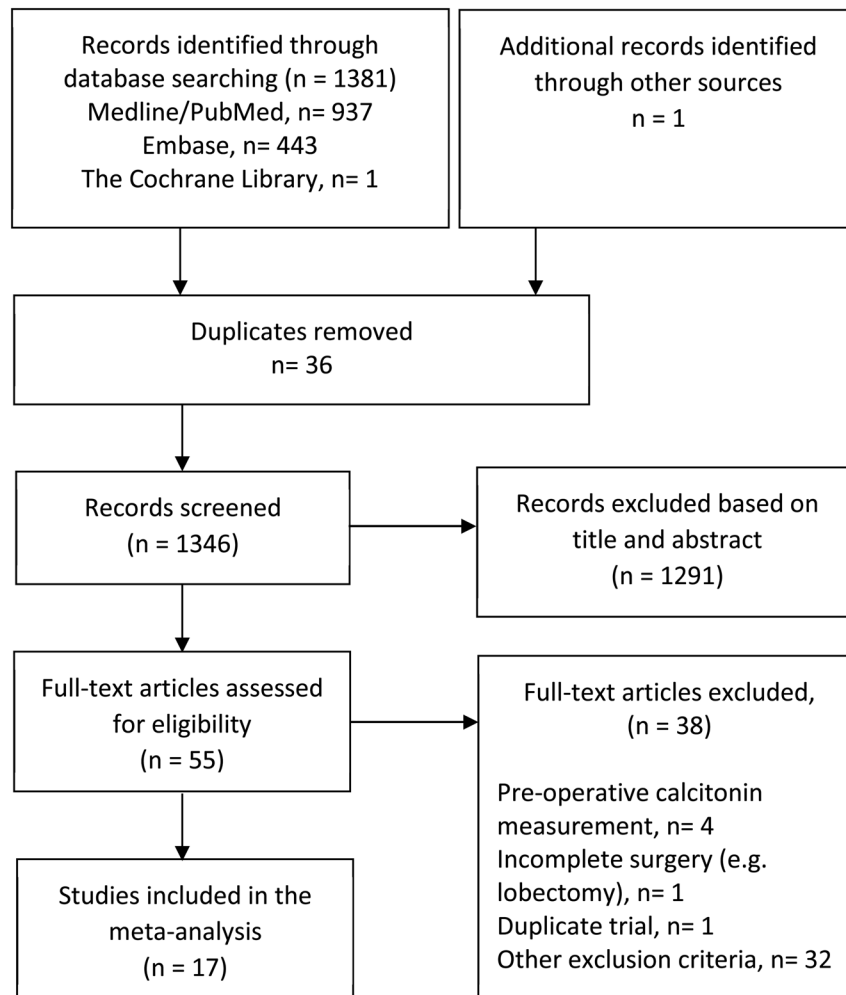

Figure 1
Flow chart for inclusion and exclusion of trials, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Table 1 Characteristics of the included studies; *n* = 17 trials.

First author year	Country	Study design	Basal Ctn threshold, pg/mL	Stimulation test (Pentagastrin) if basal Ctn is elevated	Stimulated Ctn threshold, pg/mL	Pat. total, *n*	Studies with basal calcitonin threshold				Studies with basal calcitonin threshold and stimulated Ctn threshold				Studies with basal calcitonin threshold and stimulated Ctn threshold												Nodular thyroid disease; status[&]	Calcitonin assay
															Females				Males								
							TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN		
Rieu 1995 (34)	F	PCo	RIA: 35 IRMA: 10 (m/f)	Yes	100 (m/f)	469	4	0	0	465	4	0	0	465									Uni-nodular, multi-nodular	1989: RIA[b §] 1990–1993: IRMA[c §§]
Oezgen 1999 (35)	TR	Pco	30 (m/f)	No	–	773	4	0	0	769					3	0	0	583	1	0	0	186	Uni-nodular, multi-nodular	RIA[d §]
Hahm 2001 (36)	KR	Co	10 (m/f)	Yes	100 (m/f)	1448	10	46	0	1392	10	2	0	1436									nodular	IRMA[e §]
Hatzl-Griesenhofer 2002 (37)	A	RCo	4.6 (f), 11.5 (m)	Yes (not, if bCtn is >80 pg/mL)	100 (m/f)	3899	12	218	0	3669	12	23	0	3796	7	133	0	2933	5	85	0	736	Nodular diffuse-nodular	ICMA[f §§]
Elisei 2004 (15)	I	Co	20 (m/f)	Yes (in n=44)	60 (m/f)	10864	44	3	0	10817	44	0	0	10818									Uni-nodular, multi-nodular	IRMA[g §§]
Karanikas 2004 (38)	A	Co	10 (m/f)	Yes	100 (m/f)	195	1	12	0	182	1	1	0	193									Uni-nodular, multi-nodular	ICMA[f §§]
Vierhapper 2005 (39)	A	Co	10 (m/f)	Yes	100 (m/f)	10157[a]	33	474	3	9647	31	72	3	10025	24	302	1	8487	9	172	2	1860	nodules	IRMA[c] ICMA[f §§]
Papi 2006 (40)	I	Co	5 (m/f)	Yes (not, if bCtn is ≥100 pg/mL)	100 (m/f)	1425	9	14	0	1402	9	1	0	1415	4	11	0	1129	5	3	0	273	Uni-nodular, multi-nodular	ICMA[f §§]
Costante 2007 (41)	I	Co	20 gray zone 10–<20 (m/f)	Yes (not, if bCtn is ≥100 pg/mL)	100 (m/f)	5817	15	267	0	5535	15	11	0	5791									Nodular multi-nodular	ICMA[f §§]
Rink 2009 (42)	D	Co	10 (m/f)	Yes	80 (m) 50 (f)	21928	28	857	0	21043	11	51	0	21199									nodular	IRMA[h §§]
Hasselgren 2010 (43)	DK	RCo	RIA: 100 (m/f) ICMA: 10.5(m), 7.3(f)	No	–	702	6	33	0	663													Uni-nodular, multi-nodular	IRMA[i §?] ICMA[$ §§]
Herrmann 2010 (44)	D	RCo	10 (m/f)	Yes (not, if bCtn is ≥100 pg/mL)	100 (m/f)	1007	2	15	0	990	2	3	0	1002	1	0	0	566	1	15	0	424	nodular	ICMA[j §§]
Grani 2012 (45)	I	CsRo	10 (m/f)	No	–	1073	2	39	0	1032													Uni-nodular, multi-nodular	ICMA[k §?]
Schneider 2012 (46)	D	Co	13 (m/f)	Yes (not, if bCtn is ≥100 pg/mL, *n* = 14)	100 (m/f)	11270	10	22	2	11236	9	8	2	11238									nodules	ICMA[j §§]

(Continued)

Table 1 Continued.

First author year	Country	Study design	Basal Ctn threshold, pg/mL	Stimulation test (Pentagastrin) if basal Ctn is elevated	Stimulated Ctn threshold, pg/mL	Pat. total, n	Studies with basal calcitonin threshold				Studies with basal calcitonin threshold and stimulated Ctn threshold				Studies with basal calcitonin threshold and stimulated Ctn threshold								Nodular thyroid disease; status[&]	Calcitonin assay
															Females				Males					
							TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN		
Giovanella 2013 (47)	CH	PCo	10 (m/f)	Yes	100 (m/f)	1236	2	12	0	1222	2	2	0	1232	0	5	0	669	2	7	0	553	nodular	ICMA[i]§§
Turk 2017 (48)	TR	RCo	10 (m/f)	Yes (not, if bCtn is ≥100 pg/mL)	100 (m/f)	640	4	21	0	615													nodular	ICMA[i]§§
Silvestre 2019 (49)	P	RCo	10 (m/f)	No	-	1504	12	57	0	1435													nodular	ICMA[i]§§

The ranges of the nodal sizes of the respective screening population are not given in the individual studies. Schneider *et al.* (46) included patients with a nodule size ≥2 mm. In the study by Grani *et al.* (45) only those patients were included who were referred to their institution to undergo fine-needle aspiration cytology (FNAC) of thyroid nodules because of clinical or ultrasonographic suspicion; this suggests that these nodules were larger (e.g. >1 cm). In all other studies, patients with ultrasonographically confirmed nodules irrespective of size were included. Only the retrospective analysis by Silvestre *et al.* (49) does not specifically describe that the nodules were objectified by ultrasonography (the exclusion criteria were absence of clinical information, and no evidence of NTD or individuals with a familial history of MTC). In the study by Giovanella *et al.* (47) patients who only had autonomously functioning thyroid nodules where not included. In some studies, further exclusion criteria were defined (e.g. taking proton pump inhibitors or autoimmune thyroid diseases); however, corresponding information was not made consistently in all studies. [a]Incl. 3843 patients without thyroid nodules; [b]Malinckrodt Medical SA; [c]CIS; [d]DSL 5200 Ultrasensitive calcitonin RIA kit, Diagnostic System Laboratories; [e]Medgenix CT-U.S.-IRMA kit, BioSource Europe; [f]Nichols Institute Diagnostics; [g]ELSA-hCT kit, CIS; [h]Calcitonin-IRMA, IBL or Calcitonin IRMA magnum, Medipan; [i]Double-antibody RIA MediLab A/S; [j]Immulite 2000 Calcitonin, Siemens; [k]automated two-site immunochemiluminometric assay (manufacturer not specified); [§]assay not monomer-specific, [§§]assay monomer-specific, [97]monomer-specificity unclear, [*]two different assays have been used, RIA (for n= 668, ICMA (for n= 14 patients); [&]All studies focused on patients with nodular thyroid disease (NDT; at least one thyroid nodule). Co, cohort study; CsRo, cross-sectional, retrospective observational study; Ctn, calcitonin; f, females; FN, false negative; FP, false positive; ICMA, immunochemiluminometric assay; m, males; PCo, prospective cohort study; RCo, retrospective cohort study; Study, study type; TN, true negative; TP, true positive; international country codes: A, Austria; CH, Switzerland; D, Germany; DK, Denmark; F, France; I, Italy; KR, South Korea; P, Portugal; TR, Turkey.

of Ctn testing, still questioning the value of its routine use due to the low prevalence of MTC and to the risk of overdiagnosis (19). They included the trials published until 2013, searched the electronic databases last at June 6, 2018, but not assessed the potentially relevant studies identified in their last search for inclusion. A meta-analysis on this subject has not been published until now. Therefore, we performed this meta-analysis to elucidate the diagnostic accuracy of routine serum calcitonin measurement for detection of MTC in the management of patients with nodular thyroid disease.

Patients and methods

The meta-analysis was performed according to the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATE) guideline on reporting a diagnostic test accuracy meta-analysis; an updated Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (20, 21) (the checklist is provided as Supplementary Table 1, see section on supplementary materials given at the end of this article). A predefined study protocol was created but not registered. Ethical approval or informed consent was not required for this meta-analysis.

Data search and study selection

We searched the electronic databases of PubMed/MEDLINE, EMBASE and Cochrane Library systematically (updated on December 10, 2020) with the search strategies given in Supplementary Table 2; without language and time restriction in any of these databases. Furthermore, references of retrieved studies were searched for eligible studies. Electronic archives of medical societies (Endocrine Society (https://www.endocrine.org/meetings/endo-annual-meetings; accessed December 18, 2020) and Deutsche Gesellschaft für Nuklearmedizin e.V. (https://www.nuklearmedizin.de/jahrestagungen/abstr_online2020/abstract_search.php?navId=227; accessed December 18, 2020) were also searched. Studies meeting the following inclusion criteria were included: routine calcitonin measurement in serum (with or without a pentagastrin or calcium stimulation test) was performed routinely in all included patients with nodular thyroid disease, diagnosed by palpation or ultrasonography. Exclusion criteria were: data for 2 × 2 table not provided; preoperative measurement of calcitonin in serum; calcitonin measurement as screening test, as screening is epidemiologically defined as testing in healthy people

(people with thyroid nodules are not healthy); inclusion of patients with familial history of medullary thyroid carcinoma (MTC); incomplete surgery (e.g. lobectomy); case reports or case series; case–control study; duplication of a study (in case of duplication, inclusion of the study with the longest follow-up); only meeting communication, not published as full-text article.

Data extraction and quality assessment

Two authors (I V and R G) independently reviewed all eligible articles and extracted the relevant data. In case of disagreement, after consultation with a third author

(M W) regarding the eligibility, consensus was found. We used the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (22, 23) in Review Manager (RevMan) version 5.3. (Nordic Cochrane Center), which assesses the quality of the included studies in terms of biases affecting their applicability in four domains: index test, reference standard, patient selection and flow and timing. The two authors evaluated each of the items. *Index test* was defined as measurement of basal Ctn in serum (and additionally Ctn measurement in serum after stimulation, if needed). There were various assays for this test, which has to be addressed. Histological observation was considered as the *reference standard*
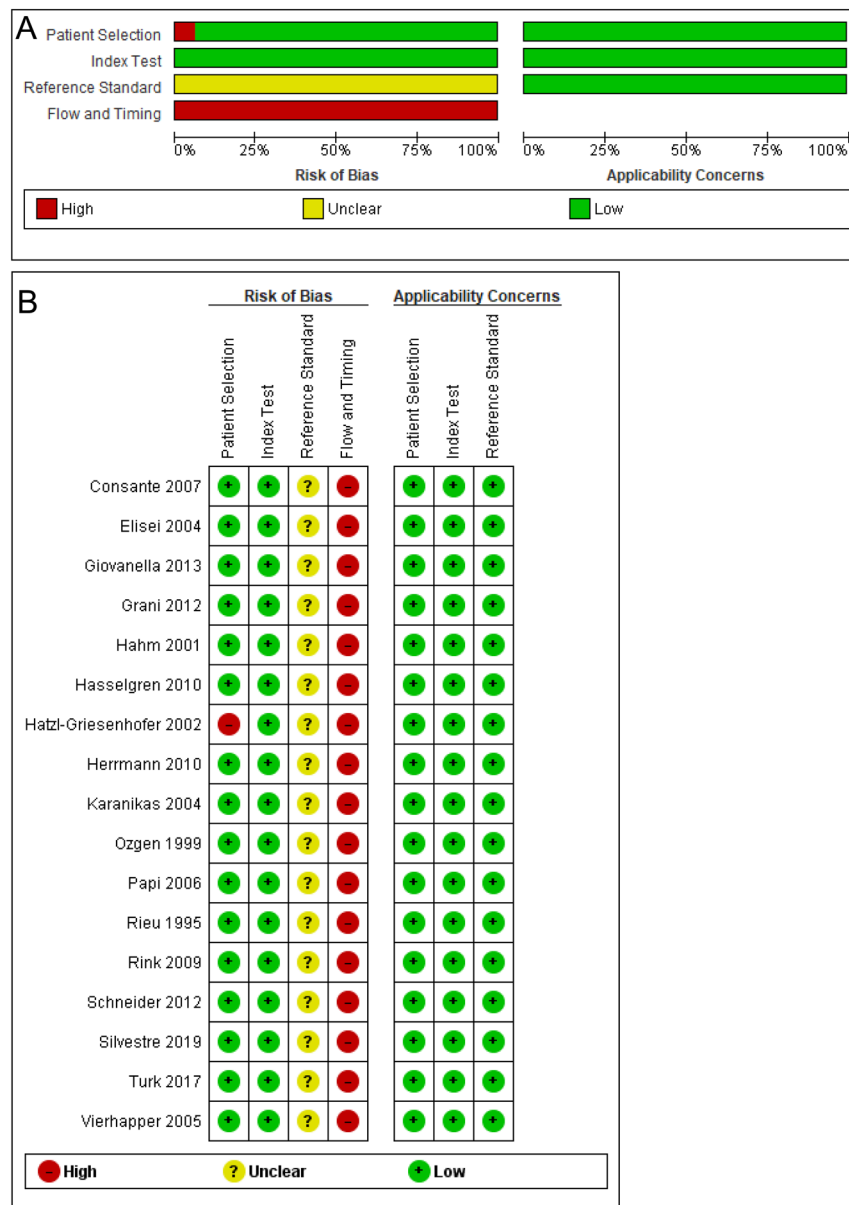

Figure 2
(A) Risk of bias and applicability concerns graph on each domain presented as percentages across all included studies. (B) Risk of bias and applicability concerns summary for each included study. *n* = 17 trials.
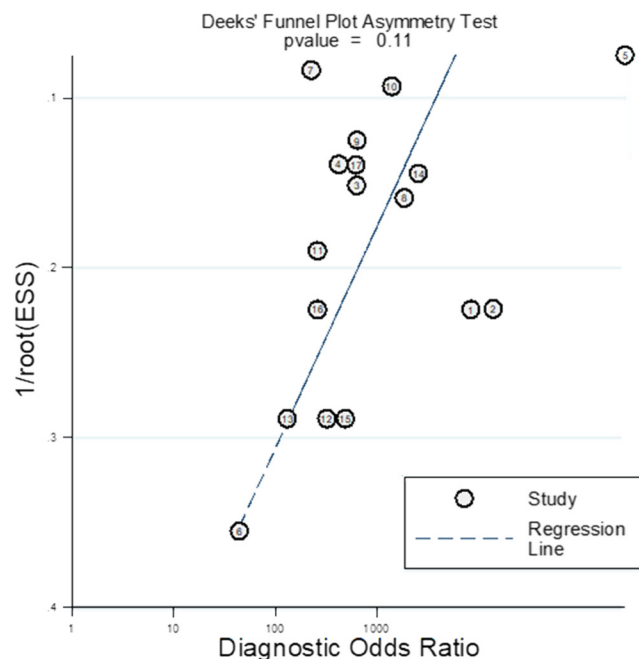
Figure 3
Deeks' funnel plot asymmetry test for all included studies (with a basal calcitonin threshold between 4.6 and 100 pg/mL); *P* < 0.1 indicates asymmetry and potential publication bias. *n*= 17 trials.

(gold standard), however in patients without calcitonin elevation surgery would be performed only due to other reasons; this is a dilemma. As a consequence, we used clinical follow-up for at least one year as an alternative. *Outcom*e was defined as the histological diagnosis of MTC after thyroidectomy.

Statistical analysis

For the meta-analysis of diagnostic test accuracy studies, the hierarchical summary receiver operating characteristic (HSROC) and bivariate methods are the most appropriate methodological approaches (https://eunethta.eu/wp-content/uploads/2018/01/2014-05-19_meta-a_diagn_draft-gl_2nd_revision_clear_0.pdf, accessed December 18, 2020). Therefore, we performed a meta-analysis using the hierarchical logistic regression modeling to determine summary estimates of the sensitivity, specificity, diagnostic odds ratio, and likelihood ratios by the bivariate random effects model (24) for calculating summary estimates of sensitivity and specificity, and the HSROC curve for modeling the parameters for the ROC curves (25, 26, 27) using Stata, version 11 (Stata Corp, College Station, Texas) with the metandi, metandiplot, and midas commands (28). Evaluation of funnel

plot asymmetry, meta-regression analysis and the funnel plots were performed using Stata, version 11 (Stata Corp) with the midas command (28). Publication bias (bias across studies) was assessed by the Deeks' funnel plot asymmetry test (28, 29) using Stata, version 11 (Stata Corp, College Station, Texas) with the midas command; *P* < 0.1 indicated publication bias. For cells containing zero 0.5 was used as the continuity correction (this is default for the metandi command in Stata), as suggested in the literature (30). Positive likelihood ratios of greater than 2.0 or negative likelihood ratios less than 0.5 with 95% CIs not including 1.0 were considered statistically significant (31, 32). The primary endpoint was defined as the sensitivity and specificity. Predefined secondary endpoints were: positive predictive value (PPV = TP/(TP + FP), whereas TP = true positives, FP = false positives, negative predictive value (NPV = TN/(FN + TN)), whereas TN = true negatives, FN = false negatives, positive likelihood ratio (L+) (=sensitivity/(1 – specificity)) and negative likelihood ratio (L–) (=1 – sensitivity)/specificity). The TN (true negative) cases were calculated using the formula TN = total number of patients – (FP + TP + FN). In studies in which Ctn-negative cases were further clarified, the (very rare) cases of proven MTC were included in the meta-analysis as FN. In studies in which the follow-up of CTn-negative patients was not reported, the FN rate in the meta-analysis was set to zero, analogous to the procedure of Verbeek *et al.* 2020 (19).

Sensitivity analyses were performed by excluding studies that are considered outliers in a statistical sense and by restricting the meta-analysis to subgroups (33). Following subgroup analyses for the primary endpoint were predefined: assay for Ctn measurement (immunochemiluminometric assays (ICMA) vs other assays), threshold for basal calcitonin (≥10 pg/mL vs between 4.6 and 100 pg/mL), using of (pentagastrin or calcium) stimulation test (stimulation test performed vs not performed); gender (females vs males); country of origin (Europe, Asia, others); if applicable. For exploring heterogeneity, a meta-regression analysis (https://methods.cochrane.org/sdt/handbook-dta-reviews, accessed December 18, 2020) with following predefined study-level covariates (potential confounders) was intended: (1) assay for calcitonin measurement (ICMA (yes) vs other assays (no)), (2) threshold for basal calcitonin (≥10 pg/mL (yes) vs other thresholds (no)), (3) using of (pentagastrin or calcium) stimulation test (stimulation test performed (yes) vs not performed (no)); (4) gender (females vs males).

Results

Study selection and characteristics

The literature search identified 1382 records with potentially relevant studies. As shown in Fig. 1, 17 studies met the inclusion and exclusion criteria and were included in the meta-analysis. The included studies had a total of 74,407 patients. None of the trials was a case-control study. The detailed characteristics of the included studies are given in Table 1 (15, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49). According to the QUADAS-2 tool (22, 23), the methodological quality of the included trials was acceptable (Fig. 2).

Risk of bias and publication bias

The Deeks' funnel plot asymmetry test suggested no significant evidence for publication bias (Fig. 3).

Meta-analysis

In our meta-analysis, we included 17 trials with in total 74,407 patients with nodular thyroid disease; 203 patients had medullary thyroid carcinoma, with a prevalence between 0.11% (in Schneider *et al.* 2012) (46) and 0.85% (in Hasselgren *et al.* 2010) (43). Regarding all included studies (*n* = 17) the summary estimates of sensitivity and specificity for the threshold between 4.6 and 100 pg/mL of basal calcitonin measurement was 0.99 (95% CI, 0.81–1.00) and 0.99 (95% CI, 0.97–0.99), respectively (Fig. 4); the pooled estimates of L+ and L− were 72.4 (95% CI, 32.3–162.1) and 0.01 (95% CI, 0.00–0.23), respectively (Supplementary Table 3). Post-test probabilities are shown in Supplementary Fig. 1. The hierarchical SROC (HSROC) curve for all included studies is depicted in Fig. 5, where the study No 7 by Vierhapper *et al.* (39) is an outlier (Supplementary Fig. 2).
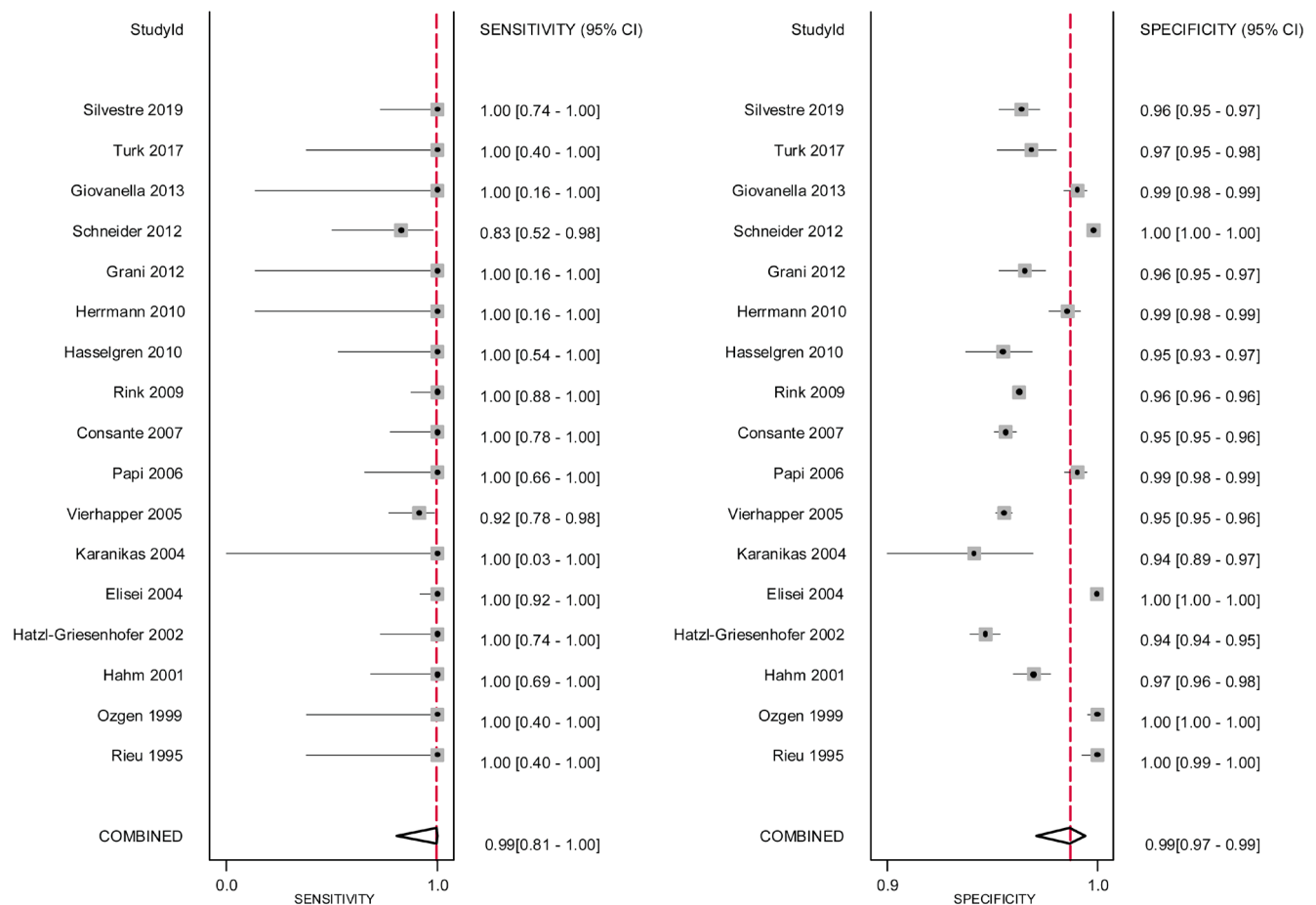

Figure 4

Coupled forest plot illustrating sensitivity and specificity for all included studies (with a basal calcitonin threshold between 4.6 and 100 pg/mL), *n* = 17. Pooled sensitivity: 0.99 (95% CI, 0.81–1.00), pooled specificity: 0.99 (95% CI, 0.97–0.99), pooled L+: 72.4 (95% CI, 32.3–162.1), pooled L−: 0.01 (95% CI, 0.00–0.23).
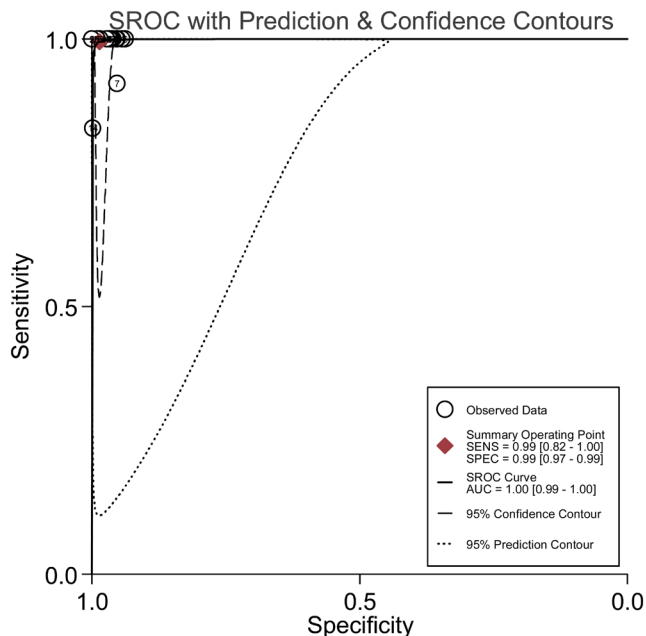
Figure 5
Hierarchical summary receiver-operating characteristics (SROC) plot for all included studies (with a basal calcitonin threshold between 4.6 and 100 pg/mL), *n* = 17 trials. Trial No 7 (39) is an outlier.

In the sensitivity analysis, exploring the possible reasons of between-study heterogeneity, after omitting the mentioned outlier trial (39), the summary estimates remained without significant changes; the summary estimates of sensitivity and specificity were 1.00 (95% CI, 0.37–1.00) and 0.99 (95% CI, 0.97–0.99), respectively (Supplementary Fig. 3); the pooled estimates of L+ and L– were 78.6 (95% CI, 33.8–182.6) and 0.00 (95% CI, 0.00–1.74), respectively (Supplementary Table 4). The hierarchical SROC (HSROC) curve for this analysis is depicted in Supplementary Fig. 4. Omitting the study by Karanakis *et al.* (38) which is not an outlier in the HSROC curve, showed no significant influence on the estimates, too (Supplementary Fig. 5); the summary estimates of sensitivity and specificity were 0.99 (95% CI, 0.81–1.0) and 0.99 (95% CI, 0.97–0.99), respectively, the pooled estimates of L+ and L– were 79.9 (95% CI, 34.3–186.2) and 0.01 (95% CI, 0.00–0.27), respectively (Supplementary Table 5). The hierarchical SROC (HSROC) curve for this analysis is depicted in Supplementary Fig. 6.

In subgroup analyses, summary estimates of sensitivity and specificity in the subgroup (*n* = 9 trials) with a threshold of 10 pg/mL of basal calcitonin measurement were 1.00 (95% CI, 0.17–1.00) and 0.97 (95% CI, 0.96–0.98), respectively (Fig. 6); the pooled estimates of L+ and L– were 32.6 (95% CI, 23.6–44.3) and 0.00 (95% CI, 0.00–4.88), respectively

(Supplementary Table 6). The hierarchical SROC (HSROC) curve for this subgroup is depicted in Fig. 7, where the study No 3 by Vierhapper *et al.* (39) is still an outlier.

Summary estimates of sensitivity and specificity in the subgroup (*n* = 12 trials) with a combined basal and stimulated calcitonin measurement with a threshold between 4.6 and 35 pg/mL of basal calcitonin, and with a threshold between 50 and 100 pg/mL of stimulated calcitonin were 0.99 (95% CI, 0.79–0.10) and 1.00 (95% CI, 1.00–1.00), respectively (Supplementary Fig. 7); the pooled estimates of L+ and L– were 690 (95% CI, 314.1–1515.6) and 0.01 (95% CI, 0.00–0.25), respectively (Supplementary Table 7). The hierarchical SROC (HSROC) curve for this subgroup is depicted in Supplementary Fig. 8. In this subgroup the specificity (1.00 (95% CI, 1.00–1.00) vs 0.97 (95% CI, 0.96–0.98) vs 0.99 (95% CI, 0.97–0.99)) and the L+ (690.0 (95 % CI, 314.1–1515.6) vs 32.6 (95% CI, 23.6–44.3) vs 72.4 (95% CI, 32.3–162.1) were superior to the findings for the basal calcitonin measurement with a threshold of ≥ 10 pg/mL and between 4.6 and 100 pg/mL, respectively. In the subgroup with combined basal and stimulated calcitonin measurement the post-predictive probability was higher (99% vs 95% as shown in the Supplementary Figs 1 and 9) than in all included studies with basal calcitonin measurement with a threshold between 4.6 and100 pg/mL; favoring the combined basal and stimulated calcitonin measurement.

The meta-regression analysis showed, that the covariate 'threshold for basal calcitonin' (≥10 pg/mL vs other thresholds), but not the covariate 'performing stimulation (pentagastrin) test' (stimulation test performed vs not performed) is an independent influencing factor (Fig. 8 and Supplementary Table 8). The latter finding is in contrast to the subgroup analysis, as shown previously.

Subgroup analysis for the influence of gender was intended, but have been not performed due to the small number of studies (*n* = 6) (35, 37, 39, 40, 44, 47) with gender-specific 2 × 2 table data. The covariate gender was therefore excluded from the intended meta-regression analysis.

Discussion

In this study, we performed a meta-analysis for the diagnostic accuracy of routine serum calcitonin measurement for the detection of medullary thyroid carcinoma in patients with nodular thyroid disease.
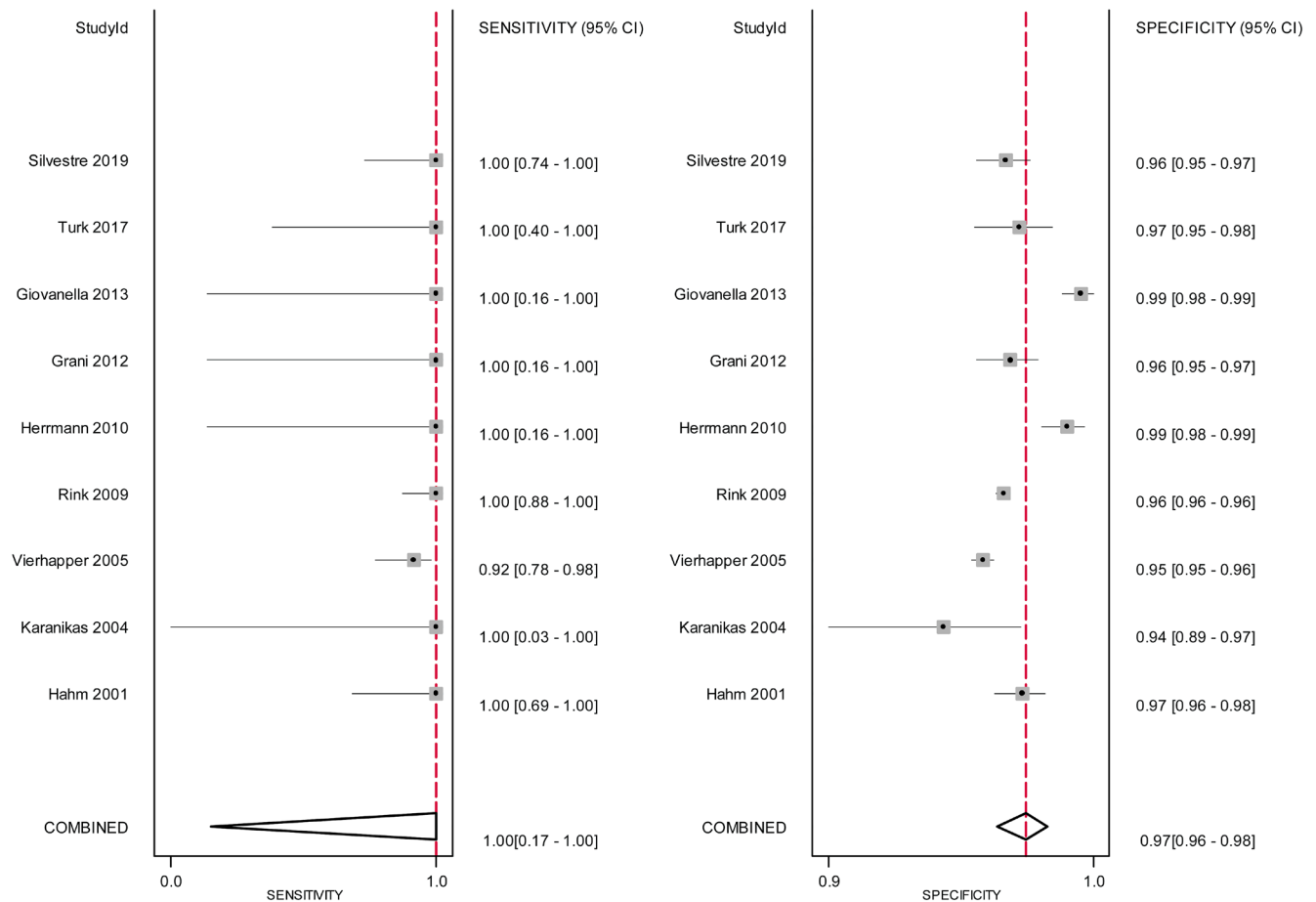
Figure 6

Coupled forest plot illustrating sensitivity and specificity for the subgroup of studies with a threshold of basal calcitonin measurement ≥10 pg/mL; *n* = 9 trials. Pooled sensitivity: 1.0 (95% CI, 0.17–1.00), pooled specificity: 0.97 (95% CI, 0.96–0.98), pooled L+: 32.6 (95% CI, 23.6–44.3), pooled L–: 0.00 (95% CI, 0.00–4.88).

Concerning all included studies, with a threshold between 4.6 and 100 pg/mL of basal calcitonin measurement, the summary estimates of sensitivity and specificity for detecting of MTC were 0.99 (95% CI, 0.81–1.00) and 0.99 (95% CI, 0.97–0.99), respectively; the pooled estimates of L+ and L– were 72.4 (95% CI, 32.3–162.1) and 0.01 (95% CI, 0.00–0.23), respectively. There was some degree of between-study heterogeneity, but no indication for publication bias. Sensitivity analysis showed no influence of particular studies on the summary estimates.

Our results indicate that both, basal calcitonin measurement as well as stimulated calcitonin measurement can cover almost 100% patients with MTC. However, particularly in iodine-replete countries where solitary MTC develops against a backdrop of normal thyroid tissue, due to the low prevalence of MTC in patients with nodular thyroid disease, the false positive rate might be high, with the risk of an unnecessary thyroidectomy, with possible risk of operative

complications and the necessity for life-long levothyroxine supplementation. In iodine-deficient countries, bilateral goiter is common, require total thyroidectomy regardless of the level of serum calcitonin. In the latter scenario, the level of calcitonin may guide the extent of node dissection at the time of thyroidectomy, as advocated in the 2015 revised ATA guidelines on MTC (2).

Studies evaluating cut-off levels for routine calcitonin measurement in patients with nodular thyroid disease concerning the recommendations of thyroidectomy due to suspicion for MTC revealed gender-specific cut-off values for basal calcitonin of >30 pg/mL for females and >60 pg/mL for males, which were not inferior to pentagastrin stimulated calcitonin levels (50, 51, 52). Almost 100% of patients with preoperative basal calcitonin values >100 pg/mL had MTC, whereas with basal calcitonin levels between 10 and 20 pg/mL only 5% of the participants had MTC (50). Due to the availability of innovative ICMAs (53), the non-availability of
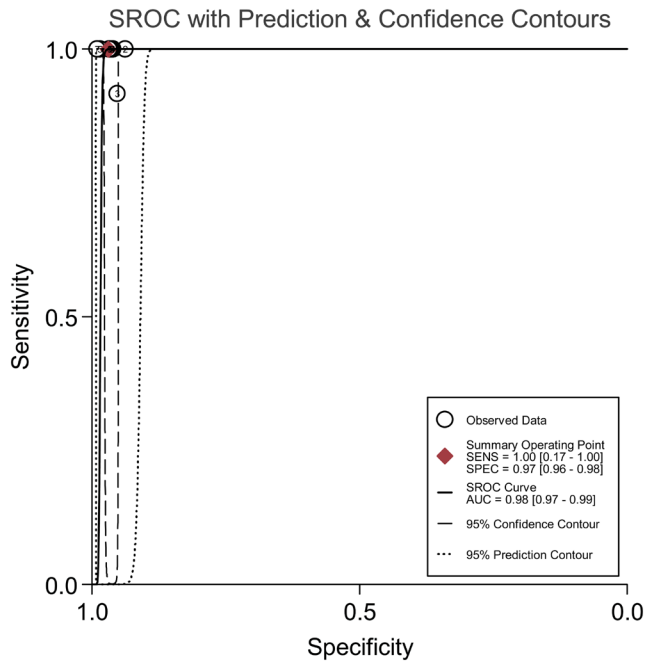
Figure 7

Hierarchical summary receiver-operating characteristics (SROC) plot for the subgroup of studies with a threshold of basal calcitonin measurement ≥10 pg/mL; *n* = 9 trials.

Figure 8

Meta-regression analysis in all included studies (*n* = 17) for the following covariates: (1) basal calcitonin threshold (>10 pg/mL (yes) vs other basal thresholds (no)), and (2) performing of stimulation test (performed (yes) vs not performed (no)) for the basal calcitonin measurement (with a threshold between 4.6 and100 pg/mL), indicating that the covariate 'basal calcitonin threshold', but not 'performing of stimulation test' is significantly influencing the sensitivity as well as specificity, as an independent influencing factor.

pentagastrin and the efforts for the calcium stimulation test, the routine measurement of basal calcitonin has been become focus of interest (54). Patients with preoperative basal calcitonin levels < 100 pg/mL may be cured in almost 100% of cases (55). Based on the available literature, some authors suggested a wait-and-see approach for patients with basal calcitonin levels < 30 pg/mL in females and < 60 pg/mL, with consequent recommendation for operative intervention in case of increasing calcitonin levels. Contrarily, females with calcitonin levels ≥30 pg/mL and males with calcitonin levels ≥ 60 pg/mL can be monitored or surgery considered, whereas surgery is recommended in patients with basal calcitonin values > 100 pg/mL (10, 54, 56). Recently, Niederle *et al.* reported, that calcitonin measurement after calcium stimulation did not improve the preoperative diagnostic; this is important and is in line with the findings in our meta-regression analysis. Niederle *et al.* additionally suggested that basal calcitonin levels >43 and >100 pg/mL for males and of >23 and 85 pg/mL for females are relevant for advising patients and planning the extent of surgery (57).

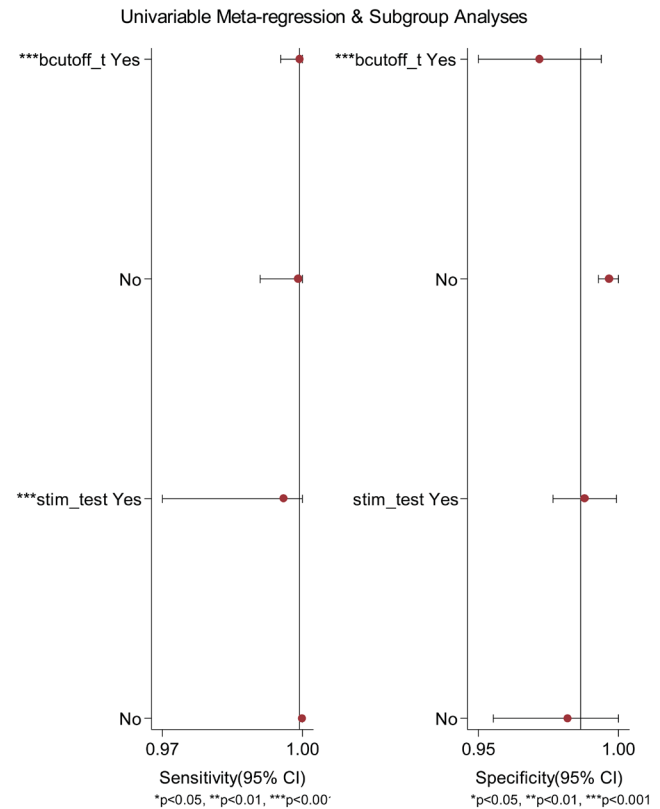There are several limitations in our study: for example, (a) The validity of the evidence is limited, as in almost all of the included studies no adequate reference standard for verification of FN and TN cases is available: ideally, this would be a histological exclusion of MTC in a representative number patients with calcitonin levels below the cut-off value after processing the entire resected tissue after total thyroidectomy using thin-layer technology. Only in a few studies the histological findings of some patients who underwent thyroid surgery despite calcitonin values below the cutoff were reported. For example, Schneider *et al.* (46) reported two patients with incidentally diagnosed MTC in patients with false-negative basal calcitonin levels. These few MTC cases in patients who were not detected with pathological screening Ctn values were assessed as FN in our meta-analysis. Because of the extreme rarity of such cases, it seemed legitimate for the meta-analysis to set the FN rate to zero in studies in which false-negative cases were not reported. The diagnostic accuracy can be affected even

when a small number of patients with very rare diseases, like the MTC, is missed. Additionally, this may lead to a high risk of bias with regard to flow and timing in the assessment of methodological quality. (b) Because of the small number of trials only few subgroup analyses could be performed. (c) There is somewhat between-study heterogeneity, in particular due to the different cut-off levels of basal calcitonin measurement and using of different assays for calcitonin measurements. (d) Included studies using disparate provocative agents for pentagastrin test were not evaluated separately but lumped together in the meta-analysis.

In conclusion, our results indicate that both basal and combined basal and stimulated calcitonin testing have a high sensitivity and specificity. We showed that routine calcitonin measurement in serum in the management of patients with thyroid nodules is valuable for the detection of medullary thyroid cancer. However, the published cut-off values should be considered and, if applicable the patients monitored, in a wait-and-see strategy, in experienced hands to avoid overtreatment.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0030.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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