



# A systematic review and meta-analysis of the Kwak TIRADS for the diagnostic assessment of indeterminate thyroid nodules

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## ARTICLE INFORMATION

### Article history:

Received 19 June 2018

Accepted 24 September 2018

**AIM:** To explore the diagnostic usefulness of the Thyroid Imaging Reporting and Data System (TIRADS) classification proposed by Kwak in indeterminate nodules using a systematic literature review.

**MATERIAL AND METHODS:** The PubMed, Cochrane database, ScienceDirect, and EMBASE databases were searched for relevant articles. A meta-analysis was performed to calculate pooled sensitivity, specificity, negative and positive likelihood ratios (LR– and LR+), diagnostic odds ratio (DOR), and area under the curve (AUC) from summarised receiver operating characteristic (SROC) curves.

**RESULTS:** Six publications describing 1,096 nodules were analysed. Overall pooled sensitivity, specificity, LR+, LR-, DOR, and AUC for SROC were 0.913, 0.347, 1.396, 0.341, 5.832, and 0.7180, respectively.

**CONCLUSIONS:** Kwak TIRADS classification with 3/4a cut-off for indeterminate lesions has high sensitivity but low specificity to exclude benign lesions. A higher Kwak TIRADS cut-off could help exclude larger numbers of benign lesions and lower the rate of unnecessary surgeries.

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## Introduction

Fine-needle aspiration biopsy (FNAB) is considered the basic invasive diagnostic tool for evaluation of thyroid nodules, reducing the number of unnecessary surgical resections.<sup>1</sup> Introduction of the six-graded classification, the

Bethesda System for Reporting Thyroid Cytopathology (BSRTC) in 2009, was an important element. It provided unified terminology of diagnoses and a standardised reporting system as well as suggestions for further proceedings, depending on the assigned category.<sup>2</sup> Three of these categories are considered indeterminate: III (atypia of undetermined significance or follicular lesion of undetermined significance [AUS/FLUS]), IV (follicular neoplasm or suspicious for follicular neoplasm [FN/SFN]), and V (suspicious for malignancy [SM]). They form a heterogeneous group of changes with approximately 20–25% of all cytology

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results, thus challenging clinicians in differentiating benign and malignant lesions.

Surgical resection is a common procedure for these lesions; however, due to the high percentage of benign results in histological examinations (80%), it is reasonable to identify predictors that can narrow the group to nodules that absolutely require resection.<sup>3,4</sup> Among the diagnostic tools widely available, ultrasonography is the first to aid in the decision of further proceedings. Ultrasonography is the basic diagnostic tool in the selection of nodules requiring cytological verification.<sup>5,6</sup> Ultrasound can be used to detect features that include solid structure; low or markedly low echogenicity; the presence of microcalcifications; lobular, irregular, or blurred margins; and a vertical shape of the nodule. Previous publications state that the coexistence of these features has more discriminatory ability than comparing each feature individually.<sup>5,7</sup>

Thyroid Imaging Reporting and Data System (TIRADS) classification has been introduced to improve the selection of thyroid lesions requiring further diagnostics and FNAB. Its concept was based on the recognised Breast Imaging Reporting and Data System (BIRADS) classification for stratification of focal lesions in the breast according to the growing risk of malignancy. The introduction of this system took place in 2009 by Horvath *et al.*<sup>8</sup> Its creation was based on 10 ultrasound patterns related to different rates of malignancy. In the same year, a different classification was proposed by Park *et al.*<sup>9</sup> This concept was based on an equation that could predict malignancy in thyroid nodules and stratify the results into TIRADS categories, reflecting the probability of malignancy.<sup>9</sup> The latest classification proposed by Kwak in 2011, K-TIRADS, has a different approach. It uses the number of suspicious ultrasound features to stratify the risk of thyroid nodules. The authors specified a group of five suspicious features as follows: solid structure; low or very low echogenicity; irregular or microlobular margins; microcalcifications; and vertical shape. The assignment of a nodule to different K-TIRADS categories proceeded according to the following scheme: TIRADS 3=no suspicious features; TIRADS 4a=one suspicious feature; TIRADS 4b=two suspicious features; TIRADS 4c=three or four suspicious features; TIRADS 5=five suspicious features.

Currently, several variants of TIRADS classification have appeared in the available literature,<sup>8–14</sup> although the most commonly used to assess indeterminate nodules is still K-TIRADS.<sup>10</sup> Overall, the TIRADS system was designed to improve nodule stratification and foster communication between clinicians.<sup>8,9,11</sup>

The aim of the present study was to explore the diagnostic usefulness of the K-TIRADS classification of indeterminate nodules via a systematic literature review.

## Materials and method

### *Eligibility criteria and data sources*

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-

Analysis (PRISMA).<sup>15</sup> Four databases (PubMed, Cochrane database, ScienceDirect, and Embase) were searched for articles dating from January 2009 to December 2017 by using key terms as related to “TIRADS”; “indeterminate cytology”; “undetermined significance”; “Bethesda system”; “Bethesda category III”, “Bethesda category IV”, Bethesda category V”, “atypia of undetermined significance”; “follicular lesion of undetermined significance”; “follicular neoplasm”; “suspicious for follicular neoplasm”; “suspicious for malignancy”. The search was conducted by two independent reviewers (B.M. and M.M.).

### *Inclusion criteria and data extraction*

The inclusion criteria were as follows: (1) adults with indeterminate nodules (belonging to category III, IV, or V according to Bethesda); (2) using the K-TIRADS classification as a tool for differentiating thyroid nodules; (3) final diagnosis based on histological or cytological examination, but only in cases of definitive diagnosis or for non-suspicious nodule ultrasound follow-up after at least 12 months with no sign of progression; (4) data in the publication had to allow for calculations based on 2×2 pivot tables; (5) studies published in English or German. Previously published material was used to obtain additional information about the group analysed. Decisions on article inclusion for further stage meta-analysis were made independently by two authors (B.M. and M.S.M.). All discrepancies were resolved in consensus.

The following information was obtained from each study included: author data, year of publication, country of origin, number of patients, number of nodules, average age of patients (in some articles, average age was only available with distribution of benign and malignant groups), number of men and women, study design, and reference method (Table 1). Each of the studies included was verified qualitatively according to Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria.<sup>16</sup>

Because heterogeneity was found in the analysed studies, the random-effects model was used. The data from the 2×2 pivot tables were used for the calculations. The following pooled values were calculated: sensitivity, specificity, positive and negative likelihood ratio, and diagnostic odds ratio (DOR). Heterogeneity was assessed using the values of  $I^2$  statistics. A funnel plot was used to evaluate the possibility of publication bias. The Begg and Mazumdar test was used for assessment of funnel plot asymmetry. To assess the diagnostic usefulness of the TIRADS classification according to nodules with indeterminate cytology, the summarised receiver operating characteristic (SROC) curve (computation method; DerSimonian–Laird for the random-effects model) was used. The results were presented as area under the SROC curve (AUC), standard error (SE) for AUC, and  $Q^*$  statistics with its standard error (SE).

To determine possible factors of heterogeneity, meta-regression was used. The following potential factors were included: reference standard, cytology (category III versus categories III–V according to Bethesda classification), and TIRADS cut-off (3/4a versus 4a/4b). A significance level below

**Table 1**  
Baseline characteristics of included studies.

Authors	Year	Origin	Patients	Nodules	Mean age (years)	Male/female	Study design	Reference standard
Yoon <sup>17</sup>	2016	Korea	188	192	50.2	43/145	Retrospective	Repeat FNAB/surgery/US follow-up
He <sup>18</sup>	2017	China	453	453	Benign 54.9; malignant 48.3	90/363	Retrospective	Surgery
Park <sup>19</sup>	2015	Korea	56	31	50.6	10/46	Retrospective	Surgery
Koh <sup>20</sup>	2016	Korea	221	221	Benign 50.3; malignant 45.3	54/167	Retrospective	Repeat FNAB/surgery/US follow-up
Rho <sup>21</sup>	2017	Korea	ND	78	48.9	ND	Retrospective	Surgery
Mao <sup>22</sup>	2017	China	121	121	Benign 55; malignant 54	18/103	Retrospective	Surgery

ND, no data; FNAB, fine-needle aspiration biopsy, US, ultrasound.

0.05 was considered statistically significant. For calculations, Statistica 13.1 (Dell Inc. 2016, Tulsa, USA) and Meta-DiSc 1.4 (freeware software) were used.

## Results

### Selection and data extraction

In accordance with the adopted criteria, 298 potential literature articles were obtained. The analysis of titles and abstracts excluded 276 studies due to different subjects, literature review, duplicates, or language (not English or German). Next, 11 publications were analysed, of which five were excluded because they did not meet the inclusion criteria (use of a different cytology classification than Bethesda and different TIRADS classification). Finally, six original studies were included, with a total of 1096 nodules, meeting the meta-analysis criteria<sup>17–22</sup> (Fig 1).

The included studies dated from 2015 to 2017. All were retrospective, and the number of nodules, depending on the article, varied between 31 and 453. In four out of six studies, all nodules were diagnosed definitively based on histopathological examination. In the remaining two studies, the verification was histopathological; cytological if the result was definitive; or, in the case of benign lesions, ultrasound follow-up after at least 12 months with no signs of

progression in US. In five studies, the authors analysed changes from category III and, in the remaining one, nodules from categories III–V.

The funnel plot showed signs of asymmetry, suggesting publication bias; however, in the Begg and Mazumdar test, the size of the calculated effect in each of the six studies was not strongly related to its standard error, and the asymmetry was found to be insignificant ( $p=0.3272$ ).

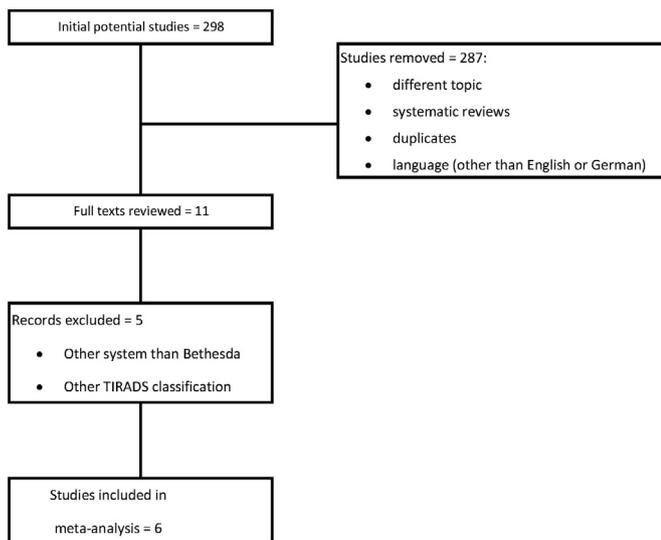
The overall pooled sensitivity and specificity for the TIRADS classification were 0.913 (95% confidence interval [CI]: 0.884–0.936) and 0.347 (95% CI: 0.311–0.386), respectively (Fig 2). The overall pooled values of the positive likelihood ratio and negative likelihood ratio were 1.396 (95% CI: 1.155–1.686) and 0.341 (95% CI: 0.179–0.649), respectively (Fig 3). The overall pooled DOR was 5.832 (95% CI: 2.517–13.515; Fig 4). The AUC was 0.7180 ( $Q^*=0.6673$ ; Fig 5).

### Subgroup analysis and meta-regression

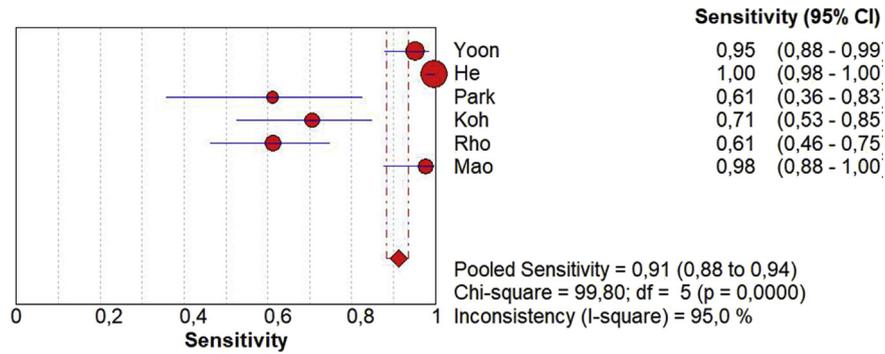
The meta-regression was made in three subgroups. Differences were found only in one group: the reference standard. In four studies, the authors used only histopathological verification with higher values of sensitivity and DOR in relation to studies that also used cytological verification and ultrasound follow-up 0.923 and 10.491 versus 0.879 and 2.706, respectively ( $p<0.05$ , Table 2). In cases of a cut-off point and cytology, the differences were insignificant ( $p>0.05$ , Table 2).

## Discussion

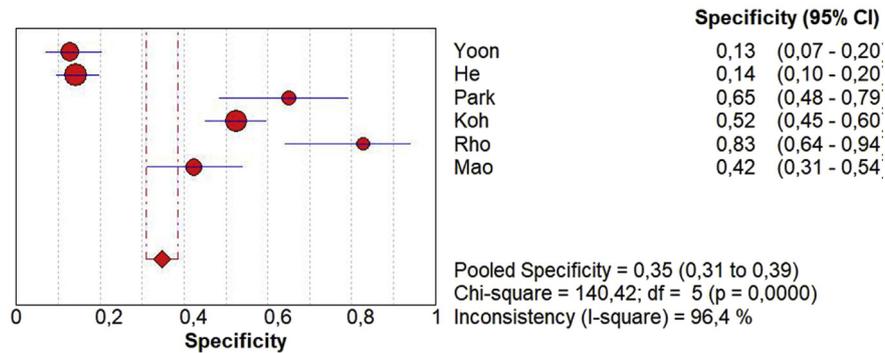
Recent publications report systems based on thyroid nodular stratification that are delivered by different scientific societies such as the American Thyroid Association (ATA), American Association of Endocrinologists, American College of Endocrinologists, and Associazione Medici Endocrinologi (AACE, ACE, and AME), and British Thyroid Association (BTA).<sup>3,23,24</sup> Independently, the TIRADS classification has been established and developed. Currently, several variants of TIRADS have been published,<sup>8–14</sup> including two new modifications recently presented by the American College of Radiology (ACR)<sup>14</sup> and the European Thyroid Association (ETA).<sup>13</sup> In the first of them, authors proposed a lexicon of descriptive terms for reporting thyroid nodules<sup>25</sup> and subsequent ACR-TIRADS that provided management recommendations (ultrasound follow-up, FNAB,



**Figure 1** Literature search and selection.

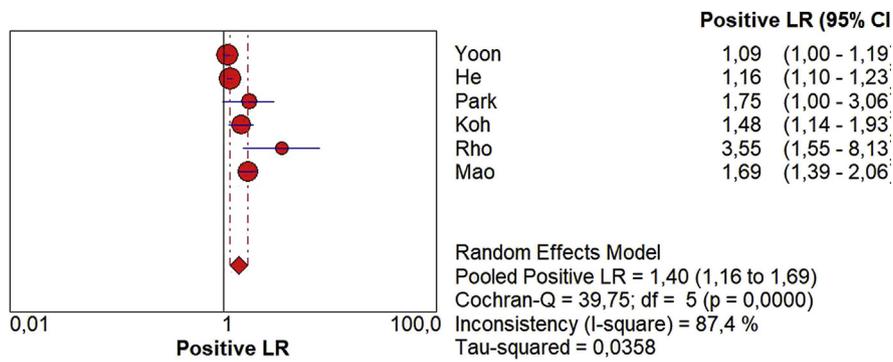


(a)

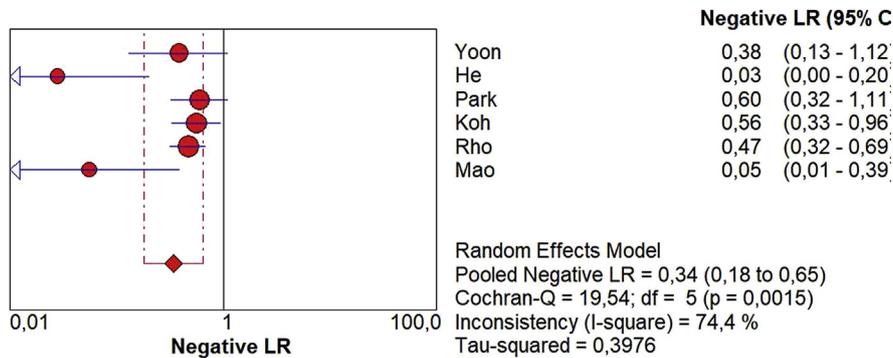


(b)

**Figure 2** Forest plots of eligible studies showing individual and pooled (a) sensitivities and (b) specificities of K-TIRADS in the differential diagnosis of indeterminate thyroid nodules. Pooled values marked by diamonds with 95% CI (in brackets).

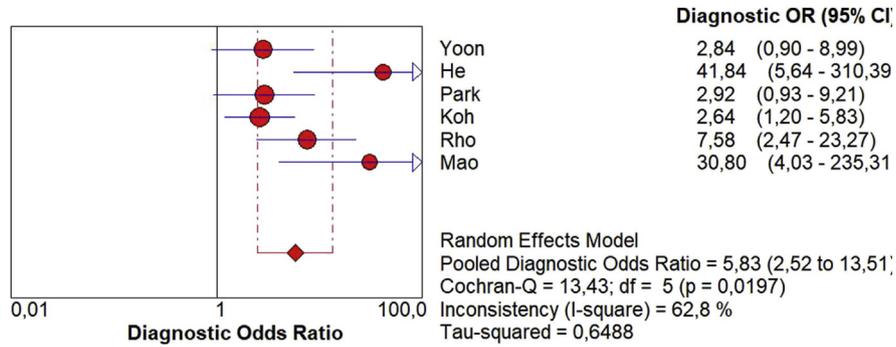


(a)



(b)

**Figure 3** Forest plots of eligible studies showing individual and pooled (a) negative and (b) positive likelihood ratios (LRs) of the K-TIRADS in the differential diagnosis of indeterminate thyroid nodules. Pooled values marked by diamonds with 95% CI (in brackets).



**Figure 4** Forest plot of eligible studies showing individual and pooled DOR of the K-TIRADS in the differential diagnosis of indeterminate thyroid nodules. Pooled value marked by diamonds with 95% CI (in brackets).

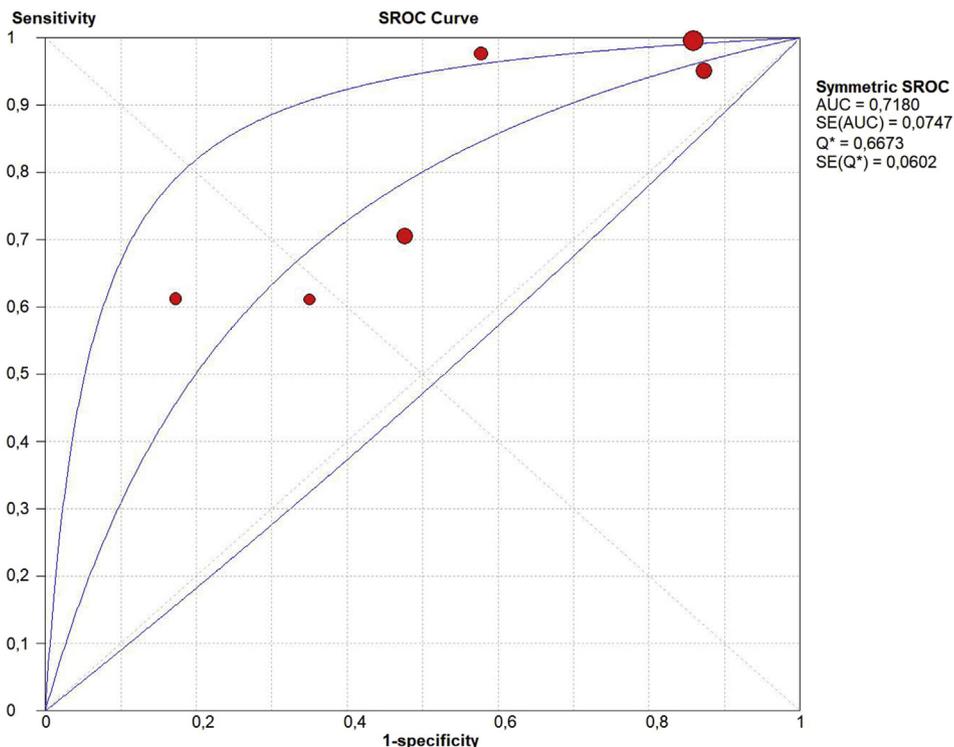
surgery) on the basis of ultrasound features, described in the lexicon, with assigned points and by size.<sup>14</sup> Assignment to a particular category was based on the number of points (TR1=0; TR2=2; TR3=3; TR4=4–6; TR5=>7) where recommendation depends on nodule size.<sup>14</sup> The second classification, proposed by the ETA (EU-TIRADS) was based on ultrasound-detected suspicious features (vertical shape; irregular margins; microcalcifications, and marked hypoechogenicity), and the recommendations (ultrasound follow-up, FNAB, surgery) depended on EU-TIRADS category and lesion size. In this work, the authors also provided recommendations for an ultrasound reporting template and how to stratify nodules in case of nodular goitre. So far, neither ACR-TIRADS nor EU-TIRADS has been tested in terms of indeterminate thyroid nodules.

Currently, the World Federation of Ultrasound in Medicine and Biology (WFUMB) guidelines, published in 2017,

recommend using K-TIRADS for better categorisation of thyroid nodules and improved communication between specialists and patients.<sup>26</sup>

An increasing number of publications assess the utility of TIRADS according to Bethesda-specific category and exploration of indeterminate lesions. While this meta-analysis was being conducted, another publication assessed ultrasonographic features in nodules that were classified as Bethesda category III.<sup>27</sup> The overall pooled sensitivity, specificity, DOR, and AUC SROC were accordingly 0.75 (95% CI: 0.72–0.78), 0.48 (95% CI: 0.45–0.50), 10.92 (95% CI: 6.04–19.74), 0.84. In addition, the authors included publications reflecting TIRADS but without further exploration of this classification, which was the subject of the present meta-analysis.

Six publications comprising 1,096 nodules were analysed, with overall pooled values of sensitivity 0.913,



**Figure 5** SROC curve for the K-TIRADS with AUC, AUC standard error [SE(AUC)], Q\*, and Q\* standard error [SE(Q\*)].

**Table 2**  
Subgroup analysis.

Subgroups	No. of studies	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	DOR	Meta-regression (p-value)
Total	6	0.913 (0.884–0.936)	0.347 (0.311–0.386)	5.832 (2.517–13.515)	
Reference standard					
Surgery	4	0.923 (0.891–0.948)	0.322 (0.273–0.374)	10.491 (3.004–36.642)	0.0316
Repeat FNAB/surgery/US follow-up	2	0.879 (0.806–0.932)	0.377 (0.322–0.435)	2.706 (1.409–5.194)	
Cytology					
III	5	0.819 (0.762–0.867)	0.439 (0.392–0.487)	4.287 (2.146–8.565)	0.06
III–V	1	0.996 (0.978–1.00)	0.141 (0.096–0.198)	41.835 (5.639–310.39)	
TIRADS cut-off					
3/4a	3	0.966 (0.942–0.982)	0.195 (0.155–0.241)	5.737 (1.275–25.825)	0.4573
4a/4b	3	0.762 (0.678–0.833)	0.527 (0.468–0.585)	6.605 (1.871–23.314)	

CI, confidence interval; DOR, diagnostic odds ratio; FNAB, fine-needle aspiration biopsy, US, ultrasound; TIRADS, Thyroid Imaging Reporting and Data System.

specificity 0.347, positive likelihood ratio 1.396, negative likelihood ratio 0.341, DOR 5.832, and AUC under the SROC 0.7180. In the publications analysed, some authors pointed to differing levels of experience of the examiners performing the ultrasound. Frequently, a higher percentage of radiologists had less experience, but difficult cases were performed under the supervision of more experienced radiologists.<sup>17,18</sup> Furthermore, those authors stated that cytology could also be dependent either from examiner or from the centre where the examinations were performed, with a possibility of low agreement in indeterminate categories compared with definitive categories such as category II, according to BSRTC, as suggested by other researchers.<sup>28</sup> This could influence the correlation of ultrasound and cytology and variance of the final results.

When comparing results from recently published meta-analyses, this analysis revealed that overall pooled sensitivity was higher and specificity was lower than in Wei *et al.* (0.913 versus 0.79 and 0.347 versus 0.71), and sensitivity and specificity were lower than in Migda *et al.* (0.913 versus 0.983 and 0.347 versus 0.552)<sup>29,30</sup>; however, compared to the second publication, the present results were also characterised by high sensitivity and lower specificity. This could be explained by the fact that Migda *et al.* also analysed the utility of K-TIRADS classification, although without specifying indeterminate nodules.

In the present analysis, the 3/4a cut-off for K-TIRADS was characterised by higher sensitivity (0.966) and lower specificity (0.195) in relation to a higher cut-off (4a/4b). A higher cut-off increased the specificity to 0.527 but decreased sensitivity to 0.762 ( $p > 0.05$ ). As a result, it was concluded that a higher cut-off could help exclude higher numbers of benign lesions and lower the rate of unnecessary surgeries.

The main factor explaining the heterogeneity of this meta-analysis based on meta-regression was the reference method. Four studies were based on surgery verification only and two on surgery, FNAB in case of definitive result, and ultrasound follow-up for non-suspicious nodules with no sign of progression. In the present analysis, pooled sensitivity for studies with surgery series was higher (0.923 versus 0.879), whereas pooled specificities were almost parallel (0.322 versus 0.377). The DOR in surgery series was significantly higher than in other groups (10.491 versus 2.706). These results could lead to the conclusion that in diagnostic protocols, cases of

indeterminate nodules should seek histopathological verification; however, it seems unethical to target all patients with BSRTC III–V nodules for surgery. FNAB is an invasive method of diagnosing thyroid cancer and is generally recommended with a higher TIRADS cut-off; on the contrary, low-suspicion nodules having low risk of malignancy (approximately <15%) can reduce unnecessary FNAB by most international society guidelines. Follicular carcinoma, or the follicular variant papillary thyroid cancer (PTC), occasionally shows an ultrasound pattern of TIRADS 3, and nodule size should be considered in the management decision regarding indeterminate nodules, because the incidence of follicular carcinoma may increase in large nodules. Therefore, TIRADS 3 may not always allow conservative follow-up without repeat FNAB in indeterminate nodules, especially in the case of large nodules in clinical practice.

In addition, the management strategy may be different according to the subtype of AUS/FLUS; however, this could not be assessed in this analysis because only one of the included studies investigated the malignancy risk of each AUS/FLUS subtype.<sup>17</sup>

Currently, in cases of indeterminate nodules, there is a different protocol, depending on the category according to the Bethesda classification.<sup>2</sup> Different diagnostic strategies are also proposed in the literature.<sup>31,32</sup>

In the studies analysed, the authors suggested: diagnostic lobectomy for AUS lesions with suspicious features classified by K-TIRADS >3, and lobectomy for FLUS independently from ultrasound-detected suspicious features<sup>17</sup>; in the case of category AUS/FLUS and repeated FNAB with a category AUS/FLUS diagnosis, a surgical approach should be considered independently from ultrasonographic features<sup>19</sup>; for AUS/FLUS category BSRTC and K-TIRADS 3, a conservative approach should be considered, but in cases of category III–V BSRTC and nodule K-TIRADS >4a, surgery is recommended.<sup>33</sup>

The BRAF V600 mutation, which is present in 70% of PTC cases, is considered an independent factor for poor prognosis.<sup>34,35</sup> According to ATA guidelines, the authors suggested BRAF V600 mutation for category III, but it has yet to be used in correlation with clinical and ultrasonographic features.<sup>23</sup> On the contrary, a meta-analysis by Trimboli *et al.* reported lower mutation percentages in indeterminate lesions and, thus, low utility of differentiation between benign and malignant in this group.<sup>36</sup>

The present meta-analysis has several limitations. First, different cut-offs were used for TIRADS. This could have some impact on statistical parameters, especially in analysed groups of indeterminate lesions with higher percentages of malignant cases (in this meta-analysis, >43.4%). Second, final histology was not always available in all studies, but publications with ultrasonographic follow-up and definitive cytology and histology are more adequate in terms of daily practice than studies based only on histology. Third, all analyses were retrospective. For future analysis, further prospective, multicentre studies are required. Fourth, five papers assessed category III and one assessed categories III–V according to Bethesda; however, this did not affect result heterogeneity.

In conclusion, K-TIRADS classification with 3/4a cut-off for indeterminate lesions has high sensitivity but low specificity to exclude benign lesions. A higher K-TIRADS cut-off could help exclude larger numbers of benign lesions and lower the rate of unnecessary surgeries.

## Conflict of interest

The authors declare no conflict of interest.

## Funding

The authors state that this work has not received any funding.

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