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A systematic review and meta-analysis of clinical trials of thyroids hormone using ultrasound based datasets

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► ***Review article***

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ABSTRACT

Background: Thyroid nodules account for 10-15 % of thyroid cancers or malignancies and ultrasound (US) is the most accurate technique for evaluating thyroid nodules. Ultrasound-based datasets aid in detecting malignancy risk and avoiding Fine Needle Aspiration (FNA) biopsy. There are several guidelines for determining thyroid nodules, and ACR-TIRADS (American College of Radiology Thyroid Imaging Reporting and Data Systems) is the most accurate and widely used. However, very few or no studies have compared various grades of ACR-TIRADS based on benign and malignant nodules. Therefore, this study aimed to investigate the predictive risk of malignant cancer in thyroid nodules obtained from an ultrasound dataset based on the ACR-TIRADS classification. ***Materials and Methods***: PubMed, Medline, EMBASE (Excerpta Medica dataBASE), Google Scholar, Cochrane Library, and Web of Science were searched for articles published between Jan 2018 to 30 June, 2022, and ultrasound-based datasets were obtained for benign and malignant thyroid nodules based on ACR -TIRADS. ***Results***: Ten articles were included with 12723 total cases of thyroid ultrasound dataset for benign and malignant thyroid nodule classification. The total number of benign was 6641 and the total number of malignant thyroid nodules was 6082 respectively (95 % CI=1.14, 0.75-1.74) with P=0.53. The number of TR4 and TR5 malignancies were 1397 and 3733 respectively (95 % CI=0.42, 0.22-0.83) with P=0.01. ***Conclusion***: The TR4 and TR5 grading of the ACR-TIRADS represents an excellent stratification system for classifying thyroid lesions thereby avoiding biopsies performed on benign nodules.

INTRODUCTION

Thyroid hormones are tyrosine-based hormones produced by the thyroid gland triiodothyronine (T_3) and thyroxine (T_4). The thyroid is a butterfly-shaped organ of the endocrine system that is present in the neck region (C5-T1 vertebral region) wrappeding around the anterior trachea and right below the larynx [1]. It is composed of two bulging lobes joined by an isthmus [2]. The organ receives blood supply from the superior and inferior thyroid arteries [3]. The normal histology of the thyroid gland consists of several follicles enclosed by a fibrous capsule that separates the parenchyma into many lobules, containing 20-40 follicles each [4]. Thyroglobulin, a thyroid hormone precursor, is present in these follicles. A healthy thyroid gland has thyroglunins that last for almost three months [5].

Thyroid disorders, hyperthyroidism, and hypothyroidism, are the most common disorders of the endocrine system [6]. These disorders can be symptomatic or asymptomatic and may even cause death in certain cases [7]. Thyroid gland disorders are characterized by altered levels of tetraiodothyronine (T_4) and triiodothyronine (T_3), which are important for normal body metabolism [8]. On the other hand, disorders of Thyroid nodules (TN) are becoming a burden with a very high frequency [9]. Moreover, implementing a proper system for risk stratification and suitable citation of circumstances decreases the number of difficulties through phaco-emulsification [10]. These citations will license harmless operations as well as augment preparation, by guaranteeing that a suitably skilled physician is accessible to work on a circumstance and accomplish and clarify the subordinate doctor [11]. "Risks" references to technical jeopardy, or the possibility of an adversative medical consequence. The risk stratification system (RSS) has allowed our preparation to deliver risk-stratified maintenance supervision such as the ability to choose patients who will assist most from occupied with the combined behaviourist, the risk to recognize patients for precaution management, scheduling the high-hazard patients for long term visits, and considering patients' risk stages after highlighting properties, viz flu shots or education courses [12, 13].

FNA employs a fine needle to pass through the skin to collect cell samples or fluid from a mass or suspected lump. FNA requires imaging if the mass or lumps cannot be felt while touching it. It does serves as an important part of handling patients with thyroid lumps, due to its safe and precise procedure and result. Owing to its guidance, non-diagnostic specimens and rare difficulties happen post-FNA [14]. FNA biopsy of the thyroid usually involves a certain risk of infection at the injection site, and injury to areas near the thyroid. Local anesthesia is usually not required; however, in the case of children, some medicines may be required to ease them while aspirating from the tissue mass. The US results for benign and malignant TNs usually overlap to some extent and the final impression depends on the radiologist [15, 16].

Several guidelines and directives have been proposed for the classification of benign and malignant TN using conventional US methods over the past two decades which seem to be inaccurate in detecting benign and malignant TNs [17, 18]. However, in the past decade, numerous guidelines have been proposed such as the Kwak TI-RADS proposed by Kwak *et al*. in 2011, which is based on the number of suspicious ultrasound features [19]. The American Thyroid Association (ATA) published guidelines for TN classification in 2015 [20]. Similarly, Koreans had KTA/KSThR and release their procedure in 2016 [21]. The EU (European) released its European Thyroid Imaging Reports and Data Systems (EU-TIRADS) in 2020 and China released Chinese Thyroid Imaging Reports and Data Systems (C-TIRADS) in 2021 [22, 23]. In 2017, the ACR updated its latest ACR-TIRADS which is based on large-scale US data and evidence-based clinical validation [24].

With an increasing number of thyroid nodule cases in recent years, there is an urgent need for its detection using high-frequency US. In most cases, the major obstacle lies in the identification of benign which comprises around 80-90 % of malignant cases [25]. Therefore, the necessity of this study is to establish the accuracy and precision of ACR-TIRADS in the disparate investigation of benign and malignant ultrasound based on data from various clinical trials. The studies also analyzed the sensitivity and specificity of the meta-analysis. The meta-analysis also aimed to compare benign and malignant risk ratios based on the sub-type classification of the ACR-TIRADS. Although, there are several comparisons based on different TIRADS classification systems, to the best of our knowledge and literature survey, there are no such comparisons based on TR sub-classification and meta-analysis. Therefore, the present study is the first to demonstrate a meta-analysis based on TR classification. This study aimed to provide accurate information for identifying the most clinically significant malignancies, thereby reducing the number of biopsies performed for benign nodules.

MATERIALS AND METHODS

Search strategy

The search strategy for the present meta-analysis was mostly based on PubMed, Google Scholar, and MEDLINE. Additional searches were performed using EMBASE, Web of Science and Cochrane. The following search terms were used: ("thyroid hormone ultrasound" or "ultrasound thyroid" or thyroid ultrasound or "ultrasound based dataset of thyroid" or "thyroid cancer" or "thyroid nodule" and "ACR-TIRADS". All relevant content and bibliographies of published articles were also manually searched for potential articles. All articles published between Jan 2018 and June 2022 were retrieved because the ACR-TIRADS was updated in 2017. The deadline search date was 30 June 2022.

Selection criteria

The selection of the study criteria was based on the following: (1) clinical study or research article based on diagnostic analysis, (2) Involvement of assessment based on ACR-TIRADS for identification of benign and malignant and (3) only histologically confirmed thyroid nodules were considered.

Exclusion criteria

The following were excluded: (1) case reports (2) animal experiments (3) review articles (4) conference abstracts (5) studies that did not follow ACR-TIRADS guidelines (6) studies without histological or pathological reference and (7) articles without informed consent.

Data extraction

Data extraction was carried out following standard procedures and all extracted information was checked independently by two different researchers based on a universal format. The standard procedure and format include (1) author details, affiliation, publication year and type of study (2) criteria of included thyroid nodules based on the ACR-TIRADS; and (3) total number of benign and malignant thyroid nodules.

Data analysis and statistical assessment

Data and statistical analysis were carried out using Review Manager, RevMan 5.0 (Cochrane Rev Manager, Inc, USA). First, a total meta-analysis was conducted for benign and malignant cases among all included studies. Second, a proportion meta-analysis for TR5, TR4, and TR3 levels in ACR-TIRADS was performed. TR1 and TR2 were not included in the study because TR1 is classified as "Benign" and TR2 is classified as "Not suspicious for malignancy". In both cases, FNA was not required and hence was not accounted in the proportion meta-analysis. For the

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statistical pooling of data, a random-effects model, Cochran's Q statistic and I0 test were applied. We used the Begger funnel test to explore publication partiality. Statistical significance was set at $p < 0.05$.

Literature search

In total, 351 articles were obtained. After removing 234 duplicates, cross-checking of the abstracts resulted in 54 articles. A check of the entire text and data for completeness resulted in the exclusion of 44 other studies, leaving ten research evaluations (figure 1).

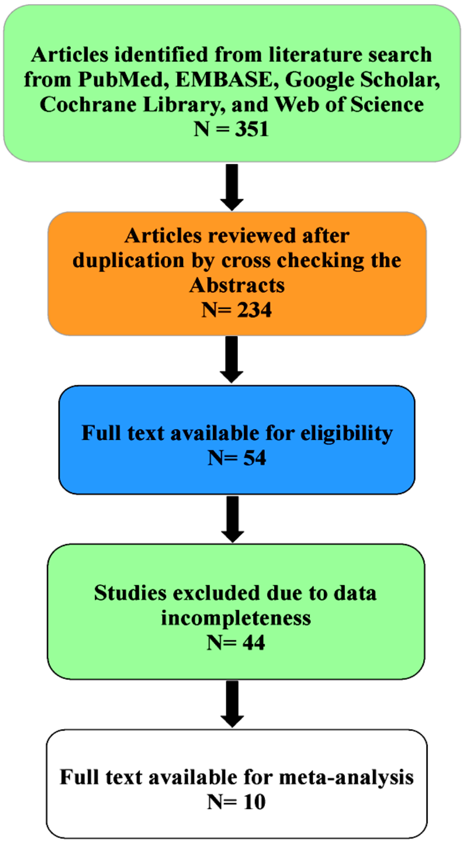

Figure 1. Flowchart of the literature search and study included.

Characteristics of the included study

The characteristics and features of the study's procedural standards are outlined in table 1. Ten articles were included with 12723 total cases. The total number of patients was 10,478 patients. The upper age was 10 years and the lower age was 93 years and the median age is 51.5 years. The total number of benign and malignant thyroid nodules was 6641 and 6082 respectively. The highest number of benign cases in a single study was 43 whereas the highest number of malignant cases was 788 cases. Table 1 also presents the relevant characteristics of the benign and malignant thyroid nodule cases in each study and their classification based on ACR-TIRADS.

Table 1. Grading based on ACR-TIRADS.

Author & Year	ACR-TIRADS Grade	Benign	Malignant
Xu 2018 [42]	TR1	62	0
	TR2	416	10
	TR3	295	24
	TR4	549	368
	TR5	138	603
Total Xu 2018	2465	1460	1005
Gao 2019 [32]	TR1	8	0
	TR2	144	2
	TR3	280	28
	TR4	252	279
	TR5	179	1372
Total Gao 2019	2544	863	1681
Ruan 2019 [41]	TR1	7	307
	TR2	183	72
	TR3	281	9
	TR4	106	4
	TR5	32	0
Total Ruan 2019	1001	609	392
Shen 2019 [40]	TR1	0	0
	TR2	6	0
	TR3	269	13
	TR4	459	78
	TR5	105	682
Total Shen 2019	1612	839	773
Wildman 2019 [45]	TR1	122	11
	TR2	181	14
	TR3	250	19
	TR4	468	32
	TR5	168	9
Total Wildman	1325	1189	136
Darota 2020 [39]	TR1	0	48
	TR2	2	64
	TR3	20	204
	TR4	108	368
	TR5	120	66
Total Darota 2020	1000	250	750
Wang 2020 [35]	TR1	2	0
	TR2	0	0
	TR3	10	0
	TR4	22	12
	TR5	7	48
Total Wang 2020	101	41	60
Zhang 2020 [43]	TR1	42	0
	TR2	82	2
	TR3	142	3
	TR4	217	114
	TR5	52	616
Total Zhang	1271	535	736
McClean 2021 [38]	TR1	7	0
	TR2	85	32
	TR3	43	30
	TR4	33	42
	TR5	5	31
Total McClean 2021	308	173	135
Qi 2021 [36]	TR1	40	0
	TR2	145	1
	TR3	54	7
	TR4	242	100
	TR5	201	306
Total Qi 2021	1096	682	414

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Qualitative and meta-analysis study

The details of the investigated articles are presented in table 1. The articles were published from Jan 2018 to 30 June 2022 and had sample sizes ranging from 41 to 2544 thyroid nodules. Overall, there were 12723 thyroid nodule cases, of which 6641 were benign and 6082 were malignant. Among the 6082 malignant nodules diagnosed by USG and histology, the number of TR3, TR4, and TR5 malignancies was 337, 1397, and 3733 respectively. The prevalence of malignancy among the investigated ten articles in the present meta-analysis were 47.80 % (95 % CI=1.14, 0.75-1.74) comprising 6082 cases (figure 2). Among the 6082 malignant cases, three different sub-meta-analyses were carried out based on the grading of TR5 (highly suspicious) 3733 cases (figure 3), and TR4 (moderately suspicious) (figure 4). Very high heterogeneity and evidence of publication bias were observed and presented as a funnel plot which is shown in figures 5 and 6 AB.

Study or Subgroup	Benign Events	Benign Total	Malignant Events	Malignant Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Xu 2018	1460	2465	1005	2465	10.1%	1.45 [1.37, 1.54]	2018
Shen 2019	839	1612	773	1612	10.1%	1.09 [1.01, 1.16]	2019
Wildman 2019	1189	1325	136	1325	10.0%	8.74 [7.45, 10.26]	2019
Gao 2019	863	2544	1681	2544	10.1%	0.51 [0.48, 0.55]	2019
Ruan 2019	609	1001	392	1001	10.1%	1.55 [1.42, 1.70]	2019
Wang 2020	41	101	60	101	9.6%	0.68 [0.51, 0.91]	2020
Zhang 2020	535	1271	736	1271	10.1%	0.73 [0.67, 0.79]	2020
Darota 2020	250	1000	750	1000	10.0%	0.33 [0.30, 0.37]	2020
McClean 2021	173	308	135	308	10.0%	1.28 [1.09, 1.50]	2021
Qi 2021	682	1096	414	1096	10.1%	1.65 [1.51, 1.80]	2021
Total (95% CI)		**12723**		**12723**	**100.0%**	**1.14 [0.75, 1.73]**	
Total events	6641		6082				

Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 1976.89$, df = 9 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 0.63 (P = 0.53)

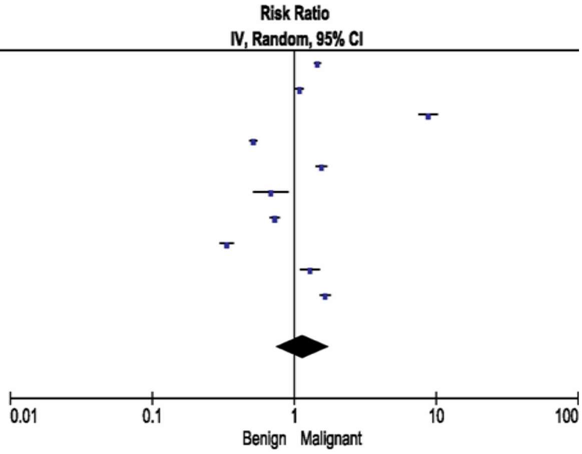

Figure 2. Forest plot of comparison TOTAL 1 USG TIRADS between benign and malignant (Risk Ratio).

Study or Subgroup	Benign Events	Benign Total	Malignant Events	Malignant Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Xu 2018	138	1460	603	1005	11.1%	0.16 [0.13, 0.19]	2018
Shen 2019	105	839	682	773	11.1%	0.14 [0.12, 0.17]	2019
Wildman 2019	168	1189	9	136	10.2%	2.14 [1.12, 4.08]	2019
Gao 2019	179	863	1372	1681	11.2%	0.25 [0.22, 0.29]	2019
Ruan 2019	32	609	0	392	3.8%	41.88 [2.57, 681.92]	2019
Zhang 2020	52	535	616	736	11.0%	0.12 [0.09, 0.15]	2020
Darota 2020	120	250	66	750	11.0%	5.45 [4.19, 7.10]	2020
Wang 2020	7	41	48	60	10.0%	0.21 [0.11, 0.42]	2020
McClean 2021	5	173	31	135	9.3%	0.13 [0.05, 0.31]	2021
Qi 2021	201	682	306	414	11.2%	0.40 [0.35, 0.45]	2021
Total (95% CI)		**6641**		**6082**	**100.0%**	**0.42 [0.22, 0.83]**	
Total events	1007		3733				

Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 713.38$, df = 9 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: Z = 2.50 (P = 0.01)

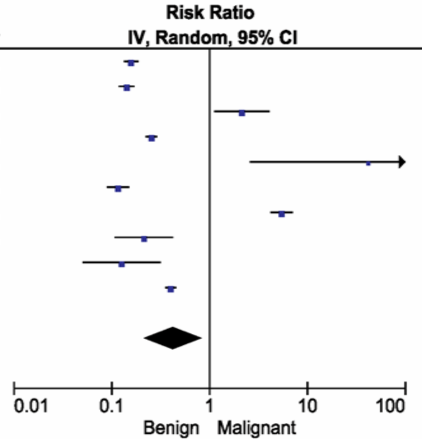

Figure 3. Forest plot of comparison of TR5 between benign and malignant (Risk Ratio).

Study or Subgroup	Benign Events	Benign Total	Malignant Events	Malignant Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Xu 2018	549	1460	368	1005	10.9%	1.03 [0.92, 1.14]	2018
Shen 2019	459	839	78	773	10.6%	5.42 [4.35, 6.75]	2019
Wildman 2019	468	1189	32	136	10.3%	1.67 [1.23, 2.28]	2019
Gao 2019	252	863	279	1681	10.8%	1.76 [1.52, 2.04]	2019
Ruan 2019	106	609	4	392	6.4%	17.06 [6.34, 45.91]	2019
Wang 2020	22	41	12	60	8.8%	2.68 [1.50, 4.79]	2020
Zhang 2020	217	535	114	736	10.7%	2.62 [2.15, 3.19]	2020
Darota 2020	108	250	368	750	10.8%	0.88 [0.75, 1.03]	2020
McClean 2021	33	173	42	135	9.9%	0.61 [0.41, 0.91]	2021
Qi 2021	242	682	100	414	10.7%	1.47 [1.20, 1.79]	2021
Total (95% CI)		**6641**		**6082**	**100.0%**	**1.91 [1.30, 2.82]**	
Total events	2456		1397				

Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 306.00$, df = 9 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: Z = 3.27 (P = 0.001)

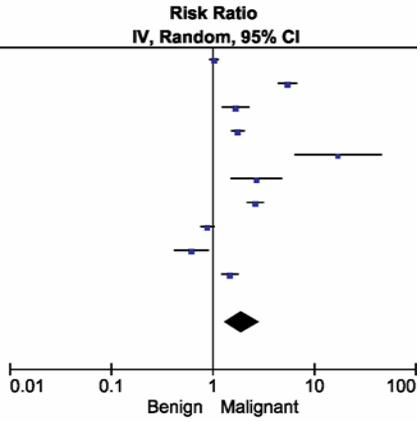

Figure 4. Forest plot of comparison of TR4 between benign and malignant (Risk Ratio).

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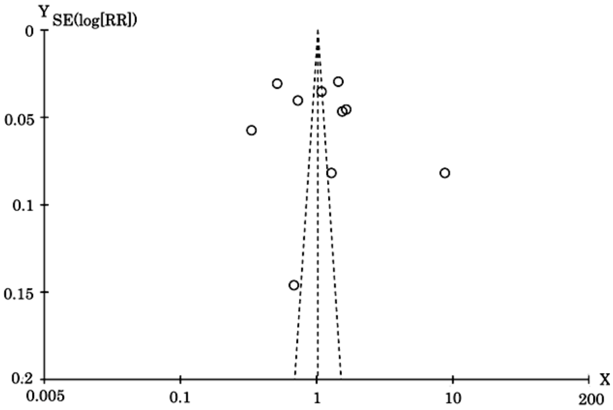

Figure 5. Funnel plot of comparison TOTAL between benign and malignant.

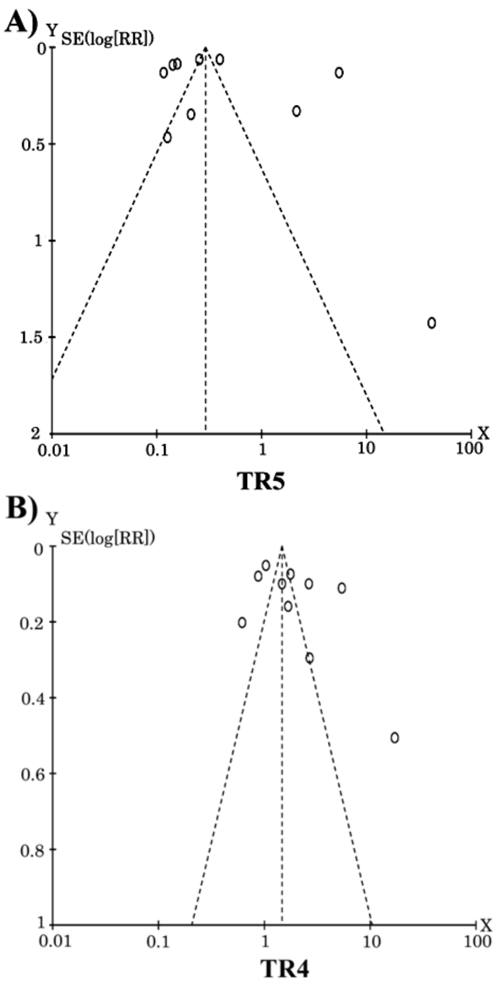

Figure 6. Funnel plot of comparison of **(A)** TR5 and **(B)** TR4 between benign and malignant.

The risk of bias and funnel plots were evaluated autonomously which included characteristics such as patient assortment, index flow, and timing. Reporting bias may arise because of variations in the direction of the results. The consequences of publication bias in the present meta-analysis include factors such as selective outcome reporting, selective analysis reporting, and asymmetrical funnel plots.

DISCUSSION

Among the general population, approximately 20-70 % of the population is having cases with thyroid nodules, out of which 10-15 % account for thyroid cancer [26]. Ultrasound imaging has become a primary tool for identifying radiologists when evaluating thyroid nodules [27]. Although there are different guidelines for ultrasound-based thyroid nodule identification, there is considerable confusion among these guidelines to establish the accuracy and precision of ACR-TIRADS in the disparate investigation of benign and malignant ultrasound based on the data of various clinical trials and to analyze their sensitivity and specificity from the meta -analysis.

The terms in the ACR-TIRADS used to define nodules were poorly defined and applied inconsistently. Manifold terminologies are often used to describe the same feature, leading to misperceptions of the real clarifications and most prominently, the precise use of the terms. These confusions lead to a consequential discrepancy in record writing and ambiguity in instructions for supplementary organization [28]. Documentation of US malignant structures is one of the challenges in ACR-TRIADS. According to the ACR thyroid ultrasound registry, there were differences among radiologists owing to the dissimilar obligations of the structures. This inter-spectator inconsistency was reliant on the knowledge and repetition of the radiologist [29]. Some of the issues that caused such variability among the spectators involved were knowledge of the pathology, and concrete skimming skills. The variation in practical scan techniques enhances inter-observer variability in the assignment of sonographic signs. The entrance of structures (e.g., ecogenicity) might differ depending on factors such as conveyance, improvement, density, and pre- and post-dispensation limitations. Images must be taken at dissimilar advanced locations with clear qualities for informal clarification by radiologists for forecasts based on ultrasonographic images. These encounters can be moderated through augmented teaching, information, and applied knowledge.

During the procurement of large tissue samples, core needle biopsy is more operative, enabling molecular testing for precise identification [30]. They further reported considerable heterogeneity that in the pooled proportions, there was considerable heterogeneity [31]. Cytologically unspecified thyroid nodules lacking doubtful USG (Ultrasonogram) patterns permit caution when examining histological thyroid nodules [17]. When assessing the correctness of RSSs, thyroid nodules analyzed as unspecified by FNA were not included until a conclusive consensus was confirmed through pathological results [17]. The

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miscellany of US sorting schemes for nodules may add to the heterogeneity of this meta-analysis; in most studies, nodules identified as malignant were considered by hypoechogenicity, taller-than-wide shape, microcalcifications, and a risked boundary [32]. RSSs were established to distinguish the distortion risk of a node and to propose the necessity for FNA and Ultrasound for threat valuation of thyroid nodes malignancy [33]. Risk stratification plays an active role in cardiac operating repetition worldwide and countless risk stratification systems have been established using logistic relapse and Bayes modelling techniques. Mathematicians also established the method to evaluate the presentation of schemes for accurately forecasting experiential significance. It has been established to decrease the amount of needless FNA [33].

A noteworthy alteration in cancer percentage occurred in these studies, and as a result, an important inconsistency was perceived in the US RSSs routine. Investigative examinations considered for choosing FNA for thyroid nodules, the query was questioned as to whether the schemes were actually similar, provided the dissimilar follows of the circulated intelligence. The final FNA consequences do not continuously contest the pre-biopsy threat allocated by the two schemes [34]. The pointer dimension or quantity of permits in every location of US-FNA would be resolve depending on the US features of thyroid swelling and the operator's inclination. Instant evaluation of cytological competence strengthens and is helpful depending on the knowledge of the worker who is handling the FNA [14]. There is also a study on thyroid tumour (TT) in 63 references that reported 43 malignant cases and further reported another 43 benign cases of which 29 were nodular goiter, 9 were thyroid adenoma, 1 was focal sub-acute thyroiditis and atypical hyperplasia of follicular cells, and 2 had chronic lymphocytic thyroiditis [35].

There are also reports of 682 cases of benign nodules and 414 cases of malignant nodules with an ICC value of 0.937 (ACR-TIRADS). It allocates scores to diagnosis efficacy and further reported that the five guidelines showed a moderate correlation coefficient among different systems [36, 37]. Thyroid nodules are well-defined by the incidence of characteristic US findings and its allotted scores [38]. They found statistically substantial alterations and their sample comprised patients who had undergone surgery. The effectiveness of TIRADS relies on the occurrence of papillary thyroid cancer; however the systems are not well-organized for running SFN/SHT nodules [39]. Another researcher encountered certain limitations in and misdiagnosis in TIRADS and ATA [32]. The ACR-TIRADS had the maximum and finest specificity (SPE) and confident analytical value (PPV) [40, 41].

In addition, it can be readily integrated into the reporting templates. A total of 1460 benign and 1005 malignant nodules were included in a study in which the circulation of tumors showed good sensitivity with the lowest specificity [42]. The ACR-TIRADS and Kwak 26 TI-RADS have shown improved investigative routines [43]. The TIRADS proposed by Kwak is referred to as (K-TIRADS), ACR-TIRADS stands for the American College of Radiology and EU-TIRADS stands for the European Thyroid Association. EU-TIRADS scoring is useful for classifying thyroid nodules in FNA [34]. It was further reported that the ACR and EU-TIRADS systems suggested FNA in 46.5% and 51.9% of the swellings, respectively. ACR TI-RADS practices consistent lexis for the valuation of thyroid nodules giving a numeric counting of structures, labelig groups of the comparative likelihood of kindliness or distortion, and delivering organization references, with the goal of plummeting needless operations and extreme investigation [44]. Accepting the ACR TI-RADS might require practice-level variation to connect the achievement of image, clarification, and commentary. ACR TI-RADS delivers an outline to produce organized broadcasting and reliably categorize nodules to deliver a suitable organization [44]. Applying the ACR TI-RADS touches manifold features of the imaging progress, likewise, it has drawbacks and contests.

Thyroid hormone ultrasound is regarded as a benchmark examination for the identification of thyroid nodule cancer and its management for risk stratification [45]. In this study, the issue of confusion between the different ACR-TIRADS classification systems was raised and TR sub-classifications or gradings were evaluated to identify different types of thyroid nodules. The ultrasound grading features in the ACR-TIRADS were classified as TR1 (benign), TR2 (minimally suspicious), TR3 (moderately suspicious), TR4 (moderately suspicious), and TR5 (highly suspicious). In the present meta-analysis two important findings were addressed: 1) the accuracy of the ACR-TIRADS and 2) the relative prevalence of thyroid nodule malignancies. The result of the meta-analysis revealed that 6082 malignant nodules in 12723 thyroid nodules. However, the present investigation has certain limitations. First, the meta-analysis was based on a sub-group analysis. Second, the meta-analysis considered factors such as age, sex, ethnicity, and disease duration. Third, the meta-analysis considered only the literature survey which was limited to English publications only which may have affected the pooled data and selection bias.

CONCLUSION

The present meta-analysis revealed an effective correlation of the thyroid ultrasound dataset reported using ACR-TIRADS grading. In fact, the TR4

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and TR5 grading of the ACR- TIRADS represents an excellent stratification system for classifying thyroid lesions thereby avoiding biopsies performed on benign nodules. These analyses suggest the accuracy of ACR-TIRADS in diagnosing malignant thyroid nodules.

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