ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ijnm.co.in/

Indian Journal of Nuclear Medicine

Original Article

Improving Thyrotoxicosis Diagnosis: The Clinical Necessity of Refining Tc-99m Pertechnetate Uptake Reference Ranges

Mohammad A. Ghanem[1,2], Shorouk F. Dannoon[1,2], Nafeesa A. Kazim[3]

[1]Department of Nuclear Medicine, College of Medicine, Kuwait University, [2]Department of Nuclear Medicine, Jabar Hospital, [3]Department of Nuclear Medicine, Mubarak Hospital, Kuwait City, Kuwait

ABSTRACT

Objectives: Accurate thyroid uptake assessment using Technetium-99m (Tc-99m) pertechnetate is essential for diagnosing thyrotoxicosis. This study evaluates the applicability of the current regional reference range (0.2%–2.0%) in Kuwait and investigates whether a refined range enhances diagnostic accuracy by reducing missed thyrotoxic cases.

Material and Methods: A retrospective study was conducted on 218 thyrotoxic patients who underwent Tc-99m pertechnetate and 131I thyroid uptake studies at a tertiary hospital between 2018 and 2024. Patients with prior thyroid surgery, iodinated contrast exposure, or interfering medications were excluded. Statistical analyses, including quartile distribution and receiver operating characteristic (ROC) curve assessment, were used to determine a more precise diagnostic threshold.

Results: Among 218 thyrotoxic patients, 56 (26%) had Tc-99m pertechnetate uptake (TU) within the current normal range, potentially leading to misdiagnosis. Refining the reference range to 0.5%–1.5% significantly reduced the number of missed thyrotoxic cases to 31 (14%). ROC analysis identified 0.5% as the optimal lower threshold, maximizing sensitivity (95.1%). The revised upper threshold of 1.5% improved the differentiation between normal and hyperfunctioning thyroid states, allowing better exclusion of non-hyperthyroid cases while maintaining high sensitivity. This refined range improved diagnostic accuracy, ensuring a more precise classification of thyrotoxic patients.

Conclusion: The existing TU reference range may lead to underdiagnosis of thyrotoxicosis. A revised range of 0.5%–1.5% enhances diagnostic precision by optimizing sensitivity and specificity, ensuring more accurate identification of hyperthyroid cases. This adjustment has significant implications for thyroid imaging protocols and clinical decision-making.

Keywords: Diagnostic accuracy, I-131 uptake, Reference range, Technetium-99m pertechnetate uptake, Thyroid scintigraphy, Thyrotoxicosis

INTRODUCTION

Thyroid imaging plays a crucial role in diagnosing and managing various thyroid disorders, such as hyperthyroidism and thyroid nodules. Radioactive iodine isotopes, particularly iodine-131 (I-131) and iodine-123 (I-123), are considered the gold standard for thyroid uptake measurements due to their high specificity for thyroid tissue and their ability to provide functional insights into the activity of the thyroid gland.[1] This technique evaluates the thyroid's capacity to trap and incorporate iodine, which is essential for hormone synthesis, making it invaluable in diagnosing hyperthyroidism, assessing thyroid nodules, and guiding treatment decisions.[2,3] The accuracy and reproducibility of radioactive iodine uptake (RAIU) tests have been extensively validated, reinforcing their vital role in evaluating thyroid

***Corresponding author:** Dr. Mohammad A. Ghanem, Department of Nuclear Medicine, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait. E-mail: mohammad.sghanem@ku.edu.kw

Received: 26 February 2025 **Accepted:** 16 June 2025 **Published:** 31 January 2026 **DOI:** 10.25259/IJNM_27_25

function. Among other available radiopharmaceuticals, Technetium-99m pertechnetate (Tc-99m pertechnetate) has become a cornerstone in clinical practice due to its availability, cost-effectiveness, and favorable characteristics, such as high count rates, efficient collimation, and low radiation exposure, rendering it a suitable alternative for radioactive iodine.[4] Similar to iodine, Tc-99m pertechnetate is taken up by the sodium-iodide symporter (NIS); however, it is not incorporated into thyroid hormones, allowing for efficient functional imaging without interference in the synthesis process.[5] Since Tc-99m pertechnetate is not incorporated into thyroid hormones, its uptake indirectly measures thyroid function, leading to discrepancies between Tc-99m pertechnetate and I-131 uptake values, necessitating a nuanced approach to diagnosis, as Tc-99m pertechnetate uptake (TU) may not always align with the patient's thyroid functional status.[6]

Determining accurate reference ranges for typical TU is crucial for reliable interpretation. Globally, the reported reference ranges for TU exhibit substantial variation, reflecting differences in dietary iodine intake and population-specific characteristics. For instance, normal uptake values range from 0.2%–2.0% in the United Kingdom (UK),[7] 0.26%–1.64% in Turkey,[8] 0.54%–1.80% in Northern Iran,[6] and 0.15%–1.69% in Namibia,[9] 0.4%–2.80% in Southern Germany,[10] all of which are lower than the previously internationally used range of 0.75%–4.5%[1,11] [Table 1]. These discrepancies underscore the need for localized reference values to ensure diagnostic accuracy and relevance across diverse populations. In Kuwait, the commonly used regional range is 0.2%–2.0%; however, we have noted that many cases are misdiagnosed, highlighting the importance of re-evaluating these ranges in our population.

Table 1: Reported ranges of Tc-99m pertechnetate uptake percentages in various geographical regions as documented in published studies from 2002 to 2024

Published papers	Area	Tc-99m pertechnetate uptake range
Paudel and Bhattarai, 2024[1]	Nepal	0.5%–2.90%
Gholami *et al*., 2024[6]	Northern Iran	0.5%–1.80%
Grunert *et al*., 2024[10]	Southern Germany	0.4%–2.80%
Alshahrani *et al*., 2021[19]	Saudi Arabia	0.2%–2.0%
Gungor, 2021[8]	Turkey	0.3%–1.64%
Macauley *et al*., 2018[7]	United Kingdom	0.2%–2.0%
Hamunyela *et al*., 2014[9]	Namibia	0.2%–1.69%
Ramos *et al*., 2002[23]	Brazil	0.4%–1.70%

A variety of patient-specific characteristics, including age, sex, ethnicity, medications, and underlying thyroid disorders, can significantly influence TU measurements.[7,9] Conditions associated with hyperthyroidism, such as Graves' disease, toxic multinodular goiter, and Hashitoxicosis, commonly exhibit elevated TU. However, the etiology and stage of thyrotoxicosis, as well as iodine turnover and the thyroid's functional reserve, can lead to uptake values that overlap with the normal range. In contrast, thyroiditis can also cause thyrotoxicosis in its early stage, but it typically presents with reduced or absent TU.[3,10,12] Consequently, the diagnostic utility of TU necessitates careful integration with clinical, laboratory, and imaging assessments to prevent misinterpretation.

This study focuses on thyrotoxic patients since existing Tc-99m pertechnetate reference ranges are primarily based on euthyroid individuals with stable iodine metabolism and normal thyroid function. However, thyrotoxic patients exhibit altered iodine kinetics, increased NIS activity, and variable uptake patterns, which may lead to misclassification under current reference thresholds. Including euthyroid individuals could broaden the range unnecessarily, reducing sensitivity in detecting hyperfunctioning thyroid states. By refining the reference range specifically for thyrotoxicosis, this study aims to improve diagnostic accuracy and reduce missed cases, ensuring more precise clinical decision-making.

To achieve this, we evaluate the diagnostic utility of TU in thyrotoxic patients in Kuwait. Specifically, the study investigates the applicability of the commonly used regional reference range of 0.2%–2.0%, considering regional variations in dietary iodine intake and Kuwait's unique demographic and clinical characteristics. Given the limitations of current reference values, this research seeks to refine the normal reference range by employing statistical analyses, including receiver operating characteristic (ROC) curve assessment and quartile distribution analysis, to determine a more clinically relevant threshold for distinguishing hyperfunctioning from nonhyperfunctioning thyroid conditions.

MATERIAL AND METHODS

Patient selection

This retrospective study was conducted at a tertiary referral hospital in Kuwait, examining 255 patients who underwent thyroid uptake assessments between January 2018 and September 2024. The study population consisted of 218 individuals with confirmed thyrotoxicosis, all of whom had undergone Tc-99m pertechnetate and I-131 24-h uptake measurements. Patients with previous thyroid surgery, pregnancy, iodinated contrast exposure, radiation therapy, I-131 treatment, or medications known to affect

thyroid function were excluded to minimize the impact of confounding factors on the uptake values. However, patients receiving antithyroid medication were included, provided they had discontinued such treatment at least 7 days before the study. Demographic and clinical data, including age, gender, and thyroid function tests, were collected for analysis. Three nuclear medicine consultants reviewed all the thyroid scans, and the final diagnoses were reached based on the scan findings and I-131 24-h uptake. Any disagreement was resolved by consensus.

Urinary iodine levels were not measured in individual patients as part of routine clinical workup during the study period. However, Kuwait is known to have adequate iodine intake at the population level, as reflected in national nutrition surveys and previous studies. This background was considered when interpreting TU values in our cohort.

Radiopharmaceutical administration

99mTcO4–imaging protocol

Tc-99m pertechnetate was administered intravenously at a standardized mean dose of 185 MBq. Thyroid uptake measurements were obtained 20 ± 5 minutes postinjection using a standard thyroid scintigraphy protocol. The images were acquired using a Siemens Intevo bold single photon emission computed tomography/computed tomography gamma camera (SPECT/CT) equipped with a low-energy, high-resolution (LEHR) parallel-hole collimator. Dynamic imaging was performed on a 128 × 128 matrix and summed over time without further processing. This was followed by acquiring anterior and lateral oblique views using a pinhole collimator. Results were expressed as the percentage of the administered activity accumulated in the thyroid gland.

Calculation of Tc-99m pertechnetate thyroid uptake

The Siemens Intevo Bold SPECT/CT gamma camera was utilized for the uptake measurement utilizing the camera method with System Sensitivity (LEHR at 10 cm) of 202 cpm/μCi (8 cpm/MBq) based on the manufacturer's data. Thyroid counts were measured by defining a region of interest around the gland's borders. A separate region of interest below the neck was used for background correction. The obtained counts were adjusted for Tc-99m pertechnetate decay and acquisition time. Residual activity from the Tc-99m pertechnetate injection was routinely measured, and injected activity was corrected based on the activity measured in the syringe before injection. The percentage of thyroid TU at 20 min was automatically calculated using the following equation:

TU = [(thyroid cpm – background cpm)/(pre-injection syringe cpm – postinjection syringe cpm)] × 100%.

I-131 thyroid uptake protocol

I-131 thyroid uptake measurements were performed following a standardized procedure. The patient ingested an I-131 Sodium Iodide (I-131 NaI) capsule dose of 0.37 MBq (sourced from the National Centre for Nuclear Research Radioisotope Centre POLATOM, Poland), measured by a dose calibrator on the day of dose administration. The thyroid uptake of I-131 was assessed after 24 h of ingesting the capsule, after correcting for decay. A scintillation probe (Atomlab 960-NaI crystal by Biodex, UK) was placed 25 cm from the patient's thyroid, and the emitted activity from the thyroid was measured for 2 minutes. The background (BKG) correction measurements were taken by positioning the probe at the patient's thigh, maintaining the same distance and measurement time as the thyroid. A subset of patients had an I-131 4-h measurement as early uptake and a next-day 24-h uptake.

Calculation of I-131 thyroid uptake

After correcting for background activity, the thyroid activity (counts per minute, cpm) was compared to the activity of a standard containing 0.37 MBq I-131, measured within an anthropomorphic Perspex thyroid/neck phantom, with adjustments made for room background activity.

The percentage of thyroid I-131 uptake (IU) by the thyroid is:

IU = [Neck cpm-Thigh cpm)/(Standard cpm-Background cpm)] × 100%

Statistical analysis

All statistical analyses were performed using IBM Statistical Package for Social Sciences version 23 (SPSS Inc., Chicago, USA). The study population was categorized into seven groups based on the etiology of hyperthyroidism: subacute thyroiditis, recovery phase of thyroiditis, Hashimoto's thyroiditis, diffuse toxic goiter (Graves' disease), toxic nodular goiter (Plummer's disease), multinodular goiter, and toxic solitary nodular disease. The mean and standard deviation (SD) were calculated for each group, and the results are presented as the mean ± SD for Tc-99m pertechnetate and I-131 thyroid uptake values.

To assess the validity of the current reference range, we conducted ROC curve analysis using TU as the predictor variable and classified patients into hyperfunctioning (Graves' disease, Plummer's disease, multinodular goiter, solitary toxic nodule) and hypofunctioning (acute thyroiditis, Hashimoto's thyroiditis) groups. The optimal threshold was determined using Youden's Index, which maximizes sensitivity and specificity. In addition, quartile analysis was performed within the currently accepted normal range (0.2%–2.0%) to assess the distribution of TU values in thyrotoxic patients.

As this was a retrospective analysis, a formal a *priori* sample size calculation was not applicable. However, a *post hoc* assessment based on the ROC analysis (AUC = 0.75) was used to estimate statistical power. At a significance level of 0.05, the achieved power exceeded 90%, supporting the adequacy of the included sample (n = 218) for identifying clinically meaningful thresholds in this population.

RESULTS

The data of two hundred fifty-five patients who underwent a thyroid uptake study for the workup of thyrotoxicosis from January 2018 to September 2024 were reviewed. This study analyzed data of two hundred eighteen thyrotoxicosis patients with Tc-99m pertechnetate and I-131 thyroid uptake studies. The mean age of this group was 40.1 ± 12.9 years, with a mean thyroid-stimulating hormone (TSH) value of 0.042 ± 0.047 and a mean Free Thyroxine (FT4) value of 42.3 ± 24.0. There were 148 females with a mean age of 38.8 ± 13.5 years, a mean TSH value of 0.041 ± 0.052, and a mean FT4 value of 43.4 ± 24.8, and 70 males with a mean age of 42.8 ± 11.2 years, a mean TSH value of 0.043 ± 0.037, and a mean FT4 value of 40.0 ± 22.1 [Table 2].

Table 2: Summary of patient demographics and thyroid function parameters (thyroid-stimulating hormone and free thyroxine 4) stratified by gender for the study population, listing the mean values±standard deviation

Gender	*n*	Age range	Mean±SD	TSH	FT4
Female	148	10–81	38.8±13.5	0.041±0.052	43.4±24.8
Male	70	22–69	42.8±11.2	0.043±0.037	40.0±22.1
Total	218	10–81	40.1±12.9	0.042±0.047	42.3±24.0

TSH: Thyroid-stimulating hormone, FT4: Free thyroxine 4, SD: Standard deviation

Among these patients, 47 had subacute thyroiditis, 6 had Hashimoto's thyroiditis, 124 had Graves' disease, 28 had Plummer's disease, 5 had multinodular goiter, and 8 had toxic solitary nodules (TSNs). Their 24-h I-131 uptake and TU mean values, along with the uptake range, are listed in Table 3.

After stratifying patients based on TU values, only those with uptake ≤2% were included in the analysis, narrowing the study population to 89 patients (41%) [Figure 1]. Within this group, 56 patients had uptake values within the currently accepted normal range of 0.2%–2.0%, with a mean uptake of 1.0 ± 0.5% [Table 4]. The TU values were compared with their I-131 uptake values, as illustrated in Figure 2. Of these 56 patients, there were 34 (61%) with normal 99mTcO4– and I-131 uptake values, 15 (27%) with normal Tc-99m pertechnetate and high I-131 uptake, and only 7 (13%) with normal Tc-99m pertechnetate and low I-131 uptake. The patients' diagnosis of each group is shown in Table 5.

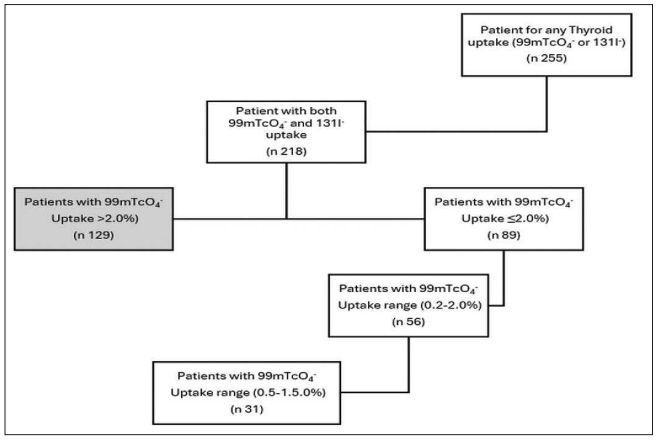

Figure 1: This flowchart illustrates the selection and stratification of patients based on Tc-99m pertechnetate and I-131 uptake. Of 255 patients who underwent thyroid uptake studies, 218 had Tc-99m pertechnetate and I-131 uptake measurements and were included in the analysis. Patients were categorized into those with Tc-99m pertechnetate uptake >2.0% (n = 129) and those with uptake ≤2.0% (n = 89). Within the latter group, 56 patients fell within the commonly accepted normal uptake range (0.2%–2.0%), while further refinement using the proposed 0.5%–1.5% range reduced the number of patients classified as normal to 31. (99mTcO4–: Tc-99m pertechnetate, 131I–: I-131)

To further evaluate the functional significance of the uptake values, Pearson correlation analysis was conducted between TU and Free T4 levels. A statistically significant moderate

Table 3: Summary of Tc-99m pertechnetate and I-131 thyroid uptake values in patients with different etiologies of thyrotoxicosis with the range of the Tc-99m pertechnetate and 24-h I-131 uptake, along with the mean values±standard deviation

Diagnosis	n	Tc-99m pertechnetate uptake range	Mean±SD	I-131 uptake range	Mean±SD
Grave's disease	124	0.7–43.5	11.3±9.5	8.3–99.0	61.2±18.2
Multinodular goiter	5	0.9–1.6	1.4±0.3	12.8–34.7	25.3±8.8
Plummers disease	28	0.3–12.8	4.1±3.7	15.0–73.0	43.9±15.5
Toxic solitary nodule	8	0.1–11.7	4.1±3.6	13.0–65.0	42.0±18.4
Subacute thyroiditis	47	0–0.1.6	0.24±0.3	0.0–5.35	6.1±8.0
Hashimoto's thyroiditis	6	0.2–1.8	0.7±0.6	16.0–29.0	21.6±5.2
Total	218				

SD: Standard deviation

positive correlation was observed (r = 0.43, P < 0.001), indicating that higher uptake values generally reflected higher circulating thyroid hormone levels. This supports the clinical applicability of the revised reference range and underscores its relevance in identifying biochemically hyperthyroid states.

Table 4: Breakdown of diagnoses for patients with Tc-99m pertechnetate uptake values between 0.2% and 20%, including the number of cases and mean uptake values±standard deviation for each diagnostic category (n=56)

Diagnosis	*n*	Mean Tc-99m pertechnetate uptake ±range
Grave's disease	19	1.3±0.4
Multinodular goiter	5	1.4±0.3
Plummers disease	10	1.0±0.5
Toxic solitary nodule	1	0.9
Subacute thyroiditis	15	0.6±0.5
Hashimoto's thyroiditis	6	0.7±0.6
Total	56	1.0±0.5

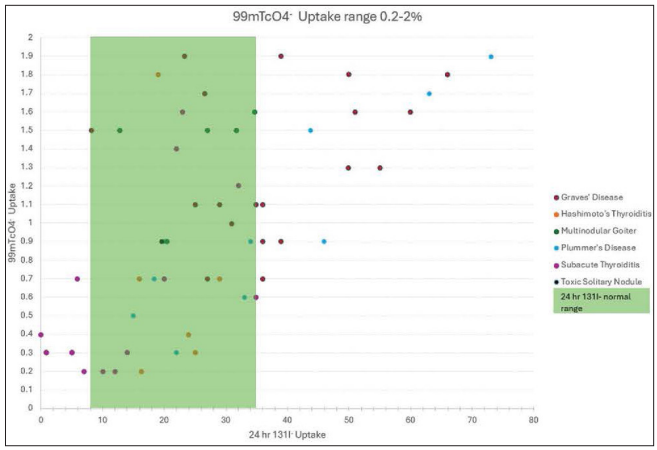

Figure 2: This scatter plot illustrates the relationship between Tc-99m pertechnetate uptake (y-axis) and 24-h I-131 uptake (x-axis) for patients with uptake values within the normal range of 0.2%–2.0%. Each dot represents an individual patient, color-coded by diagnosis: Graves' disease, Hashimoto's thyroiditis, multinodular goiter, Plummer's disease, subacute thyroiditis, and toxic solitary nodule. The green-shaded area represents the normal reference range for 24-h I-131 uptake (8%–35%). (99mTcO4–: Tc-99m pertechnetate, 131I–: I-131)

Quartile analysis of Tc-99m pertechnetate values within the normal range (0.2%–2.0%) demonstrated a 25th percentile (Q1) of 0.575%, median (Q2/50th percentile) of 0.900% and a 75th percentile (Q3) of 1.500% [Figure 3].

The ROC curve analysis identified 0.5% as the threshold with the highest sensitivity (95.1%), meaning nearly all

Table 5: Categories thyroid conditions based on their I-131 uptake levels (low, normal, and high) and correlate them with Tc-99m pertechnetate uptake in the normal range (0.2%–2%)

Diagnosis	Normal Tc-99m pertechnetate Tc-99m pertechnetate Tc-99m pertechnetate uptake (%)	
Low I-131 uptake Subacute thyroiditis	7	7 (13)
Normal I-131 uptake Subacute thyroiditis	8	34 (61)
Hashimoto's thyroiditis	6	0.9±0.3 (Mean ± SD)
Grave's disease	8	0.9
Multinodular goiter	5	0.9±0.4 (Mean ± SD)
Plummer's disease	6	0.7±0.0 (Mean ± SD)
Toxic solitary nodule	1	
High I-131 uptake Grave's disease	11	15 (27)
Plummer's disease	4	
Total		56

SD: Standard deviation

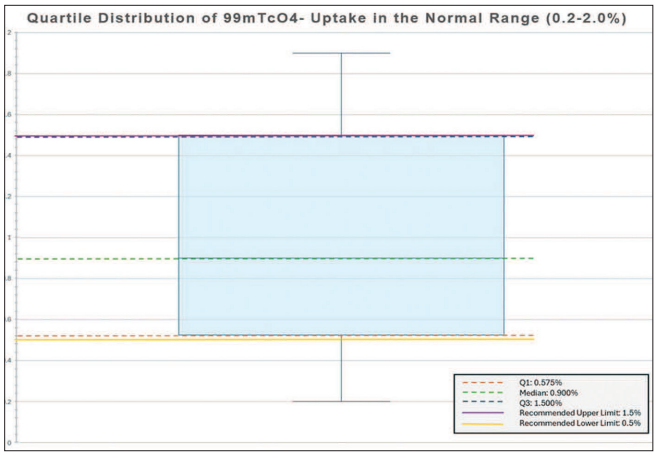

Figure 3: The box plot illustrates the quartile distribution of Tc-99m pertechnetate uptake within the normal range (0.2%–2.0%). The blue box represents the interquartile range between the first quartile (Q1) (0.575%) and third quartile (Q3) (1.500%), with the whiskers extending to the minimum and maximum non-outlier values. A grey line marks the median (0.900%). The recommended revised uptake thresholds are indicated by the solid orange line (lower limit: 0.5%) and the solid purple line (upper limit: 1.5%). These findings support refining the normal range to 0.5%–1.5% for improved diagnostic accuracy in thyrotoxicosis. (99mTcO4–: Tc-99m pertechnetate, 131I–: I-131)

hyperfunctioning cases were correctly classified [Figure 4]. However, the low specificity (24.9%) indicated that many nonhyperfunctioning cases were also classified as hyperfunctioning. A higher threshold of 1.5% was associated

with a more balanced sensitivity (75.6%) and specificity (35.0%), making it a potential upper limit for the refined reference range. The currently used threshold of 2.0% showed lower sensitivity (58.5%), indicating that it may fail to detect some hyperfunctioning cases [Figure 5].

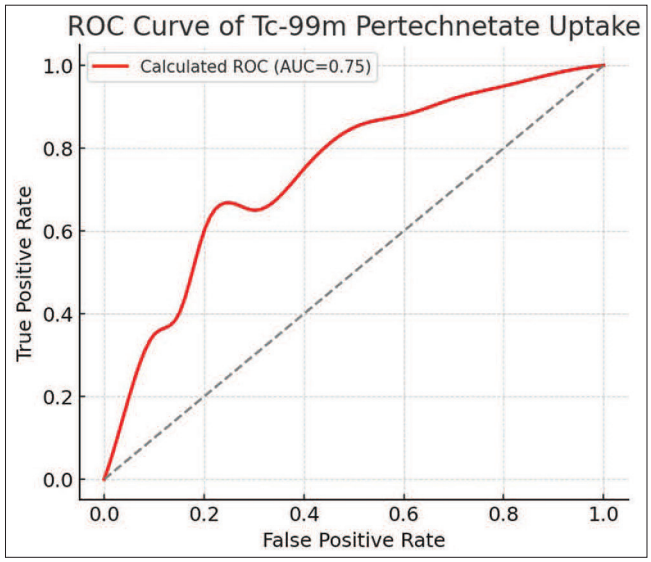

Figure 4: The receiver operating characteristic (ROC) curve illustrates the diagnostic performance of Tc-99m pertechnetate uptake in detecting thyrotoxicosis. The red line represents the calculated ROC curve, while the grey dashed line indicates the reference line for random classification. The area under the curve = 0.75 suggests moderate diagnostic accuracy of Tc-99m pertechnetate uptake in distinguishing thyrotoxic patients from non-thyrotoxic individuals. Higher true positive rates with lower false positive rates indicate better diagnostic performance

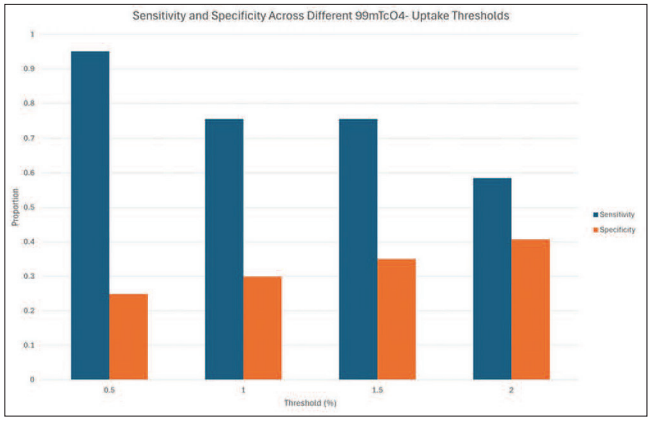

Figure 5: This bar chart shows the sensitivity (blue) and specificity (orange) at different Tc-99m pertechnetate uptake thresholds for diagnosing thyrotoxicosis. Lower thresholds (e.g., 0.5%) yield higher sensitivity but lower specificity, while higher thresholds (e.g., 2.0%) improve specificity at the cost of sensitivity. The 1.5% threshold offers a balanced diagnostic cutoff. (99mTcO4–: Tc-99m pertechnetate)

The calculation of Youden's Index demonstrated that the threshold of 0.5% yielded the highest index value, confirming its effectiveness in distinguishing hyperfunctioning from non-hyperfunctioning conditions. However, the threshold of 1.5% represented a practical balance between sensitivity and specificity, making it an appropriate upper limit for the revised reference range [Table 6].

Table 6: Youden's Index Calculation Table shows different threshold's sensitivity and specificity

Threshold (%)	Sensitivity	Specificity	Youden's Index
0.5	0.951	0.249	0.200
1.0	0.756	0.299	0.055
1.5	0.756	0.350	0.106
2.0	0.585	0.407	−0.008

The interquartile range, 0.5%–1.5%, decreased the number of patients from 56 to 31 out of the 89 patients, as illustrated in Figures 6 and 7. Within this range, 22 of the 31 (70%) patients had normal I-131 uptake values compared to 34 of the 52 (61%) patients in the earlier group. Details of the uptake with the diagnosis are listed in Table 7, and the comparison of numbers between the two reference ranges with correlation with the I-131 uptake is in Table 8.

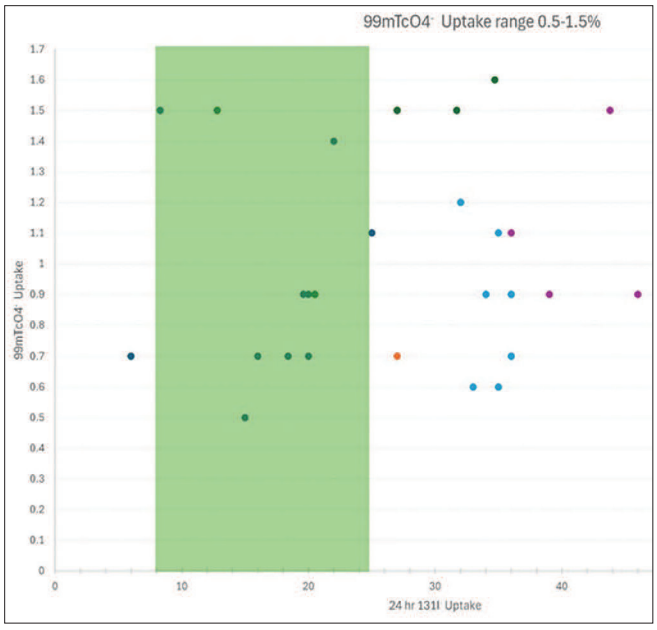

Figure 6: This scatter plot shows the relationship between Tc-99m pertechnetate uptake (y-axis) and 24-h I-131 uptake (x-axis) within the refined Tc-99m pertechnetate uptake range of 0.5%–1.5%. Each dot represents a patient, color-coded by diagnosis. The green-shaded area marks the normal reference range for 24-h I-131 uptake. (99mTcO4–: Tc-99m pertechnetate, 131I–: I-131)

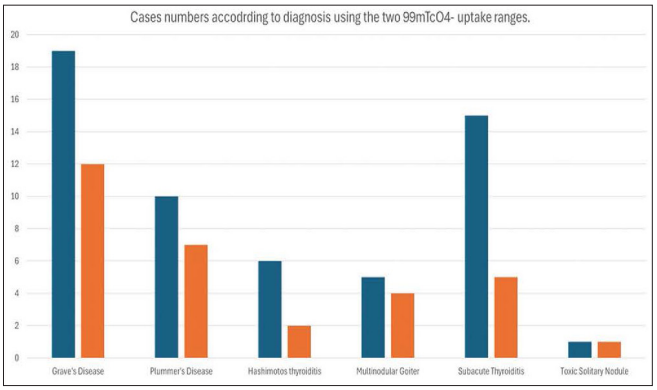

Figure 7: This bar chart compares the number of cases per diagnosis using two Tc-99m pertechnetate uptake ranges: 0.2%–2.0% (blue) and the refined 0.5%–1.5% range (orange). The refined range reduces the number of cases classified within the normal uptake category, particularly in Graves' disease, Plummer's disease, and subacute thyroiditis. (99mTcO4–: Tc-99m pertechnetate)

For patients on Carbimazole, antithyroid medication, who stopped taking their dosage 7 days before the study, there were five patients with Graves' disease and one patient with Plummer's disease in the whole studied population. Of the five Graves patients, three were within the normal range of TU values (0.2%–2%), and two had TU values >2%. The Plummer patient was also within the normal range of TU values. While using the smaller, more restricted range of TU values (0.5%–1.5%), only one patient with Graves was excluded as the value was above 1.5%.

Table 7: Breakdown of diagnoses for patients with Tc-99m pertechnetate uptake values between 0.5% and 1.5%, including the number of cases and mean uptake values±standard deviation for each diagnostic category (n=31)

Diagnosis	*n*	Mean±SD
Graves	8	1.1±0.2
Multinodular goiter	7	1.4±0.3
Plummers	4	0.9±0.3
Toxic solitary nodule	1	0.9
Subacute thyroiditis	6	0.9±0.4
Hashimoto's thyroiditis	5	0.7±0.0
Total	31	1.0 ± 0.3

SD: Standard deviation

Table 8: Number and percentage of patients with normal Tc-99m pertechnetate uptake (two defined ranges: 0.2%–2% and 0.5%–1.5%) categorized by low, normal, and high I-131 uptake levels

	Normal Tc-99m pertechnetate uptake (%)	
	Range (0.2%–2%)	Range (0.5%–1.5%)
Low I-131 uptake	3 (6)	1(2)
Normal I-131 uptake	35 (67)	23 (44)
High I-131 uptake	14 (27)	7 (13)
Total	52	31

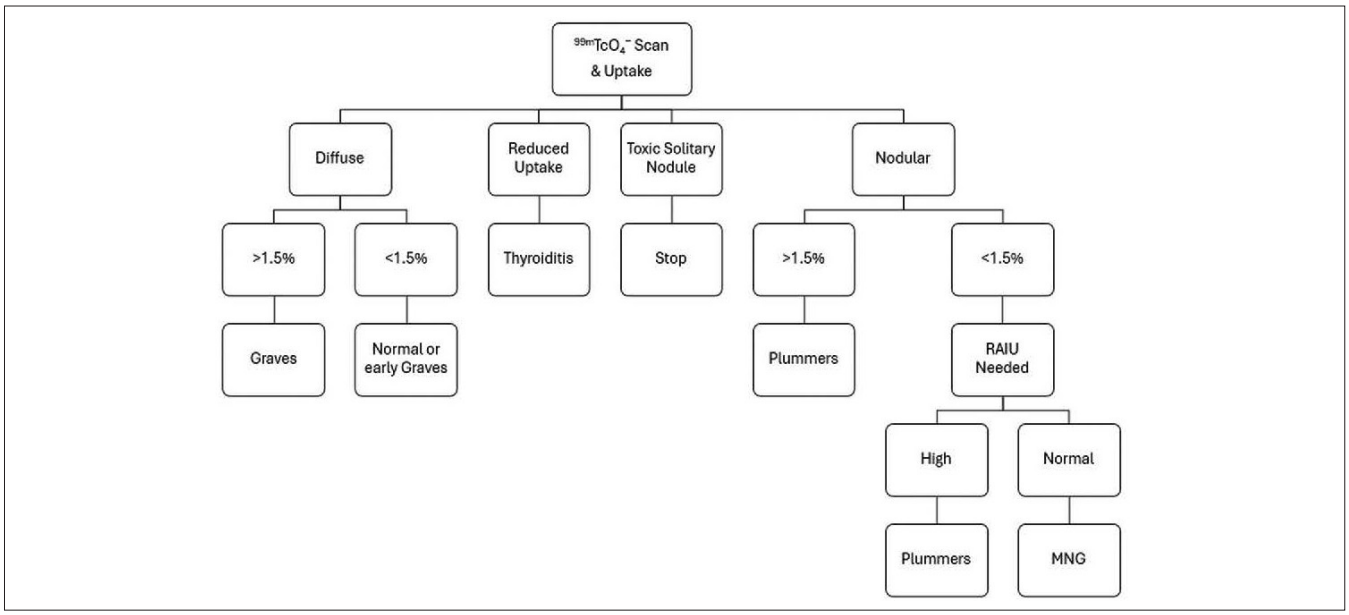

Figure 8: This flowchart outlines the diagnostic approach using Tc-99m pertechnetate uptake patterns. Diffuse uptake is classified based on the 1.5% threshold, distinguishing Graves' disease from early or normal Graves' cases. Reduced uptake suggests thyroiditis. Toxic solitary nodules lead to further evaluation. Nodular uptake is assessed using the 1.5% threshold; values above this suggest Plummer's disease, while lower values require radioactive iodine uptake testing to differentiate between multinodular Goitre and Plummer's disease. (99mTcO4–: Tc-99m pertechnetate, RAIU: Radioactive iodine uptake)

DISCUSSION

Both I-131 and Tc-99m pertechnetate are transported by the NIS, utilizing the exact mechanism to enter thyroid cells. However, Tc-99m pertechnetate has a significantly lower affinity for NIS than I-131, reducing uptake and transport efficiency. While I-131 is retained in the thyroid due to organification and its role in hormone synthesis, Tc-99m pertechnetate is not organified and is rapidly cleared.[13] Kinetic studies further demonstrate that I-131 has a higher transport capacity (Vmax) and more significant steady-state accumulation than 99mTcO4–, emphasizing their functional differences in thyroid physiology and diagnostic applications.[13]

The internationally accepted reference range for Tc-99m pertechnetate thyroid uptake is 0.75%–4.5%.[1,11] This range has been widely used in nuclear medicine to assess thyroid function; however, it includes populations with dietary iodine content ranging from inadequate to optimum. The dietary iodine intake in Kuwait is generally adequate, with a content commonly consumed in Kuwaiti dishes ranging from 7.4 μg/100g to 61.2 μg/100g.[14] The urinary iodine excretion (UIE) levels in Kuwait (UIE of 148 μg/L) align with the World Health Organization recommendations and fall in the adequate iodine nutrition category-median UIE levels between 100 and 199 μg/L-for the general population, including school-age children.[15-17] Individual UIE levels were not available in this retrospective cohort, but population-wide data were considered sufficient for contextual interpretation of uptake thresholds. Since there is an inverse relation between dietary iodine intake and thyroid TU,[18] this data supports the idea of a lower uptake value than the internationally applied one, especially in Kuwait. It is important to note that this has led to more recent studies re-evaluating this range, which have reported lower normal ranges in various populations. Thus, it reinforces the notion of a reduced uptake value compared to the internationally accepted standard. Notably, this has prompted recent studies to reassess this range, revealing lower normal ranges across different populations. As the Saudi and UK papers suggested, the regionally accepted range for pertechnetate uptake is 0.2%–2%.[7,19] This range is established for euthyroid patients, and when applied to the cohort in this paper, 56 out of the 218 patients (26%) were diagnosed with thyrotoxicosis but had normal TU.

Furthermore, the papers published to determine the normal range for TU were performed on either euthyroid patients with neither thyroid nor parathyroid disease or those referred to the nuclear medicine department to investigate parathyroid problems. Since the aim was to determine the normal range, none of the studies were conducted on patients with thyrotoxicosis. Interestingly, the studies on the Saudi Arabian population (Alshahrani *et al.*, 2021)[19] and Turkey (Gungor, 2021)[8] were conducted on patients undergoing parathyroid scintigraphy for suspected primary hyperparathyroidism. However, a crucial inclusion criterion was that these individuals were biochemically and clinically euthyroid for 12 months before the thyroid uptake scan. Including patients with parathyroid adenomas can impact the determination of the upper limit of the normal range since some adenomas have been reported to show TU.[20-22] The other studies (Paudel and Bhattarai, 2024)[1], (Gholami *et al.*, 2024)[6], (Macauley *et al.*, 2018)[7], (Hamunyela *et al.*, 2014)[9], and (Ramos *et al.*, 2002)[23] focused on establishing normal thyroid uptake ranges and specifically selected euthyroid individuals without known parathyroid issues. This method is standard practice for defining normal reference intervals, as the presence of other conditions could confound the results. Therefore, finding the proper population sample with normal thyroid glands, including function and structure, is challenging, especially if dietary iodine intake and prior episodes of thyroiditis are all considered. Not forgetting the effect of gender and age on iodine uptake.[24-27]

Furthermore, thyroid TU exhibits an inconsistent reference range pattern in the presence of thyroid nodularity. Some individuals with thyrotoxicosis may demonstrate lower TU, potentially leading to diagnostic challenges.[28,29] In such cases, I-131 uptake measurements are essential to accurately assess the thyroid gland's functional state.[26,30] Within the patient cohort of this study, 41 individuals exhibited thyroid nodularity on their scans. Twenty-four of these 41 patients had an elevated TU, while 17 were in the normal range. Further analysis revealed that 11 of the 17 patients with normal TU had a normal I-131 uptake. The remaining 6 patients, however, exhibited elevated RAIU. These findings highlight the importance of comprehensively utilizing Tc-99m pertechnetate and I-131 uptake measurements to evaluate thyroid function, especially in thyroid nodularity.[31,32]

Among the 124 patients with Graves' disease, 18 exhibited a normal TU. Further investigation revealed that 8 of these patients demonstrated elevated 4-h (early) I-131 uptake but normal 24-h (delayed) uptake, suggesting a state of rapid thyroid hormone turnover in Graves' disease. Other cases of normal pertechnetate uptake in Graves' disease patients may occur in the initial stage of the condition; therefore, complementing the TU findings with an assessment of TSH-binding inhibitor immunoglobulins is recommended to aid in the diagnostic process.[33]

Follow-up thyroid function results were available for 29 patients, mostly those with subacute thyroiditis or recovering from Graves' disease. In 27 of these, repeat testing at around 3 to 6 months showed patterns that matched what was initially seen on imaging, either normalization or progression to hypothyroidism. While this represents a smaller portion of

the cohort, it offers some reassurance that the refined uptake range corresponds with the expected clinical course. That said, we acknowledge the limitations of retrospective data and incomplete follow-up across all cases.

Our analysis focused on thyrotoxic patients within the normal range; we examined data from 56 out of 218 patients, accounting for 26%. We established a 0.5% to 1.5% range by isolating the first and fourth quartiles. Consequently, only 31 out of the 218 patients (14%) had normal TU. This revised range aligns closely with findings from Turkey and Brazil, which reported ranges of 0.3%–1.64% and 0.4%–1.70%, respectively.[8,34] Increasing the lower limit from 0.2% to 0.5% removes 13 patients from the normal uptake category, including 9 diagnosed with recovery-phase thyroiditis, 3 with Hashimoto's thyroiditis, and one with Plummer's disease. Importantly, this change will not significantly impact their clinical management since continued follow-up laboratory investigations are still planned for most of them to exclude future onset of hypothyroidism.[34-36]

In addition, reducing the upper limit from 2% to 1.5% moves 12 patients from the normal range to the high pertechnetate uptake category, reflecting their hyperthyroid condition more accurately. This change will impact many thyrotoxic patients labeled with normal uptake if the 2% upper limit is to be clinically used. This refined reference range of 0.5%–1.5% will effectively exclude as many hyperfunctioning and hypofunctioning patients as possible, ensuring a more accurate and clinically useful classification of thyroid function.

The flowchart [Figure 8] outlines a diagnostic algorithm for evaluating thyroid disorders using Tc-99m pertechnetate scintigraphy and radiotracer uptake measurements. The diagnostic process begins with a Tc-99m pertechnetate scan and subsequent quantification of radiotracer uptake. The initial branching point distinguishes four primary patterns of radiotracer distribution: diffuse, reduced, TSN, and nodular. The diffused uptake is characterized by a homogeneous distribution of the radiotracer throughout the thyroid gland, and it is further stratified based on the magnitude of uptake. If the TU exceeds 1.5%, it strongly suggests a Graves' disease diagnosis. Conversely, suppose the diffused uptake is <1.5%. In that case, it may represent either normal thyroid function or the early stages of Graves' disease, warranting further clinical correlation and potentially serial testing.[32,37,38] Reduced uptake signifies diminished overall radiotracer accumulation in the thyroid, a pattern typically observed in thyroiditis, encompassing various inflammatory thyroid conditions, such as postpartum, silent, or subacute thyroiditis.[27,39,40] A TSN, identified by intensely increased radiotracer uptake concentrated within a single, well-defined nodule with suppression of uptake in the remaining thyroid tissue, is considered diagnostic of a hyperfunctioning nodule that autonomously produces thyroid hormones and suppresses TSH. In cases of nodular uptake, where multiple areas of increased or decreased radiotracer activity are observed within the thyroid gland, the algorithm again considers the overall uptake value. If the uptake is >1.5%, it suggests Plummer's disease, also known as toxic multinodular goiter, characterized by multiple autonomously functioning nodules leading to hyperthyroidism. When nodular uptake is accompanied by an uptake value <1.5%, a RAIU test is indicated for further functional assessment of the nodules.

A high RAIU in this context reinforces the diagnosis of Plummer's disease, indicating increased iodine avidity by the hyperfunctioning nodules. This study has some important limitations. As a single-center retrospective analysis, it lacked long-term follow-up for many patients, and subgroup sizes– particularly for multinodular goiter and Hashimoto's thyroiditis–were too small to support etiology-specific conclusions. These subgroup comparisons should therefore be interpreted as exploratory. While these factors may limit generalizability, the diagnostic trends observed remain consistent and clinically meaningful. Future studies should aim to prospectively validate the proposed 0.5%–1.5% range, ideally incorporating serial follow-up and thyroid antibody profiles to improve correlation between uptake and disease trajectory. Larger, multi-institutional cohorts may also help clarify whether tailored thresholds by etiology are warranted. If validated, the revised reference range could contribute to greater standardization in nuclear medicine reporting and enable more accurate functional assessment of thyrotoxic states, thereby informing timely and appropriate therapeutic decisions.

CONCLUSION

This study underscores the complexities of interpreting Tc-99m pertechnetate thyroid uptake, particularly in thyroid dysfunction. Our findings indicate that the widely accepted regional reference range of 0.2%–2% may not be universally applicable, with emerging evidence supporting a refined range of 0.5%–1.5%. This adjustment significantly enhances the accuracy of thyrotoxicosis diagnosis by minimizing missed cases and improving patient classification. Careful consideration of additional factors, such as thyroid nodularity and rapid turnover in Graves' disease, is crucial for accurately assessing thyroid function using this diagnostic modality. While the revised range offers greater diagnostic clarity, its application should be tailored to specific populations, considering regional dietary iodine intake and clinical variability. Implementing this refined threshold in nuclear medicine practice could lead to more accurate diagnoses, optimized treatment decisions, and improved patient outcomes.

Ethical approval: Institutional Review Board approval is not required.

This study was a retrospective analysis of existing clinical data. It involved no prospective intervention, no direct patient contact, and no alteration of patient management. All data were fully anonymized prior to analysis, with no patient identifiers, names, medical record numbers, or dates of birth accessed or recorded.

According to institutional policy and local regulations, studies of this nature are exempt from formal ethical committee approval and informed consent requirements.

We therefore confirm that ethical approval was not required for this study.

Declaration of patient consent: Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI

REFERENCES

1. Paudel J, Bhattarai B. Standardizing normal reference value for thyroid uptake of technetium 99m pertechnetate in nepalese population. World J Nucl Med 2024;23:25-32.
2. Pooria A, Pourya A, Gheini A. Frequency of pathological types of hyperthyroidism in thyroid scan patients. Curr Med Imaging 2021;17:608-12.
3. Giovanella L, Avram A, Clerc J. Molecular imaging for thyrotoxicosis and thyroid nodules. J Nucl Med 2021;62:20S-5S.
4. Giovanella L, Avram AM, Iakovou I, Kwak J, Lawson SA, Lulaj E, Et Al. EANM practice guideline/snmmi procedure standard for raiu and thyroid scintigraphy. Eur J Nucl Med Mol Imaging 2019;46:2514-25.
5. Huysmans DA, Hermus AR. Iodine and technetium scintigraphy of the thyroid. In: Krenning EP, editor. Functional and morphological imaging of the endocrine system. Endocrine Updates. Berlin, Heidelberg: Springer; 2000. p. 103–24.
6. Gholami A, Armaghan N, Shirafkan H, Amiri M, Mousavie Anijdan SH. Normal reference values for tc 99m pertechnetate thyroid uptake in northern iranian population: A single center experience. Caspian J Intern Med 2024;15:459-65.
7. Macauley M, Shawgi M, Ali T, Curry A, Howe K, Howell E, *et al*. Assessment of normal reference values for thyroid uptake of technetium 99m pertechnetate in a single centre UK population. Nucl Med Commun 2018;39:834-8.
8. Güngör S. Determination of the normal range for thyroid uptake of technetium-99m pertechnetate in a turkish population. Anatolian Clinic Journal of Medical Sciences. 2021;26:265–270.
9. Hamunyela RH, Kotze T, Philotheou GM. Normal reference values for thyroid uptake of technetium 99m pertechnetate for the namibian population. J Endocrinol Metab Diabetes South Afr 2014;18:142-7.
10. Grunert M, Schenke SA, Konrad A, Schütze C, Förster S, Klemenz B, *et al*. Thyroid scintigraphy: establishing a clinically useful normal range for 99mtc pertechnetate uptake. Nuklearmedizin 2024;63:337-46.
11. Currie GM, Iqbal BM. Re-modelling 99m technetium pertechnetate thyroid uptake: statistical, machine learning, and deep learning approaches. Journal of Nuclear Medicine Technology. 2022;50(2):162–8.
12. Hoff W Van't, Pover GG, Eiser NM. Technetium 99 m in the diagnosis of thyrotoxicosis. Br Med J 1972;4:203-6.
13. Zuckier LS, Dohan O, Li Y, Chang CJ, Carrasco N, Dadachova E. Kinetics of perrhenate uptake and comparative biodistribution of perrhenate, pertechnetate, and iodide by nai symporter expressing tissues in vivo. J Nucl Med 2004;45:500-7.
14. Sawaya WN, Al Awadhi F, Aziz A, Al Rashdan A, Mahjoub BT, Al Amiri H. Nutritional profile of kuwaiti composite dishes: Minerals and vitamins. J Food Composit Anal 1998;11:70-88.
15. Al Yatama FI, Al Bader MD, Al Mazidi ZM, Ali A, Al Omair AS, Al Jehma NA, *et al*. Assessment of urinary iodine excretion among normal kuwaiti adults. Biol Trace Elem Res 2009;132:67-74.
16. Dashti B, Al Awadi F, Alkandari R, Ali A, Al Otaibi J. Macro and microelements contents of 32 kuwaiti composite dishes. Food Chem 2004;85:331-7.
17. Andersen SL, Laurberg P. Iodine supplementation in pregnancy and the dilemma of ambiguous recommendations. Eur Thyroid J 2016;5:35-43.
18. Reinhardt MJ, Högerle S, Trupkovic T, Krause TM, Moser E. Influence of urinary iodine excretion on thyroid technetium 99m pertechnetate uptake with and without tsh suppression: what happens when iodine supply increases? Eur J Nucl Med 1998;25:1475-81.
19. Alshahrani A, Syed GM, Khan AH, Numani SP, Alnaim A, Alanazi F, *et al*. Assessment of normal reference values for thyroid uptake of technetium 99m pertechnetate in a saudi population. Ann Saudi Med 2021;41:86-90.
20. Leslie WD, Riese KT, Guzman R, Dupont JO, Peterdy AE. Technetium 99m pertechnetate uptake by intrathyroidal parathyroid adenoma. J Nucl Med 1996;37:861-2.
21. Kikuchi T, Watanobe H, Suda T, Tomiyama T, Masuda M. Marked uptake of technetium 99m pertechnetate by parathyroid adenoma. Intern Med 2001;40:506-9.
22. Kiratli PO, Peksoy I, Erbaş B, Gedikoğlu G, Karabulut N. Technetium 99m pertechnetate uptake in ectopic parathyroid adenoma. Ann Nucl Med 1999;13:113-5.
23. Ramos CD, Zantut Wittmann DE, Etchebehere EC, Tambascia MA, Silva CA, Camargo EE. Thyroid uptake and scintigraphy using 99mtc pertechnetate: Standardization in normal individuals. Sao Paulo Med J 2002;120:45-8.
24. Hanson GA, Komorowski RA, Cerletty JM, Wilson SD. Thyroid gland morphology in young adults: normal subjects versus those with prior low dose neck irradiation in childhood. Surgery 1983;94:984-8.
25. Saba C, Guilmin Crepon S, Zénaty D, Martinerie L, Paulsen A, Simon D, *et al*. Early determinants of thyroid function outcomes in children with congenital hypothyroidism and a normally located thyroid gland: A regional cohort study. Thyroid 2018;28:959-67.
26. Begum R, Reza MS, Hossain MS, Haque MM, Islam FN, Islam MR. Radioiodine thyroid uptake and scintigraphy in the evaluation of hyperthyroidism with multinodular goiter. J Sci Res 2018;10:223-9.
27. Waqar M, Okaneme C, Rasthapuram S, Aadil M, Saeed T. An unusual presentation of subacute thyroiditis as pyrexia of unknown origin with normal thyroid functions. Cureus 2022;14:E28807.
28. Alonso O, Mut F, Lago G, Aznarez A, Nunez M, Canepa J, *et al*. 99Tc(M) MIBI scanning of the thyroid gland in patients with

markedly decreased pertechnetate uptake. Nucl Med Commun 1998;19:257-61.
29. Burke G, Halko A, Silverstein GE, Hilligoss M. Comparative thyroid uptake studies with 131 i and 99m tco 4. J Clin Endocrinol Metab 1972;34:630-7.
30. Şahmaran T, Gültekin SS. Least significant changes and reproducibility of 131i uptake test. Health Phys 2021;120:316-20.
31. Dodds WJ, Powell MR. Thyroid scanning with technetium 99m pertechnetate. Radiology 1968;91:27-31.
32. Atkins HL. Technetium 99m pertechnetate uptake and scanning in the evaluation of thyroid function. Semin Nucl Med 1971;1:345-55.
33. Ikekubo K, Hino M, Ito H, Koh T, Ishihara T, Kurahachi H, *et al*. Thyrotoxic graves' disease with normal thyroidal technetium 99m pertechnetate uptake. Ann Nucl Med 1990;4:43-8.
34. Bennedbaek FN, Hegedüs L. The value of ultrasonography in the diagnosis and follow up of subacute thyroiditis. Thyroid 1997;7:45-50.
35. Zhao N, Wang S, Cui XJ, Huang MS, Wang SW, Li YG, *et al*. Two years prospective follow up study of subacute thyroiditis. Front Endocrinol (Lausanne) 2020;11:47.
36. Mondal S, Dasgupta R, Lodh M, Ganguly A. Subacute thyroiditis following recovery from covid 19 infection: Novel clinical findings from an eastern indian cohort. Postgrad Med J 2023;99:558-65.
37. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, pearce sh. 2018 European thyroid association guideline for the management of graves' hyperthyroidism. Eur Thyroid J 2018;7:167-86.
38. Yang M, Perros P. Management plan and delivery of care in graves' ophthalmopathy patients. Best Pract Res Clin Endocrinol Metab 2012;26:303-11.
39. Uchida T, Suzuki R, Kasai T, Onose H, Komiya K, Goto H, *et al*. Cutoff value of thyroid uptake of (99m)tc pertechnetate to discriminate between graves' disease and painless thyroiditis: a single center retrospective study. Endocr J 2016;63:143-9.
40. Misaki T, Miyamoto S, Kasagi K, Mori T, Konishi J. Serial occurrence of two types of postpartum thyroid disorders. Usefulness of tc 99m pertechnetate uptake. Clin Nucl Med 1996;21:460-2.

How to cite this article: Ghanem MA, Dannoon SF, Kazim NA. Improving Thyrotoxicosis Diagnosis: The Clinical Necessity of Refining Tc-99m Pertechnetate Uptake Reference Ranges. Indian J Nucl Med. 2025;40:323-33. doi:10.25259/IJNM_27_25