Diagnostic performance of Thyroid Arterial Peak Systolic Velocity and Thyroxine Level as a Surrogate of Radioactive Iodine Uptake

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ABSTRACT

Introduction: Although the radioactive iodine uptake (RAIU) is regularly used for the assessment of thyrotoxicosis, its relationship with thyroxine (T4) level and the thyroid arterial peak-systolic velocity (PSV) deserves to be explored.

Patients and methods: A retrospective study was done on a dataset comprising data from clinical work-up in a small series of patients with various entities of thyrotoxicosis. The RAIU, T4 level, and PSV from the inferior thyroid artery (ITA) were evaluated against RAIU. Moreover, the PSV index, calculated by dividing the PSV of ITA with the AP diameter of the corresponding thyroid lobe, and the T4 index, calculated by dividing the T4 level by the combined length of the anteroposterior (AP) diameters of the right and left lobes of the thyroid gland, were evaluated against RAIU. Receiver-operator characteristic (ROC) analysis was done to find out cut-off values for all those parameters that can be a surrogate for the RAIU categories at two and 24 hours.

Result: The PSV of ≥ 42.6 cm/sec in the right ITA and a PSV of ≥ 36.8 cm/sec in the left ITA and a PSV index of 26 sec-1 in the left ITA were found as surrogates of RAIU ≥ 10% at two hours. The T4 index of ≥ 12.1 ng/dl/cm was found to be a surrogate of RAIU ≥ 25% at 24 hours. A PSV index of < 8.6 sec^{-1} in the right ITA and < 8.9 sec^{-1} in the left ITA were found as surrogates of RAIU < 4% at two hours.

Conclusion: The cutoff values for the primary and derived parameters were determined in comparison with RAIU as the gold standard. Application of those values is expected to be clinically meaningful for the management of thyrotoxicosis.

Keywords: Radioactive Iodine Uptake, Inferior Thyroid Artery, Peak Systolic Velocity index, T4 index

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INTRODUCTION

The current standard of management relies on radioactive iodine uptake (RAIU) for distinguishing among the three major entities of thyrotoxicosis, for determination of the administrable dose of radioactive iodine (RAIT) when the thyrotoxicosis is particularly refractory to pharmacotherapy (1), as well as a tool for prediction of response after RAIT (2, 3). The normal ranges of RAIU have varied temporally across the ethnicities (4, 5). The reference ranges for RAIU at two, four, and 24 hours are generally known as 1-7%, 6-18%, and 10-35% (4, 6). The institutes in Bangladesh measure the RAIU at two and 24 hours while considering the normal ranges as 4-10% and 10-25%, respectively (7). Although the influential guidelines tend to undermine the contributory potential of ultrasound in the differential diagnoses of thyrotoxicosis, the guidelines cannot but acknowledge the increased color Doppler flow as an adjunct for identification of the hyperactive thyroid (8). The Doppler flow and PSV of thyroid arteries are as capable as the RAIU and the 99mTc-pertechnetate uptake for the distinction between entities of thyrotoxicosis because all three parameters increase substantially in the Graves' but remain normal or go subnormal in thyroiditis (7, 9-13). Since thyroid ultrasound has emerged as an impeccable tool for the assessment of thyroid nodules (11), a provision of functional assessment within the same session of the scan can increase the management efficiency as well as the patient comfort. Moreover, the diagnosis of thyrotoxicosis in pregnant or lactating persons or in patients with recent history of excessive iodine consumption does not allow for the performance of a RAIU, shifting the dependency from RAIU towards the PSV of the thyroid artery for the assessment of thyroid functional status. The thyroid arterial PSV has undergone extensive validations for its diagnostic performance against serological biomarkers as well as radioisotope uptake (10, 14, 15), and the strands of evidence support the utility of thyroid artery PSV as a tool for

assessment of response after RAIT (16). However, the interchangeable use of ITA PSV with RAIU is still uncertain due to a lack of adequate evidence of equivalence.

The thyroid gland size is considered to have implications in the determination of the administrable dose of RAIT in the non-dosimetric method (1) as well as in the assessment of outcome at status post RAIT (17, 18). Moreover, the thyroid gland size is positively correlated with RAIU (19). Therefore, the combination of anatomical size information with the Doppler or serology-generated functional biomarkers of the thyroid, following the examples in other specialties (20), may emerge as a derived parameter with enhanced diagnostic performance. that can improve the insight about their interaction.

Thus, the aim of this study was to explore the diagnostic performance of PSV of ITA during its use as an alternative to RAIU as well as with derived parameters that combine the anteroposterior (AP) diameter of the thyroid gland with the PSV of ITA, or the thyroxine (T4) level, or the tri-iodothyronine (T3) level, while considering the RAIU as the gold standard.

PATIENTS AND METHODS

This retrospective exploratory analysis was done on data collected from a group of patients between July 2016 to June 2017 at the workplace of the third author. All patients underwent RAIU, 2D ultrasound of thyroid gland, and Doppler ultrasound of thyroid arteries as a part of their diagnostic work-up with various entities of thyrotoxicosis prior to receiving pharmacotherapy or RAIT due to thyrotoxicosis refractory to pharmacotherapy. The details of selection criteria and diagnostic procedure is described elsewhere (7).

Particularly the RAIU at two and 24 hours measured in percentage, the AP diameter of both the thyroid lobes measured in centimeters (cm) and the PSV of both the inferior thyroid arteries (ITA) measured in cm/sec were entered as variables for these analyses. Some derived parameters were created that were named as T3 index, T4 index, and PSV indices for right and left ITA. The T3 and T4 indices were calculated by dividing the T3 or T4 level (ng/dl) by combined length (cm) of anteroposterior (AP) diameters of right and left lobes of the thyroid gland. The PSV indices of right and left ITA were calculated by dividing the PSV (cm/sec) of an ITA with anteroposterior (AP) diameter (cm) of the corresponding thyroid lobe.

Receiver operator characteristic (ROC) analyses was performed on the entire dataset and then on subgroups based on the RAIU value categories with an aim to find out cut-off values for T3, T4, PSV and the derived indices that may statistically qualify as a surrogate for the RAIU value categories. > 10% at two, and > 25% at 24 hours. A significant yield was considered if the p-value for asymptotic significance was < 0.05 under the nonparametric assumption (SPSS 26). ROC curves were generated using the roc function from the pROC package (version 1.18.0) on R.

Firstly, the RAIU was categorized as high (and non-high) depending on the cut-off of > 10% for two-hours and > 25% for 24 hours. This categorization was used for the receiver operator characteristic (ROC) analyses. Secondly, the RAIU was categorized in to three categories which were <4%, 4-10% and >10% for RAIU at two hours and <10%, 10-25% and >25% for RAIU at 24 hours. This categorization was used to exclude the low RAIU cases, particularly those with <4% at 2 hours and < 10% at 24 hours. Thereafter, further ROC analyses were done. Thirdly, the PSV were categorized in to three categories which were < 20, 20-40 and >40 for both ITAs. This categorization was used to exclude the cases with PSV < 20 cm/sec. Then, ROC analyses were done once again. Finally, the characterization of the low RAIU patients were done in the subgroups devoid of RAIU > 10% at two hours followed by ROC analyses.

RESULTS

The dataset analyzed for this study consisted of investigation data from 63 patients comprising of 17 males with mean age of 39.06 ± 11.44 (18 - 56) years and 46 females with mean age of 36.0 ± 10.97 (19 - 65) years. The distribution of study patients according to RAIU and PSV of ITA below, within and above the corresponding normal limits are shown in Table 1.

Table 1. Distribution of selected biomarkers among the study patients (n=63)

	Mean ± SD	Range
RAIU at two hours (%)		
< 4 (n=6)	3.08 ± 0.66	2.15 – 3.69
4-10 (n=19)	6.52 ± 1.59	4.05 – 9.12
> 10 (n=38)	20.42 ± 9.07	10.10 – 44.58
RAIU at 24 hours (%)		
< 10 (n=17)	6.83 ± 3.08	1.14 – 9.54
10-25 (n=20)	16.31 ± 5.27	10.03 – 24.79
>25 (n=26)	36.31 ± 10.18	25.92 – 60.28
PSV in Right ITA (cm/sec)		
< 20 (n=23)	13.04 ± 3.32	5.67 – 18.87
20-40 (n=9)	24.60 ± 2.09	20.04 – 26.90
>40 (n=31)	59.41 ± 14.39	41.09 – 90.23
PSV in Left ITA (cm/sec)		
< 20 (n=22)	13.07 ± 3.38	8.41 – 19.2
20-40 (n=10)	27.79 ± 6.96	20.04 – 38.42
>40 (n=31)	61.77 ± 15.27	40.50 – 94.67

Among all the 63 patients irrespective of RAIU categories, ROC analyses could not yield any significant cut-off for PSV or the derived parameters that can be taken as surrogate for RAIU cut-offs ($p > 0.05$, results not shown for simplicity).

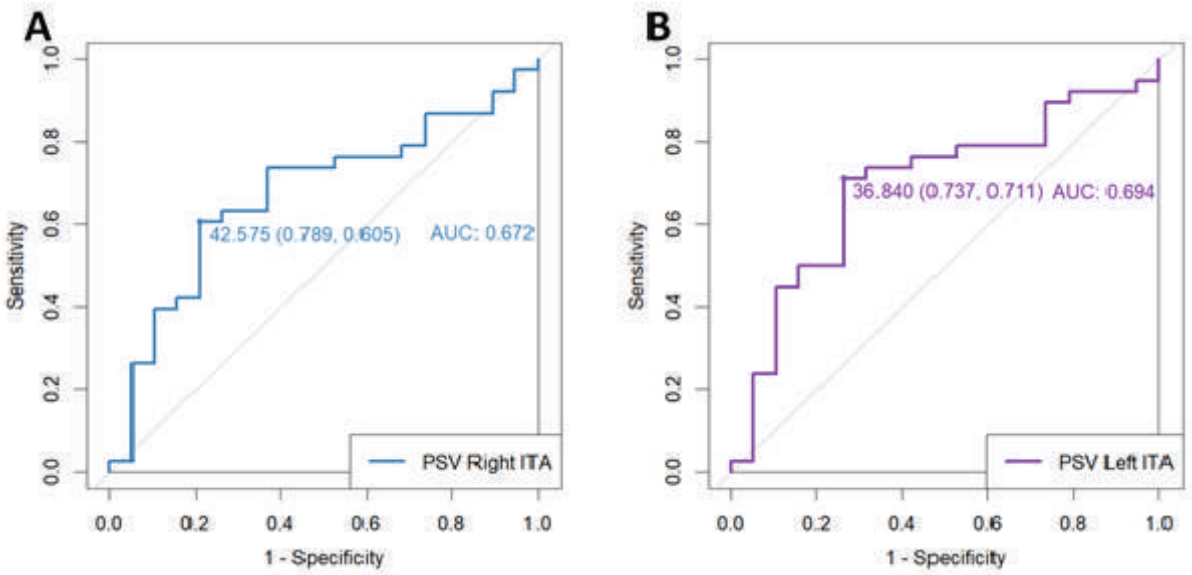

Figure 1. The PSV cut-off as surrogates of RAIU ≥ 10% at two hours, PSV ≥ 42.6 for right ITA (A) and PSV ≥ 36.8 for left ITA (B). The ROC analyses were done among the patients who had RAIU ≥ 4% (n=57) at two hours.

An ROC analyses on 57 (90.5%) patients with RAIU ≥ 4% at two hours was done. Although 43 (73%) of those patients had RAIU ≥ 10% at two hours, 38 patients were found positive by the PSV cut-off for both ITA as shown in the ROC curves in Figure 1A, and 1B, as well as by the PSV index of left ITA (Figure 2A). As the performance characteristics are shown in table 2, the PSV-index cut-off had the best sensitivity and the PSV cut-off for right ITA had the best specificity, as a surrogate of RAIU > 10% at two hours.

Table 2. Performance characteristics of selected biomarkers with significant yields

	Cut off	AUC±SE	p-value	Specificity	Sensitivity
Demarcation of RAIU > 10% at 2 hours					
PSV of right ITA (cm/sec)	42.6	0.67 ±0.08	0.036	0.79	0.61
PSV of left ITA (cm/sec)	36.8	0.69 ±0.07	0.018	0.74	0.71
PSV index of left ITA (sec^{-1})	26.0	0.71 ± 0.10	0.009	0.70	0.81
Demarcation of RAIU > 25% at 24 hours					
T4 index (ng/dl/cm)	12.1	0.73 ± 0.09	0.016	0.92	0.53
Demarcation of RAIU < 4% at 2 hours					
PSV index of right ITA (sec^{-1})	8.6	0.84 ± 0.14	0.014	0.89	0.83
PSV index of left ITA (sec^{-1})	8.9	0.83 ± 0.14	0.019	0.89	0.83

AUC Area under curve, SE Standard error

Among the 46 patients with RAIU ≥ 10% at 24 hours, T4 level was available for 30 with mean T4 index of 9.1 ± 4.2 ng/dl/cm in 13 patients having RAIU 10-25% at 24 hours and T4 index of 14.6 ± 11.7 ng/dl/cm in 17 patients having RAIU >25% at 24 hours. In these 30 patients, the cut-off for T4 index was found to be 12.1 ng/dl/cm as a surrogate of RAIU > 25% at 24 hours ($p < 0.05$). The ROC curves are shown in Figure 2B with the performance characteristics in the Table 2.

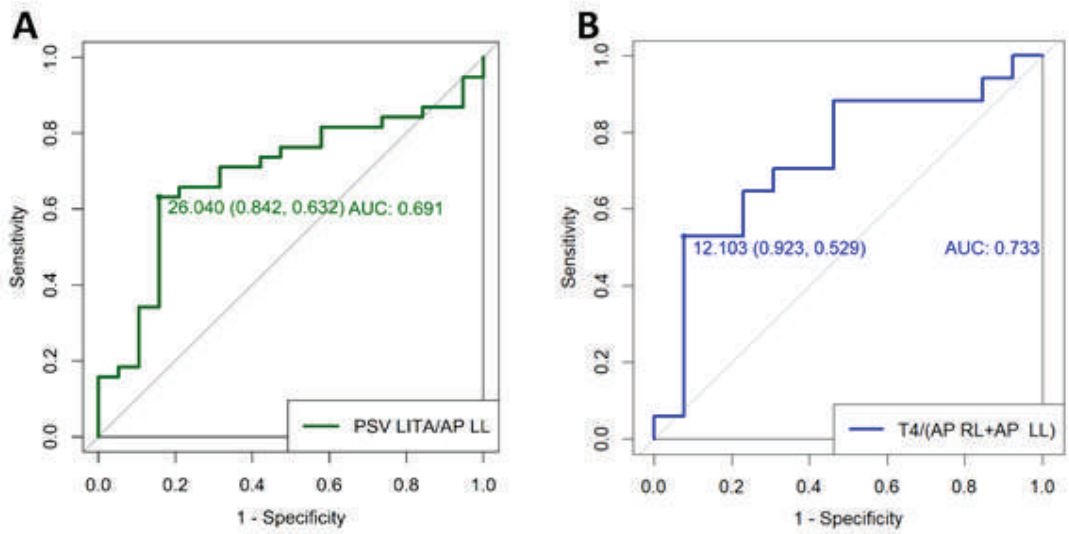

Figure 2. The PSV index ≥ 26 sec-1 as a surrogate of RAIU ≥ 10% at two hours, among the patients (n=57) who had a RAIU ≥ 4% at two hours (A), and the T4 index of ≥ 12.1 ng/dl/cm as a surrogate of RAIU ≥ 25% among patients with their T4 levels available (n=30) as well as a RAIU at 24 hours being ≥ 10% (B)

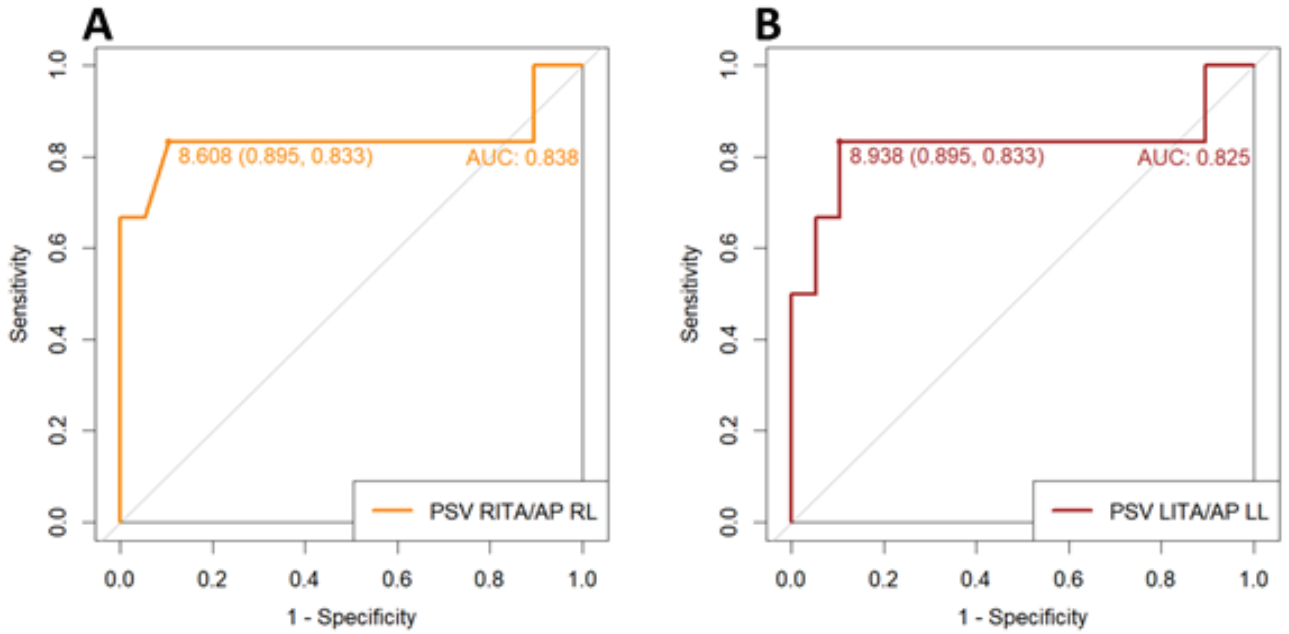

Figure 3. PSV index cut-off as surrogates of RAIU < 4% at two hours, < 8.6 sec-1 for right ITA (A), and < 8.9 sec-1 for left ITA (B). The ROC analyses is from patients (n=25) who had RAIU ≤ 10% at two hours.

Finally, an ROC analysis in 25 (39.6%) patients with RAIU ≤ 10% at two hours the PSV index cut off of < 8.6 sec-1 for right ITA and < 8.9 sec-1 for left ITA were found to be the surrogates for RAIU < 4% at two hours with identical specificity and sensitivity (Figure 3A-B and Table 2).

DISCUSSION

This retrospective exploratory analysis determined cutoff values for PSV of ITA that can represent the RAIU > 10% at two hours. Although the cut-off for PSV of the right ITA was higher than that of the left ITA, the PSV in the two ITAs is not known to be different so far (21). The cut-off values that represent a RAIU of 10% at two hours do not match with the cut-off differentiator between Graves' disease and thyroiditis, which was 30 cm/sec for the PSV of ITA (10, 22) and 45.3 cm/sec for the PSV of the superior thyroid artery (13). Since the entire patient series was comprised of patients with three categories of RAIU, the exploration of the PSV cutoff with statistical significance was done in the two adjacent subgroups of patients. In this manner, the cut-off values for primary and derived parameters came out to be exclusively applicable for the demarcation of two adjacent categories of RAIU.

The T4 index and PSV indices were found to have a significant relationship with the RAIU. The idea of combining the imaging biomarker for the anatomical dimension of the thyroid gland with the functional biomarker, such as serum levels of T3 or T4, or the Doppler-generated ITA PSV, was inspired by the recently proven diagnostic utility of prostate-specific antigen (PSA) density over PSA alone (23). The study suggests incorporating thyroid volume for more insightful analysis, which could be confirmed through a prospective study and observation on a larger cohort over longer management periods. Apart from the small sample size, the limitations of this study include the non-inclusion of thyroid volume, which could have extend the insight about PSV and T4 densities instead of PSV and T4 indices. Moreover, the subgroup comprising RAIU ≤ 4% at two hours and ≤ 10% at 24 hours was small, which precluded any statistical characterization of the relationship of low RAIU with PSV, hormone levels, and the corresponding indices.

CONCLUSION

This study determined cutoff values for PSV in ITA, the T4 index, and PSV indices as surrogates for RAIU in a small cohort of hyperthyroid patients and characterized specific conditions for suitable application of those cut off values. Although, the findings enhance our current understanding about the relationship of those biomarkers, further validation in larger cohorts may finally lead to their interchangeable use in the clinical management of thyrotoxicosis.

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