INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2025.03779
Int J Med Biochem 2025;8(4):312–317

Research Article

Adult references intervals for thyroid hormones using beckman coulter from Türkiye

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Abstract

Objectives: In this study, we aimed to establish reliable reference intervals (RIs) for free triiodothyronine (fT3), free thyroxine (fT4), and thyroid stimulating hormone (TSH) in our population using the Beckman Coulter UniCel DxI 800.

Methods: We followed the Clinical Laboratory Standards Institute (CLSI) C28-A3 guidelines to calculate RIs through both direct (DRM) and indirect methods (IDM) and compared them with the RIs provided by Beckman Coulter UniCel DxI 800 Access® immunoassay system. High sensitive (h)TSH reagent used for TSH analyses. For DM, we excluded anti thyroid peroxidase (anti-TPO) or antithyroglobulin (anti-TG) positive samples, outliers, and samples with insufficient serum, resulting in final sample sizes of 420 for TSH, 411 for fT4, and 407 for fT3. For IDM, anti-TPO or anti-TG-positive samples, repeated samples, and outliers were excluded, resulting in final sample sizes of 2874 for TSH, 2072 for fT4, and 1163 for fT3.

Results: Our study included 450 participants (225 females, 225 males) over the age of eighteen for DRM and utilized data from the Laboratory Information System (LIS) between March 1, 2018, and February 28, 2020, for IDM. After excluding certain samples and outliers, the final sample sizes were determined. The reference intervals (RIs) for TSH, fT4, and fT3 were 0.42-4.18 mIU/L, 0.41-4.45 mIU/L, 0.57–1.08 ng/dL, 0.63–1.14 ng/dL, 2.62–4.01 pg/mL, and 2.72- 4.41 pg/mL for DRM and IDM, respectively.

Conclusion: In conclusion, the RI that we will use for thyroid hormones in our laboratory is different from that provided by the manufacturer.

Keywords: Reference intervals, thyroid diseases, thyrotropin, thyroxine, triiodothyronine

How to cite this article: Sahin I, Eraldemir FC, Oztas B, Yildirim Şik B, Kir HM. Adult references intervals for thyroid hormones using beckman coulter from Türkiye. Int J Med Biochem 2025;8(4):312–317.

The clinical manifestations of thyroid diseases, especially subclinical hypothyroidism (SCH) or subclinical hyperthyroidism, are not specific. SCH is a more commonly encountered condition [1], and the disease ranges between euthyroidism and overt hypothyroidism [2–4].

The symptoms associated with hypothyroidism typically include general and mental fatigue and cognitive difficulties, referred to as brain fog, which involve problems with concentration, motivation, memory, and reasoning, thereby impairing an individual's quality of life [3]. These patients are often prone to high levels of anxiety, anddepression [4]. All of these symptoms prompt clinicians to inquire about other diseases, and the symptoms are not specific to the thyroid.

Due to the nonspecific nature of clinical symptoms, the diagnosis of thyroid dysfunction relies on laboratory results. The most sensitive and specific indicator of systemic thyroid function is thyroid-stimulating hormone (TSH). Changes in serum TSH levels act as an 'early warning system' while attempting to maintain thyroid hormone levels within healthy ranges. Thus, SCH is diagnosed by elevated TSH levels above the reference interval (RI) accompanied by normal levels of free thyroxine (fT4) and free triiodothyronine (fT3) [2].

However, reliable RIs are crucial for interpreting TSH measurements. Reporting test results with well-defined RIs is critical for correct interpretation, especially when diagnosing subclinical thyroid dysfunction [5–7].

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Submitted: February 17, 2025 **Revised:** June 02, 2025 **Accepted:** June 03, 2025 **Available Online:** October 21, 2025

For instance, a recent study was conducted in a region of China considered to have sufficient iodine levels to determine the reference intervals (RIs) for thyroid hormones using the Abbott Architect analyzer. In this study, the RIs obtained from the healthy population were inconsistent with the RIs provided by the manufacturer [8].

The laboratories typically use the RIs provided in kit inserts. However, RIs can vary depending on socioeconomic status, geographic location, exposure to environmental factors, and race. For these reasons, it is recommended by the Clinical and Laboratory Standards Institute (CLSI) and The International Federation of Clinical Chemistry (IFCC) that thesuitability of the RI provided in kit inserts for the regional population be tested or that each laboratory establish its own reference ranges [7].

Especially when developing clinical guidelines for thyroidal diseases, the RIs used should be tailored to accommodate differences in the analyzer platform on which the test will be performed. Since TSH levels are used as the basis for initiating thyroid hormone therapy and adjusting treatment doses for thyroidal diseases, the use of device- and population-specific RIs ensures that the most accurate decisions are made in managing the disease [6, 9].

The aim of this study was to calculate the RIs for fT3, fT4 and TSH using both the direct method (DRM) and the indirect method (IDM) according to the Clinical Laboratory Standards Institute (CLSI) C28-A3 guidelines and to compare them with the RIs provided by the Beckman Coulter DxI 800 [10].

Materials and Methods

This study aimed to determine the reference intervals (RIs) for fT3, fT4, and TSH in patients with DRM and IDM. All procedures performed in studies involving human participants were in accordance with the ethical standards of national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards for patient with DRM. Chief medical officer's approval was received for retrospective data (patient with IDM). This study was conducted with the approval of the Kocaeli University Ethical Committee (No: KOU GOAEK 2019/196, Date: 08/05/2019).

Reference individuals for DRM were selected among volunteers who visited our hospital's Central Laboratory Blood Collection Unit and Primary Health Care Centers in our province. Volunteers who agreed to participate were administered a questionnaire with exclusion criteria.

The questionnaire included questions about family history of thyroid disease, recent history of illness, presence of chronic disease, recent blood transfusion or donation, pregnancy and breastfeeding, drug addiction, surgery in the last 3 months, fasting for 8–12 hours, and obesity, weight gain or loss, loss of appetite, smoking (>20/day), alcohol abuse, hypotension or hypertension, vitamin use, oral contraceptive use, fatigue, irritability, insomnia, exhaustion, muscle weakness, intolerance to cold or heat, dull mood, difficulty remembering, and tremor. Individuals who were considered unsuitable for the study according to the exclusion criteria were excluded. Informed consent was obtained from individuals eligible to participate in the study. Blood samples were collected between 08:30 and 10:00, after the participants had fasted for 8–12 hours. Samples were collected using red-capped biochemistry tubes without anticoagulants or any other active substances (Plain tube, BD vacutainet, lot number 8306831). Samples were allowed to clot for 1 hour and then centrifuged at 1800 × g for 15 minutes to obtain the serum.Equal numbers of male and female reference individuals were carefully selected to ensure age and gender homogeneity. An equal number of individuals of both genders were included in each age group (1st group: 18–28 years, 2nd group: 29–38 years, 3rd group: 39–48 years, 4th group: 49–58 years, 5th group: 59 years and older).

Although participants were assumed to be healthy in terms of thyroid function, adhere to exclusion criteria, and have no history of thyroid dysfunction in themselves or their families, it is known that subclinical thyroid dysfunction may still exist. To overcome this issue and identify and exclude these individuals, thyroid antibody (TAb), anti-thyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG) antibody tests were conducted on reference individuals. Individuals with anti-TPO>9 IU/mL or anti-TG>4 IU/mL results, i.e., all individuals with positive antibody tests, were excluded from the study. Therefore, the study began with 450 individuals to ensure that results were obtained from at least 400 individuals for calculation purposes.

For IDM, data were downloaded from the Laboratory Information System (LIS) for patients who underwent simultaneous fT3, fT4, and TSH tests between March 01, 2018, and February 28, 2020. According to the CLSI's EP28-A3C guidelines, patients from oncology and intensive care units were not included in the study. Since individuals with multiple test results are likely to be healthy, the latest result in the LIS was included in the study [6].

In our study, serum fT3, fT4, TSH, anti-TPO and anti-TG data obtained from both DRM and IDM groups were analyzed with various reagents using chemiluminescence method on Beckman Coulter UniCel DxI 800 Access® immunoassay system (Beckman- CLIA, Brea, CA, USA). Access provides standardization to the World Health Organization 3rd International Standard (IS) for human TSH analysis (IRP 81/565). In our study, the TSH 3rd IS method was used for TSH analysis and hypersensitive TSH (hTSH) test results were obtained. The Access TSH (3rd IS) assay provides high functional sensitivity and precision. Calibration of anti-TPO (Access calibrator ref: A18227) and anti-TG (Access calibrator ref: A36920) were conducted using original calibrators and controls provided by Beckman Coulter. Internal quality controls were performed three times daily with SeronormTM Immunoassays (207005 Liq L-1 12×3 mL, 207105 Liq L-2 12×3 mL, and 207205 Liq L-3 12×3 mL) for all tests (Sero AS, Hvalstad, Norway). External quality controls were performed monthly using the External

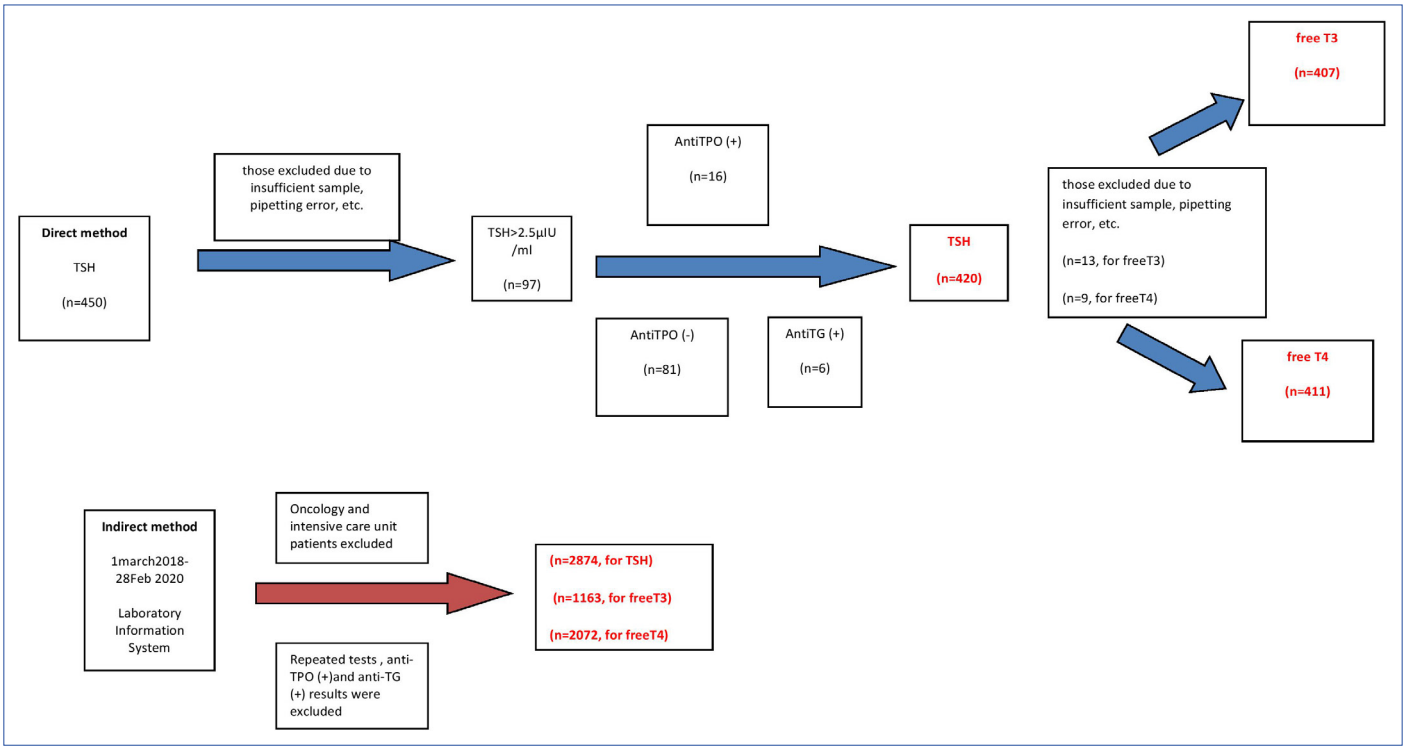

Figure 1. The algorithm graph for the number of included and excluded individuals for each parameter.
TSH: Thyroid stimulating hormone; fT4: Free thyroxine; fT3: Triiodothyronine; anti-TPO: Anti-thyroid peroxidase; anti-TG: Antithyroglobulin.

Quality Assurance Services (EQAS) Immunoassay Program. No outlier values were found in TSH, fT3 and fT4 evaluations in the EQAS reports of our laboratory.

At the end of the study, the data obtained from the DRM and IDM were transferred to the IBM SPSS Statistics 24.0 program. The histograms of the data were evaluated. The normality of the data was assessed using the Kolmogorov–Smirnov test. Outliers values were identified through histogram evaluation and by applying the Dixon method. After removing outlier values, the distribution of the remaining data was re- evaluated as visual. Independent sample t tests were conducted to determine whether there were significant differences between sexes for tests showing a normal distribution, while the Mann–Whitney U test was used for tests not conforming to a normal distribution.

The reference intervals for tests showing a normal distribution were calculated using the standard deviation (SD) (lower limit: mean - 1.96 × SD, upper limit: mean + 1.96 × SD). For tests not showing a normal distribution, the reference interval boundary values were found using the formula lower value =0.025×(n+1) and upper value =0.975×(n+1), where 'n' represents the number of data points (noninteger values were rounded to the nearest integer).

Results

After excluding inadequate samples or pipetting errors resulting in failure to obtain results, as well as data from individuals with positive Anti-TPO or Anti-TG test results and identified outliers, the following number of data points were obtained for hTSH: 420, fT3: 407, and fT4: 411 from the reference individual group formed by DRM. For IDM, following exclusion of samples according to CLSI's EP28-A3C guidelines and after removing outliers, the following number of data points were obtained for hTSH: 2874, sT3: 1163, and sT4: 2072 from the LIS. The algorithm graph for the number of included and excluded individuals for each parameter is shown in Figure 1.

When testing for normality, data with a significance level (p value) greater than 0.05 in the Kolmogorov–Smirnov test indicated a normal distribution, while those with a significance level less than 0.05 indicated a nonnormal distribution. Statistical evaluations of the data obtained from the DRM and IDM in our study revealed that the fT3 test results exhibited a normal distribution, while the hTSH and fT4 test results did not. For fT3, which showed a normal distribution, an independent sample t test was conducted to assess the significance of sex differences. The groups had a homogeneous distribution, and there was a statistically significant difference between DRM (for fT3 patients with DRM, $p<0.001$; for fT3 patients with IDM, $p<0.001$).

When examining the significance of sex differences for hTSH and fT4, which were not normally distributed, a statistically significant difference was found for both tests (for DRM, hTSH $p<0.001$, fT4 $p=0.033$; for IDM, hTSH $p=0.024$, fT4 $p<0.001$). Based on this information, RIs were calculated. The RIs at the 95% confidence intervals obtained without sex differences from the DRM and IDM data, as well as the RIs recommended

Table 1. The reference intervals obtained through direct and indirect methods for TSH, fT4, fT3, and the reference intervals provided by the manufacturer

Test	Unit	DRM		MRI		IDM	
		LL	UL	LL	UL	LL	UL
fT3	pg/mL	2.62	4.01	2.5	3.9	2.72	4.41
fT4	ng/dL	0.57	1.08	0.61	1.12	0.63	1.14
hTSH	mIU/L	0.42	4.18	0.34	5.60	0.41	4.45

hTSH: High sensitive thyroid stimulating hormone; fT4: Free thyroxine; fT3: Triiodothyronine; DRM: Direct method; MRI: The reference intervals provided by the manufacturer; IDM: Indirect method, LL: Lower limit; UL: Upper limit.

Table 2. The presentation of reference intervals obtained through DRM and IDM according to genders

Test	Gender	Unit	DRM		IDM	
			2.5th percentile	97.5th percentile	2.5th percentile	97.5th percentile
fT3	Female	pg/mL	2.54	3.99	2.62	4.29
	Male	pg/mL	2.72	4.15	2.88	4.49
fT4	Female	ng/dL	0.57	1.09	0.63	1.12
	Male	ng/dL	0.58	1.08	0.65	1.15
hTSH	Female	mIU/L	0.52	4.33	0.42	4.43
	Male	mIU/L	0.41	3.95	0.40	4.57

by the manufacturer, are presented in Table 1. The RIs obtained at the 95% confidence intervals with sex differences between the DRM and IDM groups are presented in Table 2.

Discussion

In our study, we found that gender-specific RIs were narrower than the RIs determined by DRM and IDM in all cases and that the RIs we obtained differed from those provided by the manufacturer.

For hTSH in our study, we obtained narrower RIs in females with DRM (0.52–4.33 mIU/L) than in those with IDM (0.42–4.43 mIU/L). In males, we found the RI to be particularly lower at the upper limit compared to the IDM (0.41–3.95 mIU/L for DRM versus 0.40–4.57 mIU/L for IDM). The RI provided by the manufacturer for hTSH without sex differentiation was 0.34–5.60 mIU/L. In a multicenter study conducted in Italy with IDM using the same kit and autoanalyzer as our study (Access TSH 3rd IS, using UniCel DxI), the hTSH RI without sex differences was found to be different from that in our study (0.36–5.28 mIU/L) [10].

In an RI determination study conducted with DRM in a different region of Turkey in 2010 using the same device as ours (Beckman Unicel DxI, although the generation of the kit was not emphasized), a TSH RI of 0.41–4.25 mIU/L was found [11]. Despite using the same brand of kit and autoanalyzer, there are some differences in the RIs found among regions.

In fact, according to data obtained from the Global Iodine Network in 2021, Turkey appears to be among the countries with sufficient iodine intake [12]. However, there may still be differences in dietary habits among regions. Therefore, determining RIs for a specific region or city's population is important. In particular, determining RIs with DRM ensures more reliable RI determination [13].

In a region of China reported to have sufficient iodine levels, the RIs for TSH determined with DRM using the Abbott Architect autoanalyzer were 0.67–4.62 mIU/L for males and 0.72–5.15 mIU/L for females. The RIs obtained for this study without sex differences were 0.70–4.93 mIU/L. The RI provided by the manufacturer for TSH without sex differences was 0.35–4.94 mIU/L. In particular, there was a significant difference in the lower limit of the RI compared to what was provided by the manufacturer in this study [8].

In a study conducted with IDM using the Siemens Advia Centaur XP analyzer, the RIs for TSH were found to be 0.71–4.92 mIU/L, which differs from the manufacturer's recommended TSH range (0.55–4.78 mIU/L) [14].

In another study conducted in the United Kingdom in 2017 with DRM, researchers determined RIs for TSH and fT4 through the four most commonly used analytical platforms in their country.

As seen in this study, it is obvious that the same RI cannot be used for thyroid hormones analyzed on all analytical platforms and different RIs should be used. In this study, the Beckman Unicel DxI RI for TSH was found to be 0.57–3.60 mIU/L [15].

According to the guidelines of the European and American Thyroid Associations, the serum TSH level is the most reliable test for the diagnosis of all forms of hypothyroidism and hyperthyroidism [16–18]. However, it should be noted which analytical platform the test is performed on when creating guidelines [9, 15]. Additionally, the region where the RI will be applied is also important. Reporting patient test results with RIs not determined according to regional populations may lead to the di-

agnosis of thyroid dysfunction in many individuals who do not have thyroid dysfunction, resulting in unnecessary medication use. Similarly, it may also lead to the misclassification of many individuals with thyroid dysfunction as healthy individuals. Considering the possible harmful effects of unnecessary medication use or the vital risks of not treating patients who require treatment, it is essential for each laboratory to determine its own RI to minimize these critical issues for every individual [7].

In our study, the RIs obtained for fT4 differed between DRM and IDM for females (0.57–1.09 ng/dL with DRM and 0.63–1.12 ng/dL with IDM) and males (0.58–1.08 ng/dL with DRM and 0.65–1.15 ng/dL with IDM), especially at the lower limit. The RIs obtained with both methods were also different from the values provided by the manufacturer (0.61–1.12 ng/dL). In a study conducted in a different region of Turkey with the same autoanalyzer as ours in 2010, the RI for fT4 with DRM was also different from ours (0.61–1.06 ng/dL) [11].

Another study conducted with IDM on the Siemens Advia Centaur XP analyzer showed apparent differences in RIs for fT4, with ranges of 12.2–20.1 pmol/L for males and 11.9–18.9 pmol/L for females, compared to the manufacturer's RI of 11.5–22.7 pmol/L [14]. In a study conducted in the UK in 2017 with 261 participants from the same region, different RIs were obtained for fT4 patients with DRM using four different analyzers. One of the analyzers used in this study was the same as that used in our study, and the RI for fT4 (7.9–13.0 pmol/L) was different from that used in our study [15].

As observed, different populations and different analyzers yielded different results. However, another factor to consider may be the units used. Unit differences can also lead to problems in result interpretation.

In our study, the RIs for fT3 differed between DRM and IDM, with ranges of 2.54–3.99 pg/mL for females and 2.62–4.29 pg/mL for males with DRM and 2.72–4.15 pg/mL for females and 2.88–4.49 pg/mL for males with IDM. The manufacturer's kit insert indicated a range of 2.5–3.9 pg/mL, and particularly, the upper limits of the RIs we established for males differed from those of the manufacturer.

In an RI determination study conducted with DRM in another region of our country, the RI for fT3 was found to be 2.62–3.84 pg/mL, although separate RIs for sex were not determined [11].

With IDM on the Siemens Advia Centaur XP analyzer, the RIs for fT3 were 3.9–6.0 pmol/L, while the manufacturer recommended 3.5–6.5 pmol/L for fT3. The RIs for fT3 were notably different for males (4.3–6.2 pmol/L) and females (3.8–5.5 pmol/L) [14].

The CLSI and IFCC have recommended that RI determination studies be conducted either with DRM or, if not feasible, with IDM. Therefore, many laboratories tend to prefer IDM due to concerns such as cost, time, and labor.

In our study, the RIs determined for fT3, fT4, and TSH using DRM and IDM showed statistically significant differences between sexes. As a result, separate RI values were provided for each gender in our study, as in previous similar studies [18]. The population in our study comprised individuals aged between 18 and 88 years. In our DRM-based RI determination study, care was taken to ensure an equal number of male and female reference individuals in each age group. Despite attempts to establish age-specific RIs by setting age boundaries, a definitive age cutoff could not be reached, and statistically significant differences were not obtained; therefore, age-specific RIs could not be determined. Our results were in line with the recommendation in the CLSI's EP28-A3c guidelines, emphasizing the necessity for each laboratory to establish its own RI. When comparing the RIs determined by both DRM and IDM with those provided by the manufacturer, although the RIs for fT3 and fT4 were close, the RIs we established had a narrower range. For the TSH test, while the lower limit of our RI was similar to that set by the manufacturer, there was a significant difference between the upper limit set by the manufacturer (5.60 mIU/L) and ours (DRM: 4.18 mIU/L, IDM: 4.45 mIU/L).

Subclinical thyroid dysfunction is defined by fT4 levels within the RI and TSH levels outside the RI. Studies have demonstrated an association between SCH and increased risks of hypertension, hyperlipidemia, atherosclerosis, and coronary artery disease, while subclinical hyperthyroidism has been linked to increased risks of atrial fibrillation and coronary artery disease [19].

Due to the greater number of reference individuals obtained with the IDM than with the DRM, we may have obtained wider RIs with the IDM. Additionally, the reliability of the health status of the reference individuals determined with DRM may not be ensured with IDM; therefore, we believe that the RI determined with DRM is more sensitive.

Conclusion

In conclusion, using the RI determined by us instead of the RI provided by the manufacturer for the TSH test revealed that many individuals considered normal in terms of thyroid function may actually have SCH. Therefore, we are of the opinion that the manufacturer's RI may not be suitable for our region, and it would be more appropriate to use the RI determined by our laboratory instead of the RI provided by the manufacturer.

Ethics Committee Approval: The study was approved by the Kocaeli University Non-interventional Clinical Research Ethics Committee (no: 2019/196, date: 08/05/2019).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding: This thesis project was supported by KOU BAP (Project number THD-2020-2140).

Use of AI for Writing Assistance: No AI technologies utilized.

Authorship Contributions: Concept – F.C.E., I.S.; Design – F.C.E., I.S., H.M.K.; Supervision – I.S., F.C.E.; Funding – F.C.E., I.S.; Materials – F.C.E., I.S.; Data collection and/or processing – I.S., B.O., B.Y.S.; Data analysis and/or interpretation – H.M.K., F.C.E., B.O.; Literature search – B.O., B.Y.S., I.S.; Writing – I.S., F.C.E., H.M.K.; Critical review – H.M.K., F.C.E.

Peer-review: Externally peer-reviewed.

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