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A study of the association of lipid ratios with thyroid dysfunction in a tertiary medical college in Eastern India

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ABSTRACT

Background: Thyroid hormones play a crucial role in major metabolic pathways in the body and dyslipidemia is a major metabolic abnormality seen in thyroid disorders. Cardiovascular diseases (CVDs) are now emerging as the leading cause of morbidity and mortality worldwide and the most important risk factor for CVDs is dyslipidemia. The lipid ratios that have a positive association with CVD risk are atherogenic index of plasma (AIP), Castelli's risk index (CRI)-I and II, and atherogenic coefficient (AC). Clinically, both an excess and deficiency of thyroid hormones can exacerbate or induce CVDs and lipid ratio can be used as an inexpensive marker for predicting CVD risk. **Aims and Objectives:** This study aims to evaluate the lipid ratios (AIP, CRI-I, CRI-II, AC) in patients with thyroid dysfunction and compare the results with lipid ratios in euthyroid individuals. This study also aims to find any correlation, if exists, between lipid ratios and serum thyroid-stimulating hormone (TSH) levels in thyroid dysfunction. **Materials and Methods:** The serum TSH and lipid profile were evaluated in fifty euthyroid, fifty hypothyroid, fifty subclinical hypothyroid, and fifty hyperthyroid patients. The lipid ratios (AIP, CRI-I, CRI-II, AC) were calculated from the lipid profile. **Results:** The mean lipid ratios were higher in hypothyroid, followed by subclinical hypothyroid cases when compared to euthyroid controls and hyperthyroid patients. A positive correlation was observed between the TSH and lipid ratios in euthyroid, hypothyroid, and subclinical hypothyroid subjects. There was no significant correlation between TSH and lipid ratios in hyperthyroid patients. **Conclusion:** This study demonstrates that the evaluation of lipid ratios along with TSH can provide an effective screening tool to assess the cardiovascular risk in patients with subclinical and overt hypothyroidism, especially in the absence of imaging techniques in resource-limited centers.

Key words: Hypothyroidism; Hyperthyroidism; Lipid ratios; Cardiovascular disease risk

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INTRODUCTION

Thyroid dysfunction is the most common endocrinal disorder worldwide as well as in India.[1] Thyroid disorders are primarily characterized by the abnormality in thyroid hormone production. Excess thyroid hormone production leads to hypothyroidism and diminished production causes hyperthyroidism.[2] In subclinical forms of thyroid dysfunction, the thyroid-stimulating hormone (TSH) level becomes abnormal with the T3 and T4 levels within the reference range.[3] In recent times, hypothyroidism and hyperthyroidism, diagnosed in clinical and subclinical forms, are the most common thyroid disorders.[4] The secretion of thyroid hormones, thyroxine (T4) and triiodothyronine (T3), by the thyroid gland, is under the control of TSH from the anterior pituitary gland and thyrotropin-releasing hormone from the hypothalamus.

Since thyroid hormones directly or indirectly affect almost all major metabolic pathways, thyroid dysfunction is generally associated with various metabolic abnormalities. Thyroid hormones affect the synthesis, mobilization,

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and degradation of lipids.[5] Thyroid hormones stimulate cholesterol synthesis by activating the 3-hydroxy-3-methylglutaryl-coenzyme A reductase in the liver. The lipoprotein lipase activity involved in the hydrolysis of triglycerides (TG) is also stimulated by these hormones.[4] Thyroid hormones also influence high-density lipoprotein (HDL) metabolism by increasing the activity of cholesterol ester transfer protein (CETP).[6] Thus, an imbalance in the thyroid hormone levels exerts an effect on the lipid profile. Hence, dyslipidemia has been seen as a common metabolic abnormality associated not only with overt and subclinical hypothyroidism but also with hyperthyroidism.[3]

Cardiovascular diseases (CVDs) are now emerging as the leading cause of morbidity and mortality worldwide and the most important risk factor for CVDs is dyslipidemia. In the evaluation of dyslipidemia, among all lipid profile parameters, low-density lipoprotein cholesterol (LDL-C) is emphasized as bad cholesterol and HDL cholesterol (HDL-C) as good cholesterol. However, using only LDL-C and HDL-C as diagnostic markers is inadequate when the patient is not only an intermediate risk but also has some other risk factors as well such as high plasma glucose, high blood pressure, obesity, and positive family history that exceed the desirable level. In many cases, it is seen that when the traditional lipid profile is normal, the lipid ratios have predicted the risk of developing CVD.[7] The lipid ratios that have a positive association with CVD risk are atherogenic index of plasma (AIP), Castelli's risk index (CRI)-I and II, and atherogenic coefficient (AC). Clinically, both an excess and deficiency of thyroid hormones can exacerbate or induce CVDs and lipid ratio can be used as an inexpensive marker of predicting CVD risk.

Few studies in the past have demonstrated a relationship between the TSH and lipid profile.[8] Some studies in the past have demonstrated abnormal lipid ratios in subclinical hypothyroidism[9] and hypothyroidism.[10]

On the other hand, few previous studies have found that the lipid ratios were significantly higher in hyperthyroidism and subclinical hyperthyroidism when compared to euthyroid control group patients.[11] Although a lot of research work has been done in the past, where lipid profile parameters and lipid ratios were assessed in thyroid dysfunction, the findings remain elusive.

This study aimed to evaluate the lipid ratios (AIP, CRI-I, CRI-II, AC) in patients with thyroid dysfunction (subclinical and overt hypothyroidism and hyperthyroidism) and compare the results with lipid ratios in euthyroid individuals. This study also aimed to reveal if any correlation exists between lipid ratios and serum TSH levels in euthyroid patients and patients with thyroid dysfunction.

Aims and objectives

This study aims to evaluate the lipid ratios (AIP, CRI-I, CRI-II, AC) in patients with thyroid dysfunction and compare the results with lipid ratios in euthyroid individuals. This study also aims to find any correlation, if exists, between lipid ratios and serum thyroid-stimulating hormone (TSH) levels in thyroid dysfunction.

MATERIALS AND METHODS

This is a non-interventional, observational, cross-sectional hospital-based study, conducted in the Department of Biochemistry at Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, Durgapur, from January 2024 to April 2024.

A total of fifty patients with hypothyroidism, fifty patients with subclinical hypothyroidism, and fifty patients with hyperthyroidism were included in the study. Fifty normal euthyroid patients were included as controls in this study. All subjects were above 12 years of age. Hypothyroidism was diagnosed as cases with increased TSH value (>10 μIU/mL) combined with a decreased FT4 value. Subclinical hypothyroidism was diagnosed as having high TSH levels (5–15 μIU/mL) and normal T4 levels (4.68–9.36 μg/dL) or normal FT4 levels (0.82–1.63 ng/dL). Hyperthyroidism was diagnosed as cases having a decreased TSH value (<0.27 μIU/mL) combined with FT3 or FT4 above the upper limit of the normal reference range. The normal euthyroid controls were selected from cases having normal TSH (0.27–5.0 μIU/mL) and normal T4 levels (4.68–9.36 μg/dL) or normal FT4 levels (0.82–1.63 ng/dL).

Patients having hepatic or renal dysfunction; history of heart failure, diabetes mellitus, stroke or ischemic heart disease; malignancy; and alcohol or drug abuse and blood disorders were excluded from the study. Patients who had used any medications (within the previous 6 months) that might have contained corticosteroids, antifolates or lipid-lowering agents, thyroid hormone supplements, and antithyroid drugs were excluded from the study. Neonates and infants with congenital thyroid disorders were excluded from the study.

A standardized questionnaire regarding patient demographic details, medical history, family history, anthropometric details, and drug history was collected from patients and recorded. A 5 mL blood sample, after an overnight fast of 10–12 h, was collected from the study subjects under aseptic conditions after obtaining informed consent.

The lipid ratios were calculated using the following formulas:

- AIP=Log_{10} (TG/HDL-C)
- CRI-I=Total cholesterol (TC)/HDL-C
- CRI-II=LDL-C/HDL-C
- AC=[(TC-HDL)/HDL].

Statistical analysis of the study data was performed in SPSS statistical software at the end of the study.

Ethical clearance and approval

This research study has been approved by the Institutional Ethics Committee of Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, vide reference no: SRIMS and SH/IEC/PROT/0007/2024/Approv/12022024.

RESULTS

The demographic and biochemical parameters of the study subjects are demonstrated in Table 1.

The comparison of serum TSH and lipid profile parameters among the euthyroid, hypothyroid, subclinical hypothyroid, and hyperthyroid subjects is shown in the bar diagram in Figure 1.

The bar diagram in Figure 2 shows the comparison of serum TSH and lipid ratios (AIP, CRI-I, CRI-II, AC) among the euthyroid, hypothyroid, subclinical hypothyroid, and hyperthyroid subjects.

The serum TSH value was positively correlated (P<0.05) with the lipid ratios (AIP, CRI-I, CRI-II, AC) in euthyroid, hypothyroid, and subclinical hypothyroid cases as shown in Table 2. No significant correlation (P>0.05) was found between the TSH and lipid ratios in the hyperthyroid group.

The mean difference between the lipid ratios among the euthyroid, hypothyroid, and subclinical hypothyroid study subjects was tested using One way ANOVA followed by *post hoc* Games–Howell test, and the difference in lipid ratios among these three groups was found to be statistically significant (P<0.05), as shown in Table 3.

A statistically significant positive correlation (P<0.05) was observed between TSH and AIP; TSH and CRI-I; TSH and CRI-II; TSH and AC; in overall study subjects of euthyroid, hypothyroid, and subclinical hypothyroid groups. This is shown in the scatter plots in Figures 3-6.

DISCUSSION

Dyslipidemia, a common finding in patients with thyroid disease, is predominantly due to the influence of thyroid hormones on almost all aspects of lipid metabolism. Not only overt but also subclinical hyper- and hypothyroidism, through different mechanisms, are associated with

Table 1: Demographic and biochemical parameters of different groups

Variables	Euthyroid (n=50) Mean±SD	Hypothyroid (n=50) Mean±SD	Subclinical hypothyroid (n=50) Mean±SD	Hyperthyroid (n=50) Mean±SD
Age (years)	45.04±16.3	39.08±15.19	33.1±14.25	37.38±12.07
TSH (μIU/mL)	3.0±1.26	16.94±7.85	7.36±0.94	0.12±0.07
Total cholesterol (mg/dL)	148.56±26.49	247.94±37.2	191.06±11.21	149.04±25.19
Triglyceride (mg/dL)	106.98±14.21	205.08±28.81	142.72±9.96	86.78±20.14
HDL (mg/dL)	43.36±10.19	27.62±8.35	29.9±6.84	46.88±14.5
LDL (mg/dL)	79.06±18.46	148.08±21.94	93.64±7.91	71.68±18.34
VLDL (mg/dL)	26.14±18.67	72.24±25.07	67.52±11.98	30.48±15.67
AIP	0.39±0.15	0.89±0.19	0.69±0.13	0.27±0.14
CRI-I	3.67±1.31	10.53±5.95	6.85±2.24	3.5±1.26
CRI-II	1.97±0.77	6.27±3.45	3.38±1.26	1.73±0.79
AC	2.67±1.31	9.53±5.95	5.85±2.24	2.5±1.26

SD: Standard deviation, TSH: Thyroid stimulating hormone, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, AIP: Atherogenic index of plasma, CRI-I: Castelli's risk index-I, CRI-II: Castelli's risk index-II, AC: Atherogenic coefficient

Table 2: Correlation of TSH with lipid ratios in different groups

Lipid Ratios	Euthyroid (n=50)		Hypothyroid (n=50)		Subclinical hypothyroid (n=50)		Hyperthyroid (n=50)	
	r-value	P-value	r-value	P-value	r-value	P-value	r-value	P-value
AIP	0.918	<0.05*	0.853	<0.05	0.598	<0.05	−0.067	0.645**
CRI-I	0.884	<0.05*	0.918	<0.05	0.590	<0.05	−0.249	0.081**
CRI-II	0.864	<0.05*	0.886	<0.05	0.549	<0.05	−0.229	0.110**
AC	0.884	<0.05*	0.918	<0.05	0.590	<0.05	−0.249	0.081**

TSH: Thyroid-stimulating hormone, AIP: Atherogenic index of plasma, CRI-I: Castelli's risk index-I, CRI-II: Castelli's risk index-II, AC: Atherogenic coefficient. *P<0.05 is considered statistically significant, ** Not Significant

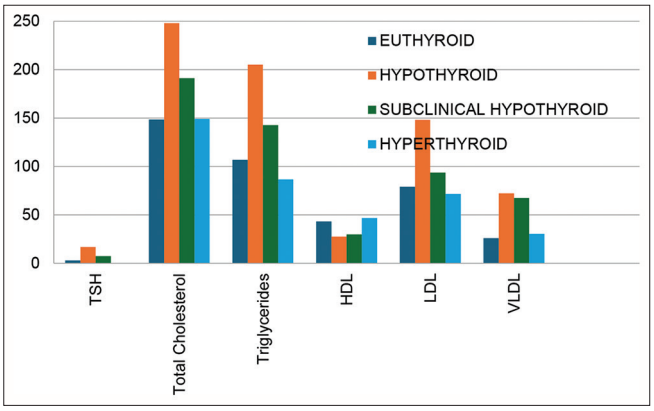

Figure 1: Comparison of thyroid-stimulating hormone and lipid parameters among the study subjects

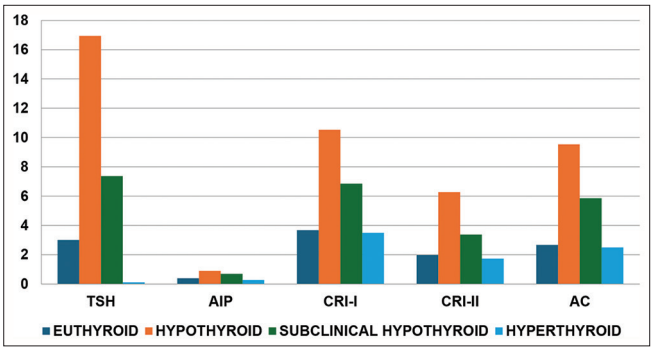

Figure 2: Comparison of thyroid-stimulating hormone and lipid ratios among the study subjects

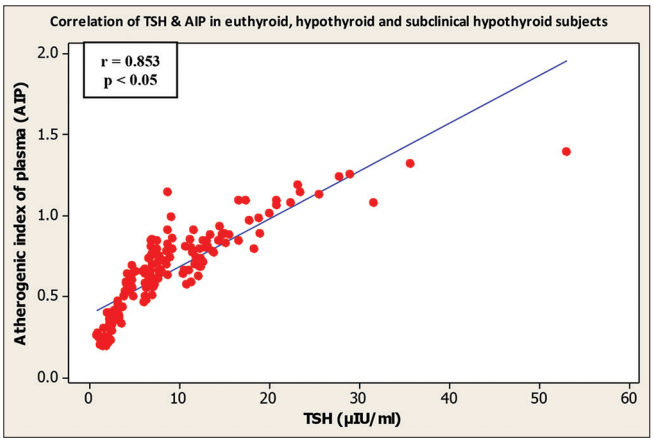

Figure 3: Scatter plot showing correlation of thyroid-stimulating hormone and atherogenic index of plasma in euthyroid, hypothyroid, and subclinical hypothyroid groups

alterations in the lipid profile. In thyroid disorder, dyslipidemia induces insulin resistance and oxidative stress through a vicious cycle.

In existing studies in the past, the lipoprotein lipase activity was found to be normal or decreased, with a decreased hepatic lipase activity, resulting in elevated levels of TG.[12] In hyperthyroidism, there is an increased fatty acid synthesis

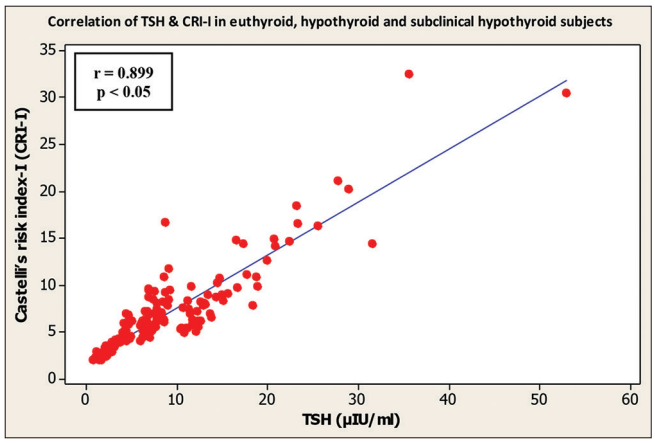

Figure 4: Scatter plot showing correlation of thyroid-stimulating hormone and Castelli's risk index-I in euthyroid, hypothyroid, and subclinical hypothyroid group

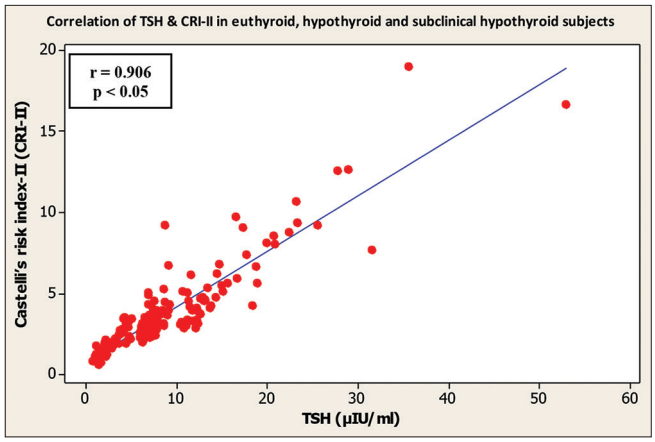

Figure 5: Scatter plot showing correlation of thyroid-stimulating hormone and Castelli's risk index-II in euthyroid, hypothyroid, and subclinical hypothyroid groups

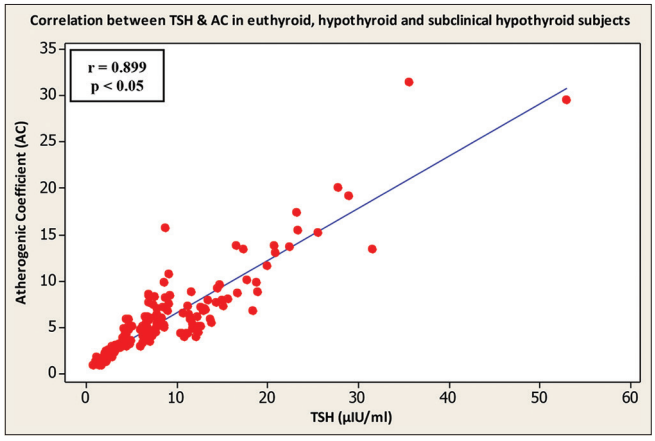

Figure 6: Scatter plot showing correlation of thyroid-stimulating hormone and atherogenic coefficient in euthyroid, hypothyroid, and subclinical hypothyroid groups

and oxidation in the liver, due to enhanced activity of acetyl CoA carboxylase and carnitine palmitoyltransferase activity, resulting in raised VLDL levels in blood.[13] Thyroid

Table 3: Comparison of mean difference of lipid ratios between euthyroid, hypothyroid, and subclinical hypothyroid subjects

Lipid ratios	One-way ANOVA		*Post hoc* Games–Howell test
	F-statistic	P-value	P-value
AIP	116.85	<0.05*	<0.05*
CRI-I	41.77	<0.05*	<0.05*
CRI-II	51.26	<0.05*	<0.05*
AC	41.78	<0.05*	<0.05*

AIP: Atherogenic index of plasma, CRI-I: Castelli's risk index-I, CRI-II: Castelli's risk index-II, AC: Atherogenic coefficient, ANOVA: Analysis of variance. *P<0.05 is considered statistically significant

hormones affect the CETP and hepatic lipase activity, which are enhanced in hyperthyroidism and suppressed in hypothyroidism, resulting in the alteration of HDL levels in the blood.[4] Furthermore, thyroid hormones by binding to the thyroid hormone receptor competitively inhibit the ATP binding cassette transporter A1 gene expression, resulting in decreased HDL in hyperthyroidism and increased HDL in hypothyroidism.[4] Along with dyslipidemia, thyroid disorder also results in insulin resistance, hypertension, inflammation, coagulation deficits, and oxidative stress, which independently contribute to the development of atherosclerosis.[14] In the present study, the TC, TG, LDL, and VLDL levels are higher in hypothyroid and subclinical hypothyroid patients than in euthyroid and hyperthyroid subjects. The HDL levels are seen to be lower in overt and subclinical hypothyroidism. The lipid parameters, except HDL, were found to be slightly lower in hyperthyroidism when compared to euthyroid patients and the findings are consistent with a previous study by Sharma et al.[15]

In a previous study, CRI-I, CRI-II, AC, and AIP were found to be significantly positively correlated with LDL in hypothyroidism when compared to euthyroid controls. The receiver operating characteristic curve analysis further revealed that CRI-I and AC were better indices for screening of early detection of cardiometabolic risk in female patients with hypothyroidism.[16] In a case–control study in a tertiary hospital in South India, it was seen that AIP was significantly higher in women with subclinical hypothyroidism than in euthyroid controls. AIP also showed a significant positive correlation with serum TSH.[10] Another study demonstrated that evaluation of lipid parameters including non-HDL-C, lipid ratios, and AIP helped in better identification of cardiovascular risk in patients with subclinical hypothyroidism who tend to have normal lipid profiles.[17] In a study by James et al., it was demonstrated that lipid ratios and AIP were significantly higher in the subclinical hypothyroid group than in euthyroid controls but there was no correlation between TSH and AIP. AIP was also found to be the significant single factor associated with subclinical hypothyroidism in multiple logistic regression analysis.[9]

In the present study, the lipid ratios (AIP, CRI-I, CRI-II, AC) are higher in hypothyroidism, followed by subclinical hypothyroidism, when compared to euthyroid controls. A statistically significant positive correlation (P<0.05) has been demonstrated between lipid ratios and serum TSH levels in euthyroid, hypothyroid, and subclinical hypothyroid subjects. The mean difference in lipid ratios and TSH between the euthyroid, hypothyroid, and subclinical hypothyroid groups is statistically significant as tested by one-way ANOVA and *post hoc* Games–Howell tests. In a previous study by Zhenjiang et al., the lipid ratios were found to be significantly higher in hyperthyroidism when compared to euthyroid controls and it was concluded that lipid ratios can predict cardiovascular complications in hyperthyroidism.[11] However, in this study, lipid ratios were found to be lower in hyperthyroid than in euthyroid controls. There was no significant correlation between serum TSH and lipid ratios in hyperthyroid cases. There was no significant difference in lipid ratios between hyperthyroid and euthyroid subjects, as tested by Independent samples t-test.

CONCLUSION

This study illustrates that dyslipidemia and abnormal lipid ratios occur in subclinical and overt hypothyroidism. Although a lot of research work has been done previously, where lipid profile parameters and lipid ratios were studied in thyroid dysfunction, the findings remain disputable. However, this study for the first time demonstrates the association of TSH with all the clinically useful lipid ratios, over the entire spectrum of thyroid disorders that include euthyroid, subclinical hypothyroid, hypothyroid, and hyperthyroid cases. Previous studies have elucidated that lipid ratios are indicative of the atherogenic potential of the blood; thyroid dysfunction is associated with dyslipidemia and dyslipidemia is one of the main risk factors for atherosclerosis. Thus, we can conclude that even when the lipid profile appears to be normal, lipid ratios can be used as an inexpensive screening tool to assess the cardiovascular risk in both subclinical and overt hypothyroidism. This will be especially useful in resource-limited centers where imaging techniques are not available and affordable. Unlike previous findings, this study demonstrates that lipid ratios are not useful to predict cardiovascular disorders in hyperthyroidism. However, a large-scale study with a larger sample size is required in this direction, to establish the diagnostic utility of lipid ratios to assess the cardiometabolic risk in thyroid dysfunction.

Limitations of the study

The lipid ratios could have been compared with echocardiographic findings in patients with CVD risk associated with thyroid dysfunction which will further

help to establish the role of lipid ratios as screening tools. However, the results of this study can be used as a reference in the future for conducting other large-scale population-based studies.

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Authors Contribution:
SC- Concept and design of the study, data analysis and result interpretation, prepared the first draft of the manuscript; **AC**- Concept and coordination, review of literature, final preparation, and critical revision of manuscript; **SB**- Concept and design of the study, critical revision of manuscript, and final approval.

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