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ORIGINAL ARTICLE

Novel Adiponectin-Resistin Indices and Ratios Predict Increased Cardiovascular Risk in Patients with Type 2 Diabetes Mellitus

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Abstract

Objectives: **Adiponectin and resistin are adipokines involved in insulin resistance, glucometabolic control and adiposity. There is evidence that hypoadiponectinemia and hyperresistinemia are associated with cardiovascular disease. Whether the ratio of Adiponectin-Resistin (AR) and Insulin Resistance Adiponectin-Resistin (IRAR) indices can be used as non-invasive biomarker of cardiovascular disease needs more attention. Therefore, the aim of this study was to assess the relationships of AR and IRAR indices with adiposity, glucometabolic control and cardiovascular risk incurred by high-sensitivity C-reactive protein (hsCRP) in healthy subjects and patients with Type 2 Diabetes Mellitus.**

Methods: **This observational case control study was conducted in the Department of Physiology and Medicine, King Saud University, Riyadh. A total of 191 (control = 84 and diabetic = 107) subjects were recruited. Body composition was assessed by bioelectrical impendence analyzer (BIA). Fasting blood samples were analyzed for glucose, glycosylated hemoglobin (HbA1c), high-sensitivity C-reactive protein (hsCRP), lipid profile, adiponectin, and resistin levels. The AR and IRAR indices were determined by formulas.**

Results: **Serum adiponectin levels were significantly lower in diabetics compared to control (95.45 ± 39.27 ng/ml vs 146.64 ± 56.36 ng/ml, $p < .001$) while serum resistin was significantly higher in diabetic when compared to control (2.94 ± 1.30 ng/ml vs 2.40 ± 1.09 ng/ml, $p = .003$). Furthermore, AR and IRAR indices were significantly increased in diabetic subjects when compared to control (.82 ± .29 vs .48 ± .35, $p < .001$) and (.30 ± .10 vs .17 ± .12, $p < .001$) respectively. ROC analysis revealed that these indices predicted increased cardiovascular risk with area under the curve (AUC) for adiponectin = .717 ($p = .001$), resistin = .635 ($p = .002$), AR index = .740 ($p < .001$), and IRAR index = .737 ($p < .001$) respectively. AR index correlated positively with Triglycerides (r = .354, $p < .01$), hsCRP (r = .264, $p < .01$), HbA1c (r = .425, $p < .01$), fat mass (r = .164, $p < .05$), Waist/Hip Ratio (WHR) (r = .248, $p < .01$), and negatively with high density lipoprotein (r = −.327, $p < .01$). Furthermore, IRAR index more strongly correlated with Triglycerides (r = .409, $p < .01$), hsCRP (r = .268, $p < .01$), HbA1c (r = .508, $p < .01$), fat mass (r = .152, $p < .05$), WHR (r = .256, $p < .01$), and negatively with high density lipoprotein (r = −.340, $p < .01$).**

Conclusions: **AR and IRAR indices correlate significantly with adiposity, glucometabolic control and cardiovascular risk in type 2 diabetic patients and non-diabetic individuals. They may prove to be useful integrated biomarkers to predict metabolic dysregulation and cardiovascular risk.**

Keywords: Adiponectin-resistin index, Insulin resistance adiponectin-resistin index, Cardiovascular risk, Diabetes mellitus, High-sensitivity C-Reactive protein

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1. Introduction

Cardiovascular diseases (CVD) remain the biggest cause of death worldwide. As the global population becomes increasingly sedentary, CVD and related diseases such as diabetes (T2DM) and obesity will increase. In 2019, according to World Health Organization (WHO), cardiovascular diseases accounted for 32% of mortality globally [1]. By 2020, cardiovascular disease was the cause of 11 million deaths worldwide and it is estimated that cardiovascular diseases would be the leading cause of death by 2030 [2,3].

One of the leading risk factors of cardiovascular diseases is diabetes mellitus which needs special concern and attention in addition to other risk factors such as increased body mass index (BMI), high level of Triglycerides and Cholesterol, and sedentary lifestyle (poor nutrition and lack of activities) [4–9]. In addition, it has been observed that Saudi Arabia has high obesity prevalence with low physical fitness score [10].

The role of adipokines, adiponectin and resistin secreted by adipocytes, is crucial in regulation of insulin sensitivity [11–13]. In addition, adiponectin plays an essential role as cardioprotective guard against inflammatory processes and hence decreases the risk of atherosclerosis [11–13]. Number of studies have reported that adiponectin concentrations are reduced in obese and cardiovascular diseases while plasma resistin concentrations are increased in metabolic syndromes and cardiovascular risk [11–14]. Not only metabolic syndrome disorders but also other diseases such as asthma [15] and polycystic ovary syndrome [16] have been mentioned in the literature to have correlation with adiponectin, resistin, and Adiponectin-Resistin (AR) index. On the other hand, resistin, secreted from white adipocytes and is involved in inflammation in humans, has been observed as an important link between obesity and T2DM and contributes harmfully to the inflammation process [17].

The chronic inflammatory process in atherosclerosis usually can be well predicted by high-sensitivity C-reactive protein (hsCRP) [18,19]. Many large prospective trials have shown that the inflammatory biomarker hsCRP is an independent predictor of future cardiovascular events [20].

An interesting study conducted by Lau et al., they proposed novel AR and Insulin Resistance Adiponectin-Resistin (IRAR) indices that can be used as valid and reliable predictors of T2DM and metabolic syndrome [21]. The scientific society aims to find trustful non-invasive biomarkers to predict cardiovascular risk and its complications. Whether AR and IRAR ratios can be used as indices for cardiovascular risk factors in healthy as well as diabetic subjects needs to be assessed. The aim of this study was to assess the relationships of AR and IRAR indices with adiposity, glucometabolic control and cardiovascular risk incurred by high-sensitivity C-reactive protein (hsCRP) in healthy subjects and patients with T2DM.

Abbreviations

ADA	American Diabetes Association
AR	Adiponectin-Resistin index
BIA	Bioelectrical Impendence Analyzer
BMI	Body Mass Index
CVD	Cardiovascular diseases
FBG	Fasting Blood Glucose
HbA1c	Glycosylated Hemoglobin
HDL	High density lipoprotein
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
hsCRP	High-sensitive C-reactive Protein
IRB	Institutional Review Board
IRAR	Insulin Resistance Adiponectin-Resistin index
QUICKI	Quantitative insulin-sensitivity check index
TC	Total cholesterol
TG	Triglycerides
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization
WHR	Waist hip ratio

2. Methods

This case control study was conducted from January 2021 to December 2021 in the Department of Physiology and Medicine, College of Medicine & King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia. The study was approved by the Institutional Review Board (IRB) of College of Medicine, King Saud University (10/2664/IRB). We had a total of 191 individuals: 107 patients with T2DM (67 males and 40 females) and control group including 84 healthy subjects (45 males and 39 females) matched for age, gender and weight recruited from patients' companions. Personal and demographic information from all subjects were obtained on a predesigned form including age, gender, Waist/Hip Ratio (WHR), weight, height, and BMI measurements. American Diabetes Association (ADA) criteria of blood glucose level were used for diagnosis and patients were in stable metabolic condition with at least one year of duration of T2DM [22]. Exclusion criteria included acute or chronic renal disorders, thyroid diseases, acute & chronic infections, stroke, acute diabetic states, and recent surgery in the last month. All subjects signed the consent form for participation in the study.

Bioelectrical impendence analysis was used to measure body composition with an InBody3.0 (BioSpace, Korea) body analyzer according to the manufacturer's instructions. All assessments were made in the early morning fasting state, wearing light clothing, and after emptying of the urinary bladder. We collected fasting venous blood samples after 10−12 h of overnight fasting and stored at −80 °C for the evaluation of total Cholesterol (TC), Triglycerides (TG), Low density Lipoprotein (LDL), High density lipoprotein (HDL), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c). Basal insulin, adiponectin and resistin levels immunoassays were carried out by a quantitative standard sandwich ELISA technique using monoclonal antibody specific for resistin with kits supplied by R&D Systems, (Abingdon, United Kingdom) were used to assess basal insulin, adiponectin and resistin levels. To maintain the overall reliability and precision of ELISA assays all tests were run in duplicate keeping inter-assay % CV<15% while intra-assay %CV<10%. To measure hsCRP, we used a turbidimetric assay (Quantex CRP ultra-sensitive kits, BIOKIT, S.A., Barcelona, Spain) on auto-analyzer Hitachi 911, (ROCHE diagnostics, Indianapolis, Indiana, USA). The US-CRP kits measured ranges from .10 to 20.0 mg/L. The outcome parameter for increased cardiovascular risk in our study was hsCRP. We followed American Heart Association criteria and guidelines for measurement, evaluation and expression of low and high-risk levels of hsCRP [23].

2.1. Formulation of the adiponectin-resistin (AR) index

$$\alpha = (1 / A_0) \times R_0 = R_0 / A_0$$

$$B = \text{Log10}(\alpha) = \text{Log10}\,(R_0 / A_0) = \text{Log10}\,(R_0) - \text{Log10}(A_0)$$

$$\text{AR index} = 1 + B = 1 + \text{Log10}\,(R_0) - \text{Log10}(A_0)$$

2.2. Formulation of the Insulin Resistance Adiponectin-Resistin (IRAR) index

$$\text{QUICKI} = 1/\text{Log10}(I_0) + \text{Log10}(G_0)$$ [quantitative insulin-sensitivity check index (QUICKI)]

2.3. IRAR index = AR index/QUICKI

{R_0 = serum total resistin (ng/mL); A_0 = serum total adiponectin (μg/mL), I_0 = fasting serum insulin (μU/mL), G_0 = fasting plasma glucose (mg/dL)} [21].

2.4. Statistical analysis

Statistical Package for Social Sciences (SPSS Version 19, Chicago, IL, USA) was used for data analysis. Descriptive characteristics were expressed as Mean ± standard deviation (SD). Group comparisons were performed using t-tests. Comparative correlation coefficients were determined using Spearman's correlations between adiponectin, resistin, AR and IRAR indices with glycemic indices, insulin resistance indices, hsCRP, and body composition. A p value $\leq$ .05 was considered significant. hsCRP was dichotomized into low and high-risk categories based on AHA guidelines cut off points (low risk $\leq$3.0 mg/L and high risk >3 mg/L) to use it as state variable for Receiver Operating Curve (ROC) analysis which was carried out to assess the performance of hsCRP in relation to adiponectin, resistin, AR and IR AR indices for increased cardiovascular risk incurred by hsCRP as standard. Since adiponectin is cardio protective at high levels, therefore, we used inverse adiponectin (invadiponectin) values in ROC predictors to keep all variables above midline.

3. Results

Comparison of demographic data and body composition analysis between control and T2DM patients is shown in Table 1. There were no significant differences in age (p = .066) and height (p = .535) between control and T2DM patients, while the diabetic patients had higher weight (p = .010), BMI (p = .017), body fat mass (p = .047), and WHR (p < .001) compared to controls. Table 2 compares HOMA-IR and hsCRP between control and patients with T2DM. HOMA-IR, and hsCRP were significantly higher in T2DM patients than control (9.52 ± 4.98 vs 5.16 ± 1.82, p < .001) and (4.53 ± 2.75 mg/L vs 3.55 ± 2.23 mg/L, p = .008) respectively.

Adiponectin, resistin, AR, IR, and IRAR indices comparisons between control and patients with T2DM are expressed in Table 3. Serum adiponectin levels were significantly lower in diabetics compared to control (95.45 ± 39.27 ng/ml vs 146.64 ± 56.36 ng/ml, p < .001) while serum resistin was significantly higher in diabetic when compared to control (2.94 ± 1.30 ng/ml vs 2.40 ± 1.09 ng/ml, p = .003). Furthermore, AR and IRAR indices were significantly increased in diabetic subjects when compared to control (.82 ± .29 vs .48 ± .35, p < .001) and (.30 ± .10 vs .17 ± .12, p < .001) respectively.

Table 1. Comparison of descriptive characteristics and body composition between control and diabetic subjects.

Variables	Total N = 191	Control n = 84	T2DM n = 107	*p*-value
Male/Female	98/93	45/39	58/49	–
Age (years)	51.15 ± 11.15	49.51 ± 11.31	52.51 ± 10.88	.066
Height (cm)	166.31 ± 11.59	166.88 ± 8.50	165.82 ± 13.68	.535
Weight (Kg)	81.41 ± 18.40	77.65 ± 14.69	84.58 ± 20.56	.010*
BMI (kg/m2)	28.94 ± 5.16	27.96 ± 4.93	29.77 ± 5.23	.017*
Intracellular fluid (ICF) (Liters)	27.43 ± 4.32	26.87 ± 4.73	27.91 ± 3.91	.100
Extracellular fluid (ECF) (Liters)	13.92 ± 7.26	13.93 ± 10.45	13.90 ± 2.38	.983
Total body water (TBW) (Liters)	42.73 ± 27.39	43.94 ± 40.11	41.70 ± 5.83	.581
Protein Mass (Kg)	10.97 ± 1.73	10.75 ± 1.89	11.16 ± 1.56	.109
Bone mass (Kg)	3.53 ± .47	3.46 ± .49	3.60 ± .43	.053*
Body Fat Mass (Kg)	25.74 ± 10.13	24.13 ± 9.09	27.09 ± 10.80	.047*
Fat mass/Muscle mass ratio	2.36 ± .89	2.28 ± .90	2.42 ± .87	.276
Soft Lean Mass (Kg)	51.80 ± 8.09	50.53 ± 8.74	52.86 ± 7.37	.050*
Lean body mass (Kg)	55.25 ± 8.60	53.87 ± 9.26	56.41 ± 7.86	.044*
Body Fat % (BF%)	31.40 ± 9.26	30.30 ± 8.13	32.34 ± 10.06	.135
Waist/Hip-Ratio (WHR)	.97 ± .11	.94 ± .12	1.00 ± .09	<.001*

Data are represented as mean and standard deviation. * Significant *p*-values of t-test, *p ≤ .05.

Table 2. Comparison of insulin resistance indices and hsCRP between control and patients with T2DM.

Variable	All N = 191	Control n = 84	T2DM n = 107	*p*-value
FBG mmol/dl	7.08 ± 3.09	5.13 ± 1.45	8.68 ± 3.16	<.001*
Insulin (μI/ml)	23.76 ± 8.09	22.64 ± 6.11	24.69 ± 9.35	.084
FBG $_{Log10}$	2.07 ± .16	1.96 ± .08	2.17 ± .14	<.001*
Insulin $_{Log10}$	1.36 ± .13	1.34 ± .11	1.37 ± .14	.133
HOMA-IR	7.55 ± 4.44	5.16 ± 1.82	9.52 ± 4.98	<.001*
HbA1c (%)	6.82 ± 2.45	5.18 ± 1.46	8.15 ± 2.29	<.001*
hsCRP mg/L	4.07 ± 2.56	3.55 ± 2.23	4.53 ± 2.75	.008*

Data are represented as Mean and standard deviation. * Significant *p*-values of t-test, *p ≤ .05, FBG: Fasting blood glucose, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HbA1c: glycosylated hemoglobin, hs-CRP: high-sensitivity C-reactive protein.

Table 3. Comparison of adiponectin, resistin, AR index and IR AR indices between control and patients with T2DM.

Variable	All N = 191	Control n = 84	T2DM n = 107	*p*-value
QUICKI	2.82 ± .17	2.71 ± .10	2.91 ± .15	<.001*
Adiponectin ng/ml	118.84 ± 54.13	146.64 ± 56.36	95.45 ± 39.27	<.001*
Resistin ng/ml	2.70 ± 1.24	2.40 ± 1.09	2.94 ± 1.30	.003*
Adiponectin $_{Log10}$	2.03 ± .19	2.14 ± .15	1.95 ± .17	<.001*
Resistin $_{Log10}$	.38 ± .22	.32 ± .24	.42 ± .20	.002*
AR index	.63 ± .36	.48 ± .35	.82 ± .29	<.001*
IR AR index	.23 ± .13	.17 ± .12	.30 ± .10	<.001*

Data are represented as mean and standard deviation. * Significant *p*-values of t-test, *p ≤ .05, AR index: Adiponectin-Resistin index, IRAR index: Insulin Resistance Adiponectin-Resistin index, QUICKI: Quantitative insulin-sensitivity check index.

Comparison of correlation coefficients of adiponectin, resistin, AR, and IRAR indices with demographic data, body composition and insulin resistance indices is revealed in Table 4. AR index correlated positively with Triglycerides (r = .354, $p < .01$), hsCRP (r = .264, $p < .01$), HbA1c (r = .425, $p < .01$), fat mass (r = .164, $p < .05$), WHR (r = .248, $p < .01$), and negatively with high density lipoprotein (r = −.327, $p < .01$). Furthermore, IRAR index was more strongly correlated with Triglycerides (r = .409, $p < .01$), hsCRP (r = .268, $p < .01$), HbA1c (r = .508, $p < .01$), fat mass (r = .152, $p < .05$), WHR (r = .256, $p < .01$), and negatively with high density lipoprotein (r = −.340, $p < .01$).

Fig. 1 shows ROC analysis comparing predictive value of adiponectin, resistin, AR, and IRAR indices for increased cardiovascular risk revealed by hsCRP high risk levels. It revealed that area under the curve (AUC) was significant for all these indices with maximum value for IRAR index. AUC values were adiponectin = .717 ($p = .001$), resistin = .635 ($p = .002$), AR index .740 ($p < .001$), and IRAR index = .737 ($p < .001$).

Table 4. Correlation coefficients of adiponectin, resistin, AR index and IRAR index with glycemic indices, insulin resistance indices, hsCRP and body composition in all subjects, N = 191.

Variable	Adiponectin	Resistin	AR index	IRAR index
FBG mmol/dl	−.422**	.101	.409**	.502**
Insulin (μI/ml)	−.180*	.157*	.209**	.170*
QUICKI	.325**	.020	.283**	.387**
HOMA-IR	−.398**	.166*	.423**	.475**
HbA1c (%)	−.490**	.079	.425**	.508**
TG mmol/L	−.358**	−.088	.354**	.409**
TC mmol/L	−.071	.009	.065	.092
HDL mmol/L	.316**	.146	−.327**	−.340**
LDL mmol/L	−.044	−.053	.026	.050
hsCRP mg/L	−.246**	.097	.264**	.268**
Body Fat Mass (Kg)	−.093	.196**	.164*	.152*
Body Fat %	.025	.166*	.090	.080
Protein Mass (Kg)	−.321**	.039	.166*	.165*
Fat mass/Muscle mass	.035	.172*	.092	.082
BMI (kg/m2)	−.158*	.141	.174*	.165*
Waist/Hip-Ratio (WHR)	−.209**	.159*	.248**	.256**

*p ≤ .05, **p < .01. FBG: Fasting blood glucose, TG: Triglycerides, TC: Total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, HbA1c: glycosylated hemoglobin, hs-CRP: high-sensitivity C-reactive protein, QUICKI: Quantitative insulin-sensitivity check index.

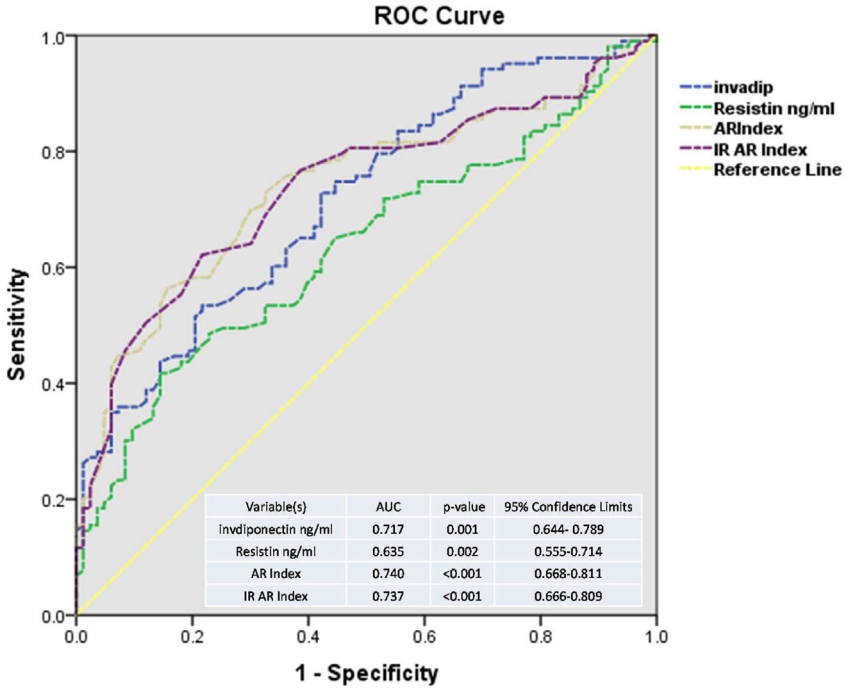

Fig. 1. ROC curve analysis comparing predictive value of adiponectin, resistin, AR and IRAR indices for increased cardiovascular risk incurred by hsCRP. AUC: area under the curve. invadip: inverse adiponectin.

4. Discussion

This study compared the relationships of adiponectin, resistin, AR, and IRAR indices with increased levels of cardiovascular risk markers and adiposity indices in healthy subjects and in patients with T2DM. We found that these composite indices are significantly related with cardiovascular risk markers and body adiposity and have better prediction of cardiovascular risk in patients with T2DM compared to adiponectin, resistin and insulin resistance alone. AR and specifically IRAR indices are significantly increased in diabetic subjects when compared to control. Furthermore, AR and IRAR indices correlated positively with Triglycerides, hsCRP, HbA1c, fat mass, WHR, and negatively with high density lipoprotein.

Our study is concomitant with the findings of Hameed et al. who reported that the AR index correlated significantly with HOMA-IR in type 2 diabetic subjects [24]. Furthermore, we found IRAR index was more positively correlated with cardiovascular biomarkers.

A study in hypertensive type 2 diabetic patients reported that AR index strongly correlated with atherosclerosis, and hence, it may be a good marker of cardiovascular risk in these patients [25]. Singh P et al. reported that AR index was the best predictor of acute coronary syndrome [26]. These studies supported our findings regarding the utility of AR and IRAR indices as cardiovascular risk biomarkers. On the other hand, our findings are not in agreement with Toczylowski et al. who found that patients with coronary artery disease who were obese, or diabetic have a limited impact on adipokines level [27]. In addition to the well-known role of adipokines, several signaling pathways still need to be studied thoroughly in order to understand the full role of adipokines. Sawaguchi et al. suggested that adiponectin could be used as a predictor of progression of heart failure in cardiovascular surgery due its link to sarcopenia, inflammation, and malnutrition [28]. Also, adiponectin and resistin can be involved in cardiac remodeling mechanism [29]. Furthermore, the relationship of adiponectin to chemerin, adiponectin/chemerin ratio, could play an important role in affecting lipids and metabolism especially in reproductive system dysfunctions such as Polycystic ovary syndrome [30]. Mooldijk et al. suggested that adipokines might participate in the pathophysiology of dementia [31]. Whether AR and IRAR indices can be used as biomarkers in these situations or not is the area of further investigations. Moreover, other adipokines like leptin, chemerin and visfatin can be targets of further research in future.

5. Conclusions and recommendations

AR and IRAR indices are more strongly associated with adiposity, glycemia, dyslipidemia and increased risk of cardiovascular diseases. They may prove to be useful integrated biomarkers to predict metabolic dysregulation and cardiovascular risk. We recommend that further, prospective study at a large scale is required to explore the true homeostatic roles of adiponectin and resistin and their correlation to each other in patients with T2DM. Since they are related to glucose and lipid metabolism, it would be worth studying them as an integrated approach with various pharmacological therapies and exercise approaches. They may prove to be useful predictive biomarkers to predict increased cardiovascular risk & metabolic dysregulation in patients with T2DM.

Author contribution

Conception and design of Study: SSH, TAK, KAR. Literature review: SSH, TAK, MAB, SMH. Acquisition of data: SSH, TAK, MAB, SMH, HAK, KAR. Analysis and interpretation of data: SSH, TAK, SMH. Research investigation and analysis: SSH, TAK, SMH. Data collection: SSH, TAK, MAB, SMH, HAK, KAR. Drafting of manuscript: SSH, TAK, MAB, SMH, HAK, KAR. Revising and editing the manuscript critically for important intellectual contents: SSH, SMH, HAK, KAR. Data preparation and presentation: SSH, TAK, MAB, SMH, HAK, KAR. Supervision of the research: SSH, TAK, KAR. Research coordination and management: SSH, TAK, KAR. Funding for the research: SSH, TAK, KAR.

Conflicts of interest

None declared.

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