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Ratios of peripheral blood mononuclear cells to lncRNA steroid receptor RNA activator as new indicators of metabolic syndrome

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Abstract

Introduction: Metabolic syndrome (MetS) is a clinical syndrome with several characteristics. Steroid receptor RNA activator (SRA) is a long non-coding RNA (lncRNA), which can increase the expression of steroid receptor-dependent gene. This study aimed to explore the changes in metabolic parameters and the predictive value of the peripheral blood mononuclear cells (PBMCs) to SRA ratios as new indicators in subjects with and without MetS in southern China.

Material and methods: There were 81 participants (39 with MetS and 42 without MetS) in this cross-sectional study. The expression of lncRNAs in PBMCs was evaluated by quantitative reverse transcription polymerase chain reaction (qRT-PCR). The risks of SRA and PBMCs to SRA ratios contributing to the presence of MetS were estimated by univariate and multivariate logistic regression models. The area under the receiver (AUC) operating characteristic curve was employed to evaluate diagnostic accuracy.

Results: MetS was positively correlated with cortisol, interleukin 6 (IL-6), white blood cell to SRA ratio (WTSR), lymphocyte to SRA ratio (LTSR), monocyte to SRA ratio (MTSR), and PBMC to SRA ratio (PTSR). A receiver operating characteristic (ROC) curve analysis was performed to assess the value of LTSR (OR: 0.722; $p < 0.001$) for predicting MetS. The area under the curve yielded a cut-off value of 0.483, with a sensitivity of 76.9% and a specificity of 71.4% ($p < 0.001$).

Conclusion: In summary, SRA in PBMCs may be an important biomarker of stress reaction and may play a role in vulnerability to MetS. Also, the lymphocyte to SRA ratio demonstrated high accuracy in the diagnosis of MetS. **(Endokrynol Pol 2022; 73 (1): 81–86)**

Key words: *lncRNA; steroid receptor RNA activator; peripheral blood mononuclear cells; metabolic syndrome; biomarkers*

Introduction

Metabolic syndrome (MetS) is a combination of several characteristics, including abdominal obesity, raised blood pressure, high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and hyperglycaemia, resulting in increased risk of type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), fatty livers, and cancers [1]. Five risk factors with different critical cut-off values are used to identify individuals with the MetS: waist circumference, circulating levels of triglycerides, HDL-C, fasting glucose, and blood pressure [2]. In China, the age-standardized prevalence of MetS was 9.8% in men and 17.8% in women in 2001, and the figures have increased to 31.0% in men and 36.8% in women in 2010 [3]. Among various risk factors of MetS, chronic stress has emerged as a contributor to the development of MetS. Psychological stress can affect health through complex interactions among neuroendocrine responses and energy homoeostasis [4]. Glucocorticoid (GC) (cortisol in human beings) is the critical matter responding to stress, which can cause central obesity, hypertension, hyperlipidaemia, and glucose intolerance. GC action is mediated by glucocorticoid receptor (GR), a nuclear receptor that regulates physiological events through activation or repression of target genes involved in inflammation, gluconeogenesis, and adipocyte differentiation [5].

Long non-coding RNA (lncRNA), a non-coding RNA with more than 200 nucleotides in length, can modify chromatin structures by interacting with polycomb repressive complex 2, enhance or reduce gene transcription by recruiting transcription factors, and regulate miRNA processing in the cell nucleus. In the cytoplasm,

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lncRNAs can mediate mRNA translation, increase or decrease mRNA stability, and act as miRNA sponges that can repress miRNAs [6]. LncRNAs have been found to be involved in various physiological and pathological cellular activities, such as adipogenesis, inflammation, cell differentiation, and tumourigenesis, via genomic expression modulation, epigenetic modification, and post-transcriptional regulation in cis or in trans by interacting with chromatins, proteins, and RNAs in the nucleus or cytoplasm. LncRNAs can participate in the pathogenesis of various human diseases, including metabolic diseases [7]. In an Indian study, the expression levels of lncRNAs HOTAIR, PANDA, and growth arrest-specific transcript 5 (GAS5) in PBMC in T2DM patients were significantly increased and positively correlated with the expression levels of inflammatory factors: tumour necrosis factor alpha (TNF-α), IL6, and MCP1. It indicates that there are abnormal expressions of various lncRNAs in the PBMC of diabetic patients, which are closely related to inflammatory factors [8]. Among the inferring lncRNAs mentioned above, GAS5 can competitively bind glucocorticoid response elements (GREs) near the promoter of the target gene that GR specifically binds, thereby inhibiting the transcription of GC-GR-GRE-dependent target genes and changing the downstream effects of GC [9]. SRA can induce the expression of steroid receptor-dependent gene, acting as a scaffold to regulate the expression of stress-related genes. SRA can co-activate GR. More and more studies have shown that SRA plays a key role in lots of diseases such as obesity, cardiomyopathy, and tumourigenesis [10].

Although lncRNAs have received widespread attention as potential and powerful biomarkers in the pathogenesis and progression of many diseases, few studies have investigated the expressions of SRA and GAS5, which can regulate GR in the MetS population. It has been suggested that the gene expression signature in PBMCs may provide an indicator of gene activation changes as a differential response to stress in humans [11]. In this study, we analysed the association between MetS and expression of SRA and GAS5 in PBMCs, which may unveil a new target for the prevention and treatment of stress-related disorders including MetS.

Material and methods

Subjects

This study was conducted among the same recruitments in our present study as described in this article [12]. Patients with acute or chronic infections or immunological diseases, obvious liver and kidney dysfunction, severe heart diseases, pregnancy, mental illness or drug abuse, gastrointestinal diseases (such as chronic gastrointestinal disorders, diarrhoea, biliary tract infection and enteritis), and serious diseases of the blood or the endocrine systems, were excluded from the study. A structured questionnaire was used to collect information on demographic data, environmental exposure, and medical histories. Current cigarette smokers were defined as those who smoked ≥ 1 cigarette/day. Alcohol use was defined as intake of wine/beer/cider/spirits ≥ 1 time per week. Physical activity was defined as walking or riding 15 min/day or doing sports or physical exercise > 2 h/week, or lifting or carrying heavy objects at work daily [13]. This study was approved by the hospital ethical committee, and informed consent was obtained from each participant.

Anthropometric measurement

Anthropometric parameters including weight, height, waist circumference (WC), hip circumference (HC), and blood pressure were obtained using standard measurement. Body mass index (BMI) was calculated by dividing the weight (kg) by the squared value of height in metres.

Blood samples collection and RNA extraction

Following an overnight fast, a 5-mL venous blood sample from each subject was collected using EDTA anticoagulant tubes and processed within three hours. A 3-mL sample was immediately centrifuged to retrieve plasma. PBMCs were isolated from 2 mL whole blood by Ficoll-Hypaque density gradient centrifugation. Immediately afterwards, total RNA was extracted from PBMCs by standard protocol of Trizol reagent (Invitrogen, New York, USA). The purity of RNA was determined using a BioPhotometer plus Eppendorf nucleic acid protein Analyzer (Hamburg, Germany), and the integrity was evaluated using agarose gel electrophoresis stained with ethidium bromide. All RNA used had OD260/OD280 ratio > 1.8, and electrophoresis showed that the integrity was acceptable. The plasma and RNA were then stored at –80°C until assayed.

Biochemical analysis

Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), and HDLC were measured using standard laboratory methods (Hitachi autoanalyzer 7060; Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDLC) was calculated using the Friedewald formula. Fasting insulin (FINS) and interleukin 6 (IL-6) was calculated by high-pressure liquid chromatography method (Tosoh Corporation, Tokyo, Japan). Plasma cortisols were measured by commercial radio immunoassays using with accounter (XH-6020; North Institute of BioTech, Beijing, China). Plasma TNF-α concentrations were evaluated by enzyme-linked immunosorbent assay using a microplate reader (STAT FAX 2100; Awareness, Palm City, FL, USA). The intra-assay and inter-assay coefficient of variation were < 5.5% and < 10.0% for these assays, respectively. The degree of IR was determined using the HOMA-IR, which was calculated using the following formula: [fasting insulin (mIU/L) *fasting glucose (mmol/L)]/22.5.

Quantitative real-time PCR

Quantification was performed with a two-step reaction process: reverse transcription (RT) and quantitative real-time PCR (qPCR). Each RT reaction consisted of 1 μg RNA, 2.0μL of 10mM dNTP (promega), 0.5μL of RNase inhibitor (promega), 0.5 μL of universal primer (Qiagen), 0.5 μL of lncRNA-specific primer, 4 μL of 5x buffer, 0.5 μL of (Moloney Murine Leukemia Virus) Reverse Transcriptase (promega), and 12.0 μL of nuclease-free water in a total volume of 20 μL. Using U6 as the internal reference of lncRNAs, the primers of GAS5 and SRA were designed and synthesized by Shanghai Sangon Biotechnology Co., Ltd. (Shanghai, China). Reactions were performed in an ABI PRISM® 7500 Sequence Detection System (Applied Biosystems, Foster City, USA) for 60 min at 42°C, followed by heat inactivation of RT for 10 min at 85°C. qPCR was performed with 20 μL PCR reaction mixture that included 5 μL of cDNA, 10 μL of 2x SYBR Green qPCR SuperMix (Invitrogen), 0.5 μL of forward primer (Qiagen), 0.5 μL of reverse primer, and 4 μL of nuclease-free

water. Reactions were incubated in a 384-well optical plate at 95°C for 5 min, followed by 40 cycles of 95°C for 15 sec and 60°C for 32 sec. The specific generation of expected PCR product was confirmed by automated melting curve analysis. All samples were performed in-triplicate (cDNA from the same PCR reaction but in separate wells). The expression levels of lncRNAs were calculated using the 2- ΔΔCt method [ΔCt = mean Ct (lncRNA of interest)- mean Ct (U6), ΔΔCt=ΔCt of lncRNA of interest in samples to be tested — ΔCt of U6 in reference samples. The up-stream primer sequences were as follows: GAS5 forward primer 5′- GCACACAGGCATTAGACAGA -3′; GAS5 reverse primer 5′-CCATACCCAAGCAAGTCATC; SRA forward primer 5′- GGCCAGTCTCTCTGTTCCAA -3′, SRA reverse primer CTTCACCTCTTTCAGCCACTT.

Statistical analysis

Normality of data distribution was assessed using the Kolmogorov–Smirnov test. The independent samples test, chi-square test, and nonparametric test were used to compare differences of demographic and clinical parameters between two groups. Spearman's correlation coefficient was used to test the correlation between lncRNA markers, inflammation cells to lncRNAs ratios, and cortisol and other clinical variables. The odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to assess the risk of lncRNAs and inflammation cells to lncRNAs ratios contributed to the presence of MetS using both univariate and binary logistic regression models with or without adjustment for covariates. ROC analysis was used to assess the biomarker potential of each lncRNA and inflammation cell to lncRNA ratios for MetS, and the area under the curve (AUC) was used as diagnostic index. The diagnostic performances of the lncRNA and ratio panels were further evaluated using the predicted probability of being diagnosed with MetS as a surrogate marker to construct ROC curve. A p value of less than 0.05 was considered statistically significant. The reported p values were two-tailed in all calculations. All statistical analyses were performed using SPSS 25.0.

Results

Basic characteristics of the study subjects

The demographic and clinical characteristics of the study participants were described in our present work [12].

Comparison of lncRNAs levels and stress hormones between two groups

The expression levels of GAS5 and SRA in PBMCs and plasma levels of stress hormones including cortisol, IL-6, and TNF-α are listed in Table 1. The expression level of SRA in MetS patients was significantly lower than that in control individuals (p = 0.036) (Fig. 1), but there was no significance shown in GAS5 (p = 0.936). Levels of plasma cortisol and IL-6 in the MetS group was significantly higher than that in the control group (p = 0.003 and p = 0.003, respectively); however, there were no significant differences of plasma TNF-α levels in the two groups (p = 0.872).

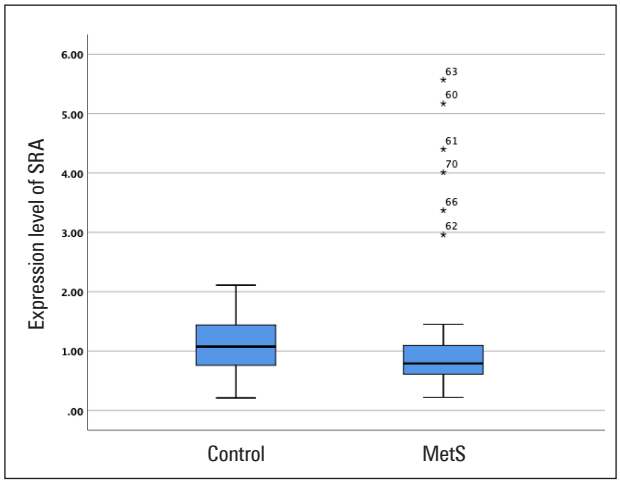

Figure 1. *Comparison of steroid receptor RNA activator (SRA) expression in peripheral blood mononuclear cells (PBMCs) between patients with metabolic syndrome (MetS) and control groups. The expression level of SRA in MetS group and control group were 0.79 ± 0.52 and 1.08 ± 0.69, respectively (median ± interquartile range), p value was 0.036, but there were no significant differences of long non-coding RNAs (lncRNA) growth arrest-specific transcript 5 (GAS5) between two groups*

Risk of SRA and the inflammatory cell to SRA ratios for MetS

Logistic regression revealed that inflammatory cells (including total WBC, LC, MC, and PBMCs) to SRA ratios were positively associated with the presence of MetS (p < 0.01) (Tab. 2). These associations were also confirmed in binary logistic regression analysis after adjustment for age and gender, and further for physical activity. With an increase of inflammatory cell

Table 1. *Long non-coding RNAs (LncRNAs) and hormonal characteristics in the two compared groups*

Variable	MetS (n = 39)	Control (n = 42)	p value
GAS5	1.16 ± 1.43	1.18 ± 1.26	0.936**
SRA	0.79 ± 0.52	1.08 ± 0.69	0.036**
Cortisol [ng/mL]	455.98 ± 93.80	393.87 ± 86.34	0.003*
IL-6 [pg/mL]	3.32 ± 3.70	2.04 ± 1.45	0.006**
TNF-α [pg/mL]	5.87 ± 2.03	5.30 ± 1.97	0.872*

*p value calculated with independent samples T test, and the data are expressed as mean ± SEM; **p value calculated with nonparametric test, and the data are expressed as median ± interquartile range; MetS — metabolic syndrome; GAS5 — growth arrest-specific transcript 5; SRA — steroid receptor RNA activator; IL-6 — interleukin 6; TNF-α — tumour necrosis factor alpha

Table 2. ***The risk of steroid receptor RNA activator (SRA) and the inflammatory cell to SRA ratios for metabolic syndrome (MetS)***

Models	OR (95% CI)	p value
SRA		
Univariate model	1.185 (0.754,1.863)	0.461*
Binary model 1	1.166 (0.699,1.947)	0.557**
Binary model 2	1.172 (0.703,1.954)	0.543***
WTSR		
Univariate model	1.103 (1.018,1.194)	0.016*
Binary model 1	1.125 (1.053,1.202)	0.001**
Binary model 2	1.111 (1.025,1.204)	0.011**
LTSR		
Univariate model	1.529 (1.13,2.069)	0.006*
Binary model 1	1.527 (1.132,2.059)	0.006**
Binary model 2	1.526 (1.13,2.059)	0.006***
MTSR		
Univariate model	3.200 (1.121,9.136)	0.030*
Binary model 1	4.376 (1.245,15.384)	0.021**
Binary model 2	4.343 (1.23,15.333)	0.022***
PTSR		
Univariate model	15.336 (4.788,49.125)	< 0.001*
Binary model 1	67.392 (8.905,509.995)	< 0.001**
Binary model 2	85.432 (9.761,747.76)	< 0.001***

This table shows the logistic regression analysis for the risk of SRA and the inflammatory cells to SRA ratios for MetS. *p value calculated without adjustment; **p value adjusted for age, gender; *** p value further adjusted for physical activity based on model 1; OR — odds ratio; CI — confidence interval; WTSR — white blood cell to SRA ratio; LTSR — lymphocyte to SRA ratio; MTSR — monocyte to SRA; PTSR — PBMCs to SRA ratio

to SRA ratios, there were 1.103 (95% CI: 1.018–1.194, p = 0.016), 1.529 (95% CI: 1.13–2.069, p = 0.006), 3.200 (95% CI: 1.121–9.136, p = 0.030), and 15.336 (95% CI: 4.788–49.125, p < 0.001) -fold greater risk of MetS, respectively. However, the expression level of SRA showed no significant risk of MetS, also after adjustment for age and gender, and further for physical activity. Taken together, inflammatory cell to SRA ratios were all independent risk factors for MetS, especially the ratio of PBMC (consisting of LC and MC) to SRA.

The diagnostic accuracy of SRA, the ratios of inflammatory cells to SRA, cortisol, and IL-6 for MetS

The diagnostic accuracy of SRA, the ratios of inflammatory cells to SRA, cortisol, and IL-6 for MetS was measured by AUC. The accuracy of SRA was 0.635 (95% CI 0.508-0.762, p = 0.036). The sensitivity and specificity were 71.4% and 69.2%, respectively (Fig. 2). The accuracy of ratios of inflammatory cells to SRA, including the lymphocyte count to SRA ratio (LT1), monocyte count to SRA ratio (MT1), and PBMC to SRA ratio (PT1) were 0.722 (95% CI: 0.603–0.841, p < 0.001), 0.664 (95% CI: 0.539–0.789, p = 0.011), and 0.718 (95% CI: 0.598–0.838, p < 0.001), respectively. The sensitivity and specificity of LT1 were 76.9% and 71.4%, respectively (Fig. 3). The sensitivity and specificity of MT1 were 66.7% and 76.2%, respectively. The sensitivity and specificity of PT1 were 79.5% and 66.7%, respectively (Fig. 4). These results revealed that the accuracy of ratios of inflammatory cells to SRA were more valuable than SRA. Among the sensitivity and specificity of ratios of inflammatory cells to SRA, the sensitivity of PT1 and the specificity of MT1 were higher. We also analysed the diagnostic accuracy of cortisol and IL-6 for MetS. The accuracy of cortisol was 0.71 (95% CI: 0.596–0.824, p = 0.001). The sensitivity and specificity were 79.5% and 59.5%, respectively. The accuracy of IL-6 was 0.676 (95% CI: 0.554–0.797, p = 0.007). The sensitivity and specificity were 79.5 % and 59.5%, respectively.

Discussion

The present study identified the relationship of expression levels of two stress-related lncRNAs in PBMCs and the PBMCs to SRA ratios between MetS patients and healthy controls in an occupational sample in Guangzhou. The expression level of SRA was negatively associated with MetS presence, and it was a significant predictor for MetS. Also, we found that the expression levels of cortisol and IL-6 in MetS were significantly higher compared with healthy controls. Our study also revealed that SRA in PBMCs were potential markers for diagnosing MetS, and the lymphocytes count to SRA ratio was identified to have the greatest accuracy for the diagnosis of MetS. Cortisol has the highest diagnostic sensitivity for MetS among these factors. The main limitation of our study was the number of participants.

GR has two splice variants: GRα and GRβ. GRα is the classical receptor, which is bound with GCs to regulate gene expression, and GRβ is served as an inhibitor of GRα, which can induce GC resistance [14]. Another study found that the expression level of GRα in myoblast under basal conditions was positively associated with levels of insulin resistance, BMI, percentage body fat, and blood pressure, which may be involved in the pathogenesis of the MetS [15]. But in another study, GRα mRNA was negatively correlated with BMI and triglycerides, and reduced in obesity subjects in the abdominal subcutaneous and omental depots, which is in contrast with the two former observations[16]. The role of GRα in metabolism remains unclear.

As a nuclear receptor coregulator of steroid receptors (including GR), lncRNA SRA can enhance the transcriptional activity of steroid receptors genes. lncRNA SRA

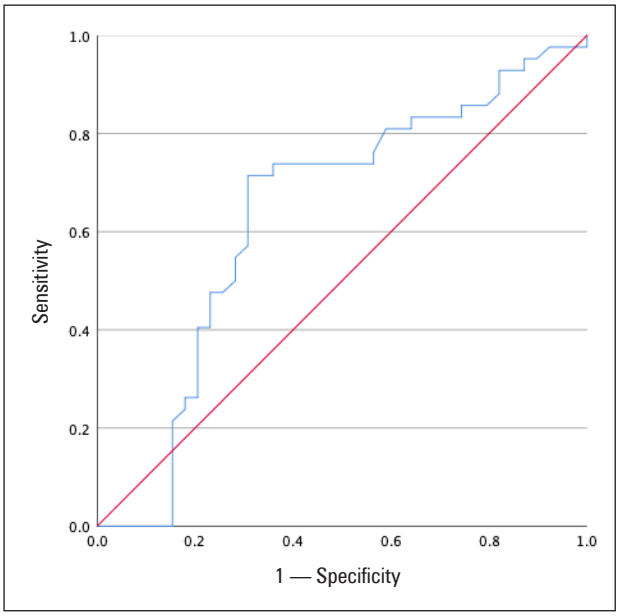

Figure 2. *Receiver operating characteristic (ROC) curve analysis of steroid receptor RNA activator (SRA) for metabolic syndrome (MetS) diagnosis. The accuracy of SRA was 0.635 (95% CI: 0.508–0.762), p = 0.036. The sensitivity and specificity were 71.4% and 69.2%, respectively. AUC — area under the curve*

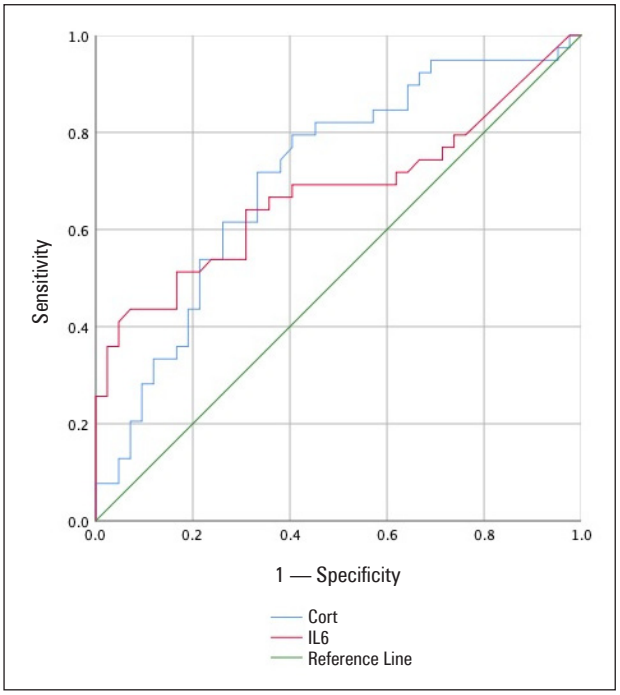

Figure 4. *Receiver operating characteristic (ROC) curve analysis of cortisol and interleukin 6 (IL-6) for metabolic syndrome (MetS) diagnosis. The accuracy of cortisol and IL-6 were 0.722 (95% CI: 0.603–0.841, p < 0.001), 0.664 (95% CI: 0.539–0.789, p = 0.011), and 0.718 (95% CI: 0.598–0.838, p < 0.001), respectively. The sensitivity and specificity of lymphocyte to SRA ratio (LTSR) were 76.9% and 71.4%, respectively. The sensitivity and specificity of monocyte to SRA ratio (MTSR) were 66.7% and 76.2%, respectively. Diagonal segments are produced by ties*

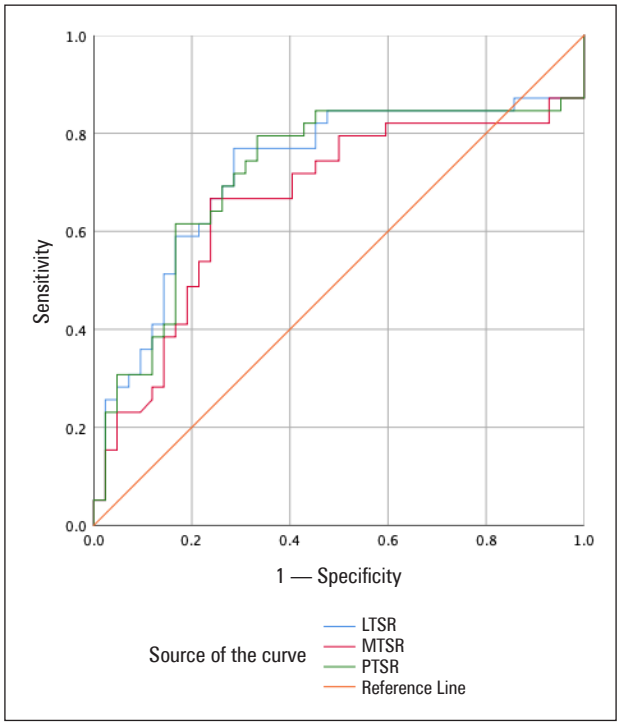

Figure 3. *Receiver operating characteristic (ROC) curve analysis of the ratios of inflammatory cells to steroid receptor RNA activator (SRA) for metabolic syndrome (MetS) diagnosis. The accuracy of lymphocyte to SRA ratio (LTSR), monocyte to SRA (MTSR), and PBMCs to SRA ratio (PTSR) were 0.722 (95% CI: 0.603–0.841, p < 0.001), 0.664 (95% CI: 0.539–0.789, p = 0.011), and 0.718 (95% CI: 0.598–0.838, p < 0.001), respectively. The sensitivity and specificity of LTSR were 76.9% and 71.4%, respectively. The sensitivity and specificity of MTSR were 66.7% and 76.2%, respectively. The sensitivity and specificity of PTSR were 79.5% and 66.7%, respectively*

coactivates GR as part of a ribonucleoprotein complex with p160 coactivators. In addition, SRA promotes GR-mediated transactivation in a ligand-dependent manner [4]. It was proven by Shannon Liu et al. that SRA gene knock-out could protect against obesity and improves glucose tolerance in high-fat-diet mice. In their study, they postulated that it might be associated with PPARγ [17]. SRA promotes adipogenesis and regulates insulin sensitivity in mouse adipocytes not only by acting as coactivator for PPARγ, but also via multiple additional mechanisms. For example, SRA can promote S-phase entry during the mitotic clonal expansion phase of adipogenesis. It can also regulate cell cycle gene expression and suppress the expression of adipocyte-related inflammatory genes. What is more, SRA can inhibit TNF-α-induced phosphorylation of c-Jun NH2-termianl kinase, which is implicated in the development of insulin resistance in mouse adipose tissue [18]. Several studies have found that SRA could regulate many inflammatory response genes such as zinc finger protein 36, toll-like receptor 4, haptoglobin, and

MCP-1. The most strongly regulated gene in this group is MCP-1, which is a macrophage-attracting chemokine highly expressed in adipose tissue. Overexpression of MCP-1 has been shown to contribute to macrophage infiltration of adipose tissue and insulin resistance. SRA may have anti-inflammatory functions within adipose tissue, which might contribute to the ability of SRA to enhance insulin sensitivity [19].

As a window, PBMCs (mostly consisting of lymphocytes) can convert psychosocial stress into cellular dysfunction and eventually contribute to the pathophysiology of lifestyle-related diseases such as DM, CVD, and atherosclerosis [11]. Chen et al. conducted a cross-sectional study on 852 participants (n = 598 with MetS and n = 254 without MetS) in southern China. They found that the severity of MetS was significantly positively associated with the WBC count, neutrophil count, and total lymphocyte count [20]. In the present study, we found that LTSR, MTSR, and PTSR can be good indicators for diagnosing MetS. It is the first time that we have investigated the relationship between SRA in PBMCs and the inflammatory cells to SRA ratios and MetS at a population level. The reasonable diagnostic accuracy of SRA and the ratios above indicate their clinical value in the diagnosis of MetS. However, well-designed prospective studies with larger sample sizes are required to validate these findings. Also, the expressions of SRA in circulation should also be detected, and the certain mechanism of SRA on GR and metabolic components need to be further identified in in vivo and in vitro levels.

Conclusion

Our findings suggest that SRA in PBMCs may play a vital role in MetS by targeting GR. What is more, the inflammatory cell to SRA ratios have demonstrated higher specificity and sensitivity in the diagnosis of MetS compared with SRA. These findings may unveil new targets for the prevention, diagnosis, and treatment of stress- and inflammation-related disorders including MetS.

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