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Mathematical Translation of Metabolic Syndrome: Assessment of siMS Score for Metabolic Syndrome and Biochemical Risks

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Abstract

Background: Metabolic syndrome over decades has undergone multiple diagnostic criteria announced by National Cholesterol Education Program (NCEP), WHO, International Diabetic Federation (IDF) and certain regional criteria. Recently, Soldatovic *et al.* have provided a mathematical model for evaluating metabolic syndrome. We aimed to compare siMS score among subjects with and without metabolic syndrome and other biochemical risks including insulin resistance. **Methods:** The study was conducted at PNS HAFEEZ hospital from July-2017 to Jan-2019. A comparative cross-sectional analysis was carried out among 232 subjects to evaluate siMS score among metabolic syndrome and those without metabolic syndrome. Pearson's correlation was performed for siMS score with other anthropometric and biochemical measures. Finally ROC curve analysis was performed to evaluate various biomarkers along with siMS score for diagnosis of metabolic syndrome. **Results:** Insulin resistance between subjects was higher among subjects with metabolic syndrome [Mean = 3.27 ± 4.45] than non-metabolic syndrome subjects [Mean = 2.10 ± 1.89] ($p = 0.012$). Differences in siMS score was higher in subjects with metabolic syndrome (Mean = 3.58 ± 0.725, N = 121) than subjects without metabolic syndrome (Mean = 2.83 ± 0.727, N = 108). AUC for various biochemical parameters was highest for sdLDL cholesterol and siMS score. **Conclusion:** siMS score has shown better performance than HOMAIR, sdLDL cholesterol, non-HDL cholesterol, HbA1c, and fasting plasma glucose in diagnosing metabolic syndrome.

Keywords

siMS Score, HOMA-IR, Metabolic Syndrome, Small Dense LDL-Cholesterol (sdLDL), Non-HDL Cholesterol, HbA1c

1. Introduction

Since the conception of the term "metabolic syndrome" various nomenclatures have been used with multiple criteria. Overtime these criteria were refined into more systematic criteria by various organizations like National Cholesterol Education Program (NCEP), World Health Organization (WHO) and International Diabetic Federation (IDF) [1] [2] [3]. Furthermore, regional criteria for labeling subjects with metabolic syndrome also appear with slight variations [4]. While being useful in many ways, there is a tangible gap between these criteria and lack of mathematically defined cut-off to unify metabolic syndrome. Recently, Soldatovic *et al.* have provided a mathematical model using parameters included in metabolic syndrome, which seems to be promising [5]. However, no local or regional study is available in literature to validate usefulness of this model in our set up.

Insulin resistance:

Why there is a need to have a simplified mathematical model in clinical practice? As highlighted above multiple criteria are there which are overlapping with slightly different cut-offs and parameters which create confusion in routine clinical practice, which may not be providing a unified diagnostic system for patients [6]. Underlying insulin resistance by using insulin-based models HOMAIR is also difficult to measure both due to cost and clinical difficulties in routine practice which makes some of the metabolic syndrome ambiguous in terms of correlation with established metabolic syndrome criteria [7]. An unmet and pushing need therefore arises to have a mathematical defined, easy to a measure and apply criteria for clinical practice.

Earlier attempts to mathematical model metabolic syndrome are also available. Gurka *et al.* have evaluated race or ethnicity specific mathematical model to predict risk in both adult and pediatric population by utilizing a "confirmatory factor analysis" in SAS program [8]. Similarly, Huh *et al.* have suggested a clinically applicable equation for continuous monitoring of metabolic syndrome risk for Korean population [9].

This study aims to evaluate the siMS scores among our sample population identified to have metabolic syndrome or otherwise as per IDF criteria and also to correlate this scoring with various biochemical risk factors including insulin resistance.

2. Methods

Study settings and design: This cross-sectional study was carried out at the

department of medicine and pathology Naval Hospital (Islamabad) in liaison with chemical pathology department at AFIP for analysis of some biochemical parameters. Referrals were also made by neighboring hospital for possible inclusion into study. The study was comparative cross-sectional and was conducted from July-2017 to Jan-2019. The study has the organizational ethical review committee approval and ensured written signed consent for all participants.

Target population & subject selection: All adults visiting hospital for executive annual medical check-up considered as target population. Patient selection was based upon the "non-probability convenience sampling" methodology. Subjects with known metabolic disorder like diabetes, hypertension, ischemic heart disease (IHD), autoimmune disorder or other acute or chronic ailments were excluded from the study. Pregnant subjects were also excluded from the study.

Sampling & general clinical examination: The study participants were requested to visit in medical fasting at the department of pathology around 08:00 to 09:00 hours from Monday to Friday. These patients were explained the medical fasting requirements along with an explanation regarding sampling strategy, purpose of research project and post-results utilization purpose of data. The subjects who finally appeared (N = 232) for study as per conditions explained to them at pathology department were fist asked to sign the written consent form. This was followed by a general history and examination to rule any signs of a chronic disease process. After this the phlebotomist collected up to 10 ml of blood from all study subjects for various biochemical parameters including fasting glucose and lipids, HbA1c and insulin in specified containers. A urine sample was collected from 171 subjects for measuring urine albumin creatinine ratio (UACR).

Clinical measurements and analysis: All anthropometric measurements were calculated as per the WHO defined criteria and Guerrero-Romero *et al.* methodology for abdominal volume index (AVI) [10] [11]. Biochemical parameters including cholesterol, triglycerides and glucose were measured by CHOD PAP, GPO PAP and GOD PAP techniques on random access clinical chemistry analyzer (Slectra ProM). HDL and LDL lipoproteins were measured using cholesterol esterase methodology on AVIDA-1800 random access clinical chemistry analyzer. HbA1c was analyzed using ion-exchange resin chromatography method. Serum insulin was analyzed using Immulite® 1000 chemiluminesence analyzer.

Outcome measures:

- Metabolic syndrome and diabetes was diagnosed as per IDF criteria, as:
  - Waist circumference ≥ 94 cm (Males) and ≥80 cm (Females), PLUS ANY OF TWO as:
  - HDLc < 1.03 mmol/L (Males) or <1.3 mmol/L (Females);
  - Triglycerides > 1.7 mmol/L;
  - Blood pressure > 130/85 mm of Hg;
  - Fasting glucose 5.6 mmol/L [12] [13].

- siMS score was calculated as per Soldatovic *et al.* formula [5], as described below:

Male:

$$\text{siMS score} = (2 \times \text{Waist/Height}) + (\text{Glucose}/5.6) + (\text{Triglyceride}/1.7) + (\text{TA}_{\text{systolic}}/130) - (\text{HDL}/1.02).$$

Female:

$$\text{siMS score} = (2 \times \text{Waist/Height}) + (\text{Glucose}/5.6) + (\text{Triglyceride}/1.7) + (\text{TA}_{\text{systolic}}/130) - (\text{HDL}/1.28).$$

- HOMA IR was calculated by the formula of Mathew's *et al.* as:

$$\text{HOMA IR} = [\{\text{Serum Insulin (mIU/L)}\} \times \{\text{Fasting Plasma Glucose (mmol/L)}\}]/22.5$$ [14].

Quality control & calibration: Internal and external laboratory testing is ensured by both external QC insurance program like "National External Quality Assurance Program Pakistan (NEQAPP)" and internal by regular monitoring and troubleshooting through Westgard's quality control rules. The usual targets for precision (%CV) and accuracy for both inter and intra batch testing are ensured on regular basis along with documentation of any error.

We lost few samples while processing and could not follow up for serum insulin (N = 4), HbA1c (N = 2), and UACR testing was only done in 174 subjects.

Statistical analysis: All data were added to Excel program and later moved to IBM-SPSS version-24. Age and gender based differences were calculated through descriptive statistics option in SPSS while the gender group wise differences between measured and calculated parameters were carried out through Independent Sample t-statistics. Independent sample t-test was used to see the differences for siMS score and insulin resistance between subjects with and without metabolic syndrome. Bivariate Pearson's correlation method between various evaluated anthropometric and biochemical risk assessment parameters. ROC curve analysis was used to measure the Area Under Curve (AUC) for various parameters in diagnosis of metabolic syndrome.

3. Results

Out of the total sample size we had 52.4% females and 47.6% males. Gender wise descriptive data is shown in Table 1 for age, anthropometric indices, biochemical measures and siMS score. Insulin resistance between study subjects is as: Metabolic syndrome subjects: Mean = 3.27 ± 4.45 and non-metabolic syndrome subjects: Mean = 2.10 ± 1.89 ($p = 0.012$) as shown in Figure 1. Figure 2 shows the differences in siMS score to be higher in subjects with metabolic syndrome (Mean = 3.58 ± 0.725, N = 121) than subjects without metabolic syndrome (Mean = 2.83 ± 0.727, N = 108) as per IDF defined criteria. Pearson's correlation between various biochemical risk predictor and siMS score suggests siMS score to be highly correlated with anthropometric, glycemic, lipid indices and insulin resistance than other parameters (Table 2). AUC for various parameters for various biochemical parameters include sdLDL cholesterol (AUC = 0.700), non-HDL

Table 1. Gender differences between subjects for various evaluated parameters.

Parameter	Gender	N	Mean	Std. Deviation	Sig. (2-tailed)*
Age (years)	Male	110	47.98	11.30	0.085
	Female	122	45.27	12.42	
Body Mass Index (BMI)	Male	110	25.98	4.83	0.001
	Female	122	28.18	5.36	
Waist to Hip Ratio (WHpR)	Male	110	0.93	0.10	0.143
	Female	122	0.94	0.06	
Waist to Height Ratio (WHtR)	Male	110	0.55	0.06	<0.001
	Female	122	0.60	0.07	
Abdominal Volume Index (AVI)	Male	110	17.48	3.72	0.087
	Female	122	18.39	4.25	
Fasting Plasma Glucose (mmol/L)	Male	110	5.86	2.61	0.127
	Female	122	5.41	1.87	
Total Cholesterol (mmol/L)	Male	110	4.54	0.59	0.173
	Female	122	4.43	0.62	
Non-HDL Cholesterol (mmol/L)	Male	110	3.63	0.58	0.009
	Female	122	3.41	0.68	
Small Dense LDL (sdLDL) as mmol/L	Male	110	0.82	0.35	0.676
	Female	122	0.80	0.35	
HbA1c (%)	Male	108	5.60	1.01	0.017
	Female	120	5.91	0.93	
Homeostasis Model Assessment for Insulin Resistance (HOMAIR)	Male	108	2.47	2.80	0.188
	Female	120	3.14	4.60	
Urine Albumin Creatinine Ratio (UACR)	Male	75	2.31	2.47	0.314
	Female	99	3.07	6.12	
siMS Score	Male	110	3.23	0.88	0.980
	Female	122	3.23	0.75	

*Independent Sample t-test.

Table 2. Correlation between non-HDL cholesterol, small dense LDL cholesterol (sdLDLc), fasting plasma glucose (FPG), homeostasis model assessment for insulin resistance (HOMA IR), urine albumin creatinine ratio (UACR) and siMS score.

		Non-HDLc	sdLDLc	HbA1c	FPG	HOMA IR	UACR	siMS score
BMI	**Pearson Correlation**	0.148*	0.076	0.185**	0.034	0.104	0.061	0.257**
	Sig. (2-tailed)	0.025	0.255	0.005	0.609	0.119	0.426	<0.001
	N	229	229	226	229	226	172	229
WHtR	**Pearson Correlation**	0.164*	0.158*	0.230**	0.102	0.205**	0.130	0.404**
	Sig. (2-tailed)	0.013	0.016	<0.001	0.125	0.002	0.088	<0.001
	N	229	229	226	229	226	172	229

Continued

	Pearson Correlation	0.214**	0.194**	0.201**	0.128	0.212**	0.073	0.429**
AVI	Sig. (2-tailed)	0.001	0.003	0.002	0.053	0.001	0.341	<0.001
	N	229	229	226	229	226	172	229
	Pearson Correlation	1	0.444**	−0.043	0.057	0.124	0.160*	0.438**
Non-HDLc	Sig. (2-tailed)		<0.001	0.518	0.392	0.062	0.036	<0.001
	N	229	229	226	229	226	172	229
	Pearson Correlation	0.444**	1	0.085	0.181**	0.145*	0.135	0.458**
SdLDLc	Sig. (2-tailed)	<0.001		0.204	0.006	0.030	0.078	<0.001
	N	229	229	226	229	226	172	229
	Pearson Correlation	−0.043	0.085	1	0.568**	0.312**	−0.016	0.410**
HbA1c	Sig. (2-tailed)	0.518	0.204		<0.001	<0.001	0.838	<0.001
	N	226	226	226	226	223	172	226
	Pearson Correlation	0.057	0.181**	0.568**	1	0.514**	0.217**	0.675**
FPG	Sig. (2-tailed)	0.392	0.006	<0.001		<0.001	0.004	<0.001
	N	229	229	226	229	226	172	229
	Pearson Correlation	0.124	0.145*	0.312**	0.514**	1	0.000	0.507**
HOMAIR	Sig. (2-tailed)	0.062	0.030	<0.001	<0.001		0.997	<0.001
	N	226	226	223	226	226	171	226
	Pearson Correlation	0.160*	0.135	−0.016	0.217**	<0.001	1	0.214**
UACR	Sig. (2-tailed)	0.036	0.078	0.838	0.004	0.997		0.005
	N	172	172	172	172	171	172	172

*p-value < 0.05. **p-value < 0.01.

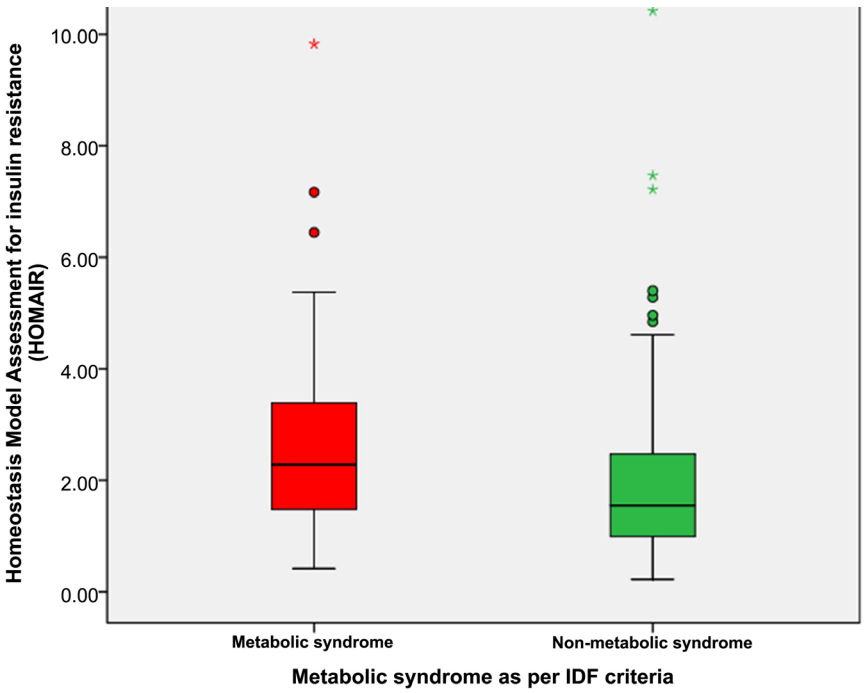

Figure 1. Differences in HOMAIR in subjects with and without metabolic syndrome (p = 0.012).

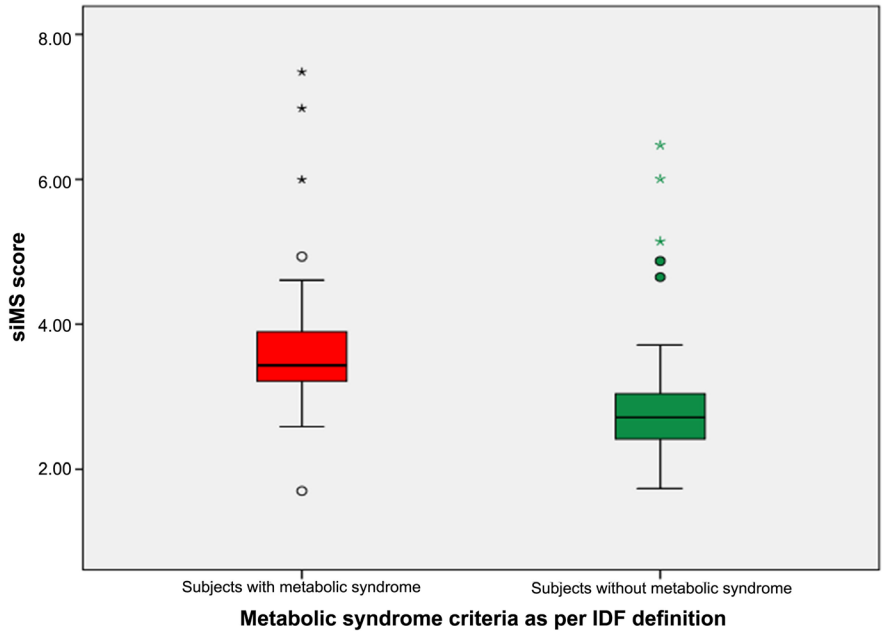

Figure 2. Differences in siMS score in subjects with and without metabolic syndrome ($p < 0.001$).

cholesterol (AUC = 0.647), HbA1c (AUC = 0.644), Fasting plasma glucose (AUC = 0.698), HOMA IR (AUC = 0.629) and siMS score (AUC = 0.866) as depicted in **Figure 3**.

4. Discussion

siMS score appeared promising in terms of mathematical translation of data from various risk biomarkers included in the definition of metabolic syndrome. Our study also confirmed that this mathematical scoring method is highly correlated with insulin resistance along with demonstrating highest area under the curve for diagnosing metabolic syndrome. Using such an index can help add to diagnostics along with its application as a measurable tool to assess the overall improvement or further worsening of the disease in a patient's prognostic monitoring. While being a simple mathematical number, it can provide the combined data from components of metabolic syndrome to simply patient management. However, Soldatovic *et al.*'s as we demonstrated seems to be very useful and in this regard there are few studies which support its use in clinical care [5]. Vukovic *et al.* have evaluated this method in pediatric population with slight modifications to conclude it as an accurate and practical measure in diagnosis of metabolic syndrome in children and adolescence [15]. Similarly, another pediatric study "the CASPIAN-V study" have also highlighted the practical usefulness in both clinics and research programs after comparing it with various principal component analysis, confirmatory component analysis and z-scores [16].

Provided clinical utility some researchers have highlighted some issues which may not be specific to siMS score, but still needs to be highlighted while using siMS score as a biomarker for metabolic syndrome. Srećković *et al.* have shown

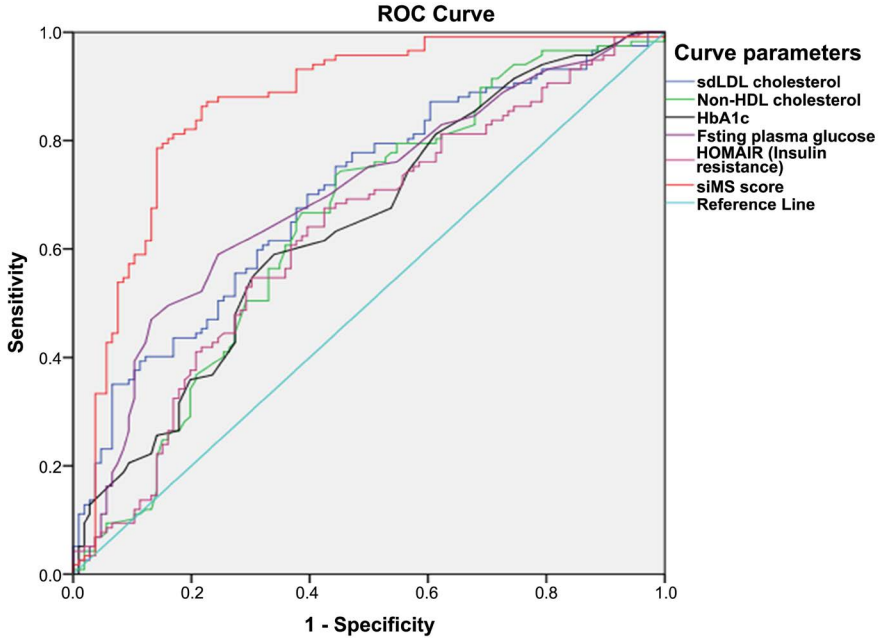

Figure 3. Receiver operating curve (ROC) curve analysis showing area under curve (AUC) for siMS score, HOMAIR, Fasting plasma glucose, HbA1c, non-HDL cholesterol and small dense LDL cholesterol (sdLDLc).

that certain acute phase reactants and cardiovascular disease (CVD) indicators like C-Reactive protein (CRP), Fibrinogen, acidum uricum, Apo-B lipoprotein and homocysteine can confound the siMS score risk prediction [17]. Furthermore Sebekova *et al.* have shown that real-time application of siMS score may label some of the subjects without criterion defined metabolic syndrome to have numerical results falling in the range of metabolic syndrome, thus can result in some false positive cases [18]. However, in the opinion of authors we agree with these later findings as metabolic risk clustering with emerging evidence is ever evolving field and more and newer CVD biomarkers depictive of underlying inflammation and atherosclerotic plaque behavior are now entering clinical market [19]. Moreover, the role of genetics and epigenetics in the absence or presence of metabolic syndrome label, as per the newer evidence is probably more informative in risk prediction than simply quantifying biochemical risk predictor [20] [21].

The study has few limitations. The authors attempted to replicate the use of siMS score in our population; however our sample size was small and the study was hospital based so a larger study in an epidemiological set up may be carried out for validating the siMS score equation for primary care set up. Moreover, as per the findings of Sebekova *et al.* we feel metabolic syndrome could have multifactorial etiology beyond what we have included in our study which thus raises the need of other factors which could lead to false negative low siMS score in the presence of a metabolic syndrome. Clinical assessment therefore must be personalized and this consideration must remain in the mind of treating physicians.

The study has significant clinical implications: The authors consider the use of

siMS score evaluation could provide a real-time assessment model for primary care physician who can not only use this equation as "Rule In" investigation for metabolic syndrome, which can also be used to monitor the treatment and assessment of prognosis for patients. Furthermore the mathematical equation may also be incorporated in hospital information system so as to calculate by the IT system to allow its simplistic application for both patients and physicians.

5. Conclusion

siMS score has shown better performance than HOMAIR, sdLDL cholesterol, non-HDL cholesterol, HbA1c, and fasting plasma glucose in diagnosing metabolic syndrome. Furthermore, the siMS score equation has moderate to high correlation with most of the anthropometric, biochemical and hormonal risk factors.

Declarations

Ethical approval: The study "Mathematical translation of metabolic syndrome by using siMS score: Assessment of siMS score for metabolic syndrome and biochemical risks" was formally approved by hospital's ethical review committee.

We confirm that our research work conforms to "World Medical Association's Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects"

Signing of inform consent by participants: All subjects were required to sign the written informed consent before inclusion into study program. All included subjects were explained about the research requirements and use of data along with confidentiality issues.

Availability of SPSS data & outputs: Subject data can be provided on formal request.

Author's Contributions

SHK: (Author for correspondence) Study idea, study conceptualization, Diagnostic lab analysis, Manuscript writing, Study finalization. **ARK:** Study sampling, analysis of data, manuscript writing. **AH:** Patient selection, examination, referrals, data output (SPSS) analysis, data analysis and manuscript writing. **RA:** Clinical evaluation of patient, statistical methods application & analysis, manuscript writing. **RS:** Sampling collection, data analysis, contribution to manuscript write up. **TC:** Overall study coordination, medical writing, study finalization. All study authors approved the final manuscript version and agreed to all aspects of contents.

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Conflicts of Interest

Authors have no competing interests to announce.

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Abbreviations

Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), siMS Score, Small Dense Low Density Lipoprotein Cholesterol (sdLDLc), Urine Albumin Creatinine Ratio (UACR), Body Mass Index (BMI), Waist to Hip Ratio (WHpR), Waist to Height Ratio (WHtR), Abdominal Volume Index (AVI)