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Longitudinal Assessment of Utility and Cut Points of Lipid Ratios in Metabolic Syndrome Prediction: the Isfahan Cohort Study

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Abstract

Introduction: Finding simple tools for prediction of metabolic syndrome (MetS) is of high interest. Role and predictive value of lipid profile in MetS prediction is still controversial. The current study aimed to compare ability of lipid ratios in prediction of MetS and also to determine cut points using longitudinal data framework in Iranian population. Materials and Methods: We studied 3212 participants of age > 35 years followed for 12 years with 3 visits at baseline, year 6 and year 12 in Iranian adults. Predictive power and optimal cut points of lipid ratios were evaluated using receiver operating characteristic (ROC) curve analysis. We also considered missing data modelling to account for cohort attrition. Results: Of total sample, 1015 (38.2%) individuals had MetS in year 6 that increased to 1288 (40.1%) in year 12. TG/HDL-C was the best predictor of MetS with AUC of 0.88 and 0.87 for 6 and 12 years of follow up. Optimal cut point in 6 and 12 years of follow-up were, respectively, 2.83 and 3.35 for TG/HDL-C, 4.22 and 4.66 for TC/HDL-C and 2.88 and 2.73 for LDL-C/HDL-C. Conclusion: lipid ratios are simple and commonly measured in primary care and could help in identifying individuals with high risk of MetS and reduce related complications and costs. Large-scale multi-ethnic studies are needed to assess generalizability of the results.

Key words: Metabolic syndrome, Lipid profile, Triglyceride, ROC curve, missing data

Introduction

Early diagnosis of metabolic syndrome (MetS) could help to reduce incidence of subsequent conditions and related costs. It is highly desirable to find simple and inexpensive methods for MetS prediction and identifying high-risk individuals using information available in primary care. Assessing single criteria such as waist circumference (WC) is more feasible than evaluating cluster of factors (Ohkubo et al., 2006; Gasevic et all., 2014). However, assessing these measures is not common in primary care and the interest revolves around the utility of routinely recorded measures. Lipid profile and ratios thereof that are examined in primary setting, have attracted great

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attention in prediction of cardiovascular events, diabetes, hypertension, chronic kidney disease and MetS (Gasevic et al., 2014; Ridker et al., 2005; Squillace et al., 2016; Kimm et al., 2010; Wen et al., 2017). The use of various lipid ratios such as TG/HDL-C, TC/HDL-C, LDL-C/HDL-C and non-HDL-C/HDL-C in MetS prediction has been suggested in the literature (Cordero et al., 2008; Kim et al., 2013). However, most of previous research are cross-sectional and this could introduce biases to the estimates. Furthermore, finding optimal cut-off points of lipid ratios in MetS prediction is still controversial (Gasevic et al. 2014; Cordero et al., 2008).

Variables are sometimes assessed repeatedly or longitudinally over time and the effect of their changes could be incorporated into the estimates. The utility of such models has been documented in various fields of medicine including diabetes (Jafari-Koshki et al., 2016; Jafari-Koshki et al., 2018).

However, longitudinal data are often incomplete due to either dropping a patient out of the study or due to missed visits. A common approach for handling incomplete longitudinal data is to exclude participants with missing data and restrict analysis to data from completers, i.e. those for whom all measurements are available (Afshari Safavi, Kazemzadeh Gharechobogh and Rezaei, 2015). This approach ignores 'informative missingness', where the value of an unmeasured variable has direct impact on its missingness. That is, a patient may refrain from a visit because of improvement or deterioration in his health status. Effect estimates obtained from complete-case analysis may be biased (Twisk J, de Vente, 2002; Fitzmaurice et al., 2008). Two analysis approaches of 'selection modelling' and 'pattern mixture' (PM) modelling have been introduced for analyzing longitudinal data with informative missingness (Little and Rubin, 2014). Recently, there has been considerable interest in PM models due to its interesting features (Liew, 2016; Post et al., 2010).

This study was conducted to evaluate the efficacy of lipids ratios and to find their optimal cut-off points in MetS prediction in Iranian adult population followed over 12 years in the Isfahan Cohort Study (ICS). The effect of missing values on the parameter estimates was also evaluated.

Materials and Methods

Participants and measurements

In this paper, we used data from participants of the Isfahan Cohort Study (ICS), a longitudinal population-based study of adults aged >35 years, living in urban and rural areas of three counties in central Iran (Sarrafzadegan et al., 2011). The ICS commenced in 2001 to evaluate impact of various risk factors on the incidence of cardiovascular events. All participants signed written informed consent before inclusion in the study. Ethical approval was obtained from the Ethics Committee of Isfahan Cardiovascular Research Center, a World Health Organization collaborating center.

Information on demographic characteristics, medical history, lifestyle behaviors including smoking, physical activity and dietary behavior and other risk factors were recorded for all participants. Self-report data on smoking status (current smokers/non-smokers), physical activity (mean hours per week) and dietary behavior of the Global Dietary Index (GDI) were recorded by using questionnaires (Roohafza et al., 2013). Participants were classified into four categories of body mass index (kg/m^2) as underweight (BMI<18), normal weight (BMI: 18-24.9), overweight (BMI: 25-29.9) and obese (BMI $\geq$ 30). Measurement of blood pressure was carried out following standard protocols and using calibrated instruments described elsewhere (Sarrafzadegan et al., 2011). Serum high-density lipoprotein-cholesterol (HDL-C) was determined after precipitation of low-density and very low-density lipoproteins with dextran sulfatemagnesium. Serum low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedwald equation. Fasting blood glucose (FBS), triglycerides (TG) and serum total cholesterol (TC) were measured enzymatically using an autoanalyzer (Eppendorf, Hamburg, Germany) (McNamara and Schaefer, 1987; Warnick, Benderson and Albers, 1982; Friedewald, Levy and Fredrickson, 1972). According to NCEP ATP III criteria, metabolic syndrome is defined as having at least three of the following criteria: i) waist circumference>102cm in men and >88 cm in women, ii) serum triglyceride>150mg/dl, iii) HDL-C<40 mg/dl in men and <50 mg/dl in women, iv) FBS>110 mg/dl, and v) Blood pressure>130/85 mmHg.

All variables were measured at baseline in 2001 and at 6 and 12 years of follow up. Some participants had missing values on one or both follow up measurements.

Statistical analysis

Descriptive statistics were expressed as mean ± SD (standard deviation) and n (%). The association of lipid ratios with the risk of MetS was determined using generalized linear model (GLM) with logit link function after adjusting for sex, age, BMI, smoking status, physical activity and global dietary index (GDI). The linear association was examined using the Jonckheere-Terpstra trend test. Receiver operating characteristic (ROC) curve analysis was performed to determine the appropriate cut-off points. Optimal values of lipid ratios

were estimated by the maximum value of Youden index (Schisterman et al., 2005). Positive predictive values (PPV) and negative predictive values (NPV) were also presented.

In this study, there was a fairly high rate of missingness in MetS measurements that deletion of corresponding individuals from the analysis could lead to biased estimates and reduction in the study sample size and power (Afshari Safavi et al., 2015). Furthermore, using generalized linear mixed model is valid only when the missing data are missing at random. This means that the mechanism of the missingness must be independent of the unobserved values (Fitzmaurice et al., 2008). In PM models, the contribution of missing data to the outcome is evaluated by including missing data patterns as a predictor in the model (Fitzmaurice et al., 2008). By definition, first, subjects are divided into groups depending on their missingness patterns and then multiple imputation was performed for each pattern by a GLM separately. For more detail see (Little and Rubin, 2014). GLM and PM models were fitted in R software version 3.3.3 using the glm and mice packages. Models were compared using Akaike information criterion (AIC). A p-value < 0.05 was considered statistically significant.

Results

Of 3212 participants included in the study, 1015 (38.2%) had MetS at 6 years from baseline, that increased to 1288 (40.1%) in year 12. There was 24.5% missing observations for MetS during follow-up, 34.6% of participants had available data on MetS at all three visits. Also, there were 17.2% and 56.5% missing subjects in year 6 and 12, respectively. The prevalence of obesity was 24.6 % at the beginning that increased to 70.3 % in year 12. Table 1 shows descriptive statistics of study participants in each visit.

Table 1. Characteristics of study participant at each time point described as n(%) and mean±SD

Variables	Baseline	6^{th} year	12^{th} year
MetS			
Yes	0 (0)	1015 (38.2)	559 (40.1)
No	3212 (100)	1644 (61.8)	834 (59.9)
Sex			
Female	1547 (48.2)	1547 (48.2)	1547 (48.2)
Male	1665 (51.8)	1665 (51.8)	1665 (51.8)
Smoke			
Yes	736 (22.9)	707 (22)	681 (21.2)
No	2476 (77.1)	2505 (78)	2531 (78.8)
BMI (kg/m^2)			
<18	61 (1.9)	43 (1.3)	25 (0.8)
18-24.9	1138 (35.4)	803 (25.0)	370 (11.5)
25-29.9	1294 (40.3)	1132 (35.2)	583 (18.2)
≥ 30	719 (22.4)	1234 (38.5)	2234 (69.5)
Age	49.06±10.55	55.06±10.55	62.06±10.55
GDI	1.10±0.25	0.93±0.28	0.89±0.32
Physical activity	15.24±9.09	13.04±11.46	13.03±10.67
Lipids (mmol/L)			
TC	210.07±49.46	214.11±44.12	201.01±40.21
TG	178.46±101.06	165.24±108.26	153.49±94.65
HDL-C	48.38±10.29	46.59±11.30	44.13±10.36
LDL-C	126.91±42.05	123.79±29.88	111.98±27.39
Lipid ratios			
TG/HDL-C	3.85±2.31	4.04±3.78	3.86±3.37
TC/HDL-C	4.48±1.22	4.82±1.43	4.72±1.17
LDL-C/HDL-C	2.73±1.04	2.78±0.84	2.63±0.73

MetS = metabolic syndrome; BMI = body mass index; GDI = global dietary index; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

Fig. 1 shows the association between lipid ratios and incidence rate of MetS in the follow-up based on the data from the first visit in 2001. Incidence of MetS was significantly increasing in both follow-up points for TG/HDL-C (p-trend=0.004 in 2006 and p-trend=0.005 in 2012) and TC/HDL-C (p-trend=0.001 in 2006 and p=0.002 in 2012). However, the association was positive and moderately significant for ratio of LDL-C/HDL-C (p=0.051 in 2006, p=0.051 in 2012).

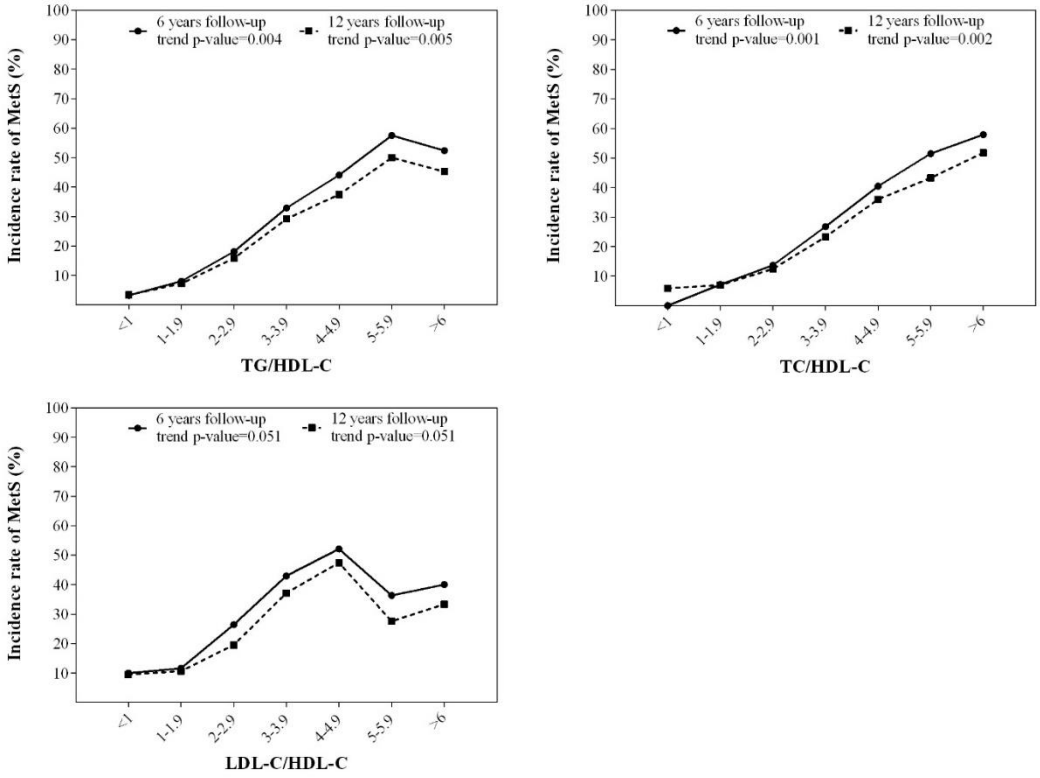

Figure 1: Association between incidence rate of metabolic syndrome and lipid ratios in 6 and 12 years of follow-up.

Diagnostic utility and cut-off values for lipid ratios from PM and GLM methods are compared in Table 2. The PM model had a better fit than GLM, both for 6 years (AIC=2642.30 vs. 2708.67) and 12 years (AIC=3324.11 vs. 3561.26) in the follow-up. The ROC curves for PM model are shown in Figure 2. The TG/HDL-C had the highest prediction ability for both follow-up time points with AUC=0.88; 95% CI= [0.86, 0.90] and AUC=0.87; 95% CI= [0.84, 0.92], respectively.

Table 2. Receiver operating characteristic (ROC) curve analysis in metabolic syndrome prediction.

Variables	GLM		PMM	
	6 years follow-up	**12 years follow-up**	**6 years follow-up**	**12 years follow-up**
TG/HDL-C				
AUC	0.882 (0.869-0.894)	0.851 (0.831-0.872)	0.884 (0.866-0.902)	0.870 (0.849-0.925)
Cut-off	>2.08	>2.63	>2.83	>3.35
Sensitivity	0.679 (0.649-0.707)	0.636 (0.593-0.676)	0.688 (0.644-0.727)	0.676 (0.579-0.759)
Specificity	0.889 (0.872-0.904)	0.875 (0.851-0.896)	0.889 (0.865-0.909)	0.876 (0.815-0.920)
PPV	0.794 (0.765-0.820)	0.764 (0.721-0.802)	0.792 (0.751-0.829)	0.781 (0.682-0.856)
NPV	0.815 (0.796-0.833)	0.791 (0.763-0.817)	0.821 (0.794-0.844)	0.805 (0.739-0.858)
TC/HDL-C				
AUC	0.846 (0.831-0.860)	0.789 (0.764-0.813)	0.848 (0.827-0.868)	0.824 (0.787-0.862)
Cut-off	>4.35	>4.71	>4.22	>4.66
Sensitivity	0.635 (0.604-0.664)	0.574 (0.531-0.616)	0.679 (0.641-0.714)	0.678 (0.583-0.761)

Specificity	0.855 (0.837-0.872)	0.828 (0.800-0.852)	0.857 (0.830-0.879)	0.843 (0.831-0.882)
PPV	0.734 (0.704-0.763)	0.679 (0.634-0.722)	0.741 (0.709-0.772)	0.723 (0.645-0.789)
NPV	0.788 (0.768-0.807)	0.754 (0.724-0.781)	0.790 (0.763-0.817)	0.782 (0.728-0.826)
LDL-C/HDL-C				
AUC	0.815 (0.799-0.831)	0.765 (0.739-0.790)	0.822 (0.800-0.844)	0.790 (0.749-0.832)
Cut-off	>3.20	>2.06	>2.88	>2.73
Sensitivity	0.592 (0.561-0.622)	0.543 (0.500-0.586)	0.635 (0.597-0.672)	0.599 (0.522-0.670)
Specificity	0.836 (0.816-0.853)	0.811 (0.782-0.836)	0.808 (0.781-0.833)	0.824 (0.770-0.865)
PPV	0.694 (0661-0.724)	0.646 (0.599-0.689)	0.707 (0.667-0.743)	0.689 (0.606-0.756)
NPV	0.765 (0.744-0.785)	0.737 (0.707-0.764)	0.754 (0.725-0.780)	0.761 (0.706-0.806)

AUC= area under curve; PPV= Positive predictive value; NPV= Negative predictive value;
Results are adjusted for sex, age, BMI and behavioral risk factors.

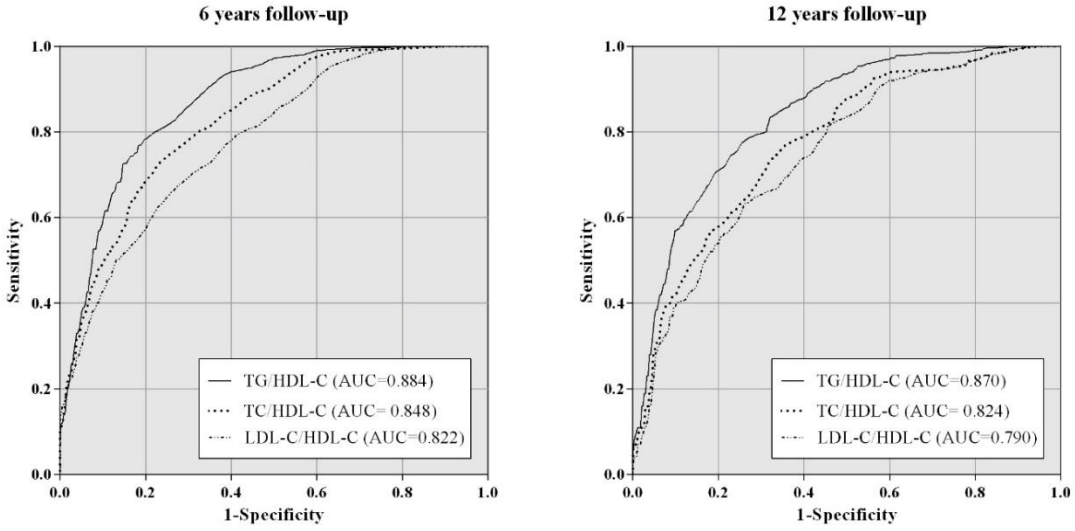

Figure 2: Receiver operating characteristic (ROC) curves of lipid ratios in metabolic syndrome prediction in 6 and 12 years of follow-up

Based on GLM, the optimal cut-off points in MetS prediction in 6 and 12 years of follow-up were, respectively, 2.08 and 2.63 for TG/HDL-C, 4.35 and 4.71 for TC/HDL-C, and 3.20 and 2.06 for LDL-C/HDL-C. The AUC values for TG/HDL-C, TC-HDL-C, and LDL-C/HDL-C were not significantly different between GLM and PM model. Using PM model in the 6 years of follow-up, TG/HDL-C had 0.68 and 0.88 of sensitivity and specificity for optimal cut-off point of 2.83, whereas these were 0.67 and 0.87 for optimal cut-off point of 3.35 in the 12 years of follow-up.

Discussion

In this study, we examined usefulness and optimal cut-off point of lipid ratios in MetS prediction in the framework of longitudinal data analysis with missing values.

After adjusting for sex, age, BMI and behavioral risk factors, compared to other lipid ratios, TG/HDL-C was found to be a better marker in MetS prediction. This is consistent with reports from other populations (Gasevic et al., 2014; Cordero et al., 2008; Kawamoto et al., 2011). In our study, the sensitivity of lipid ratios for predicting MetS was relatively less than those reported in cross-sectional studies and decreased for longer times. In a cross sectional study, the AUC for TG/HDL-C was 0.86 in men and 0.87 in women, both relatively less than the estimated AUC in 6 years of follow-up in our (Gasevic et al., 2014). In another study, estimated AUC for TG/HDL-C was 82% in men and 84% in women (Kawamoto et al., 2011). A study in Spain reported a sensitivity of 78% in men and 80% in women for TG/HDL-C. Another study in Canadian population, the sensitivity of TG/HDL-C was 84% for men and 70.2% for women. However, a recent study in South Asian population reported that the TG/HDL-C may not be a reliable risk marker for MetS (Gasevic et al., 2012).

To the best of our knowledge, this is the first study to explore the usefulness of lipid ratios and determine cut-off points for predicting MetS in longitudinal data framework. The cut-off point for TG/HDL-C was higher than previously reported estimates. In an earlier study, cut-off value of reported a TG/HDL-C value of 2.75 and 1.65 in diagnosing MetS among Spanish men and women (Cordero et al., 2008); Cut-off point of 1.62 for men and 1.18 for women have also been reported (Gasevic et al., 2014). Whilst, we have observed a similar cut-off points for TC/HDL-C and LDL-C/HDL-C, it seems that cut points for TG/HDL-C may vary between populations (Ohkubo et al., 2006;Cordero et al., 2008; Kawamoto et al., 2011).

In the present study, using PM model with multiple imputation led to more accurate estimates of cut-off points than. However, the standard error estimates from PM model tended to be slightly larger than GLM, implying that the results should be interpreted with caution.

Conclusions

Incidence and prevalence of MetS is increasing in developing and developed countries. The impact of MetS on subsequent conditions underscores the importance of its prediction and timely diagnosis using data available from routine care. Lipid ratios show significant association with risk of MetS and in this longitudinal study, TG/HDL-C appeared to be a better predictor of MetS. However, usefulness and efficient cut-off point of various lipid ratios may vary among populations. Conducting large-scale studies with multiethnic groups could help to obtain more accurate and specific estimates and provide simpler screening tool in MetS prediction and prevention.

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