A logistic regression model for microalbuminuria prediction in overweight male population

BaoDe Chen[1], WeiYi Xu[1], Yu Chen[1], ZhenYun Ni[2], XueFen Li[1], DaWei Cui[1].

[1]Department of Laboratory Medicine, The First Affiliated Hospital of Medical College, Zhejiang University, People's Republic of China and [2] Department of Endocrinology, The First Affiliated Hospital of Medical College, Zhejiang University, People's Republic of China

Correspondence: Yu Chen, Department of Laboratory Medicine, The First Affiliated Hospital of Medical College, Zhejiang University, People's Republic of China. Fax: 086-0571-87236383, Tel: +86 571-87236383. E-mail: chenyyu@hotmail.com

ABSTRACTS

Background: Obesity promotes the progression to microalbuminuria and increases the risk of chronic kidney disease. Current protocols of screening microalbuminuria are not recommended for the overweight or obesity.

Design and Methods: A cross-sectional study was conducted. The relationship between metabolic risk factors and microalbuminuria was investigated. A regression model based on metabolic risk factors was developed and evaluated for predicting microalbuminuria in the overweight or obesity

Results: The prevalence of MA was reached up to 17.6% in Chinese overweight men. Obesity, hypertension, hyperglycemia and hyperuricemia were the important risk factors of microalbuminuria in the overweight. The area under ROC curves of the

regression model based on the risk factors was 0.82 in predicting microalbuminuria, meanwhile, a decision threshold of 0.2 was found for predicting microalbuminuria with sensitivity 67.4% and specificity 79.0%, global predictive value of 75.7%; a decision threshold of 0.1 was chosen for screening microalbuminuria with sensitivity 90.0% and specificity 56.5%, global predictive value 61.7%.

Conclusions: The prediction model was an effective tool for screening microalbuminuria by using routine data among overweight populations.

Key Words: metabolism, obesity, microalbuminuria, chronic kidney disease, regression model

Introduction

Overweight or obesity is dramatically increasing in its incidence and prevalence, and has become a worldwide public health problem.[1] The overall prevalence of overweight and obesity has increased to 53.4% in middle-aged and senior Chinese people.[2] Obesity is important in the genesis of diabetes mellitus, hypertension and cardiovascular disease, all of which increase the risk of chronic kidney disease (CKD).[3] Recently, there is a growing evidence that obesity itself significantly increases CKD and accelerates its progression.[4, 5] As a result, the absolute number of CKD may be disturbing among overweight or obese populations. Unfortunately, many overweight individuals are unaware of having CKD. So early screening of CKD for the overweight may be necessary.

Microalbuminuria(MA) is the earliest sign of CKD and is a predictor of the progression of CKD to the end-stage renal disease(ESRD).[6] Currently, several screening strategies for detection of CKD have been proposed in the diverse population. For example, screening MA for all individuals with diabetes has been recommended by several international organizations.[7, 8] It is also advocated to screen MA for people with hypertension and old.[8-10] However, few recommendations have been present for the overweight. In this context, a routine, economical but comprehensive method to predict MA would be helpful to promote early awareness and better management of CKD among the overweight population.

On the other hand, evidence from clinical studies indicated that metabolic disorder is already present at an early phase of renal damage. Those metabolic factors have been implicated in the pathogenesis of chronic kidney disease and some of them can be virtually used to estimate the risk of renal damage.[11] For instance, high serum triglyceride(TG) and low high-density lipoprotein cholesterol(HDL-C) levels predict an increased risk of renal damage.[12] In addition, elevated levels of blood pressure(BP), extra large abdominal circumference, and high plasma glucose level have been associated with an increased prevalence of both MA and CKD.[13] Given the relative ease of measuring body mass index(BMI), fasting plasma glucose(FPG), BP, and lipid concentrations, and also their importance as risk factors of MA and CKD, we attempted to develop a logistic regression model based on these measurements to

identify individuals who not only have MA but also at greatest risk for CKD.

Design and Methods

Subjects The subjects were recruited from healthy volunteers who have participated in the health survey project launched in 2009. Participants used a self-report questionnaire to document the medical history, current medication, family history, clinical symptoms after they had an intimate knowledge of our study program. Participants who have cardiovascular disease, chronic kidney disease and chronic liver disease were excluded. The final study subjects have no clinically significant abnormalities and were not taking any medication known to affect renal function or lipid/glucose metabolism (such as corticosteroids and lipid/glucose-lowering drugs).This study was approved by the Ethics Committee of Medical College of Zhejiang University, and a written informed consent was obtained from each participant.

Laboratory Methods A physical examination and collection of laboratory samples (a fasting blood specimen, spot morning urine specimen) were carried out at the healthcare center of the First Affiliated Hospital of Zhejiang University. Weight and height were measured without shoes or heavy clothing using an anthropometric scale. BMI was calculated. The subjects with BMI of 25 kg/m^2 or greater, classified as overweight or obese by World Health Organization criteria,[14] were informed to collect 24-h urine of the next day and record the urine volume. BP was measured twice with

the subject seated for at least 10 minutes using a mercury sphygmomanometer. The mean of two measurements was recorded. Fasting blood sample was drawn in a vacuum tube. Spot morning urine sample was collected and immediately checked with a microscope. All samples of blood and urine collection were centrifuged within 2h and immediately frozen to −70°C. The biochemical indices such as serum creatinine(sCr) and urine creatinine(uCr), blood urea nitrogen(BUN), blood uric acid(BUA), total cholesterol(TC), FPG, TG and HDL-C were measured by a biochemical auto-analyzer (Hitachi 7600, Japan). Glomerular filtration rate(GFR) was estimated by modified MDRD equation based on Chinese population.[15] The equation is as follows: eGFR (ml/min per 1.73 m^2) =186× $Pcr^{-1.154}$ ×$age^{-0.203}$× 0.742 (if female) ×1.233 (if Chinese). Urine albumin was measured in a Beckman analyzer (Beckman Image, USA) by rate nephelometry.

Variable definitions MA was defined as urine albumin extraction(UAER)of 30 -300mg in a 24 h urine collection, urine albumin(UAlb) 20-200mg/dl in a single spot urine sample, or urine albumin/Creatinine ratio(UACR) of 20-200 mg/g for men in a single spot urine sample. These thresholds are recommended by KDIGO for detection of albuminuria.[16] According to International Diabetes Federation(IDF),[17] metabolic syndrome(MS) is defined as central obesity plus any two of the following: BP>=130/85mmHg; FPG>=5.6mmol/L; TG>1.7mmol/L; HDL-C <1.0mmol/L in men or <1.3mmol/L in women. In the present study, central obesity was defined as BMI>=25, instead of waist circumference.

Statistic analysis:

The subjects were divided into two groups, namely the normalbuminuria and the microalbuminuria. The Student's *t* test was used to compare the differences between the two groups for continuous variables. The relationship of MA with demographic and metabolic variables was analyzed by univariate and multivariate logistic regression, and the odds ratios (OR) and confidence intervals (CI) for increased risk of MA were calculated. A forward stepwise multivariate logistic regression analysis was used to build the model for predicting the risk of MA. Meanwhile, the probabilities generated from the regression model were saved and used as new input variables to meet the requirement of receiver operating characteristic (ROC) curve analysis. UAER was used as the standard method to generate binomial variables. In order to evaluate the performance of the model predicting MA, the ROC curves of lipids ratio, eGFR, UAlb, UACR and the final model were generated, respectively, and their areas under ROC curve were compared with each other. In addition, the ROC curves were used to identify the optimal decision threshold through the Youden index. Sensitivity, specificity, positive predictive value, negative predictive value and global predictive value for the thresholds chosen were calculated. Analysis was performed using SPSS software version 15.0 (SPSS Inc. Chicago, IL). All P-values were 2-sided and a *p*-value of <0.05 was considered as statistical significance.

RESULTS

Baseline characteristics of study subjects

The study subjects consisted of 245 individuals classified as overweight or obesity. All participants were adult men with a mean age (±SD) of 44±13y (range, 20 to 76y) and a mean BMI (±SD) of 26.1±2.1kg/m^2 (range, 24.5 to 40.2 kg/m^2). Participants were divided into two groups according to the status of albuminuria, namely normalbuminuria and microalbuminuria. No macroalbuminuria was included. The demographic and metabolic characteristics of the participants are detailed in Table 1. The prevalence of MA in the overweight or obesity was 17.6% (43/245). The participants' BMI, systolic pressure(SP), diastolic pressure(DP), FPG, TG, TC, BUA, uCr, UAlb, UACR and UAER differed significantly, while their age, HDL-C, LDL-C, TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, BUN, sCr and eGFR were no statistically different between the two groups.

The prevalence of abnormal metabolic components among overweight population

Figure 1 shows the prevalence of components of MS, defined by the IDF criteria, among overweight population. Abnormal metabolism was highly prevalent in the overweight population. Of the subjects, 45.7% had hypertension, 18.2% had hyperglycemia, 57.6% had high TG and 40% had low HDL-C, and the prevalence of MS was 48.2%.

Univariate and multivariate relationships between metabolic risk factors

with MA

In univariate logistic regression analysis, MA was associated with BMI, systolic and diastolic BP, FPG, BUA, TG and TC concentrations (Table 2); age, BUN, sCr, eGFR, HDL-C and LDL-C concentrations were not correlated with MA. However, in multivariate logistic regression analysis, only BMI, FPG, SP and BUA were associated with the increased prevalence of MA, the other markers did not persist as independent risk factors of the increased prevalence of MA(Table 2). Among them, FPG was the strongest and independent risk factor.

Development of the regression model for predicting MA

Table 3 shows the results of the stepwise logistic regression analysis for the subjects. There were 4 variables used in the final prediction model, namely BMI, SP, FPG and BUA. Adjusted OR values of them were 1.30, 1.05, 3.22 and 1.01, respectively. Based on β regression coefficient of each variable, the Logistic regression equation was developed as follows:

$$p = 1/[1+e^{-(-23.27+0.26*BMI+0.05*SP+1.17*FPG+0.01*BUA)}]$$

In this equation, p is the probability that a person is predicted to have MA, given independent variables BMI, SP, FPG and BUA. The corresponding regression coefficients of these variables were 0.26, 0.05, 1.17 and 0.01, respectively. Given BMI=25, SP=130, FPG=5.6 and BUA=420, the response variable p is then equal to 0.62, which indicates the person has about 62% chance of having MA. Traditionally, the logistic regression probability is given the default classification decision threshold

of 0.5, it is diagnosed as positive when the probability is greater than 50%.

Comparison of areas under the ROC curves of lipids ratio, UAlb, UACR and the regression model in predicting MA.

We performed ROC curves analysis for the regression model, UAlb, UACR and potential prediction markers (lipids ratio) in predicting MA. Their ROC curves were illustrated in Figure 2. Table 4 presents the areas under the ROC curves (AUC) of lipids ratio, UAlb, UACR and the regression model in predicting MA. According to a rough guide for classifying the accuracy of a diagnostic test, an area of 0.8-0.9 represents a good test; 0.7-0.8 represents a fair test; 0.6-0.7 represents a poor test. In this study, the AUC of UAlb, UACR and the regression model were 0.87, 0.94 and 0.82, respectively, all represented good tests, while the AUC of lipids ratio was less than 0.7, indicating poor test.

Validation of UAlb, ACR and the regression model for Predicting MA among overweight or obese male population

The traditional threshold to identify MA were the following values: UAlb of 20 mg/l or greater, UACR of 20 mg/g or greater for men, and the model of 0.5 or greater. Through the Youden index, the optimal threshold of 0.2 was found for the regression model to identify MA. Table 5 shows the results of applying these values to the study subjects. UAlb predicted MA with sensitivity 69.8% and specificity 93.1%, global predictive value of 89%. UACR predicted MA with sensitivity 79.1% and specificity

98%, global predictive value of 94.7%. The model predicted MA with sensitivity 67.4% and specificity 79.0%, global predictive value of 75.7% at the threshold of 0.2, with sensitivity 39.5% and specificity 97%, global predictive value of 86.1% at the threshold of 0.5. Additionally, through a linear interpolation, the threshold of 0.1 for the model was found to screen MA with sensitivity 90.0% and specificity 56.5%, global predictive value of 61.7%.

Discussion

Our goal was to develop a relatively simple approach allowing prediction of MA in overweight or obese persons based on some routinely available data. Early identification of high MA risk of may lead to more successful intervention and management of CKD, and is beneficial to prevent further renal damage.[18] Our findings showed that predicting MA was feasible by using routine data, such as BMI, BP, FPG and BUA. These data can be easily obtained by physical examination and laboratory tests. The potential clinical utility of our findings was highlighted by the evidence that 17.6% of the overweight might have MA, and the absolute number of MA is considerable.

Our results indicated that a considerable proportion of the overweight is accompanied by one or more metabolic disorders, including impaired glucose tolerance, dyslipidaemia and hypertension, all of which were the important components of metabolic syndrome(MS). In addition to increasing morbidity and mortality of

cardiovascular disease (CVD) and diabetes mellitus (DM),[19] MS is strongly associated with the development of renal disease.[11] It is evident that multiple metabolic disorders promote the progression of MA and CKD. Chandie Shaw PK and colleagues demonstrated that obesity was the most important contributor to the risk of MA and CKD in nondiabetic South Asians,[20] Jing Chen revealed obesity and metabolic syndrome were related to MA and renal damage in Caucasians,[13] In several epidemic investigations, hypertension, hyperglycemia and dyslipidaemia were also strongly correlated with MA and renal damage.[21-23] Moreover, a recent study reported that BUA was the independent risk factor of MA.[24] In agreement with those reports in the literatures, we identified a series of predictors including BMI, SP, FPG and BUA, predominantly contributed to the prediction of MA in the multivariable logistic regression model. Nevertheless, lipids did not have added value in our model. Our findings showed that plasma triacylglycerol levels was correlated to MA in univariate analysis, but not in multivariate analysis. Orchard TJ et al. also demonstrated the similar results in type 1 diabetes.[25] However, some studies showed that high triacylglycerol concentration was an independent predictor for the risk of progression of renal damage.[12, 26] This discrepancy could stem from lack of adequate statistical analysis, since triacylglycerol predicted progression of renal disease independently of BMI when individuals with normal BMI and microalbuminuria were pooled. In addition, our findings suggested that hyperglycaemia was the predominant risk factor, which indicated glycogenic control should be intensified for preventing MA and further renal damage, while the previous studies indicated obesity or hypertension was the most

important risk factor of MA.[13, 20] Data regarding the effect of metabolic factors on MA are controversial. It is possible that MA is associated with the race and ethnicity. Different population might confer different susceptibility on metabolic risk factors, and caused this discrepancy.[27]

Our study data showed the prevalence of MA was relatively high in the overweight, which was consistent with the results from previous studies.[28] The actual number of MA cases is disturbing. Although screening UACR has been been debated for use in the general population, it is currently still an opinion, far away from as a general practice.[18, 29] Since an annual healthcare for the overweight or obese population is available, it is unacceptable that people with MA are not identified, thus miss the chance of early prevention of CKD, and suffer from ESRD in the end. Fortunately, nowadays there have been some efforts focusing on identifying the predictors of MA and preventing the progression of CKD. Currently, the standard method for identifying MA is UAER based on a 24h urine sample collection. UAlb and UACR are recommended to use as a screening tool for MA in the diabetes and hypertension. In this study, we identified four important predictors and developed the regression model for predicting the overweight subjects with and without MA. Compared to the gold standard of UAER, the model represented a good predicting test (AUC= 0.82), and a useful examination for screening MA in the overweight. At the traditional threshold, PPV of the model was greater than of UAlb, less than of UAER. For specificity, the model had comparative performance versus UAlb and UACR in diagnosis of MA.

Furthermore, using the Youden index, we found the optimal threshold of the model for Chinese population. Compared with the traditional threshold, the model represented the optimal combination of sensitivity and specificity at the optimal threshold. For screening examination, more improvement is needed for sensitivity than specificity, so we chose a threshold of 0.1 for the model when sensitivity was 90% and specificity was 56.5%. With this threshold, 90% overweight persons with MA would be identified through the model, which would significantly reduce the proportion of missed MA.

In addition to the regression model for predicting MA, the lipids profile was also used to predict MA in the present study. A previous study reported that TG/HDL-C ratio was an alternative method to identify overweight individuals with insulin resistance.[30] Another earlier study suggested TC/HDL-C ratio can be used as a predictor of cardiovascular Disease.[31] In view of these positive data, we evaluated the performance of lipids ratio for predicting MA. Unfortunately, their performance was not ideal, and all areas of under ROC were less than 0.7(see Figure 2 and Table 4).

The present regression model has some attractive features when compared with traditional screening tool, including UAlb and UACR. Our regression model is based on routine healthcare data, therefore, it is an inexpensive tools for health care professionals and perhaps epidemiologists in identifying the overweight individuals who are at the increased risk of MA and CKD. Moreover, the probability can be predicted by computer, and therefore, the model can be easily applied in clinical

practices. We would recommend offering the overweight individual a primary screening of MA by applying the routinely available data. If it is positive, the individual with MA can be discriminated through the detection of UAER. Current screening protocols are only recommended for the diabetics, hypertension and old individuals. Using current protocol, a considerable proportion of the overweight with MA won't be identified sooner enough.

There are several potential limitations in this study. First, the study subjects consisted of Chinese adult males. Therefore, the performance of the prediction model and thresholds for overweight females needs to be further investigated. Second, because of the cumbersome and error-prone nature of 24h urine collection, the present study is only a preliminary one. A larger scale population investigation was recommended for the improvement of the prediction model in future.

In conclusion, the prevalence of MA was relatively high, reaching up to 17.6% in Chinese overweight males. BMI, FPG, SP and BUA were the important predictors of MA and renal damage. The logistic regression model, including BMI, FPG, SP and BUA, was an effective tool of prediction MA for the overweight although it was not best tool compared to UACR and UAlb.

Conflict of interest

The authors declare no conflict of interest.

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Table 1. Baseline characteristics of overweight or obese participants grouped by UAER

Characteristics	Normalbuminuria n=202	Microalbuminuria n=43	P-value
Age(*year*)	42.94(0.89)	46.42(2.43)	NS
BMI(*kg/m^2*)	25.83(0.14)	27.31(0.38)	0.001
SP (*mm/Hg*)	125.88(0.83)	136.67(2.70)	<0.001
DP (*mm/Hg*)	77.25(0.54)	83.79(1.62)	<0.001
FPG(*mmol/l*)	5.06(0.04)	5.48(0.10)	<0.001
TG (*mmol/l*)	2.11(0.10)	2.76(0.25)	0.009
TC (*mmol/L*)	4.86(0.06)	5.19(0.11)	0.026
HDL-C (*mmol/l*)	1.08(0.02)	1.09(0.04)	NS
LDL-C (*mmol/l*)	2.49(0.05)	2.59(0.10)	NS
TG/HDL-C	2.20(0.14)	2.88(0.35)	0.045
TC/HDL-C	4.64(0.08)	4.96(0.15)	NS
LDL-C/HDL-C	2.35(0.05)	2.43(0.09)	NS
BUN(mmol/l)	5.12(0.08)	5.16(0.17)	NS
BUA (umol/l)	368.85(5.67)	410.58(12.37)	0.002
sCr(umol/l)	78.69(0.67)	81.86(2.02)	NS
eGFR(ml/min/1.73m^2)	101.99(1.10)	97.71(2.99)	NS
UAlb (mg/l)	8.98(0.51)	59.81(11.28)	<0.001
uCr (umol/l)	17018.61(608.39)	13180.19(1413.74)	0.010
UACR(mg/g)	5.11(0.29)	46.47(6.43)	<0.001

UAER(mg/24h)	6.31(5.31)	51.02(25.93)	<0.001

Data were expressed as mean (SE). NS, not significant.

Normoalbuminuria: UAER<30 mg/24h; Microalbuminuria: 300 mg/24h>=UAER>=30 mg/24h.

Participants with macroalbuminuria were excluded from this analysis.

Table 2. Univariate and multivariate logistic regression relationships between MA and selected metabolic markers

Markers	**Univariate OR(95% C.I)**	**Multivariate Crude OR(95% C.I)**
Age(*year*)	1.02 (1.00-1.04)	1.05(0.99-1.12)
BMI(*kg/m^2*)	1.33(1.14-1.55)**	1.29 (1.10-1.51)**
SP (*mm/Hg*)	1.06(1.03-1.09)**	1.03(0.98-1.08)*
DP (*mm/Hg*)	1.09(1.05-1.13)**	1.04(0.97-1.11)
FPG(*mmol/l*)	3.29(1.86-5.82)**	3.46(1.70-6.57)**
TG (*mmol/l*)	1.29(1.06-1.57)*	1.20(0.50-2.69)
TC (*mmol/L*)	1.51(1.05-2.19)*	0.73(0.08-8.88)
HDL-C (*mmol/l*)	1.09(0.26-4.51)	2.25(0.14-49.23)
LDL-C (*mmol/l*)	1.26(0.77-2.07)	1.53(0.08-18.78)
BUN(mmol/l)	1.03(0.77-1.37)	1.04(0.72-1.52)
BUA (umol/l)	1.01(1.00-1.01)**	1.01(1.00-1.01)*
sCr(umol/l)	1.03(1.00-1.06)	1.21(1.00-1.46)
eGFR	0.98((0.96-1.0)	1.12(0.99-1.27)

OR, odds ratio; C.I, confidence interval. Crude OR was estimated by logistic regression

analysis without adjustments.

*p<0.05; **p<0.01

Table 3. Multi-step logistic regression models for having MA

Markers	β	Standard error	Multivariate Adjusted OR(95% CI)	P-Value
BMI(*kg/m²*)	0.26	0.08	1.30(1.11-1.52)	0.001
SP (*mm/Hg*)	0.05	0.01	1.05(1.02-1.08)	0.001
FPG(*mmol/l*)	1.17	0.33	3.22(1.71-6.05)	<0.001
BUA (umol/l)	0.01	0.00	1.01(1.00-1.01)	0.004
Constant	-23.27	3.60	0.00	<0.001

OR, odds ratio; C.I,confidence interval. Adjusted OR was adjusted for age, DP, lipids, BUN and sCr, eGFR. **β** indicated regression coefficient

Table 4. Comparison between the areas under the ROC curve constructed from output probabilities of lipids ratio, regression model and UAlb, UACR

Markers	AUC± SE	95% CI	P-Value
TG/HDLC	0.62±0.05	0.41-0.60	0.013
TC/HDLC	0.61±0.04	0.41-0.60	0.029
LDLC/HDLC	0.57±0.05	0.41-0.60	NS
Model	0.82±0.04	0.75-0.89	<0.001
UAlb	0.87±0.04	0.80-0.94	<0.001
UACR	0.94±0.03	0.89-1.00	<0.001

SE, standard error; C.I, confidence interval; NS, not significant.

Table 5. Performance of UAlb, UACR and the model for predicting MA at several cut-points in the study subjects

Markers	cut-points	Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)	GPV(%)
UAlb	20	69.8	93.1	68.2	93.5	89.0
UACR	20	79.1	98.0	89.5	95.7	94.7
Model	0.5	39.5	97.0	73.9	88.2	86.1
	0.2	67.4	79.0	40.8	91.9	75.7
	0.1	90.0	56.5	29.8	95.0	61.7

PPV, positive Predictive Value; NPV, negative Predictive Value; GPV, global predictive value

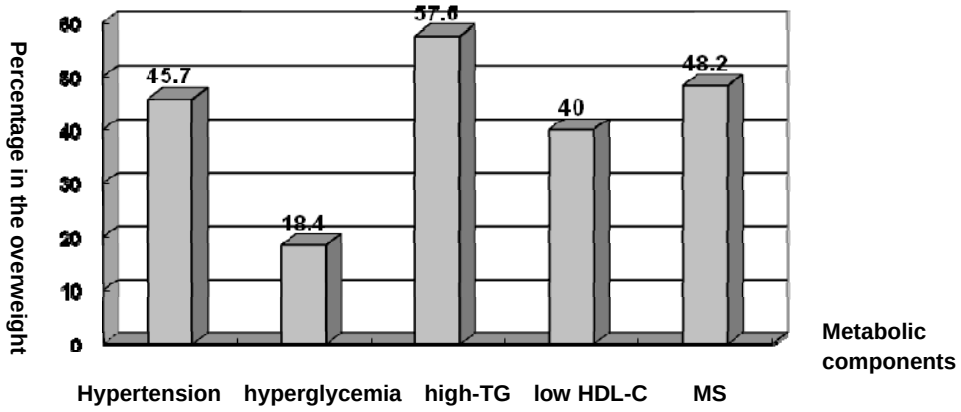

Figure 1. Prevalence of abnormal metabolic components according to IDF in the overweight /obesity. Bars are the estimated percentage of abnormal metabolic components. The prevalence of MS was 48.2% (118/245). Of all participants, 45.7% (112/245) had hypertension, 18.4% (45/245) had hyperglycemia, 57.6% (142/245) had high TG and 40%(98/245) had low HDL-C.

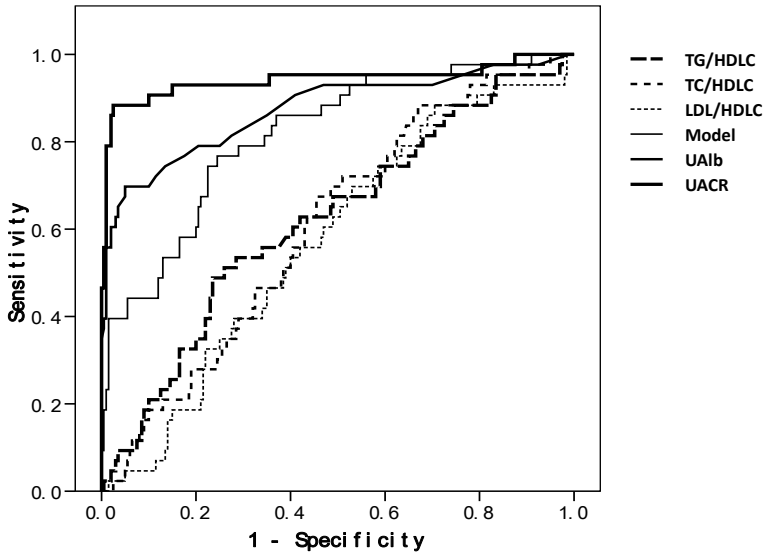

Figure 2. Comparison, in individuals with overweight or obesity , of relationships between rates of true-positive test results (sensitivity) and false-positive test results (1 - specificity) for lipids ratio, UAlb, UACR and the regression model.