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Association and diagnostic value of a novel uric acid index to cardiovascular risk

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ABSTRACT

Objectives: Cardiovascular diseases (CVD) are the leading cause of death and disability worldwide. The aim of this study was to assess the association and diagnostic value of a novel uric acid index (UA index) to cardiovascular risk (CVR).

Design: and **Methods:** An analytical cross-sectional study was performed. We analyzed data from the Plan for Prevention and Surveillance of Communicable and Non-Communicable Diseases at the Hospital de Huaycan, Peru. The QRISK model was used to measure the CVR. Stepwise regression models were performed to determine significant factors to predict CVR and formulate the UA index, then the association of UA index and high CVR was evaluated by Poisson regression models, and the diagnostic accuracy was verified through ROC curves.

Results: In total 291 participants (206 women and 85 men) were analyzed. The correlation between UA index to CVR was stronger ($R^2:0.31$, $p < 0.001$) than uric acid (UA) alone ($R^2:0.19$, $p < 0.001$), and the contribution of UA was stronger than triglycerides or glucose in the stepwise regression model. In the Poisson models, the UA index adjusted model (PR₉₅: 1.58, CI95% 1.11–2.24) presented significant independent association to CVR. The diagnostic accuracy was similar in men (cut-off: 10.8, AUC:0.81; 0.75–0.87) and women (cut-off: 10.0; AUC: 0.77, 0.71–0.84).

Conclusion: UA index presented a good diagnostic accuracy and independent significant association to high CVR in adults from Peru. This marker can be used to assess CVR and follow therapeutic progress in primary health care.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide [1]. According to the World Health Organization (WHO), the most important risk factors CVD-related in the world are high blood pressure, diabetes mellitus, central obesity, dyslipidemia, and smoking [2]. The main public health strategy to decrease CVD is the primary prevention of these risk factors in the population and cardiovascular risk assessment [3].

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Several tools for cardiovascular risk assessment have been used in clinical practice, such as the Framingham score or American College of Cardiology/American Heart Association (ACC/AHA) risk score which focus the prediction of CVD to 10 years [4,5]. This approach is appropriate for middle to older adults; meanwhile, younger adults could be considered low risk due to the limit of 10 years of prediction. For that reason, the assessment of lifetime risk of CVD is considered the best approach in a young adult to adult population [6].

Certain laboratory markers can be used for diagnostic or prognostic early detection of potential CVD in medical practice, such as high-sensitivity C-reactive protein, homocysteine, brain natriuretic peptide, apolipoprotein B, lipoprotein(a), cardiac troponin I and T, etc. [7–9]. However, in low and middle-income countries these markers are not accessible in primary health care [10].

Uric acid (UA) levels have been found to be associated with a variety of cardiometabolic risk factors, including hypertension, dyslipidemia, obesity, diabetes, and metabolic syndrome [11,12]. UA is a practical and accessible marker in primary health care. However, some markers have presented diagnostic accuracy which improves with mathematical adjustment of two or more markers related to the clinical outcome [13]. For that reason, the aim of this study was to assess the association and diagnostic value of a novel UA index to cardiovascular risk in adults from Peru.

2. Methods

2.1. Data source

This is a cross-sectional study using data from the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases at the Hospital de Huaycan II-1, Lima, Peru, in 2019. In this prevention plan, clinical evaluation and laboratory tests were performed to prevent and diagnose diseases in healthcare personnel. Workers were informed that their medical data would be used for future research and written informed consent was obtained from all participants.

This study was approved by the Ethics in Research Committee of the Universidad Peruana Union (N° 2020-CEUPEU-00017) and authorized by the Hospital de Huaycan to use data from the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases.

2.2. Eligibility criteria

We included data of health care personnel between 20 and 79 years old of both sexes from the Hospital de Huaycan. Participants who did not fill out the form, pregnant women, participants who did not do laboratory tests, those who did not sign informed consent, and participants with a medical record of antihyperlipidemic agents, myocardial infarction, coronary artery disease, cerebrovascular disease, or peripheral arterial disease were excluded.

2.3. Assessment of cardiovascular risk

The QRISK model was performed to measure the cardiovascular risk (CVR) in the population of study; this model can determine the risk of CVD up to 95 years old (Lifetime risk of CVD), and for that reason it is recommended to the young adult and adult population [14]. We used the QRISK® on-line calculator (<https://qrisk.org/lifetime/index.php>) to measure the CVR in our study.

2.4. Definition of variables

The CVR was categorized into high ($\geq 39\%$) and low ($< 39\%$) according to the Joint British Societies' consensus recommendations for the prevention of CVD with a focus on lifetime risk of CVD for early prevention of CVD in young adult and adult population [14,15]. UA index was calculated using the formula: $\text{Ln} [\text{Fasting triglycerides (mg/dL)} \times \text{fasting uric acid (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2]$ based on stepwise regression of fitted factors to CVR. Physical activity was defined as active exercise at least 20 min four or more times per week. Alcohol consumption was defined as ≥ 7 drinks (drink: 500 ml of beer) per week. Smoker, antihypertensive medication, and balanced nutrition were assessed based on the "FANTASTIC" self-reported questionnaire [16], from the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases at the Hospital de Huaycan.

2.5. Data analysis

Data analysis was performed using the R program version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>). Categorical and continuous variables were described as frequencies or median [interquartile range] (IQR). For comparative analysis, the chi-square or Mann Whitney *U* test between cardiovascular risk was performed. Then a stepwise regression was used to determine significant factors to predict CVR changes. To assess the independent association of significant factors to high CVR, the prevalence ratios (PR) and their respective 95% confidence intervals (95% CI) were determined using Poisson regression models with robust variance. Finally, Receiver operating characteristic (ROC) curve analysis was applied to estimate the diagnostic accuracy of the proposed UA index to high CVR. The diagnostic accuracy estimators were area under the curve (AUC), sensitivity (Se), specificity (Sp), positive predicted value (PPV), and negative predicted value (NPV) with their 95% CI. The optimal cut-off value was estimated using the Youden index. A $p < 0.05$ was considered statistically significant in all analyses.

3. Results

3.1. General characteristics

In total, 291 adults participated in the study, 206 (70.8%) were women and 85 (29.2%) were men with a median age of 46 [38–54] years old. The majority of the baseline values (overall population) presented in Table 1 were normal. However, body fat percentage was high (33.7%) – 50.5% of the population were overweight and 26.5% were obese.

The group with high CVR showed significant statistical differences ($p < 0.01$) compared to the group with a low CVR on the majority of variables including the UA index presented in Table 1. Balanced nutrition, physical activity, alcohol, and tobacco consumption presented no significant differences between study groups.

3.2. Main findings

After stepwise regressions of the variables, just UA, triglycerides (TG), and glucose (Glu) presented significant factors for predict CVR (AIC:1904.46, RMSE:6.32) (Fig. 1C).

In linear regression models the correlation of the UA index to CVR ($R^2:0.31$, $p < 0.001$) was stronger than UA alone ($R^2:0.19$, $p < 0.001$) (Fig. 1A and B). In the stepwise regression the contribution of UA was stronger (R -adjusted: 17%) than Glu (R -adjusted: 13%) or TG (R -adjusted: 6%) such that, to predict CVR, finally we got the fitted model: $y = -54.94 + 9.43(UA) + 3.84(TG) + 13.38(Glu)$ (Fig. 1C).

In the Poisson regression models, the independent association of UA index to high CVR was statistically significant (PR_a: 1.58, CI95% 1.11–2.24) after adjusted potential confounders. UA showed a stronger association than TG or Glu in crude analysis; however, no significant independent associations were found for UA, TG, or Glu in the multivariable analysis (Table 2).

The ROC analysis of the UA index showed that AUC for men was 0.81 (0.75–0.87), Se of 0.83 (0.72–0.91), Sp of 0.66 (0.59–0.72), PPV of 0.43 (0.36–0.61) and NPV of 0.93 (0.87–0.95) while for women the AUC was 0.77 (0.71–0.84), Se of 0.84 (0.73–0.92), Sp of 0.57 (0.51–0.64), PPV of 0.38 (0.31–0.56) and NPV of 0.92 (0.86–0.94). The estimators of diagnostic accuracy were similar between sexes and no present changes by age (>45 or <45 years old). UA index presented good diagnostic accuracy to high CVR with similar cut-off values between men (Cut-off: 10.8) and women (Cut-off: 10.0) (Fig. 2).

4. Discussion

In the present study, we found that the UA index is a good marker to complement the assessment of the CVR in Peruvian adults. Several studies showed that high levels of UA are an independent factor in dyslipidemia, metabolic syndrome, diabetes, and CVR [17,

Table 1
General characteristics in overall population and corresponding lifetime risk of CVD.

Variables	Overall (n = 291)	Cardiovascular risk		p
		High (n = 68)	Low (n = 223)	
Age (years)	46.0 [38.0–54.0]	50.0 [42.0–55.5]	44.0 [36.0–52.0]	0.001
Men ^a	85 (29.2)	40 (58.8)	45 (20.2)	<0.001
Women ^a	206 (70.8)	28 (41.2)	178 (79.8)	<0.001
Body fat (%)	33.7 [28.5–37.8]	32.0 [27.4–39.0]	34.0 [29.0–37.6]	0.477
SBP (mmHg)	110 [100–120]	120 [110–120]	100 [100–112]	<0.001
DBP (mmHg)	70 [60–80]	80 [70–80]	70 [60–70]	<0.001
Cholesterol (mg/dL)	189.0 [165.0–216.0]	214.0 [195.8–237.2]	183.0 [162.5–205.0]	<0.001
HDL-c (mg/dL)	50.0 [43.0–57.0]	45.5 [40.0–54.0]	51.0 [44.0–57.5]	0.001
LDL-c (mg/dL)	112.0 [93.0–130.0]	130.0 [117.0–155.8]	106.0 [88.5–124.0]	<0.001
Triglycerides (mg/dL)	134.0 [92.0–186.5]	172.0 [131.0–234.2]	122.0 [89.0–165.0]	<0.001
Glucose (mg/dL)	90.0 [85.0–97.0]	97.0 [89.8–109.2]	89.0 [84.0–95.0]	<0.001
HbA1c (%)	5.90 [5.60–6.20]	6.35 [5.88–6.80]	5.80 [5.50–6.00]	<0.001
Uric acid (mg/dL)	3.7 [3.1–4.5]	4.4 [3.6–5.0]	3.6 [3.0–4.2]	<0.001
UA index	10.05 [9.52–10.47]	10.46 [10.11–11.00]	9.84 [9.41–10.32]	<0.001
Diabetes ^a	39 (13.4)	32 (47.1)	7 (3.1)	<0.001
Smoker ^a	13 (4.5)	6 (8.8)	7 (3.1)	0.099
Alcohol consumption ^a	21 (7.2)	5 (7.4)	16 (7.2)	1
Balanced nutrition ^a	187 (64.3)	40 (58.8)	147 (65.9)	0.355
Physical activity ^a	190 (65.3)	45 (66.2)	145 (65.0)	0.976
Body mass index ^a				
Normal	67 (23.0)	4 (5.9)	63 (28.3)	<0.001
Overweight	147 (50.5)	31 (45.6)	116 (52.0)	
Obesity	77 (26.5)	33 (48.5)	44 (19.7)	

Data are expressed as median [RIQ] or number (%). LDL-c, Low density lipoprotein cholesterol; HDL-c, High density lipoprotein cholesterol; UA index, Uric acid index; HbA1c, Glycated hemoglobin; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

^a Frequency.

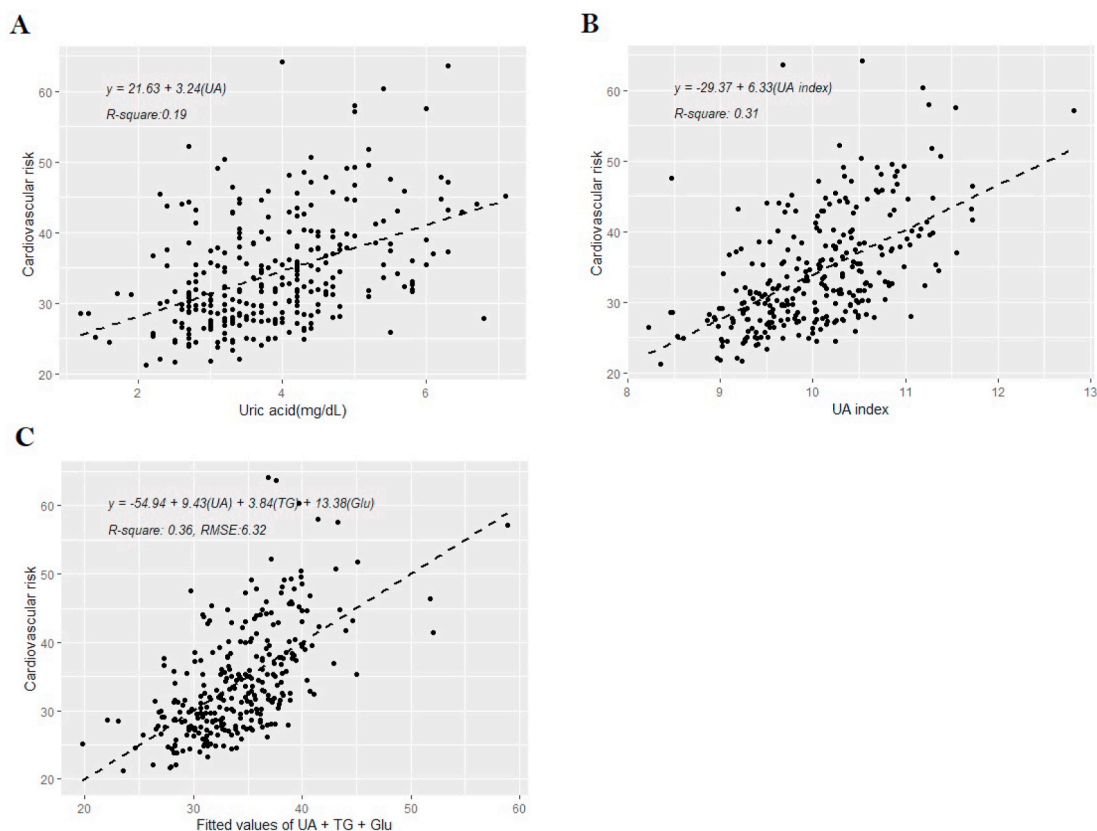


Fig. 1. Regression models between significant factors and probability of cardiovascular risk. A) Uric acid, B) UA index and C) Stepwise regression model of UA, TG, and Glu.

Table 2

Poisson regression analysis for the association of high cardiovascular risk with significant factors.

Variables	PR _c (95% CI) ^a	p-value	PR _a (95% CI) ^b	p-value
UA index	2.62 (1.93–3.50)	<0.001	1.58 (1.11–2.24)	0.012
Uric acid	1.61 (1.31–1.97)	<0.001	N-S	N-S
Triglycerides	1.01 (1.00–1.01)	<0.001	N-S	N-S
Glucose	1.01 (1.00–1.01)	<0.001	N-S	N-S

PR_c, Prevalence ratio crude; PR_a, Prevalence ratio adjusted; 95%CI, 95% confidence interval; UA index, Uric acid index; N-S, no significant.

^a Non-adjusted.

^b Adjusted by age, gender, LDL-c, balanced nutrition, alcohol consumption and physical activity.

18]. This fact can be explained because high levels of UA develop a pro-inflammatory environment with a rise of cytokines, free oxygen radicals, and endothelial damage [19]. However, the introduction of TG and Glu generates a stronger correlation than only UA for the CVR in our study. Similarly, some biochemical markers, as a product of mathematical adjusting, showed association to cardiometabolic diseases. For example, triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-c) and triglycerides to glucose index (TyG) are good markers for metabolic syndrome and CVD in different populations [20,21].

We believe that the introduction of significant factors such as TG and Glu in the adjusted mathematical formula produced synergism and explain our results [22]. There is a renewed interest that has been driven by epidemiological and genetic evidence supporting that higher levels of TG and Glu can foster and increase the risk of CVD [23]. Possible mechanisms have been suggested. High levels of TG are related to the presence of cholesterol-rich chylomicrons, which can enter the intima, leading to low-grade inflammation, induce the formation of foam cells, and atherosclerosis; furthermore, excess beta-oxidation leads to insulin resistance, hyperglycemia, and protein glycation. Finally, this leads to a CVD and increased mortality [24]. This is the reason why TG, Glu and UA, through the UA index, could be a more efficient marker in improving the assessment of CVR.

Increased levels of TG lead to the release of free fatty acids, monoacylglycerols, and other molecules, each of which could cause local damage and inflammation, and insulin resistance. Furthermore, an increased level of UA results in insulin resistance, hyperglycemia, and vice versa high levels of UA and TG [25,26], which indicates a possible synergistic effect manifested by a stronger

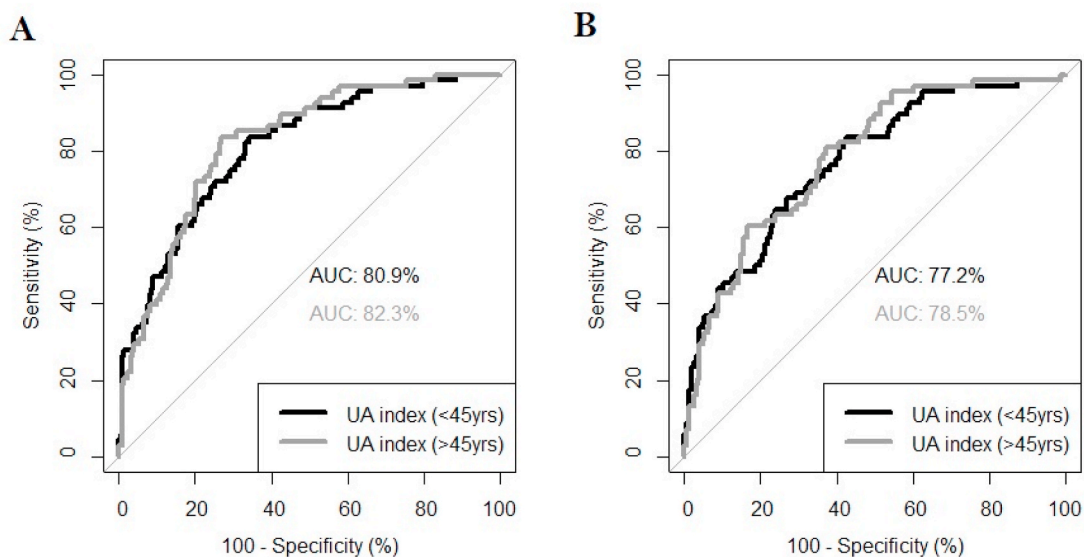


Fig. 2. ROC curve of UA index for predicting high CVR. A) UA index Men (cut-off: 10.8; Se:0.83; Sp:0.66); B) UA index Woman (cut-off: 10.0; Se:0.84; Sp:0.57).

correlation.

The diagnostic accuracy of the UA index to high CVR was good and similarly, some population studies of TG/HDL or TyG markers, both markers include triglycerides levels, showed that the AUC of TyG and TG/HDL-c for CVD were between 0.6 and 0.8 with different cut-offs values dependent of country [20,21,27,28]. In Latin-American people, genetic factors and lifestyles could change biochemical markers and differ from other populations, thus future studies should continue to assess novel markers and establish their cut-offs values [29].

This study presented some limitations; first, it was not possible to assess causality among the variables due to the nature of the cross-sectional design used. Thus, prospective future studies are required to verify our results. Second, there is a probable recall and response bias due to the self-report surveys used for some variables. Finally, the glomerular filtration rate could not be assessed in the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases at the Hospital de Huaycan. However, none of the participants presented renal pathologies in their medical records in 2019.

To our knowledge, this is the first study that assesses the association and diagnostic value of a novel UA index to CVR conducted in adults from Peru. Another strength of our study was including the adjustment of several potential confounders in the analysis and the generation of a stepwise regression to identify significant factors to CVR. The results provide evidence about a practical marker to assess CVR in primary health care and supplement the evaluation of lifetime risk of CVD through the QRISK. Quantifying metabolites like UA, TG, and Glu in rural low and middle-income countries is accessible and practical, for that reason we propose to use the proposed UA index values for following therapeutic targets by lifestyle changes or pharmacotherapy, for people with high CVR previously assessed by QRISK.

5. Conclusions

In conclusion, the UA index presented a good diagnostic accuracy and independent significant association to high cardiovascular risk in adults from Peru. The estimators of diagnostic accuracy were similar in both sexes without significant differences by age in the population of the study. This marker can be used to assess cardiovascular risk and following therapeutic progress such as a supplement of QRISK in primary health care.

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Availability of data and material

All the data analyzed during this study are included in this manuscript; the datasets are available from the corresponding author upon reasonable request.

Credit author statement

Ricardo Rojas-Humpire developed the conceptualization, formal analysis, original draft and writing - review & editing.

Keila Jauregui-Rodriguez developed the investigation, interpretation of data and the original draft.

Silvana Alborno developed the investigation, interpretation of data and the original draft.

Percy G. Ruiz Mamani developed the data curation, analysis/interpretation of data and original draft.

Rosmery Gutierrez-Ajalcrina developed the investigation, acquisition of data, original draft and writing - review & editing.

Salomón Huanchuire-Vega developed the conceptualization, analysis/interpretation of data, original draft and writing - review & editing.

All authors approved the submitted version.

Dr. Salomón Huanchuire-Vega.

Declaration of competing interest

The authors declare no conflict of interest.

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Not applicable.

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