ORIGINAL REPORT

An Iranian Scoring System for Diagnosing Buerger's Disease

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Abstract- Buerger's disease or thromboangiitis obliterans (TAO) seems to be common in IR Iran, The present study aimed to evaluate an Iranian population with Buerger's disease in order to suggest a diagnostic criterion for Buerger's disease based on the most frequent findings and to compare it with Papa diagnostic criteria. In a cross-sectional study, all patients with resting limb pain, limb ischemic ulcers, intermittent claudication and limb ischemia who referred to the Vascular Clinic of Sina Hospital during 2009-2011 were evaluated. The patients were allocated to Buerger's and non-Buerger's groups; Evaluating 122 patients (61 in each group), according to the model each clinical manifestations and risk factors in the patients with Buerger's disease obtained a score. Absent pulsation, abnormal distal Doppler sonography and ischemic ulcer were respectively present in 58 (95.1%), 58 (95.1%) and 49 (80.3%) individuals with Buerger's disease. Multivariate linear regression analysis and multivariate logistic regression analysis were used for modeling. Considering the model finding findings, diagnostic criteria including age, sex, smoking, Raynaud's phenomenon, abnormal proximal Doppler, diabetes mellitus and hyperlipidemia were suggested (R^2=0.582); the sensitivity and specificity of the criteria was respectively 95.1% and 78.7%. Compared with Papa criteria, Kappa coefficient was measured at 0.66 with a *P*-value<0.001. It seems that the recommended criteria have an acceptable accuracy in diagnosing Buerger's disease, especially in the Iranian population; however, it is necessary to conduct more studies with larger sample sizes to evaluate the criteria, especially in other populations.

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Keywords: Burger Disease; Diagnostic Criteria; Limb Ischemia; Papa Score

Introduction

Buerger's disease or thromboangiitis obliterans (TAO) is a segmental occlusive non-atherosclerotic inflammatory disease involving small and medium-size arteries and veins of upper and lower limbs (1). TAO was first introduced by Von Winiwarter in 1879; in 1908, Leo Buerger described the disease by pathological evaluation of amputated limbs (2). The prevalence of TAO is different in various parts of the world; however, the Middle East is a region with a high prevalence (2).

There is no pathognomonic clinical manifestation or specific laboratory test for TAO (3,4); therefore, the diagnosis is confirmed at the end of evaluations and after ruling out other types of vasculitis (5). Several diagnostic criteria are recommended for Buerger's disease such as Papa criteria (6), Shionoya criteria (7) and Olin's criteria (8); however, none is internationally validated resulting in various criteria to be used in different parts of the world for TAO diagnosis (5,9).

To our knowledge, there is no national study evaluating the prevalence of TAO in IR Iran but it seems that Buerger's disease is not uncommon in Iran (10). However, yet there has been no diagnostic criteria based on the evaluation of Iranian patients with TAO. As a result, this study aimed to evaluate an Iranian population with Buerger's disease in order to suggest a diagnostic criterion for Buerger's disease in Iranian patients based on the more frequent findings and to compare it with Papa diagnostic criteria.

Materials and Methods

In a stratified cross-sectional study, all patients with resting limb pain, limb ischemic ulcers, intermittent claudication and limb ischemia who referred to the vascular clinic of Sina hospital during 2009-2011 were

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evaluated. Considering at least 80% sensitivity and specificity for the suggesting criteria with an acceptable interval of 13% and an error of 5%, the sample size was measured to be 61 individuals for each group (Buerger's and non-Buerger's). As a result, 122 subjects were selected using simple non-random sequential sampling method. The inclusion criteria of the study were patients with ischemic ulcers, intermittent claudication, limb resting pain and limb ischemia. Patients with atrial fibrillation, thoracic outlet syndrome, popliteal entrapment syndrome, cystic adventitial disease, autoimmune diseases, hypercoagulability states and atherosclerosis were excluded. All of the patients were informed about the goals of the study and the privacy of their data; a written informed consent was obtained from all of them.

Patients were assigned to Buerger's and non-Buerger's groups based on clinician diagnosis and both groups were asked to quit smoking. During the follow up sessions, significant improvement or stop in progression of symptoms was observed. Accordingly, for final classification, Buerger's patients have been specified according to their response to treatment (quitting smoking).

Moreover, both groups underwent arteriography and measured for acute phase reactants and some specific auto-antibodies (including ESR, CRP, ANA, ANCA, RF, anti-phospholipid antibody, anti-cardiolipin antibody). Data collected from inpatient files and also during visits. For analysis of collected data, in first step, comparison of quantitative and qualitative variables performed between two groups by Independent sample t test and chi square test, respectively. In second step different modeling for prediction of Buerger's disease set by using multivariate linear and logistic regression analysis. In linear regression analysis each qualitative variable considered as dichotomous and valued as 0 or 1. Then the best fitted model selected according to the R^2 of the model. Many models used for finding the best fit one and the final model was based on the STEPWISE method In the third step sum score of the best fitted model (suggested criteria) calculated for each patients of both groups, then ROC analysis performed for determining the most accurate cut off point for sum score of the criteria. Consequently sensitivity and specificity of the criteria at the specified cut point calculated. In fourth step, sum scores for each patient in both groups calculated based on Papa criteria (8) and the sensitivity, specificity and accuracy of new suggested criteria compared with correspondent ones of previously suggested criteria. Besides, Kappa coefficient calculated for measurement of the non chance agreement of the novel criteria with Papa scoring. 95% confidence intervals used for comparison of sensitivity, specificity and accuracy between the novel and Papa criteria.

In suggested criteria positive scoring for each criterion indicates risk for Buerger's disease and negative sign means dissatisfactory effect on diagnosis of Buerger's disease.

All data analysis performed by SPSS software package version 16 (SPSS, Inc., Chicago, IL). *P*-values less than 0.05 were considered as statistically significant.

Results

The mean age of the patients in Buerger's and non-Buerger's groups was respectively 44 (27-75) and 58 (36-89) years old ($P<0.001$). All patients (100%) of the Buerger's group were men while there were 44 (72%) men and 17 (28%) women in the non-Buerger's group ($P<0.001$).

The studied quantitative and qualitative variables in both groups are shown in tables 1 and 2. Patients with Buerger's disease averagely smoked 24 (range 2-60) packets/year (PY) while those in the non-Buerger's group smoked 12 (range 0-40) PY ($P<0.001$). In patients with Buerger's disease 60 (98.4%) were smokers but 24 (39.3%) without Buerger's diagnosis were smokers ($P<0.001$). Thirteen (21%) and 3 patients (5%) had Reynaud's phenomenon in Buerger's and non-Buerger's groups, respectively ($P=0.007$). In the Buerger's group 6 (9.8%) patients had abnormal proximal Doppler readings while 37 (60.6%) non-Buerger's group patients had abnormal proximal Doppler results ($P<0.001$). Two patients (3.2%) with Buerger's disease and 34 (55.7%) without Buerger's disease had diabetes mellitus ($P<0.001$). Hyperlipidemia (HLP) in patients of Buerger's and non-Buerger's groups were 4 (6.5%) and 20 (32.7%), correspondingly ($P=0.001$).

In the evaluated patients, the variables of smoking, Reynaud's phenomenon, thrombophlebitis, abnormal distal vessels and normal proximal vessels in Doppler sonography of upper and lower limbs, increased level of homocystein, being at young age and male gender with other normal tests were related to the presence of Buerger's disease. In contrast, presence of any of these conditions as hypertension, diabetes mellitus, hyperlipidemia, collagen-vascular disease, ischemic changes and arrhythmia in ECG and or emboli echocardiography and other abnormal tests were not predicting Buerger's disease but atherosclerosis or

embolic origin of the disease.

The multivariate regression model for estimating Buerger's disease in the studied patients is shown in table 3, (R^2=0.584). The regression formula is as follow:

[-(0.004 * age) + (0.343 * sex) + (0.005 * PY) + (0.186 * Raynaud) - (0.322 * Proximal Doppler)- (0.319 * DM)- (0.268 * HLP)] + 0.519.

Table 1. Qualitative variables distribution in the two groups of studied patients.

Qualitative variables	Buerger's group	Non-Buerger's group	*P*-value*
Resting pain	44 (72.1%)	24 (39.3%)	<0.001
Activity pain	43 (70.5%)	40 (65.6%)	0.560
Ischemic ulcer	49 (80.3%)	27 (44.3%)	<0.001
Edema	5 (8.2%)	20 (32.8%)	<0.001
Skin color change	6 (9.8%)	31 (50.8%)	<0.001
Gangrene	39 (63.9%)	19 (31.1%)	<0.001
Reynaud's phenomenon	13 (21.3%)	3 (4.9%)	0.007
Thrombophlebitis	4 (6.6%)	2 (3.3%)	0.402
Paresthesia	40 (65.6%)	30 (49.2%)	0.067
Amputation	12 (19.7%)	7 (11.5%)	0.212
Impaired movement	1 (1.6%)	15 (24.6%)	<0.001
Temperature change	24 (39.3%)	37 (60.7%)	0.019
Trauma	0 (0%)	5 (8.2%)	0.022
Absent pulsation	58 (95.1%)	58 (95.1%)	1.00
Positive Allen test	11 (18.0%)	7 (11.5%)	0.307
Electrocardiographic change	0 (0%)	17 (27.9%)	<0.001
Abnormal proximal doppler	6 (9.8%)	37 (60.7%)	<0.001
Abnormal distal doppler	58 (95.1%)	52 (58.2%)	0.068
Hypertension	1 (1.6%)	27 (44.3%)	<0.001
Renal disease	2 (3.3%)	3 (4.9%)	0.64
Heart disease	1 (1.6%)	21 (34.4%)	<0.001
Pulmonary disease	1 (1.6%)	3 (4.9%)	0.30
Collagen-vascular disease	1 (1.6%)	3 (4.9%)	0.30

* Chi Square Test

Table 2. Comparing quantitative variables in the two groups of patients.

Quantitative variables	Buerger's group	Non-Buerger's group	*P*-value*
Age	44.2 (9.7)	58 (18)	<0.001
Cigarette (packet/)year	23.9 (21.6)	11.9 (20)	<0.001
Hemoglobin	14.8 (1.2)	12.7 (2.3)	<0.001
White blood cell	6518 (2142)	9347 (3522)	<0.00
Platelet	219721 (97095)	224922 (120386)	0.79
HDL	53.2 (20.9)	86 (314.6)	0.41
LDL	167.0 (55.8)	305 (126)	0.06
Triglyceride	114 (62.1)	164 (70)	<0.00
Cholesterol	194.5 (35.1)	253.5 (301.1)	0.06
Fasting Blood Sugar	94.8 (19)	155.5 (83.3)	<0.00
ESR	10.2 (4.6)	21.5 (18.4)	<0.00
CRP	0.00 (0.00)	0.23 (0.71)	0.014
Creatinine	1.5 (3.8)	1.2 (1)	0.65
BUN	20.4 (7.6)	43.1 (40.2)	<0.00
PT	14.4 (3.3)	13.8 (1.6)	0.23
PTT	28.9 (5.2)	34.1 (14.8)	0.01
INR	1.1 (0.14)	1.1 (0.18)	0.14
AST	23.1 (10.3)	41.9 (50.3)	0.005
ALT	26.5 (18.3)	31.3 (35.2)	0.32
ALK.ph	129.3 (45.2)	155.6 (48)	0.002
T4	8 (2.4)	7.9 (2.4)	0.84
T3	107.3 (35.6)	102.8 (44.4)	0.54
TSH	3.4 (1.4)	3.5 (1.7)	0.67
Homocystein	15.8 (8.8)	13.5 (7.0)	0.11

* Independent samples t test

Table 3. Variables involved in the suggested criteria according to the multivariate linear regression analysis (R^2=0.584).

	Unstandardized Coefficients		Standardized Coefficients	t	*P*-value	95% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	0.519	0.153		3.397	0.001	0.216	0.822
Age	-0.004	0.002	-0.141	-2.003	0.047	-0.009	0.000
Sex	0.343	0.097	0.237	3.531	0.001	0.150	0.535
PY	0.005	0.001	0.213	3.344	0.001	0.002	0.008
Reynaud's	0.186	0.092	0.125	2.013	0.046	0.003	0.368
Proximal doppler	-0.322	0.072	-0.308	-4.466	0.000	-0.465	-0.179
Diabetes mellitus	-0.319	0.084	-0.253	-3.782	0.000	-0.486	-0.152
Hyperlipidemia (HLP)	-0.268	.115	-0.153	-2.317	0.022	-0.496	-0.039

In the formula age and pack year (PY) considered as numeric and the others as dichotomous with 0 and 1 values. Considering for gender, female gender as 0 and male gender as 1, having Reynaud's phenomenon as 1 and no sign of Reynaud's phenomenon as 0, impaired proximal Doppler 1 and normal proximal Doppler as 0, presence of DM as 1 and absence of DM as 0 and Presence of Hyperlipidemia as 1 and its absence as 0.

R square of the final model was 0.582. according to the ROC analysis the best cut point for the model was 0, If the result of the formula is above 0, Buerger's disease is considered as diagnosis otherwise (including 0 summation) it should be ruled out.

As a confirmation and comparison we calculated the risk of burger both according to the Papa scoring system and ours. The ROC analysis performed for determining the accuracy of the criteria (figure 1); Accuracy of these two criteria according to the area under the curve (AUC) showed no statistical differences 0.985, CI95% (0.970-1.000) for our novel criteria vs. 0.974, CI95% (0.949-0.998) for Papa scoring. Considering the cut point for our scoring system as 0, the specificity and the sensitivity were calculated as 78.7%, CI95% (68.4-89.0%) and 95.1%, CI95% (89.7-100%), respectively, comparing those with correspondent ones of Papa criteria, with specificity and sensitivity of 82.0%, CI95% (72.4-91.6%) and 73.8%, CI95% (62.8-84.8%), respectively. These data shows that our novel scoring system has no statistically significant difference from Papa in specificity but has more sensitivity in diagnosing Buerger's disease. Kappa coefficient between these two criteria was 0.66 (P <0.001).

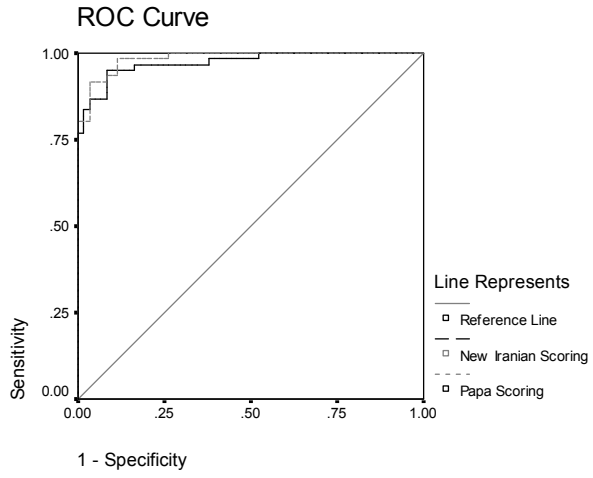

Figure 1. The ROC curve for comparison of the accuracy of the suggested novel diagnostic criteria for Buerger's disease vs. Papa scoring system.

Discussion

In the present study, the manifestations of Buerger's disease were evaluated in an Iranian population in order to determine a diagnostic criterion for the disease based on the most frequent manifestations. Absent pulsation (95.1%), abnormal distal Doppler sonography (95.1%) and ischemic ulcer (80.3%) were the most prevalent manifestations of Buerger's disease in the present study. In a study by Salimi *et al.* (10), ischemic ulcers were reported as the most frequent manifestation which is almost consistent with the findings of the present study. In another study by Laohapesang *et al.* (2), burning pain on feet and hands was the most frequent presentation in the studied patients with Buerger's disease. Moreover, Ates *et al*. indicated foot coldness (90.6%) and color changes (84.3%) as the most frequent complaints of their patients (11). Although it is reported that the prevalence of Buerger's disease is increasing in women according to the increased rate of smoking among them (6,12,13), in our study, all of the patients with TAO were men. In a study in Thailand (2), 2 patients out of 78 were women; however, in Salimi *et al.* study (10), none of the patients were women which was consistent with our study.

The mean age of the patients with TAO in the present study was 44 years old; besides, in another study in Iran (10), the mean age of the patients at the time of diagnosis was reported to be 40.5 ± 10.1 and in another study in Thailand (2) it was 34.1 ± 5.1. The older age of our patients compared with the two mentioned studies is probably due to considering the patients' age at the time of visit and not diagnosis of Buerger's disease.

Since there is no specific clinical manifestation or laboratory test for Buerger's disease, the diagnosis is confirmed based on a collection of signs and after ruling out other differential diagnoses (5). Furthermore, no diagnostic criteria is internationally accepted for Buerger's disease (5); as a result, different authors have presented various diagnostic criteria for the disease (6,7,12,14-19) among which Papa criteria (6) and Shionoya criteria (7) seem to be used more. Therefore, in the present study, the patients were allocated into Buerger's and non-Buerger's groups based on their response to treatment and then, according to the most frequent presentations in Buerger's group and by multivariate analysis and modeling, the following formula mentioned in the results was suggested for the diagnosis of Buerger's disease.

After that, the suggested criteria was compared with Papa criteria; the sensitivity and specificity of the presented criteria in diagnosing Buerger's disease in the studied population was respectively 95.1% and 78.7% while the sensitivity and specificity of Papa criteria was 73.8% and 82%, respectively. According to the 95% confidence intervals, our criteria showed a higher sensitivity than Papa which was statistically significant, with no statistically significant difference in specificity. Besides, these two criteria had a non-chance agreement in 66% of the cases diagnosing the healthy individuals and the patients with Buerger's disease which means that there was a good agreement between these two criteria.

Therefore, it seems that the recommended criteria can have an acceptable efficacy in diagnosing Buerger's disease especially in the Iranian population, with easily measuring the criteria elements, putting scores in the suggested formula and considering more than 0 results as Burger disease; however, it is necessary to conduct more studies with larger sample sizes to evaluate the criteria, further and to compare it with other diagnostic criteria for Buerger's disease. As a result, it is recommended to authors to use this criterion for diagnosing Buerger's disease in their studies in order to assess its efficacy in TAO diagnosis in other populations.

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