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Predicting arterial stiffness with multilayer perceptron; a clinical data-driven approach

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ABSTRACT

Introduction: arterial stiffness is a decrease in the elasticity of the arteries, mainly those of large caliber.

Objective: to predict the presence or absence of arterial stiffness through primary care examinations using multilayer perceptron.

Materials and methods: analytical and cross-sectional study of a secondary database made up of 801 patients undergoing estimation of cardio-ankle vascular index (CAVI) using an atherosclerosis detector. The dependent variables were left CAVI (LCAVI), right CAVI (RCAVI). The independent variables were 11 tests obtained through clinical history. Multilayer perceptron-type neural networks were used, from which the classification table, predictive capacity, and diagnostic tests were evaluated.

Results: for LCAVI, the model had an area under the curve (AUC) of 0.878. For RCAVI, the AUC was 0.869. The model test had a percentage of correct predictions for CAVI ≥ 9 of 70.70% and 67.10% for LCAVI and RCAVI, respectively. For CAVI < 9 it was 91.60% for LCAVI and 94.60% for RCAVI. The correlation between the presence and absence of arterial stiffness of the CAVI test of the atherosclerosis detector, and the CAVI obtained by multilayer perceptron was moderate for LCAVI (K = 0.579) and RCAVI (K = 0.587). Specificity values were 92% and 93% for LCAVI and RCAVI, respectively. The negative predictive value was 88% for LCAVI and 89% for RCAVI.

Conclusions: the multilayer perceptron-type neural network, based on primary care examinations, had a high predictive value for LCAVI and RCAVI to exclude the presence of arterial stiffness.

INTRODUCTION

Arterial stiffness is a natural process associated to biological ageing, accelerated by inflammation produced in a scenario of arteriosclerosis, caused by common mechanisms that include a reduced elastin/collagen ratio, due to cross linking of elastin, inflammation induced by reactive oxygen species, calcification, cell rigidity of the vascular smooth muscle and endothelial dysfunction.[1,2] Ageing causes degenerative changes coursing with contractile impairment of the elastin located in the tunica media due to repetitive cycles of mechanical stress and increase and transformations of arterial collagen proteins generated to compensate elastin loss, as well as collagen reticulation due to the final products of advanced glycation.[3] The increase in arterial stiffness is associated to a higher risk in cardiovascular disease (hypertension, myocardial infarction, heart failure, stroke), which are the first cause of death at world level, with more than 20 million yearly deaths.[4]

The determination of arterial stiffness can be made with cardio-ankle vascular index (CAVI), which measures arterial stiffness directly, is not invasive and has a high value to predict cardiovascular morbimortality, mainly in adults older than 60 years.[5] It derives from the Bramwell-Hill equation and introduces the stiffness parameter β, representing arterial dilatability, which correlates with artery diameter changes during systole and diastole.[6] CAVI can be obtained with electronic devices called "arteriosclerosis detectors", measuring blood pressure in arms and ankles, performing an ECG, phonocardiograms and determining pulse waves.

CAVI measurement is generally kept for patients with high risk factors of cardiovascular and cerebrovascular morbimortality.[7] The measurement device of arterial stiffness is not used as an instrument of regular measurement in the general population going to the primary care and cardiology medical offices; however, this population may benefit from a preventive and monitoring point of view if they knew they have arterial stiffness or not, which may present a risk of circulatory disease.

In this regard, data stated in the clinical history, and laboratory and hemodynamic results performed as a routine, could be directly or indirectly related to CAVI and could work as an indirect instrument for the estimation of arterial stiffness reaching a greater number of patients. For this reason, the aim of this investigation may predict the presence or absence of arterial stiffness through primary care tests by multilayer perceptron.

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MATERIALS AND METHODS

Study population and design

Analytical, cross-sectional study from data secondary to the Harvard Dataverse repository *(see Ethical Considerations)*, consisting of adults who underwent chest CT scan without contrast and a measurement of arterial stiffness between March 2018 and October 2019.

The database was made up by a total of 801 adults from 18 years of age, who underwent chest CT scan, from whom 791 underwent LCAVI and 786 RCAVI. The authors of the original database reported that it is made up by people who lack significant arterial anomalies or diseases that may severely affect the structure of the arteries, with those being the following: history of aortic revascularization; stent implant or replacement; genetic syndromes identified or suspected, associated to aneurysms and chest aortic dissections (Marfan syndrome, Turner syndrome); congenital variation in a complete or significant branch of the aorta in adults (abnormal right subclavian artery, coarctation of the aorta); inflammatory diseases associated to the disease in thoracic aorta disease; acute arterial syndrome (including aortic dissection and intramural hematoma); aortic aneurysms; severe hypovolemia and unstable hemodynamics; severe heart failure with low ejection fraction; patients in hemodialysis. The total population of the database was used; hence, there was no sampling or randomization technique. The characteristics of the population are in *Table 1.*

Measurements and variables

The dependent variable was the cardio-ankle vascular index (CAVI), whether right (RCAVI) or left (LCAVI); which is a test measuring the degree of arterial stiffness, and it was a qualitative dichotomous variable divided in ≥9, corresponding to values of arterial stiffness, and <9 corresponding to values of absence of arterial stiffness and pre-stiffness. According to the authors of the database, CAVI was obtained by an arteriosclerosis detector VS-1000. Before performing the measurement, the patient rested for 15 minutes, and then CAVI was measured in supine position. The device also recorded blood pressure, ECG, phonocardiogram and pulse waves, automatically estimating CAVI in the left and right sides.

The independent variables were 11 laboratory tests made as part of the patients' evaluation. Continuous variables were age (in years), body mass index (BMI), creatinine (in mg/dL), alanine aminotransferase (ALT, in U/mL), aspartate aminotransferase (AST, in U/mL), systolic and diastolic blood pressure (in mmHg), cholesterol (in mg/dL), triglycerides (in mg/dL), calcium (in mg/dL) and phosphorus (in mg/dL). These results were obtained from the clinical history.

STATISTICAL ANALYSIS

Tables were used for descriptive statistics, obtaining absolute and relative frequencies, and standard deviation. Neural networks were used of the multilayer perceptron

TABLE 1.
Characteristics of the database population

Variable	Value	n	Percentage	
LCAVI	≥ 9	204	25,50	
	<9	587	73,30	
RCAVI	≥ 9	209	26,10	
	<9	577	72	
Age group	18-48	196	24,50	
	49-54	177	22,10	
	55-66	216	27	
	>66	212	26,50	
Smoker	No	536	66,90	
	Yes	265	33,10	
Currently drinking alcohol	No	574	71,70	
	Yes	227	28,30	
HTN	Yes	513	64	
	No	288	36	
T2DM	Yes	177	22,10	
	No	624	77,90	
Coronary artery disease	No	646	80,60	
	Yes	155	19,40	
Chronic pulmonary disease*	No	772	96,40	
	Yes	29	3,60	
	Minimum	Maximum	Mean	SD
BMI	15.30	40.20	24.55	3.30
SBP (mmHg)	91	2230	148.48	20.45
DBP (mmHg)	52	118	79.30	10.27
LCAVI	3.19	14.86	8.150	1.41
RCAVI	3.24	16.95	8.22	1.46
ALT (U/mL)	10	599	27.60	30.5
AST (U/mL)	11	444	24.57	21.01
Creatinine (mg/dL)	0.05	6.25	0.85	0.31
Calcium (mg/dL)	7.21	234.47	9.22	7.98
Phosphorus (mg/dL)	1.30	7.16	3.19	0.56
Total cholesterol (mg/dL)	72.97	375.29	171.92	43.22
Triglycerides (mg/dL)	36.28	1908.85	166.26	168.73

LCAVI: left cardio-ankle vascular index; **RCAVI:** right cardio-ankle vascular index; **HTN:** hypertension (systolic blood pressure ≥140 mmHg); **T2DM:** type 2 diabetes mellitus; chronic pulmonary disease included asthma, cystic fibrosis, chronic bronchitis, bullous emphysema, atelectasis, chronic obstructive pulmonary disease; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **SD:** standard deviation.

TABLE 2.
Summary of the neural network model of the multilayer perceptron type to predict the presence or absence of arterial stiffness according to LCAVI and RCAVI

		LCAVI	RCAVI
Training	Training	564 (71,60%)	547 (69,90%)
	Testing	224 (28,40%)	236 (30,10%)
	Percentage of incorrect prognoses	15.80%	15.90%
	Stopping rule used	1 consecutive step without error decrease	1 consecutive step without error decrease
	Time of training	00:00.1	00:00.1
Testing	Percentage of incorrect prognoses	13.80%	13.60%
	Area under the curve	0,878	0,869

type. The multilayer perceptron is an artificial neural network made up by several layers of interconnected units and neurons, analogous to biological neurons. Every neuron of the hidden and output layers has a nonlinear activation function, allowing the perceptron to model complex relationships.[8] It can execute classification, prediction and regression tasks, and by backpropagation, it learns from labeled data, adjusting connection weights during training.[9] The neural network was used to predict the presence or absence of arterial stiffness (CAVI ≥9), by evaluations included in the clinical history (age, BMI, creatinine, ALT, AST, SBP, DBP, cholesterol, triglycerides, calcium and phosphorus), which was made at the right (RCAVI) and the left (LCAVI). The way to develop the neural network was (in the SPSS statistics 25 software) the following: analysis → neural networks → multilayer perceptron, where the dependent variable (CAVI) and the co-variables corresponding to the independent variables were introduced. Hyperparameters were automatically selected by the software.

The results of the perceptron included the area under the curve (AUC), which evaluated the predictive efficacy of the neural network model, and which considers values between 0.6 and 0.7 as a poor model, 0.7 to 0.8 as an acceptable model, 0.8 to 0.9 as a good model, and more than 0.9 as an outstanding model.[10] Also, a classification table was included for correct prognosis, where it was possible to determine the percentage of accurately predicted cases for CAVI values ≥9 and <9. Also, diagnostic tests were carried out for sensitivity, specificity, positive and negative predictive values between the total CAVI values predicted by the multilayer perceptron and CAVI values obtained from the arteriosclerosis detector.

Data processing and analysis, including the neural network modeling, was carried out with the SPSS statistics 25TM software.

Ethical considerations

The database was taken from the open data repository of the Harvard Dataverse, with open access under Creative Commons Zero (CC0) license, so no authorizations for use or ethical committees were required as the research was conducted based on a secondary source, as well as because of the confidential aspect of the personal information of the analysis unit (surveyed individuals). The principles of the Declaration of Helsinki were followed.

The database is available at the following link: *https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/C0YY9I*

The database specifications can be found in the following link: *https://doi.org/10.3389%2Ffcvm.2021.737161*

RESULTS

For LCAVI prediction, training was made with 564 patients, and testing with 224. For RCAVI, training was with 547 and the test with 236. For LCAVI, the percentages of incorrect prognoses were 15.80% and 13.80% in training and testing, respectively. For RCAVI, the percentage of incorrect prognoses was 15.90% in training and 13.60% in testing *(Table 2).*

The neural network for the prediction of presence or absence of left arterial stiffness (LCAVI) was made up of 3 layers, with an input layer with 11 units, a hidden layer with 9 units, and an output layer with 2 units, with hidden layer activation function of the hyperbolic tangent type and output layer activation function of the identity type. The area under the curve was 0.878, indicating a good predictive capacity for the model *(Figure 1).*

The neural network for the prediction of presence or absence of right arterial stiffness (RCAVI) was made up by 3 layers, with one input layer with 11 units, one hidden layer with 7 units, and one output layer with 2 units, with hidden layer activation function of the hyperbolic tangent type and output layer activation function of the identity type. The area under the curve was 0.869, indicating a good predictive capacity for the model *(Figure 2).*

The percentage of correct prognosis for CAVI <9 was high in the training and testing of the neural network. The testing had a percentage of correct prognosis for CAVI ≥9 of 70.70% and 67.10% for LCAVI and RCAVI, respectively. For CAVI <9 it was 91.60% for LCAVI and 94.60% for RCAVI *(Table 3).*

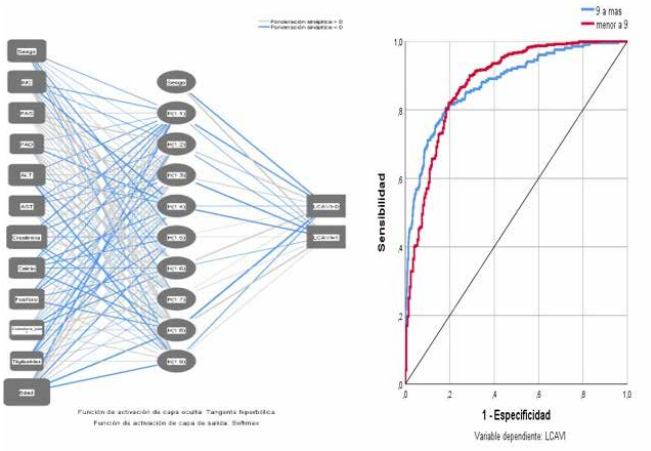

FIGURE 1
Neural network structure of the multilayer perceptron type and area under the curve for primary care tests predictors of presence or absence of arterial stiffness in the left side.

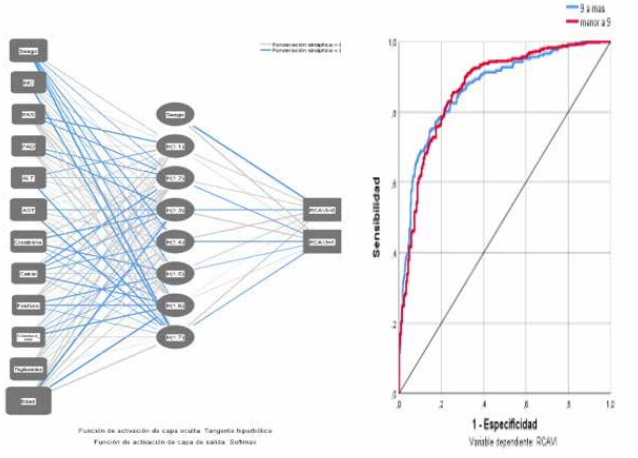

FIGURE 2
Neural network structure of the multilayer perceptron type and area under the curve for primary care tests predictors of the presence or absence of arterial stiffness of the right side.

The correspondence between the presence and absence of arterial stiffness of the CAVI testing of the arteriosclerosis detector and the CAVI obtained by multilayer perceptron was moderated for LCAVI (K=0.579) and RCAVI (K=0.587). There were high specificity values, of 92% and 93% for LCAVI and RCAVI, respectively, and high negative predictive values of 88% for LCAVI and 89% for RCAVI (Table 4).

DISCUSSION

The variables introduced in the multilayer perceptron to predict arterial stiffness by the CAVI index, besides presenting a high correlation with the Cohen's Kappa test, had a high percentage of correct prognoses to detect cases where the CAVI index was less than 9, as well as high levels of specificity and negative predictive value, indicating that this neural network was very reliable to rule out the presence of arterial stiffness. Furthermore, the area under the curve was 0.878 and 0.869 for LCAVI and RCAVI, respectively, showing a good performance of the classification model. These results allow to infer that it is feasible to create analytical models based on historical clinical data, which improve the performance of the multilayer perceptron by training the neural network for the qualitative estimation of arterial stiffness, with abilities similar to the arteriosclerosis detector test in terms of the ability to rule out arterial stiffness.

Recent studies have explored the chance of estimating arterial stiffness. Park and Shin. developed an artificial neural network to predict vascular ageing, using decomposition data of the waveform of photoplethysmogram as variables.[11] Li et al. developed a neural network to determine pulse waves based on history of cardiovascular disease and physiological parameters.[12] Hsiu et al. used the multilayer perceptron to predict arterial ageing using signals.[13] Although previous studies have used information neural networks, this is probably the first study evaluating data cross-

TABLE 3.
Classification table of correct prognoses for the presence or absence of arterial stiffness (CAVI) through primary care tests by multilayer perceptron

		LCAVI			RCAVI		
		Predicted			Predicted		
Single		≥9	<9	Correct percentage	≥9	<9	Correct percentage
Training	≥9	85	58	59.40%	83	53	61.00%
	<9	31	390	92.60%	34	377	91.70%
	Global percentage	20.60%	79.40%	84.20%	21.40%	78.60%	84.10%
Pruebas	≥9	41	17	70.70%	47	23	67.10%
	<9	14	152	91.60%	9	157	94.60%
	Global percentage	24.60%	75.40%	86.20%	23.70%	76.30%	86.40%

TABLE 4.
Sensitivity, specificity, positive and negative predictive value and correspondence between presence or absence of arterial stiffness according to CAVI obtained through primary care by multilayer perceptron

	LCAVI		RCAVI	
	Value	**95% CI**	**Value**	**95% CI**
Se	0,63	0,56-0,69	0,64	0,57-0,70
Sp	0,92	0,90-0,94	0,93	0,90-0,95
PPV	0,74	0,67-0,80	0,75	0,69-0,82
NPV	0,88	0,85-0,90	0,89	0,85-0,90
K	0,579		0,587	

SE: sensitivity; **SP:** specificity; **PPV:** positive predictive value; **NPV:** negative predictive value; **K:** Cohen's Kappa coefficient.

referencing from clinical histories to evaluate the presence or absence of arterial stiffness. The results obtained based on predictor variables are based on the relation they have with arterial stiffness from a pathophysiological view.

Age influences on arterial stiffness due to arterial wall hardening, as they lose elasticity. Constant pulsing, over time, lead to fatigue and fracture of elastin fibers, increasing vascular calcification and endothelial dysfunction.[14] BMI has been related to arterial stiffness as the increase in adipose tissue leads to dysfunction in vascular, endothelial and immune adipocytes with neurohormonal interactions that include insulin, the renin-angiotensin-aldosterone system, the sympathetic system, among others.[15] Creatinine, coming from muscle catabolism, whose serum elevation is related to inappropriate kidney function, and consequently hypertension, has been associated to a higher risk of cerebrovascular disease after 10 years of follow-up in a study.[16]

Aminotransferases, which are inflammatory markers, have been associated to arterial stiffness in observational studies, including young adults.[17,18] Lipids, such as cholesterol and triglycerides, are strongly associated to arterial stiffness, as they are deposit components in the intima layer of the arterial wall.[19] Serum calcium has been directly related to arterial stiffness as part of the atherosclerosis process, with the observation that the risk of cardiovascular disease increases in 10 years, estimated by the Framingham risk score.[20] Phosphorus had a low predictive value in the neural network; however, a study has related it to the arterial stiffness linked to the ankle-arm index, and with cardiovascular disease in healthy individuals, and it has been verified that it induces phenotypical transformation of aortic smooth muscle cells in vitro, into cells similar to osteoblasts.[21]

The tests included in the neural network have been frequently used in medical offices of primary care and specialized ones, so due to their high specificity and negative predictive value, as well as due to their high percentages of correct prognoses in CAVI values less than 9 in the classification table, they could be a means to determine the absence of arterial stiffness in patients attending medical offices, as well as in health campaigns, so using the multilayer perceptron could be a tool for a widespread use to determine the presence or absence of arterial stiffness based on the CAVI obtained by neural networks.

The limitations of this investigation were the origin of the source of information, which came from a secondary database, with the possibility of information and classification biases existing. According to the classification table, this neural network had a low percentage of correct prognoses to detect CAVI ≥9, as well as low sensitivity and positive predictive values of 75%, so it is preferable as a tool to rule out the presence of arterial stiffness, as well as for initial screening, reducing the need for additional tests in unnecessary cases. Likewise, this neural network lacks variables that could have helped to a higher prediction capacity, such as glucose, LDL, HDL, VLDL, waist circumference, among others, so we suggest future investigations that include possible predictors that could not be obtained in this investigation as they were not available in the secondary database.

To conclude, the neural network of the multilayer perceptron type, based on primary care tests, had a high predictive value for LCAVI and RCAVI to rule out the presence of arterial stiffness.

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