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Sensitivity, Specificity of Pulse Wave Velocity (PWV) test for Cerebral Small Vessel Disease (CSVD): A diagnostic Study

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ABSTRACT

Background: present study assessed the sensitivity, specificity and optimal cut-off point of Pulse Wave Velocity (PWV) test for the diagnosis of Cerebral Small Vessel Disease (CSVD).

Methods: 143 Patients candidates for brain MRI in 2022 were included in this observational, prospective diagnostic study. The MRI results were interpreted by two radiologists and the patients with lesions of small cerebral vessels were divided into three groups based on the Fazekas scale, and those diagnosed with CSVD were subjected to PWV. In order to measure the diagnostic value and cut-off point of PWV test in diagnosing CSVD, ROC diagram was used. The sensitivity and specificity of the test were also determined using a cross table and then ICC analysis. The data were analyzed using IBM SPSS Statistics v24.

Results: Rock curve for MeanPWV showed that specificity and sensitivity are 93 and 65.3, respectively. The area under the ROC curve (AUC) was equal to 0.86 with P value <0.001 and the proposed cut-off point was equal to 10.66, and the Youden index of 0.58 shows the high diagnostic value of this test.

Conclusion: The results of the present study show that PWV has sufficient diagnostic power to distinguish healthy people from patients with CSVD, and its use can help in the early diagnosis of lesions of small cerebral vessels and in the direction of Reducing the diagnostic costs of patients with brain lesions will be very useful.

Keywords: Sensitivity, Specificity, Pulse Wave Velocity (PWV), Cerebral Small vessel Disease (CSVD)

INTROCATION

Cerebral small vessel disease (CSVD) structural and functional changes in small vessels (arteries, capillaries, small cerebral arteries and their terminal branches, venules and small veins) are the result of clinical, imaging and pathological manifestations[1, 2], which the main cause of vascular cognitive impairment and is a significant cause of stroke, disability and mortality[3].

CSVD is associated with aging[4] and the increase in life expectancy worldwide has increased CSVD prevalence, affecting almost everyone older than 90 years. CSVD is the attributable cause of 25% of strokes and more than doubles the odds of recurrent stroke5; furthermore, it contributes to 45% of dementia cases[6] and to global functional decline[7]. Epidemiological studies have shown that at least 700 million people worldwide experience various forms of CSVD[8, 9].

Cerebrovascular accidents rank first among all adult neurological diseases in terms of importance and prevalence[10], their management and control can reduce the harmful effects on individuals, families and their quality of life[11, 12], Therefore, acquiring job skills in the diagnosis and treatment of these diseases needs more attention[13].

MRI brain imaging has been accepted as a marker to identify CSVD[9, 14]. MRI divides the severity of WMH lesions in T2/FLAIR of the brain into 3 grades with the Fazekas scale[15-18]. The Fazekas scale, classified by Fazekas et al. 1987, is used to quantify the amount of severe T2 white matter lesions[19]. The scale divides the white matter in periventricular white matter PVWM0 = absent; 1 = “caps” or pencil-thin lining; 2 = smooth “halo”; 3 = irregular periventricular signal extending into the deep white matter and deep white matter DWM 0 = absent; 1 = punctate foci; 2 = beginning confluence; 3 = large confluent areas and each region is given a grade depending on the size and confluence of lesions 1 [16, 19, 20].

The disadvantages of MRI include expensiveness, unavailability, patients' fear of brain MRI, long appointments, and the fact that patients sometimes need anesthesia, and the risks that anesthesia has on cardiovascular patients[13, 21-24]. in addition to other negative consequences, the use of newer approaches, can lead to better management of CSVD disease. Because aortic stiffness is one of the important indexes of blood pressure, atherosclerosis, arterial aging and diabetes[9, 11], And studies have shown the importance of evaluating PWV in patients with cerebral vascular disorders and showed that the use of other diagnostic methods in cerebral vascular disorders can improve the diagnosis of this category of cerebral vascular disorders[17, 25-27], other indicators can also be used.

Pulse wave velocity PWV is the most widely used measure of arterial stiffness[27], the gold standard for measuring arterial stiffness and also an independent predictor of stroke[28, 29]. Also, different studies showed that this index is a good predictive value for the occurrence of CVD in the general population and patients with different clinical conditions in different contexts[30-40]. Of course, what is more interesting in the studies are the different cut points that have been obtained[41-50] and it seems that the life context of the studied populations has been very influential. Therefore, the present study aims to evaluate the diagnostic value of the PWV test sensitivity, specificity, determination of the cut-off points in the diagnosis of CSVD in the context of Iran.

METHODS

Ethical issues

Ethical clearance (IR.KAUMS.MEDNT.REC.1400.208) for this study was approved by research Ethics Committees of faculty of medicine & faculty of Dentistry-kashan university of medical sciences referring to Declaration of Helsinki.(https://ethics.research.ac.ir/PortalProposalList.php?code=IR.KAUMS.MEDNT.REC.1400.208&title=&name=&stat=&isAll=&GlobalBackPage=)

Study design, Setting and duration

Prent study was observational, prospective diagnostic study. This paper refers to STARD guidelines[51] for the reporting of diagnostic test accuracy. The study was performed at Beheshti Hospital of kashan, in Iran from March 13, 2022 to December 15, 2022.

Study Cohort and Participant Recruitment

In this study, 143 patients aged 40 to 70 years with results consistent with cerebral small vessel disease (CSVD) who were candidates for MRI in the radiology department of Shahid Beheshti Hospital, Kashan, were included in the study by simple non-random sampling. Enrolment continued until completion of the required sample size.

Selection criteria

Inclusion criteria

1. Patients (in the age range of 40-70 years) who have undergone Brain MRI.
2. Not suffering from severe mental and physical illnesses that prevent the patient from cooperating.
3. There should be no brain structural disorder in the brain MRI taken from the patient.
4. Informed consent to participate in the study

Exclusion criteria

1. Incompletely completing each of the questionnaires
2. Failure to apply for the PWV test

Test Methods

Patients were subjected to MRI of the brain by PHILIPS MRI machine /1.5T/2007 in the same way as T2 sequences in T1&FLAIR sections, Axial/Cronal/Sagital in Axial sections.

(A) MRI Image

FLAIR spin echo (TE 300 ms, TR 4800 ms, TI 1660 ms, slice thickness 3mm, Filip Angle 90, Matrix size208× 206, FOV 240 mm, inter slice gap 0.3mm)

T2 Axial turbo spin echo (TE 120 ms, TR 7000 ms, slice thickness 5 mm, Filip Angle 90, Matrix size 288× 21, FOV 240 mm, inter slice gap 0.5mm)

(B) Image interpretation

Then the obtained stereotype was interpreted by an experienced radiologist.

At this stage, to increase consistency, the results were again interpreted by another radiologist.

The radiologist divided the patients with lesions of small cerebral vessels into groups based on the Fazekas scale.

Fazekas 0: absence of hyperintensity in the white matter.

Fazekas 1: point focal lesions (single lesions < 9 mm; group lesions < 20 mm).

Fazekas 2: the beginning of confluent lesions (single lesions 10-20 mm; group lesions >20 mm with any diameter).

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Fazekas 3: confluent lesions (single lesions or mixed areas with a size of more than 20 mm).

Individuals diagnosed with CSVD were then assessed with PWV. Demographic and disease related information (severity of
CSVD lesions, age, gender, history of heart disease, family history of heart disease, blood pressure and diabetes) were collected.

(C) PWV Test
It was performed by a sonologist using a fixed color doppler ultrasound machine equipped with an electrocardiogram machine with a 10 MHz transducer. After connecting the three ECG leads to the patient's chest, the Doppler spectral wave from the common carotid artery (at a distance of 10 mm from the bifurcation site) was recorded simultaneously with the ECG wave. This work was repeated 5 times and findings were recorded each time. Then, similar photos were taken of the common femoral artery at a distance of 10 mm from the separation of the superficial femoral artery 5 times. After completing the recording of the waves, the distance between the two areas (common carotid and common femoral) was also measured by a cloth meter (cm). In each photo recorded in the two mentioned areas, the distance between the peak of the R wave in the ECG and the beginning of the increase in blood velocity in the Doppler spectral wave was measured (seconds). The average of these numbers was calculated for each area, which indicates the average time for blood to reach the said area from the heart. By deducting the time for the blood to reach the common femoral artery from the time for the blood to reach the common carotid artery, the approximate time of blood movement between the two areas was obtained in seconds, and by dividing the centimeter distance between these two areas by the time obtained, the speed Wave propagation (PWV) was calculated in cm/s.

Blinding
The radiologists were not aware of the clinical data of the subjects and did not know in advance the results of MRI.

Statistical Methods and Analysis
Data analysis was done using SPSS.v24 software. Descriptive statistics were used to express demographic and clinical information; Also, the sensitivities, characteristics and predictive values of PWV were calculated based on MRI diagnosis. In order to measure the diagnostic value and the cut point of the PWV test in the diagnosis of CSVD, the ROC diagram was used. The sensitivity and specificity of the test were also determined using a cross table, and then ICC analysis and Altman's long diagram were used to evaluate the reliability of the test. All parameters were reported with 95% confidence interval (CI); A significance level of 0.05 was considered.

RESULT
Out of 143 participants in the study, 71 people were in the normal group (Fazekas=0), and 72 people were in the abnormal group (Fazekas=1,2,3). As you can see in Table 1, the mean and (standard deviation) age in the two normal and abnormal groups are 50.6 (9.87) and 60.8 (7.99), respectively, and this difference is statistically significant (P<0.001). In addition, the Mean difference between the normal and abnormal groups in the variables of height (P=0.88), weight (P=0.19) and BMI (P=0.22) was not statistically significant. The Mean difference between two normal and abnormal groups was significant in triglyceride (p=0.007), LDL (p=0.01), HDL (p<0.001), CHOL (p=0.003)) and VLDL (p=0.005) variables. Also, in the PWV mean variable, the Mean PWV was 10 in the normal group and 10.77 in the abnormal group, which is a statistically significant difference (P<0.001) (Table 1).

TABLE I. Main demographic parameters and risk factors in patients

Variable		Mean (SD)		
		Normal (N=71)	Not Normal (N=72)	P-Value
Sex (%)	Male	34(47.90)	37(51.40)	0.67
	Female	37(52.10)	35(48.60)	
Age		50.63(9.87)	60.87(7.99)	<0.001
Height(cm)		169.00(9.36)	168.00(8.29)	0.88
Weight(kg)		71.50(14.36)	73.77(13.60)	0.19
BMI		25.00(3.54)	25.76(3.88)	0.22
Triglyceride		89.52(31.95)	107.84(43.16)	0.007
LDL		101.16(23.99)	114.27(31.23)	0.01
HDL		50.33(13.09)	42.72(12.52)	<0.001
CHOL		154.92(44.83)	184.16(59.83)	0.003

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VLDL		17.74(6.46)	21.12(7.91)	0.005
CR		0.98(0.14)	1.01(0.20)	0.14
heart rate		71.49(11.64)	71.51(12.17)	0.99
PWV mean		10.00(0.51)	10.77(0.51)	<0.001
CVD (%)	Yes	4(5.6)	24(33.3)	<0.001
	No	67(94.4)	48(66.7)	
HTN (%)	Yes	28(39.4)	43(59.7)	0.01
	No	43(60.6)	29(40.3)	
Smoker (%)	Yes	11(15.5)	9(12.5)	0.6
	No	60(84.5)	63(87.5)	
DM (%)	Yes	10(14.1)	15(20.8)	0.28
	No	61(85.9)	57(79.2)	
RF (%)	Yes	2(2.8)	4(5.6)	0.41
	No	69(94.4)	68(94.4)	
Migran (%)	Yes	4(5.6)	21(29.2)	<0.001
	No	67(94.4)	51(70.8)	
FHCVD (%)	Yes	12(16.9)	18(25)	0.23
	No	59(83.1)	54(75)	
BP (%)	Yes	0	0	-
	No	71(100)	71(100)	

The difference between the two normal and abnormal groups in the variables of exposure/exposure (has-not) CVD (P<0.001), HTN (p=0.01) and migraine (P<0.001) is statistically significant and in the variables used Smoking (p=0.6), diabetes mellitus (p=0.28), RF (p=0.41), the difference between the two groups is not significant. There is also a slight difference in the FHCVD variable between the normal (16.9) and abnormal (25) groups, but this difference was not statistically significant (p=0.23). (Table 1).

Although the normal group does not have Fazekas classification, the difference between the three grades of the abnormal group is statistically significant. In such a way that the first grade of this variable includes 55.6%, the second grade equals 23.6% and the third grade equals 20.8% of the participants in the abnormal group. (Table 2).

TABLE II. The difference between the Fazekas grades in the abnormal group

Variable	grade	Normal	Not Normal	P-Value
Fazekas N (%)	0	71(100)	0	>0.001
	1	0	40(55.6)	
	2	0	17(23.6)	
	3	0	15(20.8)	

As you can see in Figure 1, the rock curve for MeanPWV shows that the points of the MeanPWV index have the highest sensitivity and Specificity that are on the left and top of the diagram so that the closer the rock curve is to this part ((corner) The left side of the diagram and the upper part) the accuracy of the diagnostic method in differentiating healthy people from the sick is higher. According to this diagram, the specificity and sensitivity of the proposed cut point are 93 and 65.3, respectively.

In order to measure the diagnostic power of PWV in order to identify patients from healthy people, the ROC curve was used, the results of which you can see in Table 3. Considering that the area under the ROC curve is equal to 0.86 and the P value is <0.001, it can be concluded that MeanPWV has sufficient diagnostic power to distinguish patients from healthy people. Also, the number 10.66, which has the highest sensitivity and specificity, can be considered as the best cut point for MeanPWV.

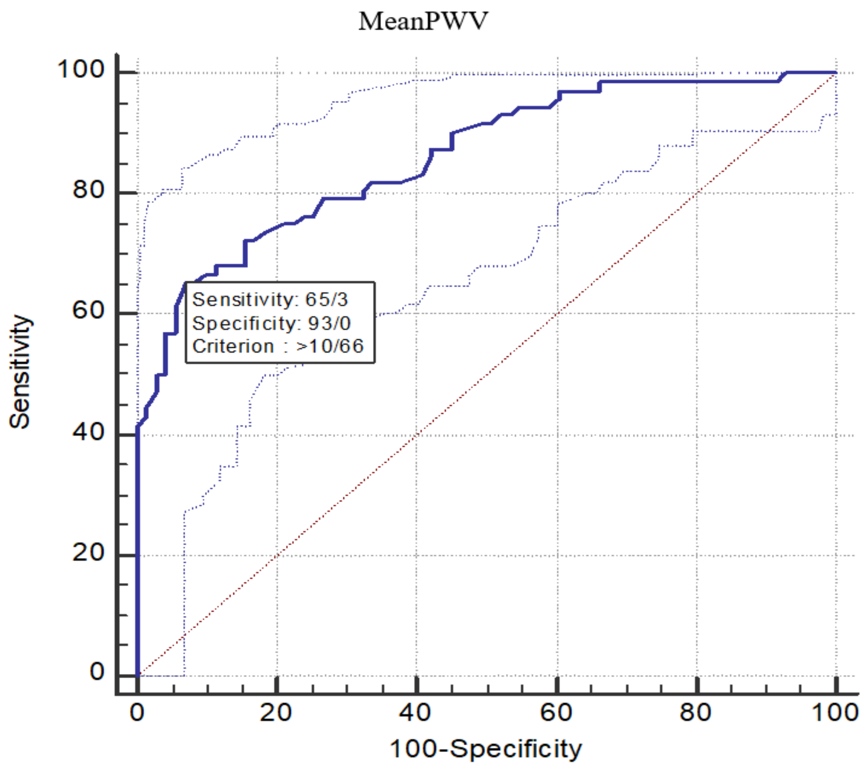

FIG 1. Rock curve for Mean PWV

TABLE III. ROC curve analysis results

Area under the ROC curve (AUC)	0/861
Standard Errora	0/0300
95% Confidence intervalb	0/793 to 0/913
z statistic	12/027
Significance level P (Area=0.5)	<0/0001

There is an important question in ROC Curve analysis and that is which point should present tsudy accept as the best cutoff point. This point should be a number that has the highest sensitivity and specificity. To determine the optimal cut-off point, present tsudy used the Yoden index, the results of which you can see in Table 4. Based on this index, our optimal and desirable cut-off point is the one with the highest sum of sensitivity and specificity. The value of 0.58 Youden index for this diagnostic test shows the good performance of PWV in differentiating between Patients and healthy people.

TABLE IV. Youden index results

Youden index J	0/5824
95% Confidence intervala	0/4411 to 0/6800
Associated criterion	>10/66
95% Confidence intervala	>10/45 to >10/84
Sensitivity	65/28
Specificity	92/96

In order to compare the Mean PWV in the normal and abnormal groups as well as the three abnormal groups based on the Fazekas variable, the Bonferroni post hoc test was used, the results of which can be seen in Table 5. According to this table, the mean difference of MeanPWV in the group whose FAZEKAS status is normal is significant compared to the other three groups. For example, the difference in the Mean PWV of the normal group compared to group 1 is -0.5, which indicates that the normal group has a lower Mean PWV, which is statistically significant. Also, the difference in the Mean PWV in group one compared to all three groups has shown a significant difference. For example, the average difference of group one compared to group three is -0.56, which indicates that group one has a lower Mean PWV compared to group three, and this difference is statistically significant (P=0.001).

Table V. Multiple comparison of mean PWV based on Fazekas variable

(I) FAZEKAS	(J) FAZEKAS	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
0	1	-.54598*	.09575	.000	-.8023	-.2897
	2	-1.00540*	.13078	.000	-1.3554	-.6554
	3	-1.11023*	.13763	.000	-1.4786	-.7419
1	0	.54598*	.09575	.000	.2897	.8023
	2	-.45943*	.14022	.008	-.8347	-.0841
	3	-.56425*	.14664	.001	-.9567	-.1718
2	0	1.00540*	.13078	.000	.6554	1.3554
	1	.45943*	.14022	.008	.0841	.8347
	3	-.10482	.17157	1.000	-.5640	.3544
3	0	1.11023*	.13763	.000	.7419	1.4786
	1	.56425*	.14664	.001	.1718	.9567
	3	.10482	.17157	1.000	-.3544	.5640

To measure the reliability of PWV, present tsudy used Intraclass Correlation Coefficient (ICC), the results of which you can see in Table 6 and Figure 2. In the first measurement with the second, the ICC value is equal to 0.43, which has poor reliability, and in the second measurement with the third, the ICC value is equal to 0.63, with moderate reliability, and in the third with the fourth measurement, this value reaches 0.93, which has excellent reliability, that You can see it clearly in Figure 2. Also, in the fourth and fifth measurements, it has an ICC value of 0.57, which has moderate reliability.

TABLE VI. intra-class correlation coefficient (reliability) of PWV

measures		Intraclass Correlation (ICC)	95% Confidence Interval		Fisher's test with True Value 0			
			Lower Bound	Upper Bound	Value	df1	df2	Sig
first with second	Single Measures	0.43	0.29	0.56	5.56	141	141	
second with third	Single Measures	0.63	0.52	0.72	4.4	142	142	0.000
Third and fourth	Single Measures	0.93	0.91	0.95	31.07	142	142	

fourth with fifth	Single Measures	0.57	0.45	0.67	7.74	142	142

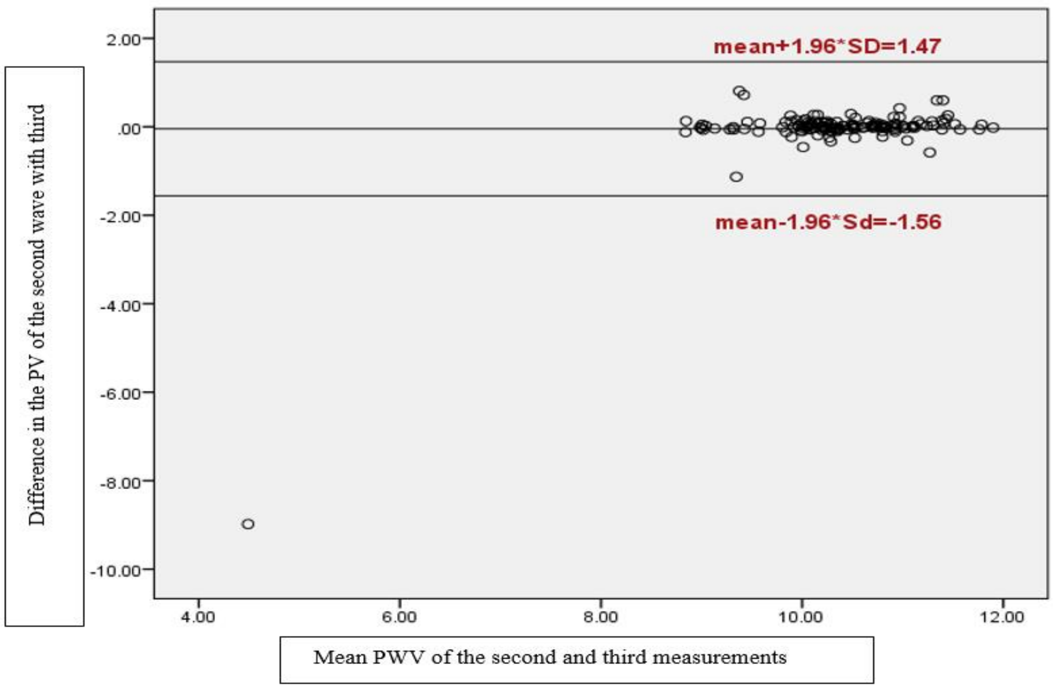

FIG 2. Blan-Alman diagram of the second and third measurements of wave propagation

DISCUSSION

This study was conducted in the context of Iran and in the city of Kashan. In two normal and abnormal groups, the average difference between height, weight and body mass index variables was not significant, and it was significant in the clinical variables of triglyceride, LDL, HDL, CHOL, VLDL. Also, there is a significant difference in CVD, hypertension, smoking and migraine, and there is no significant difference in diabetes mellitus, RF and FHCVD.

In this study, present tsudy calculated the sensitivity and specificity for MeanPWV in differentiating healthy people from patients 93 and 65.3, And since the Area under the ROC curve (AUC) was equal to 0.86, it can be concluded that MeanPWV has sufficient diagnostic power to distinguish Patients from healthy people (P Value <0.001). And because in the ROC Curve analysis, present tsudy should accept the point where the sensitivity and specificity are the highest as the best cutoff point, the number 10.66, which has the highest sensitivity and specificity, is suggested as the best cutoff point for MeanPWV. In addition, the Youden index of 0.58 indicates the good performance of the diagnostic test in differentiating between Patients and healthy people.

Ohyama study in examining the relationship between AaPWV and CVD events, stated the mean value of AaPWV as 7.4 m/s (IQR 5.6 to 10.2) and stated a significant positive relationship between AaPWV and age for outcomes and also stated showed that AaPWV assessed by MRI is a significant predictor of CVD events among middle-aged individuals (45-54 years old), meaning that PWV can distinguish Patients from healthy Peoples for CSVD with susceptibility and The high feature confirms the correct diagnosis[48].

In a study where the diagnosis of the presence and severity of CSVD was investigated based on the total score of baPWV, the optimal cut-off of baPWV for the diagnosis of CSVD was estimated at 13.12 m/s and for the diagnosis of severe CSVD at 15.63 m/s; The results showed a positive correlation of BaPWV with the total score of CSVD, therefore baPWV measurement was reported to be a useful and suitable method for early detection of CSVD; These findings are in line with the results of the present study and confirm the results[52].

Another study also showed that increased arterial stiffness has a direct relationship with CSVD imaging markers; Therefore, evaluating arterial stiffness with PWV can help distinguish CSVD patients from healthy individuals[13].

In addition, Robert study showed that increased carotid artery stiffness, caused by central aortic pressure, is associated with markers of cerebral microvascular disease, vascular dementia, and cognition, and that cerebral microvascular disease is partly due to the deleterious effects of carotid artery stiffness, and increased carotid artery stiffness may help identify patients with or at risk of developing cerebral microvascular disease, cognitive impairment, and dementia, so that timely interventions and preventive strategies can be effectively implemented be executed. Therefore, the diagnosis of patients with small cerebral vessels can be made using the PWV, which is Confirmed by our study based on accurate statistics[53]. Chang study[54], unlike our study, which emphasizes and confirms the diagnosis of CSVD by the PWV method, emphasizes that PWV does not significantly reflect the severity of CSVD.

Questioning the threshold value of 10 m/s cfPWV established by the European Society of Hypertension to classify patients into neurocardiovascular risk groups, Atef Badji reported that when white matter microstructure was considered as a basis for comparison, The threshold value of cfPWV is equal to 8.5 m/s[44]. Although the cut-off point of 10 m/s approved by the European Society of Blood Pressure is closer to the results of our study, Atef Badji's study rejects it[44].

Conclusion

The sensitivity, specificity, and also the Area under the ROC curve (AUC) show that PWV has sufficient diagnostic power to distinguish healthy people from patients with cerebral small vessel disease (CSVD). Therefore, according to the disadvantages of MRI and the risks of anesthesia has for previous patients and vessels, it is a suitable method for diagnosing the disease of small cerebral vessels, for this reason, its use can help in the early diagnosis of lesions of small cerebral vessels and in the direction of Reducing the diagnostic costs of patients with brain lesions will be very useful.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The author declares no conflicts of interest.

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