



A SAGE score cutoff that predicts high-pulse wave velocity as measured by oscillometric devices in Brazilian hypertensive patients

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Abstract

We aimed to identify the optimal cutoff SAGE score for Brazilian hypertensive patients who had their pulse wave velocity (PWV) measured with oscillometric devices. A retrospective analysis of patients who underwent central blood pressure measurement using a validated oscillometric device, the Mobil-O-Graph® (IEM, Stolberg, Germany), between 2012 and 2019 was performed. Patients with arterial hypertension and available data on all SAGE parameters were selected. An ROC curve was constructed using the Youden index to define the best score to identify patients at high risk for high PWV. A total of 837 patients met the criteria for SAGE and diagnosis of hypertension. The median age was 59.0 years (interquartile range [IQR]: 47.0–68.0), and 50.7% of the patients were women. The following comorbidities and conditions were present: dyslipidemia (37.4%), diabetes (20.7%), a body mass index score ≥ 30 kg/m² (36.6%), use of antihypertensive drugs (69.5%), and smoking (18.3%). The median peripheral blood pressure was 128 mmHg (IQR: 117–138 mmHg) for systolic and 81 mmHg (IQR: 73–90 mmHg) for diastolic blood pressure. The median PWV was 8.3 m/s (7.1–9.8 m/s), and the prevalence of high PWV (≥ 10 m/s) was 22.9% (192 patients). A cutoff SAGE score ≥ 8 was effective at identifying a high risk of PWV ≥ 10 m/s, achieving 67.19% sensitivity (95% CI: 60.1–73.8) and 93.95% specificity (95% CI: 91.8–95.7). With this cutoff point, 1 out of every 5 treated hypertensive patients would be referred for a PWV measurement. A SAGE score of ≥ 8 identified Brazilian hypertensive patients with a high risk of future cardiovascular events (PWV ≥ 10 m/s).

Keywords Arterial stiffness · Hypertension · Risk factors · Risk scores · Triage.

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Introduction

The measurement of pulse wave velocity (PWV) is an important tool for the early identification of vascular damage [1–8] caused by elevated blood pressure (BP) or the presence of other factors associated with accelerated vascular aging; carotid-femoral analysis is the gold standard method for PWV measurement [1, 9–11].

Despite growing evidence for the clinical applicability of measuring carotid-femoral PWV due to the availability of devices and software capable of obtaining this measure in a noninvasive way, its implementation in clinical practice is still incipient and restricted to tertiary and research centers. There is a significant gap between the potential clinical benefit of early damage identification and its practical use in the real world [12].

The SAGE score has been validated in European and Japanese populations and used to screen and identify hypertensive patients with an elevated likelihood of PWV

Table 1 Acronym and definition of the SAGE score

Acronym	Definition	Score
S	Peripheral systolic blood pressure	
	<140 mmHg	0
	140–159 mmHg	3
	160–179 mmHg	5
	≥180 mmHg	6
A	Age	
	<50 years	0
	50–59 years	2
	60–69 years	4
	≥70 years	6
G	Fasting glucose	
	<126 mg/dl	0
	≥126 mg/dl	2
E	CKD-EPI estimated glomerular filtration rate	
	≥90 ml/min per 1.73 m ²	0
	60–89 ml/min per 1.73 m ²	1
	30–59 ml/min per 1.73 m ²	2
	15–29 ml/min per 1.73 m ²	3
Maximum score		17

(A) was categorized as <50 years, 50–59 years, 60–69 years and ≥70 years [12]. Fasting glucose (G) was categorized according to the definition of diabetes mellitus: <126 mg/dl or ≥ 126 mg/dl [12]. Renal function, assessed by the glomerular filtration rate estimated by CKD-EPI (E), was classified according to the stages of chronic kidney disease: ≥90, 60–89, 30–59, and 15–29 ml/min per 1.73 m² [12, 14]. The SAGE score received a score from 0 to 17 points, as shown in Fig. 2 [12].

After the SAGE calculation, the overall sample of hypertensive patients and those with PWV ≥ 10 m/s were divided into score categories from 0 to 17 to analyze the frequency of the scores. PWV values ≥ 10 m/s are related to increased aortic stiffness in hypertensive patients and the presence of target organ lesions [1, 4, 21–23].

Statistical analysis

A descriptive analysis was performed with Stata®, version 14.0, using the Kolmogorov–Smirnov test to check the normal distribution of the variables. Descriptive analysis of the data was performed and presented as absolute and relative frequencies, medians, and interquartile ranges (IQRs).

For each SAGE score from 0 to 17, analysis of sensitivity, specificity, positive predictive value, and negative predictive value for PWV ≥ 10 m/s was performed, and a receiver operating characteristic (ROC) curve was constructed using MedCalc® software, version 19.1.7. The

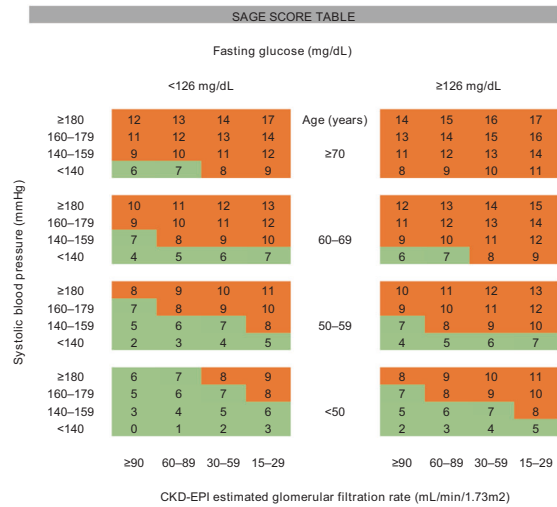


Fig. 2 SAGE score table. Orange (SAGE ≥ 8): high probability of elevated arterial stiffness (PWV ≥ 10 m/s). Green (SAGE < 8): low probability of elevated arterial stiffness. Adapted from a prior study [12]. PWV, pulse wave velocity

optimal cutoff point for the SAGE score to identify patients at high risk for high PWV was chosen using the Youden J index.

In addition to the statistical analysis obtained by the ROC curve graph, the cutoff point was also analyzed using a qualitative approach to determine the ideal cutoff point [12, 13].

Ethical aspects

The study was approved by the Ethics Committee of the Clinical Hospital, Federal University of Goiás (Opinion No. 3,792,750).

Results

A total of 837 patients with a median age of 59.0 years old evaluated (IQR: 47.0–68.0). Among cardiovascular risk factors, dyslipidemia was the most frequent. Most participants were undergoing pharmacological treatment for arterial hypertension, and the most commonly used class of antihypertensive medication was angiotensin II receptor blockers (Table 2). Approximately 39.5% (n = 331) used combinations of antihypertensive drug classes. The other medications used for this purpose were statins (35.7%, n = 299) and oral hypoglycemic agents (8.5%, n = 71).

More than half of the participants had preserved renal function: 33.6% (n = 281) were in stage G1 (≥90 ml/min per 1.73 m²), and 47.9% (n = 401) were in stage G2 (60–89 ml/min per 1.73 m²). Blood pressure was controlled in 65.1% (n = 545), while 25.3% (n = 212) of patients were

Table 2 Patient characteristics and cardiovascular and laboratory risk factors

	<i>n</i>	%	Median (IQR)		<i>n</i>	%	Median (IQR)
Demography				Glucose			
Age ≥70 years	187	22.3%		<126 mg/dl	751	89.7%	
Age 60–69 years	202	24.1%		≥126 mg/dl	86	10.3%	
Age 50–59 years	211	25.2%		LDL			
Age <50 years	237	28.3%		<50 mg/dl	55	6.6%	
Female	424	50.7%		51–69 mg/dl	99	11.8%	
Risk factors				70–99 mg/dl	177	21.1%	
Smoking	153	18.3%		100–129 mg/dl	140	16.7%	
BMI > 30 kg/m ²	306	36.6%		≥130 mg/dl	128	15.3%	
Diabetes mellitus	173	20.7%		Triglycerides			
Dyslipidaemia	438	37.4%		<150 mg/dl	365	43.6%	
Sedentary lifestyle	228	27.2%		≥150 mg/dl	220	26.3%	
Antihypertensive treatment				Blood pressure parameters			
New diagnosis, without medication	255	30.5%		pSBP (mmHg)			128 (117–138)
Prior diagnosis, with medication	582	69.5%		pDBP (mmHg)			81 (73–90)
ACEI	153	26.3%		pPP (mmHg)			56 (39–54)
ARB	294	50.5%		cSBP (mmHg)			118 (109–127)
Calcium Channel Blocker	166	28.5%		cDBP (mmHg)			83 (74–91)
Diuretic	202	34.7%		cPP (mmHg)			34 (29–41)
Alpha blocker	1	0.2%		PVR (s*mmHg/ml)			
Beta blocker	201	34.5%		AI (%)			21 (13–31)
Central action	22	3.8%		PWV (m/s)			8.3 (7.1–9.8)
Biochemical parameters (mg/dl)				Blood pressure			
Creatinine			0.9 (0.8–1.1)	SBP < 140 mmHg	640	76.5%	
Glucose			96 (88–107)	SBP 140–159 mmHg	154	18.4%	
Total cholesterol			172 (145–200)	SBP 160–179 mmHg	32	3.8%	
Triglycerides			130 (93–179)	SBP ≥ 180 mmHg	9	1.1%	
HDL			46 (39–68)	DBP < 90 mmHg	624	74.6%	
LDL			93 (68–123)	DBP 90–99 mmHg	151	18.0%	
VLDL			26 (19–36)	DBP 100–109 mmHg	43	5.1%	
Potassium			4.3 (4.0–4.6)	DBP ≥ 110 mmHg	19	2.3%	
Total cholesterol				Arterial stiffness			
<150 mg/dl	183	21.9%		PWV < 8 m/s	357	42.7%	
150–199 mg/dl	260	31.1%		PWV 8–10 m/s	288	34.4%	
200–249 mg/dl	113	13.5%		PWV > 10 m/s	192	22.9%	
250–299 mg/dl	29	3.5%					
≥300 mg/dl	8	1.0%					

BMI body mass index, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *VLDL* very low-density lipoprotein, *pSBP* peripheral systolic blood pressure, *pDBP* peripheral diastolic blood pressure, *PPP* peripheral pulse pressure, *cSBP* central systolic blood pressure, *cDBP* central diastolic blood pressure, *cPP* central pulse pressure, *pPP* peripheral pulse pressure, *PVR* peripheral vascular resistance, *AI (%)* augmentation index, *PWV* pulse wave velocity, *IQR* interquartile range

Fig. 3 Distribution of SAGE scores, with absolute and relative frequencies

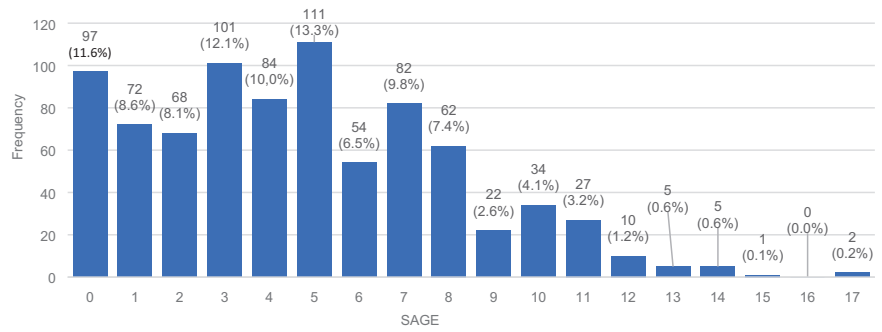


Fig. 4 Absolute and relative frequencies of SAGE scores in patients with arterial stiffness

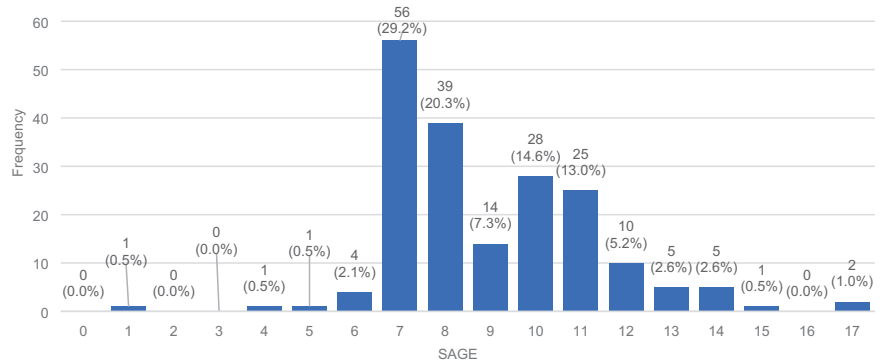


Table 3 Analysis of the sensitivity and specificity of the SAGE score points

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI
0	100.00	98.1–100.0	0.00	0.0–0.6	1.00	1.0–1.0		
1	100.00	98.1–100.0	15.04	12.4–18.0	1.18	1.1–1.2	0.00	
2	99.48	97.1–100.0	26.05	22.7–29.6	1.35	1.3–1.4	0.020	0.003–0.1
3	99.48	97.1–100.0	36.59	32.9–40.2	1.57	1.5–1.7	0.014	0.002–0.1
4	99.48	97.1–100.0	52.25	48.3–56.2	20.8	1.9–2.3	0.0100	0.001–0.07
5	98.96	96.3–99.9	65.12	61.3–68.8	2.84	2.6–3.2	0.016	0.004–0.06
6	98.44	95.5–99.7	82.17	79.0–85.0	5.52	4.7–6.5	0.019	0.006–0.06
7	96.35	92.6–98.5	89.92	87.3–92.1	9.56	7.6–12.1	0.041	0.02–0.08
8	67.19	60.1–73.8	93.95	91.8–95.7	11.11	8.1–15.3	0.35	0.3–0.4
9	46.88	39.7–54.2	97.52	96.0–98.6	18.9	11.4–31.4	0.54	0.5–0.6
10	39.58	32.6–46.9	98.76	97.6–99.5	31.91	15.7–64.9	0.61	0.5–0.7
11	25.00	19.0–31.7	99.69	98.9–100.0	80.62	19.8–328.7	0.75	0.7–0.8
12	11.98	7.7–17.4	100.00	99.4–100.0			0.88	0.8–0.9
13	6.77	3.7–11.3	100.00	99.4–100.0			0.93	0.9–1.0
14	4.17	1.8–8.0	100.00	99.4–100.0			0.96	0.9–1.0
15	1.56	0.3–4.5	100.00	99.4–100.0			0.98	1.0–1.0
16	1.04	0.1–3.7	100.00	99.4–100.0			0.99	1.0–1.0
17	0.00	0.0–1.9	100.00	99.4–100.0			1	1.0–1.0

classified as stage I hypertensive, 6.6% ($n = 55$) as stage II, and 3.0% ($n = 25$) as stage III.

The median peripheral blood pressure was 128 mmHg (IQR: 117–138 mmHg) for systolic and 81 mmHg (IQR: 73–90 mmHg) for diastolic blood pressure. The median PWV was 8.3 m/s (7.1–9.8 m/s), and the prevalence of high PWV (≥ 10 m/s) was 22.9% (192 patients).

Regarding the SAGE score categories from 0 to 17, a score of 5 was the most frequent (Fig. 3). Among hypertensive patients with $PWV \geq 10$ m/s, the most frequent SAGE score was 7 (Fig. 4).

The sensitivity and specificity of different cutoff points are shown in Table 3. In the ROC analysis, the area under the curve (AUC) was 0.95 (95% CI 0.94–0.97; Fig. 5).

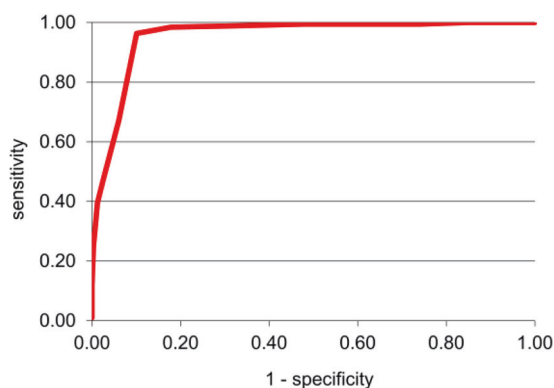


Fig. 5 SAGE score ROC curve. ROC, receiver operating characteristic

According to Youden's J statistic, a cutoff point of 7 provided the optimal combination of sensitivity and specificity for identifying patients with a PWV ≥ 10 m/s. However, the choice of a cutoff point of 8 improved the specificity to 93.95% (95% CI: 91.8–95.7) at the expense of sensitivity, which was reduced to 67.19% (95% CI: 60.1–73.8). A cutoff point of 8 (where score values of at least 8 were considered to indicate high risk) had a positive predictive value of 76.79% and a negative predictive value of 90.58%. This means that one in five hypertensive patients would be referred for PWV analysis. Thus, the use of this cutoff point would aid decision-making by accurately excluding patients who are less likely to have elevated PWV.

Discussion

In this study, the SAGE scores of 837 Brazilian hypertensive patients were determined in order to identify the cutoff point for detecting patients with increased PWV using the brachial cuff oscillometric method.

In 2019, Xaplanteris et al. reported that the SAGE score cutoff point to identify increased carotid-femoral PWV using tonometry in Greek hypertensive patients was 8 [12]. The following year, Tomiyama et al. reported a cutoff point of 7 for Japanese hypertensive patients undergoing brachial-ankle PWV measurement [13]. In this study, the cutoff point identified for Brazilian hypertensive patients was 8, which is identical to the value reported for the European population and close to the value reported for the Japanese population.

Using a quantitative approach (based on the Youden index), the cutoff point was 7. However, using a qualitative approach that prioritized achieving a satisfactory positive predictive value while maintaining a high negative predictive value, a SAGE score cutoff of 8 was selected. Thus, one in five hypertensive patients would be referred for PWV analysis. This means that patients not referred for screening

would have a low probability of high PWV and, therefore, would not be deprived of the risk-predicting value of this biomarker [12, 13].

The difference between the SAGE score cutoff values to identify increased arterial stiffness by the oscillometric method could be related to the fact that the SAGE score, designed to predict elevated values of brachial-ankle PWV in the Japanese population, was calculated based on a slight modification of the originally described method [13]. The estimated glomerular filtration rate was calculated by the CKD-EPI equation for Japanese subjects, which tends to underestimate the prevalence of chronic kidney disease [24]. In addition, the PWV value that was considered abnormal (>1800 cm/s) was slightly lower than the value established to determine the occurrence of cardiovascular disease in the Japanese population using the brachial-ankle method (>1830 cm/s) [25]. The cutoff points obtained using the same CKD-EPI equation and PWV values ≥ 10 m/s were similar [12].

Although carotid-femoral PWV (tonometry) is a cardiovascular risk marker commonly used in Europe [10] and the United States [11], the oscillometric method is more often used in Brazil [15, 18].

The oscillometric method was chosen for the assessment of PWV based on its advantages compared with the gold standard noninvasive method of carotid-femoral measurement by tonometry. The Mobil-O-Graph® is a validated oscillometric device [19, 20, 26], and a series of longitudinal studies compared the oscillometric method with arteriography [26, 27] and tonometry [20], its use in different populations [28–30], and its correlation with the risk of target organ lesions and cardiovascular events [31–33]. Devices using a brachial cuff have many advantages, such as compact and comfortable design, low cost, prevention of operator errors, ease of use, and ease of repeated measurements [1, 9, 18, 21]. However, compared with the intra-arterial measurement of aortic pressure, they tend to underestimate central arterial pressure values and arterial stiffness parameters [20, 28].

Clinical implications

PWV is the gold standard biomarker to identify arterial stiffness, which represents vascular aging [1–4]. The inclusion of PWV in traditional risk scores, such as the Framingham risk score [34] and SCORE [35], significantly increases the predictive value for cardiovascular events. In recent decades, longitudinal studies and systematic reviews have shown that increased arterial stiffness is a strong independent predictor of cardiovascular diseases and total cardiovascular mortality [22, 23]. PWV analysis improves the identification of subclinical disease and the assignment of a high-risk classification to patients who may benefit

from a more aggressive treatment regimen to control cardiovascular risk factors [3].

In the subjects of the Longitudinal Study of Adult Health (ELSA-Brasil), a 1 m/s increase in PWV was associated with a 10% increase in the chance of having a low glomerular filtration rate, a 10% increase in the chance of having a high albumin/creatinine ratio and a 12% increase in the chance of having chronic kidney disease [36]. In a subgroup within this same study, greater aortic stiffness was observed to be associated with a more pronounced decline in cognitive performance, memory and verbal fluency, regardless of systolic blood pressure levels [37]. A cross-sectional analysis of data from the Study of Pulse Wave Velocity in the Elderly in an Urban Area in Brazil (IVOPUI) found increased central arterial stiffness in diabetic hypertensive patients, regardless of systemic blood pressure control [38]. In another cross-sectional study, PWV assessed by oscillometry was the only central hemodynamic parameter correlated with carotid intima-media thickness (IMT) in prehypertensive and hypertensive patients with low cardiovascular risk [31]. In a cross-sectional study on a sample of hypertensive patients, PWV was significantly increased in subjects with left ventricular hypertrophy, IMT > 1 mm, carotid plaque, stenosis $\geq 50\%$ and target organ damage. An IMT greater than 1 mm caused a 3.94-fold increase in the chance of presenting a PWV above 10 m/s [33].

The present study makes a significant contribution to the literature because the implementation of carotid-femoral pulse wave velocity in clinical practice is still in its early stages and restricted to tertiary and research centers, despite growing evidence for the clinical applicability of carotid-femoral PWV measurement due to the availability of devices and software capable of obtaining this measure noninvasively. The SAGE score is a simple clinical score that uses clinical variables widely available in a routine diagnostic investigation of hypertensive patients to identify patients who should undergo PWV measurement [12, 13]. Our paper evaluated SAGE score cutoffs against oscillometric measurements in Brazilian hypertensive patients. Ultimately, the use of the SAGE score will result in wider acknowledgment of the role of aortic stiffness and may aid clinicians in improving the treatment and management of their patients.

Limitations

The SAGE score cutoff was obtained using cross-sectional data from a mixed population of hypertensive patients both on and off therapy and with accompanying comorbidities; although this increases the applicability of the score, it may also result in different levels of accuracy when used in populations with varying proportions of diseases and drug utilization.

Several studies have reported PWV differences between ethnicities and sexes [39, 40]. The present study was limited to the Brazilian hypertensive population, and the possible sex-specific differences in SAGE score cutoff points were not analyzed. Ethnic differences within the Brazilian population were not evaluated, as racial boundaries are ill defined in Brazil due to a high prevalence of mixed-race ancestry. Due to the obvious difficulties in classification, all systems that are used to categorize Brazilians by race have been subject to criticism, as have the reported statistics on the prevalence of arterial hypertension in the Black population in Brazil [41].

Reference values for central blood pressure measurement and arterial stiffness parameters based on the oscillometric method have been defined in the Brazilian population for categories defined by age, sex, and cardiovascular risk factors [18]. However, the present study defined PWV values greater than or equal to 10 m/s as abnormal, according to an article that validated the SAGE score for the European population [12].

Although several studies associate increased PWV with increased mortality and cardiovascular risk [22, 23], the present study focused on assessing the applicability of the SAGE score in Brazilian hypertensive patients using the oscillometric method. Future studies are necessary to analyze whether the SAGE score can modify the cardiovascular outcomes and mortality of patients with subclinical lesions who are indicated for PWV assessment.

Regarding future prospects, we believe that further studies on the application of the SAGE score in patients without a diagnosis of hypertension or use of anti-hypertensive drugs will be useful in the context of primary prevention.

Conclusion

The SAGE score performed well as a predictor of PWV measured in Brazilian hypertension patients using an oscillometric device. The cutoff point found was close to that reported in the Japanese cohort and identical to that reported in the European cohort, indicating that the SAGE score is a practical and robust screening tool to identify patients with probable high PWV, who are at risk for target organ lesions.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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