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Risk factors associated with hemorrhagic cerebrovascular accident

A cross-sectional study in patients from a hospital in Peru

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Abstract

In Peru, cardiovascular accidents (CVA) cause around 15% of premature death, with an increase in CVA due to the prevalence of risk factors for CVA in the Peruvian population. Hemorrhagic CVA presents higher mortality compared to ischemic. This research aimed to identify the risk factors associated with hemorrhagic CVA. We carried out a retrospective cross-sectional study using the medical records of patients with a diagnosis of CVA treated at the Regional Hospital of Ica during the years 2018 and 2019. Independent variables included age, sex, type 2 diabetes, dyslipidemia, hypertension, smoking, obesity, and intracranial carotid artery calcification. To identify factors associated with an increased probability for hemorrhagic CVA compared to ischemic CVA, a generalized linear model with logit link and binomial family, obtaining the odds ratio (OR) and its 95% confidence interval (CI). we evaluated the data from 132 patients. Of them, 46 (34.85%) had hemorrhagic CVA. Only systolic blood pressure (OR: 1.04; 95% CI: 1.02–1.06) and hypertension (OR: 0.29; 95% CI: 0.10–0.89) were significantly associated with hemorrhagic CVA compared to ischemic CVA. Hypertension is associated with hemorrhagic CVA compared to ischemic CVA. These results are consistent with the literature.

Abbreviatures: CI = confidence interval, CT = computed tomography, CVA = cardiovascular accidents, ICAC = intracranial carotid artery calcification, OR = odds ratio, SBP = systolic blood pressure.

Keywords: arterial calcification, Peru, stroke, tomography

1. Introduction

Cerebrovascular accident (CVA, also known as stroke) is the second cause of disability and mortality globally, especially in low-income countries, causing approximately 15 million new cases and 5 million premature deaths in patients.[1] CVA is a rapidly developing clinical syndrome due to a focal disturbance of cerebral function of vascular origin, which can trigger the sudden death of the affected person or leave temporary and permanent sequelae.[2] The most common causes are attributed to the presence of structures that obstruct blood flow in the brain or to the rupture of a blood vessel, generating ischemic and hemorrhagic CVA, respectively.[3] The most common type of CVA is ischemic.[4]

Computed tomography (CT) is one of the most critical and accurate techniques for identifying brain lesions and allows the detection of hemorrhagic CVA and differentiation from ischemic CVA.[5] Likewise, cranial CT is used to identify intracranial carotid artery calcification (ICAC) associated with cerebrovascular and CVA risk.[6] ICAC is generated in the same way as most vascular calcifications, being the product of atherosclerosis, a disease in which atheromatous plaques are generated on the walls of blood vessels made up of lipids and inflammatory cells that become rigid and swell over time and can calcify, mainly due to the accumulation of hydroxyapatite crystals.[7] Studies reveal a positive association between ICAC and the presence of ischemic CVA,[8] in addition to presenting it as a potential independent predictor of CVA.[9] In patients

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Hospital Regional de Ica, on November 24, 2021 (Resolution N° 1215-2021-HR/DE).

Patient consent was waived due to the use of medical records considering the criteria of confidentiality and security. Hence, identifiers were removed to register the analyzed data.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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with CVA evaluated by CT without contrast, it was determined that a high grade of ICAC is related to a high mortality rate.[10]

In Peru, CVA causes around 15% of premature death, harms the population, and harms the health system.[11] In this country, during 2017 and 2018, the standardized incidence of CVA was 38.1 and 44.9 per 100,000 inhabitants and almost doubled in people older than 35. The increase in CVA events in recent years is a complex problem due to its high mortality and generated disability,[12] and there has been a continuous rise in the presence of CVA since 2003.[13] Ischemic CVA in Peru has serious consequences, such as mortality, sequelae, and economic impact.[12] On the other hand, the incidence of hemorrhagic CVA in Peru is 7.82 per 100,000 person-years, and in adults over 35 years old, it increases to 18.14 per 100,000 person-years[4].

CVA has different modifiable risk factors. However, the most significant are hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, diet, alcohol consumption, and smoking,[14] which in Peru have been increasing progressively in the last decade.[15] Studies on CVA in Peru are scarce; however, they have shown that patients with CVA have a significantly reduced quality of life, and the most frequent risk factor in this population is hypertension.[16,17] Even though early detection of intracranial atherosclerotic disease allows therapeutic intervention while CVA is still asymptomatic,[18] unfortunately, CT-based diagnostic services in low-income countries are limited and found in few high-complexity hospitals, which generates a weak response for timely identification of CVA. Although hemorrhagic CVA is not the most frequent of the 2 types, it has a higher mortality rate. Identifying factors related to this type can help identify subgroups with a greater probability of death from a CVA event.[19,20] Hence, this research aimed to identify the risk factors associated with hemorrhagic CVA in patients who presented the diagnosis of CVA based on the CT study in a hospital in Peru between 2018 and 2019. Since many factors are modifiable, we consider the information relevant to improving and strengthening primary prevention actions in groups at high-risk of CVA. Likewise, we believe it is essential to promote evaluation based on images to improve the chance of a diagnosis of CVA.

2. Methodology

2.1. Study population

We carried out a retrospective cross-sectional study using the medical records of patients with a diagnosis of CVA treated at the Regional Hospital of Ica during the years 2018 and 2019. This public hospital is located approximately 300 km from Lima, the capital of Peru, and is classified as a Center of the third level of care. It is the largest in the Ica region, being the hospital with the highest resolution capacity. For the present study, 132 medical records of patients diagnosed with CVA in its 2 forms were included: ischemic and hemorrhagic. CVA diagnoses were made by the head CT, considering the history of risk factors and clinical manifestations (facial dropping, weakness in the arm or leg, sudden numbness and confusion, paralysis, problems with coordination and balance, burning sensation and tingling, nausea and vomiting). Most stroke patients were older adults of both sexes. We excluded records of patients with a history of brain surgery, thrombolytic treatment, and oral anticoagulants.

2.2. Techniques and instruments

We used a file to record the data from the review of the patient's medical history, including the evaluation reports by CT. CTs were performed without contrast, as requested in the medical order. The CTs have performed with a SOMATOM model Siemens tomograph with a definition of 64 slices, following the following tomographic technical parameters: Pitch = 1, Thickness = 1, Kv: 120, mAs: 280.

We collected data on characteristics described in the literature associated with CVA, including the diagnosis of Type 2 Diabetes (T2D), dyslipidemia, hypertension, and obesity. T2D was identified according to the presence of hyperglycemia, glycosylated hemoglobin more significant than 6.0%, and clinical manifestations, as established by the American Diabetes Association.[21] Dyslipidemia was recognized as altering at least one of the following biochemical parameters: total cholesterol >200 mg/dL, triglycerides >150 mg/dL, or HDL <40 and 45 mg/dL among women and men, respectively. Hypertension was considered the sustained elevation of systolic and diastolic blood pressure >140- and 90-mm Hg, and with a history of treatment with antihypertensive drugs. On the other hand, the weight and height at the time of the CT were obtained, and the body mass index was estimated, whose value ≥ 30 kg/m2 was considered obesity.

The evaluation of the cranial CT allowed the recognition of arterial calcification, based on the presence of intracranial calcifications evaluated according to the Hounsfield scale (for intravascular calcifications: Hounsfield Units > 90) and according to the Woodcock criteria,[6] which is divided into 5 degrees of calcification: Grade 0: without calcifications; Grade 1: thin calcifications occupying <10% of the lumen of the artery; Grade 2: thin, interrupted calcifications with a compromise between 10% to 50% of the lumen of the artery, and with a length of <1 cm; Grade 3: interrupted thin or thick calcifications, with a commitment between 10% to 50% of the lumen of the artery, if the calcification is continuous thin or more than 50% if the calcification is thick, and with a length >1 cm; and Grade 4: thick and continuous calcifications occupying more than 50% of the lumen of the artery with a length >1 cm.

The CVA was identified based on the diagnostic results recorded in the medical report. The hemorrhagic CVA was based on identifying lesions in the brain, evaluated by CT. It was identified by hyperdense images (50–100 Hounsfield Units), well-defined, homogeneous, with normal surrounding parenchyma, and surrounded by a hypodense area due to sudden onset edema. On the other hand, ischemic CVA was observed as a hypodense image 24 hours after the event occurred, and with the presence of clinical manifestations, mainly neurological, such as headache with no known cause, altered level of consciousness, visual paralysis, motor incoordination in upper and lower extremities, ataxia, dysarthria, and inattention. It is important to note that CT is one of the most appropriate procedures for diagnosing CVA. According to what was reported by Smajlović D. and Sinanović O.,[22] the sensitivity of CT in the diagnosis of CVA reaches 98.6%, which shows the high reliability of the instrument.

2.3. Data analysis

The study population was characterized using mean ± standard deviation and frequencies, depending on the study variable. The bivariate analysis between independent variables and type of CVA was conducted using Pearson chi-squared, Chi-squared Yates correction, Mann-Whitney nonparametric test, and T-test 2 sides according to the type of variables. The factors associated with CVA were calculated using a generalized linear model with logit link and binomial family, obtaining the odds ratio (OR) and its 95% confidence interval (CI), represented in a Forest Plot graph. A P value < .05 was considered statistically significant. All calculations and statistical tests were performed using Stata Version 17 software (Stata College Station, TX).

2.4. Ethical aspects

The research did not require informed consent, considering it was retrospective, using the information in the patient's medical

records. Likewise, the information obtained was used considering the criteria of confidentiality and security through coding procedures of the variables and the encryption of the files. The Hospital Regional de Ica Ethics Committee approved the study on November 24, 2021, with the resolution N° 1215-2021-HR/DE.

3. Results

We present the characteristics of the 132 patients with CVA evaluated at the Hospital Regional de Ica. The mean age was 69.2 ± 15.3 years, and 57.6% were male. Mean diastolic and systolic blood pressure was 80.2 ± 47.1 and 140.6 ± 27.3, respectively. Sixty-eight-point nine percentage of those evaluated had a diagnosis of hypertension 37.9% of those evaluated had a diagnosis of T2D. The mean body mass index was 27.3 ± 3.7 kg/m2, and 34.5% were obese. On the other hand, 98.5% of those evaluated presented calcification of the intracranial internal carotid artery, with different degrees of affection (I: 2, II: 12, III: 25, and IV: 91). Finally, 65.2% of the cases had an ischemic CVA (Table 1).

For systolic blood pressure (SBP) was identified a difference in the mean SBP among people with ischemic CVA (134.7 ± 24.9 mm Hg) compared with hemorrhagic CVA (151.7 ± 28.4 mm Hg), $P < .001$, with a higher mean un hemorrhagic CVA group (Table 2).

As a result, an increase in SBP (OR: 1.04; 95% CI: 1.02–1.06) and hypertension (OR: 0.29; 95% CI: 0.10–0.89) were significantly associated with hemorrhagic CVA compared to ischemic CVA (Table 3). Other variables had no significant association with hemorrhagic CVA (Fig. 1).

4. Discussion

In this study, hypertension was associated with a reduced probability of hemorrhagic CVA compared to ischemic CVA. A higher SBP was also found in patients with hemorrhagic CVA than

Table 1

Descriptive characteristics of the study participants.

Characteristic	n	%
Sex		
Male	76	57.58
Female	56	42.42
Age (yr)*	69.2 ± 15.3	
Hypertension		
No	41	31.06
Yes	91	68.94
Type 2 diabetes		
No	82	62.12
Yes	50	37.88
Smoking		
No	102	77.27
Yes	30	22.73
Dyslipidemia		
No	69	52.27
Yes	63	47.73
Obesity		
No	101	76.52
Yes	31	23.48
ICAC		
No	2	1.52
Yes	130	98.48
CVA		
Ischemic	86	65.15
Hemorrhagic	46	34.85

CVA = cerebrovascular accident, ICAC = intracranial carotid artery calcification.
* Mean ± standard deviation is reported.

Table 2

Characteristics of the study sample according to the type of CVA.

Variable	Cardivascular Accident, N (%)		*P* value
	Ischemic	Hemorrhagic	
Age (yr)‖	72 (63-81)	68 (58–79)	.171‡
Sex			
Male	50 (58.1)	26 (56.5)	.858*
Female	36 (41.9)	20 (43.5)	
Type 2 diabetes			
No	51 (59.3)	31 (67.4)	.361*
Yes	35 (40.7)	15 (32.6)	
DBP (mm Hg)‖	80.0 (70.0–80.0)	80.0 (70.0–90.0)	.061‡
SBP (mm Hg)¶	134.7 ± 24.9	151.7 ± 28.4	<.001§
Hypertension			
No	28 (32.6)	14 (30.4)	.194*
Yes	58 (67.4)	32 (69.6)	
Smoking			
No	69 (80.2)	33 (71.7)	.267*
Yes	17 (19.8)	13 (28.3)	
Dyslipidemia			
No	41 (47.7)	28 (60.9)	.148*
Yes	45 (52.3)	39.1)	
BMI (kg/m2)¶	27.2 ± 3.5	27.5 ± 4.1	.642§
Obesity			.007*
No	66 (76.7)	35 (76.1)	
Yes	20 (23.3)	11 (23.9)	
ICAC			
No	1 (1.2)	1 (2.2)	.768†
Yes	85 (98.8)	45 (97.8)	

BMI = body mass index, CVA = cardiovascular accidents, DBP = diastolic blood pressure, ICAC = intracranial carotid artery calcification, SBP = systolic blood pressure.
* Pearson chi-squared.
† Chi-squared Yates correction.
‡ Mann-Whitney nonparametric test.
§ t test two side.
‖ Median (interquartile range).
¶ Mean ± standard deviation.

Table 3

Identification of risk factors associated with hemorrhagic CVA in multivariate analysis.

Independent variables	Odds ratio*	CI 95%*	*P* value*
Age (yr)*	0.99	0.97-1.02	.697
Sex			
Male	Ref.	Ref.	
Female	1.01	0.45-2.27	.986
Type 2 diabetes			
No	Ref.	Ref.	
Yes	0.81	0.34-1.91	.630
DBP (mm Hg)*	1.01	0.99-1.02	.291
SBP (mm Hg)	1.04	1.02-1.06	<.001
Hypertension			
No	Ref.	Ref.	
Yes	0.28	0.09-0.87	.029
Smoking			
No	Ref.	Ref.	
Yes	1.20	0.43-3.34	.723
Dyslipidemia			
No	Ref.	Ref.	
Yes	0.69	0.31-1.55	.371
BMI (kg/m2)	1.08	0.91-1.28	.389
Obesity			
No	Ref.	Ref.	
Yes	0.60	0.14-2.58	.490
ICAC			
No	Ref.	Ref.	
Yes	0.32	0.02-5.91	.441

BMI = body mass index, CI = confidence interval, CVA = cardiovascular accidents, DBP = diastolic blood pressure, ICAC = intracranial carotid artery calcification, SBP = systolic blood pressure.
* Generalized linear model.

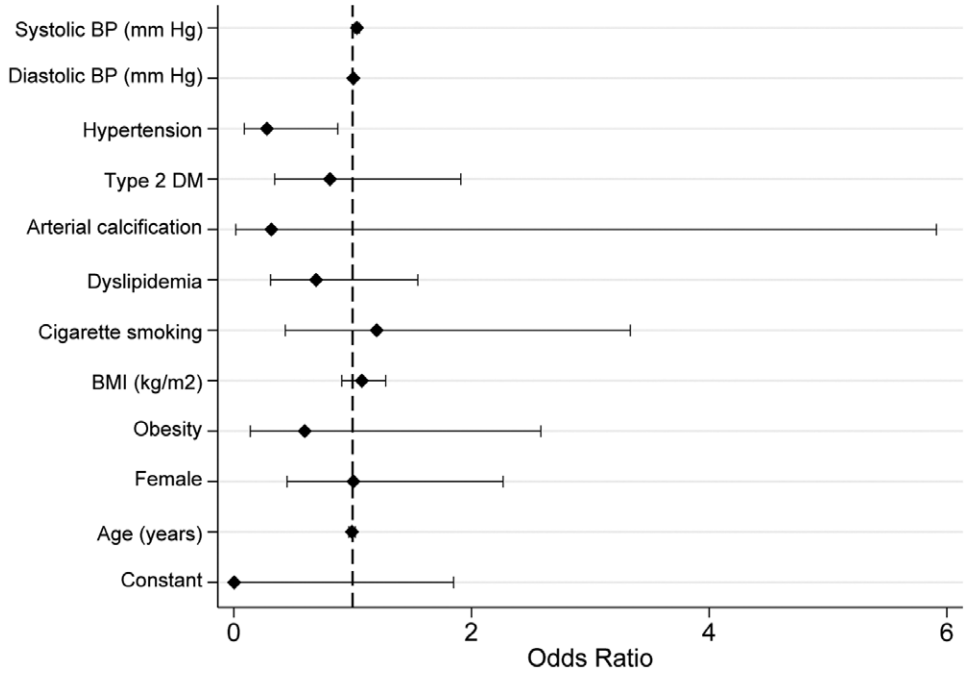


Figure 1. Forest plot of factors associated with stroke in the study population.

those with ischemic CVA. The literature indicates that hypertension is a risk factor for ischemic and hemorrhagic CVA and that untreated chronic hypertension generates endothelial damage with thrombus formation, an atherogenic process, and ischemic lesions,[23] and alters cerebral vasodilation with dysfunction in autoregulation, increasing hemodynamic compromise and even reducing the outer diameter of cerebral arterioles.[24] Even though it was found that hypertension reduced hemorrhagic CVA odds in the study sample (increasing ischemic CVA odds), hypertension has been associated with intracerebral hemorrhage at the ganglia, thalamus, pons, and cerebellum level, probably due to the extensive branching of small blood vessels.[25] It is also a predictor of subarachnoid hemorrhage,[26] evidencing aneurysms only with intima and adventitia content and fewer smooth muscle cells and external elastic lamina.[27] These pathophysiological changes associated with hypertension increase the probability of arterial rupture leading to hemorrhagic, including hemorrhagic CVA.

SBP strongly predicts cardiovascular events, especially its variability over time.[28] Most physicians evaluate SPB regarding elevation above 140 mm Hg, which is undoubtedly associated with stroke. However, there are more effective forms of use, considering that changes in SPB can occur below 140 mm Hg and still be associated with hemorrhagic stroke.[29] Likewise, a significant association has been reported between blood pressure variability and carotid intima-media thickness independently of diseases such as diabetes mellitus.[30] Furthermore, there is evidence that the thickened carotid intima-media thickness of hypertensive patients is associated with atherosclerosis.[31] These aspects are crucial since antihypertensive treatment is usually administered to severe cases. Consequently, SPB can behave independently of hypertension, even as a potential risk factor associated with hemorrhagic stroke.

Recently, researchers evidenced increased stiffness and histological changes in the inner wall of the internal carotid artery in patients with hypertension.[32] So, there could be a link between hypertension, arterial calcification, and CVA. Mak et al[33] identified a high degree of calcification associated with intracranial atherosclerosis and CVA. Regarding ICAC and the CVA subtype, this occurred in almost all the registries evaluated. Its frequency was similar in people with ischemic and hemorrhagic CVA (around 98% in both cases).

Consequently, arterial calcification was not associated with any of the types of CVA. Systematic reviews do not show a conclusive relationship between carotid artery calcification and CVA.[34,35] Despite this, it is pertinent to highlight the importance of CT in identifying the different degrees of arterial calcification, the most frequent being those classified as grade 3 and 4. Other studies have shown that the high degree of calcification of the intracranial carotid artery generates the appearance of microemboli in patients who suffered CVA,[36] so those people who presented grade 3 and 4 calcification (87% of all those evaluated) should continue with the tomographic controls to identify sequelae at the brain level or possible micro embolic events that are associated with future adverse outcomes. Furthermore, the pattern of calcification could be associated with the endovascular treatment effectiveness,[37] data not available for analysis in this study, and that could be relevant for future studies in this population as a predictor for any of the CVA's subtypes.

A Peruvian study carried out by Canchos, M. reported that ischemic CVA is more frequent (75.6%) than hemorrhagic CVA (24.4%),[38] a similar proportion than were found in this study.[39,40] In the literature, many risk factors have been reported for hemorrhagic CVA, including age, sex, T2D, and hypertension. In this study, only hypertension was found to be associated. However, it is advisable to consider other risk factors such as T2D, hypertension, age, and a previous history of CVA when providing recommendations to strengthen primary and secondary prevention actions regarding the development of future events, where according to Alvarado, M. identified out of every 5 people who present CVA for the first time, one of them dies a year following, more frequently in the elderly and in those in whom the CVA has left serious sequelae of disability.[41]

Regarding the study's limitations, it should be noted that there is no temporality due to its cross-sectional design, so causal relationships cannot be established. Likewise, some possible confounders described in the literature (ethnicity, genetics, sodium and sugar intake, physical activity, weight control program)[14] could not be included in the analysis because they needed to be recorded in the information sources. We also did

not obtain information from the historical record of blood pressure, in order to identify its variability. On the other hand, it was not possible to obtain further data from the CT report regarding the number and location of the calcifications within the trajectory of the intracranial carotid artery. The study of the factors associated with stroke must use longitudinal designs, where the behavior of strong predictors such as blood pressure and changes in lifestyle patterns are evaluated. In this way, obtaining more consistent results and improving primary prevention strategies will be possible.

One of the most important benefits of the study is identifying a single risk factor associated with CVA. Uncontrolled hypertension and even independent elevation of systolic blood pressure are modifiable factors through primary prevention strategies, such as strengthening a healthy diet, promoting physical activity, weight control, and smoking. Failure to consider these considerations can negatively impact the health of the affected person. Among the most significant outcomes found in people with CVA is the death of patients whose rate is high. On the other hand, the recurrence of CVA within the first 5 years of suffering the first event, as well as neuropsychiatric sequelae.

5. Conclusion

An association was found between SBP, hypertension, and presenting hemorrhagic CVA compared to ischemic CVA. These results are consistent with the literature. Therefore, preventive and promotional actions should be prioritized to guarantee the treatment and control of patients with hypertension, a high-risk group for this CVA subtype of higher mortality.

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