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The effect of aortic arch calcification on in-hospital mortality in patients with hemorrhagic stroke

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Abstract

Background & Objective: The association between calcifications in the aortic arch and cardiovascular, particularly cerebrovascular, diseases has been widely discussed in the literature. This study aims to investigate the impact of the severity of aortic arch calcification on mortality and morbidity in patients who have experienced a hemorrhagic stroke. *Methods:* The study included 187 patients with hemorrhagic stroke. Clinical, demographic, echocardiographic, and laboratory characteristics of patients who presented to the hospital within the first 24 hours were obtained from hospital discharge summaries and records. The study examined whether there was a difference in the severity of aortic arch calcification between survivors and the in-hospital mortality group. Additionally, the relationship between the severity of aortic arch calcification and morbidity, hemorrhage volume, and localization was investigated. *Results:* Systolic and diastolic blood pressures were found to be lower in the mortality group ($p < 0.05$). In the mortality group, total cholesterol, ejection fraction (EF), and platelet count (PLT) were significantly lower, while glucose, creatinine, NIHSS score, and modified Rankin score were significantly higher ($p<0.05$). Other epidemiological factors and risk factors did not differ from the surviving group ($p>0.05$). Aortic arch calcification was found to have no significant impact on mortality, morbidity, hemorrhage volume, or hemorrhage localization ($p>0.05$).
Conclusion: Vascular calcification is an important risk factor for stroke. Calcifications in large vessels like the aorta are expected to also develop in relatively smaller cerebral vessels. While increased vascular calcification heightens the risk of hemorrhagic stroke, higher severity of aortic arch calcification does not contribute additional risk for mortality in cases of hemorrhagic stroke.

Keywords: Hemorrhagic stroke, vascular calcification, aortic arch calcification, in-hospital mortality

INTRODUCTION

Spontaneous intracranial hemorrhages are the second most common cause of stroke. Approximately 20% of all stroke patients experience spontaneous intracranial hemorrhage.[1] Due to the high rates of mortality and morbidity associated with these events, close monitoring is required. Hypertension, the use of anticoagulant and antiplatelet medications, and vascular pathologies are among the leading causes of hemorrhage.

Atherosclerosis is a progressive disease that leads to endothelial damage in the vascular wall and causes obstruction in vascular structures.[2-4] Calcification of the arterial wall is exacerbated by factors such as hypertension, age, and obesity. Arterial wall calcification is also associated with increased cardiac complications independent of traditional cardiovascular risk factors. Calcifications in the thoracic aorta are associated with severe systemic atherosclerosis and are more prone to complications due to their extensive plaque surface area.[5] In patients undergoing open-heart surgery or requiring intervention on the aorta, those with porcelain aorta have been observed to have higher rates of postoperative cardiovascular and cerebrovascular complications.[6] Some studies have linked high rates of calcification detected in the aorta via computed tomography to increased cardiovascular mortality.[7] It is known that increased calcification rate in the aortic arch is associated with ischemic stroke. An increase in the rate of vascular calcification heightens the

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risk of dissection and hemorrhage. Pathologies observed in the aortic arch also affect intracranial vascular structures. Arterial calcifications can be detected using various imaging techniques.

Evaluation of the aortic arch in chest X-rays and detection of vascular calcifications is a cost-effective, non-invasive, and practical method. The aim of our study is to assess whether the severity of calcification in the aortic arch can predict in-hospital mortality and morbidity in patients who develop spontaneous intracranial hemorrhage.

METHODS

The study population

Approval for the study was obtained from the Ethical Committee of Necmettin Erbakan University. The study included individuals aged 18 and older who were followed in the Neurology Clinic for spontaneous intracranial hemorrhage. Patient files of those who experienced spontaneous intracranial hemorrhage between January 2019 and January 2024 were retrospectively reviewed. Patients with a history of trauma, bleeding diathesis, intracranial bleeding after hypertensive attacks, history of ischemic stroke, presence of intracranial aneurysm, previous history of intracranial hemorrhage, elevated INR, recent infection history within the last month, and malignancy were excluded from the study. Inclusion and exclusion criteria are illustrated in Figure 1.

Study protocol

A total of 187 patients were included in the study. Among these patients, 92 developed in-hospital mortality. Patients were systematically categorized according to their clinical, demographic, echocardiographic, and laboratory characteristics. Computed tomography was utilized to confirm intracranial hemorrhage. In deceased patients, the cause of death was investigated to determine whether it was related to intracranial pathology, and causes of death unrelated to intracranial pathology were excluded. Aortic arch evaluation was performed based on direct chest X-rays taken at the time of admission (Figure 2). Aortic arch calcification was classified into four grades:

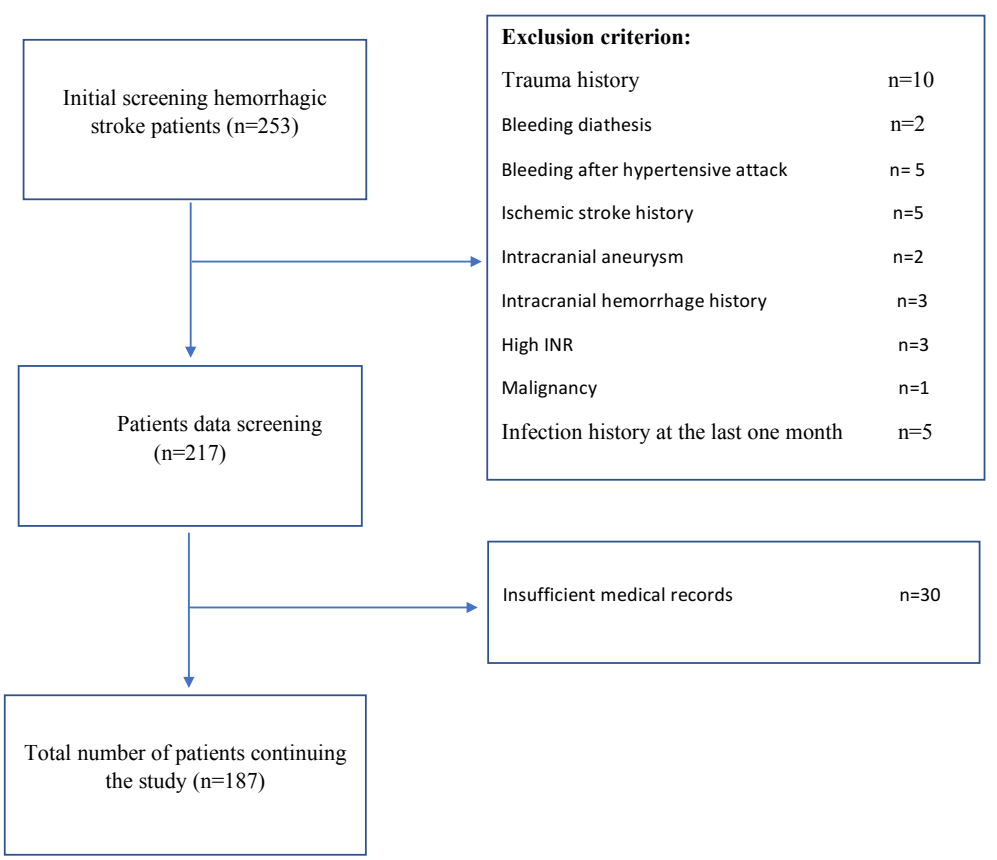

Figure 1. Study flow chart.

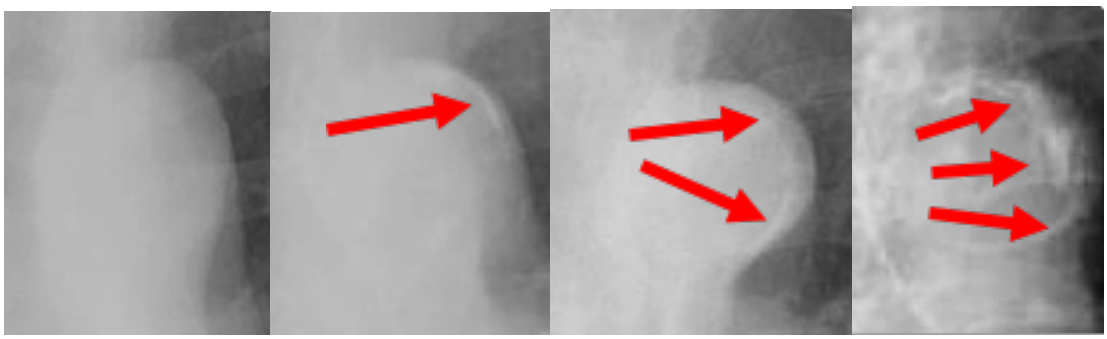

Figure 2. Grading of aortic arch calcification on plain Chest X-Ray.

Grade 0—no visible calcification; Grade 1—small calcification images or linear striations; Grade 2—one or more thickened areas of calcification; Grade 3—circular calcification images. All patients underwent echocardiography. Measurements were taken using the Philips Epiq 7C ultrasound system (Bothell, WA, USA) with a 5-1 MHz transducer. Echocardiographic measurements were performed by two experienced cardiologists following the standard techniques and images recommended by the American Echocardiography Association's guidelines.[8] The left ventricular dimensions and functions, left atrial dimensions, aortic measurements, and pulmonary artery pressures were assessed. Information such as patients' age, history of coronary artery disease, hypertension, diabetes mellitus, and use of anti-platelet and anti-coagulant drugs were obtained from hospital records. Comprehensive evaluations, including complete blood counts and biochemical tests, were conducted.

Statistical analyses

Data analysis was performed using SPSS software (version 20.0; SPSS Inc, Chicago, IL) and presented as mean ± standard deviation or median (interquartile range [IQR]). The normality of distribution was assessed using the Kolmogorov–Smirnov test. Independent Student's t-tests were utilized to compare differences between two groups, while the Mann–Whitney U test was applied for non-normally distributed variables. Differences in categorical variables were evaluated using the Chi-square test.

RESULTS

In patients with hemorrhagic stroke, the mean age of the surviving group (95 patients) was 67 ± 18.5 years, while the mean age of the mortality group (92 patients) was 69 ± 16.9 years, showing no statistically significant difference between the two groups (P value = 0.45). Among the patients included in the study, the proportion of male patients was numerically higher; however, the gender characteristics were similar between the two groups, with no statistically significant differences identified ($p = 0.46$). Traditional risk factors such as hypertension, diabetes mellitus, coronary artery disease, chronic kidney failure, and hyperlipidemia were similarly distributed between the two groups, with no statistically significant differences found ($p > 0.05$). When examining the medications used by the patients with hemorrhagic stroke (antihypertensives, antihyperlipidemics, anticoagulants, antiplatelets), no statistically significant differences were detected between the groups ($p > 0.05$).

In the mortality group, both systolic and diastolic blood pressures were found to be lower compared to the surviving group ($p = 0.016$ and $p = 0.006$, respectively). Similarly, the mortality group had statistically higher NIHSS and modified Rankin scores compared to the surviving group (both $p < 0.001$). The hemorrhagic areas were classified into anterior and posterior systems; however, no statistically significant differences were identified regarding localization between the groups ($p = 0.29$). There was no statistically significant difference between the groups in terms of hemorrhage volume ($p = 0.49$). Sperman's correlation was performed between aortic arc grade, NIHSS, modified Rankin Score and hemorrhage volume, no strong relationship was found between them [respectively, ($r=-0.126$, $p=0.138$), ($r=0.014$, $p=0.866$), ($r=-0.169$, $p=0.027$)].

However, no statistically significant differences

were found between the groups (p = 0.39). Clinical and demographic characteristics of the patients are shown in Table 1. Patients in the mortality group had higher creatinine levels (p = 0.0001). Hemoglobin and platelet counts were found to be lower in deceased patients compared to surviving patients, with statistically significant results (p = 0.025 and p = 0.001, respectively). The left ventricular ejection fraction was also found to be lower in deceased patients compared to survivors, with statistically significant results (p = 0.015). Laboratory and echocardiographic features of the patients are shown in Table 2.

DISCUSSION

Our study demonstrates that an increase in the severity of aortic arch calcification in patients with hemorrhagic stroke does not affect in-hospital mortality. The density of calcification in the aortic arch is associated with increased cardiovascular and cerebrovascular complications. It is known that patients who experience ischemic stroke have a higher prevalence of increased wall thickness in the aortic arch, carotid arteries, and subclavian arteries compared to the normal population. This condition is also associated with an increased risk of recurrent stroke in patients. In fact, the

Table 1: Demographic and clinical characteristics of the patients

Variables	Survival (n=95)	Mortality (n=92)	P value
Age, years	67±18.5	69±16.9	0.45
Sex, n, %			0.46
---Male	56(48.7)	59(51.3)	
---Female	39(54.2)	33(45.8)	
Anti-hypertensive drug, n, %	50(51)	48(49)	0.95
Anti-hyperlipidemic drug, n, %	13(43.3)	17(56.7)	0.37
Anti-aggregant drug, n, %	25(43.9)	32(56.1)	0.20
Anti-coagulan drug, n, %	17(44.7)	21(55.3)	0.40
Systolic blood pressure, mmhg	138.7±28.9	128.1±31.1	**0.016**
Diastolic blood pressure, mmhg	82.1±16.1	75.1±17.8	**0.006**
NIHSS	7±5.3	14.2±5.4	**0.0001**
Modified Rankin score	2.8±1.6	4.6±1	**0.0001**
HT, n, %	50(46.7)	57(53.3)	0.19
DM, n, %	26(55.3)	21(44.7)	0.47
Hyperlipidemia, n, %	11(42.3)	15(57.7)	0.75
CAD, n, %	26(42.6)	35(57.4)	0.16
CRF, n, %	7(36.8)	12(63.2)	0.19
Hemorrhage localization, n, %			0.29
--Anterior system	75(53.6)	65(46.4)	
--Posterior system	20(42.5)	27(57.5)	
Hemorrhage volume, ml	12.7±2	10.8±1.7	0.49
Aortic calfication grade, n, %			0.39
--Grade 0	24(45.3)	29(54.7)	
--Grade 1	38(55.9)	30(44.1)	
--Grade 2	29(53.7)	25(44.3)	
--Grade 3	4(33.3)	8(66.7)	
Aortic calfication, n, %			0.34
--with	24(45.3)	29(54.7)	
--without	71(53)	63(47)	

Notes: NIHSS: National stroke health scale; HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary arterial disease; CRF: Chronic renal failure

Table 2: Laboratory and echocardiographic characteristics of the patients

Variables	Survival (n=95)	Mortality (n=92)	P value
Total cholesterol, mg/dl	174.4±42.8	148.2±65.3	**0.047**
HDL, mg/dl	44.3±16.5	43.1±7.9	0.865
LDL, mg/dl	102.9±33.8	91.6±38.5	0.233
TG, mg/dl	147.2±107.9	148.9±60.2	0.939
Glucose, mg/dl	135.2±52.7	159.9±72	**0.009**
Creatinine, mg/dl	0.95±0.46	1.5±1.3	**0.0001**
Potassium, mmol/l	4.1±0.59	4.2±0.7	0.2
Calcium, mg/dl	9.6±1	8.4±0.6	0.2
Albumin, g/l	36±7.7	32.6±7.9	**0.006**
Hemoglobin, g/dl	12.9±2.6	11.9±2.8	**0.025**
PLT, (10^3/L)	251±101	204±87	**0.001**
CRP, mg/l	162±10.3	88.1±10.7	0.5
EF, %	56.5±5.3	51.8±10.2	**0.015**
Enddiastolic diamater, mm	44.5±9.8	44.5±12	0.98
Endsystolic diamater, mm	27.8±8.4	29±11	0.68
Left atrium, mm	35.3±8.8	34.4±9.5	0.73
Aortic diamater, mm	26.4±6.2	26.2±7.3	0.90
IVS thickness, mm	10.7±3	11.2±3.1	0.61
Posterior wall thickness, mm	9.9±2.9	9.7±2.6	0.75
E velocity	71.4±20.1	65.8±21	0.42
A velocity	79.1±20.3	78±14.2	0.89
PAP, mmhg	31.6±6.4	34.5±10.8	0.28

Notes: HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglyceride; PLT: Platelet; CRP: C-reactive proteine; EF: Ejection fraction; IVS: Interventricular septum; PAP: Pulmonary arterial pressure

pathophysiology linking vascular calcification and stroke is not clearly understood. However, one of the most commonly cited mechanisms is the disruption of endothelial structure following intimal calcification, leading to increased permeability of the blood-brain barrier.[9] The second mechanism involves increased arterial stiffness due to medial calcification, which, in turn, can lead to rupture in cerebral vessels due to elevated intravascular pressure. Patients with significant intracranial vascular calcification exhibit a higher frequency of lacunar infarcts.[10,11] primarily because calcification in these regions leads to greater disruption of endothelial structure.[12]

The literature contains numerous data on the relationship between ischemic stroke and aortic arch calcification. However, the relationship between calcification in the aortic arch and hemorrhagic stroke is not well-established. In a study by Pektezal *et al*., it was shown that patients with intracranial hemorrhage had a higher rate of cerebral hematomas in areas of dense calcification.[13] Similarly, it has been observed that regions with higher calcification rates post-ischemic stroke also had increased rates of microbleeds.[14] Following thrombolytic therapy, higher rates of hemorrhagic transformation were noted in areas with dense calcification.[15] One study found that approximately 76% of patients who developed intracranial hemorrhage also had accompanying intracranial vascular calcification.[16]

While the primary problem in patients who suffer ischemic strokes is often large vessel pathology, the underlying cause in those with hemorrhagic strokes is typically small vessel disease. It is expected that calcification in large vessels like the aorta may also develop in smaller vessels. This expectation serves as a fundamental basis for our research, particularly considering the relationship between small vessel disease and intracranial hemorrhages with vascular calcification. In a study by Acar *et al*., a correlation was found between vascular calcification parameters measured in serum and the occurrence of intracranial hemorrhage.[17] Among

these parameters, matrix Gla protein (MGP) was identified as a predictor of hemorrhagic stroke mortality. However, there are significant differences in our study. First and foremost, our study is a mortality study, which differentiates it from other studies. We examined the relationship between calcification rates observed on chest X-rays, a method that is practical, inexpensive, and easily accessible in daily clinical practice, and hemorrhagic stroke. In contrast, the literature predominantly involves studies employing more advanced imaging techniques. As a result, our findings differ from those in the existing literature.

The relationship between hemorrhagic stroke and elevated creatinine levels is a well-established area of research, particularly considering that renal dysfunction, typically indicated by high creatinine levels, may contribute to the risk of cerebrovascular events, including ischemic and hemorrhagic strokes. Several studies have shown that patients with chronic kidney disease (CKD) and elevated serum creatinine levels have an increased risk of stroke due to factors such as endothelial dysfunction, inflammation, and platelet abnormalities.[18] These factors can deteriorate cerebrovascular health and increase the likelihood of hemorrhagic events independently of traditional risk factors such as hypertension and diabetes. For example, data from the REGARDS study indicated that low estimated glomerular filtration rate (eGFR) – an inverse marker of creatinine levels – is associated with a higher incidence of hemorrhagic strokes.[19] Furthermore, elevated creatinine levels have been linked to worse outcomes in stroke patients, as higher levels often indicate greater severity of renal dysfunction, which can exacerbate complications in the cerebral blood vessels.[20]

Our study has several limitations. The single-center design, the relatively small sample size, and the retrospective nature of the study are significant factors that limit the findings. In particular, the limited number of patients in the group with grade 3 calcification—where we anticipated a stronger impact on outcomes—poses a notable restriction. Furthermore, there are gaps in the medical records regarding factors such as smoking and metabolic anomalies that could influence calcification. Additionally, the exclusion of hemorrhagic areas, particularly in high-mortality regions like the posterior fossa, and the lack of analysis regarding which arteries were associated with the bleeding focus also represent limitations in our study. The inability to radiologically visualize the state of calcification in intracranial vascular structures further contributes to these limitations. These factors highlight the need for future studies with larger cohorts, multi-center designs, and comprehensive data collection to better understand the relationships between aortic arch calcification and clinical outcomes in hemorrhagic stroke patients.

In conclusion, vascular calcification development is indeed a significant risk factor for stroke. The expectation that calcification in larger vessels, such as the aorta, can also occur in relatively smaller cerebral vessels aligns with various studies that indicate the systemic nature of atherosclerosis and vascular aging. There are publications suggesting that the increase in aortic arch calcification detected on plain radiography is an important predictor for the presence of cardiovascular and ischemic cerebrovascular disease. However, there is a need for studies to investigate its effect on the incidence of hemorrhagic stroke. However, it appears that the increase in aortic arch calcification does not add an additional risk for in-hospital mortality and morbidity in patients who have experienced hemorrhagic stroke. This finding suggests that while vascular calcification can indicate broader cardiovascular risks, it may not specifically correlate with worse outcomes in this particular patient population. Nonetheless, further large-scale randomized studies are needed to clarify this relationship and to better understand the underlying mechanisms involved in vascular calcification and hemorrhagic stroke outcomes. More comprehensive research could provide valuable insights into whether specific thresholds of calcification might affect mortality rates in these patients.

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DISCLOSURE

Ethic: Ethical approval was obtained from the Ethics Committee of Necmettin Erbakan University (approval no: 2024/5103).

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Conflict of interest: None

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