



## Plaque morphology in carotid arteries and correlation of symptoms in stroke patient study in SPRC and Neurology Hospital and BSMMU Hospital, Dhaka, Bangladesh

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### Abstract

**Purpose:** In carotid artery disease, correlation of carotid plaque morphology with the patients presenting symptoms has drawn conflicting conclusions.

**Objective:** to correlate plaque morphology in carotid arteries and correlation of symptoms in stroke patient study in SPRC and neurology hospital, Dhaka, Bangladesh.

**Methods:** All carotid endarterectomy procedures performed by one group of vascular surgeons at SPRC and Neurology Hospital and BSMMU Hospital, Dhaka, Bangladesh Dhaka, Bangladesh from January 2020 to June 2021 were included in this study. There were 551 carotid endarterectomy procedures completed within the study period. All endarterectomy specimens were inspected during the surgical procedure, and plaque characteristics were recorded by the surgeon immediately after the operation. Information related to demographics, comorbidities, and operative indications were recorded prospectively at the time of operation. All endarterectomy specimens were inspected during the procedure, and plaque characteristics were recorded immediately after operation.

**Results:** There was a higher incidence of plaque ulceration in the transiently symptomatic and prior stroke groups (260 of 335 [77.61%] and 22 of 31 [70.96%]) than in the asymptomatic cohort (110 of 185 [59.45%];  $p < 0.0001$ , X<sup>2</sup> test). There was no significant difference in the incidence of plaque hemorrhage between the transiently symptomatic and prior stroke patients compared with the asymptomatic patients. There was no statistical difference for ulcerated plaque or plaque hemorrhage between the transiently symptomatic and prior stroke groups. Intraplaque hemorrhage occurred more frequently in patients with high-grade stenosis (90% to 99%) than in those with less than 90% stenosis (123 of 185 [66.48%] versus 62 of 185 [33.51%];  $p = 0.01$ , X<sup>2</sup> test).

**Conclusions:** On gross examination of the carotid specimen in the operating room, plaque ulceration correlates with an initial presentation of amaurosis fugax, TIA, or prior stroke compared with patients operated on for asymptomatic disease. The presence of intraplaque hemorrhage is associated with more advanced stenosis of the internal carotid artery. These findings suggest that plaque morphology does play an important role in the presentation of carotid artery disease.

**Keywords:** Artery Disease, Plaque Morphology, Plaque Ulceration

### Introduction

Recent randomized, prospective trials have demonstrated the superiority of carotid endarterectomy compared with the best medical treatment for the prevention of stroke in both asymptomatic and symptomatic patients with carotid artery disease [1-4]. The challenges of proper patient selection and perfection of the surgical technique represent the next echelon in advancing treatment for this disease.

Inherent within the process of understanding which patients will have a stroke is to identify the early warning signs. Prior studies have clearly shown that patients with higher-grade stenosis and transiently symptomatic presentation are at an increased risk for subsequent cerebrovascular accidents (CVA) [5-9]. The biologic basis for this observation, however, has yet to be clearly determined. Factors that dictate the rate of progression of the disease process also are not well understood. Better insight into which patient or arterial characteristics lead to subsequent stroke would provide the surgeon with the opportunity to operate selectively on patients who are at greater risk. Alternatively, a subgroup of patients with moderate stenosis (40% to 60%) of the internal carotid artery (ICA) combined with ominous plaque characteristics may be at a high risk of progression to a stroke. These patients also might warrant surgical consideration. Pathologic investigations of the carotid plaque specimen from carotid endarterectomy have primarily involved the study of interleaflet hemorrhage and plaque ulceration. The reported incidence of plaque hemorrhage has varied from 7.4% [10] to 87% [11]. Similarly, the rate of plaque ulceration has been highly variable in the literature. 12-15 Conflicting data have been presented for and against the use of plaque morphology as an indicator for the subsequent symptomatic presentation of carotid artery disease.

### Methods

All carotid endarterectomy procedures performed by one

group of vascular surgeons at SPRC and Neurology Hospital and BSMMU Hospital, Dhaka, Bangladesh Dhaka, Bangladesh from January 2020 to June 2021 were included in this study. There were 551 carotid endarterectomy procedures completed within the study period. All endarterectomy specimens were inspected during the surgical procedure, and plaque characteristics were recorded by the surgeon immediately after the operation. Information related to demographics, comorbidities, and operative indications were recorded prospectively at the time of operation. The presenting symptoms for all patients were subdivided into one of three groups: transiently ischemic, prior stroke, or asymptomatic. The transiently ischemic patients included those with a history of amaurosis fugax or transiently ischemic symptoms ipsilateral to the affected carotid artery. A patient was considered to be transiently symptomatic if the symptoms could be documented within 4 to 6 weeks from the date of operation. Any ischemic event for which the symptoms lasted longer than 24 hours was considered to be a completed stroke. Operations for patients with completed strokes were delayed at least 6 weeks to prevent further damage to the ischemic penumbra. Furthermore, a temporary indwelling intraluminal shunt was routinely used for these patients. Reversible ischemic neurologic deficits and other intermediate categories were not considered. Any patient who was found to have carotid artery stenosis without a presenting symptom of focal neurologic deficit was classified in the asymptomatic cohort.



**Fig 1:** Angiogram of a carotid bifurcation with evidence of stenosis of the ICA and a large plaque ulceration

Preoperative angiography was routinely used in all cases. The degree of stenosis based on the preoperative angiogram was used in conjunction with the presenting symptoms as the primary criterion in the decision to operate. The degree of stenosis of the ICA was determined according to the protocol used in the North American Carotid Endarterectomy Trial; the lumen at the carotid bifurcation was compared with the distal normal ICA [1].

**Exclusions.** From the 652 carotid endarterectomies that were performed in this study period, 101 cases were excluded. Repeat operations, including 113 operations for restenosis, were specifically excluded to allow a focus on primary carotid artery stenosis. In a recent trend, 23 cases were excluded because preoperative angiography was substituted

by magnetic resonance angiography or duplex scanning alone. In 28 cases, the data for carotid plaque characteristics or presenting symptoms were not recorded or not available; thus, there were 551 primary operations for which all of the data were available for analysis.

**Plaque characteristics.** All carotid specimens were inspected by the surgeon at the time of the operative exposure and endarterectomy. The presence or absence of ulceration or intraplaque hemorrhage was documented prospectively in all cases. For some cases, more than one plaque characteristic was present in a single specimen. Throughout the 14-year study period, frequent discussions were made regarding characteristics consistent with ulceration and hemorrhage. Comparison of the incidence of plaque ulceration or plaque

hemorrhage among the transiently symptomatic, asymptomatic, and prior stroke cohorts. All p values refer to  $X^2$  statistical analysis. Percentage of patients with plaque ulceration from the groups with symptoms of transient ischemia and prior stroke were significantly greater than the asymptomatic cohort. Gross ulceration was defined as plaque surface irregularity with an opening seen by the surgeon at the time of arteriotomy. Pin holes of less than 1 mm were not considered to be ulcerations. Plaques with smooth invaginations without evidence of disruption of the fibrous cap also were not considered examples of plaque ulcers. Plaque hemorrhage was noted grossly by looking for evidence of blood within the plaque itself. Old hemosiderin-laden plaques also were considered to be examples of plaque hemorrhage. There was no attempt in this study to distinguish the age of the hemorrhage. Statistical analysis. All data were maintained in a database and analyzed with the use of Microsoft Excel or Stat View for the PC. Univariate testing included a t test for continuous variables, and  $X^2$  tests for

comparison of proportions of categorical variables were used to test statistical significance. A significance level of  $p < 0.05$  was used as a threshold for statistical significance.

## Results

Patients underwent a total of 551 primary carotid endarterectomy procedures. A high incidence of cardiovascular risk factors was present. Patient characteristics and comorbidities are expressed in (Table I). There were a total of 551 primary carotid endarterectomies for 487 patients (64 bilateral procedures). There were significantly more men (63.52%) than women (49.18%) in the study group, and the patients had a high incidence of cardiovascular risk factors. The comorbidities of smoking and hypertension were particularly remarkable, 67% with a smoking history and 41.74% with hypertension. The age of patients ranged from 40 to 75 years, with a mean age of 57.2 years.

**Table 1:** Patient characteristics (N=551)

Age	68.2 ± 8.4 yr (mean ± SD)	
Gender	Men 350 (63.52%)	Women 201 (36.48%)
Side of operation	Right 280 (50.82%)	Left 271 (49.18%)
Diabetes	Yes 90 (16.33%)	No 461 (83.67%)
Hypertension	Yes 230 (41.74%)	No 321 (58.26%)
Smokers	Active smokers 230 (41.74%)	Nonsmokers 180 (32.67%)
	Previous smokers 140 (25.40%)	

**Table 2:** Plaque characteristics versus presenting symptoms comparing transiently symptomatic and asymptomatic groups and prior stroke and asymptomatic groups (n = 551)

Plaque Characteristic	Transiently symptomatic (n = 335)	p value	Asymptomatic (n = 185)	p value	Prior stroke (n = 31)
Ulcerated (n= 385)	260 of 335 (77.61%)	<0.0001	110 of 185 (59.46%)	<0.0001	22 of 31 (70.97%)
Hemorrhage (n = 166)	75 of 335 (22.39%)	0.72	75 of 185 (40.54%)	0.06	9 of 31 (29.03%)

The overall incidence of plaque ulceration (with or without hemorrhage) was 69.87% (385 of 551). Plaque hemorrhage was found less frequently, with an incidence of 30.12% (166 of 551). Table II provides data related to the presence of plaque ulceration and hemorrhage compared with the initial clinical presentation. This comparison illustrates the higher incidence of plaque ulceration in both the transiently symptomatic patients (77.61% [260 of 335]) and the prior stroke group (70.96% [22 of 31]) compared with the asymptomatic patients (59.45% [110 of 185];  $p < 0.0001$ ,  $X^2$  test). Table II also demonstrates a nonsignificant trend of more plaque hemorrhage in the prior stroke group (23.03% [9 of 31]) compared with the asymptomatic group of patients (40.54% [75 of 185;  $p = 0.06$ , NS]). A separate comparison of carotid plaque characteristics with the presenting symptoms is given in Table III. Patients who exhibited hemorrhage and ulceration in the same plaque were considered to be in a unique category, as were those with ulcer only or hemorrhage only. There was no statistically significant difference between the transiently symptomatic

group compared with the prior stroke group on the basis of frequency of plaque ulceration, plaque hemorrhage, or both. Many more transiently symptomatic patients demonstrated a plaque ulceration alone than did the asymptomatic cohort of patients (36.71% [123 of 335] compared with 37.83% [70 of 185];  $p < 0.0001$ ,  $X^2$  test) (Table III). The incidence of plaque hemorrhage or coexisting hemorrhage and ulceration, however, was similar for the symptomatic and asymptomatic patients. There was a trend toward an increased incidence of plaque ulceration in the prior stroke group (48.38% [15 of 31]) compared with the asymptomatic patients (37.83% [70 of 185]). However, this trend was not statistically significant ( $p = 0.06$ ). Similarly, there were more patients in the prior stroke group who had coexisting plaque ulceration and hemorrhage (32.25% [10 of 31]) compared with the asymptomatic patients (24.86% [46 of 185]); this association achieved borderline statistical significance ( $p = 0.052$ ). The presence of plaque hemorrhage alone was identical in the prior stroke and asymptomatic groups of patients (4.4%).

**Table 3:** Plaque characteristics versus presenting symptoms (N=551)

Plaque characteristic	Transiently symptomatic (n = 335)	p value	Asymptomatic (n = 185)	p value	Prior stroke (n = 31)
Ulcer alone (n = 231)	123 of 335 (36.72%)	<0.0001	70 of 185 (37.84%)	0.064	15 of 31 (48.39%)
Hemorrhage alone (n = 17)	8 of 335 (2.39%)	0.28	8 of 185 (4.32%)	>0.99	2 of 31 (6.45%)
Hemorrhage and ulcer (n =180)	70 of 335 (20.89%)	0.39	46 of 185 (24.86%)	0.052	10 of 31 (32.26%)
Neither (n =123)	50 of 335 (14.93%)	<0.0001	61 of 185 (32.97%)	<0.0001	6 of 31 (19.35%)

Carotid plaque characteristics were compared with presenting symptoms. Plaques were classified into those with

ulcer alone, hemorrhage alone, both hemorrhage and ulcer, and neither hemorrhage nor ulcer.

**Table 4:** Carotid artery stenosis (N=551)

Stenosis of ICA	Asymptomatic (n = 185)	Prior stroke (n = 31)	Transiently ischemic (n = 335)
<75% (n = 76 of 551 [13.79%])	16 of 185 (8.65%)	5 of 31 (16.13%)	60 of 335 (17.91%)
75% (n = 137 of 551 [24.86%])	53 of 185 (28.65%)	8 of 31 (25.80%)	80 of 335 (23.88%)
90% (n = 327 of 551 [59.35%])	112 of 185 (60.54%)	16 of 31 (51.61%)	191 of 335 (57.01%)
99% (n = 11 of 551 [2.0%])	4 of 185 (2.16%)	2 of 31 (6.45%)	4 of 335 (1.19%)
Total (n = 551)	185	31	335
Stenosis of ICA	Asymptomatic (n = 185)		Prior stroke (n = 31)
≥90%	123 of 185 (66.49%)		18 of 31 (58.06%)
<90% X <sup>2</sup> p = 0.27 (NS)	62 of 185 (33.51%)		13 of 31 (41.94%)
Stenosis of ICA	Prior stroke (n = 31)		Symptomatic (n = 335)
≥90%	18 of 31 (58.06%)		195 of 335 (58.20%)
<90% X <sup>2</sup> p > 0.99 (NS)	13 of 31 (41.94%)		212 of 335 (41.80%)
Stenosis of ICA	Symptomatic (n = 335)		Asymptomatic (n = 185)
≥90%	195 of 335 (58.20%)		123 of 185 (66.49%)
<90% X <sup>2</sup> p = 0.07 (NS)	212 of 335 (41.80%)		62 of 185 (33.51%)

The degree of stenosis of the ICA was compared with presenting symptoms. The difference in stenosis among the various cohorts was not significantly different.

Table IV provides a comparison of the degree of stenosis by preoperative angiography of the carotid artery with the presenting symptoms. For the purpose of statistical analysis, the patients were divided into either the high-grade stenosis

(90% to 99%) group or the lower-grade stenosis (less than 90%) group. The transiently symptomatic patients and those with a history of a prior stroke were more likely to have lower-grade stenosis than was the asymptomatic cohort. This difference, however, was not statistically significant based on X<sup>2</sup> analysis. Table V expresses the relative frequencies of plaque ulceration and intraplaque hemorrhage com-

**Table 5:** Stenosis of ICA versus plaque morphology (N=551)

Stenosis of ICA	Ulcerated plaque (n = 371)	Plaque hemorrhage (n = 180)
<75% (n = 76 of 551 [13.79%])	58 of 371 (15.63%)	21 of 180 (11.67%)
75% (n = 137 of 551 [24.86%])	92 of 371 (24.8%)	38 of 180 (21.11%)
90% (n = 327 of 551 [59.35%])	218 of 371 (58.76%)	118 of 180 (65.55%)
99% (n = 11 of 551 [2.0%])	3 of 371 (0.8%)	3 of 180 (1.67%)
Total (n = 551)	371	180
Stenosis of ICA	Ulcerated plaque (n = 371)	
≥90% (n = 402)	223 of 371 (60.1%)	
<90% (n = 149) ≥2 p = 0.57 (NS)	148 of 371 (39.9%)	
Stenosis of ICA	Plaque hemorrhage (n = 180)	
≥90% (n = 149)	123 of 180 (68.33%)	
<90% (n = 397) ≥2p = 0.0038	57 of 180 (31.67%)	
	No hemorrhage (n = 371)	
	218 of 371 (58.76%)	
	153 of 371 (41.24%)	

The frequency of plaque ulceration and plaque hemorrhage by the degree of stenosis of the ICA was compared. To simplify the analysis, the patients were separated into those with less than 90% stenosis and those with 90% to 99% stenosis. Pared with the degree of ICA stenosis. There were more incidences of intraplaque hemorrhage from specimens with higher-grade stenosis (90% to 99% stenosis of ICA) than from those with less than 90% ICA stenosis ( $p < 0.005$ ,  $\geq 2$  test). Plaque ulceration was present with consistent frequency independent of the degree of stenosis of the ICA ( $p = 0.57$ , NS, X<sup>2</sup> test).

## Discussion

The present study demonstrates a strong association between gross ulceration of carotid plaque and a presentation of TIAs, amaurosis fugax, or prior stroke. The correlation of plaque hemorrhage and clinical presentation was less clear, with a trend that did not achieve statistical significance toward an association with prior stroke (Table II;  $p = 0.06$ , NS). There was no statistically significant relation between the degree of stenosis and clinical presentation among the asymptomatic, symptomatic, and prior stroke groups of patients (Table IV).

The frequency of plaque ulceration was independent of the degree of ICA stenosis, whereas plaque hemorrhage occurred more commonly in the more highly stenotic lesions (Table V). Each of these areas is discussed. The association of gross plaque ulceration with an initial presentation of TIAs, amaurosis fugax, or prior stroke is strong (Table II;  $p < 0.0001$ , X<sup>2</sup> test) and is an association that has been described previously<sup>[9, 16-19]</sup>. The importance of the present study is the large number of cases supporting this conclusion and statistical analysis that is possible with 1008 observations. The association of plaque ulcer with symptoms is believed by many to represent an anatomic etiology for the patient's intermittent transient ischemia. In a recent publication originating from the North American Symptomatic Carotid Endarterectomy Trial (NASCET), a detailed investigation of plaque ulcer in symptomatic patients was evaluated. Eliasziw *et al.*<sup>[9]</sup> reported the increased risk of subsequent stroke in patients with demonstrated plaque ulceration on preoperative angiograms. A finding of increased risk for subsequent stroke in patients known to have ulcerated plaques reinforces the argument that plaque characteristics should be used in conjunction with clinical symptoms and degree of stenosis in



the decision to operate. Prior investigators have been criticized for a lack of similarity between the degree of stenosis of the asymptomatic and symptomatic cohorts when comparing the incidence of plaque ulceration [20]. In that study, the symptomatic patients had an overall higher degree of stenosis than the asymptomatic group. However, in the present series, the lesions of the symptomatic cohort were, as a group, less stenotic than those of the asymptomatic cohort (Table IV). The correlation of ulcerated plaques to symptomatic patients is not affected by the consideration of plaques with concomitant ulceration and hemorrhage as a separate entity (Table III). A comparison of the asymptomatic group with the prior stroke group was found to be highly significant when plaque ulceration and hemorrhage were considered independently (Table II;  $p < 0.0001$ ). However, when the category for combined hemorrhage and ulceration was considered, there was a no statistically significant trend toward more ulceration (Table III;  $p = 0.064$ ) and coexisting ulceration and hemorrhage ( $p = 0.052$ ) in the prior stroke group compared with the asymptomatic group. This discrepancy may result from the creation of more subcategories. When comparing the data in Tables II and III, it becomes evident that plaque hemorrhage rarely occurs without ulceration, whereas plaque ulceration commonly occurs independently. The presence of plaque hemorrhage without ulceration was not significantly different among the symptomatic (Table III; 2.39%), prior stroke (6.45%), and asymptomatic (4.32%) cohorts. When plaque hemorrhage was considered independently, there was a trend toward increased likelihood of hemorrhage in the prior stroke group (29.03%) compared with the asymptomatic cohort (40.54%) (Table II;  $p = 0.06$ , NS, X2 test). This finding is different from the conclusions drawn by researchers who support the position that plaque hemorrhage is significantly more common in prior stroke and transiently symptomatic patients [11, 12, 17, 21-23]. On the other hand, Bassiouny *et al.* [13] in a pathologic study, concluded that plaque hemorrhage was a common occurrence in carotid lesions from both symptomatic and asymptomatic patients. Svindland and Torvik [24] described findings of plaque ulcer and hemorrhage in many asymptomatic patients with greater than (59.46%) carotid stenosis. The presence of asymptomatic patients with plaque hemorrhage or ulceration does not necessarily imply that the plaque is benign in nature. We believe that these "unstable" plaques are more common in symptomatic and prior stroke patients. The possibility of plaque hemorrhage and ulcer healing through the formation of a fibrous cap also has been suggested. More recent histologic and radiographic/imaging studies have focused on the "soft" and unstable plaque with foreboding structure, composition, or consistency [10, 25-27]. The data for ICA stenosis and clinical presentation (Table IV) demonstrate a nonsignificant trend of asymptomatic patients showing higher-grade stenosis than those with prior symptoms. This difference is likely a result of the changing indications for carotid endarterectomy during the study period. Large, randomized, prospective studies to determine the proper indications for carotid endarterectomy were not available until. Before the publication of the Asymptomatic Carotid Artery Study, [4] very few asymptomatic patients in the present series were operated on who had less than 80% stenosis. Many asymptomatic patients with stenosis of 50% to 75% were followed with duplex scanning before the completion of the Asymptomatic Carotid Artery Study report. Like- wise, before the initial reports

from the NASCET collaborators, some symptomatic patients with moderate stenosis (50% to 70%) also were operated on. This selection bias toward a higher degree of stenosis in the operated asymptomatic group accounts for the observed trend. Because the asymptomatic and symptomatic patients presented for completely different reasons, it is understandable that they might have different degrees of stenosis at the time of operation. Population studies that have controlled for this generally agree that the degree of stenosis does influence the presence of symptoms [1, 2, 9]. In this study, the relation between the degree of ICA stenosis and carotid plaque morphology demonstrates an increased frequency of plaque hemorrhage in the more highly stenosed lesions ( $p < 0.005$ , X2 test). This association has been previously described by Beach *et al.* [28] who showed that intraplaque hemorrhage occurred more frequently in more stenotic lesions. Persson *et al.* [17] proposed in 1983 that the progression of atherosclerotic plaque may depend on the development of intraplaque hemorrhage and that in turn may lead to TIAs or frank stroke. In the present study, the association of plaque hemorrhage with greater stenosis was seen in both asymptomatic and symptomatic groups. This finding, however, does not allow us to draw conclusions related to the cause-and-effect relation of plaque hemorrhage with high-grade stenosis. The incidence of plaque ulceration at all different degrees of carotid artery stenosis is less conclusive. The present study showed an overall incidence of plaque ulceration in 67.33% (371 of 551) of carotid specimens. The plaque ulcers were distributed proportionally among each of the groups of degree of ICA stenosis (Table V). The X2 analysis of plaque ulceration in which the data were divided according to whether the patient had greater or less than 90% stenosis also failed to show any differences ( $p = 0.57$ , NS). It thus appears from this study that the rate of ulceration is not affected by the degree of stenosis.

### Conclusion

There is a highly significant correlation of carotid plaque ulceration with symptomatic carotid artery disease, including patients with transient ischemia and prior stroke. The relation of plaque hemorrhage to clinical presentation is less clear, with a nonsignificant trend toward an association with prior stroke ( $p = 0.06$ ). Intraplaque hemorrhage is found more frequently in the presence of high-grade stenosis (90% to 99%) of the ICA for both symptomatic and asymptomatic patients than at lesser degrees of stenosis. These findings suggest that carotid plaque morphology does play an important role in the presentation of carotid artery disease.

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