Prevalence of peripheral arterial diseases in patients with large artery ischemic stroke and its prognostic value

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Abstract

Background: Peripheral artery disease (PAD) can be an important predictor of comorbid cerebrovascular disease (CVD). However, it is not sufficiently investigated or considered in the management and prevention of stroke.

Objectives: To study the prevalence of peripheral arterial disease in large artery ischemic stroke patients and its impact on prognosis.

Methods: This is a prospective cohort study. A total of 100 patients with large artery ischemic stroke were enrolled with assessment for signs of PAD; duplex on both lower limb arteries and measurement of ankle-brachial index (ABI), carotid duplex, and/or C.T angiography brain and neck and/or conventional angiography; functional assessment by NIHSS at days 0, 7, and 30; and follow-up for recurrence or death after 6 months.

Results: Peripheral arterial disease was found in 42% of cases. Fifty percent of patients with lower extremity arterial disease were asymptomatic. Fifty percent had significant carotid stenosis (stenosis > 50%), and 48% of patients with significant carotid stenosis had peripheral arterial disease. During our study, 8 cases had a recurrence of large artery ischemic stroke, and 5 cases (62.5%) had PAD. The recurrence rate of stroke was the highest in the asymptomatic PAD group with 19%.

Conclusion: The prevalence of PAD in large artery ischemic stroke patients is high. Asymptomatic PAD has a risk potential for large artery ischemic stroke recurrence and mortality more than symptomatic PAD and non-PAD patients.

Keywords: Peripheral artery disease, Ankle-brachial index, Stroke outcome

Introduction

The presence of vascular disease in one arterial territory strongly predicts disease in other territories, increasing the risk of vascular events in patients with previous stroke/transient ischemic attack [1].

PAD can be either asymptomatic (defined by an ABI ≤ 0.9) or symptomatic presented by intermittent claudication or acute PAD events (acute limb ischemia and critical limb ischemia). Acute limb ischemia can be viable, threatened, or irreversible. Critical limb ischemia includes rest pain and ulceration [2].

ABI is an easy way to compare the systolic pressure of the upper extremity with that of the affected lower extremity. ABI test has a sensitivity above 90% and a specificity of 95% for the diagnosis of PAD [3].

Although PAD risks poor prognosis compared with vascular disease in other territories, little attention is paid to its epidemiology, treatment, and prevention. Despite the high prevalence of PAD in patients with stroke, and of stroke in patients with PAD, PAD is not considered in the guidelines for treatment, prevention, and rehabilitation of stroke. Therefore, screening for PAD is

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not routinely considered, and so, it is probably often missed [4].

PAD affects 12 to 14% of the general population. The prevalence of PAD is age-dependent, reaching 10% in patients aged over 60 years. Unfortunately, the majority of patients are asymptomatic and undiagnosed. Also, one third of patients with symptoms do not report them to their doctor. As a result of this, a high-risk group of patients is underdiagnosed and receive no (or suboptimal) treatment or intervention [5].

The prevalence of asymptomatic carotid stenosis increases with decreasing ABI. Therefore, there may be a role for screening for asymptomatic carotid stenosis in patients with PAD, although the benefit of carotid endarterectomy in such patients is low [6].

Aim of this work
The aim of this work is to study the prevalence of peripheral arterial disease in large artery ischemic stroke patients and its impact on prognosis.

Methods
This is a prospective cohort study. One hundred cases with large artery ischemic stroke were recruited from Nasr City Insurance Hospital. Patients were subjected to *clinical assessment* including complete medical history (detailed history including personal data with a history of risk factors including hypertension, diabetes mellitus, dyslipidemia, smoking); general examination including signs suggestive of PAD; detailed neurological history, examination, and NIHSS at days 0, 7, and 30 for the assessment of stroke severity; follow-up for recurrence or death after 6 months; *laboratory assessment* full chemistry including full blood picture, liver and kidney functions, fasting and random blood sugar, PT, PTT, INR, lipid profile, collagen profile, protein C, protein S, and anti-thrombin III in cases of stroke in young without strong risk factors; *imaging* including trans-thoracic echocardiography (General electric Vivid 7, USA) and trans-esophageal echocardiography in cases of stroke in young without strong risk factors to exclude cardioembolic strokes; Duplex on the arteries of both lower limbs; and measuring of ankle brachial index (ABI). The systolic pressure in the dorsalis pedis or posterior tibial artery was measured using a handheld 8-MHz Doppler probe (model Life Dop L250R with SD8 probe product by Summit Doppler, China) and a blood pressure cuff. The higher of these two measurements was compared with a similarly taken brachial artery systolic pressure. A ratio (ankle/brachial) of 0.9 or less is considered a sign of impaired flow to the extremity [3]. MRI brain (diffusion-weighted, flair, T1, T2, and T2* images) and MRA (Philips 1.5 Tesla, Germany). Carotid duplex (General

Electric Logic 5, USA) and/or C.T angiography brain and neck and/or conventional angiography if needed.

Inclusion criteria and subject selection
Stroke patients with large artery atherosclerotic disease either intra-cranial or extra-cranial and anterior circulation or posterior circulation verified by MRI and MRA brain or CT angiography on the neck and brain vessels or conventional angiography.

Exclusion criteria
Patients were excluded from the study if they showed clinical evidence of cardio-embolic stroke as atrial fibrillation, transient ischemic attack, and intra-cerebral, subdural, or subarachnoid hemorrhage.

Statistical analysis
Data were analyzed using Stata® version 14.2 (StataCorp LLC, College Station, TX, USA). Normality of numerical data distribution was examined using the Shapiro-Wilk test. Non-normally distributed numerical data were presented as median and interquartile, and intergroup differences were compared using the Wilcoxon rank sum test (for two-group comparison) or the Jonckheere-Terpstra trend test (for comparison of multiple tanked grouped).

Categorical data were presented as the ratio or number and percentage, and intergroup differences were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data). Associations among ordinal variables were tested using the Spearman rank correlation and Kendall's tau-b.

A time-to-event analysis was done using the Kaplan-Meier (K-M) method. The log-rank test was used to compare individual K-M curves.

p value < .05 was considered statistically significant.

Results
A total of one hundred patients with acute large artery ischemic stroke were enrolled. The study included 80 males (80%) and 20 females (20%). The age of patients ranged from 36 to 85 with a mean of 62 ± 9. The most prevalent risk factor was hypertension (80%) followed by smoking (61%) followed by diabetes (50%) followed by dyslipidemia (35%) and followed by IHD (35%), and 4% had a history of CABG operation (Table 1). In the study group, 83 (83%) patients had first-ever stroke while 17(17%) presented with recurrent stroke. Eighty percent of patients had anterior circulation stroke versus 14% who had post-circulation stroke while 6% had both anterior and post-circulation; among these patients, 50% had significant extra-cranial carotid stenosis (> 50% stenosis) and 20 cases had interventional carotid angioplasty. Among our patients, 42% had PAD (defined by

Table 1 Characteristics of the study population

Variable	Ratio/mean ± SD/*n* (%)
Gender (M/F)	80/20
Age	62 ± 9 (range, 36–85)
Co-morbidities	
DM	50 (50.0%)
Hypertension	80 (80.0%)
Dyslipidemia	35 (35.0%)
Smoking	61 (61.0%)
IHD	35 (35.0%)
Previous CABG	4 (4.0%)

DM diabetes mellitus, *IHD* ischemic heart disease, *CABG* coronary artery bypass graft

Table 2 Short-term and long-term outcomes

Variable	Median (IQR)/*n* (%)
NIHSS	
Day 0	9 (5–15), range (1–23)
Day 7	5 (3–10), range (0–24)
Day 30	3 (1–6), range (0–17)
Recurrence of stroke	8 (8.0%)
Mortality	2 (2.0%)

IQR interquartile range, *NIHSS* National Institute of Health Stroke Scale

ABI ≤ 0.9), 50% of them were asymptomatic with ABI range 0.6–0.9, and 50% were symptomatic with ABI range 0.4–0.8. Among our 42 patients with PAD, 23 cases had ABI range from 0.7 to 0.9, and 18 cases had marked ABI impairment below 0.7 (Fig. 1). In the study, the median for NIHSS at day 0 was 9 and interquartile range (IQR) 5–15, 5 at day 7 and IQR 3–10 while finally the median for NIHSS after 1 month was 3 and IQR 1–6. Eight cases out of 100 had a recurrence of large artery ischemic stroke during 1 month period, and there were 2 cases of death (Table 2). We classified the severity of PAD according to ABI to mild (0.7–0.9) and moderate to severe (< 0.7) [7]. There is no satisfactory significant relation between the severity of PAD and NIHSS on admission (*p* value = .800), after 7 days (*p* value = .575), or at 1 month follow up (*p* value = .474). There is no satisfactory significant relation between PAD (symptomatic or asymptomatic) and NIHSS at day 0 (*p* value = .583), at day 7 (*p* value = .371), or at day 30 (*p* value = .382). Five of the cases (11.9%) who had recurrence had PAD (ABI ≤ 0.9) versus 3

cases (5.2%) without PAD (Fig. 2), with insignificant odds ratio, OR = 2.47 (CI = 95%), *p* = 0.23.

The 2 cases of mortality both had ABI 0.7–0.9 (Figs. 2 and 3). There was no statistical significance between ABI and recurrence of CVS or mortality probably due to the low rate of recurrence and mortality in our study. Regarding the time to recurrence of stroke by the ABI, there is no statistically significant difference among patients with ABI > 0.9, ABI of 0.7–0.9, or ABI < 0.7 (log-rank test chi-squared = 2.293, df = 2, *p* value = .318) (Fig. 4). The recurrence rate of stroke was higher in the PAD group with 11.9% versus 5.1% in the non-PAD group with insignificant *p* value due to the low rate of event. Recurrence rate was higher in the asymptomatic PAD group with 19% versus 5% in the non-PAD group and 4.8 in the symptomatic PAD group. There were 2 cases of death in the asymptomatic PAD group, one at day 14 of stroke and another 6 months later with recurrence of another large artery ischemic stroke (Table 3). There is no statistically significant relation between NIHSS and recurrence of stroke with *p* value = 0.447 at day 0, *p* value = 0.478 at day 7, and *p* value = 0.562 at day 30. Forty-eight percent of patients with significant carotid stenosis (> 50% stenosis) has PAD versus 34% who had IHD; on the other
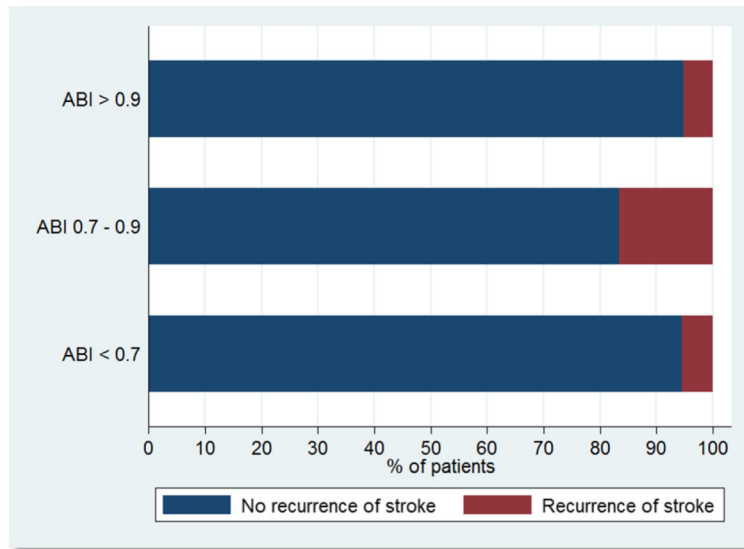

Fig. 1 a Evaluation of PAD. **b** Asymptomatic PAD versus symptomatic PAD
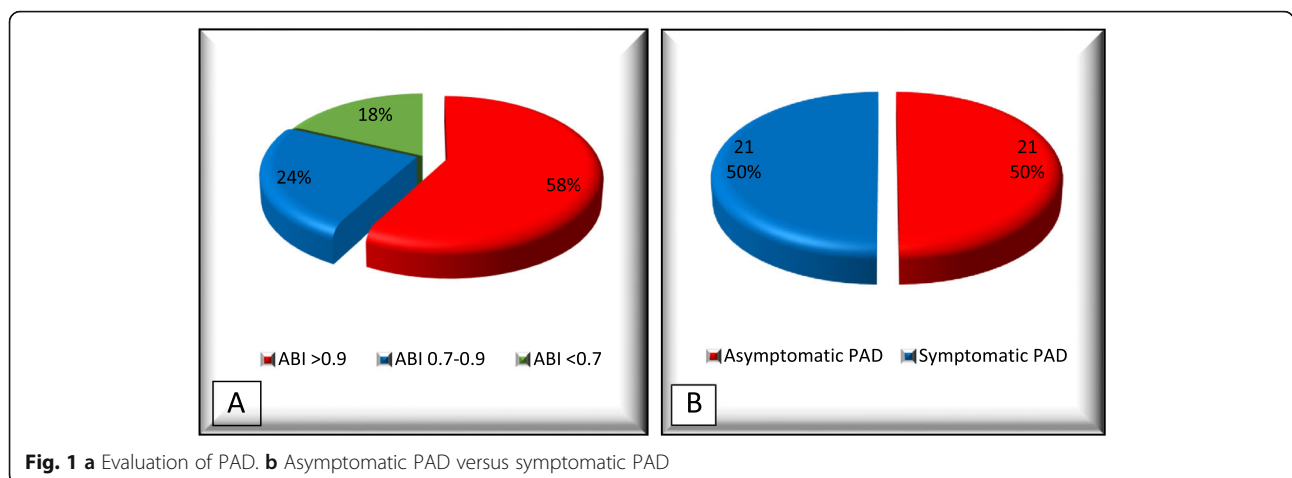
Fig. 2 Relation between ABI and recurrence of stroke

hand, there was no statistically significant relation between the severity of extra-cranial stenosis and the severity of impairment of ABI (tau-p = .099, p value = 0.263 and rho = .146).

Discussion

Our current study aimed to examine 100 cases with large artery ischemic stroke. The evaluation was done by history taking, clinical examination, echocardiography, MRI and MRA brain, carotid duplex or CT angiography or conventional angiography, duplex on arteries of both lower limbs with ABI measurement, functional assessment by NIHSS at day 0, 7, and 30, and follow-up for recurrence or death after 6 months.

PAD was found in 42% of cases. This is in agreement with the Systemic Risk Score Evaluation in Ischemic Stroke Patients (SCALA) study [8] and the Polyvascular Atherothrombosis Observational Study (PATHOS) [9]. Yet, our prevalence of PAD was higher than that of a
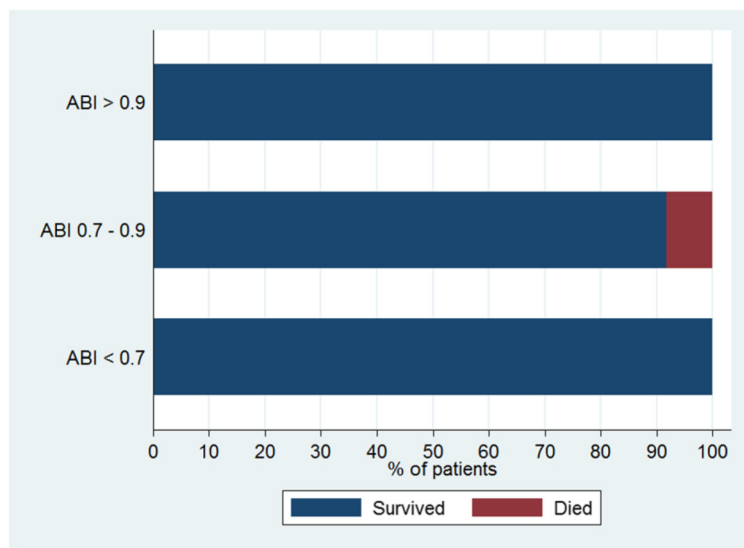

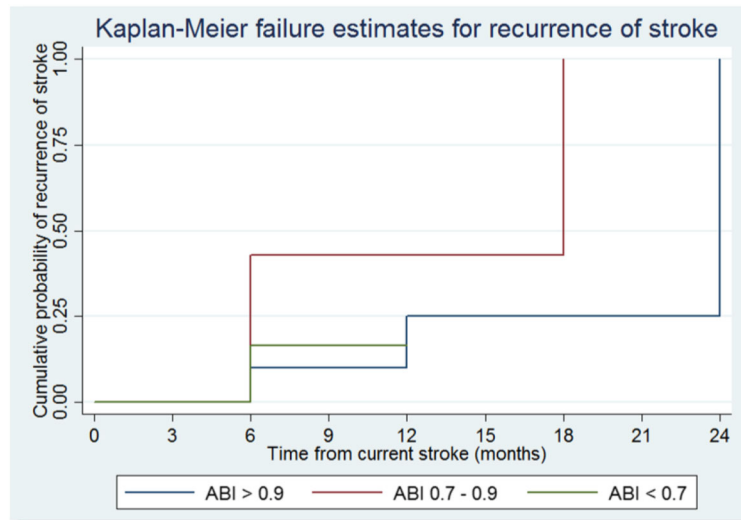**Fig. 3** Relation between ABI and mortality

Fig. 4 Kaplan-Meier curve for the time to recurrence of stroke by the ABI

Japanese study, Hoshino et al. [10], indicating the possibility of ethnic variations. During our study, 8 cases had a recurrence of large artery ischemic stroke, and 5 cases (62.5%) had PAD versus 4 cases (50%) with IHD. This is in agreement with Uchiyama et al. [11] and Beatrice et al. [12]. Fifty percent of patients with lower extremity arterial disease were asymptomatic in agreement with Sigvant et al. [13] and Alvarez-Sabín et al. [14].

Forty-eight percent of the patients with significant carotid stenosis had PAD in agreement with another study on the Egyptian population, Sayed et al. [15], and 42% of these patients with significant carotid stenosis and PAD were asymptomatic. However, our study showed a higher percentage of significant extracranial carotid stenosis as our studied sample was only large artery ischemic stroke patients, and we studied a larger sample.

The recurrence rate of stroke was the highest in the asymptomatic PAD group with 19% followed by the non-PAD group with 5.1% followed by the symptomatic PAD group with 4.8%; however, the low rate of recurrence in our study gives us non-significant statistical value. Notably, in the group of asymptomatic PAD patients, the risk increase was not significant, which may be due to small power owing to low event numbers. Several studies confirmed the positive association between ABI and stroke recurrence, yet most of them included large numbers of patients, and follow-up for recurrence and mortality was assessed at 12 and 24 months which could explain our lower events rate [16].

We strongly recommend routine screening for PAD in patients with ischemic stroke as it is a good predictor for morbidity and mortality in these patients. Once PAD is detected in ischemic stroke patients, prevention of athero-thrombtic events and treatment of atherosclerotic risk factors should be done as PAD can indicate the risk of stroke recurrence.

Conclusion

The prevalence of PAD in large artery ischemic stroke patients is high. Asymptomatic PAD has a risk potential for large artery ischemic stroke recurrence and mortality more than symptomatic PAD and non-PAD patients. ABI can be used in ischemic stroke patients as it is cheap, non-invasive, and available method for diagnosis of PAD for better management and prognosis of stroke patients.

Table 3 Relation between the symptoms of PAD and recurrence of stroke or mortality

Variable	No PAD (n = 58)		Asymptomatic PAD (n = 21)		Symptomatic PAD (n = 21)		Chi-square test, p value
	N	%	N	%	N	%	
Recurrence of stroke	3	5.1	4	19.0	1	4.8	.663
Mortality	0	0.0	2	9.6	0	0.0	.515

Availability of data and materials
The corresponding author takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; has full access to all of the data; and has the right to publish any and all data separate and apart from any sponsor.

Ethics approval and consent to participate
The study was approved by the Ain-Shams University Ethical Committee (date of approval: April 6, 2017) (reference number not available). Written informed consent was obtained from the patients participating in the study after informing them about the study rationale and their right to withdraw from the study at any time without any consequences.

Consent for publication
Not applicable

Competing interests
None of the authors has any conflict of interest.

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