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Original Article

Internal Medicine Section

Peripheral Artery Disease in Patients Presenting with Acute Coronary Syndrome in Hill Population of Northern India

NAGARAJU NAIK BANAVATH[1], MOHD IQBAL DAR[2], MOHD IQBAL WANI[3], AAMIR RASHID[4], KHURSHEED A KHAN[5]

ABSTRACT

Introduction: Acute Coronary Syndrome (ACS) and Peripheral Artery Disease (PAD) represent the serious presentations of the atherosclerotic disease spectrum. PAD due to atherosclerotic disease can lead to significant morbidity and mortality with significant medical and economic burden.

Aim: To study the prevalence of PAD in patients presenting with ACS in the Hill population of Northern India.

Materials and Methods: Patients presenting with ACS, with acute chest pain, Electrocardiogram (ECG) changes and elevated troponins were enrolled in the study. The presence of PAD was assessed with MESI Ankle Branchial Measuring Device (MESI ABPI MD® Slovenia EU) system which uses plethysmographic sensors with an inbuilt software that automatically calculates ABI with accuracy. Patients with ABI <0.91 were further evaluated by Computed Tomography (CT) Angiography of lower limb vessels.

Results: A total of 288 patients were included in the study. There were 238 (82.6%) males and 50 (17.4%) females. Majority of patients had hypertension (214, 74.3%) as the risk factor. ST-Elevation Myocardial Infarction (STEMI) was seen in 197 (68.4%) and Non-ST Elevation Myocardial Infarction (NSTEMI) in 91 (31.6%). Coronary angiography was done in 240 patients. Single vessel disease was seen in 135 (56.2%), double vessel disease in 69 (28.8%) and triple vessel disease in 36 (15%) cases. Out of overall 288 patients 9 (3.12%) had borderline ABI (ABI- >0.9 and ≤1.0) and 4 (1.38%) had abnormal ABI (ABI <0.9). CT angiography of 3 out of 4 patients with ABI <0.9 showed significant atherosclerosis of lower limb vessels.

Conclusion: There was very low prevalence of PAD with ACS in this study population.

Keywords: Ankle brachial index, Coronary angiography, Hypertension

INTRODUCTION

The Peripheral Artery Disease (PAD) generally refers to the vascular disease of an upper or lower extremity associated with decreased blood supply leading to symptoms like claudication and gangrene [1]. Atherosclerosis is the most common aetiology, but other conditions presenting with similar complaints are vasculitis, vasospasm, venous thrombosis, venous insufficiency and lymphatic disorders [2]. This disorder is most commonly asymptomatic and some patients present for the first time with a threatened ischemic limb or a nonhealing ulcer [3].

PAD is one of the most underreported diseases among the spectrum of atherosclerosis because of the low prevalence of the symptomatic disease or atypical nature of presenting symptoms and most commonly affecting elderly population with other comorbidities [4].

ACS represents the acute catastrophic presentation of the coronary atherosclerotic disease process. PAD has been found to be associated with increased risk of coronary, cerebral and carotid atherosclerotic disease which is independent of traditional atherosclerotic risk factors like smoking, diabetes and hypertension [5-7]. Additionally, impaired mobility in PAD masks the signs of early coronary artery disease like angina pectoris and patients usually present with advanced coronary atherosclerosis, adversely affecting the outcome of the ACS as depicted by multiple studies [8,9].

There are wide geographical and racial variations in the prevalence and outcome of PAD worldwide. High prevalence of PAD is seen in western population with poor outcomes in the black population than in white population [10]. Low PAD prevalence was seen in Middle Eastern population [11]. Data on Indian population is scarce with one study from southern India showing a high prevalence of PAD in the study population [12]. Hence, this study was aimed to understand the prevalence of PAD in patients presenting with ACS in a hill population of Northern India.

MATERIALS AND METHODS

Study Design

This study was an observational cross-sectional study conducted over a period of two years at Sheir-i-Kashmir Institute of Medical Sciences Srinagar, which is the lone Tertiary Care Centre of Kashmir. The ethical clearance for the study design was sought and granted by the Institutional Ethical Committee (IEC) and informed consent was obtained from patients/relatives for utilisation of data for research purposes (Ref no. IEC/SKIMS protocol101/2020).

Participants

The recruitment of patients for this study took place between February 2018 to January 2020. Patients reporting to this centre with a diagnosis of an ACS (STEMI, NSTEMI and Unstable Angina) based on American College of Cardiology (ACC)/ American Heart Association (AHA) diagnostic criteria were considered for this study [13,14]. The acceptable sample size for this study with a confidence interval of 99% and a margin of error 10% was 166.

Inclusion criteria: All consenting patients presenting as ACS were included in the study.

Exclusion criteria: Patients with deranged Kidney Function Tests, contrast allergy, denying consent for participation or coronary angiography, known PAD and patients presenting with cardiogenic shock or other structural complication were excluded from the study.

Patient Evaluation

1. Basic and coronary evaluation

Patients were evaluated for the presence of risk factors of atherosclerosis. History of smoking, diabetes mellitus, PAD and family history of coronary artery disease was noted. Patients were screened for the presence of dyslipidemia and diabetes mellitus by lipid profile testing and fasting blood sugars/HbA1c respectively according to ADA guidelines [15]. Blood sample for Lipid profile was taken on admission or within 48 hours of admission and prior to initiation of high dose statin therapy, as both of these factors (postinfraction duration >48 hours and high dose statins) cause significant alteration in lipid metabolism [16].

Definitions of risk factors:

- Diabetes- A fasting glucose of >126 mg/dL (>7 mmol/L) or an HbA1c of >6.5%, or with a RBG >200 mg/dL and with symptoms of hyperglycaemia [15].
- Hypertension- A Systolic Blood Pressure (SBP) >140 mmHg and Diastolic Blood Pressure (DBP) >90 mmHg and or already on treatment for the same [17].
- Dyslipidemia- defined as any one of the following: serum total cholesterol ≥200 mg/dL, serum LDL cholesterol ≥130 mg/dL, serum HDL cholesterol <40 mg/dL, in men or <50 mg/dL in women, or serum triglycerides ≥150 mg/dL [18].
- Body Mass Index (BMI)- defined as: normal (18.0-22.9 kg/m^2), overweight (23.0-24.9 kg/m^2), or obesity (≥25 kg/m^2) [19].

Patients included in the study underwent baseline 2D Echocardiography and coronary angiography if no contraindication to coronary angiography was present. Patients were subsequently revascularised as per ACC/AHA recommendation.

2. Evaluation of PAD

Ankle Brachial Index (ABI) assessment was performed during hospitalisation. ABI assessment was done using MESI ABPI MD® Slovenia EU. This device has three cuffs that are to be attached to the patient's extremities all at the same time and the device uses a PADsense™ algorithm which controls the inflation and deflation process of the cuffs. It works on plethysmographic sensors with an inbuilt software that automatically calculates ABI with accuracy. This device allows the operator to assess both the limbs simultaneously with no time delay contrast to handheld Doppler probe machines which takes longer duration for assessment of the same in one limb. This device was studied in various studies which have given an overall sensitivity of 85% and a specificity of 95% with good reproducibility to this device [20]. An ABI value >1.0 and ≤1.4 was considered normal, Abnormal high ABI >1.4, Borderline ABI >0.9 and ≤1.0, Abnormal low ABI ≤0.9.

All patients with an ABI <0.9 were subjected to CT angiography after 3 weeks for the assessment of PAD. Those patients found to have significant obstructive disease amenable for revascularisation were treated as per the ACC/AHA guidelines for the management of PAD.

STATISTICAL ANALYSIS

All the data was initially compiled in Microsoft Excel and then exported to SPSS. Baseline categorical data was described using numbers and percentages, continuous data was described using mean and standard deviation. Student's Independent t-test was employed for comparing continuous variables. The p-value ≤0.05 was considered significant. Statistical analysis was done using SPSS Version 23.0.

RESULTS

A total of 288 patients were included in the study. Baseline demographics and clinical features of the study population are given

Parameter		ACS (n=288) (%)	STEMI (n=197) (68.4%)	NST-ACS (n=91) (31.6%)	p-value
Age (Years)	<60 years	141 (49.0%)	90 (45.7%)	51 (56.0%)	0.461
	≥60 years	147 (51.0%)	107 (54.3%)	40 (44.0%)	
	Mean±SD	57.4±11.36	57.9±11.32	56.4±11.41	
Gender	Male	238 (82.6%)	168 (85.3%)	70 (76.9%)	0.210
	Female	50 (17.4%)	29 (14.7%)	21 (23.1%)	
BMI (kg/m^2)	18-22.9	81 (28.1%)	58 (29.4%)	23 (25.3%)	0.582
	23-24.9	96 (33.3%)	63 (32.0%)	33 (36.3%)	
	≥25	111 (38.5%)	76 (38.6%)	35 (38.5%)	
	Mean±SD	24.53±2.75	24.51±2.67	24.57±2.93	
Smoking status	Smoker	207 (71.9%)	143 (72.6%)	64 (70.3%)	0.761
	Non-smoker	81 (28.1%)	54 (27.4%)	27 (29.7%)	
Diabetes mellitus	Present	101 (35.1%)	68 (34.5%)	33 (36.3%)	0.482
	Absent	187 (64.9%)	129 (65.5%)	58 (63.7%)	
Hypertension	Present	214 (74.3%)	141 (71.6%)	73 (80.2%)	0.118
	Absent	74 (25.7%)	56 (28.4%)	18 (19.8%)	
Dyslipidemia (n=204)	Present	194 (95.1%)	133 (96.4%)	61 (92.4%)	0.363
	Absent	10 (4.9%)	5 (3.6%)	5 (7.6%)	
Family history of CAD	Present	26 (9.0%)	18 (9.1%)	8 (8.8%)	0.289
	Absent	262 (91.0%)	179 (90.9%)	83 (91.2%)	

[Table/Fig-1]: Clinical features of the study population. Continuous data was described using Mean and Standard Deviation and Student's Independent t-test was employed for comparing continuous variables.
NST-ACS: Non ST elevation-acute coronary syndrome; CAD: Coronary artery disease

Lipid profile on admission or within 24 hours of myocardial infarction and prior to high dose statin therapy was done in 204 patients. Fifty four patients had received high dose statin therapy in peripheral centres prior to referral to this centre and 30 patients presented more than 48 hours after myocardial infarction and lipid profile of these patients was not considered in the final lipid data analysis. Out of

Parameter	Levels	N (%)
TC	>200 mg/dL	30 (14.7)
	<200 mg/dL	174 (85.3)
LDL	>130 mg/dL	26 (12.7)
	<130 mg/dL	178 (87.3)
HDL	<40 mg/dL (M) + <50 mg/dL (F)	176 (86.3)
	>40 mg/dL (M) + >50 mg/dL (F)	28 (13.7)
TG	>150 mg/dL	70 (34.3)
	<150 mg/dL	134 (65.7)

[Table/Fig-2]: Lipid profile of the study population.
TC: Total cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; TG: Triglycerides; M: Males; F: Females

204 patients with lipid profile considered in the study, 95.1% (n=194) had at least one form of dyslipidemia as shown in [Table/Fig-2].

Out of 138 patients of STEMI with lipid profile, dyslipidemia was noted in 96.4% (n=133) and out of 66 patients of NST-ACS with lipid profile, 92.4% (n=61) patients were having dyslipidemia.

Coronary Angiogram (CAG) could be done in only 240 patients due to financial constraints and other contraindications. The CAG profile, syntax score and echocardiographic features of the study population are given in [Table/Fig-3].

Of the 288 patient population, 13 (4.5%) patients had an abnormal ABI value on presentation. Of this 4 (1.38%) had an ABI <0.9 suggestive of definitive PAD and 9 (3.12%) had ABI value between 0.9 and 1.0 suggestive of borderline PAD disease. Percentage of the elderly population (age group ≥60 years) with an abnormal ABI

value was 3.4% (5 out of 147) (p=0.391). Of the 238 male population 9 (3.7%, n=238) patients had abnormal ABI values and out of 50 female population 4 (8%, n=50) had abnormal ABI values with a

Parameter	ACS	STEMI	NSTEMI
Echo (EF) Mean±SD	52.5±11.28 (n=288)	50.2±10.03 (n=197)	57.4±12.24 (n=91)
Syntax score Mean±SD	7.87±7.8 (n=241)	7.09±6.49 (n=167)	9.62±9.97 (n=74)
CAG done	240	166	74
SVD	135 (56.2%)	99 (73.3%)	36 (26.7%)
DVD	69 (28.8%)	48 (69.5%)	21 (30.5%)
TVD	36 (15%)	19 (52.8%)	17 (47.2%)

[Table/Fig-3]: Coronary angiographic profile, Echo (EF) and syntax score of the patient population.
ACS: Acute coronary syndrome; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; SVD: Single vessel disease; TVD: Triple vessel disease

Demographic variables		Non-PAD (n=275) (%)	PAD (n=13) (%)	p-value
Age (Years) (n=288)	<60	133 (48.4)	8 (61.5)	0.391
	≥60	142 (51.6)	5 (38.5)	
	Mean±SD	57.5±11.35	54.8±11.49	
Gender (n=288)	Male	229 (83.3)	9 (69.2)	0.192
	Female	46 (16.7)	4 (30.8)	
BMI (n=288)	18-22.9	76 (27.6)	5 (38.5)	0.688
	23-24.9	93 (33.8)	3 (23.1)	
	≥25	106 (38.5)	5 (38.5)	
	Mean±SD	24.54±2.74	24.23±3.06	
Smoking status (n=288)	Smoker	198 (72.0)	9 (69.2)	0.828
	Non-smoker	77 (28.0)	4 (30.8)	
Hypertension (n=288)	Present	205 (74.5)	9 (69.2)	0.668
	Absent	70 (25.5)	4 (30.8)	
Diabetes (n=288)	Present	94 (34.2)	7 (53.8)	0.149
	Absent	181 (65.8)	6 (46.2)	
Dyslipidemia (n=204)	Present	184 (94.8)	10 (100)	0.462
	Absent	10 (5.2)	0 (0)	
Type of ACS (n=288)	STEMI	185 (67.3)	12 (92.3)	0.058
	NSTEMI ACS	90 (32.7)	1 (7.7)	
Family history of CAD (n=288)	Present	25 (9.1)	1 (7.7)	0.863
	Absent	250 (90.9)	12 (92.3)	
Echo (EF) (n=288)	Mean±SD	52.4±11.19	53.5±13.43	0.743
Syntax score (n=288)	Mean±SD	7.83±7.86	8.54±6.89	0.751
Lipid profile Mean±SD (n=204)	Cholesterol	150.5±47.34	152.1±72.27	0.921
	LDL	64.8±50.23	73.7±61.46	0.534
	HDL	32.5±8.93	28.2±5.59	0.137
	Triglycerides (TG)	151.4±114.81	198.1±167.01	0.221
CAG (n=240)	SVD	128 (56.4)	7 (53.8)	0.783
	DVD	68 (30)	1 (7.7)	0.476
	TVD	31 (13.7)	5 (38.5)	0.028

[Table/Fig-4]: Clinical and biochemical profile of patients with and without PAD.

male to female ratio of 2.25:1 for abnormal ABI value (p=0.192). The clinical and biochemical profile of patients with and without PAD is given in the [Table/Fig-4].

Of the 13 patients with abnormal ABI, 3 patients with an ABI <0.9 undergone CT angiography of both lower limbs and rest of the patients were kept on medical follow-up for symptoms and progression of the disease. The fourth patient with ABI <0.9 was lost to follow-up and could not turn up for lower limb CT angiography. The CT angiography and the baseline profile of the patients with ABI <0.9 is given in [Table/Fig-5].

Parameter	Patient 1	Patient 2	Patient 3	Patient 4
Age (Years)	50	49	50	65
Sex	Male	Male	Female	male
Smoking	Yes	Yes	Yes	Yes
HTN	No	Yes	Yes	Yes
DM	No	Yes (on treatment)	Yes (on treatment)	No
Dyslipidaemia	Yes	yes	-	Yes
BMI	28.2	26.4	21.8	20.4
Family history of CAD	No	No	No	No
TC (mg/dL)	200	119	-	137
LDL (mg/dL)	138	79	-	96
HDL (mg/dL)	40	23	-	26
TG (mg/dL)	190	90	-	117
Type of ACS	IWMI	AWMI	AWMI	IWMI
EF	50%	40%	40%	77%
CAG pattern	SVD	SVD	SVD	SVD
Syntax	11	5	5	2
ABI (right/left)	1.02/0.71	0.68/1.02	0.89/1.05	0.80/1.16
CT angio lower limbs	Complete occlusion of distal SFA with distal collateral formation, CA++, calcified plaques in bilateral EIA and origins of profunda femoris	Diffuse atherosclerotic narrowing of right popliteal artery and right posterior tibial artery with atherosclerotic disease without narrowing in B/L CFA/SFA.	Not done	Right CFA showing discrete Plaque, with distal diffuse plaguing bilaterally with narrowing

[Table/Fig-5]: Profile of patients with ABI <0.91.
HTN: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; EF: Ejection fraction; TC: Total cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; TG: Triglycerides

DISCUSSION

This study, conducted at this tertiary care center of the state was designed to evaluate the presence of peripheral artery in patients presenting as ACS. A total of 288 patients were includes in the study. Males constituted the majority of the study population. Dyslipidemia was the commonest risk factor identified followed by hypertension, smoking and diabetes. More than 2/3rd of the patients of ACS in the study presented as STEMI and the rest presented as NST-ACS.

Demographics and Risk Factors

The baseline characteristics of the study population were very similar to the characteristics of the study group from CREATE [21] registry, India, except for the higher prevalence of HTN and smoking habit among this study population. Compared to western data from GRACE registry [22], this study population had lower mean age group for occurrence of ACS, lower mean BMI values, higher prevalence of smoking, HTN, diabetes and higher occurrence of STEMI compared to NST-ACS. Similarly, the current study population compared to Gulf RACE registry [23], had lower mean BMI values, higher prevalence of smoking, HTN, diabetes and higher occurrence of STEMI compared to NST-ACS despite having similar mean ages for the occurrence of ACS.

In this study population, the occurrence of STEMI ACS was found to be higher compared to NST-ACS. The mean age of these groups of the population was 57.9 and 56.4 years, respectively. Males were predominant in both STEMI and NST-ACS groups. The mean BMI values of both groups were also similar. Population with obesity were also similar in both groups. Both the groups had the similar number of patients with a history of smoking, diabetes, dyslipidemia, family history of CAD but with more number of patients with hypertension (71.6% vs 80.2%; p=0.118) in NST-ACS group

compared to STEMI group.

This baseline risk profile of STEMI and NST-ACS populations is similar to CREATE registry population, except for higher smoker and hypertensive patients in the current study. Prevalence of diabetes was higher in this STEMI population than in CREATE registry but are similar in NST-ACS group. This study data when compared to western Global Registry of Acute Coronary Events (GRACE) [22] and Manejo del Síndrome Coronario Agudo. Registro Actualizado (MASCARA) [24] registries had more STEMI patients than NST-ACS, lower mean age for occurrence of ACS, more smokers, more hypertensives and lower mean BMI values for both STEMI and NST-ACS groups. STEMI population in this study had more diabetic population compared to western registries. When compared to middle-east Gulf RACE registry [23], STEMI and NST-ACS groups in the current study population had more smoker and hypertensive patients and a lower mean BMI values but had similar mean age at presentation of ACS.

Dyslipidemia in the current study was noted in >90% of study subjects. The most common abnormality noted was low HDL followed by elevated TG, elevated total cholesterol levels and elevated LDL levels. This is in contrast to western data [25] where TC and LDL were found to be independent factors for CV events.

Coronary Status

In this study, CAG of the STEMI population had a higher percentage of SVD and DVD compared to NST-ACS group, but there was not much difference for the occurrence of TVD in both the groups. One of the registry data from Spain, MASCARA [24], compared the angiographic profiles of patients of ACS and had shown more prevalence for all the three profiles in STEMI compared to NST-ACS.

Coronary Artery Disease with vs without PAD

The mean age of the patient population of ACS with PAD in this study population was the same as the mean of ACS population without a PAD. This is in contrast with other registry data available [22], where the mean age of patients with PAD was higher than those without a PAD on presentation. The male population was higher in this study similar to other registry data but its incidence was equally higher in ACS group suggestive of no statistical significance. BMI values were similar in both groups of PAD and nonPAD, similar to other studies [22,26] suggestive of no clinical influence of it on the association of PAD in an ACS.

Tobacco abuse was also similar in both groups and similar to other registry [22] suggesting no statistical significance. The occurrence of HTN was similar in both groups in this study suggestive of no statistical significance which contrasts the western data [27] where there was a higher occurrence of HTN in patients with concomitant PAD. However, the Chinese registry data [28] also has a similar occurrence of HTN in both groups of PAD and nonPAD, similar to the current study. There was a higher occurrence of diabetes in patients with PAD compared to those without a PAD (though not statistically significant) similar to all other registries where there was a significant association of DM for the occurrence of PAD [26,27].

There was no association between family history of CAD and incidence of PAD and this characteristic was the least to be reported even for ACS in this study. The definition of dyslipidemia was different for different registries with most of them addressing it for abnormal higher levels of lipid profile [21-23]. Role of HDL was assessed less in most of these registries. In this study, a low HDL level was also considered as part of dyslipidemia, which increased the number of patients having any one of this abnormality to more than 90% for both the groups. When assessed individually, there was no independent association for any of the lipid parameter for the occurrence of PAD in an ACS patient, in contrast to other data that have shown an independent association between total cholesterol and LDL levels [27,28]. However, there was an occurrence of lower levels of HDL cholesterol among patients with PAD than patients without a PAD, though there was no statistically significant association with it.

Association

In this study, the authors tried to understand the association of pattern of coronary artery disease in presence of associated PAD among patients of ACS. In this study we could establish an association between the pattern of triple vessel disease and PAD (p=0.028) similar to multiple other studies across the world [29,30]. However, a Japanese study has shown a higher association of TVD with the increasing number of extra-cardiovascular lesions [30]. This study, first of its kind in this study population showed an overall low prevalence of PAD associated with ACS.

Limitation(s)

The main limitation of the study is that it was a single centre study. A multicenter study with larger sample size is needed to validate the findings.

CONCLUSION(S)

This study concludes that in this study population STEMI is more common than NSTEMI. In this study, population of ACS, significant lower ABI values (<0.9) for a definite PAD were very low compared to many studies across the globe done in the same scenario of ACS presentation. Furthermore, PAD is associated with triple vessel disease and overall incidence of PAD with ACS is very low in this study population.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Cardiology, SKIMS, Soura, Srinagar, Jammu and Kashmir, India.
2. Senior Resident, Department of Cardiology, SKIMS, Soura, Srinagar, Jammu and Kashmir, India.
3. Senior Resident, Department of Cardiology, SKIMS, Soura, Srinagar, Jammu and Kashmir, India.
4. Assistant Professor, Department of Cardiology, SKIMS, Soura, Srinagar, Jammu and Kashmir, India.
5. Professor, Department of Cardiology, SKIMS, Soura, Srinagar, Jammu and Kashmir, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Mohd Iqbal Dar,
Room No. f04, Old Sr Hostal, SKIMS, Soura, Srinagar, Jammu and Kashmir, India.
E-mail: darmohdiqbal@yahoo.in

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