Original Research Paper

General Surgery

ASSESSMENT OF MAJOR RISK FACTORS ASSOCIATED WITH PERIPHERAL VASCULAR DISEASE: A CASE-CONTROL STUDY

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ABSTRACT **Objectives:** To assess the major risk factors which are potentially contributing to peripheral vascular disease (PVD). **Methods:** This is a case-control study conducted among inpatients of a Tertiary care hospital in the state of Andhra Pradesh who are having the risk factors that contribute to PVD. Cases and controls were selected based on the ABPI (Ankle Brachial Pressure Index). A total of 50 cases and 100 controls were included in the study i.e., in 1:2 ratio. The odds of exposure of PVD to risk factors were assessed using odds ratio. **Results:** In our study, we found that the maximum number of cases were among the age group of 51-60 years. Smoking and Alcoholism showed significantly higher odds of exposure than all others with a P-value <0.0001. Diabetes and CAD also showed significant risk with P-Values of 0.005 and 0.027 respectively. Hypertension and Platelet count posed lesser risk with P-values of 0.728 and 0.2201 respectively. Gender difference imposed insignificant odds with a P-Value of 0.550. **Conclusion:** As per the results, we demonstrate that increased risk of PVD is associated with advanced age. Sex is not having any predominant association with disease i.e., both males and females are equally prone to the disease. Alcohol and Smoking are major risk factors and the risk of disease increases with increased duration. Among diabetics, type ii diabetes contributes to increased risk of PVD. Hypertension and Dyslipidemia also contribute to the pathogenesis of PVD but not that much affiliated as others. there is a clearcut observation that the trend is shifting towards Diabetes from Smoking.

KEYWORDS : Peripheral Vascular Disease, Macrovascular disease, Risk factors, case-control study.

INTRODUCTION:

Peripheral vascular disease (PVD) is a slowly progressive macro-vascular disorder resulting from occlusion of peripheral arteries other than coronary and intracranial vasculature [1]. It is one of the systemic Atherosclerotic vascular diseases along with stroke, abdominal aortic aneurysm (AAA), coronary artery disease (CAD), cerebrovascular disease (CVD) etc [2]. The prevalence of PVD is dependent on age which is infrequent in younger individuals and common in older individuals. It is a type of Atherosclerotic syndrome marked by progressive narrowing of vasculature due to stenosis because of formation of plaque leading to diminished blood flow in vasculature particularly of lower limbs leading to acute or chronic ischemia, which may sometimes lead to amputation [3, 4].

Patients with PVD may be asymptomatic typically early in the disease. As the disease progresses they present with intermittent claudication which can be described as pain, fatigue, discomfort, cramping, tightness, weakness that occurs typically in buttocks, thigh or calf during exercise and it usually relieves when the physical activity is discontinued, atypical leg pain on exertion and rest which is generally regarded as the primary indicator of PVD [5]. Some patients may develop critical limb ischemia which is a painful condition marked by numbness or continuous pain even at rest. Resting pain is a typical symptom of critical limb ischemia due to decrease in blood perfusion and this condition most often is felt at night in the feet when the patient is lying in bed [6].

PVD is diagnosed by physical findings and invasive techniques such as peripheral Angiography/contrast arteriography or intra-arterial blood pressure measurement and non- invasive techniques such as Duplex scanning, Magnetic resonance Arteriography, Doppler study or Ankle-brachial pressure index [7]. ABI has become a standard part of the initial evaluation of patients with suspected PVD. It identifies PVD by comparing systolic blood pressures in the ankle to the higher of the brachial systolic blood pressures, which is the best estimate of central systolic blood pressure. ABPI is performed using a continuous wave Doppler, a sphygmomanometer and pressure cuffs to measure brachial and ankle systolic pressure. A patient can be diagnosed as PVD if ABPI is ≤ 0.9, it is graded as severe if ABPI < 0.40 and considered as mild to moderate if ABPI is between 0.4 to 0.9, ABPI ≥ 1.4 indicates highly non-compressible vessels [8]. Duplex ultrasonography does not use radiation or contrast agent and is safe. It is an accurate method for determining the degree of stenosis or length of occlusion of the arteries supplying the lower extremity. It is useful in the follow-up of patients who have undergone percutaneous transluminal angioplasty/stent or surgical revascularization. Magnetic resonance angiography (MRA) of the aorta and peripheral vasculature acquires angiographic-like images. The quality of MRA is so good that it has virtually replaced diagnostic angiography. The success of MRA in identifying small runoff vessels meets or exceeds that of traditional catheter-based angiography [9]. The aim of this study was to assess the association between risk factors (i.e., smoking, Alcohol, Diabetes mellitus, Hypertension, Coronary artery disease) and peripheral vascular disease

METHODOLOGY:

Study design:

This is a case-control study that was conducted on patients admitted to the General Surgery Department of NRI General Hospital, Chinakakani, Andhra Pradesh, India.

Study duration:

This study was conducted for a period of 14 months i.e., from February 2019 to March 2020.

Study population and methods:

Identification of cases and controls was based on results of Doppler study and Ankle Brachial Pressure Index (ABPI) values. Cases refer to the number of patients having ABPI value 0.85 or less in any of the lower limbs and are diagnosed with PVD by Doppler study. Controls refer to the number of patients having ABPI values within the range 1.18-1.28 in both lower limbs and are diagnosed without PVD by Doppler study.

To ensure 100% specificity and no false positives among cases, only newly identified cases are taken (incident cases). To accommodate for the low number of cases, case to control ratio was decided as 1:2, without compromising the power of the study. Thus 50 cases and 100 controls were recruited in the study. The association between risk factors and PVD is assessed by calculating odds ratio using the number of case-patients who did or did not have exposure to a specific factor and the number of controls who did or did not have the exposure.

Inclusion criteria:
• Patients who are greater than 25 years of age.
• Patients who are diagnosed with PVD and having co-morbidities as Cases.
• Patients who are not diagnosed as having PVD but who are having the following risk factors are included as controls- Advanced age, Hypertension, Smoking, Alcoholism, CAD, Dyslipidemia, Diabetes Mellitus etc.

Exclusion criteria:
• Pregnant and lactating women
• Patients who fail to give informed consent.
• Patients who are diagnosed with PVD with the history of Trauma.

Data collection:
Both cases and controls included admitted patients in different surgical units picked randomly. The required information was obtained from patient case records and through direct patient interviews. Information on demographic factors, the presence of selected non-communicable disease conditions such as Diabetes, Hypertension, Dyslipidemia, coronary artery disease and, smoking and alcohol history were obtained with duration.

Ethical Approval:
The study was conducted as per the proforma and approved by Ethical review committee of the NRI General Hospital. Informed consent was obtained from all patients prior to participation.

Statistical Analysis:
Categorical variables were described using frequencies; whereas the standard deviation and means were used for continuous variables. Multivariate logistic regression analysis was carried out to identify risk factors associated with renal toxicity. All analysis was carried out using SPSS software version 21.0 (SPSS). A P-value <0.05 was considered statistically significant.

RESULTS:
All the selected cases (50) and controls (100) participated in the study making the response rate 100%.

TABLE -1: AGE WISE INCIDENCE

Age Group in Years	No. of Patients [Cases]		Mean ± SD	Percentage	No. of Patients [Controls]		Percentage	Mean ± SD
	Male [n=33]	Female [n=17]			Male [n=61]	Female [n=39]		
30-40	1	3	58 ±12.1	8%	5	5	10%	54.9 ±13.1
41-50	7	3	58.8±11.5	20%	16	6	22%	55.8 ±12.3
51-60	12	6	58.6 ±11.7	36%	19	17	36%	55.5 ±12.2
61-70	7	4	58.6 ±11.6	22%	15	6	21%	55.9 ± 12.3
71-80	5	1	59.3±12	12%	5	5	10%	56.1± 12.4
>80	1	0	61.7 ±14.3	2%	1	0	1%	80 ± 0

Total	33	17	58.3 ±11.7	100%	61	39	100%	55.9 ±12.2

The youngest patient was of 34 years of age and the oldest patient was of 87 years of age in the case group, while the youngest patient was of 29 years of age and the oldest patient was of 85 years of age in the control group. In the case group, maximum numbers of cases were observed in the age group of 51-60 years, 18 cases (36%); followed by age group of 61-70 years, 11 cases (22%) and a minimum number of cases were seen in the age group of >80 years, 1 case (2%). In the control group, maximum numbers of cases were observed in the age group of 51-60 years, 36 cases (36%); followed by age group of 41-50 years with 22 cases (22%) and 61-70 years with 21 cases (21%)and a subtle number of cases were seen in the age group of >80 years, 1 case (1%).

TABLE -2: SEX INCIDENCE

Gender	No. of Patients [Cases] [n=50]	Percentage	Mean ± SD	No. of Patients [Controls] [n=100]	Percentage	Mean ± SD
Male	33	66%	58.4±11.8	61	61%	55.9±12.2
Female	17	34%	58.6±11.5	39	39%	55.6±12.3

Male preponderance noted with 33 out of 50 (66%) in the case group and 61 out of 100 (61%) in the control group.

TABLE -3A: RISK FACTORS

Risk Factor Duration in Years	Cases		Controls	
	Smoking [n=24]	Alcoholism [n=19]	Smoking [n=11]	Alcoholism
0-5	1	0	1	1
6-10	2	2	3	5
11-15	2	3	3	0
16-20	4	6	1	2
>20	15	8	3	2

Out of 50 patients in the case group, 24 (48%) were smokers, 19 (38%) were alcoholics and 16 patients were having both smoking and alcohol history. Out of 100 patients in the control group, 11 (11%) were smokers, 10 (10%) were alcoholics and 7 patients were having both smoking and alcohol history. Risk of smoking and alcoholism as shown in the table is dependent on duration. In the case group, 15 smokers have about >20 years of exposure and 8 alcoholics has about >20 years exposure whereas, in the control group, 3 smokers have >20 years of exposure and only 2 alcoholics has about >20 years exposure.

TABLE -3B: RISK FACTORS

Risk Factors	Cases		Controls	
	Hypertension [n=25]	Diabetes [n=42]	Hypertension [n=53]	Diabetes [n=61]
0-5	8	11	28	21
6-10	10	8	14	23
11-15	7	11	7	8
16-20	0	8	1	5
>20	0	4	3	4

Out of 50 patients in the case group, hypertensive's were 25 (50%), 41 (82%) were diabetics and 22 patients were having both hypertension and diabetes. Whereas hypertensives were 53 (53%), 61 (61%) were diabetics and 36 patients were having both hypertension and diabetes in the control group. Risk of hypertension and diabetes as shown in the table is dependent

on duration. Out of 50 cases, 10 patients were having hypertension of 6-10 years duration,11 patients were having up to 5 years of duration of diabetes and 11 were having 11-15 years of duration of diabetes. Out of 100 controls, 28 patients were having hypertension and 21 patients were having diabetes of up to 5 years of duration.

TABLE -4: CAD

CAD	No. of Patients [Cases] [n=50]	Percentage	No. of Patients [Controls] [n=50]	Percentage
Present	14	28%	13	13%
Absent	36	72%	87	87%

Out of 50 patients in the case group and 100 patients in the control group, patients having simultaneous coronary artery disease were 14 (28%) and 13 (13%) respectively. Almost all of them were hypertensive and diabetic. Most of them had a history of smoking.

TABLE-5: PLATELET COUNT

Platelet Count	No. of Patients [Cases] [n=50]	Percentage	No. of Patients [Controls] [n=100]	Percentage
>1.5L	47	94%	98	98%
<1.5L	3	6%	2	2%
Total	50	100%	100	100%

Out of 50 cases, 39 patients in the case group and 87 patients out of 100 patients in the control group were having platelet count within normal limits. Only 8 (16%)patients in the case group and 11 (11%) patients in the control group were having high platelet count.

TABLE 9: ANALYSIS OF SIGNIFICANCE OF ODDS OF EXPOSURE OF THE DISEASE TOWARDS THE RISK FACTOR

Patient characteristics	Category	Number of Patients	ADR (YES)	ADR (NO)	Odds Ratio (95% CI)	P-Value
Gender	Male	94	33	61	1 (reference)	<0.550
	Female	56	17	39	0.8(0.39to 1.63)	
Smoking	Smokers	35	24	11	1 (reference)	<0.0001
	Non-smokers	115	26	89	0.13 (0.05 to 0.30)	
Alcohol	Alcoholic	29	19	10	1 (reference)	<0.0001
	Non-Alcoholic	121	31	90	0.18 (0.07 to 0.43)	
Hypertension	HTN	78	25	53	1 (reference)	<0.728
	No HTN	72	25	47	1.12 (0.57 to 2.22)	
Diabetes	DM	103	42	61	1 (reference)	<0.005
	No DM	47	08	39	0.29 (0.12 to 0.70)	
CAD	CAD	27	14	13	1 (reference)	<0.027
	No CAD	123	36	87	0.38 (0.16 to 0.80)	
Platelet count	> 1.5	145	47	98	1 (reference)	<0.2201
	< 1.5	5	3	2	1.22(0.50-19.35)	

DISCUSSION:

Very few case-control studies on Peripheral Arterial Disease (PAD) were conducted in South Indian Population. Peripheral Vascular disease is a well-known health problem in patients who are having high risk. Most common and classical risk factors for PVD include advanced age, smoking, alcohol, hypertension, Dyslipidemia, Diabetes mellitus and renal disease. Non-classical risk factors include race and ethnicity, elevated inflammatory markers such as C-reactive proteins, fibrinogen, leucocytes, interleukin-6, genetics, and hypercoagulable states of altered levels of D- dimer. Risk factors for PVD are almost identical to Atherosclerotic disease and presence of more than one risk factor in a single patient may increase the risk to many folds [10].Risk factor identification and modification play an important role in both diagnosis and the management of PAD. This study was able to identify specific risk factors of PAD which will help to address preventive measures of PAD [11]. Andrew P Miller et al stated that PAD is common in older adults (≥25%), usually asymptomatic or associated with atypical symptoms unidentified as claudication; similar to our study which also showed an increased risk of PAD in older adults [12] Prevalence of PVD increases with advanced age because of age-related alterations in vascular structure and function such as increased calcium deposition, collagen content, increased vessel diameter and outward remodelling [13]. Schramm Ket.al., stated that PAD remains an under-recognized disease entity for women and women who present with symptomatic PAD tend to be older than their male counterparts and are more likely to present with CLI than men. Despite these differences, endovascular treatment of PAD in women remains a viable and durable option so there is a continued need for targeted health campaigns for women to promote early management of risk factors, early diagnosis, and management of PAD [14].Bennett et al reported that males are at significantly high risk for developing PAD among migrant South Asians in the UK. In the same study, they found that sex was not a significant risk factor among blacks, similarly to the results of our study which demonstrated that sex has no significant association with PAD [15].LU JT et al described that smoking is a major risk factor for PVD and there is an association between endothelial dysfunction and pack-years smoked. Smoking cessation increases long-term survival in patients with PAD by restoring some of the normal physiological responses of the vascular system and increases the probability of limb viability in patients with PAD [16]. Exposure to smoking activates a number of mechanisms that predispose to Atherosclerosis as it contains 4000 chemicals, of these polycyclic aromatic hydrocarbons, oxidising agents, nicotine are identified as potential contributors for vascular disease by inducing the release of catecholamines [17].Components of cigarette smoke, including carbon monoxide and nicotine, affect the function of endothelial cells; increase the reactivity, aggregation, and adhesion of platelets; cause vasoconstriction, and permit the migration of smooth muscle cells and oxidise low-density lipoprotein particles and leads to atherosclerosis. In our study also smoking was found to be a significant risk factor for PAD [16].Jepson RG et al investigated the relationship Alcohol intake and occurrence of peripheral arterial disease in the general population and concluded that greater alcohol consumption is related to higher ABPI. These results were similar to our study which showed alcohol usage to be a significant risk factor for PAD [18]. Alcohol, when taken in small quantities, is found to be beneficial against vascular disorders whereas heavy drinking contributes severe risk condition [19].Makin A et al., in their study evidently concluded a clear association between PVD and hypertension although its relative risk may not be as high as for smoking or diabetes mellitus. These results were similar to our study in which hypertension was found to be a non-significant risk factor for PAD [20].Hypertension and Dyslipidemia are associated with abnormalities of homeostasis and lipids and they contribute to the pathogenesis of Atherosclerosis which is the basic underlying mechanism of PVD [21]. Thiruvoipati T et al., in their study stated that DM is associated with greater severity towards PAD relative to non-diabetics. Diabetes also

correlates to a greater risk of mortality and impaired quality of life. Our study also reported a significant association between Diabetes and PAD [22]. Type II Diabetes Mellitus is majorly associated with an increased risk of PVD. Insulin resistance causes several metabolic abnormalities including suppression of lipid oxidation which then lead to Dyslipidemia and the well-known lipid triad: high levels of plasma triglycerides, low levels of high-density lipoproteins, and the appearance of low-density lipoproteins which contributes to the formation of Atherosclerosis [23]. Sarangi S et al. stated that the occurrence of CAD among patients who had PAD was 2 times more than those without PAD and in their study among PAD-positive cases, CAD was present in 46.88%. Only 20% of PAD-negative cases had CAD. A strong correlation was found to occur between PAD and CAD. Ninety-five per cent of individuals with PVD have at least one cardiovascular risk factor; the majority of patients have multiple risk factors for CVD [24].

CONCLUSION:

The results of this study demonstrate that the risk of PVD is highly associated with smoking, alcoholism, Diabetes Mellitus and CAD. PVD is also associated with hypertension but not as highly affiliated as other factors. Early diagnosis, proper treatment and modification of these risk factors may play an important role in the prevention and management of PVD.

ABBREVIATIONS:

- PVD - Peripheral Vascular Disease.
- ABPI – Ankle Brachial Pressure Index.
- CAD – Coronary Artery Disease.
- AAA- Abdominal Aortic Aneurysm.
- CVD – Coronary Vascular Disease.
- MRA – Magnetic Resonance Imaging.
- PAD – Peripheral Vascular Disease.

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