ORIGINAL ARTICLE

Epidemiology of hospitalized patients with peripheral arterial disease in Bosnia and Herzegovina

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ABSTRACT

Aim To investigate a profile of patients with peripheral artery disease (PAD) in Bosnia and Herzegovina.

Methods This observational study included 1022 patients hospitalized at the Clinical Centre University of Sarajevo in a 5-year period, 2015 to 2019.

Results Disease prevalence rises sharply after the age of 50. Most patients, 797 (78%) had proximal PAD; 658 (64.4%) were males. The death occurred in 73 (7.1%) patients, more often in females (66- 10%), and in patients with chronic kidney disease (10- 23.8%). Amputation occurred in 153 (15%) patients, where 102 (66.7%) patients had diabetes. Other surgical procedures were more common in males and smokers. Necrosis and phlegmon on lower extremities were found in 563 (55.1%) and 43 (4.2%) patients, respectively. History of tobacco use was noted in 620 (60.2%) patients, and 414 (40.8%) patients were current smokers. More than a half of patients had hypertension and diabetes, 596 (58.3%) and 513 (50.2%), respectively. One in 10 patients had a history of myocardial infarction or stroke. Most patients had high fibrinogen and blood glucose and low high-density lipoprotein (HDL).

Conclusion Patients with PAD have multiple comorbidities and risk for various complications. Primary and secondary prevention of risk factors is the mainstay of treatment.

Key words: atherosclerosis, diabetes mellitus, risk factors, tobacco use

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INTRODUCTION

Peripheral arterial disease (PAD) is a complete or partial obstruction of blood flow in major systemic arteries other than those of the cerebral and coronary circulation. The most common cause is atherosclerosis, while other, such as vasculitis, thrombosis, thromboembolism, are infrequent (1). The estimated prevalence of this disease in Europe is around 5.3% (40 million) (2). The PAD has a strong correlation with coronary artery disease (CAD) and cerebrovascular disease, as atherosclerosis is the basis of all these conditions (1). Accordingly, the main risk factors for PAD include smoking, diabetes, hypertension, hypercholesterolemia (3). The presence of three or more risk factors increases the risk of PAD ten times and smoking alone increases that risk two to four times (2,4).

The prevalence of PAD is increasing, due to the ageing of the global population and larger detection of asymptomatic cases (2). Studies show that patients with symptomatic PAD with no prior myocardial infarction (MI) or stroke had around 2 times higher risk of cardiovascular events than those with prior MI or stroke but without symptomatic PAD (5). This condition remains underdiagnosed and undertreated, and it is a very important public health problem in all countries (2,4).

The aim of this study was to present epidemiological data on PAD in Bosnia and Herzegovina (B&H) as a middle-income country, and emphasize the importance of the disease and the range of associated conditions. Such data have not been previously published in our institution and sparse data are available in the region.

PATIENTS AND METHODS

Patients and study design

This observational retrospective study included 1022 patients hospitalized at the Department of Angiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Centre University of Sarajevo from 2015 to 2019. Inclusion criteria were patients with confirmed PAD.

PAD was defined as atherosclerotic disease in the lower extremities and classified as proximal if occlusion/stenosis involves arteries above the knee and distal if the obstruction only involves popliteal arteries or those below the knee.

Data were collected from medical records of all patients hospitalized for PAD: gender, age, PAD location, number of hospitalizations, lethal outcome, Leriche syndrome, Buerger syndrome, ulcer, phlegmon, necrosis, history of smoking cigarettes (packs of cigarettes smoked per day x years; 1 pack= 20 cigarettes), comorbidities, amputation, other surgical procedures and laboratory values.

The study was completed in compliance with the Helsinki Declaration (last revised in 2013) and approved by the Institute for Scientific Research and Development of the Clinical Centre University of Sarajevo.

Methods

The diagnosis of PAD was confirmed by ultrasound VI-VID S5 with 12 L linear probe (General Electric, Boston, Massachusetts, United States) or Logiq Book XP with 8L curvilinear probe (General Electric, Boston, Massachusetts, United States), or CT angiography (Toshiba Aquilion Prime 160 Slice CT), or digital subtraction angiography (Siemens Axiom Artis or General Electric Innova).

Laboratory analysis included fibrinogen (1.8-3.8 g/L), blood glucose (3.3-6.1 mmol/L), glycated haemoglobin (HbA1C) (<6.5%) and lipoprotein fractions - total cholesterol (3.1-5.2 mmol/L), high-density lipoprotein (HDL; 1.06-1.94 mmol/L, low-density lipoprotein (LDL; 1.4-3.4 mmol/L), and triglycerides (0.11-1.70 mmol/L). Reference values were according to the Clinical Centre University of Sarajevo.

When tobacco use was compared with other conditions, both current and former smokers are considered as smokers, while non-smokers are those who have never smoked, unless otherwise noted.

Statistical analysis

The results of the descriptive analysis were displayed in frequencies and percentages. Differences between parameters were assessed using Mann Whitney U test. The correlation between parameters was assessed by the χ^2 test of independence with Yates' Correction for Continuity: the phi *coefficient* is a measure of association between two binary variables, ranging from -1 to 1 (higher number shows stronger correlation between two variables). The $p \leq 0.05$ was used for statistical significance.

RESULTS

Out of 1022 patients hospitalized with PAD in the 5 year-period, 658 (64.4%) were males and 364 (35.6%) were females. Overall average age was 68.5 (±11.3) (range 18-96) years: 66.7±10.5 (range 37-93) years for males, and 71.8±11.8 (range 18-96) years for females.

One in ten patients, 110 (10.8%), were hospitalized more than once in the five-year period; among those, 66 (60%) were hospitalized twice, 25 (22.7%) three times, 13 (11.8%) four times, six (5.5%) patients five or more times. Annually, 189 (18.5%) patients were hospitalized more than once, and most of them twice, 145 (76.7%).

Lethal outcome was registered in 73 (7.1%) hospitalized patients (Table 1), significantly more females than males, 10% and 5%, respectively (p=0.001; phi=-0.12). More deaths occurred in non-smokers than smokers, 10.7% and 4.8%, respectively (p=0.001; phi=-0.12). More deaths occurred in patients who had lower extremity necrosis than in patients without necrosis (76.5% vs. 23.5% (p=0.002; phi=0.10). Lethal outcome was more frequent in patients with chronic kidney disease (CKD) comparing the ones without CKD, 23.8% and 6.4%, respectively (p=0.00; phi=0.13).

Table 1. Conditions and outcome associated with peripheral artery disease (PAD)

Variable	No (%) of patients*			p (phi)§	No (%) of patients		p (phi)§
	Total†	Females	Males		Smokers‡	Non-smokers	
Lethal outcome	73 (7.1)	36 (10)	33 (5)	0.001 (-0.12)	30 (4.8)	43 (10.7)	0.001 (0.12)
Leriche syndrome	29 (2.8)	14 (3.8)	15 (2.3)	0.21 (-0.045)	27 (93.1)	2 (6.9)	p=0.001 (0.11)
Buerger's disease	22 (2.2)	5 (1.4)	17 (2.6)	0.29 (0.04)	21 (95.5)	1 (4.5)	p=0.002 (0.11)
Necrosis	563 (55.1)	233 (64.1)	355 (53.9)	0.003 (-0.09)	303 (53.8)	260 (46.2)	p=0.00 (-0.16)
Phlegmon	43 (4.2)	12 (3.3)	31 (4.7)	0.36 (0.034)	13 (2.1)	30 (7.5)	p=0.00 (-0.13)
Lower-extremity ulcer	60 (5.9)	21 (5.8)	39 (5.9)	1.00 (0.003)	29 (48.3)	31 (51.7)	0.06 (-0.06)
History of tobacco use	620 (60.2)	154 (42.3)	466 (70.8)	0.00 (0.28)	N/A	N/A	N/A
Amputation	153 (15)	49 (13.5)	104 (15.8)	0.36 (0.03)	85 (55.6)	68 (44.4)	0.19 (0.04)
Other surgical procedures	124 (12.1)	25 (6.9)	99 (15)	0.00 (0.12)	99 (16)	25 (6.2)	0.00 (0.15)

*Percentages are shown within gender for females and males, and within primary condition for smokers and non-smokers; †Number of patients with available data; ‡Current or former smokers; §The Phi *Coefficient* is a measure of association between two binary variables, it is in the range from -1 to 1, higher number shows stronger correlation between two variables; N/A, non applicable;

Most patients had proximal PAD (797; 78%), including patients with diabetes mellitus (72.1%) and smokers (84%) (p=0.00; phi=-0.14; p=0.00; phi=0.18, respectively). The significance of PAD location was proven in other groups of patients (Table 2).

Table 2. Peripheral artery disease (PAD) location and its significance among groups of patients according to comorbidities

Patients group	No (%) of patients in the PAD group		p (phi*)
	Proximal	Distal	
All	797 (78)	225 (22)	
Diabetes mellitus	370 (72.1)	143 (27.9)	0.00 (-0.14)
Necrosis	414 (73.5)	149 (26.5)	0.00 (-0.13)
Leg ulcer	38 (63.3)	22 (36.7)	0.008 (-0.09)
Buerger's disease	6 (27.3)	16 (72.7)	0.00 (-0.18)
Current smokers	348 (84)	66 (16)	0.00 (0.18)
Amputation	109 (71.2)	44 (28.8)	0.05 (-0.07)

*The Phi Coefficient is a measure of association between two binary variables, it is in the range from -1 to 1, higher number shows stronger correlation between two variables

Necrosis was more common in patients with a history of stroke (67.6% vs 56.2% in others), p=0.03; phi=0.07. Phlegmon was more common in non-smokers (7.5%) than smokers (2.1%) (p=0.00; phi=-0.13) (Table 1).

Tobacco use was declared by 620 (60.2%) patients: 414 (40.8%) were current smokers at the time of hospitalization, while 207 (20.2%) were former smokers; four patients were counted in both categories, due to different smoking status during rehospitalization. Among 138 patients with available data on the smoking habit, pack-years were in the range from 10 to 200. Over 90% of patients smoked 30 pack-years and 60.1% at least 50 pack-years; males significantly surpassed females (mean 76 vs 51 pack-years) (p=0.002); 81 (7.9%) were categorized as passionate smokers, without quantification (data not shown). Most of our former smokers (83.5%) quit smoking cigarettes within 20 years.

More than a half of the patients had hypertension and diabetes, 596 (58.3%) and 513 (50.2%) respectively, more frequently non-smokers (63.4% and 63.7%, respectively) than smokers (55.0% and 47.32%, respectively) (p=0.009; phi=-0.08 and p=0.00; phi=-0.22, respectively).

History of 117 (11.5%) and 116 (11.4%) patients revealed MI and stroke, respectively. Hypertension has been more often in females, while MI has been more often in males (Table 3).

A total number of 153 (15%) patients had some form of amputation on the lower extremities (Ta-

Table 3. Comorbidities of patients with peripheral artery disease (PAD)

Comorbidity	No (%) of patients*			p (phi)§	No (%) of patients*		p (phi)§
	Total†	Females	Males		Smo-kers‡	Non-smokers	
Hypertension	596 (58.3)	235 (64.6)	361 (54.9)	0.003 (-0.09)	341 (57.2)	255 (42.8)	0.009 (-0.08)
Diabetes mellitus	513 (50.2)	186 (51.1)	327 (49.7)	0.72 (-0.01)	257 (50.1)	256 (49.9)	0.00 (-0.22)
Myocardial infarction	117 (11.5)	31 (8.5)	86 (13.1)	0.04 (0.07)	73 (62.4)	44 (37.6)	0.76 (0.013)
Stroke	116 (11.4)	48 (13.2)	68 (10.3)	0.20 (-0.04)	62 (53.4)	54 (46.6)	0.12 (-0.05)
Hyperlipide-mia	43 (4.2)	14 (3.8)	29 (4.4)	0.79 (0.01)	35 (81.4)	8 (18.6)	0.007 (0.09)
Chronic kid-ney disease	42 (4.1)	9 (2.5)	33 (5.0)	0.07 (0.06)	23 (54.8)	19 (45.2)	0.52 (-0.02)
AAA	25 (2.4)	4 (1.1)	21 (3.2)	0.06 (0.06)	21 (84)	4 (16)	0.03 (0.08)
Popliteal ar-tery aneurysm	18 (1.8)	2 (0.5)	16 (2.4)	0.05 (0.07)	13 (72.2)	5 (27.8)	0.44 (0.03)
Malignancy	7 (0.7)	1 (0.3)	6 (0.9)	0.43 (0.04)	6 (85.7)	1 (14.3)	0.33 (0.43)
Pulmonary embolism	5 (0.5)	3 (0.8)	2 (0.3)	0.50 (-0.04)	1 (20)	4 (80)	0.16 (-0.06)
AIC aneu-rysm	5 (0.5)	0	5 (0.8)	N/A	5 (100)	0 (0)	N/A
Deep vein thrombosis	4 (0.4)	1 (0.3)	3 (0.5)	N/A	2 (50)	2 (50)	N/A
AFC aneu-rysm	2 (0.2)	1 (0.3)	1 (0.2)	N/A	2 (100)	0 (0)	N/A

*Percentages are shown within gender for females and males, and within comorbidity for smokers and non-smokers; †Number of patients with available data; ‡Current or former smokers; §The Phi *Coefficient* is a measure of association between two binary variables, it is in the range from -1 to 1, higher number shows stronger correlation between two variables; AAA, abdominal aortic aneurysm; AIC, arteria iliaca communis; AFC, arteria femoris communis; N/A, non applicable

ble 1), during hospitalization or earlier in history, and 102 (66.7%) had diabetes (p=0.00; phi=0.14). The most common site was partial foot amputation seen in 85 (8.4%) patients, followed by transfemoral and transitibial amputation in 44 (4.3%) and 34 (3.3%) patients, respectively.

A correlation between necrosis and amputation was found (p=0.038; phi=0.19).

Regarding other surgical procedures, peripheral artery bypass surgery was noticed in 67 (6.5%) cases (Table 4).

Table 4. Surgical procedures in patients hospitalized with peripheral artery disease (PAD)

Procedure	No (%) of patients*
Bypass procedure	67 (6.5)
PTA +/- stenting	33 (3.3)
CABG	29 (2.8)
AAA repair	7 (0.7)
PAA repair	1 (0.1)
Hip replacement	1 (0.1)

*of the total number of patients; AAA, abdominal aortic aneurysm; CABG, coronary artery bypass grafting; PAA, popliteal artery aneurysm; PTA, percutaneous transluminal angioplasty

Surgical procedures (Table 1) were more common in males (99- 15%) versus females (25- 6.9%) (p=0.00; phi=0.12), as well in smokers (99- 16%) versus non-smokers (25- 6.2%) (p=0.00; phi=0.15). Patients with hypertension and a history of MI had more often surgical procedures (p=0.01; phi=0.08 and p=0.00; phi=0.17, respectively).

High fibrinogen level was detected in 657 (82.8%) patients. Patients with a history of amputation and patients with distal PAD had higher fibrinogen values than patients without a history of amputation (p=0.00; p=0.014; respectively) (Table 5).

Table 5. Laboratory values of patients hospitalized with peripheral artery disease (PAD)

Parameter (reference values)	Mean (±SD)	Range	No (%) of patients* with		
			High value	Normal value	Low value
Fibrinogen (1.8-3.8 g/L)	4.9 (±1.6)	0.8-13.5	657 (82.8)	134 (16.9)	2 (0.3)
Blood glucose 3.3-6.1 (mmol/L)	9.8 (±5.7)	2.5-37.5	665 (66.8)	327 (32.9)	3 (0.3)
HbA1C (<6.5%)	8.4 (±1.93)	4.5-14.8	227 (81.2)	64 (18.8)	N/A
Total cholesterol (3.1-5.2 mmol/L)	4.2 (±1.38)	1.7-16	168 (18.1)	570 (61.4)	191 (20.6)
HDL cholesterol (1.06-1.94 mmol/L)	0.98 (±0.37)	0.1-2.9	9 (1.3)	224 (33.1)	444 (65.6)
LDL cholesterol (1.4-3.4 mmol/L)	2.43 (±0.89)	0.6-5.7	94 (14.1)	482 (72)	93 (13.9)
Trigycerides (0.11-1.70 mmol/L)	1.85 (±1.2)	0.5-14.56	374 (40.4)	552 (59.6)	0

*Within patients with available data; HbA1C, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable

Blood glucose >6.1 mmol/L was detected in 665 (65.1%) patients; patients with amputation had higher blood glucose level (mean 5.80 mmol/L) than the ones without amputation (mean 4.83 mmol/L) (p=0.00).

HbA1C ≥6.5% was determined in 277 (81.2%) patients; 76 (21.9%) patients had HbA1C ≥10%.

Most patients had total and LDL cholesterol in the reference range, 570 (61.4%) and 482 (72%) (mean value of 4.2 mmol/L and 2.43 mmol/L, respectively). Lower HDL cholesterol was found in 444 (65.6%) patients; 552 (59.6%) patients had triglycerides in the reference range (Table 5).

DISCUSSION

PAD is more common among the elderly population. After the age of 50, the prevalence of this disease increases sharply (6), similarly to our results. Most of our patients were ≥50 years old (a mean age of 68 years), similar to the age distribution in other studies (2,7,8).

Fewer PAD-related hospitalizations and procedures were found in females, as it was previously reported (9). Females had higher mortality than males in our study. Several studies have reported higher mortality in females who undergo a vascular procedure (9-11). On the other hand, some studies found higher rates of amputation in males (9,12), however, we did not prove this.

More than 40% of our patients were current smokers, which is much more compared to the Rotterdam study where around 24% and 17% males and females, respectively, were current smokers, and compared to the National Health and Nutrition Examination Survey (NHANES) where around 34% were current smokers (7,8). If we consider that these studies were published at the beginning of the 21st century, when the prevalence of tobacco use in the West countries was higher than today and that over 90% of our patients had 30 or more pack-years, the tobacco use frequency in B&H is an even a more worrying fact. Our study showed a much lower percentage of former smokers in relation to the other studies (7,8). The risk for PAD associated with the smoking remains elevated even 20 years after cessation, although this risk is significantly reduced 10 years after smoking cessation (13). Most smokers in our study had proximal PAD, which is consistent with earlier data (14). Lethal outcome and phlegmon were more common in non-smokers in our study; a possible explanation is that non-smokers had diabetes and hypertension more often, which are the main risk factors for PAD as well.

Studies, including ours, reported that more than half patients with PAD have hypertension (8). Half of our patients had diabetes, which is a much higher percentage than in other studies, around 8% and 26% in the Rotterdam Study and the NHANES, respectively (7,8). The prevalence of diabetes in the USA is estimated to be higher than in B&H, which makes this data more unclear, while the prevalence of diabetes in the Netherlands is lower, but not enough to explain this discrepancy (15). A possible explanation is poorer diabetes control in B&H due to lack of population awareness, lack of educational programs for people with diabetes, inability to afford medication and others. Another reason could be the clinical setting of this study including more severe patients. Most of our diabetic patients had proximal PAD, which is inconsistent with earlier evidence that diabetes is related to atherosclerosis in arteries distal to the knee (14).

Males in our study were more likely to have a history of MI than females. Similarly, prior studies demonstrated more males with a history of CAD (10,11). Prior studies also demonstrated a higher prevalence of diabetes in males (10,11), which we did not prove.

Approximately one in ten patients with PAD has a history of stroke, considering that 11.6% patients in our study and 11.2% patients in NHANES had a history of stroke (7).

Chronic kidney disease was associated with PAD in several studies and now is considered one of the independent risk factors for the disease (16-18). More lethal outcomes are reported in patients with concomitant CKD (16,19,20), which was proved in our study (almost four times more deaths in patients with CKD). Some studies also reported a higher risk for limb amputation in patients with CKD (21-23). We did not prove this association, neither did a French study which concluded that CKD was not an independent predictor of limb amputation (20). One study determined that only patients receiving dialysis have a higher risk for amputation, and not patients with milder kidney disease (21).

Limb amputation was noted in 15% of our patients and two-thirds of those patients had diabetes. This association was significant and reported in other studies (7,8,24,25). Diabetes is the most common cause of non-traumatic amputation (24). One study reveals that diabetic patients with PAD have a five times higher risk to have an amputation (26).

Several studies determined a strong positive association between fibrinogen level and PAD (8,27,28). We confirmed high fibrinogen level in more than 80% of our patients. Fibrinogen has a possible role as a biomarker for the detection of subclinical arterial disease (29). Most of our patients had normal total cholesterol with a mean value of 4.2 mmol/L compared to around 6.5 mmol/L in the Rotterdam Study (weak association between PAD and serum cholesterol), which is incompatible (8). Normal total cholesterol, LDL and triglycerides in our study could be explained by an effect of statin therapy. Other studies determined that high HDL cholesterol level protects against PAD (8,29), accordingly, most of our patients had lower HDL level. Many studies confirm that any arterial disease is significantly associated with high HbA1C and plasma glucose (30,31); we found those values to be high in most patients.

The role of elevated triglycerides as an independent risk factor for PAD has been rejected in some studies (27,32), but has been confirmed in others (33,34). This question remains controversial.

The main limitation of this study is that patients were from the clinical setting from one institution and established epidemiological data could overestimate the burden of the disease in the general population. Our results represent severe cases of this disease in need of hospitalization, not considering those with subclinical or asymptomatic PAD.

In conclusion, the impact of PAD is higher than the importance attached to it. These are commonly the patients with multiple comorbidities and risk for various complications. These findings highlight the importance of primary and secondary prevention of atherosclerosis. Smoking cessation, exercise and other lifestyle modifications, as well as usage of antihypertensives, statins, antiplatelets and other medication, depending on comorbidities, is a mainstay of treatment. This study is, to the best of our knowledge, the first study that clearly describes the profile of patients with PAD in Bosnia and Herzegovina.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

REFERENCES

1. Conte SM, Vale PR. Peripheral arterial disease. Heart Lung Circ 2018; 27:427-32.
2. Olinic DM, Spinu M, Olinic M, Homorodean C, Tataru DA, Liew A, Schernthaner GH, Stanek A, Fowkes G, Catalano M. Epidemiology of peripheral artery disease in Europe: VAS Educational Paper. Int Angiol 2018; 37:327-34.
3. Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol 2017; 14:156-70.
4. Firnhaber JM, Powell CS. Lower extremity peripheral artery disease: diagnosis and treatment. Am Fam Physician 2019; 99:362-9.
5. Tada H, Usui S, Sakata K, Takamura M, Kawashiri MA. Low-density lipoprotein cholesterol level cannot be too low: considerations from clinical trials, human genetics, and biology. J Atheroscler Thromb 2020; 27:489-98.
6. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med 2007; 32:328-33.
7. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 2004; 110:738-43.
8. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: The Rotterdam Study. Arterioscler Thromb Vasc Biol 1998; 18:185-92.
9. Egorova N, Vouyouka AG, Quin J, Guillerme S, Moskowitz A, Marin M, Faries PL. Analysis of gender-related differences in lower extremity peripheral arterial disease. J Vasc Surg 2010; 51:372-8.e1.
10. McCoach CE, Armstrong EJ, Singh S, Javed U, Anderson D, Yeo KK, Westin GG, Hedayati N, Amsterdam EA, Laird JR. Gender-related variation in the clinical presentation and outcomes of critical limb ischemia. Vasc Med 2013; 18:19-26.
11. Vouyouka AG, Egorova NN, Salloum A, Kleinman L, Marin M, Faries PL, Moscowitz A. Lessons learned from the analysis of gender effect on risk factors and procedural outcomes of lower extremity arterial disease. J Vasc Surg 2010; 52:1196-202.
12. Feinglass J, Kaushik S, Handel D, Kosifas A, Martin GJ, Pearce WH. Peripheral bypass surgery and amputation: northern Illinois demographics, 1993 to 1997. Arch Surg 2000; 135:75-80.
13. Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, Mukamal KJ. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. JAMA 2012; 308:1660-7.
14. Haltmayer M, Mueller T, Horvath W, Luft C, Poelz W, Haidinger D. Impact of atherosclerotic risk factors on the anatomical distribution of peripheral arterial disease. Int Angiol 2001; 20:200-7.
15. The World Bank Data. Diabetes prevalence (% of population ages 20 to 79) 2019. https://data.worldbank.org/indicator/SH.STA.DIAB.ZS (01 March 2021)
16. Liew YP, Bartholomew JR, Demirjian S, Michaels J, Schreiber MJ. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high-risk population. Clin J Am Soc Nephrol 2008; 3:1084-9.
17. O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. Circulation 2004; 109:320-3.

18. O'Hare AM, Vittinghoff E, Hsia J, Shlipak MG. Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the Heart and Estrogen/Progestin Replacement Study (HERS). J Am Soc Nephrol 2004; 15:1046-51.
19. Pasqualini L, Schillaci G, Pirro M, Vaudo G, Siepi D, Innocente S, Ciuffetti G, Mannarino E. Renal dysfunction predicts long-term mortality in patients with lower extremity arterial disease. J Intern Med 2007; 262:668-77.
20. Lacroix P, Aboyans V, Desormais I, Kowalsky T, Cambou JP, Constans J, Rivière AB, COPART investigators. Chronic kidney disease and the short-term risk of mortality and amputation in patients hospitalized for peripheral artery disease. J Vasc Surg 2013; 58:966-71.
21. O'Hare AM, Sidawy AN, Feinglass J, Merine KM, Daley J, Khuri S, Henderson WG, Johansen KL. Influence of renal insufficiency on limb loss and mortality after initial lower extremity surgical revascularization. J Vasc Surg 2004; 39:709-16.
22. O'Hare AM, Bertenthal D, Sidawy AN, Shlipak MG, Sen S, Chren MM. Renal insufficiency and use of revascularization among a national cohort of men with advanced lower extremity peripheral arterial disease. Clin J Am Soc Nephrol 2006; 1:297-304.
23. Landray MJ, Thambyrajah J, McGlynn FJ, Jones HJ, Baigent C, Kendall MJ, Townend JN, Wheeler DC. Epidemiological evaluation of known and suspected cardiovascular risk factors in chronic renal impairment. Am J Kidney Dis 2001; 38:537-46.
24. Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Eur Heart J 2013; 34:2444-52.
25. Abbott RD, Brand FN, Kannel WB. Epidemiology of some peripheral arterial findings in diabetic men and women: experiences from the Framingham Study. Am J Med 1990; 88:376-81.
26. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care 2001; 24:1433-7.
27. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J 2002; 143:961-5.
28. Allison MA, Criqui MH, McClelland RL, Scott JM, McDermott MM, Liu K, Folsom AR, Bertoni AG, Sharrett AR, Homma S, Kori S. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol 2006; 48:1190-7.
29. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001; 285:2481-5.
30. Beks PJ, Mackaay AJ, de Neeling JN, de Vries H, Bouter LM, Heine RJ. Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn study. Diabetologia 1995; 38:86-96.
31. Criqui MH, Browner D, Fronek A, Klauber MR, Coughlin SS, Barrett-Connor E, Gabriel S. Peripheral arterial disease in large vessels is epidemiologically distinct from small vessel disease. An analysis of risk factors. Am J Epidemiol 1989; 129:1110-9.
32. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, Ruckley CV. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol 1992; 135:331-40.
33. Katsilambros NL, Tsapogas PC, Arvanitis MP, Tritos NA, Alexiou ZP, Rigas KL. Risk factors for lower extremity arterial disease in non-insulin-dependent diabetic persons. Diabet Med 1996; 13:243-6.
34. Bainton D, Sweetnam P, Baker I, Elwood P. Peripheral vascular disease: consequence for survival and association with risk factors in the Speedwell prospective heart disease study. Br Heart J 1994; 72:128-32.