ISSN 1669-9106 MEDICINA (Buenos Aires) 2023: 83: 910-917

Original article

PROGNOSTIC RELEVANCE OF FEMALE GENDER ON MORTALITY AFTER PERIPHERAL ARTERY DISEASE REVASCULARIZATION

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Received: 5-V-2023
Accepted: 19-VII-2023

Abstract

Introduction: Lower limb peripheral artery disease (PAD) presents high morbidity and mortality. Women represent a small subgroup in different studies, with scarce evidence regarding the prognosis of this gender on PAD. The aim of the present work was to determine the prognostic impact of female gender on lower limb PAD revascularization.

Methods: This was a retrospective, single-center study, including patients undergoing symptomatic lower limb PAD revascularization.

Results: Among a total of 309 patients included in the study, 109 belonged to the female gender (35%). Women were older and presented lower prevalence of cardiovascular risk factors compared with the male gender. All-cause mortality (22% vs. 12%, p = 0.02) and re-hospitalizations for chronic limb-threatening ischemia (18% vs. 10%, p = 0.04) rates were significantly higher in women. In a multivariate regression model, female gender was independently associated with all-cause mortality (OR 2.19 [95% CI: 1.06-4.51], p = 0.03). The time-to-event showed that women exhibited 93% more risk of suffering death than men, after adjusting for clinically relevant variables (HR 1.93 [95% CI: 1.04-3.56], p = 0.04).

Discussion: Women with symptomatic PAD revascularization presented worse prognosis than men in terms of all-cause mortality and re-hospitalizations for chronic limb-threatening ischemia rates. Therefore, it is essential to achieve an adequate control of cardiovascular risk factors, as well as to optimize medical treatment in female patients.

Key words: peripheral artery disease, female gender, mortality, chronic limb-threatening ischemia

Resumen

Relevancia pronóstica del género femenino en la mortalidad luego de la revascularización de la enfermedad arterial periférica

Introducción: La enfermedad arterial de miembros inferiores (EAMI) presenta elevada morbimortalidad. Las mujeres constituyen un subgrupo minoritario en distintos estudios, con escasa evidencia acerca del pronóstico por género en EAMI. Nuestro objetivo fue determinar el impacto pronóstico del género femenino en la revascularización de EAMI.

Métodos: Estudio de cohorte retrospectivo y unicéntrico, que incluyó pacientes con EAMI sintomática y revascularizada.

Resultados: Se incluyeron 309 pacientes, de los cuales 109 (35%) eran mujeres. Las mujeres fueron más añosas y presentaron menor prevalencia de factores de riesgo cardiovascular en comparación a los hombres. Las tasas de mortalidad por todas las causas (22% vs. 12%, p = 0.02) y de hospitalizaciones por isquemia crítica (18% vs. 10%, p 0.04) fueron significativamente mayores en mujeres. En

el modelo de regresión multivariado, el sexo femenino se asoció de forma independiente con mortalidad por todas las causas (OR 2.19 [IC 95%: 1.06-4.51], p = 0.03). En el análisis de tiempo al evento, las mujeres tuvieron 93% más riesgo de morir que los hombres, luego de ajustar por variables clínicamente relevantes (HR 1.93 [IC 95%: 1.04-3.56], p = 0.04).

Discusión: Las mujeres con EAMI sintomática y revascularizada presentaron un peor pronóstico en comparación a los hombres en términos de tasas de mortalidad por todas las causas y de hospitalizaciones por isquemia crítica de miembros inferiores. Por lo tanto, es fundamental lograr un adecuado control de factores de riesgo cardiovascular, como así también, optimizar el tratamiento médico en el género femenino.

Palabras clave: enfermedad arterial periférica, género femenino, mortalidad, isquemia crítica de miembros inferiores

KEY POINTS

Current knowledge

- Lower limb peripheral artery disease (PAD) is associated with an increase in morbidity and mortality in the general population. However, women have been underrepresented in the different studies, with scarce evidence regarding the prognosis of this gender on PAD.

Article contribution

- Women with symptomatic PAD undergoing lower limb revascularization are older and present a more advanced disease with worse prognosis than men in terms of all-cause mortality and re-hospitalizations for chronic limb-threatening ischemia rates. Therefore, it is essential to achieve an adequate control of cardiovascular risk factors, as well as to optimize medical treatment in female patients.

Introduction

Lower limb peripheral artery disease (PAD) is characterized by stenosis or occlusion of one or more arteries from the aortic-iliac segment to the foot, with clinical manifestation of intermittent claudication (IC), chronic limb-threatening ischemia (CLTI) or acute limb ischemia (ALI)[1]. Although numerous etiologies may explain PAD, atherosclerosis stands out as its main cause[2,3].

Despite the growing understanding of PAD as an important cause of cardiovascular morbidity and mortality, it has been less studied than coronary or cerebrovascular diseases[4]. Effectively, the global prevalence of PAD has increased by 45% from the year 2000 to 2015, with a greater impact in underdeveloped countries (58% vs. 18%, respectively)[5].

Women are frequently underrepresented in scientific studies concerning the efficacy and safety of symptomatic lower limb PAD revascularization. In addition, there are few studies of cohorts evaluating PAD differences between genders. This is mainly due to its oligo symptomatic course or with atypical symptoms in women, favoring underdiagnosis[6]. In this sense, the American Heart Association (AHA) has postulated strategies to improve the knowledge of basic and clinical vascular biology as a function of gender for a correct PAD diagnosis and treatment[7].

Additionally, the fact that PAD is a disease whose incidence increases with age and that the female gender prevails in a predominantly older population represents an opportunity to better understand the prognosis of women undergoing symptomatic PAD interventions[8].

The purpose of this study was thus to determine the prognosis and outcome of women undergoing a symptomatic PAD revascularization procedure.

Materials and methods

Study population and design

This was a retrospective cohort study including patients over 18 years of age with symptomatic lower limb PAD requiring percutaneous or surgical revascularization carried out at a university hospital of the Autonomous City of Buenos Aires from 2014 to 2020.

Symptomatic PAD was defined as the presence of pain during exertion or at rest and/or trophic lesion of the lower limbs associated with angiographic documentation of hemodynamically significant lesion[9]. The clinical presentation of symptomatic PAD was classified as IC, CLTI or ALI. IC was described as lower limb fatigue, discomfort or pain manifested during activity and relieved by rest[10]. CLTI was considered as the presence of pain at rest and/

or cutaneous lesions (ulcer or gangrene) of more than 2-week evolution[11]. ALI was defined as the sudden decrease of perfusion of less than 2-week evolution, typically characterized by pain, paresis or paralysis, paresthesia, pulselessness, lower temperature and/or pallor, threatening limb viability[12].

Cases of lower limb revascularization secondary to iatrogenic, inflammatory or traumatic causes were excluded from the study, as atherosclerosis was the main focus of the analysis.

Endpoints of the study

The primary endpoint was the comparison of all-cause mortality between men and women undergoing symptomatic lower limb PAD revascularization. The secondary endpoints considered were: re-hospitalization for CLTI, major amputation (defined as supra-malleolar amputation)[13], non-fatal stroke (both ischemic-classified as cerebral ischemia due to thrombosis, embolism or hypo-perfusion- and hemorrhagic due to non-fatal intracranial bleeding or subarachnoid hemorrhage)[14], non-fatal acute myocardial infarction (AMI) (described as acute myocardial injury with elevated biomarkers and evidence of nonfatal myocardial ischemia)[15] and MACE (composite endpoint of death, nonfatal AMI and nonfatal stroke).

Data were collected from the electronic medical records of our center.

Statistical analysis

The Kolmogorov-Smirnov test was used to analyze Gaussian distribution of the variables. Continuous variables were expressed as mean ± standard deviation or as median and interquartile range (IQR), as appropriate, and compared using Student's t test in the former case and the Man Whitney test in the latter.

Categorical variables were presented as absolute value and percentage, and were compared using the chi-square test or Fisher´s exact test, as appropriate. A bivariate logistic regression analysis was performed to assess the independent association between different variables and the endpoint of interest. Variables presenting $p < 0.1$ or considered as potential confounders were included in the multivariate logistic regression. Likelihood-ratio test was performed to compare multivariate analysis models. Survival was expressed using the Kaplan-Meier curve and the Log-Rank test. Hazard Ratio was estimated by multiple Cox regression, also adjusting by the same variables. Statistical significance was considered for $p < 0.05$. SPSS 25 (IBM, Armonk, NY, USA) was used for the statistical analyses.

Ethical considerations

The present study complies with the principles described in the Declaration of Helsinki[16]. This study was approved by the *Hospital Italiano* Institutional Review Board (protocol number 6792 and PRIISA registration code 10354). The informed consent was waived considering the retrospective nature of the study.

Results

A total of 309 patients were included in the study with median follow-up of 1.9 years (IQR 25-75%: 0.3-3.7 years). In 35.3% of cases (N = 109) patients belonged to the female gender. The general population characteristics are described in Table 1. Women were older compared with men (75.6 ± 11.2 years vs. 69.8±10.6 years, $p < 0.01$). Conversely, women presented lower prevalence of smoking (48.6% vs. 67.5%, $p < 0.01$), diabetes (18.3% vs. 37.2%, $p < 0.01$), chronic kidney disease (8.3% vs. 25.8%, $p < 0.01$) and myocardial infarction (11% vs. 28.4%, $p < 0.01$) than men. Medical treatment prior to lower limb revascularization showed no statistically significant differences in the use of antiplatelet agents (aspirin: 76.4% vs. 67.9%, $p = 0.11$; clopidogrel: 54.6% vs. 51.4%, $p = 0.59$) or statins (77.9% vs. 70.6%, $p = 0.16$). Neither were there differences in the form of clinical presentation (Table 2) and type of revascularization procedure (percutaneous or surgical) (Table 3) between both genders.

Regarding the primary endpoint, women presented greater rate of all-cause mortality than men (22% vs. 12%, $p = 0.02$) (Table 4, Fig. 1). Mortality was significantly higher among women after adjusting for age and chronic kidney disease (OR 2.19 [95% CI: 1.06-4.51], $p = 0.03$). In addition, in the analysis of time-to-event (all-cause death), female gender exhibited 93% higher risk of suffering death than men, when adjusting by the above-mentioned relevant clinical variables (HR 1.93 [95% CI: 1.04-3.56], $p = 0.04$) (Table 5).

Regarding the secondary endpoints, women evidenced higher rate of re-hospitalization for CLTI (18.3% vs. 10%, $p = 0.04$), without statistically significant differences in the rest of the final

Table 1 | Baseline characteristics of the study population, according to gender

	Male gender (n:200)	Female gender (n:109)	p-value
Age (years), mean ± SD	69.8 ± 10.6	75.6 ± 11.2	< 0.01
Hypertension (%)	170 (85)	87 (79.8)	0.25
Diabetes (%)	74 (37.2) n: 199	20 (18.3)	<0.01
Dyslipidemia (%)	136 (68)	66 (60.5)	0.15
Smoking habit (%)	135 (67.5)	53 (48.6)	<0.01
- Current smokers (%)	42 (21)	26 (23.8)	0.56
- Former smokers (%)	93 (46.5)	27 (24.8)	< 0.01
Chronic kidney disease (%)	51 (25.8) n:198	9 (8.3) n:108	< 0.01
Coronary heart disease (%)	56 (28.4) n:197	12 (11)	< 0.01
Stroke/TIA (%)	22 (11.1) n:199	7 (6.5) n:108	0.19
Symptomatic PAD (%)	62 (31.2) n:199	25 (23.2) n:108	0.14
Atrial fibrillation (%)	34 (17.1) n:199	18 (16.7) n:108	0.93
Laboratory values			
Glycated hemoglobin (%), median [IQR]	6.95 [6.20-7.78]	7.1 [5.38-9.20]	0.89
Creatinine serum (mg/dl), median [IQR]	1.02 [0.84-1.38]	0.82 [0.66-1.07]	< 0.01
Medical treatment prior to lower limb PAD revascularization			
Anticoagulants (%)	44 (22) n: 199	23 (21.4) n: 107	0.90
- VKAs (%)	37 (18.6)	20 (18.7)	0.97
- DOACs (%)	7 (3.5)	3 (2.8)	1
Aspirin (%)	152 (76.4) n:199	74 (67.9)	0.11
Clopidogrel (%)	108 (54.6) n:198	56 (51.4)	0.59
Cilostazol (%)	88 (44.4) n:198	41 (37.6)	0.25
ACEi/ARBs (%)	124 (62.6) n:198	63 (57.8)	0.41
Beta-blockers (%)	105 (53) n:198	63 (57.8)	0.42
Statins (%)	155 (77.9) n:199	77 (70.6)	0.16
Metformin (%)	43 (21.6) n:199	9 (8.5) n:106	<0.01
Insulin (%)	20 (10.1) n:199	13 (11.9)	0.61

SD: standard deviation; TIA: transient ischemic attack; PAD: peripheral artery disease; IQR: interquartile range; VKAs: vitamin K antagonists; DOACs: direct oral anticoagulants; ACEi/ARBs: angiotensin-converting enzyme inhibitors / angiotensin receptor blockers

Table 2 | Clinical presentation according to Rutherford classification and traditional clinical classification

Rutherford classification	Male gender (n: 147)	Female gender (n: 76)	p-value
Mild claudication (%)	6 (4.1)	3 (3.9)	1
Moderate claudication (%)	28 (19)	10 (13.2)	0.27
Severe claudication (%)	81 (55.1)	38 (50)	0.47
Rest pain/tissue loss (%)	32 (21.8)	25 (32.9)	0.07
Traditional clinical classification	**Male gender (n: 200)**	**Female gender (n: 109)**	**p-value**
Intermittent claudication (%)	118 (59)	55 (50.1)	0.15
Chronic limb-threatening ischemia (%)	58 (29)	33 (30.3)	0.81
Acute limb ischemia (%)	24 (12)	21 (19.3)	0.08

Table 3 | Type of revascularization according to gender

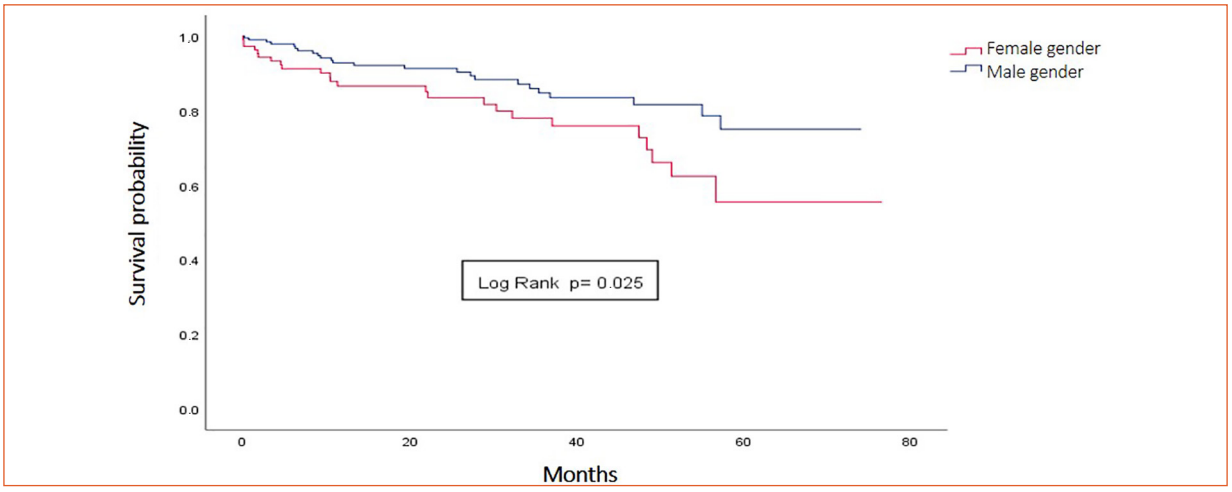
	Male gender (n: 200)	Female gender (n: 109)	p-value
Endovascular revascularization (%)	170 (85)	87 (80)	0.25
Surgical revascularization (%)	30 (15)	22 (20)	0.25

Table 4 | Endpoints according to gender

	Male gender (n: 200)	Female gender (n: 109)	p-value
All-cause mortality (%)	24 (12)	24 (22)	0.02
Fatal AMI (%)	1 (0.5)	0	0.35
Non-fatal AMI (%)	11 (5.5)	3 (2.8)	0.39
Fatal stroke (%)	2 (1)	3 (2.8)	0.35
Non-fatal stroke (%)	5 (2.5)	4 (3.7)	0.72
MACE (%)	36 (18)	30 (27.5)	0.05
Major amputation (%)	22 (11)	10 (9.2)	0.62
Re-hospitalization for CLTI	20 (10)	20 (18.3)	0.04

AMI: acute myocardial infarction; MACE: composite endpoint of death, nonfatal AMI and nonfatal stroke ; CLTI: chronic limb-threatening ischemia

Figure 1 | Kaplan-Meier survival curve according to gender



endpoints analyzed, such as major amputation, AMI, stroke and MACE (Table 4).

Discussion

The present work analyzed the underlying comorbidities, the different forms of clinical presentation, and the prognosis of lower limb PAD revascularization according to gender. The main findings of our study were: a) women were older but with less comorbid conditions (lower prevalence of smoking, diabetes, chronic kidney disease and myocardial infarction); and b) women presented higher rate of all-cause mortality and re-hospitalization for CLTI compared with

Table 5 | Multivariate analysis and Cox regression model

Multivariate analysis Model 1			
	OR	**95% CI**	**p-value**
Female gender	2.16	1.05-4.47	0.04
Age	1.05	1.01-1.08	<0.01
CKD	3.39	1.57-7.31	<0.01
Diabetes	0.86	0.39-1.90	0.71
Model 2			
Female gender	2.19	1.06-4.51	0.03
Age	1.05	1.01-1.08	<0.01
CKD	3.33	1.56-7.14	<0.01
Model 1 Likelihood-ratio value: 26.7 vs. Model 2 Likelihood-ratio value: 26.5			
Likelihood-ratio test (Model 1 vs. Model 2): p=0.71			
Cox regression model			
	HR	**95% CI**	**p-value**
Female gender	1.93	1.04-3.56	0.04
Age	1.04	1.01-1.08	<0.01
CKD	2.68	1.41-5.07	<0.01

CKD: Chronic kidney disease

men. This difference in all-cause mortality was preserved even after adjusting for age and presence of chronic kidney disease.

In our study, female gender represented 35.3% of the population, in agreement with previous randomized and prospective cohort studies of subjects undergoing symptomatic lower limb PAD revascularization, where women represent 32% to 43% of the population[7, 17]. The results of the present study are similar to previously published works regarding the clinical characteristics according to gender at the time of revascularization. Women undergoing lower limb revascularization are generally older and have less comorbidities (including diabetes, smoking and coronary heart disease)[8]. The manifest relationship between age and female gender in lower limb PAD development is of particular interest. In this sense, evidence suggests that the hormonal factor plays a key role in its etiopathogenesis. Effectively, estrogens act as a protective factor reducing the risk of developing atherosclerosis until menopause, time in which this "protection" is lost and the risk of cardiovascular risk increases[18]. The fact that women with lower limb PAD who will undergo revascularization present with older age could be the reason for a more advanced disease in this group, explaining in part the greater rates of mortality and re-hospitalization for CLTI observed in our study. Moreover, these results are similar to evidence reported in the literature[8, 19-21]. On the one hand, although we did not find differences between genders in antiplatelet, lipid-lowering and hypertensive treatment, the degree of control of the different cardiovascular risk factors and the compliance with blood pressure and metabolic (such as LDL cholesterol levels) objectives were not explored in our study, and there is evidence that women have less probability of attaining these goals[19]. Because medical treatment in women is less optimal than that in men places the former at higher risk of cardiovascular events and death after lower limb revascularization[19]. Another hypothesis could consist in the factors that delay the time to diagnosis. Since oligosymptomatic PAD manifestation mainly occurs in women, it could justify a later consultation and consequently worse outcomes as a result

of disease progression[22]. However, we have not found differences in terms of presentation symptoms according to the Rutherford classification. On the other hand, symptoms could initially be masked or misinterpreted as arthritis, osteoporosis, or spinal stenosis, which are more prominent in female gender. In addition, there are differences in the distribution of body fat among men and women: the latter tend to have more fatty deposits in the lower limbs and hips. These sex-related characteristics may lead an erroneous conclusion when examining a woman with PAD[22]. In addition, there is evidence that women with PAD present greater prevalence of depression. The presence of this condition would facilitate the underdiagnosis of peripheral vascular disease in women due to the absence of controls and timely consultation, thus delaying diagnosis, as well as favoring lower adhesion to medical treatment[23].

Finally, despite our study has limitations due to its design and variables analyzed (the associated depression, the control of cardiovascular risk factors and the anatomical characteristics of vascular lesions between both genders were not evaluated), we believe that it is relevant, as it allows assessing PAD behavior (less studied compared with coronary and cerebrovascular disease) in a gender underrepresented in most studies.

In conclusion, women with symptomatic PAD undergoing lower limb revascularization are older and present a more advanced disease with worse prognosis than men. It is therefore essential to achieve medical treatment optimization in the female gender, since PAD not only has a negative impact on the quality of life, but also on women survival, which is independent of age.

Conflict of interest: None to declare

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