

DIFERENÇAS DE GÉNERO NA APRESENTAÇÃO DE ISQUÊMIA CRÔNICA DE MEMBRO INFERIOR E NOS RESULTADOS APÓS REVASCULARIZAÇÃO

GENDER DIFFERENCES IN CHRONIC LOWER LIMB ISCHEMIA PRESENTATION AND REVASCULARIZATION OUTCOMES

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RESUMO

Introdução: Os resultados após revascularização de membro inferior, quando estratificados por sexo, são piores no sexo feminino, particularmente após procedimentos convencionais. As mulheres parecem ter maior probabilidade de complicações do procedimento, amputação e morte quando comparadas com os homens. Este estudo pretende identificar as diferenças nas características demográficas, apresentação clínica e principais *outcomes* após revascularização de membro inferior, entre doentes do sexo masculino e feminino.

Métodos: Este estudo unicêntrico retrospectivo observacional incluiu todos os membros inferiores sem revascularização prévia em doentes com diagnóstico de DAP, que foram submetidos a um procedimento terapêutico vascular num hospital terciário, entre Janeiro de 2017 e Dezembro de 2018. O grupo do sexo feminino (Grupo F) foi comparado com o grupo do sexo masculino (Grupo M). O *endpoint* primário foi a amputação *major* e os *endpoints* secundários foram a restenose/oclusão diagnosticada, reintervenção vascular e sobrevida. A análise de subgrupos foi realizada após estratificação em procedimentos convencionais, endovasculares ou híbridos.

Resultados: O Grupo M incluiu 324 membros inferiores de doentes do sexo masculino, com uma idade média de 67,5 anos. O Grupo F incluiu 96 membros inferiores de doentes do sexo feminino, com uma idade média de 71,7 anos ($p < 0,001$). Não foi encontrada diferença estatisticamente significativa nos fatores de risco cardiovascular entre os grupos, com exceção de uma maior prevalência de tabagismo no Grupo M e de hipertensão no Grupo F ($p < 0,001$). 83% dos procedimentos no Grupo F e 79% dos procedimentos no grupo M foram realizados devido a isquemia crônica com compromisso do membro (ICCM; $p = 0,321$). Não foi encontrada diferença estatisticamente significativa no que diz respeito ao grau de ferida ou infeção (WIFI) e ao estadiamento anatómico de doença femoropoplíteia ou abaixo do tornozelo (GLASS). O Grupo M apresentou maior prevalência de doença aorto-iliaca ($p = 0,014$) e da artéria femoral comum ($p = 0,001$) e o Grupo F apresentou doença abaixo-do-jelho mais grave ($p = 0,012$). No Grupo F observou-se uma maior proporção de procedimentos endovasculares ($p < 0,001$). A taxa de amputação do Grupo M e no Grupo F foi de $8 \pm 2\%$ e $7 \pm 3\%$ a 1 mês, $14 \pm 2\%$ e $16 \pm 4\%$ a 1 ano, e $15 \pm 2\%$ e $19 \pm 4\%$ a 2 anos, respetivamente ($p = 0,564$). Não houve diferenças significativas nas taxas de restenose/oclusão entre os grupos ($p = 0,395$). As taxas de reintervenção no Grupo M e no Grupo F foram $13 \pm 2\%$ e $13 \pm 3\%$ a 1 mês, $21 \pm 2\%$ e $20 \pm 4\%$ a 1 ano, e $25 \pm 3\%$ e $24 \pm 5\%$ a 2 anos, respetivamente ($p = 0,74$). A sobrevida no Grupo M e no Grupo F foi de $97 \pm 1\%$ e $93 \pm 3\%$ a 1 mês, $84 \pm 2\%$ e $84 \pm 4\%$ a 1 ano, e $77 \pm 3\%$ e $72 \pm 5\%$ a 2 anos, respetivamente ($p = 0,443$). Estratificando de acordo com o tipo de procedimento vascular (convencional, endovascular ou híbrido), não se verificou diferença estatisticamente significativa entre os grupos nos *endpoints* acima mencionados.

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Conclusão: De acordo com este estudo, as doentes do sexo feminino apresentam idade mais avançada e doença abaixo-do-jelho mais grave. São mais frequentemente submetidas a procedimentos endovasculares. Contudo, não parecem existir diferenças importantes nos *outcomes* de membro para as mulheres submetidas a procedimentos de revascularização de membro inferior.

Palavras-chave

Gênero; Doença arterial periférica (DAP); Isquemia crônica com compromisso do membro (ICCM); Revascularização de membro inferior

ABSTRACT

Introduction: Sex-specific data on outcomes after lower limb revascularization associate the female gender with worse surgical outcomes, particularly after open procedures. Women were found to be more likely to suffer from procedure complications, limb loss, and mortality than their male counterparts. This study aims to identify differences in demographic characteristics, clinical presentation and all major outcomes after lower limb revascularization between female and male patients.

Methods: This retrospective, single-center study comprises all never-revascularized lower limbs in patients with clinically diagnosed PAD who underwent a lower limb therapeutic vascular intervention in a tertiary hospital between January 2017 and December 2018. Women's limbs Group (F) was compared against men's limbs Group (M). The primary endpoint was major amputation, and the secondary endpoints were restenosis/occlusion, vascular reintervention and overall survival. Subgroup analysis was undertaken considering open, endovascular or hybrid procedures.

Results: Group M included 324 male lower limbs; patients had a mean age of 67,5 years. Group F included 96 female lower limbs; patients had a mean age of 71,7 years ($p < 0,001$). There were no significant differences in cardiovascular risk factors between groups, aside from a higher prevalence of smoking in Group M and hypertension in Group F ($p < 0,001$). 83% of Group F procedures and 79% of procedures in Group M were performed due to CLTI ($p = 0,321$). We found no statistically significant difference between groups regarding wound or infection grading (WIFI) and femoropopliteal or BTA anatomic disease staging (GLASS). Group M was more likely to have aortoiliac ($p = 0,014$) and common femoral artery disease ($p = 0,001$), and Group F to have more severe BTK disease ($p = 0,012$). Group F had a higher proportion of endovascular procedures ($p < 0,001$). Amputation rates in Group M and Group F were 8±2% and 7±3% at 1 month, 14±2% and 16±4% at 1 year, 15±2% and 19±4% at 2 years, respectively ($p = 0,564$). There were no significant differences in rates of procedure restenosis/occlusion between groups ($p = 0,395$). Reintervention rates in Group M and Group F were 13±2% and 13±3% at 1 month, 21±2% and 20±4% at 1 year, 25±3% and 24±5% at 2 years, respectively ($p = 0,74$). Overall survival in Group M and Group F was 97±1% and 93±3% at 1 month, 84±2% and 84±4% at 1 year, 77±3% and 72±5% at 2 years, respectively ($p = 0,443$). Stratifying according to the type of vascular procedure (open, endovascular or hybrid), we found no significant difference between groups in the outcomes mentioned above.

Conclusion: Overall, women were more likely to be older, to have more severe BTK disease, and to undergo endovascular procedures. However, this study suggests no major differences in limb outcomes for women who undergo lower limb revascularization procedures.

Keywords

Gender; Peripheral arterial disease (PAD); Chronic limb-threatening ischemia (CLTI); Lower limb revascularization

INTRODUCTION

Peripheral artery disease (PAD) has traditionally been identified as a male-dominant disease. However, PAD prevalence increases with age, and a larger percentage of the elderly patients are women. On the other hand,

there has been a steeper decline in male smoking rates compared with female smoking. Nowadays, the incidence of PAD in men and women is similar⁽¹⁾.

Sex-specific data on outcomes after lower limb revascularization associate the female gender with worse surgical outcomes, particularly after open procedures.

Women were found to be more likely to suffer from procedure complications, limb loss, and mortality than their male counterparts^(1,2).

These differences may be related to an older age at presentation, smaller vessel size, poorer overall health status, or a more severe clinical and anatomical disease burden at presentation in female patients⁽²⁾.

This study aims to identify differences in all major outcomes after lower limb revascularization between female and male patients (primary goals). It also aims to identify sex-associated dissimilarities in demographic characteristics and clinical presentation (secondary goals).

METHODS

This is a retrospective, observational, single-center study. It includes all lower limbs without prior revascularization procedures in patients with diagnosed PAD, which underwent a revascularization procedure in a tertiary university hospital between January 2017 and December 2018. Exclusion criteria comprised lower limbs that had previously undergone a revascularization procedure and lower limbs that underwent a revascularization attempt without success in treating or bypassing the occlusive lesion.

Patient, procedure and outcome details were collected from medical records. It included analysis of admission and discharge documents, hospitalization and outpatient registries, and review of available follow-up exams (ultrasound, CTA or invasive angiography). Chronic limb-threatening ischemia (CLTI) was defined as objectively documented atherosclerotic PAD in association with ischemic rest pain or tissue loss (ulceration or gangrene). In the presence of CLTI, limbs and wounds were classified according to Wifl (wound, ischemia, foot infection) system, and PAD was staged according to the GLASS (Global Limb Anatomical Staging) system after arteriography evaluation. Women's limbs Group (F) was compared against men's limbs Group (M).

The primary endpoint was major amputation, and secondary endpoints were diagnosed vascular procedure restenosis/occlusion, vascular reintervention and overall survival.

Diagnosed vascular procedure restenosis/occlusion was determined on follow-up exams, including ultrasound, CTA or invasive arteriography. In our department, patients undergo vascular surgeon observation and lower limb vascular ultrasound on an outpatient basis a month after discharge, six months after discharge, yearly after that, and every time symptoms

recur or become more severe. If the patients have healing wounds, they are clinically followed closer, usually every two weeks.

A vascular reintervention was defined as a vascular revascularization procedure performed on the same limb. It included procedures performed: 1) after a diagnosis of vascular procedure restenosis/occlusion associated with life-limiting claudication or CLTI; 2) after a diagnosis of asymptomatic failing-graft; 3) after vascular procedures that did not relieve previous symptoms, despite having treated arterial anatomic lesions; 4) after symptoms recurrence due to atherosclerosis progression in another sector.

Subgroup analysis was undertaken considering open, endovascular or hybrid procedures. It was also performed for procedures addressing inflow, outflow, or simultaneous inflow and outflow disease.

Written consent was obtained from the patient for the planned procedure and anonymous data usage for scientific purposes.

Quantitative variables are expressed as mean \pm standard deviations (SD) or median (interquartile range – IQR), as appropriate. Qualitative variables are expressed as absolute values and percentages. Shapiro-Wilk normative tests were used to assess distribution patterns in quantitative variables. Student's t-test, A-nova one way, and respective non-parametric tests and χ^2 and proper adjustments were used on univariate analysis. Correlations tests have been applied when relating quantitative variables. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Group M included 324 male lower limbs. Group F included 96 female lower limbs.

Group F included older patients than group M ($p<0,001$). Group F had a mean age of $71,7\pm 1,2$ years, and Group M had a mean age of $67,5\pm 0,6$ years.

Baseline characteristics are depicted in TABLE 1. There were no significant differences between groups, aside from a higher prevalence of smoking in Group M (70% vs. 21%; $p<0,001$) and hypertension in Group F (90% vs. 80%; $p=0,031$).

The severity of limb ischemia was not different between groups. 83% of procedures in Group F ($N=80$) and 79% of procedures in Group M ($N=255$) were performed due to chronic limb-threatening ischemia (CLTI). 17% ($N=16$) and 21% ($N=69$) of procedures were performed due to lifestyle-limiting claudication in Group F and Group M, respectively ($p=0,321$).

TABLE 1 Baseline characteristics

Variable	Group M (N=324)	Group F (N=96)	p-value
	N (%)	N (%)	
Smoking	224 (70)	20 (21)	<0,001
Hypertension	256 (80)	86 (90)	0,031
Dyslipidemia	151 (47)	52 (54)	0,230
Diabetes mellitus	179 (56)	54 (56)	0,981
Chronic kidney disease	65 (20)	20 (21)	0,912
under dialysis	33 (10)	10 (10)	0,977
Coronary disease or congestive heart failure	116 (36)	32 (33)	0,601
Previous cerebrovascular event or carotid artery stenosis	49 (15)	18 (19)	0,422
Chronic limb-threatening ischemia (CLTI)	255 (79)	80 (83)	0,321

TABLE 2 Clinical grading and anatomic disease staging if CLTI

Variable	Group M with CLTI (N=255)	Group F with CLTI (N=80)	p-value
Wound grade in Wifl, median (IQR)	2 (1)	2 (1)	0,896
Infection grade in Wifl, median (IQR)	1 (1)	1 (1)	0,708
Aortoiliac disease stage in GLASS, median (IQR)	0 (0)	0 (0)	0,014
CFA disease, N (%)	51 (20)	3 (4)	0,001
Femoropopliteal disease stage in GLASS, median (IQR)	3 (4)	3 (3)	0,845
BTK disease stage in GLASS, median (IQR)	4 (4)	4 (1)	0,012
Infrainguinal GLASS, median (IQR)	3 (0)	3 (0)	0,941
BTA disease stage, N (%)			0,215
0	19 (12)	2 (4)	
1	63 (39)	22 (41)	
2	79 (49)	30 (56)	

If CLTI, we found no statistically significant difference between groups regarding wound or infection grading (in Wifl system) and femoropopliteal or below-the-ankle (BTA) anatomic disease staging (in GLASS system) – TABLE 2. Group M was more likely to have common femoral artery (CFA) disease ($p=0,001$) and higher stages of aortoiliac disease (in GLASS system; $p=0,014$). Group F had more severe below-the-knee (BTK) disease ($p=0,012$). The median follow-up was 22 months. The vascular procedures to treat different levels affected by occlusive disease were associated with

gender (TABLE 3; $p=0,016$). Group F underwent more outflow procedures (78% vs. 68% in Group M) and fewer simultaneous inflow and outflow procedures (3% vs. 14% in Group M).

We found an association between gender and the type of revascularization procedure performed (TABLE 4; $p<0,001$). Group F had a higher proportion of endovascular procedures (84% vs. 65% in Group M).

Major amputation rates in Group M and Group F were $8\pm 2\%$ and $8\pm 3\%$ at 1 month, $14\pm 2\%$ and $16\pm 4\%$ at 1 year, and $15\pm 2\%$ and $19\pm 4\%$ at 2 years, respectively (Image 1; $p=0,564$).

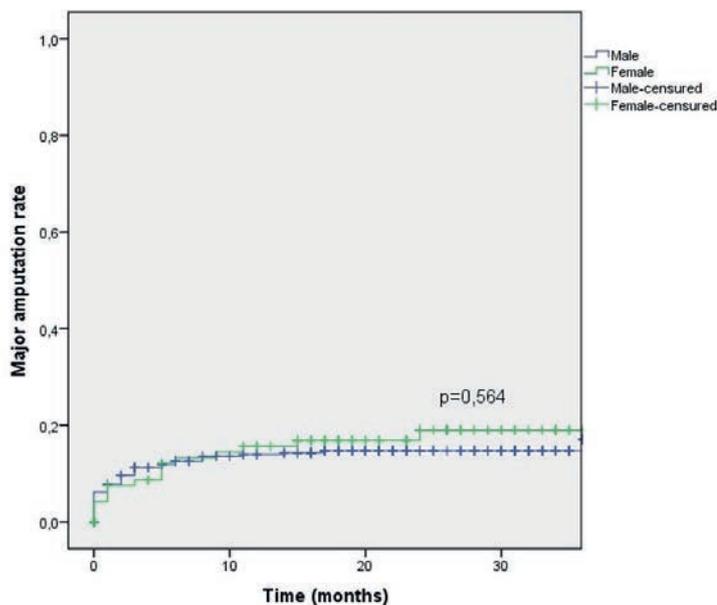
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TABLE 3 Target disease of the revascularization procedure performed

Vascular procedure target	Group M (N=324)	Group F (N=96)	p-value
	N (%)	N (%)	
Inflow disease	59 (18)	18 (19)	0,016
Outflow disease	221 (68)	75 (78)	
Inflow and outflow disease	44 (14)	3 (3)	

TABLE 4 Type of revascularization procedure performed

Vascular procedure type	Group M (N=324)	Group F (N=96)	p-value
	N (%)	N (%)	
Open	81 (25)	14 (15)	<0,001
Endovascular	209 (65)	81 (84)	
Hybrid	34 (11)	1 (1)	



Vascular reintervention rates in Group M and Group F were 13±2% and 13±3% at 1 month, 21±2% and 20±4% at 1 year, and 25±3% and 24±5% at 2 years, respectively (Image 3; $p=0,74$).

Overall survival in Group M and Group F was 97±1% and 93±3% at 1 month, 83±2% and 82±4% at 1 year, and 77±3% and 72±5% at 2 years, respectively (Image 4; $p=0,443$). After group stratification according to the vascular procedure (open, endovascular or hybrid procedure) and according to the treated level affected by occlusive disease (inflow, outflow, or simultaneous inflow and outflow procedure), we found no significant difference between Groups M and F in the outcomes mentioned above (major amputation rate, diagnosed restenosis/occlusion procedure rate, reintervention rate, overall survival).

DISCUSSION

Our study's main finding is that women and men have a similar prognosis after lower limb revascularization. Female patients who underwent lower limb revascularization tend to be older and have a more distal PAD distribution pattern. They undergo more frequent endovascular procedures and vascular procedures to treat outflow disease.

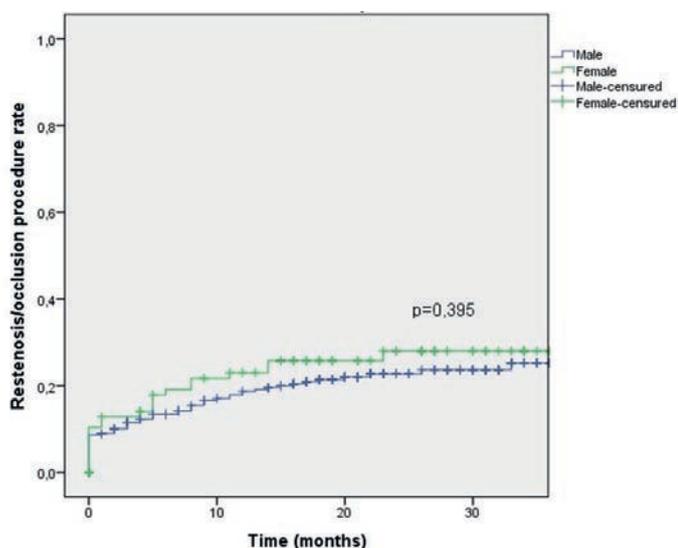
It has been suggested that, in women, there is a prolonged latent phase in the progression of PAD from asymptomatic to symptomatic. Notably, women tend to be older at the time of diagnosis than men, as in this study^(1,3). Classic symptoms of PAD may be masked in this age group by increasing prevalence of osteoarthritis or a decrease in activity levels that occur with aging.

Group M	323	248	170	89
	0,06 (0,01)	0,14 (0,02)	0,15 (0,02)	0,15 (0,02)
N at risk, major amputation rate, (SE)				
Group F	95	73	46	21
	0,04 (0,02)	0,15 (0,04)	0,27 (0,04)	0,19 (0,04)

Image 1 Kaplan-Meier estimates of major amputation rates

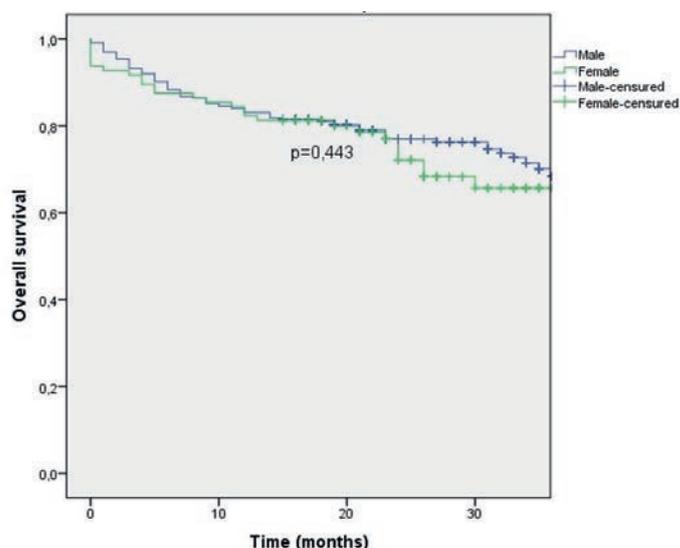
Diagnosed procedure restenosis/occlusion rates in Group M and Group F were 9±2% and 13±4% at 1 month, 19±2% and 23±5% at 1 year, and 23±3% and 28±5% at 2 years, respectively (Image 2; $p=0,395$).

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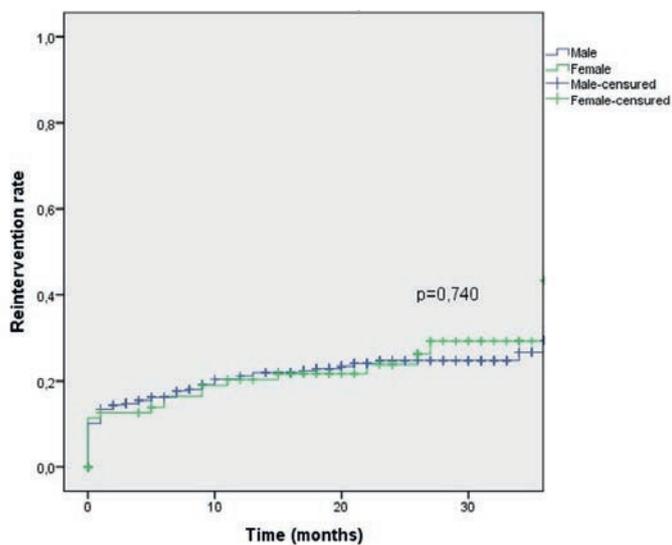
	323	202	131	66
Group M	0,09 (0,02)	0,17 (0,02)	0,22 (0,03)	0,24 (0,03)
	N at risk, restenosis/occlusion procedure rate, (SE)			
Group F	95 (0,03)	60 (0,05)	36 (0,05)	18 (0,05)

Image 2 Kaplan-Meier estimates of diagnosed vascular procedure restenosis/occlusion rates



	323	275	193	98
Group M	0,99 (0,01)	0,85 (0,02)	0,80 (0,02)	0,76 (0,03)
	N at risk, overall survival, (SE)			
Group F	95 (0,03)	82 (0,04)	57 (0,04)	24 (0,06)

Image 4 Kaplan-Meier estimates of overall survival



	323	208	138	71
Group M	0,10 (0,02)	0,20 (0,02)	0,23 (0,03)	0,25 (0,03)
	N at risk, reintervention rate, (SE)			
Group F	95 (0,03)	62 (0,04)	38 (0,05)	19 (0,06)

Image 3 Kaplan-Meier estimates of vascular reintervention rates

Other factors such as less physical activity and smaller calf muscle mass may also contribute to the delay in detecting PAD in women⁽¹⁾.

In Portugal, smoking is still more common in men⁽⁴⁾. Increased smoking prevalence in Group M of this study may explain the increased burden of aortoiliac and CFA disease in male revascularized limbs, as smoking is associated with a proximal distribution of lower limb PAD⁽⁵⁾.

The longer latent phase of PAD in women may lead to delayed diagnosis of PAD and greater risk of severe and complex anatomic disease burden⁽¹⁻³⁾. Below-knee arteries typically become increasingly involved as the overall severity of the disease worsens⁽⁵⁾. Besides this, some authors state that women may be more prone to the development of FP disease⁽⁵⁾. This can explain higher stages of BTK disease in Group F in this study. However, as PAD progresses, we should expect an increased prevalence of CLTI at presentation, and Groups F and M had similar CLTI prevalence.

Therefore, given the relative prevalence of asymptomatic PAD in women, early detection of asymptomatic PAD in this group can help control risk factors and inhibit disease progression⁽¹⁾.

In this study, women underwent endovascular and procedures to treat outflow disease more frequently than men. A possible explanation is the high

experience of our vascular department on endovascular treatment of severe BTK disease. Other reasons may include the traditional belief that the female gender is associated with worse surgical outcomes, particularly after open procedures^(1,2). These worse outcomes may be related to the above-mentioned older age of presentation, a smaller vessel size, a poorer overall health status, or a more severe clinical and anatomical disease burden at presentation in female patients⁽²⁾.

On the other hand, some studies point out that endovascular intervention in females appears to be associated with better patency rates and better outcomes when compared with males^(1,2).

After lower limb revascularization procedures, we found similar outcomes in males and females, even after stratifying by open, endovascular or hybrid procedures. Group F and M had no different rates of amputation, restenosis/occlusion and reintervention. There was also no difference in overall survival between groups. Ferranti et al. showed comparable results⁽³⁾.

Despite similar outcomes in this study, Group F comprised only 23% of all revascularized lower limbs. In an analysis of 2.4 million PAD-related inpatient admissions, women were significantly less likely than men to receive a surgical revascularization procedure⁽⁶⁾. This study presents some limitations. It is dependent on appropriate medical records and patient clinical and imagiological follow-up. Department protocols do not include ankle-brachial index measurements, ankle pressure, or other parameters to evaluate ischemia grade in Wlfl. Vascular procedure selection is dependent on surgeon experience. Power calculation was not produced to ascertain a sufficient sample size. Small sample size and lower prevalence of open, hybrid, inflow, and simultaneous inflow and outflow procedures on female limbs influence the statistical significance of outcomes differences. Gender-differences in baseline characteristics and in clinical grading and anatomic disease staging, if CLTI, may be confounding factors.

CONCLUSION

Overall, this study suggests no major difference in limb outcomes for women who undergo lower limb revascularization procedures. Women were more likely to be older, have more severe BTK disease, and undergo endovascular procedures. This absence of difference in outcomes may be explained by the high proportion of endovascular revascularization procedures due to CLTI in our population.

According to this study, we find no reason to expect worse limb outcomes in women.

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