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Risk factors for reamputation in patients with diabetic foot: A case-control study

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ABSTRACT

Background: Reamputation as a complication of diabetic foot ulcers presents a high economic burden and represents a therapeutic failure. It is paramount to identify as early as possible patients in whom a minor amputation may not be the best option. The purpose of this investigation was to do a case-controlled study to determine risk factors associated with re-amputation in patients with DFU (diabetic foot ulcers) at two University Hospitals.

Methods: Multicentric, observational, retrospective, case-control study from clinical records of 2 university hospitals. Our study included 420 patients, with 171 cases (re-amputations), and 249 controls. We performed a multivariate logistic regression analysis and time-to-event survival analysis to identify re-amputation risk factors.

Results: Statistically significant risk factors were artery history of tobacco use ($p = 0.001$); male sex ($p = 0.048$); arterial occlusion in Doppler ultrasound ($p = 0.001$); percentage of stenosis in arterial ultrasound > 50 % ($p = 0.053$); requirement of vascular intervention ($p = 0.01$); and microvascular involvement in photoplethysmography ($p = 0.033$). The most parsimonious regression model suggests that history of tobacco use, male sex, arterial occlusion in ultrasound, and percentage of stenosis in arterial ultrasound > 50 % remained statistically significant. The survival analysis identified earlier amputations in patients with larger occlusion in arterial ultrasound, high leukocyte count, and elevated ESR.

Conclusion: Direct and surrogate outcomes in patients with diabetic foot ulcers identify vascular involvement as an important risk factor for reamputation.

Level of evidence: III

1. Introduction

Diabetic foot ulcers (DFU) account for approximately 50 % of non-traumatic lower extremity amputations and nearly 75 % of foot amputations [1–12]. The latter is associated with high morbidity in diabetic patients and carries additional costs for the health system, especially when reamputations or other reinterventions are required [13].

A major challenge for the orthopedic surgeon aiming for successful treatment in a patient with DFU is to define the proper amputation level [2,3,6,8,11,14–21]. Multiple studies have focused on the prediction of amputation and reamputation, though with very heterogeneous variables [1,2,11,15,17,20,22–25]. Those descriptive studies report variables associated with re-amputation, but few of them determine risk factors with statistical certainty. Some authors have associated the reamputation risk with severe peripheral arterial disease, male gender, older age, initial lesion in the heel, and infection [1,8,9,16,23,26]. Additionally, the definition of reamputation varies in the literature, which makes comparison among publications difficult [1,2,11,14,16,18,20,25,27].

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The amputation level carries economic consequences for both the healthcare system and the patient. Some reports indicate that the yearly cost of diabetes mellitus management can be 5.4 times higher in patients with DFU and could become 8 times higher in severe DFU [29]. Woods et al. performed a systematic review assessing 19 studies concerning the cost of interventions for infection management in DFU. The review concluded that regardless of the quality of the studies, results were highly variable and not comparable [28]. In Colombia, direct medical cost *per capita* of diabetic foot (DF) complication management was USD 1947,01 (United States dollar) (COP 3894,023 - Colombian Peso) and minor amputation at USD 782,60 (COP 1565,199) [30]. Above-the-knee amputation (AKA) could be a definitive approach that avoids the need for further ablative procedures, yet it could carry a far more "expensive" cost for the patient's functionality. Perhaps the goal should be somewhere in between, an optimal solution that seeks a balance between the number of operations and the desire to preserve lower extremity function.

The purpose of this investigation was to do a case-controlled study to determine risk factors associated with re-amputation in patients with DFU at two University Hospitals.

2. Methods

This case-control study performed a secondary analysis of a database of patients hospitalized for DFU treatment in the 2 participating hospitals.

The study included patients older than age 18 who had required lower extremity amputation from January 2013 to March 2021. Patients with lower extremity amputation due to causes different from DF complications were excluded. Cases were defined as those who required a new amputation at a proximal level in the same extremity or at the same or more proximal level in the opposite extremity. This definition for re-amputation was adapted considering that both extremities are at risk for these kinds of patients [2,14,16,37,40]. Controls were those patients who did not require a new amputation. Case-control match was done according to age, sex, and time of duration of diabetes mellitus (DM). We identified 573 patients, of which 420 fulfilled inclusion criteria, with 171 in the group of cases (reamputations) and 249 in the group of controls.

The assessed variables included age, sex, previous amputation, reamputation, Wagner classification, arterial assessment, leucocyte count, CRP (C Reactive Protein), ESR (Erythrocyte Sedimentation rate), time of DM, diagnosis for hypertension, chronic kidney disease and dialysis requirement.

The study collected data from the admission for the first amputation. In patients who underwent the first amputation in another institution, data were collected from the first admission to the Department of Orthopedics and Traumatology at the participating hospitals.

The study was approved by the Ethics and Research committees of the participating hospitals.

2.1. Statistical methods

Descriptive statistics were used. For categorical variables, proportions and frequencies were used. For continuous variables, central tendency and dispersion measures were used. Statistical significance was calculated using Fisher's exact test for categorical data. Wilcoxon signed-rank test evaluated independence between samples.

A multivariate logistic regression analysis model was used. The analysis identified odds ratio (OR) for variables with statistical relevance in the univariate analysis, controlling for confounding variables. Also, the study performed a time-to-event survival analysis for variables included in the regression model. All tests used a 0.05 statistical significance level with the statistical software [31].

Table 1
Patient characteristics.

	Amputation n = 249	Reamputation n = 171	Total n = 420	p-value
Age				**0.44**
Average (SD)	62.76 (± 12.02)	64.60 (± 10.18)	64.21 (± 10.58)	
Median (Q1-Q3)	65.00 (54.00–70.00)	64.00 (59.00–72.00)	64.00 (58.00–71.00)	
[Min-Max]	[38–88]	[27–95]	[27–95]	
Sex				**0.05***
Male	156 (62.65 %)	123 (71.92 %)	279 (66.42 %)	
Female	93 (37.34 %)	48 (28.07 %)	141 (33.57 %)	
HBP History				**0.39**
Yes	183 (73.49 %)	132 (77.19 %)	315 (75 %)	
No	66 (26.51 %)	39 (22.81 %)	105 (25 %)	
DM duration				**0.23**
Average (SD)	14.32 (± 6.24)	14.28 (± 8.40)	14.29 (± 7.98)	
Median (Q1-Q3)	15.00 (11.00–18.00)	13.00 (10.00–20.00)	14.00 (10.00–19.75)	
[Min-Max]	[0–25]	[0–40]	[0–40]	
History of tobacco use				**0.001***
Yes	87 (34.94 %)	85 (49.70 %)	172 (40.95 %)	
No	144 (57.83 %)	71 (41.52 %)	215 (51.19 %)	
ND	18 (7.23 %)	15 (8.77 %)	33 (7.86 %)	
History of dialysis in CKD				**0.76**
Yes	41 (16.47 %)	29 (16.96 %)	70 (16.67 %)	
No	208 (83.53 %)	142 (83.04 %)	350 (83.33 %)	

* Statistically significant; HBP (High blood pressure); DM (Diabetes mellitus); CRI (Chronic Kidney Disease); SD (standard deviation); ND (No data).

3. Results

3.1. Patient characteristics

Sociodemographic characteristics are shown in Table 1.

3.2. Amputation, reamputation, and vascular/surgical interventions

The initial amputation level was most frequently the toes for both groups (67.25 % of cases and 40.56 % of controls). For reamputation, above-the-knee amputation was the most frequent level (54.39 %). Interventions, such as VAC (Vacuum-assisted closure) therapy, were used in 18.13 % of cases and 12.05 % of controls. Regarding vascular interventions, a stent was used in 19.88 % of cases and 14.06 % of controls. Bypass was performed in 14.08 % of cases, compared to 7.23 % of controls (Table 2). Both stent and bypass were statistically significant.

3.3. Vascular involvement

For reamputations, arterial occlusion demonstrated in ultrasound was present in more than 70 % of individuals, with statistical significance ($p < 0.05$). Furthermore, half of the cases had a reported occlusion of more than 50 % which was also statistically significant ($p < 0.05$). Microvascular compromise reported in photoplethysmography was found to be statistically significant when information was available (Table 3).

Table 2
Distribution of patients according to interventions.

	Amputation	Reamputation	Total	p-value
	n = 249	n = 171	n = 420	
First amputation				
Level				**0.10**
Supracondylar	92 (36.94 %)	27 (15.79 %)	119 (28.33 %)	
Transtibial	40 (16.06 %)	11 (6.43 %)	51 (12.14 %)	
Syme	2 (0.08 %)	5 (2.92 %)	7 (1.66 %)	
Chopart	4 (1.60 %)	4 (2.3 %)	8 (1.90 %)	
Lisfranc	10 (4.02 %)	9 (5.26 %)	19 (4.52 %)	
Toe	101 (40.56 %)	115 (67.25 %)	216 (51.43 %)	
Reamputation				
Level				**0.59**
Disarticulation		5 (2.92 %)		
Supracondylar		93 (54.39 %)		
Transtibial		38 (22.22 %)		
Syme		8 (4.7 %)		
Chopart		1 (0.06 %)		
Lisfranc		13 (7.60 %)		
Toe		13 (7.60 %)		
Other interventions				
Use of vacuum therapy				**0.09**
Yes	30 (12.05 %)	31 (18.13 %)	61 (14.52 %)	
No	216 (86.75 %)	139 (81.29 %)	355 (84.52 %)	
ND	3 (1.21 %)	1 (0.06 %)	4 (0.96 %)	
Vascular surgery				
Stent	35 (14.06 %)	34 (19.88 %)	69 (16.42 %)	**0.009***
Bypass	18 (7.23 %)	24 (14.04 %)	42 (10 %)	**0.002***
Medical	40 (16.06 %)	40 (23.39 %)	80 (19.04 %)	**0.9**
NR	156 (62.65 %)	73 (42.69 %)	229 (54.52 %)	

ND (No data); NR (Not required).
* Statistically significant

3.4. Ulcer characteristics and infectious involvement

Wagner classification was most frequently grade 4 (58.48 % of cases and 53.41 % of controls). For leukocyte count, a median of 12,400 u/mm3 was reported in cases, compared to a median of 10,300 u/mm3 in controls, but these differences did not quite reach statistical significance. Regarding other variables, neither ESR, CRP nor HbA1 reached statistical significance.

The multivariate logistic regression model used variables with statistical significance and clinical relevance (Table 4).

3.5. Multivariate logistic regression model

The complete model included the history of tobacco use, male sex, use of stent and bypass, arterial occlusion in ultrasound, percentage of stenosis > 50 % in ultrasound, microvascular compromise in photoplethysmography and Wagner classification (this last one was included for its clinical relevance rather than its statistical significance in the univariate analysis). However, the most parsimonious regression formula revealed that history of tobacco use, male sex, arterial occlusion in ultrasound, and percentage of stenosis > 50 % in ultrasound were the most relevant risk factors for re-amputation.

3.6. Time-to-event survival analysis (Kaplan Meier curve)

The study performed a survival analysis between the first and the second amputation for the statistically significant variables. Such analysis showed a tendency to an earlier reamputation outcome in

Table 3
Characteristics of vascular, ulcers and infectious compromise.

	Amputation **n = 249**	Reamputation **n = 171**	Total **n = 420**	p-value
Arterial occlusion in Doppler ultrasound				**0.0013***
Yes	160 (64.26 %)	127 (74.26 %)	287 (68.33 %)	
No	48 (19.28 %)	13 (7.60 %)	40 (9.52 %)	
No hemodynamic repercussion	41(16.47 %)	31 (18.12 %)	72 (17.14 %)	
Occlusion percentage in Doppler ultrasound > 50 %				**0.05***
Yes	100 (40.16 %)	86 (50.29 %)	186 (44.28 %)	
No	149 (59.84 %)	85 (49.71 %)	234 (55.71 %)	
Microvascular involvement in photoplethysmography				**0.039***
Yes	68 (27.30 %)	39 (22.81 %)	107 (25.48 %)	
No	7 (2.81 %)	12 (7.01 %)	19 (4.52 %)	
Undetermined	6 (2.41 %)	2 (1.16 %)	8 (1.9 %)	
ND	168 (67.50 %)	118 (69 %)	286 (68.09 %)	
Wagner grade				**0.31**
0	8 (3.21 %)	-	8 (1.90 %)	
1	1 (0.04 %)	-	1 (0.02 %)	
2	27 (10.84 %)	15 (8.77 %)	42 (10 %)	
3	71 (28.51 %)	50 (29.24 %)	121 (28.81 %)	
4	133 (53.41 %)	100 (58.48 %)	233 (55.48 %)	
5	9 (3.61 %)	6 (3.51 %)	15 (3.57 %)	
Leukocyte count in a complete blood count (u/mm^3)				**0.67**
Average (SD)	11544 (± 4759)	14038 (± 5801)	13520 (± 5680)	
Median (Q1-Q3)	10300 (8490–14350)	12400 (10300–17460)	12315 (9517–16590)	
[Min-Max]	[5050–29230]	[5730–40932]	[5050–40932]	
CRP (mg/dL)				**0.83**
Average (SD)	60.81 (± 71.58)	73.25 (± 88.05)	70.66 (± 84.85)	
Median (Q1-Q3)	29.29 (14.03–82.80)	28.60 (13.59–98.80)	29.20 (13.60–98.77)	
[Min-Max]	[2.8–338]	[0–361.9]	[0–361.9]	
ESR (mm/seg)				**0.123**
Average (DE)	65.31 (± 63.71)	76.93 (± 36.96)	74.51 (± 43.91)	
Median (Q1-Q3)	65.00 (15.00–90.00)	81.00 (48.00–101.00)	75.50 (46.00–99.75)	
[Min-Max]	[0–358.3]	[0–161]	[0–358.3]	
HbA1c (%)				**0.78**
Average (SD)	7.33 (± 3.52)	7.32 (± 4.28)	7.32 (± 4.12)	
Median (Q1-Q3)	7.50 (6.60–9.10)	7.60 (6.10–9.40)	7.50 (6.20–9.40)	
[Min-Max]	[0–13.5]	[0–21.4]	[0–21.4]	

CRP (C-reactive protein); ESR (erythrocyte sedimentation rate); HbA1c % (glycated hemoglobin).
* Statistically significant; ND (No data)

Table 4
Multivariate logistic regression model for statistically and clinically significant variables.

	Complete model			Reduced model		
	OR	CI	p-value	OR	CI	p-value
History of tobacco use	1.98	1.31–2.99	**0.001***	1.75	1.31–2.99	**0.022***
Sex (Male)	1.53	1.00–2.32	**0.048***	1.50	1.00–2.32	**0.037***
Vascular surgery (Stent)	1,48	1.28–1.83	**0.009***			
Vascular surgery (Bypass)	1,35	1.18–1.69	**0.002***			
Arterial occlusion in Doppler ultrasound	2.93	1.56–5.86	**0.001***	1.95	1.56–5.86	**0.035***
Percentage of stenosis > 50 % in doppler ultrasound	1.79	1.14–2.80	**0.053***	1.60	1.14–2.80	**0.037***
Microvascular compromise in photoplethysmography	1.71	1.11–4.66	**0.033***			
Wagner grade	1.22	0.82–1.82	0.312			

* Statistically significant; CI (confidence interval); OR (odds ratio)

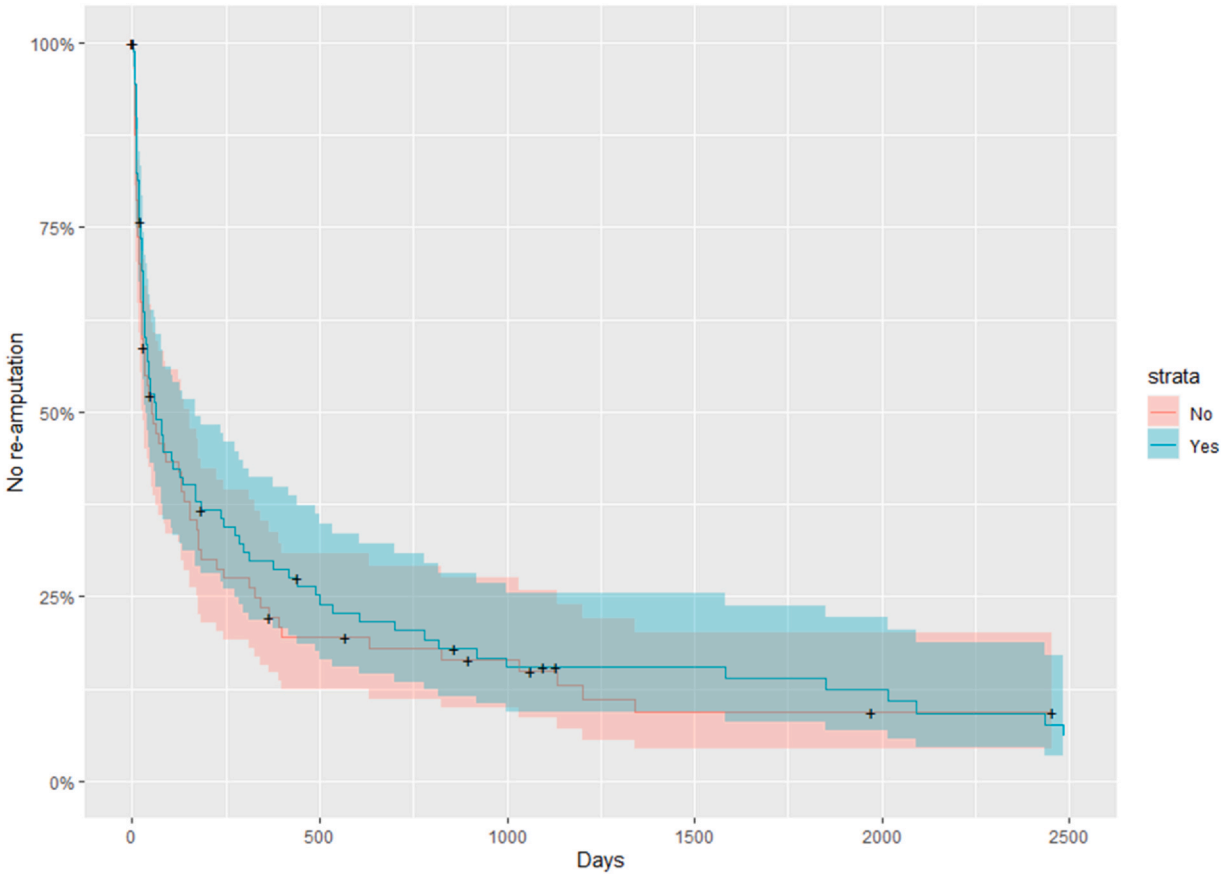

Fig. 1. Kaplan Meier curve for survival between amputations and history of tobacco use.

individuals with a history of tobacco use (Fig. 1), male sex (Fig. 2), occlusion in ultrasound, and occlusion higher than 50 % (Figs. 3 and 4).

4. Discussion

Multiple studies have attempted to identify variables associated as risk factors for reamputation, aiming for a better therapeutic approach [1,2,11,15,17,20,22–25]. The results of these papers are heterogeneous and, despite methodological rigor, comparison among models is difficult. This limits their applicability in clinical practice. Our study aimed to determine risk factors associated with re-amputation in patients with DFU. Previous risk factors identified by prediction models include age; male sex; length of the disease; hemoglobin A1C (HbA1C %) levels; leukocyte count; classification of DF lesions; chronic arterial occlusive disease (CAOD); lack of foot sensibility and pulse; C-reactive protein (CRP) level; fasting glucose level; ulcer extension and depth; and dialysis requirement due to CKD [2,8,32]. The great variety of variables is evident. They can be classified into 3 groups: metabolic, infectious, and vascular. In our study, the most relevant variables were the ones associated with vascular compromise. These are usually associated with reamputation in literature.

The literature establishes that infectious processes in the intervened extremity perpetuate DFU. Even with antibiotic therapy, when the inflammatory response is not controlled, the risk of therapeutic failure and so the risk of reamputation is increased by 14-fold [1,2,18,20,23,32–35]. Though ESR is a highly unspecific marker, previous studies suggest it could be a marker for reamputation [3,6]. Results in this study did not show an association to re- amputation in our population.

The Wagner classification did not show statistical significance in the study. It has been reported, however, that patients with initial Wagner grade 3 or higher may require initial amputation at a higher level on the extremity. With a more distal amputation, the reamputation risk increases, especially when there is vascular and

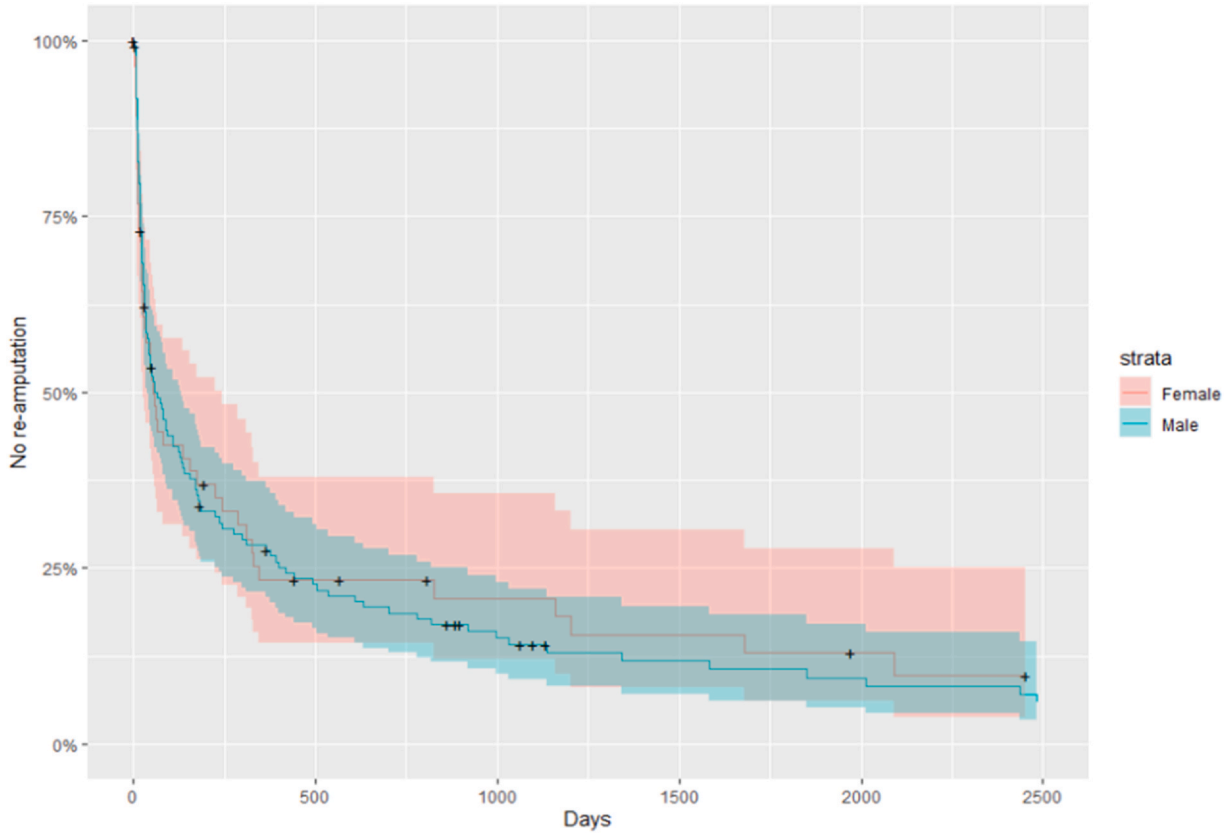

Fig. 2. Kaplan Meier curve for survival between amputations sex.

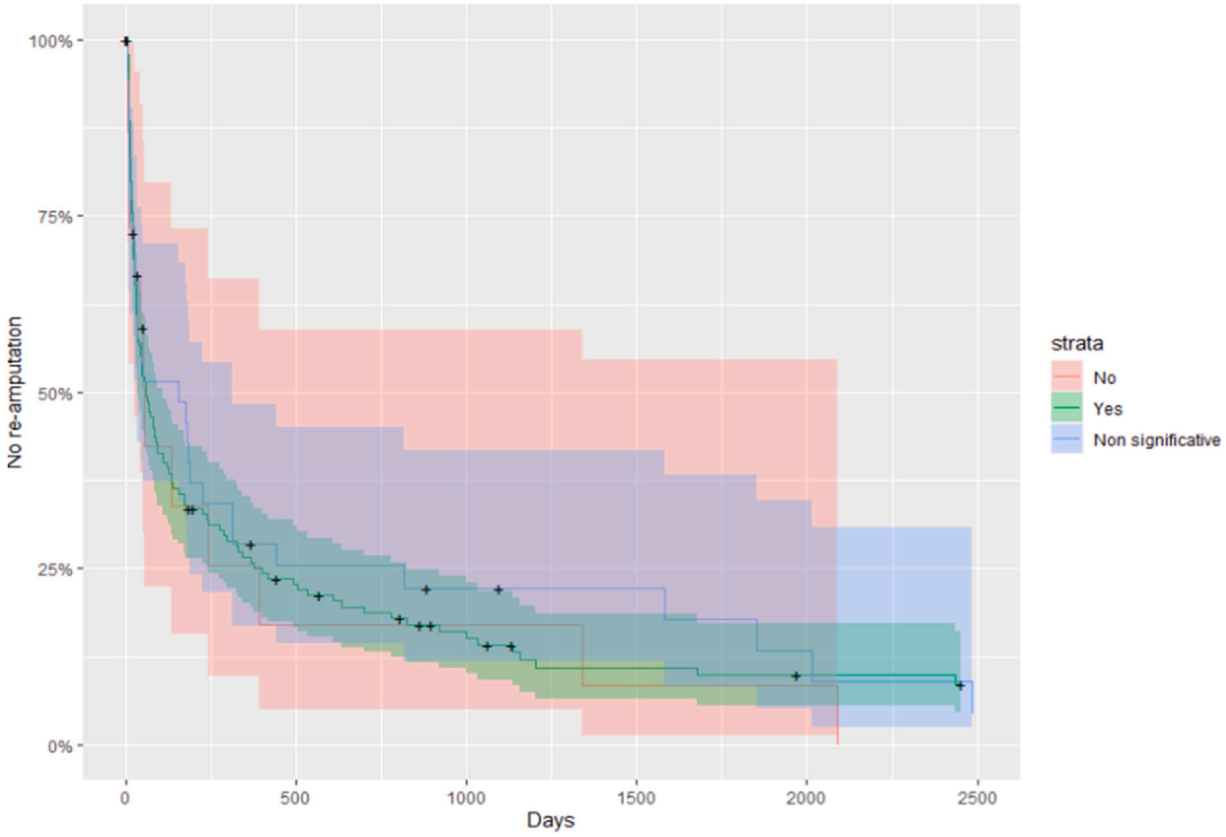

Fig. 3. Kaplan Meier curve for survival between amputations and arterial occlusion in doppler ultrasound.

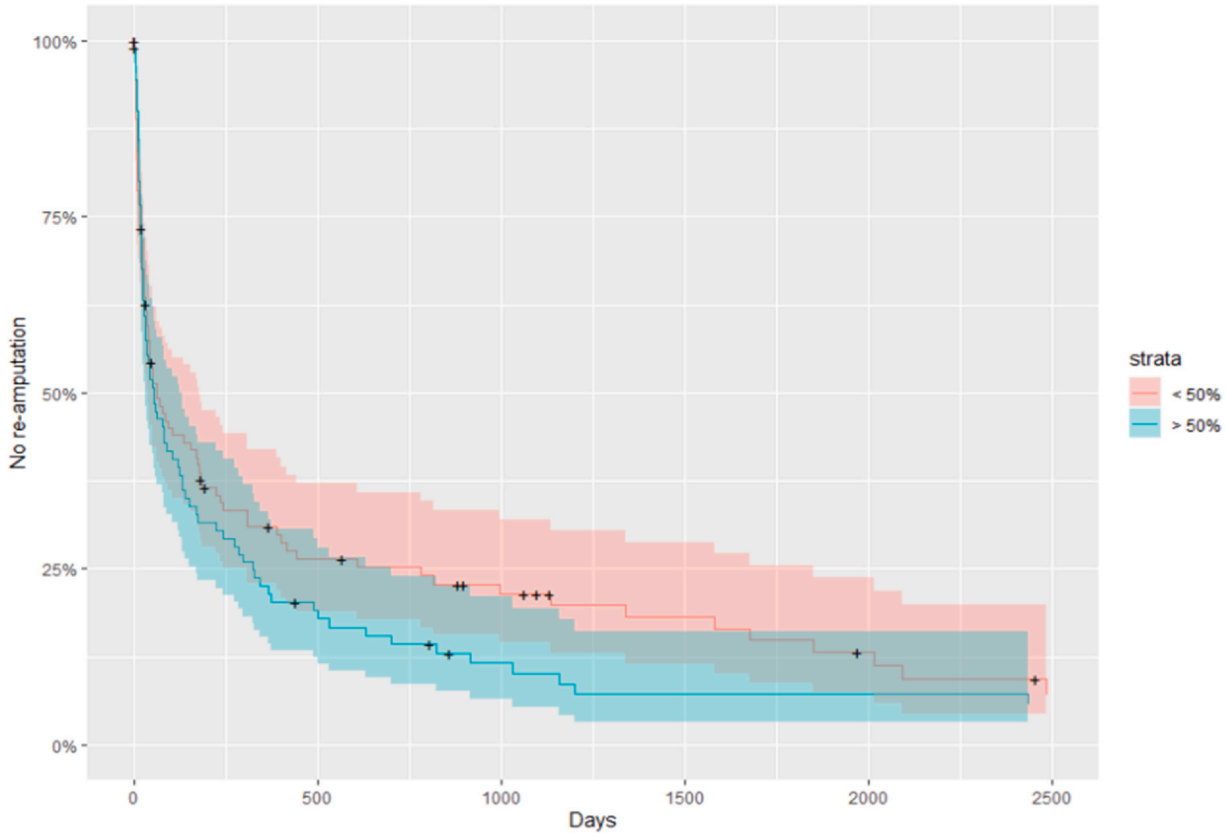

Fig. 4. Kaplan Meier curve for survival between amputations percentage of stenosis in doppler ultrasound.

infectious involvement [10,15,16,23,33]. Despite not being a predictive factor, classification may be a fundamental consideration for the initial approach of patients, based on their vascular and infectious states. Microbial isolation in intraoperative culture does not represent a predictive factor for reamputation. Skoutas et al. also reported low statistical significance for this variable [23]. Early empiric use of wide-spectrum antibiotics may be an important factor of confusion leading to false negatives, as Ceballos et al. reported [36]. Nonetheless, despite the typification of the microbial agent in the sample is not a determinant variable for re- amputation it aids in selecting the adequate antimicrobial agent for each patient.

Vascular involvement has been assessed in multiple publications, and it is reported as a factor frequently associated with the outcome of amputation and reamputation [1,6,7,15,16,21–23,25,37]. Thorud et al. and Shin et al. identified the peripheral arterial disease and vascular involvement in other organs (coronary disease, CKD, high blood pressure, among others) as high-risk factors for re- amputation [16,22]. It is important to stress that in available studies the method of vascular involvement assessment is heterogeneous, either by physical examination (pulse palpation, ankle-brachial index [ABI]) or diagnostic aids, such as angiography reported [1,6,7,15,21,37]. This study described vascular involvement with the occlusion percentage gauged by arterial ultrasound. Vascular occlusion was revealed as a statistically significant risk factor for reamputation.

Vascular occlusion may also impact reamputation timing, primarily by shortening the interval between procedures. Izumi et al. and Skoutas et al., report similar reamputation rates around 6 months after the first procedure in patients with more pervasive vascular involvement [23,25]. Other studies report amputation rates varying from 25 % at one year to 60 % at 5 years in patients with peripheral arterial disease (PAD), a history of re-interventions for revascularization, or vascular comorbidities [1,16,37].

There are few systematic reviews and meta-analyses assessing reamputation risk factors. Like the studies referenced in this paper, they present heterogeneous results. Publications in the last 2 years identify male gender, tobacco smoking history, amputation history, DFU history, osteomyelitis, CAOD, retinopathy, gangrene, leukocytosis, Wagner grades 4 and 5, International Working Group on the Diabetic Foot (IWGDF) classifications 3 and 4, elevated ESR/CRP, positive cultures, and presence of gram-negative germs, as re- amputation risk factors with highest statistical weight [38,39]. Again, variables associated with vascular involvement dominate among risk factors, as this study reports.

A strength of this study is the case-control design. By having a control group, findings regarding risk factors are considered relevant. This is an advantage, as there are few case-control studies of reamputation in the literature and the majority are studies based in cohorts with retrospective data, especially regarding reamputation.

Limitations of the study include its observational and retrospective nature which creates an important bias in selection and data collection. Also, some variables are limited by a lack of data in the database, such as the patient's desire to "save their body parts" or ABI.

5. Conclusion

This study identified that vascular compromise (including possible damage from tobacco smoking) is the variable with the highest relevance in determining the risk of reamputation. Identification of risk factors for reamputation in patients with DFU is growing in frequency in the literature. Reports with the methodological rigor of the case and control studies, however, are not frequent. Finally, the development of prospective studies and predictive models may allow a better approach to the management of this complication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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