

WOUND, ISCHEMIA, FOOT INFECTION (WIFI) CLASSIFICATION SYSTEM AND ITS PREDICTIVE ABILITY CONCERNING AMPUTATION-FREE SURVIVAL, MORTALITY AND MAJOR LIMB AMPUTATION IN A PORTUGUESE POPULATION: A SINGLE CENTER EXPERIENCE

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Abstract

Introduction: Commonly used chronic limb-threatening ischemia (CLTI) classifications lack granularity and detail to precisely stratify patients according to risk of limb loss, expected revascularization benefit and mortality. The aim of this study is to evaluate in a Portuguese population the prognostic value of an updated CLTI classification based on Wound, Ischemia, and foot Infection (Wifi) proposed by the Society for Vascular Surgery.

Materials and Methods: Single-center retrospective evaluation of prospectively collected data of consecutive patients with CLTI submitted to lower limb revascularization from January to December of 2017. All consecutive patients with chronic peripheral artery disease with ischemic rest pain or tissue loss were included. The exclusion criteria were patients with intermittent claudication, vascular trauma, acute ischemia, non-atherosclerotic arterial disease and isolated iliac intervention. The primary end-point was major limb amputation, mortality and amputation-free survival (AFS) at 30 days, 1 year and 2 year follow-up. Secondary end-points were minor amputation, wound healing time (WHT) and rate (WHR).

Results: A total of 111 patients with CLTI were submitted to infra-inguinal revascularization: 91 endovascular and 20 open surgery. After categorizing them according to the Wifi: 20 had stage 1 (18.52%), 29 stage 2 (26.85%), 38 stage 3 (35.19%) and 21 stage 4 (19.44%). Overall mortality rate was 1.8%, 17% and 22.3% at 30 days, 1 year and 2 years follow-up. Major amputation rate was 0.9%, 2.7% and 2.7% at 30 days, 1 year and 2 years follow-up. AFS rate was 97.3%, 82.1%, and 76.8% at 30 days, 1 year, 2 years follow-up. In multi-variable analysis, higher Wifi score was the only predictive factor for mortality and AFS. Wifi 3 and 4 were also associated with increased risk of non-healing ulcer.

Conclusion: This study proved the prognostic value of the Wifi classification in a Portuguese population by showing an association between higher scores and increased mortality, lower AFS and non-healing ulcer.

Keywords: Ischemia; Foot Ulcer; Infection; Diabetic foot; Amputation; Peripheral Arterial Disease.

INTRODUCTION

Critical limb ischemia (CLI) was a term initially defined in 1982, to describe patients without diabetes, with severe chronic ischemia¹. Since then, there has been a noticeable demographic shift, mostly due to greater diabetes incidence².

This paradigm shift underscores the need to recognize the profound impact of the diabetes pandemic on peripheral arterial disease presentation. A more recent terminology, chronic limb threatening ischemia (CLTI) was proposed to overcome some of the limitations of previous CLI. Older classifications that were used to classify a mainly smoking

related CLTI such as Rutherford³ and Fontaine⁴ that would define CLTI as stages 4 to 6 and stages 3 or 4, respectively, are no longer precise enough to stratify patients according to their morbidity, mortality and risk of limb loss.

When assessing limb salvage in individuals with diabetes, neuropathy or wound related infections, over a wide range of peripheral arterial disease (PAD) severities, limb perfusion is a crucial factor to consider, albeit not the only one. Previous CLTI classification systems do not provide enough information regarding the level of tissue damage and degree of infection, usually reducing ischemia to a dichotomic variable. Thus, the Society for Vascular Surgery (SVS) developed in 2014 an updated classification system that takes into account Wound, Ischemia, and foot Infection (WIFI)⁵.

The SVS WIFI classification system assigns a grade based on the combination of wound, ischemia, and infection. These grades correspond to one of four clinical limb stages, numbered 1 through 4, correlating to the likelihood of wound healing and the one-year risk of amputation⁵. Numerous studies have been conducted to test the effectiveness of this system and it has been proven reliable as a practical way to evaluate the potential for wound healing and the risk of amputation in patients with different levels of chronic limb-threatening ischemia⁶⁻⁸.

The use of WIFI to stratify amputation risk has been reported by multiple centers⁹, there are currently, however, no reports in the medical literature that have applied WIFI classification as a prognostic tool in a Portuguese center. Therefore, this study aims to investigate whether the SVS WIFI classification can accurately predict clinically relevant outcomes, in a Portuguese population.

MATERIALS AND METHODS

Study design and patient selections. Authors reviewed surgical records of all consecutive procedures performed from January to December 2017 in a single-center in Portugal. Authors performed a retrospective analysis of prospectively collected data. A comprehensive chart review was done to extract demographics, comorbidities, cardiovascular disease risk factors and clinical outcomes during the study period. The treatment strategy (endovascular or open) was performed by the choice of the case physician.

The inclusion criteria were all consecutive patients with ischemic rest pain or with tissue loss coexisting with chronic peripheral artery disease (PAD). To avoid bias caused by previous vascular interventions at the index limb, only patients with new-onset of chronic limb-threatening ischemia (CLTI) after the last previous vascular intervention were included.

The study excluded patients with acute ischemia (embolic or thrombotic), nonatherosclerotic disease, intermittent claudication, isolated iliac interventions, vascular trauma at the index leg, and documented hypercoagulable states. Clinic records and admission letters were reviewed

for demographic data, history, comorbidities, and physical examination findings, including wound state, ischemia index, and the extent of foot infection. The wound documentation included detailed wound evaluation, photographs and reporting of local or systemic infection.

The WIFI score was assigned for each patient prior to the intervention and an ankle-brachial index was calculated before and after each procedure. The baseline WIFI score was used to classify the patients into four groups according to the risk for amputation as reported by Mills et al⁵: group 1, very low risk, clinical stage 1; group 2, low risk, clinical stage 2; group 3, moderate risk, clinical stage 3; and group 4, high risk, clinical stage 4.

End points. The primary end point of the study was major limb amputation, amputation-free survival (AFS) and mortality. Secondary end points were minor amputation, wound healing time (WHT) and wound healing rate (WHR).

Statistical analysis. Authors compared major/minor amputation, amputation-free survival, overall mortality, WHT and WHR according to the different WIFI clinical stages. Categorical variables are presented as percentages. Authors performed Student t-test for age and gender distribution. Ordinal data (four groups) were compared with the Pearson chi-square test, and continuous data were compared with Kruskal-Wallis or one-way analysis of variance test. Since the authors intended to inference about the study end points as a function of time, the primary outcomes are presented as survival analysis. Thus, AFS, major amputation and mortality survival rates were calculated using the Kaplan-Meier method and compared by the log-rank test. A multivariate Cox regression analysis was also performed to adjust to possible confounding factors. A value of $p \leq 0.05$ was considered as statistically significant for individual tests.

RESULTS

During the study period, 267 patients were submitted to infra-inguinal revascularization. Of those, 111 patients fit our inclusion/exclusion criteria and were included in the study (Table 1). They initially were categorized according to the type of treatment: 91 (82%) were submitted to endovascular approach and the remaining 20 (18%) to open surgery (Table 2).

The demographics of our study population consisted of 72 (64,3%) males and 39 (35,7%) females, with an average age of 71 years old. A total of 80 (71,4%) patients had diabetes and a strong association ($p=0,01$) was discovered between diabetes and advanced stages of WIFI, specifically stages 3 and 4. Female gender was also associated with higher WIFI stage. This difference was also statistically significant, with a p-value of 0.036.

A baseline patient stratification following to the WIFI classification was performed: 20 (17.9%) had WIFI stage 1, 29 (25.9%) stage 2, 38 (33.9%) WIFI stage 3 and 21 (18.8%) WIFI stage 4. Table 3 provides a comprehensive characterization of the patient's demographics and comorbidities analysed. In

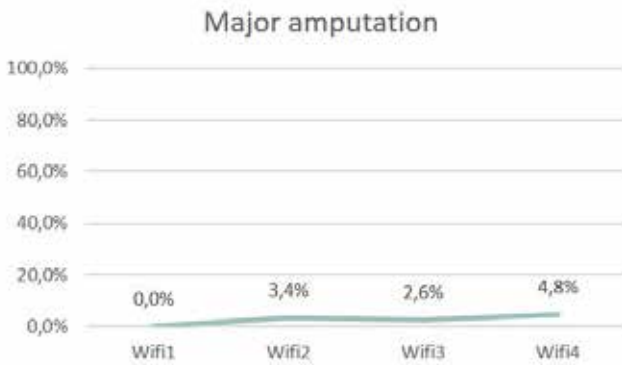


Figure 1 Major amputation categorized by Wifi stage group.

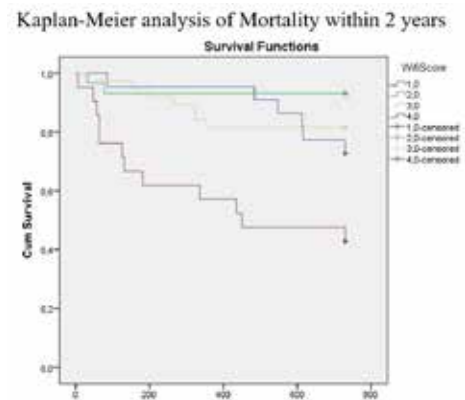


Figure 4 Kaplan-Meier analysis of Mortality within 2 years.

Kaplan-Meier analysis of Major Amputation within 2 years

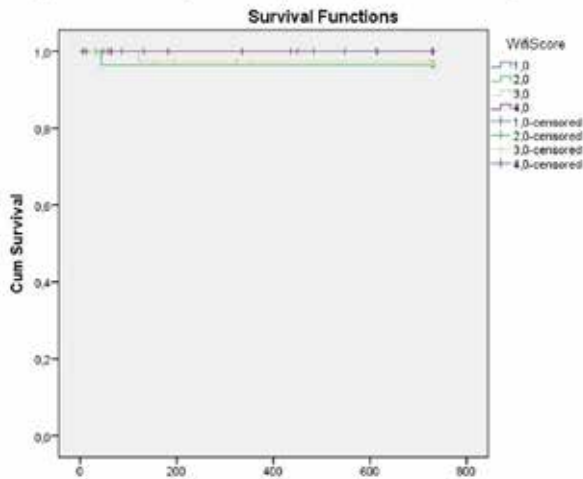


Figure 2 Kaplan-Meier analysis of Major Amputation within 2 years



Figure 5 Amputation free survival by Wifi stage group.

2 year all cause mortality



Figure 3 Mortality within 2 years of follow-up within each Wifi stage group.

Kaplan-Meier analysis of Amputation Free Survival

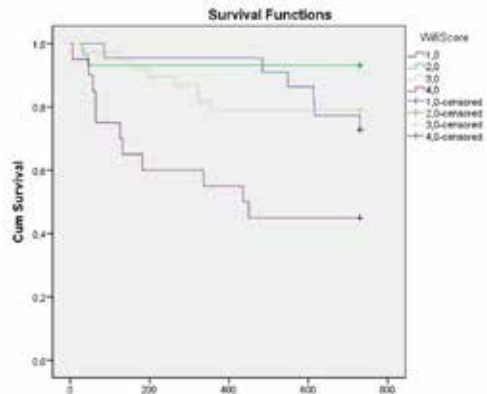


Figure 6 Kaplan-Meier analysis of Amputation Free Survival.

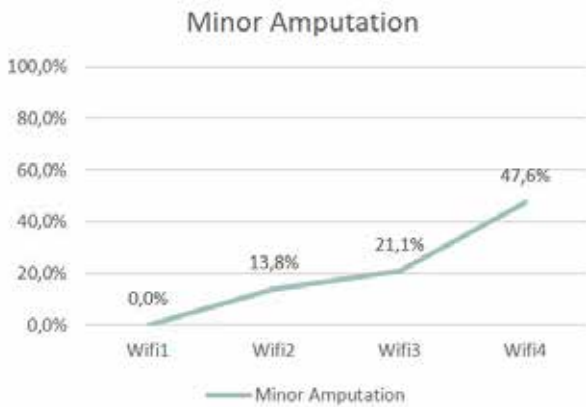


Figure 7 Minor Amputation by Wifi stage group.

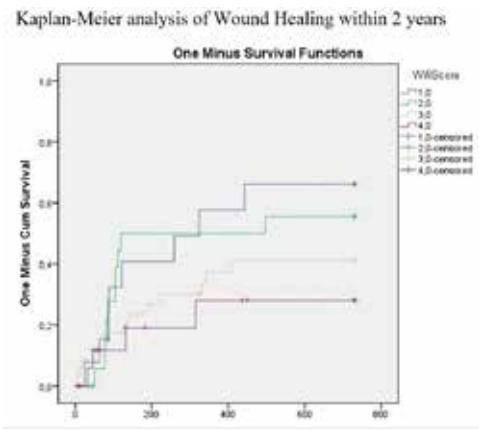


Figure 10 Kaplan-Meier analysis of Wound Healing Rate within 2 years.

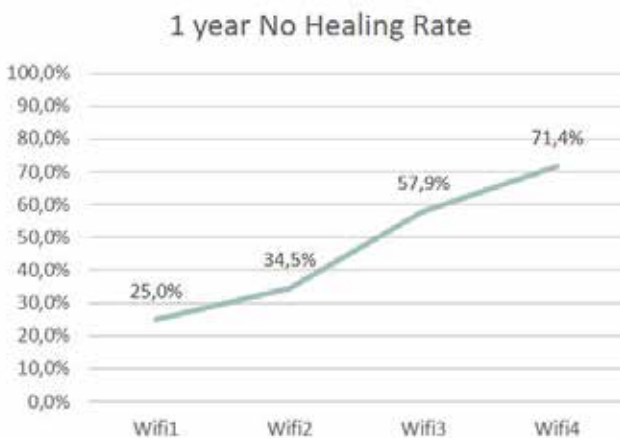


Figure 8 Wound Healing Time by Wifi stage group.



Figure 9 Wound Healing Rate by Wifi stage group.

the Wifi stage 4 group, a larger proportion of individuals was submitted to open surgery (23,8%) compared with the other groups, however not statistically significant.

During the follow-up period, major amputation was 0,9% within 30 days, 2,7% after a year and 2,7% after 2 years (Figure 1). Kaplan-Meier analysis for major amputation had a test statistic of 1.264 and a p-value of 0.738 (Figure 2). Mortality was 1.8%, 17% and 22.3% at 30 days, 1 year and 2 years follow-up, respectively (Figure 3). The Kaplan-Meier curves for mortality had a test statistic of 21.570 and statistically significant differences were observed between Wifi scores (p-value 0) (Figure 4). Depicted in figure 5, amputation free survival reached 97,3% at 30 days, 82,1% at 1 year and 76,8% at 2 years. A Kaplan-Meier analysis was performed for AFS with a test statistic of 18.277 and a statistically significant result was obtained (p-value 0) (Figure 6).

To adjust to possible confounding variables, a multivariate Cox regression was performed. Variables included in this model were Wifi score, gender, type of revascularization (open vs endovascular), preoperative ABI, DM and age. The model was statistically significant with overall χ^2 19,182, $p=0.014$. The only predictive variable of 2 year AFS was $Wifi \geq 3$ ($B -2.674$, $p=0.013$, $Exp(B)=0.069$ (95% CI 0.005-0.572)

Secondary end-points results such as minor amputation, wound healing time (WHT) and rate (WHR) are illustrated in figures 7, 8 and 9. The Kaplan-Meier curves for wound healing rate had a test statistic of 4.176 and statistically significant difference were observed (p-value 0.246) (Figure 10). A strong correlation was found to exist between Wifi stages 3 and 4 and an increased risk of non-healing ulcers ($p \leq 0.05$).

Fontaine and Rutherford classifications were not predictive of mortality, AFS, and amputation risks.

Concerning the ankle-brachial index (ABI) before and after each intervention, as expected, open surgery was

Table 1 Excluded patients

	Excluded patients (n)	Excluded patients (%)
1	156	58,4%
AI embolic	2	1,28%
AI thrombotic	13	8,33%
NAADs	10	6,41%
IC	111	71,15%
IN	2	1,28%
VT	18	11,54%

AI - Acute ischemia; NAADs - Non-atherosclerotic arterial disorders; IC - Intermittent claudication; IN - Isolated iliac interventions; VT - Vascular trauma at the index leg

Table 2 Demographics and cardiovascular risk factors analyzed by the type of revascularization

	Endovascular (n)	Open Surgery (n)	p
n	81% (91)	18% (20)	
Male	61,5% (56)	80% (16)	0.131
Female	38,5 (35)	20% (4)	0.131
Age (range)	71,6 (50,4-92,6)	70,1 (55,1-84,7)	0.578
ABI			
Pre-Operative	0.55	0.34	0.008
Post-Operative	0,72	0,75	0.679
Average change	30,4%	118 5%	0.001
WifT			
Average score	2,5	2,5	0.702
WifT 1	18,7% (17)	25% (5)	0,702
Wifl 2	26,4% (24)	25% (5)	0.702
Wif 3	36,3% (33)	25% (5)	0.702
WifT 4	17,6% (16)	25% (5)	
DM	75,8% (69)	55% (11)	0.060
Hypertension	85,7% (78)	85% (17)	0.934
Dyslipidemia	74,7% (68)	80% (16)	0.619
Active smoking	24,2% (22)	50% (10)	0.021
CKD	18,7% (17)	0% (0)	0.017
CVD	69,2% (63)	50% (10)	0.107
COPD	9,9% (9)	15% (3)	0.464
CAD	45,9% (39)	45% (9)	0.808

ABI - Ankle-Brachial Index; CAD - Coronary artery disease; CKD - Chronic Kidney Disease; COPD - Chronic obstructive pulmonary disease; CVD - Cerebrovascular disease; DM - Diabetes mellitus.

Table 3

Demographics and cardiovascular risk factors analyzed by Wifl score

	Wifl 1 (n)	Wifl 2 (n)	Wifl 3 (n)	Wifl 4 (n)	p
n	19,8% (22)	26.1% (29)	34,2% (38)	18,9% (21)	
Male	77,3% (17)	72.4% (21)	57,9% (22)	57,1% (12)	0.310
Female	22,7% (5)	27,6% (8)	42,1% (16)	45,9% (9)	0.310
Age (range)	71,8 (50,7-86,2)	69.8 (50,4-89,6)	70.9 (52.2-90.1)	70,9 (51,2-92,7)	0,582
ABI					
Pre-Operative	0.63	0.47	0.47	0.52	0.277
Post-Operative	0,74	0,72	0,74	0,70	0,955
Average change	18,1%	52.5%	55.9%	33.6%	0.116
DM	45,5% (10)	65,5% (19)	86.8% (33)	81,0% (17)	0.004
Hypertension	90,9% (20)	86.2% (25)	81,6% (31)	85,7% (18)	0,801
Dyslipidemia	72,7% (16)	86.2% (25)	78.9% (30)	57,1% (12)	0.114
Active smoking	27,3% (6)	44,8% (13)	15,8% (6)	33,3% (7)	0.073
CKD	27,3% (6)	10,3% (3)	18,4% (7)	4,8% (1)	0.057
CVD	59,1 (13%)	69,0% (20)	71,1% (27)	57,1% (12)	0.694
COPD	22,7% (5)	10,3% (3)	0,0% (0)	19,0% (4)	0.023
CAD	50,0% (11)	31,0% (9)	47.4% (18)	47,6% (10)	0.350

ABI - Ankle-Brachial Index; CAD - Coronary artery disease;
 CKD - Chronic Kidney Disease; COPD - Chronic obstructive pulmonary disease;
 CVD - Cerebrovascular disease; DM - Diabetes mellitus.

found to have a higher impact on limb perfusion (118,5%) compared to the endovascular results (30,4%), with a p-value of 0,017. Initially, the average ABI of the study population was 0,51, reaching a mean 0,72 after revascularization (41,1%).

DISCUSSION

Using previous CLI classifications, all patients included in this study, would be classified as Fontaine grade 3 and 4 or Rutherford 4, 5 and 6, even though their presentation is much more diverse, with different severities of ischemia, different wound complexities and some would present with infection. The more recent Wifl classification aims to integrate all these different variables into an intuitive, daily use tool, and offering increased granularity, allowing to more precisely define the risk of limb loss, mortality and the potential benefit of revascularization. In this study, the Fontaine and Rutherford classifications were not predictive of these clinically relevant outcomes. We could demonstrate

however that Wifl was of prognostic value, and a higher Wifl score was the only predictive variable of increased mortality and AFS.

The SVS Wifl classification system revealed an association of higher Wifl scores with lower amputation free survival, longer wound healing times, increased mortality and high major amputation rates, striking similarities to conclusions previously drawn by Darling et al⁹ and Zhan et al¹⁰.

Although the female gender was less represented (35,7%), a strong association was observed with higher Wifl stage. While women often present fewer risk factors and are healthier when contrasted with their male counterparts¹¹, they tend to develop chronic limb threatening ischemia at a later age. This critical factor is linked to both short- and mid-term mortality¹². Additionally, it's well-documented that women with peripheral arterial disease and intermittent claudication have longer asymptomatic periods. This pattern of presentation often results in substantial delays in diagnosis, thus a worse prognosis^{13,14}.

Diabetes was also found to have a strong association to advanced stages of Wlfl. Even though this comorbidity seems to have a minimal effect on the mortality rate of patients with peripheral arterial disease and intermittent claudication^{15,16}, it has been independently associated with a higher risk of amputation by Cull et al⁶ and higher risk of cardiovascular events by Matsuo et al¹⁷.

The SVS Wlfl classification system has been systematically associated with poorer prognosis, higher risks of frailty and malnutrition^{6,9,10,18,19}. However, further research is needed to validate its applicability in a broader spectrum of clinical settings and heterogeneous populations⁸. By performing a retrospective evaluation and stratifying patients according to the Wlfl classification clinical stages, this study was able to address those two purposes.

However, the SVS Wlfl classification system is meant to provide additional information to healthcare providers in order to assist with clinical decision-making and it should not be used as the sole basis for treatment decisions. Other factors such as the patient's overall health and comorbidities, as well as the specific characteristics of the ulcer and anatomical extent, should also be taken into account.

In our study, major amputation within one year was found to be null in Wlfl stages 1, while it reached 5% in Wlfl stages 4. Although they follow a consistent order of size, these percentages differ considerably from the major amputation rates of the study of Zhan et al¹⁰ (0% in Wlfl stages 1 and 64% in Wlfl stages 4) and the study of Beropoulos et al¹⁸ (0% in Wlfl stages 1 and 12% in Wlfl stages 4). It is worth highlighting that while the mentioned studies either focused in mostly diabetic patients or in a non-diabetic population, respectively, our study encompassed a highly diverse population. In our cohort, authors included both outpatient and hospitalised patients, diabetics and non-diabetic, smokers and non-smokers, as well as patients treated with endovascular approaches and open surgery.

Regarding WHR, our study's findings are consistent with prior research observations. Within one year, 75% of wounds were healed in Wlfl stages 1, in contrast with only 28,6% of wounds healed in Wlfl stages 4. Van Haelst et al²⁰ observed 100% of wound healing in Wlfl stages 1 and 19% in Wlfl stages 4. This alignment proves the SVS Wlfl classification system predicting ability of wound healing outcomes, emphasizing the link between higher Wlfl scores and higher risk of non-healing ulcer.

The mortality prediction within the context of the SVS Wlfl classification system is a subject that elicits different conclusions in the existing literature. While a number of studies failed to establish a strong correlation between higher Wlfl scores and increased mortality^{7,9,21}, similarly to Beropoulos et al.¹⁸ and Hicks et al.²², authors were able to validate the prognostic value of the SVS Wlfl classification system concerning this outcome.

Since this was a retrospective study, it ultimately inherits some of its limitations such as lack of information available and selection bias. Besides functioning as a referral

hospital, authors chose to only include patients submitted to revascularization. By excluding patients under medical treatment or submitted to primary amputation, authors made the sample of subjects less representative of the population. By leaving up to the responsible surgeon decision and his experience the choice of treatment, no conclusion can be drawn from the efficacy of each revascularization strategies, open or endovascular, concerning the different Wlfl stages.

One other limitation presented by this cohort is the use of the ankle-brachial index (ABI) as a way to determine the degree of ischemia for each patient. Given the prevalence of diabetic individuals in this study (71,4%), ideally, authors should have used TBI (Toe Brachial Index) or TcPO₂ (Transcutaneous oxygen Partial Pressure) as a way to assess the severity of peripheral artery disease (PAD).

With a higher prevalence of diabetes mellitus, smoking history, chronic kidney disease, and other cardiovascular diseases, chronic limb threatening ischemia (CLTI) is considered a significant public health problem. On a personal level, it leads to functional impairment and decreased quality of life, but it is also a burden on society and its health related costs^{23, 24}.

Having recognized the high risk of morbidity and mortality associated with CLTI, moving forward, physicians should strive to use standardized ways to evaluate and risk stratify patients. Only then will we be able to assess more homogeneous clinical outcomes and decide upon the best revascularization approach.

CONCLUSION

The presented data successfully demonstrates the prognostic value of the Wlfl classification in a Portuguese population. In this study, higher Wlfl scores are associated with higher mortality and lower amputation free survival. High Wlfl stage was also associated with higher risk of non-healing ulcer risk of non-healing ulcer. This data reinforces the advantages of the use of the SVS Wlfl classification system on a day to day decision making.

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