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Chapter

Chronic Limb-Threatening Ischemia (CLTI) in Diabetic Patients: Looking at the Big Picture beyond Wound, Ischemia and Foot Infection (WIFI) Classification System

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Abstract

During the 1990s, most diabetic ulcers were considered neuropathic, but the Eurodiale study showed that more than 50% of these were non-plantar (neuro-ischaemic and ischaemic). According to the International Guidelines, the neuro-ischaemic and ischaemic diabetic foot ulcer (DFU) outcomes are connected to factors related to the wound, leg-associated factors and patients' comorbidities. We used wound, ischaemia and foot infection (WIFI) classification system; Trans-Atlantic Inter-Society Consensus-II (TASC-II) arterial lesion score; and Kaiser Permanente pyramid (stratification of patients according to their complexity) for assessing these parameters. From February 2011 to June 2012, we collected 124 episodes of neuro-ischaemic and ischaemic active ulcer in 100 patients: 18 required major amputation, 14 of them were in WIFI stage 4 and 4 in WIFI stage 3. Ten patients (over 14 in WIFI stage 4) were classified as TASC-II D. Eight patients (over the same 14) were classified as the higher risk of Kaiser Permanente pyramid. In line with other studies, our data support that the WIFI classification correlates well regarding risk of amputation at 1 year. However, when adding TASC-II and Kaiser Permanente pyramid assessment, the outcome is even more accurate not only for limb salvage but also for patients' survival.

Keywords: critical limb ischaemia, chronic limb-threatening ischaemia, diabetic foot ulcers, diabetic foot ulcer classification systems, outcome predictors

1. Introduction

Nowadays, diabetes is considered as a leading cause of non-traumatic amputation all around the world. Despite the high morbidity and mortality associated with diseases of the foot in diabetes and although it is costly to both healthcare providers and the patient and their families [1], it is a topic that has generally failed to attract

the same level of interest by healthcare professionals as other diabetes complications.

The concept of critical limb ischaemia (CLI) implies that there are objective values that inform about the perfusion below which, if we do not increase the blood supply, the limb will be lost. CLI was defined for the first time in 1982 as rest pain with ankle pressure < 40 mmHg or necrosis and ankle pressure < 60 mmHg [2]. In 2017 the European Society of Cardiology and the European Society for Vascular Surgery (ESC/ESVS) guidelines on the diagnosis and treatment of peripheral arterial disease (PAD) have replaced the term critical limb ischaemia with chronic limb-threatening ischaemia (CLTI). The authors gave three arguments for this change: first, not all patients are in a “critical” situation even if they are not revascularized. Second, due to change in the population affected, mostly diabetics with neuro-ischaemic ulcers, it was recognized that severe ischaemia was not the only underlying cause. And finally, the risk of amputation does not only depend on the extent of ischaemia but also on the presence of wound and infection [3].

According to the World Health Organization (WHO), the diabetic foot may be defined as a group of syndromes in which neuropathy, ischaemia and infection lead to tissue breakdown, resulting in morbidity, possible amputation and mortality [4].

It is admitted that ischaemic and neuro-ischaemic ulcers have similar behaviour to each other compared to the neuropathic ones referred to major amputation and survival [5].

Before the Eurodiale study, published in 2007 [6], it was widely believed that most diabetic ulcers were neuropathic, but this study found that:

- More than 50% (52%) of the foot ulcers were non-plantar (ischaemic and neuro-ischaemic).
- More than 50% (58%) of patients with an ulcer had signs of infection.
- One third of the patients (31%) had signs of both peripheral arterial disease and infection. These patients have a worse prognosis; they take longer to heal and have more amputations and more risk of dying. They have a distinct profile: they are older and have more non-plantar ulcers, greater tissue loss and more serious comorbidities.

The results from the Eurodiale study underlined that not only ulcer healing depends on the wound, the limb and the patient, but also the future of the extremity and patient survival too.

The International Guidelines [7] have published similar results: the neuro-ischaemic and ischaemic diabetic ulcer outcome is connected to:

- Factors related to the wound (the most important is the extent of tissue involvement).
- Limb-related factors (in these cases severity of PAD).
- Patients’ comorbidities (see **Figure 1**).

Apelqvist in 1151 patients with diabetes and CLTI confirmed the three above-mentioned factors. Moreover, revascularization is the major driver for ulcer healing. In fact, both percutaneous transluminal angioplasty (PTA) and open vascular surgery increased the probability for primary healing with an odds ratio (OR) of 1.77 and 2.05, respectively [8].

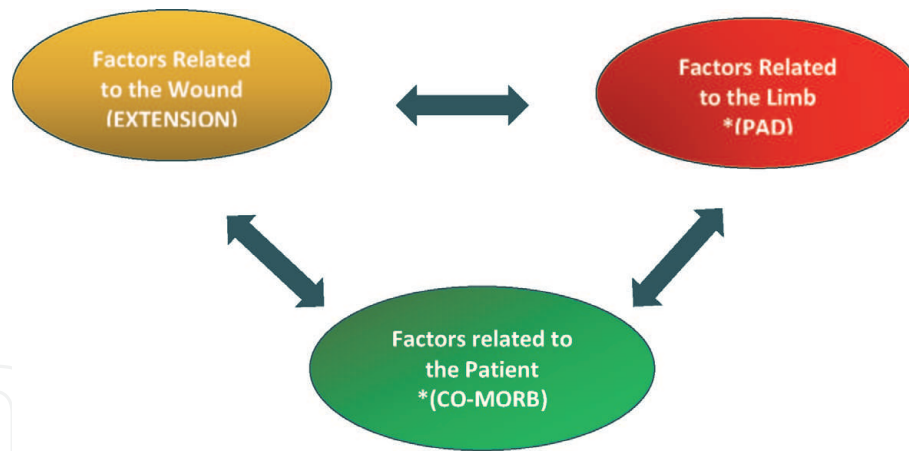


Figure 1. Contributors to the neuro-*ischaemic* and *ischaemic* diabetic foot ulcers (DFUs) outcomes. *PAD, peripheral arterial disease; **CO-MORB, comorbidities.

However, data about natural history of the disease are scarce. Elgzyri in 602 patients with diabetic foot ulcer (DFU) who had been considered as CLTI and were not revascularized reported that [9]:

- 50% healed primarily with wound care or with minor amputation
- 17% healed, but after a major amputation
- 33% died with limbs intact but with unhealed wounds

1.1 Multidisciplinary team approach

Dr. Joslin, the famous American diabetologist, observed that after the introduction of insulin, “the mortality from diabetic coma had fallen dramatically (from 60 to 5%) yet deaths from diabetic gangrene of the foot and leg had risen significantly”. He believed that diabetic gangrene was preventable and his remedy was a team approach involving nurses, surgeons and podiatrists for limb salvage and foot care. He was also the first to advocate for teaching patients to care for their own diabetes and the first who named diabetes as a serious public health issue that was becoming a pandemic [10].

Dr. Edmonds in 1979 in UK recognized the need for coordinated intensive care of patients with diabetic foot with input from several disciplines, including diabetology, medicine, orthopedics and vascular surgery as well as podiatrists, orthotists and nurses. This initiative resulted in an immediate 50% reduction in major amputations (1984). Specific emphasis was placed on podiatric debridement, off-loading, infection control and diabetes care [11].

The diabetic rapid response acute foot team (DRRAFT) guidelines [12], published in 2009, suggest that the vascular surgeon and diabetic podiatrist constitute the minimum in the formation of a diabetic foot team.

The authors defined seven vital skills for such a team to be able to effectively manage the lower-extremity complications of diabetes (see **Table 1**).

The Multidisciplinary Diabetic Foot Unit (MDFU) was introduced at our institution in February 2011. The team was working in three levels of care: primary prevention, acute patients’ treatment and outpatient postoperative management. Day-to-day care was carried out by a podiatrist and a vascular surgeon, the basic American “toe and flow” approach [13]. An algorithm for urgent referral was introduced in our Unit regarding the ulcer, the leg and the patient (see **Figure 2**).

Haemodynamic and anatomic vascular assessment with revascularization, as necessary
Biomechanical and podiatric assessment with surgical and non-surgical intervention as necessary
Peripheral neurological examinations
Wound assessment and staging/grading of infection and ischaemia
Site-specific bedside and intraoperative incisions and debridement, taking samples for culture using an appropriate technique
Initiate and modify culture-specific and patient-appropriate antibiotic therapy
Conduct appropriate postoperative monitoring to reduce risks of re-ulceration

Table 1.
Minimum skills for constituting a diabetic foot team from DRRAFT [12].

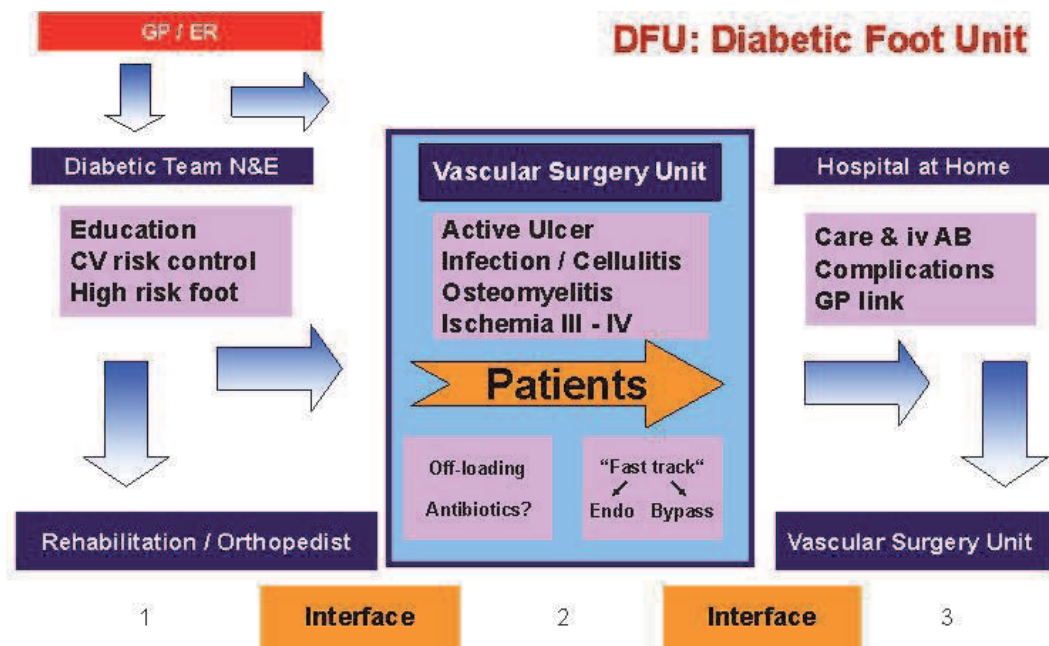


Figure 2.
Multidisciplinary diabetic foot unit organization (toe and flow inspired). GP, general practitioner; ER, emergency room; N&E, nurses and endocrinologist; CV, cardio vascular; iv AB, intravenous antibiotics.

1.2 Understanding diabetic foot ulcer classifications

Classifications that we use in daily clinical practice are compartmentalized: some refer only to infection, and others only to ischaemia or only treat descriptive aspect of ulcers [14] (see **Table 2**).

Monteiro-Soares in a meta-analysis published in 2014 identified 25 different classification systems for diabetic foot ulcers. Of those, eight used a descriptive basis, and seven utilized prognostic stratification classification systems, but few studies evaluated their reliability or external validity [15].

The International Working Group on Diabetic Foot (IWGDF) has published in 2019 his updated guidelines on the prevention and management of diabetic foot disease with a new and special chapter focus on the classification of active diabetic foot ulcers. The authors identified eight key factors judged to contribute to the scoring of classifications: some are patient-related (e.g., end-stage renal failure

Classification system	Main points	Pros/cons
Meggitt-Wagner	Assesses ulcer depth plus the presence of gangrene and loss of perfusion using six grades (0–5)	Well established Conversely, infection and ischaemia are not fully addressed
Texas University	Assesses ulcer depth, infection and ischaemia using a matrix of four grades combined with four stages	Well established Describes infection and ischaemia better than Meggitt-Wagner but informs only about yes or no (is not categorized). May help in predicting the outcome of DFUs
PEDIS Perfusion, extent (size), depth (tissue loss), infection and sensation (neuropathy)	Developed by IWGDF Uses four grades (1–4)	User-friendly (clear definitions, few categories) for practitioners with a lower level of experience with diabetic foot management
SINBAD Site, ischaemia, neuropathy, bacterial infection, area and depth	It grades area, depth, infection arteriopathy and neuropathy and site. Uses a scoring system to help predict outcomes and enable comparisons between different settings and countries	Simplified version of the S (AD) SAD classification system. Includes ulcer site as data suggests this might be an important determinant of outcome

Table 2.
Pros and cons of some common wound classification systems for DFUs [14].

Clinical scenario	Classification recommended
Communication among health professionals	*SINBAD
Predicting the outcome of an individual ulcer	None
Assessment of infection	**IDSA/IWGDF [#]
Assessment of perfusion and the likely benefit of revascularization	WIFI ^{##}
Audit of outcome in local, regional or national populations	SINBAD

*SINBAD, site, ischaemia, neuropathy, bacterial infection, area and depth.

**IDSA, Infectious Diseases Society of America.

[#]IWGDF, International Working Group on Diabetic Foot.

^{##}WIFI, Wound, Ischaemia and foot Infection.

Table 3.
IWGDF classification system recommendations [16].

(ESRF)); others, limb-related (e.g., PAD and loss of protective sensation) and lastly ulcer-related (area, depth, site, single or multiple and infection). They identified five clinical key situations too and recommended one specific classification for each one: communication among health professionals; predicting the outcome of an individual ulcer; aid to clinical decision-making for an individual case; assessment of a wound, with or without infection, and peripheral artery disease; and audit of outcome in local, regional or national populations [16–18] (see **Tables 3–5**).

In order for a stratification system of a disease to be relevant, it is expected that it will give us a risk scale with respect to natural history and that the classification is detailed enough to compare different treatments. Thus, the scale could be descriptive and predictive at the same time. In January 2014 the Society for Vascular Surgery (SVS) published the new classification system for CLTI based on wound extent, degree of ischaemia and foot infection (WIFI), with scales from 0 to 3, for each one of these parameters [19].

Category	Definition	Score
Site	Forefoot	0
	Midfoot and hindfoot	1
Ischemia	Pedal blood flow intact (at least one palpable pulse)	0
	Clinical evidence of reduced pedal flow	1
Neuropathy	Protective sensation intact	0
	Protective sensation lost	1
Bacterial infection	None	0
	Present	1
Area	Ulcer <1 cm ²	0
	Ulcer >1 cm ²	1
Depth	Ulcer confined to the skin and subcutaneous tissue	0
	Ulcer reaching the muscle, tendon or deeper	1
Total possible score		6

Table 4.
SINBAD classification system [17].

Clinical manifestations	Infection severity	PEDIS grade
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of >2 manifestations of inflammation (purulence, erythema, tenderness, warmth or induration), but any cellulitis/erythema extends <2 cm around the ulcer, and the infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but which has >1 of the following characteristics: cellulitis extending >2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep tissue abscess, gangrene and involvement of muscle, tendon, joint or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (e.g. fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia or azotemia)	Severe	4

Table 5.
IDSA/IWGDF system [18].

WIFI classification represents a summary of multiple previously published classifications focused on diabetic foot ulcers and pure ischaemia or infection models and is the first one which reports on the risk of amputation and benefit of revascularization at 1 year.

With respect to the wound, WIFI integrates the Texas University classification that is validated and adds the gangrene component. The authors include pain at rest and gangrene of ischaemic cause. Depth takes preference over extension, and there is a measure of what is going to lose (see **Table 6**).

WIFI ischaemia is stratified not only according to ankle-brachial index (ABI) figures but also ankle pressure and digital pressure. They are categorized up to moderate degrees of ischaemia. Alternatives to the ABI are included, and digital pressure is considered mandatory in diabetic patients (see **Table 7**).

WIFI collects the characteristics of the Infectious Diseases Society of America (IDSA) (validated) and the IWGDF (see **Table 8**).

Based on the results obtained in each parameter, a Delphi survey among 12 experts was conducted. A table for estimating the risk of major amputation over the first year and the theoretical benefit of revascularization was elaborated.

Wound grade	Diabetic foot ulcer (DFU)	Gangrene
0	No ulcer Clinical description: minor tissue loss (1 or 2 digits)	No gangrene Salvageable with simple digital amputation or skin coverage
1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to the distal phalanx Clinical description: minor tissue loss (1 or 2 digits)	No gangrene Salvageable with simple digital amputation or skin coverage
2	Deeper ulcer with exposed bone, joint or tendon; generally, not involving the heel; shallow heel ulcer, without calcaneal involvement Clinical description: major tissue loss	Gangrenous changes limited to digits Salvageable with multiple (>3) digital amputation or standard trans-metatarsal amputation (TMA) ± skin coverage
3	Extensive, deep ulcer involving the forefoot and/or midfoot; deep full-thickness heel ulcer ± calcaneal involvement Clinical description: extensive tissue loss	Extensive gangrene involving the forefoot and/or midfoot; full-thickness heel necrosis and calcaneal involvement Salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc) flap coverage or complex wound management needed for large soft tissue defect

Table 6.
 Wound from WIfI system [19].

Ischemia grade	Ankle-brachial index	Ankle systolic pressure (mmHg)	Toe pressure, trans-cutaneous oxygen pressure (mmHg)
0	>0.80	>100	>60
1	0.6–0.79	70–100	40–59
2	0.4–0.59	50–70	30–39
3	<0.39	<50	<30

Table 7.
 Ischemia from WIfI system [19].

Foot infection grade	Clinical manifestations
0	No symptoms or signs of infection Infection present, as defined by the presence of at least 2 of the following items: local swelling or induration; erythema >0.5 to <2 cm around the ulcer; local tenderness or pain; local warmth; purulent discharge: thick, opaque to white or sanguineous secretion
1	Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (e.g. trauma, gout, acute Charcot, neuro-osteoarthropathy, fracture, thrombosis, venous stasis)
2	Local infection (as described above) with erythema >2 cm, or involving structures deeper than the skin and subcutaneous tissues (e.g. abscess, osteomyelitis, septic arthritis, fasciitis), and no systemic inflammatory response signs (as described below)
3	Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: temperature > 38°C or < 36°C; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or PaCO ₂ < 32 mmHg; white blood cell count >12,000 or < 4000 cu/mm or 10% immature (band) forms

Table 8.
 Foot infection from WIfI system [19].

a, Estimate risk of amputation at 1 year for each combination

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	L	M	H	VL	L	M	H	VL	L	M	H	VL	L	M	H
W-1	VL	L	M	H	VL	L	M	H	VL	L	M	H	VL	L	M	H
W-2	VL	L	M	H	VL	L	M	H	VL	L	M	H	VL	L	M	H
W-3	VL	L	M	H	VL	L	M	H	VL	L	M	H	VL	L	M	H
	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3

b, Estimate likelihood of benefit of/requirement for revascularization (assuming infection can be controlled first)

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	L	M	H	VL	L	M	H	VL	L	M	H	VL	L	M	H
W-1	VL	L	M	H	VL	L	M	H	VL	L	M	H	VL	L	M	H
W-2	VL	L	M	H	VL	L	M	H	VL	L	M	H	VL	L	M	H
W-3	VL	L	M	H	VL	L	M	H	VL	L	M	H	VL	L	M	H
	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3

fl, foot Infection; I, Ischemia; W, Wound.

Premises:

1. Increase in wound class increases risk of amputation (based on PEDIS, UT, and other wound classification systems)
2. PAD and infection are synergistic (Eurodiale); infected wound + PAD increases likelihood revascularization will be needed to heal wound
3. Infection 3 category (systemic/metabolic instability): moderate to high-risk of amputation regardless of other factors (validated IDSA guidelines)

Very low = VL = clinical stage 1
 Low = L = clinical stage 2
 Moderate = M = clinical stage 3
 High = H = clinical stage 4
 Clinical stage 5 would signify an unsalvageable foot

Table 9. Wifl prediction tables. Adapted from the original [19].

When calculating the benefit of revascularization, they assume that the infection is controlled. Intraclass correlation coefficient for the amputation in the first year was 0.81/0.98 and for the benefit of revascularization 0.76/0.97 (see Table 9).

2. Looking at the big picture

In a recent meta-analysis published in 2019 regarding the prognostic value of the Wifl classification in patients with CLTI and where 12 studies comprising 2669 patients were evaluated, the authors conclude that “the likelihood of an amputation after 1 year in patients with CLTI increases with higher Wifl stages”. But, “the current evidence is not sufficient for the instrument to be helpful in clinical decision making for patients with CLTI and prospective studies are needed to determine its role in clinical practice” [20]. We are aware that the risk of amputation increases as the Wifl clinical stage progresses from stage 1 to stage 4. However, data regarding those with PAD and their anatomical conditions and patients’ comorbidities are lacking in Wifl classification system. By better defining and understanding CLTI spectrum, we need to include arterial lesion classification and patients’ comorbidities.

Existing systems of classification of critical ischaemia (e.g., classical Fontaine and Rutherford) do not adequately explain the extent of tissue loss or the presence and severity of infection. In recent years, most classifications have focused on anatomical details extracted from arteriography without paying attention to the physiological state of the limb, for example, the Bollinger, Graziani and Trans-Atlantic Inter-Society Consensus (TASC-I and TASC-II) classifications. Although there are criticisms, the TASC-I and TASC-II classifications are the only ones that carry recommendations for treatment [21] (see **Figure 3**). And we should also use a classification that describes the state of the arteries in the foot [22].

If we assume that in ulcer healing, factors are related not only to the wound itself but also to the limb and the patients are involved, we need an objective scale that indicates the type of patient we are treating. For this purpose, among other scales (e.g. Prevent III and Finnvasc), we have included the categorization of the chronic pluripathological patient adopted by Osakidetza-Servicio Vasco de Salud (Osakidetza-SVS, Basque Country National Health Service) in 2011 based on the good practice model of Kaiser Permanente. Chronic patients are stratified into three levels of intervention depending on the complexity of the case. At the baseline of the Kaiser Permanente pyramid, the healthy members of the population are located for whom prevention, health promotion and risk factor control interventions are a priority. In the first level, where the majority of chronic patients we find concentrated, the interest is focused on promoting self-care. In the second level are chronic patients with the prominence of a particular disease or organ and who can benefit from the “disease management”, and, finally, in the highest level of the pyramid are those patients with very complex cases that need integral management. Although they are not the most numerous, these are the ones that consume the most resources [23] (see **Figure 4**).

Other scales used in vascular surgery units are Prevent III and Finnvasc. Prevent III was designed to calculate the amputation-free time after revascularization surgery and consists of a scoring system on various pathologies: dialysis 4 points, tissue loss 3 points, age ≥ 75 years 2 points, hematocrit $\leq 30\%$ 2 points and coronary disease 1 point. A low risk ≤ 3 , medium risk 4–7 or severe risk ≥ 8 points is attributed according to the score obtained [24]. Finnvasc score seems to behave better also when predicting the immediate postoperative outcome [25]. The accuracy of these scales is acceptable. They are easy to use and very valuable in clinical practice, especially to help us decide when not to revascularize.

2.1 Population in our study

Based on this background, as part of a doctoral thesis [26], we collected retrospectively our data. The aim of the study was to evaluate the implementation of the WIfI classification mainly on the risk of major amputation and benefit of revascularization at 1 year in a population diagnosed with CLTI and neuro-ischaemic or pure ischaemic wounds and diabetes. Adding up the TASC-II classification to have more information on the arterial status of the limb and the result of applying the Kaiser Permanente pyramid to better profile the type of patient affected.

It is a retrospective and observational study based on episodes of active ulcer in patients with diabetes collected in a prospective database open from the beginning of the care activity related to the creation of the Multidisciplinary Diabetic Foot Unit at Cruces University Hospital.

From February 2011 to June 2012, we treated 122 consecutive patients (151 episodes) with diabetic foot ulcer. The median age was 70 years (SD 11.35). Men are 73.8%. The median HbA1c was 62.8 mmol/mol (7.9%). Hypertension was present in 82% of our population, coronary artery disease in 53%, chronic kidney disease in 38%

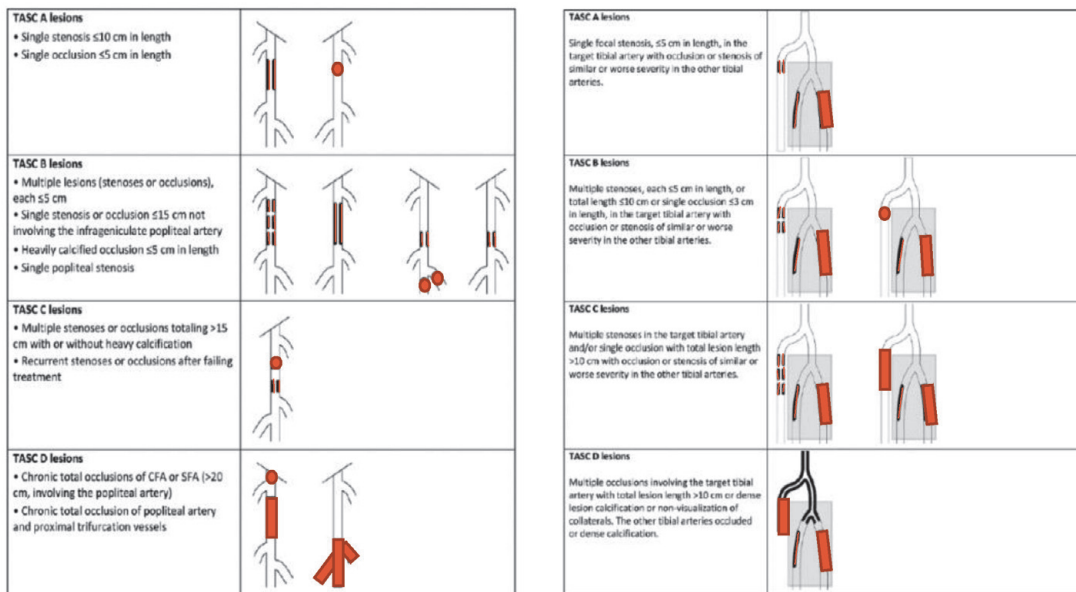


Figure 3. Modified from TASC-II classification system including below the knee (BTK) lesions [21].

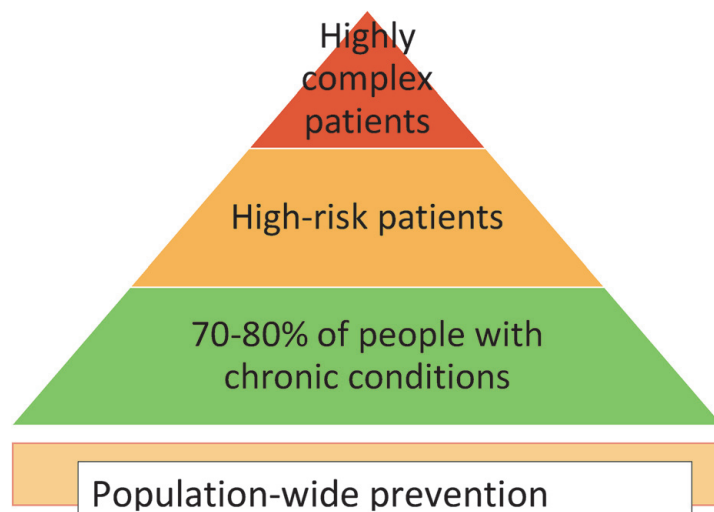


Figure 4. Adapted from the Kaiser Permanente pyramid model [23].

and 6.0% on dialysis. We retrospectively collected data on 124 (82.11%) ischaemic and neuro-ischaemic ulcers; 27 pure neuropathic (17.89%) were excluded from the study. Therefore 115 ulcers in 93 patients were the final population (see **Figure 5**).

To verify the influence of the different factors on the time to amputation, the survival of the patients or until healing, we make use of Kaplan–Meier tables. A univariate and multivariate Cox regression has also been carried out using a non-automatic stepping method. A level of statistical significance $p < 0.05$ has been considered for all tests. The statistical analysis was carried out with the SPSS program vs. 22.0.

2.2 Our results

In our study 72.6% of patients were revascularized. We follow the “endovascular-first” policy, but whether the intervention was endovascular or open is not specified. We had 18 (14.5%) major amputations at one year. Fourteen of them (78%) were in Wifl stage 4 and 4 (22%) in Wifl stage 3 (see **Table 10**). The positive likelihood ratio (LR) was 1.40 (95% CI = 1.04–1.89); and the negative LR

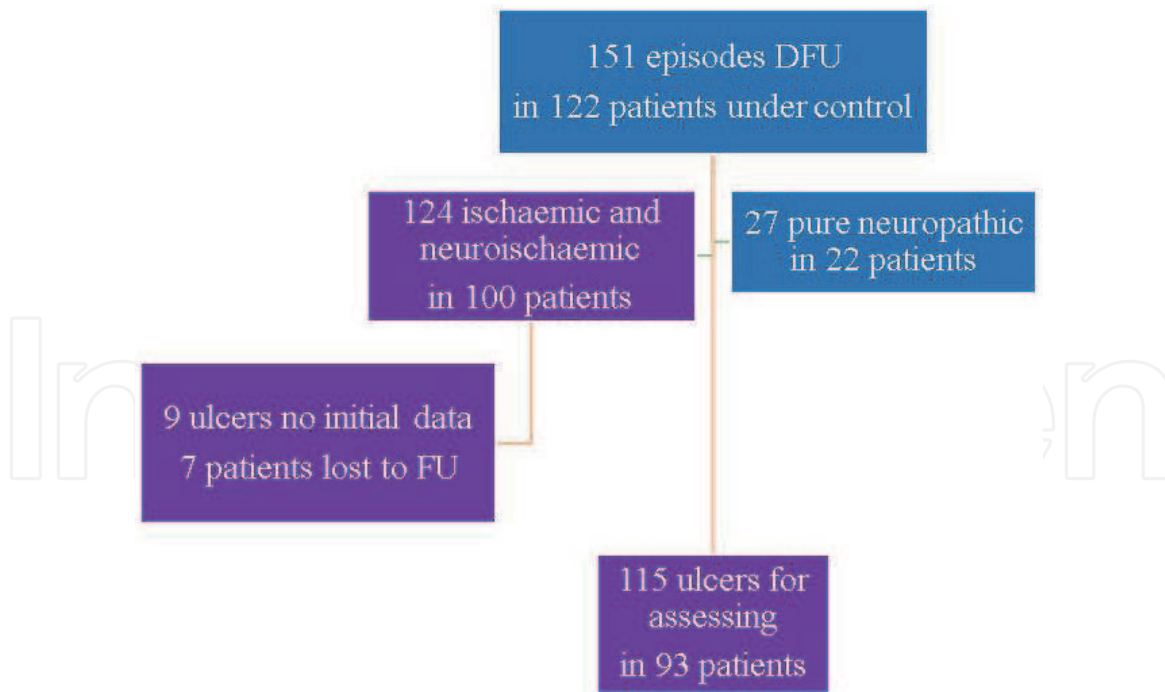


Figure 5.
 Population under study [26].

was 0.5 (95% CI = 0.20–1.23). In the negative LR, if a patient was in stage 1, 2 or 3, he/she had double probability for limb salvage than in stage 4.

Regarding the benefit of revascularization, we compared patients classified as high benefit versus those of moderate and low benefit. Those of very low benefit were excluded because the intervention would not really be indicated. The positive LR was 2.08 (95% CI = 1.39–3.13) and negative LR 0.00. Thus, the probability that a patient with a high benefit of being revascularized according to the WIfI scale, if this intervention is performed, saves the limb is 73.1%.

In our study the analysis of the area under the receiver operating characteristic (ROC) curve (AUC) regarding the predictive ability related to amputation risk at 1 year was 0.61 (95% CI = 0.47–0.74) (see **Figure 6**).

2.2.1 Survival function for major amputation

In our population the median time for suffering a major amputation was 4.01 years (95% CI = 3.69–4.31). Patients who had not undergone prior amputation

WifI amputation risk at 1 year	No	Yes	Total
Very low, Number	5	0	5
%	100.0	0.0	100.0
Low, Number	12	0	12
%	100.0	0.0	100.0
Moderate, Number	30	4	34
%	88.2	11.8	100.0
High, Number	59	14	73
%	80.8	19.2	100.0
Total Number	106	18	124
%	85.5	14.5	100.0

Table 10.
 Number of major amputations at 1 year according to WIfI [26].

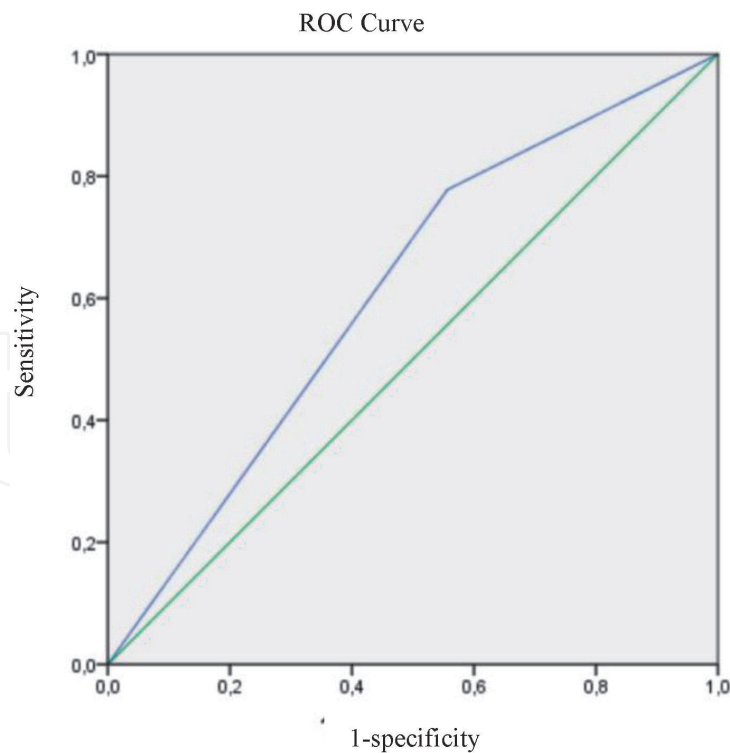


Figure 6.
Area under the ROC curve [26].

and those who had only a minor one take a median of 4.08 years (95% CI = 3.77–4.40) and (95% CI = 3.47–4.69), respectively. Patients who had suffered a previous major amputation were amputated in a median of 1.76 years (95% CI = 0.76–2.77); the difference was statistically significant $p < 0.001$ (see **Figure 7**).

Patients in TASC A, B and C take a median of 4.14 years (95% CI = 3.921–4.367) to suffer a major amputation, whereas patients classified as TASC D took a median of 3.75 years (95% CI = 3.306–4.200). The difference was statistically significant $p = 0.009$ (see **Figure 8**).

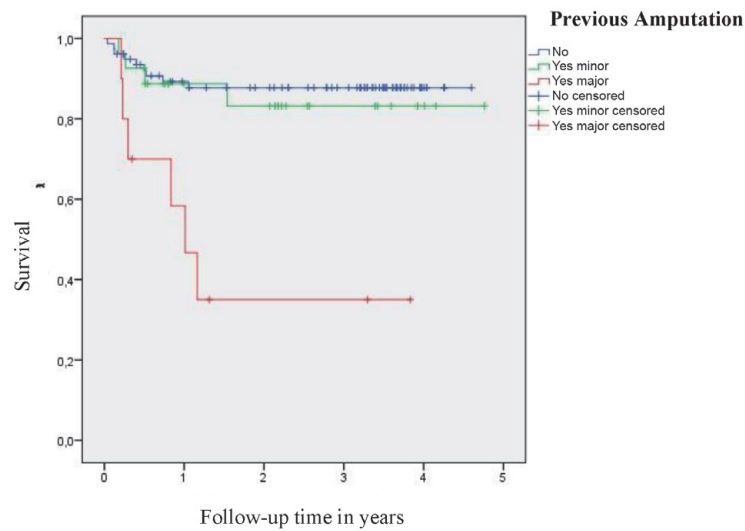
We found statistical differences regarding the amputation rate only when Wifl stages 1, 2 and 3 were compared with stage 4. Patients classified according to the Wifl scale as very low, low and moderate risk of being amputated during the first year underwent such amputation in a median of 3.92 years (95% CI = 3.60–4.23). And those classified as high risk presented it in a median of 3.73 years (95% CI = 3.27–4.18), $p = 0.044$ (see **Figure 9**).

Patients with small lesions take a median of 3.90 years to be amputated (95% CI = 3.58–4.23); those with a major lesion took 4.01 years (95% CI = 3.58–4.43) compared to those who had extensive wound that took 1.35 years (95% CI = 0.21–2.48); the difference was statistically significant $p < 0.001$ (see **Figure 10**).

Cox regression multivariate analysis identified previous major amputation, TASC D arterial lesions and extensive ulcer from Wifl (but no global Wifl) as independent risk factors for major amputation (see **Table 11**).

2.2.2 Survival function for survival

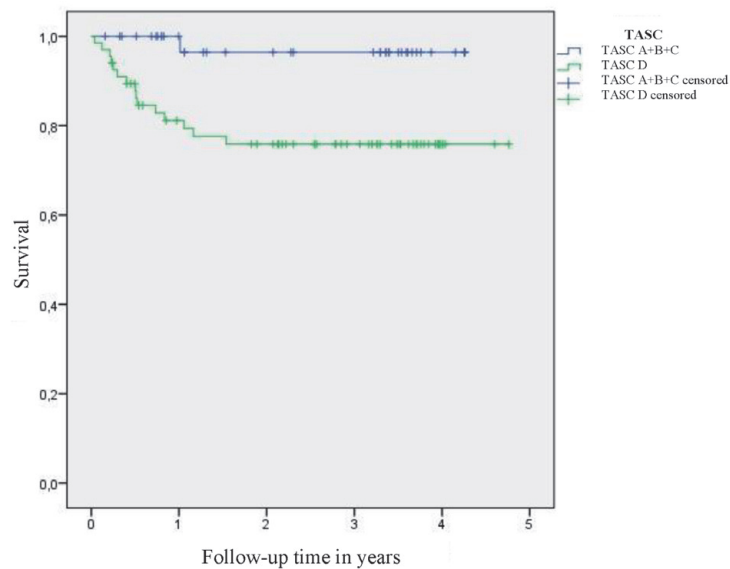
We must not forget that we are facing elderly and pluripathological patients. The median survival was 3.42 years (95% CI = 3.08–3.76). Patient's survival was 84% at 1 year, 66% at 3 years and 50% at 5 years. Five years after the diagnosis of CLTI, only half of the population survived regardless of whether the limb was saved or amputated (see **Figure 11**).



Previous Amputation	Total Number	Events Number	Censored	
			Number	Percentage
No	78	9	69	88.5%
Yes, minor	27	4	23	85.2%
Yes, major	10	6	4	40.0%
Global	115	*19	96	83.5%

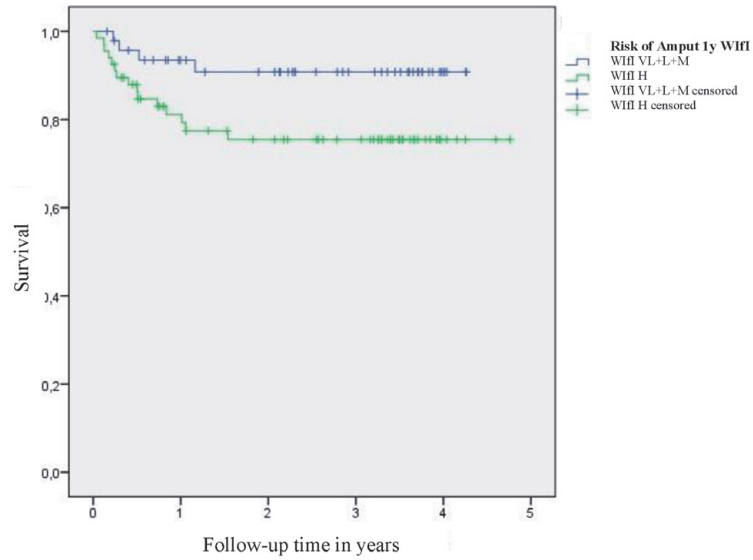
*19 Events: One amputation was excluded because it happened after the first year

Figure 7.
 Survival function for major amputation according to previous one [26].



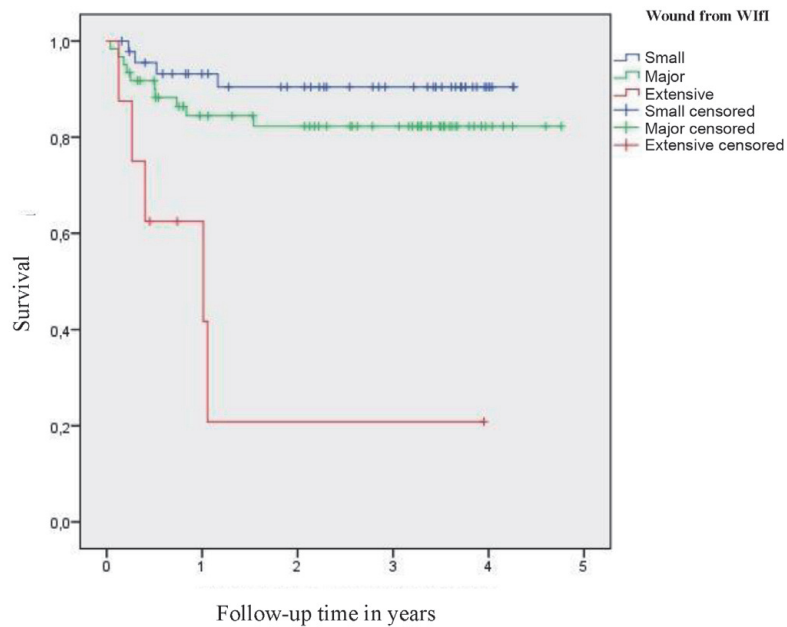
TASC Recoded	Total Number	Events Number	Censored	
			Number	Percentage
TASC A+B+C	39	1	38	97.4%
TASC D	67	15	52	77.6%
Global	106	16	90	84.9%

Figure 8.
 Survival function for TASC-II major amputation risk at 1 year comparing a, B and C versus D.



WIfI Recoded	Total Number	Events Number	Censored	
			Number	Percentage
WIfI 1,2,3	48	4	44	91.7%
WIfI 4	67	15	52	77.6%
Global	115	*19	96	83.5%

Figure 9. Survival function for WIfI major amputation risk at 1 year stages 1, 2 and 3 compared with stage 4 [26].



Wound	Total Number	Events Number	Censored	
			Number	Percentage
Small Lesion	46	4	42	91.3%
Major Lesion	61	10	51	83.6%
Extensive Lesion	8	5	3	37.5%
Global	115	19	96	83.5%

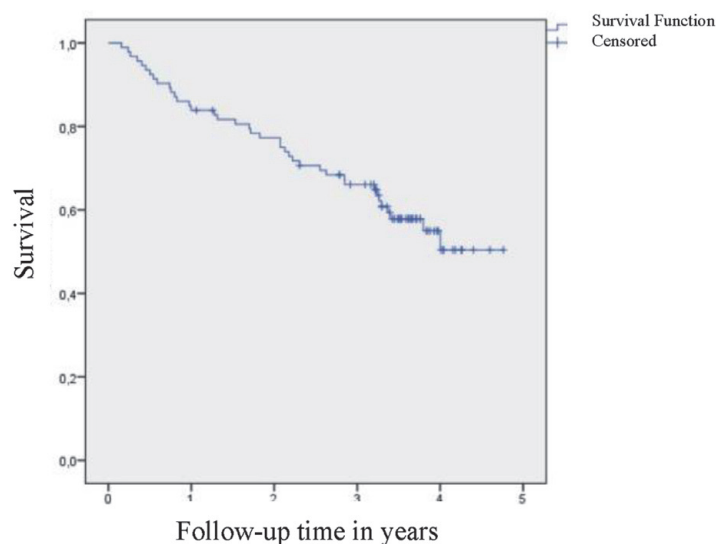
Figure 10. Survival function for major amputation according to wound from WIfI.

	p-value	HR	HR 95% CI	
			Inferior	Superior
No previous amputation (reference)	<0.001			
Yes, minor	0.987	0.987	0.197	4.934
Yes, major	<0.001	20.720	6.013	71.406
TASC D (recoded)	0.003	27.952	3.000	260.452
Wifl extensive lesion (reference)	0.016			
Small lesion	0.194	2.248	0.662	7.632
Major lesion	0.004	11.868	2.184	64.490

Table 11.
 Cox regression multivariate analysis for major amputation.

In our study, 51% of patients were in the Kaiser Permanente pyramid highest risk zone. Patients who did not reach the top of the pyramid survive a median of 4.25 years (95% CI = 3.88–4.62), and those who accumulate more pathology survive a median of 3.30 years (95% CI = 2.90–3.70), $p < 0.001$ (see **Figure 12**).

The Cox regression multivariate analysis has shown that only the stratification of the pluripathological patient according to the Kaiser Permanente model is an independent risk factor for death. The most pluripathological patients are classified at the top of the pyramid (red color) and have a risk of dying 8.27 times higher (95% CI = 2.48–27.59).



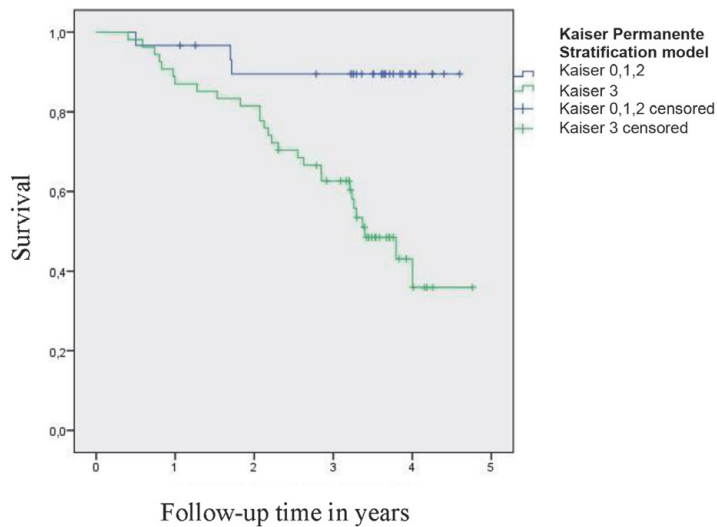
Survival Function	Total Number	Events Number	Censored	
			Number	Percentage
	93	39	54	58.1%

Figure 11.
 Patient's survival function [26].

2.2.3 Survival function for wound healing time (WHT)

The median time for ulcer healing, in our study, was 7.65 months (95% CI = 5.723–9.587) which is equal to 230 days.

Previous history of amputation influences wound healing time. Thus, in patients with no past history of amputation, the median WHT was 13.4 months (95% CI = 9.65–17.20); in those with a minor amputation, 15.7 months (95% CI = 10.34–21.20); and in patients with a major one, 34.5 months (95% CI = 23.50–45.55), $p = 0.006$.



Kaiser Permanent Pyramid	Total N	Events N	Censored	
			N	Percentage
Kaiser 0,1,2	30	3	27	90.0%
Kaiser 3	54	28	26	48.1%
Global	84	31	53	63.1%

Figure 12. Survival function comparing low and median levels with high level at Kaiser Permanente pyramid [26].

As the arterial lesions become more complex according to TASC-II and more extensive according to Wifl, wound healing time is longer, $p = 0.005$ and $p < 0.001$, respectively. There is more information about WHT in a previous paper published by our group in 2017 [27].

Patients who followed podiatric treatment take a median of 7.5 months in healing (95% CI = 6.14–9.03) and those who did not take a median of 12 months (95% CI = 2.18–22.00), $p = 0.012$. Unfortunately, this factor was only significant at Cox regression univariate analysis.

Cox regression multivariate analysis identified previous amputation, TASC-II classification and wound from Wifl (but no global Wifl) as independent risk factors for wound healing (see **Table 12**).

	p-value	HR	HR 95% CI	
			Inferior	Superior
TASC D (reference)	<0.001			
TASC A	0.001	6.672	2.206	20.181
TASC B	<0.001	5.517	2.208	13.783
TASC C	0.028	1.828	1.068	3.126
Extensive lesion (reference)	0.040			
Small	0.025	9.959	1.336	74.252
Major	0.057	6.985	0.946	51.580
Previous major amputation (reference)	0.008			
No amputation	0.010	13.696	1.868	100.391
Minor amputation	0.044	8.099	1.060	61.874

Table 12. Cox regression multivariate analysis for wound healing time [26].

2.3 Discussion

Reviewing the van Reijen meta-analysis which compares the best methodological 12 scientific papers published until June 2018 focused on the prognostic value of the Wifl classification in patients with CLTI, only one study included exclusively patients with diabetes, whereas others excluded them.

Regarding treatment, six studies included revascularized patients in different ways, and the other six also included patients with conservative treatment.

The prognostic value of the Wifl classification was studied retrospectively (as in our study) in all but one which implies a certain risk of information bias. Five studies performed a multivariate analysis for the Wifl classification on major amputation, but in four of them, clinical stage or reference was not reported.

The authors recognize that the likelihood of a major amputation after 1 year in patients with CLTI increases with higher clinical Wifl stages, especially in stage 4 in spite of diverging range of patients included (hospitalized/outpatients; requiring hemodialysis or not; invasively or conservative treatment; diabetics/non-diabetics; etc.). This could, partly, explain the statistical heterogeneity that they found. Although the concept of the Wifl classification is well designed, it only considers the status of the affected limb with neither additional information related to vascular anatomy involved nor patients' comorbidities [20] (see **Tables 13** and **14**).

2.4 Conclusions

In conclusion, in our study, we identified a previous amputation, TASC-II classification and wound from Wifl (but no global Wifl) as independent risk factors for major amputation and wound healing time. And, among other comorbidities, only

	% Major amputation >1 year	% AFS >1 year	% Limb salvage >1 year
Wifl I	0	83	95
Wifl II	8	76	92
Wifl III	11	75	91
Wifl IV	38	55	61

Table 13.
 Results of van Reijen meta-analysis [20].

	Cull	Zhan	Causey	Beropoulos	Darling	Ward	Vela
Age (years)	70 +/- 11	58 +/- 16	66	77 +/- 15	71 +/- 12	62.8	70 +/- 11
Males %	62	79	62	61	53	—	74
HbA1c %	—	—	—	—	—	—	7.9
DM %	66	93	76	0	77	72	100
Prevent III at high risk	—	—	17%	5.2 +/- 2.4	—	—	—
Kaiser high risk level %	—	—	—	—	—	—	51
Hypertension %	93	86	85	—	84	84	82
CAD %	63	55	47	54	49	—	53
CKD %	—	41	—	37.5	23	—	38
Dialysis %	14	20	23	15.5	18	—	6

Table 14.
 Population comparison from some studies included on van Reijen meta-analysis and our study.

the stratification of the pluripathological patient according to the Kaiser Permanente model was recognized as an independent risk factor for death.

Of course, our study has certain limitations: it is retrospective but is based on test and images included in our electronic database. The population is small, and we need to recode some items in order to increase statistical significance. Moreover, our patients are in-hospital, with CLTI and diabetes. But our goal was “the better definition of the population, the better accuracy of the results”. Infection was not significant because it was controlled on antibiotics.

In line with other publications, our data support that the Wifl classification system correlates well with clinical outcomes regarding risk of amputation at one year and WHT. However, when adding TASC-II and, in our case, Kaiser Permanente pyramid assessment, the outcome is even more accurate not only for limb salvage but also for patients' survival.

Considering all this information, not only more prospective studies if not a new three-dimensional score capable to predicting the outcome of an individual ulcer paying attention to the better characterization of the population involved should be implemented.

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Conflict of interest

The authors declare no conflict of interest.

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