Title: Outcome of diabetic foot ulcer management in a French multidisciplinary foot center: one year healing, amputation and mortality rate

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ABSTRACT

Objective

To describe the rates of healing, major amputation and mortality after 12 months in patients with a new diabetic foot ulcer (DFU) and their care in a French Diabetic Foot Service (DFS).

Research design and methods

A prospective single center study including patients from March 2009 to December 2010. The length of time of healing, minor amputation, major amputation and mortality rate after inclusion were analyzed using the Kaplan Meier method.

Results

347 patients were included (3% loss to follow up), with a median follow up (Q1;Q3) of 19 months [12 ; 24] ; the mean age was 65 ± 12 years, 68% of men, and the median duration of the ulcer was 49 [19; 120] days. Complications of the DFU were ischemia (70%), infection (55%), osteomyelitis (47%). Fifty percent of hospitalization in the DFS (median duration of 26 (15; 41) days). The rate of healing at 1 year was 67% (95% CI 61; 72), major amputation 10% (95% CI 7;17), minor amputation 19% (95% CI 14; 25), and death rate 9% (95% CI 7; 13). Using an adjusted Hazard Ratio the predictive factors of healing were perfusion and the

area of the wound. The risk factors for a major amputation were active smoking and osteomyelitis. The risk factors for mortality were perfusion and age

Conclusion

This study confirms the need to treat these DFU rapidly, in a multidisciplinary DFS.

INTRODUCTION

Diabetic foot ulcers (DFU) are characterized by slow healing and a high risk of amputation in patients with many co-morbidities and high mortality rates (1,2,3). International guidelines recommend a rapid access to expertise in a multidisciplinary diabetic foot service (DFS) in order to decrease the risk of major amputation (4,5,6,7,8). Treatment in this type of care structure might be essential in the control of infection, metabolic disorder, and peripheral vascular disease, in addition to optimizing offloading and wound care (4,9). In France the amputation rate in patients with diabetes is still high, and a recent epidemiological study has shown considerable differences between regions (10).

However, to date, no data has been available on the outcome of the management of DFU in a French DFS, to allow comparison between French care units and European centers. However, a major 14-center European study (11) has already reported some data in this respect, although no French center participated in it.

The aim of the present study was to report on the population attending a French DFS and to evaluate the rates of healing, of major amputations and of mortality one year after admission.

Research design and methods

The DFS at a University Hospital is organized with an outpatient unit which can attend to patients within 48 hours if necessary, as well as a 13 bed inpatient unit dedicated to DFU. The multidisciplinary team is composed of diabetologists, vascular

and orthopedic surgeons, rehabilitation specialists, radiologists, infectious disease specialists, chiropodists, shoe makers and nurses highly specialized in DFU.

Population studied

Between March 2009 and December 2010 all patients who attended the DFS as in or out-patients with a DFU seen for the first time in the DFS were prospectively included in the study, and were followed every 6 weeks until healing or major amputation, for at least 12 months. Data were prospectively (at each visit) collected and recorded in a dedicated clinical research file by the investigators. At the end of the study, all data from the clinical research files were input on informatics tables to be analyzed. If data on mortality was missing after one year from admission, patients or their relatives or their family physician were contacted by phone. When necessary, clinical files or registry office files of the patient's city of birth, were consulted. If there was no mention of death on their birth certificate, the patient was considered as still alive. If the patient was not born in France, and the information could not be obtained, the patient was considered lost to follow-up. The study was in accordance with the French Ethics guidelines, and patients gave their oral consent.

A DFU was defined as a full-thickness new lesion on or below the ankle. All patients with acute Charcot foot without ulcer, and skin disease were excluded. In cases where several ulcers were presented, the most extended was included. The PEDIS classification was used for graduation of the wound (12), as follows: P1 = absence of peripheral arterial disease (PAD), P2 = PAD without critical ischemia, P3 = critical ischemia; ulcer extension E1 <1cm², E2: 1-5 cm², E3: >5cm² ; ulcer Depth: D1= superficial, D2= muscle or tendon exposed , D3 = bone exposed.

- Infections were clinically evaluated into 4 grades (I1 to I4) according to the criteria of IWGDF (13).

- Sensitivity was measured with a monofilament of 10g under the Hallux and under the first and the fifth metatarsal heads: S1 corresponded to no anomaly, S2 to loss of sensitivity. We added S3 to correspond to chronic Charcot foot.

The treatment was based on the IWGDF recommendations (4). A half-shoe was prescribed for the offload of fore-foot DFUs, or an open-backed shoe for heel DFUs. A windowed irremovable fiberglass boot (14) was supplied for plantar ulcers of the mid-foot on a Charcot foot or other neuropathic plantar ulcers for patients with poor

offloading adhesion after 3 months of follow up. Sick leave was systematically prescribed for patients who worked.

Reasons for hospitalization were: IWGDF grade 3 or 4 infection, suspicion of osteomyelitis, need for revascularization (in PAD P2 and P3 cases) or surgical debridement. The diagnosis of osteomyelitis was based on positive probe to bone test with typical radiological signs (permeative radiolucencies, destructive changes, cortical defects) and in case of doubt, by MRI. Surgical treatment of osteomyelitis was minimal: partial ostectomy of the toe or of a metatarsal (15,16, 17).

The decision of amputation was made only after a multidisciplinary discussion with a view to conserve as much of the foot as possible and the level of amputation was decided jointly with the surgeon and a Rehabilitation specialist.

After hospitalization, patients went back home or were rehospitalized in a post-care section (post acute hospitalization, which is covered 100% by the French Social Security System) when their DFU needed heavy local care or if the patient was isolated socially or domestically.

Study outcomes

The primary outcome was healing at 12 months. Healing was defined by complete epithelialization without any discharge. Patients who healed after a minor amputation to do with their DFU at the time of inclusion were also counted as healed patients. The date of healing was noted on the day of the consultation in the DFS.

Secondary endpoints were minor amputation rates, major amputation rates and death rates at 12 months.

Minor amputations were defined by the following levels: toes, transmetatarsal, Chopart and Lisfranc. Major amputations were defined by the following levels: transtibial or transfemoral.

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation (SD) or median [Q1: first quartile; Q3: third quartile]. Categorical variables are reported as numbers and percentages (percentages were calculated excluding any missing data). Missing data were not handled.

Time of healing, minor amputation, major amputation and death after inclusion were analyzed using the Kaplan Meier method. Rate estimates at 12 months and their 95% confidence interval (CI) were presented. Censor rules were detailed in the appendix.

Predictive factors of healing, risk factors of major amputations and of death were looked for, amongst the patient and disease characteristics (age, sex, type of diabetes, diabetes duration, ulcer duration, hemodialysis, organ transplant, active smoking, PEDIS perfusion, PEDIS surface area, PEDIS depth, PEDIS infection, PEDIS sensation, osteomyelitis), using the Cox proportional Hazard model. Univariate analyses ($p < 0.10$) were used to select the explanatory variables to include in the multivariate model. The results were interpreted in terms of adjusted hazard ratios (aHR) with their associated 95% CI.

A p-value < 0.05 was considered as significant. All statistical analyses were carried out using the SAS release 9.4 (SAS Institute Inc, Cary, NC) statistical software package.

Results

Patient characterization (table 1)

At the DFS, 347 patients were successively included for new DFUs. Data on outcome were recorded in 336 patients (3.2 % lost to follow up), with a median follow up [Q1; Q3] of 19 months [12; 24].

The average age of the patients was 65 ± 12 years with 68% of men. The majority of the diabetes was of type 2 (89%), for a median length of time [Q1; Q3] of 16 years [10; 27], a dialysis rate of 13% and organ transplant of 7%.

Ulcer characteristics

The DFUs at the time of inclusion were a median [Q1; Q3] of 49 days old [19; 120], and 11% of the patients included had ulcers longer than 1 year.

The ulcers were localized to the toes (53%), forefoot (20%), midfoot (11%) or the heel (12%). The areas of the foot affected were: plantar (49%), dorsal (22%), lateral (16%) or distal (11%). Complications of the ulcers included, 47% of osteomyelitis and 33% of ischemic and infected wounds.

According to the PEDIS classification (table 2), 70% of the patients had a PAD including 17% with a necrosis (P3), 55% had an infected wound, 70% had ulcers of $>1\text{cm}^2$ and, 51% had deep sores (D2 and D3).

Surgical treatment

Of all the patients, 42 underwent an angioplasty of the lower members (14%), with a failure rate of 19% (8/42), and 5% had a distal by-pass surgery. 23 Patients had a partial toe ostectomy (8%) and 15 patients had a partial metatarsal ostectomy (5%) (Appendix S1).

Healing

The rate of healing was 67% at 12 months (95% CI: 61; 72). The median [Q1; Q3] healing time was 6.6 [5.5; 9.1] months (Figure 1a). The rate of healing after angioplasty, was 33% (14/42) and after distal bypass 50% (8/16).

Predictive factors of healing (table 3) were the degree of perfusion (P1 vs P3 : aHR 2.34 [1.34 ; 4.07] and P2 vs P3 : aHR = 2.42 [1.43 ; 4.10]), and the ulcer surface area (Extension): (E1 vs E3 : aHR = 1.82 [1.23 ; 2.70] , E2 vs E3 : aHR =1.51 [1.04 ; 2.19].

Amputations

The rate of minor amputations after 1 year was 19% [95% CI : 14; 25] (47 minor amputations: 27 toes, 17 transmetatarsal, 2 Chopart, 1 Lisfranc).

The rate of major amputations after 12 months was 10%: (95% CI 7; 17] (19 major amputations: 16 transtibial and 3 transfemoral). (Figure 1b)

The risk factors of major amputations (table 4) were active smoking: aHR = 2.89 [95% CI 1.09; 7.70] and the presence of osteomyelitis: aHR 2.89 [95% CI: 1.03-8.10].

Mortality

The rate of mortality at 12 months was 9% (95% CI 7; 13) (Figure 1c). All the deceased patients had a PAD. Risk factors of mortality were the degree of perfusion

P3 vs. P1-P2: aHR 4.52 [95% CI 2.16 ;9.46] and age (per additional year) : aHR 1.05 [95% CI 1.02-1.09] (table S2).

DISCUSSION

Diabetic foot ulcer is just as much a major public health problem in France as it is in other countries (1,10,19), and for several years now, many French multidisciplinary foot units have been set up to deal with them according to international guidelines. But to our knowledge, to date, no exhaustive data have been published from these French centers. The objective of the present study was to evaluate the results from one of these centers, to allow comparisons in centers in France, as well as, with the rest of Europe. After a median delay of 7 weeks of DFU before treatment in our DFS, a healing rate of 67%, a major amputation rate of 10% and a mortality rate of 9% was obtained after 1 year. The rate of minor amputations was relatively high (19%) but were mainly of the toes, which was due to a therapeutic strategy aiming to conserve as much of the foot as possible and to reduce the rate of major amputations (18,19,20,21) and hind foot or transmetatarsal amputations. The population studied at the DFS was of a similar age group (65 years old) as other European cohorts (11, 23-25) and had the same rate of wound infection (around 55%). Our population was comparable to that of the Morbach study (24,) with a prevalence of peripheral arterial disease (PAD) much higher than the Eurodiale study (11), a high number of patients on dialysis (13% versus 3 to 6% in others studies) (11,24) or with an organ transplant (7%). This difference explains why the healing rate obtained in our center (67%) was lower than that of the Eurodiale study (77%) but comparable to the result of the sub group of patients with PAD in this study. However, the rate of minor amputations was the same in our center as in Eurodiale centers (19%), but the rate of major amputations was higher in our population. This can be explained by the high prevalence and severity of PAD in our population. PAD is a well-known risk factor for major amputations (24), as was confirmed in our study.

As for the mortality rate of the whole cohort after one year, comparison with other publications is difficult because this data has not always been reported. In the Jeffcoate (23) and Morbach (24) populations, the mortality rate was much higher (16,7% and 15,4% respectively) than our center (9%). This could be related to the increase of life expectancy observed in patients with diabetes these last years (27), or to differences in parameters that influence mortality but are not recorded in these

studies, like the number of cardiovascular risk factors, socio-economical problems, smoking or depression. The lower mortality rate in our population can probably explain why, conversely, we find a higher rate of major amputations than Jeffcoate and Morbach studies (10% versus 5% and 8,7% respectively). This end point might have been observed in our center in patients who perhaps would not have survived several years ago.

Concerning the risk factors for major amputations, PAD has already been described as crucial (24). In addition, we found that bone infection can also increase this risk in patients with PAD, and overall we found that the significant association of major amputations with active smoking was persistent after adjustment with PAD. It is important to highlight this latter result because it suggests that in patients with severe PAD, active smoking, which is responsible for tissue hypoxemia (26) increases the risk of major amputation substantially.

The limits of this study are the absence of a record of the causes of mortality and of cardiovascular risk factors other than smoking, and the monocentric design. In addition, the small number of patients with major amputations and mortality makes it difficult to draw hard conclusions on predictive factors. The strengths of this study are the low number of patients lost during the study and the high cohort.

In conclusion, the results obtained in our French DFS where international guidelines are implemented, are indeed comparable to those of other European centers. The results from this French DFS center confirm that a multidisciplinary treatment of the DFU in an expert center is essential to the healing of more than two thirds of the patients and reduces the rate of major amputations despite the delay in treatment. The relatively low mortality rate after a year, despite the severity of the condition of the population studied, is in accordance with the increase in life expectancy recently observed in patients with diabetes.

REFERENCES

1. Richard JL, Lavigne JP, Got I, Hartemann A, Malgrange D, Tsirtsikolou D, Baleyrier A, Senneville E. Management of patients hospitalized for diabetic foot infection: results of the French OPIDIA study. *Diabetes & Metabolism*, 2011; 37: 208-215

2. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease *Lancet*. 2005; 366:1719-24.
3. Ghanassia E , Villon L, Thuan Dit Dieudonné JF, Boegner C, Avignon A, Sultan A.
Long-term outcome and disability of diabetic patients hospitalized for diabetic foot ulcers: a 6.5-year follow-up study. *Diabetes Care*. 2008; 31:1288-92.
4. Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Baker on behalf of the International Working Group on the Diabetic Foot (IWGDF) Prevention and management of foot problems in diabetes: a summary guidance for daily practice 2015, based on the IWGDF Guidance documents. *Diabetes Metab Res Rev*, 2016;32 S1: 7-15
5. Basit A. Setting up a diabetic foot service in: Hinchliffe RJ, Schaper NC, Thompson MM, Tripathi RK, Timaran CHe diabetic Foot 2014 eds JP medical 21-26
6. Jeffcoate WJ, Harding KG Diabetic foot ulcers. *Lancet*. 2003 ; 361:1545-51.
7. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. *Lancet*. 2005 ;366:1725-35.
8. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes.*JAMA*. 2005;293:217-28.
9. Wukich DK, Armstrong DG, Attinger CE, Boulton AJ, Burns PR, Frykberg RG, Hellman R, Kim PJ, Lipsky BA, Pile JC, Pinzur MS, Siminerio L. Inpatient management of diabetic foot disorders: a clinical guide. *Diabetes Care*. 2013; 36:2862-71
10. Fosse-Edorh S, Mandereau-Bruno L, Hartmann-Heurtier A. Les hospitalisations pour complications podologiques chez les personnes diabétiques traitées pharmacologiquement, en France en 2013. *Bull Epidemiol Hebd*. 2015;(34-35):638-44.
http://www.invs.sante.fr/beh/2015/34-35/2015_34-35_4.html
11. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, Uccioli L, Urbancic V, Bakker K, Holstein P, Jirkovska A, Piaggese A, Ragnarson-Tennvall G, Reike H, Spraul M, Van Acker K, Van Baal J, Van Merode F, Ferreira I, Huijberts M. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia*. 2008;51 :747-55.
12. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev*. 2004;20 Suppl 1:S90-5
13. Lipsky BA, Aragón-Sánchez J, Diggle M, Embil J, Kono S' Lavery L, Senneville É, Urbancic-Rovan V, Van Asten S. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. *Diabetes Metab Res Rev*. 2016 Jan;32 Suppl 1:45-74. doi: 10.1002/dmrr.2699.
14. Ha Van G, Michaux C, Parquet H, Bourron O, Pradat-Diehl P, Hartemann A. Treatment of chronic plantar ulcer of the diabetic foot using an irremovable windowed fiberglass cast boot: prospective study of 177

- patients. *Diabetes Metab Res Rev*. 2015; 31:691-8. doi: 10.1002/dmrr.2657
15. Ha Van G, Siney H, Danan JP, Sachon C, Grimaldi A Treatment of osteomyelitis in the diabetic foot. Contribution of conservative surgery. *Diabetes Care*. 1996; 19:1257-60.
 16. Aragon-Sanchez FJ, Cabrera-Galvan JJ, Quintana-Marrero Y, Hernandez-Herrero MJ, Lazaro-Martínez JL, García-Morales E, Beneit-Montesinos JV, Armstrong DG. Outcomes of surgical treatment of diabetic foot osteomyelitis: a serie of 185 patients with histopathological confirmation of bone involvement. *Diabetologia*. 2008;51:1962-70
 17. Lazaro-Martínez JL, Aragon-Sanchez J, García-Morales E. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. *Diabetes Care*. 2014 ; 37:789-95.
 18. Beckert S, Witte M, Wicke C, Konigsrainer A, Coerper S. A new wound-based severity score for diabetic foot ulcers : a prospective analysis of 1000 patients. *Diabetes Care*, 2006; 29: 988-992
 19. Hartemann-Heurtier A, Ha Van G, Danan JP, Koskas F, Jacqueminet S, Golmard JL, Grimaldi A. Outcome of severe diabetic foot ulcers after standardised management in a specialised unit. *Diabetes Metab*. 2002; 28:477-84.
 20. Margolis DJ, Allen-Taylor I, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers and amputation. *Wound repair Regen*. 2005; 13: 230-236
 21. Holstein P, Ellitsgaard N, Olsen BB, Ellitsgaard V. decreasing incidence of major amputations in people with diabetes . *Diabetologia*. 2000;43:844-847
 22. Apelqvist J. Wound healing in diabetes. Outcome and costs. *Clin Podiatr Med Surg*. 1998; 15:21-39
 23. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. *Diabetes Care* 2006;29: 1784-1786,
 24. Morbach S, Furchert H, Gröblinghoff U, Hoffmeier H, Kersten K, Klauke G-T, Klemp U, Roden T, Icks A, Haastert B, Rumenapf G, Abbas ZG, Bharara M, Armstrong DG. Long-term prognosis of diabetic foot patients and their limbs Amputation and death over the course of a decade *Diabetes Care*. 2012, 35: 2021-2027
 25. Young MJ1, McCardle JE, Randall LE, Barclay JI. Improved survival of diabetic foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk management. *Diabetes Care*. 2008 ;31:2143–2147
 26. Santilli SM, Kronson JW, Payne WD. Cigarette smoking alters the rabbit transarterial wall oxygen gradient. [Ann Vasc Surg](#). 1998; 12:174-81.

Table I : Patient characteristics at inclusion (N=347):

Age (years)*	65.4 ± 12.4
Sex (Male)**	237 (68.3)
BMI (kg/m ²)*	28.5 ± 6.0
Type 2 diabetes **	308 (89.0)
Diabetes duration (years)***	16.0 [10.0 ; 27.0]
Insulin treatment**	245 (71.4)
Hemodialysis **	44 (12.7)
Organ transplant**	23 (6.6)
Active smoking**	48 (14.4)
PY***	30.0 [15.0 ; 50.0]

* mean ± SD

** n(%)

*** median [Q1; Q3]

BMI: Body Mass Index

PY : pack-years of cigarettes

Table II : PEDIS classification of the ulcers at inclusion (N=347)

n(%)	Perfusion	Extent	Depth	Infection	Sensation
1	105(30.3)	104(30)	170(49.0)	155(44.7)	58(16.7)
2	184(53.0)	150(43.2)	71(20.5)	91(26.2)	259(74.6)
3	58(16.7)	93(26.8)	106(30.5)	97(28.0)	30(8.6)
4	NA	NA	NA	4(1.2)	NA

NA : not applicable

Table III : Predictive factors of healing (N=347)

Factors	Univariate analysis HR [95% CI]	p-value	Multivariate analysis aHR [95% CI]	p-value
Age (per additional year)	1.00 [0.99; 1.01]	0.645		
Sex				
Male	1.00			
Female	1.19 [0.88; 1.60]	0.255		
Type 2 diabetes				
No	1.16 [0.77; 1.77]	0.478		
Yes	1.00			
Duration of diabetes (per additional year)	1.01 [1.00; 1.02]	0.121		
Duration of ulcer (per additional day)	1.00 [1.00; 1.00]	0.938		
Hemodialysis				
No	1.44 [0. 90; 2.32]	0.129		
Yes	1.00			
Organ transplant				
No	1.32 [0.72; 2.43]	0.370		
Yes	1.00			
Active smoker				
No	1.38 [0.88; 2.15]	0.158		
Yes	1.00			
PEDIS Perfusion				
1	2.60 [1.51; 4.49]	<0.001	2.34 [1.34; 4.07]	0.003
2	2.59 [1.54; 4.37]	<0.001	2.42 [1.43; 4.10]	0.001
3	1.00		1.00	
PEDIS Extent				
1	2.12 [1.44; 3.13]	<0.001	1.82 [1.23; 2.70]	0.003
2	1.65 [1.14; 2.39]	0.008	1.51 [1.04; 2.19]	0.029
3	1.00		1.00	
PEDIS Depth				
1	1.09 [0.79; 1.49]	0.608		
2	0.74 [0.49; 1.12]	0.153		
3	1.00			
PEDIS Infection				
1	1.36 [0.34; 5.54]	0.664		
2	1.54 [0.38; 6.33]	0.546		
3	1.25 [0.31; 5.14]	0.753		
4	1.00			
PEDIS Sensation				
1	1.47 [0.84; 2.57]	0.180		
2	1.18 [0.72; 1.93]	0.503		
3	1.00			
Osteomyelitis				
No	1.31 [0.99; 1.74]	0.057	1.31 [0.99; 1.74]	0.061
Yes	1.00		1.00	

aHR : adjusted Hazard Ratio

Table IV: Risks Factors of major amputation (n=347)

Factors	Univariate Analysis HR [95% CI]	p	Multivar. Analysis. aHR [95% CI]	p
Age (per additional year)	0.99 [0.95; 1.03]	0.557		
Sex Male	1.00			
Sex Female	0.89 [0.32; 2.46]	0.817		
Type 2 Diabetes = No	1.00			
Type 2 Diabetes = Yes	2.17 [0.29; 16.26]	0.451		
Duration of Diabetes (Per additional year)	0.98 [0.94; 1.02]	0.353		
Duration of Ulcer (Per additional day)	1.00 [1.00; 1.00]	0.774		
Hemodialysis No	1.00			
Hemodialysis Yes	1.23 [0.36; 4.22]	0.744		
Organ Transplant No	1.00			
Organ Transplant Yes	0.74 [0.10; 5.57]	0.773		
Active smoker No	1.00		1.00	
Active smoker Yes	2.61 [0.99; 6.68]	0.052	2.89 [1.09; 7.70]	0.034
PEDIS Perfusion				
P1	1.00		1.00	
P2	1.74 [0.47; 6.44]	0.406	1.48 [0.40; 5.49]	0.562
P3	3.83 [0.99; 14.84]	0.052	3.48 [0.89;13.51]	0.072
PEDIS Extent				
E1	1.00			
E2	1.60 [0.42; 6.02]	0.490		
E3	2.16 [0.57; 8.17]	0.258		
PEDIS Depth				
D1	1.00			
D2	1.33 [0.37; 4.70]	0.664		
D3	2.30 [0.82; 6.45]	0.115		
PEDIS Infection				
I1	1.00			
I2	2.16 [0.72; 6.42]	0.168		
I3-I4	1.44 [0.46;4.47]	0.528		
PEDIS Sensation				
S1	1.00			
S2	1.08 [0.31; 3.74]	0.902		
S3	0.48 [0.05; 4.65]	0.529		
Osteomyelitis				
No	1.00		1.00	
Yes	2.92 [1.05; 8.13]	0.040	2.89 [1.03;8.10]	0.044

aHR: adjusted Hazard Ratio

Figure 1 : Kaplan-Meier plots of time to healing (a), time to major amputation (b) and time to death (c). Estimated rate after 12 months [95% CI]