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A Complication of the Complications: The Complexity of Pathogenesis and the Role of Co-Morbidities in the Diabetic Foot Syndrome

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Diabetic foot syndrome (DFS) is considered the most severe and complicated framework of 2 diabetes-related long-term complications, peripheral neuropathy and peripheral arterial disease, and foot ulceration is usually their main clinical expression. Due to the presence of several co-morbidities, diabetic foot patients are often very fragile subjects and foot ulceration is usually only an aspect of a complex clinical condition. Diabetes-related chronic complications affecting other organs, mainly kidneys and heart, can deeply influence not only the patient's general health but also the outcomes of foot ulcers. Ulcer-related outcomes may be deeply influenced by co-morbidities associated with diabetic foot disease. Therefore, DFS not only requires a treatment plan addressing ulcers characteristics but also the assessment method of all co-morbidities that may influence the outcomes. A global approach is mandatory to reduce major amputations and increase survival among diabetic patients. The aim of this review is to describe the co-morbidities that influence the pathophysiology of the DFS and its outcomes.

*La sindrome del piede diabetico **è il quadro più severo** tra le complicanze croniche del diabete e l'**ulcera** è spesso la sua principale **espressione clinica***

*I pazienti con piede diabetico sono spesso soggetti fragili e l'ulcera al piede rappresenta solitamente solo uno degli aspetti di questa **condizione clinica complessa***

Il piede diabetico: una sindrome complessa

- Età
- Fragilità
- Comorbilità
- Limitazione funzionale
- Alterazioni cognitive

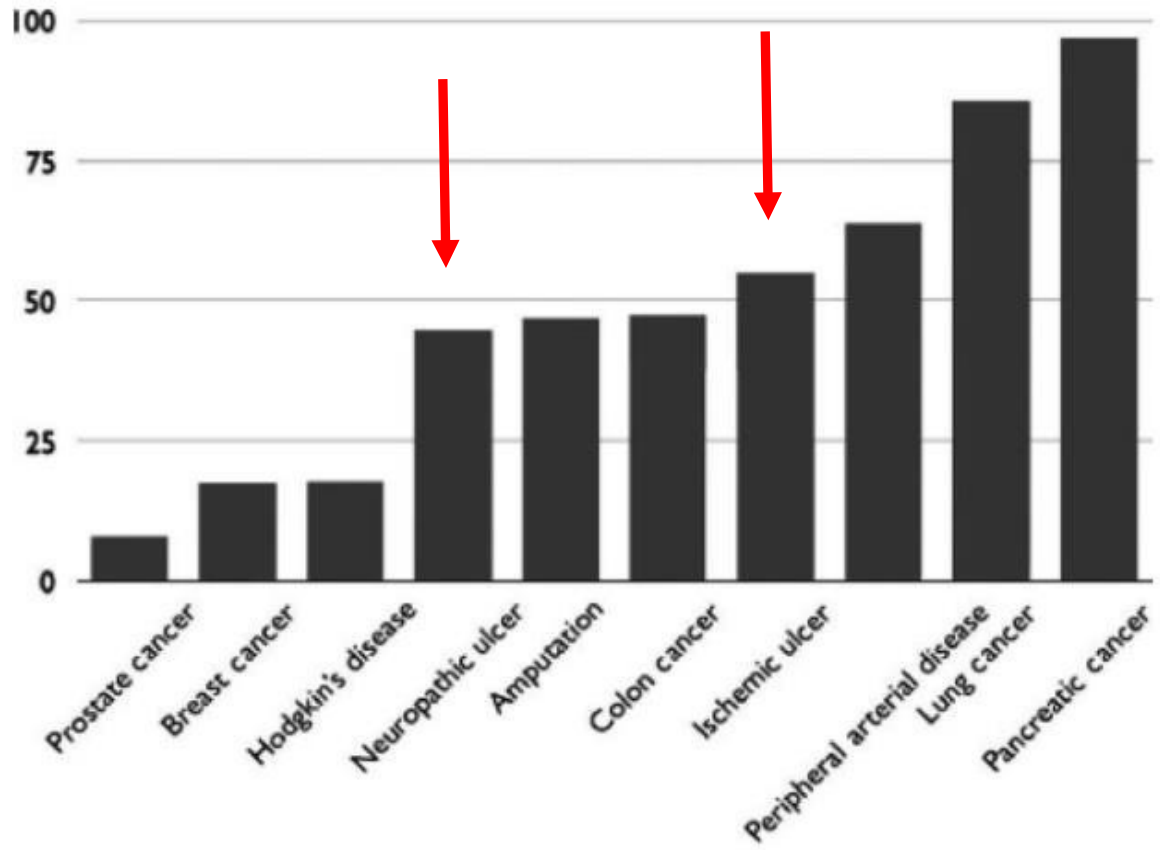
SPECIAL COMMUNICATION

Mortality Rates and Diabetic Foot Ulcers

Is it Time to Communicate Mortality Risk to Patients with Diabetic Foot Ulceration?

Robbins et al, Journal of American Podiatry 2008

La sopravviveza a 5 anni dopo la presentazione di una nuova ulcera al piede è di solo il 50-60, inferiore a molte forme comuni di tumori...



Caratteristiche dei pazienti con piede diabetico: lo studio EURODIALE

Variable	Included (n=1,088)	Dropouts (n=144)	p value
Age (years)	64.7±12.5	68.0±11.6	0.003
Male sex, n (%)[a]	703 (64.6)	85 (59.0)	0.189
Duration of diabetes, n (%)[a]			0.418
<5 years	148 (14.1)	19 (13.5)	
5–10 years	169 (16.1)	17 (12.1)	
>10 years	731 (69.8)	105 (74.5)	
Deep ulcer, n (%)[a]	476 (43.8)	80 (55.6)	0.007
Size of ulcer, n (%)[a]			0.843
<1 cm^2	403 (37.2)	50 (35.0)	
1–5 cm^2	563 (52.0)	76 (53.1)	
>5 cm^2	117 (10.8)	17 (11.9)	
Duration of ulcer, n (%)[a]			<0.001
<1 week	184 (17.0)	10 (7.0)	
1 week–3 months	627 (58.1)	68 (47.6)	
>3 months	269 (24.9)	65 (45.5)	
Plantar location, n (%)[a]	493 (48.2)	62 (46.3)	0.675
Pretibial oedema, n (%)[a]	197 (18.2)	29 (20.3)	0.538
Heart failure NYHA III–IV, n (%)[a]	117 (10.9)	23 (16.1)	0.065
Neurological disorder, n (%)[a]	70 (6.5)	9 (6.3)	0.918
Inability to stand or walk without help, n (%)[a]	107 (9.9)	15 (10.4)	0.843
Visual impairment, n (%)[a]	164 (15.3)	19 (13.2)	0.507
ESRD, n (%)[a]	63 (5.8)	7 (4.9)	0.639
Polyneuropathy, n (%)[a]	826 (78.5)	105 (76.1)	0.515
Infection, n (%)[a]	591 (57.2)	82 (61.2)	0.380
PAD, n (%)[a]	505 (47.5)	78 (56.1)	0.056

Il **5.8%** presentavano IRC in **dialisi**

Il **10.9%** presentavano **scompenso cardiaco**

Prompers L et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007

Caratteristiche dei pazienti con piede diabetico: lo studio EURODIALE

Variable	Patients with PAD (n=505)	Patients without PAD (n=558)	p value
Age (years)	69.1±11.2	60.5±12.3	<0.001
Male sex, n (%)[a]	321 (65.6)	366 (63.6)	0.490
Duration of diabetes, n (%)[a]			0.265
<5 years	63 (12.9)	80 (14.9)	
5–10 years	72 (14.7)	93 (17.4)	
>10 years	354 (72.4)	363 (67.7)	
Deep ulcer, n (%)[a]	266 (52.7)	200 (35.8)	<0.001
Size of ulcer, n (%)[a]			0.002
<1 cm^2	173 (34.4)	219 (39.5)	
1–5 cm^2	259 (51.5)	294 (53.0)	
>5 cm^2	71 (14.2)	42 (7.5)	
Duration of ulcer, n (%)[a]			<0.001
<1 week	58 (11.5)	120 (21.7)	
1 week–3 months	296 (58.0)	318 (57.5)	
>3 months	148 (29.5)	115 (20.8)	
Plantar location, n (%)[a]	197 (40.9)	284 (55.0)	<0.001
Pretibial oedema, n (%)[a]	111 (22.0)	83 (14.9)	0.002
Heart failure NYHA III–IV, n (%)[a]	64 (12.7)	47 (8.5)	0.027
Neurological disorder, n (%)[a]	40 (8.0)	27 (4.9)	0.039
Inability to stand or walk without help, n (%)[a]	65 (12.9)	36 (6.5)	<0.001
Visual impairment, n (%)[a]	89 (17.9)	66 (12.0)	0.007
ESRD, n (%)[a]	35 (7.0)	25 (4.5)	0.082
Polyneuropathy, n (%)[a]	383 (77.2)	424 (79.3)	0.429
Infection, n (%)[a]	293 (60.9)	282 (53.4)	0.016

IRC in dialisi: Incidenza di circa il 7% nei pazienti ischemici vs 4.5% nei pazienti neuropatici (p=0.08)

Scompenso cardiaco: Incidenza di circa il 12.7% nei pazienti ischemici vs 8.5% nei pazienti neuropatici (p=0.02)

Prompers L et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007

Insufficienza renale e piede diabetico: studio EURODIALE

Table 4 Multivariable models with independent predictors of non-healing in the whole study population and in patients with and without PAD

Variable	All patients			Patients with PAD			Patients without PAD		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Age, per 10 year increase	1.28	1.11–1.47	0.001	1.42	0.17–1.73	<0.001	1.55	0.91–2.63	0.105
Sex, men vs women	1.72	1.23–2.40	0.002	1.97	1.25–3.11	0.003	–	–	–
Size of ulcer			<0.001			<0.001			0.008
1–5 vs <1 cm^2[a]	2.26	1.58–3.22		3.22	1.95–5.32		1.25	0.74–2.12	
>5 vs <1 cm^2[a]	3.88	2.37–6.34		3.84	1.97–7.48		3.48	1.62–7.46	
Duration of ulcer			–			–			0.086
1 week to 3 months vs <1 week[a]	–	–		–	–		2.14	1.05–4.36	
>3 months vs <1 week[a]	–	–		–	–		2.18	0.98–4.84	
Heart failure (NYHA III–IV), yes vs no	1.55	0.99–2.43	0.054	1.54	0.87–2.74	0.141	–	–	–
Inability to stand or walk without help, yes vs no	2.00	1.27–3.14	0.003	2.36	1.34–4.17	0.003	1.91	0.86–4.24	0.112
ESRD, yes vs no	2.51	1.41–4.48	0.002	3.04	1.38–6.70	0.006	2.00	0.76–5.25	0.161
Polyneuropathy, yes vs no	1.42	0.96–2.08	0.078	–	–	–	1.70	0.89–3.25	0.108
Infection, yes vs no	–	–	–	1.63	1.03–2.58	0.036	–	–	–
PAD, yes vs no	1.71	1.23–2.37	0.001	N/A			N/A		

[a] Reference category
N/A, not applicable

Una fotografia attuale del paziente con piede diabetico

Journal of
Clinical Medicine

MDPI

Article

Prevalence, Clinical Aspects and Outcomes in a Large Cohort of Persons with Diabetic Foot Disease: Comparison between Neuropathic and Ischemic Ulcers

Marco Meloni [1,*], Valentina Izzo [1], Laura Giurato [1], José Luis Lázaro-Martínez [2] and Luigi Uccioli [1]

Received: 25 May 2020; Accepted: 4 June 2020; Published: 8 June 2020

Una fotografia attuale del paziente con piede diabetico

SCOPO

- Valutare caratteristiche cliniche dei pazienti neuropatici ed ischemici/neuro-ischemici
- Valutare caratteristiche ulcerative dei pazienti neuropatici ed ischemici/neuro-ischemici
- Valutare gli esiti a medio-lungo termine dei due gruppi di studio

Che tipo di paziente abbiamo trattato/stiamo attualmente trattando?

Meloni M., Izzo V, Giurato L, Lazaro-Martinez JL, Uccioli L. 2020

Una fotografia attuale del paziente con piede diabetico

METODI

- Inclusione: pazienti diabetici con ulcera al piede
- Esclusione: pazienti con indicazione ad amputazione maggiore alla prima valutazione (unsalvageable foot), aspettativa di vita <6 mesi, lost follow-up
- Periodo: 2010-2018

Una fotografia attuale del paziente con piede diabetico

METODI

- Limb salvage protocol (nel rispetto delle linee guida):
  - Rivascolarizzazione (ischemici/neuro-ischemici)
  - Gestione infezione
  - offloading
  - int. Chirurgico/wound care
  - gestione condizioni cliniche generali (diabete, ip. Arteriosa, dislipidemia, protezione renale)

Table 2. Microvascular and Macrovascular related complications, and concomitant comorbidities.

Microvas. Complications	*n* = 1198	Neuropathic DF (*n* = 386)	Ischemic DF (*n* = 812)	*p*-Value
Retinopathy	612 (51.2%)	194 (50.2%)	420 (51.7%)	0.7
Nephropathy	410 (34.2%)	88 (22.8%)	321 (39.6%)	<0.0001
Peripheral neuropathy	1102 (92%)	386 (100%)	716 (88.2)	0.0002
Macrovas. Complications				
Ischemic heart disease	388 (32.4%)	88 (22.8%)	(299) 36.9%	0.0004
Cerebrovascular disease	192 (14.3%)	8.3%	(140) 17.2%	0.002
Peripheral arterial disease	812 (67.8%)	–	812 (100%)	
Comorbidities				
Hypertension	950 (79.3%)	284 (73.6%)	666 (82%)	0.01
Dyslipidemia	482 (40.2%)	168 (43.5%)	314 (38.7%)	0.2
Heart failure	269 (22.4%)	68 (10.1%)	201 (24.7%)	0.0002
ESRD	240 (20%)	21 (5.4%)	219 (27%)	0.0001
Anemia	226 (18.8%)	31 (8%)	195 (24%)	0.0003
Smoke	90 (7.5%)	24 (6.2%)	66 (8.1%)	0.4

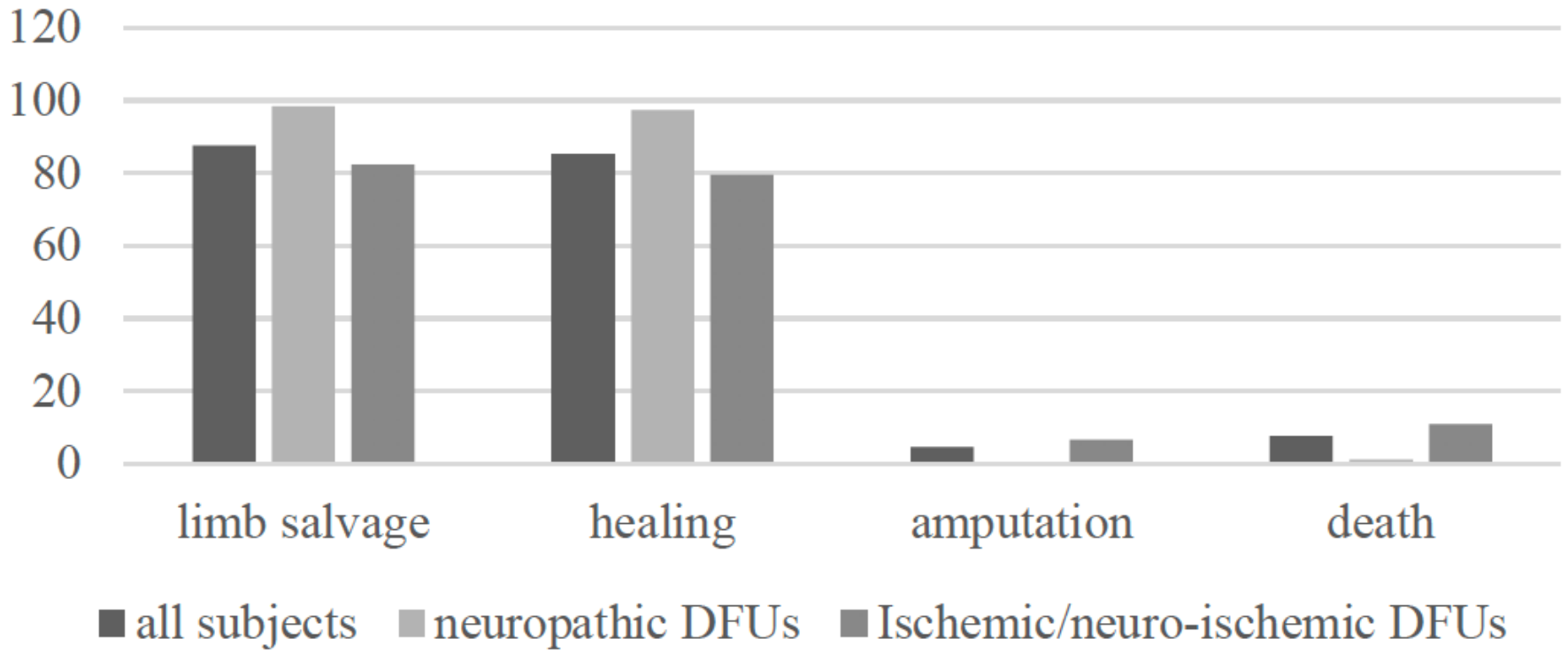
Microvasc.: microvascular; macrovasc.: macrovascular; ESRD: end-stage-renal-disease.

Meloni M., Izzo V, Giurato L, Lazaro-Martinez JL, Uccioli L. 2020

Table 3. Rate of co-diseases in all subjects, neuropathic and ischemic DF groups.

Co-diseases (n) (%)	*n* = 1198	Neuropathic DF (*n* = 387)	Ischemic DF (*n* = 812)	*p*-Values
0 co-disease	70 (5.8%)	34(8.8%)	36 (4.4)	0.1
1 co-disease	190 (15.8%)	72 (18.6%)	118(14.5%)	0.2
2 co-disease	206 (25.5%)	94 (24.3%)	212(26.1)	0.8
3 co-disease	298 (24.9%)	122 (31.6%)	176 (21.7%)	0.06
4 co-disease	198 (16.5%)	46 (11.9%)	152 (18.7%)	0.005
≥5 co-disease	136 (10.8%)	18 (4.6%)	118 (13.6%)	0.0003

I pazienti **ischemici** presentavano nel **32.3% dei casi almeno 4 o 5 comorbilità** oltre il diabete, i neuropatici 16.5%



Gli esiti per i **neuropatici** e gli **ischemici** a 1 anno di follow-up erano rispettivamente:

- Guarigione (97.3 vs. 79.6%, $p < 0.0001$),
- Amputazione (0.5 vs. 6.6%, $p = 0.0001$)
- Mortalità (1.1%vs. 11%, $p < 0.0001$)

Table 6. Multivariate analysis of independent predictors of outcome (major amputation and death) found at univariate analysis.

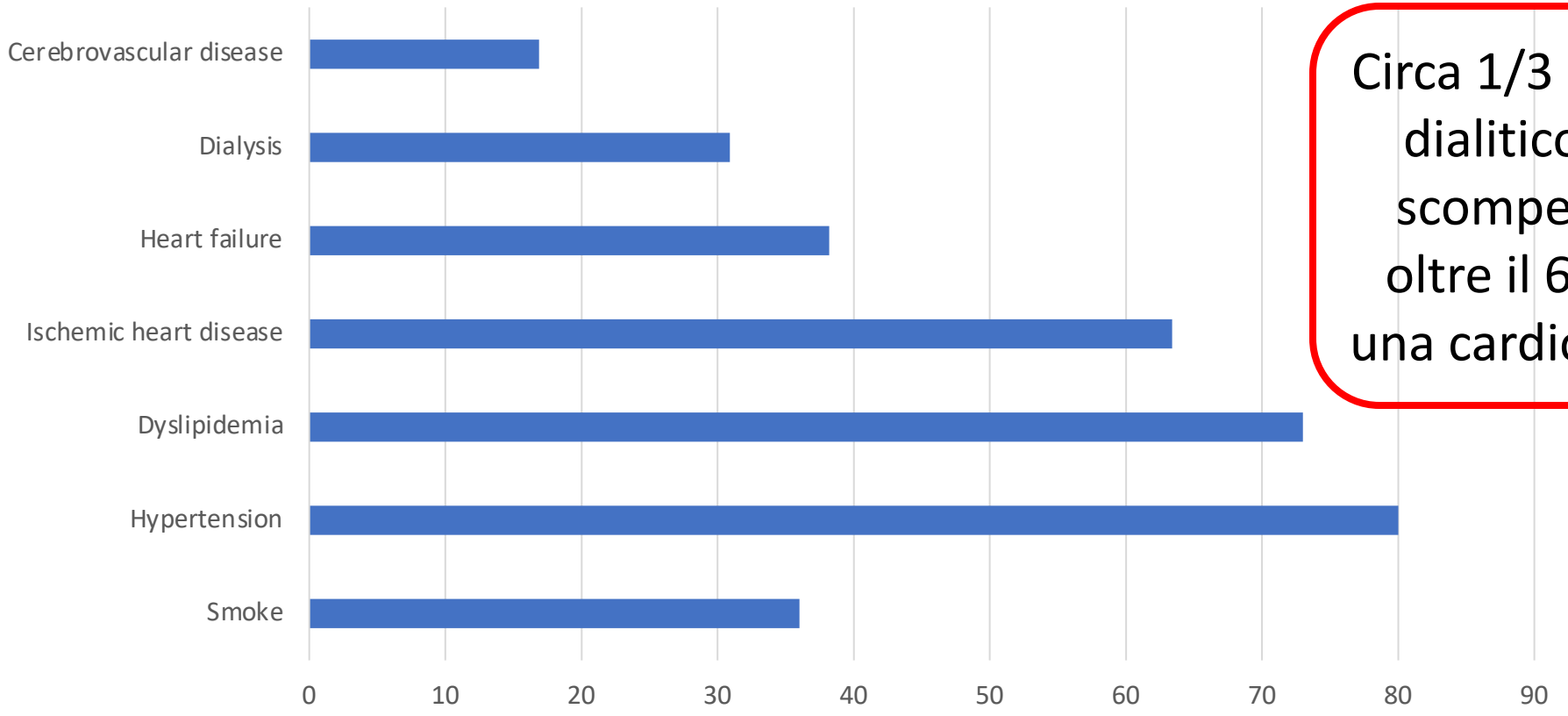
Variables	Major Amputation			Death		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Ulcer size (>5 cm²)	1.1	0.7–1.6	0.2			
Heel ulcer	1.2	0.8–1.8	0.08			
Infection	0.9	0.6–1.4	0.6	1.4	0.9–1.7	0.06
Revascularization failure	5.7	2.9–11.5	0.001			
ESRD	2.1	1.7–5.8	0.02	0.8	0.5–1.9	0.1
IHD				1.5	0.8–2.2	0.07
Heart failure				6.4	2.1–14.5	0.0001
Number of co-diseases (≥5)				3.4	1.8–7.7	0.0001

ESRD: end-stage-renal-disease; IHD: ischemic heart disease.

Amputazione: ulcere calcagno, fallimento rivascolarizzazione, dialisi

Mortalità: scompenso cardiaco, **numero comorbilità (>5)**

Comorbilità nel piede diabetico neuro-ischemico



Circa 1/3 è in trattamento dialitico e/o presenta scompenso cardicaco, oltre il 60% presentava una cardiopatia ischemica

Data 2015-2021, Diabetic Foot Unit, Policlinico Tor Vergata Roma

Contents available at ScienceDirect
Diabetes Research and Clinical Practice
journal homepage: www.elsevier.com/locate/diabres
International Diabetes Federation

Long term outcomes of diabetic haemodialysis patients with critical limb ischemia and foot ulcer ☆

Marco Meloni, Laura Giurato, Valentina Izzo, Matteo Stefanini, Enrico Pampana, Roberto Gandini, Luigi Uccioli*

599 pazienti
Dialisi si: 99 pazienti
Dialisi no: 500 pazienti
Follow-up: 15±13 mesi

DIALISI SI
33,3% guarigione
14,4% amputazione
21,1% decesso
31,2% mancata guarigione

DIALISI NO
52,6% guarigione
10,8% amputazione
11% decesso
25,6% mancata guarigione

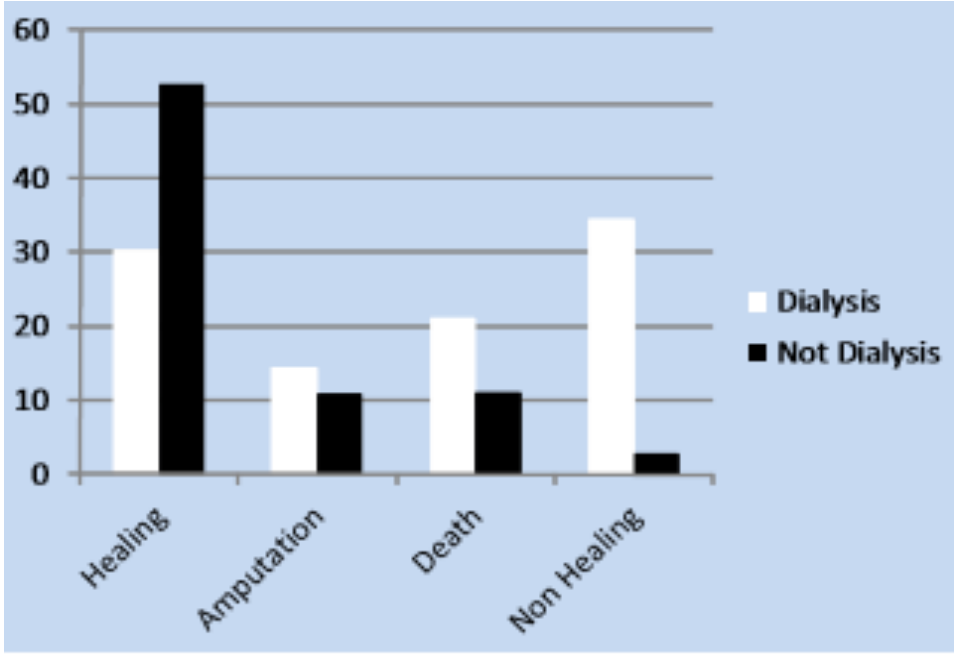


Fig. 1 – Outcomes in dialysis group and not dialysis group. $X^2 = 0.0004$.

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

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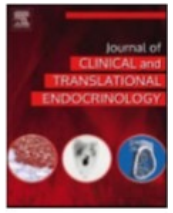


Original research

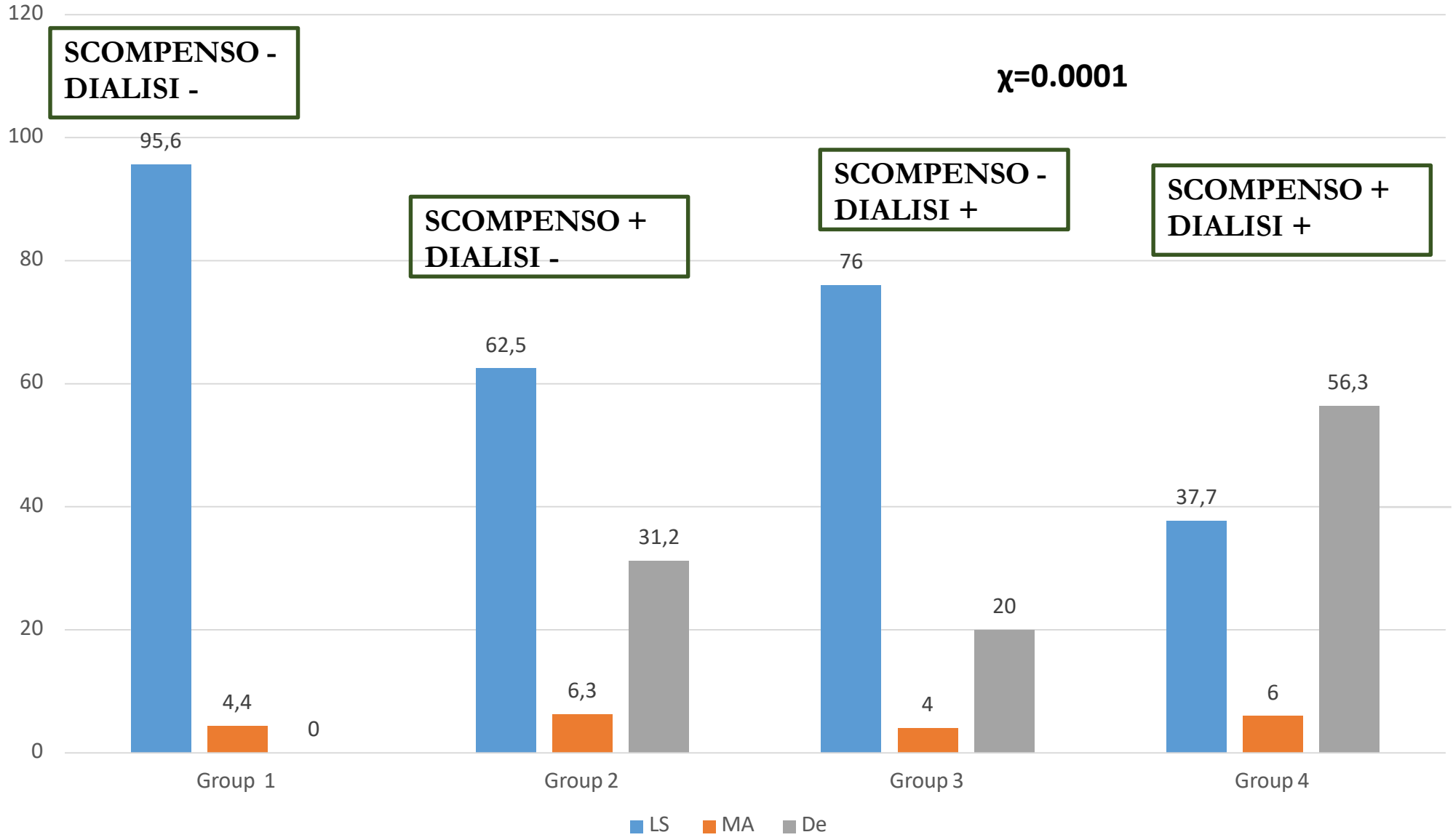
Impact of heart failure and dialysis in the prognosis of diabetic patients with ischemic foot ulcers

Marco Meloni[a,*], Valentina Izzo[a], Laura Giurato[a], Valerio Cervelli[b], Roberto Gandini[c], Luigi Uccioli[a]

136 pazienti diabetici con ischemia critica d'arto e ulcera ischemica, suddivisi in **4 gruppi**:

- **Gruppo 1:** Pazienti non in dialisi e senza scompenso cardiaco (49 pazienti, 47.1%)
- **Gruppo 2:** Pazienti con scompenso cardiaco (20 pazienti, 19.2%)
- **Gruppo 3:** Pazienti in dialisi (20 pazienti, 19.2%)
- **Gruppo 4:** Pazienti in dialisi e con scompenso cardiaco (15 pazienti, 14.5%)

2018



LS: salvataggio d'arto MA: amputazione De: Mortalità

- Group 1 (HF-, D-): - amputazione 4.4%
  - mortalità 0%

Low risk patients

- Group 2 (HF+, D-): - amputazione 6.3%
  - mortalità 31.2
- Group 3 (HF-, D+): - amputazione 4%
  - mortalità 20%

High risk patients

- Group 4 (HF+, D+): - amputazione 6%
  - mortalità 56.3%

Highest risk patients

FAST-TRACK PATHWAY FOR DIABETIC FOOT ULCERATION

Meloni et al, The Diabetic Foot Journal 2019

D-FOOT international

International Diabetic Foot Care Group

FIRST ASSESSMENT

CO-MORBIDITIES
- HEART FAILURE CLASS
- END STAGE RENAL FAILURE
- DEPRESSION

HOLISTIC APPROACH*
- MEDICAL HISTORY
- CLINICAL EXAM.
- BIOLOGY

* : take care of psycho-social context of patient

ASSESSMENT OF DIABETIC FOOT LESION AND LOWER LIMB

Absence of necrosis/gangrene
Absence of bone, muscle and/or tendon exposure
Normal pulses
Absence of signs of infection*

NON COMPLICATED DFU

STANDARD OF CARE

max. 2 weeks of observation and treatment

outcome : 30% decrease of ulcer area
signs of granulation or reepithelisation

YES — **FOLLOW UP WITH RECHECK STANDARD OF CARE**

NO

Necrosis
Bone, muscle and/or tendon exposure
Absence of abnormal pulses
Sign of infection*

OR

DM Patient with lesion with dialysis or heart failure

COMPLICATED DFU

STANDARD OF CARE ⊕ referral with a max. delay of 4 days

REFERRAL TO DF CENTERS OF REFERENCE

IN COOPERATION WITH FIRST LINE FURTHER FOLLOW UP

⊕ Gangrene /
Phlegmone /
Fever or other signs of sepsis

SEVERE COMPLICATED DFU

STANDARD OF CARE

URGENT HOSPITALISATION IN 24H TO SPECIALISED DF CLINIC

GOALS

- **REDUCE HEALING TIME**
- **LIMB SALVAGE / ↑QUALITY of LIFE**
- **DECREASE MORTALITY + LIMB SALVAGE**

PRINCIPLES OF STANDARD OF CARE

Offloading: Reduction of extrinsic and/or intrinsic biomechanical stress/plantar pressure is essential for ulcer protection and healing. The use of Non-removable knee-high offloading devices, total contact casts (TCC), removable walkers or specific footwear should be used tailored to individual need and according to local available resources. Patients should be educated to minimise standing and walking. Regular follow -up should be undertaken to ensure clinical effectiveness and compliance.

Restoration of foot perfusion: In patients with peripheral arterial disease (ankle pressure <50mm Hg, ABI <0.5, toe pressure <30mmHg or TcpO2 <25 mmHg), revascularisation should be considered. When an ulcer does not show signs of healing within 4 weeks, despite optimal management, further vascular assesment and revascularisation should be considered (even if the tests above fall within acceptable /normal ranges).

Treatment of infection: When there are clinical signs of infection, empiric and broad-spectrum antibiotic therapy should be administered after obtaining microbiological samples (ideally deep tissue), followed by adjustments according to clinical response and microbiological results. Removal of any necrotic or non-viable tissue following comprehensive assessment of infection severity is required.

Metabolic control/Holistic management: Metabolic approach requires optimisation of glycaemic control (if necessary with insulin), the treatment of malnutrition and oedema if present. Optimal management of relevant co-morbidities is mandatory.

Local wound care: Frequent ulcer inspection/assessment, debridement and redressings should be undertaken. Dressing selection is based upon ulcer findings (characteristics of wound bed, exudation, size, depth, local pain). In case of neuro-ischemic ulcers, dressings with TLC-NOSF (Lipid-Colloid Technology with Nano-OligoSaccharide Factor) should be considered.

Complessità del paziente con piede diabetico e fattori correlati agli esiti

- Ci sono una **complessità di fattori** correlati agli esiti dei pazienti con Piede diabetico, fra i quali le comorbilità, la vasculopatia periferica, l'infezione, la dimensione della lesione sono fortemente correlate alla possibilità di guarigione

- Le **comorbilità** in particolare sono strettamente correlata al rischio di **amputazione e mortalità**

- Questi elementi sottolineano la necessità di riconoscere il **Piede diabetico** come una sottostante **malattia multi-organo**

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