Foot and Ankle Surgery 30 (2024) 471–479

Contents lists available at ScienceDirect

Foot and Ankle Surgery

journal homepage: www.journals.elsevier.com/foot-and-ankle-surgery

Prediction model for lower limb amputation in hospitalized diabetic foot patients using classification and regression trees

CA Sánchez [a,b,*], E. De Vries [a], F. Gil [a], ME Niño [c]

[a] Department of Clinical Epidemiology and Biostatistics, Pontificia Universidad Javeriana, Bogotá, Colombia
[b] Department of Orthopaedics and Traumatology, Hospital Universitario de la Samaritana, Bogotá, Colombia
[c] Foot and ankle surgery, Clínica del Country and Hospital Militar Central, Bogotá, Colombia

ARTICLE INFO

Article history:
Received 17 November 2023
Received in revised form 1 March 2024
Accepted 16 March 2024

Keywords:
Foot ulcer
Wagner
Amputation
Forecasting
Machine learning

ABSTRACT

Background: The decision to perform amputation of a limb in a patient with diabetic foot ulcer (DFU) is not an easy task. Prediction models aim to help the surgeon in decision making scenarios. Currently there are no prediction model to determine lower limb amputation during the first 30 days of hospitalization for patients with DFU.
Methods: Classification And Regression Tree analysis was applied on data from a retrospective cohort of patients hospitalized for the management of diabetic foot ulcer, using an existing database from two Orthopaedics and Traumatology departments. The secondary analysis identified independent variables that can predict lower limb amputation (mayor or minor) during the first 30 days of hospitalization.
Results: Of the 573 patients in the database, 290 feet underwent a lower limb amputation during the first 30 days of hospitalization. Six different models were developed using a loss matrix to evaluate the error of not detecting false negatives. The selected tree produced 13 terminal nodes and after the pruning process, only one division remained in the optimal tree (Sensitivity: 69%, Specificity: 75%, Area Under the Curve: 0.76, Complexity Parameter: 0.01, Error: 0.85). Among the studied variables, the *Wagner classification* with a cut-off grade of 3 exceeded others in its predicting capacity.
Conclusions: Wagner classification was the variable with the best capacity for predicting amputation within 30 days. Infectious state and vascular occlusion described indirectly by this classification reflects the importance of taking quick decisions in those patients with a higher compromise of these two conditions. Finally, an external validation of the model is still required.
Level of evidence: III

1. Introduction

Diabetes mellitus (DM) is a chronic disease that compromises different organ systems and whose global incidence shows a sustained annual increase [1–4]. According to the International Diabetes Federation (IDF), in Central and South America alone, approximately 32 million people aged 20 to 79 years suffered from DM during 2019 [4].

The decision to perform amputation of a limb in a patient with diabetic foot ulcer (DFU) is not an easy task. The debate has focused on determining the appropriate surgical management for each foot, whether it be amputation or limb preservation without jeopardizing the patient's life [5–7]. Prediction models aim to assist in decision-making by offering tools to make the specialist's decision more objective. Although there are models for predicting risk factors for lower limb amputation in DFU, they have not described factors related to the risk of amputation within the first 30 days after hospital admission [8–18]. This initial hospitalization period is of great importance, considering that the initial surgical interventions performed can impact long-term outcomes such as mobility, the need for reintervention, and healthcare system costs [8–18].

Existing prediction models include a wide range of variables, making standardization for clinical practice challenging and rather than guiding specialists, they could potentially confuse them due to the abundance of information [8–18]. Moreover, some of them are based on observational studies that aim to identify risk factors, yet it remains uncertain whether the intervention of these factors can impact on the amputation outcome within the first 30 days of admission to the Orthopedics service [8–18]. Given this lack of information, decision-making in managing this condition

* Correspondence to: Cra 18 # 88 – 10, Bogotá, Colombia.
E-mail address: csanchezc@javeriana.edu.co (C. Sánchez).

https://doi.org/10.1016/j.fas.2024.03.007

Table 1
Reported risk factors for lower limb amputation in Diabetic Foot (Most important risk factor included, full version in supplementary material).

	Study	Year	Study design	Sample size	Amputated n (%)	Non amputated n (%)	Measure of association for risk factor (OR/ HR [IC 95%])	p- value
1	Acar [8]	2017	PC	132	110 (83)	22 (17)	Male 5.1 [1.6 – 13.0]	0.05
2	Pickwel[9]	2015	RC	575	159 (27.6)	416 (72.4)	Positive bone probe 6.8 [3.8–12.2]	-
3	Ferreira[41]	2018	RO	479	48 (10)	431 (90)	Moderate – severe infection 5.2 [2.5-10.8]	< 0.001
4	Yang[10]	2011	RC	44917	1457 (3.2)	43460 (96.7)	CKD 3.2 [2.8–3.6]	< 0.001
5	Guo[11]	2019	RC	475	59 (12.4)	416 (87.6)	Wagner 20.9 [4.2-104.1]	< 0.001
6	Morbach[12]	2012	RC	247	38 (15.4)	209 (84.6)	PAD 35.3 [4.8–259.8]	< 0.001
7	Ahmed[13]	2009	PC	2321	661 (28.5)	1660 (71.5)	Critical extremity ischemia 5.1 [2.6–10.1]	< 0.001
8	Pemayun[36]	2015	CC	94	47 (50)	47 (50)	HbA1c > =8% 20.5 [3.1- 134.3]	0.002
9	Hippisley-Cox[14]	2015	PC	454575	4822 (1)	449753 (99)	PAD 4.3 [3.6 - 5.0]	-
10	Czerniecki[15]	2019	RC	5260	1283 (24.4)	3977 (75.6)	Amputation level	-
11	O'Hare[16]	2003	RC	2665	183 (6.8)	2482 (93.2)	PAD 3.2 [2.3 - 4.4]	< 0.001
12	Hüsers[17]	2020	PC	254	104 (40.9)	150 (59.1)	Ulcer extension 3.6 [1.8 – 9.3]	-
13	Barbern[27]	2010	RC	78	26 (33.3)	52 (66.7)	Wagner 4 & 5 20.0 [3.6 – 111.1]	0.001
14	Li[18]	2020	RC	21484	504 (2.3)	20980 (97.7)	DFU 7.5 [3.3 – 16.7]	< 0.001
15	Lipsky[22]	2011	RC	3018	646 (21.4)	2372 (78.6)	Surgical site infection 4.0 [2.4 – 6.6]	< 0.0001
16	Choi[7]	2014	RC	154	30 (19.5)	124 (80.5)	3 vessels 21.5 [6.5 - 71.9]	< 0.01
17	Endoh[37]	2017	RC	13774	782 (5.7)	12992 (94.3)	Hemodialysis 2.1 [1.9 – 2.4]	< 0.001
18	Skoutas[38]	2009	PC	121	26 (21.5)	95 (78.5)	Heel injury 2.7	0.05
19	Shin[39]	2017	SR - MA	51034	654 (1.2)	50380 (98.8)	Stroke 2.2	0.025
20	Izumi[40]	2006	RC	277	168 (60.6)	109 (39.4)	Amputation level	< 0.001
21	Lin[23]	2020	SR - MA	6505	2006 (30.8)	4499 (69.2)	Gangrene 10.9 [5.7 - 21.0]	< 0.00001
22	Sen[49]	2019	SR - MA	6132	1873 (30.5)	4259 (69.5)	Gangrene/ necrosis 9.9 [6.2 - 15.7]	< 0.001

BMI (Body Mass Index); CC (Case control); CKD (chronic kidney disease); CRP (C Reactive Protein); DFU (Diabetic Foot Ulcer); DM (Diabetes Mellitus); ESR (Erythrocyte Sedimentation Rate); GFR (Glomerular Filtration Rate); GN (Gram Negative); HbA1c% (Glycated hemoglobin); HBP (High Blood Pressure); LL (Lower Limb); LLA (Lower Limb Amputation); PAD (Peripheral Artery disease); PC (Prospective cohort); RA (Rheumatoid Arthritis); RC (Retrospective cohort); RO (Retrospective Observational); SBP (Systolic Blood Pressure); SR – MA (Systematic Revie & Meta Analysis)

Table 2
Patients' characteristics.

	Group A (n = 290)	Group B (n = 263)	OR [95% CI]	p – value
	n (%)	n (%)		
Age (years)			2.4 [0.8; 3.3]	0.2
mean ± SD	66.1 (11.7)	63.7 (12.4)		
Median (1Q, 3Q)	66.0 (58.3, 75)	65.0 (55.5, 72.5)		
Hospital				
HUS	182 (63)	162 (62)	1.1 [0.7; 1.5]	0.9
HUSI	108 (37)	101 (38)	1.0 [0.7; 1.4]	
Sex				
Male	191 (66)	181 (69)	0.9 [0.6; 1.3]	0.5
Female	99 (34)	82 (31)	1.1 [0.8; 1.7]	
Smoking history				
Yes	115 (40)	111 (42)	0.8 [0.6; 1.2]	0.6
No	155 (53)	120 (46)	1.2 [0.9; 1.8]	
ND	20 (7)	32 (12)		
HBP history				
Yes	212 (73)	188 (72)	1.1 [0.7; 1.6]	0.7
No	78 (27)	75 (28)	1.0 [0.6; 1.4]	0.7
Time since DM diagnosis (years)				
< 10	66 (23)	76 (29)	0.7 [0.5; 1.1]	0.1
> 10	224 (77)	187 (71)	1.4 [0.9; 2.1]	0.1
CKD history				
Yes	178 (61)	143 (54)	1.3 [0.9; 1.9]	0.1
No	112 (39)	120 (46)	0.8 [0.5; 1.0]	0.1
Dialysis in CKD				
Yes	46 (16)	30 (11)	1.3 [0.8; 2.3]	0.2
No	133 (46)	113 (43)	0.8 [0.4; 1.3]	0.6
NA	111 (38)	120 (46)		
Death during follow up				
Yes	16 (6)	21 (8)	0.7 [0.3; 1.4]	0.3
No	274 (94)	242 (92)	1.5 [0.7; 3.1]	0.3

*Statistically significant variable (alfa < 0.05); NA (Non applicable); ND (No Data); OR (Odds ratio); SD (Standard deviation); HbA1c% (Glycated hemoglobin); CKD (chronic kidney disease); DM (Diabetes Mellitus); HBP (High Blood Pressure); HUS (Hospital Universitario de la Samaritana); HUSI (Hospital Universitario San Ignacio).

Table 3
Lower limb amputation characteristics.

	Group A (n = 290)	Group B (n = 263)	OR [95% CI]	p - value	
	n (%)	n (%)			
Previous LLA					
Yes	111 (38)	117 (45)	0.8 [0.5; 1.1]	0.2	
No	179 (62)	146 (55)	1.3 [0.9; 1.8]		
Previous LLA side					
Right	60 (20)	72 (27)	0.7 [0.4; 1.3]	1.0	
Left	51 (18)	45 (17)	1.4 [0.8; 2.4]		
NA	179 (62)	146 (56)	-		
Previous LLA level					
Supracondylar	15 (5)	26 (10)	0.6 [0.3; 1.2]	0.05	
Transtibial	9 (3)	8 (3)	1.2 [0.4; 3.7]	1.0	
Syme	5 (2)	0	-	-	
Chopart	2 (1)	2 (1)	1.1 [0.1; 14.8]	1.0	
Lisfranc	7 (2)	5 (2)	1.5 [0.4; 6.2]	0.9	
Toes	73 (25)	76 (29)	1.0 [0.6; 1.9]	0.4	
None	179 (62)	146 (55)	-		
Reamputation					*
Yes	102 (35)	67 (26)	0.4 [0.3; 0.6]	< 0.01	
No	188 (65)	50 (19)	2.5 [1.6; 3.9]		
NA	-	146 (56)			
Total number of amputations			0.4 [0.2; 0.6]	< 0.01	*
mean ± SD	1.5 (0.74)	1.1 (1.2)			
Cardinal amputation side					
Right	147 (51)	57 (22)	1.1 [0.6; 1.5]	0.8	
Left	143 (49)	60 (23)	0.9 [0.6; 1.5]		
NA	-	146 (55)			
Cardinal amputation level					
Supracondylar	119 (41)	60 (51)	0.7 [0.4; 1.0]	0.1	
Transtibial	60 (21)	18 (15)	1.4 [0.8; 2.7]	0.3	
Syme	6 (2)	4 (3)	0.6 [0.1; 2.9]	0.7	
Chopart	4 (1)	1 (1)	1.6 [0.2; 80.5]	1.0	
Lisfranc	16 (5)	6 (5)	1.1 [0.4; 3.5]	1.0	
Toes	80 (28)	27 (23)	1.3 [0.8; 2.2]	0.4	
Disarticulation	5 (2)	1 (1)	2.0 [0.2; 97]	0.8	
None	-	-	-		
Total number of surgeries			1.0 [0.2; 1.1]	0.1	
mean ± SD	3.0 (2.2)	3.5 (3.2)			
Median (1Q, 3Q)	2.0 (1, 4)	3.0 (1, 5)			
Time from admission to amputation (days)			-	< 0.01	*
mean ± SD	9.0 (7.1)	374 (7.1)			
Median (1Q, 3Q)	7.0 (4, 12)	105 (52, 314)			

* Statistically significant variable (alfa < 0.05); NA (Non applicable); ND (No Data); OR (Odds ratio); SD (Standard deviation); LLA (Lower limb amputation)

lacks enough high-quality studies to provide a better understanding of risk factors and the amputation in DFU. Furthermore, the time to reach the outcome in these studies varies, and in hospitalized patients, there is a lack of studies that assess variables associated with the need for amputation in the first 30 days of hospitalization [8–18,20–24,41].

Consequently, a retrospective cohort study was conducted to identify the clinical variables that best predict the amputation outcome in lower limbs within the first 30 days of hospitalization using a machine learning approach.

2. Methodology

A retrospective cohort study was conducted using information from clinical records of two university institutions in Bogota, Colombia. "Time 0" (or the moment of cohort entry) was defined as the first admission to the orthopaedics service for the management of DFU in hospitalization. Follow-up was conducted until the occurrence of the primary event of interest (lower limb amputation at any level within the first 30 days of admission to the service) or up to 30 days after admission if amputation had not occurred, whichever came first.

The research protocol was submitted to the research and ethics committee of the participating institutions, which approved the project.

The study included patients aged 18 y and older with DFU managed in hospitalization between 2006 and 2022 due to infection, ischemia, or gangrene, and who may require amputation (or not) of the affected lower limb as a result. Patients who, despite meeting inclusion criteria, had undergone surgical interventions for causes other than those mentioned earlier (e.g., oncology patients, vasculitis, or trauma) were excluded. Patients who did not have an amputation and had died before completing 30 days from admission to the service were also excluded.

2.1. CART

In the current literature, most published studies on risk factors or prediction in this condition use techniques such as logistic regression [7–18,22,23,27,36–41,49] (Table 1). Therefore, a different approach was proposed using Classification and Regression Trees (CART). This technique developed by Breiman and colleagues, is used for predictive modelling through machine learning in various fields, including public health, medicine, and monetary policy development [28–30].

Table 4
Vascular and therapeutical characteristics of DFU patients.

	Group A (n = 290)	Group B (n = 263)	Difference/ OR [95% CI]	p - value	
	n (%)	n (%)			
Use of vacuum therapy					
Yes	34 (12)	64 (24)	0.4 [0.2; 0.6]	< 0.01	*
No	253 (87)	186 (71)	2.6 [1.6; 1.2]		
ND	3 (1)	13 (5)	-		
Vascular surgery intervention					
Stent	45 (15)	44 (17)	1.1 [0.6; 1.9]	0.8	
Bypass	22 (8)	23 (9)	1.0 [0.5; 2.0]	0.7	
Medical	46 (16)	48 (18)	1.0 [0.5; 1.7]	0.5	
None	177 (61)	148 (56)	-		
Microvascular damage in photoplethysmography					
Yes	77 (27)	52 (20)	2.0 [1.0; 4.0]	0.1	
No	14 (5)	23 (9)	0.4 [0.2; 0.9]	< 0.05	*
Undetermined	7 (2)	5 (2)	1.2 [0.3; 4.8]	0.9	
ND	192 (66)	183 (69)	-		
Arterial occlusion in Doppler ultrasound					
Yes	187 (65)	150 (57)	1.4 [1.0; 2.0]	0.1	
No	55 (19)	46 (17)	1.1 [0.7; 1.8]	0.7	
No hemodynamic repercussion	48 (16)	67 (26)	0.6 [0.4; 1.0]	0.1	
Arterial occlusion in Doppler ultrasound per side					
Right	71 (25)	47 (18)	1.6 [1.0; 2.5]	0.07	
Left	66 (23)	58 (22)	1.1 [0.7; 1.7]	0.9	
Bilateral	98 (34)	112 (43)	0.7 [0.5; 1.0]	0.05	
`NA	55 (18)	46 (17)	-		
Arterial occlusion in Doppler ultrasound per level in right LL					
Superficial femoral	26 (9)	21 (8)	0.9 [0.5; 1.9]	0.8	
Deep femoral	4 (1)	1 (0)	3.1 [0.3; 156.2]	0.4	
Popliteal	9 (3)	10 (4)	0.7 [0.2; 1.9]	0.8	
Fibular	13 (5)	5 (2)	2.1 [0.7; 7.8]	0.14	
Anterior tibial	18 (6)	9 (3)	1.6 [0.7; 4.3]	0.19	
Posterior tibial	14 (5)	9 (3)	1.2 [0.5; 3.3]	0.5	
3 or > vessels	51 (18)	49 (19)	0.7 [0.4; 1.2]	0.8	
No hemodynamic repercussion	155 (53)	159 (61)	0.8 [0.5; 1.1]	0.11	
Right LL arterial occlusion (%)					
< 50	170 (59)	171 (65)	0.8 [0.5; 1.1]	0.11	
> 50	120 (41)	92 (35)	1.3 [0.9; 1.9]		
Arterial occlusion in Doppler ultrasound per level in left LL					
Superficial femoral	25 (9)	23 (9)	1.0 [0.5; 1.9]	1.00	
Deep femoral	2 (1)	0	-		
Popliteal	13 (4)	10 (4)	1.2 [0.5; 3.2]	0.9	
Fibular	11 (4)	10 (4)	1.0 [0.4; 2.7]	1.0	
Anterior tibial	15 (5)	14 (5)	1.0 [0.4; 2.3]	1.0	
Posterior tibial	13 (4)	3 (1)	4.2 [1.1; 23.6]	< 0.05	*
3 or > vessels	48 (17)	54 (20)	0.7 [0.4; 1.2]	0.3	
No hemodynamic repercussion	163 (56)	149 (57)	1.0 [0.7; 1.4]	0.9	
Left LL arterial occlusion (%)					
< 50	175 (60)	163 (62)	0.9 [0.7; 1.3]	0.4	
> 50	115 (40)	100 (38)	1.1 [0.8; 1.5]		

* Statistically significant variable (alfa < 0.05); NA (Non applicable); ND (No Data); OR (Odds ratio); SD (Standard deviation); LL (Lower limb)

A classification tree was developed using the CART methodology, considering the primary outcome as a categorical-dichotomous variable (amputation within 30 days, yes or no) [30]. This methodology is based on binary partitions in a predictor variable that produce an end node that contains a prediction for the outcome variable. Hence, the model included those variables that could best predict the outcome [28,31]. The classification tree selected during the construction process was chosen considering the most appropriate complexity parameter, as well as receiver operating characteristic (ROC) curves and their respective area under the curve (AUC) calculations after the pruning process done by the algorithm [32–34]. Additionally, a sensitivity analysis was conducted using a loss matrix that considered the error of misclassification that could have existed in the original model (1.5 and 2 times the error of not correctly classifying the outcome). The model was evaluated through cross validation developing different models on subsets of the available data and evaluating them on the complementary subset of the data [31,35].

2.2. Statistical analysis

Initially, a descriptive analysis of the variables studied was performed according to feet who were amputated before 30 days (Group A) and those who were not (Group B). The second group included patients amputated after the initial 30 days of hospitalization and those who were not amputated during the follow-up. Quantitative variables were summarized using measures of central tendency and dispersion (mean, SD, median, 1Q and 3Q), while qualitative variables were described using frequency tables. The comparison of quantitative and qualitative variables between Groups A and B was performed using the Student's T-test for independent groups and the chi-squared test for independence, in case of a normal distribution; otherwise, the Mann-Whitney and Kruskal-Wallis tests were employed. A significance level of 5% was used to determine statistically significant differences between the two groups.

Table 5
Infectious and metabolic characteristics of DFU patients.

	Group A (n = 290)	Group B (n = 263)	Difference/ OR [95% CI]	p - value	
	n (%)	n (%)			
Wagner					
0	4 (1)	5 (2)	0.7 [0.1; 3.4]	0.9	
1	1 (0)	7 (2)	0.1 [0.003; 1.0]	0.06	
2	28 (10)	60 (23)	0.4 [0.2; 0.6]	< 0.05	*
3	74 (26)	99 (38)	0.6 [0.4; 0.8]	< 0.01	*
4	172 (59)	87 (33)	2.9 [2.0; 4.2]	< 0.01	*
5	11 (4)	5 (2)	2.0 [0.6; 7.6]	0.3	
Leucocyte count (cel/mm^3)			1933.68 [921.2; 2946.1]	< 0.01	*
mean ± SD	13965.0 (6262.2)	11970.1 (5807.8)			
Median (1Q, 3Q)	12465.0 (9732.0, 17238.0)	10750.0 (8625.0, 14100.0)			
CRP (mg/dL)			31.3 [17.6; 45.1]	< 0.01	*
mean ± SD	89.3 (89.9)	58.4 (73.7)			
Median (1Q, 3Q)	44.8 (16.6, 153)	23.0 (9.3, 78.9)			
ESR (mm/h)			4.2 [- 3.1; 11.4]	0.3	
mean ± SD	66.2 (42.8)	61.2 (44.2)			
Median (1Q, 3Q)	64.0 (29.3, 97.8)	60.0 (24.5, 87.5)			
Time of ulcer development					
Days	42 (14)	39 (15)	1.0 [0.6; 1.6]	1.00	
Weeks	84 (29)	80 (30)	1.0 [0.7; 1.4]	0.78	
Months	130 (45)	120 (46)	1.0 [0.7; 1.4]	0.9	
Years	25 (9)	19 (7)	1.2 [0.6; 2.4]	0.70	
ND	9 (3)	5 (2)			
HbA1c (%)			0.1 [- 0.8; 0.6]	0.9	
mean ± SD	7.7 (4.4)	7.7 (4.0)			
Median (1Q, 3Q)	8.2 (6, 10.5)	7.9 (6.2, 10.2)			
Glucose (mg/dL)			3.0 [−16.6; 22.6]	0.8	
mean ± SD	214.1 (120.1)	212.4 (114.8)			
Median (1Q, 3Q)	196.0 (124.2, 280.2)	189.0 (124, 283.5)			
Leucocyte count (cel/mm^3)				< 0.01	
< 11000	100 (35)	134 (51)	0.5 [0.4; 0.7]		*
> 11000	190 (65)	129 (49)	2.0 [1.4; 2.8]		
CRP (mg/dL)				< 0.01	
< 10	39 (14)	64 (24)	0.5 [0.3; 0.8]		*
> 10	251 (86)	199 (76)	2.1 [1.3; 3.3]		
ESR (mm/h)					
< 15	39 (14)	44 (17)	0.8 [0.5; 1.3]	0.3	
> 15	251 (86)	218 (83)	1.3 [0.8; 2.1]	0.3	
ND		1 (0)			
HbA1c (%)					
< 7	99 (34)	93 (35)	1.0 [0.7; 1.4]	0.8	
> 7	187 (64)	168 (64)	1.0 [0.7; 1.5]	0.1	
ND	4 (2)	2 (1)			
Glucose (mg/dL)					
> 126	77 (26)	70 (27)	1.0 [0.7; 1.5]	1.0	
< 126	213 (74)	193 (73)	1.0 [0.7; 1.5]	1.0	

* Statistically significant variable (alfa < 0.05); NA (Non applicable); ND (No Data); OR (Odds ratio); SD (Standard deviation); HbA1c% (Glycated hemoglobin); CKD (chronic kidney disease); DM (Diabetes Mellitus); ESR (Erythrocyte Sedimentation Rate); CRP (C Reactive Protein)

3. Results

The database initially included 573 extremities at the time of modelling. After assessing inclusion and exclusion criteria, 20 patients who died before reaching the minimum follow-up period were excluded. Thus, there were 553 feet available for model development. A total of 290 extremities with the outcome of interest were identified, resulting in an incidence of 0.52 amputations per person-year (52 cases per 100 person-years) for the outcome.

3.1. Sample characteristics and initial variable analysis

The characteristics of groups A and B are presented in Table 2. When conducting exploratory analysis, statistically significant differences were found between the two groups. In Group A, there was a higher occurrence of: reamputation, total number of amputations, posterior tibial artery stenosis on Doppler in left lower limb, DFU Wagner 4, leukocyte count > 11,000 cells/mL, and C-reactive protein (CRP) > 10 mg/dL (Tables 3, 4 and 5). The entire set of patients in Group B showed a longer time between admission and amputation, use of VAC (Vacuum Assisted Closure), uncompromised photoplethysmography, DFU Wagner 2 & 3, and isolation of S. Aureus (Table 6).

3.2. Modelling and evaluation of Classification of Tree

The modelling of the tree is presented in Fig. 1. This 13-terminal node model reports a complexity parameter (CP) of 0.010 with an error of 0.85 (error corresponding to the cross-validation process) for the complete model. However, an optimal tree with a single split was identified after the pruning process (Fig. 2), corresponding to the Wagner score, with the lowest CP (0.01) and error (0.76) (Table 7; Fig. 3). When evaluating this model using a ROC curve, a sensitivity and specificity of 69% and 75% were detected (AUC = 0.764) (Fig. 4).

4. Discussion

The results of the study indicate that, despite the large number of variables included in the model, amputation for feet in this cohort is primarily determined by grade 3 ulcers in the Wagner classification. Several studies reveal that developing a prediction model for

Table 6
Microorganism in monomicrobial ulcer culture.

	Group A (n = 290)	Group B (n = 263)	Difference/ OR [95% CI]	p - value
	n (%)	n (%)		
Escherichia coli	19 (7)	19 (7)	0.9 [0.4; 1.9]	0.89
Proteus Mirabilis	15 (5)	8 (3)	1.8 [0.7; 5.2]	0.30
Pseudomona Aeruginosa	11 (4)	8 (3)	1.3 [0.4; 3.8]	0.80
Streptococcus anginosus	7 (3)	1 (0)	6.7 [0.8; 304]	0.1
Streptococcus agalactiae	5 (2)	5 (2)	0.9 [0.2; 4.0]	1.00
Proteus Vulgaris	1 (0)	1 (0)	1.0 [0.01; 71.4]	1.00
Staphylococcus aureus	5 (2)	18 (7)	0.2 [0.1; 0.6]	< 0.01*
Enterococcus Faecalis	7 (2)	4 (2)	1.6 [0.4; 7.8]	0.66
Staphylococcus epidermidis	2 (1)	2 (1)	0.9 [0.1; 12.6]	1.00
Klebsiella pneumoniae	6 (2)	3 (1)	1.9 [0.4; 11.8]	0.60
Serratia liquefaciens	1 (0)	0	-	
Morganella morganii	9 (3)	6 (3)	1.4 [0.4; 4.9]	0.74
Citrobacter freudii	1 (0)	1 (0)	0.9 [0.01; 71.4]	1.00
Klebsiella oxytoca	0	2 (1)	-	
Serratia marcescens	1 (0)	2 (1)	0.5 [0.01; 8.7]	0.9
Enterobacter cloacae complex	3 (1)	1 (0)	2.7 [0.2; 146]	0.69
Enterococcus faecium	3 (1)	0	-	
Staphylococcus lugdunensis	0	2 (1)	-	
Streptococcus pyogenes	0	2 (1)	-	
Enterobacter aerogenes	0	1 (0)	-	
Negative	5 (2)	5 (2)	0.9 [0.2; 4.0]	1.00
NA	189 (65)	172 (65)	-	

* Statistically significant variable (alfa < 0.05); NA (Non applicable); ND (No Data); OR (Odds ratio); SD (Standard deviation)

amputation in a multifactorial condition like DFU is a challenging task [8–27,36–40].

Results of previous studies agree that infection in DFU and vascular involvement of the limb are variables that may carry a major effect as prognostic components in managing this condition [7–18,22,23,27,36–41,49]. These elements can be homogenized through the classifications used to categorize the severity of the lesions, as the Wagner classification does. Despite its limitations, the Wagner classification remains the most widely known and used in the literature [42–46]. Additionally, studies report that this classification offers advantages over other classifications, including moderate to excellent inter- and intra-observer agreement (regardless of the examiner's experience) and high sensitivity and specificity as a predictor of amputation [44,46,47]. It is even considered that the Wagner classification does not perform worse than other classifications in predicting amputation [48].

This aligns with previous studies reporting odds ratio (OR) of approximately 20 times higher concerning risk of amputation as severity of a DFU increases [11,27]. These observational studies are complemented by the results of a meta-analysis which identified

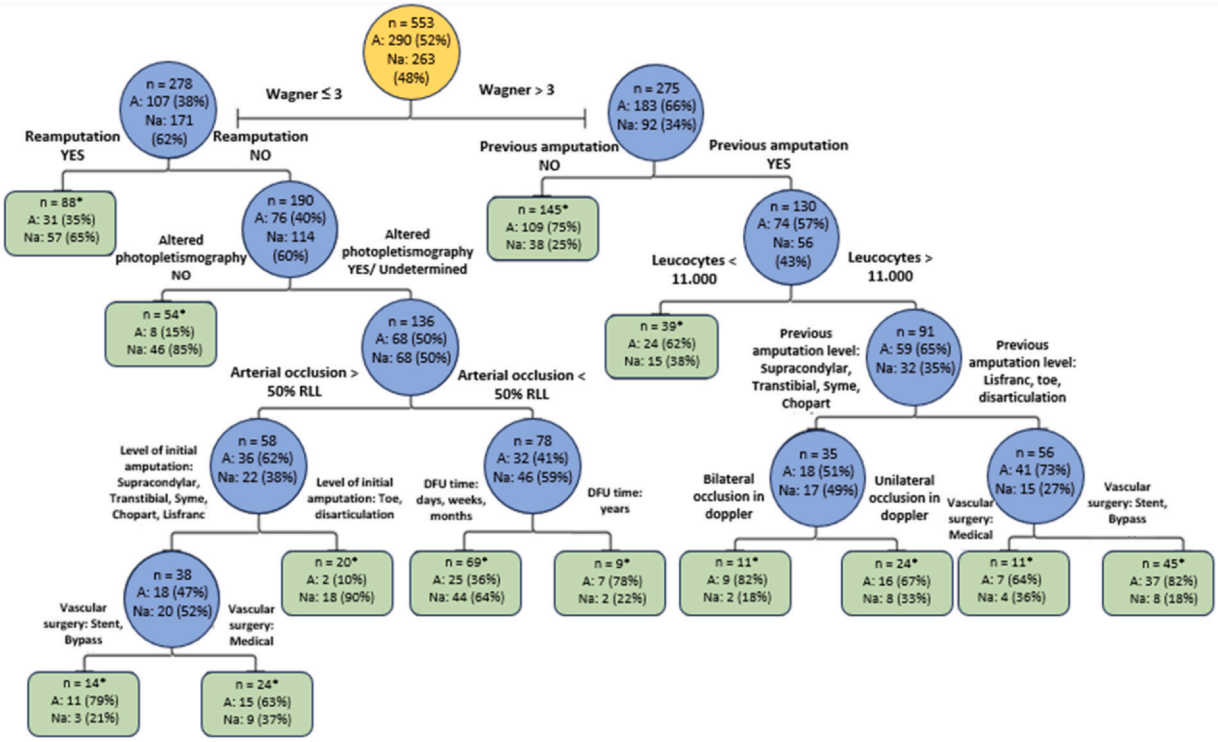

Fig. 1. ***Classification And Regression Tree for predicting lower limb amputation.*** **Nodes: yellow (root), blue (internal), green (terminal);** n (Total individuals in a node); A (Individuals with LLA < 30 days); Na (Individuals not amputated < 30 days); RLL (Right Lower Limb); *Terminal node.

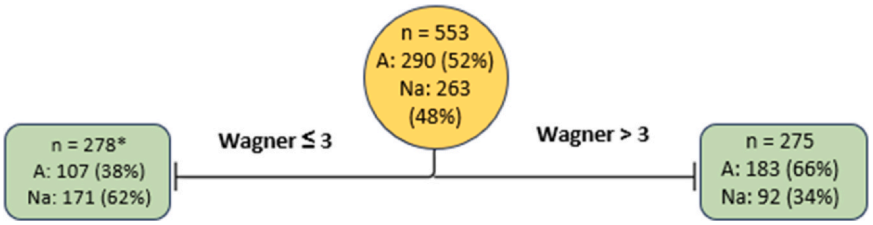

Fig. 2.. ***Classification And Regression Tree for predicting lower limb amputation after pruning.*** **Nodes: yellow (root), blue (internal), green (terminal);** n (Total individuals in a node); A (Individuals with LLA < 30 days); Na (Individuals not amputated < 30 days); *Terminal node.

Table 7
Classification And Regression Tree characteristics.

Complexity parameter	Divisions	Relative error	Cross validation error	Cross validation SD	
0.24	0	1	1	0.05	
0.01	1	0.76	0.76	0.04	*
0.02	5	0.68	0.78	0.04	
0.02	7	0.65	0.82	0.04	
0.01	9	0.62	0.81	0.04	
0.01	11	0.59	0.85	0.04	
0.01	12	0.58	0.85	0.04	

SD (Standard deviation);
* Best model for predicting amputation according to cross validation.

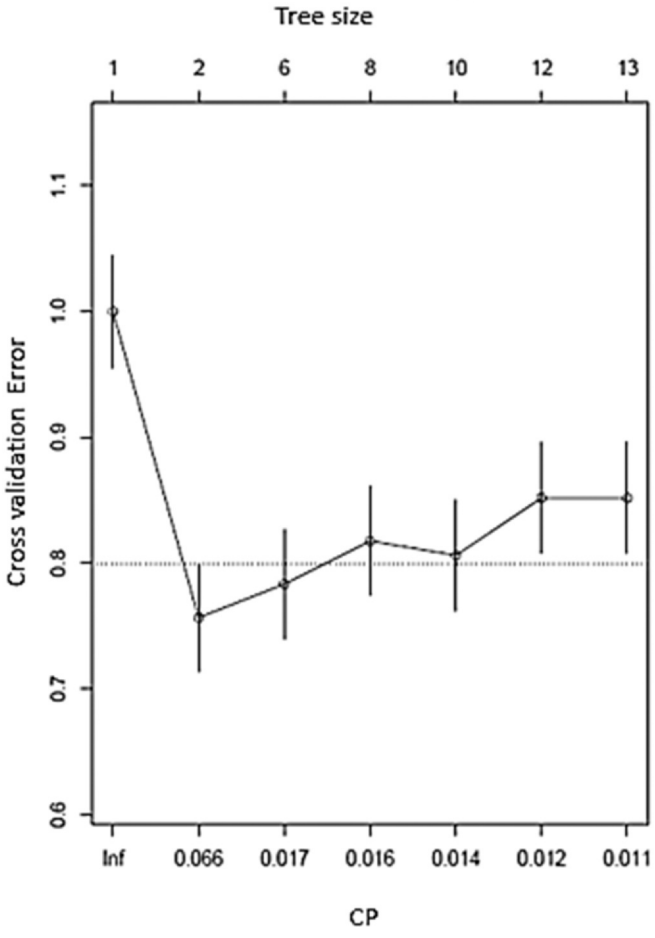

Fig. 3. Complexity Parameter and cross validation error graph. CP (Complexity Parameter).

Wagner 4 or 5 as a risk factor for amputation [49]. Similarly, this and other studies report other risk factors that indirectly reinforce the significance of the Wagner classification [13,15,49].

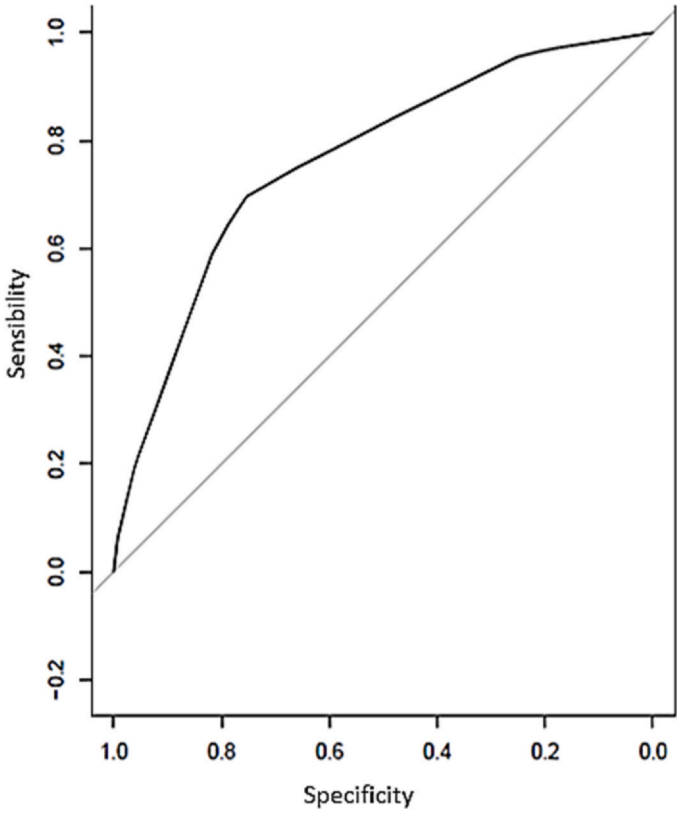

Fig. 4. Receiver Operating Characteristic Curve.

Furthermore, it is important to consider that variables that indirectly indicate infectious and vascular damage such as gangrene/necrosis, leukocytosis > 11,000 mm3, elevated ESR, and positive CRP are highly related to the outcome of amputation [13,15,49]. Moreover, other relevant variables that showed differences between the two groups but were not as determinant as Wagner classification for predicting the outcome should not be disregarded. For instance, a compromised photoplethysmography, the presence of stenosis in Doppler, the need for limb revascularization, and bilateral arterial involvement reflect direct or indirect vascular damage and have been widely described in the literature as a prognostic element [12,14–16,22,27,36,39–41,49]. In contrast, variables such as previous amputation and positive infection with S. Aureus could indirectly represent infectious involvement and have also been described as prognostic elements in the literature [15,22,41,49].

This is not the first study attempting to develop a predictive model for management of DFU, but it represents an approach using machine learning-based modelling for outcome prediction. The model developed has the advantage of being easy to understand and highly intuitive for decision-making, resembling the process of diagnosing and treating patients in clinical practice while it offers the best diagnostic performance based on the balance between

sensitivity and specificity [28,30,31]. Due to its graphical nature, it allows for a more user-friendly exercise for understanding the condition and the variables involved in the decision-making process, just like previous publications on DFU prediction [50–53]. This model could facilitate decision-making in healthcare institutions, reducing hospitalization times, procedure-related complications, and even direct and indirect costs. Additionally, a novel aspect of the study was the use of variables such as "percentage of arterial occlusion in Doppler" and "level of occlusion" based on the affected side in the analysis. These variables are not typically included in published studies and, while they did not provide guidance on decision-making for amputations within the first 30 days, they open the door to new research projects.

Limitations of the present study included the fact that assembling the cohort retrospectively involves a sacrifice in terms of data loss, such as the history of smoking and photoplethysmography involvement, as well as the inability to measure certain variables, for example, the patient's decision/wish to accept an ablative procedure. This latter variable is rarely evaluated in publications and could be critical in decision-making. Once again, this last idea could be another starting point for new studies. Additionally, as the use of classifications in the study of DFU is highly debated, and although the Wagner classification is widely used, publications seem to use it less frequently [45]. Despite de above-mentioned, it is important to remember that there is no existing classification for individual outcome prognosis, as the International Working Group on the Diabetic Foot (IWGDF) states in its latest update [54]. Furthermore, developing the model based on information from two institutions with different populations does not constitute a representative sample, especially as hospitalization is typically reserved for advanced cases (excluding patients with low complexity conditions e.g., Wagner 0–1). This could limit the ability to generalize the results to other populations. Finally, external validation of the model is pending to assess its performance.

5. Conclusions

Wagner's classification demonstrated the best ability to predict the outcome with a grade 3 ulcer. Despite being questioned in the literature for its lack of specificity, this classification indirectly reflects the damage from infection and vascular injury that the patient may experience, in agreement with risk factors previously described in the literature. The results suggest that the development of a prediction model using a machine learning technique such as CART to foresee amputation for feet with DFU within the first 30 days of hospitalization is limited by the multifactorial nature of the pathology and, therefore, should be interpreted with caution. Finally, external validation of the model is still required to assess its true performance.

Declaration of Competing Interest

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.fas.2024.03.007.

References

[1] Spoden M, Nimptsch U, Mansky T. Amputation rates of the lower limb by amputation level - observational study using German national hospital discharge data from 2005 to 2015 (BMC Health Services Research. BMC Health Serv Res 2019;19(1):1–9. https://doi.org/10.1186/s12913-018-3759-5)

[2] Johannesson A, Larsson GU, Ramstrand N, Turkiewicz A, Wiréhn AB, Atroshi I. Incidence of lower-limb amputation in the diabetic and nondiabetic general population: a 10-year population-based cohort study of initial unilateral and contralateral amputations and reamputations. Diabetes Care 2009;32(2):275–80.

[3] Chun D il, Kim S, Kim J, Yang HJ, Kim JH, Cho J ho, et al. Epidemiology and burden of diabetic foot ulcer and peripheral arterial disease in Korea. J Clin Med 2019;8(5):748.

[4] ⟨https://idf.org/our-network/regions-members/south-and-central-america/diabetes-in-saca.html⟩.

[5] Triana-Ricci R. Pie diabético. Fisiopatología y consecuencias. Revista Colombiana de Ortopedia y Traumatología [Internet]. 2014 Dec 1 [cited 2022 Oct 4];28(4):143–53. Available from: ⟨https://www.elsevier.es/es-revista-revista-colombiana-ortopedia-traumatologia-380-articulo-pie-diabetico-fisiopatologia-consecuencias-S0120884515000486⟩.

[6] Dillon MP, Quigley M, Fatone S. Outcomes of dysvascular partial foot amputation and how these compare to transtibial amputation: a systematic review for the development of shared decision-making resources. Syst Rev 2017;6(1):1–20.

[7] Choi MSS, Jeon SB, Lee JH. Predictive factors for successful limb salvage surgery in diabetic foot patients. BMC Surg 2014;14(1):1–6.

[8] Acar E, Kacıra BK. Predictors of lower extremity amputation and reamputation associated with the diabetic foot. J Foot Ankle Surg 2017;56(6):1218–22.

[9] Pickwell K, Siersma V, Kars M, Apelqvist J, Bakker K, Edmonds M, et al. Predictors of lower-extremity amputation in patients with an infected diabetic foot ulcer. Diabetes Care 2015;38(5):852–7.

[10] Yang Y, Østbye T, Tan SB, Abdul Salam ZH, Yang KS, Ong BC. Risk factors for lower extremity amputation among patients with diabetes in Singapore. J Diabetes Complicat 2011;25(6):382–6.

[11] Guo Z, Yue C, Qian Q, He H, Mo Z. Factors associated with lower-extremity amputation in patients with diabetic foot ulcers in a Chinese tertiary care hospital. Int Wound J 2019;16(6):1304–13.

[12] Morbach S, Furchert H, Gröblinghoff U, Hoffmeier H, Kersten K, Klauke GT, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. Diabetes Care 2012;35(10):2021–7.

[13] Ahmed M, Widatalla A, Mahadi SE, Shawer M, Elsayem H. Implementation of diabetic foot ulcer classification system for research purposes to predict lower extremity amputation. Int J Diabetes Dev Ctries 2009;29(1):1.

[14] Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate future risk of blindness and lower limb amputation in patients with diabetes: Cohort study. BMJ 2015;351.

[15] Czerniecki JM, Thompson ML, Littman AJ, Boyko EJ, Landry GJ, Henderson WG, et al. Predicting reamputation risk in patients undergoing lower extremity amputation due to the complications of peripheral artery disease and/or diabetes. Br J Surg 2019;106(8):1026–34.

[16] O'Hare AM, Bacchetti P, Segal M, Hsu C yuan, Johansen KL. Factors associated with future amputation among patients undergoing hemodialysis: results from the dialysis morbidity and mortality study waves 3 and 4. Am J Kidney Dis 2003;41(1):162–70.

[17] Hüsers J, Hafer G, Heggemann J, Wiemeyer S, John SM, Hübner U. Predicting the amputation risk for patients with diabetic foot ulceration - a Bayesian decision support tool. BMC Med Inf Decis Mak 2020;20(1):1–10.

[18] Li CI, Lin CC, Cheng HM, Liu CS, Lin CH, Lin WY, et al. Derivation and validation of a clinical prediction model for assessing the risk of lower extremity amputation in patients with type 2 diabetes. Diabetes Res Clin Pr 2020;165:108231.

[19] Landry GJ, Silverman DA, Liem TK, Mitchell EL, Moneta GL. Predictors of healing and functional outcome following transmetatarsal amputations. Arch Surg 2011;146(9):1005–9.

[20] Beckert S, Witte M, Wicke C, Königsrainer A, Coerper S. A new wound-based severity score for diabetic foot ulcers: a prospective analysis of 1,000 patients. Diabetes Care 2006;29(5):988–92.

[21] Shammas AN, Jeon-Slaughter H, Tsai S, Khalili H, Ali M, Xu H, et al. Major limb outcomes following lower extremity endovascular revascularization in patients with and without diabetes mellitus. J Endovasc Ther 2017;24(3):376–82.

[22] Lipsky BA, Weigelt JA, Sun X, Johannes RS, Derby KG, Tabak YP. Developing and validating a risk score for lower-extremity amputation in patients hospitalized for a diabetic foot infection. Diabetes Care 2011;34(8):1695–700.

[23] Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a meta-analysis. PLoS One 2020;15(9 September):1–15.

[24] Orduz A, Tique C, Stetphens I, González A, Noel B, Tamayo D. Pie risk, una herramienta para la prevención del pie diabético. Revista Colombiana de Endocrinología. Diabetes amp; Metab 2016;Vol 3(Núm 1). Revista ACE Vol3 No1. 2017.

[25] Crawford F, Cezard G, Chappell FM, Young MJ, Abbott CA, Boulton AJM, et al. The development and validation of a multivariable prognostic model to predict foot ulceration in diabetes using a systematic review and individual patient data meta-analyses. Diabet Med 2018;35(11):1480–93.

[26] Tardivo JP, Baptista MS, Correa JA, Adami F, Pinhal MAS. Development of the tardivo algorithm to predict amputation risk of diabetic foot. PLoS One 2015;10(8):1–10.

[27] Barbern J, Granizo JJ, Aguilar L, Alguacil R, Sainz F, Menndez MA, et al. Predictive model of short-term amputation during hospitalization of patients due to acute diabetic foot infections. Enferm Infecc Microbiol Clin 2010;28(10):680–4.

[28] Venkatasubramaniam A, Wolfson J, Mitchell N, Barnes T, Jaka M, French S. Decision trees in epidemiological research. Emerg Themes Epidemiol 2017;14(1):1–12.
[29] Barlin JN, Zhou Q, St. Clair CM, Iasonos A, Soslow RA, Alektiar KM, et al. Classification and regression tree (CART) analysis of endometrial Carcinoma: seeing the forest for the trees. Gynecol Oncol 2013 Sep;130(3):452.
[30] Breiman L., Friedman J., Stone C.J.O.R.. Classification and Regression Trees by Leo Breiman. Chapter 7. 1999;(January):1–7.
[31] Classification and regression trees, CART | IFPRI: International Food Policy Research Institute [Internet]. [cited 2022 Oct 13]. Available from: ⟨https://www.ifpri.org/publication/classification-and-regression-trees-cart⟩.
[32] Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35(29):1925–31.
[33] Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21(1):128–38.
[34] Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. J Clin Epidemiol 2016;69:245–7.
[35] Song YY, Lu Y. Decision tree methods: applications for classification and prediction. Shanghai Arch Psychiatry 2015;27(2):130.
[36] Pemayun T.G.D., Naibaho R.M., Novitasari D., Amin N., Minuljo T.T. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a hospital-based case-control study. Diabet Foot Ankle [Internet]. 2015 Dec 7 [cited 2022 Jul 2];6. Available from: ⟨https://pubmed.ncbi.nlm.nih.gov/26651032/⟩.
[37] Endoh S, Yamana H, Nakahara Y, Matsui H, Fushimi K, Yasunaga H, et al. Risk factors for in-hospital mortality and reamputation following lower limb amputation. Prog Rehabil Med 2017;2(0):n/a.
[38] Skoutas D, Papanas N, Georgiadis GS, Zervas V, Manes C, Maltezos E, et al. Risk factors for ipsilateral reamputation in patients with diabetic foot lesions. Int J Low Extrem Wounds 2009;8(2):69–74.
[39] Shin JY, Roh SG, Sharaf B, Lee NH. Risk of major limb amputation in diabetic foot ulcer and accompanying disease: a meta-analysis. (Available from:). J Plast, Reconstr Aesthetic Surg 2017;70(12):1681–8. https://doi.org/10.1016/j.bjps.2017.07.015
[40] Izumi Y, Satterfield K, Lee S, Harkless L. Risk of reamputation in diabetic patients. Diabetes Care 2006;29:566–70.
[41] Ferreira L, Carvalho A, Carvalho R. Short-term predictors of amputation in patients with diabetic foot ulcers. Diabetes Metab Syndr: Clin Res Rev 2018;12(6):875–9.
[42] Santema TB, Lenselink EA, Balm R, Ubbink DT. Comparing the Meggitt-Wagner and the University of Texas wound classification systems for diabetic foot ulcers: inter-observer analyses. Int Wound J 2016;13(6):1137.
[43] Shah P, Inturi R, Anne D, Jadhav D, Viswambharan V, Khadilkar R, et al. Wagner's classification as a tool for treating diabetic foot ulcers: our observations at a suburban teaching hospital. Cureus 2022;14(1).
[44] Jeon BJ, Choi HJ, Kang JS, Tak MS, Park ES. Comparison of five systems of classification of diabetic foot ulcers and predictive factors for amputation. Int Wound J 2017;14(3):537–45.
[45] Monteiro-Soares M, Boyko EJ, Jeffcoate W, Mills JL, Russell D, Morbach S, et al. Diabetic foot ulcer classifications: a critical review. Diabetes Metab Res Rev 2020;36(S1):1–16.
[46] Camilleri A, Gatt A, Formosa C. Inter-rater reliability of four validated diabetic foot ulcer classification systems. (Available from:). J Tissue Viability [Internet] 2020;29(4):284–90. https://doi.org/10.1016/j.jtv.2020.09.002
[47] Bravo-Molina A, Linares-Palomino JP, Vera-Arroyo B, Salmerón-Febres LM, Ros-Díe E. Inter-observer agreement of the Wagner, University of Texas and PEDIS classification systems for the diabetic foot syndrome. (Available from:). Foot Ankle Surg 2018;24(1):60–4. https://doi.org/10.1016/j.fas.2016.10.009
[48] Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio MDR S. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. Diabetes Metab Res Rev [Internet] 2014;32(30):13–23. (Available from). ⟨http://libweb.anglia.ac.uk/⟩.
[49] Sen P, Demirdal T, Emir B. Meta-analysis of risk factors for amputation in diabetic foot infections. Diabetes Metab Res Rev 2019;35(7):1–16.
[50] Chemello G, Salvatori B, Morettini M, Tura A. Artificial intelligence methodologies applied to technologies for screening, diagnosis and care of the diabetic foot: a narrative review. Biosens 2022;12(11):985.
[51] Jian Y, Pasquier M, Sagahyroon A, Aloul F. A machine learning approach to predicting diabetes complications. Healthcare 2021;9(12):1712. 9.
[52] Mousa KM, Mousa FA, Mohamed HS, Elsawy MM. Prediction of foot ulcers using artificial intelligence for diabetic patients at Cairo University Hospital, Egypt. SAGE Open Nurs 2023;9.
[53] Power M, Fell G, Wright M. Principles for high-quality, high-value testing. Evid-Based Med 2013;Vol. 18:5–10.
[54] IWGDF Guidelines, Classification [Internet]. [cited 2024 Jan 06]. Available from: ⟨https://iwgdfguidelines.org/classification-2023/⟩.