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Development of a Prediction Model for Lower Limb Amputation in Hospitalized Diabetic Foot Patients Using Classification Trees (CART)

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Abstract:	Background The decision to perform ablative management of a limb in a patient with diabetic foot ulceration (DFU) has never been 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 underwent a lower limb amputation during the first 30 days of hospitalization. Six different models were developed using a loss matrix to evaluate the cost 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 exceeded others in its predicting capacity. Conclusions Wagner classification was the variable with the best capacity for predicting amputation within 30 days with a cut-off score of 3. 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.
Suggested Reviewers:	

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Dear Editor in chief,

The manuscript being submitted is the result of an independent research developed in two teaching hospitals in Bogotá - Colombia and received no funding at all. This retrospective cohort study aims to develop a prediction model for 30-day lower limb amputation for patients with diabetic foot ulceration (DFU) using machine learning. Though prediction models for this outcome have been studied previously in literature, results of these studies are heterogeneous and comparison among models is difficult. Furthermore, none of them use a 30-day time frame and, regretfully, some of them lack statistical rigor which limits the applicability of such results in different contexts in clinical practice. Our study aimed to provide a better understanding of the risk factors that should be considered when treating DFU.

We hope that our manuscript will be considered for publication.

If there are any doubts regarding the manuscript, in representation of my research team, I will be glad to answer your queries.

Kind regards,

Carlos Alberto Sánchez.

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Abstract

Background

To develop a prediction model to determine lower limb amputation during the first 30 days of hospitalization for patients with diabetic foot ulcer (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 underwent a lower limb amputation during the first 30 days of hospitalization. Six different models were developed using a loss matrix to evaluate the cost 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* exceeded others in its predicting capacity.

Conclusions

Wagner classification was the variable with the best capacity for predicting amputation within 30 days with a cut-off score of 3. 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.

Key words: Diabetic Foot; Foot ulcer; Wagner; Amputation; Forecasting; Classification And Regression Trees; Machine learning.

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 ablative management of a limb in a patient with diabetic foot ulceration (DFU) has never been an easy task. The debate has focused on determining the "appropriate" surgical management for each patient, 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. While there are models for predicting risk factors for lower limb amputation in DFU patients, 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 lacks meta-analyses, sufficient systematic reviews, and clinical experiments to provide a better understanding of risk factors and the amputation in DFU.

Consequently, a retrospective cohort study was conducted to develop a prediction model using classification trees to identify the clinical variables that best predict the amputation outcome in lower limbs within the first 30 days of hospitalization in the study population.

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 study included patients aged 18 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 were not amputated and had died before completing 30 days from admission to the service were also excluded.

2.1 Statistical Analysis

Initially, a descriptive analysis of the variables studied was performed according to patients 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, 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, respectively, 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.

2.2 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 in 1984 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).

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). 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 (32–34). Additionally, a sensitivity analysis was conducted using a loss matrix that considered the cost of misclassification that could have existed in the original model (1.5 and 2 times the cost of not correctly classifying the outcome). Finally, the model was evaluated through cross-validation (31,35).

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

3. Results

The database initially included 573 patients 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 individuals available for model

development. A total of 290 patients with the outcome of interest were identified, resulting in an incidence of 0.52 cases 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 (**Table 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 **Figure 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, corresponding to the Wagner score, with the lowest CP and error (0.018 and 0.76, respectively) (**Table 7; Figure 2**).

When evaluating this model using a ROC curve, a sensitivity and specificity of 69% and 75% were detected (AUC = 0.764) (**Figure 3**).

4. Discussion

The results of the study indicate that, despite the large amount of variables included in the model, amputation for patients in this cohort is primarily determined by the Wagner classification with a cut-off score of 3. Several studies reveal that developing a prediction model for amputation in a multifactorial condition like DFU is a challenging task (8–27,36–40). The time to reach the outcome in these studies varies, and in the context of 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).

Literature agrees that infection in DFU and vascular involvement of the limb are variables that may carry significant weight 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-Meggitt classification remains the most widely known and used in the literature (42–46). Additionally, studies by Jeon, Camilleri, and Bravo-Molina et al 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, as described by Monteiro-Soares et al in 2014 (48).

This aligns with what has been described by Guo and Barbern et al, who report an odds ratio (OR) of around 20 times higher concerning risk of amputation as severity of a DFU increases (11,27). These observational studies are complemented by the results of the meta-analysis published by Sen et al in 2019, which identified 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).

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 (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 (50–52). This model could facilitate decision-making in healthcare institutions, reducing hospitalization times, procedure-related

complications, and even direct and indirect costs. This goes beyond the scope of this study but raises new research hypotheses. 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.

Our study is not without limitations. The sample size and available data allowed for the development of various models; however, the model with the best diagnostic performance had an AUC of 0.764. This does not provide a high discriminatory capacity and is far from being a perfect tool; nevertheless, it was the model that offered the best diagnostic performance based on the balance between sensitivity and specificity (53). On the other hand, 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 avoid using it (45). 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 cut- off score of 3. 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 in patients with UPD within the first 30 days of hospitalization is limited by the multifactorial nature of the pathology and, therefore, should be interpreted with caution. Finally, this study raises new hypotheses for the development of further research, and external validation of the model is still required to assess its true performance.

6. 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.

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Declaration of interests

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Table 1. Reported risk factors for lower limb amputation in Diabetic Foot.

	Study	Year	Study design	Sample size	Risk factors	Amputated	Non amputated	Measure of association (OR/ HR [IC 95%])	p- value
1	Acar et al (8)	2017	Retrospective cohort	132	Male, long standing DM, infected DFU, Diabetic neuropathy, smoking	110	22	Male 5.12 [1.56 – 13.04]; long standing DM 4.22 [2.01 - 12.95]; infected DFU 3.94 [1.04 - 9.00]; diabetic neuropathy 3.53 [1.07 - 9.11]; Smoking 3.04 [1.55 - 9.89]	0.05
2	Pickwel et al (9)	2015	Retrospective cohort	575	Perilesional edema, foul odor, purulent or non- purulent drainage, Deep ulcer, positive bone probe, fever, high CRP (higher than 3 times normal value).	159	416	Perilesional edema HR 2.01 [1.33–3.03]; Foul odor 1.74 [1.17–2.57]; Purulent or non- purulent drainage 1.67 [1.17–2.37] & 1.49 [1.02–2.18]; Deep ulcer 3.49 [1.84–6.60]; positive bone probe 6.78 [3.79–12.15]; Fever 2.00 [1.15–3.48]; High CRP 3.84 [2.07–7.12]	-
3	Ferreira et al (41)	2018	Retrospective observational	479	Moderate – severe infection, previous LLA, PAD, any gait abnormality	48	431	Moderate – severe infection 5.23 [2.51-10.80]; Previous LLA 3.93 [1.81-8.53]; PAD 3.51 [1.29-9.58]; Any gait abnormality 3.35 [1.58-7.13]	Moderate – severe infection (< 0.001); Previous LLA (0.001); PAD (0.014); Any gait abnormality (0.002)

	Study	Year	Study design	Sample size	Risk factors	Amputated	Non amputated	Measure of association (OR/ HR [IC 95%])	p- value
4	Yang et al (10)	2011	Retrospective cohort	44917	CKD, ethnicity	1457	43460	CKD 3.2 [2.8–3.6]; Ethnicity 1.6, Malayans vs. Chinese/ 1.0, Indians vs. Chinese	< 0.001
5	Guo et al (11)	2019	Retrospective cohort	475	HbA1c, low triglycerides, Wagner	59	416	HbA1c 1.37 [1.015-1.709]; Low Triglycerides 0.255 [0.067-0.975]; Wagner 20.94 [4.216-104.080]	HbA1c (0,039), Low triglycerides (0,046), Wagner (< 0,001)
6	Morbach et al (12)	2012	Retrospective cohort	247	Age, dialysis, PAD	38	209	Age 1.05 [1.01–1.10]; Dialysis 3.51 [1.02–12.07]; PAD 35.34 [4.81–259.79]	Age (0.023), dialysis (0.046), PAD (< 0.001)
7	Ahmed et al (13)	2009	Prospective cohort	2321	Critical extremity ischemia, terminal CKD, Deep DFU, sepsis	661	1660	Critical extremity ischemia 5.08 [2.56–10.07]; Terminal CKD 4.39 [1.53–12.61]; Deep DFU 3.45 [2.02–5.88]; Sepsis 2.4 [1.55–3.7]	Critical extremity ischemia (0,000), Terminal CKD (0.003), Deep DFU (< 0.005), sepsis (< 0.005)
8	Pemayun et al (36)	2015	Case - control	94	HbA1c >=8%, PAD, Hypertriglyceridemia, HBP	47	47	HbA1c >=8% 20.47 [3.12- 134.31]; EAP 12.97 [3.44 - 48.88]; Hipertrigliceridemia 5.58 [1.74 - 17.91]; HTA 3.67 [1.14 - 11.79]	HbA1c >=8% (0.002), PAD (<0.001), Hypertriglyceridemia (0.004), HBP (0.028)
9	Hippisley-Cox et al (14)	2015	Prospective cohort	454575	DM diagnosis > 10 years, smoking, RA, CHF, PAD, CKD	4822	449753	DM diagnosis > 10 years 3.49 [3.15 - 3.86]; Smoking 1.89 [1.49 - 2.41]; RA 1.50 [1.19 - 1.90]; CHF 1.79 [1.44 - 2.22]; PAD 4.26 [3.63 - 4.99]; CKD 2.68 [1.96 - 3.66]	-

	Study	Year	Study design	Sample size	Risk factors	Amputated	Non amputated	Measure of association (OR/ HR [IC 95%])	p- value
10	Czerniecki et al (15)	2019	Retrospective cohort	5260	Male, smoking, alcohol, resting pain, gangrene, DM, revascularization, CKD, leucocyte count >11,000	1283	3977	-	-
11	O'Hare et al (16)	2003	Retrospective cohort	2665	Male, PAD, high SBP, high phosphorus	183	2482	Male 1.42 [1.03-1.96]; PAD 3.18 [2.31-4.39], high SBP 1.11 [1.03-1.20]; High phosphorus 1.82 [1.17-2.83]	Male (0.031), PAD (<0.001), High SBP (0.007), High phosphorus (0.008)
12	Hüsers et al (17)	2020	Prospective cohort	254	PEDIS (Perfusion, Extension, Depth, Infection, Sensation)	104	150	Perfusion 2.020 [1.422–3.052]; Extension 3.609 [1.754–9.326]; Depth 1.927 [1.183–3.677]; Infection 0.979 [0.644–1.446]; Sensation 1.675 [0.738–3.397]	-
13	Barbern et al (27)	2010	Retrospective cohort	78	Wagner 4 & 5, arterial occlusion in Doppler, ESR	26	52	Wagner 4 & 5 20.00 [3.62–111.11]; Arterial occlusion in Doppler 12.50 [1.42–66.67]; ESR 1.06 [1.01–1.10]	Wagner 4 & 5 (0.001); Arterial occlusion in Doppler (0.003); ESR (0.013)

	Study	Year	Study design	Sample size	Risk factors	Amputated	Non amputated	Measure of association (OR/ HR [IC 95%])	p- value
14	Li et al (18)	2020	Retrospective cohort	21484	Age, male, 1 to 5-year DM diagnosis, DM diagnosis >5 years, BMI <25 kg/m2, HbA1c > 7%, triglyceride > 150 mg/dL, GFR <60 mL/min/1.73 m2, change in fasting glucose >34.9%, stroke, diabetic retinopathy, hypoglycemia, DFU, insulin use, insulin + oral hypoglycemics, + diuretics, + nitrates	504	20980	Age 1.04 [1.03–1.05]; Male1.33 [1.08–165]; 1 to 5-year DM diagnosis 2.80 [1.42–5.55]; DM diagnosis >5 years 6.55 [3.36–12.75]; BMI <25 kg/m2 1.48 [1.18–1.87], HbA1c > 7% 1.94 [1.47–2.57]; Triglyceride > 150 mg/dL 1.43 [1.15–1.77]; GFR <60 mL/min/1.73 m2 3.13 [2.53–3.88]; change in fasting glucose >34.9% 2.07 [1.58–2.71]; stroke 2.84 [2.03–3.98], Diabetic retinopathy 2.75 [1.89-4.00]; Hypoglycemia 2.71 [3.33–16.71], DFU 7.46 [3.33–16.71]; insulin use 7.03 [3.27–15.13], insulin + oral hypoglycemics 5.22 [2.49–10.96]; + Diuretics 2.25 [1.75-2.90]; + Nitrates 2.77 [1.76–4.35]	Age (<0,001), Male (0,009), 1 to 5- year DM diagnosis (0,003), DM diagnosis >5 years (<0,001), BMI <25 kg/m2 (<0,001), HbA1c > 7% (<0,001), triglyceride > 150 mg/dL (0,001), GFR <60 mL/min/1.73 m2 (<0,001), change in fasting glucose >34.9% (<0,001), stroke (<0,001), diabetic retinopathy (<0,001), hypoglycemia (<0,001), DFU (<0,001), insulin use (<0,001), insulin + oral hypoglycemics (<0,001), + diuretics (<0,001), + nitrates (<0,001)

	Study	Year	Study design	Sample size	Risk factors	Amputated	Non amputated	Measure of association (OR/ HR [IC 95%])	p- value
15	Lipsky et al (22)	2011	Retrospective cohort	3018	Surgical site infection, PAD, Previous LLA, leucocyte >11,000/mm3	646	2372	Surgical site infection 3.99 [2.44–6.55]; PAD 2.11 [1.66–2.69]; Previous LLA 1.65 [1.29–2.11]; leucocyte >11,000/mm3 2.61 [2.07–3.30]	< 0,0001
16	Choi et al (7)	2014	Retrospective cohort	154	Hb, leucocyte, CRP, number of affected vessels (1 to 3)	30	124	2 vessels 16,7 [4,98 - 55,8]; 3 vessels 21,5 [6,48 - 71,86]; Anterior tibial artery 10,40 [4,08 - 26,48]; Posterior tibial artery5,06 [2,63 - 9,73]; Peroneal artery 4,22 [2,24 - 7,98]	< 0,01
17	Endoh et al (37)	2017	Retrospective cohort	13774	Male, old age, PAD, insulin use, hemodialysis, high Charlson Comorbidity index (CCI)	782	12992	Male 1.14 [1.03 – 1.26]; Old age 1.03 [1.03 – 1.04]; PAD 1.21 [1.05 – 1.39]; Insulin use 1.38 [1.24 – 1.53]; Hemodialysis 2.10 [1.87 – 2.35]; High CCI 1.50 [1.27 – 1.76]	< 0,001
18	Skoutas et al (38)	2009	Prospective cohort	121	Age, heel injury	26	95	Age 1.06; Heel injury 2.69	Age (0,01); Heel injury (0,05)
19	Shin et al (39)	2017	Systematic review and meta-analysis	51034	HBP, coronary artery disease, stroke, PAD	654	50380	HBP 2,078; Coronary disease 1,971; Stroke 2,242; PAD 2,004	HBP (0,038); coronary artery disease (0,049); Stroke (0,025); PAD (0.045)
20	Izumi et al (40)	2006	Retrospective cohort	277	Age, PAD, CKD	168	109	-	< 0,001
21	Lin et al (23)	2020	Systematic review and meta-analysis	6505	Male, smoking, previous DFU, osteomyelitis, gangrene, low BMI, leukocytosis	2006	4499	Male 1.30 [1.16 - 1.46]; Smoking 1.19 [1.04 -1.35]; Previous DFU 2.48 [2.00 - 3.07]; Osteomyelitis 3.70 [3.02 - 4.53]; Gangrene 10.90 [5.73 - 20.8]; Low BMI -0.88 [-1.30 - -0.47]; Leukocytosis 2.42 [2.02 - 2.82]	Male (<0.00001); Smoking (0.009); Previous DFU (<0.00001); Osteomyelitis (<0.00001); Gangrene (<0.00001); Low BMI (<0.0001); Leukocytosis (<0.00001)

	Study	Year	Study design	Sample size	Risk factors	Amputated	Non amputated	Measure of association (OR/ HR [IC 95%])	p- value
22	Sen et al (49)	2019	Systematic review and meta-analysis	6132	Male, smoking, previous amputation, osteomyelitis, PAD, International Working Group on the Diabetic Foot (IWGDF) 3 & 4, Wagner 4 & 5, gangrene/ necrosis, neuro-ischemic infection, severe infection, hospitalization time, leukocytes >11 000/mm3, ESR, CRP, positive infection in culture, GN in culture	1873	4259	Male 1.31 [1.138-1.509]; smoking 1.38 [1.032 - 1.838]; Previous Amputation 1.47 [1.242-1.734]; Osteomyelitis 1.94 [1.336-2.826]; PAD 2.35 [1.484-3.718]; IWGDF 3 1.7 [1.398-2.061] & 4 2.5 [1.647-3.823]; Wagner 4 4.3 [1.090-17.166] & 5 6.4 [2.535-16.134]; Gangrene/ necrosis 9.9 [6.243-15.699]; Neuro- ischemic infection 3.06 [1.433-6.532]; Severe infection 3.12 [2.008-4.855]; Hospitalization time 0.7 [0.45-0.95]; Leucocytes >11 000/mm3 1.76 [1.209-2.550], ESR 0.5 [0.236-0.761]; CRP 0.8 [0.561-1.035]; Positive infection in culture 1.61 [1.096-2.363]; GN in culture 1.5 [1.029-2.160]	Male (< 0.001); Smoking (0.03); Previous Amputation (< 0.001); Osteomyelitis (0.001); PAD (< 0.001); IWGDF 3 & 4 (< 0.001); Wagner 4 (0.03) & 5 (< 0.001); Gangrene/ necrosis (< 0.001); Neuro-ischemic infection (0.004); Severe infection (< 0.001); Hospitalization time (< 0.001); Leucocytes >11 000/mm3 (0.003); ESR (< 0.001); CRP (< 0.001); Positive infection in culture (0.01); GN in culture 1.5 (0.03)

HbA1c% (Glycated hemoglobin); CKD (chronic kidney disease); DM (Diabetes Mellitus); BMI (Body Mass Index); PAD (Peripheral Artery disease); CRP (C Reactive Protein); ESR (Erythrocyte Sedimentation Rate); GN (Gram Negative); HBP (High Blood Pressure); RA (Rheumatoid Arthritis); LL (Lower Limb); LLA (Lower Limb Amputation); DFU (Diabetic Foot Ulcer); GFR (Glomerular Filtration Rate); SBP (Systolic Blood Pressure)

Table 2. *Patients' characteristics*

	Group A (n = 290)		Group B (n = 263)		OR	CI 95%	p – value
	n	%	n	%			
Age (years)					2.4	0.8; 3.3	0.2
Mean	66.1		63.7				
SD	11.7		12.4				
Median	66.0		65.0				
1q	58.3		55.5				
3q	75.0		72.5				
Hospital							
HUS	182	62.8	162	61.6	1.1	0.7; 1.5	0.9
HUSI	108	37.2	101	38.4	1.0	0.7; 1.4	
Sex							
Male	191	65.9	181	68.8	0.9	0.6; 1.3	0.5
Female	99	34.1	82	31.2	1.1	0.8; 1.7	
Smoking history							
Yes	115	39.7	111	42.2	0.8	0.6; 1.2	0.6
No	155	53.4	120	45.6	1.2	0.9; 1.8	
ND	20	6.9	32	12.2			
HBP history							
Yes	212	73.0	188	71.5	1.1	0.7; 1.6	0.7
No	78	27.0	75	28.5	1.0	0.6; 1.4	0.7
Time since DM diagnosis (years)							
<10	66	22.8	76	28.9	0.7	0.5; 1.1	0.1
>10	224	77.2	187	71.1	1.4	0.9; 2.1	0.1
CKD history							
Yes	178	61.4	143	54.4	1.3	0.9; 1.9	0.1
No	112	38.6	120	45.6	0.8	0.5; 1.0	0.1
Dialysis in CKD							
Yes	46	15.9	30	11.4	1.3	0.8; 2.3	0.2
No	133	45.9	113	43.0	0.8	0.4; 1.3	0.6
NA	111	38.2	120	45.6			
Death during follow up							
Yes	16	5.5	21	8.0	0.7	0.3; 1.4	0.3
No	274	94.5	242	92.0	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)**

Table 3. *Lower limb amputation characteristics*

	Group A (n = 290)		Group B (n = 263)		OR	CI 95%	p - value	
	n	%	n	%				
Previous LLA								
Yes	111	38.3	117	44.5	0.8	0.5; 1.1	0.2	
No	179	61.7	146	55.5	1.3	0.9; 1.8		
Previous LLA side								
Right	60	20.7	72	27.4	0.7	0.4; 1.3	1.0	
Left	51	17.6	45	17.1	1.4	0.8; 2.4		
NA	179	61.7	146	55.5	-	-		
Previous LLA level								
Supracondylar	15	5.2	26	9.9	0.6	0.3; 1.2	0.05	
Transtibial	9	3.1	8	3.0	1.2	0.4; 3.7	1.0	
Syme	5	1.7	0	0.0	-	-	-	
Chopart	2	0.7	2	0.8	1.1	0.1; 14.8	1.0	
Lisfranc	7	2.4	5	1.9	1.5	0.4; 6.2	0.9	
Toes	73	25.2	76	28.9	1.0	0.6; 1.9	0.4	
Disarticulation	0	0.0	0	0.0	-	-		
None	179	61.7	146	55.5	-	-		
Reamputation								*
Yes	102	35.2	67	25.5	0.4	0.3; 0.6	<0.01	
No	188	64.8	50	19.0	2.5	1.6; 3.9		
NA	-	-	146	55.5				
Total number of amputations					0.4	0.2; 0.6	<0.01	*
Mean	1.5		1.1					
SD	0.74		1.2					
Cardinal amputation side								
Right	147	50.7	57	22.0	1.1	0.6; 1.5	0.8	
Left	143	49.3	60	22.5	0.9	0.6; 1.5		
NA	-	-	146	55.5				
Cardinal amputation level								
Supracondylar	119	41.0	60	51.3	0.7	0.4; 1.0	0.1	
Transtibial	60	20.7	18	15.4	1.4	0.8; 2.7	0.3	
Syme	6	2.1	4	3.4	0.6	0.1; 2.9	0.7	
Chopart	4	1.4	1	0.9	1.6	0.2; 80.5	1.0	
Lisfranc	16	5.5	6	5.0	1.1	0.4; 3.5	1.0	
Toes	80	27.6	27	23.1	1.3	0.8; 2.2	0.4	

Disarticulation	5	1.7	1	0.9	2.0	0.2; 97	0.8	
None	-	-	-	-	-	-		
Total number of surgeries					1.0	0.2; 1.1	0.1	
Mean	3.0		3.5					
SD	2.2		3.2					
Median	2.0		3.0					
1q	1.0		1.0					
3q	4.0		5.0					
Time from admission to amputation (days)					-	277.9; 452.5	<0.01	*
Mean	9.0		374					
SD	7.1		7.1					
Median	7.0		105					
1q	4.0		52.0					
3q	12.0		314.0					

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

Table 4. *Vascular and therapeutical characteristics of DFU patients*

	Group A (n = 290)		Group B (n = 263)		Difference/ OR	CI 95%	p - value	
	n	%	n	%				
Use of vacuum therapy								
Yes	34	11.7	64	24.3	0.4	0.2; 0.6	<0.01	*
No	253	87.3	186	70.7	2.6	1.6; 1.2		
ND	3	1.0	13	4.9	-	-		
Vascular surgery intervention								
Stent	45	15.5	44	16.7	1.1	0.6; 1.9	0.8	
Bypass	22	7.6	23	8.7	1.0	0.5; 2.0	0.7	
Medical	46	15.9	48	18.3	1.0	0.5; 1.7	0.5	
None	177	61.0	148	56.3	-	-		
Microvascular damage in photoplethysmography								
Yes	77	26.6	52	19.8	2.0	1.0; 4.0	0.1	
No	14	4.8	23	8.7	0.4	0.2; 0.9	<0.05	*
Undetermined	7	2.4	5	1.9	1.2	0.3; 4.8	0.9	
ND	192	66.2	183	69.6	-	-		
Arterial occlusion in Doppler ultrasound								
Yes	187	64.5	150	57.0	1.4	1.0; 2.0	0.1	
No	55	19.0	46	17.5	1.1	0.7; 1.8	0.7	
No hemodynamic repercussion	48	16.5	67	25.5	0.6	0.4; 1.0	0.1	
Arterial occlusion in Doppler ultrasound per side								
Right	71	24.5	47	17.9	1.6	1.0; 2.5	0.07	
Left	66	22.8	58	22.1	1.1	0.7; 1.7	0.9	
Bilateral	98	33.7	112	42.6	0.7	0.5; 1.0	0.05	
NA	55	19.0	46	17.5	-	-		
Arterial occlusion in Doppler ultrasound per level in right LL								
Superficial femoral	26	9.0	21	8.0	0.9	0.5; 1.9	0.8	
Deep femoral	4	1.4	1	0.4	3.1	0.3; 156.2	0.4	
Popliteal	9	3.1	10	3.8	0.7	0.2; 1.9	0.8	
Fibular	13	4.5	5	1.9	2.1	0.7; 7.8	0.14	
Anterior tibial	18	6.2	9	3.4	1.6	0.7; 4.3	0.19	
Posterior tibial	14	4.8	9	3.4	1.2	0.5; 3.3	0.5	
3 or > vessels	51	17.6	49	18.6	0.7	0.4; 1.2	0.8	

No hemodynamic repercussion	155	53.4	159	60.5	0.8	0.5; 1.1	0.11	
Right LL arterial occlusion (%)								
<50	170	58.6	171	65.0	0.8	0.5; 1.1	0.11	
>50	120	41.4	92	35.0	1.3	0.9; 1.9		
Arterial occlusion in Doppler ultrasound per level in left LL								
Superficial femoral	25	8.6	23	8.8	1.0	0.5; 1.9	1.00	
Deep femoral	2	0.7	0	0.0	-	-		
Popliteal	13	4.5	10	3.8	1.2	0.5; 3.2	0.9	
Fibular	11	3.8	10	3.8	1.0	0.4; 2.7	1.0	
Anterior tibial	15	5.2	14	5.3	1.0	0.4; 2.3	1.0	
Posterior tibial	13	4.5	3	1.1	4.2	1.1; 23.6	<0.05	*
3 or > vessels	48	16.6	54	20.5	0.7	0.4; 1.2	0.3	
No hemodynamic repercussion	163	56.1	149	56.7	1.0	0.7; 1.4	0.9	
Left LL arterial occlusion (%)								
<50	175		163		0.9	0.7; 1.3	0.4	
>50	115		100		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)**

Table 5. *Infectious and metabolic characteristics of DFU patients*

	Group A (n = 290)		Group B (n = 263)		Difference/ OR	CI 95%	p - value	
	n	%	n	%				
Wagner								
0	4	1.4	5	1.9	0.7	0.1; 3.4	0.9	
1	1	0.3	7	2.7	0.1	0.003; 1.0	0.06	
2	28	9.7	60	22.8	0.4	0.2; 0.6	<0.05	*
3	74	25.5	99	37.6	0.6	0.4; 0.8	<0.01	*
4	172	59.3	87	33.1	2.9	2.0; 4.2	<0.01	*
5	11	3.8	5	1.9	2.0	0.6; 7.6	0.3	
Leucocyte count (cel/mm^3)					1933.68	921.2; 2946.1	<0.01	*
Mean	13965.0		11970.1					
SD	6262.2		5807.8					
Median	12465.0		10750.0					
1q	9732.0		8625.0					
3q	17238.0		14100.0					
CRP (mg/dL)					31.3	17.6; 45.1	<0.01	*
Mean	89.3		58.4					
SD	89.9		73.7					
Median	44.8		23.0					
1q	16.6		9.3					
3q	153.0		78.9					
ESR (mm/h)					4.2	- 3.1; 11.4	0.3	
Mean	66.2		61.2					
SD	42.8		44.2					
Median	64.0		60.0					
1q	29.3		24.5					
3q	97.8		87.5					
Time of ulcer development								
Days	42	14.5	39	14.8	1.0	0.6; 1.6	1.00	
Weeks	84	29.0	80	30.4	1.0	0.7; 1.4	0.78	
Months	130	44.8	120	45.6	1.0	0.7; 1.4	0.9	
Years	25	8.6	19	7.3	1.2	0.6; 2.4	0.70	
ND	9	3.1	5	1.9				
HbA1c (%)					0.1	- 0.8; 0.6	0.9	
Mean	7.7		7.7					
SD	4.4		4.0					
Median	8.2		7.9					
1q	6.0		6.2					
3q	10.5		10.2					
Glucose (mg/dL)					3.0	-16.6; 22.6	0.8	
Mean	214.1		212.4					
SD	120.1		114.8					
Median	196.0		189.0					

1q	124.2		124.0					
3q	280.2		283.5					
Leucocyte count (cel/mm^3)							<0.01	
<11000	100	34.5	134	51.0	0.5	0.4; 0.7		*
>11000	190	65.5	129	49.0	2.0	1.4; 2.8		
CRP (mg/dL)							<0.01	
<10	39	13.5	64	24.3	0.5	0.3; 0.8		*
>10	251	86.5	199	75.7	2.1	1.3; 3.3		
ESR (mm/h)								
<15	39	13.5	44	16.7	0.8	0.5; 1.3	0.3	
>15	251	86.5	218	82.9	1.3	0.8; 2.1	0.3	
ND			1	0.4				
HbA1c (%)								
<7	99	34.1	93	35.4	1.0	0.7; 1.4	0.8	
>7	187	64.5	168	63.9	1.0	0.7; 1.5	0.1	
ND	4	1.4	2	0.7				
Glucose (mg/dL)								
>126	77	26.5	70	26.6	1.0	0.7; 1.5	1.0	
<126	213	73.5	193	73.4	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)**

Table 6. *Microorganism in monomicrobial ulcer culture*

	Group A (n = 290)		Group B (n = 263)		Difference/ OR	CI 95%	p - value	
	n	%	n	%				
Escherichia coli	19	6.6	19	7.2	0.9	0.4; 1.9	0.89	
Proteus Mirabilis	15	5.2	8	3.0	1.8	0.7; 5.2	0.30	
Pseudomona Aeruginosa	11	3.8	8	3.0	1.3	0.4; 3.8	0.80	
Streptococcus anginosus	7	2.4	1	0.4	6.7	0.8; 304	0.1	
Streptococcus agalactiae	5	1.7	5	1.9	0.9	0.2; 4.0	1.00	
Proteus Vulgaris	1	0.3	1	0.4	1.0	0.01; 71.4	1.00	
Staphylococcus Aureus	5	1.7	18	6.8	0.2	0.1; 0.6	<0.01	*
Enterococcus Faecalis	7	2.4	4	6.8	1.6	0.4; 7.8	0.66	
Staphylococcus Epidermidis	2	0.7	2	1.5	0.9	0.1; 12.6	1.00	
Klebsiella pneumoniae	6	2.1	3	1.1	1.9	0.4; 11.8	0.60	
Pseudomonas putida	0	0.0	0	0.0	-			
Serratia liquefaciens	1	0.3	0	0.0	-			
Morganella morganii	9	3.2	6	2.3	1.4	0.4; 4.9	0.74	
Citrobacter Freudii	1	0.3	1	0.4	0.9	0.01; 71.4	1.00	
Klebsiella oxytoca	0	0.0	2	0.8	-	-		
Serratia marcescens	1	0.3	2	0.8	0.5	0.01; 8.7	0.9	
Enterobacter cloacae complex	3	1.1	1	0.4	2.7	0.2; 146	0.69	
Aeromonas hydrophila	0	0.0	0	0.0	-	-		
Enterococcus faecium	3	1.0	0	0.0	-	-		
Staphylococcus lugdunensis	0	0.0	2	0.8	-	-		
Streptococcus pyogenes	0	0.0	2	0.8	-	-		
Enterobacter aerogenes	0	0.0	1	0.4	-	-		
Acinetobacter baumannii	0	0.0	0	0.0	-	-		
Negative	5	1.7	5	1.9	0.9	0.2; 4.0	1.00	
NA	189	65.2	172	65.4	-	-		

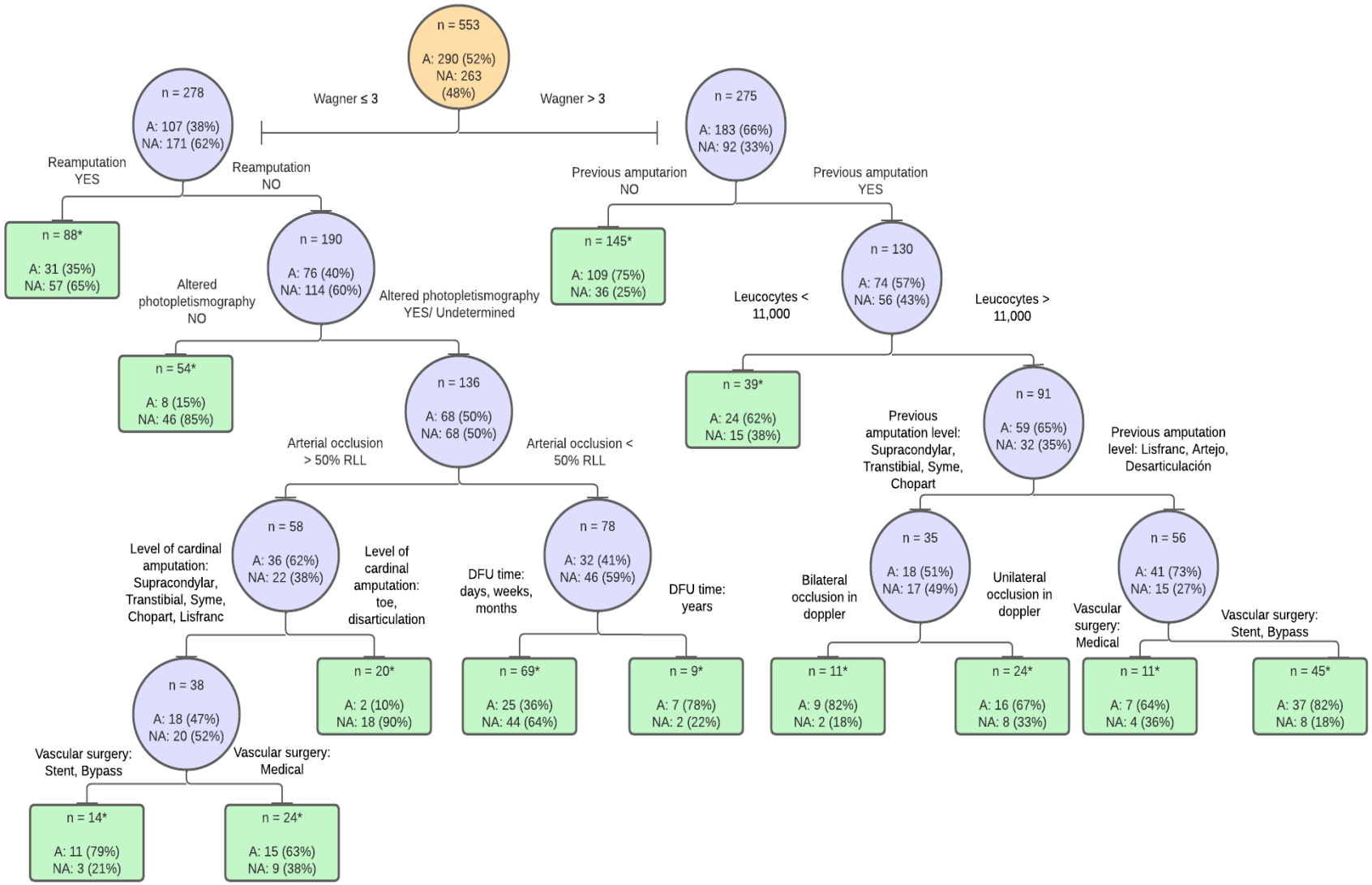
***Statistically significant variable (alfa <0.05); NA (Non applicable); ND (No Data); OR (Odds ratio); SD (Standard deviation)**

Table 7. CART characteristics

Complexity parameter	Divisions	Relative error	Cross validation error	Cross validation SD	
0.243346	0	1	1	0.044654	
0.017744	1	0.75665	0.75665	0.042915	*
0.017110	5	0.68441	0.78327	0.043229	
0.015209	7	0.65019	0.81749	0.043587	
0.013308	9	0.61977	0.80608	0.043474	
0.011407	11	0.59316	0.85171	0.043894	
0.010000	12	0.58175	0.85171	0.043894	

*** Best model**

Figure 1. CART for predicting lower limb amputation.



n (Total individuals in a node); A (Individuals with LLA < 30 days); NA (Individuals not amputated < 30 days); RLL (Right Lower Limb); * Terminal node

Figure 2. CP and cross validation error graph

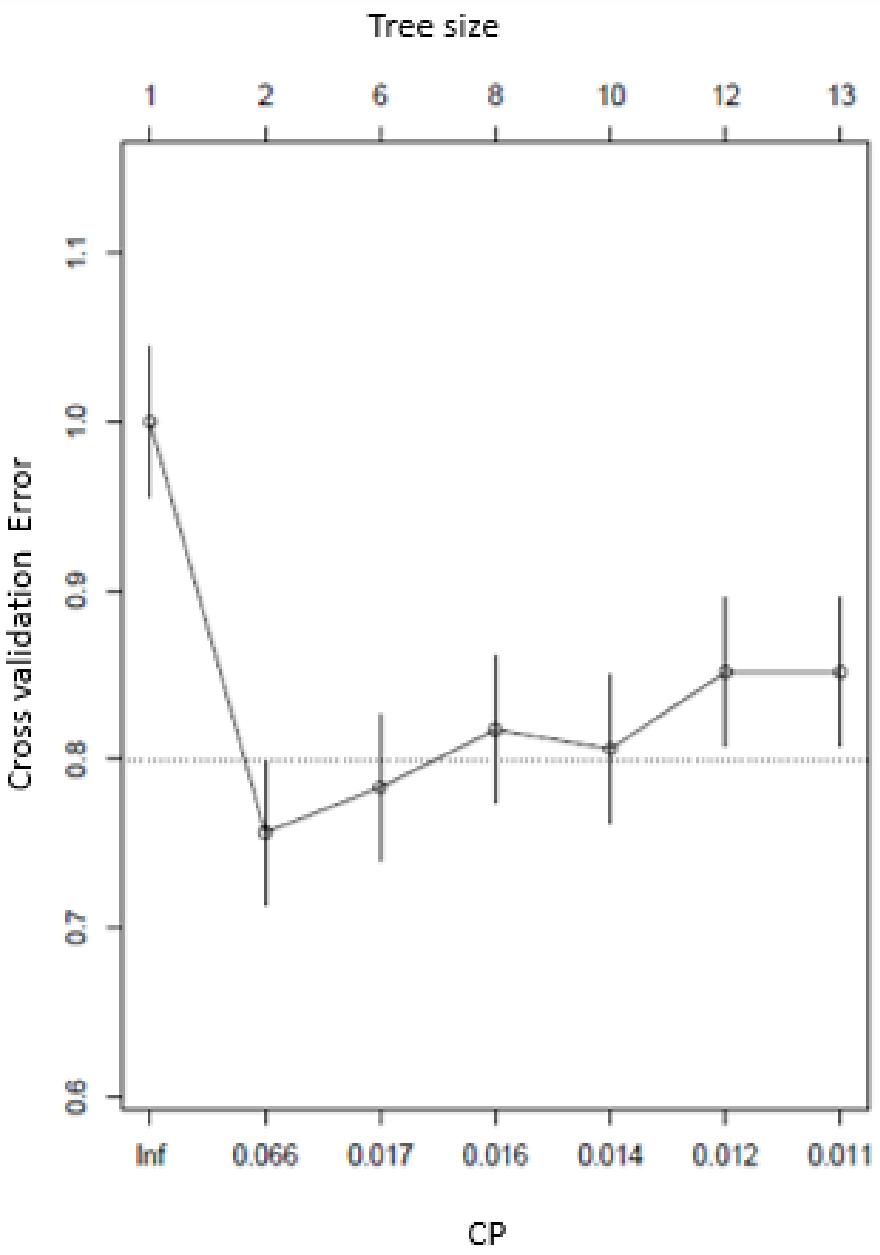


Figure 3. ROC Curve