Risk assessment of amputation in patients with diabetic foot

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Abstract. The prevalence of diabetes has increased dramatically over the past decade, especially in developing countries, reaching pandemic proportions. Although has been the most important factor influencing the prevalence of type 2 diabetes, the prevalence of type 2 diabetes is on the increase among younger adults. The subsequent rate of increase with age is variable, which is more evident in societies where the general prevalence of the disease is higher. Based on clinical and statistical data obtained from the patients who were admitted to The First and Second Surgery Wards in the Sibiu County Emergency University Clinical Hospital (Sibiu, Romania) and the Proctoven Clinic (Sibiu, Romania) between January 2018 and December 2020, the present study attempted to devise a risk score that can be applied for the benefit of patients. The ultimate aim was that this risk score may be eventually applied by diabetologists and surgeons to assess the risk of amputation in patients with diabetic foot lesions. An important part in the therapeutic management of diabetic foot injuries is the assessment of risk factors. Using this risk score system devised, the risk factors that were found to exert influence in aggravating diabetic foot injuries are smoking, obesity, dyslipidaemia, unbalanced diabetes mellitus (glycated haemoglobin ≥7.5%), duration of diabetes >5 years, hepatic steatosis and the co-existence of various heart diseases. To conclude, all these risk factors aforementioned can decrease the effectiveness of treatment and can have a significant impact on the quality of life, if they are not well known.

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Introduction

Diabetic foot is one of the most mutilating and severe complications of diabetes, the prevalence of which is gradually increasing over the past decade. The global prevalence of diabetic foot ulcer in 2019 is estimated to be 463 million, which is expected to rise to 578 million by 2030 (1,2). In 2015, the International Diabetes Federation estimated that diabetic foot ulcers develop in 9.1-26.1 million individuals worldwide annually (2). The prevalence of both type 1 and type 2 diabetes is increasing, such that in 2019, 463 million adult individuals were afflicted with diabetes worldwide (3). In addition, diabetes is now becoming a increasingly common pathological condition because the lifestyle of the world population is becoming increasingly problematic (4). Diabetes is known to be associated with obesity and a sedentary lifestyle (5). The prevalence of diabetes has increased dramatically over recent decades especially in developing countries, reaching global pandemic proportions. The International Diabetes Federation estimated that 451 million adults live with diabetes worldwide in 2017, with a projected increase to 693 million by 2,045 if no effective prevention methods are adopted (6). Age is the most important factor influencing the prevalence of type 2 diabetes (7). However, the prevalence of type 2 diabetes is also increasing among young adults aged ≤20 years (8). In the USA, estimates are as high as 5,000 new cases every year (8). Type 2 diabetes is increasingly diagnosed in young adults, which now accounts for 20-50% of all patients with new-onset diabetes (8). The subsequent growth rate of the incidence increases with age, which is typically more evident in societies where the general prevalence of the disease is higher (9).

It has been found that as the cardiovascular event risk decreases, so does the risk of mortality (10). In a previous study conducted by Pinto et al (11), patients with type 2 diabetes mellitus and diabetic foot were predicted to have worse prognoses in terms of faster progression of cardiovascular damage and are at higher risks of cardiovascular morbidity. This previous study also proposed that the main cause of mortality in these patients was coronary artery disease (11). However, the
average healing time of diabetic foot ulcers without surgery is ~12 weeks, but it is associated with an exceptionally high risk of amputation (12). The latest data regarding mortality due to diabetic foot ulcers, according to the Veterans Health Administration Population, reported that the 1-year survival rate in patients with diabetic foot ulcer is 81%, 69% survive up to 2 years and only 29% survive up to 5 years (13,14).

Complications in the leg are among the most severe and costly complications of diabetes (15). Amputation of the entire or part of the leg is frequently caused by diabetic ulcers (16). A strategy for tackling this includes preventative interventions, methods of educating both the patient and the medical staff, multidisciplinary treatments of the diabetic foot, such as pharmacological treatment, treatment of oedema and malnutrition, local wound care and careful monitoring (17). Altogether, they have been reported to reduce the rate of amputations by 49-85% (17).

Neuropathy and ischemia are two of the main etiological causes of diabetic foot, which together lead to ulceration and Charcot neuroarthropathy (18). A triad of neuropathy, trauma with secondary infection and peripheral arterial disease all account for the pathophysiology of diabetic foot ulcer (19). Peripheral neuropathy produces intrinsic muscle atrophy, leading to functional anatomical changes in hammner toe formation and the development of ‘high-pressure’ zones on the plantar surface of the foot at the metatarsal heads (19). By contrast, repetitive trauma whilst walking, in association with decreased sensation and proprioception, predisposes the skin to injury by producing atrophy and dislocation of the protective plantar fat pads, leading to ulceration and infection (19). In association with the infection, it increases the risk of mortality among the diabetic population, having an adverse impact both clinically and economically (20).

Ischemia in the form of peripheral arterial disease provides an important contribution to causing diabetic foot, which mainly affects the lower limb, specifically the parts distal to the knee joint (21). In patients with diabetes, the risk of developing a diabetic foot ulcer is between 19 and 34% (18). However, relapse is common after a healed episode. In total, typically ~40% of patients experience recurrence of a diabetic ulcer within 1 year of healing, ~60% within 3 years and 65% within 5 years (18,22). Therefore, it is a common and highly severe complication given its deforming nature, with an incidence of 3-4% among patients already diagnosed with diabetes (23). In addition to impairments in insulin signalling, environmental factors, such as sedentary lifestyles or an unhealthy diet coupled with genetic predispositions, have all been reported to be involved in altering glucose homeostasis (24). Diabetic foot is also one of the most expensive complications of diabetes. The burden it places on medical services is enormous, with the overall cost estimated to be ~$1.3 trillion in 2015 worldwide (25). The latest studies in the UK estimate an annual cost of >£1 billion ($1.32 billion) for diabetic foot management alone, which is ~1% of the budget of the National Health Service (25).

In particular, the association of diabetic foot with various risk factors or comorbidities can accelerate its deterioration. Therefore, the present study performed a comprehensive analysis of the risk factors of patients with diabetic foot injuries. The present study also assessed the risk of a diabetic patient who has already developed diabetic foot injuries requiring amputation. Therefore, the diabetologist or surgeon treating the patient would have the opportunity to input the patient’s risk factors into a working model that can automatically calculate the risk of amputation. The main objective of the present study is to assess the impact of individual risk factors on surgical treatment and the risk of amputation.

The present study starts from the hypothesis that a system of classification, grading or description of foot injuries in the practice of the clinician would facilitate the placement of patients and interdisciplinary communication between diabetologists and surgeons. The inclusion of a scoring system can provide an estimated prognosis useful for optimizing the management protocol of the appropriate treatment schemes. Numerous classification schemes have been introduced over time, with the most well-known being the Size (Area, Depth), Sepsis, Arteriopathy and Denervation (SAD) system (26), which grades the diabetic foot ulceration according to five ulcer features (size, depth, sepsis, arteriopathy, and denervation) on a 4-point scale (0-3). In addition, there is also the Sanders-Eichenholz-Rogers-Wagner (SERW) system (27), which describes the entire complex of pathological changes in neuropathic diabetic foot and offer a combination of classification. The SERW system is typically used to describe the anatomical division of the foot, pathophysiological stage of the process, clinical degree of deformation, the presence and depth of the wound and the infection process (27). Other systems used include the Meggitt-Wagner System (28) and the Site, Ischemia, Neuropathy, Bacterial Infection, Area and Depth system (29).

Patients and methods

Study design. The present retrospective, observational and longitudinal cohort study was performed between 1st January 2018 and 31st December 2020. The present study included a group of 181 patients with diabetes from the first and second surgery wards in the Sibiu County Emergency University Clinical Hospital (Sibiu, Romania) and a group of 47 patients with diabetes from the Proctoven Clinic (Sibiu, Romania). Therefore, the present study included a total number of 228 patients.

All patients involved in the present study met the main criterion for inclusion, which was the presence of lesions in the sphere of the diabetic foot (ischemia, ulceration, gangrene, neuropathy, callus and arteriopathy). All patients were between the ages of 18 and 90 years, including both 178 males and 50 females. In terms of pathology, all patients had either type I or II diabetes with a diabetic foot complication. All patients who underwent surgery for diabetic foot lesions by various methods, such as amputation, necrectomy, debridement, disarticulation and lower limb by-pass, were also included. Patients aged <18 or >90 years, those with incomplete medical records and those without diabetic foot lesions were excluded from the present study. The present study followed international regulations under the Declaration of Helsinki. The present study was approved by the Ethics Committee of the Sibiu County Clinical Emergency University Hospital (approval no. 5281; Sibiu, Romania) and the Ethics Committee of the Proctoven Clinic Sibiu (approval no. 314; Sibiu, Romania). Written
informed consent for publication was obtained from all the patients involved in the present study.

Analysis. Data collection and integration were performed based on the medical records that were extracted from the database of the Sibiu County Emergency University Clinical Hospital and Proctoven Clinic in addition to the clinical observation sheets of each of the patients hospitalized in both wards. Based on the collected data, analysis was performed and a comparison of the cases was represented in the tables and figures generated. These results were then associated with the most up-to-date data from the international literature on the complications of diabetes, specifically the diabetic foot.

Regarding the search strategy, to associate data from the present study with those from the internationally specialized literature, the following online databases were used: PubMed (https://pubmed.ncbi.nlm.nih.gov); Elsevier (https://www.elsevier.com); Springer (https://link.springer.com) and Research gate (https://www.researchgate.net). In these databases, the following search terms were used: ‘Diabetic foot injuries’, ‘diabetic foot complications’, ‘surgical treatment of diabetic foot complications’, ‘risk factors in diabetic foot injuries’, ‘importance of risk factors in surgical treatment of diabetic foot injuries’. Systematic reviews and meta-analyses on the treatment of the diabetic foot, articles that analysed the influence of risk factors in the diabetic foot and those that analysed the complications of the diabetic foot were included. Studies and articles that did not refer to the surgical treatment of the diabetic foot, case reports and those that did not report concrete conclusions were excluded. Regarding data restrictions, for the most up-to-date information, articles and specialized studies published online between 2015 and 2022 were searched.

Assessment methods. The following parameters were studied: Age, sex, living environment, comorbidities, the presence or absence of risk factors, their influence on the occurrence of lesions grouped under the name of diabetic foot, type of diabetes, therapy applied, type of surgery performed and their relationship with risk factors and comorbidities.

Statistical methods. P<0.05 was considered to indicate a statistically significant association or significant difference between means/percentages. Following statistical analysis of the processed data, the risk score was obtained using the following formula: \( X = \frac{Y \times 100}{Z} \), where X represents the amputation risk percentage, Y represents patients who received amputation from the risk group and Z represents the total number of patients in the risk group. This formula was used in the Microsoft Excel 2016 program (Microsoft Corporation) to calculate the risk score using Pearson’s \( \chi^2 \) test.

In addition, the binary logistic regression model implemented in SPSS version 22 (IBM Corp.) was used for the multidimensional evaluation of amputation risk factors.

Results

Baseline data. The present study was conducted over a period of three years between 2018 and 2020, which included a total of 228 patients diagnosed with diabetes who had associated complications in the area of the foot treated and hospitalized within the Sibiu County Emergency University Clinical Hospital and Proctoven Clinic (Sibiu, Romania).

After dividing the patients by age groups, a predominance of the number of cases was observed in the 60-70 years age group (n=103; 45%), followed by the 70-80 years age group (n=66; 29%). In particular, patients aged between 60 and 80 years represent >74% of the total cases included in the present study group. In the 80-90 years age group, 20 patients (9%) were identified whereas 32 cases (14%) belonged to the 50-60 years age group. The fewest cases were observed in the 40-50 years (n=6; 2.6%) and 30-40 years (n=1; 0.4%) age groups (Table I). The statistical analysis revealed significant differences between the percentages (P=0.0285, Pearson’s \( \chi^2 \) test).

The patients included in the study group were also divided into two groups according to their sex. Among all the patients included in the study group, the diabetic foot was predominantly more common among males (n=178; 78%) compared with females (n=50; 22%) during the 3 years of study (P=0.0097, Pearson’s \( \chi^2 \) test; Table I).

Regarding the distribution of patients according to the living environment, among the 228 patients included in the present study, 182 (80%) lived in an urban environment, whereas 46 (20%) patients came from the rural area (P=0.0091; Table I). This increased incidence of cases in urban areas can be explained by the greater accessibility and addressability to more specialized medical care but also by the more developed medical knowledge, compared with patients from rural areas. It has been observed that patients in rural areas in the present study frequently approached the institutions already at advanced stages of the underlying disease. Consequently, they typically present with acute complications and require emergency surgery because of the lack of easy access to specialized consultations.

After grouping the patients according to the type of diabetes, a predominance of type II diabetes was observed in close association with the diabetic foot (n=198; 87%). Only 30 patients (13%) in the study group were diagnosed with type I diabetes. In addition, the prevalence of type II diabetes was observed in each year of the study (P=0.0074, Pearson’s \( \chi^2 \) test; Table I). In addition, there was a steady, annual decrease in the number of patients admitted to the institutions involved in the present study. This can be explained by the Coronavirus pandemic and the low addressability of patients to medical services during this period.

The diabetic foot can affect either one or both of the lower limbs. Therefore, the present study also analysed the prevalence of unilateral and bilateral lesions. Amongst the 228 patients included in the present study, 178 (78%) have one affected limb, whereas 50 (22%) had both affected limbs (P=0.0099, Pearson’s \( \chi^2 \) test; Fig. 1).

Comorbidities. The following comorbidities were observed in the patients included in the present study: i) High blood pressure; ii) chronic ischemic heart disease; iii) heart failure; iv) chronic kidney failure; v) chronic venous insufficiency; vi) macroangiopathy in chronic oblitative arteriopathy; vii) stroke; viii) chronic obstructive pulmonary disease; ix) hepatitis; and x) neoplasia (Fig. 2)

Following the analysis of comorbidities associated with diabetic foot, high blood pressure was observed in 171 cases
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(75.13%), followed by arteriopathy [122 (53.5%)] and chronic ischemic heart disease [104 (45.8%)], whereas heart failure was present in 87 (38.1%) patients. Chronic kidney failure and chronic venous insufficiency were present in 64 (28.17%) and 60 (26.5%) patients, respectively. Other pathologies, such as hepatitis, neoplasia, stroke and chronic obstructive pulmonary disease, have also been identified, but with relatively smaller percentages (<10%) compared with the others. The results were found to be statistically significant (P<0.0001, Pearson's χ² test; Fig. 2).

Risk factors. The risk factors identified in the patients included in the present study were subsequently analysed. These included smoking, obesity, dyslipidaemia, duration of diabetes >5 years, hepatic steatosis, various pre-existing heart conditions and unbalanced diabetes [glycated haemoglobin (HbA1c) >7.5%; Table II].

Following the analysis of the risk factors associated with diabetic foot, the prevalence of pre-existing cardiac pathologies was 83.4%, whilst the prevalence for obesity and dyslipidaemia was 55.8 and 49.1%, respectively. The prevalence of diabetes with a duration >5 years was 40.3%, whereas 36.4% of patients had unbalanced diabetes (HbA1c >7.5%). The risk factors with the lowest cases were hepatic steatosis and smoking, with a share of 13.2 and 7.1% of the studied group, respectively. The results were found to be statistically significant (P<0.001, Pearson's χ² test; Table II).

Type of surgery. During the present study, analysis of the type of surgery performed was then performed. Therefore, for the 3-year study period, five types of classical types of surgeries were performed, namely debridement, amputation, disarticulation, lower limb bypass and necrectomy. Following analysis of the interventions, it was observed that amputation and debridement represented 40 and 26% of all cases, respectively. These were followed by disarticulation and necrectomy, with 17 with 14% prevalence, respectively. The least common intervention was represented by the bypass of the lower limb, with a prevalence of 3%. The statistical analysis revealed significant differences among the interventions (P=0.0123, Pearson's χ² test; Fig. 3).

The types of amputations performed in the two institutions in the present study were also analysed. Finger amputation was performed in 26 patients (29%), followed by amputation above the knee in 24 cases (26%) and amputation below the knee in 17 cases (18%). Transmetatarsal and mediotalarsal amputations were performed in 14 (15%) and 11 (12%) patients, respectively (P=0.0413, Pearson's χ² test; Table III).

Association analysis. Taking into account that risk factors and comorbidities serve a major role in the evolution of diabetes and indirectly of the diabetic foot, the association between

| Parameter | 2018 | 2019 | 2020 | No. of cases | Percentage, % | P-value |
|-----------|------|------|------|-------------|---------------|---------|
| Age group, years |
| 30-40 | 0 | 0 | 1 | 1 | 0.4 | 0.0285 |
| 40-50 | 0 | 6 | 0 | 6 | 2.6 |
| 50-60 | 18 | 9 | 5 | 32 | 14 |
| 60-70 | 49 | 38 | 16 | 103 | 45 |
| 70-80 | 39 | 14 | 13 | 66 | 29 |
| 80-90 | 9 | 7 | 4 | 20 | 9 |
| Sex |
| Male | 86 | 53 | 39 | 178 | 78 | 0.0097 |
| Female | 26 | 14 | 10 | 50 | 22 |
| Living environment |
| Urban | 77 | 64 | 41 | 182 | 80 | 0.0091 |
| Rural | 29 | 11 | 6 | 46 | 20 |
| Type of diabetes |
| Type I | 18 | 9 | 3 | 30 | 13 | 0.0074 |
| Type II | 83 | 61 | 54 | 198 | 87 |

P-value was obtained using Pearson's χ² test.
surgeries and the risk factors/comorbidities were studied. The risk factors analysed were the following: i) Smoking; ii) obesity; iii) heart disease; iv) dyslipidaemia; v) duration of diabetes >5 years; vi) hepatic steatosis; and vii) HbA1c >7.5% (Table IV).

In the present study, amputation was the most common surgical intervention in patients with the aforementioned risk factors, followed by necrectomy, debridement, disarticulation and by-pass. There was also an increased prevalence of heart disease among all patients who underwent surgery, followed by obesity and dyslipidaemia. Amputation (P=0.0257, Pearson’s χ² test) and necrectomy (P=0.001, Pearson’s χ² test) were observed more frequently in patients with HbA1c >7.5%, in those with a duration of diabetes >5 years and those with dyslipidaemia. Surgical debridement was more associated with patients with heart disease and duration of diabetes >5 years, HbA1c >7.5% and hepatic steatosis (P<0.001, Pearson’s χ² test). The incidence of disarticulation (P=0.0123, Pearson’s χ² test) and bypass (P=0.0439, Pearson’s χ² test) was most common in cases of heart disease, obesity and diabetics with HbA1c >7.5% (Table IV).

Age-related amputation analysis was particularly beneficial for analysing assess the most affected age groups. The same age groups as aforementioned in the demographic data were used for analysis. This analysis was performed on the 92 patients in the study group who underwent amputation surgery. The majority of the amputations were performed in the 60-70 years age group with 52 cases (56.5%), followed by the 70-80 years age group with 21 cases (22.8%). By contrast, 14 amputations (15.2%) were performed in the 80-90 years age group. Amputations were less common in the 50-60 and 40-50 years age groups with three (3.3%) and two cases (2.2%), respectively (P=0.008, Pearson’s χ² test; Fig. 4).

**Risk score analysis.** The risk score system constructed in the present study was designed for patients with diabetes who already developed diabetic foot-specific lesions to assess their risk of amputation due to the associated risk factors (Table IV). To achieve this score on the risk of amputation in patients with diabetes, the risk factors that were analysed and presented in the study were incorporated. They are represented by the following: i) Smoking, 16 cases (7.1%); ii) obesity, 127 cases...
Table II. Distribution of patients according to associated risk factors.

| Risk factors          | No. of cases | Percentage, % | P-value<sup>a</sup> |
|-----------------------|-------------|---------------|---------------------|
| Smoking               | 16          | 7.1           | <0.001              |
| Obesity               | 127         | 55.8          |                     |
| Pre-existing heart    | 190         | 83.4          |                     |
| conditions            |             |               |                     |
| Dyslipidaemia         | 112         | 49.1          |                     |
| Duration of diabetes  | 92          | 40.3          |                     |
| >5 years              |             |               |                     |
| Hepatic steatosis     | 30          | 13.2          |                     |
| Glycated              | 83          | 36.4          |                     |
| haemoglobin >7.5%     |             |               |                     |

<sup>a</sup>Calculated using Pearson’s χ² test.

Table III. Distribution of patients according to the type of amputation.

| Amputation            | No. of cases | Percentage, % | P-value<sup>a</sup> |
|-----------------------|-------------|---------------|---------------------|
| Finger                | 26          | 29            | 0.0413              |
| Below the knee        | 17          | 18            |                     |
| Above the knee        | 24          | 26            |                     |
| Mediotarsal           | 11          | 12            |                     |
| Transmetatarsal       | 14          | 15            |                     |
| Total                 | 92          | 100           |                     |

Distribution of patients according to the type of amputation. *Calculated using Pearson’s χ² test.

![Percentage distribution of types of surgery as a result of diabetic foot.](image)

P=0.0123 for Pearson χ² test

Figure 3. Percentage distribution of types of surgery as a result of diabetic foot. It can be observed that amputation and debridement together represent 66% of the total surgical procedures in the diabetic foot. Necrectomy, disarticulation and by-pass of the lower limb represent together represent only 34% of the performed surgical procedures.

(55.8%); iii) pre-existing heart conditions, 190 cases (83.4%); iv) dyslipidaemia, 112 cases (49.1%); v) duration of diabetes >5 years, 92 cases (40.3%); vi) hepatic steatosis, 30 cases (13.2%); and vii) HbA1c >7.5%, 83 cases (36.4%). To create the model for calculating the risk score based on the seven risk factors and the data obtained from the 228 patients with diabetes who developed specific lesions of the diabetic foot, the patients were divided into four risk stratification groups as follows: i) Group A, patients who have zero or one risk factor; ii) group B, patients who have two or three risk factors; iii) group C, patients who have four or five risk factors; and v) group D, patients who have > five risk factors (Table V).

The present study revealed that the risk of amputation among patients who have at most one risk factor was low at 12.2% (Table V). By contrast, the simultaneous presence of two or three risk factors in the same patient increased the risk of amputation to 67.11%. The risk of amputation was 85.71% in patients in group C with four or five risk factors whilst the highest risk was shown in patients with > five risk factors, with a risk of amputation of 90%. It can therefore be concluded that the simultaneous presence of a greater number of risk factors in the same patient is directly proportional to the increase in the risk of amputation.

All data collected were used to construct the risk score system. Therefore, to calculate it, a database with the patients in the present study and the risk factors they presented was constructed according to the model shown in Table SI.

Table SI contains all patients included in the study group along with the risk factors identified for each patient, their total number of risk factors and the risk group they are assigned to. In addition, the last column mentions patients who have had undergone amputation (Yes/No). For columns two to eight, which correspond to each of the risk factors, the following applies: 1=true and 0=false. Therefore, patients who presented with one of the risk factors studied were marked with ‘1’, whereas those without risk factors were marked with ‘0’. Table SI continues up to patient 228.

Statistical analysis. All data collected were extracted from clinical observation sheets and surgical protocols. These data were also analysed and entered into a table using Microsoft Office Excel 2016 (Microsoft Corporation). An additional column was then inserted, representing the risk group for amputation in percentages, based on the number of risk factors present on each patient. A statistically significant association between the risk groups and amputation was found (P<0.001,
The risk of amputation is found to be 12.4% in cases with up to one risk factor, which increased up to 85.71‑90% in cases that have ≥ four risk factors. Based on the number of risk factors encountered in any single patient which, combined with the statistical analysis results previously performed on the database used in the present study, the clinician may use this system to automatically generate an estimation of the risk of amputation. This may serve to be a beneficial tool for planning the individualized therapeutic strategy. In order to be able to use this functionality, Table SII is available as an additional Excel file.

The present study didn’t demonstrate if all analysed risk factors can significantly increase the amputation risk. The binary logistic regression model was implemented with the dependent variable of amputation (1=true or 0=false) and the following independent variables: i) HbA1c >7.5%; ii) duration of diabetes >5 years; iii) smoking; iv) hepatic steatosis; v) obesity; vi) dyslipidaemia; and vii) pre-existing heart conditions. The minimal value of the confidence interval for each OR is >1, except for ‘duration of diabetes >5 years’, B was found to be 0.923 with 95% CI of -0.16‑2.01 and an OR=2.52 and CI: (e^0.923=−0.16 ‑ e2.01)=(0.85‑7.44). Therefore, OR>1 but the left side of 95% CI is 0.85<1 (i.e. the risk of OR <1 is >5%). This meant that each risk factor listed in Table VII adds a 95%‑significant extra hazard, except for ‘duration of diabetes >5 years’.

**Table IV. Distribution of surgical interventions in relation to risk factors.**

| Risk factors                          | Debridement | Amputation | Disarticulation | Necrectomy | By-pass | Total, N |
|---------------------------------------|-------------|------------|-----------------|------------|---------|----------|
| Smoking                               | 0           | 8          | 0               | 4          | 4       | 16       |
| Obesity                               | 4           | 74         | 18              | 23         | 8       | 127      |
| Pre-existing heart conditions          | 41          | 84         | 31              | 18         | 16      | 190      |
| Dyslipidaemia                          | 7           | 58         | 2               | 9          | 6       | 112      |
| Duration of diabetes >5 years          | 16          | 39         | 9               | 23         | 5       | 92       |
| Hepatic steatosis                      | 10          | 12         | 2               | 6          | 0       | 30       |
| HbA1c >7.5%                            | 15          | 29         | 9               | 20         | 10      | 83       |

**Table V. Risk factor stratification for amputation.**

| Risk group | No. of risk factors | No. of patients | Patients who received amputation | Risk of amputation, % | P-value a |
|------------|---------------------|-----------------|---------------------------------|-----------------------|-----------|
| A          | 0-1                 | 121             | 15                              | 12.40                 | <0.001    |
| B          | 2-3                 | 76              | 51                              | 67.11                 |           |
| C          | 4-5                 | 21              | 18                              | 85.71                 |           |
| D          | >5                  | 10              | 8                               | 90.00                 |           |

**Table VI. Calculating the risk score using Microsoft Excel 2016.**

| Risk Factors | Duration Hepatic Glycated | Total | Risk of amputation, % |
|--------------|---------------------------|-------|-----------------------|
| Patient No.  | Smoking | Obesity | Heart conditions | Dyslipidaemia | of diabetes >5 years | Hepatic steatosis | of glycated haemoglobin >7,5% | Risk factors | Risk group | %       |
| 1            | 1       | 0       | 1                   | 1           | 1                   | 1                | 1                      | 6           | D         | 87.5    |

From column two to column 8, the following applies: 1=true, 0=false. The total number of risk factors must also be changed when entering the data in Microsoft Excel 2016. After that, by using the formula, the percentage changes automatically.
Table VII. Logistic regression model for the dependent variable of amputation.

| Risk                        | Estimated co-efficient | Standard error | Wald  | Degrees of freedom | P-value | OR    | Lower 95% CI | Upper 95% CI |
|-----------------------------|------------------------|----------------|-------|--------------------|---------|-------|--------------|--------------|
| HbA1c >7.5%                 | 2.001                  | 0.614          | 10.611| 1                  | 0.001   | 7.393 | 2.219        | 24.638       |
| Dyslipidaemia               | 0.988                  | 0.468          | 4.465 | 1                  | 0.035   | 2.687 | 1.074        | 6.721        |
| Duration of diabetes >5 years | 0.923                  | 0.553          | 2.787 | 1                  | 0.095<sup>a</sup> | 2.517 | 0.852<sup>a</sup> | 7.441        |
| Smoking                     | 2.983                  | 0.807          | 13.626| 1                  | 0.000   | 19.740| 4.058        | 96.026       |
| Obesity                     | 1.658                  | 0.533          | 9.627 | 1                  | 0.002   | 5.250 | 1.847        | 14.924       |
| Pre-existing heart conditions | 1.890                  | 0.516          | 13.387| 1                  | 0.000   | 6.616 | 2.405        | 18.206       |
| Hepatic steatosis           | 2.577                  | 0.702          | 13.458| 1                  | 0.000   | 13.156| 3.321        | 52.123       |
| Constant                    | -3.750                 | 0.552          | 46.153| 1                  | 0.000   | 0.024 |             |              |

<sup>a</sup>Non-significant. <sup>b</sup>INPUT description: Amputation variable is binary (1=amputation/0=no amputation) and all risks are binary (1=yes/0=no). OR, estimated odd ratio; CI, confidence interval.

This table shows the logistic regression model for the dependent variable of amputation, which has been used to determine the probability of amputation for a new patient. The model includes various risks such as HbA1c >7.5%, dyslipidaemia, duration of diabetes >5 years, smoking, obesity, pre-existing heart conditions, hepatic steatosis, and constant. The model uses the logistic regression formula:

\[ S_k = B_0 + \sum_i B_{xi} \cdot \text{prob(Event}_i=1) = \exp(S_k)/[1 + \exp(S_k)] \]

In this formula, \( S_k \) represents the total risk for patient \( k \), \( B_0 \) and \( B_{xi} \) are the estimated coefficients of the logistic regression model, and \( i \) is the index for risks. The sum is computed for all risks, where \( x_{ki} \) is the value of risk \( i \) for patient \( k \) (in this present case, \( x_{ki} \) is 1 or 0 depending on presence/absence of risk \( i \)) and \( \exp(z) = e^z \) is the natural exponential function. Subsequently, knowing the risk values for a new patient, the probability of \( \text{Event}_k=1 \) can be computed. In the present case, the prediction would yield Amputation=yes if \( \text{prob(Event}_k=1) > 0.5 \) or Amputation=no if \( \text{prob(Event}_k=1) < 0.5 \). Therefore, except for the duration of diabetes >5 years, each risk factor listed in Table VII added an extra hazard, whether or not these risk factors are statistically associated.

**Discussion**

Diabetes rarely presents a ‘one-size-fits-all’ pathology. Patients with diabetes frequently present with a unique but diverse series of comorbidities and complications (30). They can also present numerous risk factors for the occurrence of diabetic foot lesions, which may accumulate over time due to an inappropriate lifestyle (31). As a result, comorbidities that can accelerate progression to diabetic foot have to be identified and analysed, since they can serve a significant role in increasing the risk of patient mortality (32).

The majority of the patients investigated in the present study had ≥ one associated comorbidity. Several studies had previously shown that comorbidities associated with diabetes increase the demand for medical care, cost of hospitalization, and frequency of medical follow-ups (33,34). Therefore, a deeper understanding of the comorbidities and associated factors may improve the management of patients with diabetes and the selection of individualized treatment protocols (33,34).

The occurrence of diabetic foot injuries is dependent on a number of risk factors, especially those related to lifestyle (35). Although the number of smoking patients identified in the present study was small, there is a close association between smoking and diabetic foot. Smoking is an important risk factor in the development of peripheral vascular disease in patients with diabetes. In addition, it was found to exacerbate the risk of peripheral neuropathy by 12-fold compared with that in non-smokers (36,37).

Dyslipidaemia also serves an important role in the progression of vascular complications caused by diabetes. A recent study indicated a high prevalence of dyslipidaemia among patients with diabetes (38). Sex, advancing age, long duration of diabetes, increased body-mass index (BMI) and high blood pressure were risk factors associated with the prevalence of dyslipidaemia (39). In addition, dyslipidaemia has been previously considered to be an independent predictor of the development of cardiovascular diseases (40,41). In the present study, a close association between obesity (translated into high BMI) and diabetic foot was found, which was consistent with findings from specialized studies (42,43). It has also been previously concluded that obesity is a major risk factor for the development and progression of macrovascular complications of diabetes, such as coronary heart disease, peripheral arterial disease and hypertension (44,45).

The duration of diabetes is a major contributing factor to the increased incidence of diabetic foot disorders (46). In the present study, 92 patients with a duration of diabetes >5 years were identified. In particular, diabetic foot disorders are common among patients with diabetes even during the early stages of diabetes or when they are first diagnosed (47). Although the duration of diabetes is not a modifiable risk factor, it is of great importance for the early identification and management of diabetic foot, as previously stated by Fawzy et al (48) and Alzahrani et al (49).

In the present study, it was highly important to identify patients with unbalanced diabetes because longer exposure to high HbA1c levels is associated with complications in patients with diabetes (50). In total, 83 patients had HbA1c >7.5%. Poor glycaemic control is strongly associated with the development of diabetic foot over time (50). Although the prevalence of unbalanced diabetes was only 36.4% in the present study, previous
studies by Fawzy et al (48) and Abdissa and Hirpa (41), show a much higher frequency among patients with diabetic feet, at 89 and 63.8%, respectively. These same studies showed that high levels of HbA1c can contribute to the development of the diabetic foot. This may be due to hyperglycaemia, which is considered a risk factor for diabetic foot due to its contribution to the development of peripheral neuropathy and microvascular complications (49,51).

Another risk factor identified in the present study is hepatic steatosis, which was found in 30 patients. Previous studies mentioned the existence of a bidirectional relationship between hepatic steatosis and type 2 diabetes, given the vital role of the liver in the pathophysiology of both conditions (52). This in turn leads to the development of insulin resistance and aggravation of hepatic steatosis and type 2 diabetes (52). The presence of hepatic steatosis increases the likelihood of complications of type 2 diabetes, which likely explains the increased screening rates for this disease in patients with type 2 diabetes (52,53). Several studies previously indicated that hepatic steatosis is closely associated with an increased risk of chronic vascular complications of diabetes (54-56). In addition, other studies on patients with type 2 diabetes found that the prevalence of vascular disease is higher in patients with hepatic steatosis compared with that among healthy individuals (52,53).

Treatment of diabetic foot ulcers is complex and typically involves both conventional and innovative methods, such as antibiotic therapy, wound dressing, negative pressure therapy, necrotic tissue debridement, hyperbaric oxygen therapy, stem cell therapy, growth factor therapy and maggot therapy, all to prevent amputation (57,58). However, the use of any of the aforementioned methods alone may not be effective in preventing pain and/or mechanical damage in the healthy underlying tissues. In the majority of cases, it may be advisable to combine different therapeutic strategies according to the particularities of the patient and the therapeutic possibilities available (57-59).

Early recognition and management of risk factors associated with the diabetic foot can influence the decision on the type of surgery but also the subsequent outcome for patients, thereby preventing major debilitating amputations (60-63). Diabetic foot ulcers remain to be a major public health issue, being one of the most debilitating chronic complications of diabetes, the prevalence of which has been increasing exponentially globally (20,64). In addition, the annual decrease in the number of cases admitted to our service can be at least partially explained by the Coronavirus pandemic, which led to a decrease in the addressability of patients to medical services during this period.

The most affected age group found in the present study was the 60-70 years age, followed by the 70-80 years age group. Therefore, age was considered to be an important aggravating factor in the evolution of diabetic foot, which could be seen in the present study, since the majority of amputations were performed in the 60-70 age group.

Risk factors serve an important role in the occurrence of diabetic foot injuries. The results of the present study, in terms of risk factors, were in agreement with the literature and previous studies (6.65-67). The identification of risk factors and types of treatment, in addition to their analysis, allowed the development of the risk score. The novelty of the present findings consists of the establishment of a risk score system that enables clinicians to have, from the time of admission, a perspective on the prospective outcome and complications to guide the designation of personalized treatment methods for patients with diabetic foot injuries. This risk score system enables the early identification of patients with diabetes who have developed diabetic foot injuries and are at high risk of amputation, allowing them to take preventive measures. A limitation of the present study is that this risk score system has not been tested on another independent patient cohort. Patients with diabetes should pursue a self-care education, since successful control of the disease depends to a large extent on the application of this behaviour throughout the life of the patients. In the future, the study will be expanded to other medical facilities to increase the size of the cohort.

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Availability of the data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CT, AM and DT contributed substantially to the conception and design of the study, the acquisition, analysis and interpretation of the data. DS, CG, RF and CB contributed substantially to the analysis and interpretation of the data. CT, CM, AM and CB contributed substantially to the interpretation of the data and were involved in the critical revisions of the manuscript for important intellectual content. CB, CM and CT confirm the authenticity of all the raw data. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study followed international regulations under the Declaration of Helsinki. The present study was approved by the Ethics Committee of the Sibiu County Clinical Emergency University Hospital (approval no. 5281; Sibiu, Romania) and the Ethics Committee of the Proctoven Clinic Sibiu (approval no. 314; Sibiu, Romania). Written patient informed consent for publication of the data associated with the manuscript was obtained.
Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Armstrong DG, Boulton AJM and Bus SA: Diabetic foot ulcers and their recurrence. N Engl J Med 376: 2367-2375, 2017.

2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Uncer I, Choblete L, Mota LA, Ogurtsova K, et al: Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International diabetes federation diabetes atlas, 9th edition. Diabetes Res Clin Pract 157: 107843, 2020.

3. Adem AM, Andargie AA, Teshale AB and Wolde HF: Incidence of diabetic foot ulcer and its predictors among diabetes mellitus patients at felege hiwot referral hospital, Bahir Dar, Northwest Ethiopia: A retrospective follow-up study. Diabetes Metab Syndr Obes 13: 3703-3711, 2020.

4. Nkiajav KV, Narayana KMV, Lobelo F and Weber MB: Lifestyle and the prevention of type 2 diabetes: A Status Report. Am J Lifestyle Med 12: 4-20, 2015.

5. Park JH, Moon JH, Kim HJ, Kong MH and Oh YH: Sedentary lifestyle: Overview of updated evidence of potential health risks. Korean J Fam Med 41: 365-373, 2020.

6. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW and Malanda B: IDF diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 138: 271-281, 2018.

7. Selvin E and Parrinello CM: Age-related differences in glycaemic control in diabetes. Diabetologia 56: 2549-2551, 2013.

8. Nadeau KJ, Anderson BJ, Berg EG, Chiang JL, Chou H, Chou I, Copeland KC, Hannon TS, Huang TT, Lynch JL, Powell J, et al: Youth-Onset type 2 diabetes consensus report: Current status, challenges, and priorities. Diabetes Care 39: 1635-1642, 2016.

9. Sinnott SJ, McHugh S, Whelton H, Layte R, Barron S and Kearney PM: Estimating the prevalence and incidence of type 2 diabetes using population level pharmacy claims data: A cross-sectional study. BMJ Open Diabetes Res Care 5: e000288, 2017.

10. Rubio JA, Jimenez S and Lazaro-Martinez JL: Mortality in patients with diabetic foot ulcers: Causes, risk factors, and their association with evolution and severity of ulcer. J Clin Med 9: 3009, 2020.

11. Pinto A, Tuttolomando A, Di Raimondo D, Fernandez P, Tannasecu et al: Type 2 diabetes mellitus and the prevention of type 2 diabetes: An overview of evidence from the International diabetes federation. Diabetes Res Clin Pract 157: 107843, 2020.

12. Al-Rubeaan K, Al Derwish M, Ouizi S, Youssef AM, Subhani SN, Ibrahim HM and Alami BN: Diabetic foot complications and their risk factors from a large retrospective cohort study. PLoS One 10: e0124446, 2015.

13. Al-Derwish M, Al-Obeidan K and Al-Zahrani NA: Prevalence and associated factors of dyslipidemia among adults with type 2 diabetes in Riyadh, Saudi Arabia. Metabolism 58: 1366-1372, 2009.

14. Boulton AJM, Armstrong DG and Moncrieff J: Hyperglycaemia: A major risk factor for the development of diabetic foot lesions. Diabetes Metab Rev 28 (Suppl 1): S225-S231, 2012.

15. Edmonds M, Muni C and Vas P: The current burden of diabetic foot disease. J Clin Orthop Trauma 17: 88-93, 2021.

16. Bandy DF: The diabetic foot: Pathophysiology, evaluation, and treatment. Semin Vasc Surg 31: 43-48, 2018.

17. Jeyaraman K, Berthane T, Hamilton M, Chandra AP and Falhammer M: Mortality in patients with diabetic foot ulcer: A retrospective study of 515 cases from a single Centre in the Northern Territory of Australia. BMC Endor Disord 19: 1, 2019.

18. Boyko EJ, Monteiro-Saares M and Wheeler SGB: Peripheral arterial disease, foot ulcers, lower extremity amputations, and diabetes. In: Diabetes in America, Cowie CC, Casagrande SS, Woolf SH, Bergstralh EJ, Whelton PK, Cutler JA (eds). National Institute of Diabetes and Kidney Diseases (US), Bethesda, MD, 2018.

19. Chandrake C: The P value and statistical significance: Misunderstandings, explanations, challenges, and alternatives. Indian J Psychol Med 41: 210-215, 2019.

20. Yazdanpanah L, Shahbaziand N, Nazari I, Arti HR, Ahmadf M, Mohammadianinajaf SE, Cheraghian B and Hesam S: Incidence and risk factors of diabetic foot ulcer: A population-based diabetic foot cohort (ADFC Study)-two-year follow-up study. Int J Endocrinol 2018: 7631659, 2018.

21. DeFranoza RA, Ferranini E, Groop L, Henry RR, Herman WH, Holst JJ, Hu FB, Kahn CR, Raz I, Shulman GI, et al: Type 2 diabetes mellitus. Nat Rev Dis Primers 1: 15019, 2015.

22. Jeffcoat WJ, Vileikyte L, Boyko EJ, Armstrong DG and Boulton AJM: Current challenges and opportunities in the prevention and management of diabetic foot ulcers. Diabetes Care 41: 645-652, 2018.

23. Ttreeke KA, Macfarlane RM, Pourn N, Game FL and Jeffcoat WJ: Validation of a system of foot ulcer classification in diabetes mellitus. Diabet Med 21: 987-991, 2004.

24. Obolensky NV, Protsko VG and Komelyagina LY: Classification of diabetic foot, revisited. Wound Med 18: 1-7, 2017.

25. Ohyio SO, Jude EB, Tarawneh I, Nguyen HC, Barkless LB and Boulton AJ: A comparison of two diabetic foot ulcer classification systems: The Wagner and the University of Texas wound classification systems. Diabetes Care 24: 88, 2001.

26. Ince P, Abbas ZG, Lutale JK, Bastian A, Ali SM, Chohan F, Morbach S, Möllenberg J, Game FL and Jeffcoate WJ: Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care 31: 964-967, 2008.

27. Cho YY and Cho SI: Treatment variation related to comorbidity and complications in type 2 diabetes: A real world analysis. Medicine (Baltimore) 97: el2435, 2018.

28. Al-Rubeaan K, AlDerwish M, Ouizi S, Youssef AM, Subhani SN, Ibrahim HM and Alami BN: Diabetic foot complications and their risk factors from a large retrospective cohort study. PLoS One 10: e0124446, 2015.

29. Al-Derwish M, Al-Obeidan K and Al-Zahrani NA: Prevalence and associated factors of dyslipidemia among adults with type 2 diabetes in Riyadh, Saudi Arabia. Metabolism 58: 1366-1372, 2009.

30. Piette JD and Kerr EA: The impact of comorbid chronic conditions on diabetes care. Diabetes Care 29: 725-731, 2006.

31. Boulton AJM: Management of diabetes mellitus in older people with comorbidities. BMJ 353: i2200, 2016.

32. Adeyemi TM, Olajumobi TL, Adejumobi AE and Rehal S: Knowledge, practice and attitude towards foot ulcers and foot care among adults living with diabetes in Tobago: A qualitative study. Int J Environ Res Public Health 18: 8021, 2021.

33. Mantey F, Foster AV, Spurrier DM, Smith MD and Edmunds ME: Why do foot ulcers recur in diabetic patients? Diabet Med 16: 245-249, 1999.

34. Xia N, Moretza A, Yang F, Cao H and Wang A: Review of the role of cigarette smoking in diabetic foot. J Diabetes Invest 10: 210-215, 2019.

35. Pitsos M, Mofokeng TR and Nel R: Dyslipidaemia pattern and prevalence among type 2 diabetes mellitus patients on lipid-lowering therapy at a tertiary hospital in Central South Africa. BMC Endor Disord 21: 159, 2021.

36. Al-Zaarafa H, Alzahabi K, Alhajimah A, Almomani MM, Alzahabi AS and Almomani AH: Prevalence and associated factors of dyslipidemia among adults with type 2 diabetes mellitus in Saudi Arabia. Diabetes Metab Syndr Obes 13: 4033-4040, 2020.

37. Bekele S, Johannes T and Mohammed AE: Dyslipidemia and associated factors among diabetic patients attending Durame General Hospital in Southern Nations, Nationalities, and People’s Region. Diabetes Metab Syndr Obes 10: 265-271, 2017.
41. Abdissa D and Hirpa D: Dyslipidemia and its associated factors among adult diabetes outpatients in West Shewa zone public hospitals, Ethiopia. BMC Cardiovasc Disord 22: 39, 2022.

42. Sohn MW, Budiman-Mak E, Lee TA, Oh E and Stuck RM: Significant J-shaped association between body mass index (BMI) and diabetic foot ulcers. Diabetes Metab Res Rev 27: 402-409, 2011.

43. Zantour B, Bouchareb S, El Atti Z, Boubaker F, Alaya W, Kossomtini W and Star MH: Risk assessment for foot ulcers among Tunisian subjects with diabetes: A cross sectional outpatient study. BMC Endocr Disord 20: 128, 2020.

44. Rizk MN and Ameen AL: Comorbidities associated with Egyptian diabetic foot disease subtypes. Egypt J Intern Med 25: 154-158, 2013.

45. Galal YS, Khairy WA, Taha AA and Amin TT: Predictors of foot ulcers among diabetic patients at a tertiary care center, Egypt. Risk Manag Healthc Policy 14: 3817-3827, 2021.

46. Almobarak AO, Awadalla H, Osman M and Ahmed MH: Prevalence of diabetic foot ulceration and associated risk factors: An old and still major public health problem in Khartoum, Sudan? Ann Transl Med 5: 340, 2017.

47. Ming A, Walter I, Alhajjar A, Leuckert M and Mertens PR: Study protocol for a randomized controlled trial to test for preventive effects of diabetic foot ulceration by telemedicine that includes sensor-equipped insoles combined with photo documentation. Trials 20: 521, 2019.

48. Fawzy MS, Alshammari MA, Alruwaili AA, Alanazi RTR, Alharbi JAM, Almasoud AMR, Alshammari RA and Toraih EA: Factors associated with diabetic foot among type 2 diabetes in Northern area of Saudi Arabia: A descriptive study. BMC Res Notes 12: 51, 2019.

49. Alzahrani HA, Wang D, Alzahrani AH and Hu FB: Incidence of diabetic foot disorders in patients with diabetes in Jeddah, Saudi Arabia. Int J Diab Dev Countries 35: 115-122, 2015.

50. Rossboth S, Lechleitner M and Oberaigner W: Risk factors for diabetic foot complications in type 2 diabetes-A systematic review. Endocrinol Diabetes Metab 4: e00175, 2020.

51. Al Kafrawy NA, Mustafa EA, Dawood ADA, Ebad OM and Ahmed Zidane OM: Study of risk factors of diabetic foot ulcers. Memoufia Med J 27: 28-34, 2014.

52. Padja J, Khalid K, Khedr A, Tasnim F, Al-Ewaidat OA, Cooper AC and Jean-Charles G: Non-Alcoholic fatty liver disease and its association with diabetes Mellitus. Cureus 13: e17321, 2021.

53. Khneizer G, Rizvi S and Gawrieh S: Non-alcoholic fatty liver disease: A non-alcoholic fatty liver disease and its association with diabetes Mellitus. Adv Skin Wound Care 38: 77, 2021.

54. Targher G and Byrne CD: Clinical review: Nonalcoholic fatty liver disease: A novel cardiometabolic risk factor for type 2 diabetes and its complications. J Clin Endocrinol Metab 98: 483-495, 2013.

55. Targher G, Byrne CD, Lonardo A, Zoppini G and Barbui C: Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol 65: 589-600, 2016.

56. Guo K, Zhang L, Lu J, Yu H, Wu M, Bao Y, Chen H and Jia W: Non-alcoholic fatty liver disease is associated with late but not early atherosclerotic lesions in Chinese inpatients with type 2 diabetes. J Diabetes Complications 31: 80-85, 2017.

57. Boulton AJM, Armstrong DG, Hardman MJ, Malone M, Embil JM, Attinger CE, Lipsky BA, Aрангón-Sánchez J, Li HK, Schultz G and Kirnser RS: Diagnosis and management of diabetic foot infections. American Diabetes Association, Arlington, VA, 2020.

58. Serban D, Papanas N, Dascalu AM, Stana D, Nicolae VA, Vanea G, Badiu CD, Tanasec D, Tudor C, Balaseca SA and Pantea-Stoian A: Diabetic retinopathy in patients with diabetic foot ulcer: A systematic review. Int J Low Extrem Wounds 20: 98-103, 2021.

59. Mponponsoo K, Sibbalb RG and Somayaji R: A comprehensive review of the pathogenesis, diagnosis, and management of diabetic foot infections. Adv Skin Wound Care 34: 574-581, 2021.

60. Shojaiefard A, Khorgami Z and Larijani B: Independent risk factors for amputation in diabetic foot. Int J Diabetes Dev Cities 28: 32-37, 2008.

61. Rismayanti IDA, Nursalam N, Farida VN, Dewi NWS, Utami R, Aris A and Agustini NLPIB: Early detection to prevent foot ulceration among type 2 diabetes mellitus patient: A multi-intervention review. J Public Health Res 11: 2752, 2022.

62. Serban D, Papanas N, Dascalu AM, Kempler P, Raz I, Rizvi AA, Rizzo M, Tudor C, Silviu Tudosie M, Tanasec D, et al: Significance of neutrophil to lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) in diabetic foot ulcer and potential new therapeutic targets. Int J Low Extrem Wounds: Nov 18, 2021 (Epub ahead of print).

63. Brănescu C, Serban D, Dascălău AM, Oprescu SM and Savlovschi C: Interleukin 6 and lipopolysaccharide binding protein-markers of inflammation in acute appendicitis. Chirurgia (Bucur) 108: 206-214, 2013.

64. Adeleye OO, Úgwú ET, Gezawa ID, Okpe I, Ezeani I and Enamino M: Predictors of intra-hospital mortality in patients with diabetic foot ulcers in Nigeria: Data from the MÉDFUN study. BMC Endocr Disord 20: 134, 2020.

65. Shi L, Wei H, Zhang T, Li Z, Chi X, Liu D, Chang D, Zhang Y, Wang X and Zhao Q: A potent weighted risk model for evaluating the occurrence and severity of diabetic foot ulcers. Diabetol Metab Syndr 13: 92, 2021.

66. Huang ZH, Li SQ, Kou Y, Huang L, Yu T and Hu A: Risk factors for the recurrence of diabetic foot ulcers among diabetic patients: A meta-analysis. Int Wound J 16: 1373-1382, 2019.

67. Tolossa T, Mengist B, Mulisa D, Fetensa G, Turi E and Abajobir A: Prevalence and associated factors of foot ulceration among type 2 diabetic patients in Ethiopia: A systematic review and meta-analysis. BMC Public Health 20: 41, 2020.

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