**RISK FACTORS FOR INFECTION DEVELOPMENT IN PATIENTS WITH DIABETIC FOOT ULCERS**

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**Факторы риска развития инфекции у пациентов с диабетическими язвами стопы**

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**Абстракт**

Использование алгоритмов по оценке риска инфицирования диабетической язвы и выявление предикторов инфицирования может быть весьма полезным для сортировки пациентов по степени риска осложнений диабетической язвы, адекватного ведения и выбора соответствующей лечебной помощи. Своевременное выявление пациентов с неосложненными диабетическими язвами может быть крайне важно для дальнейшего адекватного амбулаторного лечения, не допуская госпитализации. Считается, что при эффективном вмешательстве в лечении СДС можно предотвратить ампутации, снизив долгосрочную нагрузку на экономику и систему здравоохранения.

**Материалы и методы**

Были отобраны амбулаторные пациенты с диабетическими язвами. Далее после скрининга по форме оценки синдрома диабетической стопы и стратификации риска инфицирования диабетической язвы по разработанному алгоритму, будут выявлены факторы риска инфицирования и определены пациенты с низким риском инфицирования диабетической язвы по клиническим признакам. Далее будет определен риск инфицирования диабетической язвы по лабораторным и микробиологическим признакам.

**Результаты**

При первичном скрининге 33,1% диабетических язв имели клинические признаки инфицирования. Выявлены независимые факторы риска инфицирования, такие как глубина диабетической язвы r = 0,909, р <0,01, микробная нагрузка и уровень лейкоцитов в крови (𝑟 = 0,273, р = 0,032).

**Заключение**

Структурированная стратегия мониторинга и профилактики риска инфицирования диабетической язвы помогает в выборе тактики лечения и снижении риска осложнений синдрома диабетической стопы.

**Ключевые слова: язва диабетической стопы, факторы риска, инфекции, заживление ран.**

**Диабеттік табан жарасы бар науқастарда инфекцияның дамуының қауіп факторлары**

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**Тұжырым**

Диабеттік ойық жараның инфекциялануы қаупін бағалау және инфекцияның болжаушыларын анықтау алгоритмдерін пайдалану диабеттік ойық жараның асқыну қаупінің дәрежесі бойынша пациенттерді сұрыптау, барабар басқару және тиісті медициналық көмекті таңдау үшін өте пайдалы болуы мүмкін. Асқынбаған диабеттік ойық жарасы бар науқастарды уақтылы анықтау ауруханаға жатқызуды болдырмай, одан әрі барабар амбулаторлық емдеу үшін маңызды болуы мүмкін. Диабеттік табан емдеу барысында тиімді араласулар арқылы ампутациялардың алдын алуға, экономика мен денсаулық сақтау жүйесіне ұзақ мерзімді жүктемені азайтуға болады деп саналады.

**Материалдар мен тәсілдер**

Диабеттік ойық жарасы бар амбулаториялық науқастар таңдалды. Одан әрі диабеттік табан синдромын бағалау нысаны және әзірленген алгоритм бойынша диабеттік ойық жара инфекциясының қауіп-қатер стратификациясы бойынша скринингтен кейін инфекциялық қауіп факторлары анықталады және клиникалық белгілері бойынша диабеттік ойық жара инфекциясының қаупі төмен науқастар анықталады. Әрі қарай, диабеттік ойық жараны жұқтыру қаупі зертханалық және микробиологиялық белгілермен анықталады.

**Нәтижелер**

Алғашқы скрининг кезінде диабеттік ойық жаралардың 33,1% инфекцияның клиникалық белгілеріне ие болды. Инфекцияның тәуелсіз қауіп факторлары анықталды, мысалы, диабеттік ойық жараның тереңдігі r = 0,909, p < 0,01, микробтық жүктеме және қандағы лейкоциттердің деңгейі (𝑟 = 0,273, p = 0,032).

**Қорытынды**

Диабеттік ойық жара инфекциясының қаупін бақылау және алдын алудың құрылымдық стратегиясы емдеу тактикасын таңдауға және диабеттік табан синдромының асқыну қаупін азайтуға көмектеседі.

**Негізгі сөздер: диабеттік табан жарасы, қауіп факторлары, инфекциялар, жараларды емдеу**.

**Abstract**

The use of algorithms to assess the risk of diabetic ulcer infection and identify predictors of infection can be highly useful for sorting patients by the degree of diabetic ulcer complication risk, appropriate management, and the selection of suitable medical care. Timely detection of patients with uncomplicated diabetic ulcers may be extremely important for further adequate outpatient treatment, avoiding hospitalization. It is believed that effective intervention in diabetes foot syndrome treatment can prevent amputations, reducing the long-term burden on the economy and healthcare system.

**Materials and Methods.** Outpatient patients with diabetic foot ulcers were selected. After screening using the diabetic foot syndrome assessment form and risk stratification of diabetic ulcer infection using the developed algorithm, infection risk factors will be identified and patients with low risk of diabetic ulcer infection will be determined based on clinical signs. Subsequently, the risk of diabetic ulcer infection will be determined by laboratory and microbiological characteristics.

**Results.** At the initial screening, 33.1% of diabetic ulcers had clinical signs of infection. Independent risk factors for infection were identified, such as the depth of the diabetic ulcer r = 0.909, p <0.01, microbial load, and the level of leukocytes in the blood (r = 0.273, p = 0.032).

**Conclusion.** A structured strategy of monitoring and prevention of diabetic ulcer infection risk assists in treatment strategy selection and reduces the risk of diabetic foot syndrome complications.

**Keywords: diabetic foot ulcer, risk factors, infections, wound healing**

**Introduction**

According to the International Diabetes Federation, in 2019 there were 463 million people living with diabetes worldwide. The prevalence of diabetes is expected to increase rapidly, with over 700 million people predicted to be living with diabetes by 2045 [1]. It is reported that people with diabetes have a lifetime risk of developing Diabetic Foot Syndrome (DFS) of about 25%, and the risk of lower limb amputation can reach up to 40%. Several risk factors for limb loss have been identified, including type 2 diabetes, age, a longer history of diabetes, male sex, Body Mass Index, smoking, and the presence of complications such as diabetic nephropathy and peripheral vascular disease. In people living with diabetes, lower limb amputations positively correlate with peripheral artery disease (PAD), diabetic ulcers, or infections [2].

It has also been found that nearly 50% of patients with DFS suffer from foot infections [3]. About 20% of moderate to severe diabetic foot ulcer infections lead to minor or major amputations [4]. A diabetic foot ulcer infection is a risk factor for prolonged wound healing in diabetic ulcers, amputation, and premature mortality. If the diabetic foot ulcer infection is not detected at an early stage and brought under control in time, it can spread from superficial tissues to deeper structures such as bones and joints, complicating the disease course. Therefore, the infection of a diabetic foot ulcer is a significant primary event from which further DFS complications progress if comprehensive treatment is insufficiently effective. Individual studies have investigated the incidence and risk factors for infection development in the population of patients with uninfected diabetic ulcers. Thus, the primary objective of our study was to examine the risk factors for infection development in patients with uninfected diabetic foot ulcers.

The distinction between mild infection and the absence of infection in diabetic foot ulcers can be challenging due to the lack of objective data available at the point of care. Upon identifying signs of infection, the spectrum of its spread is broad, ranging from local manifestations to soft tissue infection, osteomyelitis, and sepsis. Apart from clinical signs of infection, inflammatory biomarkers can also play a crucial role in the pathogenesis of the infection and, hence, they may serve as useful tools for monitoring the onset and progression of diabetic ulcer infection.

Assessment of inflammatory biomarker indicators can be employed in the diagnosis of patients with diabetic ulcers, aiding clinicians in preventing infection and other complications. This study examines the relationship between certain inflammatory biomarkers and bacterial balance in uninfected diabetic ulcers. Both inflammatory biomarkers and bacterial load may serve as additional criteria for assessing the risk of diabetic foot ulcer infection.

We believe that more effective management would involve adequate monitoring and treatment of uncomplicated diabetic ulcers at the outpatient stage, to prevent the inevitable onset of infection and as a result, the further progression of complications that could lead to limb loss and increased risk of fatality.

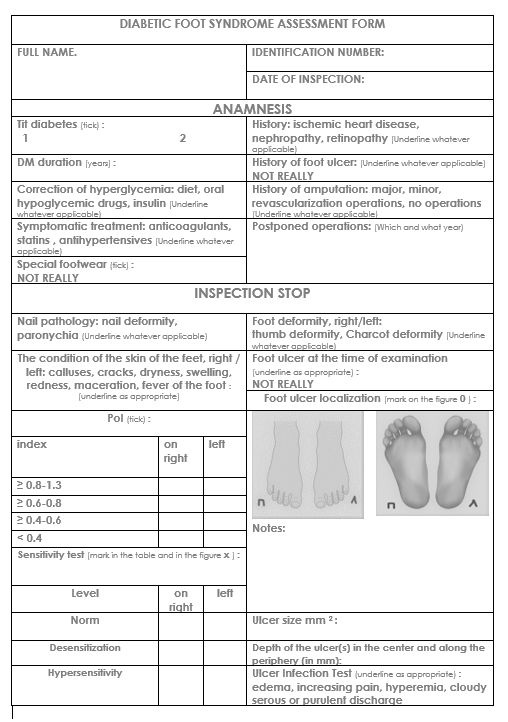
**Results**

*Monitoring and Prevention Strategy for Diabetic Foot Syndrome (DFS) Complications*

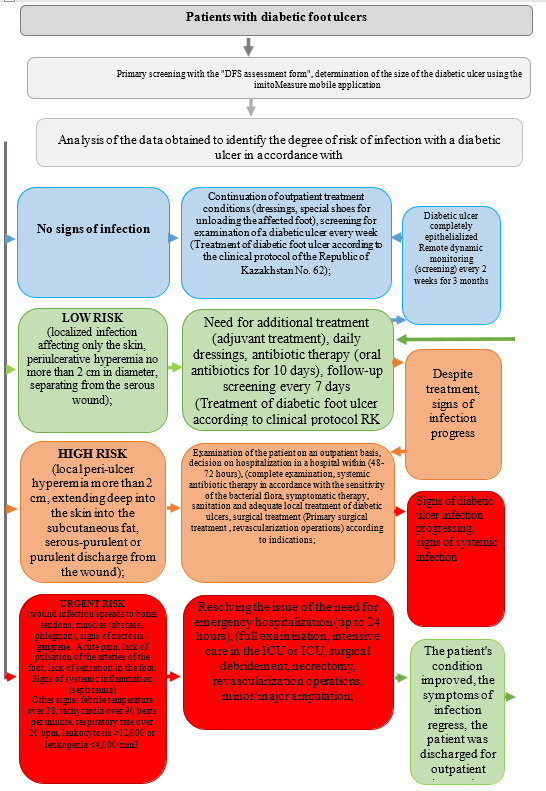
For this study, a "DFS Assessment Form" was developed to screen for diabetic foot and an algorithm to assess the risk of infecting a diabetic foot ulcer (Certificate of Authorship No. 11670 dated August 18, 2020).

For the purpose of the study, the explanatory variables were data collected using the developed DFS assessment form and the diabetic foot ulcer infection risk algorithm during the patient's first clinical visit. If data for a variable were missing, data for that variable (variables) from the second visit were used, if available, provided that the second visit occurred within two weeks after the first visit. The DFS Assessment Form is a tool for collecting multiple patient-reported and clinically diagnosed variables when they are collected by clinicians with different diabetic foot treatment experience. A diabetic foot ulcer was defined as a full-thickness wound on the foot of a patient with diabetes [5]. Non-infected diabetic foot ulcers were defined according to the classification system of the International Working Group on the Diabetic Foot as having no clinical signs or symptoms of infection. Patients with infected ulcers were not included in further research [4]. Patient-reported variables included: demographics (age, sex); diabetes history (type of diabetes, duration of diabetes, current blood glucose level and over the preceding 14 days); life history (hypertension, cardiovascular disease, chronic kidney disease, smoking); DFS history (previous foot ulcer and previous amputation, previous lower limb revascularization surgeries); and past foot treatment within the preceding 30 days (by a podiatrist, physician, surgeon, or other specialists). Clinically diagnosed variables included: foot risk factors (peripheral neuropathy, absence of protective sensitivity to a 10-gram monofilament in at least 2 plantar areas of the forefoot [6], foot ulcer characteristics (surface area of the ulcer (cm2); degree and depth according to the Texas University Diabetic Wound Classification System [5]. Treatment of the diabetic foot ulcer conducted during the first clinical visit was also recorded, including: debridement; appropriate wound dressings; prescribed antibiotics; optimal foot off-loading; suitable footwear; and patient education on diabetic ulcer care.

Figure 1 shows the DFS assessment form for the physician and research team to register patient data.



The presence of a diabetic foot ulcer infection was determined by the diabetic foot ulcer infection risk algorithm in accordance with the classification system of the International Working Group on the Diabetic Foot as at least two clinical signs or symptoms of infection in the diabetic ulcer, including purulent discharge, erythema, pain, swelling, increased temperature, and/or induration of the tissue surrounding the ulcer. The study included patients without signs of infection of the diabetic ulcer according to this algorithm. The developed strategy for monitoring and prevention of the risk of developing DFS complications appears to be the first multi-stage tool developed for identifying multiple high-risk factors for foot disease complications. Figure 2 shows the algorithm for stratification of the risk of DFS complications.



Thus, overall, the strategy for monitoring and preventing complications of DFS seems to be a valid and reliable tool for collecting the vast majority of elements contained in the construction of the diabetic foot syndrome.

**Assessment of risk factors for infection of a diabetic foot ulcer**

*Patient set and inclusion in the study*

From September 30, 2021, to November 30, 2021, 413 patients with diabetic foot ulcers were recruited. The participants were recruited from clinics in Astana, namely (City Polyclinic No. 2, "City Polyclinic No. 4, City Polyclinic No. 5, City Polyclinic No. 6, City Polyclinic No. 7, City Polyclinic No. 9, City Polyclinic No. 10, City Polyclinic No. 13); The average number of participants consenting from each clinic was 18.5 (SD 8.5, range 1-78).

**Clinical risk factors for diabetic foot ulcer infection**

*General patient characteristics*

Out of 350 patients with diabetic ulcers, 116 (33.1%) patients showed clinical signs of diabetic ulcer infection (higher than average risk of DFS complications). The analysis of patients by the DFS assessment form and the diabetic foot ulcer infection algorithm is presented in Table 1.

Table 1. Analysis of patients at stage 1 according to the DFS assessment form and the algorithm for diabetic ulcer infection

|  |  |  |  |
| --- | --- | --- | --- |
| **Patients** | **All** | **Clinically uninfected diabetic ulcers (low risk of infection)** | **Clinically diagnosed diabetic ulcers (medium, high, urgent risk)** |
| **Number of participants** | 350 | 234 | 116 |
| **DEMOGRAPHIC DATA** | | | |
| **age (SD)** | (62.2)(±4.1) | 62.4 (± 4.0 ) | 61.9 (± 4.5 ) |
| **sex n (%)** |  | | |
| female | 126 (36%) | 82 (35%) | 44 (37.9%) |
| male | 224 (64%) | 152 (65%) | 72 (62.1%) |
| **History of diabetes** | | | |
| duration of diabetes (years) (IQR) | 12.9 (4-18) | 12.6 (4–18) | 13.1 (7–18) |
| **Anamnesis of life** | | | |
| CVD a | 239 (68.2%) | 179 (76%) | 60 (51.7) |
| CKD b | 61 (17.4%) | 30 (12.8%) | 31 (26.7%) |
| smoking | 42 (12%) | 18 (7.7%) | 24 (20.7%) |
| **Previous treatment for DFS** | | | |
| GP | 216 (61.7%) | 132 (56.4%) | 84 (72.4%) |
| endocrinologist | 342 (97.7%) | 229 (97.9%) | 113 (97.4%) |
| surgeon | 50 (14.2%) | 30 (12.8%) | 20 (17.2%) |
| vascular surgeon | 106 (30.2%) | 78 (33.3%) | 28 (24.1%) |
| podiatrist | 9 (2.5%) | 6 (2.6%) | 3 (2.5%) |
| other | 22 (6.2%) | 15 (6.4%) | 7 (6.0%) |
| **History of DFS** |  |  |  |
| history of diabetic ulcer | 34 (9.7%) | 17 (7.3%) | 17 (14.7%) |
| history of amputation | 7 (2%) | 2 (0.9%) | 5 (4.3%) |
| **Risk factors for DFS** |  |  |  |
| peripheral neuropathy (decreased peripheral sensation at 2 or more points) | 234 (66.8%) | 134 (57.3%) | 100 (86.2%) |
| PAD | 110 (31.4%) | 81 (34.6%) | 29 (25.0%) |
| ABPI: |  |  |  |
| 0.5–0.79 | 110 (31.4%) | 52 (22.2%) | 58 (50%) |
| 0.8–0.99 | 129 (36.8%) | 101 (43.2%) | 28 (24.1%) |
| 1.0–1.4 | 93 (26.5%) | 74 (31.6%) | 19 (16.4%) |
| >1.4 | 18 (5.1%) | 7 (3.0%) | 11 (9.5%) |
| foot deformities | 6 (1.7%) | 2 (0.9%) | 4 (3.4%) |
| Charcot's sharp foot | 0 | 0 | 0 |
| **Characteristics of a diabetic ulcer** |  |  |  |
| ulcer area (cm 2 ) (±SD) c | 15.18 (1.85) | 15.54 (1.83) | 15.34 (1.87) |
| ulcer depth n (%) | | | |
| superficial | 342 (97.7%) | 231 (98.7%) | 111 (95.7%) |
| deep ulcer d | 9 (2.5%) | 3 (1.3%) | 6 (5.2%) |
| **Standard treatment** n (%) | | | |
| Debridement | 340 (97.1%) | 227 (97%) | 113 (97.4%) |
| Matching dressings | 336 (96%) | 226 (96.6%) | 110 (94.8%) |
| Antibacterial therapy | 75 (52.4%) | 31 (13.2%) | 44 (37.9%) |
| Foot unloading | 46 (13.1%) | 24 (10.3%) | 22 (19.0%) |
| Optimal footwear | 15 (4.2%) | 9 (3.8%) | 6 (5.2%) |
| Patient education in foot care | 350 (100%) | 234 (100%) | 116 (100%) |
| a CVD: cardiovascular diseases including arterial hypertension;  b CKD is a combination of CKD and ESRD (end-stage kidney disease).  c Ulcer area was measured using the imitoMeasure application Wounds .  d A deep ulcer is an ulcer that scores 2 or 3 on the University of Texas Diabetic Wound Grading System.  CKD: chronic kidney disease;  CVD: cardiovascular diseases;  GP: general practitioner;  cm2: centimeters squared;  PAD: peripheral arterial disease;  SD: standard deviation | | | |

In the group of patients with clinical signs of infection in a diabetic ulcer, the average age/standard deviation (SD) was 61.9 (4.5) years, 62.1% were male. Neuropathic ulcers were present in 100 (86.2%) patients and ischemic ulcers in 29 (25.0%). Differences between patients with different types of diabetic ulcers included: patients with ischemic ulcers were older (p<0.05), a larger number of patients had arterial hypertension and cardiovascular diseases, and fewer had previous foot ulcers (all p<0.005); patients with neuroischemic ulcers were also older (p<0.05), and a larger number of patients had previous amputations (p<0.005);

Correlation analysis of clinical risk factors for developing infection in a diabetic ulcer.

The Pearson correlation coefficients between various variables related to the development of diabetic foot ulcer infection are presented in Table 2.

Table 2. Correlations of the risk of developing diabetic foot ulcers with some demographic and clinical data

|  |  |
| --- | --- |
| **Index** | **P value** |
| Age | r=0.228, p=0.014 |
| foot deformity | r = 0.322, p < 0.01 |
| History of diabetic ulcer | r=0.088, p=0.348 |
| Characteristics of a diabetic ulcer: | |
| Depth of diabetic ulcer | r = 0.909, p < 0.01 |
| Diabetic ulcer area | r=0.228, p=0.014 |
|  | |

A weak positive correlation was observed between age and the area of the diabetic ulcer, whereas a significant correlation between gender and other variables related to the development of infection was not found, nor was there a significant correlation between the history of neuropathy and other variables related to the development of infection. A strong negative correlation was observed between the depth of the diabetic ulcer r = 0.909, p<0.01 and diabetic foot ulcer infection. This suggests that the presence of a superficial diabetic ulcer is less associated with the risk of developing an infection in the wound.

**Laboratory and microbiological risk factors for diabetic foot ulcer infection**

*Biochemical investigations (baseline levels of biomarkers of clinically non-infected diabetic foot ulcers)*

Biomarker levels in patients are shown in Table 3.

Table 3. Biomarker levels of clinically uninfected diabetic foot ulcers

|  |  |
| --- | --- |
| **Biomarker :** | **Mean (± SD)** |
| Blood sugar ( mmol /l) | 9.1 (±4.2) |
| Albumin (g/l) | 44.6 (±7.2) |
| Leukocytes (×10 9 /l) | 7.2 (±1.9) |
| Neutrophils (×10 9 /l) | 59.6 (±8.7) |
| C-reactive protein (mg/l) | 3.3 (±1.8) |
| Procalcitonin ( ng /ml) | 0.07 (±0.04) |

Following laboratory screening (inflammation biomarker study and microbiological study of the diabetic ulcer biopsy), the following predictors of infection were found - hyperglycemia more than 15 mmol/L in 38 patients (11.7%), elevated levels of inflammatory biomarkers in 22 patients (6.7%).

Microbiological study (baseline bioburden of clinically non-infected diabetic foot ulcers)

This was used to determine the degree of bacterial burden in the wound. The bacterial burden indicators in the biopsies of the diabetic ulcers of patients are presented in Table 4.

Table 4. Indicators of bacterial load in biopsy specimens of diabetic ulcers

|  |  |  |
| --- | --- | --- |
| **Index** | **Mean (± SD)** | **Median (range)** |
| Bacterial load | 1.0×10 4 (±3.75×10 5 ) | 5.1 × 10 3 (0–2.7 × 10 6 ) |

Six patients out of 234 had no growth on culture dishes. Therefore, the microbial load for these subjects was 0. Mean and median microbial load and microbial diversity were calculated for the entire sample, including those with no growth. Therefore, the range included 0 as the low level.

In 12 patients (5.1%), according to the microbiological study, the degree of bacterial load in the diabetic ulcer exceeded 10 5 per gram of biopsy, that is, the microbiological risk of infection of the diabetic ulcer was 5.1%.

- Correlation analysis of total microbial load in diabetic ulcer

Correlation analysis of the total microbial load with other clinical and laboratory parameters is presented in Table 5.

Table 5. Correlations of total microbial load with some demographic, clinical and biomarker data

|  |  |
| --- | --- |
| **Index** | **P value** |
| Microbial load | 𝑟 𝑠 = 0.544, p <0.001 |
| leukocytes | 𝑟 𝑠 = 0.273, p =0.032 |
| neutrophils | 𝑟 𝑠 = 0.306, p =0.015 |
| depth of diabetic ulcer | 𝑟 𝑠 = 0.246, p =0.053 |
| age | 𝑟 𝑠 = -0.147, p =0.253 |
| duration of diabetes | 𝑟 𝑠 = −0.20, p =0.880 |
| duration of diabetic ulcer ∗ | 𝑟 𝑠 = 0.048, p =0.712 |
| ABPI | 𝑟 𝑠 = -0.032, p =0.806 |
| CRP | 𝑟 𝑠 = 0.140, p =0.278 |
| blood sugar | 𝑟 𝑠 = 0.228, p =0.075 |
| albumen | 𝑟 𝑠 = 0.130, p =0.315 |
| procalcitonin | 𝑟 𝑠 = 0.104, p=0.420 |
| ∗ ulcer duration in months  ABPI - ankle -brachial pressure index  CRP - C reactive protein | |

The overall microbial load was positively correlated with the number of leukocytes (rs = 0.273, P = 0.032). The analysis also showed a borderline insignificant positive correlation with the depth of the diabetic ulcer (rs = 0.246, p = 0.053).

**Discussion**

The treatment of diabetic foot requires a multi-profile team to treat diabetic ulcer complications, metabolic disorders, deficiency or improper nutrition, comorbidities, and surgeries (surgical revascularization). Recently, several intensive therapy strategies have been developed to avoid amputation [7] [8]. It is important to note that for any diabetic foot treatment strategy, there is always an amputation risk, which has yet to be defined by the medical community. Understanding the chances of cure helps to make a therapeutic decision and can reduce the number of diabetic ulcer complications, the number of amputations, and expenses related to hospitalization and long-term treatment. The physician's role in making a decision about amputation or continuing conservative treatment is not easy [8]. The decision often rests on how bad the wound looks. However, this visual observation often hampers the decision-making process because the appearance of the wound is definitely not a factor correlating with amputation. Several authors have contributed to the development of tools for identifying risk factors and the chances of healing diabetic foot wounds. In his research, Lipsky developed and approved an amputation risk scale for hospitalized patients (more than 3000 patients) with an infected diabetic foot. This research considered fourteen different factors associated with the risk of amputation. The most significant analyzed factors were diabetic ulcer infection, vasculopathy, previous amputation, and leukocytosis over 11,000/mm3 [9]. The Lipsky scale represents a five-layer prognostic system with scores ranging from 0 to 21 and more. However, there is no practical guidance regarding how to use these indicators to determine the risk of amputation. While all these strategies provided important information for assessing the possible outcome of the diabetic foot, they are cumbersome, and physicians tend to use empirical evaluation instead of conducting the necessary quantitative assessments. Therefore, new strategies need to be developed to classify the diabetic foot to improve healing, speed up the regeneration process, and avoid amputation, regardless of the type of intervention or treatment.

Evidence supporting the risk classification of diabetic foot development has been obtained from a series of large cross-sectional and prospective studies, as well as the identification of clinical features in individual patients related to the relative risk of forming a diabetic ulcer in the future. If the risk classification of the diabetic foot is linked to preventive strategies, the incidence of new foot diseases should decrease. Therefore, foot risk classification may become a routine part of diabetes treatment 10]. A multidisciplinary approach is needed in conjunction with a vascular surgeon, as peripheral artery occlusive disease and foot ulcers in diabetic patients increase the risk of foot complications and amputation [11]. The goals of the current research are to develop a simple prognostic scale for the diabetic foot, using which the doctor can quickly obtain the necessary information using individual indicators for each patient, stratify the risk of infecting a diabetic ulcer and the risks of more serious complications, allowing decisions to be made based on the likelihood of outcome. Our aim was to conduct structured observation and care for patients with DFS by evaluating the risk of infection and other complications of the developed risk stratification algorithm and tactics of patient management to reduce DFS complications, improve patient quality of life, and reduce social costs associated with these diseases, using this specific strategy [12].

In this study, the total microbial load showed a positive correlation with some inflammatory markers, i.e., with leukocytes, but not with CRP and procalcitonin, this confirms data that inflammation markers can predict wound infection, and in the absence of signs of infection their indicators will be normal. Essentially, several factors can influence the clinical manifestations of infection, especially ischemia and neuropathy, both of which can blunt the inflammatory response [13]. An alternative explanation for the lack of significant correlation is the homogeneity of our study population, as the selected patients had a mild risk of diabetic ulcer infection. Conversely, the total microbial load was not associated with ulcer duration. Typically, long-existing chronic ulcers are predisposed to colonization and infection [14]. However, this propensity does not equate to the development of a high microbial load, as our results showed.

*Limitations*

This DFS complication risk monitoring and prevention strategy has not been validated; this study is the first where it has been.

**Conclusion**

In this study, we propose a developed strategy for screening and risk stratification for the development of DFS complications. This strategy helps to identify the risk of complications and, depending on the identified risk, to form a further management strategy for adequate treatment and reducing the risk of lower limb amputation. Timely identification of patients with uncomplicated diabetic ulcers can be extremely important for further adequate outpatient treatment, without hospitalization. With effective intervention in the treatment of DFS, it is possible to prevent the progression of complications and the frequency of lower limb amputations. This study revealed a strong relationship between the depth of the diabetic ulcer and the risk of infection. This suggests that early identification of patients with diabetic ulcers, while the risk of complications is low, are less susceptible to the development of infection in the diabetic ulcer, and therefore will respond better to treatment.

Attention should be paid to structuring the process of providing care to patients with DFS. The available data indicate that very significant improvements in the quality of medical care for patients with DFS may accompany a structured approach and constant monitoring of the patient.

**Declaration of conflicting interests**

The authors declared no potential conflicts of interest with respect to the research, authoship, and/or publication of this article.

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