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Inflammatory Markers Influencing Mortality Rates in Diabetic Foot Ulcer—A Prospective Study

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Abstract: This study aimed to explore the relationship between inflammatory markers, apolipoprotein E (ApoE) levels, renal function, and mortality in patients with diabetic foot ulcers (DFUs). Conducted as a single-center prospective study at the Clinical County Emergency Hospital of Arad, Romania, the study included 90 patients diagnosed with infected DFUs. The main objective was to determine the risk factors for mortality over a three-year follow-up period, focusing on early versus late deaths. The results indicate a significant correlation between elevated levels of ApoE, pentraxin 3 (PTX3), procalcitonin (PCT), and impaired renal function with increased mortality. Patients with higher levels of these biomarkers, particularly those with impaired renal function, were more likely to experience early death, especially within the first 90 days after surgery. The findings underscore the critical role of these factors in predicting mortality, and they highlight the need for early intervention and aggressive management of these risk factors to improve outcomes in this vulnerable population. Despite advancements in medical and surgical care, the prognosis for patients with DFUs remains poor, particularly due to the recurrent nature of ulcers and the presence of comorbidities like chronic kidney disease.

Keywords: diabetic foot ulcer; mortality; inflammatory markers; apolipoprotein E; pentraxin 3

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1. Introduction

The global prevalence of diabetes mellitus (DM) has reached concerning levels, putting immense pressure on public health systems worldwide [1]. The chronic nature of the disease and its tendency to cause various

complications present significant challenges to both individuals and healthcare providers [1]. The impact of DM goes beyond just metabolic issues, often leading to a range of serious microvascular and macrovascular complications that significantly reduce patients' quality of life [2].

One of the most serious complications of DM is the development of diabetic foot ulcers (DFUs). These minor wounds, often caused by small injuries or infections, can quickly become complex and difficult to heal [3]. The impaired ability to heal in DM, combined with the possibility of nerve damage and poor blood circulation, creates a high risk for infection, tissue death, and, eventually, amputation. The burden of DFUs is not just physical; it also causes significant emotional and financial stress for patients and their families [4].

The strong connection between DFUs and mortality has been well documented in the literature. Studies consistently show a much higher risk of early death among individuals with DFUs compared to those without it, with a 2.5 hazard ratio [5,6]. This increased risk of death highlights the broader impact of DFUs, indicating its role as a sign of a more severe decline in overall health. The complex relationship between DFUs and other diabetes-related complications, such as heart disease and kidney problems, further complicates the situation and adds to the increased risk of death reaching up to 50% at 5 years, a higher risk than that of many cancers [7].

Several factors have been identified to contribute to the higher mortality seen in patients with DFUs. Older age, the presence of poor blood circulation, chronic kidney disease, and poor blood sugar control have all been recognized as independent predictors of mortality. Additionally, the severity and extent of the DFU, along with the presence of infection, further increases the risk. Understanding how these risk factors interact is essential for developing effective strategies to reduce mortality in this vulnerable population [8].

This study aims to explore the complex relationship between inflammatory markers and early and late mortality in diabetic patients with DFUs. While previous research has looked at the importance of various clinical and demographic factors, the role of inflammatory markers in predicting long-term mortality has not been as thoroughly investigated. By examining a broad range of inflammatory markers, we hope to identify potential biomarkers that could serve as early warning signs of a worsening condition, allowing for timely interventions and better patient outcomes. The main goal of this study is to determine the risk factors for mortality over a 3-year follow-up period, with a particular focus on the predictive value of inflammatory markers.

2. Materials and Methods

2.1. Study Design and Participants

This research was conducted as a single-center, prospective study at the Clinical County Emergency Hospital of Arad, Romania, spanning from March 2020 to March 2021. The study's objective was to explore the relationship between inflammatory markers and mortality in patients with diabetic foot ulcers (DFUs). Prior to participation, all subjects were fully informed about the study's purpose and provided written consent.

The study population was based upon a group of 90 patients diagnosed with infected diabetic foot ulcers (IDFUs). The participants were further categorized based on their outcomes at the 90 days after index DFU admission and three-year follow-up (survivors versus non-survivors, early deaths versus late deaths):

- Distal interventions: Procedures performed below the ankle, including soft tissue debridement without bone removal, toe amputations, transmetatarsal amputations, and midtarsal amputations.

—Proximal interventions: Procedures performed above the ankle, such as below-knee and above-knee amputations.
—Outcome subgroups: Patients who survived versus those who did not survive during the follow-up period, before-90-days deaths and later deaths.

The classification of foot infections in diabetic patients followed the criteria outlined in the 2019 guidelines developed by the International Working Group on the Diabetic Foot (IWGDF).

2.2. Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Participants aged 18 years or older.
2. Ability to understand and provide informed consent.
3. Presence of an IDFU at initial hospital presentation, without prior surgical or antibiotic treatment.
4. Classification of the foot ulcer as mild to moderate according to the IWGDF guidelines.
5. Positive microbiological culture from the wound site.

Exclusion Criteria:

1. Presence of any other infections.
2. Death due to COVID-19 during the study period or follow-up.
3. Diagnosis of cancer either before or during the study period.
4. Patients who were lost to follow-up at three years.
5. Candidates for major vascular reconstructive surgery.

2.3. Ethical Considerations

The study protocol received approval from the Institutional Review Board and Ethics Committee of the Clinical County Emergency Hospital of Arad (Approval No. 51, dated February 24, 2020). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. All participants provided written consent for the collection, analysis, and anonymous publication of their data.

2.4. Data Collection

Demographic information (age, gender, place of residence), comorbid conditions, location of the foot infection, details of any amputations performed, and length of hospital stay were extracted from patient medical records. Decisions regarding amputation, including the level at which it was performed, were made following comprehensive clinical assessments conducted during daily meetings by the medical team.

Routine laboratory tests were conducted upon admission, including those that examine white blood cell count (WBC), hemoglobin A1c (HbA1c), hemoglobin levels, fibrinogen levels, procalcitonin levels, pentraxin 3 levels, apo-3 levels, creatinine, and urea.

2.5. Follow-Up

The final follow-up occurred three years after the initial hospital admission. This involved outpatient clinic visits and recording any subsequent hospitalizations or procedures. Mortality data were obtained from the local death registry.

2.6. Data Analysis

Statistical analysis was performed using MedCalc software version 21. The distribution of numerical data was evaluated using the Kolmogorov–Smirnov test. Data that followed a normal distribution are reported as mean ± standard deviation (SD), while non-normally distributed data are presented as median values with interquartile ranges (IQR). Comparisons of continuous variables were performed using the t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Categorical variables were compared using the Chi-square test. Correlations between continuous variables were assessed using Pearson (r) or Spearman (rho) coefficients. A p-value of less than 0.05 was considered statistically significant.

3. Results

During the study period, we enrolled 90 patients; for the final analysis, after applying the inclusion and exclusion criteria, 74 patients remained (as shown in Figure 1).

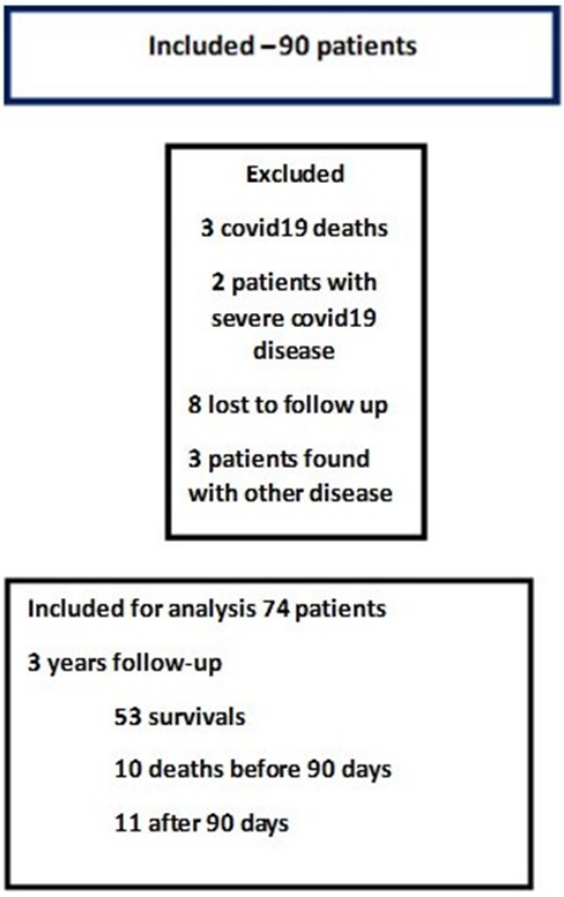

Figure 1. Flow-chart of patients' inclusion in the study.

The total number of deaths recorded in the study was 21 out of 74, 28% of total number of patients analyzed.

Comparing the survivors with the total death group, we found several significant differences in inflammatory markers and some laboratory blood tests (Table 1).

Table 1. Survivors versus non-survivors at three years follow-up.

Variables	Survivors (n = 53)	Non-Survivors (n = 21)	*p*
Median age in years (95% Cl)	63 (60–68)	68 (63–71)	0.1
Male % (male/n)	75% (40/53)	52% (11/21)	0.05
Rural % (rural/n)	66% (35/53)	52% (11/21)	0.2
Type of surgery			
Proximal % (proximal/n)	90% (48/53)	80% (17/21)	0.2
Distal % (distal/n)	10% (5/53)	20% (4/21)	0.2
Number of days in hospital (mean ± SD)	10 ± 5	14 ± 8	0.03
WBC (mean ± SD) (number × 10^9/L)	14.9 ± 5	17 ± 7	0.1
RDW (mean ± SD) (%)	61 ± 21	60.9 ± 23	0.9
Fibrinogen (mean ± SD) (mg/dL)	689 ± 147	642 ± 169	0.2
C reactive protein (mean ± SD) (mg/dL)	123 ± 104	142 ± 71	0.4
Procalcitonin (mean ± SD) (ng/mL)	0.4 ± 0.6	0.5 ± 0.7	0.3
Apo E (mean ± SD) [mg/dL]	6.2 ± 1	18.9 ± 6.7	<0.0001
Pentraxin 3 (mean ± SD) (pg/mL)	1955 ± 1580	3096 ± 1525	0.006
HbA1c (mean ± SD) (%)	9.7 ± 7.2	9 ± 2.7	0.6
Years since diabetes diagnosis			
<5 years	30% (16/53)	4.7% (1/21)	0.02
5–10 years	30% (16/53)	42.8% (9/21)	0.2
>10 years	39% (21/53)	52.3% (11/21)	0.3
HDLc (mean ± SD) [mg/dL]	30 ±10	30 ±14	0.9
Creatinine (mean ± SD) [mg/dL]	1.1 ± 0.5	1.4 ± 1.4	0.05
Urea (mean ± SD) [mg/dL]	50 ± 30.8	67.3 ± 53.5	0.06
Hgb (mean ± SD) (g/dL)	11.6 ± 1.7	10 ± 2.3	0.004

Female sex was a risk factor for death.

When comparing the patients who died before 90 days after surgery with the patients who died later, we found more significant differences in the inflammatory markers' values (Table 2).

Table 2. Deaths 90 days after surgery compared with deaths before three-year follow-up.

Variables	Death before 90 Days after Surgery (n = 10)	Death after 90 Days (n = 11)	*p*
Median age in years (95% Cl)	66 (60–70)	70 (63–80)	0.1
Male % (male/n)	50% (5/10)	54% (6/11)	0.8
Rural % (rural/n)	30 % (3/10)	36% (4/11)	0.7
Type of surgery			
Proximal % (proximal/n)	20% (2/10)	18% (2/11)	0.9
Distal % (distal/n)	80% (8/10)	82% (9/11)	0.9
Hospital days (mean ± SD)	17.2 ± 10.2	12.4 ± 5.4	0.1
WBC (mean ± SD) (number × 10^9/L)	16.26 ± 7.50	17.84 ± 7.64	0.6
RDW (mean ± SD) (%)	71 ± 17.59	51.81 ± 25.08	0.05
Fibrinogen (mean ± SD) (mg/dL)	657.60 ± 133.14	629.09 ± 203.30	0.7
CRP (mean ± SD) (mg/dL)	179.52 ± 75.44	112.66 ± 76.28	0.05
Procalcitonin (mean ± SD) (ng/mL)	1.02 ± 0.89	0.18 ± 0.15	0.006
Apo E (mean ± SD) [mg/dL]	18.9 ± 6.6	19.72 ± 7.28	0.8
Pentraxin3 (mean ± SD) (pg/mL)	4013.60 ± 1832.38	3171.09 ± 1496.93	0.26
HbA1c (mean ± SD) (%)	10.48 ± 3.04	7.79 ± 1.87	0.02
Years since diabetes diagnosis			
<5 years	0	9% (1/11)	0.3
5–10 years	50% (5/10)	36% (4/11)	0.5
>10 years	50% (5/10)	54% (6/11)	0.8
HDLc (mean ± SD) [mg/dL]	25.5 ± 10.1	38.60 ± 16.48	0.1
Creatinine (mean ± SD) [mg/dL]	1.90 ± 0.88	1.12 ± 0.44	0.01
Urea (mean ± SD) [mg/dL]	100.0 ± 62.0	37.46 ± 14.41	0.04
Hgb (mean ± SD) (g/dL) [mg/dL]	9.4 ± 2.3	10.82 ± 2.13	0.1

4. Discussion

DFUs are a severe complication in patients with diabetes, often leading to significant morbidity and mortality. The mortality rate among individuals with DFUs is notably high, with studies indicating that the death rate can reach alarming levels within a few years of diagnosis [7]. In our study, we observed that the death rate was 28% at three years for diabetic individuals with infected foot ulcers. This statistic underscores the grave prognosis associated with DFUs, reflecting a broader trend seen in the literature.

The five-year mortality rate associated with diabetic foot complications is comparable to that of some of the most aggressive forms of cancer [7]. For instance, the five-year mortality rate for patients with DFUs has been reported to range from 30% to 68%, depending on various factors such as the presence of additional comorbidities, the severity of the ulceration, and whether the patient underwent an amputation [9]. Specifically, major amputations are associated with a five-year mortality rate that can exceed 50%, illustrating the severe impact of this condition [7].

Several factors contribute to the high mortality rate observed in patients with DFUs. First, DFUs are often indicative of advanced systemic disease, including peripheral neuropathy and peripheral arterial disease, both of which are associated with increased cardiovascular mortality [10].

In our study, female sex was identified as a significant risk factor for mortality among patients with DFUs. More than half of the women included in our cohort died within the study period, highlighting the severe impact of DFUs on female patients. The mortality rate among women with DFUs was lower than in men, but still significant, with around 16.1% of women dying during the follow-up period versus 24.5% men [11]. Another study suggested a slightly higher mortality rate for women compared to men in certain contexts, emphasizing the variability in outcomes based on the population and healthcare setting [12].

In our cohort, the mortality rate for women exceeded 50%, underscoring the heightened vulnerability of female patients in our study compared to those in other studies. This discrepancy might be due to differences in comorbidities, access to care, or severity of the disease at presentation.

In our study, we found that 20 out of 21 deaths occurred in patients who had a history of diabetes mellitus for longer than five years. This finding suggests a strong correlation between the duration of diabetes and the risk of mortality in patients with DFUs.

Comparing this to other studies, a similar trend is observed. For instance, in one study, the median duration of diabetes among patients who died was around seven years, with the majority of deaths occurring in patients who had diabetes for several years before the onset of DFUs [13]. This aligns with our observation that prolonged exposure to the complications of diabetes, such as vascular and neuropathic damage, significantly increases the risk of mortality.

Another study reported that the duration of diabetes was a critical factor in determining the outcomes for patients with DFUs. Patients with a longer history of diabetes were more likely to experience severe complications and had higher mortality rates [14]. These findings reinforce the importance of early intervention and aggressive management of diabetes to prevent the progression to severe complications like DFUs, which are closely linked to higher mortality, especially in those with a longer history of the disease.

In our study, we found a significant association between apolipoprotein E (ApoE) levels and mortality in patients with diabetic foot ulcers (DFUs). ApoE plays a crucial role in lipid metabolism by mediating the

clearance of lipoprotein remnants from the bloodstream, which is essential in maintaining lipid homeostasis. Variations in ApoE can lead to dyslipidemia, contributing to the development and progression of atherosclerosis, a major risk factor for neuropathy and cardiovascular complications in diabetic patients [15].

In patients with DFUs, impaired lipid metabolism due to ApoE dysfunction can exacerbate peripheral neuropathy by increasing oxidative stress and inflammation, further compromising blood flow to the extremities and hindering wound healing [16]. This pathological process likely contributes to the higher mortality observed in our study, as patients with altered ApoE function are more prone to severe vascular complications. Thus, monitoring ApoE levels could be useful in managing and predicting outcomes in diabetic patients with DFUs.

In our study, we observed a significant correlation between elevated levels of pentraxin 3 (PTX3) and increased mortality in patients with diabetic foot ulcers (DFUs). PTX3 is an acute-phase protein involved in the body's immune response and plays a critical role in inflammation and vascular health [17]. Elevated PTX3 levels are indicative of systemic inflammation, which is a common complication in diabetic patients, particularly those with DFUs. In the context of DFUs, high PTX3 levels may reflect ongoing vascular inflammation and endothelial dysfunction, which can exacerbate peripheral artery disease and impair wound healing [17]. The persistent inflammatory state associated with elevated PTX3 can lead to more severe infections and slower recovery, increasing the risk of sepsis and other life-threatening complications. PTX3 serves not only as a biomarker of inflammation but also as a potential predictor of poor outcomes [18].

In our study, we observed that patients with infected diabetic foot ulcers (DFUs) who had elevated procalcitonin (PCT) levels were more likely to experience early mortality, specifically within the first 90 days after surgery. Procalcitonin is a biomarker that rises significantly in response to bacterial infections and systemic inflammation, making it a useful indicator of the severity of infection.

Higher PCT levels suggest a more aggressive infection and a heightened systemic inflammatory response, which can lead to rapid deterioration in patients with DFUs. The early deaths observed in those with elevated PCT may be due to the overwhelming infection and ensuing sepsis, which can cause multi-organ failure and death if not swiftly managed. The elevated PCT levels in these patients likely reflect the severity of their condition, indicating that the infection was more extensive and harder to control, leading to poor outcomes despite surgical intervention [19].

In our study, impaired renal function emerged as a significant risk factor for mortality in patients with diabetic foot ulcers (DFUs), with differences between survivors and overall deaths, but also between early and later deaths. Patients with compromised renal function are more vulnerable to complications due to the kidneys' reduced ability to filter waste and manage electrolyte balance, which exacerbates the systemic effects of diabetes. Renal impairment also contributes to poor wound healing and increased susceptibility to infections, both of which are critical in the context of DFUs [20,21].

The significance of renal dysfunction in both early and later deaths suggests that kidney health plays a crucial role throughout the disease course. Early deaths may result from acute complications like sepsis, while later deaths could be linked to chronic issues such as cardiovascular disease, both of which are exacerbated by renal insufficiency.

The prognosis for patients with DFUs remains poor despite advances in medical and surgical care. The recurrent nature of foot ulcers, with a high likelihood of re-ulceration even after successful initial healing,

places patients in a continuous state of risk. This ongoing risk, coupled with the underlying diabetes and associated comorbidities, means that patients with DFUs face a substantially shortened life expectancy compared to the general population or even diabetics without foot complications.

Our study has several limitations that must be acknowledged. As a single-center study, the findings may not be generalizable to broader populations or different healthcare settings. The sample size was relatively small, limiting the statistical power of our analyses. Additionally, the study's observational design introduces potential biases, such as selection bias. Recall bias could also affect the accuracy of patient-reported data. Furthermore, the reliance on retrospective data from medical records might have led to incomplete or inaccurate information, affecting the validity of our conclusions.

5. Conclusions

This study highlights the significant impact of inflammatory markers, apolipoprotein E levels, and renal function on the mortality of patients with diabetic foot ulcers. Despite advances in treatment, the prognosis for patients with diabetic foot ulcers remains poor, underscoring the importance of early detection and aggressive management of risk factors to improve outcomes and reduce mortality in this vulnerable population.

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