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ORIGINAL: Evaluation of Prognostic Risk Factors in Patients with Diabetic Foot Ulcers Admitted to Sayyad Shirazi Hospital in Gorgan during 2018-2020

Roghieh Golsha	Infectious Diseases Research Center, Golestan University of Medical Science, Gorgan, Iran.
Zeynab Baylari	General Practitioner, Golestan University of Medical Sciences, Gorgan, Iran.
Mohammad Tajik	Medical Student, School of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran.
Ahmad Sohrabi	Cancer Control Research Center, Cancer Control Foundation, Iran University of Medical Sciences, Tehran, Iran.
Maryam Montazeri	General Practitioner, Infectious Diseases Research Center, Golestan University of Medical Science, Gorgan, Iran.

Correspondence:

Maryam Montazeri, Infectious Diseases Research Center, Golestan University of Medical Science, Gorgan, Iran.

Email: Marine.montazeri@yahoo.com
ORCID: 0000-0003-1699-3361

ABSTRACT

Introduction: Diabetes mellitus (DM) is one of the most common diseases in the world and diabetic foot ulcer (DFU) is one of the main causes of mortality and morbidity. This study was done for the evaluation of prognostic risk factors in hospitalized patients with DFU.

Material and Methods: In this cross-sectional study, the records of all patients with DFU referred to Sayyad Shirazi Hospital in Gorgan during 2018-2020 were reviewed to determine the demographic characteristics, paraclinical findings, and clinical features. All information of patients was entered into the checklist. Frequency, percentage, mean± standard deviation (SD) were used to describe the data. Chi-square and ANOVA tests were used to investigate the relationship between each. SPSS software version 20 was used for data analysis.

Results: In this study 379 patient with DFU were studied that 54.1% were female. 62.3% of patients were in the age group of 45 -65 years. In these patients, 64.9% had hypertension and 37.7% had cardiovascular disease. 6.8% and 21.2% were smokers and drug addicts, respectively and 17.7% had history of lower limb amputation .76% of patient had grade 2 and 3 Wagner's DFUs. According to the statistical analysis, there was no significant relationship between insulin treatment, smoking and opium use, and patient's age with the final outcome of discharge. The chi-square test showed the relationship between white blood cells (WBCs) erythrocyte sedimentation rate (ESR) level and final outcome.

Conclusion: DFU prognosis may be related to WBC and ESR, grading of DFU, and history of lower limb amputation.

Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia. This disease is one of the main problems of health care systems in Iran and the world. According to the world health organization (WHO) report, the prevalence of diabetes in Iran in 2016 was 10.3% and its global prevalence will increase from 176 million in 2000 to 366 million in 2030 (1). The prevalence of diabetes in the world is increasing, and type II diabetes is more prevalent than the other types, which

can be due to increased obesity, aging, and decreased physical activity in modern societies (2, 3).

DFU is one of the most serious chronic complications of diabetes which, if not controlled, can lead to disability, severe loss of quality of life, and amputation (4). The increasing incidence of this disorder is due to the interference of several factors such as neuropathy, poor gait, peripheral vascular disease, and poor ulcer healing (1). Sensory and motor neuropathy cause structural changes in the foot such as a hammer toe, and autonomic neuropathy causes dry skin and Skin changes. Peripheral vascular disease (PVD) and poor ulcer healing cause small ulcers to become larger and infected (5). DFU is the most common cause of hospitalization in diabetics and is expensive to treat worldwide. In developed countries, more than 5% of diabetic's patients develop foot ulcers. In the United States, the treatment of DFUs costs $ 7,000 to $ 10,000 a year, and this cost increases by $ 65,000 in *complicated* cases needing amputation, which indicates the high costs of healthcare. Currently, one foot is amputated every 30 seconds, 85% of which is due to a DFU (6).

The risk of non-thrombotic amputation in diabetic patients is higher than normal people in the community and amputation itself can be a surplus factor in diabetic patients in addition to determining prognostic factors for DFU patients, which is an inevitable challenge for physicians and surgeons treating diabetic foot (7). Therefore, more attention to foot problems and their timely treatment is necessary. In Iran, we are also witnessing a progressive incidence of DFUs (8). The evaluation of the condition of diabetics in recent years and its comparison with previous years is necessary to show the decreased or increased prevalence of DFUs and lower-limb amputations and to evaluate success rates in educating patients their treatment (9).The risk and prognostic factors of diabetic foot ulcers (clinical, laboratory, and pharmacological) can greatly help prevent this serious complication. For this purpose, the present study was conducted to evaluate the levels of laboratory and pharmacological variables of Hemoglobin A1c (HbA1c), inflammatory indices of erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP), and antibiotic regimen to design a protocol to prevent chronic and progressive DFUs and amputation of diabetic limbs.

Methods

In this cross-sectional descriptive-analytic study, the records of all patients with DFUs referred to Sayyad Shirazi Hospital in Gorgan during 2018-2020 were reviewed to determine the demographic characteristics, paraclinical findings, and clinical features of the disease including duration of disease, atherosclerosis, type of antibiotic regimen used in ulcer healing, and the patients' health behaviors including smoking. All information of patients recorded in the interview, as well as the first paraclinical findings at the time of admission, were entered into the checklist. Finally, prognostic factors were determined according to the outcome of treatment (complete recovery, partial recovery, and amputation).

To present the descriptive characteristics of the study population based on the type of variable (quantitative/qualitative), tables and graphs of frequency, as well as mean and standard deviation were used, and X2 and ANOVA tests were used to investigate the relationship between each variable and the outcome evaluated as univariate, and if the variables were not normal, the nonparametric equivalent of these tests was used. According to the type of outcome evaluated, the rank regression model was used, SPSS software version 20 was used for data analysis, and a p-value of less than 0.05 was considered significant.

Results

In the present study, 379 patients with DFUs were evaluated, of which 174 (46%) were male and 205 (54%) were female. The mean age of participants was about 60 years with a minimum age of 31 years and a maximum age

of 89 years. 371 (98%) subjects were married and 8 (2 %) were single.

The results of the present study showed that approximately 253 (67%) and 126 (33%) patients were residents of the city and village, respectively. Also, 327 people (86.3%) were of Persian ethnicity and 38 people (10%) were of Turkmen ethnicity.

According to the table below, of the 173 people whose body mass index (BMI) data were available, 31.8% had normal weight and 68.2% had high BMI (overweight and obesity).

The results of a family history study in diabetic patients showed that about 50% of the subjects had a family history of diabetes. In addition, 246 patients (65%) had a history of hypertension (HTN), 142 (38%) were with a history of heart disease, 2 patients (0.5%) with a history of collagen vascular disease, 137 patients (36%) with a history of chronic kidney disease, and 100 patients (26.5 %) had a history of dyslipidemia.

In this study, it was found that out of 377 patients, 227 (60%) were taking insulin and 67 (18%) had a history of previous leg amputation.

The results of the table below show that about 6% of the subjects were addicted to cigarettes and about 21% were addicted to other drugs.

In evaluating the type of treatment selected to heal the ulcers of patients, it was determined that among 377 patients, in 342 (90%) the standard method and in 37 patients (10%) the new and standard method was used.

In evaluating the degree of ulcer, about 75% of the subjects had grade 2 and 3 ulcers (*Table 1*).

The results show that approximately 48% of hospitalized patients with diabetic ulcers were discharged with no complications (n=179, 47.7%) and only 3.2% died. Also, 143 (37.8%) and 45 (11.3%) patients had discharge with complications and with personal consent, respectively.

In this study, among the 327 patients who received clindamycin injections, 52.91% were discharged with no complications, 43.5% with complications, and 3.67% died. Of 247 patients who received ciprofloxacin

Table 1. Distribution of subjects according to BMI, Grading of Wound, Smoking and Addiction

	variation	Frequency (percent)
BMI	normal	55 (31.8%)
	Overweight	56 (32.4%)
	Fat	62 (35.8%)
Grading of Wound	Grade 1	21 (5.5%)
	Grade2	214 (56.5%)
	Grade3	74 (19.5%)
	Grade4	55 (14.5%)
	Grade5	15 (4%)
Smoker	No	344 (93.2%)
	Yes	25 (6.8%)
Addiction	No	290 (78.8%)
	Yes	78 (21.2%)

injections, 53.63% were discharged with no complication, 43.72% with complications, and 9% died. Therefore, it can be concluded that injecting clindamycin and ciprofloxacin can improve the patient's prognosis.

Of 57 patients who received fluconazole capsules, 56.14% were discharged with no complications, so it may be concluded that antifungal administration may improve the patient's prognosis.

The highest use of vancomycin, tazocin, and penicillin G was observed in people who were discharged with no complication, which may be justified by the severity of the disease. (*Table 2*)

According to the results, the distribution of the final outcome based on the duration of the ulcer is almost the same, and the result of Fisher's exact test also showed no correlation between the duration of the ulcer and the final outcome (p-value = 0.257). Also, from the table below, it is observed that the distribution of the final outcome in different age groups is almost the same, and the result of the chi-square test also showed no relationship between age groups and the final outcome (p-value = 0.432) (*Table 3*).

As shown in the *Table 4*, the distribution of the final outcome differs between normal and abnormal levels. The more we look at the number of people in the uncomplicated-to-death discharge group, the higher the number of people in the group with abnormal white blood cell (WBC) levels. The result of the

Table 2. Distribution of antibiotics by the final outcome

Antibiotic Type	Uncomplicated Discharge	Complicated Discharge	Dead	Total
Clindamycin	173 (52.91%)	142 (43.43%)	12 (3.67%)	327
Ciprofloxacin	130 (52.63%)	108 (43.72%)	9 (3.64%)	247
Cap fluconazole	32 (56.14%)	22 (38.6%)	3 (5.29%)	57
Vancomycin	31 (32.63%)	57 (60%)	7 (7.37%)	95
Meropenem	27 (39.13%)	38 (55.07%)	4 (5.8%)	69
Ceftazidime	27 (52.94%)	21 (41.18%)	3 (5.88%)	51
Targosid	18 (41.86%)	23 (53.49%)	2 (4.65%)	43
Tazocin	17 (32.69%)	32 (61.54%)	3 (5.77%)	52
Metronidazole	15 (44.12%)	17 (50%)	2 (5.88%)	34
Cap rifampin	14 (46.67%)	15 (50%)	1 (3.33%)	30
Cefepime	12 (46.15%)	14 (53.85%)	0 (0%)	26
Cefazolin	11 (47.83%)	11 (47.83%)	1 (4.35%)	23
Ceftriaxone	9 (64.29%)	4 (28.57%)	1 (7.14%)	14
Cap Azithromycin	4 (100%)	0 (0%)	0 (0%)	4
Penicillin	3 (27.27%)	7 (63.64%)	1 (9.09%)	11
Tavanex	3 (100 %)	0 (0%)	0 (0%)	3
Amikacin	2 (28.57%)	4 (28.54%)	1 (14.29%)	7
Tab ciprofloxacin	2 (28.57%)	4 (57.14%)	1 (14.29%)	7
Cap clindamycin	2 (50%)	1 (25%)	1 (25%)	4
Tab metronidazole	2 (40%)	3 (60%)	0 (0%)	5
Cloxacillin	2 (100%)	0 (0%)	0 (0%)	2
Imipenem	0 (0%)	2 (100%)	0 (0%)	2

Table 3. Distribution of final outcomes by the age groups

Final Outcomes	age groups			ulcer duration		
	≤45 years	45-60 years	≥60 years	Less than 10 days	10-60 days	More than 60 days
Uncomplicated discharge	19 (10.6%)	113 (63.1%)	47 (26.3%)	42 (28%)	76 (50.7%)	32 (21.3%)
Complicated discharge	21 (14.9%)	82 (58.2%)	38 (27%)	28 (23.3%)	64 (53.4%)	28 (23.3%)
dead	1 (8.3%)	10 (83.3%)	1 (8.3%)	0 (0%)	4 (50%)	4 (50%)

Table 4. Distribution of final outcomes by white blood cell level and ESR level

final outcomes	WBC Level				ESR Level			
	≤ Normal		Normal		≤ Normal		Normal	
Uncomplicated discharge	26.6	47	73.4	130	88.8	142	11.3	18
Complicated discharge	49.6	70	50.4	71	97	131	3	4
dead	83.3	10	16.7	2	100	11	0	0

chi-square test also showed the relationship between the WBC level and the final outcome (p-value <0.001).

Also, it is observed that the distribution of the final outcome at both normal and abnormal levels of ESR was not different, although the result of the chi-square test showed the relationship between ESR level and final outcome (p-value = 0.018) (*Table 4*).

According to the results of the below table, the distribution of final outcome in the two groups with and without a history of amputation is not much different, although in patients with death outcome, it was observed

that the distribution of people with a previous history of amputation was about 20% higher and the result of chi-square test showed a relationship between the history of amputation and the final outcome (P-value = 0.048) (*Table 5*).

Table 5. Distribution of final outcome based on amputation history

Final Outcomes	History of Amputation			
	yes		no	
Uncomplicated discharge	14.30	26	85.5	153
Complicated discharge	18.2	26	81.8	117
dead	41.7	5	58.3	7

Table 6. Summary of the results of the study of the relationship between the studied variables and the final outcome

Final Outcomes	Grade 1	Grade2	Grade3	Grade4	Grade5
Uncomplicated discharge	20 (100%)	154 (78.2%)	5 (7.4%)	0 (0%)	0 (0%)
Complicated discharge	0 (0%)	39 (19.8%)	60 (88.2%)	39 (95.1%)	5 (62.5%)
dead	0 (0%)	4 (2%)	3 (4.4%)	2 (4.9%)	3 (37.5%)

According to the results of the table below, the distribution of the final outcome is different in the five groups of ulcer degrees, and as we move towards death, the distribution of people in groups with higher ulcer degree increases. The result of chi-square test also shows a relationship between the history of amputation and the final outcome (P-value <0.001) (*Table 6*).

In general, in the present study, it was found that according to the statistical analysis, there is a significant relationship between the history of amputation, WBC, and ESR levels with the final outcome of discharge.

Discussion

In this study, it was found that there is a meaningful relationship between amputation history, WBC level, and ESR with the final result of the discharge. In other words, ESR, WBC, and history of amputation can be considered as prognostic risk factors in patients with diabetic foot ulcers. Most of the diabetic patients who underwent lower limb amputation were of Persian descent and lived in the city. About 65% had high blood pressure. In other words, in patients with DFUs, people with a history of high blood pressure were twice as likely as people without a history of high blood pressure, and generally HTN was the most common underlying disease. However, in the statistical analysis showed no significant relationship between high blood pressure and the final outcome of discharge. Moreover, the statistical analysis showed no significant relationship between the final outcome of discharge and a history of chronic kidney disease.

In this study, it was found that receiving clindamycin and ciprofloxacin injection and antifungal could improve the patient's prognosis. The highest use of vancomycin, tazocin and penicillin G was in people who had a discharge with complication, which may be justified by the severity of the disease. In the present study, more than 75% of the subjects had Wegner grade 2 and 3 ulcers. In the statistical analysis, there was a significant relationship between the degree of ulcer and the final outcome of discharge (0.001). In this regard, in a study conducted by Mashayekhi et al. in 2011 in Tehran on 699 patients with DFUs, the average severity of patients' ulcer based on Wegner grading system was 3 (10). In the present study, in the group of dead patients, the distribution of people with a previous history of amputation was about 20% higher than that of the group of patients discharged with a complication and 25% higher than patients discharged without a complication and the result of chi-square test also showed the relationship between the history of amputation and the final outcome (P-value = 0.048). In this regard, in a study conducted by Leila Yazdanpanah et al. with the aim of investigating the prevalence and risk factors for diabetic foot ulcers, one of the independent risk factors for developing DFU was a previous history of DFU or amputation. Also, in a study conducted by Mashayekhi et al. in 2011 in Tehran on 699 patients with DFUs, a statistically significant relationship was observed between the previous history of amputation and the frequency of amputation (11).

In the present study, according to the statistical analysis, it was found that there is no significant relationship between age and gender with the final outcome of discharge. In the prospective study of Gubara Musa et al. (2012) with the aim of determining risk factors and clinical features and their relationship with a history of 6 months of diabetic foot ulcer in 108 patients, the size,

depth and infection of the wound and associated diseases including eye, Heart, and kidney disorders were studied and showed that age and sex of the patients had no significant effect on the healing process of diabetic foot ulcers (12).

In the present study, the distribution of the final outcome differed between normal and abnormal (leukocytosis) WBC levels and as we look at the number of people in the discharge with no complication towards the death group, the number of people in the high WBC (leukocytosis) group increased. The result of chi-square test also showed the relationship between white blood cell level and the final outcome (P-value <0.001). In this study, Imad R. Musa et al. studied the factors associated with amputation among patients with diabetic foot ulcers in a Saudi population between January 2015 and December 2016, and showed by univariate analysis that the high number of white blood cells (WBC) was associated with amputation (13). Due to the increased inflammation in individuals with DFUs, an increase in WBC is observed in these patients. Therefore, the increase in WBC can be considered as one of the prognostic risk factors for DFUs (14). The results of our study showed that the increase in ESR is seen in abundance in patients with DFUs, which is most likely related to inflammatory and infectious processes occurring in DFUs (15).

In the present study, according to the statistical analysis, it was found that there was no significant relationship between degree of ulcer and patient's age with the final outcome of discharge; while Shahi et al. (2012) in India conducted a prospective study on 678 patients with diabetic foot to determine the risk factors and the results showed that age over 50 years, insulin therapy, and tobacco use were of the significant risk factors of developing diabetic foot ulcers in northern India (16).

Conclusion

According to this cross-sectional study, white blood cells, ESR level, previous history of amputationو and the grade of ulcer were significantly associated with the final outcome of discharge, which can be effective in the prognosis of patients with hospitalized diabetic foot ulcers.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authors' contributions

All the authors contributed equally to this manuscript.

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