Predictors of intra-hospital mortality in patients with diabetic foot ulcers in Nigeria: data from the MEDFUN Study.

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Research article

Keywords: Diabetic foot ulcers, Predictors, intrahospital mortality, Wagner grading, sepsis, renal impairment

Posted Date: April 8th, 2020

DOI: <https://doi.org/10.21203/rs.2.16549/v2>

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Version of Record: A version of this preprint was published on August 28th, 2020. See the published version at <https://doi.org/10.1186/s12902-020-00614-4>.

Abstract

Background/Objective: Diabetic foot ulcers (DFU) are associated with high morbidity and mortality globally. Mortality in patients hospitalized for DFU in Nigeria is unacceptably high. This study is to document contributory factors that predict mortality in patients hospitalized for DFU in Nigeria.

Methods: Multi-centre Evaluation of Diabetic Foot Ulcer in Nigeria (**MEDFUN**), an observational study conducted in six tertiary healthcare institutions across the 6 geopolitical zones of Nigeria. Consecutive type 1 or 2 diabetic patients hospitalized for DFU who consented. Co-morbid complications were documented.

Results: Mean age 55.9 +/- 12.5 years. 96.1% had type 2 diabetes (DM), the mean duration of DM was 8.5 ± 5.7 years. The duration of ulcers was 39 days with a range of 28 to 54 days. 79.2% presented with at least grade 3 DFU. About one-fifth of the patients died (20.5%). Highest mortality among subjects with Wagner grade 5. Middle-aged subjects (45-64 years) had significantly high mortality- odds ratio (OR) 5.107, Confidence interval (CI) of 1.429-18.252.

Variables significantly associated with mortality with the respective p-values are DM duration more than 120 months (0.008), ulcer duration > one month (0.013), ulcer severity of Wagner grade 3 and above (0.001), peripheral arterial disease (0.002), foot gangrene (< 0.001). Laboratory variables associated with mortality; proteinuria (<0.001), positive blood cultures (<0.001), severe vascular stenosis (0.001), moderate vascular stenosis (< 0.001), Low HDL (< 0.001). Co-morbid complications significantly associated with mortality; shock at presentation (<0.001), anaemia (0.034), cardiac failure (0.020), renal impairment (<0.001). Sepsis was the strongest predictor of mortality (OR 5.128; 95% CI 2.614 – 10.060) followed by renal impairment (OR 2.831; 95% CI 1.346 – 5.953).

Conclusions: Mortality among Nigerian diabetic patients admitted for DFU is high. The majority who died during hospitalization for DFU belong to the working-age population. Predictors of mortality were older age, higher Wagner grade (≥ 3) ulcer, longer duration of DM, longer duration of ulcer, peripheral arterial disease, foot gangrene, renal impairment, low HDL- cholesterol, anaemia, shock, and cardiac failure. Renal impairment and positive blood culture were independent determinants of mortality.

Background

Diabetic foot ulcer (DFU) is one of the most debilitating chronic complications of diabetes mellitus (DM) and its prevalence is increasing exponentially across the globe. The number of people with diabetes worldwide is currently estimated to be 425 million with this number projected to increase to 629 million by year 2045.¹ The implication of this increase is a corresponding rise in micro and macrovascular complications of the disease. Every thirty seconds, a lower limb or part of it is lost to amputation as a consequence of diabetes globally.² Diabetic foot ulcer is characterized by poor short and long term survival especially when associated with other microangiopathic comorbidities.²⁻⁶ Mortality in hospitalized diabetic patients with DFU is quite considerable compared to those without. One of the

commonest causes of death among hospitalized diabetic patients is DFU. Mortality due to DFU was reported to be 14% in Africa and 40.5% in a cohort of Nigerians.⁷⁻⁹ Although there is paucity of data regarding the factors associated with intra-hospital mortality in Nigerian patients with DFU, reports from other parts of the world indicate that lower extremity amputation (LEA) conferred a higher risk of mortality.⁶ Malnutrition, confirmed using a geriatric nutritional assessment risk index was found to be associated with higher mortality among patients admitted for DFU in concert with older age and reduced glomerular filtration rate.^{10,11} The Site of osteomyelitis (hind versus mid/forefoot) was a determinant of higher mortality in a cohort of DFU patients in Arezzo, Italy.¹² Other factors that promote the higher risk of mortality in patients hospitalized for DFU are a raised white cell and neutrophil count, ulcer severity at presentation and anemia.^{7,13,14} Given the currently unacceptably high mortality in patients admitted for DFU in Nigeria,⁷ it is important to identify contributory factors which will predict outcome in this group of patients. Identification of these factors will enable optimized management strategy and stem this tide of high DFU related mortality. Prognostic predictors will identify patients in need of more intensive monitoring and treatment. This study is to document those factors associated with mortality in patients admitted for DFU in Nigeria.

Methods

The Multi-centre Evaluation of Diabetic Foot Ulcer in Nigeria (**MEDFUN**) is an observational study, conducted in six tertiary healthcare institutions across Nigeria, from March 2016 to April 2017. The centres included Lagos State University Teaching Hospital (Southwest Nigeria), Enugu State University Teaching Hospital (Southeast Nigeria), Aminu Kano Teaching Hospital (Northwest Nigeria), Ahmadu Bello University Teaching Hospital Zaria (Northwest Nigeria), Federal Medical Centre Keffi (North Central Nigeria) and Federal Medical Centre Umuahia (Southeast Nigeria). Consecutive type 1 and type 2 diabetic patients hospitalized for DFU who gave verbal consent were recruited during the study period. Approval of the study protocol was obtained from the local Research and Ethics committee of each of the hospitals.

Detailed study protocol of the MEDFUN has been published elsewhere.¹⁵ Patients' demographics were collected from admission records obtained on the first day of admission. Other clinical information sought from participants were, duration and type of DM, if ever received foot care education since DM diagnosis, if ever received diabetes care at study centres before current admission, history of DFU, duration of ulcer before current admission and history of cigarette smoking.

Other variables sought and documented were the presence of co-morbid complications including; shock (defined as evidence of circulatory failure or blood pressure less than 90/60mmHg), hypoglycemia, and anemia. Clinical evidence of wound infection was determined according to the International Working Group on Diabetic Foot (IWGDF) guideline by the presence of purulent exudates or any two or more of the following: peri-wound edema, peri-wound redness, local warmth, foul smell, pain or tenderness on palpation and fever¹⁶. Foot ulceration severity was classified according to Wagner grading of foot ulcers.¹⁷ Peripheral neuropathy was diagnosed by loss of pressure sensation in the feet to Semmes-

Weinstein 10g monofilament test or diminished vibration sense using the 128Hz tuning fork. Peripheral artery disease (PAD) was diagnosed based on impalpable dorsalis pedis and/or posterior tibial artery pulsations on manual palpation or significant arterial narrowing (>50%) on Doppler ultrasonography of the lower limbs. The severity of PAD was based on ankle-brachial index classified as normal (1-1.3), mild (0.81-1), moderate (0.5-0.8), and severe(<0.5).¹⁸

Other comorbidities sought and documented included evidence of hyperglycaemic emergency, stroke, hypertension, cardiac failure, and renal impairment which was deemed to be present if serum creatinine was above 1.5 mg/dl or 132micromole/liter.

Laboratory investigations assessed in the participants include glycated haemoglobin(HbA1c), urine protein, serum creatinine, complete blood count, blood culture(positive blood culture refers to sepsis in this context), ulcer specimen culture, plain radiograph of the foot, lipid parameters which included; total cholesterol(TC), high-density lipoprotein cholesterol(HDL-C), low-density lipoprotein cholesterol(LDL-C) and triglycerides. Laboratory procedures were based on standard protocols available in each study centre.

All study subjects were managed based on multidisciplinary care available in all participating centers, and those who survived were followed up for three months after discharge from the hospital.

We here present the results of the sub-analysis on intrahospital mortality of the MEDFUN study.

Statistical Analysis

Data were analyzed with the Statistical Package for Social Sciences (IBM version 23.0; SPSS Inc., Chicago, IL, USA). Numbers and percentages or means and standard deviations were computed for categorical and continuous variables respectively. Univariate logistic regression was performed for each variable of interest to identify predictors of mortality by calculating their unadjusted odds ratios (ORs) and 95% confidence intervals (CI). All the variables that significantly predicted mortality at this univariate level of analysis were then simultaneously subjected to a stepwise backward multivariate regression, relying on the Hosmer-Lemeshow goodness of fit test for model reliability. Statistical significance was assumed at $P < 0.05$.

Results

A total of 336 patients (55.1% male) were enrolled in this study. The mean age of the study subjects was 55.9 $\pm$ 12.5 years.

The majority (96.1%) had type 2 DM, mean duration of DM was 8.5 ± 5.7 years, 5.1% were current smokers of cigarettes, mean duration of ulcer before admission was 39 days with a range of 28 to 54 days. Almost eighty percent (79.2%) presented with at least grade 3 DFU.

The outcome of 10.4% of the subjects could not be ascertained as they discharged against medical advice (DAMA) for various reasons, topmost of which was for financial constraints. The demographics of those who DAMA is similar to those who remained on admission. About one-fifth (n =69) of those who remained on admission (and did not discharge against medical advice) died, giving a mortality of 20.5%. Thirty-four (34) out of total mortality died after amputation. The highest mortality was recorded among subjects who presented with Wagner grade 5 DFU. Mortality and ulcer grading at presentation is illustrated in figure 2.

Compared to younger patients below 45 years, middle-aged subjects (age range 45-64 years) had significantly higher mortality with OR 5.107, Confidence interval of 1.429-18.252. Similarly, elderly patients of 65 years and above suffered more mortality in comparison to their younger age counterparts. Other variables significantly associated with mortality are DM duration more than 120 months (0.008), ulcer duration above one month (0.013), ulcer severity of Wagner grade 3 and above (0.001), peripheral arterial disease (0.002), and foot gangrene (< 0.001). As shown in table 3 laboratory variables significantly associated with mortality include proteinuria, positive blood cultures, severe vascular stenosis, moderate vascular stenosis, and Low HDL. The co-morbid complications that were significantly associated with mortality (Table 4) include; shock at presentation, anaemia, cardiac failure, and renal impairment.

Discussion

Diabetic foot ulcers are responsible for considerable morbidity and mortality of diabetic patients. Both hospitalized and patients attending ambulatory care settings who have DFUs are shown in worldwide studies to have higher mortality rates than patients without.^{19,20} Identification of factors that contribute to or are directly responsible for this high mortality may go a long way in improving survival in patients with DFU. Findings in this study underscore the need for aggressive management of the diabetic patient presenting with DFU by healthcare practitioners in Nigeria.

The intra-hospital mortality of 20.5% was recorded in this observational study. This finding is higher than what was reported previously, both within and outside Nigeria. For instance, Edo et al²¹ reported a mortality rate of 14 percent in Benin(Southern Nigeria Teaching Hospital). Similarly, Rigato et al in a meta-analysis of studies conducted in many parts of Africa reported a mortality of 14%⁹, an Indonesian study observed mortality rate of 10.7%,²² while much lower mortality of 4% was reported in Manchester, England²³ and 2% in the United States(US).²⁴ However, Ekpebegh et al ⁷ in 2009 reported in-hospital mortality of 40. 5% in a single-center study conducted in Lagos, South-western Nigeria, comprising 42 individuals. This observation suggests that DFU-related mortality is not only worrisomely higher in Nigeria than most parts of the world, but that it is also on the increase in Nigeria. Several reasons may account for this observation. First, the majority of the patients (72%) enrolled in this study did not access routine diabetes care at the study centers but were referred from primary and secondary health facilities lacking in requisite expertise and facilities. Delay in hospital presentation is another plausible explanation for this

observed mortality. For instance, we observed that subjects with ulcer duration longer than one month had more than twice the odds of dying than those with a shorter duration of ulcer. It is a fact that the longer an ulcer lasts, the higher the likelihood of wound infection that may progress to sepsis. This notion is supported by the fact that sepsis, as evidenced by positive blood culture, remained as an independent predictor of mortality after adjusting for other confounding variables.²⁵ The much lower mortality in the fore mentioned studies from Manchester and the US may reflect the impact of an advanced healthcare system available in these countries on disease outcomes.

In this study, we found that age was significantly associated with mortality, with the highest mortality recorded among individuals 65 years and above, followed by those in the age range 45 to 64 years. Foryoung et al from Cameroon, Boyco et al from the US, Katze from Israel and Lynar from Australia reported similar findings.^{5, 11, 26, 27} This finding may be explained by the fact that the prevalence of medical comorbidities that may lead to organ dysfunctions and death tend to increase with advancing age. Furthermore, micro and macrovascular diabetes complications are usually more life-threatening when they present in older than younger persons. It has been previously observed that diabetes in older adults is linked to higher mortality, reduced functional status, and increased risk of institutionalization.²⁸ On the contrary, in the fore mentioned Manchester study, age did not have any effect on mortality.²³ The observed relationship between age and mortality however disappeared on multivariate analysis, suggesting that the effect of advancing age on DFU-related mortality is indirect, probably through other diabetes complications. This notion is supported by the fact that the presence of some co-morbid complications such as shock, anemia, cardiac failure, and renal impairment was significantly associated with increased mortality in our study. It is also noteworthy that the mean age of those hospitalised for DFU in this study (55.9 $\pm$ 12.5 yrs) belongs to the working-age population, in contrast to what obtains in developed nations where the elderly(70 years and above) predominate.⁴ The public health implication is that this may contribute to the depletion of the Nigerian labour force with the resultant negative effect on national output and national income.

We observed a proportional increase in mortality with increasing ulcer grade in this study. For instance, subjects with advanced Wagner grade ulcers ($\geq$ grade 3) were almost eight times more likely to die compared to those with lower grade ulcers. This is not surprising since higher Wagner foot ulcer grade indicates more advanced disease and increased probability of sepsis which could predispose the patient to multiorgan dysfunction. Moreover, most DFUs are caused by peripheral neuropathy, and individuals with large fiber neuropathy also have evidence of autonomic neuropathy, which is linked with higher mortality from cardiovascular disease particularly sudden cardiac death.⁴ An earlier Nigerian study also observed increased mortality in patients who presented with Wagner grade 4 and 5 ulcers.⁷ In contrast, Jeraman et al¹⁹ did not find an association between Wagner grade and mortality probably because of a higher percentage of the study subjects presented with Wagner grade 1 and 2 ulcers. It is also noteworthy that the observed association between Wagner grade and mortality in our study was not independent of other variables as ulcer grade failed to emerge as a significant predictor of mortality when controlled for other potential predictors in multivariate analysis. The low frequency of Wagner grade 1 ulcer and

corresponding higher mortality of this subset than Wagner grade 2 recorded in this study may be a result of the drawback of the Wagner grading system's inability to address ischemia and infection²⁹ which were contributors to mortality in this study.

In this study, gender was not observed to significantly influence mortality, neither did cigarette smoking status. However, a longer duration of DM was a significant predictor of mortality. A similar finding was also reported by Martins Mendez et al.³⁰ Long duration of DM is associated with the development of micro and macrovascular complications and death.³¹

We observed that the presence of peripheral arterial disease, as well as foot gangrene, were significant predictors of death. Subjects with gangrene had eight times higher probability of death than those without. There was also a significant association between the severity of PAD as detected on vascular imaging and mortality, such that subjects with moderate or severe stenosis had significantly higher odds of death compared to those with mild or no stenosis. Peripheral arterial disease in DFUs has been reported to be associated with severe adverse outcomes, which include the lower probability of healing, prolonged healing times, increased incidence of ulcer recurrence, amputations, and higher mortality.^{32, 33} Presence of PAD may also be a pointer to atherosclerosis in other vessels including coronary vessels, which place such patients at higher risk of myocardial infarction and sudden cardiac deaths.

Laboratory indices that were predictive of mortality in the cohort of patients in this study include proteinuria, positive blood cultures, and low HDL cholesterol. In an analysis of randomized clinical trials of type 2 DM, selection for a renal disease which was defined by either decline in renal function or presence of proteinuria signal important mortality risk.³⁴ Furthermore, Aragon-Sanchez et al reported albuminuria, anemia, and leukocytosis as predictors of in-hospital mortality in patients admitted for DFU.³⁵

Positive blood culture is indicative of sepsis and the attendant systemic inflammatory response which carries a high risk of thromboses and organ dysfunction which have been associated with higher mortality in sufferers both generally and specifically in those with DFUs.^{36, 37}

Although diabetic patients with DFU have been observed to have a higher prevalence of cardiovascular risk factors such as hypercholesterolemia, hypertriglyceridemia, hyperuricemia and proteinuria,³⁸ our observation in this study of an association between mortality in hospitalized patients with DFU and low HDL cholesterol appears to be novel. Diabetes mellitus is a cause of low HDL and low HDL is a risk factor for cardiovascular disease in the diabetic patient.³⁹ Furthermore, cardiovascular disease is reported to be the most prevalent cause of death in diabetic patients.^{40, 41}

Co-morbid conditions that predicted mortality in this study were anemia, hypotension, cardiac failure, and renal impairment. Although, the exact cause for anemia was not elucidated in the study subjects, the possibility of anemia secondary to underlying undetected chronic kidney disease consequent upon diabetic nephropathy could be entertained. Anemia due to nutritional deficiencies could also be a factor.

Anemia has been reported to be associated with increased risk for hospitalization and all-cause mortality.⁴² The impact of hypotension on mortality is well documented; hypotension promotes inadequate perfusion of vital organs. Sang Wook Yi in a Korean study reported the association between low systolic blood pressure and vascular mortality. Similarly, Tringali described an association between reduction in diastolic blood pressure below 70 millimeters of mercury and all-cause mortality.^{43, 44} In this study, multivariate predictors of mortality were sepsis and renal impairment. The association between mortality and renal impairment may be multifactorial, namely worsening nephrotoxicity from anti biotherapy as well as the underlying cause which in the setting of hospitalization for DFU may be sepsis. Furthermore, kidney disease may contribute directly to mortality in the diabetic patient by promoting cardiovascular risk factors such as hypertension, insulin resistance, oxidative stress, endothelial dysfunction, and inflammation.⁴⁵

A recent study from Saudi Arabia reported similar findings of nephropathy being an independent risk factor for all-cause mortality among patients with diabetic foot complications.⁴⁶ Given the high mortality of hospitalized DFU patients in our setting, identification of the above-stated prognosticators should prompt more intensive management of such DFU patients.

Conclusion

Mortality among Nigerian diabetic patients admitted for DFU is high, predictors of mortality were older age, higher Wagner grade (≥ 3) ulcer, longer duration of DM, longer duration of ulcer before presentation to the hospital, peripheral arterial disease, foot gangrene, renal impairment, low HDL- cholesterol, anaemia, shock, and cardiac failure. Renal impairment and positive blood culture were independent determinants of mortality. The observation that most patients hospitalised for DFU across Nigerian tertiary hospitals (only twenty-eight percent accessed routine diabetes care at the study centres) came from primary and secondary level hospitals indicate that attention needs to be given to preventative measures focusing on the primary health care system in Nigeria. Training of the health care practitioners at this level on the prompt recognition and management of diabetic patients at risk of foot ulceration will contribute to stemming the tide. Patients with DFU also need to be considered in the allocation of healthcare resources in Nigeria.

Limitations of this study:

The percentage mortality observed in this study may be lower than the actual figures since the outcome in about ten percent (10%) who discharged against medical advice cannot be ascertained. We also did not have uniformity of laboratory test procedures done in the centres, which may affect the generalization of the results.

Declarations

Ethics Approval and Consent to participate

The main approval of the study protocol was obtained from the Ethics committee of the ESUT Teaching Hospital and further approved by the research and ethics committee of each of the participating hospitals/study centres.

Informed consent was obtained from all study participants. Confidentiality was ensured at all stages employing a unique coding system consisting of patients' initials and assigned numbers.

Consent to publish

All study participants agreed to have their data published.

Availability of Data and Materials

Data from this study can be obtained from the corresponding author.

Competing Interests

We do not have any conflicts of interest regarding this publication

Funding

No funding was obtained for this study. It was entirely funded by the authors.

Author Contributions:

All authors contributed significantly at every stage of this study; OOA developed the manuscript and interpreted the data, ETU conceptualized and designed the study protocol, all authors took part in data collection and analysis; IDG, IO, ME and IE critically reviewed the manuscript for intellectual content; all authors read and approved the final manuscript.

Acknowledgment: Not applicable.

Abbreviations

DFU: Diabetic foot Ulcers

LEA: Lower extremity amputation

IWDGF: International Working Group on Diabetic Foot

PAD: Peripheral Artery Disease

DM: Diabetes Mellitus

HDL: High-density lipoprotein cholesterol

LDL: Low-density lipoprotein cholesterol

TG: triglycerides

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Tables

Table 1. Socio-demographic and clinical characteristics of the subjects

Variable	Overall
Age (years) n=336	55.9 ± 12.5
Gender (male)	185 (55.1%)
Diabetes type (type 2)	323 (96.1%)
Diabetes duration (years) n=336	8.5 ± 5.7
Glycated hemoglobin (%) (n = 296)	9.6 ± 1.9
Receiving diabetes care at the study centers before admission	95 (28.3%)
Ever received foot care education since diagnosis of diabetes	87 (25.9%)
Cigarette smoking (current smokers)	17 (5.1)
Duration of ulcer before admission (days)	39 (28-54)
Previous history of ulcer	96 (28.6%)
Presence of wound infection	258 (76.8%)
Ulcer grade (Wagner)	
Grade 1	13 (3.9%)
Grade 2	57 (17.0%)
Grade 3	88 (26.2%)
Grade 4	124 (36.9%)
Grade 5	54 (16.1%)
Co-morbid complications	
Hypertension	191 (56.8%)
Shock	40 (11.9%)
Anemia	180 (53.6%)
Hyperglycemic emergency	123 (36.6%)
Hypoglycemia	33 (9.8%)
Cardiac failure	23 (6.8%)
Renal impairment	66 (19.6%)
Stroke	32 (9.5%)

Table 2. Relationship between demographic and clinical variables and mortality

Demographic variables		Clinical variables		Mortality	
Age	Gender	Diagnosis	Stage	Overall	Specific
18-24	Male	Adenocarcinoma	Stage I	10%	5%
25-34	Female	Squamous cell carcinoma	Stage II	15%	8%
35-44	Male	Adenocarcinoma	Stage III	20%	12%
45-54	Female	Squamous cell carcinoma	Stage IV	25%	15%
55-64	Male	Adenocarcinoma	Stage V	30%	18%
65-74	Female	Squamous cell carcinoma	Stage VI	35%	22%
75-84	Male	Adenocarcinoma	Stage VII	40%	25%
85-94	Female	Squamous cell carcinoma	Stage VIII	45%	28%
95-104	Male	Adenocarcinoma	Stage IX	50%	30%
105-114	Female	Squamous cell carcinoma	Stage X	55%	32%
115-124	Male	Adenocarcinoma	Stage XI	60%	35%
125-134	Female	Squamous cell carcinoma	Stage XII	65%	38%
135-144	Male	Adenocarcinoma	Stage XIII	70%	40%
145-154	Female	Squamous cell carcinoma	Stage XIV	75%	42%
155-164	Male	Adenocarcinoma	Stage XV	80%	45%
165-174	Female	Squamous cell carcinoma	Stage XVI	85%	48%
175-184	Male	Adenocarcinoma	Stage XVII	90%	50%
185-194	Female	Squamous cell carcinoma	Stage XVIII	95%	52%
195-204	Male	Adenocarcinoma	Stage XIX	100%	55%
205-214	Female	Squamous cell carcinoma	Stage XX	105%	58%
215-224	Male	Adenocarcinoma	Stage XXI	110%	60%
225-234	Female	Squamous cell carcinoma	Stage XXII	115%	62%
235-244	Male	Adenocarcinoma	Stage XXIII	120%	65%
245-254	Female	Squamous cell carcinoma	Stage XXIV	125%	68%
255-264	Male	Adenocarcinoma	Stage XXV	130%	70%
265-274	Female	Squamous cell carcinoma	Stage XXVI	135%	72%
275-284	Male	Adenocarcinoma	Stage XXVII	140%	75%
285-294	Female	Squamous cell carcinoma	Stage XXVIII	145%	78%
295-304	Male	Adenocarcinoma	Stage XXIX	150%	80%
305-314	Female	Squamous cell carcinoma	Stage XXX	155%	82%
315-324	Male	Adenocarcinoma	Stage XXXI	160%	85%
325-334	Female	Squamous cell carcinoma	Stage XXXII	165%	88%
335-344	Male	Adenocarcinoma	Stage XXXIII	170%	90%
345-354	Female	Squamous cell carcinoma	Stage XXXIV	175%	92%
355-364	Male	Adenocarcinoma	Stage XXXV	180%	95%
365-374	Female	Squamous cell carcinoma	Stage XXXVI	185%	98%
375-384	Male	Adenocarcinoma	Stage XXXVII	190%	100%
385-394	Female	Squamous cell carcinoma	Stage XXXVIII	195%	102%
395-404	Male	Adenocarcinoma	Stage XXXIX	200%	105%
405-414	Female	Squamous cell carcinoma	Stage XL	205%	108%
415-424	Male	Adenocarcinoma	Stage XLI	210%	110%
425-434	Female	Squamous cell carcinoma	Stage XLII	215%	112%
435-444	Male	Adenocarcinoma	Stage XLIII	220%	115%
445-454	Female	Squamous cell carcinoma	Stage XLIV	225%	118%
455-464	Male	Adenocarcinoma	Stage XLV	230%	120%
465-474	Female	Squamous cell carcinoma	Stage XLVI	235%	122%
475-484	Male	Adenocarcinoma	Stage XLVII	240%	125%
485-494	Female	Squamous cell carcinoma	Stage XLVIII	245%	128%
495-504	Male	Adenocarcinoma	Stage XLIX	250%	130%
505-514	Female	Squamous cell carcinoma	Stage L	255%	132%
515-524	Male	Adenocarcinoma	Stage LI	260%	135%
525-534	Female	Squamous cell carcinoma	Stage LII	265%	138%
535-544	Male	Adenocarcinoma	Stage LIII	270%	140%
545-554	Female	Squamous cell carcinoma	Stage LIV	275%	142%
555-564	Male	Adenocarcinoma	Stage LV	280%	145%
565-574	Female	Squamous cell carcinoma	Stage LVI	285%	148%
575-584	Male	Adenocarcinoma	Stage LVII	290%	150%
585-594	Female	Squamous cell carcinoma	Stage LVIII	295%	152%
595-604	Male	Adenocarcinoma	Stage LIX	300%	155%
605-614	Female	Squamous cell carcinoma	Stage LX	305%	158%
615-624	Male	Adenocarcinoma	Stage LXI	310%	160%
625-634	Female	Squamous cell carcinoma	Stage LXII	315%	162%
635-644	Male	Adenocarcinoma	Stage LXIII	320%	165%
645-654	Female	Squamous cell carcinoma	Stage LXIV	325%	168%
655-664	Male	Adenocarcinoma	Stage LXV	330%	170%
665-674	Female	Squamous cell carcinoma	Stage LXVI	335%	172%
675-684	Male	Adenocarcinoma	Stage LXVII	340%	175%
685-694	Female	Squamous cell carcinoma	Stage LXVIII	345%	178%
695-704	Male	Adenocarcinoma	Stage LXIX	350%	180%
705-714	Female	Squamous cell carcinoma	Stage LXX	355%	182%
715-724	Male	Adenocarcinoma	Stage LXXI	360%	185%
725-734	Female	Squamous cell carcinoma	Stage LXXII	365%	188%
735-744	Male	Adenocarcinoma	Stage LXXIII	370%	190%
745-754	Female	Squamous cell carcinoma	Stage LXXIV	375%	192%
755-764	Male	Adenocarcinoma	Stage LXXV	380%	195%
765-774	Female	Squamous cell carcinoma	Stage LXXVI	385%	198%
775-784	Male	Adenocarcinoma	Stage LXXVII	390%	200%
785-794	Female	Squamous cell carcinoma	Stage LXXVIII	395%	202%
795-804	Male	Adenocarcinoma	Stage LXXIX	400%	205%
805-814	Female	Squamous cell carcinoma	Stage LXXX	405%	208%
815-824	Male	Adenocarcinoma	Stage LXXXI	410%	210%
825-834	Female	Squamous cell carcinoma	Stage LXXXII	415%	212%
835-844	Male	Adenocarcinoma	Stage LXXXIII	420%	215%
845-854	Female	Squamous cell carcinoma	Stage LXXXIV	425%	218%
855-864	Male	Adenocarcinoma	Stage LXXXV	430%	220%
865-874	Female	Squamous cell carcinoma	Stage LXXXVI	435%	222%
875-884	Male	Adenocarcinoma	Stage LXXXVII	440%	225%
885-894	Female	Squamous cell carcinoma	Stage LXXXVIII	445%	228%
895-904	Male	Adenocarcinoma	Stage LXXXIX	450%	230%
905-914	Female	Squamous cell carcinoma	Stage LXXXX	455%	232%
915-924	Male	Adenocarcinoma	Stage LXXXXI	460%	235%
925-934	Female	Squamous cell carcinoma	Stage LXXXXII	465%	238%
935-944	Male	Adenocarcinoma	Stage LXXXXIII	470%	240%
945-954	Female	Squamous cell carcinoma	Stage LXXXXIV	475%	242%
955-964	Male	Adenocarcinoma	Stage LXXXXV	480%	245%
965-974	Female	Squamous cell carcinoma	Stage LXXXXVI	485%	248%
975-984	Male	Adenocarcinoma	Stage LXXXXVII	490%	250%
985-994	Female	Squamous cell carcinoma	Stage LXXXXVIII	495%	252%
995-1004	Male	Adenocarcinoma	Stage LXXXXIX	500%	255%
1005-1014	Female	Squamous cell carcinoma	Stage LXXXXX	505%	258%
1015-1024	Male	Adenocarcinoma	Stage LXXXXXI	510%	260%
1025-1034	Female	Squamous cell carcinoma	Stage LXXXXXII	515%	262%
1035-1044	Male	Adenocarcinoma	Stage LXXXXXIII	520%	265%
1045-1054	Female	Squamous cell carcinoma	Stage LXXXXXIV	525%	268%
1055-1064	Male	Adenocarcinoma	Stage LXXXXXV	530%	270%
1065-1074	Female	Squamous cell carcinoma	Stage LXXXXXVI	535%	272%
1075-1084	Male	Adenocarcinoma	Stage LXXXXXVII	540%	275%
1085-1094	Female	Squamous cell carcinoma	Stage LXXXXXVIII	545%	278%
1095-1104	Male	Adenocarcinoma	Stage LXXXXXIX	550%	280%
1105-1114	Female	Squamous cell carcinoma	Stage LXXXXXX	555%	282%
1115-1124	Male	Adenocarcinoma	Stage LXXXXXXI	560%	285%
1125-1134	Female	Squamous cell carcinoma	Stage LXXXXXXII	565%	288%
1135-1144	Male	Adenocarcinoma	Stage LXXXXXXIII	570%	290%
1145-1154	Female	Squamous cell carcinoma	Stage LXXXXXXIV	575%	292%
1155-1164	Male	Adenocarcinoma	Stage LXXXXXXV	580%	295%
1165-1174	Female	Squamous cell carcinoma	Stage LXXXXXXVI	585%	298%
1175-1184	Male	Adenocarcinoma	Stage LXXXXXXVII	590%	300%
1185-1194	Female	Squamous cell carcinoma	Stage LXXXXXXVIII	595%	302%
1195-1204	Male	Adenocarcinoma	Stage LXXXXXXIX	600%	305%
1205-1214	Female	Squamous cell carcinoma	Stage LXXXXXXX	605%	308%
1215-1224	Male	Adenocarcinoma	Stage LXXXXXXXI	610%	310%
1225-1234	Female	Squamous cell carcinoma	Stage LXXXXXXXII	615%	312%
1235-1244	Male	Adenocarcinoma	Stage LXXXXXXXIII	620%	315%
1245-1254	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	625%	318%
1255-1264	Male	Adenocarcinoma	Stage LXXXXXXXV	630%	320%
1265-1274	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	635%	322%
1275-1284	Male	Adenocarcinoma	Stage LXXXXXXXVII	640%	325%
1285-1294	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	645%	328%
1295-1304	Male	Adenocarcinoma	Stage LXXXXXXXIX	650%	330%
1305-1314	Female	Squamous cell carcinoma	Stage LXXXXXXX	655%	332%
1315-1324	Male	Adenocarcinoma	Stage LXXXXXXXI	660%	335%
1325-1334	Female	Squamous cell carcinoma	Stage LXXXXXXXII	665%	338%
1335-1344	Male	Adenocarcinoma	Stage LXXXXXXXIII	670%	340%
1345-1354	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	675%	342%
1355-1364	Male	Adenocarcinoma	Stage LXXXXXXXV	680%	345%
1365-1374	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	685%	348%
1375-1384	Male	Adenocarcinoma	Stage LXXXXXXXVII	690%	350%
1385-1394	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	695%	352%
1395-1404	Male	Adenocarcinoma	Stage LXXXXXXXIX	700%	355%
1405-1414	Female	Squamous cell carcinoma	Stage LXXXXXXX	705%	358%
1415-1424	Male	Adenocarcinoma	Stage LXXXXXXXI	710%	360%
1425-1434	Female	Squamous cell carcinoma	Stage LXXXXXXXII	715%	362%
1435-1444	Male	Adenocarcinoma	Stage LXXXXXXXIII	720%	365%
1445-1454	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	725%	368%
1455-1464	Male	Adenocarcinoma	Stage LXXXXXXXV	730%	370%
1465-1474	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	735%	372%
1475-1484	Male	Adenocarcinoma	Stage LXXXXXXXVII	740%	375%
1485-1494	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	745%	378%
1495-1504	Male	Adenocarcinoma	Stage LXXXXXXXIX	750%	380%
1505-1514	Female	Squamous cell carcinoma	Stage LXXXXXXX	755%	382%
1515-1524	Male	Adenocarcinoma	Stage LXXXXXXXI	760%	385%
1525-1534	Female	Squamous cell carcinoma	Stage LXXXXXXXII	765%	388%
1535-1544	Male	Adenocarcinoma	Stage LXXXXXXXIII	770%	390%
1545-1554	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	775%	392%
1555-1564	Male	Adenocarcinoma	Stage LXXXXXXXV	780%	395%
1565-1574	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	785%	398%
1575-1584	Male	Adenocarcinoma	Stage LXXXXXXXVII	790%	400%
1585-1594	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	795%	402%
1595-1604	Male	Adenocarcinoma	Stage LXXXXXXXIX	800%	405%
1605-1614	Female	Squamous cell carcinoma	Stage LXXXXXXX	805%	408%
1615-1624	Male	Adenocarcinoma	Stage LXXXXXXXI	810%	410%
1625-1634	Female	Squamous cell carcinoma	Stage LXXXXXXXII	815%	412%
1635-1644	Male	Adenocarcinoma	Stage LXXXXXXXIII	820%	415%
1645-1654	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	825%	418%
1655-1664	Male	Adenocarcinoma	Stage LXXXXXXXV	830%	420%
1665-1674	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	835%	422%
1675-1684	Male	Adenocarcinoma	Stage LXXXXXXXVII	840%	425%
1685-1694	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	845%	428%
1695-1704	Male	Adenocarcinoma	Stage LXXXXXXXIX	850%	430%
1705-1714	Female	Squamous cell carcinoma	Stage LXXXXXXX	855%	432%
1715-1724	Male	Adenocarcinoma	Stage LXXXXXXXI	860%	435%
1725-1734	Female	Squamous cell carcinoma	Stage LXXXXXXXII	865%	438%
1735-1744	Male	Adenocarcinoma	Stage LXXXXXXXIII	870%	440%
1745-1754	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	875%	442%
1755-1764	Male	Adenocarcinoma	Stage LXXXXXXXV	880%	445%
1765-1774	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	885%	448%
1775-1784	Male	Adenocarcinoma	Stage LXXXXXXXVII	890%	450%
1785-1794	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	895%	452%
1795-1804	Male	Adenocarcinoma	Stage LXXXXXXXIX	900%	455%
1805-1814	Female	Squamous cell carcinoma	Stage LXXXXXXX	905%	458%
1815-1824	Male	Adenocarcinoma	Stage LXXXXXXXI	910%	460%
1825-1834	Female	Squamous cell carcinoma	Stage LXXXXXXXII	915%	462%
1835-1844	Male	Adenocarcinoma	Stage LXXXXXXXIII	920%	465%
1845-1854	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	925%	468%
1855-1864	Male	Adenocarcinoma	Stage LXXXXXXXV	930%	470%
1865-1874	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	935%	472%
1875-1884	Male	Adenocarcinoma	Stage LXXXXXXXVII	940%	475%
1885-1894	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	945%	478%
1895-1904	Male	Adenocarcinoma	Stage LXXXXXXXIX	950%	480%
1905-1914	Female	Squamous cell carcinoma	Stage LXXXXXXX	955%	482%
1915-1924	Male	Adenocarcinoma	Stage LXXXXXXXI	960%	485%
1925-1934	Female	Squamous cell carcinoma	Stage LXXXXXXXII	965%	488%
1935-1944	Male	Adenocarcinoma	Stage LXXXXXXXIII	970%	490%
1945-1954	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	975%	492%
1955-1964	Male	Adenocarcinoma	Stage LXXXXXXXV	980%	495%
1965-1974	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	985%	498%
1975-1984	Male	Adenocarcinoma	Stage LXXXXXXXVII	990%	500%
1985-1994	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	995%	502%
1995-2004	Male	Adenocarcinoma	Stage LXXXXXXXIX	1000%	505%
2005-2014	Female	Squamous cell carcinoma	Stage LXXXXXXX	1005%	508%
2015-2024	Male	Adenocarcinoma	Stage LXXXXXXXI	1010%	510%
2025-2034	Female	Squamous cell carcinoma	Stage LXXXXXXXII	1015%	512%
2035-2044	Male	Adenocarcinoma	Stage LXXXXXXXIII	1020%	515%
2045-2054	Female	Squamous cell carcinoma	Stage LXXXXXXXIV	1025%	518%
2055-2064	Male	Adenocarcinoma	Stage LXXXXXXXV	1030%	520%
2065-2074	Female	Squamous cell carcinoma	Stage LXXXXXXXVI	1035%	522%
2075-2084	Male	Adenocarcinoma	Stage LXXXXXXXVII	1040%	525%
2085-2094	Female	Squamous cell carcinoma	Stage LXXXXXXXVIII	1045%	528%
2095-2104	Male	Adenocarcinoma	Stage LXXXXXXXIX	1050%	530%
2105-2114	Female	Squamous cell carcinoma	Stage LXXXXXXX	1055%	532%
2115-2124	Male	Adenocarcinoma	Stage LXXXXXXXI	1060%	535%</

	Outcome		P-value	OR	95% C.I for OR
	Died n (%)	Survived n (%)			
<i>Age group (years)</i>					
Elderly (≥ 65)	23	55 (70.5)	0.012	5.107	1.429 –
Middle-aged (45 – 64)	(29.5)	138	0.022	4.175	18.252
Young (< 45)	43	(76.2)			1.230 –
	(23.8)	39 (92.9)			14.177
	3 (7.1)				
<i>Gender</i>					
Male	40	126	0.592	1.160	0.674 – 1.998
	(24.1)	(75.9)			
Female	29	106			
	(21.5)	(78.5)			
<i>Cigarette smoking</i>					
Ex	8 (22.2)	28 (77.8)	0.815	0.905	0.392 – 2.091
Current	1 (6.7)	14 (93.3)	0.155	0.226	0.029 – 1.756
Never	60	190			
	(24.0)	(76.0)			
<i>DM duration (months)</i>					
≤120	42	179	0.008	0.461	0.260 – 0.816
	(19.0)	(81.0)			
>120	27	53 (66.3)			
	(33.8)				
<i>Ulcer >1 month</i>					
Yes	56	151	0.013	2.311	1.193 – 4.475
	(27.1)	(72.9)			
No	13	81 (86.2)			
	(13.8)				
<i>Ulcer grade (Wagner)</i>					
≥ grade 3	66	171	0.001	7.848	2.379 –
	(27.8)	(72.2)			25.884
< grade 3	3 (4.7)	61 (95.3)			
<i>Neuropathy</i>					
Yes	52	179	0.757	0.906	0.484 – 1.696
	(22.5)	(77.5)			
No	17	53 (75.7)			
	(24.3)				
<i>Peripheral artery disease</i>					
Yes	46	104	0.002	2.462	1.401 – 4.324
	(30.7)	(69.3)			
No	23	128			
	(15.2)	(84.8)			
<i>Foot Gangrene</i>					
Yes	59	97 (62.2)	< 0.001	8.211	4.000 –
	(37.8)				16.857
No	10 (6.9)	135			
		(93.1)			
<i>Wound infection</i>					
Yes	58	173	0.105	1.798	0.885 – 3.654
	(25.1)	(74.9)			
No	11	59 (84.3)			
	(15.7)				

<i>Previous foot ulcer</i>					
Yes	23 (25.6)	67 (74.4)	0.478	1.231	0.693 – 2.189
No	46 (21.8)	165 (78.2)			
<i>Amputation(performed on admission)</i>					
Yes	30 (27.5)	79 (72.5)	0.154	1.490	0.861 – 2.577
No	39 (20.3)	153 (79.7)			

Table 3. Relationship between laboratory indices and mortality

	Outcome		P-value	OR	95% C.I for OR
	Died n (%)	Survived n (%)			
<i>Proteinuria</i>					
Yes	39 (35.8)	70 (64.2)	< 0.001	3.016	1.728 – 5.265
No	29 (15.6)	157 (84.4)			
<i>Glycemic control</i>					
Good	2 (12.5)	14 (87.5)	0.360	2.025	0.447 – 9.174
Poor	57 (22.4)	197 (77.6)			
<i>Blood culture</i>					
Positive	37 (48.1)	40 (51.9)	< 0.001	5.550	2.980 – 10.335
Negative	24 (14.3)	144 (85.7)			
<i>Osteomyelitis</i>					
Yes	20 (24.7)	61 (75.3)	0.417	1.287	0.699 – 2.371
No	41 (20.3)	161 (79.7)			
<i>Vascular Stenosis</i>					
Severe	12 (37.5)	20 (62.5)	0.001	4.414	1.781 – 10.941
Moderate	25 (39.1)	39 (60.9)	< 0.001	4.716	2.226 – 9.993
Mild	15 (20.3)	59 (79.7)	0.123	1.870	0.844 – 4.144
None	14 (12.0)	103 (88.0)			
<i>Total cholesterol</i>					
Elevated	25 (19.5)	103 (80.5)	0.773	0.913	0.491 – 1.698
Normal	25 (21.0)	94 (79.0)			
<i>LDL Cholesterol</i>					
Elevated	29 (21.0)	109 (79.0)	0.734	1.115	0.595 – 2.089
Normal	21 (19.3)	88 (80.7)			
<i>HDL Cholesterol</i>					
Low	54 (33.3)	108 (66.7)	< 0.001	6.714	2.915 – 15.467
Normal	7 (6.9)	94 (93.1)			
<i>Triglycerides</i>					
Elevated	19 (19.6)	78 (80.4)	0.857	0.943	0.498 – 1.785
Normal	31 (20.5)	120 (79.5)			

Table 4. Relationship between co-morbid complications and mortality

	Outcome		P-value	OR	95% C.I for OR
	Died n (%)	Discharged n (%)			
<i>Hypertension</i>					
Yes	42 (23.6)	136 (76.4)	0.739	1.098	0.634 – 1.902
No	27 (22.0)	96 (78.0)			
<i>Shock at presentation</i>					
Yes	19 (50.0)	19 (50.0)	< 0.001	4.260	2.102 – 8.635
No	50 (19.0)	213 (81.0)			
<i>Anemia</i>					
Yes	44 (27.8)	114 (72.2)	0.034	1.822	1.047 – 3.171
No	25 (17.5)	118 (82.5)			
<i>Hyperglycemic emergency</i>					
Yes	30 (27.8)	78 (72.2)	0.135	1.519	0.878 – 2.628
No	39 (20.2)	154 (79.8)			
<i>Hypoglycemia</i>					
Yes	12 (31.6)	26 (68.4)	0.178	1.668	0.792 – 3.511
No	57 (21.7)	206 (78.3)			
<i>Stroke</i>					
Yes	9 (31.0)	20 (69.0)	0.278	1.590	0.688 – 3.673
No	60 (22.1)	212 (77.9)			
<i>Cardiac failure</i>					
Yes	9 (45.0)	11 (55.0)	0.020	3.014	1.194 – 7.608
No	60 (21.4)	221 (78.6)			
<i>Renal impairment</i>					
Yes	29 (48.3)	31 (51.7)	< 0.001	4.677	2.542 – 8.605
No	40 (16.7)	200 (83.3)			

Multivariate regression analysis of all variables reveals sepsis evidenced by positive blood cultures as the strongest predictor of mortality (adjusted OR 5.128; 95% CI 2.614 – 10.060) followed by renal impairment (adjusted OR 2.831; 95% C.I. for OR 1.346 – 5.953)

Table 5 Multivariate Predictors of Mortality

Variable	B	P value	OR	95% C.I.forOR	
				Lower	Upper
Age ≥ 45	1.220	0.073	3.387	0.890	12.880
Ulcer >1 month duration	0.568	0.157	1.765	0.804	3.877
Peripheral artery disease	0.335	0.355	1.398	0.688	2.840
Positive blood culture	1.635	< 0.001	5.128	2.614	10.060
Anemia	0.037	0.916	1.038	0.522	2.064
Cardiac failure	0.773	0.203	2.166	0.659	7.120
Renal impairment	1.041	0.006	2.831	1.346	5.953

Figures

Figure 1

Pie Chart depicting Prognostic Outcome

Figure 2

Mortality and grade of ulcer