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ORIGINAL ARTICLE

Factors associated with In-Hospital Mortality among Patients with Diabetes Admitted for Lower Extremity Infections

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Abstract

Objective. To determine the factors associated with in-hospital mortality among diabetic patients admitted for lower extremity infection.

Methodology. This is a retrospective analysis of diabetic patients with lower extremity infection admitted at the UP-Philippine General Hospital. Data was analyzed through multiple logistic regression after multiple imputation was performed for missing data.

Results. 441 patients with diabetes were included in the analysis, of which 98.1% have Type 2 diabetes mellitus; 58.1% were males and the mean age of the cohort was 56.7±11.1 years. The mortality rate was 11.1% over the 3-year period from 2015 to 2017, of which 46% died from myocardial infarction (MI). Multivariate logistic regression showed the following were associated with increased likelihood of in-hospital mortality: non-performance of surgery (OR=4.22, 95%CI 1.10-16.27, *p*=0.036), elevated BUN (OR=1.06, 95%CI 1.01-1.11, *p*=0.016), MI (OR=27.19, 95%CI 6.38-115.94, *p*=0.000), respiratory failure requiring mechanical ventilation (OR=26.14, 95%CI 6.28-108.80, *p*=0.000), gastrointestinal bleeding (OR=10.08, 95%CI 1.87-54.38, *p*=0.007), hospital-acquired pneumonia (OR=9.46, 95%CI 2.52-35.51, *p*=0.001) and shock (OR=7.09, 95%CI 2.17-23.22, *p*=0.001).

Conclusion. In the in-patient setting, morbidity and mortality is high among diabetic patients with lower extremity infection. Non-performance of surgery, elevated BUN, MI, respiratory failure requiring mechanical ventilation, gastrointestinal bleeding, hospital acquired pneumonia and shock are associated with in-hospital death.

Key words: diabetes, diabetic foot infection, mortality, hospitalization

INTRODUCTION

Diabetic foot disease remains the leading cause of non-traumatic lower extremity amputation. Foot ulcers, in association with infection or gangrene, precede amputations in 75-85% of cases.[1] Approximately 9% of patients with diabetes admitted at hospitals have active foot disease. Half of this group will have active foot disease as the reason for admission.[2] After an initial event of hospitalization for diabetic foot ulcer, the rates are high for ulcer recurrence (60.9%) and amputations (43.8%). Furthermore, long-term studies have found poor quality of life and increased mortality among these patients even after amputation and discharge.[1,3,4]

Management of diabetic foot disease requires a multidisciplinary approach to adequately address the various pathological processes contributing to the disease. At the University of the Philippines-Philippine General Hospital (UP-PGH), the Diabetes Extremity Care Team (DECT) was established in 1996 with the aim of providing comprehensive surgical and medical care. The major objective of this team approach is to decrease the rates of major amputations and mortality. A retrospective study done 3 years after the formation of the DECT reported a decrease in the mortality rate of patients from 13.8% to 8%. However, no decrease in major amputation rate was observed.[5] Furthermore, additional retrospective studies published last 1999 and 2009 showed suboptimal quality of care in this patient group.[6,7] There was a non-significant trend in mortality increase during 2005, 2006 and 2007 (2.6%, 9% and 8.5%, respectively) compared to 1999 (4.6%). From 1998 to 2007, the time from admission to surgery ranged from 7.5 to 10.9 days. In addition, the mean time to antibiotic administration ranged from 7.5 to 16.7 hours. This is far from the recommended window of 1 hour from recognition of severe sepsis/septic shock to first antibiotic administration and likely contributed to increased mortality.[8] Department data from June 2014 to August 2016 showed a significantly higher mortality rate compared to previous reports, wherein there were 53 in-hospital deaths among 445 admissions (11.9%) under the DECT.

Diabetic patients with foot disease have prolonged hospital stay and greater in-hospital mortality, which widely ranged from 1.1% to 40.5%.[9-13] Few studies have

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examined the factors that are associated with mortality among hospitalized diabetic patients with foot disease.[12-15] However, potential factors such as delay in surgery and initiation of antibiotics, and development of in-hospital complications such as infection, hypoglycemia, MI, renal failure, stroke and respiratory failure and their influence on in-hospital death among diabetic patients with lower extremity infection has not been adequately studied.

The present study was undertaken to examine the factors potentially associated with in-hospital mortality such as clinical and biochemical characteristics, type of surgical treatment received and in-hospital complications. Furthermore, the mortality rate and causes of death among diabetic patients admitted with lower extremity infection were also studied. The early recognition and management of the identified in-hospital complication may help decrease the mortality rate among these patients. Findings of this study will aid in the creation of a risk stratification strategy that will identify high risk patients needing urgent medical and surgical care as well as provide data that will inform an institution-based treatment pathway.

METHODOLOGY

Study design and study population

This is a retrospective analytical study conducted at the UP-PGH, a tertiary government hospital in Manila, Philippines. The records of 506 consecutive admitted patients with diabetes referred to the DECT from January 2015 to December 2017 were reviewed. All patients were ≥18 years old, diagnosed with diabetes mellitus according to the American Diabetes Association (ADA) criteria and had signs of infection involving the lower extremity. Patients who refused treatment for infection control, life-extending measures, or those who were discharged against medical advice were excluded from the analysis.

The sample size calculation was estimated based on the risk of dying among diabetic patients with extremity infection who develop in-hospital MI from our registry. A logistic regression of death on occurrence of MI with a sample size of 435 admitted patients with diabetic foot infection (of which 89% are without MI and 11% had MI) achieves 90% power at 5% significance level to detect a change in probability of death from the baseline value of 0.16 to 0.50. This change corresponds to an odds ratio of 5.25. An adjustment was made since a multiple regression of MI on the other independent variables in the logistic regression is assumed to have an R-squared of 0.60.

This study was approved by the University of the Philippine Manila Research Ethics Board (UPREB) Panel. Since the research was limited to use of existing records, informed consent was waived. Patient codes were used to de-identify patients in the data collection forms. All data gathered was kept strictly confidential.

Data collection

The in-hospital charts of all patients admitted under the DECT from January 2015 to December 2017 were screened for eligibility. The patient's demographic profiles, clinical presentation, medical history and physical findings were reviewed from the medical records. This included the patient's age, sex, smoking status and medical conditions. Patients were classified as smokers if they smoked ≥100 cigarettes per lifetime, currently smoking or stopped less than 1 year. They were considered former smokers if they smoked ≤100 cigarettes per lifetime, quit ≥1 year. Those who smoked <100 cigarettes per lifetime were considered never smokers. Patients were diagnosed with diabetes based on medical history, present intake of diabetes medications or if they fulfill the ADA criteria for the diagnosis of diabetes mellitus. Those who had a blood pressure of ≥140/90 mmHg or were taking antihypertensive medications were diagnosed with hypertension. The diagnosis of coronary heart disease was based on the presence of anginal chest pain, exertional dyspnea, history of MI, unstable angina, prior revascularization procedures or as diagnosed by a physician. Neuropathy was considered present if the patient had evidence of loss of sensation using the monofilament test, vibration sense on tuning fork test or as diagnosed by a physician based on symptoms. Retinopathy was diagnosed based on funduscopic examination by an ophthalmologist or history of retinal surgery. Peripheral arterial disease was diagnosed by an ankle brachial index of <0.9 with claudication, significant occlusion on arterial Doppler studies or as diagnosed by a physician based on symptoms. Cerebrovascular disease was defined as a history of an acute focal neurologic deficit of sudden onset that was irreversible within 24 hours, evidence of stroke on neuro-imaging or as assessed by a physician.

The wound classification was based on the University of Texas Diabetic Foot Classification System. Classification of Body Mass Index (BMI) was based on the World Health Organization/International Association for the Study of Obesity/International Obesity Task Force (WHO/IASO/IOTF).

Values of routine laboratory tests taken on admission were documented and included the following: complete blood count, creatinine, calculated eGFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, blood urea nitrogen, alanine transaminase, aspartate transaminase, serum sodium, potassium, albumin, total calcium, magnesium, chloride, international normalized ratio (INR), random blood sugar, capillary blood glucose on admission, HBA1c and lipid profile results. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated by dividing the neutrophil or platelet counts, respectively, by the number of lymphocytes from the initial complete blood count.

The hospital course of each patient was followed from admission until death or discharge. Amputations above the ankle were classified as major amputations. Digit, ray and trans-metatarsal amputations were considered minor amputations. The time intervals from admission to the first antibiotic dose and first surgery were documented. In-hospital complications were reviewed based on the medical records and include the following: hypoglycemia, hospital-acquired pneumonia, MI, stroke, transfusion of packed red blood cell (PRBC), gastrointestinal bleeding, renal failure requiring dialysis and respiratory failure needing assisted ventilation. Hypoglycemia was defined based on the ADA classification of hypoglycemia.[16] Hospital-acquired pneumonia was defined as

development of new lung infiltrates with clinical evidence that the infiltrate was infectious in origin, associated with new-onset fever, purulent sputum, leukocytosis or decrease in oxygenation presenting 2 or more days after hospitalization or as diagnosed by the attending physician. Stroke was defined as an acute focal neurologic deficit of sudden onset that is irreversible for 24 hours or results in death not due to other non-vascular cause, or evidence of infarction or intracerebral hemorrhage by neuro-imaging. Myocardial infarction was defined based on an elevated cardiac troponin (>99th percentile or a >20% increase if with elevated baseline value) associated with at least one of the following: symptoms of myocardial ischemia, new ischemic electrocardiogram (ECG) changes or new left bundle branch block, development of pathological Q-waves on the ECG, imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality or identification of intracoronary thrombus by angiography. Patients with sudden death but without biomarkers were diagnosed to have had MI if attending physician deemed it was the cause of death. Shock was defined as systolic arterial pressure less than 90 mmHg or mean arterial pressure less than 70 mmHg associated with evidence of tissue hypoperfusion. Gastrointestinal bleeding was defined as a clinical event documented by the attending physician such as coffee-ground emesis, hematemesis, hematochezia or melena, or endoscopic evidence of active bleeding from the upper or lower gastrointestinal tract.

Data analysis

The demographic, clinical and laboratory characteristics of patients who were discharged or who died during admission were summarized using means and standard deviations (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed using frequencies and percentages. Shapiro-Wilks test was used to test for normality of data.

Pearson chi-square and Fisher's exact tests were used to compare categorical parametric and nonparametric data, respectively. Independent t-test was used to compare continuous variables. Variables were assessed for collinearity and excluded in the multivariate logistic regression. We used multiple imputation by chained equation (MICE) to impute missing data in the covariates. All available auxiliary variables capturing the clinical profiles of the patients were included in the imputation to support missing-at-random assumption. We estimated average associations across 10 imputed data sets. The effect size from the multivariate analyses was reported as odds ratios (OR) for inpatient mortality. Confidence intervals (CI) are given at 95% and p-values less than 0.05 were considered significant. STATA 13 was used for data analysis.

RESULTS

From January 2015 to December 2017, there were 506 diabetic patients with lower extremity infection referred to the DECT. Four hundred and seventy-one records were reviewed and 35 charts could not be retrieved. Out of the 471 patients, 30 were excluded from the study. Of the final 441 patients, 49 (11%) died during hospitalization. The causes of deaths were as follows: 23 (46.9%) due to MI, 13 (26.5%) from refractory septic shock, 7 (14.3%) with respiratory failure and 6 (12.2%) with fatal arrhythmia. The death occurred prior to any surgical intervention in 35 (71.4%) patients and 14 (28.6%) were post-operative mortalities. The mean duration from admission to death was 17.7±14.4 days.

The demographic and clinical characteristics are summarized in Table 1. The mean patient age of the cohort was 56.7±11.1 years. Patients who died were significantly older than those who were discharged with mean ages of 55.2±10.9 and 60.6±11.9 years old, respectively. Overall, majority of patients were males (58.1%) and were within the normal BMI category for Asians (46%). Almost all patients had type 2 diabetes mellitus (98.1%), with 57 (13%) patients diagnosed within one month from admission and four of whom eventually died.

Microvascular and macrovascular complications were common in both groups. The most common microvascular complication was neuropathy, which was present in 287 (65.1%) patients. Likewise, the most common macrovascular complication among the cohort was peripheral arterial disease which was present in 110 patients (24.9%). The presence of retinopathy, pre-existing coronary heart disease and peripheral arterial disease was more frequent in the mortality group. Other common comorbidities were hypertension, renal disease and dyslipidemia which were present in 239 (54.2%), 190 (43.1%) and 188 (42.6%), respectively. Eighty patients (18%) already had a prior amputation.

Table 2 summarizes the laboratory results of the patient cohort. Patients had leukocytosis and anemia on admission. Renal function was significantly poorer in the mortality group as shown by the higher BUN and creatinine, as well as a lower eGFR. Overall, glycemic control was poor as reflected by the RBS [median 9.9 mmol/L (IQR 9.7)] and HBA1c (mean 9.85±3.4%).

The wound classification of diabetic foot ulcers in patients with foot involvement is presented in Appendix A. Majority of the wounds were University of Texas stage 3 (69.6%) and grade C (51.3%). 22 patients (5%) presented with necrotizing fasciitis, four of whom died during admission.

All patients received antibiotic treatment. The median time to first antibiotic administration was longer among those who were discharged alive but the observed difference between the two groups was not statistically significant [4.3 hours (IQR 13.6) vs 6.3 hours (IQR 11.6), p=0.2]. The median length of hospital stay was 17 days (IQR 13) for the entire cohort.

Table 3 summarizes the surgical procedures performed during hospital stay. Any form of surgery for infection control was performed in 315 patients (71.4%). Major amputation was performed in 233 patients (50.6%). There were fewer deaths among patients who underwent BKA. Overall, surgery was performed 11 days (IQR 10) after admission and did not significantly differ between two groups.

The in-hospital complications are summarized in Table 4. Occurrence of at least one hypoglycemic episode

Table 1. Demographic and clinical characteristics of diabetic patients with lower extremity infection

	Total n=441	Discharged n=392	Mortality n=49
Age in years, mean (SD)	56.7 (11.1)	56.2 (10.9)	60.6 (11.9)
Sex, n (%)			
Male	256 (58.1)	224 (57.1)	32 (65.3)
Female	185 (41.9)	168 (42.9)	17 (34.7)
BMI (kg/m^2), mean (SD)	23.50 (3.9)	22.54 (3.6)	23.58 (3.9)
<18.5	12 (4.4)	11 (4.5)	1 (3.3)
18.5-22.9	127 (46.0)	108 (43.9)	1 (63.3)
23-24.9	62(22.5)	58 (23.5)	4 (13.3)
25-29.9	58 (21.0)	54(22.0)	4 (13.3)
>30	17 (6.16)	15 (6.1)	2 (6.7)
Smoking, n (%)			
Smoker	92 (20.9)	82 (20.9)	10 (20.4)
Previous smoker	107 (24.3)	97 (24.7)	10 (20.4)
Never smoker	242 (54.9)	213 (54.4)	29 (59.2)
Type of Diabetes, n (%)			
Type 1 DM	6 (1.4)	6 (1.5)	0
Type 2 DM	433 (98.1)	385 (98.2)	48 (98)
Secondary diabetes*	2 (0.5)	1 (0.3)	1 (2)
Newly-Diagnosed Diabetes**, n (%)	57 (12.9)	53 (13.5)	4 (8.2)
Duration of Diabetes in months (SD)	93.37 (94.5)	93.44 (95.5)	92.86 (87.9)
Treatment of diabetes, n (%)			
Insulin Only	42 (9.5)	38 (9.7)	4 (8.2)
Oral diabetes medication only	238 (54.0)	212 (54.1)	26 (53)
Insulin and oral medication	55 (12.5)	50 (12.8)	5 (10.2)
None	106 (24)	92 (23.4)	14 (28.6)
Microvascular complications, n (%)			
Retinopathy	205 (46.5)	185 (47.19%)	20 (40.82%)
Nephropathy	226 (51.3)	197 (50.26%)	29 (59.18%)
Neuropathy	287 (65.1)	261 (66.58%)	26 (53.06%)
Macrovascular complications, n (%)			
Cerebrovascular disease	43 (9.8)	36 (9.2)	7 (14.3)
Coronary heart disease	63 (14.3)	48 (12.2)	15 (30.6)
Peripheral arterial disease	110 (24.9)	92 (23.5)	18 (36.7)
Co-morbidities, n (%)			
Hypertension	239 (54.2)	207 (52.8)	32 (65.3)
Renal Disease	190 (43.1)	163 (41.6)	27 (55.1)
Dyslipidemia	188 (42.6)	168 (42.7)	20 (40.8)
Prior amputation	80 (18.1)	67 (17.1)	13 (26.5)
Dialysis prior to admission	48 (10.9)	38 (9.7)	10 (20.4)
Liver Disease	16 (3.6)	11 (2.8)	5 (10.2)
Pulmonary Tuberculosis	16 (3.6)	13 (3.3)	3 (6.1)
COPD	7 (1.6)	5 (1.3)	2 (4.1)

COPD - Chronic Obstructive Pulmonary Disease
* 1 patient with Acromegaly and 1 patient with Steroid-induced Diabetes
** Diagnosed within 1 month from admission

was common and occurred in 160 of patients (36.3%), with 27 episodes (6.1%) classified as severe hypoglycemia based on the ADA classification. Blood transfusion was required in 285 patients (65.4%). Development of shock, renal failure requiring dialysis, blood transfusion, respiratory failure requiring mechanical ventilation, hospital-acquired pneumonia, MI, and gastrointestinal bleeding were more frequent in the mortality group.

Univariate analysis revealed 22 factors with crude association with mortality as shown in Appendix B. After removal of collinear variables and adjusting for covariates, analysis showed that in-hospital complications increased the likelihood of dying during hospitalization due to lower extremity infection among patients with diabetes. Myocardial infarction, respiratory failure requiring mechanical ventilation, gastrointestinal bleeding, hospital-acquired pneumonia and shock were found to be associated with higher risk of in-hospital mortality (Table 5). Similarly, for every 1 mmol/L increase in BUN seen on admission, there is a corresponding 6% increase in the odds of dying. Likewise, patients who did not undergo any form of surgery for source control were also 4.2 times more likely to die during hospitalization.

DISCUSSION

This study shows that the in-hospital mortality rate among patients with diabetes admitted for lower extremity infection was 11.1%. This figure is comparable to that reported by Costa et al., in a Brazilian cohort of patients.[15] However, the reported in-hospital mortality rates vary widely from 1.1% to as high as 40.5% depending on the hospital setting.[9-13] Majority of our patients had cardiac or pulmonary complications as the underlying causes of death. This is similar to a study involving 283 predominantly diabetic patients who underwent major lower extremity amputation wherein cardiac and respiratory complications were significant risk factors for death during hospitalization.[14]

Table 2. Laboratory characteristics of diabetic patients with lower extremity infections

	Total n=441	Discharged n=392	Mortality n=49	*p*-value
WBC (10^9/L), median (IQR)	17.1 (13.6)	16.7 (13.7)	20.3 (12.9)	0.032
Hemoglobin g/L, median (IQR)	9.9 (3.4)	10(3.5)	8.9 (3.8)	0.172
Platelet (10^9/L), mean (SD)	402.3 (168.4)	409.3 (169.4)	346.7 (150.4)	0.014
Neutrophil (%), mean (SD)	80.3 (11.1)	79.6 (11.2)	86.2 (8.2)	0.0001
Lymphocyte (%), median (IQR)	10(10)	11(10)	6(5)	0.000
N-L Ratio, median (IQR)	8.3 (10.5)	7.5(10.3)	14.8(13.5)	0.000
P-L Ratio, median (IQR)	224.7(172.9)	221.5(165)	263.3(201.9)	0.099
Creatinine (mmol/L), median (IQR)	110(139)	103(264.5)	199(234)	0.000
BUN (mmol/L), median (IQR)	8.5(9)	7.7(8.2)	14.2(15.2)	0.000
eGFR (ml/min/1.73 m^2), median (IQR)	54.7 (63.6)	58.9(60.9)	24 (34.6)	0.000
Na (mmol/L), mean (SD)	131.5(10.4)	131.5 (10.6)	131.6 (8.5)	0.930
K (mmol/L), median (IQR)	4.3 (1.2)	4.3(1.2)	4.5(1.1)	0.241
Cl (mmol/L), mean (SD)	95.7 (10.2)	95.4 (10.2)	97.8 (10.2)	0.125
Albumin (g/L), mean (SD)	28.7 (12.2)	28.6 (7.2)	29.9 (29.8)	0.496
Calcium (mmol/)L, mean (SD)	2.29 (0.29)	2.30 (0.20)	2.20 (0.66)	0.018
Mg (mmol/L), mean (SD)	0.79 (0.34)	0.78 (0.36)	0.85 (0.21)	0.175
HBA1c (%), mean (SD)	9.85 (3.40)	9.93 (3.40)	8.75 (3.25)	0.155
ALT (U/L), median (IQR)	31 (28)	30.5 (27)	39 (31)	0.070
AST (U/L), median (IQR)	32 (25)	32 (24.5)	43 (40)	0.011
INR, mean (SD)	1.19 (0.40)	1.17 (0.36)	1.38 (0.64)	0.001
RBS (mmol/L), median (IQR)	9.9 (9.7)	10.3 (9.6)	8.1 (6.6)	0.565
CBG (mmol/L), median (IQR)	11.6 (10.2)	11.9 (10.2)	10.9 (10.9)	0.082
Cholesterol (mmol/L), mean (SD)	3.55 (1.40)	3.62 (1.43)	2.85 (0.73)	0.004
Triglyceride (mmol/L), median (IQR)	1.3 (0.9)	1.31(0.9)	1.4(0.82)	0.486
HDL (mmol/L), median (IQR)	0.59 (0.3)	0.61 (0.4)	0.51(0.3)	0.026
LDL (mmol/L), mean (SD)	2.18 (0.95)	2.23 (0.96)	1.63 (0.59)	0.001

WBC - white blood cell count; N-L ratio - Neutrophil to Lymphocyte Ratio; P-L ratio - Platelet to Lymphocyte ratio; BUN - Blood urea nitrogen; eGFR - estimated glomerular filtration rate; Na - Sodium; K - Potassium; Cl - Chloride; Mg - Magnesium; HBA1c - Hemoglobin A1c; ALT - alanine aminotransferase; AST - aspartate aminotransferase; INR - international normalized ratio; RBS - random blood sugar; CBG - capillary blood glucose; HDL - High-Density Lipoprotein; LDL - Low-Density Lipoprotein

Table 3. Surgical procedures performed

	Total n=441	Discharged n=392	Mortality n=49	*p*-value
Number of patients who had surgery, n (%)	315 (71.4)	297 (75.8)	18 (36.7)	0.000
Debridement, n (%)	49 (11.1)	45 (11.4)	4 (8.2)	0.486
Minor amputation, n (%)	42 (9.5)	41 (10.5)	1 (2.0)	0.058
Major amputation, n (%)	223 (50.6)	210 (53.6)	13 (26.5)	0.000
BKA	178 (40.4)	173 (44.1)	5 (10.2)	0.000
AKA	46 (10.4)	38 (9.7)	8 (16.3)	0.152
Hip disarticulation	2 (0.4)	2 (0.5)	0	-
Revascularization, n (%)	2 (0.4)	2 (0.5)	0	-
Time from admission to first surgery (days), median (IQR)*	11(10)	13(14)	11(17)	0.653

BKA - Below Knee Amputation; AKA - Above Knee Amputation
* n=302

Our subjects had a mean age of 56.7±11.1 years and were predominantly males. The cohort is slightly older than the previous population of diabetic patients with foot infection in our hospital described in 2007, wherein the mean age was 55±11 years old.[17] In other reports, the age of diabetic patients admitted for foot disease varies between 54.3 to 64.3 years.[13,15,18,19] Increasing age has been found to be a risk factor for in-hospital mortality among diabetic patients with foot disease.[12,15] One study reported that age >75 years old was associated with increased in-hospital mortality in diabetic patients admitted for foot disease.[12] However, our study did not find age as a factor for in-hospital death. This may be due to dissimilarities in the ages of the population. Our patient cohort is younger and only 5% were more than 75 years of age.

Majority of our patients had microvascular complications, with retinopathy documented in 46.5%, nephropathy in 51.3% and neuropathy in 65%. These complications are commonly observed in patients with long-standing diabetes (>10 years) and these numbers likely underestimate the true prevalence of these conditions due to the retrospective design of the study. The high prevalence of microvascular complications highlights the need for routine screening for such conditions during hospitalization of patients with diabetes mellitus as hospital stay is a good opportunity for these patients to be assessed by different specialists involved in their care. PAD was observed in 24.9% of the study population. The presence of both neuropathy and PAD are independent risk factors for ulcer development and limb loss in diabetic patients.[15] This relationship between PAD and increased risk of amputation emphasizes the need for a comprehensive vascular assessment among diabetic foot patients. Coronary heart disease was present in 14.3% of patients but this likely underestimates the true prevalence of this disorder as patients may have occult disease. In our study, the presence of PAD and pre-existing coronary heart disease was crudely associated with mortality in univariate analysis but the association was not significant after correcting for multiple variables.

Table 4. In-hospital complications among diabetic patients with lower extremity infection

	Total n=441	Discharged n=392	Mortality n=49	*p*-value
Any hypoglycemia episode, n (%)	160 (36.3)	137 (35)	23 (46.9)	0.100
Severe hypoglycemia, n (%)	27 (6.1)	20 (5.1)	7 (14.3)	0.011
PRBC transfusion, n (%)	285 (65.4)	247 (63.5)	38 (80.9)	0.018
Shock, n (%)	71 (16.1)	37 (9.4)	34 (69.4)	0.000
Respiratory failure requiring mechanical Ventilation, n (%)	52 (11.8)	19 (4.9)	33 (67.4)	0.000
Myocardial infarction, n (%)	51 (11.6)	22 (5.6)	29 (59.2)	0.000
Hospital-acquired pneumonia, n (%)	51 (11.6)	27 (6.9)	24 (49)	0.000
Renal failure requiring dialysis, n (%)	38 (8.6)	25 (6.4)	13 (26.5)	0.000
Gastrointestinal bleeding, n (%)*	25 (5.7)	13 (3.3)	12 (24.5)	0.000
Stroke, n (%)	4 (0.9)	2 (4.1)	2 (0.5)	0.063

PRBC - Packed Red Blood Cell
* Includes both upper and lower gastrointestinal bleeding

Table 5. Multivariate analysis of factors associated with in-hospital mortality

Variable	OR	95% CI	*p*-value
Myocardial infarction	27.19	6.38 to 1115.94	0.000
Respiratory failure requiring mechanical ventilation	26.14	6.28 to 108.80	0.000
Gastrointestinal bleeding	10.08	1.87 to 54.38	0.007
Hospital-acquired pneumonia	9.46	2.52 to 35.51	0.001
Shock	7.09	2.17 to 23.22	0.001
No surgery	4.22	1.10 to 16.27	0.036
Blood urea nitrogen	1.06	1.01 to 1.11	0.016

In terms of laboratory parameters, both groups were anemic on admission (hemoglobin <11 g/dL) and required transfusion with packed red blood cells in two-thirds of patients (65.4%). The anemia is likely multifactorial resulting from infection, chronic kidney disease or poor nutrition. When analyzed in our multiple logistic model, anemia did not increase the likelihood of mortality contrary to another report.[15] Both groups had elevated creatinine and BUN, with eGFR <60ml/min during admission. These findings are likely secondary to sepsis, preexisting renal disease and/or volume depletion. Of interest, elevated BUN was found to be associated with in-hospital mortality in this study and has not been previously reported in this patient population. The elevated BUN and its relationship to increased mortality in this population is uncertain. However, in a study involving 4176 critically ill patients admitted to the ICU due to various medical conditions, BUN was independently associated with a higher risk of death.[20] As BUN levels are routinely taken during hospitalization, this laboratory test represents a readily available tool to risk stratify patients who have a higher risk of in-hospital death. This can be used in combination with other reported laboratory parameters associated with in-hospital death such as albuminuria and elevated WBC count (>12.0 x10^9/L) in this patient population.[12]

In our study, the grade and stage of the diabetic foot ulcer were not associated with mortality. There was a slight increase in the major amputation rate from 48.6% in 2008 to 50.6% in this study.[17] This rate is higher compared to international reports that ranged from 21% to 24.4%.[14,18] Overall, the median time interval from admission to surgery for source control was 11 days (IQR 10), which is even longer compared to the 9.8 days last 2007.[17] The delay in intervention in our hospital setting is mainly due to the lack of an available operating room, the need for medical optimization of the patient, correction of anemia or no initial consent for surgery.

Patients who did not undergo any surgical intervention had an increased likelihood of mortality of 3.5 times. This finding supports the notion that prompt source control of infection should be done as soon as medically practical after the diagnosis of sepsis has been made to improve outcomes.[21,22] Furthermore, after initial resuscitation and stabilization of the patients with septic shock, source control should be done within 6-12 hours.[8] However, our study did not show any association between delayed time to first antibiotic treatment (>60 minutes) and surgery with mortality. This may be due to the fact that majority of the patients in both groups had delayed antibiotic treatment and surgery hence there was no adequate comparator to assess this association.

Severe hypoglycemia occurred more frequently in the mortality group (14.3% vs 5.1%). There was crude association between severe hypoglycemia and mortality in our study but this was not significant after adjusting for confounders. Hypoglycemia has been linked to higher mortality rates in hospitalized patients with diabetes, while hyperglycemia has been linked to impaired wound healing.[23,24] This stresses the importance of carefully balancing glycemic control with hypoglycemia avoidance.

In this study, gastrointestinal bleeding was associated with 10-fold increase in the likelihood of death during hospitalization and highlights the need for routine stress ulcer prophylaxis. The development of shock, respiratory failure requiring assisted ventilation, hospital-acquired pneumonia and MI also markedly increased the odds of dying among diabetic patients with lower extremity infection. Development of these in-hospital complications indicate a need for more aggressive treatment and possible early subspecialty referral if necessary. In particular, those who are high risk for adverse cardiovascular events based on clinical risk stratification may warrant additional non-invasive testing for proper risk stratification.

This study has several limitations. First, due to the retrospective nature of the study design, missing data is inevitable when reviewing medical records. However, we tried to offset this by doing multiple imputation of missing data. Second, important physical findings such as the ankle brachial index, test for loss of proprioception and funduscopic examination were not performed in all of the patients and the true incidence of PAD, neuropathy and retinopathy are likely underestimated. Third, findings of this study apply to diabetic patients admitted in a tertiary hospital with limited resources and

availability of operating rooms allotted for infectious cases such as diabetic foot ulcers. This limits the applicability of our data to patients with similar situations. Fourth, the odds ratios of the factors associated with in-hospital death are broad indicating that the precision is low or that the sample size for logistic regression analysis may be small. Hence, these findings should be confirmed through studies with a larger population. Finally, causality cannot be established between the factors identified and death due to the retrospective nature of the study. However, this study was able to analyze a comprehensive set of multiple variables including in-hospital complications as it relates to mortality thereby adding to our understanding of the hospital course of this patient group. Furthermore, our data highlights the complex nature of lower extremity infections among patients with diabetes mellitus wherein patients present with multiple diabetes complications, comorbidities and frequent hospital complications that need to be considered in treating this population.

CONCLUSION

In our setting, the in-hospital mortality rate among patients with diabetes admitted for lower extremity infection was 11.1%. In-hospital complications such as development of shock, MI, respiratory failure, hospital-acquired pneumonia and gastrointestinal bleeding were associated with increased risk of in-patient death. Additionally, elevated baseline BUN and non-performance of surgery for source control were also associated with increased likelihood of death. Patients identified to have high risk for cardiovascular events, and those who develop in-hospital complications, warrant more aggressive approach to treatment, including source control.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

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APPENDIX

Appendix A. University of Texas wound classification for infections with foot involvement*

	Total n=392	Discharged n=344	Mortality n=48	*p*-value
UT Grade				
A	0 (0)	0 (0)	0 (0)	0.887
B	21 (5.3)	19 (5.5)	2 (4.2)	
C	201 (51.3)	177 (51.5)	24 (50)	
D	170 (43.4)	148 (43)	22 (45.8)	
UT Stage				
1	65 (16.6)	61 (17.7)	4 (8.3)	0.246
2	54 (13.8)	46 (13.4)	8 (16.7)	
3	273 (69.6)	237 (68.9)	36 (75)	
Necrotizing Fasciitis	22 (5.6)	18 (5.2)	4 (8.3)	0.329

UT - University of Texas
* Data presented as n(%)

Appendix B. Univariate analysis of factors associated with in-hospital mortality

Variable	Crude OR	95% CI	*p*-value
Respiratory failure requiring mechanical ventilation	40.49	19.04 to 86.09	0.000
Myocardial infarction	24.39	11.94 to 49.79	0.000
Shock	21.75	10.85 to 43.60	0.000
Hospital acquired pneumonia	12.98	6.55 to 25.69	0.000
Gastrointestinal bleeding	9.46	4.02 to 22.21	0.000
Stroke	8.30	1.14 to 60.29	0.037
No surgery	5.38	2.88 to 10.06	0.000
Renal failure requiring dialysis	5.30	2.50 to 11.25	0.000
Coronary heart disease	3.16	1.60 to 6.23	0.001
eGFR ≤15 (ml/min/1.73 m^2) on admission	2.80	1.23 to 6.39	0.014
Severe hypoglycemia	2.80	1.13 to 6.95	0.026
PRBC transfusion	2.29	1.09 to 4.82	0.029
INR	2.26	1.13 to 4.52	0.021
Peripheral arterial disease	1.89	1.01 to 3.54	0.046
Blood urea nitrogen	1.06	1.03 to 1.08	0.000
Age (years)	1.04	1.01 to 1.07	0.008
Neutrophil lymphocyte ratio	1.03	1.02 to 1.05	0.000
Creatinine	1.002	1.001 to 1.003	0.003
Platelet count	0.997	0.995 to 0.999	0.015
Cholesterol	0.671	0.506 to 0.891	0.007
Low density lipoprotein	0.525	0.359 to 0.768	0.001
Major amputation	0.313	0.161 to 0.608	0.001

OR - Odds ratio
eGFR - estimated glomerular filtration rate; INR - international normalized ratio