

Predictive factors for lower extremity amputations in diabetic foot infections

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The objective of this study was to evaluate the epidemiology of diabetic foot infections (DFIs) and its predictive factors for lower extremity amputations. A prospective study of 100 patients with DFIs treated at the National University Hospital of Singapore were recruited in the study during the period of January 2005-June 2005. A protocol was designed to document patient's demographics, type of DFI, presence of neuropathy and/or vasculopathy and its final outcome. Predictive factors for limb loss were determined using univariate and stepwise logistic regression analysis. The mean age of the study population was 59.8 years with a male to female ratio of about 1:1 and with a mean follow-up duration of about 24 months. All patients had type 2 diabetes mellitus. Common DFIs included abscess (32%), wet gangrene (29%), infected ulcers (19%), osteomyelitis (13%), necrotizing fasciitis (4%) and cellulitis (3%). Thirteen patients were treated conservatively, while surgical debridement or distal amputation was performed in 59 patients. Twenty-eight patients had major amputations (below or above knee) performed. Forty-eight percent had monomicrobial infections compared with 52% with polymicrobial infections. The most common pathogens found in all infections (both monomicrobial and polymicrobial) were *Staphylococcus aureus* (39.7%), *Bacteroides fragilis* (30.3%), *Pseudomonas aeruginosa* (26.0%) and *Streptococcus agalactiae* (21.0%). Significant univariate predictive factors for limb loss included age above 60 years, gangrene, ankle-brachial index (ABI) <0.8, monomicrobial infections, white blood cell (WBC) count $\geq 15.0 \times 10^9/L$, erythrocyte sedimentation rate ≥ 100 mm/hr, C-reactive protein ≥ 15.0 mg/dL, hemoglobin (Hb) ≤ 10.0 g/dL and creatinine ≥ 150 μ mol/L. Upon stepwise logistic regression, only gangrene, ABI <0.8, WBC $\geq 15.0 \times 10^9/L$ and Hb ≤ 10.0 g/dL were significant.

Keywords: gangrene; diabetes mellitus; amputation; ulceration

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With a prevalence of 8.2% in 2004 (1), diabetes is one of the leading causes of lower limb amputations in Singapore. Diabetes mellitus itself accounts for almost 700 amputations annually (2). Its devastating complications, including peripheral vascular disease and neuropathy, predispose patients to having diabetic foot infections (DFIs) that most commonly require urgent attention in order to avoid a lower extremity amputation (3). In the past two decades, publications from Singapore concerning diabetes mellitus underscored the alarming prevalence of its complications in the republic (4–6). However, the only studies on DFI in Singapore were undertaken in the 1970s and 1980s (7–9). These studies mainly concentrated on the pathophysiology of DFI, such as the defective function of the polymorphonuclear leukocytes and the benefits of

maintaining optimal blood glucose levels, along with discussions on criteria for conservative versus ablative surgery. In Singapore, there had been no latest literature studying DFI and predictive factors for limb loss, which would provide an insight to better optimization of patients with DFIs. Our study is the most comprehensive study on DFI undertaken in Singapore recently.

The aim of this study was to evaluate the epidemiology of DFI and to determine its parameters that could be predictive factors for limb loss resulting from major below and above the knee amputations (AKA).

Methods and materials

This is a prospective study of 100 patients diagnosed and treated with DFI in the National University Hospital of Singapore during the period of January 2005-June 2005.

Medical and surgical treatment was provided by our multidisciplinary team approach for the treatment of the diabetic foot. Data on all patients were documented using a carefully designed study protocol. Ethics approval was sought prior to commencement of the study and informed consent was obtained from all subjects studied in this cohort.

Documentation included patient demographics such as age, sex, race and type of DFI (abscess, wet gangrene, infected ulcers, osteomyelitis, necrotizing fasciitis and cellulitis). Objective clinical data such as clinical examination for fever, neuropathy and vasculopathy were also collected. Neuropathy was assessed using the 5.07 Semmes-Weinstein Monofilament Test (SWMT). Ability to detect seven or less sites out of a total of ten sites indicated the presence of peripheral neuropathy. The ankle-brachial index (ABI) measured was used to determine if a patient had vasculopathy. Patients with a recorded ABI value of <0.8 were considered to have vasculopathy. Laboratory investigations, including glycosylated hemoglobin (HbA1c), erythrocyte sedimentation rate (ESR), hemoglobin level (Hb), white blood cell (WBC) count, creatinine (Cr) and C-reactive protein (CRP) levels were recorded and documented. Blood cultures were performed for all patients and swabs were taken from the local infection sites for culture of aerobic and anaerobic organisms. In patients undergoing debridement or amputation, intra-operative infected tissue was examined for culture and sensitivities.

The treatment administered to each patient was also recorded. Conservative treatment included, but was not limited to intravenous antibiotics, bedside wound debridement and local wound care, whereas surgical treatment included debridement or distal foot amputation versus major below the knee amputation (BKA) or AKA. Patients were considered to have a successful limb salvage procedure when they received conservative treatment only, or had undergone operations such as wound debridement, incision and drainage, and distal amputations such as toe disarticulation and ray amputation. Patients who had undergone major amputations (BKA or AKA) were classified as having a non-salvageable procedure performed. All patients were reviewed weekly or fortnightly for the first two months and subsequently monthly for a minimum of two years.

In this cohort, the following factors were studied to see if they were significant predictive factors of limb loss: age, sex, ethnicity, type of DFI, fever, type of pathogen(s) encountered, presence of neuropathy and vasculopathy, WBC, ESR, CRP, Hb, HbA1c and Cr. All statistical analysis were performed using SPSS 14.0 with statistical significance set at ($P < 0.050$). Predictive factors for limb loss were determined using univariate and stepwise logistic regression analysis.

Results

The ages of our patients ranged between 21 and 91 years with a mean of 59.8 years. The majority were in their 5th and 6th decades of life (59.0%). Nineteen percent were in their 1st-4th decades of life, and the remaining 22.0% were in their 7th-9th decades of life. The ratio of male to female patients was approximately 1:1. Forty-nine percent of the patients were females and 51% were males. Racial distribution was 46% Chinese, 39% Malays and 15% Indians. In comparison with the national racial distribution of Singapore (10), which reported 75.6% Chinese, 13.6% Malays and 8.7% Indians, there was a significant increased representation in Malays ($P < 0.001$) and a significant decreased representation in Chinese ($P < 0.001$). All patients had type 2 diabetes mellitus for at least 5 years in duration. The most common DFIs were abscess (32%), wet gangrene (29%), infected ulcers (19%) and osteomyelitis (13%). Other infections included necrotizing fasciitis (4%) and cellulitis (3%).

Culture swabs from ulcers or from infected tissues sent for bacterial cultures intra-operatively showed that 48% of the infections were monomicrobial and 52% were polymicrobial. For monomicrobial infections, the most common pathogens were *Staphylococcus aureus* (31.3%), methicillin-resistant *S. aureus* (MRSA) (16.7%) and *Pseudomonas aeruginosa* (16.7%). Other pathogens included *Streptococcus agalactiae* (12.5%), *Bacteroides fragilis* (12.5%), beta-haemolytic *Streptococcus* (4.1%), *Peptostreptococcus* (2.1%) and others (4.1%). For polymicrobial infections, the most common organisms found were *S. aureus* (48.1%), *B. fragilis* (46.2%) and *P. aeruginosa* (34.6%). Other pathogens included *S. agalactiae* (28.9%), *Peptostreptococcus* (19.2%), beta-haemolytic *Streptococcus* (15.4%), MRSA (13.5%) and others (13.5%). The commonest pathogens found in all infections (both monomicrobial and polymicrobial) were *S. aureus* (39.7%), *B. fragilis* (30.3%), *P. aeruginosa* (26.0%) and *S. agalactiae* (21.0%). Others included MRSA (15.0%), *Peptostreptococcus* (11.0%), beta-haemolytic *Streptococcus* (10.4%) and others (9.6%). Bose (11) and Frykberg (12) reported similar findings to our study. They found *S. aureus* to be the most common pathogen as in this study.

With regards to the markers of infection, 62.0% had elevated WBC counts ($WBC \geq 11.0 \times 10^9$), and 38.0% had $WBC \geq 15.0 \times 10^9/L$. Ninety-seven percent had raised ESR ($ESR \geq 16 \text{ mm/hr}$ for males and $ESR \geq 19 \text{ mm/hr}$ for females) and 53.0% had $ESR \geq 100 \text{ mm/hr}$. Ninety-five percent had elevated CRP ($CRP \geq 1.0 \text{ mg/dL}$) and 26.0% had $CRP \geq 15.0 \text{ mg/dL}$. Seventy-seven percent had reduced Hb levels ($Hb \leq 13.1 \text{ g/dL}$) and 31.0% had $Hb \leq 10.0 \text{ g/dL}$. Thirty-nine percent had elevated Cr levels ($Cr \geq 115 \mu\text{mol/l}$) and 29.0% had $Cr \geq 150 \mu\text{mol/l}$. The majority (79.0%) of the patients had poor control of diabetes, as indicated by their HbA1c level ($>7.0\%$).

Fifteen percent of patients had HbA1c >13.0%. Of the 100 patients documented, 37.0% experienced fever, 67.0% had ABI <0.8 (indicating vasculopathy), and 84.0% were found to have sensory neuropathy based on SWMT.

All patients had no prior surgical intervention performed for their DFI. The mean follow-up duration was 24 months. This was a single surgeon series, who dictated which procedure to perform and the surgical procedures were not staged. Thirteen patients were treated conservatively with intravenous antibiotics, bedside wound debridement and local wound care. Surgery was required in 87 patients, including 21 ray amputations, 18 debridements, 14 incisions and drainage, 6 toe disarticulations and 28 major amputations (24 BKA and 4 AKA). There were no re-infections or secondary surgical procedures required for patients who underwent surgery. The amputation rate of 28% is much lower than the higher amputation rate of 40% reported by Bose (7).

Discussion

Predictive factors for lower extremity amputations (Table 1)

Age

Thirty-eight percent of patients older than age 60 suffered limb loss in comparison to 18.0% of patients younger than age 60 y. Patients older than age 60 were found to be a significant predictive factor for limb loss ($P = 0.026$), similar to findings by Leung et al. (13) and Santos et al. (14).

Gender

Gender was not found to be an important predictive factor for limb loss ($P = 0.310$). This is similar to findings by Miyajima et al. (15) and Gurlek et al. (16), although Hamalainen et al (17) showed otherwise, indicating that the male gender has a higher risk of undergoing lower extremity amputations.

Ethnicity

Ethnicity was also not a predictive factor for limb loss ($P > 0.050$) for all three major races in Singapore. This is in contrast to studies conducted in the United States, where Resnick et al. (18) showed that people of African American descent with diabetes have a much higher amputation risk than whites, as well as studies conducted in the United Kingdom, which showed that African Caribbean men had a lower risk of amputation than European men (19). In a recent study carried out on a larger cohort of 234 patients, Nather et al., however, have recently reported that the Malay ethnicity, along with a low-level of education and low average household income, were found to have a significantly higher incidence of diabetic foot problems (20).

Type of diabetic foot infection

Among the types of DFI present, only gangrene was found to be highly significant as a predictive factor for limb loss ($P < 0.001$). Approximately 58.6% of cases involving wet gangrene had major amputations. Pittet et al. (21) also reported a similar finding, although their study showed that in addition to gangrene, plantar ulcers, deep tissue infections and osteomyelitis were also highly significant as predictive factors for limb loss. The significance of gangrene as a predictive factor for limb loss and the lack of significance for other types of DFI indicated urgency to actively treat infections with gangrene.

Fever

Out of 37 patients presented with fever (temperature $\geq 38C$), twelve had major lower extremity amputations (32.4%). Fever was not found to be a predictive factor for limb loss ($P = 0.449$).

Neuropathy

Approximately 29.8% of patients with sensory neuropathy had a major amputation in comparison with 18.8% of those without neuropathy who had a major amputation. Neuropathy was not found to be a significant factor in predicting limb loss ($P = 0.546$). As neuropathy is commonly regarded as a major factor that predisposes diabetic patients to lower extremity amputations, as shown by Reiber et al. (22) and Hamalainen et al. (17), it was surprising that neuropathy was not found to be significant in our study.

ABI measurements

About 38.8% of patients with ABI <0.8 (indicating vasculopathy) underwent major amputations, in comparison with 6.1% of patients with ABI ≥ 0.8 who had major amputations performed.

The ABI <0.8 was found to be highly significant in predicting limb loss ($P = 0.001$), similar to findings by Pittet et al. (21) and Hamalainen et al. (17). Medial arterial calcinosis (MAC) occurs frequently and unpredictably in diabetic patients, and this may result in non-compressible arteries and artificially elevated ABI. Mayfield et al. (23) found that MAC is associated with an increased risk of ulceration, amputation and mortality. Hence, one should not be re-assured by a normal ABI in diabetic foot disease.

Type of pathogen

Approximately 37.5% of patients with monomicrobial infections suffered from limb loss, in contrast to 19.2% of patients with polymicrobial infections. Comparison of monomicrobial versus polymicrobial infections as a predictive factor for limb loss showed that the former was significant ($P = 0.042$). Frykberg (12) reported in a

Table 1. Evaluation of factors as predictive factors for limb loss

Risk factor	Limb Loss		Unadjusted		Stepwise analysis	
	Positive	Negative	OR (95% CI)	P value	OR (95% CI)	P value
<i>Age</i>						
> 60 years	19 (38.0)	31 (62.0)	2.8 (1.1–7.0)	0.029		
≤ 60 years	9 (18.0)	41 (82.0)	1.0			
<i>Gender</i>						
Male	12 (23.5)	39 (76.5)	0.6 (0.3–1.5)	0.310		
Female	16 (32.7)	33 (67.3)	1.0			
<i>Ethnicity</i>						
Chinese	16 (34.8)	30 (65.2)	2.1 (0.8–5.5)	0.149		
Malay	8 (20.5)	31 (79.5)	1.0			
Indian	4 (26.7)	11 (73.3)	1.4 (0.4–5.6)	0.627		
<i>Type of DFI</i>						
<i>Abscess</i>						
	Yes	2 (6.3)	30 (93.8)	0.1 (0.0–0.5)	0.001	
	No	26 (38.2)	42 (61.8)	1.0		
<i>Gangrene</i>						
	Yes	17 (58.6)	12 (41.4)	7.7 (2.9–20.6)	< 0.001	5.6 (1.7–18.7) 0.005
	No	11 (15.5)	60 (84.5)	1.0		
<i>Infected ulcer</i>						
	Yes	5 (26.3)	14 (73.7)	0.9 (0.3–2.8)	0.856	
	No	23 (28.4)	58 (71.6)	1.0		
<i>Osteomyelitis</i>						
	Yes	2 (15.4)	11 (84.6)	0.4 (0.1–2.1)	0.342	
	No	26 (29.9)	61 (70.1)	1.0		
<i>Necrotising fasciitis</i>						
	Yes	2 (50.0)	2 (50.0)	2.7 (0.4–20.1)	0.312	
	No	26 (27.1)	70 (72.9)	1.0		
<i>Cellulitis</i>						
	Yes	0 (0.0)	30 (100.0)	NA	0.557	
	No	28 (38.2)	42 (61.8)	1.0	0.001	
<i>Complications</i>						
<i>Fever</i>						
	Yes	12 (32.4)	25 (67.6)	1.4 (0.6–3.4)	0.449	
	No	16 (25.4)	47 (74.6)	1.0		
<i>ABI <0.8</i>						
	Yes	26 (38.8)	41 (61.2)	9.8 (2.2–44.6)	0.001	19.9 (2.8–139.6) 0.003
	No	2 (6.1)	31 (93.9)	1.0		
<i>Neuropathy</i>						
	Yes	25 (29.8)	59 (70.2)	1.8 (0.5–7.0)	0.546	
	No	3 (18.8)	13 (81.2)	1.0		
<i>Type of pathogens</i>						
<i>Staphylococcus aureus</i>						
	Yes	9 (22.5)	31 (77.5)	0.6 (0.3–1.6)	0.317	
	No	19 (31.7)	41 (68.3)	1.0		
<i>Bacteriodes fragilis</i>						
	Yes	8 (26.7)	22 (73.3)	0.9 (0.4–2.4)	0.846	
	No	20 (28.6)	50 (71.4)	1.0		
<i>Pseudomonas aeruginosa</i>						
	Yes	10 (38.5)	16 (61.5)	1.9 (0.8–5.0)	0.167	
	No	18 (24.3)	56 (75.7)	1.0		
<i>Streptococcus agalactiae Group B</i>						
	Yes	2 (9.5)	19 (90.5)	0.2 (0.1–1.0)	0.034	
	No	26 (32.9)	53 (67.1)	1.0		
<i>MRSA</i>						
	Yes	7 (46.7)	8 (53.3)	2.7 (0.9–8.2)	0.117	
	No	21 (24.7)	64 (75.3)	1.0		
<i>Peptostreptococcus</i>						
	Yes	2 (18.2)	9 (81.8)	0.5 (0.1–2.7)	0.723	
	No	26 (29.2)	63 (70.8)	1.0		
<i>Beta-Haemolytic Streptococcus sp.</i>						
	Yes	1 (10.0)	9 (90.0)	0.3 (0.0–2.1)	0.275	
	No	27 (30.0)	63 (70.0)	1.0		

Table 1 (Continued)

Risk factor		Limb Loss		Unadjusted		Stepwise analysis	
		Positive	Negative	OR (95% CI)	P value	OR (95% CI)	P value
Monomicrobial	Yes	18 (37.5)	30 (62.5)	2.5 (1.0–6.2)	0.042		
	No	10 (19.2)	42 (80.8)	1.0			
Polymicrobial	Yes	10 (19.2)	42 (80.8)	0.4 (0.2–1.0)	0.042	0.2 (0.1–0.7)	0.010
	No	18 (37.5)	30 (62.5)	1.0			
<i>Markers of infection</i>							
WBC $\geq 15.0 \times 10^9/L$	Yes	16 (42.1)	22 (57.9)	3.0 (1.2–7.5)	0.014	4.7 (1.3–16.8)	0.016
	No	12 (19.4)	50 (80.6)	1.0			
ESR ≥ 100 mm/hr	Yes	22 (41.5)	31 (58.5)	4.8 (1.7–7.5)	0.001		
	No	6 (12.8)	41 (87.2)	1.0			
CRP ≥ 15.0 mg/dL	Yes	12 (46.2)	14 (53.8)	3.1 (1.2–8.0)	0.017		
	No	16 (21.6)	58 (78.4)	1.0			
Hb ≤ 10.0 g/dL	Yes	16 (51.6)	15 (48.4)	5.1 (2.0–13.0)	< 0.001	5.2 (1.5–17.7)	0.008
	No	12 (17.4)	57 (82.6)	1.0			
HbA1C $> 7.0\%$	Yes	19 (24.1)	60 (75.9)	2.4 (0.9–6.5)	0.093		
	No	9 (42.9)	12 (57.1)	1.0			
Cr ≥ 150 $\mu\text{mol/l}$	Yes	15 (51.7)	14 (48.3)	4.8 (1.9–12.3)	0.001		
	No	13 (18.3)	58 (81.7)	1.0			

review that severe infections are characterized by polymicrobial involvement, but our findings showed monomicrobial infections to be significant as a predictive factor of limb loss. When individual pathogens were studied as predictive factors for limb loss, none were found to be predictive of limb loss ($P > 0.050$). However, Fejfarova et al. (24) found *S. aureus* to be a significant predictive factor for limb loss.

Wheat et al. (25) has shown that deep-tissue biopsy were likely to contain a single organism, as compared to superficial wound culture, which were more likely to be polymicrobial. Hence, the higher amputation rate in patients having monomicrobial infections could be contributed by the fact that patients with more severe infections often undergo surgical intervention and more likely to have deep tissue (intra-operative) cultures.

Markers of infection

White blood cells $\geq 15.0 \times 10^9/L$

Limb loss occurred in 42.1% of patients with WBC $\geq 15.0 \times 10^9/L$. WBC $\geq 15.0 \times 10^9/L$ was found to be a significant predictive factor for limb loss ($P = 0.014$).

Erythrocyte sedimentation rate ≥ 100 mm/hr

Limb loss occurred in 41.5% of patients with ESR ≥ 100 mm/hr. Table 1 showed that ESR ≥ 100 mm/hr was also a significant predictive factor for limb loss ($P = 0.001$).

C-reactive protein ≥ 15.0 mg/dL

Limb loss occurred in 46.2% of patients with CRP ≥ 15.0 mg/dL. CRP ≥ 15.0 mg/dL was also found to be a significant predictive factor for limb loss ($P = 0.017$).

Hemoglobin ≤ 10.0 g/dL

Limb loss occurred in 51.6% of patients with Hb ≤ 10.0 g/dL. It was interesting to note that Hb ≤ 10.0 g/dL was a highly significant predictive factor for limb loss ($P < 0.001$).

Creatinine ≥ 150 $\mu\text{mol/l}$

Limb loss occurred in 51.7% of patients with Cr ≥ 150 $\mu\text{mol/l}$. Cr ≥ 150 $\mu\text{mol/l}$ was found, as shown in Table 1, to be a highly significant predictive factor for limb loss ($P = 0.001$). Pittet et al. (21) and Upchurch et al. (26) showed that elevated CRP levels and elevated Cr levels were useful in signalling severe infection and predicting limb loss. However, a study by Santos et al. (14) did not find Cr, glucose and WBC levels to be significant risk factors for major amputations.

Glycosylated hemoglobin $> 7.0\%$

Limb loss occurred in 24.1% of patients with HbA1c $> 7.0\%$. Table 1 showed that HbA1c was not found to be a predictive factor for limb loss ($P > 0.050$). Glycemic control is commonly found to be of key importance to the prevention of major amputations (8, 27), although

HbA1c was not found to be a predictive factor in our study.

Conclusion

This is the most comprehensive study about DFIs undertaken in Singapore in recent years and hope that it will provide awareness of the rising rate of diabetes mellitus and its related lower extremity amputations.

Conflict of interest and funding

The authors have not received any funding or benefits from industry to conduct this study.

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