Risk factors that predict major amputations and amputation time intervals for hospitalised diabetic patients with foot complications

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Abstract
Diabetes-related lower extremity amputations are an enormous burden on global health care and social resources because of the rapid worldwide growth of the diabetic population. This research aimed to determine risk factors that predict major amputation and analyse the time interval from first hospitalisation to amputation by using standard management protocols and Kaplan–Meier survival curves. Data from 246 patients with diabetes mellitus and diabetic foot ulcers from the Division of Plastic and Reconstructive Surgery of the Department of Surgery at XXX Hospital between January 2016 and May 2020 were analysed. Univariate and multivariate analyses of 44 potential risk factors, including invasive ulcer depth and C-reactive protein levels, showed statistically significant differences for those at increased risk for major amputation. The median time from hospitalisation to lower extremity amputation was approximately 35 days. Most patients with abnormal C-reactive protein levels and approximately 70% of patients with ulcers invading the bone were at risk for lower extremity amputations within 35 days. Therefore, invasive ulcer depth and C-reactive protein levels are significant risk factors. Other potential risk factors for major amputation and the time intervals from first hospitalisation to amputation should be analysed to establish further prediction strategies.

KEYWORDS
amputation, diabetes mellitus, diabetic foot, lower extremity, risk factors

Key Messages
• diabetes-related lower extremity amputations are an enormous burden on global health care and social resources because of the rapid worldwide growth of the diabetic population
1 | INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent and debilitating metabolic disorders, and its high incidence is sustained in most countries.\(^1\) Recently, the total number of DM patients has reached approximately 463 million, and it is predicted to exceed 700 million by 2045.\(^2\) The defining clinical characteristic of DM is abnormal blood glucose regulation with deficient insulin signalling over a prolonged period of time.\(^3\) Patients with DM experience many disabling and even life-threatening complications. The major complications resulting in disability and mortality for DM patients are diabetic foot ulcers (DFUs), long-term cardiovascular disease, neural disease, and renal failure.\(^4\) DFUs are recognised as markers of increased mortality rates by the International Working Group on the Diabetic Foot.\(^5\) DFUs comprise a full-thickness wound penetrating the dermis and a combination of peripheral neuropathy and peripheral vascular disease; furthermore, they often deteriorate into serious infections.\(^6\) The healing of DFUs is difficult because of the lack of haemoglobin A1c (HbA1c) control and poor blood circulation, which lead to insufficient oxygen and nutrient supplies.\(^7\) Because of their poor healing and associated recurrent infections, DFUs weaken the immune system, subsequently resulting in a greater risk of lower extremity amputations (LEAs).\(^8\)

During the past 5 years, the risk of LEAs increased to 56% because of poorly healing DFUs. Nearly 130,000 LEAs in the United States are performed annually for DM patients, and the mortality rate of LEA patients is approximately 70%.\(^8,9\) Diabetes-related LEAs create an enormous burden on global health care and social resources because of the rapid worldwide growth of the diabetic population.\(^10\) Among the numerous diabetes patients with DFUs, several risk factors for LEAs have been studied and suggested as characteristics that require preventive health care; these risk factors include bony invasions, dialysis, and gastrointestinal disorders.\(^11,12\) Retrospective cross-sectional studies have provided inconsistent results because of different selective biases and inherent limitations.\(^13\) However, risk factors for amputation analysed using the time interval from first hospitalisation to amputation may help further estimate the severity of DFUs and determine further medical predictions and strategies.\(^14\)

This longitudinal research study used standard management protocols and Kaplan–Meier (KM) survival curves to determine the risk factors that predict major amputation and analyse the time interval from first hospitalisation to amputation.

2 | MATERIALS AND METHODS

2.1 | Management protocol

Patients were hospitalised with severe DFUs or severely infected ulcers. Outpatient clinic-based treatment was not possible. Patients who required surgical debridement with systemic intravenous antibiotic therapy were also hospitalised, and some required immediate angioplasty because of severe vasculopathy. General serological tests of blood glucose and other ambulatory markers were performed.

Percutaneous transluminal angioplasty was performed for patients with peripheral arterial disease. Deep tissue cultures were performed to manage the wound bioburden and adjust antibiotic treatment. Serial surgical debridement was performed according to the wound condition whenever necessary during therapy. Patients were discharged when outpatient treatment was possible. If the wound condition worsened despite appropriate treatment for more than 4 weeks and if the wound could not be closed by a split-thickness skin graft, then a full-thickness skin graft, local flap, or minor amputation were considered before major amputation to prevent exacerbation of the general condition.

2.2 | Patients

A retrospective cohort study was conducted to collect clinical data from 246 DM patients who visited the Division of Plastic and Reconstructive Surgery of the Department of Surgery at XXX Hospital. Thirty-five patients
who attended the clinic for other management purposes and those with incomplete medical records were excluded from the study. Although there is no specific International Classification of Diseases 10th revision (ICD-10) code for diabetic foot complications, our patient inclusion criteria followed the ICD-10 codes for diabetic foot complications based on the study by Lauterbach et al\textsuperscript{15}:

- ICD-10 code E10 indicates insulin-dependent DM (type 1).
- ICD-10 code E11 indicates non-insulin-dependent DM (type 2).
- ICD-10 code E13 indicates other DM.
- ICD-10 codes E10621, E11621, and E13621 were used for DM with DFUs.
- ICD-10 codes E1052, E1152, and E1352 were used for DM with gangrene, and code I702 was defined as the occurrence of atherosclerosis.
- ICD-10 codes E1069, E1169, and E1369 were used for DM with other specified complications (M726 for necrotizing fasciitis and M86 for osteomyelitis).
- ICD-10 codes E10628, E11628, and E13628 were used for DM with other skin complications (L03115 for cellulitis of the right lower limb and L03116 for cellulitis of the left lower limb).
- ICD-10 codes E105, E115, and E135 were used for DM with circulatory complications.

Finally, 211 patients (147 men and 64 women) with a confirmed diagnosis of either type 1 or type 2 DM and an average age of 67 years were successfully observed until complete recovery. Among the included patients, 44 potential risk factors that were considered demographic and clinical characteristics of patients in the amputation and non-amputation groups were investigated to analyse the probability of amputation.

2.3 | Outcome measures

We used code ICD-10-PCS “0Y6...” in the surgical records to determine whether the patients underwent amputation. All patients with a diagnosis of defined diabetic complications or foot problems at the time of the first hospitalisation (baseline) were recorded and continuously tracked for amputation between January 2016 and May 2020.

2.4 | Independent variables

Baseline characteristics and time-dependent variables were collected and analysed in this study. Potential risk factors for amputation included sex, age, type of diabetes, pre-treatment, smoking, height, weight, ulcer cause (trauma or pressure), ulcer side, ulcer depth, ulcer location, ulcer level (forefoot, midfoot, hindfoot, or above the ankle), inflammatory signs, cardiac disorder, hypertension, pulmonary disorder, gastrointestinal disorder, ophthalmic disorder, hepatobiliary disorder, central nervous system disorder, musculoskeletal disorder, arthritis, malignant tumour, metabolic disorder, acute myocardial infarction, ischemic heart disease, cerebrovascular accident, chronic kidney disease, peripheral vascular disease, osteomyelitis, white blood cell count, platelet count, haemoglobin level, glucose level, blood urea nitrogen level, creatinine level, aspartate aminotransferase level, C-reactive protein (CRP) level, alanine transaminase level, erythrocyte sedimentation rate, albumin level, and HbA1c level.

2.5 | Statistical analyses

Categorical data regarding the frequency, percentage, mean (±SD), and interquartile range for continuous variables are presented. A Cox proportional hazards regression model was used to analyse the correlation between the predictors and amputation. Potentially significant risk factors were chosen using univariate Cox regression models with a value of $P < .05$ during the initial multivariable analyses. In the multivariable analyses, risk factor variables for amputation with a two-sided $P < .05$ were considered statistically significant. Hazard ratios (HRs) were also used to quantify the relationship between the predictors and amputation. A survival curve for amputation was performed using the KM survivor function to demonstrate and analyse the time interval from the first hospitalisation to amputation.

3 | RESULTS

The overall demographics and clinical characteristics of 211 patients were collected during the analysis. Of these patients, 69.7% were male ($n = 147$) and 30.3% were female ($n = 64$); their mean (SD) age was 67.39 years (13.45 years) (Table 1). Most patients (98.1%) were diagnosed with type 2 DM. Patients were categorised into the amputation group ($n = 85$; 40.3%) or the non-amputation group ($n = 126$; 59.7%) at the end of this study. The mean (SD) age of the amputation cohort was 66.91 years (14.44 years). Ulcers invading the bone were the most common indicator for amputation (45.2% of 76 patients with ulcers invading the bone), compared with ulcers invading the tendon/joint (22.6% of 38 patients with...
| Characteristics                      | Total patients (n = 219) | Non-amputation (n = 131) | Amputation (n = 88) | P-value |
|--------------------------------------|--------------------------|--------------------------|---------------------|---------|
| **Sex**                              |                          |                          |                     | .853*   |
| Male                                 | 149 (68.0)               | 88 (59.1)                | 61 (40.9)           |         |
| Female                               | 70 (32.0)                | 43 (61.4)                | 27 (38.6)           |         |
| **Age, years**                       | 67.35 ± 13.43            | 67.59 ± 12.85            | 66.98 ± 14.32       | .738b   |
| **Type of diabetes**                 |                          |                          |                     | .924*   |
| 1                                    | 4 (1.8)                  | 3 (75.0)                 | 1 (25.0)            |         |
| 2                                    | 217 (98.2)               | 130 (59.9)               | 87 (40.1)           |         |
| **Pre-treatment**                    |                          |                          |                     | .568a   |
| No                                   | 87 (49.2)                | 53 (60.9)                | 34 (39.1)           |         |
| Yes                                  | 90 (50.8)                | 50 (55.6)                | 40 (44.4)           |         |
| **Smoker**                           |                          |                          |                     | .139a   |
| No                                   | 152 (69.7)               | 96 (63.2)                | 56 (36.8)           |         |
| Yes                                  | 66 (30.3)                | 33 (50.0)                | 33 (50.0)           |         |
| **Height, cm**                       | 165.49 ± 8.40            | 164.83 ± 9.35            | 166.38 ± 6.91       | .248b   |
| **Weight, kg**                       | 68.99 ± 15.19            | 69.4 ± 16.14             | 68.53 ± 13.87       | .724b   |
| **Cause**                            |                          |                          |                     | .865a   |
| Trauma                               | 54 (27.4)                | 32 (59.3)                | 22 (40.7)           |         |
| Pressure                             | 143 (72.6)               | 81 (56.6)                | 62 (43.4)           |         |
| **Side**                             |                          |                          |                     | .629a   |
| Left                                 | 102 (48.6)               | 61 (59.8)                | 41 (40.2)           |         |
| Right                                | 108 (51.4)               | 60 (55.6)                | 48 (44.4)           |         |
| **Depth**                            |                          |                          |                     | <.001a  |
| Dermis                               | 0                        | 0                        | 0                   |         |
| Subcutaneous tissue                 | 59 (33.3)                | 43 (72.9)                | 16 (27.1)           |         |
| Tendon/joint                         | 39 (22.0)                | 27 (69.2)                | 12 (30.8)           |         |
| Bone                                 | 79 (44.6)                | 26 (32.9)                | 53 (67.1)           |         |
| **Location**                         |                          |                          |                     | .612a   |
| Dorsal foot                          | 42 (21.1)                | 22 (52.4)                | 20 (47.6)           |         |
| Plantar foot                         | 50 (25.1)                | 31 (62.0)                | 19 (38.0)           |         |
| Border                               | 107 (53.8)               | 59 (55.1)                | 48 (44.9)           |         |
| **Level**                            |                          |                          |                     | .463a   |
| Forefoot                             | 113 (62.8)               | 57 (50.4)                | 56 (49.6)           |         |
| Midfoot                              | 22 (12.2)                | 14 (63.6)                | 8 (36.4)            |         |
| Hindfoot                             | 19 (10.6)                | 12 (63.2)                | 7 (36.8)            |         |
| Above the ankle                      | 26 (14.4)                | 16 (61.5)                | 10 (38.5)           |         |
| **Inflammatory signs**               |                          |                          |                     | .139a   |
| No                                   | 8 (4.1)                  | 7 (87.5)                 | 1 (12.5)            |         |
| Yes                                  | 189 (95.9)               | 103 (54.5)               | 86 (45.5)           |         |
| **Cardiac disorder**                 | 116 (53.2)               | 68 (59.8)                | 48 (40.2)           | .969a   |
| Hypertension                         | 161 (73.9)               | 89 (55.3)                | 72 (44.7)           | .070a   |
| Pulmonary disorder                   | 22 (10.1)                | 12 (54.5)                | 10 (45.5)           | .813a   |
| Renal disorder                       | 83 (38.1)                | 45 (54.2)                | 38 (45.8)           | .305a   |
| GI disorder                          | 32 (14.7)                | 19 (59.4)                | 13 (40.6)           | 1.000a  |

* Significant at the 0.05 level.
| Characteristics                  | Total patients (n = 219) | Non-amputation (n = 131) | Amputation (n = 88) | P-value |
|---------------------------------|--------------------------|--------------------------|---------------------|---------|
| Hepatobiliary disorder          | 18 (8.3)                 | 11 (61.1)                | 7 (38.9)            | 1.000^a |
| Ophthalmic disorder             | 35 (16.1)                | 20 (57.1)                | 15 (42.9)           | .957^a  |
| CNS disorder                    | 14 (6.4)                 | 7 (50.0)                 | 7 (50.0)            | .659^a  |
| Arthritis                       | 16 (7.4)                 | 11 (68.8)                | 5 (31.3)            | .575^a  |
| Musculoskeletal disorder        | 20 (9.2)                 | 11 (55.0)                | 9 (45.0)            | .873^a  |
| Genitourinary disorder          | 15 (6.9)                 | 7 (46.7)                 | 8 (53.3)            | .454^a  |
| Metabolic disorder              | 7 (13.2)                 | 7 (100.0)                | 0                   | .182^a  |
| Malignant tumour                | 11 (5.0)                 | 6 (54.5)                 | 5 (45.5)            | .995^a  |
| Ischemic heart disease          | 48 (22.0)                | 21 (43.8)                | 27 (56.3)           | .022^a  |
| Acute myocardial infarction     | 28 (12.8)                | 10 (35.7)                | 18 (64.3)           | .012^a  |
| Cerebrovascular accident        | 22 (10.1)                | 9 (40.9)                 | 13 (59.1)           | .108^a  |
| Chronic kidney disease          | 88 (40.4)                | 47 (53.4)                | 41 (46.6)           | .199^a  |
| Peripheral vascular disease     | 120 (54.1)               | 64 (53.3)                | 56 (46.7)           | .042^a  |
| Osteomyelitis                   | 31 (14.0)                | 16 (51.6)                | 15 (48.4)           | .413^a  |
| WBCs (× 10^3)/μL                |                          |                          |                     | .171^a  |
| Normal                          | 94 (45.4)                | 51 (54.3)                | 43 (45.7)           |         |
| Abnormal                         | 113 (54.6)               | 73 (64.6)                | 40 (35.4)           |         |
| Hb (g/dL)                       |                          |                          |                     | .465^a  |
| Normal                          | 145 (70.0)               | 84 (57.9)                | 61 (42.1)           |         |
| Abnormal                         | 62 (30.0)                | 40 (64.5)                | 22 (35.5)           |         |
| Platelets (× 10^3)/μL           |                          |                          |                     | .734^a  |
| Normal                          | 56 (27.2)                | 35 (62.5)                | 21 (37.5)           |         |
| Abnormal                         | 150 (72.8)               | 88 (58.7)                | 62 (41.3)           |         |
| Glucose (mg/dL)                 |                          |                          |                     | .635^a  |
| Normal                          | 201 (97.6)               | 119 (59.2)               | 82 (40.8)           |         |
| Abnormal                         | 5 (2.4)                  | 4 (80.0)                 | 1 (20.0)            |         |
| BUN (mg/dL)                     |                          |                          |                     | 1.000^a |
| Normal                          | 93 (46.7)                | 57 (61.3)                | 36 (38.7)           |         |
| Abnormal                         | 106 (53.3)               | 64 (60.4)                | 42 (39.6)           |         |
| Creatinine (mg/dL)              |                          |                          |                     | .169^a  |
| Normal                          | 154 (74.8)               | 88 (57.1)                | 66 (42.9)           |         |
| Abnormal                         | 52 (25.2)                | 36 (69.2)                | 16 (30.8)           |         |
| AST (U/L)                       |                          |                          |                     | .365^a  |
| Normal                          | 19 (9.7)                 | 9 (47.4)                 | 10 (52.6)           |         |
| Abnormal                         | 177 (90.3)               | 108 (61.0)               | 69 (39.0)           |         |
| ALT (U/L)                       |                          |                          |                     | .273^a  |
| Normal                          | 10 (5.4)                 | 4 (40.0)                 | 6 (60.0)            |         |
| Abnormal                         | 174 (94.6)               | 109 (62.6)               | 65 (37.4)           |         |
| CRP (mg/dL)                     |                          |                          |                     | .515^a  |
| Normal                          | 151 (87.3)               | 88 (58.3)                | 63 (41.7)           |         |
| Abnormal                         | 22 (12.7)                | 15 (68.2)                | 7 (31.8)            |         |
| ESR (mm/h)                      |                          |                          |                     | .501^a  |
| Normal                          | 60 (96.8)                | 30 (50.0)                | 30 (50.0)           |         |

(Continues)
ulcers invading the tendon/joint) and ulcers invading subcutaneous tissue (32.1% of 54 patients with ulcers invading subcutaneous tissue). Amputation rates were significantly higher in patients with ischemic heart disease (55.3% of 47 patients; \( P = .037 \)) and acute myocardial infarction (63.0% of 27 patients; \( P = .023 \)).

During this study, 40.3% (85 of 211) of patients underwent amputation. The major amputation-free survival rate for the amputation group was demonstrated using KM survival curves (Figure 1A). The median time from hospitalisation to major amputation was 35 days (interquartile range, 29.2-40.8 days). Major amputation results were analysed using univariate and multivariate analyses (Table 2). Of the 44 risk factors in the univariate analysis, ulcer depth and CRP level were significantly correlated with an increased risk of major amputation (\( P < .05 \)). Potentially significant risk factors for major amputation, including CRP level (HR, 0.248; 95% confidence interval [CI], 0.096-0.638; \( P = .004 \)) and ulcer depth (bone vs subcutaneous tissue; HR, 2.258; 95% CI, 1.135-4.494; \( P = .020 \)), were also significantly correlated in the multivariable analyses. The major amputation-free survival rate was as low as approximately 0% at 39 days in the amputation group with abnormal CRP levels (Figure 1B). The major amputation-free survival rate was approximately 30% at 35 days in the amputation group with deep ulcers invading the bone (Figure 1C).

4 | DISCUSSION

Previous studies have indicated that DM increases the risk of diabetes-related LEAs by 20-fold, which may cause disability, affect quality of life, increase burden and medical expenditures, and further influence the entire health care system. Various risk factors, such as Wagner grade, dementia, leukocytosis, and peripheral arterial occlusive disease, have been investigated extensively and have been identified as characteristics that are possibly associated with diabetes-related LEAs and can predict the probability of amputation. However, each predictor may yield inconsistent results with different study

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**TABLE 1 (Continued)**

| Characteristics | Total patients (n = 219) | Non-amputation (n = 131) | Amputation (n = 88) | \( P \)-value |
|-----------------|--------------------------|--------------------------|---------------------|-------------|
| Abnormal       | 2 (3.2)                  | 2 (100.0)                | 0 (0)               |             |
| Albumin (g/dL) |                          |                          |                     | .681*       |
| Normal         | 104 (75.9)               | 63 (60.6)                | 41 (39.4)           |             |
| Abnormal       | 33 (24.1)                | 18 (54.5)                | 15 (45.5)           |             |
| HbA1c (%)      |                          |                          |                     | .486*       |
| Normal         | 123 (91.1)               | 74 (60.2)                | 49 (39.8)           |             |
| Abnormal       | 12 (8.9)                 | 9 (75.0)                 | 3 (25.0)            |             |

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; Hb, haemoglobin; HbA1c, haemoglobin A1c; SD, standard deviation; WBC, white blood cell.

*aChi-square test.

*bIndependent Student’s \( t \)-test. Values are presented as number (%) or mean ± SD.

**FIGURE 1** Major amputation-free survival for the amputation cohort. A, The Kaplan–Meier (KM) survival curve demonstrates survival for the amputation cohort. B, The KM survival curves indicate survival for the amputation cohort with normal and abnormal C-reactive protein (CRP) levels. C, The KM survival curves show major amputation-free survival for the amputation cohort with deep ulcers with different depths of invasion.
| Independent variables | Amputation |  |  |  |
|-----------------------|------------|---|---|---|
|                       | Univariate analysis | Multivariate analysis |  |
|                       | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Sex                   |  |  |  |  |
| Male                  | Ref.       |  | Ref.       |  |
| Female                | 1.556 (0.961-2.520) | .072 |  |  |
| Age                   | 1.015 (0.998-1.033) | .084 |  |  |
| Type of diabetes      |  |  |  |  |
| 1                     | Ref.       |  | Ref.       |  |
| 2                     | 0.570 (0.078-4.145) | .579 |  |  |
| Pre-treatment         |  |  |  |  |
| No                    | Ref.       |  | Ref.       |  |
| Yes                   | 1.374 (0.857-2.203) | .187 |  |  |
| Smoker                |  |  |  |  |
| No                    | Ref.       |  | Ref.       |  |
| Yes                   | 1.088 (0.698-1.695) | .710 |  |  |
| Height                |  |  |  |  |
|  | 0.972 (0.936-1.010) | .142 |  |  |
| Weight                |  |  |  |  |
|  | 0.994 (0.975-1.014) | .545 |  |  |
| Cause                 |  |  |  |  |
| Trauma                | Ref.       |  | Ref.       |  |
| Pressure              | 1.300 (0.788-2.144) | .305 |  |  |
| Side                  |  |  |  |  |
| Left                  | Ref.       |  | Ref.       |  |
| Right                 | 1.001 (0.652-1.537) | .996 |  |  |
| Depth                 |  |  |  |  |
| Subcutaneous tissue   | Ref.       |  | Ref.       |  |
| Tendon/joint          | 1.023 (0.472-2.217) | .954 | 1.099 (0.461-2.617) | .832 |
| Bone                  | 1.932 (1.065-3.505) | .030 | 2.258 (1.135-4.494) | .020 |
| Location              |  |  |  |  |
| Dorsal foot           | Ref.       |  | Ref.       |  |
| Plantar foot          | 0.938 (0.485-1.814) | .849 |  |  |
| Border                | 1.223 (0.719-2.079) | .458 |  |  |
| Level                 |  |  |  |  |
| Forefoot              | Ref.       |  | Ref.       |  |
| Midfoot               | 0.524 (0.238-1.153) | .108 |  |  |
| Hindfoot              | 0.561 (0.236-1.334) | .191 |  |  |
| Above the ankle       | 0.511 (0.240-1.089) | .082 |  |  |
| Inflammatory signs    |  |  |  |  |
| No                    | Ref.       |  | Ref.       |  |
| Yes                   | 1.430 (0.199-10.299) | .723 |  |  |
| Cardiac disorder      | 0.970 (0.630-1.494) | .891 |  |  |
| Hypertension          | 1.622 (0.938-2.803) | .083 |  |  |
| Pulmonary disorder    | 0.965 (0.482-1.933) | .920 |  |  |
| Renal disorder        | 1.402 (0.907-2.169) | .129 |  |  |
designs. Population studies may also be affected by different inherent factors and social cultures. Moreover, health care quality and protocols vary among different studies. Few studies have investigated the risk factors that predict amputation and simultaneously evaluated the time interval from the first hospitalisation to amputation for patients with diabetes-related LEAs. Our data from the XXX Hospital between January 2016 and May 2020 demonstrated that the amputation rate in our study patients was approximately 40.1%, which was higher than those of previous studies (24.6% and 34.1%).\textsuperscript{13,14} The relatively high amputation rate in our study occurred because most patients with severe DFUs and debridement difficulty were advised to undergo amputation and presented to our medical centre for optional treatment according to the hierarchy of medical services in Taiwan. The patients included in the study had to be admitted for LEAs because they experienced severe DFUs for many years, and it was determined that there was no alternative method of saving the foot according to the rigorous limb

| Independent variables                | Univariate analysis | Multivariate analysis |
|--------------------------------------|---------------------|-----------------------|
|                                      | HR (95% CI)         | P-value               | HR (95% CI)         | P-value               |
| GI disorder                          | 0.742 (0.409-1.346) | .326                  |                       |                       |
| Hepatobiliary disorder               | 0.819 (0.377-1.782) | .615                  |                       |                       |
| Ophthalmic disorder                  | 0.833 (0.470-1.476) | .532                  |                       |                       |
| CNS disorder                         | 1.114 (0.506-2.453) | .788                  |                       |                       |
| Arthritis                            | 1.027 (0.414-2.545) | .955                  |                       |                       |
| Musculoskeletal disorder             | 1.269 (0.583-2.761) | .549                  |                       |                       |
| Genitourinary disorder               | 1.162 (0.533-2.534) | .706                  |                       |                       |
| Metabolic disorder                   | 0.039 (<0.001-27.920) | .333                  |                       |                       |
| Malignant tumour                     | 0.971 (0.392-2.405) | .950                  |                       |                       |
| Ischemic heart disease               | 1.438 (0.901-2.296) | .128                  |                       |                       |
| Acute myocardial infarction          | 1.051 (0.610-1.811) | .857                  |                       |                       |
| Cerebrovascular accidents            | 1.513 (0.817-2.804) | .188                  |                       |                       |
| Chronic kidney disease               | 0.977 (0.633-1.509) | .917                  |                       |                       |
| Peripheral vascular disease          | 1.375 (0.882-2.143) | .159                  |                       |                       |
| Osteomyelitis                        | 1.368 (0.780-2.399) | .274                  |                       |                       |
| WBC                                  | 0.825 (0.535-1.271) | .383                  |                       |                       |
| Hb                                    | 0.996 (0.612-1.620) | .986                  |                       |                       |
| Platelet                             | 0.722 (0.439-1.189) | .201                  |                       |                       |
| Glucose                              | 2.651 (0.368-19.088) | .333                  |                       |                       |
| BUN                                   | 0.958 (0.611-1.502) | .851                  |                       |                       |
| Creatinine                           | 1.215 (0.711-2.077) | .477                  |                       |                       |
| AST                                   | 1.018 (0.537-1.931) | .956                  |                       |                       |
| ALT                                   | 1.206 (0.520-2.798) | .662                  |                       |                       |
| CRP                                  | 0.399 (0.177-0.896) | .026                  | 0.248 (0.096-0.638) | .004                  |
| ESR                                  | 21.400 (0.002-203333.076) | .512                  |                       |                       |
| Albumin                              | 0.680 (0.371-1.244) | .211                  |                       |                       |
| HbA1c                                | 1.076 (0.333-3.476) | .903                  |                       |                       |

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CI, confidence interval; CNS, central nervous system; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; Hb, haemoglobin; HbA1c, haemoglobin A1c; HR, hazard ratio; WBC, white blood cell.
salvage policy. All efforts to save the limb using minor amputation, skin grafts, and serial debridement were performed before the patients finally decided to undergo LEAs.

In this longitudinal study, out of 44 risk factors in our multivariate stepwise logistic regression analysis, invasive ulcer depth and CRP level were identified as the most significant risk factors predicting diabetic LEAs. The invasive depth of the ulcers was separated into four categories (dermis, <5 mm; subcutaneous tissue, 5-10 mm; tendon/joint, 10-20 mm; bone, >20 mm) in the SIDESTEP study to determine the prognosis.20 Namgoong et al found that severe ulcers with bone invasion resulted in a high risk for major amputation in DM patients; this was consistent with our clinical observations.12

Increased CRP levels in serum are widely associated with infection, inflammation, tissue necrosis, autoimmune disorders, and severe infectious diseases such as dengue and coronavirus disease 2019 (COVID-19) pneumonia.21,22 Although CRP is not specific, it is still used as an important management guide and potential predictor for many diabetic diseases. CRP levels have a good response to diabetic foot disease monitoring and have been reported to be more effective and sensitive after appropriate therapy than the erythrocyte sedimentation rate.23 In our study, the univariate and multivariate analyses demonstrated that the baseline CRP levels of patients with long-term DM were strongly predictive indicators for major amputation.

Previous studies of the potential influences of hypertension, fasting blood glucose level, and HbA1c level on the increased rate of LEAs in DM patients with foot complications showed conflicting results; therefore, further clinical data and evidence are needed.24-26 Hypertension was an insignificant predictor of amputation during our study, which is consistent with the findings of Gürlek et al.27 Some studies indicated that patients with an average HbA1c ≤7.5% were at higher risk for LEA (approximately 52%) than those with an average HbA1c >7.5%. However, other studies showed that patients with an average HbA1c <7.5% were at lower risk for LEA (approximately 20%) than those with an average HbA1c >7.5%.28 Additionally, Kim et al indicated that patients with HbA1c levels ≤9% were at lower risk for LEA than patients with HbA1c levels >9% (39.7% with HbA1c ≤9% vs 42.9% with HbA1c >9%); however, this difference was not statistically significant.18

Some diseases, such as peripheral vascular disease, have been reported as potential risk indicators for LEA in patients with DM.29,30 However, our data showed non-statistically significant positive correlations with ischemic heart disease, acute myocardial infarction, and cerebrovascular accidents. These divergent results may be attributed to different management protocols and therapy during regular examinations during the healing process.

Statistical information regarding the time interval from first hospitalisation to amputation may be a helpful reference for physicians when making medical decisions and providing patients with their options. Furthermore, alternative treatment may be a potentially effective method of replacing amputation if the therapy duration exceeds the predictive time for amputation. Therefore, we used KM survival curves to determine and analyse the survival rates following amputation for our patients who underwent LEA. During our study, the median time from hospitalisation to LEA was approximately 35 days, and approximately 60% of patients underwent LEA within 50 days. Most patients with abnormal CRP levels underwent LEA within 35 days, as did approximately 70% of patients with deep ulcers invading the bone. The results suggested that most patients have approximately 30 to 50 days from the first hospitalisation to try alternative therapy. However, the time interval from the first hospitalisation to amputation based on various risk factors should be studied in more patients.

In conclusion, diabetes-related LEAs remain common medical and public health issues. Various potential risk factors such as the ulcer depth and CRP level of DM patients who require major amputation should be further studied and analysed along with the time intervals from first hospitalisation to amputation so that further medical predictions and strategies can be created.

ACKNOWLEDGEMENTS
The authors wish to thank members of the Burn Injury & Chronic Wound/Scar Care Center of Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, who provided ongoing support. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from Tri-Service General Hospital. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from Dr. Yu-Lung Chiu with the permission of Tri-Service General Hospital.

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How to cite this article: Chou Y-Y, Hou C-C, Wu C-W, et al. Risk factors that predict major amputations and amputation time intervals for hospitalised diabetic patients with foot complications. *Int Wound J.* 2022;19(6):1329-1338. doi:10.1111/iwj.13727