INTRODUCTION

Diabetic foot wound (DFW), including diabetic foot ulcer (DFU) and diabetic foot gangrene (DFG), is a relatively common complication of diabetic mellitus (DM). It has known to be the main cause of non-traumatic lower extremity amputation. Several studies have reported that diabetic patients have a 10-15 times risk of lower extremity amputation compared to patients without DM [1,2]. It has been estimated that approximately 15% of all diabetic patients...
develop DFU during their lifetime and 5% to 8% of DFU will require major amputation within one year despite of aggressive wound management treatment and recent advanced revascularization techniques, especially in patients with peripheral arterial occlusive disease (PAOD) [3-6]. DFG is also one of critical limb manifestations of DFW. It can be caused by PAOD or bacterial infections. In clinical practice, most DFGs require major amputation, such as below-knee amputation or above-knee amputation with poor functional prognosis because proper antibiotic treatment and aggressive wound management may not be effective. DFU is at increased risk of DFG mainly due to PAOD and foot infections [7,8]. Although most DFW patients have diabetic polyneuropathy, PAOD is also present in one-half of all DFU patients. It is considered an important predictor of overall outcomes [9-11].

DFW is not only a serious health problem, but also poses socioeconomic burden to the patient and the county because of prolonged hospitalization and rehabilitation time [12]. Therefore, early recognition and proper management of risk factors for amputation in DFW patients may reduce major amputations and prevent adverse outcome.

However, despite well-defined risk factors for the development of DFW, there are little data on overall amputation rates or predictors of DFW. Therefore, the objective of the present study was to evaluate overall amputation rates and risk factors of major amputation in DFW patients and in DFW with PAOD patients. In addition, in patients with DFU, overall rates of amputation and major amputation were investigated and potential predictors for amputation were also determined.

### Table 1. Clinical characteristics and risk factors for major amputation in DFW

| Risk factor                          | DFW (n=141) | Major amputation (n=37, 26.2%) | Univariate | Multivariate |
|--------------------------------------|-------------|--------------------------------|------------|-------------|
|                                      |             |                                | P-value    | P-value     |
| Age (y) ≥60                         | 86 (61.0)   | 27 (31.4)                      | 0.082      | 0.485       |
| Male                                 | 71 (50.4)   | 16 (22.5)                      | 0.314      | 0.227       |
| Site, right                          | 68 (48.2)   | 19 (27.9)                      | 0.658      | 0.787       |
| Wagner classification                |             |                                |            |             |
| Wagner grade 0                       | 3 (2.1)     | 0 (0.0)                        | 0.001      | 0.001       |
| Wagner grade 1                       | 19 (13.5)   | 0 (0.0)                        |            |             |
| Wagner grade 2                       | 1 (0.7)     | 0 (0.0)                        |            |             |
| Wagner grade 3                       | 50 (35.5)   | 5 (10.0)                       |            |             |
| Wagner grade 4                       | 45 (31.9)   | 9 (20.0)                       |            |             |
| Wagner grade 5                       | 23 (16.3)   | 23 (100.0)                     |            |             |
| Wound infection                      | 102 (72.3)  | 29 (28.4)                      | 0.339      | 0.476       |
| Hypertension                         | 92 (65.2)   | 25 (27.2)                      | 0.730      | 0.839       |
| DM control                           | 40 (28.4)   | 9 (22.5)                       | 0.525      | 0.690       |
| Insulin                              |             |                                |            |             |
| Coronary artery disease              | 36 (25.5)   | 14 (38.9)                      | 0.046      | 0.322       |
| Congestive heart failure             | 18 (12.8)   | 10 (55.6)                      | 0.002      | 0.028       |
| Cerebrovascular disease              | 35 (24.8)   | 11 (31.4)                      | 0.421      | 0.706       |
| Chronic kidney diseasea              | 31 (22.0)   | 11 (35.5)                      | 0.185      | 0.754       |
| COPD                                 | 41 (29.1)   | 13 (31.7)                      | 0.345      | 0.667       |
| Leukocytosis                         | 68 (48.2)   | 25 (36.8)                      | 0.006      | 0.047       |
| HbA1c >9                             | 40 (28.4)   | 10 (25.0)                      | 0.833      | 0.894       |
| Smoking                              | 81 (57.4)   | 21 (25.9)                      | 0.921      | 0.319       |
| Dementia                             | 23 (16.3)   | 10 (43.5)                      | 0.040      | 0.071       |
| Economic state                       | 79 (56.0)   | 24 (30.4)                      | 0.207      | 0.140       |
| PAOD                                 | 76 (53.9)   | 29 (38.2)                      | 0.001      | 0.034       |

Values are presented as number (%). DFU, diabetic foot wound; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.

*aGlomerular filtration rate <30.
MATERIALS AND METHODS

From January 2014 to December 2017, a total of 141 DFW patients who underwent lower extremity computed tomography (CT) angiography for assessing PAOD were enrolled in this study. First, all DFWs were classified into DFU group and DFG group based on clinical findings and its symptoms presented for the first time within six months. Next, we reclassified all DFWs according to Wagner classification [13] system based on clinical and radiologic findings. All DFW patients had aggressive wound dressing and/or debridement. They received initially empirical broad-spectrum antibiotics with specific antibiotics thereafter based on culture and sensitivity results if wound infection or concomitant osteomyelitis (OM) was suspected. In this study, the presence of PAOD was determined by findings of lower extremity CT angiography that indicated at least one severe stenotic or occlusive lesion of iliac arteries, femoropopliteal arteries, and tibioperoneal arteries. All CT angiography results were assessed by two board-certified radiologists specializing in vascular imaging. Based on findings of CT angiography, patients with PAOD were divided into three groups based on PAOD location: 1) proximal location defined as the iliac or femoropopliteal arteries involved, 2) distal location when tibioperonal arteries were involved and 3) multiple (proximal and distal) locations. PAODs were also classified into single arterial stenotic/occlusive lesion and multiple arterial stenotic/occlusive lesions. Basically, revascularization procedures were performed for proximal location of PAOD or when all run-off vessels showed significant stenosis or occlusion in patients with DFW and PAOD. In addition, demographic features and potential risk factors were investigated to predict major amputation in DFW group and amputation in DFU group, including age, gender, hypertension, coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular disease, chronic kidney disease (CKD), hemodialysis (HD), HbA1c, DM medication, concomitant OM, smoking status, and dementia. OM was confirmed based on the findings of magnetic resonance imaging and 3-phase bone scan in DFW patients with an ulcer when the tract extended to the bone and the presence of bony destruction and the involvement of periosteal and bone surface in foot X-ray.

In this study, we firstly determined overall rates of major amputation in patients with DFW and DFW with PAOD. Moreover, additional risk factors as independent predictors for major amputation were analyzed in DFW group and DFW with PAOD group using logistic regression model. Major amputation-free survival was also calculated in DFW and DFW with PAOD by Kaplan-Meier survival curves. Next, for DFU only group, we investigated rates of amputation and major amputation and then analyzed potential predictors that showed statistically significant correlations with amputation by univariate and multivariate analyses. Multivariate analysis was used to evaluate odds ratio (OR) for statistically significant correlation between potential risk factors and amputation or major amputation with 95% confidence interval (CI). A P-value of less than 0.005 was considered to indicate statistical significance. All statistical analyses were performed with IBM SPSS Statistics ver. 20.0 software (IBM Co., Armonk, NY, USA).

RESULTS

1) Major amputation in DFW

In this study, major amputation in patients with DFW

![Fig. 1. Major amputation-free survival rates for diabetic foot wound (DFW). (A) Kaplan-Meier survival curves showing major amputation-free survival rate for DFW; DFW patients are divided into two groups as diabetic foot ulcer and diabetic foot gangrene. (B) Kaplan-Meier survival curves demonstrating major amputation-free survival rate in DFW with and without peripheral arterial occlusive disease (PAOD).](https://doi.org/10.5758/vsi.2018.34.4.109)
was performed for 37 of 141 patients (26.2%). Moreover, the rates of major amputation in were 6.8% in DFU group and 47.1% in DFG group. Wound state according to Wagner classification grade, CAD, CHF, leukocytosis, dementia, and PAOD showed statistically significant differences between the non-major amputation group and the major amputation group (Table 1). Our multivariate analysis indicated that wound state (OR, 12.155; 95% CI, 3.427-43.106; P=0.001), CHF (OR, 4.486; 95% CI, 1.180-17.061; P=0.028), leukocytosis (OR, 2.661; 95% CI, 1.012-6.995; P=0.047), and PAOD (OR, 3.727; 95% CI, 1.101-12.615; P=0.034) were significant risk factors for major amputation in patients with DFW (Table 1). Major amputation-free survival was 83.9% at 1 year in DFW group and 56.7% at 1 year in DFW with PAOD group and showed statistically significant difference (P=0.001) (Fig. 1).

2) Major amputation in DFW with PAOD

Among a total of 141 DFW patients, 76 patients (53.9%) had PAOD and 29 of 76 PAOD patients (38.2%) underwent

| Table 2. Risk factors for major amputation in DFW with PAOD |
|-----------------|-----------------|-----------------|-----------------|
| Risk factor     | DFW with PAOD (n=76) | Major amputation (n=29, 38.2%) | Univariate | Multivariate |
| Age (y)         |                  |                               | P-value | P-value | OR (95% CI) |
| ≥60             | 64 (84.2)        | 25 (39.1)                   | 0.708   | 0.110   | 0.008-1.435 |
| Male            | 38 (50.0)        | 12 (31.6)                   | 0.238   | 0.080   | 6.096 (0.806-46.079) |
| Site, right     | 32 (42.1)        | 14 (43.8)                   | 0.392   | 0.595   | 1.557 (0.304-7.966) |
| Wound infection | 57 (75.0)        | 23 (40.4)                   | 0.495   | 0.375   | 0.363 (0.039-3.410) |
| Hypertension    | 52 (68.4)        | 19 (36.5)                   | 0.669   | 0.957   | 0.952 (0.154-5.885) |
| DM control      | 17 (22.4)        | 7 (41.2)                    | 0.771   | 0.126   | 5.436 (0.623-47.428) |
| Insulin         | 17 (22.4)        | 7 (41.2)                    | 0.392   | 0.375   | 0.363 (0.039-3.410) |
| Coronary artery disease | 26 (34.2) | 13 (50.0)                   | 0.125   | 0.074   | 5.502 (0.849-35.672) |
| Congestive heart failure | 15 (19.7) | 9 (60.0)                   | 0.052   | 0.171   | 4.259 (0.534-33.962) |
| Cerebrovascular disease | 20 (26.3) | 10 (50.0)                   | 0.204   | 0.398   | 2.402 (0.315-18.382) |
| Chronic kidney disease | 20 (26.3) | 10 (50.0)                   | 0.204   | 0.467   | 0.500 (0.077-3.240) |
| COPD            | 24 (31.6)        | 9 (37.5)                    | 0.936   | 0.589   | 1.681 (0.256-11.052) |
| Leukocytosis    | 42 (55.3)        | 22 (52.4)                   | 0.005   | 0.019   | 8.457 (1.410-50.716) |
| HbA1c >9        | 18 (23.7)        | 7 (38.9)                    | 0.942   | 0.855   | 1.231 (0.133-11.368) |
| Smoking         | 36 (47.4)        | 14 (38.9)                   | 0.901   | 0.884   | 0.867 (0.127-5.902) |
| Dementia        | 20 (26.3)        | 10 (50.0)                   | 0.204   | 0.167   | 3.859 (0.569-26.162) |
| Economic state  | 37 (48.7)        | 17 (45.9)                   | 0.173   | 0.247   | 2.847 (0.484-16.749) |
| PAOD location   |                  |                               | 0.802   | 0.705   | 0.046-10.812 |
| Proximal        | 7 (9.2)          | 3 (42.9)                    | 0.802   | 0.705   | 0.046-10.812 |
| Distal          | 27 (35.5)        | 9 (33.3)                    | 0.802   | 0.705   | 0.046-10.812 |
| Proximal & distal | 42 (55.3) | 5 (26.3)                    | 0.802   | 0.705   | 0.046-10.812 |
| Arterial stenotic/occlusive lesion | 61 (80.3) | 24 (39.3)                   | 0.668   | 0.802   | 0.705 (0.046-10812) |
| Multiple lesions | 61 (80.3) | 24 (39.3)                   | 0.668   | 0.802   | 0.705 (0.046-10812) |
| Revascularization | 16 (21.1) | 4 (25.0)                    | 0.223   | 0.156   | 4.415 (0.566-34.431) |
| Wagner classification | 0.001 | 0.003 | 97.257 (4.807-1,967.729) |
| Wagner grade 0  | 1 (1.3)          | 0 (0.0)                     | 0.001   | 0.003   | 97.257 (4.807-1,967.729) |
| Wagner grade 1  | 6 (7.9)          | 0 (0.0)                     | 0.001   | 0.003   | 97.257 (4.807-1,967.729) |
| Wagner grade 2  | 0 (0.0)          | 0 (0.0)                     | 0.001   | 0.003   | 97.257 (4.807-1,967.729) |
| Wagner grade 3  | 17 (22.4)        | 2 (11.8)                    | 0.001   | 0.003   | 97.257 (4.807-1,967.729) |
| Wagner grade 4  | 34 (44.7)        | 9 (26.5)                    | 0.001   | 0.003   | 97.257 (4.807-1,967.729) |
| Wagner grade 5  | 18 (23.7)        | 18 (100.0)                  | 0.001   | 0.003   | 97.257 (4.807-1,967.729) |

Values are presented as number (%).
DFW, diabetic foot wound; PAOD, peripheral arterial occlusive disease; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

*Glomerular filtration rate <30.
major amputation. Wound state according to Wagner classification grades (OR, 97.257; 95% CI, 4.807-1,967.729, \( P=0.003 \)) and leukocytosis (OR, 8.457; 95% CI, 1.410-50.716; \( P=0.019 \)) were found to be statistically significant predictors for major amputation in patients with DFW with PAOD by univariate and multivariate analyses (Table 2). In terms of PAOD location, proximal location in 7 patients (9.2%), distal location in 27 patients (35.5%), and multiple locations in 42 patients (55.3%) were found. Among 42 patients with multiple locations, 17 patients (40.5%) underwent major amputation. However, these findings did not show statistically significant relationship according to PAOD location. In this study, two-thirds of DFW patients with PAOD had multiple stenotic/occlusive lesions. Although the presence of multiple arterial stenotic/occlusive lesions showed higher rate of major amputation (33.3% in single arterial lesion vs. 39.3% in multiple arterial lesion), there was no statistically significant difference between two groups (\( P=0.668 \)). Moreover, vascular/endovascular procedure was performed in 16 of 76 DFW patients (21.1%) with PAOD and all procedures were clinically and radiologically successful. Rates of major amputation were 41.7% in non-vascular/endovascular procedure group and 25.0% in vascular/endovascular procedure group. In addition, we performed a subgroup analysis of PAOD patients except Wagner classification 5 (n=18) and bedridden state (n=3) to assess the effect of vascular/endovascular procedure on major amputation. Among 55 patients with DFW and PAOD, revascularization procedures were performed in 13 patients (23.6%) and major amputations were done in 9 patients (16.4%). The rates of major amputation were 16.7% in non-vascular/endovascular procedure group and 15.4% in vascular/endovascular procedure group. We did not find any statistical significances among two groups by univariate (\( P=1.000 \)) and multivariate (\( P=0.999 \)) analyses.

Freedom from major amputation was 62.2% at 1 year in no procedure group and 58.2% at 1 year in procedure group (\( P=0.321 \)) (Fig. 2). However, univariate or multivariate analysis for major amputation did not identify any statistical significance between the two groups (\( P=0.156 \)) (Table 2).

3) Amputation in DFU

Of 73 patients with DFU, amputation was performed for 28 patients (38.4%) while major amputation was performed for 5 patients (6.8%). Age (\( P=0.044 \)) and OM (\( P=0.021 \)) showed statistically significant differences between the non-amputation group and the amputation group (Table 3). Amputation-free survival rate was 68.3% at 1 year in non-OM group and 41.6% at 1 year in OM group (\( P=0.010 \)). The presence of PAOD of DFU patients showed similar rate in the amputation group (33.3% in non-amputation vs. 32.1% in amputation) and there was no significant difference between the presence of PAOD and amputation (\( P=0.916 \)).

DISCUSSION

DM is known to increase the risk of major amputation by 20 times [14]. However, few studies have evaluated amputation rates or predictors in overall DFW patients. Miyajima et al. [15] have reported that 45 of 210 patients (21.4%) with diabetic foot lesion require major amputation and atherosclerosis obliterans with multiple stenosis, HD, and HbA1C are risk factors for major amputation. In the present study, the overall rate of major amputation in patients with DFW was 26.4% with wound state according to Wagner classification grade, CHF, leukocytosis, dementia, and

Fig. 2. Major amputation-free survival rates for diabetic foot wound with peripheral arterial occlusive disease (PAOD). (A) Kaplan-Meier survival curves demonstrating major amputation-free survival rate in patients with PAOD as the presence of diabetic foot ulcer or diabetic foot gangrene. (B) Kaplan-Meier survival curves illustrating major amputation-free survival rate in PAOD patients with and without revascularization.

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PAOD being identified as significant risk factors for major amputation. These findings indicated that systemic factors such as CHF, leukocytosis, and dementia might affect major amputation in patients with DFW rather than local wound factors. Huang et al. [16] have also reported a major amputation rate of 57.3% in patients with infectious DFG. Our results showed similar rate of 47.1% in DFG (32 of 68 DFG patients). In addition, we also identified that wound state according to Wagner classification grades was a major predictor for major amputation in all DFW and DFW with PAOD, as previous studies reported that Wagner classification system was significantly correlated to the amputation in DFW [17,18]. Our current study demonstrated that about half of DFW patients (76 of 141 DFWs) had PAOD and 38.2% of all PAOD patients needed major amputation. Several studies have established that PAOD is a significant risk factor in diabetic foot lesions [15,16,19]. Our analyses also supported that the presence of PAOD was the predictor for major amputation in patients with DFW. In terms of PAOD severity, the major amputation group had higher rates of multiple locations and multiple arterial stenotic/occlusive lesions of PAOD. However, the present study failed to prove statistically significant relationship between major amputation and PAOD severity. Furthermore, current guideline recommends revascularization procedures with either bypass surgery or endovascular treatment for functional limb salvage in patients with diabetes and lower extremity wounds [20]. On the contrary, Claesson et al. [21] have reported that there is no difference in major amputation between conservative management and endovascular treatment or in unreconstructable patients. In our study, the rate of major amputation in DFW patients was lower in the vascular/endovascular procedure group (25.0% in procedure group vs. 41.7% in non-procedure group). However, subgroup analysis except extensive foot necrosis and bedridden state showed similar rate of major amputation between non-procedure group (16.7%) and procedure group (15.4%).

Severe CKD and dialysis are known to be independent risk factors for major amputation in DFW [15,22,23]. Our results showed that DFW patients with severe CKD and HD had higher rate of major amputation (35.5% in severe CKD and HD vs. 23.6% in non-severe CKD and HD). In addition, high HbA1c is a potential risk factor for non-healing and amputation in DFW. Good glycemic control is also important to reduce amputation risk [18,24,25]. We analyzed HbA1c >9% as a risk factor for amputation and found that HbA1c >9%
showed slightly higher rate of amputation in DFU patients (42.9% in HbA1c >9% vs. 39.7% in HbA1c ≤9%), although there was no statistical significance between the two groups. The EURODIALE study reported that 77% of DFU patients healed and 5% underwent major amputation [5]. However, among DFU patients healed, 17% underwent minor amputation. They also found that patients with PAOD and major amputation had worse wound rates with higher mortality rates in PAOD patients. Another large cohort study stated that overall amputation rate in patients with DFU was 37.1% with limb ischemia, OM, presence of gangrene, and ulcer depth being identified as major predictors of overall and major amputation [25]. Our present study showed that overall amputation and major amputation rates were 38.4% and 6.8%, respectively, in DFU patients, similar to the amputation rates reported in previous studies. Twenty-four of 79 DFU patients (32.9%) had PAOD. Our results revealed that DFU patients with the presence of PAOD had similar rate of amputation (amputation rate of 33.3%) compared to DFU patients without PAOD (amputation rate of 32.1%). In addition, more than half of DFU patients with OM underwent amputation and showed statistically significant difference between DFU with OM and DFU without OM. Previous studies have reported a significant association of OM with overall and major amputations although our multivariate analysis failed to be identified that OM was a major predictor for amputation in DFU patients. These findings indicated that the presence of deep infection involving the bone is a major risk factor for amputation in patients with DFU despite aggressive surgical debridement to control deep infection.

This present study has several potential limitations. First, the number of patients with DFW was small. Therefore, we found a relatively higher rate of major amputation. However, we failed to prove PAOD severity as a risk factor for major amputation, although the presence of PAOD was identified as a predictor for major amputation in patients with DFW. Second, it had a retrospective study design to investigate predictors for major amputation in DFW and amputation in DFU. Especially, the classification system for detailed local wound state including WIFI grading classification could not be applied to analyze risk factors for amputation. The presence of wound infection or OM was analyzed as potential predictors for amputation. Another limitation of this study was a relatively lower rate of vascular/endovascular procedure in patients with DFW and PAOD. Although the procedure group showed lower rate of major amputation, our analyses did not show statistically significant correlation between vascular/endovascular procedure and major amputation. This result might be caused by the small number of patients and the lower rate of vascular/endovascular procedure in DFW patients with PAOD.

In conclusion, our findings showed that 37 of 141 DFW patients (26.2%) underwent major amputation with wound state by Wagner classification system, CHF, leukocytosis, dementia, and PAOD as significant risk factors for major amputation. Moreover, over half of DFW patients had PAOD and about 38.2% of them underwent major amputation. Higher grade of Wagner classification and leukocytosis were found to be significant predictors for major amputation in patients with DFW with PAOD. In addition, among DFU patients, 38.4% underwent amputation. The presence of OM showed significant difference for amputation in DFU patients. In summary, our present study indicates that wound state and the presence of PAOD are major predictors for major amputation in patients with DFW. Moreover, systemic factors such as CHF, leukocytosis, and dementia can affect major amputation in DFW. In terms of DFU, local wound state, such as OM rather than systemic factors is a determinant for amputation.

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