EnM
Endocrinology and Metabolism

Original Article

Endocrinol Metab 2025;40:574-582
https://doi.org/10.3803/EnM.2024.2266
pISSN 2093-596X · eISSN 2093-5978

The Severity of Diabetes and the Risk of Diabetic Foot Amputation: A National Cohort Study

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Background: This study aimed to assess whether markers of diabetes severity could serve as predictors for foot amputation risk among patients with type 2 diabetes mellitus.

Methods: We analyzed data from the nationally representative Korean National Health Insurance System database, tracking 2,544,077 patients with type 2 diabetes mellitus who participated in routine health check-ups between 2009 and 2012, with follow-up extending through the end of 2018. The parameters used to define the diabetes severity score encompassed diabetes duration, insulin usage, the number of oral glucose-lowering medications, the presence of chronic kidney disease, diabetic retinopathy, and cardiovascular disease. Each factor was assigned one point, yielding a cumulative severity score ranging from 0 to 6.

Results: The risk of diabetic foot amputation was predominantly predicted by insulin therapy, diabetic retinopathy, and a prolonged duration of diabetes. The hazard ratios for foot amputation increased with the severity score as follows: 2.31 (95% confidence interval [CI], 2.15 to 2.47) for a score of 1, 4.73 (95% CI, 4.42 to 5.07) for a score of 2, 8.86 (95% CI, 8.24 to 9.53) for a score of 3, 16.95 (95% CI, 15.60 to 18.4) for a score of 4, 23.98 (95% CI, 21.25 to 27.05) for a score of 5, and 37.87 (95% CI, 28.93 to 49.57) for a score of 6.

Conclusion: Specific markers of advanced diabetes effectively identified patients at an elevated risk for diabetic foot amputation.

Keywords: Diabetes mellitus, type 2; Diabetic foot; Amputation, surgical

INTRODUCTION

Individuals with diabetes mellitus (DM) who develop foot ulcers face a 10- to 20-fold increased risk of amputation compared to those without DM. Furthermore, diabetic patients with a history of foot ulcers that have led to amputation experience even higher mortality rates than those without such complications [1-3]. Given that a previous episode of diabetic foot complications predisposes patients to future re-ulceration and amputation [1-3], it is crucial to prevent foot ulcers from developing in the first place. Therefore, establishing risk profiles is essential to identify high-risk patients who have not yet experienced a foot ulcer or

Received: 28 November 2024, **Revised:** 17 January 2025,
Accepted: 4 February 2025

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amputation.

A systematic review examining risk factors for diabetic foot complications consistently found that male sex, peripheral neuropathy, retinopathy, nephropathy, inadequate glycemic control, insulin therapy, longer diabetes duration, smoking, and increased height were positively correlated with these complications [2]. Excluding gender, height, and smoking, these factors also serve as indicators of diabetes severity [3-5]. Recently, a diabetes severity index was introduced that integrates insulin use, duration of diabetes, treatment complexity, and the presence of diabetic complications [4,5]. This suggests that identifying patients at risk for diabetic foot complications might be more effective when using markers of severe diabetes rather than focusing solely on poor glycemic control. In fact, one study reported no significant association between glycemic control and wound outcomes in diabetic patients [6]; neither baseline levels nor changes in glycosylated hemoglobin A1c (HbA1c) were clinically linked with wound healing in cases of diabetic foot ulcers.

The Korean National Health Information Database (NHID) is a comprehensive, prospective population-based cohort that includes detailed baseline biochemical measurements (e.g., fasting blood glucose [FBG], renal function) along with complete medical usage and prescription data for roughly five million individuals [7-10]. In this study, we utilized NHID data to examine the relationship between diabetes severity and the risk of diabetic foot amputation.

METHODS

Study population

The Korean National Health Insurance Service (NHIS) offers a single-payer insurance system covering all South Korean residents (approximately 50 million individuals) and provides free health examinations every 2 years. These examinations include anthropometric measurements, laboratory tests, health behavior surveys (covering smoking, alcohol consumption, and exercise habits), and medical as well as family histories, as previously described [7-10]. The NHID holds comprehensive health examination records for all insured individuals along with demographic details and diagnostic codes related to inpatient and outpatient services, which facilitates the evaluation of diabetes-related complications.

We included patients with type 2 DM aged 20 years or older who participated in the NHIS health examinations between 2009 and 2012 (n=2,745,689). We excluded individuals with missing data (n=171,129), those with a history of foot amputations (n=3,947), and individuals who experienced an amputation event or died during the first year of follow-up (n=26,536). This process resulted in a final cohort of 2,544,077 participants (Fig. 1). The Institutional Review Board of Yeouido St. Mary's Hospital, The Catholic University of Korea (No. SC23ZISE0043), approved this study. Anonymous and deidentified information was used for analysis and, therefore, informed consent was not obtained.

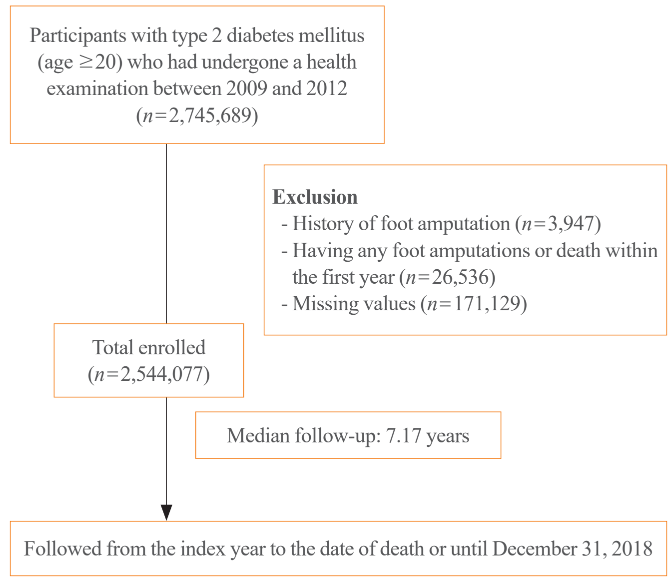

Fig. 1. Study flow chart.

Data collection and definitions

Covariate information was obtained from the health examinations conducted between 2009 and 2012 and encompassed variables such as age, sex, socioeconomic status (determined by income level), body mass index (BMI in kg/m²), current smoking status, alcohol use, exercise habits (yes/no), and both systolic and diastolic blood pressure (measured in mm Hg). Blood samples for serum glucose and creatinine levels were collected after an overnight fast. Glucose-lowering medications were categorized into six classes: insulin, sulfonylureas, metformin, thiazolidinediones, dipeptidyl-peptidase-4 inhibitors, and alpha-glucosidase inhibitors. Prescription details—including drug class, prescription date, duration of supply, and quantity dispensed—were also retrieved.

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2. Cardiovascular disease (CVD) was identified as a history of myocardial infarction or stroke, confirmed by one or more inpatient or outpatient International Statistical Classification of Diseases 10th Revision (ICD-10) codes within the 3 years preceding the index date [4,5,7,8]. Diabetic retinopathy was determined by the presence of the relevant ICD-10 code during hospitalization or by recording this code at least twice in an outpatient setting for patients with type 2 DM within 3 years prior to the index date [8].

Definition of parameters comprising the diabetes severity score

The components of the diabetes severity score in this study included the complexity of diabetes medications (specifically, insulin use or the use of multiple oral glucose-lowering drugs [GLDs]), an extended duration of diabetes, the presence of diabetic retinopathy, diabetes-associated renal complications (i.e., CKD), and the presence of CVD [4,5]. Each factor was assigned one point, resulting in a cumulative diabetes severity score ranging from 0 to 6. For example, if a patient was taking three or more oral GLDs, they were assigned one point; similarly, a diabetes duration of 5 years or more contributed one point. Thus, a patient on insulin with diabetic retinopathy and a diabetes duration of at least 5 years would have a severity score of 3.

Definition of diabetic foot amputation

The primary endpoint of the study was the occurrence of a new, nontraumatic foot amputation, identified using ICD-10 codes N0562, N0564-6, and N0571-5 [11]. Participants who did not undergo foot amputation were censored at the time of death or at the study's end, whichever occurred first. Follow-up continued from baseline until the date of death, foot amputation, or December 31, 2018, whichever came first. The median follow-up period was 7.17 years, with an interquartile range of 6.02 to 8.10 years.

Statistical analysis

All statistical analyses were conducted with SAS software version 9.4 (SAS Institute, Cary, NC, USA), considering a *P* value below 0.05 as statistically significant. Baseline characteristics are reported as mean±standard deviation or as counts (number) and percentages. Participants were categorized into seven groups based on their diabetes severity score. The incidence rate of foot amputations was determined by dividing the number of new cases by 1,000 person-years. Unadjusted Kaplan–Meier curves illustrated the cumulative incidence of the primary outcome by diabetes severity score, and differences between groups were assessed using the log-rank test. Cox proportional hazard models were utilized to explore the relationship between the diabetes severity score (and its individual components) and the incidence of foot amputation, yielding hazard ratios (HRs) with 95% confidence intervals (CIs). Model 1 adjusted for age and sex, while model 2 further adjusted for smoking status, alcohol consumption, regular exercise, BMI, hypertension, dyslipidemia, and depression. Potential effect modification by age, sex, and obesity was examined through stratified analyses and interaction testing using a likelihood ratio test.

RESULTS

Baseline characteristics

Patients who experienced foot amputations were older, predominantly male, and had higher rates of current smoking compared to those who did not undergo amputation (Table 1). Among type 2 DM patients, those who developed foot amputations exhibited higher FBG levels, reduced eGFR values, and a greater prevalence of CKD, diabetic retinopathy, and CVD. They were also more likely to be treated with insulin or to be on multiple oral GLDs.

Risk of diabetic foot amputation according to the clinical characteristics of type 2 DM

Table 2 presents the incremental risk of foot amputation corresponding to the presence or absence of each component of the DM severity score. All factors remained significantly associated with an elevated risk of foot amputation even after adjusting for confounding variables (Table 2). Among these, insulin use emerged as the strongest predictor (HR, 5.43; 95% CI, 5.18 to 5.69), followed by diabetic retinopathy (HR, 4.03; 95% CI, 3.84 to 4.23). A longer duration of diabetes was also an independent risk factor (HR, 3.79; 95% CI, 3.62 to 3.97) (Table 2). Both CKD and the use of three or more GLDs were linked to more than a 2-fold increase in foot amputation risk.

We further evaluated foot amputation risk in relation to the presence of peripheral artery disease (PAD), which has been recognized in earlier studies as a key factor in diabetic foot [2]. Both PAD (HR, 1.59; 95% CI, 1.51 to 1.67) and prior CVD (HR, 1.56; 95% CI, 1.47 to 1.66) were similarly associated with an elevated risk. Because CVD was already included in our analysis, PAD was not incorporated into the severity score.

Risk of diabetic foot amputation according to diabetes severity score

The foot amputation incidence rate was 0.173 per 1,000 person-years among patients with a diabetes severity score of zero. This rate increased progressively, reaching 1.576 per 1,000 person-

Table 1. Baseline Characteristics of the Study Participants

Characteristic	Diabetic foot amputation		*P* value
	No	Yes	
Number	2,535,606	8,471	
Age, yr	57.35±12.33	61.53±10.81	<0.001
Male sex	1,518,886 (59.9)	6,497 (76.7)	<0.001
Body mass index, kg/m^2	25.07±3.4	23.97±3.34	<0.001
Smoking			<0.001
Non-smoker	1,411,607 (55.67)	3,987 (47.07)	
Ex-smoker	468,160 (18.46)	1,595 (18.83)	
Current smoker	655,839 (25.87)	2,889 (34.1)	
Alcohol drinking	251,574 (9.92)	975 (11.51)	<0.001
Regular exercise	522,473 (20.61)	1,595 (18.83)	0.014
Income (lower 25%)	531,196 (20.95)	2,128 (25.12)	<0.001
Systolic BP, mm Hg	129.03±15.82	131.51±18.34	<0.001
Diastolic BP, mm Hg	79.05±10.27	78.8±11.12	0.022
Fasting glucose, mg/dL	144.57±46.65	176.12±82.17	<0.001
eGFR, mL/min/1.73 m^2	85.01±36.26	77.49±45.64	<0.001
Baseline TC, mg/dL	196.52±42.45	194.21±46.51	<0.001
Dyslipidemia	1,057,535 (41.71)	3,694 (43.61)	<0.001
Hypertension	1,434,044 (56.56)	5,908 (69.74)	<0.001
Chronic kidney disease	288,637 (11.38)	2,237 (26.41)	<0.001
Diabetic retinopathy	202,504 (7.99)	2,433 (28.72)	<0.001
Myocardial infarction	54,920 (2.17)	371 (4.38)	<0.001
Stroke	179,052 (7.06)	1,183 (13.97)	<0.001
Depression	253,386 (9.99)	1,221 (14.41)	<0.001
Duration of diabetes ≥5 years	774,843 (30.56)	5,608 (66.2)	<0.001
Pharmacologic therapy for DM			
Insulin	200,181 (7.89)	2,882 (34.02)	<0.001
No. of oral GLDs ≥3	337,701 (13.32)	2,431 (28.7)	<0.001
Medication			
Metformin	1,049,731 (41.4)	4,957 (58.52)	<0.001
Sulfonylurea	987,882 (38.96)	5,243 (61.89)	<0.001
DPP4-inhibitors	157,885 (6.23)	577 (6.81)	0.026
Thiazolidinedione	156,608 (6.18)	772 (9.11)	<0.001
Alpha-glucosidase inhibitors	281,430 (11.1)	2,310 (27.27)	<0.001

Values are expressed as mean±standard deviation or number (%).
BP, blood pressure; eGFR, estimated glomerular filtration rate; TC, total cholesterol; DM, diabetes mellitus; GLD, glucose-lowering drug; DPP4, dipeptidyl-peptidase 4.

years in patients with three severity factors and 6.546 per 1,000 person-years in those with all six factors (Table 3, Fig. 2). After adjusting for potential confounders, the HR for foot amputation rose with the number of severity parameters: 2.31 (95% CI, 2.15 to 2.47) for one parameter, 4.73 (95% CI, 4.42 to 5.07) for two, 8.86 (95% CI, 8.24 to 9.53) for three, 16.95 (95% CI, 15.60 to 18.4) for four, 23.98 (95% CI, 21.25 to 27.05) for five, and 37.87 (95% CI, 28.93 to 49.57) for six, relative to individuals with a severity score of zero.

Effect of FBG level on the risk of diabetic foot amputation in patients with type 2 DM

FBG was measured once during the baseline health check-ups conducted between 2009 and 2012. A J-shaped relationship emerged between glycemic control and foot amputation risk (Table 4), with the lowest risk occurring in the 120 to 139 mg/dL FBG range. In comparison, an FBG level below 100 mg/dL was associated with a higher risk (HR, 2.14; 95% CI, 1.94 to 2.35) relative to the 120 to 129 mg/dL range. Similarly, an FBG level of 180 to 189 mg/dL corresponded to nearly a 3-fold in-

Table 2. Risk of Diabetic Foot Amputation by Diabetes Characteristics Indicative of Severity

Variable	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)	
			Model 1	Model 2
Duration of diabetes, yr				
<5	2,863	0.236	1 (ref)	1 (ref)
≥5	5,608	1.045	4.03 (3.84–4.22)	3.79 (3.62–3.97)
No. of oral glucose-lowering drugs				
<3	6,040	0.399	1 (ref)	1 (ref)
≥3	2,431	1.026	2.40 (2.29–2.51)	2.21 (2.11–2.32)
Use of insulin				
No	5,589	0.345	1 (ref)	1 (ref)
Yes	2,882	2.151	6.02 (5.75–6.30)	5.43 (5.18–5.69)
Chronic kidney disease				
No	6,234	0.400	1 (ref)	1 (ref)
Yes	2,237	1.157	2.57 (2.44–2.70)	2.48 (2.36–2.61)
Cardiovascular disease				
No	7,026	0.438	1 (ref)	1 (ref)
Yes	1,445	0.984	1.78 (1.68–1.89)	1.56 (1.47–1.66)
Diabetic retinopathy				
No	6,038	0.375	1 (ref)	1 (ref)
Yes	2,433	1.739	4.34 (4.14–4.55)	4.03 (3.84–4.23)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, smoking, alcohol drinking, regular exercise, body mass index, hypertension, dyslipidemia, and depression history.
HR, hazard ratio; CI, confidence interval.

Table 3. Risk of Diabetic Foot Amputation according to Diabetes Severity Score

	Total	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)	
				Model 1	Model 2
0	1,380,356	1,647	0.173	1 (ref)	1 (ref)
1	598,973	1,706	0.409	2.30 (2.15–2.46)	2.31 (2.15–2.47)
2	337,767	1,979	0.851	4.83 (4.52–5.17)	4.73 (4.42–5.07)
3	155,387	1,648	1.576	9.19 (8.56–9.87)	8.86 (8.24–9.53)
4	56,318	1,083	2.986	17.87 (16.49–19.36)	16.95 (15.60–18.4)
5	13,785	352	4.178	25.69 (22.83–28.91)	23.98 (21.25–27.05)
6	1,491	56	6.546	41.59 (31.83–54.36)	37.87 (28.93–49.57)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, smoking, alcohol drinking, regular exercise, body mass index, hypertension, dyslipidemia, and depression history.
HR, hazard ratio; CI, confidence interval.

Table 4. The Risk of Diabetic Foot Amputation by Fasting Blood Glucose Category in Patients with Type 2 Diabetes Mellitus

Fasting blood glucose, mg/dL	No. of events	Incidence rate, /1,000 person-yr	HR (95% CI)	
			Model 1	Model 2
<100	1,110	0.668	2.39 (2.17–2.63)	2.14 (1.94–2.35)
100–109	410	0.364	1.33 (1.17–1.50)	1.25 (1.10–1.41)
110–119	548	0.416	1.52 (1.36–1.70)	1.46 (1.30–1.64)
120–129	677	0.242	1 (ref)	1 (ref)
130–139	733	0.218	0.94 (0.84–1.04)	0.95 (0.85–1.05)
140–149	562	0.285	1.20 (1.07–1.34)	1.20 (1.07–1.34)
150–159	516	0.407	1.70 (1.52–1.91)	1.69 (1.51–1.90)
160–169	401	0.467	1.96 (1.73–2.21)	1.92 (1.70–2.18)
170–179	378	0.609	2.57 (2.26–2.91)	2.51 (2.21–2.85)
180–189	335	0.711	3.03 (2.66–3.45)	2.94 (2.58–3.35)
190–199	277	0.759	3.28 (2.85–3.77)	3.17 (2.75–3.64)
≥200	2,524	1.479	6.80 (6.24–7.40)	6.27 (5.76–6.83)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, smoking, alcohol drinking, regular exercise, body mass index, hypertension, dyslipidemia, and depression history.
HR, hazard ratio; CI, confidence interval.

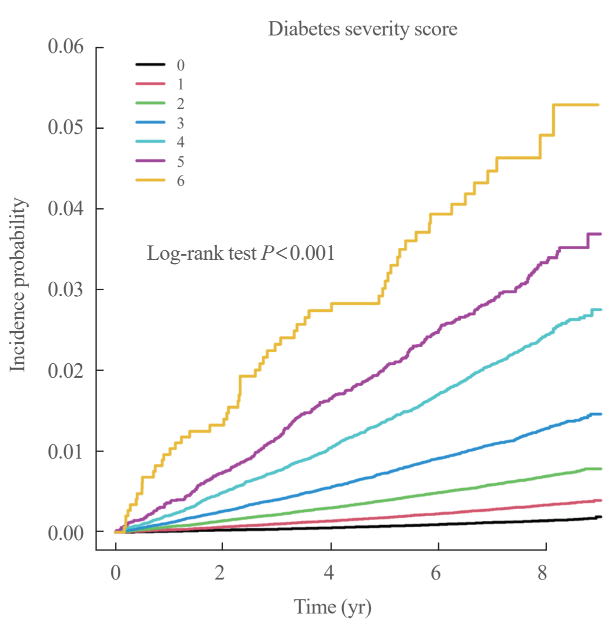

Fig. 2. Kaplan–Meier estimates of the cumulative incidence of diabetic foot amputation according to the diabetes severity score (0–6).

crease in risk (HR, 2.94; 95% CI, 2.58 to 3.35).

Subgroup analyses

Across all subgroups, a higher number of diabetes severity indicators was linked to an elevated risk of foot amputation (Supplemental Fig. S1). Notably, the association between the diabetes severity score and foot amputation risk was more pronounced in younger individuals (<65 years), women, and obese patients (all *P* values for interaction <0.001).

DISCUSSION

This study demonstrated that patients with a diabetes severity score of zero had a low foot amputation incidence rate of 0.173 per 1,000 person-years. In contrast, the rate increased to 1.576 per 1,000 person-years in those with three severity factors and reached 6.546 per 1,000 person-years in patients with all six factors. A diabetes severity score of 3 or higher elevated the risk of diabetic foot amputation by nearly 9-fold compared to those with a score of zero, while a score of 6 was associated with an almost 40-fold increased risk. Readily available clinical information—such as insulin use, treatment complexity, diabetes duration, and the presence of diabetic retinopathy or nephropathy—can thus aid in predicting the development of foot amputation in type 2 DM patients. Notably, the diabetes severity risk score can be derived from clinical data alone without additional laboratory tests. Additionally, our findings indicate that both hyperglycemia and hypoglycemia contribute to an increased risk of foot amputation, with the lowest risk observed in the FBG range of 120 to 139 mg/dL.

Insulin therapy often reflects the severity of diabetes because patients who cannot achieve glycemic control through lifestyle modifications or oral GLDs are typically transitioned to insulin. Although the link between age and foot complications is somewhat variable, the association between diabetes duration and foot complications remains consistently positive—even after adjustment for age [2]. This indicates that cumulative exposure to hyperglycemia over time may be more critical in developing diabetic foot complications than age *per se*.

Although one might expect a strong correlation between poor glycemic control and diabetes complications, existing findings are inconsistent. Recent reports have shown that patients undergoing major amputations spent significantly less time within the target glucose range (70 to 180 mg/dL) and more time below range (<70 mg/dL) [12]. Inpatient hypoglycemia has also been identified as an independent risk factor for amputations in patients with diabetic foot ulcers [13]. Our results indicate that both low (<100 mg/dL) and high (>140 mg/dL) FBG levels are linked to an elevated risk of diabetic foot amputation, underscoring the importance of optimal glycemic management. Although an FBG level below 100 mg/dL likely reflects mild hypoglycemia, the absence of data on severe hypoglycemia (e.g., <70 mg/dL) limits our ability to assess its impact. Future research incorporating more detailed glucose measurements and records of hypoglycemic episodes is needed to better understand this relationship. Hypoglycemia might simply indicate a more severe underlying illness, predisposing patients to a higher risk of amputation. For instance, one study found that hospitalized patients who experienced hypoglycemia were more frequently on dialysis for end-stage renal disease, had PAD, and were receiving insulin therapy [13]. Additionally, other research did not find a clinically significant association between baseline or changes in HbA1c and wound healing in diabetic foot ulcer patients [6]—possibly because HbA1c does not capture the nuances of hyperglycemia, hypoglycemia, or glucose variability as effectively as continuous glucose monitoring.

Our study also revealed a strong association between diabetic retinopathy and the risk of foot amputation, possibly attributable to a shared physiological basis. Diabetic neuropathy, like retinopathy and nephropathy, is a microvascular complication resulting from damage to small blood vessels [2,14]. Nevertheless, diabetic retinopathy exhibited a much stronger association with foot amputation risk compared to diabetic nephropathy. Previous longitudinal studies have linked poor vision to an increased likelihood of developing diabetic foot ulcers and subsequent amputations [3]. Inadequate perfusion in small blood vessels—closely associated with retinopathy—can hinder the healing of minor wounds, eventually leading to foot ulcers independent of neuropathy and macrovascular disease.

Could the occurrence of one diabetes complication predict the occurrence of another diabetic complication? Microvascular and macrovascular complications frequently coexist and share common risk factors and pathological mechanisms. However, the influence of macrovascular disease on the occurrence of microvascular events remains less clear. In type 2 DM patients, both microvascular and macrovascular diseases independently predict a 10-year risk of mortality, major adverse cardiovascular events, and significant clinical microvascular outcomes (such as end-stage renal disease or the need for retinal photocoagulation) [15]. The simultaneous presence of these conditions corresponds to the highest risk levels [15]. It appears that macrovascular disease exerts a weaker influence on major microvascular events than microvascular disease does on cardiovascular risk. Diabetic foot, regarded as a macrovascular complication secondary to arterial insufficiency, typically develops following foot ulceration or injury from diabetic neuropathy. In our analysis, diabetes severity—reflected by treatment complexity, diabetes duration, and the presence of diabetic retinopathy, nephropathy, and CVD—was robustly associated with an increased risk of foot amputation.

Our findings further indicate that the relationship between increasing diabetes severity and foot amputation risk was more consistent in younger individuals. This suggests that, in younger patients, diabetes itself may be the primary contributor to foot complications, whereas in older patients, other comorbid conditions might also influence the risk. Young-onset diabetes is often characterized by higher obesity rates, poorer adherence to treatment, a more rapid decline in beta-cell function, and earlier initiation of insulin therapy compared to later-onset type 2 DM [16,17]. Consequently, the adverse impact of diabetes on both morbidity and mortality is most pronounced in those diagnosed at a younger age [16,17].

This study has several limitations. First, as an observational investigation, the associations observed between severity parameters and outcomes may not imply causation. Second, we were unable to accurately assess the impact of diabetic neuropathy because the insurance claim database lacks precise diagnostic data for this condition. Third, data on HbA1c and postprandial glucose levels were not analyzed, as it is challenging to perform these tests on all participants in a mass screening context. Finally, although we classified the complexity of oral GLDs, we could not examine specific insulin regimens (e.g., basal-only vs. basal-bolus therapy) due to insufficient detailed data. Given that insulin dosing is often tailored dynamically to individual needs, consistent classification is further complicated. It is also important to note that individuals with type 1 DM were excluded from our study.

In summary, diabetic foot ulcers and subsequent amputations represent some of the most severe yet preventable complications of diabetes. In addition to regular foot examinations, enhanced strategies for prevention and early detection are imperative. A crucial component of prevention is the early identification of severe diabetes, enabling clinicians to pinpoint patients at high risk for foot complications [18]. We are confident that the diabetes severity score proposed in this study will prove valuable in this effort.

CONFLICTS OF INTEREST

Mee Kyoung Kim is a deputy editor of the journal. But she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

ACKNOWLEDGMENTS

This research was supported by grant from the Institute of Clinical Medicine Research in the Yeouido St. Mary's Hospital, The Catholic University of Korea. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. We would like to thank the Medical Library of the Catholic University of Korea for assisting with the manuscript formatting and the Research Support Team of the Catholic University of Korea for providing English proofreading support.

AUTHOR CONTRIBUTIONS

Conception or design: J.H.K., M.K.K. Acquisition, analysis, or interpretation of data: J.Y., J.H.K., B.K., K.H., S.H.L., M.K.K. Drafting the work or revising: J.Y., J.H.K., M.K.K. Final approval of the manuscript: J.Y., J.H.K., B.K., K.H., S.H.L., M.K.K.

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