Three Years Survival and Factor Predicting Amputation or Mortality in Patients with High Risk for Diabetic Foot Ulcer in Fatmawati General Hospital, Jakarta

Em Yunir1,2, Canggih Dian Hidayah3, Kuntjoro Harimurti4,5, and Ida Ayu Made Kshanti6

Abstract

Background: Diabetic foot is one of major complication in diabetes patients with unfavorable outcome. Survival study in outpatients is limited and factors related are inconsistent. Survival and its modifiable risk factors should be identified early since the foot at risk status to reduce amputation/mortality in type 2 diabetes mellitus (T2DM). Objective: The aims of this study were to investigate survival probability for amputation or mortality, compare different ulcer risk classification, and figure out the relation of status of ulcer risk, age, gender, diabetes duration, body mass index, fasting plasma glucose, HbA1C, and LDL with amputation or mortality. Methods: This is a retrospective cohort study of 487 T2DM subjects who visited internal medicine outpatient clinic in Fatmawati General Hospital since January-December 2016. Status of ulcer risk and risk factors were extracted from medical record and lower-extremity amputation or mortality was observed in 3 years from baseline. Result: Three years overall survival is 85.7% (SE 0.17). Patients with high risk for foot ulcer have survival probability of 80.2% (SE 0.027), which is lower compared to non-high risk for foot ulcer with survival probability of 91.8% (SE 0.019). Patients with high risk for foot ulcer (aHR 2.386 [95% CI 1.356-4.20]; P = .003), aged ≥60 years old (aHR 2.051 [95% CI 1.173-3.585]; P = .012), and HbA1C ≥7% (aHR 2.022 [95% CI 1.067-3.830]; P = .031) were independently associated with amputation or mortality. Conclusion. T2DM patients with high risk for foot ulcer have lower survival probability and higher risk for amputation or mortality in 3 years compared to patients with non-high risk for foot ulcer. Status of ulcer risk, age ≥60 years, and HbA1C ≥7% were associated with amputation or mortality in 3 years observation.

Keywords
diabetic foot, ulcer risk, survival, age, HbA1C, amputation, mortality, Jakarta

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1Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
2Metabolic, Cardiovascular and Aging Cluster, The Indonesian Medical Education and Research Institute, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
3Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
4Clinical Epidemiological Unit, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia
5Division of Geriatrics, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
6Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Fatmawati General Hospital, Jakarta, Indonesia

Corresponding Author: Em Yunir, Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jalan Diponegoro No. 71, Central Jakarta, Jakarta 10430, Indonesia.
Email: e.yunir@ui.ac.id
Introduction

Diabetes mellitus is one of the most prevalent chronic diseases. One study reported 463 million cases worldwide in 2019 and 16 million cases in Indonesia by 2018. This profound prevalence of diabetes ultimately increases prevalence of diabetes complication, such as diabetic foot—as one of its major devastating complication. The global prevalence of diabetic foot is 6.4% of all cases and 8.7% nationally. It is estimated that 1 out of 4 patients living with diabetes will soon develop ulcer in their lifetime that associated with high rate of hospital admission, medical cost, socioeconomic burden, and finally, mortality and morbidity. Diabetic foot could increase risk of limb or life threatening up to 2 times higher, and hence should have received serious attention.

International Working Group on Diabetic Foot (IWGDF) has provided a simple and implementable framework to classify patients with diabetic foot, according to patient-related factors, limb-related factors, and ulcer-related factors. This classification aimed for better risk assessment, prevention, management, and, later expected, long-term outcome of diabetic foot. Several other studies showed the importance of foot risk stratification, not only to prevent diabetic foot, but also to predict future major outcome in T2DM patients.

Studies reported that majority of T2DM patients were presented with various comorbidities, which could attribute to worse outcome, even though those factors are inconsistent among studies. Unfortunately, long-term outcome of T2DM patients with high risk for foot ulcer are not reported adequately in Indonesia. The present analysis aims to assess long-term outcome of T2DM patients with high risk for foot ulcer and the associated factors.

Methods

This was a cohort retrospective study as continuation of previous report “Diabetic Foot Ulcer in High Risk Patient: the Role of Internist in Providing Adequate Foot Care” by Kshanti et al. reviewing 487 outpatient’s medical records in Fatmawati General Hospital who visited internal medicine clinic during January to December 2016. The inclusion criteria for this study were: patients with T2DM, aged ≥18 years old, visiting the clinic during study period, and was registered to the previous research database. The exclusion criteria were unavailable medical records and unequipped data. Ethical clearance was obtained from hospital authority prior to the commencement of the study (number 11/KEP/III/2021).

The main outcome of this study was any amputation or mortality included in this study were age, sex, diabetes duration, any foot appearance that could lead to DFU (such as foot deformities, nail abnormalities, dry cracked skin, peripheral neuropathy, peripheral artery disease (PAD), and callus), body mass index (BMI), hypertension, fasting plasma glucose (FPG), HbA1C, LDL. Data regarding those risk factors were taken from subjects’ medical records at study entry, except for HbA1C and LDL were taking 6 months within study entry. We did not have reliable data on smoking, diet, physical activity, and socioeconomic profile including job or income.

According to IWGDF 2019 risk stratification system, Subjects were classified as high risk for ulcer if they exhibited either loss of protective sensation (LOPS) or PAD and at least 1 history of foot ulcer or lower-extremity amputation or end-stage renal disease. Subjects with very low, low or moderate risk for ulcer were classified as non-high risk. LOPS was assessed with a 10-g Semmes Weinstein monofilament and or the 128-Hz tuning fork. PAD was assessed with ankle brachial index (ABI) or Doppler ultrasound of lower extremity. The results of BMI was stratified using the World Health Organization (WHO) Asia-Pacific classifications. Hypertension was defined as JNC-8 categories. Glycemic control represented by HbA1C in percentage and FPG as our national guidelines: HbA1C ≥7% and FPG ≥130 mg/dl were classified as poor glycemic control, while HbA1C <7% and FPG <130 mg/dl were classified as good glycemic control. LDL level <100 mg/dl were classified as controlled dyslipidemia.

The minimum sample size required for this study was calculated based on comparison of survival in 2 group formula.

\[ n_1 = n_2 = \left( \frac{Z_{\alpha} + Z_{\beta}}{\sqrt{\theta_{\lambda_2} - \theta_{\lambda_1}}} \right) \]

\[ \theta_{\lambda} = \frac{\lambda^2}{(1 - e^{-\lambda t})} \]

\[ n_1 = n_2 = \left( 1.96 + 0.842 \right) \left( 0.022 + 0.062 \right) \left( 0.15 - 0.25 \right) \]

\[ \theta_{\lambda_1} = \frac{(0.25)^2}{(1 - e^{(0.25)t_{36}})} \]

\[ \theta_{\lambda_2} = \frac{(0.15)^2}{(1 - e^{(0.15)t_{36}})} \]

Consider that value of \( \alpha \), the probability of type I error (5%), value of \( \beta \), the probability of type II error or (1-power), the standard normal deviate for \( \alpha \) (Z\( \alpha \)), the standard normal deviate for \( \beta \) (Z\( \beta \)) with hazard assumption in patients with high risk for foot ulcer group (\( \lambda_2 \)) and patients with non-high risk for foot ulcer (\( \lambda_1 \)), exponential (e), and follow up duration (t) in months.
The survival rate of patients with diabetic ulcers who are hospitalized to amputation or mortality in 3 years in Indonesia is 36%, while there is no research data in outpatients so it is estimated at 20%, with an estimated hazard in patients with high risk for foot ulcer group of 25% and patients with non-high risk for foot ulcer of 15%. The minimum number of sample needed for each group of patients with high risk for foot ulcer and patients with non-high risk for foot ulcer is 132 patients.

Samples were selected using stratified random sampling with status of ulcer risk as stratum. Kaplan-Meier survival curves were plotted showing probabilities over the whole follow-up period between groups. Cox proportional hazards model was used to compare hazard between the 2 groups. Independent variables were transformed into nominal scale and bivariate analysis was done using cox proportional hazard regression test. All variables with HR $\geq 1.5$ or $P$ value $<.25$ were included in multivariate analysis using cox regression hazard test. All analyses were conducted by SPSS Statistics 25.0 program.

**Results**

There were total of 1002 patients with T2DM who visited internal medicine outpatient clinic in Fatmawati General Hospital from January to December 2016. Of these patients, 487 subjects met the inclusion and exclusion criteria (Figure S1).

Mean age of the subjects was 61 (IQR: 13; 27-85) years old and more than half of them were obese (51.1%), having hypertension (67.4%), and had previous foot ulcer (51.7%). Less than 5% subjects had previous lower extremity amputation (LEA). There were 54.8% subjects who were classified as high risk for DFU (Table 1).

Subject characteristics based on status of ulcer risk were shown in Table 2. We found that the majority of patients with high risk for DFU were male (50.2%), having longer diabetes duration (54.3%), obese (51.3%), diagnosed with hypertension (71.9%), and HbA1c level $\geq 7\%$ (71.4%).

Total amputation or mortality in our study were 62 cases (12.74%) (Table 3). There were 2 cases of amputation in each group and all cases were related to diabetic foot ulcer. Three years overall survival probability is 85.7% (SE 0.17) with mean survival 34.97 months (95% CI 34.38-35.56). Cause of mortality in this study were multi-organ failure (48%), coronary heart disease (22.4%), respiratory infection (8.6%), cerebrovascular accident (6.9%), malignancy (3.4%) and accident (10.3%).

Survival probability of patients with high risk and non-high risk for foot ulcer were 80.2% (SE 0.027) and 91.8% (SE 0.019), respectively. Patients with high risk for foot ulcer were associated with amputation or mortality (HR 2.60 [95% CI 1.49-4.54]; $P=.001$). The Kaplan-Meier curves showed for the outcome that compare different categories high risk and non-high risk for foot ulcer group (Figure S2).

We found that age $\geq$60 years old was the only factor related to amputation or mortality in bivariate analysis (cHR 1.91 [95% CI 1.11-3.31]; $P=.02$) (Table 4). In our multivariate analysis, patients with high risk for foot ulcer (aHR 2.39 [95% CI 1.36-4.20]; $P=.003$), aged $\geq$60 years old (aHR 2.05 [95% CI 1.17-3.59]; $P=.012$), and HbA1C $\geq 7\%$ (aHR

| Table 1. Baseline Characteristics of the Subjects. |
|-----------------------------------------------|
| Characteristic | Value |
|----------------|-------|
| N=487          |       |
| Sex, n (%)     |       |
| Male           | 217 (44.6) |
| Female         | 270 (55.4) |
| Age, median (IQR; range), years old | 61 (13, 27-85) |
| Duration T2DM, median (IQR; range), years | 9 (11, 1-37) |
| Education, n (%) |     |
| Elementary school | 64 (13.1) |
| Junior high school | 56 (11.5) |
| Senior high school | 204 (41.9) |
| Bachelor       | 163 (33.5) |
| T2DM therapy, n (%) |   |
| Diet           | 14 (2.9) |
| OAD            | 297 (61.0) |
| Insulin        | 90 (18.5) |
| Insulin and OAD | 86 (17.6) |
| BMI, median (IQR; range) (kg/m²) | 25.1 (4.84; 14.1-37.1) |
| Underweight, n (%) | 16 (3.3) |
| Normoweight, n (%) | 120 (24.7) |
| Overweight, n (%) | 102 (20.9) |
| Obese, n (%)   | 249 (51.1) |
| Comorbidities, n (%) |       |
| Hypertension   | 328 (67.3) |
| CVD            | 21 (4.3) |
| CAD            | 86 (17.6) |
| Heart Failure  | 13 (2.6) |
| ESRD           | 29 (5.9) |
| Malignancy     | 11 (2.3) |
| History of foot ulcer, n (%) | 252 (51.7) |
| History of LEA, n (%) | 22 (4.5) |
| FPG, median (IQR; range), (mg/dl) | 127 (57; 58-364) |
| Hba1C, median (IQR; range), (%) | 7.7 (2.2; 5.1-15.7) |
| LDL, median (IQR; range), (mg/dl) | 122 (43; 63-267) |
| Status of ulcer risk, n (%) |       |
| High risk      | 267 (54.83) |
| Non-high risk  | 220 (45.17) |
| Amputation or mortality, n (%) | 62 (12.7) |

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; ESRD, end-stage renal disease; FPG, fasting plasma glucose; IQR, interquartile range; LDL, low-density lipoprotein; LEA, lower extremity amputation; OAD: oral antidiabetic drug; T2DM: type-2 diabetes mellitus.
2.02 [95% CI 1.07-3.83]; *P* = .03) were significantly associated to 3 years amputation or mortality (Table 5).

**Discussion**

This study aimed to investigate long-term outcome, either amputation or mortality, of T2DM patients who were at high risk for foot ulcer. We also aimed to compare outcome among subjects with high risk and non-high risk for diabetic foot ulcer and factors related to it. The 3-years overall survival probability in T2DM outpatient was 85.7% (SE 0.17). Survival probability in T2DM patients with high risk for DFU was lower than patients with non-high risk for DFU. Thus, patients with high risk for DFU had worse outcome than patients with non-high risk for DFU. DFU, in most of the time, is limb-threatening and may also become life-threatening.

This study took place in the internal medicine outpatients clinic in Fatmawati General Hospital, a tertiary referral hospital. Majority of subjects were having comorbidities such as obesity, hypertension, poor glycemic control and elevated LDL level, similar to other study in T2DM outpatient in tertiary-hospital by Pscherer et al and Mader et al. This investigation showed that subjects at high risk for DFU were mostly male, having longer duration of T2DM, obese, and HbA1C ≥7%. These characteristics were similar to previous studies showing worse outcome in patients with factors mentioned above.6-9

Three years survival probability for amputation or mortality in patients with high risk for DFU was lower compared to other study (80.2% vs 84.5%).9 This may be because of the difference in our status of ulcer risk classification and study duration, which was 1 year shorter. Mader et al6 reported similar result, in which mortality rate was 80% in high risk group for individual with older age, neuropathy, and had history of ulceration. Unfortunately, studies involving subjects without active ulcer were still limited.

Several authors had proposed different classification system, mostly according to neuropathy, deformity, history of ulceration or amputation, or any combination of these.6,8-10 Previous studies also found that neuropathy, peripheral artery disease,6,8,22-24 and chronic kidney disease,5,6,25,26 were related to amputation or mortality in patients with diabetic foot. IWGDF provides evidence-based guidelines that have been updated in 2019 producing a simple and implementable framework for assessment, prevention, and management of diabetic foot disease and later expected to predict long-term outcome.4 Peters and Lavery7 previously evaluated the effectiveness of IWGDF classification system to predict diabetic foot complication. They reported that patient with high risk for foot ulcer had 17 times higher risk for amputation in 3 years (*P* < .001). This study however was conducted more than decade ago and had different classification from our study. There are development in foot care programs and facilities through years globally in order to prevent and treat diabetic foot disease.3 In this study, hazard ratio for amputation or mortality in patients with high risk for foot ulcer showed similar result with study by Vidiveloo,9 even though it had shorter study duration. This result is also supported by Saluja et al.5

This research showed a significant association between age ≥60 years and amputation or mortality in multivariate analysis. These finding were similar according to ADVANCE study reported that age has lower association to macrovascular complication and mortality, not only in diabetes patients but also in general population.27 Older patients generally have multiple risk factors for macrovascular and microvascular complication. Mader et al6 and Pscherer et al8 reported that older age had significantly associated with amputation and mortality, due to the presence of early macrovascular complication prior to the study. Meanwhile, Won et al22 study showed that younger subjects with active ulcer have more severe complication than older.

The correlation of high blood sugar values and amputation or mortality is consistent with 2 previous studies by Mader et al6 and Pscherer et al8. HbA1C reflect average glucose concentration to hemoglobin lifespan in several months before examination,18 which is more reliable than

| Variable                  | Total | Status of ulcer risk |
|---------------------------|-------|----------------------|
|                           | N = 487 | High risk | Non-high risk |
| Sex, n (%)                |        |           |               |
| Male                      | 217 (44.6) | 134 (50.2) | 83 (37.7) |
| Female                    | 270 (55.4) | 133 (49.8) | 137 (62.3) |
| Age, n (%)                |        |           |               |
| ≥60 years                 | 278 (57.1) | 152 (56.9) | 126 (57.3) |
| <60 years                 | 209 (42.9) | 115 (43.1) | 94 (42.7) |
| Diabetes duration, n (%)  |        |           |               |
| ≥10 years                 | 229 (47.0) | 145 (54.3) | 84 (38.2) |
| <10 years                 | 258 (53.0) | 122 (45.7) | 136 (61.8) |
| BMI, n (%)                |        |           |               |
| Obese                     | 249 (51.1) | 137 (51.3) | 112 (50.9) |
| Non-obese                 | 238 (48.9) | 130 (48.7) | 108 (49.1) |
| Hypertension, n (%)       |        |           |               |
| Yes                       | 328 (67.4) | 192 (71.9) | 136 (61.8) |
| No                        | 159 (32.6) | 75 (28.1)  | 84 (38.2)  |
| FPG, n (%)                |        |           |               |
| ≥130 mg/dl                | 229 (47.0) | 124 (46.4) | 105 (47.7) |
| <130 mg/dl                | 258 (53.0) | 143 (53.6) | 115 (52.3) |
| HbA1C, n (%)              |        |           |               |
| ≥7%                       | 332 (68.5) | 190 (71.4) | 142 (64.8) |
| <7%                       | 153 (31.5) | 76 (28.6)  | 77 (35.2)  |
| LDL, n (%)                |        |           |               |
| ≥100 mg/dl                | 373 (76.6) | 199 (74.5) | 174 (79.1) |
| <100 mg/dl                | 114 (23.4)  | 68 (25.5)  | 46 (20.9)  |

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; LDL, low-density lipoprotein.
random plasma glucose. Chronic hyperglycemia was represented by elevated HbA1C and would progress to macrovascular and microvascular complication. Correlation between HbA1c values and outcomes can also be seen in ADVANCE Study, in which HbA1C variability can reduce microvascular and macrovascular complication. In contrast, HbA1C level cannot well-represent glucose concentration in patients with CKD or malnutrition. Our study used HbA1C level from 6 months prior to recruitment as baseline HbA1C level. ADVANCE study also mentioned that there would be no significant change in the average HbA1C level for up to 5 years if there was no intensive blood glucose control treatment.

Our study failed to find significant association between male sex and amputation or mortality, as mentioned in studies by Al-Rubeaan et al and Won et al. However, other previous study stated that male subjects tend to have lower health seeking behavior regarding foot ulcer. Theoretically,

### Table 3. Comparison of Amputation or Mortality According to Status of Ulcer Risk.

| Status of ulcer risk | Total N=487 | Amputation or mortality | cHR (95% CI) | P |
|----------------------|-------------|-------------------------|--------------|---|
| High risk, n (%)     | 267         | 45 (16.9) | 222 (83.1) | 2.60 (1.49-4.54) | .001* |
| Non-high risk, n (%) | 220         | 17 (7.7)  | 203 (92.3) |              |      |

Abbreviations: cHR, crude hazard ratio; CI, confidence interval.
*Statistically significant.

### Table 4. Factors Related to 3 years Amputation or Mortality.

| Variable                  | Total N=487 | Amputation or mortality | cHR (95% CI) | P |
|---------------------------|-------------|-------------------------|--------------|---|
| Sex, n (%)                |             |                        |              |   |
| Male                      | 217         | 33 (15.2) | 184 (84.8) | 1.51 (0.92-2.49) | .11** |
| Female                    | 270         | 29 (10.7) | 241 (89.3) |              |      |
| Age, n (%)                |             |                        |              |   |
| ≥60 years                 | 278         | 44 (15.8) | 234 (84.2) | 1.91 (1.11-3.31) | .02* |
| <60 years                 | 209         | 18 (8.6)  | 191 (91.4) |              |      |
| Diabetes duration, n (%)  |             |                        |              |   |
| ≥10 years                 | 229         | 30 (13.1) | 199 (86.9) | 1.11 (0.67-1.82) | .69  |
| <10 years                 | 258         | 32 (12.4) | 226 (87.6) |              |      |
| BMI, n (%)                |             |                        |              |   |
| Obese                     | 249         | 26 (10.4) | 23 (89.6)  | 0.68 (0.41-1.12) | .13** |
| Non-obese                 | 238         | 36 (15.1) | 202 (84.9) |              |      |
| Hypertension, n (%)       |             |                        |              |   |
| Yes                       | 328         | 45 (13.7) | 283 (86.3) | 1.39 (0.79-2.41) | .26  |
| No                        | 159         | 17 (10.7) | 142 (89.3) |              |      |
| FPG, n (%)                |             |                        |              |   |
| ≥130 mg/dl                | 229         | 31 (13.5) | 198 (86.5) | 1.14 (0.69-1.88) | .60  |
| <130 mg/dl                | 258         | 31 (12.0) | 227 (88.0) |              |      |
| HbA1C, n (%)              |             |                        |              |   |
| ≥7%                       | 337         | 50 (14.8) | 287 (85.2) | 1.84 (0.98-3.46) | .06** |
| <7%                       | 150         | 12 (8.0)  | 138 (92.0) |              |      |
| LDL, n (%)                |             |                        |              |   |
| ≥100 mg/dl                | 373         | 45 (12.1) | 328 (87.9) | 0.79 (0.45-1.39) | .42  |
| <100 mg/dl                | 114         | 17 (14.9) | 97 (85.1)  |              |      |

### Table 5. Multivariate Analysis Factors Related to 3 Years Amputation or Mortality.

| Variable                      | aHR     | 95% CI     | P     |
|-------------------------------|---------|------------|-------|
| High risk for foot ulcer      | 2.39    | 1.36-4.20  | .003* |
| Male                          | 1.24    | 0.75-2.06  | .405  |
| Age ≥ 60 years                | 2.05    | 1.17-3.59  | .012* |
| Obese                         | 0.64    | 0.39-1.06  | .850  |
| HbA1C ≥7%                     | 2.02    | 1.07-3.83  | .031* |

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.
*Statistically significant.
male subjects also had higher traumatic exposures toward their foot, which often lead to more amputation and death.\textsuperscript{8,27}

The initial diagnosis of diabetes does not always coincide with the onset of metabolic disease, yet in this study duration of diabetes is defined as time period from first diagnosis of T2DM to study entry. According to Indonesian Basic Health Research (RISKESDAS) 2018 there were up to 70\% cases of undiagnosed T2DM in our country,\textsuperscript{2} which could explain why duration of diabetes in our study was shorter than other study. This might also explained why we found no significant correlation between diabetes duration and outcome in this work, although longer diabetes duration is well known to increase all-cause mortality among patients with diabetes.\textsuperscript{9,27}

It is interesting that obesity had protective effect in this investigation, similar to the study by Al-Rubeaan et al.\textsuperscript{10} Obesity paradox theory mentioned that obese patients with diabetes had reduce mortality risk based on several hypothesis, including better mobilization of progenitor cells, decreased thromboxane production which may contribute to survival from cardiovascular disease, and better wound healing among those subjects.\textsuperscript{28,29}

Hypertension and dyslipidemia theoretically lead to endothelial dysfunction and systemic atherosclerosis, ultimately result to cardiovascular events or systemic peripheral artery disease (PAD).\textsuperscript{5,10,14,30,31} In this study we found no association between hypertension and amputation or mortality, similar to Huang et al.\textsuperscript{32} Diagnosis of hypertension extremely depended on measurement technique and races, so comparison among study were difficult. ABI was more reliable to represent PAD than hypertension alone,\textsuperscript{23} while Al-Rubeaan et al\textsuperscript{10} said otherwise. Surprisingly, dyslipidemia became a protective factor in reducing risk of amputation or mortality among our subjects even though it did not statistically significant. Noting that our study was conducted in hospital-based, most of the patients are consuming statin. ADVANCE study found that LDL levels were affected by statin therapy,\textsuperscript{28} which has pleiotropic effect that could reduce all-cause mortality effect, improved insulin sensitivity, and reduced endothelial inflammation and nitric oxide production.\textsuperscript{33} Other reason might be because the LDL level in our research were taken from data 6 months prior to the study.\textsuperscript{28}

This investigation used data registry from daily practice in a tertiary-referral hospital setting to develop not only health service policy in our hospital but also future researches. To the extent of our knowledge, this is the first study reporting long-term survival and factors associated with amputation or mortality in T2DM outpatients in a tertiary care hospital in Indonesia. However, our study has several limitation, including: (1) research method was cohort retrospective, where recall bias might occurred, (2) subjects were only taken from one tertiary health care center in Indonesia where experts, facilities, and procedures might be different from other centers, (3) baseline HbA1C and LDL level were taken from data 6 months prior to the study, (4) unavailable data related to other risk factors such as history of smoking, diet, physical activity, socioeconomic, hemoglobin, and albumin—all which might have affected our outcome. Future study should be conducted prospectively to further assess risk factors toward amputation or mortality in T2DM patients.

**Conclusion**

Three years overall survival probability is 85.7\%. T2DM patients with high risk for foot ulcer have lower 3 years survival probability compared to patients with non-high risk for foot ulcer. Status of ulcer risk, age $\geq 60$ years, and HbA1C $\geq 7\%$ were associated with amputation or mortality in 3 years observation.

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**Author Contribution**

Idea and study design: EY, CDH, IAMK, KH; Data collection: CDH; Data analysis: CDH, KH; Article draft writing: CDH; Draft revision: KH, EY, IAMK; Writing supervision: EY, KH

**Declaration of Conflicting Interests**

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**ORCID iDs**

Em Yunir \(\text{https://orcid.org/0000-0002-2004-9050}\)

Ida Ayu Made Kshanti \(\text{https://orcid.org/0000-0002-7918-2411}\)

**Supplemental Material**

Supplemental material for this article is available online.

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