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Mortality Prediction Model in Patients with Diabetic Foot Ulcer: A Case-Control Study from a Tertiary Referral Hospital in Surabaya, Indonesia

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Abstract:

Objective: Diabetic foot ulcers (DFUs) are a diabetes mellitus (DM) complication with a high mortality rate. This research aimed to demonstrate a mortality prediction model in patients with DFUs.

Material and Methods: This research conducted a case-control study based on secondary data from the medical records of DFU patients in Dr. Soetomo General Hospital, a tertiary referral hospital in Surabaya, Indonesia, between 2016-2018. The association between various risk factors and mortality was analyzed using bivariate and multivariate analyses to make a mortality prediction model.

Results: 358 subjects (179 cases and 179 controls) were included in the final analysis. Septic shock was the major cause of DFU death. Both bivariate and multivariate analyses determined that 5 independent variables were associated with the mortality in DFU patients, namely albumin level (p-value<0.001 OR 16.52 CI 95% 3.42–79.86), sepsis (p-value<0.001 OR 23.47 CI 95% 5.80–26.85), renal function impairment (p-value<0.001 OR 3.41 CI 95% 1.87–6.21), cardiovascular complications (p-value<0.001 OR 2.93 CI 95% 1.64–5.25), and the severity level of the ulcers using Wagner's classification (p-value<0.001 OR 6.80 CI 95% 3.77–12.27). The mortality prediction model showed a maximum score of 7, indicating a 98.4% mortality risk.

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Conclusion: Low albumin level, sepsis, renal function impairment, cardiovascular complications, and Wagner's severity level IV–V of the DF ulcers were the predictors of mortality in DFUs.

Keywords: diabetes mellitus, diabetic foot ulcer, mortality, risk factors

Introduction

Diabetic foot ulcers (DFUs) are the leading cause of diabetic patients requiring hospitalization in Indonesia. DFUs are painful for the patient and expensive for both the patient and the healthcare system. More than one million people worldwide have lower extremities amputation due to diabetes every year, and DFU patients have a higher risk of death which is increased by the presence of additional factors such as other DM complications.[1,2]

The major underlying causes of DFU are peripheral neuropathy and ischemia from peripheral vascular disease. Various intrinsic and extrinsic factors such as trauma, infection, poor glycemic control, and nutrition also contribute to the pathogenesis of DFU.[3–5] These factors can lead to delayed wound healing and worsen the infection, leading to sepsis and death immediate treatment with debridement, amputation, and effective revascularization procedures are required to prevent sepsis and death.[6]

The lack of an easy-to-use and practical mortality prediction model that can comprehensively risk-stratify patients with DFU has led to delayed aggressive and intensive treatment. This research aimed to identify mortality risk factors and create a prediction model with a DFU scoring system.

Material and Methods

This research was a case-control study of type 2 DM (T2DM) patients with DFU hospitalized in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from 2016 to 2018. Data were obtained from the hospital's medical records. Dr. Soetomo General Academic Hospital is a tertiary referral hospital in the Eastern part of Indonesia. The Medical Ethics Committee of Dr. Soetomo General Hospital approved this study (approval #1379/KEPK/VIII/2019), which further agreed that this study was exempt from the requirement for patient consent because of the use of retrospective analysis data. This study complied with the 1975 Declaration of Helsinki.

The ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) code of E11.5 (Diabetic Ulcer) was entered into the medical records database. Among the diabetic ulcer patients, patients ≥18 years with a DFU diagnosis were selected for the study. Patients with incomplete data were excluded, and hypoglycemic patients were excluded due to the influence of this condition on blood glucose.

The dependent variable was the mortality of DFU patients during hospitalization. The cause of death was obtained from the death certificates in medical records. Eight risk predictors age, random blood glucose (RBS), albumin level, and hemoglobin level. Sepsis, renal function, cardiovascular risk factors, and Wagner's severity of ulcers were analyzed. All data are presented categorically on nominal scales.

Age was classified into 18–54 and ≥55 years groups.[7] Random blood glucose was used since it is the most common blood glucose test, first immediately done in diabetic patients. RBS was classified into <200 mg/dL and ≥200 mg/dL.[8] Albumin and hemoglobin levels were used to determine nutrition status and the presence of chronic disease. Albumin levels were classified into <3.4 mg/dL and ≥3.4 mg/dL. Anemia was defined by hemoglobin <11 g/dL.[7]

Sepsis criteria were assessed using the quick Sequential Organ Failure Assessment (qSOFA) score, which consisted of respiratory rate ≥22, GCS <15, systolic blood pressure ≤100 mmHg calculated in suspected infection patients, which was defined using abnormal leukocytes.[8,9] We chose the qSOFA score to diagnose sepsis because it has been used as a mortality predictor in several previous studies.[10–12]

Renal function was determined using the estimated Glomerular Filtration Rate (eGFR) calculated by the MDRD-4 (Modification of Diet in Renal Disease) formula. 10 The data of age, creatinine serum levels, gender, and African-American ethnicity were required for the calculation. Renal function impairment was defined if eGFR <60 mL/minutes/1.73 m^2.[12]

Cardiovascular risk factors were diagnosed if the patient had one or more cardiovascular diseases: hypertension, dyslipidemia, macrovascular disease (stroke, coronary artery disease, congestive heart disease), PVD, cardiac autonomic neuropathy, diabetic cardiomyopathy, or valvular heart disease.[13–15]

Assessing the severity of ulcers in Dr. Soetomo General Hospital employs Wagner's severity levels. At these levels, DFUs were categorized as I–III (early/mild lesion) and IV–V (severe lesions with gangrene).[16]

A Receiver Operating Curve (ROC) with Hosmer–Lemeshow analysis for calibration was employed to evaluate the performance of the mortality prediction model. The bivariate analysis identified associations between independent variables and mortality using Chi-Square. The significance level was α=0.05, and a significant association was defined as a p-value<0.05. Chi-square analysis was followed by multivariate analysis using logistic regression. The multivariate analysis employed all variables with p-value<0.25 in bivariate analysis with a cut-off point of p-value<0.25. Furthermore, to generate the mortality prediction, we divided the coefficient B by the standard error (SE) of all predictive variables, i.e., p-value<0.05, for scoring purposes.

Results

We found 210 deceased DFU cases, of whom 31 were subsequently excluded (21 for incomplete data and ten for hypoglycaemic complications). Thus 179 deceased DFU cases were analyzed, along with 179 control cases randomly selected from 2103 living DFU patients, leaving a total of 358 DFU patients in the final analysis (Table 1). The deceased group's most common causes of death were septic shock, cardiovascular events, and respiratory failure (Table 2).

Table 1 Characteristics of study subjects

Variables	Cases (n=179)		Controls (n=179)	
	Mean±S.D.	Median	Mean±S.D.	Median
Age (years)	57.71±9.83		55.84±9.80	
Duration of DM (years)		5.00		3.00
Hospital stay duration (days)		2.00	9.36±4.66	
RBG (mg/dL)	260.38±171.59		254.77±140.03	
Plasma albumin (mg/dL)	2.38±0.49		2.91±0.57	
Hemoglobin (g/dL)	9.41±2.34		9.99±2.16	
WBC (nx10^9/L)	23.61±12.94		18.30±8.66	
eGFR (mL/min)	39.73±37.83		64.60±40.15	

S.D.=standard deviation, DM=diabetes mellitus, WBC=White Blood Cell Count, eGFR=estimated Glomerular Filtration Rate

Table 2 Causes of deaths in study patients with DFUs

Cause of death	Frequency	Percentage* (%)
Septic shock	123	68.70
Cardiovascular event	23	12.80
Respiratory failure	15	8.40
Cerebrovascular event	3	1.70
Multi-organ failure	2	1.10
Cerebral herniation	2	1.10
Hypovolemic shock	1	0.50
Unknown	9	5.00

DFUs=diabetic foot ulcers
*The number of the case sample group instead of the number of the causes of death

Bivariate analysis (Table 3) showed that age, random blood glucose, and anemia were not significantly associated with mortality in DFU patients. Variables with p-value<0.25 in the bivariate analysis were included in the multivariate analysis, and in both bivariate and multivariate analysis, plasma albumin, sepsis, renal function, cardiovascular complications, and Wagner's severity level of ulcer were the risk factors and predictors of mortality in the DFU patients (Table 3; Table 4).

Table 3 Bivariate analysis of independent variables

Variable	Cases (n)	Controls (n)	OR (CI 95%)	p-value
Age (years old)			1.39 (0.91–2.14)	0.128
18–54	62	76		
≥55	117	103		
RBS (mg/dL)			0.82 (0.54–1.24)	0.338
<200	83	74		
≥200	96	105		
Plasma albumin (mg/dL)			20.00 (4.72–84.77)	<0.001*
<3.4	177	146		
≥3.4	2	33		
Anemia (g/dL)			1.46 (0.93–2.32)	0.103
<11	134	120		
≥11	45	59		
Sepsis (qSOFA score)			12.04 (6.39–23.69)	<0.001*
qSOFA score <2	84	12		
qSOFA score ≥2	95	167		
Renal function			3.51 (2.22–5.55)	<0.001*
Low (eGFR <60 mL/min/1.73 m^2)	139	89		
Normal (eGFR ≥60 mL/min/1.73 m^2)	40	90		
Cardiovascular risk factors			2.02 (1.33–3.08)	0.001*
Yes	99	68		
No	80	111		
Wagner's severity level of ulcer			5.20 (3.30–8.18)	<0.001*
Wagner I–III	64	133		
Wagner IV–V	115	46		

OR=odds ratio, CI=confidence interval, RBS=random blood glucose, qSOFA=quick Sequential Organ Failure Assessment, eGFR=estimated Glomerular Filtration Rate
*Significance (p-value<0.05)

The multivariate analysis used significant variables to create a mortality prediction model (Table 5). The predictive variable scores are calculated using the division of coefficient B by each predictor's SE. Next, the least B/SE is utilized as the divider of all variable B/SE. Plasma albumin had the smallest B/SE (3.5), then the final score was counted. The prediction model's performance was based on the calibration and discrimination measures of logistic regression analysis of the total score (Table 6). The Hosmer–Lemeshow test to measure the goodness of fit of logistic regression models showed a fit regression (p–value=0.74) in this study. Model validation can be identified in the Receiver Operating Curve (Figure 1). This predictor model gave an area under curve (AUC) value of 0.87, indicating good performance in predicting mortality. The maximum score obtained from this model was 7, which indicated a 98.4% probability of death (Table 7).

Table 4 Multivariate analysis of independent variables

Variable	B	SE	Wald	OR (CI 95%)	p–value
Age	0.14	0.29	0.25	1.16 (0.66–2.03)	0.617
Plasma albumin	2.81	0.80	12.17	16.52 (3.42–79.86)	<0.001*
Anemia	–0.11	0.32	0.11	0.90 (0.48–1.69)	0.740
Sepsis (qSOFA score)	2.52	0.39	41.65	12.47 (5.80–26.87)	<0.001*
Renal function (eGFR)	1.23	0.31	16.14	3.41 (1.87–6.21)	<0.001*
Cardiovascular risk factors	1.08	0.30	13.08	2.93 (1.64–5.25)	<0.001*
Wagner's severity level of ulcer	1.92	0.30	40.51	6.80 (3.77–12.27)	<0.001*

B=Coefficient B, SE=standard error, OR=odds ratio, CI=confidence interval, qSOFA=quick Sequential Organ Failure Assessment, eGFR=estimated Glomerular Filtration Rate
*Significance (p–value<0.05)

Table 5 Mortality prediction model

No.	Variable	Yes	No
1.	Plasma albumin <3.4 mg/dL	1	0
2.	Sepsis (qSOFA score ≥2)	2	0
3.	Renal function impairment (eGFR <60 mL/minute/1.73 m^2)	1	0
4.	Cardiovascular risk factors	1	0
5.	Wagner's severity level of ulcer IV–V	2	0

eGFR=estimated Glomerular Filtration Rate

Table 6 Logistic regression analysis of the total score

Variable	B	p-value	Odds ratio	EXP (B) CI 95%	
				Minimal	Maximal
Total score	1.05	<0.001	2.87	2.30	3.57
Constant	-3.63	<0.001	0.03		

EXP (B)=exponentiation of B coefficient, CI=confidence interval

Table 7 The scoring and probability of death

Total score	y=-3.850+1.139 (total score)	Probability ($p=1/(1+e^{-y})$) (%)
0	-3.85	2.08
1	-2.71	6.23
2	-1.57	17.19
3	-0.43	39.34
4	0.71	66.95
5	1.85	86.35
6	2.98	95.18
7	4.12	98.41

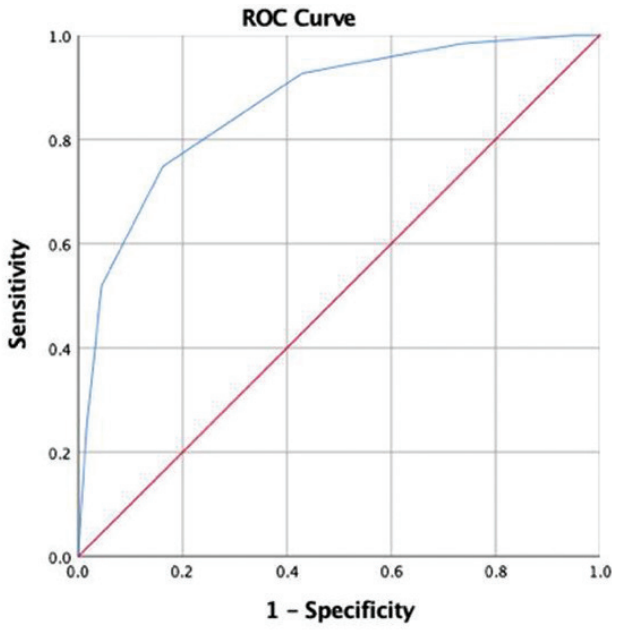

Figure 1 Receiver operating characteristic (ROC) validation of the mortality risk prediction of diabetic foot ulcer (DFU) nomogram

Discussion

This research aimed to create a tool to predict mortality in DFU patients in a tertiary hospital in Indonesia. Older age, high random blood glucose, and anemia had no association with DFU mortality. Both bivariate and multivariate analyses identified low albumin level, sepsis, renal function impairment, cardiovascular complications, and Wagner's severity level IV–V of ulcer as predictors of mortality in DFU patients. 68.7% of our patients died due to septic shock. Another case-control study in a developed country found sepsis the most common cause of death. 17 The severity of DFU is also associated with sepsis and septic shock, which also contributed as the leading cause of death.[18]

Hyperglycemia can lead to malnutrition in diabetic patients.[19] The plasma albumin level is a marker of malnutrition or the presence of chronic disease. The low albumin level is a mortality predictor in DFU patients with amputation. Patients with DFU and amputation with lower albumin levels have higher mortality than average albumin levels[7,19] Most of the deceased patients in this study died from septic shock, mainly caused by an infection of DFU. The inflammatory response to infection requires more nutrients for wound healing, leading to metabolic stress-reducing plasma albumin levels.[19] Moreover, rapid elevated kinetic protein metabolism alterations in DFU patients have been associated with a higher resting energy expenditure that could lead to insulin resistance and lack of insulin secretion. These alterations could worsen hyperglycemia in DFU patients and increase the risk of morbidity and mortality.[20] This multivariate analysis demonstrated a significant association between low albumin levels and death. Patients with low plasma albumin levels had 16.52 times higher mortality risk than patients with normal plasma albumin levels. Other recent studies have reported that underweight BMI, another indication of malnutrition, predicted worse outcomes for DFU patients.[21,22]

Sepsis caused by infection of DFU leads to septic shock, with abnormalities manifestations in the circulation, cellular, or metabolic systems. 23 Septic shock is the leading cause of death in DFU patients in this study (68.7%). This research employed the qSOFA questionnaire to define sepsis. Other studies have found that the qSOFA scores are significantly associated with mortality in pre-hospitalized and hospitalized patients with suspected infection.[11,24] One study reported that sepsis could elevate blood glucose, which leads to decreased immune function.[25] Another study found that sepsis also caused microcirculation dysfunctions due to impaired endothelial barriers, leukocyte adhesion, platelet activation, microvascular coagulation, and vascular tone.26 Diabetic foot sepsis reduces the blood oxygenation supply for natural healing and the delivery of antibiotics to the infected site.[6] This research found that the sepsis variable had the strongest predictor of mortality in DFU patients. This study's patients with DFU with sepsis had 12.47 times higher mortality risk than those without sepsis.

Impaired renal function has been reported to have significant associations with DFU deaths and kidney failure.[12,19] This current study also found that impaired renal function was a predictor of mortality in DFU patients. Multivariate analysis demonstrated that DFU patients with impaired renal function had 3.41 times higher mortality risk than those with normal renal function. The increase in creatinine serum level used in the MDRD-4 formula was related to the increased number of microbiological agents that grow in diabetic foot infections, leading to worse conditions until death.[1] Hyperammonemia, another marker for impaired renal function, may contribute to a worse prognosis of DFU patients due to uncontrolled T2DM. It has been associated with a link between ammonia and brain function, leading to a higher risk for morbidity and mortality[27,28], This study did not use ammonia level as a variable because it is not a routine examination in DFU patients. A further factor contributing to chronic kidney

disease (CKD) is reduced renal function. CKD is an independent predictor of mortality in DFU patients and the primary cause of death. Patients with CKD and dialysis have a lower chance of survival after amputation.29,30 Microvascular damage that occurs in patients with CKD later has a high risk of leading to neuropathy and vascular insufficiency related to poor wound healing and survival.[31]

Previous studies have investigated cardiovascular complications as a bivariate predictive mortality variable in DFUs.[31–33] This research emphasized cardiovascular risk factors as the multivariate predictive variable with the weakest association (p-value<0.001 and Wald=13.08). Multivariate analysis confirmed that DFU patients with cardiovascular risk factors had 2.93 times higher mortality risk than those. The cardiovascular risk factors in this research included PVD, while other studies commonly considered it separately.[32,34] PVD was used as a bivariate predictor of mortality in DFU patients in other studies.[31,33,34] The other studies have found that severe PVD (Ankle-Brachial Index <4) had the strongest association with DFU mortality both in bivariate and multivariate analysis and in the Asian population.[17,35,36] In another study, hypertension was investigated separately, and a significant association with mortality in DFU patients was found.[32] The development of microangiopathy and macroangiopathy lead to lipotoxicity and chronic inflammation and represent the correlation between cardiovascular risk factors and death in patients with DFUs.[37] PVD combined with chronic renal insufficiency is one of the diabetic microvascular complications which one study reported increased the risk of death using multivariate analysis.[17]

This research found a significant association between a higher Wagner's severity level of ulcer and death in both bivariate and multivariate analyses. The multivariate analysis resulted in a higher Wagner's severity level of ulcer as the second strongest predictor of mortality in DFU patients (p-value<0.001 Wald –40.51). DFU patients with Wagner level IV-V of ulcer had 6.80 times higher mortality risk than DFU patients with Wagner level I-III of ulcer. Wagner level IV–V is defined as gangrene in DFU patients.[18] Lesion severity and gangrene are strongly associated with mortality in DFU patients even if the cardiovascular diseases are controlled.[38]

Furthermore, gangrene leads to sepsis, the strongest mortality predictor in this study. It confirms that DFU patients cannot be ignored and must be treated immediately, even if they have a mild level of ulcers on the first arrival. The pathogenesis of gangrene initiated by PVD is associated with mortality in DFUs.[18] The DFU patients with Wagner level of IV–V severity accompanied by PVD had higher mortality. Research conducted by Kusnanto et al. found that the respondents involved in the study had the most DFU complications at degree 4 Wagner (38 people, 54.3%).[39] This study found a strong association of Wagner severity level IV-V of ulcer with mortality in DFU patients by employing multivariate analysis.

Most patients with dire prognoses, who represent the worst-case scenario in the medical industry due to DFUs, are treated at Dr. Soetomo General Hospital, the first referral tertiary hospital in East Indonesia. The mortality prediction model developed in this research demonstrated exemplary performance in Hosmer-Lemeshow and Receiver Operating Curve of logistic regression analysis of the total score. This research increases the domain awareness of medical workers and patients never to ignore DFU. Furthermore, the predictor variables could help the physician predict the patient's prognosis and decide the priority of treatment. Identifying priority candidates would be easier and faster to provide proper treatment based on the prognosis and priority of DFUs calculated by our mortality prediction model. This research had several limitations regarding the objectivity and reliability of the data obtained from the medical records in Dr. Soetomo General Hospital. Due to the case-control approach employed, there were possible

biases since unconfirmed and uncompleted data could affect the analysis result. Some required data to corroborate the research findings were unavailable, i.e., albumin levels in urine to evaluate the renal function. Moreover, the prediction model could only be implemented in T2DM patients. Due to these limitations, further studies with prospective cohort designs are required to obtain more valid mortality prediction models in DFU patients.

Conclusion

Predictive variables associated with mortality in DFU patients in Dr. Soetomo General Hospital were low albumin level, sepsis, renal function impairment, cardiovascular complications, and Wagner's severity level IV–V of ulcers. These variables were used in a prediction model for mortality in DFU patients with a maximum total score of 7, which indicated a 98.2% probability of death. The model had a reliable performance confirmed by Hosmer–Lemeshow as the calibration value of the model showed a fit regression of (p–value=0.74) and discrimination value the Area Under Curve value of 0.87.

Conflict of interest

There is no conflict interest to declare.

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