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High serum C-reactive protein level predicts mortality in patients with stage 3 chronic kidney disease or higher and diabetic foot infections

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Abstract

Background: Diabetic patients are predisposed to foot infections because of vascular insufficiency and peripheral neuropathy. Diabetic foot infection is a common cause of mortality and lower extremity amputations (LEAs) in patients with chronic kidney disease (CKD). We evaluated the risk factors for mortality and LEAs in patients with stage 3 CKD or higher with diabetic foot infections.

Methods: We retrospectively evaluated a cohort of 105 CKD patients with diabetic foot infections between July 1998 and December 2011. We reviewed their demographic characteristics and laboratory parameters to evaluate the risk factors for mortality and amputations at 24 weeks after diagnosis of a diabetic foot infection.

Results: The mortality of the 105 enrolled CKD patients was 21% at 24 weeks after the diagnosis of a diabetic foot infection. Cox proportional regression analyses revealed that age 60 years or older [odds ratio (OR) 3.03, 95% confidence interval (CI) = 1.02-9.02, P = 0.047] and initial serum C-reactive protein (CRP) level ≥ 3 mg/dL (OR 3.97, 95% CI = 1.17-13.43, P = 0.027) were independent risk factors for mortality at 24 weeks. Twenty-four patients (23%) underwent LEAs. On Cox proportional regression analyses, peripheral vascular disease (OR=4.49, 95% CI=1.98–10.17, P=0.01) and cerebrovascular accident (OR 2.42, 95% CI=1.09–5.39, P=0.03) were independently associated with LEAs.

Conclusion: This study showed that age and serum CRP level, were independent risk factors for mortality at 24 weeks in patients with stage 3–5 CKD with diabetic foot infections. Peripheral vascular disease and cerebrovascular accident were significantly associated with LEAs.

Introduction

Diabetic foot ulceration is one of the main causes of morbidity and mortality that leads to nontraumatic lower extremity amputations (LEAs) [1,2]. Foot ulcers can become life-threatening when complicated by infection and might result in amputation when lesions do not heal [2]. Diabetic patients are predisposed to foot ulcers and infections because of impaired immunity, vascular insufficiency, and peripheral neuropathy [1,2]. The annual incidence of diabetic foot ulcers is between 1.5% and 4% [3]. Diabetic patients have at least a 10-fold greater risk of hospitalization for foot infections compared with individuals without diabetes [1]. Nontraumatic LEAs are at least 15 times more prevalent in those with diabetes than in

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those without diabetes [3,4]. Furthermore, 5-year mortality rate after LEAs is up to 50% [5], and the mortality risk is higher for diabetic patients compared with nondiabetic patients [6].

Chronic kidney disease (CKD) has been associated with diabetic foot ulceration and LEAs [3]. Foot complications are encountered more than 2-fold in diabetic patients with CKD, and the rate of LEAs is 6.5–10 times greater in comparison to the general diabetic population [7]. One-year survival was 71% among diabetic patients on dialysis with foot lesions compared with 94% among their counterparts without renal impairment [8]. Even CKD stage 3 was independently associated with higher mortality within 30 days after nontraumatic LEAs [9].

There are only a few studies on the risk factors for mortality and amputations in patients with stage 3–5 CKD with diabetic foot infections. Therefore, the purpose of this study was to identify risk factors for mortality and LEAs within 24 weeks after the diagnosis of diabetic foot infection in patients with CKD stage 3–5.

Methods

Study population

This study investigated CKD patients with an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 and diabetic foot infections who were attending Bundang Jesaeng General Hospital (Sungnam, South Korea) from July 1998 to December 2011. We identified and enrolled 105 patients, all of whom had been followed for 24 weeks.

Data collection

The clinical characteristics at diagnosis of a diabetic foot infection in patients with CKD stage 3–5 were collected. The potential clinical risk factors were recorded, including demographic features (age and sex) and the presence of medical conditions such as hypertension (HTN), peripheral vascular disease (PVD), cerebrovascular accident (CVA), cardiovascular disease (CVD), systemic inflammatory response syndrome, peripheral neuropathy, diabetic retinopathy, and smoking. Laboratory data were also reviewed including blood urea nitrogen, creatinine, white blood cell (WBC), hemoglobin, C-reactive protein (CRP), hemoglobin A1c, glucose, total cholesterol, albumin, calcium, and phosphorus.

Assessment of renal function

Renal function was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation and categorized according to CKD stage in compliance with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [10]. Patients with CKD were indicated as those who had stage 3, 4, or 5 CKD with an eGFR less than 60 mL/min/1.73 m^2.

Definition

Diabetes mellitus was defined by physician's diagnosis or current treatment with hypoglycemic medication. PVD was defined as a narrowing of blood vessels documented on angiography or computerized tomographic angiography. Peripheral neuropathy was assessed by vibratory, monofilament, muscle strength, and tendon reflex testing. The definition of diabetic foot infection was foot ulceration, soft tissue infection, or bone infection with elevated serum CRP level [1]. LEA was defined as a surgical removal of part of a lower extremity. CVD was defined as a history of acute coronary syndrome, or according to previous coronary angiographic findings ($\geq$ 50% stenosis in one or more of the coronary arteries) [11]. A history of CVA was confirmed by computed tomographic scans or magnetic resonance images. HTN was diagnosed as a systolic blood pressure of 140 mmHg or more, or a diastolic blood pressure of 90 mmHg or more on three separate visits, or when the enrolled patients received antihypertensive agents. Patients were considered to have systemic inflammatory response syndrome if they had two or more of the following criteria: body temperature $< 36\,^{\circ}$C or $> 38\,^{\circ}$C, heart rate > 90 beats/min, tachypnea with > 20 breaths/min or an arterial partial pressure of carbon dioxide < 32 mmHg, WBC count < 4000 cells/mm^3 or $> 12{,}000$ cells/mm^3 or the presence of $> 10\%$ immature neutrophils (band forms).

Statistical analysis

The clinical characteristics of the patients were presented as means $\pm$ standard deviations for continuous variables or as

Table 1. Baseline demographics and characteristics of patients (N=105)

Variable	Value
Demographics	
Male	62 (59)
Age (y)	61.6 $\pm$ 13.5
60 y or older group	62 (59)
Medical conditions	
HTN	82 (78)
PVD	18 (17)
CVA	33 (31)
CVD	20 (19)
SIRS	21 (20)
Peripheral neuropathy	41 (39)
Diabetic retinopathy	55 (52)
Smoking	32 (31)
CKD stage	
Stage 3	18 (17)
Stage 4	10 (10)
Stage 5	77 (73)
Laboratory data	
White blood cell (/mm^3)	12,502.1 $\pm$ 8230.5
White blood cell (/mm^3; 2 wks later)	10,361.4 $\pm$ 4921.9
White blood cell (/mm^3; 4 wks later)	9188.6 $\pm$ 3694.2
Hemoglobin (g/dL)	9.6 $\pm$ 1.9
BUN (mg/dL)	45.8 $\pm$ 23.7
Cr (mg/dL)	4.6 $\pm$ 2.9
CRP (mg/dL)	7.6 $\pm$ 7.2
CRP (mg/dL; 2 wks later)	4.8 $\pm$ 5.2
CRP (mg/dL; 4 wks later)	3.9 $\pm$ 4.6
HbA1c (%)	7.7 $\pm$ 2.9
Glucose(mg/dL)	219 $\pm$ 137.9
Cholesterol (mg/dL)	145.5 $\pm$ 47.7
Albumin (g/dL)	3.3 $\pm$ 0.5
Ca (mg/dL)	8.7 $\pm$ 0.9
P (mg/dL)	4.1 $\pm$ 1.6
Ca $\times$ P (mg^2/dL^2)	35.4 $\pm$ 14.3

Data are presented as mean $\pm$ SD or n (%).
BUN, blood urea nitrogen; Ca, calcium; CKD, chronic kidney disease; Cr, creatinine; CRP, C-reactive protein; CVA, cerebrovascular accident; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HTN, hypertension; P, phosphorus; PVD, peripheral vascular disease; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

percentages for categorical variables. Categorical variables were assessed using the Chi-square test, and continuous variables were compared with independent t tests. The Kaplan–Meier method with the log-rank test and multivariate Cox proportional regression analyses were performed to identify the factors independently associated with mortality and amputations. Variables with $P < 0.05$ on univariate analysis were included in the multivariate Cox proportional model, and odds ratios (OR) and 95% confidence intervals (CI) were calculated. The receiver operating characteristic curve analysis was used to estimate the area under the curve of the model predicting the mortality of serum CRP level. Risk estimates were presented as OR with 95% CI, and $P < 0.05$ were considered statistically significant. Statistical analyses were performed using the SPSS statistical software (Version 16.0.1; SPSS Inc., Chicago, IL, USA).

Results

We assessed a group of 105 CKD stage 3–5 patients (62 males, 59%) with diabetic foot infections with a mean age of 61.6 ± 13.5 years. Based on the patients' medical records, the prevalence of HTN was 78%, and 18 patients (17%) had PVD. A total of 33 patients (31%) had a history of CVA and 20 patients (19%) had CVD.

Of the enrolled patients, 18 had CKD stage 3, 10 patients had stage 4, and 77 patients (73%) had stage 5. A total of 73 patients (70%) were receiving renal replacement therapy. Hemodialysis was used in 62 patients (85%), whereas the remaining patients were treated with peritoneal dialysis. The mean laboratory values included an initial plasma CRP of 7.6 ± 7.2 mg/dL and a hemoglobin A1c of 7.7 ± 2.9%. The mean baseline plasma albumin was 3.3 ± 0.5 g/dL, whereas serum calcium and phosphate levels were 8.7 ± 0.9 mg/dL and 4.1 ± 1.6 mg/dL, respectively (Table 1).

The overall mortality was 21% (22 patients), and the mean duration from diagnosis until death was 8.7 ± 6.5 weeks (range, 1–20 weeks). The leading cause of death was CVD (14 patients, 64%), followed by infection (8 patients, 36%), including pneumonia (3 patients), sepsis secondary to foot infection (4 patients), and catheter-related infection (1 patient). A total of 24 patients (23%) underwent LEAs during the study period. The median time from diagnosis to amputation was 5 ± 4.7 weeks (range, 1–19 weeks).

On univariate analysis, the proportion of patients aged 60 years or older was higher in the nonsurviving group compared with the survivors. The prevalence of CVD and CKD stage 5 were higher in the nonsurviving group of patients. Initial and follow up CRP levels and WBC counts at 4 weeks were higher in the nonsurviving group of patients. There are more patients with initial serum CRP $\geq$ 3mg/dL in the nonsurviving group than survivors (Table 2). Additionally, the prevalence rates of PVD and CVA were higher in the group of amputees compared with the nonamputees (Table 3).

We computed the area under the receiver operating characteristic associated with mortality-prediction models based on serum CRP levels. In this analysis, the initial serum CRP level was shown

Table 2. Comparison of clinical characteristics between nonsurvival and survival groups

Characteristic	Nonsurvival (n = 22)	Survival (n = 83)	P
Male sex	12 (55)	50 (60)	0.63
Age (y)	66.4 ± 12.9	60.4 ± 13.4	0.06
60 y or older	18 (82)	44 (53)	0.02
HTN	18 (82)	64 (77)	0.77
PVD	6 (27)	12 (15)	0.47
CVD	8 (36)	12 (15)	0.02
Stage 5 CKD	20 (91)	57 (69)	0.04
CRP ≥ 3 mg/dL	19 (86)	48 (59)	0.02
Peripheral neuropathy	7 (32)	34 (4)	0.47
Diabetic retinopathy	11 (50)	44 (53)	0.81
SIRS	6 (27)	15 (18)	0.37
Smoking	8 (35)	24 (29)	0.60
Amputation	6 (27)	18 (22)	0.57
White blood cell (/mm^3)	12,490.9 ± 5709.2	12,505.1 ± 8807.2	0.99
White blood cell (/mm^3; 2 wks later)	12,805 ± 6923.5	9585.7 ± 3848.7	0.06
White blood cell (/mm^3; 4 wks later)	11,517.6 ± 5024.9	8441.5 ± 2827.9	0.03
Hemoglobin (g/dL)	9.1 ± 1.7	9.7 ± 1.9	0.14
BUN (mg/dL)	51.5 ± 23	44.3 ± 23.8	0.20
Cr (mg/dL)	4.4 ± 1.8	4.7 ± 3.1	0.65
CRP (mg/dL)	10.7 ± 7.1	6.8 ± 7.1	0.03
CRP (mg/dL; 2 wks later)	7.5 ± 6.1	3.8 ± 4.5	0.01
CRP (mg/dL; 4 wks later)	7.4 ± 5.5	2.6 ± 3.5	0.01
HbA1C	6.7 ± 2.6	7.8 ± 2.9	0.11
Glucose (mg/dL)	215.6 ± 92.6	219.9 ± 148	0.86
Cholesterol (mg/dL)	131.8 ± 43.2	149.1 ± 48.4	0.11
Albumin (g/dL)	3.2 ± 0.5	3.3 ± 0.6	0.13
Ca (mg/dL)	8.8 ± 0.9	8.6 ± 0.9	0.36
P (mg/dL)	4.1 ± 1.3	4.1 ± 1.7	0.91
Ca × P (mg^2/dL^2)	35.9 ± 11.9	35.3 ± 14.9	0.85

Data are presented as mean ± SD or n (%).

BUN, blood urea nitrogen; Ca, calcium; CKD, chronic kidney disease; Cr, creatinine; CRP, C-reactive protein; CVA, cerebrovascular accident; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HTN, hypertension; P, phosphorus; PVD, peripheral vascular disease; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Table 3. Comparison of clinical characteristics between amputees and nonamputees

Characteristic	Amputees (n = 24)	Nonamputees (n = 81)	P
Male sex	14 (58.3)	48 (59.3)	0.93
Age (y)	64.8 ± 11.4	60.7 ± 13.9	0.18
60 y or older	17 (70.8)	45 (55.6)	0.23
HTN	20 (83.3)	62 (76.5)	0.58
PVD	10 (41.7)	8 (9.9)	0.001
CVA	12 (50.0)	21 (25.9)	0.026
CVD	4 (16.7)	16 (19.8)	0.73
Stage 5 CKD	17 (70.8)	60 (74.1)	0.79
CRP ≥3 mg/dL	18 (75)	49 (62)	0.33
Peripheral neuropathy	6 (25)	35 (43.2)	0.15
Diabetic retinopathy	10 (41.7)	45 (55.6)	0.25
SIRS	6 (25)	15 (18.5)	0.56
Smoking	9(37.5)	23 (28.4)	0.45
White blood cell (/mm^3)	16,500 ± 12,310.2	11,317.5 ± 6187	0.06
White blood cell (/mm^3; 2 wks later)	11,245.5 ± 5050.8	10,042.6 ± 4877.4	0.32
White blood cell (/mm^3; 4 wks later)	9077.3 ± 3611.5	9239.6 ± 3768.2	0.86
Hemoglobin (g/dL)	9.9 ± 1.1	9.5 ± 2.0	0.16
BUN (mg/dL)	43.5 ± 20.3	46.5 ± 24.7	0.59
Cr (mg/dL)	4.5 ± 2.8	4.7 ± 2.9	0.80
CRP (mg/dL)	8.9 ± 8.0	7.3 ± 7.0	0.33
CRP (mg/dL; 2 wks later)	5.7 ± 5.1	4.4 ± 5.3	0.33
CRP (mg/dL; 4 wks later)	4.5 ± 4.9	3.5 ± 4.4	0.42
HbA1C	7.2 ± 3.0	7.7 ± 2.9	0.51
Glucose (mg/dL)	189.8 ± 112.4	227.7 ± 144	0.23
Cholesterol (mg/dL)	135.3 ± 39.6	148.5 ± 49.6	0.23
Albumin (g/dL)	3.4 ± 0.5	3.3 ± 0.6	0.23
Ca (mg/dL)	8.9 ± 1.1	8.6 ± 0.9	0.24
P (mg/dL)	4.2 ± 1.6	4.1 ± 1.6	0.83
Ca × P (mg^2/dL^2)	36.5 ± 13.2	35.1 ± 14.7	0.69

Data are presented as mean ± SD or n (%).
BUN, blood urea nitrogen; Ca, calcium; CKD, chronic kidney disease; Cr, creatinine; CRP, C-reactive protein; CVA, cerebrovascular accident; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HTN, hypertension; P, phosphorus; PVD, peripheral vascular disease; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Table 4. Multivariate Cox proportional regression analysis of risk factors associated with mortality

Variable	P	Odds ratio	95% CI
60 y or older	0.047	3.03	1.02–9.02
CRP ≥ 3 mg/dL	0.027	3.97	1.17–13.43
CVD	0.062	2.31	0.96–5.55

CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease.

Table 5. Multivariate Cox proportional regression analysis of risk factors associated with amputations

Variable	P	Odds ratio	95% CI
PVD	0.010	4.49	1.98–10.17
CVA	0.030	2.42	1.09–5.39

CI, confidence interval; CVA, cerebrovascular accident; PVD, peripheral vascular disease.

to be related to mortality. The area under the curve for CRP was 0.678 (95% CI=0.560–0.797, P=0.01), and the best predictive value was 3.26 mg/dL (sensitivity 47%, specificity 86%). The Kaplan–Meier survival curves demonstrated that high initial serum CRP (≥ 3.0 mg/dL) was associated with higher mortality than low initial serum CRP (< 3.0 mg/dL; log rank 5.14, P=0.02).

The multivariate Cox proportional analysis revealed that age ≥ 60 years (OR 3.03, 95% CI 1.02-9.02, P = 0.047) and initial serum CRP ≥ 3 mg/dL (OR 3.97, 95% CI 1.17-13.43, P = 0.027) were independently associated with mortality within 24 weeks of the diagnosis of diabetic foot infection (Table 4). To determine the independent risk factors for LEAs, we performed a series of multivariable Cox proportional analyses. Consequently, we found that PVD (OR 4.49, 95% CI 1.98–10.17, P=0.01) and CVA (OR 2.42, 95% CI 1.09–5.39, P=0.03) were significantly associated with LEAs (Table 5).

In our study, contrast-induced nephropathy occurred in 12 patients after the administration of a contrast medium. However, the prevalence of contrast-induced nephropathy was not statistically significantly associated with mortality.

Discussion

This study showed that in patients with stage 3–5 CKD with diabetic foot infections, mortality was associated with old age, serum CRP level after adjusting for potential confounders. We also found that PVD and CVA were independent risk factors for LEAs.

Old age is a risk factor for CKD and CVD. Shlipak et al [12] showed that elderly patients with mild to moderate CKD had a substantial risk for cardiovascular mortality. The 1-year mortality of elderly patients with moderate CKD after myocardial infarction is nearly 3-fold compared to those with normal renal function [13].

Our study showed that patients with CVD had a tendency to higher mortality. Patients with CKD had a significant

tendency to develop arrhythmia, congestive heart failure, and cardiogenic shock after myocardial infarction [14]. Death from cardiac causes is 10–20 times more common in CKD [15].

Serum CRP level is elevated in patients with CKD [16] and is an independent predictor of cardiovascular mortality in this population [17]. Serum CRP level, a circulating marker of inflammation, is closely linked to CVD [18]. Recent data from the MDRD study showed that high serum CRP was an independent risk factor for all-cause mortality in patients with CKD stages 3 and 4 [19]. Zimmerman et al [20] showed that high serum CRP was an independent predictor of 2-year all-cause mortality in 280 stable hemodialysis patients. Our current results showed that initial serum CRP $\geq$ 3.0 mg/dL was a strong predictor of 24-week mortality in CKD stage 3–5 patients with diabetic foot infections. This finding may have implications for early risk identification and for targeted interventions to reduce the risk of mortality in high-risk patients.

We found that PVD was independently associated with an increased risk of LEAs. Some previous studies suggest that the risk factors of LEAs are PVD, peripheral neuropathy, retinopathy, minor trauma, infection, impaired wound healing, and limited joint mobility [21,22]. PVD is a major component factor for LEAs [23]. Insufficient blood supply is an important contributor to foot ulceration and plays a significant role in the delayed healing of an ulcer once it developed. American Diabetes Association emphasized the need for the prevention of PVD in patients with CKD stage 3 or higher with diabetic foot infections.

The result of our study is consistent with those of previous studies that reported CVA as a significant risk factor for LEAs [24,25]. The kidney and the brain share unique susceptibilities to vascular injury. Therefore, some risk factors for atherosclerosis such as HTN, diabetes, and dyslipidemia may result in similar vascular injuries in both organs [26]. The mechanisms involved in this association may be related to traditional and nontraditional risk factors, such as endothelial dysfunction, oxidative stress, inflammation, hyperhomocysteinemia, and thrombogenic factors [27,28]. All of these factors may play a role in accelerated atherosclerosis in the arteries of the kidney and the brain.

The current study has several limitations. First, this study has a retrospective, observational, single-center design. Second, the use of statins and angiotensin-converting enzyme inhibitors may be associated with lower serum CRP levels in patients with ischemic heart disease, stroke, or CKD [29,30]. Therefore, our study might have underestimated the serum CRP level.

Our study result suggests that an initial serum CRP $\geq$ 3 mg/dL may predict mortality in patients with stage 3–5 CKD with diabetic foot infections.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

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