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ORIGINAL ARTICLE

Incidence and associated risk factors for limb amputation among sepsis survivors in South Korea

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Abstract

Purpose Peripheral gangrene (PG) is a known complication requiring limb amputation among sepsis survivors; however, its incidence and associated risk factors remain controversial. We aimed to examine the incidence of limb amputation among sepsis survivors, and to investigate factors independently associated with limb amputation.

Methods In this population-based cohort study, data obtained from the South Korean national health insurance service database between 2015 and 2016 were analyzed. A sepsis survivor was defined as someone having survived > 90 days after initiation of treatment for sepsis.

Results Of 19,906 sepsis survivors, 163 (0.8%) had undergone surgical limb amputation. In a multivariable model, male sex (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.26–2.40; $P = 0.001$), dopamine infusion (OR 1.78, 95% CI 1.22–2.60; $P = 0.003$), epinephrine infusion (OR 2.04, 95% CI 1.30–3.20; $P = 0.002$), continuous renal replacement therapy (OR 3.34, 95% CI 2.01–3.20; $P < 0.001$), diabetes mellitus (DM) without chronic complication (OR 1.73, 95% CI 1.19–2.51; $P = 0.004$), DM with chronic complication (OR 3.49, 95% CI 2.32–5.26; $P < 0.001$), and peripheral arterial disease (OR 6.79, 95% CO 3.70–12.46; $P < 0.001$) were associated with a higher incidence of limb amputation among sepsis survivors.

Conclusions In South Korea, 0.8% of sepsis survivors underwent limb amputation for the treatment of PG. Furthermore, the incidence of limb amputation was higher among the sepsis survivors having some underlying diseases (DM and peripheral arterial diseases) or receiving certain vasopressor treatments (epinephrine and dopamine).

Keywords Amputation · Reconstructive surgical procedures · Sepsis · Shock · septic

Introduction

Sepsis is defined as a life-threatening illness attributable to a dysregulated host immune response due to infection [1], with a reported incidence rate of 6% of all hospitalized adults in the United States [2], and its incidence is continuing to increase [3]. Moreover, a retrospective inpatient study in the United States in 2011 reported an all-cause mortality rate for sepsis of 14.8% [4]. However, there have been many efforts to treat sepsis globally [5], and recent cohort studies have reported improvements in survival for patients with sepsis due to advancements in medical management and treatment [6, 7]. Therefore, quality of life and return to work have emerged as important issues for sepsis survivors.

Sepsis survivors have been reported to have a higher risk of cardiovascular events [8] and all-cause mortality at 5 years post-discharge [9]. Moreover, survivors have shown an increase in healthcare use following discharge from hospitals due to various causes, including complications of sepsis [10]. One important challenge to improve the quality of life in sepsis survivors is limb amputation, undertaken as treatment for peripheral gangrene (PG). This clinical syndrome is characterized as bilateral distal ischemic damage leading to gangrene in the absence of major vascular occlusive disease [11]. Intensive care physicians usually administer vasopressors for the treatment of septic shock, which is known to cause PG [12, 13]. Moreover, disseminated intravascular coagulation (DIC), which is also a known complication of sepsis [14], has been reported to be a factor

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related to the development of PG [15]. Therefore, PG is a severe complication for sepsis survivors and several studies have reported treating PG with limb amputation [11, 16, 17]. In South Korea, the incidence rate and associated risk factors for limb amputation in sepsis survivors is not known. Therefore, this study aimed to examine the incidence of limb amputation among sepsis survivors in South Korea, and to investigate risk factors independently associated with limb amputation.

Methods

Ethical statement

As a population-based cohort study, this study was conducted according to the Reporting of Observational Studies in Epidemiology guidelines. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (X-1912-580-902) and the Health Insurance Review and Assessment Service (NHIS-2019-1-275). Informed consent was waived, because data analyses were performed retrospectively, using anonymous data derived from the South Korean National Health Insurance Service (NHIS) database.

Data source

This study used health records obtained from the NHIS database. In South Korea, all disease diagnoses and prescription information concerning drugs and/or procedures are required to be registered with the NHIS database. Data were extracted by an independent medical record technician at the NHIS center who was unaffiliated to this study.

Study population

All adult patients (≥ 18 years of age) who had been admitted to any hospital in South Korea between 2015 and 2016 with a main diagnosis of sepsis (A40*, A41*) or septic shock (R65.2), according to International Classification of Diseases 10th revision (ICD-10) codes, were initially screened for this study. Where a patient had been admitted to hospital for treatment of another main disease, and sepsis had developed as a complication during the treatment, the patient was excluded from our analysis.

Among patients diagnosed with sepsis at their initial treatment during hospitalization, a sepsis survivor was defined as someone who had survived > 90 days after initiation of treatment for sepsis and who, therefore, was eligible for inclusion in this study. Furthermore, among the sepsis survivors, cases of limb amputation due to trauma were excluded.

Study endpoint

The primary endpoint of this study was limb amputation in a sepsis survivor. Limb amputation was classified into four categories according to procedural codes in the NHIS database, as follows: thigh-level amputation; upper arm, forearm, lower leg-level amputation; hand- or foot-level amputation, and finger- or toe-level amputation.

Measurements as confounders

Confounding data for this study included demographic information such as age, sex, place of residence (Seoul, metropolitan cities, and other), and quartile ratio income levels. The Charlson comorbidity index (CCI) at diagnosis of sepsis was calculated based on ICD-10 codes recorded during 2014–2015 (e-Appendix 1), duration of treatment for sepsis (day), and treatment of sepsis during hospitalization. Treatment for sepsis during hospitalization included infusions of norepinephrine, vasopressin, dopamine, dobutamine, epinephrine, and corticosteroid medications, the use of continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), and mechanical ventilator in the intensive care unit (ICU) for over 8 h.

Statistical analysis

Participant baseline characteristics are presented as means with standard deviations for continuous variables, and as numbers with percentages for categorical variables. As 8.7% of the cohort had data missing concerning income levels prior to the diagnosis of sepsis, we performed multiple imputation (MI) with the fully conditional specification method to replace the missing data, using the PROC MI [18]. All covariates were included in the imputation model to improve the accuracy of generating replacements for the missing values. Five imputations were performed to generate five datasets, and each missing value was replaced with the average of the five values in each of the five datasets.

We performed univariable and multivariable logistic regression analyses in relation to limb amputation among sepsis survivors to identify which variables were associated with limb amputation. Based on the results of univariable logistic regression analysis, all variables except rheumatic disease, moderate or severe liver disease, metastatic solid tumor, and acquired immune deficiency syndrome were included in the final multivariable logistic regression model. These specific variables were excluded from the model due to a high P value of 0.999. Furthermore, we constructed three separate multivariable models to avoid multi-collinearity in the models. The first model included the CCI and

underlying diseases used to calculate the CCI; vasopressor infusions and combination of vasopressor infusions were included in separate models, because the variance inflation factor between the variables was > 10. The results of logistic regression analysis presented as odds ratios (OR) with 95% confidence intervals (CI), confirmed that there was no multi-collinearity between the variables in each of the multivariable models as the variance inflation factor was < 2.0. Finally, we performed receiver operating characteristic (ROC) analysis to investigate the validity of the multivariable logistic regression models in predicting limb amputation among sepsis survivors. The results of ROC analysis are presented as areas under the curve (AUC) with 95% CIs. All statistical analyses were performed using R software (version 3.6.1 with R packages), and a P value < 0.05 was considered statistically significant.

Results

From 2015 to 2016 in South Korea, 75,207 patients were registered for sepsis in the NHIS database, based on the ICD-10 codes. In this study, we initially screened 37,285 of these patients who had been hospitalized with the main diagnosis of sepsis. Among them, 20,890 patients had survived for > 90 days after initiation of treatment for sepsis, of which we excluded 984 pediatric patients. Finally, 19,906 sepsis survivors were included in the analysis and of these 163 (0.8%) patients had undergone surgical limb amputation. Specifically, 81 (0.4%) patients had undergone surgical limb amputation at the finger or toe level, 42 (0.2%) at the upper arm, forearm, and lower leg level, 23 (0.1%) at the thigh level, and 17 (0.1%) at the hand or foot level. Moreover, these 163 patients were not diagnosed with any trauma to the limbs, suggesting that all limb amputations were due to PG. A flowchart depicting the patient selection process for this study is presented in Fig. 1. The baseline characteristics of the sepsis survivors included in the final analysis are shown in Table 1.

Associated risk factors for limb amputation in sepsis survivors

Tables 2 and 3 show the results of univariable and multivariable logistic regression analyses for limb amputation among sepsis survivors. In multivariable model 1, male sex (OR 1.74, 95% CI 1.26–2.40; $P = 0.001$), dopamine infusion (OR 1.78, 95% CI 1.22–2.60; $P = 0.003$), epinephrine

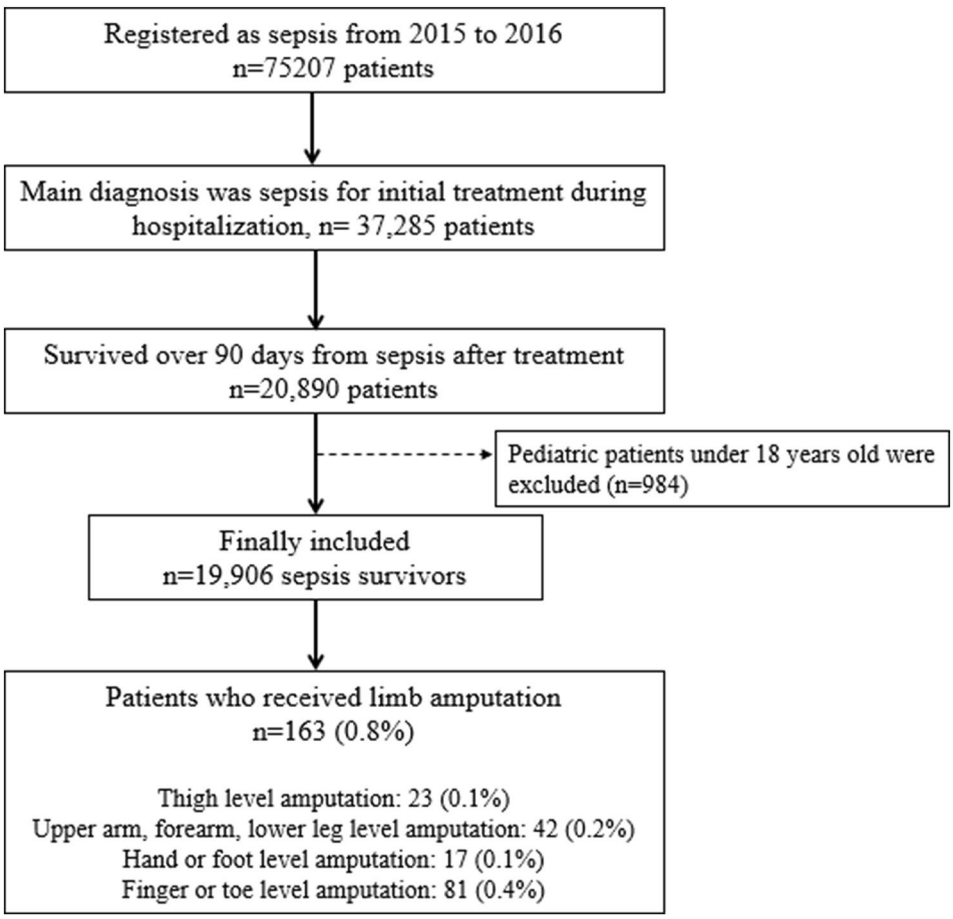

Fig. 1 Flowchart depicting patient selection

Table 1 Baseline characteristics of sepsis survivor from 2015 to 2016 in South Korea ($n = 19,906$)

Variable	Number (%)	Mean (SD)
Age, year		74.2 (13.7)
Sex, male	7.943 (39.9)	
Residence at diagnosis		
Capital city, Seoul		
Other metropolitan city		
Others		
Income level at diagnosis in quartile		
Q1 (lowest)	3304 (16.6)	
Q2	3558 (17.9)	
Q3	5655 (28.4)	
Q4 (highest)	7389 (37.1)	
Duration of treatment for sepsis, day		11.5 (10.8)
CCI at diagnosis of sepsis		0.9 (1.2)
Comorbidities for calculating CCI		
Myocardial infarction	67 (0.3)	
Congestive heart failure	279 (1.4)	
Peripheral vascular disease	256 (1.3)	
Cerebrovascular disease	1392 (7.0)	
Dementia	3237 (16.3)	
Chronic pulmonary disease	866 (4.4)	
Rheumatic disease	155 (0.8)	
Peptic ulcer disease	332 (1.7)	
Mild liver disease	730 (3.7)	
DM without chronic complication	3072 (15.4)	
DM with chronic complication	1197 (6.0)	
Hemiplegia or paraplegia	1042 (5.2)	
Renal disease	283 (1.4)	
Malignancy	1184 (5.9)	
Moderate or severe liver disease	17 (0.1)	
Metastatic solid tumor	56 (0.3)	
AIDS/HIV	6 (0.0)	
Treatment of sepsis		
Norepinephrine infusion	6497 (32.6)	
Vasopressin infusion	248 (1.2)	
Dopamine infusion	2882 (14.5)	
Dobutamine infusion	530 (2.7)	
Epinephrine infusion	1295 (6.5)	
IV corticosteroid	2126 (10.7)	
CRRT use	630 (3.2)	
ECMO use	3 (0.0)	
Mechanical ventilator use in ICU > 8 h	2443 (12.3)	

SD standard deviation, *CCI* Charlson comorbidity index, *DM* diabetes mellitus, *AIDS* acquired immune deficiency syndrome, *HIV* human immunodeficiency virus, *IV* intravenous, *CRRT* continuous renal replacement therapy, *ECMO* Extracorporeal membrane oxygenation

infusion (OR 2.04, 95% CI 1.30–3.20; $P = 0.002$), CRRT use (OR 3.34, 95% CI 2.01–3.20; $P < 0.001$), and a 1-point increase in the CCI (OR 1.24, 95% CI 1.13–1.36; $P < 0.001$)

Table 2 Univariable logistic regression analysis for limb amputation among sepsis survivor

Variable	Univariable model OR (95% CI)	*P* value
Age, year	0.98 (0.97, 0.99)	< 0.001
Sex, male	2.12 (1.55, 2.90)	< 0.001
Residence at diagnosis		
Capital city, Seoul	1	
Other metropolitan city	0.67 (0.39, 1.15)	0.147
Others	0.76 (0.53, 1.11)	0.153
Income level at diagnosis in quartile		
Q1 (lowest)	1	
Q2	1.35 (0.82, 2.20)	0.239
Q3	0.84 (0.52, 1.38)	0.496
Q4 (highest)	0.96 (0.61, 1.52)	0.862
Duration of treatment for sepsis, day	1.01 (0.99, 1.02)	0.486
CCI at diagnosis of sepsis, per 1 point	1.25 (1.14, 1.38)	< 0.001
Comorbidities for calculating CCI		
Myocardial infarction	1.84 (0.25, 13.34)	0.546
Congestive heart failure	1.78 (0.66, 4.84)	0.258
Peripheral vascular disease	7.57 (4.32, 13.29)	< 0.001
Cerebrovascular disease	0.78 (0.40, 1.52)	0.461
Dementia	0.52 (0.31, 0.89)	0.016
Chronic pulmonary disease	1.29 (0.66, 2.53)	0.463
Rheumatic disease	0.00 (0.00–)	0.996
Peptic ulcer disease	2.28 (1.10, 5.18)	0.050
Mild liver disease	2.11 (1.16, 3.81)	0.014
DM without chronic complication	1.67 (1.16, 2.41)	0.006
DM with chronic complication	3.90 (2.64, 5.76)	< 0.001
Hemiplegia or paraplegia	0.81 (0.38, 1.73)	0.589
Renal disease	3.17 (1.47, 6.81)	0.003
Malignancy	0.82 (0.40, 1.66)	0.574
Moderate or severe liver disease	0.00 (0.00–)	0.999
Metastatic solid tumor	0.00 (0.00–)	0.999
AIDS/HIV	0.00 (0.00–)	0.999
Treatment of sepsis		
Norepinephrine infusion	2.15 (1.54, 3.01)	< 0.001
Vasopressin infusion	3.63 (1.69, 7.83)	0.001
Dopamine infusion	2.49 (1.77, 3.50)	< 0.001
Dobutamine infusion	3.50 (2.01, 6.10)	< 0.001
Epinephrine infusion	3.57 (2.42, 5.28)	< 0.001
IV corticosteroid	1.98 (1.33, 2.93)	0.001
CRRT use	5.73 (3.71, 8.84)	< 0.001
ECMO use	0.00 (0.00–)	0.999
Mechanical ventilator use > 8hrs	2.01 (1.28, 3.16)	0.002
Combination of vasopressors		
Norepinephrine + vasopressin infusion	4.63 (2.72, 8.95)	< 0.001
Norepinephrine + dopamine infusion	4.79 (3.50, 7.75)	< 0.001
Norepinephrine + dobutamine infusion	4.50 (3.50, 7.10)	< 0.001
Dopamine + epinephrine infusion	6.75 (4.80, 9.84)	< 0.001

Table 2 (continued)

Variable	Univariable model OR (95% CI)	*P* value
Dobutamine + epinephrine infusion	4.55 (3.05, 7.10)	< 0.001
Norepinephrine + epinephrine infusion	4.85 (4.41, 5.34)	< 0.001

OR odds ratio, *CI* confidence interval, *CCI* Charlson comorbidity index, *DM* diabetes mellitus, *AIDS* acquired immune deficiency syndrome, *HIV* human immunodeficiency virus, *IV* intravenous, *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation

were associated with a higher incidence of limb amputation among sepsis survivors. Hosmer–Lemeshow statistics indicated a goodness-of-fit for multivariable model 1 ($P > 0.05$), and the AUC for multivariable model 1 was 0.74 (95% CI 0.69–0.79) according to ROC analysis.

In multivariable model 2, diabetes mellitus (DM) without chronic complication (OR 1.73, 95% CI 1.19–2.51; $P = 0.004$), DM with chronic complication (OR 3.49, 95% CI 2.32–5.26; $P < 0.001$), and peripheral arterial disease (PAD) (OR 6.79, 95% CI 3.70–12.46; $P < 0.001$) were associated with a higher incidence of limb amputation among sepsis survivors. Hosmer–Lemeshow statistics indicated a goodness-of-fit for multivariable model 2 ($P > 0.05$), and the AUC of multivariable model 2 was 0.78 (95% CI 0.74–0.82) according to ROC analysis.

In multivariable model 3, the combination of norepinephrine and dopamine (OR 1.87, 95% CI 1.10–3.55; $P = 0.025$), dopamine and epinephrine (OR 3.25, 95% CI 2.02–5.95; $P < 0.001$), dobutamine and epinephrine (OR 1.52, 95% CI 1.20–4.88; $P = 0.005$), and norepinephrine and epinephrine (OR 2.10, 95% CI 1.35–3.40; $P < 0.005$) infusions were associated with a higher incidence of limb amputation among sepsis survivors. Hosmer–Lemeshow statistics indicated a goodness-of-fit for multivariable model 3 ($P > 0.05$), and the AUC of multivariable model 3 was 0.75 (95% CI 0.70–0.79) according to ROC analysis.

Discussion

In this population-based cohort study, limb amputation to treat PG in sepsis survivors, was performed at a low rate of 0.8%, and amputations at the finger and toe level were the most common (0.4%). Male sex, vasopressor infusion (epinephrine and dopamine), CRRT use for sepsis treatment, and a pre-diagnosis of PAD and DM were associated with a higher incidence of limb amputation among the sepsis survivors.

According to this study, the 90-day mortality rate in South Korean patients with sepsis was 44.0%. In a recent study, the average 90-day mortality rate due to sepsis in Europe, North America, and Australia between 2009 and 2019, was reported as 32.2% (95% CI 27.0–37.5%) [19]. The 90-day mortality rate in our cohort seems relatively higher owing to the inclusion of patients diagnosed with septic shock in addition to those with sepsis. Another study in Germany reported that the 90-day mortality rate among patients with severe sepsis or septic shock, decreased from 64.2 to 45.0% [20]. From this perspective, the 90-day mortality rate in our study may be justifiable.

The incidence of limb amputation per 100,000 person-years was reported as 195 in a diabetic population (0.19%) and 23 in a non-diabetic population (0.23%) in Sweden [21]. Another review article reported the incidence of lower extremity amputation in a diabetic population to be 78–704 per 100,000 person-years (0.08–0.7%) [22]. In addition, the incidence of major lower extremity amputation in patients with PAD, was reported to be 4.92–5.41 per 100,000 person-years (0.0049–0.0054%) [23]. Therefore, the 0.8% incidence rate of limb amputation among sepsis survivors in our study was not low when compared with that of other diabetic or general populations. Although there have been case reports of limb amputation among sepsis survivors [11, 16, 17], our study was the first to report the incidence of limb amputation for the treatment of PG in sepsis survivors in South Korea.

PG development after treatment for sepsis has been reported in many case reports and, while relatively rare, has serious sequelae [11, 17, 24, 25]. Our study findings highlight the risk factors associated with limb amputation among sepsis survivors; however, they require careful interpretation. First, our results showed that the use of dopamine and epinephrine infusion was associated with a higher incidence of limb amputation among sepsis survivors. Our study focused on sepsis patients who had been treated for a main diagnosis of sepsis from 2015 to 2016. However, in 2017, a campaign to improve sepsis survival rates was introduced [5], based on the Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock (2016) [5] that recommended norepinephrine and vasopressin as the first treatment, followed by other vasoactive medications. Epinephrine was not included in the guidelines, and dopamine was recommended for highly selective patients with a low risk of tachyarrhythmia. Therefore, it is possible that many patients with sepsis in our study have been treated with dopamine as the first vasoactive medication. Furthermore, patients with sepsis treated with epinephrine and dopamine in our study may have been refractory to norepinephrine, suggesting that they had a more severe status. Moreover, results of a multivariable model used in a recent retrospective cohort study reported that only dopamine among all the vasopressors, was associated with PG development in ICU patients [26].

Table 3 Multivariable logistic regression analysis for limb amputation among sepsis survivor

Variable	Multivariable model OR (95% CI)	*P* value
Age, year	0.98 (0.97, 0.99)	0.004
Sex, male	1.74 (1.26, 2.40)	0.001
Residence at diagnosis		
Capital city, Seoul	1	
Other metropolitan city	0.75 (0.43, 1.30)	0.307
Others	0.86 (0.59, 1.25)	0.433
Income level at diagnosis in quartile		
Q1 (lowest)	1	
Q2	1.25 (0.76, 2.06)	0.382
Q3	0.83 (0.50, 1.36)	0.452
Q4 (highest)	1.05 (0.66, 1.68)	0.831
Duration of treatment for sepsis, day	1.00 (0.98, 1.01)	0.708
Treatment of sepsis		
Norepinephrine infusion	1.10 (0.73, 1.64)	0.651
Vasopressin infusion	0.77 (0.32, 1.86)	0.565
Dopamine infusion	1.78 (1.22, 2.60)	0.003
Dobutamine infusion	1.63 (0.87, 3.02)	0.125
Epinephrine infusion	2.04 (1.30, 3.20)	0.002
IV corticosteroid	1.21 (0.79, 1.86)	0.383
CRRT use	3.34 (2.01, 5.53)	< 0.001
Mechanical ventilator use > 8 h	0.85 (0.51, 1.40)	0.514
CCI at diagnosis of sepsis, per 1 point (Model 1)	1.24 (1.13, 1.36)	< 0.001
Comorbidities for calculating CCI (Model 2)		
Myocardial infarction	0.91 (0.092, 9.04)	0.936
Congestive heart failure	1.70 (0.59, 4.88)	0.324
Peripheral vascular disease	6.79 (3.70, 12.46)	< 0.001
Cerebrovascular disease	0.80 (0.40, 1.59)	0.522
Dementia	0.77 (0.45, 1.34)	0.361
Chronic pulmonary disease	1.30 (0.65, 2.62)	0.461
Peptic ulcer disease	1.87 (0.75, 4.63)	0.177
Mild liver disease	1.40 (0.73, 2.66)	0.312
DM without chronic complication	1.73 (1.19, 2.51)	0.004
DM with chronic complication	3.49 (2.32, 5.26)	< 0.001
Hemiplegia or paraplegia	0.90 (0.41, 1.96)	0.789
Renal disease	1.65 (0.71, 3.85)	0.243
Malignancy	0.81 (0.39, 1.67)	0.572
Combination of vasopressors (Model 3)		
Norepinephrine + vasopressin infusion	1.38 (0.65, 2.67)	0.215
Norepinephrine + dopamine infusion	1.87 (1.10, 3.55)	0.025
Norepinephrine + dobutamine infusion	1.42 (0.75, 2.75)	0.285
Dopamine + epinephrine infusion	3.25 (2.02, 5.95)	< 0.001
Dobutamine + epinephrine infusion	1.52 (1.20, 4.88)	0.005
Norepinephrine + epinephrine infusion	2.10 (1.35, 3.40)	< 0.001

AUC of multivariable model 1: 0.74, (95% CI 0.69, 0.79), model 2: 0.78 (0.74, 0.82), and model 3: 0.75 (95% CI: 0.70, 0.79)

Hosmer Lemeshow Model1: Chi-square, 3.88, $df = 8$, $P = 0.868$, Model 2: Chi-square:5.60, df: 8, $P = 0.692$, and Model 3: Chi-square: 4.20, $df = 8$, $P = 0.527$

OR odds ratio, *CI* confidence interval, *CCI* Charlson comorbidity index, *DM* diabetes mellitus, *IV* intravenous, *CRRT* continuous renal replacement therapy

We also found that underlying PAD or DM were independent risk factors for limb amputation in sepsis survivors. Since PG is known to be caused due to a low-flow state in terms of the microcirculation to affected regions, leading to vessel occlusion [27], an underlying PAD might influence the development of PG in patients with sepsis. Furthermore, DM is a well-known risk factor for PAD [28], and has also been associated with the development of PG [29]. Therefore, patients with sepsis who have underlying PAD or DM should be carefully treated considering the higher risk of PG.

Our study findings regarding age and use of CRRT should be carefully interpreted. Our results focused on amputation surgery, and not on the development of PG. Therefore, there may have been older sepsis survivors with PG who did not undergo surgical limb amputation due to the risks pertaining to surgery. Additionally, it is possible that younger sepsis survivors may have undergone surgical limb amputation to facilitate rehabilitation and return to work. CRRT is usually used to treat sepsis-associated acute kidney injury [30]; its use indicates that patients treated with CRRT may have had a more severe status than other patients with sepsis not requiring CRRT treatment. Therefore, CRRT was not a causal factor but rather an associated factor for both the development of PG and limb amputation.

Our study had several limitations. First, important physiologic variables, such as body mass index, were not included in the analysis, because the NHIS database does not contain this information. Second, we used the ICD-10 codes registered in the NHIS database to calculate the CCI of sepsis survivors. However, there is a possibility that the underlying diseases specified by the ICD-10 codes may have differed from the actual underlying diseases. Third, we did not include some important patient parameters. For example, Acute Physiology and Chronic Health Disease Classification System II and The Simplified Acute Physiology Score II scores for patients with sepsis were not included in our analysis, because the NHIS database only provides data regarding the prescription of drugs, procedural information, and registered ICD-10 codes of the disease. Fourth, DIC in patients with sepsis was not considered as it is not commonly registered in the database with ICD-10 codes. Thus, the effect of DIC on PG development was not established in this study. Fifth, although we performed multivariable adjustments to control for confounders in this study, there may have been some residual and unknown confounders that could have affected our results. Lastly, there were important changes in the definition of sepsis in 2016 [31] which may have affected the results of our study, as we included sepsis patients from 2015 to 2016.

In conclusion, in this population-based cohort study in South Korea, 0.8% of sepsis survivors underwent limb amputation for treatment of PG. In addition, limb amputation was found to be more prevalent in sepsis survivors having some underlying diseases (DM and PAD) or receiving certain vasopressor treatments (epinephrine and dopamine).

Author contributions TKO designed the study, analyzed the data, interpreted the data, and drafted the manuscript; I-AS contributed to the study conceptualization, acquisition of data, and review of manuscript. All authors have given final approval for the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest The author declares that they have no competing interest.

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