Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Risk factors for extremity ischaemia in patients with septic shock: A retrospective study

Liying Gong
Chengdu Fifth People's Hospital
Taojiang Chen
Chengdu Fifth People's Hospital
Xuelian Li
Chengdu Fifth People's Hospital
Qiang Han
qianghan2023@126.com

Chengdu Fifth People's Hospital

Research Article

Keywords: Extremity Ischaemia, Septic Shock, Agranulocytosis, Vasopressors, Symmetrical peripheral gangrene

Posted Date: May 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9388121/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Extremity ischaemia is a rare but disabling complication of sepsis. Owing to the low incidence rate, data concerning the causes of extremity ischaemia among septic shock patients are lacking. The aim of this study was to explore the risk factors for extremity ischaemia in septic shock patients.

Methods

This retrospective study included patients who were diagnosed with septic shock according to the Sepsis 3.0 criteria from January 1, 2023, to June 30, 2024. The patients' demographic characteristics, laboratory test results and records of vasopressor use were collected. Logistic regression was used to identify the independent risk factors for extremity ischaemia among septic shock patients. The results of the regression analysis are shown as adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Results

The final analysis included 639 patients (median age: 73 years; 194 females), among whom 86 experienced extremity ischaemia, resulting in an incidence rate of 13.5%. Symmetrical peripheral gangrene was identified in 34 patients, corresponding to an incidence rate of 5.3%. In the multivariate analysis, age (aOR 1.026, 95% CI: 1.004–1.048; p = 0.018), international normalized ratio (INR) (aOR 1.134, 95% CI: 1.013–1.269; p = 0.029), acute physiology and chronic health evaluation II (APACHE II) score (aOR 1.034, 95% CI: 1.005–1.065; p = 0.021), agranulocytosis (aOR 2.543, 95% CI: 1.506–4.293; p < 0.001), maximum norepinephrine dosage (aOR 1.190, 95% CI: 1.033–1.372; p = 0.016) and combination vasopressor therapy (aOR 2.927, 95% CI: 1.778–4.820; p < 0.001) were independent risk factors for extremity ischaemia in septic shock patients.

Conclusions

Certain risk factors, including norepinephrine dosage, agranulocytosis, and combination vasopressor therapy, contributed to the development of extremity ischaemia. Improved blood pressure management and early recognition and removal of underlying causes are crucial for arresting the development of extremity ischaemia.

IINTRODUCTION

Sepsis is a life-threatening response to infection[1]. It affects millions of individuals worldwide annually and results in devastating complications[2].

Extremity ischaemia is known as symmetrical peripheral gangrene (SPG) and is characterized by distal ischaemia affecting two or more extremities without the occlusion of large vessels or vasculitis[3, 4].

Although rare, it is a disabling complication that affects approximately 1.6% to 8% of patients with septic shock, with 0.2% to 0.8% of these patients ultimately requiring surgical amputation [5–7]. Various infective and noninfective factors contribute to the development of SPG, which has a high mortality rate of 35% and frequently occurs in the context of disseminated intravascular coagulation (DIC) and liver shock, often secondary to sepsis and trauma[8–10]. The pathophysiology of ischaemia of the extremities remains uncertain, but it is presumed to be intricately linked to three primary factors: DIC, shock and natural anticoagulant depletion[11]. Disruption of the procoagulant–anticoagulant balance caused by DIC, combined with the persistent low-flow state induced by shock and natural anticoagulant depletion, leads to the formation of microthrombi in blood vessels[11–13].

Apart from known risk factors (such as vasopressor use, arterial line placement, elevated serum lactate levels, and bacteraemia), other factors can lead to the development of SPG since only a minority of patients with DIC and shock develop SPG[5, 14, 15]. Hence, given the high risk of disability associated with this condition, we conducted a retrospective study to not only provide additional data on this topic but also provide guidance on the prompt recognition and early identification of the underlying causes of the condition to ultimately assist in the prevention of this life-threatening complication and the prevention of limb loss.

MATERIALS AND METHODS

STUDY DESIGN AND PATIENTS

For this retrospective study, the medical records of patients diagnosed with extremity ischaemia after septic shock at Chengdu Fifth People's Hospital, Chengdu, China, from January 1, 2023, to June 30, 2024, were reviewed. All the patients with septic shock who met the International Consensus Criteria for Sepsis-3 were included in the study[1]. Extremity ischaemia was defined as the acute onset of ischaemia, with manifestations that included cold skin, bluish discolouration, acrocyanosis, and SPG[16–19]. Patients with the following conditions were excluded: extremity ischaemia due to diabetes, vascular disease and infection; age less than 18 years; pregnancy; and extremity ischaemia before admission. All information, including demographic characteristics, laboratory test results and use of vasopressors, was gathered for each patient. This study was approved by the Medical Ethics Committee for Clinical Studies of Chengdu Fifth People's Hospital and was conducted in adherence with the Declaration of Helsinki.

STATISTICAL ANALYSIS

All data were analysed with IBM SPSS statistics version 22.0 software (IBM SPSS, Armonk, NY, USA). Categorical variables were compared by Pearson's $\chi 2$ test or Fisher's exact test when appropriate. Normally distributed and nonnormally distributed continuous variables are presented as the means ± SDs and medians and quartiles [M (Q1, Q3)], respectively. Differences between the groups were compared by t tests and Mann–Whitney U tests. Logistic regression was used for univariate and multivariate analyses. Variables with a p value < 0.05 in the univariate analysis were included in the subsequent multivariate analysis based on logistic regression. All p values < 0.05 were considered to indicate statistical significance. The results of the regression analysis are presented as adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

RESULTS

From January 1, 2023, to June 30, 2024, we identified 661 patients with septic shock, among whom 108 had extremity ischaemia (EI). After 22 patients (12 with preadmission extremity ischaemia, 9 with diabetes, and 1 with arterial occlusion) were excluded, 86 patients were included in the EI group. The demographic and basic characteristics of the 639 patients with septic shock are displayed in Table 1, with an incidence rate of 13.5% (86/639) for extremity ischaemia. Among these, 34 patients experienced gangrene, resulting in an incidence rate of 5.3% (34/639). The median age of the septic shock patients was 73 years (interquartile range [IQR], 65–81), with a predominance of male patients. The most common comorbidity was hypertension, affecting 47.9% of the patients. Patients who developed extremity ischaemia had a higher mortality rate (68.6%; 59/86) than patients without extremity ischaemia did (55%; 304/553).

Table 1
The demographic and clinical characteristics of patients with sepsis shock

variable	Total (n = 639)	EI group (n = 86)	Non-EI group (n = 553)	statistics	p
Age, year	73(65,81)	77.5(68, 84)	73(65, 81)	Z = 2.415	0.016*
Sex, female	194	27	167	χ2 = 0.05	0.822
Comorbidities					
Diabetes	210	29	181	χ2 = 0.033	0.856
hypotension	306	35	271	χ2 = 2.058	0.151
CKD	55	12	43	χ2 = 3.611	0.057
Cancer	120	20	100	χ2 = 1.306	0.253
COPD	136	21	115	χ2 = 0.583	0.445
CAHD	67	12	55	χ2 = 1.274	0.259
Liver disease	41	5	36	χ2 = 0.06	0.806
Cerebral stoke	80	12	68	χ2 = 0.187	0.666
Laboratory test					
AST	145(72,431)	110(50,281)	122(69,289)	Z = 0.193	0.847
ALT	119.5(66,285.75)	144(71.8,548)	147(72,424)	Z = 1.820	0.069
Albumin	24.2(21.95,25.9)	24.5(21.8,26.6)	24.1(22.25.8)	Z = 0.737	0.461
APTT	50.9(40.02,65.8)	52.2(42.8,72.6)	50.7(40,63.6)	Z = 1.438	0.150
PT	18.4(16.1,22.1)	20(17.4,23.6)	18.1(16.1,21.7)	Z = 2.712	0.007*
D-dimer	16(8.1,30.9)	19.7(6,42.2)	15.8(8.3,29.8)	Z = 0.937	0.349
INR	1.53(1.34,1.83)	1.67(1.46,1.96)	1.5(1.32,1.8)	Z = 3.108	0.002*
Ccr	25.63(15.16,43.73)	22.9(14.5,30.5)	26.5(15.3,45.1)	Z = 2.330	0.020*
Lactate	5.9(4.110.6)	6.75(4.48,11)	5.8(4,10.5)	Z = 1.091	0.275

Abbreviations: CKD: chronic kidney disease; CAHD: coronary atherosclerotic heart disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; APTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; Ccr: creatinine clearance rate; CRP: C-reactive protein; VA: vasoconstriction agent; NE: norepinephrine

variable	Total (n = 639)	EI group (n = 86)	Non-EI group (n = 553)	statistics	p
Na	151.1(146.95,159)	150.8(146.9,159)	151.2(146.9,159.2)	Z = 0.082	0.935
CRP	237(151,280.6)	235.5(151,283.3)	238.5(151,280)	Z = 0.208	0.835
Platelet	60(25,99.5)	49.5(24.8,87.5)	62(25,101)	Z = 1.073	0.283
Agranulocytosis	141	32	99	$\chi2$ = 57.827	< 0.001*
APACHE II	29(22,34)	32.5(22.8,38)	29(22,34)	Z = 3.469	< 0.001*
Hypothermia	84	21	63	$\chi2$ = 17.022	< 0.001*
NE dose max	0.741(0.364,1.67)	1.24(0.51,2.45)	0.67(0.36,1.55)	Z = 3.017	0.003*
VA combination	194	43	151	$\chi2$ = 18.130	< 0.001*
NE day	3(2,6)	3(2,5.25)	4(2,6)	Z = 1.719	0.086
Ventilation day	6(2,13)	5(3,14)	6(2,13)	Z = 0.442	0.658
Hospitalization	12(6,19)	11(4,20)	12(6,19)	Z = 0.836	0.403
Mortality	363	59	304	$\chi2$ = 5.637	0.018*

Abbreviations: CKD: chronic kidney disease; CAHD: coronary atherosclerotic heart disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; APTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; Ccr: creatinine clearance rate; CRP: C-reactive protein; VA: vasoconstriction agent; NE: norepinephrine

All patients were categorized into the EI group or the non-EI group according to whether they had extremity ischaemia. Differences in demographics, laboratory test results and use of vasopressors between the groups are summarized in Table 2. The univariate analysis revealed that compared with the non-EI group, the EI group had a greater mean age (77.5 years vs. 73 years; OR 1.022, 95% CI: 1.003–1.042; p = 0.022), higher D-dimer levels (19.7 mg/l vs. 15.8 mg/l; OR 1.007, 95% CI: 1.014; p = 0.040), higher international normalized ratios (INRs) (1.67 vs. 1.5; OR 1.156, 95% CI: 1.033–1.294; p = 0.011), higher acute physiology and chronic health evaluation II (APACHE II) scores (32.5 score vs. 29 score; OR 1.046, 95% CI: 1.019–1.073; p = 0.001), greater maximum norepinephrine (NE) dosages (1.24 mg/kg/min vs. 0.67 mg/kg/min; OR 1.266, 95% CI: 1.112–1.021; p < 0.001), a higher incidence of hypothermia (21/86 [24.4%] vs. 63/553 [11.4%]; OR 2.513, 95% CI: 1.439–4.388; p = 0.001), a higher incidence of agranulocytosis (32/86 [37.2%] vs. 99/553 [17.9%]; OR 1.046 2.718, 95% CI: 1.668–4.428; p < 0.001), a greater percentage of patients receiving combination vasopressor therapy (43/86 [50.0%] vs. 43/553 [7.8%]; OR 2.978, 95% CI: 1.872–4.438; p < 0.001)), and poorer creatinine clearance (22.9 ml/min vs. 26.5 ml/min; OR 0.985, 95% CI: 0.973–0.997; p = 0.013). The rate of diabetes, duration of vasoconstrictor agent use, platelet counts, liver function, and duration of ventilation were comparable between the two groups.

Table 2
Univariate analysis and multivariate analysis of risk factors associated with the incidence of extremity ischemia of sepsis shock patients

variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Age, year	1.022(1.003 ~ 1.042)	0.022*	1.026(1.004 ~ 1.048)	0.018*
Sex, female	0.945(0.579 ~ 1.544)	0.822		
Comorbidities				
Diabetes	1.046(0.646 ~ 1.692)	0.856		
Hypertention	0.714(0.450 ~ 1.133)	0.153		
CKD	1.923(0.970 ~ 3.815)	0.061		
Cancer	1.373(0.796 ~ 2.368)	0.255		
COPD	1.231(0.722 ~ 2.097)	0.446		
CAHD	1.468(0.751 ~ 2.871)	0.262		
Liver disease	0.886(0.338 ~ 2.325)	0.807		
Cerebral stoke	1.157(0.597 ~ 2.239)	0.666		
Laboratory test				
AST	1.000(1.000 ~ 1.000)	0.461		
ALT	1.000(0.999 ~ 1.000)	0.272		
Albumin	1.013(0.945 ~ 1.085)	0.725		
APTT	1.003(0.998 ~ 1.008)	0.214		
PT	1.009(0.996 ~ 1.021)	0.183		
D-dimer	1.007(1.000 ~ 1.014)	0.040*	1.006(0.998 ~ 1.013)	0.135
INR	1.156(1.033 ~ 1.294)	0.011*	1.134(1.013 ~ 1.269)	0.029*
Ccr	0.985(0.973 ~ 0.997)	0.013*	0.996(0.982 ~ 1.009)	0.552
Lac	1.022(0.969 ~ 1.078)	0.426		
NA	0.996(0.971 ~ 1.021)	0.741		
CRP	1.000(0.997 ~ 1.003)	0.951		
Platelet	0.999(0.995 ~ 1.003)	0.687		

Abbreviations: CKD: chronic kidney disease; CAHD: coronary atherosclerotic heart disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; APTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; Ccr: creatinine clearance rate; Lac: lactic acid; CRP: C-reactive protein; NE: norepinephrine

variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Agranulocytosis	2.718(1.668 ~ 4.428)	0.000*	2.543(1506 ~ 4.293)	0.000*
APACHE II	1.046(1.019 ~ 1.073)	0.001*	1.034(1.005 ~ 1.065)	0.021*
Hypothermia	2.513(1.439 ~ 4.388)	0.001*	1.576(0.846 ~ 2.933)	0.152
NE dose max	1.266(1.112 ~ 1.021)	0.000*	1.190(1.033 ~ 1.372)	0.016*
VA combination	2.662(1.667 ~ 4.227)	0.000*	2.927(1.778 ~ 4.820)	0.000*
NE day	0.956(0.894 ~ 1.021)	0.178		
Ventilation day	1.017(0.995 ~ 1.039)	0.129		
Hospitalization	1.006(0.989 ~ 1.024)	0.486		

Abbreviations: CKD: chronic kidney disease; CAHD: coronary atherosclerotic heart disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; APTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; Ccr: creatinine clearance rate; Lac: lactic acid; CRP: C-reactive protein; NE: norepinephrine

In the multivariate analysis, age (aOR 1.026; 95% CI: 1.004–1.048; p = 0.018), INR (aOR 1.134, 95% CI: 1.013–1.269; p = 0.029), APACHE II score (aOR 1.034, 95% CI: 1.005–1.065; p = 0.021), agranulocytosis (aOR 2.543, 95% CI: 1.506–4.293; p < 0.001), maximum NE dosage (aOR 1.190, 95% CI: 1.033–1.372; p = 0.016) and combination vasopressor therapy (aOR 2.927, 95% CI: 1.778–4.820; p < 0.001) were identified as independent risk factors for extremity ischaemia in septic shock patients (Table 2).

DISCUSSION

Our analysis of 86 patients with extremity ischaemia revealed that although the duration of NE was not significantly associated with extremity ischaemia, the dosage of NE and combination vasopressor therapy significantly contributed to the development of extremity ischaemia. Age, INR, and agranulocytosis are also risk factors for SPG. The APACHE II score can also predict the incidence of SPG.

Furthermore, septic shock (or the initiation of NE) occurs a median of 3 days before SPG occurs[11, 20]. Theoretically, the duration of NE and the development of SPG may be correlated to some extent. However, a matched case–control study revealed that the duration of vasopressor usage has no effect on the occurrence of SPG[14]. Several studies further revealed that the time between the start of vasopressor therapy and the onset of limb ischemic necrosis is associated with a time-dependent decrease in natural anticoagulants synthesized by the liver[13, 20].

The maximum vasopressor dose and duration are not mentioned in consensus recommendations or the Survival Sepsis Campaign guidelines[21]. The role of vasopressors in septic shock patients with extremity ischaemia is controversial. Jerrold H conducted a meta-analysis and reported that there is no evidence to support that ischaemic limb necrosis is a complication of high-dose vasopressor therapy and that its

incidence cannot be accurately estimated in this high-risk population[22]. Theoretically, the use of vasopressors can contribute to extremity ischaemia, as they can induce a persistent low-flow state by activating alpha-adrenergic receptors that restrict the delivery of oxygen and nutrients[23]. Numerous studies, including the present work, have corroborated this assertion. The use of vasopressors (such as NE, dopamine, and epinephrine) is most frequently attributed to the occurrence of SPG, with phenylephrine and NE being the most frequently noted[14, 15]. Specifically, doses exceeding 0.5 mcg/kg/min are associated with ischaemic necrosis of the limbs and digits[7]. Furthermore, higher dosages are associated with a higher risk of amputation[5]. The primary approach to managing vasopressor-related extremity ischaemia involves reducing the dosage of the vasopressor according to individual tolerances[24].

During sepsis, both the immune system and coagulation system are activated, resulting in the transition of endothelial cells from anticoagulant states to procoagulant states[25]. A prolonged INR indicates the consumption of clotting factors and serves as a critical criterion for evaluating DIC[26]. The coagulopathy associated with sepsis results from the interplay between the immune system and coagulation system, which facilitates the formation of extensive thrombi in the microvasculature[9, 27]. While this response can help contain infections, it also damages endothelial cells and obstructs blood flow.

Neutrophils are pivotal in the immune response against invading pathogens. However, in patients with neutropenia and agranulocytosis, neutrophil functions[28] such as extracellular trap formation, phagocytosis, and degranulation are compromised. Consequently, invading bacteria cannot be effectively captured or eliminated in the circulation, leading to persistent damage to endothelial and tissue cells[29].

Microvascular endothelial dysfunction and microangiopathy, which arise from insulin resistance and unstable glucose levels or hyperglycaemia, render diabetes a risk factor for peripheral vascular disease[30, 31]. However, in our study, diabetes was not linked to the onset of ischaemia. These findings suggest that even patients without complicating risk factors remain susceptible to ischaemia in the context of infection.

Evidence-based recommendations for the treatment of limb ischaemia are limited. The management of underlying causes and the maintenance of haemodynamic stability are widely accepted practices. Various therapeutic interventions, including epoprostenol[32], sympathetic blockades[33], vasodilators, nitroglycerin[34], hyperbaric oxygen, and heparin[35], have been reported. However, most of these therapies are tailored to the individual, thus robust evidence of their efficacy is lacking. Additionally, early recognition and prompt management of sepsis are critical for preventing extremity ischaemia.

This study has several limitations. First, this was a single-centre retrospective study, thus the applicability of our findings to other populations is limited. Furthermore, owing to the retrospective nature of the study, some data, such as the percentage of patients with DIC, SOFA scores, and the duration of low perfusion, were not included because of objective reasons, such as limitations of the medical records system; however, we included indicators related to coagulation function, such as the APACHE II score, to reduce bias.

CONCLUSION

Extremity ischaemia is an uncommon complication among septic shock patients, and the high risk of amputation is associated with a high mortality rate. Certain risk factors, including norepinephrine dosage, agranulocytosis and combination vasopressor therapy, contributed to the development of extremity ischaemia. Since there is still no effective treatment for extremity ischaemia, improved blood pressure management and early recognition and removal of underlying causes are crucial for arresting the development of extremity ischaemia. Further clinical trials on therapy are warranted to improve the prognosis of sepsis patients at risk of extremity ischaemia.

Abbreviations

SPG
Symmetrical peripheral gangrene
DIC
Disseminated intravascular coagulation
aORs
Adjusted odds ratios
Cis
Confidence intervals
EI
Extremity ischaemia
IQR
Interquartile range
CKD
Chronic kidney disease
CAHD
Coronary atherosclerotic heart disease
ALT
Alanine aminotransferase
AST
Aspartate aminotransferase
APTT
Activated partial thromboplastin time
PT
Prothrombin time
INRs
International normalized ratios
Ccr
Creatinine clearance rate
CRP
C-reactive protein
VA
vasoconstriction agent

NE
norepinephrine
APACHE II
Acute physiology and chronic health evaluation II

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee for Clinical Studies of Chengdu Fifth People's Hospital and was conducted in adherence with the Declaration of Helsinki. The requirement for individual informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable. This study does not contain any individual person's data in any form (including images, videos, or other identifiable information).

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to privacy and ethical restrictions related to patient data but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

Not applicable.

Authors' contributions

Liying Gong and Qiang Han designed the study. Liying Gong and Taojiang Chen collected and analysed the data. Liying Gong and Xuelian Li contributed to the interpretation of results and manuscript writing. All authors read and approved the final manuscript.

Acknowledgments

Not applicable.

References

1. Seymour C, Liu V, Iwashyna T, Brunkhorst F, Rea T, Scherag A, Rubenfeld G, Kahn J, Shankar-Hari M, Singer M *et al*: **Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *JAMA* 2016, **315**(8):762-774.
2. Carolin F, André S, Neill K J A, Christiane S H, Thomas T, Peter S, Derek C A, Konrad R: **Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations**. *Am J Respir Crit Care Med* 2015, **193**(3).
3. Hutchinson J: **Notes of Uncommon Cases**. *Br Med J* 1891, **2**(1592):8-9.
4. Yuanyuan C, Kai L, Xiujuan X, Gaofei W, Lianghua Z, Junjing Z, Chuji C: **Symmetrical peripheral gangrene caused by urosepsis: Case reports and literature review**. *Medicine (Baltimore)* 2024, **103**(40).
5. Reitz K, Kennedy J, Rieser C, Hlavin C, Gershengorn H, Neal M, Bensen N, Linstrum K, Prescott H, Rosengart M *et al*: **The Epidemiology of Extremity Threat and Amputation after Vasopressor-Dependent Sepsis**. *Annals of the American Thoracic Society* 2022, **19**(4):625-632.
6. Oh TK, Song I-A: **Incidence and associated risk factors for limb amputation among sepsis survivors in South Korea**. *Journal of Anesthesia* 2020, **35**(1):51-58.
7. Levy JH, Ghadimi K, Faraoni D, van Diepen S, Levy B, Hotchkiss R, Connors JM, Iba T, Warkentin TE: **Ischemic limb necrosis in septic shock: What is the role of high-dose vasopressor therapy?** *Journal of Thrombosis and Haemostasis* 2019, **17**(11):1973-1978.
8. Subhadarshani S, Aggarwal M, Kumar V: **Symmetrical Peripheral Gangrene Due to Disseminated Intravascular Coagulation**. *Dermatology practical & conceptual* 2019, **9**(3):220-221.
9. Iba T, Levy JH: **Sepsis-induced Coagulopathy and Disseminated Intravascular Coagulation**. *Anesthesiology* 2020, **132**(5):1238-1245.
10. Molos M, Hall J: **Symmetrical peripheral gangrene and disseminated intravascular coagulation**. *Archives of dermatology* 1985, **121**(8):1057-1061.
11. Warkentin TE: **Limb Ischemic Necrosis Secondary to Microvascular Thrombosis: A Brief Historical Review**. *Semin Thromb Hemost* 2024, **50**(5):760-772.
12. Alhumam T, Alhumam AA, Alhumaidi I, Al Rajeh I, Alduhailan Y: **Relationship Between Symmetrical Peripheral Gangrene Patients and Using Vasopressors in the Intensive Care Unit**. *Cureus* 2024, **16**(4):e58117.
13. Theodore E W, Shuoyan N: **Symmetrical peripheral gangrene in critical illness**. *Transfus Apher Sci* 2021, **60**(2).
14. Kwon JW, Hong MK, Park BY: **Risk Factors of Vasopressor-Induced Symmetrical Peripheral Gangrene**. *Ann Plast Surg* 2018, **80**(6):622-627.
15. Landry GJ, Mostul CJ, Ahn DS, McLafferty BJ, Liem TK, Mitchell EL, Jung E, Abraham CZ, Azarbal AF, McLafferty RB *et al*: **Causes and outcomes of finger ischemia in hospitalized patients in the intensive care unit**. *J Vasc Surg* 2018, **68**(5):1499-1504.
16. Santistevan J: **Acute Limb Ischemia: An Emergency Medicine Approach**. *Emergency medicine clinics of North America* 2017, **35**(4):889-909.
17. Jung K, Nho J, Cho H, Hong S, Won S, Chun D, Kim B: **Amputation of multiple limbs caused by use of inotropics: Case report, a report of 4 cases**. *Medicine* 2018, **97**(5):e9800.

18. Wang M, Sun T, Dong L, Huang S, Liu J: **Symmetrical peripheral gangrene: potential mechanisms and therapeutic approaches in severe COVID-19**. *Frontiers in cardiovascular medicine* 2023, **10**:1280625.
19. Uncu Ulu B, Yiğenoğlu TN, Hacıbekiroğlu T, Sağlam DA, Kılınç A, İskender G, Çakar MK, Dal MS, Altuntaş F: **Recovery of Symmetrical Peripheral Gangrene of Limbs in a Patient After Performing Hemoadsorption in Septic Shock**. *Journal of Clinical Apheresis* 2021, **36**(4):649-653.
20. Warkentin T: **Symmetrical Peripheral Gangrene: Mechanisms for Limb Loss in the ICU in Patients With Retained Pulses**. *Clinical Pulmonary Medicine* 2018, **25**:61-66.
21. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, McIntyre L, Ostermann M, Prescott HC *et al*: **Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021**. *Intensive Care Med* 2021, **47**(11):1181-1247.
22. Jerrold H L, Kamrouz G, David F, Sean vD, Bruno L, Richard H, Jean M C, Toshiaki I, Theodore E W: **Ischemic limb necrosis in septic shock: What is the role of high-dose vasopressor therapy?** *J Thromb Haemost* 2019, **17**(11).
23. Anastassia N, Katharine D H, Arianna T, Frederick V R, Joseph J T: **Why Not Life and Limb? Vasopressor Use in Intensive Care Unit Patients the Cause of Acute Limb Ischemia**. *Hand (N Y)* 2018, **15**(2).
24. Noura A, Esraa H, Abbas B J, Shikha J, Mohamed E, Renee G, Sadik A, Mool C, Nitesh K J, Syed Anjum K: **Management of Vasopressor-Induced Acute Limb Ischemia (VIALI) in Septic Shock**. *Cureus* 2023, **14**(12).
25. Jérémie J, Judith H, Can I, Hafid A-O: **Endothelial Responses in Sepsis**. *Am J Respir Crit Care Med* 2020, **202**(3).
26. Iba T, Umemura Y, Watanabe E, Wada T, Hayashida K, Kushimoto S: **Diagnosis of sepsis-induced disseminated intravascular coagulation and coagulopathy**. *Acute Med Surg* 2019, **6**(3):223-232.
27. Marcel L, Tom vdP: **Inflammation and coagulation**. *Crit Care Med* 2010, **38**(0).
28. Maria Florencia D, Do-Hoon K, Suk-Joong L, Hee-June K, Erica K, Hyun-Joo L: **Identification of risk factors and clinical outcomes for symmetric peripheral gangrene: A new scoring system using a common data model database**. *J Orthop Surg (Hong Kong)* 2024, **32**(2).
29. Zhang H, Wang Y, Qu M, Li W, Wu D, Cata JP, Miao C: **Neutrophil, neutrophil extracellular traps and endothelial cell dysfunction in sepsis**. *Clinical and Translational Medicine* 2023, **13**(1).
30. Caporali A, Pani E, Horrevoets AJ, Kraenkel N, Oikawa A, Sala-Newby GB, Meloni M, Cristofaro B, Graiani G, Leroyer AS *et al*: **Neurotrophin p75 receptor (p75NTR) promotes endothelial cell apoptosis and inhibits angiogenesis: implications for diabetes-induced impaired neovascularization in ischemic limb muscles**. *Circ Res* 2008, **103**(2):e15-26.
31. Shi Y, Vanhoutte PM: **Macro- and microvascular endothelial dysfunction in diabetes**. *J Diabetes* 2017, **9**(5):434-449.
32. Hayes M, Yau E, Hinds C, Watson J: **Symmetrical peripheral gangrene: association with noradrenaline administration**. *Intensive care medicine* 1992, **18**(7):433-436.
33. Kuberski T, Robinson L, Schurgin A: **A case of plague successfully treated with ciprofloxacin and sympathetic blockade for treatment of gangrene**. *Clin Infect Dis* 2003, **36**(4):521-523.

34. Jadhav DV, Mendonca D, Kotinatot S, Shankar S, Mazmi MA: **Nitroglycerin patch use in digital ischemia secondary to sepsis: a case report**. *Pan Afr Med J* 2021, **38**:114.
35. Vishnu K, R Scott S: **Sepsis-induced digital ischaemia in a professional pianist, in the absence of vasopressors**. *BMJ Case Rep* 2019, **12**(10).