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Predictors of sepsis, intensive care unit admission, and death in patients hospitalized for complicated skin and soft tissue infections: Retrospective study at a large tertiary-care center

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Abstract

Background: Complicated skin and soft tissue infections often lead to poor health outcomes, with necrotizing skin and soft tissue infections occurring in 70%–80% of hospitalized patients and a mortality rate typically exceeding 20%. The current study's main objective was to identify early predictors of sepsis, intensive care unit admission, and mortality in hospitalized complicated skin and soft tissue infection patients.

Methods: A retrospective review of records from 235 adult complicated skin and soft tissue infection patients admitted from 2012 to 2022 was conducted. Collected data included demographics, medical history, clinical presentation, treatment, and outcomes. Laboratory results were used to calculate the Laboratory Risk Indicator for Necrotizing Fasciitis score for diagnosing necrotizing fasciitis. Predictors of sepsis, intensive care unit admission, and death were identified using logistic regression analysis.

Results: Of the 235 patients, 42.1% were wheelchair-bound or bedridden; 93.2% had diabetes, 76.2% had cardiovascular disease, and 33.6% had kidney disease. Necrotizing fasciitis criteria were met by 75% of patients. Sepsis was diagnosed in 27.7% of patients, while 30.6% required intensive care unit admission, and 20.4% did not survive hospital discharge. Low mean arterial pressure and vasopressor use were significant predictors of all three severe outcomes, with pre-existing kidney disease also a predictor of in-hospital death. The Glasgow Coma Scale predicted both intensive care unit admission and sepsis, but not death.

Conclusions: Low mean arterial pressure, vasopressor use, and pre-existing kidney disease are key predictors of in-hospital death in patients hospitalized for complicated skin and soft tissue infection. The former two, and the patient's Glasgow Coma Scale, also appear to predict both intensive care unit admission and sepsis.

Keywords

Skin and soft tissue infection, necrotizing fasciitis, sepsis, critical care, mortality, risk factors, multivariable analysis

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Introduction

Bacterial skin and soft tissue infections (SSTIs), defined as bacterial invasion of the epidermis, dermis, and subcutaneous tissue, are common, accounting for roughly 2 million visits to emergency departments annually in the United States alone.[1,2] Though most are managed out of hospital, they account for roughly 6% of all hospital admissions for

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infection, and the emergence of antibiotic-resistant bacterial strains has caused this percentage to steadily increase.[3] Complicated skin and soft tissue infections (cSSTIs) are those that include a range of clinical presentations, often in the presence of complicating comorbidities.[1,4–7] Presentations include deep-seated infection; tissue injury to the point of necrosis, including necrotizing fasciitis; the need for surgical debridement that may be extensive, ultimately requiring surgical reconstruction; neutropenia; signs of systemic sepsis, including septic shock; and a high rate of mortality.[1,8–10] For such patients, hospitalization is usually required.

Sepsis caused by a cSSTI is a particularly serious clinical scenario, associated with prolonged hospital stays; the potential for repeated surgical debridement procedures, including amputation; and mortality rates that, though most commonly reported in the 20% range, can be 50% or greater, depending on the causative organism.[8–10] Though most SSTIs are caused by Staphylococcus species organisms,[1,11,12] gram-negative organisms, including atypical organisms like *Acinetobacter baumannii* and *Vibrio vulnificus*, also are seen that are especially difficult to treat and associated with particularly high rates of mortality.[8,13–16] Necrotizing soft tissue infections are especially aggressive and rapidly progressive. Yet, they are often missed early in a patient's clinical course, significantly increasing the risk of poor and even catastrophic outcomes.[10,14,17,18] Despite this, relatively sparse research exists on risk factors for cSSTI associated with sepsis, as well as for poor outcomes, including mortality, in patients admitted to hospital with a cSSTI and sepsis or septic shock.

The primary objective of the current study was to characterize patients with a cSSTI admitted to one of Saudi Arabia's largest tertiary care centers over a decade. More specifically, we sought to characterize the clinical presentation of cSSTI patients, distinguishing (a) between those requiring versus not requiring admission to the intensive care unit (ICU); (b) between those ultimately diagnosed versus not diagnosed with sepsis; and (c) between those who survive to hospital discharge versus those who do not. We also sought to assess the impact of several previously reported risk factors for sepsis, ICU admission, and death.

Methods

All data were collected retrospectively on patients presenting with an SSTI between 2012 and 2022 to King Abdulaziz University Hospital (KAUH), in Jeddah, Saudi Arabia. The KAUH is one of the largest tertiary care centers in the Middle East with almost 900 inpatient beds.

To be eligible for inclusion, patients had to have been admitted between January 1st, 2012 and December 31st, 2022, for management of an SSTI and to be at least 18 years old. Patients not meeting either of these two criteria, and patients being treated for major trauma or other major illness (e.g., end-stage cancer) were excluded. In the absence of widely recognized diagnostic criteria for SSTI, all initial diagnoses of SSTI were made based on physical examination findings, supplemented by laboratory analysis and imaging, as deemed appropriate, as recommended in numerous international guidelines published over the past decade.[19–23] Complicated SSTI was diagnosed in patients diagnosed with an SSTI who (a) met the criteria for necrotizing fasciitis using the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, a tool first described by Wong et al.[24] as a means to diagnose necrotizing fasciitis (NF), (b) developed signs of and were diagnosed with systemic sepsis, or (c) required admission to the ICU for treatment of their SSTI.

Data collected included data on patient demographics (age, sex, nationality) and morphometrics (height, weight, body mass index (BMI)); past and concurrent illnesses, including diabetes mellitus, other endocrine disease, cardiovascular disease (CVD), gastrointestinal or liver disease, kidney disease, hematological disease or cancer, other cancer, pre-existing infectious disease, neurological disease, and autoimmune disease; Glasgow Coma Scale (GCS) score; recent hospitalization or surgery, defined as having occurred within 30 days of the index admission; risk factors for infection; initial site of infection (e.g., foot, sacral ulcer); admission service; admission vital signs; specific baseline laboratories obtained within the first 24 h of hospitalization; SSTI treatment administered; whether admission to the ICU was required; whether vasopressor circulatory support was required (e.g., dopamine, epinephrine, or norepinephrine); and clinical outcomes, including sepsis, ICU admission, length of ICU stay, length of hospital stay, mortality, and hospital re-admission for the same SSTI. Sepsis was determined by the clinical team according to the international consensus on sepsis and septic shock definition. Specific laboratories obtained at baseline were the six components of the LRINEC score, a tool first described by Wong et al.[24] as a means to diagnose NF and subsequently found to be moderately to highly accurate for this purpose.[25,26]

Because data collection was retrospective and no patients were identified, upon ethics approval, the institutional review board informed the investigators that they did not require patient consent.

Data analysis

The sample size we selected was based on the two premises that (a) 10–15 patients are needed per independent variable entered into regression analysis and (b) roughly 10–15 variables would meet our entry criterion (see below) into the regression models. Hence, we determined that a maximum of 225 patients would be needed.

All data were imported into SPSS version 28 from Excel, then screened for outliers (e.g., age < 18), and missing or improperly entered values using both descriptive analysis and the Explore function. All continuous variables were assessed for normal versus non-normal distribution using the Shapiro–Wilk's test to determine whether inferential

analysis would require parametric or non-parametric tests. Continuous variables were then summarized as means with standard deviation, minimum, and maximum values, while categorical variables were summarized as absolute numbers with percentages.

For bivariate analysis, since almost all the continuous variables were found to be non-normally distributed and all comparisons were limited to two groups, inter-group comparisons were performed using the Mann–Whitney *U* test. Since no data cells were found to contain fewer than five patients, all inter-group comparisons of categorical variables were performed using Pearson χ^2 analysis, as opposed to Fisher's Exact test. For bivariate analysis, the criterion for statistical significance was a two-tailed *p*-value set at $\leqslant 0.001$ to adjust for multiple comparisons.

Multivariable analysis was also performed to identify variables statistically impacting sepsis, ICU admission, and death (each absent vs present = 0/1), using hierarchical logistic regression analysis with independent variables identified as different between groups at $p \leqslant 0.20$ entered by forward entry, and variables with $p \leqslant 0.10$ retained in final models. Risk factors of primary interest included both (a) previously reported risk factors like patient age, sex, BMI, diabetes, CVD, and GCS score at the time of hospital admission; and (b) any variables identified as different between each pair of patients groups (e.g., requiring vs not requiring ICU admission). Since an LRINEC score was only computable for $N = 118$ of the 235 patients ultimately included in analysis (mostly due to missing C-reactive protein (CRP) values), and because LRINEC scores of both 6 and 7 have been proposed as the cutoff distinguishing NF from other SSTI,[24–30] for each of the multivariable models, the LRINEC score was only entered into models for testing after they had already been evaluated with all 235 patients, to prevent the loss of data caused by only 118 LRINEC scores; once in each model with the classification threshold set at 6, and once with the threshold set at 7.

Results

A total of 235 patients met the study's eligibility criteria and were entered into analysis, among whom 166 (70.6%) were males and 69 (29.4%) females, ranging from 18 to 93 years old. Almost 60% either were overweight ($n = 73$, 31.1%) or had class I through class III obesity ($n = 67$, 28.5%). Diabetes mellitus ($n = 170$, 93.2%) and hypertension ($n = 165$, 70.2%) were highly prevalent. Almost three in four ($n = 170$, 72.3%) had both diabetes and some form of CVD. Roughly one in four ($n = 59$, 25.1%) had either been hospitalized or had an inpatient or outpatient surgical procedure within the preceding 30 days. Six in 10 ($n = 142$, 60.4%) were admitted to the hospital already on one or more antibiotics, while 9.4% ($n = 22$) were taking a systemic corticosteroid. Further baseline characteristics of the patient cohort are summarized in Table 1.

Ninety-five percent ($n = 223$) of the SSTI involved the lower extremity, most commonly the foot ($n = 162$, 68.9%). Eight patients presented with sacral ulcers (3.4%), three of these patients being wheelchair-bound and two bedridden. Seventy-one patients (32.2%) presented with a baseline systolic blood pressure (SBP) that was elevated, and 32 (14.5%) with a diastolic blood pressure (DBP) that was elevated. However, another 73 patients (33.2%) had mean arterial pressures (MAPs) that were either from 65 to 85 mmHg ($N = 65$, 27.7%) or under 65 mmHg ($N = 8$, 3.4%); and 48 (21.5%) required early circulatory support with one or more vasopressor drugs. Twenty-six patients (11.9%) had a GCS score either from 9 to 12, signifying moderate coma, or from 3 to 8, signifying deep coma. Sepsis was diagnosed in 65 patients (27.7%), and 72 patients (30.6%) required either immediate admission or later transfer to the ICU. Among the 118 patients with data adequate to permit the calculation of an LRINEC score, 89 (75.4%) met the 7-point and 97 (82.2%) the 6-point classification threshold for NF. Forty-eight patients died during their initial hospitalization (20.4% of the cohort), a rate that was virtually identical to the 20.2% ($n = 89$) and 20.6% ($n = 97$) of patients with presumed NF using the 7-point and 6-point classification thresholds, respectively. In total, 28 patients (11.9%) required hospital re-admission after their index admission for SSTI, with no deaths. The results of initial evaluations and baseline laboratories are summarized in Table 2.

Tables 3–5 summarize the results of bivariate comparisons. Since all inter-group comparisons of continuous variables were performed using the Mann–Whitney *U* test, the test statistic "*U*" is used in Tables 3–5. Inter-group differences at $p < 0.001$ included more sepsis patients taking preadmission systemic corticosteroids. Sepsis patients also had more than a 50-fold higher rate of vasopressor use, an eight-fold higher rate of a GCS < 13, and an 82% increase in baseline serum creatinine level. They also were more than seven-fold as likely to require ICU admission (83.1% vs 11.2%), and over five-fold as likely to die in a hospital (49.2% vs 9.4%). They also, even considering deaths, spent an average of 10.5 extra days in the hospital (Table 3).

Comparing patients admitted versus not admitted to the ICU, and again using $p < 0.001$ as the adjusted criterion for statistical significance, bivariate analysis found ICU patients to have significantly higher rates of being underweight; having pre-existing hypertension, kidney disease, lung disease, and the triad of diabetes, CVD, and kidney disease; having an indwelling urinary catheter; requiring vasopressor support; and having a GCS < 13 (Table 4). Their respiratory rate also was higher, and their serum creatinine level was 94% higher; the rate of sepsis was almost 11-fold as high; hospital stay almost twice as long (40.1 vs 20.8 days); and mortality rate 24-fold as high as patients not requiring ICU admission.

Table 1. Baseline characteristics of the sample, $N = 235$.

Characteristics	Number	Percentage (%)
Demographic characteristics		
Females	69	29.4
Males	166	70.6
Age < 30	4	1.7
Age 30–49	34	14.5
Age 50–69	139	59.1
Age 70+	58	24.7
Saudi	88	37.4
Non-Saudi	142	60.4
Unknown	5	2.1
Morphometric characteristics and ambulatory status		
Underweight (BMI < 18.5 kg/m^2)	8	3.4
Normal weight (BMI 18.5–24.9)	87	37.0
Overweight (BMI 25–29.9)	73	31.1
Class I obesity (BMI 30–34.9)	34	14.5
Class II obesity (BMI 35–39.9)	25	10.6
Class III obesity (BMI 40+)	8	3.4
Ambulatory (± assistance)	136	57.9
Wheelchair-bound	70	29.8
Bedridden	29	12.3
Comorbid conditions		
Diabetes mellitus	219	93.2
Hypertension	165	70.2
Ischemic heart disease	68	28.9
Heart failure	53	22.6
Kidney disease	79	33.6
Diabetes and CVD	170	72.3
Diabetes and kidney disease	71	30.2
Diabetes, CVD, and kidney disease	65	27.7
Thyroid or parathyroid disease	12	5.1
Neurological disease	55	23.4
Gastrointestinal and/or liver disease	14	6.0
Pre-existing infectious disease	32	13.6
Hematological disease/cancer	21	8.9
Other cancer	11	4.7
Other risk factors		
Smoking history	36	15.3
Healthcare worker	3	1.3
Recent hospitalization or surgery	59	25.1
Indwelling catheter	32	13.6
Antibacterial drug use pre-admission	142	60.4
Antifungal use pre-admission	10	4.3
Antiviral use pre-admission	4	1.7
Systemic corticosteroid	22	9.4

The greatest number of significant inter-group differences (16 of them) was identified comparing patients who died versus survived hospital discharge, as summarized in Table 5. They include statistically higher rates of numerous pre-morbid conditions in patients who died, including ischemic heart disease (52.1% vs 23.0%), heart failure (41.7% vs 17.6%), chronic kidney disease (CKD, 60.4% vs 26.7%), and lung disease (18.5% vs 8.0%), as well as higher rates of the combinations of diabetes and CKD, and diabetes, CKD, and CVD. More patients who died had an indwelling urinary catheter prior to ICU admission (33.3% vs 8.6%). They had lower mean systolic (119.4 vs 133.9) and diastolic (66.5 vs 77.1) blood pressures upon hospital admission and more required a vasopressor after hospital admission (60.9% vs 11.3%). Their mean GCS was lower (13.0 vs 14.5), and 10-fold as many had a GCS < 13 (30.4% vs 2.7%). They also had an 85% increase in serum creatinine relative to survivors (300.6 vs 161.8 μmol/L). In addition, they were almost six-fold as likely to have been admitted to an ICU (91.7% vs 15.5%), and almost four times as likely to have been diagnosed with sepsis (66.7% vs 17.6%). They spent an average of 19 more days in the hospital before death than patients who survived to discharge (41.8 vs 23.0 days). Neither the total LRINEC score, nor either LRINEC threshold score (6 or 7) met the adjusted $p < 0.001$ criterion for statistical significance for sepsis, ICU admission, or death.

Relative to bivariate analysis, multivariable analysis identified far fewer variables being statistically linked to sepsis, ICU admission, or death. The strongest predictor for all three outcomes was the need for circulatory support with one or more vasopressor drugs, always significant at $p < 0.001$. Low MAP was the only other variable to remain in all three binary logistic regression models. GCS under 13 was linked to both sepsis and ICU admission, but not death. The only three predictors of death were the need for vasopressor support, low MAP, and pre-existing kidney disease. No iteration of the LRINEC score—total score, 6-point threshold, or 7-point threshold—exerted any impact upon the models for sepsis, ICU admission, or death. The full results of the multivariable analysis are summarized in Table 6.

Discussion

cSSTI accounts for just 2%–6% of all hospital admissions among patients admitted for infectious reasons.[3,4,7] However, most cSSTI patients have multiple pre-existing morbidities—especially diabetes and CVD—and most are seniors, all of which renders them particularly susceptible to poorer outcomes.[4–7] This is further complicated by a strong tendency for clinicians to overlook severe, necrotizing infections early during a patient's clinical course, and necrotizing SSTIs have mortality rates exceeding 50% in some settings, depending on each patient's underlying health status and the causative organism(s).[6,8] Several classification tools have been developed to assist in recognizing necrotizing infections, to serve as adjuncts to generally non-specific physical findings.[6] However, debate remains as to which tool is the most accurate, and which threshold score to use within particular tools.[26,27,29] Moreover, very little research has been published to guide clinicians in determining which hospitalized SSTI patients, with or without necrotizing infections, are at greater than average risk of adverse outcomes, including death, and hence, warrant more aggressive management.

Table 2. Clinical characteristics and outcomes.

Characteristics	Number	Percentage (%)	Total
Site of infection			
Foot	162	68.9	235
Lower extremity ± foot	61	26.0	
Sacrum	8	3.4*	
Other	4	1.7	
Baseline cardiovascular status			
Systolic BP < 90 mmHg	3	1.4	221
Systolic BP 90–140 mmHg	147	66.5	
Systolic BP 140–180 mmHg	68	30.8	
Systolic BP > 180 mmHg	3	1.4	
Diastolic BP < 60 mmHg	39	17.7	220
Diastolic BP 60–90 mmHg	149	67.7	
Diastolic BP 91–120 mmHg	30	13.6	
Diastolic BP > 120 mmHg	2	0.9	
Mean arterial pressure (MAP) < 65	8	3.6	220
MAP 65–85	65	29.5	
MAP 86–105	106	48.2	
MAP 106–130	39	17.7	
MAP > 130	2	0.9	
Vasopressor used	48	21.5	223
Vasopressor not used	175	78.5	
Baseline neurological status			
Glasgow coma scale (GCS) score 3–8	9	4.1	219
Glasgow coma scale (GCS) score 9–12	17	7.8	
Glasgow coma scale (GCS) score 13–15	193	88.1	
Baseline laboratory results			
WBC < 15 cells/μL	133	57.6	232
WBC 15–25 cells/μL	67	29.0	
WBC > 25 cells/μL	32	13.9	
Hemoglobin > 13 g/dL	13	5.6	233
Hemoglobin 11–13.5 g/dL	55	23.6	
Hemoglobin < 11 g/dL	165	70.8	
C-reactive protein ⩽ 141 mg/L	19	15.0	127
C-reactive protein > 141 mg/L	108	85.0	
Blood glucose ⩽ 10 mg/dL	89	42.0	212
Blood glucose > 10 mg/dL	123	58.0	
Serum sodium ⩾ 135 mEq/L	118	50.6	233
Serum sodium < 135 mEq/L	115	49.4	
Serum creatinine ⩽ 141 μmol/L	31	13.4	89
Serum creatinine > 141 μmol/L	58	25.0	
LRINEC score ⩾ 7	89	75.4	118
LRINEC score ⩾ 6	97	82.2	
Outcomes			
Sepsis diagnosed	65	27.7	235
ICU admission	72	30.6	
Death during 1st admission	48	20.4	235
Hospital discharge (home or other care)	188	80.0	
Hospital readmission	28	11.9	28
Death during repeat admission	0	0.0	

Source: Glasgow Coma Scale per Teasdale et al.[31]
The term "pre-admission" refers to occurrences that extended over time prior to hospital admission; while "baseline" refers to characteristics present at the time of admission.
BP: blood pressure; HTN: hypertension; WBC: white blood Cell; ICU: intensive care unit.
*3.4% = 1 of the 29 patients readmitted to the hospital.

Table 3. Comparing septic versus non-septic patients.

Characteristics	No sepsis	Sepsis	Test statistic*	Significance
Number of patients	170	65		
% Male	70.6%	70.8%	$\chi^2 = 0.008$	$p = 0.98$
Mean age (years)	60.0	61.5	$U = 0.008$	$p = 0.93$
% Age > 50 years	82.9%	86.2%	$\chi^2 = 0.358$	$p = 0.55$
% Saudi	42.9%	23.1%	$\chi^2 = 7.921$	$p = 0.005$
Mean body mass index (BMI)	28.0	26.3	$U = 2.446$	$p = 0.12$
% Underweight	1.2%	9.2%	$\chi^2 = 9.276$	$p = 0.002$
% Overweight	34.1%	23.1%	$\chi^2 = 2.667$	$p = 0.10$
% Obesity	30.6%	23.1%	$\chi^2 = 1.302$	$p = 0.25$
% Either wheelchair-bound or bedridden	40.0%	47.7%	$\chi^2 = 1.141$	$p = 0.29$
% Diabetes[32]	93.5%	92.3%	$\chi^2 = 0.110$	$p = 0.74$
% Cardiovascular disease (CVD)	71.2%	89.2%	$\chi^2 = 8.444$	$p = 0.004$
% Hypertension	66.5%	80.0%	$\chi^2 = 4.115$	$p = 0.042$
% Ischemic heart disease	27.1%	33.8%	$\chi^2 = 1.053$	$p = 0.31$
% Heart failure	22.4%	23.1%	$\chi^2 = 0.014$	$p = 0.91$
% Chronic kidney disease (CKD)	27.6%	49.2%	$\chi^2 = 9.816$	$p = 0.002$
% Lung disease	8.8%	18.5%	$\chi^2 = 4.295$	$p = 0.038$
% With DM and CVD	67.6%	84.6%	$\chi^2 = 7.448$ ($df = 2$)	$p = 0.024$
% With DM and CKD	70.6%	55.4%	$\chi^2 = 7.478$ ($df = 2$)	$p = 0.024$
% With DM, CVD, and CKD	21.8%	43.1%	$\chi^2 = 13.619$ ($df = 3$)	$p = 0.003$
% Smoking history	13.5%	20.0%	$\chi^2 = 1.518$	$p = 0.22$
% With recent hospitalization or surgery	25.9%	24.6%	$\chi^2 = 0.040$	$p = 0.84$
% With catheter in place	10.0%	23.1%	$\chi^2 = 6.836$	$p = 0.009$
% With pre-admission antibiotics	59.4%	63.1%	$\chi^2 = 0.264$	$p = 0.61$
% With pre-admission corticosteroids	4.7%	21.5%	$\chi^2 = 15.701$	$p < 0.001$
% With foot ulcer	68.8%	69.2%	$\chi^2 = 1.919$ ($df = 3$)	$p = 0.59$
% With leg ulcer	25.9%	26.2%		
% With sacral or another ulcer	5.3%	4.6%		
Mean SBP	133.81	123.6	$U = 3.748$	$p = 0.053$
Mean DBP	76.7	70.41	$U = 8.012$	$p = 0.005$
Mean pulse pressure	57.11	52.67	$U = 0.023$	$p = 0.88$
Mean MAP	95.55	87.79	$U = 4.311$	$p = 0.038$
% Started on a vasopressor	1.3%	70.8%	$\chi^2 = 131.707$	$p < 0.001$
Mean respiratory rate	20.24	21.89	$U = 10.946$	$p < 0.001$
Mean Glasgow coma score (GCS)	14.77	12.83	$U = 5.627$	$p < 0.001$
% With GCS < 13	3.8%	31.7%	$\chi^2 = 33.387$	$p < 0.001$
Mean WBC count (cells/μL)	14.2	18.9	$U = 16.177$	$p = 0.013$
Mean serum hemoglobin (g/dL)	10.2	9.0	$U = 8.676$	$p = 0.003$
Mean C-reactive protein (mg/L)	107.9	150.7	$U = 2.028$	$p = 0.15$
Mean serum glucose (mg/dL)	12.6	11.9	$U = 1.674$	$p = 0.196$
Mean serum sodium (mEq/L)	133.6	135.9	$U = 1.265$	$p = 0.26$
Mean serum creatinine (μmol/L)	155.2	283.2	$U = 15.213$	$p < 0.001$
Mean blood lactate (mmol/L)	2.5	3.9	$U = 2.158$	$p = 0.14$
LRINEC score ⩾ 6	75.9%	97.1%	$\chi^2 = 7.591$	$p = 0.006$
LRINEC score ⩾ 7	67.5%	94.3%	$\chi^2 = 9.550$	$p = 0.002$
% Admitted to the ICU	11.2%	83.1%	$\chi^2 = 113.516$	$p < 0.001$
Mean length of hospital stay (days)	23.9	34.4	$U = 13.558$	$p < 0.001$
% Re-hospitalized	14.3%	17.6%	$\chi^2 = 0.248$	$p = 0.62$
% Mortality	9.4%	49.2%	$\chi^2 = 45.870$	$p < 0.001$

Source: Glasgow Coma Scale per Teasdale et al.[31]

The term "pre-admission" refers to occurrences that extended over time prior to hospital admission, while "baseline" refers to characteristics present at the time of admission.

*All tests to one degree of statistical freedom ($df = 1$) unless otherwise specified.

Table 4. Comparing patients admitted versus not admitted to the intensive care unit (ICU).

Characteristics	No ICU	ICU	Test statistic*	Significance
Number of patients	162	73		
% Male	69.1%	74.0%	$\chi^2 = 0.568$	$p = 0.45$
Mean age (years)	59.1	63.4	$U = 0.506$ ($df = 1$)	$p = 0.48$
% Age > 50 years	81.5%	89.0%	$\chi^2 = 2.122$	$p = 0.15$
% Saudi	43.2%	24.7%	$\chi^2 = 8.627$	$p = 0.013$
Mean body mass index (BMI)	28.1	26.4	$U = 0.889$ ($df = 1$)	$p = 0.35$
% Underweight	0.6%	9.6%	$\chi^2 = 12.318$	$p < 0.001$
% Overweight	31.5%	30.1%	$\chi^2 = 0.042$	$p = 0.84$
% Obesity	31.5%	21.9%	$\chi^2 = 2.258$	$p = 0.13$
% Either wheelchair-bound or bedridden	39.5%	47.9%	$\chi^2 = 1.470$	$p = 0.23$
% Diabetes mellitus	92.6%	94.5%	$\chi^2 = 0.295$	$p = 0.59$
% Cardiovascular disease (CVD)	69.1%	91.8%	$\chi^2 = 14.217$	$p = 0.004$
% Hypertension	63.0%	86.3%	$\chi^2 = 13.106$	$p < 0.001$
% Ischemic heart disease	23.5%	41.1%	$\chi^2 = 7.614$	$p = 0.006$
% Heart failure	17.9%	32.9%	$\chi^2 = 6.461$	$p = 0.011$
% Chronic kidney disease (CKD)	26.5%	49.3%	$\chi^2 = 11.694$	$p < 0.001$
% Lung disease	6.2%	23.3%	$\chi^2 = 14.495$	$p < 0.001$
% Hematological disease or cancer	5.6%	16.4%	$\chi^2 = 7.324$	$p = 0.007$
% With DM and cardiovascular disease (CVD)	66.0%	86.3%	$\chi^2 = 11.182$ ($df = 2$)	$p = 0.004$
% With DM and chronic kidney disease (CKD)	23.5%	45.2%	$\chi 2 = 11.845$ ($df = 2$)	$p = 0.003$
% With DM, CVD, and CKD	19.8%	45.2%	$\chi^2 = 20.574$ ($df = 3$)	$p < 0.001$
% Smoking history	13.0%	20.5%	$\chi^2 = 2.232$	$p = 0.14$
% With recent hospitalization or surgery	23.5%	28.8%	$\chi^2 = 0.755$	$p = 0.39$
% With the catheter in place	6.8%	28.8%	$\chi^2 = 20.663$	$p < 0.001$
% With pre-admission antibiotics	61.1%	58.9%	$\chi^2 = 0.103$	$p = 0.75$
% With pre-admission corticosteroids	5.6%	17.8%	$\chi^2 = 8.904$	$p = 0.003$
% With foot ulcer	71.0%	64.4%	$\chi^2 = 1.838$ ($df = 3$)	$p = 0.61$
% With leg ulcer	24.1%	30.1%		
% With sacral or another ulcer	4.9%	5.4%		
Mean SBP	133.36	125.62	$U = 3.887$	$p = 0.049$
Mean DBP	76.8	70.82	$U = 6.547$	$p = 0.011$
Mean pulse pressure	56.56	54.37	$U = 0.653$	$p = 0.51$
Mean MAP	95.47	88.76	$U = 6.250$	$p = 0.012$
% Started on vasopressor	3.3%	59.7%	$\chi^2 = 91.846$	$p < 0.001$
Mean respiratory rate	20.21	21.78	$U = 13.674$	$p < 0.001$
Mean Glasgow coma score (GCS)	14.82	12.91	$U = 6.088$	$p < 0.001$
% With GCS < 13	2.7%	31.4%	$\chi^2 = 37.609$	$p < 0.001$
Mean WBC count (cells/μL)	14.4	17.9	$U = 2.419$	$p = 0.12$
Mean serum hemoglobin (g/dL)	10.2	9.0	$U = 8.029$	$p = 0.005$
Mean C-reactive protein (mg/L)	105.6	153.1	$U = 3.206$	$p = 0.07$
Mean serum glucose (mg/dL)	12.8	11.7	$U = 0.885$	$p = 0.35$
Mean serum sodium (mEq/L)	133.0	136.9	$U = 7.558$	$p = 0.006$
Mean serum creatinine (μmol/L)	146.9	285.6	$U = 19.998$	$p < 0.001$
Mean blood lactate (mmol/L)	2.3	4.0	$U = 4.255$	$p = 0.039$
LRINEC score ⩾ 6	77.5%	92.1%	$\chi^2 = 3.756$	$p = 0.053$
LRINEC score ⩾ 7	68.8%	89.5%	$\chi^2 = 5.969$	$p = 0.015$
% With sepsis	6.8%	74.0%	$\chi^2 = 113.516$	$p < 0.001$
Mean length of hospital stay (days)	20.8	40.1	$U = 27.663$	$p < 0.001$
% Re-hospitalized	13.9%	20.0%	$\chi^2 = 0.734$	$p = 0.39$
% Mortality	2.5%	60.3%	$\chi^2 = 103.455$	$p < 0.001$

Source: Glasgow Coma Scale per Teasdale et al.[31]

The term "pre-admission" refers to occurrences that extended over time prior to hospital admission, while "baseline" refers to characteristics present at the time of admission.

*All tests to one degree of statistical freedom ($df = 1$) unless otherwise specified.

Table 5. Comparing patients who survive to discharge versus die in hospital.

Characteristics	Survival	Death	Test statistic*	Significance
Number of patients	187	48		
% Male	71.7%	66.7%	$\chi^2 = 0.459$	$p = 0.50$
Mean age (years)	59.1	65.5	$U = 1.967$	$p = 0.16$
% Age > 50 years	82.9%	87.5%	$\chi^2 = 0.599$	$p = 0.44$
% Saudi	41.2%	22.9%	$\chi^2 = 5.437$	$p = 0.020$
Mean body mass index (BMI)	27.6	27.3	$U = 0.127$	$p = 0.72$
% Underweight	2.7%	6.3%	$\chi^2 = 1.486$	$p = 0.22$
% Overweight	31.6%	29.2%	$\chi^2 = 0.101$	$p = 0.75$
% Obesity	28.9%	27.1%	$\chi^2 = 0.060$	$p = 0.81$
% Either wheelchair-bound or bedridden	38.5%	56.3%	$\chi^2 = 4.934$	$p = 0.026$
% Diabetes mellitus	94.1%	89.6%	$\chi^2 = 1.238$	$p = 0.27$
% Cardiovascular disease (CVD)	72.2%	91.7%	$\chi^2 = 7.980$	$p = 0.005$
% Hypertension	65.8%	87.5%	$\chi^2 = 8.619$	$p = 0.003$
% Ischemic heart disease	23.0%	52.1%	$\chi^2 = 15.717$	$p < 0.001$
% Heart failure	17.6%	41.7%	$\chi^2 = 12.616$	$p < 0.001$
% Chronic kidney disease (CKD)	26.7%	60.4%	$\chi^2 = 19.414$	$p < 0.001$
% Lung disease	8.0%	18.5%	$\chi^2 = 10.827$	$p = 0.001$
% With DM and CVD	69.5%	83.3%	$\chi^2 = 3.662$ ($df = 2$)	$p = 0.16$
% With DM and CKD	24.1%	54.2%	$\chi^2 = 17.110$ ($df = 2$)	$p < 0.001$
% With DM, CVD, and CKD	21.4%	52.1%	$\chi^2 = 20.205$ ($df = 3$)	$p < 0.001$
% Smoking history	14.4%	18.8%	$\chi^2 = 0.547$	$p = 0.46$
% With recent hospitalization or surgery	23.0%	33.3%	$\chi^2 = 2.171$	$p = 0.14$
% With the catheter in place	8.6%	33.3%	$\chi^2 = 19.935$	$p < 0.001$
% With pre-admission antibiotics	59.9%	62.5%	$\chi^2 = 0.109$	$p = 0.74$
% With pre-admission corticosteroids	7.5%	16.7%	$\chi^2 = 3.793$	$p = 0.051$
% With foot ulcer	71.1%	60.4%	$\chi^2 = 2.054$ ($df = 3$)	$p = 0.56$
% With leg ulcer	24.1%	33.3%		
% With sacral or another ulcer	4.8%	6.3%		
Mean SBP	133.9	119.4	$U = 14.491$	$p < 0.001$
Mean DBP	77.13	66.49	$U = 10.489$	$p = 0.001$
Mean pulse pressure	56.65	52.91	$U = 0.251$	$p = 0.62$
Mean MAP	95.82	83.95	$U = 7.514$	$p = 0.006$
% Started on vasopressor	11.3%	60.9%	$\chi^2 = 53.113$	$p < 0.001$
Mean respiratory rate	20.4	21.86	$U = 8.046$	$p = 0.005$
Mean Glasgow coma score (GCS)	14.54	12.98	$U = 3.861$	$p < 0.001$
% With GCS < 13	2.7%	30.4%	$\chi^2 = 37.609$	$p < 0.001$
Mean WBC count (cells/μL)	15.4	15.8	$U = 0.420$	$p = 0.52$
Mean serum hemoglobin (g/dL)	10.1	9.0	$U = 7.929$	$p = 0.005$
Mean C-reactive protein (mg/L)	113.1	154.2	$U = 0.958$	$p = 0.33$
Mean serum glucose (mg/dL)	13.1	9.8	$U = 4.628$	$p = 0.031$
Mean serum sodium (mEq/L)	133.8	135.9	$U = 2.342$	$p = 0.13$
Mean serum creatinine (μmol/L)	161.8	300.6	$U = 10.947$	$p < 0.001$
Mean blood lactate (mmol/L)	2.2	5.0	$U = 2.832$	$p = 0./09$
LRINEC score ⩾ 6	80.2%	90.9%	$\chi^2 = 1.401$	$p = 0.24$
LRINEC score ⩾ 7	74.0%	81.8%	$\chi^2 = 0.597$	$p = 0.44$
% Admitted to the ICU	15.5%	91.7%	$\chi^2 = 103.455$	$p < 0.001$
% With sepsis	17.6%	66.7%	$\chi^2 = 45.870$	$p < 0.001$
Mean length of hospital stay (days)	23.0	41.8	$U = 15.338$	$p < 0.001$

Source: Glasgow Coma Scale per Teasdale et al.[31]

The term "pre-admission" refers to occurrences that extended over time prior to hospital admission, while "baseline" refers to characteristics present at the time of admission.

*All tests to one degree of statistical freedom ($df = 1$) unless otherwise specified.

Table 6. Predictors of sepsis, ICU admission, and death.

Variable	Statistical significance
SEPSIS	
Vasopressor needed for cardiovascular support	$p < 0.001$
Low mean arterial pressure	$p = 0.001$
Glasgow coma score < 13	$p = 0.001$
Elevated WBC count	$p = 0.002$
Anemia	$p = 0.069$
Non-Saudi citizenship	$p = 0.095$
ICU admission	
Vasopressor needed for cardiovascular support	$p < 0.001$
Glasgow coma score < 13	$p = 0.001$
Pre-existing cardiovascular disease	$p = 0.022$
Being underweight	$p = 0.039$
Low mean arterial pressure	$p = 0.063$
Death prior to hospital discharge	
Vasopressor needed for cardiovascular support	$p < 0.001$
Low mean arterial pressure	$p = 0.001$
Pre-existing kidney disease	$p = 0.045$

Source: Glasgow Coma Scale per Teasdale et al.[31]
The term "pre-admission" refers to occurrences that extended over time prior to hospital admission.

In the current study, the vast majority of hospitalized SSTI patients were at least 50 years old and had previously been diagnosed with diabetes. More than 7/10 had both diabetes and one or more CVDs. Pre-existing kidney disease also was documented in roughly one-third, suggesting that most of these patients had potential explanations both for their SSTI (e.g., diabetic foot ulcers, atherosclerosis) and for being more physically frail and, hence, more likely to require more intensive healthcare to manage their SSTI. Consistent with this, roughly 30% required either direct admission or eventual transfer to the ICU, and 20% died, a mortality rate highly consistent with rates in the 20%–30% range reported in prior series.[10,12,28] Though calculation of an LRINEC score was only possible in half of our patients, among that half, the 75% and 82% rates of NF estimated using the 7-point and 6-point LRINEC threshold scores also were highly consistent with rates reported elsewhere among patients hospitalized for cSSTI.[12]

One shortfall our study had is that, given its retrospective nature, we were only able to characterize roughly half the patients (118/235) as having a necrotizing versus non-necrotizing SSTI, especially due to the routine absence of CRP measurements. However, among the 118 patients for whom an LRINEC score was calculable, neither the total LRINEC score nor either of the two classification thresholds commonly used to diagnose NF was statistically associated with the presence of sepsis, need for ICU admission, or death, which is inconsistent with prior claims of its use predicting clinical severity and mortality risk.[27,30] That said, in one of these earlier studies, the sensitivity and specificity of the 6-point LRINEC threshold for mortality were just 70% and 60%, respectively.[27]

Two factors we identified that were statistically linked to all three outcomes of interest on multivariable analysis—sepsis, ICU admission, and death—were the early need for circulatory support with one or more vasopressor drugs and a low MAP. Very sparse data exist on predictors of sepsis or ICU admission in patients with SSTI. Data also are limited on the need for vasopressor support and mortality risk, instead focusing on the effectiveness of various vasopressors influencing mortality in patients already in need of circulatory support. Conversely, increased mortality risk from a low MAP—below 65 mmHg and especially below 50 mmHg—has been well documented across a range of ICU scenarios, including patients with sepsis.[33–38] Low MAP is also included as a component of both the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scales widely used to predict mortality risk in critically ill patients.[39,40]

Interestingly, several other variables we identified as predictors of mortality risk to $p < 0.001$ on bivariate analysis also are components of the APACHE II, SOFA, or both, including the GCS, serum creatinine, and initiation of circulatory support with either dopamine, epinephrine, or norepinephrine.[41,42]

Considerable research has already been published documenting the association between acute kidney injury and mortality in critically ill patients.[32,43–45] However, how pre-existing diabetic nephropathy affects survival in ICU patients remains relatively undocumented, especially in patients with a cSSTI.

We also found being underweight to predict ICU admission—which likely reflected disease severity—but not to predict either sepsis or mortality, as reported elsewhere.[46–49] Our failure to identify below-normal weight as a predictor of

mortality might merely reflect the very small number ($N=8$) of underweight patients in our sample. Unfortunately, the very small number of underweight patients prohibited any further analysis of this factor. As in numerous other studies,[46,47,49–52] however, in our cohort obesity was not associated with any increase in mortality risk; nor was it statistically linked to either sepsis or ICU admission.

Somewhat unexpectedly, sepsis itself dropped out of our predictive models for ICU admission and mortality, despite being statistically associated ($p<0.001$) with both outcomes on bivariate analysis. The likely reason for this dropout is that the major consequence of sepsis—septic shock—was reflected in both the need for vasopressor drug support and low MAP.

Most limitations of the current study stem from the retrospective nature of data collection, which resulted in missing data particularly for CRP—thereby halving the number of patients for whom a LRINEC score could be calculated to suggest NF—and the absence of any other universally accepted way to diagnose NF. As such, one major reason we failed to identify any significant link between NF (based on the LRINEC score) and mortality might merely be insufficient statistical power to do so. Among patients with an LRINEC score $\geqslant 7$, the mortality rate was 20.2%, versus just 13.8% in those with a score of 6 or less; however, this difference was far from statistically significant ($p=0.44$).

Also exacerbated by the retrospective nature of patient recruitment and data collection, we also, despite culture swabs being obtained for every patient, lacked organism confirmation for the majority of patients, likely because 60% already were receiving an antibiotic prior to hospital admission, a percentage that likely is secondary to the very high percentages of patients with diabetes and foot ulcers (93.2% and 68.9%, respectively), since the early initiation of antibiotics is considered standard of care at our hospital for diabetic foot ulcers. And, as stated in the introduction, certain organisms—like methicillin-resistant *Staphylococcus* sp., *Acinetobacter baumannii*, and *Vibrio vulnificus*—have been linked to especially high mortality rates.[8,14,53–58] Moreover, *Acinetobacter baumannii* appears to be particularly common in ICUs across Saudi Arabia.[56,59] As such, we similarly lacked information on antibiotic resistance, which could have impacted our results. That said, the percentage of missing data for virtually every other variable we studied was under 2%.

Finally, our patient sample included 60.4% patients of non-Saudi versus just 37.4% of Saudi descent raises concerns about the generalizability of our data. One possible reason for this could be the disproportionate number of Saudis who work in government jobs, versus the disproportionately high percentage of non-Saudis who work in the agriculture, cleaning, and domestic industries, where the risk of skin trauma on septic equipment is higher.[60]

Limitations notwithstanding, our study is one of the first to examine not just predictors of mortality, but also sepsis and ICU admission (as proxies of disease severity) in hospitalized patients with cSSTI, and identified one predictor that, to our knowledge, has not been previously reported—vasopressor use. Low MAP also was predictive of all three of these study outcomes, as opposed to a diagnosis of NF based upon LRINEC scores, which predicted none. Further research into patient and clinical parameters that make certain SSTI patients at particularly high risk of more severe disease, beyond relying solely on an NF diagnosis, remains necessary.

Conclusion

This study identified low MAP, vasopressor use, and pre-existing kidney disease as critical predictors of mortality in patients with cSSTI, with low MAP, vasopressor use, and a low GCS score predictive of both sepsis and ICU admission. These findings underscore the need for rapid hemodynamic assessments and interventions, as well as vigilant renal function monitoring, to improve patient outcomes. The LRINEC score, while useful for diagnosing NF, did not predict any of our three outcomes, though we lacked scores for almost half our patient sample. As such, further studies will be necessary to assess its role as a predictor of outcomes.

Future research should focus on prospective studies with larger cohorts to validate our findings and explore additional predictors. Integrating comprehensive care approaches that address common comorbidities such as diabetes and CVD is essential. Developing and implementing new risk stratification models could enhance the early identification and management of high-risk patients, ultimately reducing the high rates of morbidity and mortality associated with cSSTI.

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Ethical considerations

This study was approved by the institutional review board at King Abdulaziz University (Reference No: 608-23).

Consent to participate

Because data collection was retrospective and no patients were identified, upon ethics approval, the institutional review board informed the investigators that they did not require consent to participate.

Consent for publication

No consent was required from the patients for retrospective data collection based on our IRB recommendations.

Author contributions

HMA, AMA, YAO, and SYB: Proposal writing, Proposal editing, Data analysis, Manuscript writing, Manuscript editing, and Manuscript submission. RNA, FKA, NMB, LBA, SKD, RAS, and RAM: Proposal writing, Proposal editing, Data collection, Data analysis, Manuscript writing, and Manuscript editing. All authors read and approved the final manuscript.

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Data availability

Data will be available by Haifa M. Algethamy upon reasonable request.

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