BMC Infectious Diseases

RESEARCH

Open Access

Clinical and inflammatory predictors of outpatient treatment failure in uncomplicated skin and soft tissue infections: a prospective multicenter study from Türkiye

Melike Nur Özçelik[1,2*], Merve Sefa Sayar[3], Nurten Nur Aydın[4], Dilşah Başkol Elik[5], Özgür Günal[6], Pınar Yürük Atasoy[7], Ayşegül Tuna[8], Cihan Semet[9], Serpil Erol[10], Azize Yetişgen[11], Yakup Gezer[12], Muhammet Rıdvan Tayşi[12], Naciye Betül Baysal[13], Gülden Eser Karlıdağ[14], Muammer Çelik[15], Emsal Aydın[16], Yeşim Kürekçi[17], Yasemin Akkoyunlu[18], Özay Akyıldız[19], Ayşe Serra Özel[20], Oktay Yapıcı[21], Deniz Özer[22], Şafak Kaya[23], Tuba Damar Çakırca[24], Şafak Balın Özer[25] and İsmail Necati Hakyemez[3]

Abstract

Background Uncomplicated skin and soft tissue infections (uSSTIs) are highly prevalent; however, factors associated with outpatient treatment failure and subsequent hospitalization remain poorly defined in the existing literature. This prospective, multicenter observational study aimed to identify clinical and laboratory predictors of outpatient treatment failure in uSSTIs.

Methods Adult patients diagnosed with uSSTIs were enrolled from 24 infectious diseases departments across Türkiye between April 1st and September 30th, 2024, and their demographic, comorbidity, clinical, and laboratory data were systematically recorded. Hospitalization after initial outpatient therapy was considered a proxy for treatment failure, based on clinical judgment. Multivariable logistic regression was used to identify independent predictors of hospitalization following outpatient treatment failure, while receiver operating characteristic (ROC) analysis was performed to assess their discriminative performance.

Results Of 599 patients, 263 completed outpatient therapy, 169 were hospitalized at presentation, and 167 required hospitalization after initial outpatient treatment. Univariate analysis identified higher body mass index (BMI, $P = .015$), chronic kidney disease ($P = .044$), immunodeficiency ($P = .026$), insect bite etiology ($P = .047$), and smoking ($P = .019$) as associated with hospitalization. Clinical predictors included lesion size > 10% body surface area (BSA, $P < .001$), and elevated pulse rate ($P < .001$). Laboratory predictors included elevated neutrophil-to-lymphocyte ratio (NLR > 4.37, $P < .001$), C-reactive protein (CRP > 67.5 mg/L, $P < .001$), and other inflammatory markers. Multivariable analysis

*Correspondence:
Melike Nur Özçelik
drmelikenozcelik@gmail.com

Full list of author information is available at the end of the article

confirmed smoking (OR: 3.403, 95% CI: 1.535–7.542), preseptal cellulitis (OR: 42.354, 95% CI: 4.178–429.336), lesion size > 10% BSA (OR: 3.898, 95% CI: 1.598–9.509), elevated CRP (OR: 1.005, 95% CI: 1.001–1.008), NLR (OR: 1.073, 95% CI: 1.012–1.138), and pulse rate (OR: 1.027, 95% CI: 1.004–1.051) as independent predictors. ROC analysis demonstrated moderate discriminative ability with AUC values for CRP, NLR, pulse rate of 0.695, 0.672 and 0.615, respectively.

Conclusions Smoking, preseptal cellulitis, extensive lesions, and elevated NLR, CRP, and pulse rate may be associated with an increased likelihood of hospitalization in patients with uSSTIs. Early identification may guide initial management, favoring intravenous therapy in high-risk patients to reduce treatment failure.

Clinical trial Not applicable.

Keywords Uncomplicated skin and soft tissue infections, Hospitalization, Neutrophil-to-lymphocyte ratio, C-reactive protein, Pulse rate, Outpatient treatment failure

Introduction

Skin and soft tissue infections (SSTIs) exhibit diverse clinical presentations, microbial etiologies, and severity levels. Gram-positive bacteria, particularly *Staphylococcus aureus* and beta-hemolytic streptococci, are primary causative agents [1]. Cellulitis often requires hospitalization for intravenous antibiotics, especially in patients with comorbidities or severe presentations, contributing to significant healthcare costs [2]. In the United States, over 14 million individuals are treated for cellulitis annually, accounting for >1% of hospital admissions and costs exceeding $7 billion [3]. Antibiotic resistance, particularly methicillin-resistant *S. aureus* (MRSA), has reduced antimicrobial efficacy, necessitating judicious use to curb resistance and side effects [4, 5].

Evidence supports a 5-7-day antibiotic course for uncomplicated SSTIs [uSSTIs], yet clinical practice often extends treatment to ≥ 14 days [6–9]. Predominant uSSTI pathogens are aerobic Gram-positive bacteria, but broad-spectrum antibiotics targeting Gram-negative or anaerobic bacteria are frequently overused, potentially exacerbating resistance [1, 6].

Despite the high prevalence of SSTIs, the predictors of outpatient treatment failure leading to hospitalization remain poorly defined. Previous studies have mostly been retrospective, single-center, or based on heterogeneous populations, which limits their generalizability [10–12]. This study aims to optimize treatment duration through the early identification of high-risk patients who may benefit from intravenous therapy and hospitalization. It is anticipated that this approach will result in reduced treatment duration, minimized antibiotic use, and enhanced cost-effectiveness.

Materials and methods

This prospective, multicenter observational study was conducted across 24 infectious diseases departments in Türkiye from April 1st to September 30th, 2024. A total of 599 adult patients (≥ 18 years) diagnosed with such as uSTTIs cellulitis or erysipelas were enrolled. Exclusion criteria included complicated SSTIS (large or deep soft tissue abscesses, surgical site infections, chronic wounds or ulcers present ≥ 28 days or unknown duration), necrotizing SSTIs (SSTIs involving deeper structures such as tendon, fascia, or bone), diabetic foot infections, osteomyelitis, septic arthritis or prior antibiotic use for uSSTIs due to their distinct clinical management. Patients with uSSTIs received empirical treatment in accordance with the 2014 IDSA and 2021 Turkish guidelines for skin and soft tissue infections [6, 13].

Data on demographics, comorbidities, clinical characteristics (e.g., lesion size, location), laboratory parameters (e.g., white blood cell count [WBC], C-reactive protein [CRP], neutrophil-to-lymphocyte ratio [NLR]), and initial treatment setting (outpatient vs. inpatient) were collected using a standardized case report form. For patients initially managed as outpatients but later hospitalized, persistent uSSTI symptoms were the primary indication for admission, often due to inadequate oral antibiotic dosing or insufficient antimicrobial coverage. Outpatient treatment failure was defined as clinical deterioration requiring inpatient care, as determined primarily by clinician judgment and supported by standardized criteria such as worsening clinical symptoms, persistent fever, or systemic signs (e.g., sepsis) and elevation of acute phase reactants in the blood.

Statistical analysis

Analyses were performed using R version 4.3.0. Data preprocessing involved variable type checks, outlier detection via the interquartile range method, and handling missing data through multiple imputation. Categorical variables were reported as frequencies and percentages; continuous variables were assessed for normality using the Shapiro-Wilk test, Q-Q plots, and histograms. Normally distributed variables were presented as mean ± standard deviation, non-normally distributed as median (interquartile range).

Group comparisons used the t-test or Mann-Whitney U-test for two groups, and ANOVA with Tukey's HSD or Kruskal-Wallis with Dunn's test for ≥ 3 groups, based on normality and variance (Levene's test). Multivariable logistic regression identified independent predictors of hospitalization, with variable selection based on clinical relevance and univariate analyses ($p < .20$). Models were fitted to imputed datasets and pooled using Rubin's rules. Significance was set at $\alpha = 0.05$.

Sample size adequacy was evaluated using the Events Per Variable (EPV) ratio. Which was 5.57. This meets contemporary guidelines recommending EPV ≥ 5 for multivariable logistic regression [14, 15].

Results

Of 599 patients, 263 completed outpatient therapy, 169 were hospitalized at presentation, and 167 required hospitalization after initial outpatient treatment (Fig. 1). Outpatient antibiotics were administered orally or intramuscularly; inpatients received intravenous antibiotics. Mean antibiotic duration was 11.1 ± 2.3 days for outpatient-only, 14.7 ± 3.1 days for direct hospitalization, and 17.3 ± 4.0 days for those initially outpatient but later hospitalized (Fig. 2).

Univariate analysis identified higher BMI (median 28.7 vs. 27.0 kg/m², $P = .015$), chronic kidney disease (12.6% vs. 6.8%, $P = .044$), immunodeficiency (6.6% vs. 2.3%, $P = .026$), insect bite etiology (5.4% vs. 1.9%, $P = .047$), and smoking (16.2% vs. 8.7%, $P = .019$) as risk factors for hospitalization (Table 1). Clinical predictors included preseptal cellulitis (4.2% vs. 0.4%, $P < .001$), lesion size > 10% BSA (18.6% vs. 4.6%, $P < .001$), elevated pulse rate (median 81.0 vs. 76.0 beats/min, $P < .001$), and higher LRINEC (median 3.0 vs. 1.0, $P < .001$), CREST/ERON (median 2.0 vs. 1.0, $P = .001$), and modified Dundee (median 2.0 vs. 2.0, $P = .001$) scores. The majority of outpatients received empirical antibiotics with extended Gram-negative coverage (87.7%), while 69.1% had anaerobic coverage. Anti-Pseudomonal and anti-MRSA agents were included in 25.3% and 15.1% of outpatient regimens, respectively. There was no statistically significant difference in the

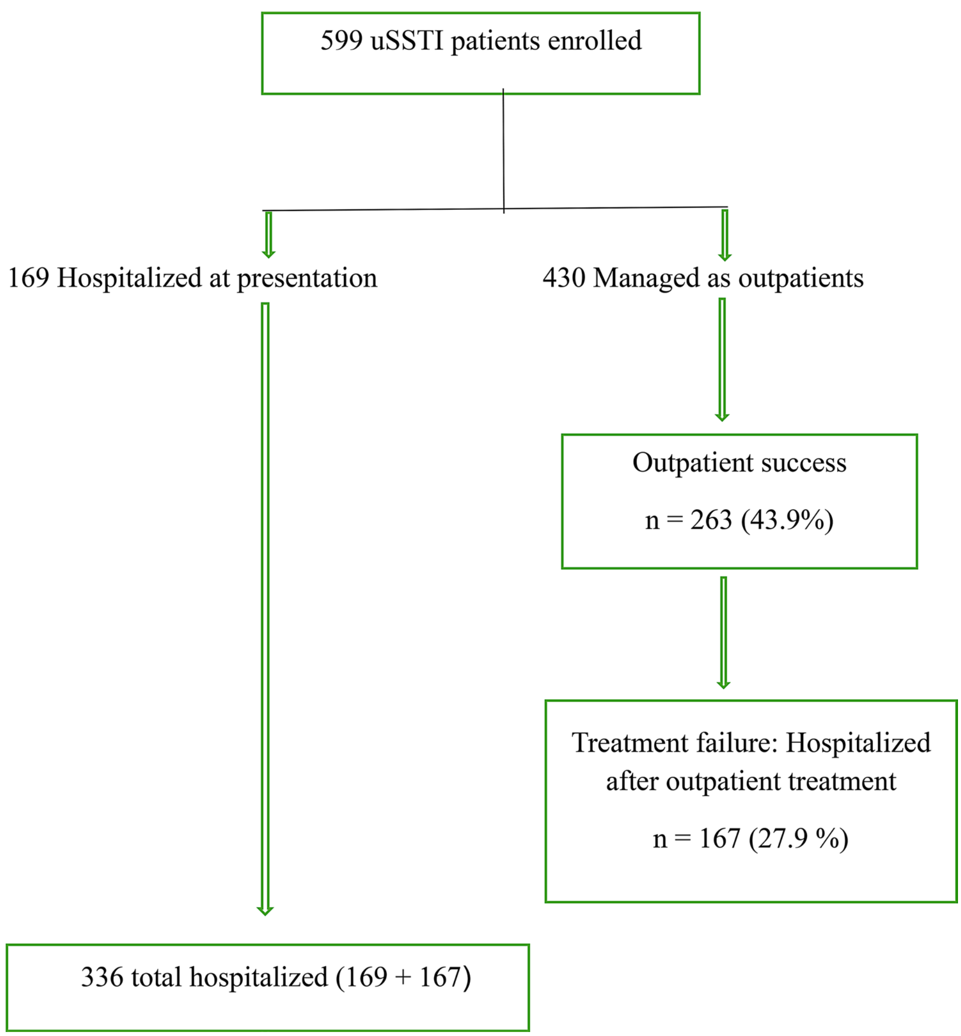


Fig. 1 Flowchart illustrating the patient's initial admission status, treatment protocol, and clinical outcomes. Abbreviations: uSSTI: uncomplicated skin and soft tissue infections

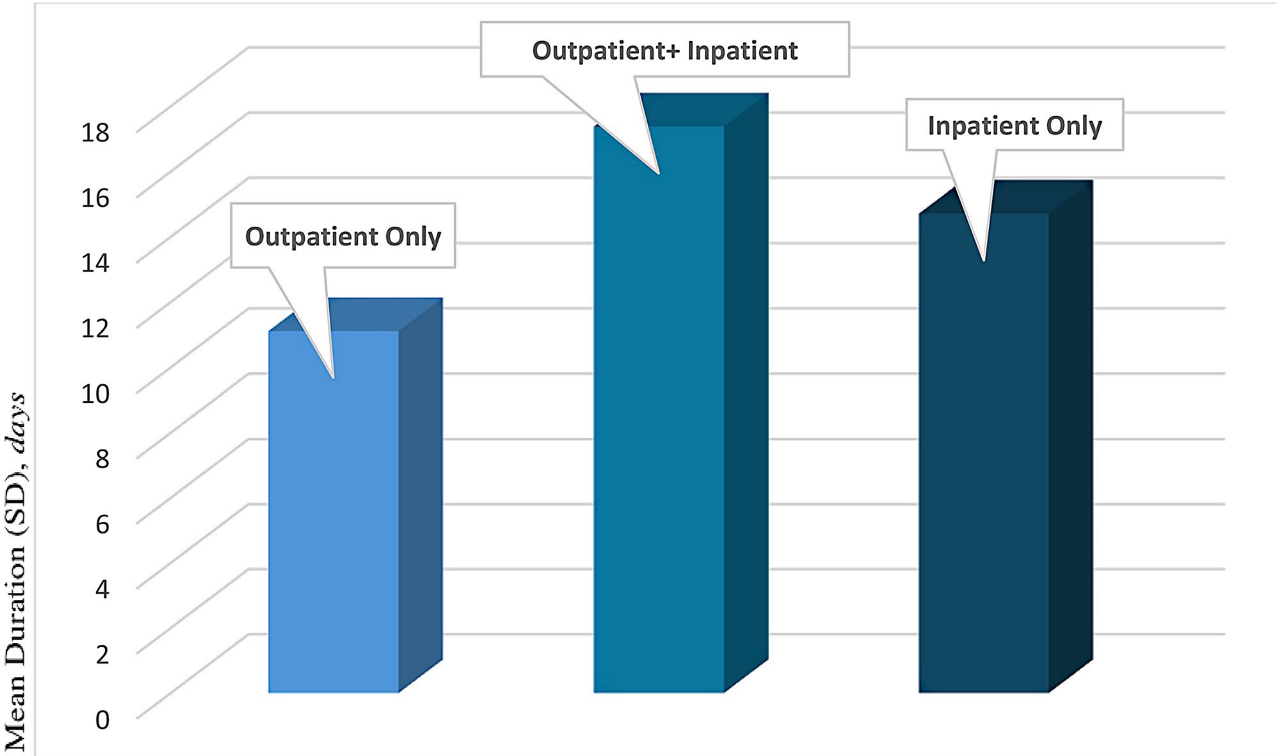


Fig. 2 Antibiotic treatment duration in patients with uncomplicated skin and soft tissue infections. Bar chart comparing mean antibiotic treatment duration (days) for uncomplicated skin and soft tissue infections patients treated entirely as outpatients (11.1 ± 2.3 days), hospitalized at presentation (14.7 ± 3.1 days), and transitioned from outpatient to inpatient care (17.3 ± 4.0 days) in a multicenter study in Türkiye

antibiotic spectrum between patients who completed outpatient therapy and those who subsequently required hospitalization (Table 2).

Microbiological data were limited as the study included only patients eligible for culture, such as those with fever exceeding 38 °C or wound discharge. Wound cultures from 74 patients yielded bacterial growth in 31, with methicillin-susceptible *S. aureus* (MSSA) predominant (45.1%). Blood cultures from 195 patients showed growth in 24, with 16 clinically significant (8 MSSA).

Laboratory predictors included elevated WBC (median 11,000 vs. 9,490/μL, $P < .001$), NLR (median 6.0 vs. 3.1, $P < .001$), CRP (median 124.0 vs. 47.9 mg/L, $P < .001$), procalcitonin (median 0.4 vs. 0.1 ng/mL, $P = .001$), and decreased hemoglobin (median 12.4 vs. 13.3 g/dL, $P < .001$) (Table 3).

Multivariable logistic regression confirmed smoking (OR: 3.403, 95% CI: 1.535–7.542, $P = .003$), preseptal cellulitis (OR: 42.354, 95% CI: 4.178–429.336, $P = .002$) lesion size > 10% BSA (OR: 3.898, 95% CI: 1.598–9.509, $P = .003$), elevated NLR (OR: 1.073, 95% CI: 1.012–1.138, $P = .018$), CRP (OR: 1.005, 95% CI: 1.001–1.008, $P = .006$), and pulse rate (OR: 1.027, 95% CI: 1.004–1.051, $P = .021$) as independent predictors (Table 4).

Receiver Operating Characteristic (ROC) analysis Clarify AUCs in results identified cutoffs of > 4.37 for NLR (sensitivity 61.1%, specificity 69.5%), > 67.5 mg/L for CRP (sensitivity 68.9%, specificity 59.0%), and > 80.5 beats/min for pulse rate (sensitivity 50.9%, specificity 69.9%). Although statistically significant, the ROC curves showed only moderate discriminatory power for CRP (AUC: 0.695), NLR (AUC: 0.672), and pulse rate (AUC: 0.615) (Fig. 3).

Discussion

This study identified smoking, preseptal cellulitis, lesion size > 10% body surface area (BSA), and elevated NLR, CRP, and pulse rate as independent predictors of hospitalization in uSSTIs.

The median age (62.0–64.0 years) was higher than reported elsewhere (41.1–61.6 years), with a female predominance (51.8% vs. 37.0–50.3%) [10–12]. Lower extremity infections aligned with prior reports (74.9% in hospitalized vs. 58.6% in outpatient, $P < .001$) [16, 17]. Facial involvement (preseptal cellulitis, was a key determinant of hospitalization, suggesting its role in severity assessment in this study ($P < .001$).

While erythrocyte sedimentation rate (ESR) and CRP are not routinely recommended for uSSTI diagnosis [18], our findings highlight CRP's predictive value (median 124.0 vs. 47.9 mg/L, $P < .001$). From a mechanistic perspective, a high NLR indicates a shift toward

Table 1 Risk factors associated with outpatient treatment failure in uncomplicated skin and soft tissue infections

Variable	Completed Outpatient Treatment (*n* = 263)	Initially Outpatient, Later Hospitalized (*n* = 167)	*P*-value
Age, years, median (Q1-Q3)	62.0 (49.0-71.8)	64.0 (55.0–74.0)	0.062†
BMI, kg/m², median (Q1-Q3)	27.00 (24.3–30.0)	28.7 (24.9–33.1)	0.015†
Gender, n (%)			0.267*
Male	121 (46.0)	86 (51.5)	
Female	142 (54.0)	81 (48.5)	
Comorbidities, n (%)			
Diabetes mellitus	100 (38.0)	70 (41.9)	0.421*
Chronic kidney disease	18 (6.8)	21 (12.6)	0.044*
Immunodeficiency	6 (2.3)	11 (6.6)	0.026*
Peripheral vascular disease	52 (19.8)	32 (19.2)	0.876*
Underlying history, n (%)			
Trauma	50 (19.0)	36 (21.6)	0.520*
Insect bite	5 (1.9)	9 (5.4)	0.047*
Contact with contaminated water	1 (0.4)	0 (0)	0.425*
Animal bite	4 (1.5)	2 (1.2)	0.781*
Tinea pedis/unguinum	112 (42.6)	65 (38.9)	0.452*
Saphenous vein graft	8 (3.0)	10 (6.0)	0.137*
Smoking	23 (8.7)	27 (16.2)	0.019*
Secondary infection	0 (0)	1 (0.6)	0.209*

Variables are compared between patients who completed outpatient treatment (*n* = 263) and those who were initially treated as outpatients but subsequently hospitalized (*n* = 167). Continuous variables are presented as medians with interquartile ranges (Q1–Q3) and expressed in appropriate units (e.g., age in years, BMI in kg/m²). *P*-values were calculated using the Chi-square test for categorical variables (*) and the Mann–Whitney U test for continuous variables (†).Significance set at $P < .05$

Abbreviations: BMI, body mass index; Q1-Q3, interquartile range; uSSTIs, uncomplicated skin and soft tissue infections

neutrophil-dominant innate immune activation accompanied by relative lymphopenia, suggesting an increased inflammatory burden and potential impairment of adaptive immunity [19]. At the same time, elevated CRP, produced by the liver in response to pro-inflammatory cytokines such as IL-6, signals a heightened systemic acute-phase response [20]. Elevated NLR and C-reactive protein CRP levels indicate an enhanced systemic inflammatory response, which may reflect a more severe or rapidly progressing infection that is less likely to respond to outpatient management. Our findings suggest that NLR (>4.37), CRP (>67.5 mg/L), and pulse rate (>80.5 beats/min) may be useful components of a clinical risk score to help identify high-risk uSSTI patients in emergency departments or outpatient settings. While these parameters were associated with hospitalization, the results are preliminary and require confirmation through external validation before they can be integrated into a clinical scoring system.

Randomized trials have reported lower response rates in older patients, those with high BMI, or diabetes [21, 22]. Collazos et al. (2018) found age and immunosuppression linked to reduced treatment response in 606 episodes [23]. Similarly, Haran et al. (2017) reported higher outpatient treatment failure in elderly patients [24]. However, Esposito et al. (2023) suggested age is not an independent predictor, though comorbidities like immunosuppression may increase risk [5]. Our study found no association between age ($P = .584$) or immunosuppression ($P = .381$) and treatment failure, possibly due to Türkiye's older patient demographic or study design differences.

Broad-spectrum antibiotic use, including anti-MRSA agents (17.4% in outpatients vs. 13.2% in hospitalized patients, $P = .269$) and Gram-negative coverage (91.5% vs. 92.7%, $P = .664$), did not result in improved clinical outcomes in this study. Given the relatively low prevalence of MRSA in Türkiye compared to global rates, the frequent use of broad-spectrum antibiotics may contribute to the development of antimicrobial resistance, underscoring the importance of more targeted treatment strategies for uSSTIs [24, 25]. The Infectious Diseases Society of America (IDSA) classifies outpatient treatment failure as severe SSTIs and recommends broad-spectrum therapy [6]; however, treatment failure is often related to patient-specific factors or diagnostic uncertainty rather than resistant pathogens [24, 26–28]. Despite broad-spectrum antibiotic use in most cases, no significant difference in treatment outcomes was observed, highlighting the need for more targeted stewardship.

Although outpatient treatment approaches for uSSTI patients offer greater comfort for the patient and cost-effectiveness for the healthcare system, failure to achieve the expected therapeutic response may necessitate hospitalization, thereby prolonging the overall course of management. In line with this, the mean duration of antibiotic therapy among patients who required hospitalization after initial outpatient treatment (17.3 days) was significantly longer than the guideline-recommended 5–7 days, suggesting that delayed hospitalization may contribute to unnecessary prolongation of therapy [6, 18]. These findings underscore the need for early risk stratification to optimize initial management and minimize resource utilization [9, 18, 28]. Consequently, early decision-making regarding the need for hospitalization and the selection of the appropriate antibiotic spectrum play a crucial role in determining the duration of treatment.

Recurrent SSTIs pose ongoing challenges, with morbidity and costs associated with repeated episodes [6]. For necrotizing infections, intensive care units (ICU) admission is frequent due to clinical severity, reinforcing the importance of early markers like NLR [29]. Türkiye's aging population (median age 62.0–64.0 years) and high

Table 2 Clinical characteristics of patients with uncomplicated skin and soft tissue infections

Variable	Completed Outpatient Treatment ($n=263$)	Initially Outpatient, Later Hospitalized ($n=167$)	P-value
Diagnosis, n (%)			0.764*
Cellulitis	247 (93.9)	158 (94.6)	
Erysipelas	16 (6.1)	9 (5.4)	
Number of uSSTIs (last year), n (%)			0.995*
One attack	218 (83.8)	130 (83.9)	
Two or more	42 (16.2)	25 (16.1)	
Skin involvement, n (%)			0.754*
Unilateral	253 (97.3)	150 (96.8)	
Bilateral	7 (2.7)	5 (3.2)	
Anatomical site, n (%)			< 0.001*
Foot	80 (30.4) [a]	17 (10.2) [b]	
Lower extremity	154 (58.6) [a]	125 (74.9) [b]	
Upper extremity	26 (9.9) [a]	13 (7.8) [a]	
Abdomen	0 (0.0) [a]	3 (1.8) [b]	
Face (preseptal)	1 (0.4) [a]	7 (4.2) [b]	
Gluteus	1 (0.4) [a]	0 (0.0) [a]	
Breast	1 (0.4) [a]	2 (1.2) [a]	
Local clinical findings, n (%)			
Redness	252 (95.8)	166 (99.4)	0.028*
Swelling	221 (84.0)	156 (93.4)	0.004*
Local warmth	226 (85.9)	159 (95.2)	0.002*
Tenderness on palpation	216 (82.1)	132 (79.0)	0.427*
Pain	174 (66.2)	111 (66.5)	0.948*
Lesion size, n (%)			< 0.001*
<%5	207 (78.7) [a]	93 (55.7) [b]	
%5-%10	44 (16.7) [a]	43 (25.7) [b]	
>%10	12 (4.6) [a]	31 (18.6) [b]	
Outpatient Antibiotic Type, n (%)			
Gram-negative coverage	237 (91.5%)	140 (92.7%)	0.664*
Anaerobic coverage	196 (75.7%)	101 (66.9%)	0.055*
Anti-Pseudomonas	70 (27.0%)	39 (25.8%)	0.791*
Anti-MRSA	45 (17.4%)	20 (13.2%)	0.269*
Systemic symptoms			
Fever, °C, median (Q1-Q3)	36.7 (36.4–37.4)	36.7 (36.3–37.3)	0.799†
Pulse rate, beats/min, median (Q1-Q3)	76.0 (70.0–84.0)	81.0 (74.0–90.0)	< 0.001†
Respiratory rate, breaths/min, median (Q1-Q3)	18.0 (16.0–20.0)	18.0 (16.0–20.0)	0.883†
Systolic blood pressure, mmHg, median (Q1-Q3)	120.0 (110.0-127.5)	120.0 (110.0-130.0)	0.102†
Diastolic blood pressure, mmHg, median (Q1-Q3)	70.0 (65.0–80.0)	74.0 (70.0–80.0)	0.002†
SaO_2, %, median (Q1-Q3)	96.0 (95.0–98.0)	96.0 (94.0–98.0)	0.612†
Scores			
qSOFA, median (Q1-Q3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.061†
LRINEC, median (Q1-Q3)	1.0 (0.0–3.0)	3.0 (1.0–6.0)	< 0.001†
CREST/ERON, median (Q1-Q3)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	0.001†
Modified Dundee, median (Q1-Q3)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.001†

Variables are compared between patients who completed outpatient treatment ($n=263$) and those who were initially treated as outpatients but subsequently hospitalized ($n=167$). P-values calculated using Chi-square test (*) for categorical variables and Mann-Whitney U test (†) for continuous variables. Different superscripts (a, b) indicate significant differences between groups ($P<.05$). Significance set at $P<.05$

Abbreviations: BSA, body surface area; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; CREST/ERON, severity classification systems; MRSA, methicillin-resistant Staphylococcus aureus; qSOFA, quick Sequential Organ Failure Assessment; SaO_2, oxygen saturation; uSSTIs, uncomplicated skin and soft tissue infections

Table 3 Laboratory parameters in uncomplicated skin and soft tissue infections

Variable	Completed Outpatient Treatment ($n=263$), median (Q1-Q3)	Initially Outpatient, Later Hospitalized ($n=167$), median (Q1-Q3)	*P*-value*
White blood cell count, $\times10^9$/L	9490.0 (7170.0-12600.0)	11000.0 (8380.0-15900.0)	< 0.001
Hemoglobin, g/dL	13.3 (11.9–14.6)	12.4 (11.2–13.6)	< 0.001
Neutrophil count, $\times10^9$/L	6240.0 (4390.0-9590.0)	8310.0 (5340.0-13160.0)	< 0.001
Neutrophil percentage, %	67.3 (60.1–78.3)	76.0 (65.0-86.5)	< 0.001
Neutrophil-to-lymphocyte ratio (NLR)	3.1 (2.1–5.5)	6.0 (2.9–10.6)	< 0.001
Platelet, $\times10^9$/L	248.0 (194.8-309.5)	240.0 (188.0-307.0)	0.395
Blood glucose, mg/dL	112.0 (94.0-153.0)	128.0 (101.0-179.0)	0.008
Glomerular filtration rate, mL/min	85.0 (68.0-100.0)	80.0 (58.0–97.0)	0.100
ALT, IU/L	22.0 (15.0–33.0)	20.0 (14.0–34.0)	0.907
AST, IU/L	19.2 (14.0-31.3)	24.0 (16.5–33.0)	0.005
Serum lactate, mmol/L	1.8 (1.2–2.1)	1.9 (1.4–2.5)	0.139
Erythrocyte sedimentation rate, mm/h	38.5 (24.0–56.0)	52.5 (32.0–75.0)	< 0.001
C-reactive protein, mg/L	47.9 (13.0-110.5)	124.0 (58.8-243.3)	< 0.001
Procalcitonin, ng/mL	0.1 (0.0-0.8)	0.4 (0.1–2.1)	0.001

Data are presented as medians with interquartile ranges (Q1–Q3). Laboratory parameters were compared between patients who completed outpatient treatment ($n=263$) and those who were initially treated as outpatients but later hospitalized ($n=167$). Units for laboratory values are as follows: white blood cell count, neutrophil count, and platelet count in $\times10^9$/L; hemoglobin in g/dL; blood glucose in mg/dL; glomerular filtration rate in mL/min; ALT and AST in IU/L; serum lactate in mmol/L; ESR in mm/h; CRP in mg/L; procalcitonin in ng/mL. *P*-values calculated using Chi-square test (*) for categorical variables and Mann-Whitney U test (†) for continuous variables. Different superscripts (a, b) indicate significant differences between groups ($P<.05$). Significance set at $P<.05$

P-values calculated using Mann-Whitney U test (*). Significance set at $P<.05$

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; uSSTIs, uncomplicated skin and soft tissue infections

rates of comorbidities (e.g., diabetes 41.9%, Table 1), coupled with limited healthcare access, may further elevate the risk of hospitalization. The study underscores the need for personalized management programs to address regional variations in patient demographics and pathogen profiles in Türkiye.

Early risk stratification may facilitate the identification of high-risk patients and has the potential to reduce treatment failure and associated healthcare costs by guiding timely hospitalization. However, while our findings suggest that certain patients may benefit from early hospitalization, this remains a hypothesis that requires validation through randomized controlled trials. Future research should assess the feasibility and effectiveness of such an approach across different healthcare systems, considering resource limitations and regional disparities that may influence clinical decision-making and access to care. Integrating predictive models with management strategies could enable more personalized, risk-based management in multicenter settings. This approach is also in line with the WHO Global Antimicrobial Resistance Action Plan (2023–2024), which advocates for optimized antibiotic use and early risk assessment to mitigate the global threat of antimicrobial resistance [30].

Limitations

The absence of a standardized treatment protocol across 24 centers may have introduced variability, and differences in local clinical practices could have affected patient management. Additionally, potential unmeasured confounders such as socioeconomic status and variability in clinicians' decisions regarding hospitalization may have influenced outcomes. Finally, the observational nature of the study limits the ability to establish causal relationships.

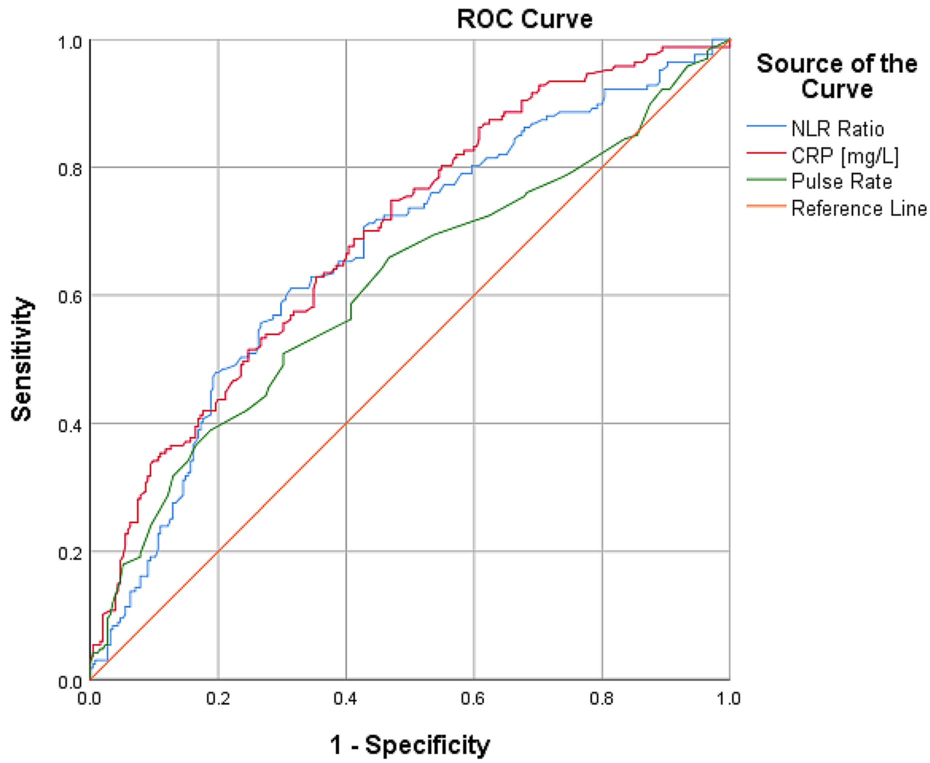
Conclusions

Smoking, preseptal cellulitis, larger BSA, and elevated inflammatory markers were associated with hospitalization following initial outpatient treatment, which served as a proxy for treatment failure in uSSTIs. These findings may assist in identifying patients at higher risk of outpatient treatment failure; however, causal relationships cannot be established due to the observational nature of the study.

Table 4 Multivariate logistic regression analysis of predictors of hospitalization in patients with uncomplicated skin and soft tissue infections initially managed as outpatients

Variable	OR (95% CI)	*P*-value
Chronic kidney disease	1.219 (0.495–3.004)	0.667
Immunodeficiency	1.971 (0.433–8.968)	0.381
Insect bite	3.219 (0.811–12.777)	0.097
Saphenous vein graft	1.682 (0.541–5.230)	0.370
Smoking	3.403 (1.535–7.542)	0.003
Site of infection		
Lower extremity	1.891 (0.910–3.930)	0.089
Upper extremity	2.077 (0.733–5.886)	0.170
Facial (preseptal)	42.354 (4.178-429.336)	0.002
Gluteus	0.000 (0.000-Inf)	0.993
Breast	5.960 (0.290-122.405)	0.248
Skin redness	3.234 (0.326–32.037)	0.316
Lesion size		
5%–10%	1.517 (0.799–2.879)	0.204
> 10%	3.898 (1.598–9.509)	0.003
Swelling	1.441 (0.581–3.572)	0.431
Local warmth	1.671 (0.523–5.344)	0.387
Age, years	1.006 (0.986–1.026)	0.584
BMI, kg/m^2	0.996 (0.945–1.050)	0.884
Pulse rate, beats/min	1.027 (1.004–1.051)	0.021
Systolic blood pressure, mmHg	1.016 (0.994–1.039)	0.154
Diastolic blood pressure, mmHg	1.022 (0.990–1.055)	0.178
White blood cell count, ×10^9/L	1.000 (1.000–1.000)	0.447
Hemoglobin, g/dL	0.928 (0.804–1.071)	0.305
Neutrophil percentage, %	0.984 (0.940–1.029)	0.476
Neutrophil count, ×10^9/L	1.000 (1.000–1.000)	0.682
NLR	1.073 (1.012–1.138)	0.018
Blood glucose, mg/dL	1.003 (0.999–1.007)	0.144
Glomerular filtration rate, mL/min	1.009 (0.998–1.020)	0.121
AST, IU/L	1.004 (0.990–1.018)	0.571
CRP, mg/L	1.005 (1.001–1.008)	0.006
ESR, mm/h	1.010 (0.996–1.024)	0.164
qSOFA score	0.904 (0.375–2.177)	0.821
LRINEC score	1.025 (0.873–1.205)	0.760
CREST/ERON score	0.625 (0.272–1.437)	0.270
Modified Dundee score	1.970 (0.880–4.412)	0.100

The analysis includes a total of 430 patients: 263 who successfully completed outpatient treatment and 167 who required subsequent hospitalization following initial outpatient management. Continuous variables were included in the model using their original units, as follows: Age (years), BMI (kg/m^2), Pulse rate (beats/min), Blood pressure (mmHg), White blood cell count and neutrophil count (×10^9/L), Hemoglobin (g/dL), Neutrophil percentage (%), NLR (unitless), Blood glucose (mg/dL), Glomerular filtration rate (mL/min), AST (IU/L), CRP (mg/L), ESR (mm/h). Significance set at $P < .05$. Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; BSA, body surface area; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; qSOFA, quick Sequential Organ Failure Assessment; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; CREST/ERON, severity classification systems; uSSTIs, uncomplicated skin and soft tissue infections



Predictors	AUC (%95 CI)	*p*-value	Cut-Off	Sensitivity	Specificity
NLR	0.672 (0.619-0.724)	<0.001	4.37	61.1 (49.7-67.7)	69.5 (56.1-76.7)
CRP, mg/L	0.695 (0.645-0.746)	<0.001	67.5	68.9 (57.5-77.2)	59.0 (47.5-67.4)
Pulse rate, beats/min	0.615 (0.558-0.671)	<0.001	80.5	50.9 (38.3-58.3)	69.9 (56.5-76.4)

Fig. 3 Receiver operating characteristic curves illustrating the predictive performance of neutrophil-to-lymphocyte ratio, C-reactive protein, and pulse rate for outpatient treatment failure in patients with uncomplicated skin and soft tissue infections. Abbreviations: AUC indicates area under the curve; CI, confidence interval NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; uSSTIs, uncomplicated skin and soft tissue infections. Significance set at $P < .001$. Note: The large odds ratio observed for preseptal cellulitis (OR = 42.354, 95% CI = 4.178–429.336, $P = .002$) likely reflects the small number of cases, as indicated by the wide confidence intervals

Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Indicates area under the curve
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
LRINEC	Laboratory Risk Indicator for Necrotizing Fasciitis
MRSA	Methicillin-resistant S. aureus
MSSA	Methicillin-susceptible S. aureus
NLR	Neutrophil-to-lymphocyte ratio
ROC	Receiver Operating Characteristic
SSTIs	Skin and soft tissue infections
uSSTIs	Uncomplicated skin and soft tissue infections
WBC	White blood cell count
QSofa	Quick Sequential Organ Failure Assessment

Author contributions

(I) Conception and design: MNÖ, MSS, İNH; (II) Provision of study material: MNÖ, MSS, NNA, DBE, ÖG, PYA, AT, CS, SE, AY, YG, MRT, NBB, GEK, MÇ, EA, YK, YA, ÖA, ASÖ, OY, DÖ, ŞK, TDÇ, ŞBÖ, İNH; (III) Collection and assembly of data: MNÖ, MSS; (IV) Data analysis and interpretation: NNA, DBE, ÖG; (V) Manuscript writing: MNÖ, MSS, İNH; (VI) Final approval of manuscript: All authors.

Funding

There was no specific funding received for this study.

Data availability

Data are available from the corresponding author upon request, subject to privacy and ethical restrictions.

Declarations

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital, Türkiye, on March 6, 2024 (2024-TBEK 2024/03–03). Written informed consent was obtained for prospectively included patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Infectious Diseases and Clinical Microbiology, Iskenderun State Hospital, Hatay, Türkiye
[2]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Tekirdag Namik Kemal University, Namık Kemal Mahallesi Kampüs Street 1/14, Tekirdağ, Süleymanpaşa 59100, Türkiye
[3]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital, Bursa, Türkiye
[4]Department of Infectious Diseases and Clinical Microbiology, Erzurum Regional Training and Research Hospital, Erzurum, Türkiye
[5]Department of Infectious Diseases and Clinical Microbiology, Manisa Turgutlu State Hospital, Manisa, Türkiye
[6]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Samsun Training and Research Hospital, Samsun, Türkiye
[7]Department of Infectious Diseases and Clinical Microbiology, Ankara City Hospital, Ankara, Türkiye
[8]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Kırıkkale University, Kırıkkale, Türkiye
[9]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Bandirma Onyedi Eylul University, Balikesir, Türkiye
[10]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Istanbul, Türkiye
[11]Department of Infectious Diseases and Clinical Microbiology, Malatya Training and Research Hospital, Malatya, Türkiye
[12]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Konya City Hospital, Konya, Türkiye
[13]Department of Infectious Diseases and Clinical Microbiology, Yunus Emre State Hospital, Eskisehir, Türkiye
[14]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Fethi Sekin City Hospital, Elazig, Türkiye
[15]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Dokuz Eylül University, İzmir, Türkiye
[16]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Giresun University, Giresun, Türkiye
[17]Department of Infectious Diseases and Clinical Microbiology, Arnavutköy State Hospital, Istanbul, Türkiye
[18]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Bezmialem Vakıf University, Istanbul, Türkiye
[19]Department of Infectious Diseases and Clinical Microbiology, Acıbadem Hospital, Adana, Türkiye
[20]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Türkiye
[21]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Balıkesir University, Balıkesir, Türkiye
[22]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Manisa Celal Bayar University, Manisa, Türkiye
[23]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences Diyarbakır Gazi Yasargil Training and Research Hospital, Diyarbakır, Türkiye
[24]Department of Infectious Diseases and Clinical Microbiology, Sanliurfa Training and Research Hospital, Sanliurfa, Türkiye
[25]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Fırat University, Elazıg, Türkiye

Received: 3 September 2025 / Accepted: 12 November 2025
Published online: 27 December 2025

References

1. Poulakou G, Giannitsioti E, Tsiodras S. What is new in the management of skin and soft tissue infections in 2016? Curr Opin Infect Dis. 2017;30(2):158–71. https://doi.org/10.1097/QCO.0000000000000360.
2. Li DG, Xia FD, Khosravi H, et al. Outcomes of early dermatology consultation for inpatients diagnosed with cellulitis. JAMA Dermatol. 2018;154(5):537–43. https://doi.org/10.1001/jamadermatol.2017.6197.
3. Peterson RA, Polgreen LA, Cavanaugh JE, et al. Increasing incidence, cost, and seasonality in patients hospitalized for cellulitis. Open Forum Infect Dis. 2017;4(1):ofx008. https://doi.org/10.1093/ofid/ofx008.
4. Diekema DJ, Pfaller MA, Shortridge D, et al. Twenty-year trends in antimicrobial susceptibilities among *Staphylococcus aureus* from the SENTRY antimicrobial surveillance program. Open Forum Infect Dis. 2019;6(Suppl 1):S47–53. https://doi.org/10.1093/ofid/ofy270.
5. Esposito S, Bassetti M, Concia E, et al. Diagnosis and management of skin and soft tissue infections (SSTI). A literature review and consensus statement: an update. J Chemother. 2017;29(4):197–214. https://doi.org/10.1080/1120009X.2017.1311398.
6. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59(2):e10–52. https://doi.org/10.1093/cid/ciu296.
7. Schuler CL, Courter JD, Conneely SE, et al. Decreasing duration of antibiotic prescribing for uncomplicated skin and soft tissue infection. Pediatrics. 2016;137(2):e20151223. https://doi.org/10.1542/peds.2015-1223.
8. Hurley HJ, Knepper BC, Price CS, et al. Avoidable antibiotic exposure for uncomplicated skin and soft tissue infections in ambulatory care setting. Am J Med. 2013;126(12):1099–106. https://doi.org/10.1016/j.amjmed.2013.08.016.
9. Moore SJ, O'Leary ST, Caldwell B, et al. Clinical characteristics and antibiotic utilization in pediatric patients hospitalized with acute bacterial skin and skin structure infection. Pediatr Infect Dis J. 2014;33(8):825–8. https://doi.org/10.1097/INF.0000000000000304.
10. Chan M, Ooi CK, Wong J, et al. Role of outpatient parenteral antibiotic therapy in the treatment of community-acquired skin and soft tissue infections in Singapore. BMC Infect Dis. 2017;6(1):474. https://doi.org/10.1186/s12879-017-2569-4.
11. Grossi AP, Ruggieri A, Del Vecchio A, et al. Skin infections in europe: a retrospective study of incidence, patient characteristics and practice patterns. Int J Antimicrob Agents. 2022;60(3):106637. https://doi.org/10.1016/j.ijantimicag.2022.106637.
12. Ebied AM, Antonelli P. Optimization of antibiotic selection in the emergency department for adult skin and soft tissue infections. Hosp Pharm. 2022;57(1):83–7. https://doi.org/10.1177/0018578720985425.
13. Ak Ö, Diktaş H, Şenbayrak S, Saltoğlu N. Skin and soft tissue infections: Deri ve yumuşak doku infeksiyonları: Tanı ve tedavi. Klimik Derg. 2020;33(3):200–12. https://doi.org/10.5152/kd.2020.45
14. van Smeden M, Moons KG, Ah de Groot J. Sample size for binary logistic prediction models: beyond events per variable criteria. Stat Methods Med Res. 2019;28(8):2455–74. https://doi.org/10.1177/0962280218784726.
15. Riley RD, Moons KGM, Snell KIE. A guide to systematic review and meta-analysis of prognostic factor studies. BMJ. 2019 Jan;30:364k4597. https://doi.org/10.1136/bmj.k4597
16. Raya-Cruz M, Payeras-Cifre A, Ventayol-Aguiló L, et al. Factors associated with readmission and mortality in adult patients with skin and soft tissue infections. Int J Dermatol. 2019;58(8):916–24. https://doi.org/10.1111/ijd.14390.
17. Sutton JD, Carico R, Burk M, et al. Inpatient management of uncomplicated skin and soft tissue infections in 34 veterans affairs medical centers: a medication use evaluation. Open Forum Infect Dis. 2020;7(1):ofz554. https://doi.org/10.1093/ofid/ofz554.
18. Jenkins TC, Sabel AL, Sarcone EE, et al. Skin and soft-tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship. Clin Infect Dis. 2010;51(8):895–903. https://doi.org/10.1086/656431.
19. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases. Int J Mol Sci. 2022;26(7):3636. https://doi.org/10.3390/ijms23073636.
20. Nakamura T, Asanuma K, Hagi T, Sudo A. C-reactive protein and related predictors in soft tissue sarcoma (Review). Mol Clin Oncol. 2023;24(1):6. https://doi.org/10.3892/mco.2023.2704.
21. Corey GR, Kabler H, Mehra P, et al. Single-dose Oritavancin in the treatment of acute bacterial skin infections. N Engl J Med. 2014;370(23):2180–90. https://doi.org/10.1056/NEJMoa1310422.
22. Corey GR, Good S, Jiang H, et al. Single-dose Oritavancin versus 7–10 days of Vancomycin in the treatment of gram-positive acute bacterial skin and

skin structure infections: the SOLO II noninferiority study. Clin Infect Dis. 2015;60(2):254–62. https://doi.org/10.1093/cid/ciu778.
23. Collazos J, de la Fuente B, García A, et al. Cellulitis in adult patients: a large, multicenter, observational, prospective study of 606 episodes and analysis of the factors related to the response to treatment. PLoS ONE. 2018;27(9):e0204036. https://doi.org/10.1371/journal.pone.0204036.
24. Haran JP, Wilsterman E, Zeoli T, et al. Elderly patients are at increased risk for treatment failure in outpatient management of purulent skin infections. Am J Emerg Med. 2017;35(2):249–54. https://doi.org/10.1016/j.ajem.2016.10.060.
25. Linz MS, Mattappallil A, Finkel D, Parker D. Clinical impact of *Staphylococcus aureus* skin and soft tissue infections. Antibiotics (Basel). 2023;12(3):557. https://doi.org/10.3390/antibiotics12030557.
26. Nathwani D, Corey R, Das AF, et al. Early clinical response as a predictor of late treatment success in patients with acute bacterial skin and skin structure infections: retrospective analysis of 2 randomized controlled trials. Clin Infect Dis. 2017;15(2):214–7. https://doi.org/10.1093/cid/ciw750.
27. Cannon J, Dyer J, Carapetis J, Manning L. Epidemiology and risk factors for recurrent severe lower limb cellulitis: a longitudinal cohort study. Clin Microbiol Infect. 2018;24(10):1084–8. https://doi.org/10.1016/j.cmi.2018.01.023.
28. Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. Population: a retrospective population-based study. BMC Infect Dis. 2013;3013:252. https://doi.org/10.1186/1471-2334-13-252.
29. Jenkins TC, Knepper BC, McCollister BD, et al. Failure of outpatient antibiotics among patients hospitalized for acute bacterial skin infections: what is the clinical relevance? Am J Emerg Med. 2016;34(6):957–62. https://doi.org/10.1016/j.ajem.2016.02.013.
30. WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS). (2023). Available on line at: https://www.paho.org/sites/default/files/2023-10/p2-20223-cde-relavra-d2-sesion-3-achievements-lessons-learned-glass-carmen-pessoa.pdf

Publisher's note