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ASSOCIATION BETWEEN C-REACTIVE PROTEIN AND CELLULITIS IN PATIENTS PRESENTING TO EMERGENCY DEPARTMENT

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Abstract

Objective: *To determine association between serum C-reactive protein (CRP) concentration and cellulitis severity assessed with Dundee classification in patients presenting to emergency department.*

Study Design: *Cross-sectional study.*

Place and Duration of Study: *Tertiary Care Hospital in Pakistan from November 2023 to April 2024.*

Methodology: *Seventy patients with clinical diagnosis of cellulitis were enrolled. Demographic variables, vital signs, white blood cell count, high-risk comorbidity, systemic inflammatory response syndrome count, Standardized Early Warning Score and serum CRP were recorded at patient presentation. Dundee classes I-IV were assigned from sepsis status, comorbidity and early warning score. Because CRP was non-normally distributed, association with ordinal Dundee class was assessed by Spearman correlation and Kruskal-Wallis test. Exploratory ordinal logistic regression estimated odds of higher Dundee class per 10 mg/L increase in CRP.*

Results: *Mean age was 50.1±14.7 years and 45 (64.3%) participants were male. Dundee class distribution was I in 37 (52.9%), II in 18 (25.7%), III in 12 (17.1%) and IV in 3 (4.3%) patients. Median CRP increased across classes were 29.8 mg/L in class I, 39.3 mg/L in class II, 77.6 mg/L in class III and 100.6 mg/L in class IV. CRP had moderate positive correlation with Dundee class (Spearman ρ=0.503; 95% CI 0.298-0.671; $p<0.001$). CRP differed significantly across four classes (Kruskal-Wallis H=19.00; $p<0.001$). Each 10 mg/L increase in CRP was associated with 1.50-fold higher odds of belonging to more severe Dundee category (OR=1.50; 95% CI 1.27-1.77; $p<0.001$).*

Conclusion: *Higher serum CRP was associated with greater Dundee-classified cellulitis severity.*

INTRODUCTION

Cellulitis is acute bacterial infection involving dermis and subcutaneous tissue and is frequent reason for emergency department assessment. Recent United States surveillance confirms that abscess and cellulitis continue to account for substantial volume of emergency care[1]. Although clinical picture often includes erythema, warmth, oedema and tenderness, syndrome overlaps with venous stasis dermatitis, lymphoedema, deep venous thrombosis and other inflammatory disorders. Evidence-based emergency medicine review emphasizes that initial distinction between non-purulent cellulitis, abscess and non-infectious mimics remains primarily clinical.[2]

In prospective validation study, thermal imaging and ALT-70 score improved discrimination between cellulitis and pseudo cellulitis but neither approach eliminated need for clinical judgement[3]. Two recent systematic reviews found that meaningful proportion of patients initially labelled as having uncomplicated cellulitis were later given alternative diagnosis after specialist reassessment[4,5]. Further review of diagnostic methods concluded that no single laboratory or imaging test currently serves as universally accepted confirmatory standard for non-purulent cellulitis[2,4]. This uncertainty can lead both to unnecessary antibiotic exposure in mimics and delayed escalation in genuinely severe infection.

Severity assessment is therefore separate and important task after working diagnosis has been made. Dundee classification combines systemic inflammatory response, comorbidity and early warning score to place patients into four clinical classes. Its value is pragmatic; it converts bedside findings into ordered estimate of illness burden that may inform site-of-care and treatment decisions. However, external evaluation has shown that predictive scores including Dundee and ALT-70, have limitations when compared with microbiological or specialist assessment[6]. Dermatology consultation and diagnostic stewardship can reduce avoidable treatment and admissions, further supporting combined rather than single-test approach[4,5].

C-reactive protein is hepatic acute-phase reactant that rises in response to inflammatory cytokine signaling. It is inexpensive, widely available and commonly requested when patients with suspected infection are assessed. Contemporary emergency department cohorts show that CRP is routinely incorporated into cellulitis work-up, although its interpretation and influence on treatment vary.[7] Current emergency department best-practice recommendations place laboratory testing within wider clinical context rather than treating any single biomarker as diagnostic[8]. This is biologically sensible because obesity, venous or lymphatic disease, host response, timing of sampling and concurrent inflammation can affect observed CRP value.

Present study was conducted to determine association between serum CRP concentration and Dundee classification among patients presenting with cellulitis to emergency department.

MATERIAL AND METHODS

This cross-sectional study was conducted in the ED of a tertiary care hospital between November 2023 to April 2024. Sample size (n = 70) was calculated by using G*Power (version 3.1.9.7), assuming as expected correlation of r = 0.33 between serum CRP and clinical severity, assuming null correlation of zero, two-sided alpha of 0.05, 80% power and 95% confidence.[9] Minimum calculated sample was 70 patients. Participants were selected by non-probability consecutive sampling from patients presenting with clinical diagnosis of cellulitis.

Inclusion Criteria

Patients aged 18 years or older were eligible when treating clinician diagnosed cellulitis on basis of compatible local findings and when serum CRP and variables required to assign Dundee class were available at emergency department assessment.

Exclusion Criteria

Patients were excluded when final diagnosis was non-infectious, drainable abscess without surrounding cellulitis, necrotizing soft-tissue infection, infection related to recent major surgery or trauma or when concurrent inflammatory, malignant or autoimmune condition was judged likely to independently raise CRP. Records with incomplete CRP or Dundee-classification data were also excluded.

At presentation, age, sex, temperature, heart rate, respiratory rate, oxygen saturation, systolic blood pressure, AVPU level and white blood cell count were recorded on structured form. Peripheral vascular disease, chronic venous insufficiency or lymphoedema and morbid obesity (body mass index >40 kg/m^2) were documented as relevant comorbid states. Serum CRP was measured by hospital laboratory using analyzer.

Sepsis was operationalized as two or more systemic inflammatory response syndrome criteria, in keeping with data collection tool. Standardized Early Warning Score (SEWS) was calculated from physiological observations. Dundee class I indicated absence of sepsis and high-risk comorbidity, class II indicated high-risk

comorbidity without sepsis, class III indicated sepsis with SEWS below 4 and class IV indicated sepsis with SEWS of 4 or more. Primary study variable was admission CRP concentration in mg/L and primary outcome was ordinal Dundee severity class.

Data were analyzed by using IBM Statistical Package for the Social Sciences (version 25.0). Continuous data were summarized as mean±standard deviation when approximately symmetric and as median with interquartile range (IQR) when skewed. Categorical data were reported as frequency and percentage. Normality of CRP was examined with Shapiro-Wilk test. Prespecified primary analysis used Spearman rank correlation because Dundee class was ordinal and CRP was non-normal. 95% confidence interval for Spearman's rho was obtained by 20,000 bootstrap resamples. Kruskal-Wallis test compared CRP distributions across four classes. As exploratory effect-size analysis, univariable proportional-odds logistic model estimated odds ratio (OR) for membership in higher Dundee category per 10 mg/L rise in CRP. All tests were two-sided and $p<0.05$ was considered statistically significant.

RESULTS

For patients (n = 70) mean age was 50.1±14.7 years (range 19-83 years) and 45 (64.3%) participants were male. Median CRP concentration was 37.3 mg/L (IQR 18.8-59.1) with range from 3.6 to 134.8 mg/L. Fifteen (21.4%) patients met study definition of sepsis while 20 (28.6%) had high-risk comorbidity. Chronic venous insufficiency or lymphoedema was documented in 12 (17.1%), morbid obesity in 8 (11.4%) and peripheral vascular disease in 3 (4.3%) patients. Overall clinical and laboratory profile is shown in Table I.

Table I: Baseline characteristics of participants (n=70)

Characteristic	Value
Age, years	50.1±14.7; range 19-83
Male sex	45 (64.3%)
CRP, mg/L	37.3 (18.8-59.1); range 3.6-134.8
White blood cell count, $\times 10^9$/L	9.0 (6.8-11.7)
Sepsis (≥2 SIRS criteria)	15 (21.4%)
High-risk comorbidity	20 (28.6%)

Values are mean±standard deviation, median (interquartile range) or n (%), as appropriate.
CRP: C-reactive protein; SIRS: systemic inflammatory response syndrome.

Dundee class I was assigned to 37 (52.9%) patients, class II to 18 (25.7%), class III to 12 (17.1%) and class IV to 3 (4.3%). Median CRP increased in ordered pattern from 29.8 mg/L in class I to 100.6 mg/L in class IV. However, ranges overlapped were class I included values as high as 86.4 mg/L while lowest class IV value was 38.4 mg/L. Class-specific distributions are presented in Table II.

Table II: Serum CRP concentration according to Dundee severity class

Dundee class	n (%)	Mean±SD, mg/L	Median (IQR), mg/L	Range, mg/L
I	37 (52.9)	29.3±20.5	29.8 (10.4-43.0)	3.6-86.4
II	18 (25.7)	44.3±27.8	39.3 (21.0-74.4)	5.5-84.5
III	12 (17.1)	74.7±34.3	77.6 (41.4-96.6)	27.7-133.3
IV	3 (4.3)	91.3±48.9	100.6 (69.5-117.7)	38.4-134.8

CRP: C-reactive protein; IQR: interquartile range; SD: standard deviation.

CRP departed significantly from normality (Shapiro-Wilk W=0.911; $p<0.001$). Primary analysis showed moderate positive monotonic association between CRP and Dundee class (Spearman $\rho=0.503$; bootstrap 95% CI 0.298-0.671; $p<0.001$). Kruskal-Wallis test also demonstrated difference in CRP distribution across four classes ($H=19.00$; 3 degrees of freedom; $p<0.001$). In exploratory proportional-odds model, each 10 mg/L increase in CRP was

associated with 50% higher odds of being in more severe Dundee category (OR=1.50; 95% CI 1.27-1.77; p<0.001). These inferential findings are summarized in Table III.

Table III: Association between serum CRP and Dundee severity class

Analysis	Effect estimate	95% CI	p-value
Spearman rank correlation	ρ=0.503	0.298-0.671	<0.001
Kruskal-Wallis test	H=19.00; df=3	–	<0.001
Ordinal logistic regression*	OR=1.50	1.27-1.77	<0.001

*Univariable proportional-odds model; OR represents odds of membership in higher Dundee class per 10 mg/L increase in CRP. CI: confidence interval; CRP: C-reactive protein; df: degrees of freedom; OR: odds ratio.

DISCUSSION

Principal finding was statistically significant, moderate positive association between admission CRP and cellulitis severity measured by Dundee classification. CRP rose in ordered manner across four classes and effect remained clear when data were examined through rank correlation non-parametric group comparison and ordinal regression model.

Result fits of contemporary cellulitis research.[10] Recent prediction studies have moved away from isolated bedside impressions toward combined models incorporating physiology, inflammatory variables and comorbidity. Chen and colleagues used routinely available clinical data to predict sepsis developing during hospitalization while Tienpratarn and colleagues developed a score for cellulitis-related complications using multiple risk domains[11,12]. In tropical Australia admission early warning score predicted prolonged stay and readmission underscoring prognostic relevance of systemic physiological disturbance[13]. Our study adds focused estimate of how one commonly available inflammatory marker tracks with structured severity scale at emergency department.

Median CRP approx. tripled from class I to class IV but class-specific ranges overlapped substantially. Patient with high CRP may remain hemodynamically stable while early severe infection may present before CRP has reached its peak. Work on CRP kinetics has shown that rate of change can provide information not captured by single measurement.[14] One-time value also reflects host characteristics and sampling time. Therefore, low result should not reassure clinicians when there are concerning physiological or local features and high result should not automatically determine admission or intravenous therapy.

Class I and class II medians were relatively close which is consistent with structure of Dundee system. Distinction between these classes depends mainly on high-risk comorbidity rather than mandatory difference in acute systemic response. Obesity is associated with cellulitis occurrences and chronic venous or lymphatic disease may contribute to both susceptibility and recurrent inflammation.[15] Present cohort included these conditions but its size did not permit reliable stratified analysis. BRRISC study similarly demonstrated that recurrence risk reflects several clinical phenotypes rather than single laboratory measure[16].

Our findings also align with research in other bacterial soft-tissue infections. Admission CRP and leukocyte measures have been associated with disease burden in orofacial infection and combined CRP-neutrophil-to-lymphocyte measure showed good discrimination for severe odontogenic infection.[17,18] These studies are not directly interchangeable with limb or truncal cellulitis because anatomy, source control and microbiology differ. They nevertheless support broader concept that acute-phase response contains severity information.

Emergency department implication is practical rather than prescriptive. CRP may strengthen confidence that patient classified clinically as Dundee III or IV has substantial inflammatory burden, prompt reassessment of apparently discordant cases and provide baseline for follow-up. It should not replace examination for abscess, necrotizing infection or pseudo cellulitis. Current diagnostic reviews emphasize that specialist reassessment, in selected cases and structured clinical tools can reduce misdiagnosis[2-8]. Similarly, treatment decisions should follow the whole clinical picture, a pilot

randomized trial of high-dose cephalexin illustrated that even apparently straightforward outpatient cellulitis requires attention to treatment response and adverse effects rather than biomarker thresholds alone.[19]

This study has several strengths. It analyzed complete dataset, used an ordinal severity outcome rather than arbitrary binary split, selected non-parametric methods appropriate for CRP distribution and reported effect sizes with confidence intervals. Bootstrap interval around Spearman's rho provides more informative estimate than p-value alone. Ordinal regression result, expressed per 10 mg/L increase also gives association clinically interpretable scale.

Several limitations require emphasis. First, single-center sample was small, particularly Dundee class IV, which contained only three patients, upper-severity estimates are therefore imprecise. Second, this was cross-sectional association and cannot establish that CRP predicts later deterioration, admission, treatment failure or recurrence. Third, CRP may be influenced by unrecorded inflammatory conditions, symptom duration and prior treatment.

CONCLUSION

Serum CRP concentration was moderately and positively associated with Dundee-classified cellulitis severity in patients presenting to emergency department. Median CRP increased across classes and each 10 mg/L rise was associated with higher odds of membership in more severe category. Because individual values overlapped and most severe group was small, CRP is best interpreted as adjunct to physiological assessment, comorbidity review and careful clinical examination rather than as independent severity rule.

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