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Original research

# THE ROLE OF C - REACTIVE PROTEIN AND NEUTROPHIL TO LYMPHOCYTE RATIO IN PREDICTING THE SEVERITY OF PEDIATRIC CELLULITIS

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**ABSTRACT**

***Background:*** *Cellulitis has caused a significant burden on the pediatric hospital system around the world, including Vietnam. However, there are no reliable clinical and laboratory features to predict the severity. This research was pursued to describe the clinical and laboratory characteristics and to determine if the combination of C-reactive protein (CRP) and Neutrophil to Lymphocyte Ratio (NLR) (CRP - NLR) may serve as potential severity predictors in pediatric cellulitis.*

***Methods:*** *A cross - sectional descriptive analysis on 50 children hospitalized for cellulitis from 01/2021 to 01/2023 was conducted at the Pediatric Center, Hue Central Hospital.*

***Results:*** *The mean age was 3.54 ± 2.82. The most risk factors were wounds (10%), insect bites (8%), other dermatological diseases (6%). Most children hospitalized with conscious consciousness (49/50, 98%), fever (36/50, 72%) and no signs of infection (46/50, 92%), 80.6% of children had high fever ≥ 39 ºC. The most affected body location was the extremities (70%). Clinical features were swelling (98%), redness (90%), pain (90%), warmth (72%). The white blood cell count (WBC) increased > 11 k/µl in 76% cases, 60% cases had CRP > 8 mg/dl. Wound cultures yielded pathogens in 6/7 cases (42.85% MSSA; 42.85% MRSA). Blood cultures were performed in 13/50 cases with no positive result. CRP was the most significant test for predicting a severe cellulitis (Area Under the Curve - AUC = 0.846; 95% [CI], 0.734 - 0.959; p - value < 0.001). We selected optimal threshold values (CRP > 23.3 mg/dl and NLR > 2.54), then CRP - NLR was associated with the severity of cellulitis (OR = 42.5; p - value < 0.001).*

***Conclusions:*** *Therefore, it can be concluded that CRP - NLR is a reliable and affordable biomarker for determining the severity of pediatric cellulitis.*

***Keywords:*** *Pediatric cellulitis, cellulitis in children, CRP - NLR.*

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## I. INTRODUCTION

Cellulitis is an infection of the dermis and subcutaneous tissue that has poorly demarcated borders and is usually caused by Streptococcus or Staphylococcus species [1]. Cellulitis is a common reason for presentation to a tertiary pediatric hospital. The most affected body location was the face and the extremities [2].

Cellulitis has an important public health impact globally. In United States, the mean annual incidence of emergency department (ED) visits with a primary diagnosis of cellulitis/erysipelas was 1.14 to 2.09 per million pediatric ED visits [3]. We confirmed a very high burden of hospital admissions due to cellulitis in children in Western Australia because cellulitis is the second common diagnosis in 3% of children hospitalized for skin and soft tissue infections per year [4]. The "Cellulitis at Home or Inpatient in Children from the Emergency Department" (CHOICE) trial in

Melbourne reported 700 presentations of cellulitis to the Royal Children's Hospital over 17 months, with 304 (43%) admissions [5].

In recent years, there has been an increasing number of pediatric patients being admitted to the Pediatric Center of Hue Central Hospital due to cellulitis. In order to assist clinicians in making accurate diagnoses, providing timely treatment to prevent complications, and offering recommendations for high - risk patients in preventing cellulitis, we conducted the present study to describe the epidemiology, clinical and laboratory features of pediatric cellulitis; and identify factors associated with the severity of cellulitis in children.

## II. MATERIAL AND METHODS

### 2.1. Study population

All patients under 16 years old hospitalized for cellulitis at the Pediatric Center, Hue Central Hospital from January 2021 to January 2023.

Selection criteria were records with a primary diagnosis of cellulitis were identified using the International Classification of Disease (ICD) 10 coding

Exclusion criteria were patients with parents or caregivers did not agree to participate in the study.

### 2.2. Study design

Cross - sectional study: All admitted patients were asked about their medical history. Data were extracted from paper and electronic hospital records, including demographics, admission duration, clinical findings and results of laboratory tests.

Sample size: Convenience sample. This study included 50 admitted patients.

Data collection techniques: A prospective descriptive series of cases and face - to - face interviews.

### 2.3. Data analysis

Data were analyzed using SPSS 20.0 software. The qualitative variables were described by frequency and percentage; the quantitative variables were described as mean ± standard deviation (SD). The Chi - square test and Fisher exact test were used to identify factors related to infection severity. The AUC was plotted for CRP and NLR to determine their accuracy in predicting the severity of cellulitis. A p - value < 0.05 was considered statistically significant when comparing the study variables.

## III. RESULTS

**Table 1:** Demographic characteristics of the study population (Total n = 50)

| Variables | Values | n | % |
|---|---|---|---|
| Age group (years) | < 1<br>1 - 6<br>7 - 14<br>> 14 | 7<br>37<br>5<br>1 | 14<br>74<br>10<br>2 |
| | Mean (± SD) | 3.54 ± 2.82 | |
| Gender | Male<br>Female | 31<br>19 | 62<br>38 |
| Geographical location | Urban<br>Rural | 21<br>29 | 42<br>58 |
| Z - scores | -3 < Z - scores ≤ -2<br>-2 < Z - scores < 2 | 1<br>49 | 2<br>98 |
| Risk factors | Wounds<br>Insect bites<br>Other dermatological diseases<br>Using immunosuppressants<br>After vaccination<br>Unknown | 5<br>4<br>3<br>1<br>1<br>36 | 10<br>8<br>6<br>2<br>2<br>72 |

A total of 50 children participated in the study. Children aged 1 - 6 (74%) and were male (62%) were over - represented in the study population. The majority of children had normal nutritional status (98%). The main identified risk factors were wounds (10%), insect bites (8%), other dermatological diseases (6%). The other dermatological diseases included eczema, furuncles, and atopic dermatitis.

**Table 2:** Clinical features of cellulitis

| Variables | Values | n | % |
|---|---|---|---|
| Level of consciousness | Normal<br>Confusions | 49<br>1 | 98<br>2 |
| Temperature | 37- < 38ºC<br>38 ≤ t < 39ºC<br>t ≥ 39ºC | 14<br>7<br>29 | 28<br>14<br>58 |
| Signs of infection | Yes<br>No | 4<br>46 | 8<br>92 |
| Lymph nodes | Yes<br>No | 13<br>37 | 26<br>74 |
| Location | Face<br>Upper limbs<br>Torso<br>Groin and buttocks<br>Lower limbs | 10<br>11<br>4<br>6<br>24 | 20<br>22<br>8<br>12<br>48 |
| Local symptoms | Swelling<br>Pain<br>Warmth<br>Redness<br>Limit clearly<br>Spots<br>Blisters<br>Ulcers<br>Purulence | 49<br>45<br>36<br>45<br>16<br>9<br>4<br>5<br>16 | 98<br>90<br>72<br>90<br>32<br>18<br>8<br>10<br>32 |
| Severity | Mild<br>Moderate<br>Severe | 13<br>23<br>14 | 26<br>46<br>28 |

Most children had conscious consciousness (49/50, 98%), fever (36/50, 72%) and no signs of infection (46/50, 92%). There were 29/36 children (80.6%) had high fever ≥ 39ºC; 13/50 (26%) had lymph nodes. The most affected body location was the extremities (70%). There were 5 children (10%) had two infection sites which were consecutive sites such as feet and toes, feet and legs, hands and forearms. Local symptoms were characterized by swelling (98%), redness (90%), pain (90%), warmth (72%). Other skin lesions such as spots, blisters, and ulcers were less frequently observed. The infection sites were purulent in 32% of cases. 14/50 children (28%) were hospitalized for severe cellulitis.

**Table 2:** Laboratory features of cellulitis.

| Variables | Values | n | % |
|---|---|---|---|
| WBC | ≥ 11 k/µl<br>< 11 k/µl | 38<br>12 | 76<br>24 |
| | Mean (± SD) | 14.8 ± 5.9 k/µl | |
| NEU% | ≥ 80 %<br>< 80% | 12<br>38 | 24<br>76 |
| | Mean (± SD) | 59.2 ± 18.4 % | |
| NLR | ≤ 2.54<br>> 2.54 | 26<br>24 | 52<br>48 |
| | Mean (± SD) | 3.4 ± 2.9 | |
| CRP | < 8 mg/dl<br>8 ≤ CRP ≤ 23.3 mg/dl<br>CRP > 23.3 mg/dl | 20<br>11<br>19 | 40<br>22<br>38 |
| | Mean (± SD) | 30.4 ± 40.8 mg/dl | |
| Wound culture results | No growth<br>MSSA<br>MRSA | 1<br>3<br>3 | 2<br>6<br>6 |
| Blood culture results | No growth | 13 | 26 |

76% of cases increased white blood cell count > 11 k/µl; 24% increased NEU%; 48% of patients had NLR > 2.54, 52% had NLR < 2.54; 60% of patients had CRP elevation, of which 38% had CRP > 23.3 mg/dl. Wound cultures obtained in 7/50 cases, of which most frequently growing MSSA (42.85%) and MRSA (42.85). There were 13 cases obtained blood cultures with 100% results as no growth.

Described the predictive of biological markers on the severity of cellulitis:

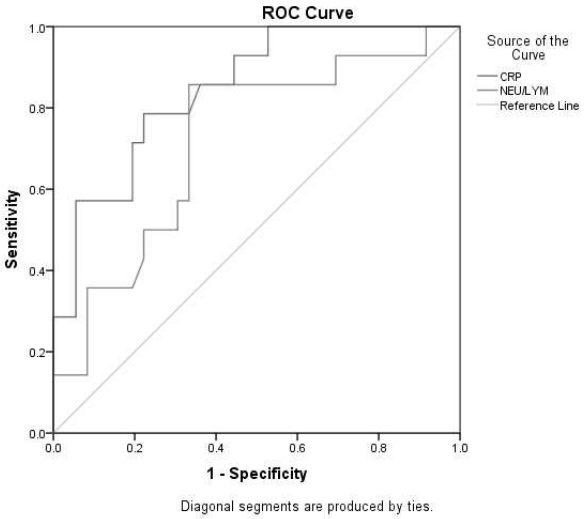


**Chart 1:** ROC curve analysis of CRP and NLR

**Table 4:** AUC and related values

| Test | AUC (95% [CI]) | p - value | Cutoff point | Sensitivity | Specificity |
|---|---|---|---|---|---|
| CRP | 0.846 (0.734 - 0.959) | 0.000 | 23.3 mg/dl | 79% | 78% |
| NLR | 0.715 (0.553 - 0.878) | 0.019 | 2.54 | 86% | 67% |

The receiver operating curve (ROC) analysis of CRP yielded an AUC value of 0.846 (95% [CI] 0.734 - 0.959), with high sensitivity (79%) and high specificity (78%), for predicting a severe cellulitis using biomarkers measured at hospital admission (p - value < 0.001). NLR has a mean prognostic value with AUC = 0.715 (95% [CI]: 0.553 - 0.878, p-value < 0.05). NLR > 2.54 is the optimal threshold value with sensitivity 86% and specificity 67%.

**Table 5:** The factors related to the severity of cellulitis

| Variables | Non-severe n = 36 (%) | Severe n = 14 (%) | p | OR (95%[CI]) |
|---|---|---|---|---|
| ≤ 6 years old | 32 (99.8) | 12 (85.7) | 1.000 | 1.333 (0.216 - 8.249) |
| Male gender | 25 (69.4) | 6 (42.9) | 0.082 | 3.030 (0.848 - 10.835) |
| Z - score < -2 | 0 (0) | 1 (7.1) | 0.280 | NA |
| High fever ≥ 39ºC | 18 (50.0) | 11 (78.6) | 0.066 | 0.273 (0.065 - 1.144) |
| Lymph nodes | 9 (25.0) | 4 (28.6) | 1.000 | 0.833 (0.209 - 3.323) |
| Indistinct border | 26 (72.2) | 8 (57.1) | 0.330 | 0,513 (0.142 - 1.854) |
| Had ulcers | 3 (8.3) | 2 (14.3) | 0.611 | 0.545 (0.081 - 3.674) |
| Purulence | 11 (30.5) | 5 (35.7) | 0.742 | 0.792 (0.215 - 2.915) |
| WBC > 11 k/µl | 25 (69.4) | 13 (92.9) | 0.140 | 0.175 (0.020 - 1.507) |
| *CRP - NLR* | *2 (5.6)* | *10 (71.4)* | *0.000* | *42,5 (6.763 - 267.067)* |
| Wound culture MRSA | 1 (2.8) | 2 (14.3) | 0.186 | 0.171 (0.014 - 2.064) |

The CRP - NLR association determined a 42.5 - fold increased risk of severe cellulitis (p - value < 0.001). There was no relationship between being ≤ 6 years old, male sex, Z - scores < -2, high fever ≥ 39ºC, having lymph nodes, indistinct border, having ulcers, purulence, WBC > 11 k/µl, wound culture MRSA and severe cellulitis.

## IV. DISCUSSION

Children aged 1 - 6 (74%) and were male (62%) were over - represented in the study population **(Table 1)**. The mean age of children admitted to hospital was 3.54 ± 2.82 years, the male/female ratio was 1.63/1. According to the study results of Salleo et al with n = 302, children ≤ 5 years old made up the majority of the study population with 48.7%, the median age was 5 years old, the male/female ratio was 1.48 : 1 [2]. More than half (55.7%) of patients were male and the mean age was 4.1 years in Chand's study which included 343 patients with non-abscess cellulitis [6]. The most commonly known risk factors of cellulitis in the study group were wounds (10%), insect bites (8%), other dermatological diseases (6%) which included eczema, furuncles, and atopic dermatitis. Using immunosuppressants (2%) and after vaccination (2%) were uncommon. Quirke's study showed that an increased risk of developing non - purulent cellulitis of the leg was associated with previous cellulitis (OR = 40.3), wound (OR = 19.1), current leg ulcers (OR = 13.7), lymphoedema/chronic leg oedema (OR = 6.8), excoriating skin diseases (OR = 4.4), tinea pedis (OR = 3.2) and body mass index > 30 kg m - 2 (OR = 2.4) [7]. In early childhood and preschool age, children begin to have extensive exposure to the external environment, which makes them more susceptible to disease transmission. They are typically lively, active, and inclined to engage in independent activities. However, due to their limited awareness of potential hazards in their surroundings, they are more prone to accidents, injuries, and insect bites, which create favorable conditions for the development of cellulitis. The studies have identified diverse risk factors contributing to the occurrence of cellulitis, with a notable proportion attributed to trauma and insect bites. This poses a challenge for parents in effectively managing their children's well - being and reducing the incidence of this condition. Although less common, factors such as needle punctures and surgical wounds are associated with medical care and must be taken into account. Additionally, timely diagnosis and treatment of other dermatological conditions, such as eczema, impetigo, blisters, and atopic dermatitis, are crucial. The Infectious Diseases Society of America (IDSA) strongly advises clinical practitioners to thoroughly examine the interdigital spaces in cases of subcutaneous cellulitis, aiming to address any cracks or fissures to prevent the infiltration of disease - causing bacteria and reduce the risk of recurrent infections (strong/moderate recommendation) [8].

Most children had conscious consciousness (49/50, 98%), fever (36/50, 72%), high fever ≥ 39ºC (29/36, 80.6%) and no signs of infection (46/50, 92%) **(Table 2)**. These results indicate that the prominent systemic symptoms of children with cellulitis upon hospital admission are fever, and the majority of these children have high - grade fever ≥ 39ºC. Fever is the most common reason for children and infants to be brought to the emergency department [9]. However, the severity of the underlying condition in children is not necessarily correlated with the degree of fever they experience [10].

The most affected body location was the extremities (70%). This result demonstrates similarities with the studies conducted by Chand (47.6%) [6] and Salleo (73.1%) [2], respectively. Local symptoms were characterized by swelling (98%), redness (90%), pain (90%), warmth (72%). Other skin lesions such as spots, blisters, and ulcers were uncommon. Infections were purulent in 32% of cases. The study conducted by Yueh et al. revealed the following results: swelling (85.1%), redness (89.1%), pain (55.6%), warmth (35.4%), purulence (50.1%), rare occurrence of skin rashes, and no petechiae [11]. From these findings, it can be concluded that the clinical features of cellulitis include swelling, pain, redness, and other skin lesions such as rashes, blisters, and ulcers, with or without purulence, but no petechiae.

The most frequent investigations were full blood count and CRP with a relatively high percentage of abnormalities (WBC 76%, CRP 58%) (Table 3). Wound cultures obtained in 7/50 cases, of which most frequently growing MSSA (42.85%) and MRSA (42.85). Chand's study conducted wound culture in 130 cases, yielding the following results: 42 cases tested positive for MSSA (32.31%), 40 cases for MRSA (30.8%), 15 cases for Streptococcus spp. (11.54%), 12 cases for gram - negative bacteria (9.23%), 13 cases

for other gram - positive bacteria (10%), and the remaining cases were presumed contaminants/ unspecified other [6]. It can be observed that MSSA and MRSA are the leading pathogens responsible for causing purulent cellulitis in children.

There were 13 cases obtained blood cultures with 100% results as no growth. In Salleo' study, blood cultures were performed in 45.6% (94/206) of admitted cases with only one positive results: coagulase negative Staphylococcus, a probable skin contaminant [2]. Five cultures (2%) were positive, and 13 (5.4%) were contaminants in 243/381 cases of Sadow and Chamberlain study [12]. In the study conducted by Chand involving 559 pediatric patients, positive blood cultures were identified in 12/302 cases (3.97%). There were 5/12 (41.6%) were MSSA, 2/12 (16.6%) were Streptococcus pyogenes, and the remaining cases involved other bacteria including Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus mitis, Micrococcus luteus, and Pseudomonas aeruginosa [13]. We identified the difficulties in determining the etiological agents of cellulitis. Wound culture may be more useful than blood culture because of over 80% of tested individuals yielding positive results. This method is particularly effective in cases of purulent cellulitis.

CRP > 23.3 mg/dL had been determined as the optimal threshold for distinguishing between severe and non - severe cellulitis in children, with the sensitivity of 79% and specificity of 78%. The cutoff value for NLR (> 2.54) showed higher sensitivity (86%) compared to CRP but lower specificity (67%). The CRP AUC (0.846; 95% [CI] 0.734 - 0.959; p - value < 0.001) was greater than NLR (AUC = 0.715; 95% [CI] 0.553 - 0.878; p - value < 0.05). The CRP AUC is also significantly greater than the WBC (AUC = 0.667; 95% [CI] 0.508 - 0.825) and NEU% (AUC = 0.740; 95% [CI] 0.580 - 0.900, p - value < 0.01). Therefore, CRP is the most reliable test for predicting the severity of cellulitis in children.

When analyzing the factors in Table 5, we found that combining the optimal thresholds of CRP (CRP > 23.3 mg/dL) and NLR (NLR > 2.54) results in a new variable called CRP - NLR, which had a strong correlation with severe cellulitis [OR = 42.5; p - value < 0.001]. The CRP and NLR values used were the results of the initial tests conducted when the patients were admitted to the hospital.

There was no relationship between being ≤ 6 years old, male sex, Z - score < -2, high fever ≥ 39ºC, having lymph nodes, indistinct border, having ulcers, purulence, WBC > 11 k/µl, wound culture MRSA and severe cellulitis.

## V. CONCLUSIONS

Therefore, it can be concluded that CRP-NLR is a reliable and affordable biomarker for determining the severity of cellulitis in children so it should be used to improve treatment choices for the disease.

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