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Research Article

Predictive Value of the Systemic Immune-Inflammation Index for Early Clinical Deterioration in Children Hospitalized With Severe Pneumonia: A Prospective Cohort Study

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Abstract

Background:

Severe community-acquired pneumonia remains a leading cause of pediatric morbidity and mortality worldwide. Early identification of children at risk for rapid clinical deterioration is essential for timely escalation of care. The Systemic Immune-Inflammation Index (SII)—calculated as (Neutrophils × Platelets)/Lymphocytes—combines systemic inflammation and immune status, but its prognostic utility in pediatric severe pneumonia has not been comprehensively established.

Objective:

To evaluate the predictive value of admission SII for early clinical deterioration in children hospitalized with severe pneumonia.

Methods:

A prospective cohort study was conducted at Gujranwala Medical College and Teaching Hospital involving 160 pediatric patients aged 1 month to 12 years admitted with severe pneumonia. Demographics, clinical characteristics, primary laboratory parameters, and baseline SII values

were obtained at admission. Early clinical deterioration was defined as transfer to the pediatric intensive care unit (PICU), requirement for non-invasive or invasive mechanical ventilation, or dynamic physiological instability within 48 hours of admission. Receiver Operating Characteristic (ROC) curve analysis, multivariate binary logistic regression, and dynamic risk stratification were performed.

Results:
Among 160 pediatric participants (mean age 3.4 ± 2.1 years; 55.6% male), early clinical deterioration occurred in 38 children (23.8%). Baseline SII was significantly higher in patients who experienced deterioration compared to those who remained stable (1482.5 ± 520.4 vs. $612.3 \pm 210.8 \times 10^9$/L, $p < 0.001$). ROC curve analysis demonstrated that an admission SII threshold $> 950 \times 10^9$/L yielded an area under the curve (AUC) of 0.88 (95% CI: 0.82–0.94), with a sensitivity of 84.2% and specificity of 81.1% for predicting early deterioration. In multivariable logistic regression, an elevated SII remained an independent predictor of deterioration (adjusted OR = 4.12, 95% CI: 2.15–7.89, $p < 0.001$) after adjusting for age, C-reactive protein (CRP), and baseline Pediatric Respiratory Severity Score.

Conclusion:
Admission SII is a highly accurate, accessible, and independent predictive biomarker for early clinical deterioration in pediatric patients hospitalized with severe pneumonia. Incorporating SII into initial clinical triage can facilitate prompt risk stratification and optimize intensive monitoring resources.

Keywords: Systemic immune-inflammation index; Severe pneumonia; Pediatrics; Early clinical deterioration; Intensive care; Biomarkers; Risk stratification.

1. Introduction

Severe pneumonia remains the single largest infectious cause of death in children under 5 years of age globally, accounting for hundreds of thousands of deaths annually, predominantly in low- and middle-income regions [1, 2]. Pediatric severe pneumonia is characterized by localized alveolar inflammation, systemic release of inflammatory cytokines, variable lung parenchymal consolidation, and impending respiratory failure [3, 4]. While a substantial proportion of children respond rapidly to standard parenteral antimicrobial and supportive therapy, a subset experiences rapid early clinical deterioration within the first 24 to 48 hours of hospitalization [4, 5].

Early clinical deterioration often entails respiratory pump fatigue, worsening hypoxemia, systemic sepsis, acute respiratory distress syndrome (ARDS), or hemodynamic collapse requiring urgent escalation to high-dependency or pediatric intensive care unit (PICU) settings [5, 6]. Delayed recognition of impending failure contributes to increased duration of mechanical ventilation, prolonged hospital stay, and higher mortality [6, 7]. Traditional clinical scoring tools—such as the Pediatric Early Warning Score (PEWS) and Pediatric Respiratory Severity Score—rely on physiological parameters that may fluctuate dynamically or present late in the disease process [7, 8].

Consequently, there is growing interest in identifying novel, cost-effective inflammatory biomarkers derived from routine complete blood counts (CBC) to enhance objective risk stratification [9, 10]. The Systemic Immune-Inflammation Index (SII) is an integrated inflammatory index introduced to assess systemic immune-inflammatory homeostasis [11, 12]. Mathematically defined as:

$$\text{SII} = \frac{\text{Absolute Neutrophil Count} \times \text{Absolute Platelet Count}}{\text{Absolute Lymphocyte Count}}$$

SII simultaneously reflects three immunological pathways: neutrophils drive innate inflammatory tissue damage, platelets mediate vascular endothelial reactivity and immunothrombosis, and lymphocytes represent adaptive immune responses and host resistance [11, 13]. While SII has demonstrated prognostic utility in adult sepsis, acute respiratory failure, and oncological states, its specific predictive value for early clinical deterioration in hospitalized pediatric pneumonia remains to be fully elucidated [14, 15].

Therefore, this prospective cohort study was conducted to evaluate the predictive capacity of admission SII for early clinical deterioration in children admitted with severe pneumonia and to define optimal diagnostic cutoff values for clinical decision-making.

2. Rationale of the Study

Pediatric severe pneumonia can deteriorate rapidly, challenging clinical monitoring in busy inpatient wards [4, 5]. While conventional phase reactants like C-reactive protein (CRP) and procalcitonin offer diagnostic insight, they do not directly integrate the tripartite relationship between innate inflammation, thrombotic pathway activation, and host lymphocyte exhaustion [9, 10]. The Systemic Immune-Inflammation Index (SII) utilizes parameters from a standard, inexpensive Complete Blood Count (CBC) with differential, making it universally accessible across diverse clinical settings [11, 12]. Establishing its prognostic accuracy for early deterioration provides a quantitative, objective tool for early risk stratification.

3. Objectives

Primary Objective

- To assess the predictive accuracy of admission Systemic Immune-Inflammation Index (SII) for early clinical deterioration (within 48 hours of admission) in pediatric patients hospitalized with severe pneumonia.

Secondary Objectives

1. To compare admission SII levels between pediatric severe pneumonia patients who experience early clinical deterioration and those who maintain clinical stability.

2. To establish an optimal SII cutoff threshold for clinical deterioration using Receiver Operating Characteristic (ROC) curve analysis.

3. To determine whether elevated SII is an independent predictor of early deterioration after controlling for age, baseline clinical severity scores, and C-reactive protein.

4. To evaluate secondary clinical outcomes, including PICU length of stay and duration of supplemental oxygen therapy across SII risk tiers.

4. Materials and Methods

4.1 Study Design and Setting

A hospital-based prospective cohort study was conducted at Gujranwala Medical College and Teaching Hospital.

4.2 Study Duration

The study was conducted over a eight-month period, encompassing prospective patient enrollment, baseline biological sampling, daily physiological monitoring, outcome tracking, and statistical modeling.

4.3 Study Population

Children aged 1 month to 12 years admitted to the pediatric inpatient ward with a primary clinical diagnosis of severe community-acquired pneumonia according to World Health Organization (WHO) and Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) clinical criteria [2, 3].

4.4 Sample Size

A sample size of 160 pediatric participants was enrolled. The sample size calculation was based on expecting an area under the ROC curve (AUC) of at least 0.80 for SII predicting clinical deterioration, assuming an early deterioration event rate of 20–25% in severe pediatric pneumonia, an alpha level of 0.05, and statistical power of 85%.

4.5 Inclusion Criteria

1. Age between 1 month and 12 years.

2. Clinical and radiological confirmation of severe pneumonia, defined by cough/difficulty breathing plus at least one of the following severe signs: severe respiratory distress (e.g., severe chest indrawing, nasal flaring, grunting), central cyanosis, oxygen saturation (SpO_2) $< 90\%$ on room air, or inability to feed/lethargy [2, 3].

3. Enrollment within 6 hours of hospital admission.

4. Complete blood count with differential performed at admission prior to starting intravenous second-line immunomodulatory therapies.

5. Written informed consent provided by parents or legal guardians.

4.6 Exclusion Criteria

1. Known congenital heart disease, chronic neuromuscular disease, or underlying bronchopulmonary dysplasia/chronic lung disease.

2. Primary immunodeficiency disorders or active immunosuppressive therapy.

3. Hematological malignancies, primary bone marrow disorders, or baseline thrombocytopenia/thrombocytosis unrelated to acute infection.

4. Hospital-acquired (nosocomial) pneumonia or transfer from an outside intensive care unit after > 24 hours of hospitalization.

5. Incomplete clinical records or missing baseline differential leukocyte parameters.

4.7 Clinical Data Collection and Baseline Evaluation

At admission, detailed demographic characteristics, illness duration prior to presentation, previous antibiotic exposure, vital signs, physical examination findings, and baseline Pediatric Respiratory Severity Scores (PRSS) were recorded. Standard empirical treatment regimens (parenteral antimicrobials, antipyretics, and age-appropriate oxygen/fluid therapy) were initiated per institutional guidelines.

4.8 Laboratory Investigations and SII Calculation

Venous blood samples were collected at hospital presentation. Complete blood counts—including absolute neutrophil count (ANC, $\times 10^9$/L), absolute lymphocyte count (ALC, $\times 10^9$/L), and total platelet count (PLT, $\times 10^9$/L)—were measured using automated hematology analyzers (Sysmex XN-Series). Serum C-reactive protein (CRP, mg/L) was measured using turbidimetric immunoassay.

The Systemic Immune-Inflammation Index (SII) was calculated as follows:

$$\text{SII} = \frac{\text{Absolute Neutrophil Count } (\times 10^9/\text{L}) \times \text{Absolute Platelet Count } (\times 10^9/\text{L})}{\text{Absolute Lymphocyte Count } (\times 10^9/\text{L})}$$

The Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) were calculated as secondary comparative inflammatory indices.

4.9 Primary and Secondary Endpoints

- **Primary Endpoint:** Early clinical deterioration occurring within the first 48 hours of inpatient hospitalization. Early clinical deterioration was defined as the composite of any of the following events:

1. Unplanned transfer to the Pediatric Intensive Care Unit (PICU).

2. Escalation to non-invasive positive pressure ventilation (NIV/CPAP/HFNC) or invasive mechanical ventilation due to refractory respiratory failure ($PaO_2/FiO_2 < 200$ or persistent $SpO_2 < 88\%$ despite high-flow oxygen).

3. Development of fluid-refractory septic shock requiring vasopressor/inotropic support.

- **Secondary Endpoints:** Total PICU length of stay (days), total duration of mechanical ventilation, total duration of oxygen therapy, and overall in-hospital mortality.

4.10 Statistical Analysis

Data were analyzed using SPSS version 26.0 and MedCalc version 20.0. Continuous variables were checked for normality using the Kolmogorov-Smirnov test and expressed as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for skewed data. Categorical variables were presented as frequencies and percentages (n, %).

Inter-group comparisons between the clinical deterioration group and the stable group were conducted using Student's t-test or Mann-Whitney U test for continuous variables and Pearson's Chi-square or Fisher's exact test for categorical variables.

Receiver Operating Characteristic (ROC) curve analysis was constructed to assess the diagnostic accuracy of SII, NLR, PLR, and CRP. Area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were derived, with the optimal cutoff threshold identified via Youden's index. Multivariable binary logistic regression models were developed to evaluate independent associations between elevated SII and clinical deterioration. Statistical significance was defined as $p < 0.05$.

5. Results

5.1 Demographic and Baseline Clinical Characteristics

The study included 160 pediatric patients (mean age 3.4 ± 2.1 years; 89 males [55.6%]). Early clinical deterioration within 48 hours occurred in 38 children (23.8%), while 122 children (76.2%) achieved stability on routine ward care. Baseline demographics and clinical presentations between the two groups are presented in Table 1.

Variable	Clinically Stable (n = 122)	Early Deterioration (n = 38)	Total Cohort (n = 160)	p-value
Age, years	3.6 ± 2.2	2.8 ± 1.8	3.4 ± 2.1	0.042
Male sex, n (%)	66 (54.1)	23 (60.5)	89 (55.6)	0.488
Female sex, n (%)	56 (45.9)	15 (39.5)	71 (44.4)	0.488
Duration of fever prior to admission, days	3.2 ± 1.1	4.1 ± 1.4	3.4 ± 1.2	<0.001
Baseline Respiratory Rate, breaths/min	48.2 ± 8.4	58.6 ± 10.2	50.7 ± 9.8	<0.001
Baseline SpO_2 on room air, %	88.4 ± 3.1	82.1 ± 4.2	86.9 ± 4.3	<0.001
Pediatric Respiratory Severity Score	5.2 ± 1.2	8.4 ± 1.6	6.0 ± 1.8	<0.001
Multlobar consolidation on CXR, n (%)	31 (25.4)	27 (71.1)	58 (36.3)	<0.001

Table 1: Baseline demographic and clinical parameters of the study cohort.

5.2 Admission Laboratory Parameters and Inflammatory Indices

Children who experienced early clinical deterioration demonstrated significantly higher absolute neutrophil counts, elevated platelet counts, decreased absolute lymphocyte counts, and marked

elevations in systemic inflammatory indices compared to stable patients ($p < 0.001$). Mean admission SII in the deterioration group was $1482.5 \pm 520.4 \times 10^9/L$ versus $612.3 \pm 210.8 \times 10^9/L$ in the stable group ($p < 0.001$).

Laboratory Parameter	**Clinically Stable (n = 122)**	**Early Deterioration (n = 38)**	**p-value**
White Blood Cell Count ($\times 10^9/L$)	11.4 ± 3.2	18.6 ± 5.4	<0.001
Absolute Neutrophil Count ($\times 10^9/L$)	6.2 ± 2.1	12.8 ± 3.9	<0.001
Absolute Lymphocyte Count ($\times 10^9/L$)	3.8 ± 1.2	2.1 ± 0.8	<0.001
Absolute Platelet Count ($\times 10^9/L$)	345.2 ± 82.6	468.4 ± 112.3	<0.001
C-Reactive Protein (mg/L)	28.4 ± 12.6	74.2 ± 28.1	<0.001
Neutrophil-to-Lymphocyte Ratio (NLR)	1.80 ± 0.65	6.82 ± 2.41	<0.001
Platelet-to-Lymphocyte Ratio (PLR)	98.2 ± 32.4	242.1 ± 78.5	<0.001
Systemic Immune-Inflammation Index ($\times 10^9/L$)	612.3 ± 210.8	1482.5 ± 520.4	<0.001

Table 2: Comparison of laboratory parameters and systemic inflammatory indices at admission.

5.3 ROC Curve Analysis for Predicting Early Clinical Deterioration

ROC curve analysis demonstrated that admission SII possessed superior diagnostic power for predicting early clinical deterioration compared to traditional single-marker or dual-ratio parameters. An SII cutoff threshold of $> 950 \times 10^9/\mathrm{L}$ achieved an AUC of 0.88 (95% CI: 0.82–0.94), with a sensitivity of 84.2% and a specificity of 81.1%.

Biomarker	Optimal Cutoff	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SII ($\times 10^9/\mathrm{L}$)	**> 950**	**0.88 (0.82–0.94)**	**84.2**	**81.1**	**58.2**	**94.3**
NLR	> 3.8	0.82 (0.75–0.89)	78.9	77.0	51.7	92.2
PLR	> 165	0.78 (0.70–0.86)	73.7	74.6	47.5	90.1
C-Reactive Protein (mg/L)	> 48	0.79 (0.71–0.87)	76.3	75.4	49.2	91.1

Biomarker	Optimal Cutoff	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Absolute Neutrophil Count ($\times 10^9$/L)	> 9.5	0.76 (0.68–0.84)	71.1	73.8	45.8	89.1

Table 3: ROC curve metrics for admission inflammatory markers in predicting early clinical deterioration.

5.4 Multivariable Binary Logistic Regression Analysis

In multivariable logistic regression incorporating clinical and biological markers, an admission SII $> 950 \times 10^9$/L remained an independent predictor of early clinical deterioration (adjusted OR = 4.12, 95% CI: 2.15–7.89, $p < 0.001$). Baseline PRSS and CRP levels > 48 mg/L also retained independent predictive significance.

Predictor Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Admission SII $> 950 \times 10^9$/L	**6.48 (3.22–13.04)**	**<0.001**	**4.12 (2.15–7.89)**	**<0.001**
Baseline PRSS Score (per 1-point increase)	1.84 (1.42–2.38)	<0.001	1.51 (1.18–1.93)	0.001
CRP > 48 mg/L	3.82 (2.01–7.26)	<0.001	2.18 (1.12–4.25)	0.022

Predictor Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age < 2 years	2.14 (1.02–4.48)	0.044	1.34 (0.62–2.91)	0.458
Multilobar Consolidation on CXR	7.12 (3.24–15.65)	<0.001	2.84 (1.28–6.31)	0.010

Table 4: Multivariable logistic regression analysis for risk factors associated with early clinical deterioration.

5.5 Secondary Clinical Outcomes Stratified by SII Risk Tiers

Patients were stratified into High SII ($> 950 \times 10^9$/L, n = 55) and Low SII ($\leq 950 \times 10^9$/L, n = 105) cohorts. The High SII group demonstrated significantly higher PICU admission rates (58.2% vs. 5.7%, $p < 0.001$), longer total duration of supplemental oxygen therapy (6.8 ± 2.4 vs. 3.2 ± 1.1 days, $p < 0.001$), and prolonged hospital length of stay (9.4 ± 3.1 vs. 4.8 ± 1.5 days, $p < 0.001$).

Clinical Outcome	Low SII (≤950×109/L) (n = 105)	High SII (>950×109/L) (n = 55)	p-value
PICU Transfer Rate, n (%)	6 (5.7)	32 (58.2)	<0.001
Requirement for Mechanical Ventilation (NIV/Invasive), n (%)	4 (3.8)	22 (40.0)	<0.001

Clinical Outcome	Low SII (≤950×109/L) (n = 105)	High SII (>950×109/L) (n = 55)	p-value
Duration of Oxygen Therapy, days	3.2 ± 1.1	6.8 ± 2.4	<0.001
Total Hospital Length of Stay, days	4.8 ± 1.5	9.4 ± 3.1	<0.001
Overall In-Hospital Mortality, n (%)	0 (0.0)	3 (5.5)	0.038

Table 5: Secondary clinical outcomes stratified by admission SII risk tier.

6. Discussion

This prospective cohort study evaluated the predictive capacity of the Systemic Immune-Inflammation Index (SII) for early clinical deterioration in children hospitalized with severe pneumonia. The primary finding indicates that an elevated admission SII ($> 950 \times 10^9$/L) is an accurate, independent predictor of deterioration within 48 hours of admission [11, 14]. Incorporating SII into routine pediatric admission protocols offers a simple, automated quantitative metric that enhances clinical alertness [8, 15].

6.1 Pathophysiological Underpinnings of SII in Severe Pneumonia

The marked diagnostic performance of SII stems from its integration of three cellular mediators involved in severe pulmonary inflammation [11, 13]:

1. **Neutrophils:** Accelerated neutrophil recruitment to infected alveolar spaces releases reactive oxygen species, matrix metalloproteinases, and neutrophil extracellular traps (NETs), driving tissue injury and alveolar capillary leak [3, 9].

2. **Platelets:** Activated platelets aggregate within damaged pulmonary microvasculature, exacerbating immunothrombosis, worsening ventilation-perfusion mismatch, and amplifying systemic cytokine cascades [12, 13].

3. **Lymphocytes:** Relative lymphopenia reflects stress-induced cortisol release, enhanced cell death, and immune exhaustion, leaving the host vulnerable to unsuppressed viral/bacterial replication [10, 14].

By multiplying neutrophil and platelet counts and dividing by lymphocyte counts, SII amplifies signals of hyperinflammation and host immune suppression, providing superior discrimination compared to single cell counts or basic dual ratios (NLR, PLR) [11, 15].

6.2 Comparison with Existing Inflammatory Biomarkers

While classical acute-phase reactants like CRP and procalcitonin are routinely measured in pediatric severe pneumonia, their kinetics can lag behind physiological changes or vary based on bacterial versus viral etiology [9, 10]. In our cohort, SII demonstrated a higher AUC (0.88) compared to CRP (0.79) and NLR (0.82) [10, 14]. Furthermore, because SII is calculated directly from a standard differential CBC, it requires no additional blood volume or specialized assay reagents, rendering it suitable for resource-constrained clinical settings [11, 12].

6.3 Clinical Application and Triage Utility

Early identification of high-risk pediatric pneumonia patients enables timely intervention [5, 8]. Patients presenting with an admission SII $> 950 \times 10^9$/L exhibited a 10-fold higher rate of PICU transfer and significantly longer durations of supplemental oxygen and hospital stay. Using SII as an objective trigger upon admission can guide triage decisions, such as placing patients in step-

down units, initiating early non-invasive respiratory support, or increasing vital sign monitoring frequency [7, 8].

6.4 Limitations

Several study limitations should be acknowledged. First, while prospective, the single-center study design warrants external validation across multi-center pediatric cohorts. Second, viral versus bacterial pathogen panel testing was not performed for all participants, which could influence cellular differential dynamics. Third, repeat sequential SII measurements during hospitalization were not systematically evaluated to assess treatment response trajectories.

7. Conclusion

The Systemic Immune-Inflammation Index (SII) measured at admission is an accurate, independent, and accessible predictor of early clinical deterioration in children hospitalized with severe pneumonia. An admission SII threshold $> 950 \times 10^9/\mathrm{L}$ effectively identifies pediatric patients at high risk for PICU transfer, ventilatory failure, and prolonged oxygen dependency. Routine automated calculation of SII from baseline blood counts can strengthen emergency triage and clinical monitoring in pediatric inpatient care.

8. Recommendations

1. Integrate automated calculation of the Systemic Immune-Inflammation Index (SII) into electronic complete blood count reporting systems for pediatric emergency admissions.

2. Establish a high-risk admission threshold ($\mathrm{SII} > 950 \times 10^9/\mathrm{L}$) to identify children requiring continuous monitoring or early high-dependency bed allocation.

3. Combine SII evaluation with established clinical scoring systems (such as PEWS or PRSS) to enhance predictive sensitivity for early respiratory failure.

4. Conduct prospective multi-center studies to externally validate SII cutoff values across diverse pediatric populations and distinct microbial etiologies.

5. Investigate serial longitudinal monitoring of SII at 24 and 48 hours post-admission to assess therapeutic response to antimicrobial and anti-inflammatory therapies.

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