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Utility of systemic immune-inflammation index as a serum biomarker to differentiate between complicated and simple para-pneumonic effusion

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Abstract

The systemic immune-inflammation index (SII) is a novel inflammatory biomarker. Simple and complicated para-pneumonic effusion (PPE) are two significant complications of pneumonia. We evaluated the efficacy of the SII to differentiate between the two. Records of all children up to 18 years of age admitted between April 2019 and September 2022 and diagnosed with simple or complicated PPE were retrospectively evaluated. SII and other biomarkers were compared between both groups. Receiver operating characteristics with the Youden index were used to estimate the discriminative value of SII. 50 children were enrolled with a median (interquartile range) age of 81.5 (36.7, 133.5) months; 31 (62%) were male. 31 (62%) had complicated PPE, and 19 (38%) had simple PPE. SII was significantly higher in complicated PPE (p=0.007). Good areas under the curve were found for C-reactive protein (0.771) and SII (0.736) to differentiate complicated from simple PPE. The best cut-off value for SII to differentiate complicated PPE from simple PPE was 1557×103µL, with a sensitivity of 82.4% and specificity of 57.6%. SII can be used as a screening tool to differentiate between complicated and simple PPE at the time of presentation.

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Introduction

Pneumonia is a significant cause of morbidity and mortality in children. It contributed to 14% of all under-5-year-old mortality in 2019 [1]. It is even significantly higher in complicated pneumonia and is one of the most common reasons for hospitalization. The most common complications include simple para-pneumonic effusion (PPE) and complicated PPE, which may further progress to empyema [2]. PPE has been reported in up to 20-40% of cases and empyema in 2-12% of patients with pneumonia [3,4]. Early differentiation between simple and complicated PPE is crucial. Morbidity and mortality are significantly higher in complicated PPE if not treated timely. Intercostal drainage (ICD) and fibrinolytic are mainly required for complicated PPE, whereas simple PPE can be managed conservatively [5].

Radio imaging and pleural tap facilities for differentiating simple and complicated PPE are not widely available in developing countries. There is a need for a simple and less invasive modality to determine the same for time management. It can facilitate early intervention in the emergency department for complicated PPE. Acute phase reactants have been used to assess severity, predict outcomes in community-acquired pneumonia, and differentiate between complicated and simple PPE [6,7]. The systemic immune inflammation index (SII) is a novel serum biomarker derived from the neutrophil count, platelets, and lymphocyte count [8]. Increased pleural fluid production occurs due to a dysregulated inflammatory process secondary to pneumonia. The proliferation of microorganisms due to poor host immune response results in the invasion of bacteria into the pleural fluid, leading to complicated PPE [9]. As SII is a marker of weak immune response and elevated inflammatory status in the host, it is a potential bio-

marker to differentiate complicated and uncomplicated PPE [8]. SII has recently been used for prognostication and predicting mortality in various other diseases associated with dysregulated inflammatory and immune responses, like COVID-19 infection in hemodialysis patients, bell's palsy, cardiovascular diseases, *etc*. [10]. This study aimed to determine the effectiveness of the SII in differentiating between simple and complicated PPE.

Materials and Methods

We reviewed the medical case records of all admitted children diagnosed with complicated or simple PPE up to 18 between April 2019 and September 2022 after the institution's ethical clearance (IEC/2019/844) from a single tertiary care center. Children with underlying chronic illnesses like congenital lung malformation, immunodeficiency, chronic renal or liver diseases, *etc.*, were excluded. Simple *versus* complicated PPE diagnosis was based on ultrasound thorax and/or pleural fluid analysis. Complicated PPE was diagnosed by demonstration of frank pus (empyema) or microorganism in gram stain or bacterial growth in pleural fluid culture or ultrasound findings suggestive of echogenic material in the pleural cavity, septations or loculations or thick pleural peel [2,9,11]. Pleural collections without any of these findings were considered simple PPE. Demographic details, clinical features, investigations, length of hospital stay, and treatment details were recorded in predesigned proforma.

Serum biomarkers done at the time of presentation included total white blood cells (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count, platelets, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), inflammatory markers including C-reactive protein (CRP), procalcitonin (PCT), and erythrocyte sedimentation rate (ESR). SII was calculated from the neutrophil count, platelets, and lymphocyte count (platelet× neutrophil/lymphocyte count). The treatment protocol consisted of symptomatic and supportive treatment, intravenous antibiotics, intercostal chest tube drainage, and fibrinolytic in cases of complicated PPE. Video-assisted thoracoscopic surgery (VATS) was done if the patient did not respond to medical treatment.

Continuous data were expressed as median [interquartile range (IQR)], and categorical variables were expressed as numbers (n) with percentages. For comparing categorical and continuous data, chi-square and independent student t-tests were used, respectively. The receiver operating characteristic (ROC) curve with the Youden index was derived to determine the optimal cut-off values of various indices to differentiate complicated and simple PPE. A p-value of less than 0.05 was considered significant.

Results

A total of 50 children (33 boys and 17 girls) were included. 31 (62%) had complicated PPE, and 19 (38%) had simple PPE. Median (IQR) age was 81.5 (36.7, 133.5) months. Completed hemogram, CRP, and ultrasound thorax were done in all the patients. Pleural fluid analysis was done in 32 (64%) children. PCT was done in 34 children (complicated PPE: 24 and simple PPE: 10), and ESR was available for 26 children (complicated PPE: 18 and simple PPE: 8). An ICD tube was inserted in 28 (90%) out of 31 children with complicated PPE, and all cases of simple pleural effusion were managed conservatively. Intrapleural fibrinolysis with urokinase was done in 14 (45%) children with complicated PPE. A total of 6 doses were planned and completed in 8 children, whereas 6 out of 14 (42.8%) children developed hemorrhage after starting urokinase; hence therapy had to be discontinued. VATS was done in 9 (29%) out of 31 children with complicated PPE after the failure of medical treatment. Table 1 compares the clinical and laboratory findings between the complicated and simple PPE groups. The area under the ROC curve (AUC) of serum biomark-

Table 1. Clinical and laboratory findings in children with complicated and simple para-pneumonic effusion (n=50).

Characteristics	Empyema (n=31)	Para-pneumonic effusion (n=19)	p
Clinical characteristics			
Age (months)	70 (36-134)	97 (57-134)	0.23
BMI (z score)	-1.57 (-2.6, -0.88)	-1.49 (-2.37, -0.23)	0.55
Male	19 (61.2)	14 (73.6)	0.39
Fever	31 (100)	19 (100)	1.00
Cough	29 (93.5)	16 (84.2)	0.33
Laboratory characteristics			
WBC ($\times 10^3/\mu L$)	15 (10, 26)	12 (7, 17.5)	0.42
ANC ($\times 10^3/\mu L$)	10 (6, 21)	7 (2.5, 11.5)	0.017*
ALC ($\times 10^3/\mu L$)	3 (2, 5)	3 (2, 4)	0.55
NLR	4 (2, 5)	2 (1, 3)	0.017*
LMR	3 (1, 4.5)	3 (2.5, 9)	0.52
Platelets ($\times 10^3/\mu L$)	399 (288, 762)	275 (144, 588)	0.55
SII ($\times 10^3/\mu L$)	1761 (638, 3440)	827 (91, 1369)	0.007*
CRP (mg/L)	171 (126, 191)	56 (7.7, 169)	0.042*
ESR (mm/h)	56 (34, 81)	69 (15,80)	1.0
PCT (mg/dL)	4 (0.5, 15.7)	1 (0.0, 18.7)	0.25

Values in number (%) or median (interquartile range). ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; PCT, procalcitonin; PPE, para-pneumonic effusion; SII, serum immune inflammation index; WBC, white blood cell; *p<0.05.

ers for differentiating complicated from simple PPE has been shown in Figure 1. The best cut-off value using Youden's index for SII to diagnose complicated PPE was 1557×10^3/microliter, with a sensitivity of 82.4% and specificity of 57.6% (Table 2).

Discussion and Conclusions

SII was developed in 2014 by Hu *et al*. to predict the prognosis of patients with hepatocellular carcinoma. The prediction ability of SII was shown to be higher than other inflammatory biomarkers [8]. They also found that patients with elevated SII mostly had neutrophilia, lymphocytopenia, or thrombocytopenia and hypothesized that it reflects altered immune as well as inflammatory responses of the host.

In this study, SII was significantly higher in the complicated PPE than in the simple PPE group. Complications in pneumonia depend on two main factors, *i.e.*, the organism's virulence and the host's immune response. SII is a marker of the inflammation and immune response in the host. Güneylioğlu *et al.* also evaluated the efficiency of SII in differentiating empyema from simple PPE [4]. They enrolled 59 children, with only 16 children in the empyema group. SII was significantly higher in the empyema group (6899.98±6678 *versus* 1902.73±1588.87; p=0.009). Other useful serum biomarkers for the prediction of empyema were LMR, CRP, and ANC, and they concluded that SII could be used to predict empyema in children.

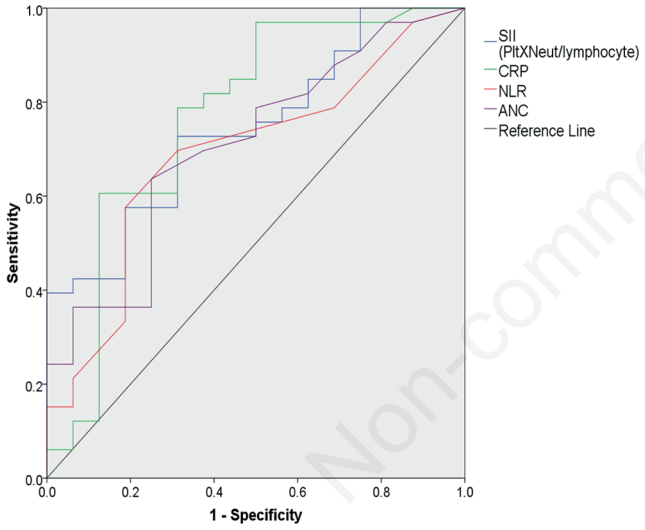

Figure 1. Receiver operating characteristic curves of serum biomarkers for differentiating complicated and simple para-pneumonic effusion. SII, serum immune inflammation index; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; ANC, absolute neutrophil count.

Studies have been done to determine the role of other inflammatory markers in complicated or simple PPE with variable findings. WBC, ALC, and LMR were significantly higher in complicated PPE compared to simple PPE in one study among 80 adult patients [12]. They concluded that LMR could be used for differentiation combined with WBC, ALC, and CRP, along with clinical and radiologic findings [12]. In contrast, LMR was significantly lower in children with empyema than PPE in the study by Güneylioğlu *et al*. [4]. In the current study, WBC, ALC, and LMR were not significantly different among the groups. In one study, serum CRP was higher in children with complicated PPE than in uncomplicated pneumonia (234 mg/L *versus* 178 mg/L; p=0.037) [7]. A meta-analysis by Li *et al*. included 18 studies evaluating the role of serum and pleural fluid CRP in differentiating complicated and uncomplicated PPE [13]. They concluded that serum CRP could aid in diagnosing PPE with an AUC of 0.79, and pleural CRP can predict complicated PPE. Additional biomarkers help further enhance CRP assay accuracy and should be interpreted together. CRP also had the highest specificity (78.8%) and AUC of 0.77 in the current study (Table 2).

Similarly, a prospective cohort study was conducted on 477 children, 3 months to 18 years of age, to correlate serum biomarkers with the disease severity of pneumonia. No serum biomarker was found to have adequate discriminatory ability for severe disease. However, in children with complicated PPE, serum CPR, and PCT had good predictions for sepsis requiring inotropes and chest drainage [6]. In our study, ANC, NLR, and CRP were significantly higher in the complicated PPE group. These findings correlate with those of Güneylioğlu *et al*., where WBC, ANC, NLR, PLR, CRP, and ESR were significantly higher in empyema [4]. However, the current study did not show elevated WBC, PLR, and ESR values.

Our study has some limitations. It was a retrospective study; therefore, some data were missing. The sample size was small, and only 19 children with simple PPE were enrolled, as children with uncomplicated effusion mainly did not require hospitalization. Pleural fluid analysis was available for only 64% of children. Furthermore, PCT and ESR were not done for all the patients, which may be a potential source of bias in results regarding these markers.

To conclude, SII can be used as a screening tool to differentiate between complicated and simple PPE at the presentation time to start appropriate treatment. SII can be derived from hemogram reports and has a potential role in screening these children, especially in settings where definitive tests for diagnosing complicated PPE, like bedside imaging or pleural fluid analysis, are not widely available. It would be better to consider various inflammatory indices together to improve diagnostic accuracy. More studies with larger sample sizes are required to determine the role of SII as a diagnostic and prognostic marker in children with complicated PPE.

Table 2. Efficacy of serum biomarkers in predicting complicated parapneumonic effusion.

Parameter	AUC n (95% CI)	Cut-off value	Sensitivity (%)	Specificity (%)
SII, 10^3/μL	0.736 [0.598-0.874]	1557	82.4	57.6
CRP, mg/L	0.771 [0.620-0.922]	121.5	70.6	78.8
ANC, 10^3/μL	0.706 [0.558-0.854]	9.5	76.5	63.6
NLR	0.693 [0.539-0.846]	2.5	70.6	69.7

ANC, absolute neutrophil count; AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; SII, serum immune inflammation index.

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