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Inflammatory biomarkers associated with surgical intervention in pediatric pneumococcal pneumonia: a five-year retrospective cohort study

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Informed consent: written informed consent was not required for this study because it was retrospective in nature and based solely on anonymized medical records. According to institutional policy and national regulations in Bulgaria, retrospective chart reviews that do not involve direct patient contact or intervention are exempt from the requirement for individual informed consent.

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Abstract

Streptococcus pneumoniae remains an important cause of community-acquired pneumonia (CAP) in children, with complicated cases sometimes requiring surgical intervention. This 5-year retrospective cohort study included 104 children aged 1 month to 18 years hospitalized with microbiologically confirmed pneumococcal pneumonia at a tertiary referral center. We evaluated clinical and laboratory factors associated with surgical intervention, with particular emphasis on the C-reactive protein-to-albumin ratio (CAR) and fibrinogen-to-albumin ratio (FAR). Complications occurred in 72.1% of patients, and 45.2% required surgical intervention. Children requiring surgery were younger, had a longer duration of symptoms before hospitalization, and showed greater alterations in inflammatory biomarkers. In multivariable analysis, CAR [adjusted odds ratio (aOR) 1.29 per unit increase; 95% confidence interval (CI) 1.12-1.52; $p=0.001$] and FAR (aOR 1.14 per unit increase; 95% CI 1.03-1.28; $p=0.021$) remained independently associated with surgical intervention in separate adjusted models. Receiver operating characteristic curve analysis showed moderate discriminatory ability for CAR [area under the curve (AUC) 0.714; 95% CI 0.615-0.813] and FAR (AUC 0.701; 95% CI 0.580-0.822), while serum albumin showed the highest overall AUC (0.783; 95% CI 0.695-0.871). FAR demonstrated significantly greater discrimination than fibrinogen alone ($p=0.005$), whereas CAR did not significantly outperform CRP or albumin. These findings suggest that CAR and FAR may provide complementary information for identifying children at increased risk of surgical intervention. However, their clinical utility should be interpreted alongside clinical and radiological findings and requires prospective multicenter validation.

Key words: *Streptococcus pneumoniae*, community-acquired pneumonia, pediatric infection, C-reactive protein-to-albumin ratio, fibrinogen-to-albumin ratio.

Introduction

Community acquired pneumonia remains a leading cause of morbidity and mortality in children worldwide, with *Streptococcus pneumoniae* as a principal bacterial pathogen. Despite the availability of vaccines and antibiotics, complicated forms of pneumococcal pneumonia—such as pleural effusion, necrotizing pneumonia, and lung abscess—continue to pose therapeutic challenges and may necessitate surgical management.

The progression from uncomplicated pneumonia to pleural organization and surgical indication is not solely determined by bacterial load, but also by the host's systemic inflammatory response. In pneumococcal infection, proinflammatory cytokines such as interleukin (IL)-6, IL-1 β , and tumor necrosis factor- α stimulate hepatic synthesis of acute-phase proteins, including C-reactive protein (CRP) and fibrinogen, while concurrently suppressing albumin production. These acute-phase changes reflect the intensity of the systemic inflammatory response and may accompany more severe and complicated disease.

Recent evidence suggests that composite indices integrating positive and negative acute-phase reactants, such as the CRP-to-albumin ratio (CAR) and fibrinogen-to-albumin ratio (FAR), may provide additional information on the systemic inflammatory response compared with individual biomarkers. However, their association with surgical intervention in pediatric pneumococcal pneumonia remains insufficiently studied. This provides the rationale for evaluating CAR and FAR in the present cohort.

This study aimed to evaluate clinical and laboratory factors associated with surgical intervention in children with pneumococcal pneumonia over a five-year period at a tertiary care center.

Materials and Methods

Study design and setting

This was a retrospective observational study conducted at the University Hospital “St. George” in Plovdiv, Bulgaria—a tertiary pediatric referral center. The study covered a five-year period from January 1, 2020, to February 28, 2025.

Study population

The study included pediatric patients aged 1 month to 18 years who were hospitalized with pneumococcal pneumonia. The diagnosis was based on a combination of

compatible clinical presentation (fever, respiratory distress, and cough), radiological findings consistent with pneumonia, and microbiological confirmation of *Streptococcus pneumoniae*. Microbiological confirmation was obtained from sputum in 85 patients, blood in 6 patients, and pleural fluid in 22 patients. In some patients, *Streptococcus pneumoniae* was identified in more than one type of clinical specimen; therefore, the total number of positive specimens exceeded the number of patients included in the study.

No formal sample size calculation was performed. All consecutive pediatric patients meeting the eligibility criteria and hospitalized with pneumococcal pneumonia during the study period (n=104) were included.

Inclusion and exclusion criteria

Patients were eligible for inclusion if they met the following criteria: age between 1 month and 18 years; a confirmed diagnosis of pneumococcal pneumonia based on consistent clinical presentation, laboratory findings, and radiological evidence; and hospitalization during the study period from January 2020 to February 2025.

Exclusion criteria comprised pneumonia attributed to pathogens other than *Streptococcus pneumoniae*, including *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella* species, and *Pseudomonas aeruginosa*. Patients with viral respiratory infections, such as COVID-19 or influenza A/B, were also excluded.

Data collection

Patient data were retrospectively extracted from the electronic medical records of the hospital. The following variables were collected and analyzed:

Demographic data included patient age and sex. Clinical data encompassed the duration of symptoms prior to admission, pneumococcal vaccination status, history of prior outpatient antibiotic therapy, and whether surgical intervention was required during hospitalization. Laboratory parameters at the time of admission included white blood cell (WBC) count, C-reactive protein (CRP), serum albumin, total protein, fibrinogen, and ferritin levels. Derived indices such as the CRP-to-albumin ratio (CAR) and the fibrinogen-to-albumin ratio (FAR) were calculated as composite indices of the systemic acute-phase response.

Radiological data were obtained from chest imaging and included information on the localization and extent of pneumonia, as well as the presence of complications such as pleural effusion, lung abscess, or necrotizing pneumonia.

Outcome measures were defined as the presence of pneumonia-related complications and the need for surgical treatment, including procedures such as pleural drainage, decortication, or lobectomy.

Bias

As a retrospective single-center study, potential sources of bias include selection bias due to referral patterns to a tertiary hospital and information bias from incomplete or inconsistent documentation in medical records. To minimize bias, only cases with complete clinical, laboratory, and radiological data were included.

Outcome definitions

Complicated pneumonia was defined by the presence of pleural effusion, empyema, lung abscess, necrotizing pneumonia, pneumothorax, or multi-organ failure. Chest radiography was the initial imaging modality in all patients, followed by chest ultrasonography in cases of suspected pleural effusion. Computed tomography (CT) was performed selectively when necrotizing pneumonia, lung abscess, or other complex pleuropulmonary complications were suspected. The decision to proceed with surgical intervention was based on clinical and radiological findings following multidisciplinary evaluation by the pediatric and pediatric surgical teams. Indications included clinically significant pleural complications, particularly empyema or complicated pleural effusion, and clinical or radiological progression despite appropriate conservative treatment. The timing and type of intervention were individualized according to disease severity and clinical evolution. Owing to the retrospective design, detailed data on the specific procedure, exact timing, and indication were not consistently available for all surgically treated patients and were therefore not included in the comparative analyses.

Statistical analysis

Statistical analyses were performed using SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA), and R. Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical variables as frequencies and percentages. Between-group

comparisons were performed using appropriate parametric or non-parametric tests, with chi-square or Fisher's exact test for categorical variables.

Univariable and multivariable logistic regression analyses were performed to identify factors associated with surgical intervention, with adjusted odds ratios (aORs) and 95% confidence intervals (CIs) reported. CAR and FAR were analyzed in separate models from their individual components to minimize collinearity and mathematical coupling.

ROC analysis was used to assess the discriminatory ability of CRP, albumin, fibrinogen, CAR, and FAR. AUCs with 95% CIs, optimal Youden index cut-offs, sensitivity, and specificity were calculated, and AUCs were compared using DeLong's test. Fibrinogen and FAR were analyzed using available-case data. A two-sided p-value < 0.05 was considered statistically significant.

Results

Study population

A total of 104 children hospitalized with pneumococcal pneumonia were included in the study. The demographic and clinical characteristics of the study cohort are summarized in Table 1. The mean age was 6 years and 4 months (± 4.6 years), ranging from 11 months to 17 years. There was a male predominance (57.7%; n=60), with a male-to-female ratio of 1.36:1. The majority of patients (53.8%) were aged 0–5 years.

Disease severity and complications

Out of the 104 children, 75 (72.1%) developed complications of pneumococcal pneumonia. The most common complications were pleural effusion (63%), lung abscess (20%), and necrotizing pneumonia (12%). Less frequent complications included pneumothorax (1%) and multi-organ failure (4%).

Surgical intervention was required in 47 patients (45.2%), all of whom had complicated pneumonia. The most common indication for surgery was empyema requiring thoracic drainage or decortication.

Age and risk of complications

Children with complicated pneumonia were significantly younger than those with uncomplicated disease (mean age 5.8 ± 4.4 years vs. 7.9 ± 5.0 years; p = 0.009).

Similarly, patients requiring surgery were younger than those managed conservatively (5.4 ± 4.1 years vs. 7.2 ± 4.9 years; $p = 0.046$).

Duration of symptoms prior to hospitalization

The average duration of symptoms at home prior to hospitalization was 5.7 ± 2.7 days. Patients with uncomplicated pneumonia had the shortest duration (4.5 ± 2.3 days), while those with complications and surgical treatment had longer delays (6.2 ± 2.6 days and 6.9 ± 2.6 days, respectively; $p < 0.001$ for both comparisons). A symptom duration >5 days was observed in 65.4% of all patients and was strongly associated with both complications and need for surgery ($p < 0.001$).

Inflammatory and biochemical markers

The association between laboratory parameters on admission, disease complications, and surgical treatment is presented in Table 2.

At the time of hospital admission, the mean C-reactive protein (CRP) level across the entire cohort was 205.1 ± 100.3 mg/L. Patients with complicated pneumonia demonstrated significantly higher CRP values (223.6 ± 101.4 mg/L) compared to those without complications (157.4 ± 80.8 mg/L; $p = 0.002$). The highest CRP concentrations were observed among patients who required surgical intervention, with a mean of 240.3 ± 102.9 mg/L ($p = 0.001$).

The mean serum albumin level was 34.6 ± 5.8 g/L. Children with complications had significantly lower albumin levels (32.8 ± 5.3 g/L) compared to those with uncomplicated pneumonia (39.4 ± 4.1 g/L; $p < 0.001$). Among patients who underwent surgery, albumin levels were further reduced (31.8 ± 3.9 g/L; $p < 0.001$). Hypoalbuminemia, defined as serum albumin <35 g/L, was significantly associated with both disease complications and the need for surgical management.

Total protein levels were also lower in patients with complications (62 ± 10 g/L) than in those without (67.9 ± 7.4 g/L; $p = 0.021$). However, this difference did not reach statistical significance when comparing surgical and non-surgical groups ($p > 0.05$).

Fibrinogen levels were markedly elevated in children with complications (6.64 ± 1.07 g/L) compared to those without complications (5.69 ± 1.5 g/L; $p = 0.001$). A similar trend was observed in relation to surgical intervention, with significantly higher fibrinogen levels among those requiring surgery ($p < 0.001$).

Other clinical factors

There was no statistically significant difference in the rate of complications or surgical intervention between male and female patients ($p > 0.05$).

Pneumococcal vaccination had been administered to most patients (79.8%); however, no significant associations were identified between vaccination status and the severity of illness, the occurrence of complications, or the need for surgery ($p > 0.05$).

Nearly half of the children (46.2%) had received outpatient antibiotic therapy prior to hospitalization. This variable was not significantly associated with the presence of complications or the likelihood of undergoing surgical treatment ($p > 0.05$).

Comorbidities were present in only 7.7% of the study population and included conditions such as adenoidal hypertrophy, epilepsy, and cerebral palsy. No significant correlation was found between the presence of comorbidities and clinical outcomes.

Hospitalization duration

The average hospital stay for all patients was 14 ± 7 days. Children with uncomplicated pneumonia had a shorter stay (9 days) compared to those with complications (16 days; $p < 0.001$), and those who required surgery had the longest stays (18 days; $p < 0.001$).

Factors associated with surgical intervention and ROC analysis

In univariable logistic regression analysis, younger age, longer duration of symptoms before hospitalization, higher CRP, lower serum albumin, higher CAR, and higher FAR were significantly associated with surgical intervention. Fibrinogen alone was not significantly associated with surgical treatment.

In the multivariable model including age, duration of symptoms before hospitalization, and CAR, both longer symptom duration (aOR 1.49 per additional day; 95% CI 1.22–1.87; $p < 0.001$) and higher CAR (aOR 1.29 per unit increase; 95% CI 1.12–1.52; $p = 0.001$) remained independently associated with surgical intervention, whereas age was no longer statistically significant (aOR 0.95; 95% CI 0.85–1.05; $p = 0.298$).

In the corresponding FAR model, longer symptom duration (aOR 1.45 per additional day; 95% CI 1.19–1.84; $p < 0.001$), younger age (aOR 0.87 per year; 95% CI 0.77–0.97; $p = 0.018$), and higher FAR (aOR 1.14 per unit increase; 95% CI 1.03–1.28; $p = 0.021$) were independently associated with surgical intervention. In a separate model evaluating the individual biomarker components, lower serum albumin remained independently

associated with surgical intervention (aOR 0.82 per g/L increase; 95% CI 0.70–0.94; $p = 0.006$), whereas CRP ($p = 0.073$) and fibrinogen ($p = 0.708$) did not retain statistical significance.

Table 3 details the multivariable logistic regression models for surgical intervention.

ROC analysis demonstrated the highest AUC for serum albumin (AUC 0.783; 95% CI 0.695–0.871), followed by CAR (AUC 0.714; 95% CI 0.615–0.813), FAR (AUC 0.701; 95% CI 0.580–0.822), CRP (AUC 0.684; 95% CI 0.580–0.787), and fibrinogen (AUC 0.596; 95% CI 0.472–0.721). The optimal cut-off values according to the Youden index were 176.5 mg/L for CRP (sensitivity 72.3%, specificity 59.6%), 36.5 g/L for albumin (sensitivity 93.6%, specificity 57.9%), 5.9 g/L for fibrinogen (sensitivity 46.3%, specificity 46.5%), 6.85 for CAR (sensitivity 59.6%, specificity 73.7%), and 18.50 for FAR (sensitivity 80.9%, specificity 69.8%).

Table 4 reports the ROC analysis of laboratory markers for surgical intervention.

DeLong comparisons showed no statistically significant difference between the AUC of CAR and CRP ($p = 0.073$) or between CAR and albumin ($p = 0.171$). Similarly, the AUC of FAR did not differ significantly from that of albumin in the complete-case subgroup ($p = 0.082$). However, FAR demonstrated a significantly greater AUC than fibrinogen (0.701 vs. 0.596; $p = 0.005$).

Discussion

This study highlights important predictors of complications and surgical intervention in pediatric patients hospitalized with pneumococcal pneumonia. More than two-thirds of the patients (72.1%) developed complications, and nearly half (45.2%) required surgical procedures. These rates exceed those in some previous series, likely reflecting our tertiary setting and late presentation.

Younger age was a significant predictor of both complications and the need for surgery. Children under five are known to have increased susceptibility to severe pneumococcal infections due to their immature immune systems and anatomical predispositions such as narrower airways [1-4].

Another key factor was delayed presentation. Patients with symptoms for more than 5 days before admission had significantly higher rates of complications and surgical intervention. Similar associations have been reported in children with empyema and

necrotizing pneumonia, where late presentation is linked to greater disease severity and increased need for invasive procedures [5,6].

Our findings are consistent with the recent study by Heinige et al. [7], which reported an increasing frequency of complicated pediatric pneumonia and invasive interventions, particularly in the post-pandemic period. These observations highlight the importance of early identification of children at risk of a severe disease course.

Inflammatory biomarkers, particularly CRP, were significantly associated with surgical intervention. Surgical patients had significantly higher mean CRP levels (~240 mg/L). Elevated CRP has been associated with the severity of pneumonia and the need for chest drainage in several pediatric studies [8-11]. However, CRP alone may lack specificity, and its value improves when interpreted alongside other markers.

Hypoalbuminemia, defined as serum albumin <35 g/L, was also significantly associated with complications and the need for surgery. Albumin is a negative acute-phase reactant, and low levels may reflect systemic inflammation, which impair immune response and healing [12,13].

The observed combination of elevated CRP and fibrinogen levels with reduced serum albumin is consistent with the systemic acute-phase response accompanying severe bacterial infection. These changes may reflect greater inflammatory burden and disease severity and may partly explain their association with complicated pneumonia and the need for surgical intervention [14,15].

Importantly, in the setting of acute bacterial infection, serum albumin should primarily be interpreted as a negative acute-phase reactant rather than as a direct marker of nutritional status. Accordingly, the associations observed in the present cohort are more likely to reflect the magnitude of the systemic inflammatory response than underlying nutritional status.

In this context, composite indices such as the CRP-to-albumin ratio (CAR) have gained interest. The clinical reflection of this cytokine-driven metabolic shift can be quantified through composite indices that integrate inflammatory and nutritional markers, providing a dynamic representation of the host response intensity. CAR has shown superior prognostic value over CRP or albumin alone in predicting severe pneumonia and sepsis in children [16-18]. In our study, the derived CAR values were higher among children with surgical outcomes, suggesting their potential clinical relevance.

Similarly, the fibrinogen-to-albumin ratio (FAR) may reflect the combined effects of inflammation and nutritional depletion. While few studies have evaluated FAR in bacterial pneumonia, pediatric studies in RSV and neonatal sepsis have demonstrated FAR's utility in identifying more severe cases and predicting longer hospital stays [12,18,19].

Radiological features such as pleural effusion and multilobar infiltrates were common among those requiring surgery. These findings align with prior research identifying these as risk factors for poor outcomes and prolonged hospitalization in pediatric pneumonia [15,20].

In contrast, factors like prior pneumococcal vaccination, previous outpatient antibiotics, sex, and minor comorbidities were not significantly associated with complications or surgical needs. Recent trends in complicated community-acquired pneumonia (CAP) reveal both the success and complexity of pneumococcal conjugate vaccine (PCV) implementation. While vaccination significantly reduced severe pediatric CAP, paradoxical findings have emerged in some studies, with higher rates of pleural effusion observed in certain vaccinated children [21,22]. This suggests that host inflammatory response and timing of care may be more critical than demographic or historical variables, a finding echoed in other pediatric CAP cohorts [1].

The length of hospital stay was significantly longer in patients requiring surgery (mean 18 days). This is consistent with systematic reviews demonstrating that early surgical intervention, such as video-assisted thoracoscopic surgery (VATS), may reduce hospital duration and re-intervention rates compared to prolonged conservative therapy [23].

Strengths and limitations

The strengths of this study include a relatively large pediatric cohort and comprehensive evaluation of routinely available inflammatory biomarkers. However, the retrospective, single-center design limits the generalizability of the findings. Fibrinogen and FAR data, as well as detailed information on the type, timing, and indication for surgical intervention, were not available for all patients. Larger prospective multicenter studies are needed to validate these findings and the proposed cut-off values.

Clinical implications

These findings suggest that routinely available inflammatory biomarkers, including CRP, albumin, CAR, and FAR, may complement clinical and radiological assessment in children with pneumococcal pneumonia. Higher CAR and FAR values, particularly in patients with prolonged symptom duration, may help identify children who warrant closer monitoring, early imaging, and timely multidisciplinary evaluation. However, these biomarkers should not be used as stand-alone criteria for surgical intervention, and their incorporation into future risk-stratification algorithms requires prospective validation.

Conclusions

In this five-year retrospective study of children with pneumococcal pneumonia, longer symptom duration before hospitalization and greater alterations in inflammatory biomarkers were associated with the need for surgical intervention. CAR and FAR remained independently associated with surgical intervention in adjusted models and showed moderate discriminatory ability. However, neither ratio consistently outperformed its individual components, although FAR demonstrated better discrimination than fibrinogen alone. These readily available biomarkers may complement clinical and radiological assessment, but their clinical utility and proposed cut-off values require validation in larger prospective multicenter studies.

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Table 1. Demographic and clinical characteristics of the study population.

Variable	Total (n=104)	With complications (n=75)	Without complications (n=29)	p
Age [mean ± SD], years	6.3±4.6	5.8±4.4	7.9±5.0	<0.05
Age group [0–5 years], n [%]	56 [53.8]	45 [60.0]	11 [37.9]	<0.05
Male sex, n [%]	60 [57.7]	42 [56.0]	18 [62.1]	NS
Duration of symptoms at home [>5 days], n [%]	68 [65.4]	56 [74.7]	12 [41.4]	<0.05
Hospital stay [mean ± SD], days	14±7	16±7	9±2	<0.05
Pneumococcal vaccination, n [%]	83 [79.8]	60 [80.0]	23 [79.3]	NS
Prior antibiotic therapy, n [%]	48 [46.2]	35 [46.7]	13 [44.8]	NS

Table 2. Laboratory markers on admission and their association with complications and surgical treatment.

Parameter	No Complications (n=29)	With complications (n=75)	p	Conservative treatment (n=57)	Surgical treatment (n=47)	p
CRP [mg/L], mean ± SD	157.4±80.8	223.6±101.4	<0.05	184.3±90.9	240.3±102.9	<0.05
Albumin [g/L], mean ± SD	39.4±4.1	32.8±5.3	<0.05	36.4±5.2	31.8±3.9	<0.05
Fibrinogen [g/L], mean ± SD	5.69±1.5	6.64±1.07	<0.05	6.07±1.3	6.79±0.93	<0.05
Total Protein [g/L], mean ± SD	67.9±7.4	62±10	<0.05	63.4±10.6	61.7±9.8	NS
WBC [10 ⁹ /L], mean ± SD	17.2±8.6	19.9±9.2	NS	17.9±8.9	21.5±8.9	0,043
CRP/Albumin Ratio [CAR]	4.04±2.05	6.99±2.91	<0.05	5.4±2.5	7.7±2.9	<0.05
Fibrinogen/Albumin Ratio [FAR]	14.78±5.32	20.56±4.44	<0.05	17.46±5,87	21.06±3.77	<0.05

Table 3. Multivariable logistic regression models for surgical intervention.

Variable	Adjusted OR	95% CI	p
Model 1 – CAR			
Age, per year	0.95	0.85–1.05	0.298
Symptom duration, per day	1.49	1.22–1.87	<0.001
CAR, per unit	1.29	1.12–1.52	0.001
Model 2 – FAR			
Age, per year	0.87	0.77–0.97	0.018
Symptom duration, per day	1.45	1.19–1.84	<0.001
FAR, per unit	1.14	1.03–1.28	0.021
Model 3 – Individual biomarkers			
Age, per year	0.94	0.82–1.07	0.342
Symptom duration, per day	1.51	1.20–2.01	0.001
CRP, per mg/L	1.01	1.00–1.01	0.073
Albumin, per g/L	0.82	0.70–0.94	0.006
Fibrinogen, per g/L	0.91	0.55–1.48	0.708

Table 4. ROC analysis of laboratory markers for surgical intervention.

c	AUC	95% CI	Cut-off	Sensitivity	Specificity
CRP	0.684	0.580-0.787	176.5 mg/L	72.30%	59.60%
Albumin	0.783	0.695-0.871	36.5 g/L	93.60%	57.90%
Fibrinogen	0.596	0.472-0.721	5.9 g/L	46.30%	46.50%
CAR	0.714	0.615-0.813	6.85	59.60%	73.70%
FAR	0.701	0.580-0.822	18.5	80.90%	69.80%

Optimal cut-off values were determined using the Youden index. Fibrinogen and FAR analyses were based on 90 patients with available measurements.