doi.org/10.36721/PJPS.2025.38.4.REG.14144.1

The impact of antibiotic use on children's recovery from community-acquired pneumonia

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Abstract: This retrospective study aims to explore the impact of rational antibiotic use on community-acquired pneumonia (CAP) children's recuperation. A retrospective analysis was performed on clinical data of 1078 children with CAP treated in Nanjing First Hospital, Nanjing Medical University from May 2021 to October 2024. Children were divided into good and poor recovery outcome groups. Related datas were compared between groups. Parameters with statistical significance ($P < 0.05$) underwent logistic regression. A predictive model for poor outcomes was developed and evaluated using ROC curve, AUC and DCA for combined predictive efficacy. The poor-recovery group had a higher proportion of children with parental smoking history, severe pneumonia, mixed infections, longer antibiotic use, CRP and PCT levels (all $P < 0.05$), but a lower rate of combined drug treatment ($P < 0.05$). Multivariate Logistic regression identified severe pneumonia (OR=1.554, 95% CI: 1.136-2.124), longer antibiotic courses (OR=1.254, 95% CI: 1.152-1.364) and elevated CRP/PCT levels as independent risk factors. The predictive model showed an AUC of 0.847 (95% CI: 0.802-0.893), with a 23.8% recovery difference between groups. Combined antibiotic use, antibiotic duration and inflammation level were independent factors significantly affecting CAP children's recovery, highlighting the critical role of rational medication in CAP outcomes.

Keywords: Community - acquired pneumonia; antibiotics; treatment; efficacy

Submitted on 18-02-2025 – Revised on 19-04-2025 – Accepted on 26-05-2025

INTRODUCTION

The World Health Organization (WHO) reports that an estimated 156 million children worldwide are afflicted with community-acquired pneumonia (CAP) annually, resulting the primary cause of death among children under the age of 5, with a global prevalence and profound implications (Meyer *et al*., 2024; Mao *et al*., 2024). The incidence of CAP among children in China is equally concerning. Studies have shown that in urban areas, the yearly occurrence rate of CAP among children aged 0 - 2 years ranges from approximately 120% to 230%, while in rural areas, it escalates to between 150% and 300% (Vaughn *et al*., 2024).

The etiology of CAP in children is intricate and varied, encompassing bacteria, viruses, mycoplasmas, chlamydias, etc. The distribution of causative agents among children of different age groups exhibits unique patterns. Viral infections predominate in infants and young children, with prevalent pathogens like respiratory syncytial virus and influenza virus. Conversely, the incidence of *Mycoplasma pneumoniae* infection tends to rise in older children (Calabretta *et al*., 2024). Rational use of antibiotics herein refers to evidence-based practices including appropriate agent selection, dosage, duration and route of administration, in accordance with clinical guidelines to avoid overuse, misuse, or underuse (Carella *et al*., 2024). However, the inappropriate use of antibiotics is a pressing issue in current clinical scenarios. Owing to the diagnostic challenges in identifying causative agents promptly, many practitioners resort to empirical broad-spectrum antibiotics, lacking specificity (Daley *et al*., 2024). Furthermore, the irrational utilization of antibiotics accelerates the evolution of bacterial resistance (Del *et al*., 2024; Bassetti *et al*., 2024). Faced with the antibiotic pressure, bacteria develop resistance mechanisms like the production of inactivating enzymes, altering drug targets and reducing cell membrane permeability. Consequently, this resistance leads to the inefficacy of treating CAP, prolonging the illness duration, extending hospital stays for children and presenting a significant challenge to public health security (Fésüs A *et al*., 2024).

Building upon this foundation, the current research endeavors to investigate how the judicious utilization of antibiotics influences the recuperation process of pediatric patients with CAP by conducting a retrospective analysis. This investigation holds significant implications in enhancing the therapeutic outcomes for children diagnosed with CAP, mitigating unfavorable reactions and curbing bacterial resistance, thereby facilitating the holistic recuperation of pediatric patients.

MATERIALS AND METHODS

Study design and participants

This is an analytical, observational and open retrospective study. The experiment designers, data collectors and statistical analysts were independent of each other and the

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data collectors and statistical analysts were blinded to the experimental design. The clinical data of 1078 children with CAP treated in Nanjing First Hospital, Nanjing Medical University from May 2021 to October 2024 were retrospectively analyzed.

Inclusion criteria

(1) Children with typical symptoms such as fever, cough, expectoration, shortness of breath and dyspnea and physical signs such as medium and fine moist rales or unfixed coarse moist rales in lung auscultation; (2) Chest X-ray or CT showing pulmonary inflammatory infiltrates; (3) Meeting the clinical diagnostic criteria of CAP; (4) Children aged 1 month - 14 years.

Exclusion criteria

(1) Special infections such as tuberculosis and fungal pneumonia; (2) Severe underlying diseases such as congenital heart disease, immunodeficiency disease, or malignant tumor; (3) Use of immunosuppressants, glucocorticoids, or long-term use of antibiotics within the last month; (4) Other chronic lung diseases such as bronchial asthma and bronchopulmonary dysplasia; (5) Children who required admission to the ICU due to severe illness or did not need special treatment due to mild illness at admission; (6) Those who were transferred to another hospital or lost to follow-up.

This study only retrospectively analyzed the data of the previous inpatient database. The names and contact information of the patients were kept confidential and the ethics committee waived any paper application requirements for this study.

Prognosis and grouping

According to the recovery status of the children, they were divided into a good-recovery group and a poor-recovery group. The evaluation of the recovery status was mainly based on the remission of clinical symptoms, such as the disappearance time of symptoms such as fever, cough and wheezing; the improvement of physical signs, such as the disappearance of lung rales; the recovery of laboratory test indicators, such as the return of white blood cell count, neutrophil ratio, C-reactive protein and other indicators in the blood routine to the normal range; and the improvement of chest imaging examination results, such as the absorption degree of pulmonary inflammatory infiltrates. If the above symptoms, physical signs and laboratory test indicators were significantly improved within 1 week after treatment and the chest imaging examination showed that the absorption of pulmonary inflammation was more than 50%, the child was judged to have a good recovery and was included in the good-recovery group.

If there were still symptoms such as fever and cough after 1 week of treatment, the lung rales did not disappear, the laboratory test indicators did not return to normal, or the chest imaging examination showed that the absorption of pulmonary inflammation was less than 50%, the child was judged to have a poor recovery and was included in the poor-recovery group.

Observed index

Information such as the gender, age, underlying diseases (malnutrition, rickets and congenital airway malformations), family monthly income (less than 10,000 yuan, 10,000 yuan and above), family location (rural, urban), parental smoking status, the severity of pneumonia (mild, moderate, severe), types of infecting pathogens (bacteria, viruses, mycoplasmas/chlamydias). Detailed information on the dose, course, combination and route of antibiotic use (oral, intravenous infusion) was recorded. The routine clinical test indicators of children at admission were mainly detected, including white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), hemoglobin (Hb), albumin (ALB), C-reactive protein (CRP), procalcitonin (PCT) and erythrocyte sedimentation rate (ESR).

Ethical approval

This study was approved by the Ethics Committee of the Nanjing First Hospital, Nanjing Medical University (KY20210416-08).

STATISTICAL ANALYSIS

All data in this study were analyzed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, N.Y., USA) software. The measurement data, which included the mean ± standard deviation, were expressed as ($\bar{x}\pm s$) or median [interquartile range (IQR)]. Statistical calculations were conducted using the T-test or Mann–Whitney test. Categorical variables were expressed as frequencies (%) and compared using the χ^2 test. The indicators with $P < 0.05$ in the univariate analysis between groups were further analyzed by univariate and multivariate Logistic regression analysis to confirm whether they were influencing factors for poor recovery in children with CAP. Univariate/multivariate Logistic regression: $\log(\text{Odds})=\beta 0+\beta 1X1+\beta 2X2+...+\beta nXn$, where $\text{Odds}= P(Y=1)/[1-P(Y=1)]$, $Y=1$ for poor recovery. A nomogram model was constructed based on the main influencing factors and the goodness-of-fit of the model was evaluated by the calibration curve and Hosmer-Lemeshow test. The prediction efficacy of the model was evaluated by the receiver operating characteristic curve (ROC), the area under the curve (AUC) and the decision curve (DCA). $P < 0.05$ was considered statistically significant.

RESULTS

Analysis of general clinical data among children with different recovery statuses

The poor-recovery group exhibited a higher incidence of parental smoking status, severe pneumonia in children, mixed infections, prolonged antibiotic treatment, CRP and PCT levels compared to the good-recovery group.

Conversely, the incidence of combined drug utilization was lower in the poor-recovery group compared to the good-recovery group ($P < 0.05$, as indicated in table 1).

Analysis of influencing factors for the recovery of children with cap

Taking the recovery status of children with CAP during hospitalization as the dependent variable (assigned as 0 for good recovery and 1 for poor recovery) and the differential indicators with $P < 0.05$ in the univariate analysis as the independent variables (assigned as 1 for parental smoking history, severe pneumonia, mixed infection and combined drug use and 0 for no parental smoking history, mild/moderate pneumonia, no mixed infection and no combined drug use; the antibiotic treatment course, CRP before treatment and PCT were assigned with their original values), the results of univariate Logistic regression analysis showed that parental smoking, severe pneumonia, mixed infection, combined drug use, antibiotic treatment duration, CRP before treatment and PCT were all potential influencing factors for poor recovery in children with CAP ($P < 0.05$, table 2).

The results of the univariate Logistic regression analysis were further included in the multivariate Logistic regression analysis and the results showed that severe pneumonia, combined drug use, antibiotic treatment course, CRP before treatment and PCT were all independent influencing factors for poor recovery in children with CAP ($P < 0.05$, table 3).

Prediction model and goodness-of-fit analysis for the recovery of children with cap

Based on the results of the multivariate Logistic regression analysis, a prediction model for the recovery of children with CAP was further constructed: log(Odds) = -5.455 + 0.441×(severe pneumonia) + -0.400×(combined drug use) + 0.226×(antibiotic treatment course) + 0.078×(CRP) + 0.501×(PCT). The calibration curve showed that the Hosmer-Lemeshow χ^2 of the prediction model was 5.863 and $P = 0.545$, indicating that there was no significant difference between the predicted values and the observed values and the prediction model had a good goodness-of-fit (see fig. 1).

Prediction model efficacy analysis for the recovery of children with cap

The results of the ROC analysis showed that the AUC(95%CI) of the prediction efficacy of the model constructed based on severe pneumonia, combined drug use, antibiotic treatment course, CRP before treatment and PCT for the recovery of children with CAP was 0.847 (0.802 - 0.893). An AUC > 0.7 indicates that the model has good prediction efficacy (see fig. 2).

Clinical Net Benefit of the Prediction Model for the Recovery of Children with CAP. The DCA curve suggested that within the threshold probability range of 0.00 - 0.90, the clinical net benefit of the prediction model for the recovery of children with CAP was > 0, indicating that the model has high clinical application value (see fig. 3).

DISCUSSION

In this retrospective analysis, it was observed that the percentage of children with a parental history of smoking, the rate of severe pneumonia cases, the incidence of mixed infections, the duration of antibiotic therapy and the levels of serum CRP and PCT prior to treatment were significantly elevated in the group of children with CAP showing poor recovery compared to those in the group exhibiting good recovery. Conversely, the utilization of combined medications was lower in the poor-recovery group when compared to the good-recovery group. The recovery outcomes of children with CAP can be influenced by both the appropriate dosage and duration of antibiotic treatment. The group with good recovery demonstrated a relatively sensible dosage and treatment duration.

A proper dosage is essential to ensure that the medication attains an effective bactericidal concentration in the body, thereby preventing inadequate treatment outcomes due to underdosing or escalating adverse reactions due to overdosing. The prolonged treatment duration observed in the poor-recovery group may signify potential overtreatment, which not only exacerbates the discomfort of children and the financial burden on families but also fosters the emergence of bacterial resistance. Moreover, the comparatively higher incidence of combined medication usage in the poor-recovery group may indicate the presence of inappropriate drug combinations. Unwarranted combined drug administration can heighten the risk of drug interactions and result in a higher incidence of adverse reactions (Puzz *et al*., 2023). Our findings align with a 2024 multicenter study showing that prolonged antibiotic use (≥7 days) and high CRP independently predict poor CAP recovery in children (Cotter *et al*., 2024). However, unlike prior reports, we identified combined drug use as a protective factor, possibly due to synergistic effects in mixed infections.

Prior research has indicated a correlation between the administration of antibiotics to children of varying age groups and their recuperation process. Infants aged between 1 month and 3 years typically possess underdeveloped liver and kidney functions, leading to a limited capacity for drug metabolism and excretion. Overusing antibiotics in this age group may surpass their metabolic capabilities, consequently elevating the likelihood of adverse reactions such as impaired liver and kidney functions as well as disruptions in intestinal flora balance (Nguyen *et al*., 2023). Conversely, insufficient dosage or a brief antibiotic regimen may fail to adequately manage the infection, leading to an extended period of illness (Yarahuan *et al*., 2023).

Table1: Analysis of General Clinical Data among Children with Different Recovery Statuses

Index	Poor-recovery group (n = 247)	Good-recovery group (n = 831)	t/χ^2	P
Age (years)	6.66±1.81	6.87±1.88	1.509	0.132
Gender			2.808	0.094
Male	147	543		
Female	100	288		
Underlying diseases	78	224	2.018	0.155
Family monthly income			0.001	0.973
10,000 yuan and above	129	433		
10,000 yuan below	118	398		
Family location			1.007	0.316
Urban	124	387		
Rural	123	444		
Parental smoking status			3.898	0.048
Non-smoking	150	561		
Smoking	97	270		
Pneumonia severity			7.358	0.025
Mild	108	443		
Moderate	92	267		
Severe	47	121		
Pathogen type			0.069	0.966
Bacterial infection	100	333		
Viral infection	106	364		
Mycoplasma/Chlamydia infection	41	134		
Mixed infection	43	103	4.088	0.043
Antibiotic dose [mg/(kg · d)]	24.66±5.00	24.46±5.06	0.543	0.587
Antibiotic treatment course (days)	7.73±2.21	7.01±1.60	5.611	<0.001
Combined drug use	157	601	7.000	0.008
Route of administration			1.491	0.222
Oral	170	605		
Intravenous infusion	77	226		
WBC($\times10^9$/L)	8.89±1.45	8.90±1.35	0.034	0.973
NEU($\times10^9$/L)	6.83±1.53	6.67±1.54	1.488	0.137
LYM($\times10^9$/L)	2.20±0.39	2.19±0.39	0.113	0.910
Hb(g/L)	138.06±8.75	138.02±8.90	0.059	0.953
ALB(g/L)	34.20±4.01	33.71±4.02	1.689	0.092
CRP(mg/L)	13.71±5.98	11.94±4.01	5.373	<0.001
PCT(ng/mL)	3.18±0.95	2.83±0.80	5.864	<0.001
ESR(mm/h)	17.07±4.80	17.06±5.10	0.011	0.992

Note: WBC: white blood cell count; NEU: neutrophil count; LYM: lymphocyte count; Hb: hemoglobin; ALB: albumin; CRP: C-reactive protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate

Table 2: Univariate Logistic Regression Analysis of the Recovery of Children with CAP

Variables	β	S.E	Wald χ^2	*P*	OR (95%CI)
Parental smoking status (Smoking)	0.295	0.150	1.971	0.049	1.344 (1.002 ~ 1.802)
Pneumonia severity (Severe)	0.466	0.203	2.299	0.022	1.593 (1.071 ~ 2.370)
Mixed infection	0.399	0.198	2.012	0.044	1.490 (1.010 ~ 2.197)
Combined drug use	-0.404	0.153	-2.636	0.008	0.668 (0.494 ~ 0.902)
Antibiotic treatment course	0.226	0.042	5.443	<0.001	1.254 (1.156 ~ 1.361)
CRP	0.083	0.016	5.214	<0.001	1.087 (1.053 ~ 1.122)
PCT	0.506	0.089	5.682	<0.001	1.658 (1.393 ~ 1.975)

Note: CRP: C-reactive protein; PCT: procalcitonin; OR: Odds Ratio, CI: Confidence Interval

Table 3: Multivariate Logistic Regression Analysis of the Recovery of Children with CAP

Variables	β	S.E	Wald χ^2	*P*	OR (95%CI)
Intercept	-5.455	0.522	-10.445	<0.001	0.004 (0.002 ~ 0.012)
Parental smoking status (Smoking)	0.340	0.213	1.597	0.110	1.405 (0.926 ~ 2.132)
Pneumonia severity (Severe)	0.441	0.160	2.761	0.006	1.554 (1.136 ~ 2.124)
Mixed infection	0.264	0.211	1.252	0.211	1.303 (0.861 ~ 1.970)
Combined drug use	-0.400	0.163	-2.454	0.014	0.670 (0.487 ~ 0.923)
Antibiotic treatment course	0.226	0.043	5.255	<0.001	1.254 (1.152 ~ 1.364)
CRP	0.078	0.016	4.743	<0.001	1.081 (1.047 ~ 1.116)
PCT	0.501	0.093	5.407	<0.001	1.651 (1.377 ~ 1.980)

Note: CRP: C-reactive protein; PCT: procalcitonin; OR: Odds Ratio, CI: Confidence Interval

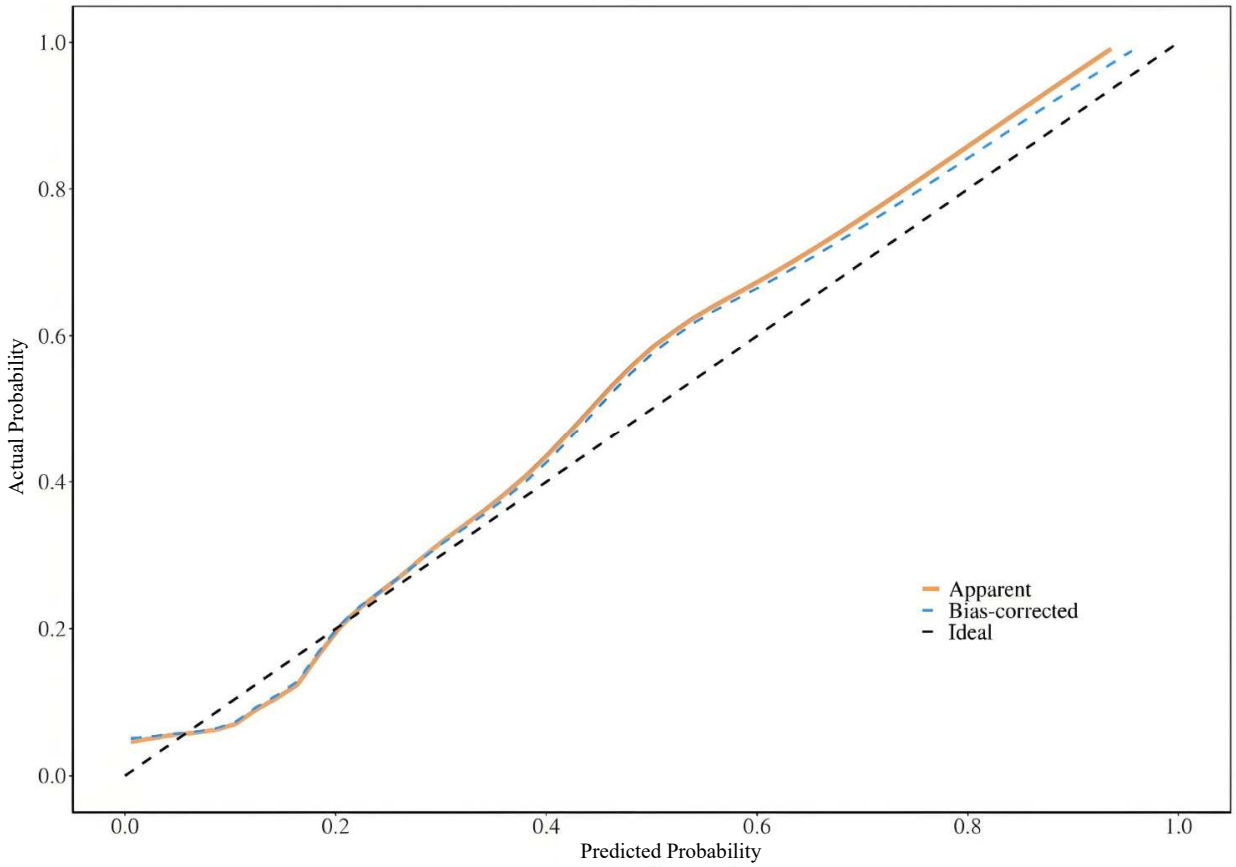

Fig. 1: Calibration curve analysis of the prediction model for the recovery of children with CAP

During the early years of childhood (3 - 6 years old), the immune system of preschool children is still in the process of gradual development and is not yet fully mature. The choice of antibiotics during this stage plays a significant role in the recovery process.

Common pathogen infections in this age group tend to be relatively focused, such as *Streptococcus pneumoniae* and mycoplasma infections being prevalent (Singla *et al*., 2023). It is essential to carefully select antibiotics that are sensitive to these common pathogens. Macrolide antibiotics are typically the preferred option for treating mycoplasma infections. However, in practical clinical scenarios, some healthcare providers may prescribe the incorrect antibiotics due to the misjudgment of the pathogens involved, consequently impacting the effectiveness of the treatment (Westerdahl and Giezeman, 2024). As for school-age children (6-12 years old) and adolescents (12-14 years old), although they generally possess stronger immunity, there are specific considerations regarding antibiotic usage (Ryu *et al*., 2024). Therefore, it is important for medical professionals to accurately determine the specific pathogen affecting children within these age brackets by carefully evaluating clinical manifestations, laboratory findings and epidemiological features. Additionally, when prescribing antibiotics, they should take into account considerations such as the child's academic commitments, ensuring that

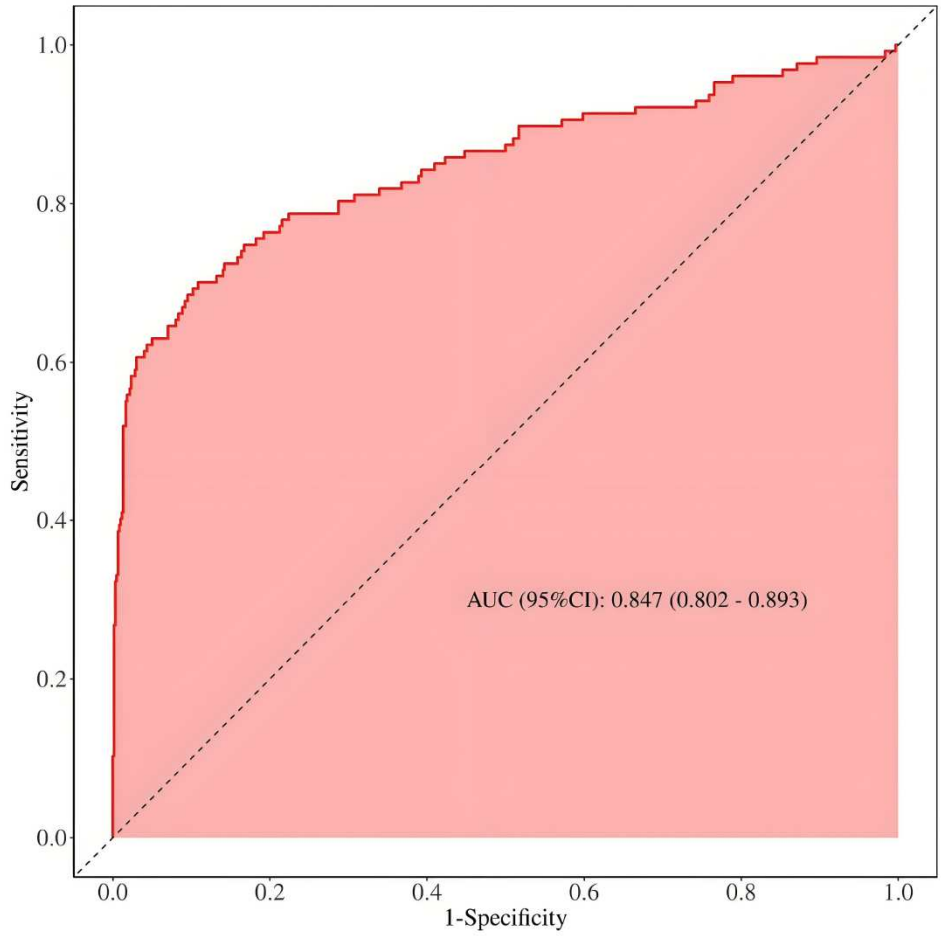

Fig. 2: ROC curve analysis of the prediction model for the recovery of children with CAP

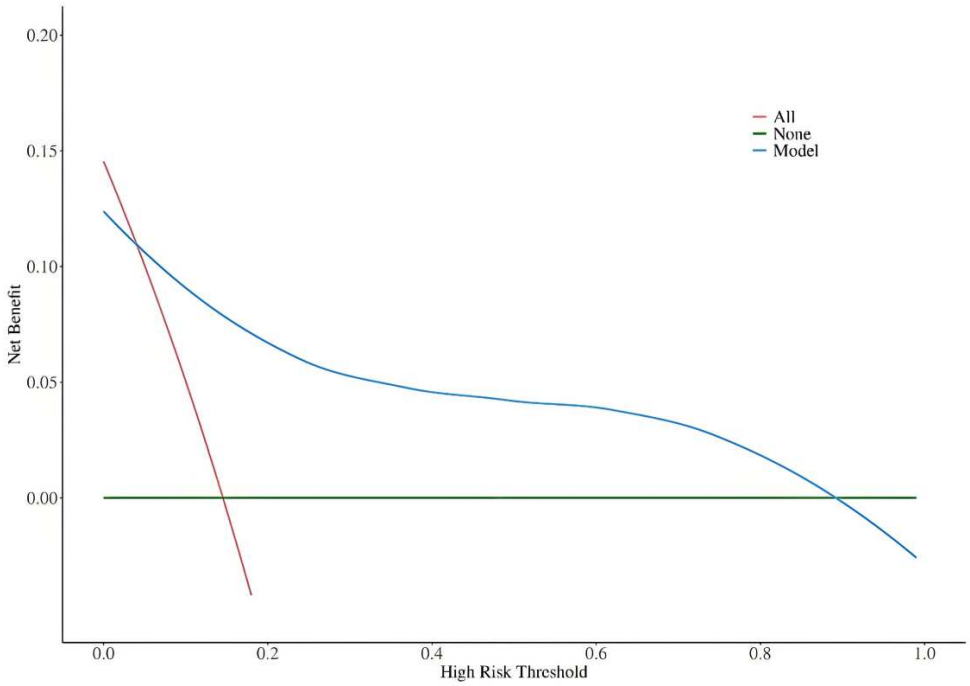

Fig. 3: DCA curve analysis of the prediction model for the recovery of children with CAP

The chosen medication is both convenient and safe to administer. In cases of mild infections, preference may be given to oral antibiotics with minimal adverse effects to minimize disruptions to the child's daily routine and academic performance.

The association between antibiotic treatment features and recuperation varies among children with varying degrees of pneumonia severity. In cases of mild pneumonia, the type and duration of antibiotic administration play a significant role in the recovery process. Mild pneumonia, being relatively less severe, can be effectively managed by selecting the suitable antibiotic type and closely monitoring the treatment duration, thereby treating the illness effectively and preventing unnecessary overtreatment (Cotter *et al*., 2024). Yet, prolonging the treatment duration might result in an imbalance of intestinal flora, triggering diarrhea and other unfavorable responses. Based on clinical observations, a 5-7 day regimen of penicillin antibiotics is typically deemed suitable for mild *Streptococcus pneumoniae* infections (Kuitunen and Renko, 2024).

The recovery of children with moderate pneumonia is closely linked to the combination and type of antibiotics used. Combining different antibiotics can have a synergistic effect, enhancing the overall treatment outcome (Zusman *et al*., 2013). When β-lactams and macrolides are combined, they can effectively target bacteria like *Streptococcus pneumoniae* and atypical pathogens such as mycoplasma, providing a beneficial treatment approach for common mixed infections in children with moderate pneumonia. According to WHO guidelines, rational antibiotic use for pediatric CAP emphasizes pathogen-directed therapy and standardized durations (5-7 days for uncomplicated cases), which our model supports by linking prolonged courses to worse outcomes. Nevertheless, caution is advised when it comes to combined drug therapy, as haphazard combinations may heighten the likelihood of adverse drug reactions (Gao *et al*., 2023). Therefore, when devising a combined drug regimen for children with moderate pneumonia, healthcare providers should possess a thorough understanding of the antibacterial spectrum, pharmacokinetic properties and potential drug interactions of various antibiotics. They should judiciously choose the type and dosage of the combined medications based on the child's specific circumstances, including the pathogen involved and the disease's severity (Rosenberg *et al*., 2023).

Based on the results of the univariate analysis, this study further confirmed through univariate and multivariate logistic regression analysis that severe pneumonia, combined drug use, antibiotic treatment course, CRP before treatment and PCT were all independent influencing factors for poor recovery in children with CAP. The DCA curve verified that the prediction model for poor recovery in children with CAP constructed based on the above five factors had a good goodness-of-fit and the ROC curve also showed that the AUC (95%CI) of the prediction model for poor recovery in children with CAP was 0.847 (0.802 - 0.893), indicating high prediction efficacy and the clinical net benefit of the model was high within the threshold probability range of 0.00 - 0.90.

This research study has solidly confirmed the crucial significance of prudent antibiotic administration in the recuperation of pediatric patients with CAP. Therefore, healthcare providers should prioritize the judicious utilization of antibiotics. When managing children diagnosed with CAP, it is imperative to strictly adhere to relevant diagnostic and treatment protocols. A thorough assessment considering factors like the child's health status, age and pathogen identification is essential for the precise selection of the suitable type, dosage, duration, combination and method of antibiotic delivery. Concurrently, healthcare institutions should establish and enhance oversight mechanisms for antibiotic usage to reinforce the evaluation and monitoring of the appropriateness of antibiotic administration, ensuring that healthcare providers genuinely practice prudent antibiotic use in clinical settings.

Limitations

However, it is important to acknowledge that this study does have some limitations. For instance, the samples used in this research were specifically collected from a single hospital, which could potentially impact the generalizability of the findings due to regional constraints. Disparities in environmental conditions, weather patterns, lifestyle choices and the prevalence of pathogens across different areas may play a role in shaping the characteristics of pediatric community-acquired pneumonia and the administration of antibiotics. To enhance the overall representativeness of the outcomes, forthcoming investigations should broaden the pool of participants to encompass children from diverse geographical locations. Moreover, this study predominantly concentrated on variables such as clinical data, pneumonia-related features, antibiotic treatment protocols and levels of inflammation without fully taking into account the potential influence of variables like the socioeconomic status of families and the health literacy levels of parents on treatment adherence and recovery rates. It is plausible that the financial situation of families could impact the timely and adequate administration of medications, as well as the accessibility to comprehensive medical assessments and therapies. Similarly, the health literacy levels of parents might affect their comprehension of the illness and their adherence to medical guidance. Future research endeavors could delve deeper into these aspects to conduct a more thorough analysis.

CONCLUSION

The recovery status of children with CAP is significantly influenced by the independent factors of using antibiotics

in combination, the duration of antibiotic therapy and the level of inflammation. The predictive model may assist clinicians in tailoring antibiotic strategies to improve recovery and reduce resistance.

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

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