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ARTICLE

# Exploration of the Therapeutic Efficacy of Azithromycin Sequential Therapy in Children With Mycoplasma Pneumonia

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## Abstract

**Aims/Background** Mycoplasma pneumonia (MP) is a relatively common infection in children. While sequential treatment with azithromycin is a commonly used regimen, therapeutic response varies substantially among children. This study aims to establish a column chart prediction model based on the clinical characteristics and pathogenic outcomes of Mycoplasma pneumonia in children, enabling accurate decision-making for clinical interventions.

**Methods** This retrospective study analysed the clinical data of 234 children with Mycoplasma pneumonia admitted to Cangnan Hospital of Wenzhou Medical University between March 2021 and October 2023. The data included general information, clinical symptoms, laboratory examination, and pathogenic profiles. The children were randomly divided into a training set (n = 164) and a validation set (n = 70) in a 7:3 ratio. Based on the efficacy of azithromycin sequential therapy, children in the training set were further divided into a poor efficacy group (n = 36) and a good efficacy group (n = 128). Independent risk factors for Mycoplasma pneumonia in the training set were identified using multiple logistic regression analysis. Furthermore, a column chart prediction model was constructed, and the model's performance was evaluated using receiver operating characteristic (ROC) curve analysis, followed by calibration curves. The predictive model was validated using an independent validation set, and decision curve analysis (DCA) assessed the model's clinical utility.

**Results** In the training set, 36 cases (21.95%) showed poor therapeutic effects, while 24 cases (34.29%) in the validation set exhibited poor treatment response. There was no significant difference in clinical data between the two groups ($p > 0.05$). Univariate analysis showed significant differences ($p < 0.05$) across several factors, such as fever duration, cough severity, presence of pulmonary wet rales, white blood cell count, C-reactive protein (CRP) levels, Mycoplasma antibody titers, and Mycoplasma nucleic acid test findings among different treatment groups. Logistic regression analysis revealed prolonged fever duration, severe cough, presence of wet rales in the lungs, high white blood cell count, high CRP levels, high Mycoplasma antibody titers, and positive Mycoplasma nucleic acid test as independent risk factors of poor efficacy for azithromycin sequential treatment ($p < 0.05$). The Concordance index (C-index) of the column chart model was 0.804 in the training set and 0.861 in the validation set. The average absolute errors of the predicted and actual values were 0.129 and 0.081, respectively. The Hosmer-Lemeshow test results were $\chi^2 = 10.288$, $p = 0.245$ for the training set and $\chi^2 = 7.922$, $p = 0.441$ for the validation set, suggesting good model calibration. The ROC curve analysis revealed that the area under the ROC curve (AUC) for predicting the poor efficacy of azithromycin sequential therapy was 0.802 (95% confidence interval [CI]: 0.698–0.907) and 0.861 (95% CI: 0.704–1.000) for training and validation sets, respectively. Sensitivity and specificity were 0.655 and 0.907 in the training set and 0.898 and 0.952 in the validation set. Sensitivity analysis revealed that the model performed well across the decision subgroups, and the decision curve analysis indicated that the model demonstrated significant advantages when the threshold probability ranged between 0.1 and 0.98.

**Conclusion** This study is the first to construct a column chart prediction model using the clinical characteristics of Mycoplasma pneumonia in children, addressing the lack of prediction tools in this area.

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This model can offer a valuable reference for assessing the prognosis of azithromycin sequential treatment, helping clinicians develop more targeted and individualised treatment strategies.

**Key words: mycoplasma pneumonia; azithromycin; sequential therapy; clinical characteristics; prediction models**

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# Introduction

Mycoplasma pneumonia (MP) infection is a primary contributor to Mycoplasma pneumonia in children with community-acquired pneumonia. In recent years, the incidence of MP in children has gradually increased. In many regions worldwide, the proportion of pediatric community-acquired pneumonia has increased, with some regions reporting it as the leading cause, posing a serious health threat (Hu et al, 2022). The MP diagnosis mainly relies on clinical symptoms, imaging examinations, and laboratory tests. However, the clinical symptoms are nonspecific and can be easily mistaken for other types of pneumonia; imaging manifestations are variable, making the diagnosis challenging; and Mycoplasma antibody testing (laboratory testing) is vulnerable to false positives or negatives. While nucleic acid testing offers high sensitivity, its requirements of advanced technology and equipment restrain its accessibility in primary health settings (Yin, 2021).

Azithromycin sequential therapy is the primary treatment for MP due to its high efficacy and minimal adverse effects. It effectively alleviates symptoms, reduces lung inflammation, and has a low physiological burden on children. However, therapeutic responses vary substantially among pediatric patients. While some children experience significant improvement, including obvious symptom relief, resolution of clinical signs, and effective absorption of lung inflammation, other children show poor treatment outcomes, without any improvement in symptoms and with persistent or worsening symptoms. Previous studies on the differences in azithromycin efficacy primarily focused on factors such as drug dosage, treatment duration, and the use of concomitant medications (Li et al, 2024).

However, there is currently no predictive model to evaluate the therapeutic efficacy of azithromycin in children with MP infection. Existing studies focus on isolated or limited influencing factors, without integrating multiple clinical and pathogenic variables to construct comprehensive and effective predictive tools. Moreover, clinical treatment faces significant challenges, with drug resistance becoming an increasingly serious concern. In some regions, the resistance rate of Mycoplasma pneumonia to azithromycin is increasing, directly affecting treatment efficacy. Furthermore, differences in individual immune status play a vital role, as children with weaker immune function respond poorly to treatment. Despite their clinical relevance, such factors have not been adequately considered in clinical decision-making (Zhao et al, 2022).

This study aims to establish and validate a predictive model for evaluating the efficacy of azithromycin sequential therapy in children based on clinical character-

istics and pathogen results. This model would enable early detection of high-risk children who may have a poor therapeutic response, allowing clinicians to optimise treatment plans, such as adjusting the dosage, extending treatment duration, or applying combination therapy tailored to patients' requirements. In contrast, children predicted to have promising therapeutic responses can follow the standard treatment protocol with close monitoring, facilitating personalised treatment, improving therapeutic efficacy, reducing unnecessary use of medical resources, and minimising health-related costs.

# Methods

## Recruitment of Research Participants

This retrospective study analysed the clinical records of 234 children diagnosed with Mycoplasma pneumonia and treated at the Cangnan Hospital of Wenzhou Medical University between March 2021 and October 2023. The inclusion criteria for patient selection were as follows: ① Presence of typical MP symptoms (such as intractable severe cough and fever) confirmed through clinical examination. ② Eligibility for azithromycin sequential therapy. ③ Chest X-ray or computed tomography (CT) examination indicating pulmonary inflammatory changes consistent with MP. ④ Informed consent was obtained from the patient's guardian. ⑤ Availability of complete clinical data. Exclusion criteria set for the study included: ① Presence of other primary respiratory diseases (such as bacterial pneumonia, tuberculosis, or viral pneumonia), ② prior use of other anti-infective drugs before recruitment, and ③ patients with known allergies to azithromycin. The study participants consisted of children aged 0.5–17 years, including both preschool and school-aged groups.

The aim was to comprehensively assess the differences in the efficacy of azithromycin sequential therapy for Mycoplasma pneumonia across different age groups. Therefore, patients were randomly divided into a training set (n = 164) and a validation set (n = 70) in a 7:3 ratio using a completely randomised method. Specifically, each patient was assigned a computer-generated random number between 0 and 1. The patients were then sorted based on these random numbers, with the top 70% (164 cases) assigned to the training set and the remaining 30% (70 cases) to the validation set. This study design ensured true randomisation, balancing the training and validation sets across various features while reducing the impact of potential confounding factors on the research findings.

This study strictly followed the ethical principles outlined in the Declaration of Helsinki and obtained ethical approval from the Cangnan Hospital of Wenzhou Medical University (Approval No.: 2024123). Throughout the research process, strict adherence to medical ethical principles was ensured to protect the rights and interests of the children and their guardians. Before collecting clinical data, the research objectives, methods, potential risks, and benefits were thoroughly explained to their guardians, and informed consent forms were signed by the guardians, ensuring compliance with ethical standards.

### Data Collection

General clinical data were collected for all patients, including age, sex, weight, duration of fever, cough frequency, underlying medical history (like asthma, congenital heart disease), cough severity (determined using the visual analogue scale (VAS)) (Green et al, 2024), presence of lung moist rales, routine blood indices (white blood cell count, neutrophil ratio, lymphocyte ratio), C-reactive protein (CRP) levels, and pathogen detection results (e.g., Mycoplasma antibody titer, Mycoplasma nucleic acid detection results). To ensure accuracy and consistency, clinical data collection was performed by two independently trained researchers. Throughout the data collection process, they strictly followed the predefined data collection standards and operational procedures. After data collection, two researchers cross-verified the data, and any inconsistencies or uncertainties were resolved through a joint review of the original medical records for confirmation and correction.

### Treatment Protocols

All patients included in the study received azithromycin-based sequential therapy. The specific treatment protocol was as follows: initially, azithromycin (Qi Longmai, Hainan Hailing Chemical Pharmaceutical Co., Ltd., Hainan Hailing Pharmaceutical Factory, National Medicine Zhunzi H20000083, Haikou, China) was intravenously administered at a dose of 10 mg/kg/day, once daily for 5 days. After this, intravenous administration was discontinued, and replaced with oral azithromycin (Xishumei, Pfizer Pharmaceutical Co., Ltd., Dalian Factory, National Medicine Zhunzi H10960112, Dalian, China) was given at a dose of 10 mg/kg/day, once daily for 3 days. This therapeutic regimen was repeated for three treatment cycles. During the treatment, symptomatic supportive care, such as cough relief, phlegm reduction, and oxygen inhalation therapy, was provided based on each patient's specific clinical conditions.

### Observation Indicators

The severity of the cough was evaluated using the visual analogue scale (VAS), a 10-cm linear scale with one end marked as 0, indicating no cough and the other marked as 10, indicating the most severe cough. The child or their guardian marked a point on a straight line that represented the actual cough intensity, with the corresponding numerical value serving as the cough severity score. A score of 0–3 indicates mild cough, 4–6 indicates moderate cough, and 7–10 represents severe cough.

Treatment efficacy was assessed by a professional team consisting of a chief physician and a deputy chief physician with more than 10 years of pediatric clinical experience. The assessment criteria were based on relevant clinical research consensus published in internationally recognised medical journals such as "*The New England Journal of Medicine*" and "*The Lancet*" (Willis et al, 2024). The efficacy of azithromycin sequential treatment was divided into two groups: good efficacy and poor efficacy.

### *Criteria for Good Efficacy*

• The fever completely resolved, and body temperature was stabilised within the normal range (36–37 °C) for at least 48 hours without recurrence.

• Cough frequency significantly reduced from more than 15 times a day to less than or equal to 15 times, or a substantial decrease in cough severity that no longer affects daily activities and sleep. Cough features also improved, transitioning from a severe, irritating dry cough to occasional mild cough or from a productive cough with excessive sputum to mild cough with minimal or no sputum.

• Respiratory symptom relief included complete resolution of shortness of breath, with respiratory rate returning to normal range for the patient's age (reference values for children of different ages (Ding et al, 2024): newborns, 40–45 breaths/minute; infants <1 year, 30–40 breaths/minute; 1–3 years, 25–30 breaths/minute; 4–7 years, 20–25 breaths/minute; 8–14 years, 18–20 breaths/minute). Breathing was smooth, with no wheezing and dyspnea (such as nasal flaring or chest retractions).

• Expectoration frequency was significantly reduced or completely resolved, and sputum became thinner and easier to expel, ensuring an unobstructed respiratory tract.

• Associated symptoms substantially improved or completely resolved, such as headache, rhinorrhea, pharyngitis, and otalgia. The children exhibited a good mental status, normal appetite, and normal sleep patterns.

• Lung auscultation findings revealed significant alleviation in wet rales, with reduced intensity and distribution, or complete rale disappearance with clear breath sounds. Thoracic dilatation was symmetrical and within the normal range, with balanced and stable respiratory movement on both sides and without limitation or abnormal respiratory effort.

• Chest X-ray or CT showed a significant decrease in the inflammatory area of the lung, with the original large-scale consolidation shadow reduced by at least 50%, decreased density, and clearer margins. The extent of ground-glass opacity obviously reduced, with decreased density. Moreover, bronchial wall thickening and lung texture abnormalities significantly improved, with bronchial morphology returning to normal or near-normal, and lung texture appearing improved significantly.

### *Criteria for Poor Efficacy*

If these improvement criteria were not observed, the therapeutic outcomes were classified as poor. In assessing the efficacy of sequential azithromycin therapy, various blood indicators were used to predict prognosis. A persistently increased white blood cell count ($>10 \times 10^9$/L), high C-reactive protein levels (>30 mg/L), abnormally high Mycoplasma antibody titer (>1:160), and an imbalanced lymphocyte ratio (<20%) indicated poor prognosis. However, good prognosis outcomes were suggested by the opposite trends in these variables.

## Handling Missing Values in Baseline Data

When handling missing values in baseline data, the first step is to evaluate the pattern and proportion of the missing data. For variables with <5% miss-

ing data, imputation methods were applied based on data type: the mean imputation method was used for continuous variables by replacing missing values with the mean of the complete dataset, while mode imputation was applied to categorical variables by filling in missing values with the most frequently occurring category. For variables with missing ratios between 5% and 20%, multiple imputation methods were conducted using the MICE package (version 3.16.0, developed by Stef van Buuren and Karin Groothuis-Oudshoorn, Leiden, Netherlands; available at https://cran.r-project.org/web/packages/mice/index.html) in R software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria), generating multiple simulated datasets based on relevant variables to fill in missing values and performing a comprehensive analysis of the results to reduce bias. If a variable has >20% missing data, with minimal effect on the study outcomes, it was excluded from the analysis.

### Identifying Influencing Risk Factors

In the training set, a univariate analysis was first performed to assess the clinical features and pathogenic factors affecting the efficacy of azithromycin sequential therapy. Factors with statistically significant influence ($p < 0.05$) on treatment outcomes were identified. Using these factors as independent variables, with treatment effect as dependent variables, multivariate logistic regression analysis was conducted to determine independent risk factors.

### Establishment of Nomogram Predictive Model

Based on the results of multivariate logistic regression analysis, independent risk factors with substantial predictive value were determined, and a nomogram prediction model for azithromycin sequential therapy was constructed. Each independent risk factor was assigned a specific score in the model, and the total predictive score was calculated to evaluate the curative effect. The probability of successful treatment was determined based on the total score, with a higher score indicating a greater accuracy in predicting the treatment outcomes of azithromycin sequential therapy.

### Model Evaluation and Verification

The predictive efficiency of the monogram model was evaluated using the receiver operating characteristic (ROC) curve and the calibration curve in the training dataset. The area under the ROC curve (AUC) was used to quantify the prediction accuracy of the model, with the AUC value closer to 1 indicating better predictive efficiency. The calibration curve was used to evaluate the consistency between the predicted outcomes of the model and actual clinical results. Furthermore, the model was validated in the verification dataset, and key performance indices were compared between the training and validation sets. Additionally, decision curve analysis was performed to evaluate the clinical application of the model, determining its advantage in clinical decision-making across different probability thresholds.

### Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 software (IBM, located in Armonk, NY, USA). The normality of data was determined using the Shapiro-Wilk (SW) test. Normally distributed measurement data was expressed as mean ± standard deviation ($\bar{x} \pm s$), and an independent sample *t*-test was applied for inter-group comparison. However, non-normally distributed data was presented as the median (M) and quartiles (Q1, Q3), and the Mann-Whitney U test was used for inter-group comparison. When the theoretical frequency (T) was $\geq$5 and the sample size (N) was $\geq$40, the chi-square test was used for analysis. When $1 \leq T < 5$ and $N \geq 40$, a chi-square test with continuity correction was applied. Fisher's exact test was applied when $T < 1$, $N < 40$, or the frequency was zero.

In multiple logistic regression analysis, the variance inflation factor (VIF) and tolerance were estimated for each variable to evaluate multicollinearity. VIF measures the degree of multicollinearity between explanatory variables, with VIF values greater than 10 indicating severe multicollinearity, and a tolerance value <0.1 indicating strong multicollinearity. Meanwhile, the Hosmer-Lemeshow test was used to evaluate the goodness of fit for the logistic regression model. This test divides observation data into groups based on predicted probabilities and compares the observed frequencies within each group to the expected frequencies. The null hypothesis assumes a good model fit, and if the *p*-value $> 0.05$, the model is considered to fit well. On the contrary, if the *p*-value $< 0.05$, the model shows insufficient fit.

Furthermore, R software (version 3.5.2, an open-source tool developed and maintained by the R language core team, available at https://www.r-project.org/) was used to construct a column chart prediction model. The model's performance was evaluated using the Concordance index (C-index), calibration curve, and decision curve analysis (DCA). A *p*-value of less than 0.05 determined statistical significance.

## Results

### Comparison of Clinical Data Between the Training and Verification Datasets

There was no significant difference in clinical data between the training and validation sets ($p > 0.05$, Table 1).

### Univariate Analysis of the Effect of Azithromycin Sequential Therapy in the Training Set

In the training set, 36 cases (21.95%) showed poor treatment response, while in the validation set, 24 cases (34.29%) exhibited poor curative effects. Univariate analysis demonstrated significant differences in various factors between the good and poor curative outcome groups, such as fever duration, cough severity, presence of lung moist rales, white blood cell count, C-reactive protein levels, Mycoplasma antibody titer, and Mycoplasma nucleic acid test findings ($p < 0.05$, Table 2).

**Table 1. Comparison of clinical data between the training and verification datasets.**

| Baseline characteristics | | Training set (n = 164) | Verification set (n = 70) | $t/\chi^2$ | *p*-value |
|---|---|---|---|---|---|
| Age | ≤5 years old | 98 (59.76) | 45 (64.29) | 0.423 | 0.515 |
| | >5 years old | 66 (40.24) | 25 (35.71) | | |
| Weight (kg) | | 20.34 ± 4.87 | 21.16 ± 4.69 | 1.192 | 0.234 |
| Fever duration (d) | | 6.62 ± 2.58 | 6.28 ± 1.60 | 1.021 | 0.308 |
| Gender | Man | 88 (53.66) | 38 (54.29) | 0.008 | 0.930 |
| | Woman | 76 (46.34) | 32 (45.71) | | |
| Basic medical history of children | Asthma | 12 (7.32) | 6 (8.57) | 0.141 | 0.706 |
| | Congenital heart disease | 6 (3.66) | 3 (4.29) | 0.020 | 0.886 |
| Cough frequency (times/day) | ≤15 | 86 (52.44) | 37 (52.86) | 0.003 | 0.953 |
| | >15 | 78 (47.56) | 33 (47.14) | | |
| Cough severity (VAS score) | ≤3 | 87 (53.05) | 30 (42.86) | 2.038 | 0.153 |
| | >3 | 77 (46.95) | 40 (57.14) | | |
| Lung moist rale | Have | 90 (54.88) | 29 (41.43) | 3.551 | 0.060 |
| | Without | 74 (45.12) | 41 (58.57) | | |
| Neutrophils (%) | | 62.37 ± 10.12 | 60.32 ± 9.98 | 1.424 | 0.155 |
| Lymphocyte ratio ($\times 10^9$/L) | | 8.26 ± 1.24 | 7.98 ± 1.33 | 1.547 | 0.123 |
| C-reactive protein (mg/L) | | 56.47 ± 12.31 | 55.36 ± 10.78 | 0.654 | 0.513 |
| Mycoplasma antibody titer | ≤1:160 | 85 (51.82) | 39 (55.71) | 0.297 | 0.585 |
| | >1:160 | 79 (48.17) | 31 (44.29) | | |
| White blood cell count ($\times 10^9$/L) | | 8.23 ± 2.31 | 8.11 ± 2.42 | 0.358 | 0.720 |
| Mycoplasma nucleic acid detection | Negative | 91 (55.49) | 41 (58.57) | 0.189 | 0.663 |
| | Positive | 73 (44.51) | 29 (41.43) | | |

VAS, visual analogue scale.

**Table 2. Univariate analysis of ineffective training set efficacy.**

| Clinical variables | | Poor curative effect (n = 36) | Good curative effect (n = 128) | $t/\chi^2$ | *p*-value |
|---|---|---|---|---|---|
| Age | ≤5 years old | 21 (58.33) | 85 (66.41) | 0.801 | 0.370 |
| | >5 years old | 15 (41.67) | 43 (33.59) | | |
| Weight (kg) | | 22.18 ± 4.68 | 21.33 ± 4.59 | 0.997 | 0.329 |
| Fever duration (d) | | 5.51 ± 2.34 | 4.63 ± 1.56 | 2.653 | 0.008 |
| Gender | Man | 20 (55.56) | 69 (53.91) | 0.030 | 0.860 |
| | Woman | 16 (44.44) | 59 (39.84) | | |
| Basic medical history of children | Asthma | 4 (11.11) | 8 (6.25) | 0.393 | 0.530 |
| | Congenital heart disease | 2 (5.56) | 4 (3.13) | 0.033 | 0.854 |
| Cough frequency (times/day) | ≤15 | 22 (61.11) | 82 (64.06) | 0.105 | 0.745 |
| | >15 | 14 (38.89) | 46 (35.94) | | |
| Cough severity (VAS score) | ≤3 | 7 (19.44) | 70 (54.69) | 14.011 | 0.001 |
| | >3 | 29 (80.56) | 58 (45.31) | | |
| Lung moist rale | Without | 12 (33.33) | 70 (54.69) | 5.125 | 0.023 |
| | Have | 24 (66.67) | 58 (45.31) | | |
| Neutrophils (%) | | 59.42 ± 10.15 | 60.08 ± 10.05 | 0.347 | 0.728 |
| Lymphocyte ratio ($\times 10^9$/L) | | 8.33 ± 1.37 | 7.89 ± 1.41 | 1.692 | 0.092 |
| C-reactive protein (mg/L) | | 44.62 ± 10.23 | 39.51 ± 8.55 | 3.029 | 0.002 |
| Mycoplasma antibody titer | ≤1:160 | 10 (27.78) | 60 (46.88) | 4.188 | 0.040 |
| | >1:160 | 26 (72.22) | 68 (53.13) | | |
| White blood cell count ($\times 10^9$/L) | | 10.51 ± 3.22 | 9.42 ± 2.22 | 2.338 | 0.020 |
| Mycoplasma nucleic acid detection | Negative | 8 (22.22) | 72 (56.25) | 13.021 | 0.001 |
| | Positive | 28 (77.78) | 56 (43.75) | | |

**Table 3. Assignment variable table.**

| Variable | Meaning | Evaluation |
|---|---|---|
| X1 | Fever duration | continuous variable |
| X2 | Cough severity | 0 = ≤3, 1 = >3 |
| X3 | Lung moist rale | 0 = None, 1 = Yes |
| X4 | White cell count | continuous variable |
| X5 | C-reactive protein levels | continuous variable |
| X6 | Mycoplasma antibody titer | 0 = ≤1:160, 1 = >1:160 |
| X7 | Mycoplasma nucleic acid test findings | 0 = negative, 1 = positive |
| Y | Treatment effect | 0 = Good, 1 = poor |

## Logistic Regression Analysis of Influencing Factors of Azithromycin Sequential Therapy in Training Set

The curative effect was used as the dependent variable (1 = poor, 0 = good), while the statistically significant indicators observed in univariate analysis of the effect of azithromycin sequential therapy in the training set (fever duration, cough severity, presence of lung moist rales, white blood cell count, C-reactive protein levels, Mycoplasma antibody titer, Mycoplasma nucleic acid test findings) were used as covariates. Variable assignments were conducted according to Table 3, where continuous variables were transformed into binary variables and assigned, and binary variables were numerically coded. A multivariate stepwise logistic regression analysis was then performed. The results revealed that longer fever duration, more severe cough, presence of moist rales in the lungs, higher white blood cell count, elevated C-reactive protein levels, higher Mycoplasma antibody titer, and positive Mycoplasma nucleic acid test were common independent risk factors for poor efficacy of azithromycin sequential therapy ($p < 0.05$). In the regression model, each variable showed a tolerance value >0.1, a VIF <10, a conditional index <30, and a variance ratio of multiple covariates without the same eigenvalue >50%, indicating no collinearity among the covariates. Logistic regression analysis of factors affecting poor treatment outcomes in the training set is shown in Table 4.

## Establishment of Nomogram Predictive Model for Azithromycin Sequential Therapy

A nomogram prediction model for azithromycin sequential therapy was established based on the independent risk factors identified through multivariate logistic regression analysis. The model includes factors such as fever duration, cough severity, presence of lung rales, white blood cell count, CRP levels, Mycoplasma antibody titer, and Mycoplasma nucleic acid test findings. Each factor was assigned a specific score, and the total score was calculated based on the scores of each clinical indicator. A higher total score indicated a greater probability of predicting poor efficacy in azithromycin sequential therapy (Fig. 1).

**Table 4. Logistic regression analysis of factors affecting poor curative effect in training set.**

| Variable | $\beta$ | Standard error | Wald | $p$-value | OR | 95% confidence interval |
|---|---|---|---|---|---|---|
| Fever duration | 0.282 | 0.110 | 6.521 | 0.011 | 1.325 | 1.068–1.645 |
| Cough severity | 1.609 | 0.457 | 12.402 | 0.001 | 5.000 | 2.042–12.246 |
| Lung moist rale | 0.881 | 0.396 | 4.961 | 0.026 | 2.414 | 1.112–5.242 |
| White cell count | 0.178 | 0.078 | 5.162 | 0.023 | 1.195 | 1.025–1.393 |
| C-reactive protein levels | 0.064 | 0.022 | 8.262 | 0.004 | 1.066 | 1.020–1.113 |
| Mycoplasma antibody titer | 0.830 | 0.412 | 4.060 | 0.044 | 2.294 | 1.023–5.145 |
| Mycoplasma nucleic acid test findings | 1.504 | 0.439 | 11.754 | 0.001 | 4.500 | 1.905–10.633 |

OR indicates Odds Ratio, which is used to measure the strength of association between a factor and an outcome. An OR $>1$ indicates an increased risk of the outcome associated with the factor, while an OR $<1$ indicates a decreased risk.

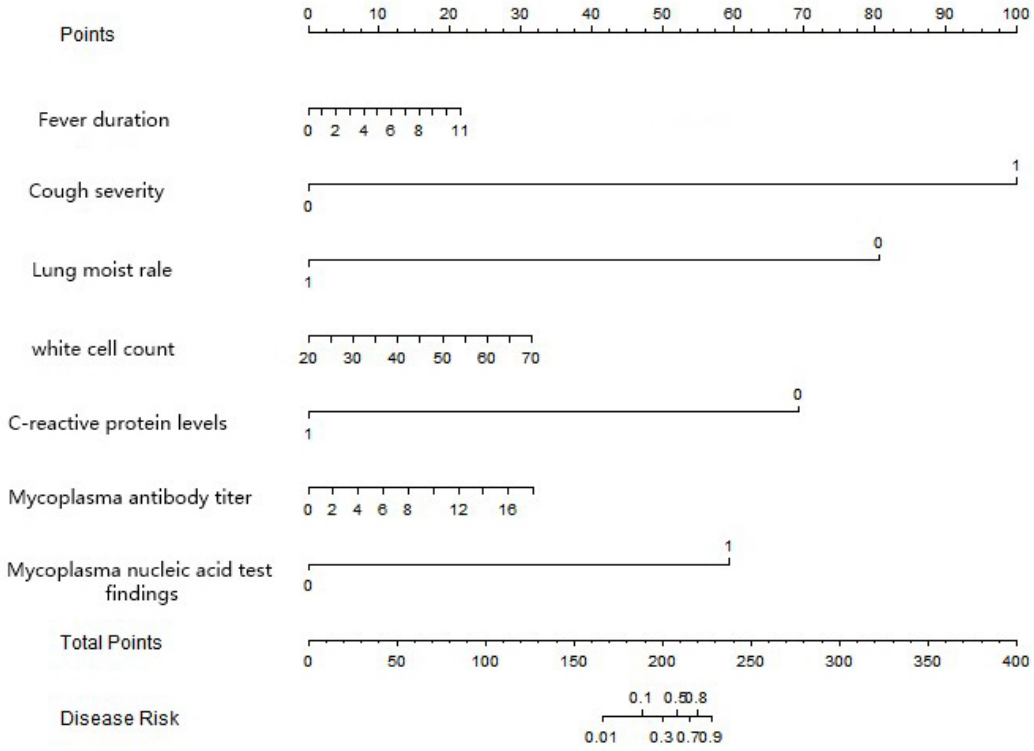


**Fig. 1. A nomogram for azithromycin sequential therapy efficacy prediction model.**

## Evaluation and Validation of the Nomogram Prediction Model for Azithromycin Sequential Therapy

In the training and verification sets, the C-index of the nomogram model was 0.804 and 0.861, respectively. The average absolute error between the predicted and real values was 0.129 and 0.081, respectively. The Hosmer-Lemeshow test results were $\chi^2 = 10.288$, $p = 0.245$ for the training set and $\chi^2 = 7.922$, $p = 0.441$ for the validation set, suggesting good model calibration. The ROC curve analysis revealed that the AUC for predicting poor efficacy of azithromycin sequential therapy was 0.802 (95% confidence interval [CI]: 0.698–0.907) and 0.861 (95% CI: 0.704–1.000) for training and validation sets, respectively. The sensitivity and

specificity were 0.655 and 0.907 in the training set and 0.898 and 0.952 in the validation set. The calibration curve analysis is shown in Fig. 2, and the ROC curve in Fig. 3.

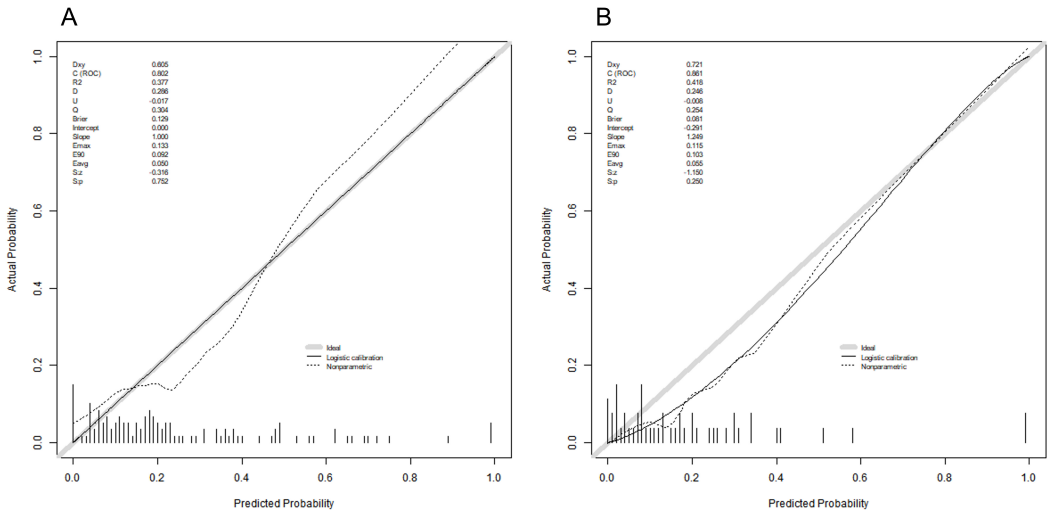


**Fig. 2. Calibration curve analysis of the prediction model.** (A) is the training set, and (B) is the verification set.

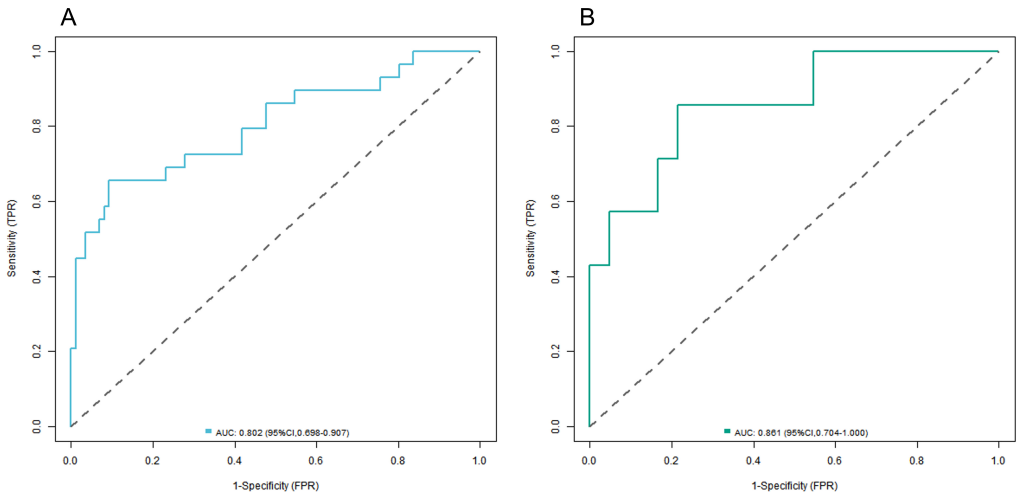


**Fig. 3. Receiver operating characteristic (ROC) curve analysis of the prediction model.** (A) is the training set, and (B) is the verification set. The term 'FPR' appearing in the figure refers to the 'False Positive Rate', which is one of the important indicators for evaluating the performance of the model. AUC, area under the ROC curve; TPR, True Positive Rate.

## Decision Curve Analysis of Nomogram Prediction Model

The decision curve showed that when the threshold probability ranges between 0.1 and 0.98, using the nomogram model to predict the efficacy of azithromycin sequential therapy provides greater clinical benefits than assuming that all cases are effective or none are effective before treatment (Fig. 4).

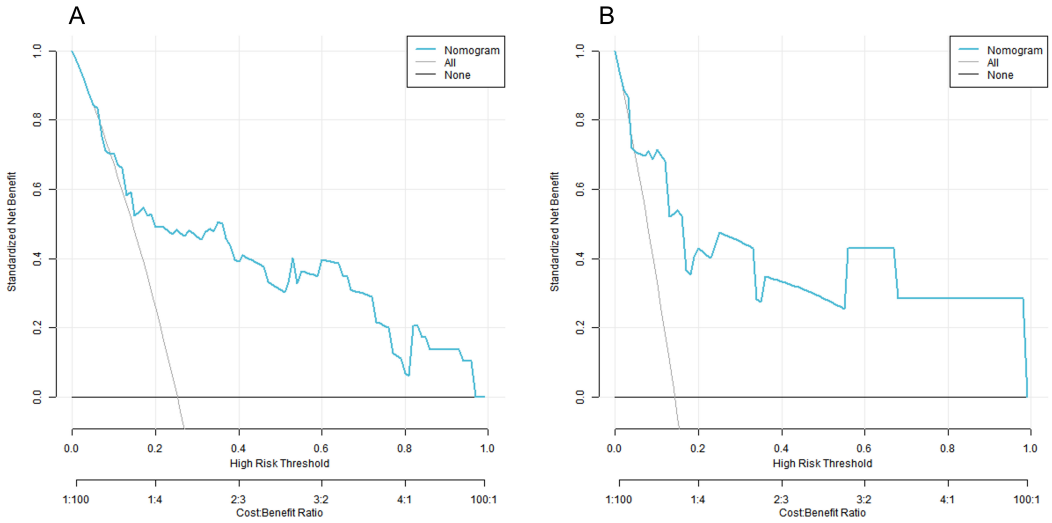


**Fig. 4. Calibration curve analysis of the prediction model.** (A) is the training set, and (B) is the verification set.

## Discussion

This study aims to construct a nomogram prediction model for azithromycin sequential therapy based on the clinical characteristics and pathogenic results of children with Mycoplasma pneumonia, providing decision support for clinicians. The clinical data of 234 children with Mycoplasma pneumonia treated in our hospital between March 2021 and October 2023 were retrospectively analysed. A series of independent risk factors correlated with the efficacy of azithromycin sequential therapy was identified, resulting in the successful development of a prediction model. This model showed strong predictive efficiency in the training set and was validated in the verification set, confirming its stability and reliability.

In children with Mycoplasma pneumonia, fever is one of the common clinical manifestations. A long fever duration often indicates a prolonged infection, suggesting that the pathogen may have triggered a complex immune response and inflammatory process. This may lead to immune system fatigue, potentially alleviating the therapeutic response to azithromycin. Additionally, long-term fever may indicate that the pathogen has established a stable infection site, making it difficult for azithromycin to completely eliminate the infection, thereby affecting the therapeutic efficacy (Zhai et al, 2020). Severe coughing may be associated with extensive lung inflammation and bronchial damage. The expansion of pulmonary inflammation increases the distribution of pathogens, making it difficult for azithromycin to fully cover and eliminate them. Furthermore, bronchial mucosal damage caused by persistent coughing can affect the local absorption and distribution of drugs, limiting azithromycin from effectively reaching the infection site and ultimately reducing its therapeutic outcome.

Additionally, excessive coughing may result in increased mucus secretion in the respiratory tract, which can encapsulate pathogens and hinder their contact with drugs (Ruan et al, 2024; Zhao et al, 2024). Lung moist rales indicate lung inflammation and exudation. A greater presence of moist rales indicates an elevated ac-

cumulation of inflammatory exudates in the lungs, which can affect the gas exchange and develop a microenvironment unfavourable to azithromycin's antibacterial effect. Furthermore, a large volume of inflammatory exudate may enclose pathogens, hindering direct contact with azithromycin and reducing its bactericidal effect (Wang et al, 2024). An increased white blood cell count indicates the body's active immune response to infection. However, excessive leukocytosis can result in the overproduction of inflammatory mediators such as tumour necrosis factor-alpha and interleukin-6. These inflammatory mediators can interfere with the binding of azithromycin to Mycoplasma or alter the surrounding microenvironment, thereby reducing its antibacterial activity. Furthermore, inflammatory mediators can stimulate immune cells to produce more reactive oxygen species and nitrogen compounds. While these molecules are crucial in pathogen control, they may damage host tissues, further affecting the body's response to treatment and reducing the therapeutic effectiveness of azithromycin (Chen et al, 2022a).

Elevated CRP levels indicate a more severe inflammatory burden. CRP not only serves as a biomarker of inflammation but also actively participates in immune regulation and amplifies inflammatory responses. High CRP levels indicate a strong inflammatory cascade, which can lead to pulmonary edema and congestion, thereby affecting drug distribution and penetration within lung tissues. Additionally, excessive inflammatory response may trigger resistance mechanisms against azithromycin, such as upregulating certain efflux pump proteins, which prevent intracellular drug accumulation, thereby reducing its therapeutic efficacy (Fan et al, 2023). Under these conditions, effective inflammation control with azithromycin may need a higher dose or an extended treatment duration. However, it may introduce complexities and challenges in treatment, such as potential drug tolerance and an increased likelihood of adverse reactions, which may affect curative effects. A high Mycoplasma antibody titer reflects either a severe Mycoplasma infection or a strong immune response against Mycoplasma. An increase in antibody titer indicates extensive Mycoplasma proliferation *in vivo*, leading to immune complexes that may hinder azithromycin's antibacterial effect (Chen et al, 2022b). Moreover, a strong immune response to Mycoplasma infection may lead to persistent inflammation even after Mycoplasma growth is inhibited, delaying the resolution of symptoms and resulting in poor therapeutic efficacy (Wang et al, 2021).

A positive nucleic acid test confirms the persistent Mycoplasma infection, indicating that azithromycin has not effectively eliminated the pathogen. Various factors contribute to this, such as mutations in Mycoplasma resistance genes, biofilm formation, or impaired immune clearance. Resistance gene mutations can change target structures, decreasing azithromycin's target-binding affinity; biofilm formation provides a protective barrier that hinders drug penetration and bacterial elimination; and immune deficiency prevents synergistic pathogen elimination, resulting in poor treatment outcomes with azithromycin sequential therapy (Tran Quang et al, 2022). The nomogram prediction model constructed in this study integrates various clinical and pathogenic factors to predict the curative effect of azithromycin sequential therapy at an early stage. This model serves as a valuable tool for clinicians, enabling them to predict therapeutic responses in children at the initial stage

of treatment according to the prediction conclusion of the model. If the model predicts a poor curative effect, doctors can proactively adjust the treatment plan, such as increasing drug dosage, prolonging the treatment duration, or using combination therapy, thereby improving the treatment success rate and reducing disease progression or complications (Sheng et al, 2024).

To evaluate the robustness of the model, a sensitivity analysis was conducted. After excluding outliers, key performance indicators such as the C-index and AUC showed no significant differences compared to the original model, indicating that the outliers had minimal impact. Additionally, re-grouping some variables, such as dividing fever duration into short, medium, and long groups, and reconstructing the model revealed stable performance across different subgroups, further confirming the model's reliability. The AUC in the validation set was slightly higher than in the training set, possibly due to the smaller sample size of the validation set, which may have resulted in a more representative selection of data features and a more uniform data distribution, improving model adaptability. The good performance in the validation set highlights the model's external validity, demonstrating its strong predictive accuracy for new cases. Under the threshold probability of 0.1–0.98, decision curve analysis confirmed the model's clinical significance. Compared with other models predicting the treatment outcomes for Mycoplasma pneumonia, the monogram developed in this study is the first to comprehensively integrate multiple clinical features and pathogenic factors, enabling a more individualised strategy to treating Mycoplasma pneumonia infection in children.

Existing models often focus on a limited number of factors, whereas this model incorporates a wide range of variables, enabling a more comprehensive evaluation of the patient's condition and improving prediction accuracy. Through rigorous training and validation using multiple evaluation metrics, the model has been well-calibrated and demonstrates high applicability in clinical settings. By using model predictions, physicians can adjust treatment plans at an early stage. If the model predicts poor efficacy, adjustments like increasing the dosage of azithromycin or combining it with other antibiotics, such as tetracycline or quinolone (where appropriate for children), can be considered. This approach helps avoid ineffective treatment, reduces drug waste and unnecessary medical resources, lowers medical costs, reduces overtreatment, lowers the risk of adverse drug reactions, and improves treatment outcomes and overall quality of life for children (Duan et al, 2019). Given that each patient presents with different clinical features and pathogenic profiles, the nomogram prediction model predicts individualised therapy by tailoring treatment approaches to the specific needs of each child. This tailored approach improves treatment accuracy and effectiveness, reduces unnecessary drug use and treatment duration, lowers medical costs and optimises healthcare resource allocation, and improves patient satisfaction and overall quality of life. Through the individualised comprehensive evaluation of each child, this model moves away from a one-size-fits-all treatment model, ultimately improving the treatment success and therapeutic outcomes (Pei et al, 2021).

This study adopts a retrospective analysis method, which allows for the collection of extensive clinical data, but it also has certain inevitable limitations. In

retrospective studies, there is a possibility of selection bias; for example, cases with complete clinical data may be preferentially selected, while cases with incomplete data (possibly containing important information) may be excluded. Additionally, retrospective studies only analyse outcomes that have already occurred, which may impact the accuracy and credibility of the research conclusions (Li et al, 2023). Although the study included 234 children with Mycoplasma pneumoniae infection, the sample size remains relatively limited. A limited sample size may not capture all potential factors affecting the efficacy of azithromycin sequential therapy, leaving some influencing factors unidentified. Moreover, the smaller sample size may contribute to statistical instability, potentially affecting the accuracy and reliability of the predictive model. As the sample size increases, the predicted efficiency of the model may improve, resulting in more precise and reliable findings (Chang et al, 2022). This study mainly assesses the influence of clinical characteristics and pathogenic factors on the efficacy of azithromycin sequential therapy without incorporating other factors, such as underlying comorbidities, differences in pharmacokinetics, differences in individual immune status, or environmental factors (Ni et al, 2023). These factors may influence the therapeutic effect to some extent. Future research should explore the relationship between these additional factors and curative effects, improve the prediction model, and enhance its accuracy and clinical applicability.

## Conclusion

In summary, the column chart prediction model holds significant clinical value, enabling early evaluation of the efficacy of azithromycin sequential therapy, assisting doctors in adjusting treatment plans and facilitating personalised therapy. However, this research has certain limitations, such as a retrospective design, a relatively limited sample size, and omitting additional factors. Future studies should expand the sample size, apply a prospective study design, and further optimise the model to enhance its predictive accuracy and clinical applicability.

### Key Points

- This retrospective study analysed 234 pediatric patients with Mycoplasma pneumoniae infection.
- A nomogram prediction model for azithromycin sequential treatment was developed based on their clinical characteristics and pathogenic profiles.
- Several factors were identified as independent risk factors for poor efficacy, and the model demonstrated high clinical value upon evaluation.
- However, this study had certain limitations and warrants further elucidation in future studies.

## Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

## Author Contributions

HH: Conceptualisation, Methodology, Validation, Writing—original draft, Review & editing. FJ: Formal analysis, Project administration, Writing—original draft, Review & editing. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

The study was reviewed and approved by the Ethics Committee of Cangnan Hospital of Wenzhou Medical University (Approval No.: 2024123), and informed consent forms were signed by the guardians. This study was conducted in accordance with the Declaration of Helsinki.

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## Conflict of Interest

The authors declare no conflict of interest.

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