Research Square

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Decreased high-density lipoprotein cholesterol is associated with severe community-acquired pneumonia in children: a single-center retrospective cohort study

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Abstract

Background

Community-acquired pneumonia (CAP) is a leading infectious cause of death among children. Recent evidence suggests that blood lipid levels are correlated with disease severity in sepsis and other inflammatory conditions; however, evidence on the association between lipid levels and severe CAP in children remains limited. This study aimed to evaluate the association between blood lipid levels and severe CAP in children and the discriminative ability of lipid parameters for severe CAP.

Methods

In this single-center retrospective cohort study, we included 1588 hospitalized children with CAP between September 2023 and September 2024. The children were divided into a severe pneumonia group (*n* = 400) and a nonsevere pneumonia group (*n* = 1188) according to disease severity. Clinical characteristics and serum lipid levels measured within 24 hours of admission were compared between the two groups. Receiver operating characteristic (ROC) analyses and multivariable logistic regression adjusted for age, sex, and body mass index (BMI) were used to evaluate the discriminative ability of each lipid parameter for severe pneumonia. A combined model including high-density lipoprotein cholesterol (HDL-C), procalcitonin, C-reactive protein, and neutrophil count was further evaluated. .

Results

Children with severe CAP had lower total cholesterol, HDL-C, low-density lipoprotein cholesterol, and apolipoprotein A1 levels than those with non-severe CAP (all $P < 0.05$). Among the lipid parameters, HDL-C showed the best discriminative performance for severe pneumonia, with an area under the ROC curve (AUC) of 0.705 (95% CI: 0.674 − 0.735, $P < 0.001$). In multivariable analysis, higher HDL-C was independently associated with lower odds of severe CAP (OR = 0.086, 95% CI:0.052–0.142), whereas higher procalcitonin, C-reactive protein, and neutrophil count were associated with higher odds. Adding HDL-C to the inflammatory marker-based model improved the AUC from 0.696 to 0.757.

Conclusions

Children with severe CAP exhibit an abnormal lipid profile characterized by decreased TC, HDL-C, LDL-C, and ApoA1. HDL-C was independently associated with severe CAP and improved discrimination when combined with PCT, CRP, and the neutrophil count.

Background

Community-acquired pneumonia (CAP) is a common infectious disease in children and is defined as pneumonia acquired outside the hospital by otherwise healthy children, or pneumonia caused by a pathogen with a clearly defined incubation period that develops within the incubation period after admission. It is the leading infectious cause of death among children under five years of age worldwide [1].

Recent studies have shown that blood lipid levels are correlated with the severity of several diseases, including sepsis, acute pancreatitis, and rheumatoid arthritis [2–4]. Patients with sepsis have significantly lower lipid levels than patients without sepsis, and these changes are correlated with disease severity and prognosis [5]. In adults with bacterial CAP, blood lipid levels are negatively correlated with inflammatory markers (procalcitonin [PCT], C-reactive protein [CRP], erythrocyte sedimentation rate, and white blood cell [WBC] count) [6]. However, studies on blood lipid levels in pediatric CAP patients are scarce and limited by small sample sizes.

We therefore performed a retrospective analysis of 1588 hospitalized children with CAP to assess whether lipid profiles are associated with disease severity and could aid in identifying severe CAP.

Methods

Study design and participants

We conducted a single-center retrospective cohort study including consecutive hospitalized children with CAP admitted to Suining Central Hospital between September 2023 and September 2024. The inclusion criteria were as follows: (1) aged ≤ 14 years; and (2) met the diagnostic criteria for pediatric CAP according to the *Guidelines for the Management of Community-Acquired Pneumonia in Children (2024 Revision)* [7]. The exclusion criteria were as follows: (1) diseases that may affect blood lipid metabolism, such as hepatitis, nephrotic syndrome, or chromosomal abnormalities; (2) recent use of glucocorticoids, lipid-regulating drugs, or other medications that affect blood lipid metabolism; and (3) incomplete clinical data.

The following data were collected: sex, age, height, weight, body mass index (BMI, calculated as weight [kg]/[height (m)]^2), length of hospital stay, duration of fever, presence of pulmonary consolidation on imaging, and serum laboratory parameters obtained within 24 hours of admission, including PCT, CRP, WBC count, neutrophil count (N), lymphocyte count (L), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and triglycerides (TG). Serum LDL-C was measured directly in blood samples. Etiological information was collected for children whose pathogens were identified via targeted next-generation sequencing (tNGS) of bronchoalveolar lavage fluid or sputum. Because tNGS was performed only in children with a prolonged disease course, severe illness, or a poor response after three days of treatment, the pathogen subgroups should be interpreted as exploratory. This retrospective study was granted a waiver of informed consent and was approved by the Ethics Committee of Suining Central

Hospital (approval no. KYLLKS20250034). All the children who met the inclusion criteria and met none of the exclusion criteria during the study period were consecutively enrolled; no formal sample size calculation was performed given the retrospective design. To reduce potential selection and information bias, diagnoses and severity classification were based on uniform guideline criteria, and all clinical and laboratory data were extracted from the electronic medical record system via standardized definitions.

Grouping

According to the *Guidelines for the Management of Community-Acquired Pneumonia in Children (2024 Revision)* [7], severe pneumonia was defined as the presence of any one of the following: poor general condition, refusal to feed or dehydration, altered consciousness, respiratory distress, oxygen saturation ≤ 92%, involvement of multiple lobes or more than two-thirds of a single lobe, or the presence of pleural effusion or extrapulmonary complications. The children were divided into a severe pneumonia group (n = 400) and a nonsevere pneumonia group (n = 1188). On the basis of etiological results, the children were further divided into a viral group (n = 122), a bacterial group (n = 141), a *Mycoplasma pneumoniae* group (n = 252), a *Mycoplasma pneumoniae* mixed infection group (*M. pneumoniae* coinfection with bacteria or viruses; n = 244), and a bacterial–viral mixed infection group (n = 153). According to the *Expert Consensus on the Diagnosis and Treatment of Dyslipidemia in Children (2022)* [8], children with HDL-C < 1.03 mmol/L (40 mg/dL) were classified into the low-HDL-C group (n = 640), and those with HDL-C ≥ 1.03 mmol/L were classified into the high-HDL-C group (n = 948).

Statistical analysis

Statistical analyses were performed via SPSS version 26.0. Normality was assessed with the Shapiro–Wilk test, together with inspection of histograms and Q – Q plots. As all continuous variables deviated from a normal distribution, they were reported as medians (P25, P75), and between-group differences were examined via the Mann–Whitney U test. Categorical variables are expressed as counts (percentages) and were compared via the chi-square test. Partial correlation analysis was used to examine the correlations between PCT, CRP, and the lipid parameters, with sex, age, and BMI as control variables. Variables with $P < 0.10$ in the univariable analysis were considered candidate predictors for the multivariable model. Collinear variables were excluded on the basis of clinical relevance and the variance inflation factor (VIF) before inclusion. Age, sex, and BMI were forced into the model as covariates regardless of their univariable significance. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic performance of the lipid parameters for severe pneumonia. The DeLong test was performed via R software (version 4.5.0) to compare the area under the ROC curve (AUC) among different markers or models within the same patients. For comparisons of the discriminative ability of a single marker (HDL-C) across pathogen subgroups, the Hanley–McNeil test for independent ROC curves was used. Pairwise P values were adjusted via the Benjamini–Hochberg method and were further verified via bootstrap resampling (2000 resamples). To assess the incremental discriminative value of HDL-C beyond conventional inflammatory markers, a base model including age, sex, BMI, CRP, PCT, and

neutrophil count was compared with an extended model additionally including HDL-C. Net reclassification improvement and integrated discrimination improvement were calculated, with confidence intervals derived from 2,000 bootstrap resamples. Model calibration was assessed using calibration curves, the Brier score, and calibration slope and intercept. Internal validation was performed using stratified bootstrap resampling (stratified by outcome; sampled with replacement; 1000 replications (for AUC and calibration metrics)) to quantify optimism. In each resample, the model was refitted in the bootstrap (in-bag) sample, and the AUC, Brier score, and calibration slope and intercept were computed in the out-of-bag (OOB) sample. A two-sided $P < 0.05$ was considered statistically significant. Patients with incomplete key clinical or laboratory data were excluded before analysis according to the predefined criteria; therefore, a complete-case analysis was performed and no missing-data imputation was undertaken.

Results

Study participants

During the study period, 1901 children with CAP were screened. After excluding 8 children with nephrotic syndrome or chromosomal abnormalities, 136 children who had recently received glucocorticoid therapy, and 169 children whose clinical data were incomplete, 1588 children were ultimately included and assigned to the severe pneumonia group (n = 400) or the nonsevere pneumonia group (n = 1188) (Fig. 1).

Comparison of clinical characteristics and laboratory parameters between the severe pneumonia and nonsevere pneumonia groups

Sex, age, and BMI did not differ significantly between the two groups, indicating comparability. The severe pneumonia group had significantly lower TC, HDL-C, LDL-C, and ApoA1 levels and higher inflammatory marker levels than the nonsevere group (all $P < 0.05$) (Table 1).

Table 1
Comparison of clinical characteristics and laboratory parameters between the severe pneumonia and nonsevere pneumonia groups.

Parameter	**Nonsevere pneumonia group (*n* = 1188)**	**Severe pneumonia group (*n* = 400)**	***χ²/z***	***P value***
Sex (male, %)	636 (53.50)	201 (50.30)	1.296	0.271
Age (years)	3.00 (2.00, 5.00)	4.00 (1.00, 7.00)	-0.336	0.737
BMI (kg/m²)	15.71 (14.57, 17.30)	15.74 (14.46, 17.36)	-0.105	0.916
Length of hospital stay (days)	6.00 (5.00, 7.00)	7.00 (6.00, 7.00)	-13.339	< 0.001
Duration of fever (days)	1.00 (0.00, 1.00)	4.00 (1.00, 6.00)	-10.407	< 0.001
Pulmonary consolidation (present, %)	234 (19.70)	239 (59.80)	229.54	< 0.001
PCT (ng/mL)	0.13 (0.05, 0.55)	0.17 (0.05, 0.93)	-2.84	0.004
CRP (mg/L)	2.16 (0.50, 9.33)	13.26 (0.61, 36.32)	-10.62	< 0.001
WBC (×10⁹/L)	9.20 (6.90, 12.15)	9.50 (7.05, 13.20)	-2.284	0.022
Neutrophil count (×10⁹/L)	4.62 (3.06, 6.81)	5.51 (3.76, 8.13)	-4.725	< 0.001
Lymphocyte count (×10⁹/L)	2.99 (2.05, 4.39)	2.40 (1.74, 3.72)	-4.669	< 0.001
TC (mmol/L)	3.98 (3.45, 4.48)	3.63 (3.07, 4.16)	-7.209	< 0.001
TG (mmol/L)	0.99 (0.76, 1.32)	1.00 (0.79, 1.33)	-0.475	0.635
HDL-C (mmol/L)	1.16 (0.97, 1.38)	0.94 (0.78, 1.13)	-12.252	< 0.001
LDL-C (mmol/L)	2.17 (1.79, 2.58)	2.12 (1.65, 2.56)	-2.085	0.037
ApoA1 (g/L)	1.22 (1.07, 1.39)	1.07 (0.90, 1.25)	-9.893	< 0.001
ApoB (g/L)	0.71 (0.59, 0.84)	0.73 (0.57, 0.87)	-0.568	0.477

All continuous variables were nonnormally distributed and are presented as medians (P25, P75) (Mann–Whitney U test); categorical data are presented as n (%) (chi-square test).

Correlations between PCT, CRP, and lipid levels

Partial correlation analysis revealed that, after controlling for sex, age, and BMI, PCT was negatively correlated with TC and LDL-C (r = − 0.05 and − 0.07, respectively; P < 0.05), and CRP was negatively correlated with TC, HDL-C, and ApoA1 (r = − 0.10, − 0.18, and − 0.23, respectively; P < 0.05) (Table 2).

Table 2
Correlations between PCT, CRP, and blood lipid parameters.

Marker		TC	HDL-C	LDL-C	ApoA1
PCT	*r*	-0.05	-0.01	-0.07	-0.04
	P	0.04	0.79	< 0.01	0.10
CRP	*r*	-0.10	-0.18	-0.01	-0.23
	P	< 0.01	< 0.01	0.90	< 0.01

Partial correlation analysis with sex, age, and BMI as control variables.

ROC analysis of the discriminative value of each parameter for severe pneumonia

HDL-C showed the highest discriminative value for severe pneumonia (AUC = 0.705, 95% CI: 0.674 − 0.735) (Table 3). In the DeLong test, the discriminative ability of HDL-C was significantly superior to that of TC, ApoA1, and LDL-C (Fig. 2).

Table 3
Discriminative performance of clinical and lipid parameters for severe pneumonia.

Parameter	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	Youden index	*P value*
PCT	0.548	0.514–0.581	0.690	31.8	79.4	0.112	0.004
CRP	0.673	0.640–0.706	11.155	53.5	78.4	0.319	< 0.001
WBC	0.538	0.505–0.572	16.950	14.8	93.5	0.083	0.022
Neutrophil count	0.579	0.546–0.612	5.645	48.8	64.9	0.137	< 0.001
Lymphocyte count	0.578	0.545–0.611	2.395	64.8	49.8	0.146	< 0.001
HDL-C	0.705	0.674–0.735	1.015	68.5	61.8	0.303	< 0.001
LDL-C	0.534	0.501–0.569	1.565	87.5	21.5	0.090	0.017
ApoA1	0.665	0.633–0.698	1.045	78.7	46.4	0.251	< 0.001
TC	0.620	0.588–0.653	3.355	79.3	38.3	0.176	< 0.001

Analysis of factors influencing the occurrence of severe pneumonia

Variables with $P < 0.10$ in the univariable analysis were entered into the multivariable logistic regression. Because of strong collinearity among the lipid parameters (TC, HDL-C, LDL-C, and ApoA1) and among the blood cell parameters (WBC, neutrophil count, and lymphocyte count), TC, LDL-C, and ApoA1 (collinear with HDL-C) and WBC and lymphocyte count (collinear with neutrophil count) were excluded. Age, sex, and BMI were forced into the model as covariates regardless of their univariable significance, and the remaining candidate predictors (HDL-C, PCT, CRP, and neutrophil count) were simultaneously entered into the final model. Among the independent factors, higher HDL-C was associated with lower odds of severe pneumonia (OR = 0.086, 95% CI: 0.052 − 0.142), whereas higher PCT (OR = 1.054), CRP (OR = 1.030), and neutrophil count (OR = 1.058) were associated with higher odds (Table 4).

According to the DeLong test, the AUC of the combined model for identifying severe pneumonia (0.757) was significantly greater than that of HDL-C alone (0.705; $z = 4.884$, $P < 0.001$). To quantify the incremental value of HDL-C beyond conventional inflammatory markers, a base model comprising age, sex, BMI, CRP, PCT, and neutrophil count (Model 1) was compared with an extended model that

additionally included HDL-C (Model 2). Adding HDL-C significantly increased the AUC from 0.696 (95% CI: 0.664 – 0.727) to 0.757 (95% CI: 0.727 – 0.786; DeLong test, z = 4.393, *P* < 0.001; Fig. 3). The IDI was 0.070 (95% CI: 0.057 – 0.084; *P* < 0.001), and the categorical and continuous NRIs were 0.298 (95% CI: 0.237 – 0.361; *P* < 0.001) and 0.531 (95% CI: 0.421 – 0.639; *P* < 0.001), respectively (Table 5), indicating that HDL-C significantly improved risk reclassification and discrimination beyond age, sex, BMI, CRP, PCT, and neutrophil count.

The apparent discrimination of Model 2, as measured by the AUC, was 0.757. The calibration plot showed good agreement between the predicted probabilities and observed rates of severe pneumonia; the Brier score was 0.148, and the calibration slope and intercept were 1.000 and 0.000, respectively. After internal validation with 1000 stratified bootstrap resamples, the optimism-corrected calibration slope was 0.963 (95% CI: 0.689 – 1.305), the intercept was – 0.038 (95% CI: –0.333 – 0.297), the Brier score was 0.151 (95% CI: 0.139 – 0.163), and the corrected AUC was 0.748 (95% CI: 0.712 – 0.788). The corrected calibration slope remained close to 1 and the intercept was close to 0, suggesting minimal overfitting and robust calibration (Fig. 4).

Table 4
Multivariate logistic regression analysis of factors associated with severe pneumonia.

Variable	**B**	**Wald**	***P***	**OR**	**95% CI**
Sex (female)	0.081	0.382	0.536	1.084	0.839 – 1.401
Age(years)	-0.006	0.084	0.772	0.994	0.951 – 1.038
BMI(kg/m²)	0.000	0.000	0.996	1.000	0.949 – 1.054
HDL-C (mmol/L)	−2.456	92.204	< 0.001	0.086	0.052 – 0.142
PCT (ng/mL)	0.053	7.953	0.005	1.054	1.016 – 1.094
CRP (mg/L)	0.029	73.596	< 0.001	1.030	1.023 – 1.037
Neutrophil count(×10⁹/L)	0.056	10.947	0.001	1.058	1.023 – 1.093
Constant	0.750	1.992	0.158	2.116	—

Table 5
NRI and IDI for adding HDL-C to the base model.

Index	**Estimate**	**95% CI**	***P* value**
IDI	0.070	0.057 – 0.084	< 0.001
Categorical NRI (cut 0.2 / 0.3)	0.298	0.237 – 0.361	< 0.001
Continuous (category-free) NRI	0.531	0.421 – 0.639	< 0.001

Confidence intervals were derived from 2000 bootstrap resamples.

Discriminative value of HDL-C across pathogen groups

For exploratory analysis, etiological testing was performed in 912 children, who were divided into five groups according to the pathogen. The AUCs of HDL-C for identifying severe pneumonia in each group are shown in Table 6. Pairwise Hanley–McNeil tests for independent ROC curves among the five groups revealed no significant differences in AUC (all $|z| \leq 1.473$, all $P \geq 0.141$; all Benjamini–Hochberg-adjusted $P \geq 0.48$).

Table 6
Discriminative value of HDL-C for severe pneumonia in different pathogen groups.

Group	**AUC**	**95% *CI***	***P value***
Viral group (*n* = 122)	0.681	0.563–0.799	0.002
Bacterial group (*n* = 141)	0.694	0.586–0.803	0.001
M. pneumoniae group (n = 252)	0.705	0.640–0.771	< 0.001
M. pneumoniae mixed infection group (*n* = 244)	0.775	0.712–0.838	< 0.001
Bacterial-viral mixed infection group (*n* = 153)	0.690	0.589–0.791	< 0.001

Pairwise Hanley–McNeil tests for independent ROC curves among the five groups revealed no significant differences in AUC (all |z| ≤ 1.473, all P ≥ 0.141; all Benjamini–Hochberg-adjusted P ≥ 0.48).

Comparison of clinical parameters between the high-HDL-C and low-HDL-C groups

Sex, age, and BMI did not differ significantly between the two groups. Compared with the high-HDL-C group, the low-HDL-C group had a significantly longer hospital stay, longer fever duration, higher proportions of severe pneumonia and pulmonary consolidation, and higher PCT and CRP levels (all $P < 0.05$) (Table 7).

Table 7
Comparison of clinical parameters between the high-HDL-C and low-HDL-C groups.

Sex (male, %)	**Low-HDL-C group (*n* = 640)**	**High-HDL-C group (*n* = 948)**	***χ²/z***	***P value***
	326 (50.90)	**511 (53.90)**	**1.348**	**0.260**
Age (years)	3.00 (1.00, 6.00)	3.00 (2.00, 6.00)	−1.555	0.120
BMI (kg/m²)	15.72 (14.57, 17.35)	15.71 (14.53, 17.34)	-0.239	0.811
Length of hospital stay (days)	7.00 (6.00, 8.00)	7.00 (6.00, 7.00)	-2.671	0.008
Duration of fever (days)	4.00 (1.00, 5.00)	1.00 (0.00, 3.00)	-13.045	< 0.001
Severe pneumonia (yes, %)	252 (39.40)	148 (15.60)	114.490	< 0.001
Pulmonary consolidation (present, %)	247 (38.60)	226 (23.80)	39.760	< 0.001
PCT	0.18 (0.06, 0.81)	0.12 (0.05, 0.51)	−3.356	0.001
CRP	5.21 (0.50, 21.57)	1.90 (0.50, 9.96)	−6.704	< 0.001

All continuous variables were nonnormally distributed and are presented as medians (P25, P75) (Mann−Whitney U test); categorical data are presented as n (%) (chi-square test).

Discussion

Pneumonia is a common respiratory disease. Its severity depends on both direct pathogen invasion and the intensity of the secondary inflammatory response. Children with severe pneumonia may develop complications such as pleural effusion, empyema, necrotizing pneumonia, and encephalitis, and have a high mortality rate; survivors may be left with sequelae such as bronchiolitis obliterans and bronchiectasis [7]. Early identification of severe cases and timely selection of appropriate treatment are important for shortening the hospital stay, reducing costs, and improving outcomes. In the present study, HDL-C was independently associated with severe CAP in children, and children with low HDL-C had more severe clinical manifestations. Moreover, HDL-C showed consistent discriminative value for severe pneumonia across different pathogen groups, with comparable performance among groups.

Previous studies have shown that blood lipid levels are associated with immune and inflammatory responses: patients with sepsis have decreased HDL-C levels, which correlate with prognosis [5, 9]; in adults with bacterial CAP, blood lipid levels are negatively correlated with inflammatory markers (PCT, CRP, erythrocyte sedimentation rate, and WBC count) [6]. In addition, blood lipid levels have been found to be correlated with disease severity and prognosis in immune-mediated diseases such as rheumatoid arthritis and Crohn’s disease, as well as in cancer and pancreatitis [2, 3].

The possible mechanisms by which lipids participate in the inflammatory response are as follows. (1) During bacterial infection, lipopolysaccharide (LPS) from gram-negative bacteria binds to Toll-like receptor 4 (TLR4), activating downstream signaling that generates inflammatory cytokines. HDL can competitively bind LPS to form HDL – LPS complexes, attenuating LPS–TLR4 inflammatory signaling, and can also bind scavenger receptor class B type I (SR-BI) to promote LPS clearance [10]. Lipoteichoic acid (LTA) released by gram-positive bacteria activates the TLR2/6 pathway, resulting in high levels of inflammatory cytokines and cell damage, whereas HDL can bind LTA to form HDL – LTA complexes, neutralizing and clearing LTA [11]. (2) ApoA1 is the main protein component of HDL, and during inflammation it regulates cell function mainly by altering the cellular cholesterol content [12, 13]. HDL-C inhibits macrophage inflammatory responses and endothelial cell activation [11]. (3) ApoA1 regulates the expression of inflammatory cytokines through signaling pathways, suppresses excessive immune and inflammatory responses [14, 15], and reduces neutrophil production by decreasing granulocyte colony-stimulating factor and attenuating the chemotaxis, adhesion, and activation of monocytes and neutrophils [16].

In both infection-induced and immune-mediated inflammation, lipids—especially HDL and ApoA1—play important regulatory roles. In this study, children with severe CAP had lower TC, HDL-C, LDL-C, and ApoA1 levels than those with nonsevere CAP. Correlation analysis revealed that lipid levels were correlated with the inflammatory markers PCT and CRP; however, the absolute correlation coefficients were small, suggesting a weak association between inflammatory markers and lipid parameters. This finding implies that disturbed lipid metabolism may contribute to the development and progression of severe pediatric pneumonia through pathways that are independent of the classical inflammatory signaling pathways represented by CRP and PCT [17, 18],providing a new direction for exploring the underlying pathophysiological mechanisms of this condition. In this study, HDL-C was not correlated with PCT, which is inconsistent with previous reports; a possible explanation is that PCT mainly reflects the severity of bacterial infection and increases only modestly in viral and *Mycoplasma pneumoniae* infections. We therefore separately analyzed the correlation between PCT and HDL-C in the bacterial group and found a weak negative correlation after controlling for sex, age, and BMI ($r = -0.168$, $P = 0.04$). Multivariate logistic regression revealed that HDL-C, PCT, CRP, and neutrophil count were independent factors associated with severe pneumonia after adjustment for age, sex, and BMI, and the model had moderate discriminative ability (AUC = 0.757; Brier score = 0.148).

Furthermore, when the children were divided according to HDL-C level, the low-HDL-C group had a significantly longer hospital stay and longer fever duration, higher proportions of severe pneumonia and pulmonary consolidation, and higher PCT and CRP levels, suggesting that low lipid levels and severe pneumonia may be interrelated. On the one hand, severe infection triggers a systemic inflammatory stress state, which may lower blood lipid levels by promoting lipid oxidation and energy consumption and by reducing lipid synthesis. Reduced food intake in severely ill children further decreases lipid intake and synthesis, and high concentrations of inflammatory cytokines (TNF-α, IL-6) inhibit lipoprotein production and promote lipoprotein degradation, which is consistent with previous findings that infusion of recombinant TNF-α or IL-6 lowers plasma cholesterol [19, 20]. On the other hand, because lipids exert

important anti-inflammatory effects, children with low lipid levels may have a weaker anti-inflammatory response, thereby contributing to a severe disease state.

These findings raise the hypothesis that lipid metabolism may be involved in the pathophysiology of severe pediatric CAP and may warrant further mechanistic and interventional studies. Although our findings do not imply causality, they support a link between lipid disturbances and disease severity in pediatric CAP. Several studies have explored the role of maintaining lipid metabolic homeostasis in the treatment and management of diseases such as pneumonia, sepsis, diabetes, and cancer [21–26]. In pediatric CAP, whether interventions targeting lipid metabolism could improve clinical outcomes remains unknown. Future mechanistic studies and prospective interventional research are needed before any therapeutic implications can be considered.

This study has several limitations. First, it was a single-center, retrospective study, and selection bias may have been present. Second, because there were fewer severe cases, the sample sizes of the two groups differed considerably, which may have affected the stability of the results. Third, healthy control data were lacking. Fourth, because critically ill children often cannot meet strict fasting requirements, the fasting status of blood samples could not be fully standardized. However, the main parameters used for assessment (HDL-C, TC, LDL-C, and ApoA1) are minimally affected by fasting status [27, 28], and TG was analyzed descriptively only, so this is unlikely to materially bias our conclusions. In addition, pathogen identification by tNGS was selective rather than universal, being restricted to children with a prolonged course, severe disease, or a poor treatment response; this indication-based testing may introduce selection bias, meaning that the pathogen subgroups may not be representative of all children with CAP. Larger, prospective, multicenter studies are needed to confirm these findings. Moreover, the prediction model was not externally validated, and because the study was conducted at a single center, the generalizability of the findings to other regions and populations remains to be established.

Conclusions

Children with severe CAP exhibit an abnormal lipid profile characterized by decreased TC, HDL-C, LDL-C, and ApoA1. HDL-C has discriminative value for severe pneumonia and is independently associated with severe CAP in children. Because the discriminative ability of a single marker is limited, HDL-C may be more useful when combined with PCT, CRP, and the neutrophil count. These findings support further prospective multicenter validation and mechanistic studies on the role of lipid metabolism in pediatric CAP.

Abbreviations

CAP
community-acquired pneumonia
PCT
procalcitonin

CRP
C-reactive protein
WBC
white blood cell
N
neutrophil count
L
lymphocyte count
TC
total cholesterol
HDL-C
high-density lipoprotein cholesterol
LDL-C
low-density lipoprotein cholesterol
ApoA1
apolipoprotein A1
ApoB
apolipoprotein B
TG
triglyceride
BMI
body mass index
SD
standard deviation
ROC
receiver operating characteristic
AUC
area under the ROC curve
CI
confidence interval
OR
odds ratio
tNGS
targeted next-generation sequencing
LPS
lipopolysaccharide
LTA
lipoteichoic acid
TLR
Toll-like receptor

SR-BI
scavenger receptor class B type I
TNF-α
tumor necrosis factor-alpha
IL-6
interleukin-6
VIF
variance inflation factor.

Declarations

Ethics approval and consent to participate:

This retrospective study was approved by the Ethics Committee of Suining Central Hospital (KYLLKS20250034). The requirement for informed consent was waived by the Ethics Committee because of the retrospective nature of the study.

Clinical trial number

Not applicable.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

Y.L. Liu: conceptualization, data curation, formal analysis, writing–original draft. Y.Y. Lei: conceptualization, formal analysis, writing–original draft. L. L., A.H., X. L., T.Z.: data curation. F. Z.: methodology, formal analysis, writing–review & editing. P.Y.: conceptualization, supervision, writing–review & editing. All the authors read and approved the final manuscript.

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Not applicable.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

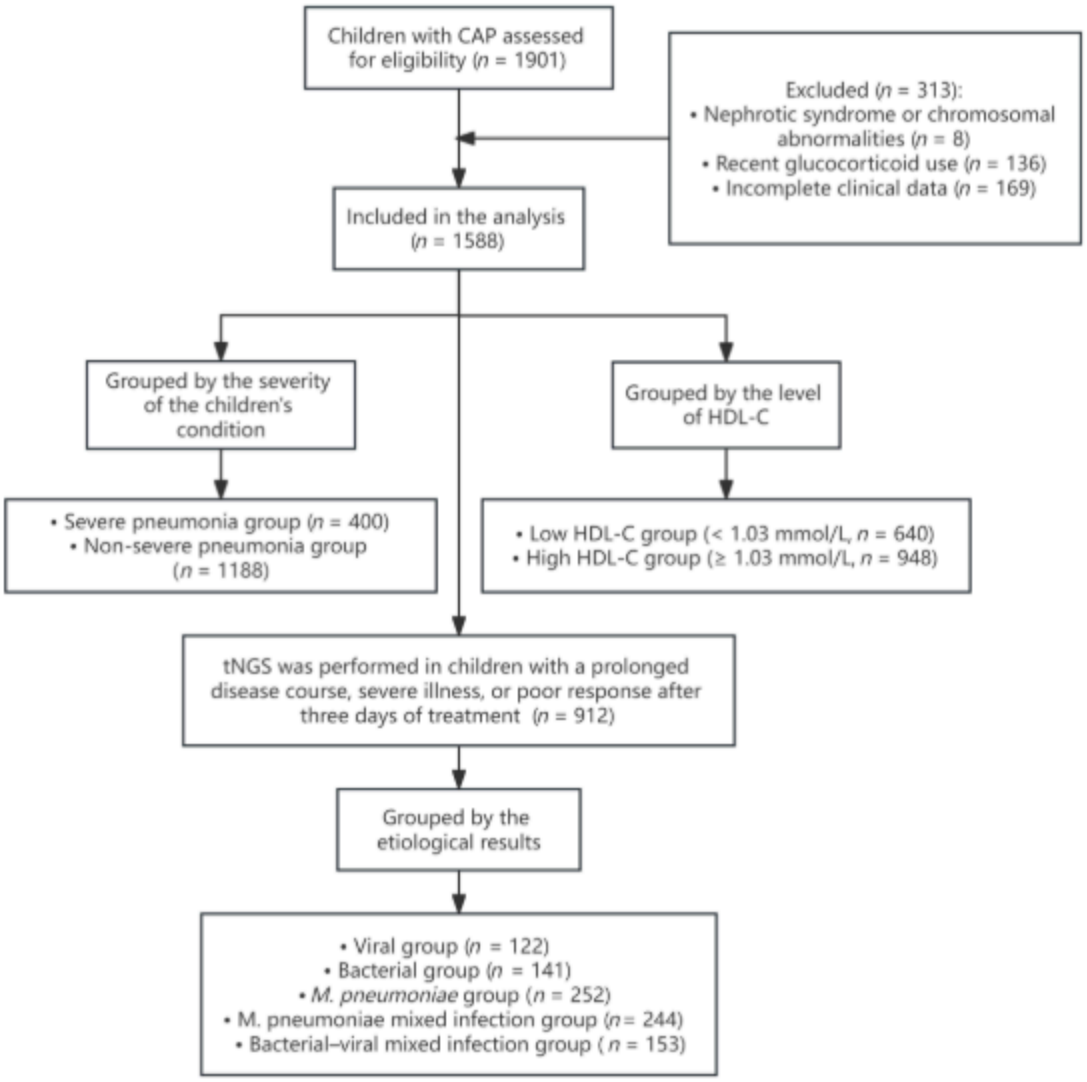


Figure 1

Flow chart of patient inclusion and exclusion criteria. A total of 1901 children with CAP were screened, and 1588 children were ultimately included.

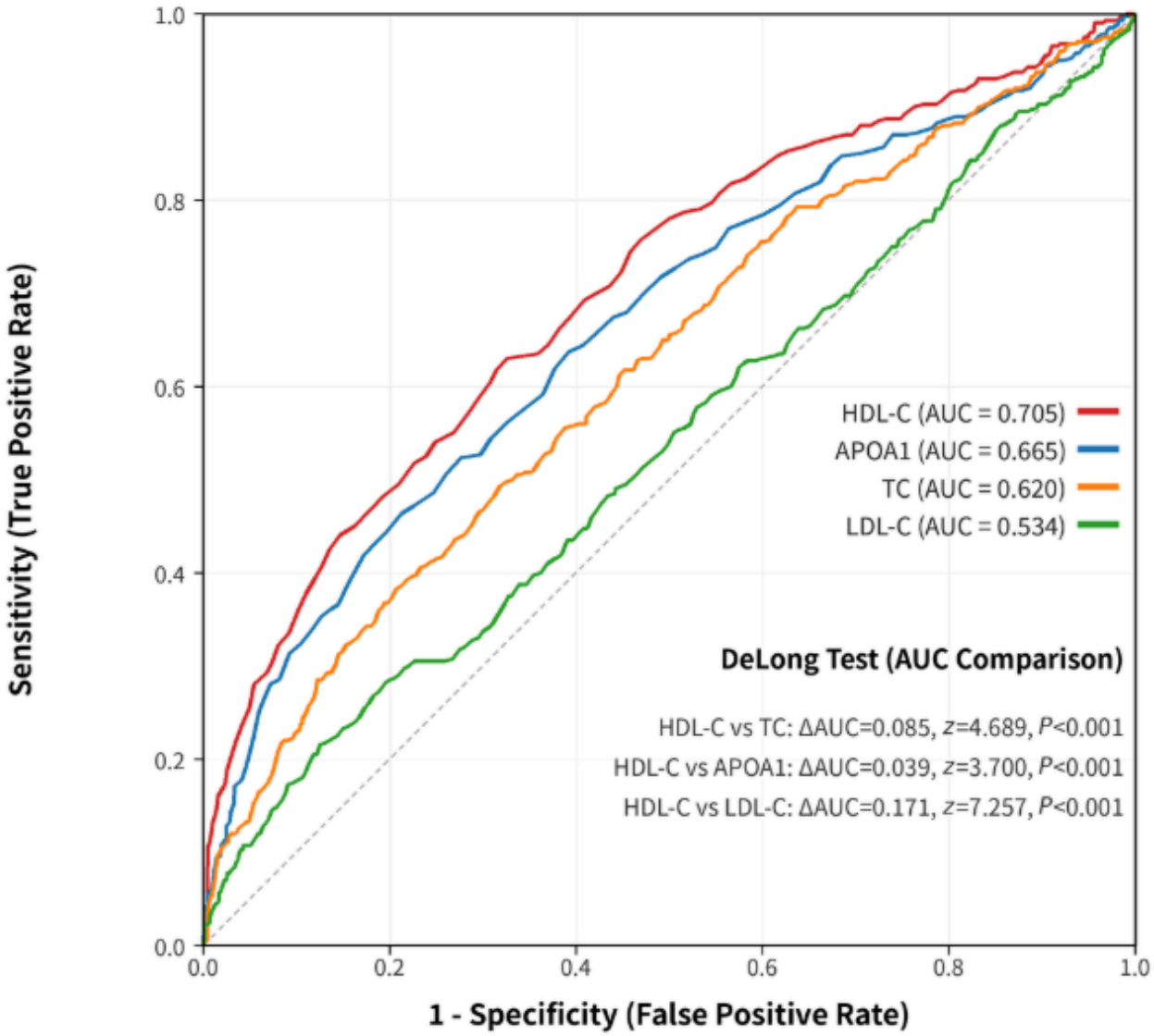


Figure 2

Receiver operating characteristic curves of lipid parameters for identifying severe pneumonia.The AUC was 0.705 for HDL-C, 0.665 for ApoA1, 0.620 for TC, and 0.534 for LDL-C. Pairwise comparisons via the DeLong test were as follows: HDL-C vs. TC, $z = 4.689$, $P < 0.001$; HDL-C vs. ApoA1, $z = 3.700$, $P < 0.001$; and HDL-C vs. LDL-C, $z = 7.257$, $P < 0.001$. Among the lipid parameters, HDL-C showed the highest discriminative value and, in the DeLong test, was significantly superior to TC, ApoA1, and LDL-C.

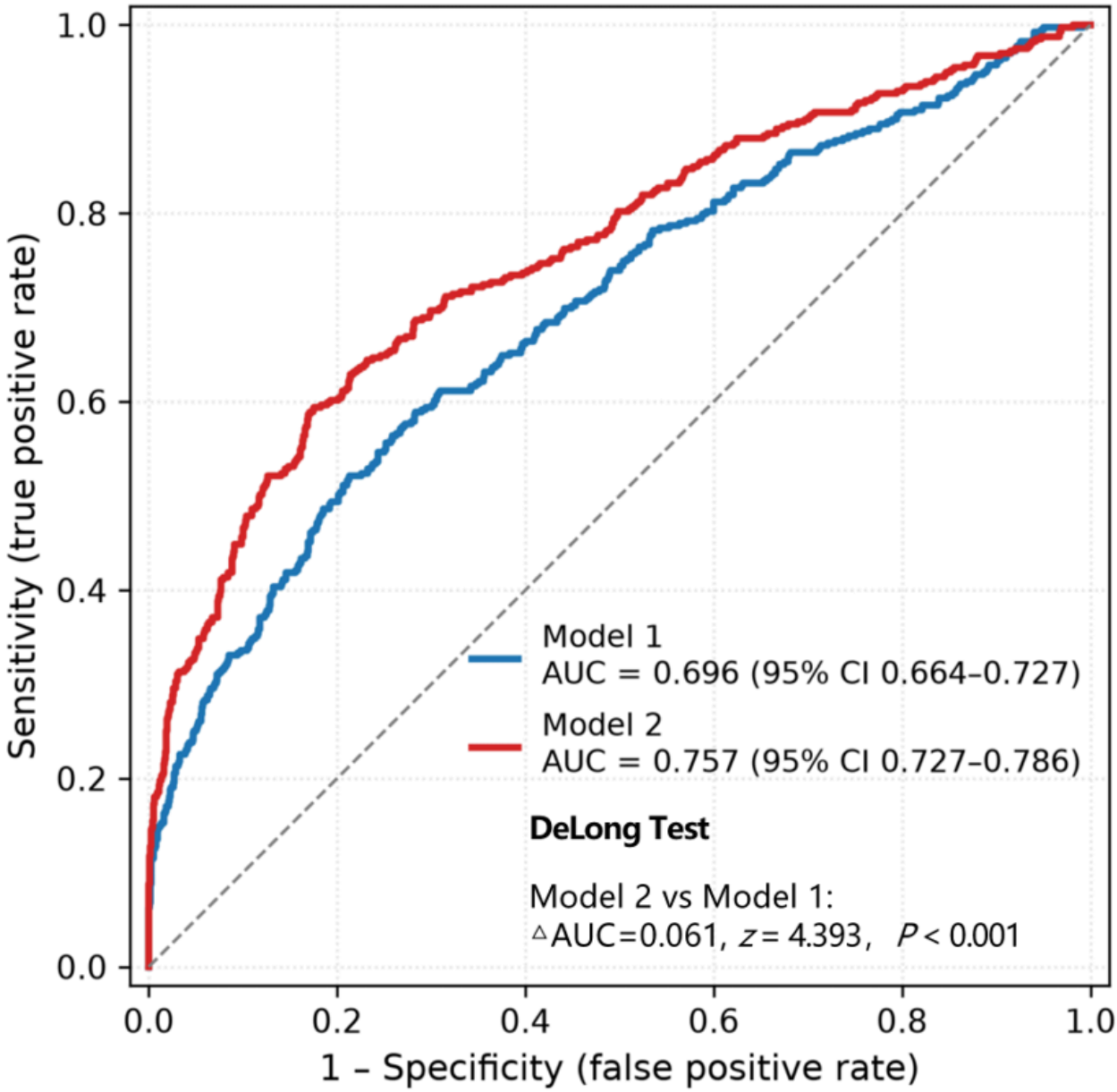


Figure 3

Receiver operating characteristic (ROC) curves of Model 1(sex, age, BMI, CRP, PCT, and neutrophil count) and Model 2 (Model 1 plus HDL-C) for discriminating severe community-acquired pneumonia in children.

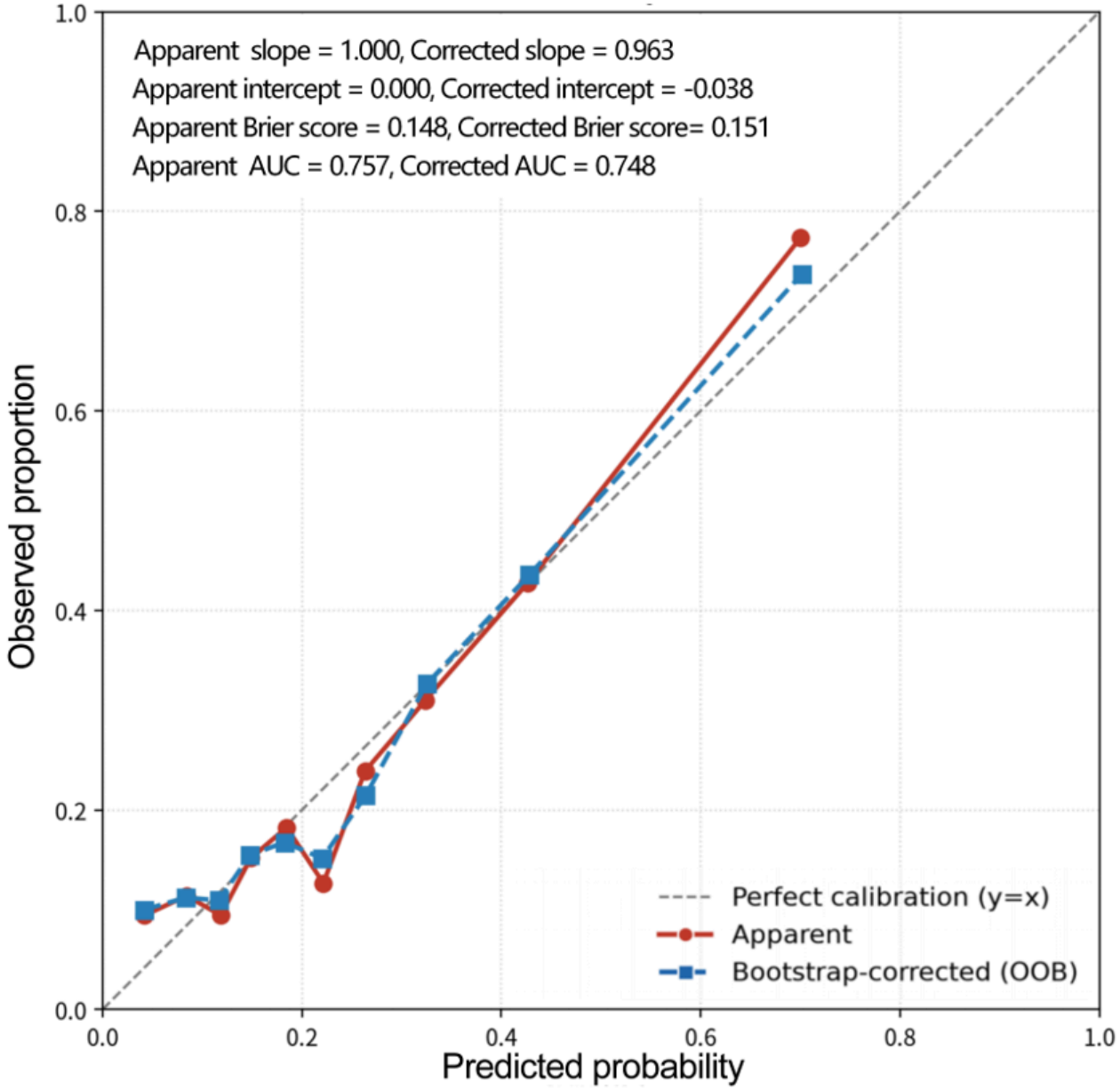


Figure 4

Calibration curve for Model 2 in discriminating severe pneumonia. The red line with circles shows the apparent calibration, and the blue dashed line with squares shows the calibration curve after internal validation with 1000 bootstrap resamples (mean of out-of-bag predictions). The gray dashed line indicates perfect calibration (y = x).