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Original Article

Factors based on Cox regression modeling to analyze the prognostic impact of fiberoptic bronchoscopic bronchoalveolar lavage on children with severe pneumonia

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Abstract: Objective: This study aimed to identify factors influencing the prognosis of children with severe pneumonia (SP) after fiberoptic bronchoscopic bronchoalveolar lavage (BAL). Methods: The clinical data of 155 children with SP treated with fiberoptic bronchoscopic BAL at Xi'an International Medical Center Hospital between January 2022 and January 2024 were retrospectively analyzed. Children were categorized into the survival group (n = 122) and the death group (n = 33) according to their clinical outcomes within 28 days after treatment. General patient data and the initial laboratory results after admission were collected. Univariate and multivariate Cox regression analyses were performed to identify independent predictors of 28-day prognosis. The predictive ability of each index was evaluated using the receiver operating characteristic (ROC) curve analysis and the Delong test. The relationship between each index and the prognosis of children with SP was analyzed using the Kaplan-Meier curve. Results: The death group had significantly younger patients, longer pneumonia course, shorter pregnancy cycle, and higher levels of procalcitonin (PCT), white blood cell count (WBC), C-protein reaction (CPR), and systemic immune-inflammation index (SII) compared to the survival group (P<0.05). Cox regression analysis identified age (HR = 0.959, P = 0.014), pneumonia course (HR = 2.270, P<0.001), pregnancy cycle (HR = 2.736, P = 0.015), PCT (HR = 2.728, P = 0.001), WBC (HR = 1.283, P = 0.001), and SII (HR = 1.009, P<0.001) as independent predictors of 28-day mortality in children with SP. Among these, pneumonia course, PCT, and SII demonstrated higher predictive efficacy in adverse outcomes, with areas under the ROC curve (AUC) of 0.827, 0.822, and 0.868, respectively, outperforming age, pregnancy cycle, and WBC (P<0.05). Kaplan-Meier survival curves showed that patients with older age, shorter pneumonia course, full-term birth, and those with lower WBC, PCT, and SII levels had significantly higher survival rates compared to their counterparts (P<0.05). Conclusion: Age, pneumonia course, pregnancy cycle, WBC, PCT, and SII were independent predictors of survival in children with SP after fiberoptic bronchoscopic BAL, among which pneumonia course, PCT, and SII showed a higher predictive efficacy for the prognosis of children with SP.

Keywords: Cox regression, bronchoalveolar lavage, severe pneumonia, prognosis, systemic immune-inflammation index

Introduction

Severe pneumonia (SP) is a common respiratory infection among children, especially those under the age of five, and remains a leading cause of child mortality worldwide [1-3]. Children are more susceptible to SP due to the immaturity of their respiratory and immune systems compared to adults. Without timely and effective treatment, SP may lead to serious complications and even be life-threatening [4].

In the era of precision medicine, it is crucial to avoid overtreatment in children with mild community-acquired pneumonia while ensuring timely interventions in those with severe cases. The early manifestations of SP may mimic mild pneumonia, making early and accurate assess-

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ment of its severity and prognosis essential to control disease progression, minimize complications, and reduce the incidence of sequelae [5]. Current therapeutic strategies for SP include mechanical ventilation, antibiotic therapy, glucocorticoid therapy, antiviral nebulization, and more recently, fiberoptic bronchoscopic bronchoalveolar lavage (BAL) [2, 6-8]. BAL has been shown to improve clinical outcomes by clearing airway inflammatory secretions and improving ventilation [9].

Despite advancements in medical technology and the clinical care of children with SP, morbidity and mortality remain high. This is partly due to the challenges in accurately assessing disease severity and initiating intensive treatment or preventive measures promptly. In adults, factors such as age, dependence on lung function support, heart rate, and oxygen saturation-to-respiratory rate ratio are associated with SP-related mortality [10]. However, there are relatively few studies related to SP in children. Clinically, elevated serum inflammatory markers and a higher respiratory rate are often considered predictors of poor outcomes in children with SP, such as delayed recovery or death [11, 12]. Common markers of inflammation, such as C-reactive protein (CRP), white blood cell count (WBC), and procalcitonin (PCT), are routinely used, yet newer indicators like the systemic immune-inflammation index (SII) have not been widely adopted in pediatric SP [13-19].

In this context, our study retrospectively analyzed the clinical and laboratory data of 155 children with SP treated with BAL at Xi'an International Medical Center Hospital. Using Cox regression modeling, we aimed to comprehensively investigate, for the first time, the various factors influencing the prognosis of SP children following fiberoptic bronchoscopic BAL. The findings of this research will enhance the existing clinical indicators used to predict mortality risk in children with SP and provide a basis for physicians to develop more precise prevention and treatment strategies, ultimately improving the overall outcome for children with SP.

Subjects and methods

Sample size calculation

Previous Literature [20] reported that the mortality rate of SP in children can be as high as 9.4%. The total sample size required for this study was calculated using the formula: $n = \left(\frac{Z_{1-a/2} \times \sqrt{p(1-p)}}{E} \right)^2$, where p is the expected incidence rate (0.094), Z1−α/2 corresponds to the 97.5% percentile of the normal distribution (significance level α = 0.05), approximately 1.96, and E is the effect size for mortality, set at 5% (0.05). Substituting these values into the formula gives a minimum sample size of 131 cases. The actual sample size was 155 cases based on available clinical data.

Sample acquisition information

This retrospective study included a total of 155 children with SP who were admitted to Xi'an International Medical Center Hospital from January 2022 to January 2024. The cohort consisted of 82 males and 73 females. Based on survival outcomes within 28 days of hospitalization, the children were divided into two groups: the survival group (n = 122) and the death group (n = 33). The study was reviewed and approved by the Medical Ethics Committee of Xi'an International Medical Center Hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients met the diagnostic criteria outlined in the Diagnostic Norms for Community-Acquired Pneumonia in Children (2019 edition) [21]: ① Symptoms including fever, cough, wheezing, increased respiration rate, and the presence of wet rales; ② Clinical signs of inspiratory depression of the chest wall, nasal flaring, three-concave signs, and cyanosis; ③ Behavioral signs including irritability, depression, lethargy, and refusal to eat; ④ Abnormal blood tests showing elevated peripheral leukocyte counts and increased neutrophil ratios; ⑤ Intrapulmonary complications, such as pleural effusion, pyothorax, and pneumothorax; (2) Patients who received fiberoptic bronchoscopic BAL during hospitalization; (3) Patients with complete clinical data and who were hospitalized for one month.

Exclusion criteria: Children were excluded from the study if they met any of the following criteria: (1) Allergy to the drugs used in this study; (2) Inability to cooperate with bronchoscopy procedures; (3) Pre-existing congenital lung dis-

Table 1. Comparison of basic clinical data of the children in both groups

Norm	Survival group (n = 122)	Death group (n = 33)	t/χ^2 value	*P* value
Gender [n (%)]			0.934	0.334
Male	67 (54.9)	15 (45.5)		
Female	55 (45.1)	18 (54.5)		
Age ($\bar{x}$±s, months)	33.65 ± 14.43	24.21 ± 10.54	-4.189	<0.001
Weight ($\bar{x}$±s, kg)	11.90 ± 5.22	12.59 ± 6.04	0.597	0.553
Pneumonia course ($\bar{x}$±s, d)	3.21 ± 1.11	4.82 ± 1.16	7.129	<0.001
Feeding history [n (%)]			1.439	0.230
Breast feeding	51 (41.8)	10 (30.3)		
Artificial feeding	71 (58.2)	23 (69.7)		
Parental education [n (%)]			2.574	0.109
Junior high school and below	34 (27.9)	14 (42.4)		
High school/secondary school and above	88 (72.1)	19 (57.6)		
Pregnancy cycle [n (%)]			15.316	<0.001
Full term	89 (73.0)	12 (36.4)		
Preterm brith	33 (27.0)	21 (63.6)		
Mode of delivery [n (%)]			0.022	0.881
Natural childbirth	72 (59.0)	19 (57.6)		
Cesarean section	50 (41.0)	14 (42.4)		

Table 2. Comparison of laboratory test data between the two groups

Norm	Survival group (n = 122)	Death group (n = 33)	t value	*P* value
PCT ($\bar{x}$±s, μg/L)	1.73 ± 0.76	2.64 ± 0.68	6.635	<0.001
NEUR ($\bar{x}$±s, %)	67.39 ± 18.11	70.11 ± 16.15	0.836	0.407
PLTC ($\bar{x}$±s, 10^9/L)	287.87 ± 59.54	275.26 ± 43.00	-1.367	0.176
WBC ($\bar{x}$±s, 10^9/L)	10.15 ± 3.76	12.06 ± 2.30	3.645	<0.001
CRP ($\bar{x}$±s, mg/L)	9.42 ± 2.39	11.19 ± 2.43	3.719	<0.001
SII ($\bar{x}$±s)	467.52 ± 46.90	563.57 ± 69.89	7.454	<0.001

PCT, procalcitonin; NEUR, neutrophil ratio; PLTC, platelet count; WBC, white blood cell count; CRP, C-reactive protein; SII, systemic immunoinflammatory index.

ease, congenital heart disease, or immune dysfunction; (4) Presence of infectious diseases.

Observation of clinical and laboratory indicators

General data collection: Electronic medical records of the selected children were retrieved from the hospital's pathology management system, including information on gender, age, weight, course of pneumonia before hospital admission, feeding history, parental education, pregnancy cycle, and mode of delivery.

Laboratory indicator testing: (1) Blood collection and analysis: A 4 ml sample of morning fasting venous blood was collected from each child on the day of hospital admission. Blood samples were placed in test tubes containing anticoagulants to prevent clotting. A routine blood analysis was performed using an automated hematology analyzer in the clinical laboratory. The following parameters were recorded: neutrophil percentage (NEUR), platelet count (PLTC), WBC, and CRP levels. The SII was calculated using the following formula:

$$SII = \frac{platelet\ count \times Neutrophil\ count}{Lymphocyte\ count}$$

(2) Serum collection and analysis: Venous blood samples were collected from children with SP.

Table 3. Univariate Cox regression analysis of factors affecting the prognosis of children

Factor	β value	S.E.	*P* value	HR value	95% CI
Gender	-0.340	0.350	0.331	0.712	0.359-1.412
Age	-0.045	0.013	0.001	0.956	0.931-0.981
Weight	0.019	0.032	0.550	1.020	0.957-1.087
Pneumonia course	1.024	0.158	<0.001	2.783	2.042-3.793
Feeding history	-0.466	0.379	0.219	0.628	0.299-1.319
Parental education	0.574	0.352	0.103	1.775	0.890-3.541
Pregnancy cycle	-1.389	0.362	<0.001	0.249	0.094-0.418
Mode of delivery	-0.079	0.352	0.822	0.924	0.463-1.842
PCT	1.270	0.212	<0.001	3.559	2.347-5.398
NEUR	0.006	0.010	0.513	1.006	0.987-1.026
PLCT	-0.003	0.003	0.270	0.997	0.991-1.003
WBC	0.131	0.049	0.007	1.140	1.036-1.254
CRP	0.294	0.081	<0.001	1.342	1.146-1.573
SII	0.016	0.002	<0.001	1.016	1.012-1.020

PCT, procalcitonin; NEUR, neutrophil ratio; PLTC, platelet count; WBC, white blood cell count; CRP, C-reactive protein; SII, systemic immune-inflammation index.

Table 4. Multivariate Cox regression analysis of factors affecting the prognosis of children

Factor	beta value	S.E.	*P* value	HR value	95% CI
Age	-0.056	0.016	0.001	0.945	0.915-0.976
Pneumonia course	0.734	0.160	<0.001	2.083	1.522-2.850
Pregnancy cycle	-0.868	0.417	0.037	0.420	0.185-0.950
PCT	0.815	0.294	0.006	2.259	1.268-4.024
WBC	0.319	0.080	<0.001	1.376	1.176-1.611
CRP	0.084	0.080	0.294	1.088	0.930-1.273
SII	0.010	0.002	<0.001	1.010	1.005-1.014

PCT, procalcitonin; WBC, white blood cell count; CRP, C-reactive protein; SII, systemic immune-inflammation.

Table 5. ROC curve analysis of independent prognostic factors

Marker	AUC	Cut-off	Sensitivity	Specificity	Youden index
Age	0.693	34.5	87.88%	49.18%	37.06%
Pneumonia course	0.827	4.5	57.58%	90.98%	48.56%
Pregnancy cycle	0.683	-	63.64%	72.95%	36.59%
PCT	0.822	2.335	72.73%	81.15%	53.87%
WBC	0.679	9.855	84.85%	48.36%	33.21%
SII	0.868	530.86	66.67%	90.16%	56.83%

PCT, procalcitonin; WBC, white blood cell count; SII, systemic immune-inflammation.

The samples were centrifuged using a centrifuge at 3000 r/min, for 10 min with an 8 cm rotor radius. The supernatant was then collected for further analysis. The PCT levels in the serum were detected using an enzyme-linked immunosorbent assay (ELISA) kit purchased from Shanghai Enzyme Link Biotechnology Co. Ltd. The manufacturer's instructions were strictly followed.

Statistical analysis

Data were analyzed using GraphPad Prism 7 software. Measurement data conforming to normal distribution were expressed as mean ± standard deviation ($\overline{x}\pm s$), and the independent samples t-test was used for comparison between groups. Count data were expressed as number of cases and percentage [n (%)], and χ^2

Table 6. Delong-test for independent prognostic factors

Marker1	Marker2	AUC difference	*P* value
Age	Pneumonia course	-0.134	0.033
Age	PCT	-0.129	0.030
Age	WBC	0.014	0.847
Age	SII	-0.175	0.005
Age	Pregnancy cycle	0.010	0.876
Pneumonia course	PCT	0.005	0.926
Pneumonia course	WBC	0.148	0.021
Pneumonia course	SII	-0.041	0.473
Pneumonia course	Pregnancy cycle	0.144	0.025
PCT	WBC	0.143	0.032
PCT	SII	-0.046	0.386
PCT	Pregnancy cycle	0.139	0.008
WBC	SII	-0.189	0.003
WBC	Pregnancy cycle	-0.004	0.957
SII	Pregnancy cycle	0.185	0.003

PCT, procalcitonin; WBC, white blood cell count; SII, systemic immune-inflammation.

test was used for comparison between groups. Factors influencing the survival of children with SP after BAL were analyzed by Cox regression modeling. Receiver operating characteristic (ROC) curves were used to assess the predictive efficacy of independent prognostic factors, and comparisons between curves were made using the Delong-test. Kaplan-Meier survival curves were generated to analyze the relationship between each index and the prognosis of children with SP. Differences were considered statistically significant at P<0.05.

Results

Comparison of baseline information

Baseline data of the two groups revealed no statistical differences in terms of gender, weight, feeding history, parental education level, or mode of delivery (P>0.05). However, the mean age of the death group (24.21 ± 10.54 months) was significantly lower than that of the survival group (33.65 ± 14.43 months), and the pneumonia course (4.82 ± 1.16 days) was longer than that of the survival group (3.21 ± 1.11 days) (P<0.05). In addition, the proportion of preterm births was significantly higher in the death group than in the survival group (P<0.05) (**Table 1**).

Comparison of laboratory data

There were no statistically significant differences in NEUR and PLTC between the two groups (P>0.05). However, the levels of PCT, WBC, CPR, and SII were significantly higher in the death group compared to the survival group: PCT (2.64 ± 0.68 μg/L vs. 1.73 ± 0.76 μg/L), WBC (12.06 ± 2.30 10^9/L vs. 10.15 ± 3.76 10^9/L), CRP (11.19 ± 2.43 mg/L vs. 9.42 ± 2.39 mg/L), and SII (563.57 ± 69.89 vs. 467.52 ± 46.90) (P<0.05) (**Table 2**).

Cox regression analysis

The survival status of SP children receiving BAL treatment under fiberoptic bronchoscopy was used as the dependent variable (0 = death, 1 = survival). Independent variables included gender, age, weight, pneumonia course, PCT, WBC, and other indicators. A Cox regression model was employed to analyze the statistical correlation between each independent variable and the survival status of the children.

Univariate Cox regression analysis

Univariate Cox regression analysis revealed that age (HR = 0.956, P = 0.001), pneumonia course (HR = 2.783, P<0.001), pregnancy cycle (HR = 2.249, P<0.001), PCT (HR = 3.559, P<0.001), WBC (HR = 1.140, P<0.001), CRP (HR = 1.342, P<0.001), and SII (HR = 1.016, P<0.001) were significantly associated with the survival of children with SP (**Table 3**).

Multivariate Cox regression analysis

Multivariate Cox regression analysis, including variables with P<0.05 from the univariate analysis, identified age (HR = 0.945, P = 0.001), pneumonia course (HR = 2.083, P<0.001), pregnancy cycle (HR = 0.420, P = 0.037), PCT (HR = 2.259, P = 0.006), WBC (HR = 1.376, P<0.001), and SII (HR = 1.010, P<0.001) as independent factors affecting the prognosis of children with SP after BAL (**Table 4**).

The value of independent prognostic factors in assessing the prognosis

The ROC graph was created with the 28-day survival status of children with SP used as the dependent variable (death = 0, survival = 1) and the independent prognostic factor as the test variable. The results showed that the AUC

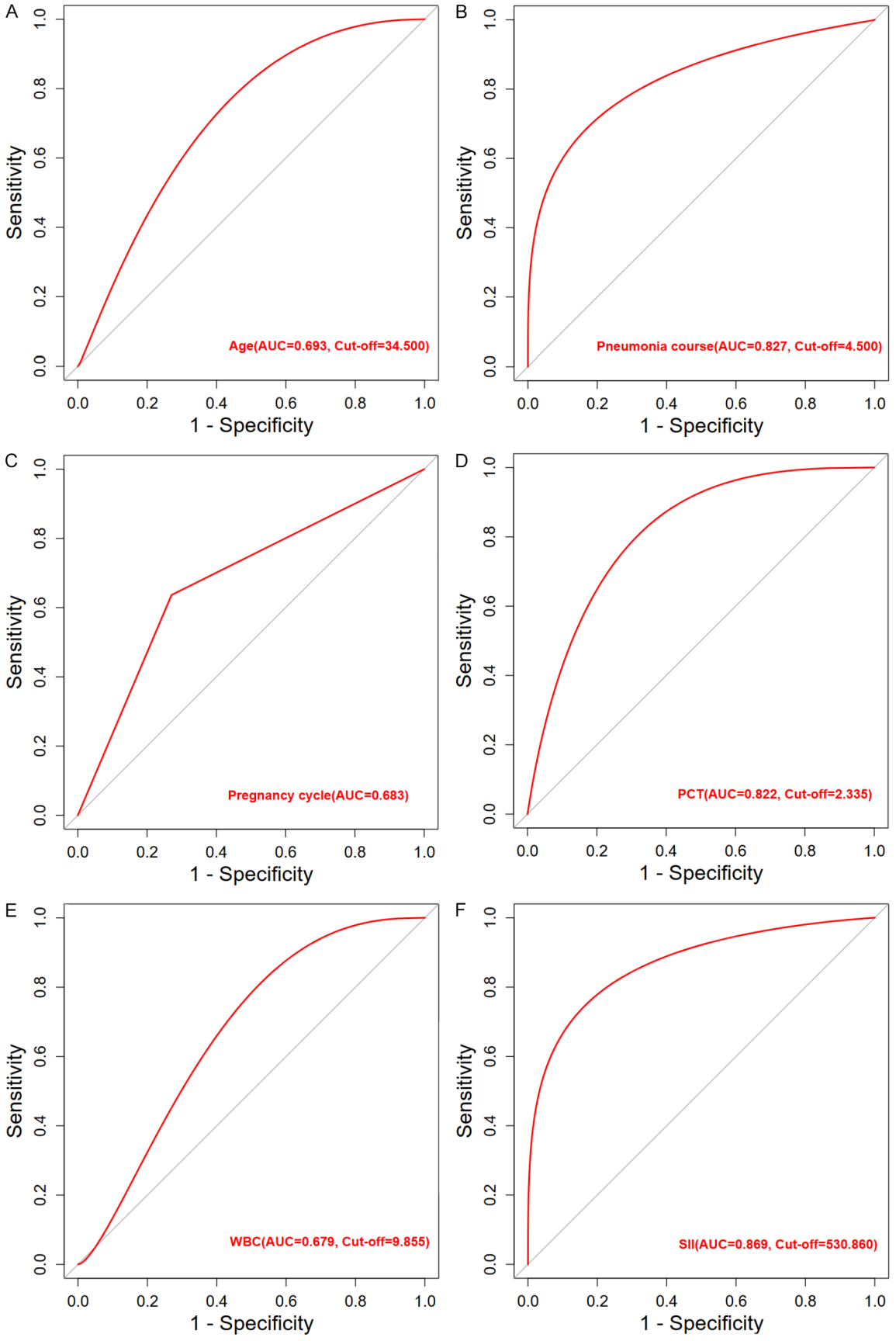
A
Sensitivity
1 - Specificity
Age(AUC=0.693, Cut-off=34.500)
B
Sensitivity
1 - Specificity
Pneumonia course(AUC=0.827, Cut-off=4.500)
C
Sensitivity
1 - Specificity
Pregnancy cycle(AUC=0.683)
D
Sensitivity
1 - Specificity
PCT(AUC=0.822, Cut-off=2.335)
E
Sensitivity
1 - Specificity
WBC(AUC=0.679, Cut-off=9.855)
F
Sensitivity
1 - Specificity
SII(AUC=0.869, Cut-off=530.860)

Figure 1. The ROC curves for independent prognostic factors. A: Age; B: Pneumonia course; C: Pregnancy cycle; D: Procalcitonin (PCT); E: White blood cell count (WBC); F: Systemic immune-inflammation index (SII).

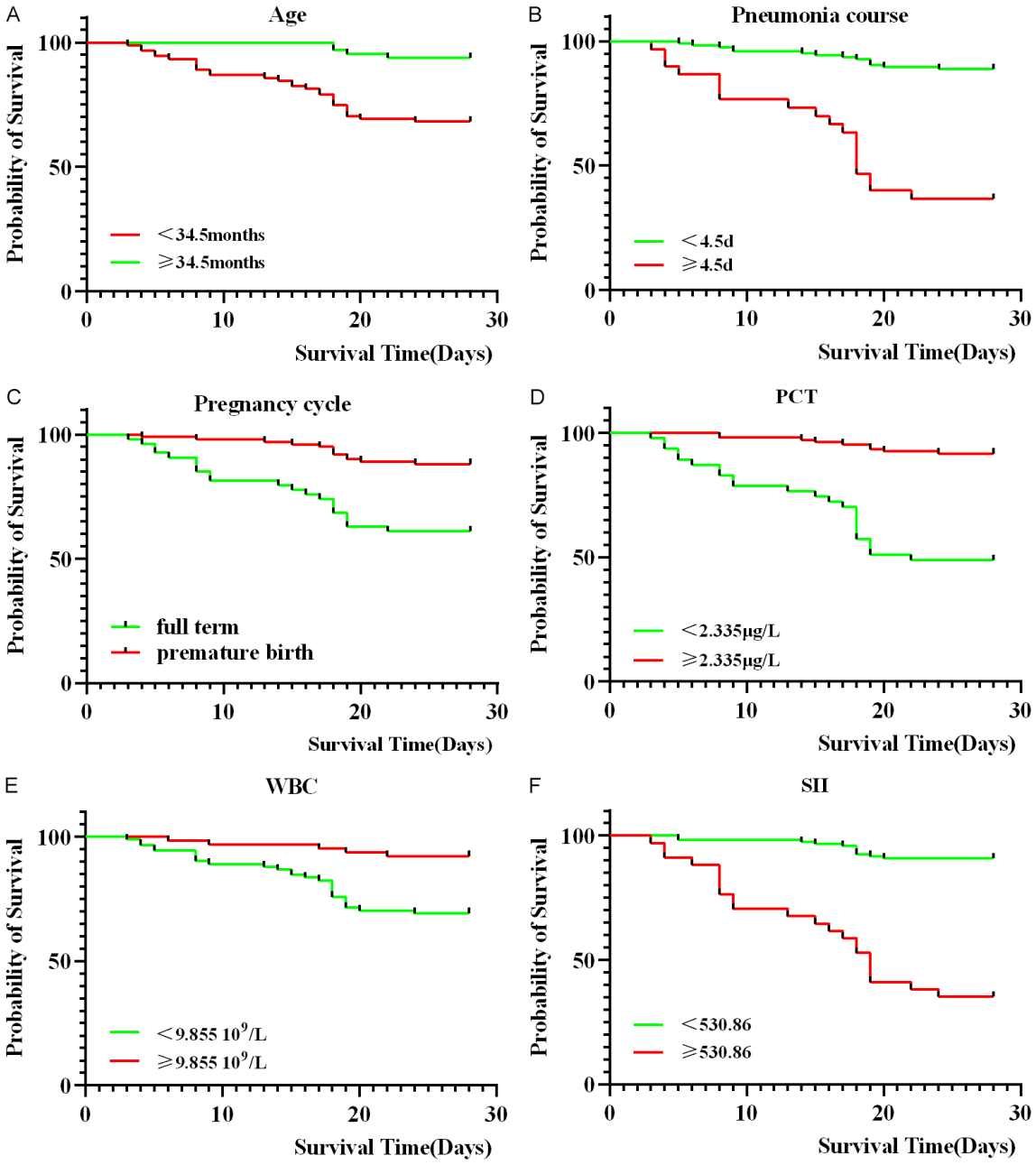

Figure 2. Kaplan-Meier survival curves for 28-day mortality in children with SP. Cut-off values for each factor were calculated using X-tile software. A: Age cut-off value was 34.5 months; B: Pneumonia course cut-off value was 4.5 d; C: Pregnancy cycle, which was categorized into full-term and preterm birth; D: Calcitoninogen (PCT) had a cut-off value of 2.335 μg/L; E: White blood cell count (WBC) cut-off value was 9.855 10^9/L; F: Cut-off value of systemic immune-inflammation index (SII) was 530.86.

values for pneumonia course (AUC = 0.827), PCT (AUC = 0.822), and SII (AUC = 0.868) demonstrated high diagnostic efficacy, outperforming age (AUC = 0.693), pregnancy cycle (AUC = 0.683), and WBC (AUC = 0.679) ($P<0.05$). The AUC differences between age, pregnancy cycle, and WBC were not statistically significant ($P>0.05$) (**Tables 5**, **6**; **Figure 1**).

28-day survival analysis

Kaplan-Meier survival curve analysis showed that children with SP younger than 34.5 months had a higher mortality rate compared to those older than 34.5 months. Similarly, children with a pneumonia course ≥4.5 days, preterm birth, PCT≥2.335 μg/L, WBC≥9.855 10^9/L, and SII≥ 530.86 had higher mortality rates compared to children with values below these thresholds (**Figure 2**).

Discussion

SP is an acute and fatal respiratory disease characterized by rapid onset, swift progression, and an extremely high mortality rate. Common symptoms include fever, cough, and dyspnea, with severe cases potentially leading to respiratory failure [22-24]. SP primarily affects the elderly, children, and individuals with compromised immune systems. Preterm newborns and infants are especially susceptible due to underdeveloped immune systems and incomplete lung maturation [2, 25-27]. SP-related infections may lead to airway tissue edema and increased secretions, causing obstruction and potentially triggering vegetative nervous system imbalances that lead to the contraction of bronchial smooth muscle, further exacerbating the obstruction [28]. As the obstruction worsens, complications such as emphysema or atelectasis may arise, often indicating a more severe condition with a poor prognosis [29]. BAL, performed via fiberoptic bronchoscopy, is a novel technique to control SP and collect pathogen information. It involves the infusion of saline into the alveoli, followed by repeated flushing and suctioning to collect the instilled fluid [30, 31]. Studies have shown that early BAL can effectively reduce hospital stays and mitigate disease progression [9]. BAL also enables direct drug delivery to lung lesions, making it a favorable option due to its non-invasive nature and safety. However, its therapeutic efficacy varies in children with SP, particularly in cases with rapid progression and high mortality. This variability underscores the importance of early prediction of disease progression and prognosis, as well as timely intervention to improve clinical outcomes. This study aimed to investigate the factors influencing the prognosis of children with SP undergoing fiberoptic bronchoscopy BAL, with the expectation of providing a reference for clinicians.

Our findings revealed statistically significant differences in age, pneumonia course, pregnancy cycle, PCT, WBC, CRP, and SII between survivors and non-survivors ($P<0.05$). The death group was younger, had a shorter pregnancy cycle and longer pneumonia course, and showed higher PCT, WBC, CRP, and SII levels compared to the survival group. Further Cox regression analysis confirmed that age, pneumonia course, pregnancy cycle, PCT, WBC, and SII were independent factors affecting the survival outcome of the children. The vulnerability of preterm infants and younger children to SP likely stems from their immature immune systems and underdeveloped lungs. Moreover, some studies suggest that early hospital visits for SP children are crucial, especially in preterm infants and younger children, where close monitoring of disease progression is imperative [32, 33]. The onset of SP is often accompanied by a persistent inflammatory response, marked by increased neutrophil counts and significantly higher serum CRP levels due to the body's immune defenses against microbial infections [34, 35]. PCT, mainly secreted by thyroid cells, is also produced by the kidneys, lungs, and liver during SP, resulting in a significant increase in serum concentrations [36]. SII, an index derived from PLT, neutrophils, and lymphocytes, reflects cell ratio imbalance and the balance between pro- and anti-inflammatory responses. Higher SII scores indicate a stronger inflammatory response or a weakened immune response [16]. It has been shown that serum levels of CRP and PCT are significantly elevated in children with SP, supporting their use as an inflammatory indicator for diagnosing SP in children [37]. This is similar to the results of our study.

Our ROC curve analysis identified age ≥34.5 months, pneumonia course ≥4.5 days, PCT≥ 2.335 μg/L, WBC≥9.855 10^9/L, SII≥530.86, and preterm birth as optimal cut-off values for predicting mortality in SP children within 28 days of fiberoptic bronchoscopy BAL treatment. The corresponding AUC values were 0.693, 0.827, 0.822, 0.679, 0.868, and 0.683, respectively. Of these, pneumonia course, PCT, and SII demonstrated good value in predicting treatment outcomes for children with SP. A study by Guozhu Sun [38] reported an AUC of 0.811 in predicting mortality in patients with severe bacterial pneumonia. Linwei Li [39] found the AUC of SII in diagnosing SP severity to be 0.813, with an optimal cut-off value of 823.41, higher

than the value observed in our study, which also showed a high predictive value. The above studies corroborate the results of this study. Kaplan-Meier survival analysis revealed higher survival rates in the older age group, shorter pneumonia course group, full-term birth group, and groups with lower WBC, PCT, and SII levels compared to their counterparts. These results underscore the importance of early recognition of factors including age, pneumonia course, and preterm birth, alongside monitoring serum WBC, PCT, and SII levels in children with SP. When significant abnormal changes are detected, early intervention can improve the prognosis of patients.

Our study establishes that pneumonia course, PCT, and SII are strong prognostic indicators for children with SP treated with fiberoptic bronchoscopic BAL, providing crucial guidance for clinicians in the diagnosis and treatment of children with SP. However, this study has some limitations. The small sample size limits the generalizability of the results, and the retrospective design may introduce information bias. Additionally, the single-center nature of the study may affect the representativeness of the results. Although Cox regression models were used for multivariate analysis, prospective validation and further exploration of potential confounders are required. Future studies should expand the sample sizes and adopt multicenter designs to improve the generalizability and reliability of the findings. Meanwhile, assessing potential confounders could enable more precise treatment strategies and comprehensive evaluation of treatment outcomes.

In summary, age, pneumonia course, pregnancy cycle, PCT, WBC, and SII were independent prognostic factors for children with SP undergoing BAL. Among them, pneumonia course, PCT, and SII have high predictive value for clinical outcomes. This predictive capability facilitates the early implementation of preventive measures and improves treatment protocols, thereby providing an important reference for the clinical treatment of SP.

Disclosure of conflict of interest

None.

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