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ORIGINAL RESEARCH

Clinical Value of Coagulation Function Indicators in Children with Severe Pneumonia

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Objective: This study aimed to probe the changes in coagulation function-related indicators (prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer (D-D), and fibrinogen degradation product (FDP)) in severe pneumonia and their clinical significance.

Methods: The levels of coagulation function indicators of all the children were measured within 24 hours of admission. Pearson correlation analysis was utilized to analyze the correlation between PT, APTT, FIB, D-D, FDP and PCIS in children with severe pneumonia. The ROC curve was drawn to assess the power of PT, APTT, FIB, D-D and FDP in diagnosing severe pneumonia and predicting the prognosis of severe pneumonia. A logistic regression analysis was implemented to analyze the factors influencing the prognosis of children with severe pneumonia.

Results: PT, APTT, FIB, FDP, and D-D in the critically severe pneumonia and the extremely severe pneumonia groups were higher versus the common pneumonia group ($P < 0.05$). FDP and D-D levels in children with severe pneumonia were negatively correlated with PCIS. PT, APTT, FIB, FDP, and D-D of children in the poor prognosis group were higher compared with those in the good prognosis group ($P < 0.05$). Further logistic regression analysis unveiled that FDP and APTT were influential factors impacting the prognosis of severe pneumonia.

Conclusion: The levels of D-D, FDP, FIB, APTT, and PT in severe pneumonia are increased. Detecting the contents of coagulation function indicators can help clinical judgment of the changes in the condition of severe pneumonia and evaluate prognosis.

Keywords: severe pneumonia, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, fibrinogen degradation product, pediatric critical illness score

Introduction

Pneumonia is one of the most severe inflammatory diseases of the respiratory system.[1] Pneumonia continues to be a common infectious disease which often results in hospital admissions and is occasionally lethal.[2] Severe pneumonia is a widely-known disorder that intensive care physicians have to face.[3] Severe pneumonia is a prevalent acute respiratory disorder in children, with a rapid onset and violent onset, and it often impacts the whole body. In addition, typical clinical manifestations and signs often cannot be recognized clinically. Because of the short time for treatment, it is easy to lead to improper diagnosis and treatment, worsen the disease condition, and even threaten the life of children.[4] Pediatric pneumonia is the main reason for childhood infection requiring hospitalization.[5] Even now, pneumonia still occupies a prominent place in clinical medicine and public health.[1] Therefore, it is important to discover new biomarkers that can help clinicians make correct diagnosis of severe pneumonia at an early stage and timely detect changes in disease severity, which can improve the survival rate and reduce the incidence of sequelae in children with severe pneumonia.

Systemic coagulation pathways possess the potential to affect pulmonary function since the lungs are a high-vascular organ, and in addition to the exchange of gas, they also function in filtering the venous blood, thereby avoiding thrombotic micro-emboli from entering the arterial circulation.[6] The activation of the coagulation system occurs in response to a pro-inflammatory state that is triggered by endotoxin and other inflammation mediators.[7] Systemically,

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coagulation system activation may result in disseminated intravascular coagulation in severe pneumonia with laboratory results of elevated coagulation activation markers and reduced natural anticoagulant defence.[8] A previous study has also demonstrated that there are notable differences in coagulation function between acute respiratory distress syndrome patients triggered by pulmonary infection.[9] Coagulation indices such as prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer (D-D), platelets and fibrinogen degradation product (FDP) are often adopted to probe the differences in coagulation in patients with acute respiratory distress syndrome due to pulmonary infections and their correlation with prognosis.[10] In addition, prolonged clotting times such as APTT and prothrombin time are common in patients infected with severe fever with thrombocytopenia syndrome virus, and previous studies have confirmed that this is associated with poor patient prognosis.[11] In addition to this, it has been shown that pediatric critical illness score (PCIS) can effectively reflect the clinical characteristics of children with severe mycoplasma pneumoniae pneumonia.[12] The PSCI score consists of 10 items, including heart rate, pH, blood sodium, blood potassium, blood pressure, hemoglobin, respiratory rate, urea nitrogen, creatinine and oxygen saturation. Each item is worth 10 points and the total score is 100 points.[12] The PCIS was adopted as the basis for the grouping in this study, aiming to assess the condition and prognosis of children with severe pneumonia by comparing the coagulation-related indices between children with severe pneumonia and children with common pneumonia, children with severe pneumonia of different degrees of illness, and children with good and poor prognosis of pneumonia, so as to provide theoretical bases for early prediction of the severity of the condition of children with severe pneumonia. This study focused on children with severe pneumonia, a group with high morbidity and mortality in pediatrics, whose coagulation changes were crucial to the assessment of their condition and treatment selection. Moreover, this study not only analyzed the conventional coagulation indices (eg, PT, APTT, FIB, etc)., but also delved into the changes of plasma D-D and fibrinogen degradation product (FDP). These indicators perform an important role in reflecting the balance status of the coagulation and fibrinolytic systems. This indicates that our study is unique in exploring the clinical value of coagulation indices in children with severe pneumonia.

Materials and Methods

Ethics Statement

The study complied with the Declaration of Helsinki and got approval from the Medical Ethics Committee of the Anhui Children's Hospital, and the families of the children gave written informed consent.

Study Subjects

A total of 218 children with pneumonia admitted to the Anhui Children's Hospital around May 2020 to May 2023 were recruited for the study, of whom 98 with common pneumonia were recorded as the common pneumonia group, and 120 with severe pneumonia were recorded as the severe pneumonia group. On this basis, children in the severe pneumonia group were grouped into the critically severe pneumonia group (79 cases, 80 points $\geq$ PCIS $>$ 70) and the extremely severe pneumonia group (41 cases, PCIS $\leq$ 70 points) according to the PCIS.[13,14]

Inclusion and Exclusion Criteria

Inclusion criteria: ① children with pneumonia who were admitted to our hospital for more than 24 h and whose diagnostic criteria for pneumonia confirmed to the criteria of the pediatric textbook; ② children with complete medical records; ③ children with clinical manifestations such as fever, cough and wheezing, and examined with hypopnea, fine rales and wheezing sounds or with pneumonia imaging; ④ children aged $\leq$ 12 years. Exclusion criteria: ① patients treated with antibiotic, immunosuppressive or hormonal therapy prior to hospitalization; ② those combined with basic diseases of other systems (digestive, hematological, central nervous and cardiovascular systems); ③ those combined with malignancy, end-stage chronic disease, multiple infections or sepsis; ④ those combined with other lung diseases (history of lung surgery, pulmonary edema, or tuberculosis); ⑤ those with severe or common pneumonia complicated by the children's surgical diseases.

PCIS Score

The PSCI score consisted of 10 items of heart rate, pH, blood sodium, blood potassium, blood pressure, hemoglobin, respiratory rate, urea nitrogen, creatinine, and oxygen saturation, with 10 points for each item and a total score of 100. Children with a PCIS score of 71–80 were included in the critically severe pneumonia group, and those with a score ≤ 70 were included in the extremely severe pneumonia group.[12]

Detection of Coagulation Function-Related Indicators

Fasting venous blood was taken from all children within 24 h of admission, and the blood samples were immediately sent to our laboratory and biochemistry department for testing. Coagulation function-related indicators including PT, APTT, FIB, D-D and FDP were measured utilizing a fully automated coagulation analyzer (CS5100, SYSMEX, Japan).

Treatment and Prognosis

All cases in the severe pneumonia group were empirically selected second- to third-generation cephalosporins for anti-infection along with active symptomatic supportive therapy, which was mainly directed at the relevant complications that occurred in each case, such as respiratory failure, toxic encephalopathy, coagulation dysfunction, gastrointestinal dysfunction, acid-base imbalance and electrolyte disorders. The treatment also included mechanical ventilation, improvement of microcirculation, dehydration and lowering of cranial pressure, sedation, hemostasis, correction of acid-base imbalance and electrolyte disturbance. Within one month, the children were categorized as the good prognosis group if they had a reduction in the size of the imaging lesion, an improvement in cough and fever, an improvement in symptoms such as decreased respiratory sounds, fine moist rales, and wheezing compared with that on admission, or were discharged from the hospital after recovering from the disease, and with the disappearance of the relevant symptoms; children whose condition did not improve from the time of admission, whose condition worsened, whose symptoms worsened, or who died were classified as the poor prognosis group.[15]

Statistics

SPSS 21.0 software (SPSS Inc, Chicago, IL, USA) combined with GraphPad Prism 6.0 software (Graph Pad Inc., La Jolla, CA, USA) were utilized for statistical processing and analysis of the data in this paper. Different statistical analysis approaches were employed for measurement data with different distribution characteristics. Specifically, if measurement data obeyed normal distribution, they were expressed as mean ± standard deviation (mean ± SD), and the independent samples *t*-test was utilized for two-group comparisons; if they did not obey normal distribution, they were expressed as median (interquartile spacing) [M (Q1, Q3)], and the Wilcoxon rank sum test was conducted for two-group comparisons. Numeration data were expressed as the number of cases (percentage) [n (%)], and the χ^2 test was implemented for two-group comparisons. Pearson's test was applied for correlation analysis. Assessment value analysis was performed utilizing ROC curve analysis. A logistic regression model was implemented to analyze the risk factors impacting the prognosis of children with severe pneumonia. In terms of significance level, $P < 0.05$ was considered with a notable difference.

Results

Clinical Data of Study Subjects

The comparison of age and gender of the children in the common pneumonia group, critically severe pneumonia group and extremely severe pneumonia group showed no statistically significant difference ($P > 0.05$) and were comparable. The PCIS scores of children in the extremely severe pneumonia group were lower than those in the critically severe pneumonia group (Table 1).

Coagulation Function Indicators in Children with Pneumonia

The levels of PT, APTT, FIB, D-D and FDP in the serum of children with common pneumonia and children with severe pneumonia were examined, and the results unveiled that the levels of PT, APTT, FIB, FDP and D-D in the critical severe

Table 1 Clinical Data of Study Subjects

Indicators	The Common Pneumonia Group (n = 98)	The Critically Severe Pneumonia Group (n = 79)	The Extremely Severe Pneumonia Group (n = 41)	*P* value
Age (years)	5.26 ± 2.15	5.35 ± 2.13	5.20 ± 2.09	0.888
Gender [n(%)]				0.736
Male	53 (54.08)	43 (54.43)	25 (60.98)	
Female	45 (45.92)	36 (45.57)	16 (39.02)	
PCIS score (scores)	/	75.47 ± 1.76	65.20 ± 2.42	

pneumonia group and in the extremely severe pneumonia group were higher versus those in the common pneumonia group ($P < 0.05$). PT, FIB, FDP and D-D levels in the extremely severe pneumonia group were higher versus those in the critically severe pneumonia group ($P < 0.05$), while the difference in APTT level between the critically severe pneumonia group and extremely severe pneumonia group was statistically insignificant ($P > 0.05$) (Table 2).

Coagulation Function Indicators and Children's Disease Severity

To evaluate the significance of changes in the levels of coagulation function indicators in children with severe pneumonia, the correlation between PT, APTT, FIB, FDP, D-D levels and PCIS was analyzed. The results unraveled (Figure 1) that FDP ($r = -0.660$, $P < 0.001$), D-D ($r = -0.482$, $P < 0.001$) and FIB levels ($r = -0.184$, $P = 0.045$) in children with severe pneumonia were strongly and negatively correlated with PCIS. In contrast, PT ($r = -0.054$, $P = 0.557$) and APTT ($r = -0.093$, $P = 0.311$) levels were not significantly related to PCIS, suggesting that some of the coagulation function indicators can better reflect the severity of the children's disease.

Diagnostic Value of Coagulation Function Indicators in Children with Severe Pneumonia

ROC curve analysis disclosed that when testing each indicator, the area under the ROC curve (AUC) of FDP was the largest (ie, highest diagnostic efficacy), followed by D-D, FIB, PT, and APTT in that order. The AUC and 95% confidence interval (95% CI) of each indicator, the critical value at the maximum of the Jorden index, sensitivity and specificity were shown in Table 3. The AUCs of FDP and D-D were 0.976 and 0.948, respectively, with high diagnostic accuracy; the AUCs of PT and FIB were 0.838 and 0.880, respectively, with moderate diagnostic accuracy; the AUC of APTT was 0.675, with low diagnostic accuracy (Figure 2).

Coagulation Function Indicators in Children with Different Prognosis

The prognosis of the children was evaluated at 1 month and the children were allocated into the good prognosis group (82 cases) and the poor prognosis group (38 cases) following the evaluation results. The admission coagulation indicators of the two groups of children were compared and analyzed, and the findings unearthed that PT, APTT, FIB, FDP, and

Table 2 Coagulation Function-Related Indicators (Mean ± SD)

Indicators	The Common Pneumonia Group (n = 98)	The Critically Severe Pneumonia group (n = 79)	The Extremely Severe Pneumonia Group (n = 41)	*P* value
PT (s)	12.03 ± 2.21	14.59 ± 1.97#	15.69 ± 2.12#*	< 0.001
APTT (s)	32.43 ± 7.05	35.98 ± 5.34#	37.26 ± 6.89#	< 0.001
FIB (g/L)	3.47 ± 0.92	4.72 ± 0.76#	5.32 ± 0.83#*	< 0.001
D-D (mg/L)	3.23 ± 1.27	6.24 ± 1.67#	9.30 ± 2.20#*	< 0.001
FDP (mg/L)	0.51 ± 0.17	1.57 ± 0.55#	3.44 ± 1.23#*	< 0.001

Note: #*P* < 0.0 5 vs the common pneumonia group, **P* < 0.0 5 vs the critically severe pneumonia group.

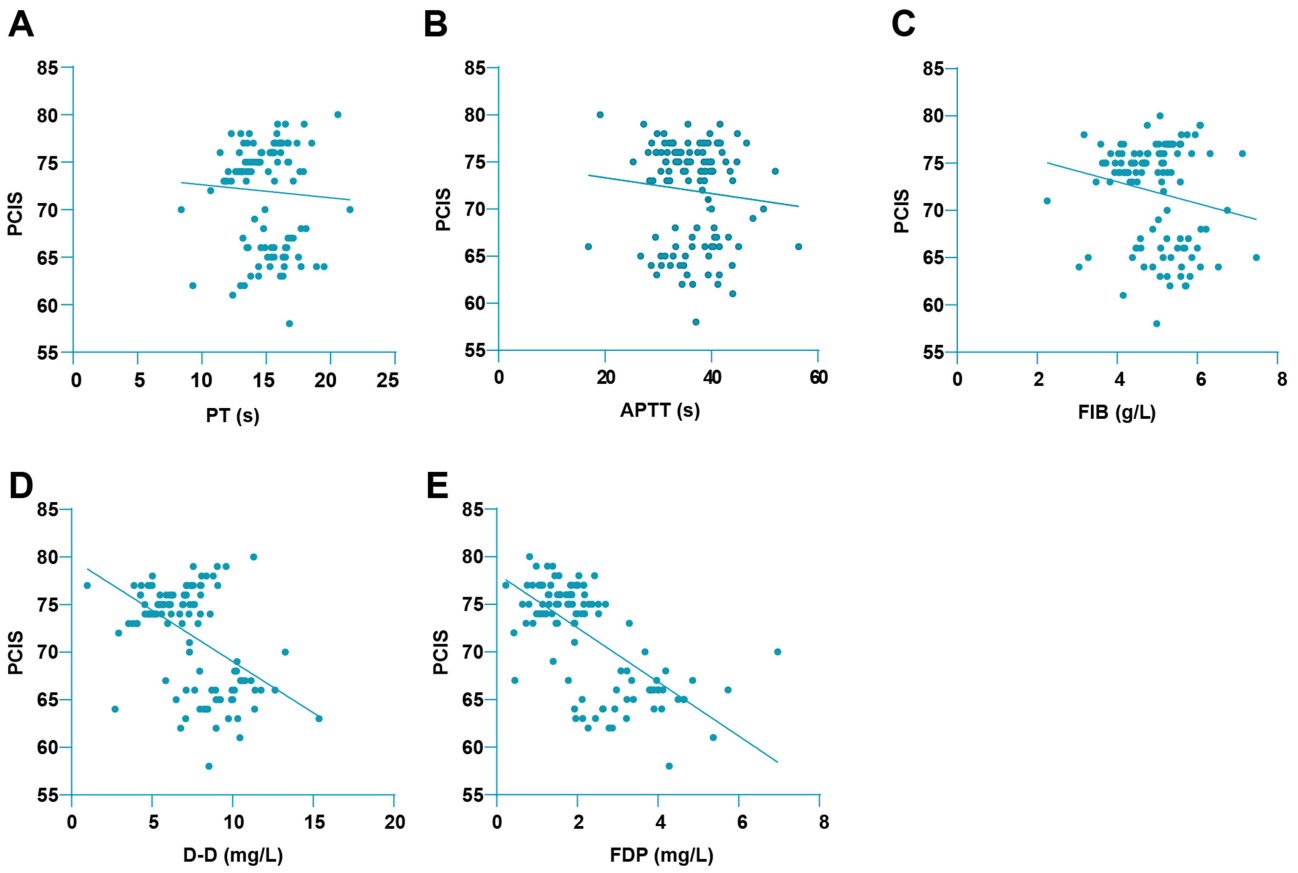

Figure 1 Correlation analysis between coagulation function indicators and children's disease severity. (**A**): The correlation between PT and PCIS was analyzed by Pearson analysis; (**B**): The correlation between APTT and PCIS was analyzed by Pearson analysis; (**C**): The correlation between FIB and PCIS was analyzed by Pearson analysis; (**D**): The correlation between D-D and PCIS was analyzed by Pearson analysis; (**E**): The correlation between FDP and PCIS was analyzed by Pearson analysis.

D-D in the poor prognosis group were higher versus those in the good prognosis group ($P < 0.05$), which suggested that coagulation function indicators had a correlation with the prognosis of children with severe pneumonia (Table 4).

Predictive Value of Coagulation Function Indicators on the Prognosis of Children with Severe Pneumonia

ROC curve analysis revealed that the AUC of FDP was the largest (ie, the highest predictive efficacy) when testing each indicator, followed by FIB, PT, D-D, and APTT in descending order. The AUC and 95% CI for each indicator, the critical value at the maximum of the Jorden index, sensitivity, and specificity were displayed in Table 5. The AUC of FDP was 0.689, with high diagnostic accuracy; the AUCs of PT, APTT, FIB, and D-D were 0.594, 0.646, 0.654, and 0.591, respectively, with lower diagnostic accuracy, as shown in Figure 3, suggesting that coagulation function indicators possessed some predictive value for the prognosis of children with severe pneumonia.

Table 3 Diagnostic Characteristics of Each Indicator for Children with Severe Pneumonia

Indicators	AUC	95% CI	The Critical Value	Sensitivity (%)	Specificity (%)
PT	0.838	0.786~0.891	13.61 s	72.50	78.57
APTT	0.675	0.603~0.747	29.55 s	90.83	37.76
FIB	0.880	0.832~0.928	3.80 g/L	92.50	76.53
D-D	0.948	0.920~0.977	4.81 mg/L	87.50	92.86
FDP	0.976	0.953~0.999	0.79 mg/L	95.00	95.92

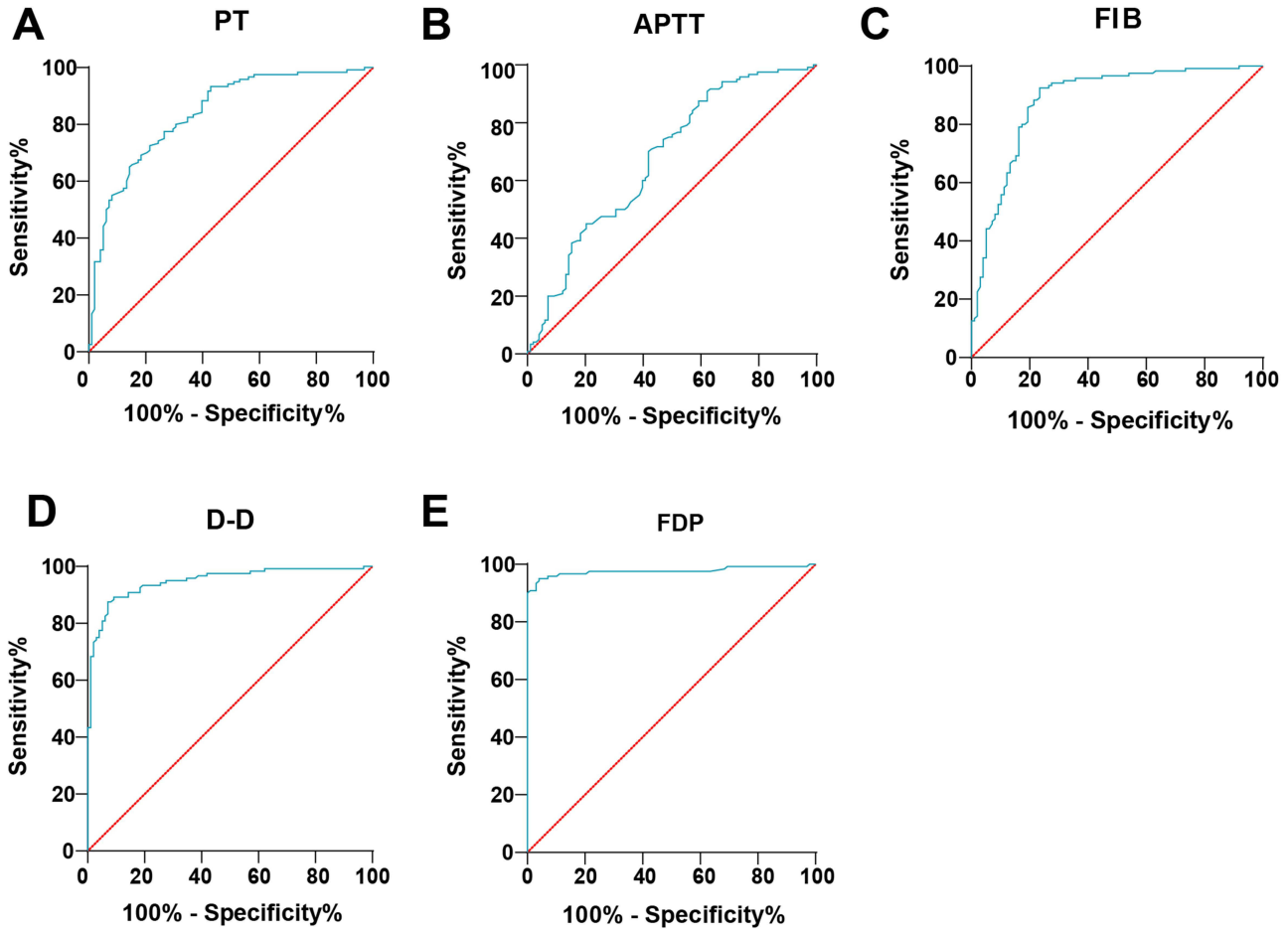

Figure 2 ROC curves of children with severe pneumonia detected by coagulation function indicators. (**A**): Value of PT detection of severe pneumonia was analyzed by ROC curve; (**B**): Value of APTT detection of severe pneumonia was analyzed by ROC curve; (**C**): Value of FIB detection of severe pneumonia was analyzed by ROC curve; (**D**): Value of D-D detection of severe pneumonia was analyzed by ROC curve; (**E**): Value of FDP detection of severe pneumonia was analyzed by ROC curve.

A Logistic Regression Analysis to Determine Independent Prognostic Factors in Children with Severe Pneumonia

To study the factors that influence the prognosis of children with severe pneumonia, these children were allocated into the good prognosis group and the poor prognosis group. Coagulation function indicators PT, APTT, FIB, D-D, and FDP were included for a logistic regression analysis, and the results demonstrated that FIB, FDP and APTT were influential factors affecting the prognosis of children with severe pneumonia ($P < 0.05$, Table 6).

Table 4 Coagulation Function-Related Indicators in Children with Severe Pneumonia with Different Prognosis (Mean ± SD)

Indicators	The Good Prognosis Group (n = 82)	The Poor Prognosis Group (n = 38)	*P* value
PT (s)	14.79 ± 2.02	15.34 ± 2.18	0.045
APTT (s)	35.63 ± 5.27	38.12 ± 6.88	0.031
FIB (g/L)	4.82 ± 0.89	5.20 ± 0.70	0.020
D-D (mg/L)	7.05 ± 2.09	7.79 ± 2.83	0.036
FDP (mg/L)	1.92 ± 0.97	2.83 ± 1.48	< 0.001

Table 5 Predictive Characteristics of Each Indicator for Poor Prognosis in Children with Severe Pneumonia

Indicators	AUC	95% CI	The Critical Value	Sensitivity (%)	Specificity (%)
PT	0.594	0.485~0.702	14.57 s	71.10	50.00
APTT	0.646	0.533~0.759	35.80 s	76.32	58.54
FIB	0.654	0.552~0.756	4.98 g/L	78.95	58.54
D-D	0.591	0.473~0.709	9.99 mg/L	31.60	92.70
FDP	0.689	0.576~0.802	2.83 mg/L	55.26	89.02

Discussion

Pneumonia is a chief reason for morbidity and mortality in children, and the characterization of pathogens that trigger infections are vital for accurate treatment and quick recovery.[16] Recently, attention has shifted to coagulation activation, and the systemic overspill and disturbed coagulation response after infection might be responsible for the pathogenesis of organ dysfunction.[17] Coagulation disorders are common in the pathology of children with severe pneumonia. Therefore, it is of great clinical value to investigate whether coagulation indicators can effectively and accurately assess the condition, severity and prognosis of children with severe pneumonia. This study focused on the changes in coagulation

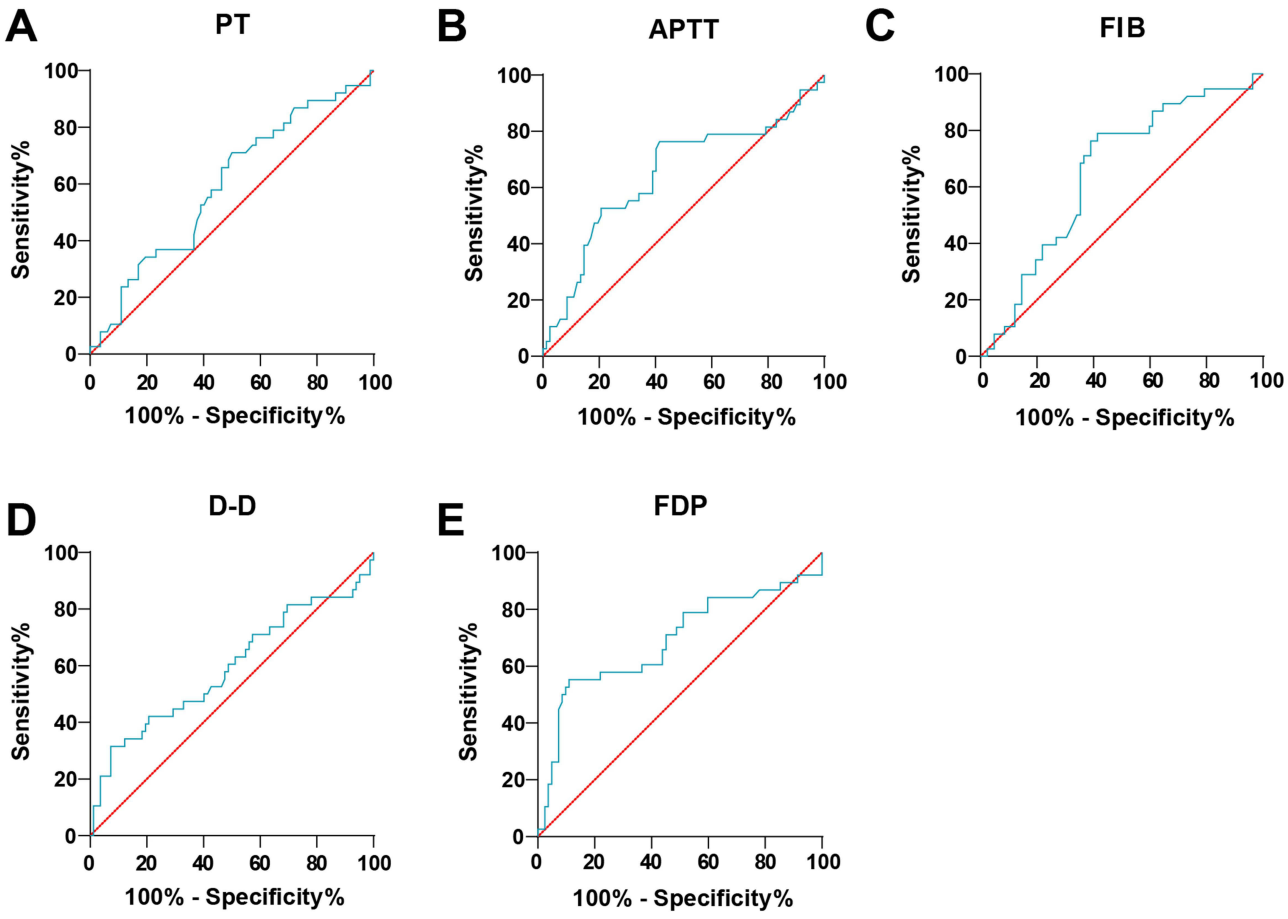

Figure 3 ROC curve of prognosis of children with severe pneumonia detected by coagulation function indicators. (**A**): The predictive value of PT on the prognosis of children with severe pneumonia was analyzed by ROC curve; (**B**): The predictive value of APTT on the prognosis of children with severe pneumonia was analyzed by ROC curve; (**C**): The predictive value of FIB on the prognosis of children with severe pneumonia was analyzed by ROC curve; (**D**): The predictive value of D-D on the prognosis of children with severe pneumonia was analyzed by ROC curve; (**E**): The predictive value of FDP on the prognosis of children with severe pneumonia was analyzed by ROC curve.

Table 6 Logistic Regression Analysis to Determine Independent Prognostic Factors in Children with Severe Pneumonia

Indicators	B	SE	Wald	*P*	OR	95% CI	
						Lower Limit	Upper Limit
PT	0.067	0.117	0.324	0.569	1.069	0.850	1.344
APTT	0.080	0.039	4.151	0.042	1.084	1.003	1.1717
FIB	0.623	0.301	4.277	0.039	1.865	1.033	3.368
D-D	−0.168	0.123	1.845	0.174	0.846	0.664	1.077
FDP	0.735	0.229	10.275	0.001	2.086	1.331	3.269

function-related indicators (PT, APTT, FIB, D-D, and FDP) in children with severe pneumonia and their clinical significance.

A study has shown that elevated D-D is positively correlated with disease severity, and patients with a prolonged PT have an increased risk of admission to the intensive care unit and an increased risk of death, while an increased FDP and an antithrombin decrease may also indicate deterioration.[18] In clinical work, PT, APTT, FIB, FDP, and D-D are commonly used indicators to evaluate the coagulation function of patients. PT can represent the most commonly utilized coagulation test in clinical laboratories.[19] In a previous study, it is also observed that FIB and D-D levels change most significantly in patients with mycoplasma pneumoniae.[20] D-D is a soluble fibrin degradation product and it functions as a valuable marker of coagulation and fibrinolysis activation.[21] The produced plasmin solubilizes the cross-linked fibrin polymers, thereby forming FDPs such as D-D, which is broadly utilized as a specific parameter for thrombosis together with physiological fibrinolysis.[22] FIB can be utilized as a cofactor of platelet aggregation, which elevates to varying degrees in multiple diseases.[23] It is reported that when the body is severely infected, the patients present blood coagulation dysfunction, and relevant coagulation indicators such as FIB may suggest pneumonia.[24] The chief mechanisms (pathways) that trigger coagulation consist of intrinsic and extrinsic pathways, and APTT and PT tests mainly measure the activity of coagulation proteins involved in both pathways, respectively.[25]

Our study revealed that PT, APTT, FIB, FDP and D-D were higher in the critically severe pneumonia and extremely severe pneumonia groups than in the common pneumonia group, while PT, FIB, FDP, D-D were higher in the extremely severe pneumonia group versus in the critically severe pneumonia group, and that FDP, D-D and FIB were negatively correlated with PCIS score in children with severe pneumonia. We also disclosed that FDP had the highest diagnostic efficacy in the analysis of the diagnostic value of coagulation function indices for severe pneumonia in children, followed by D-D, FIB, PT and APTT. Secondly, we observed that PT, APTT, FIB, FDP, and D-D were higher in the poor prognosis group than in the good prognosis group, and that FDP had the highest predictive efficacy in the analysis of the predictive value of coagulation function indices for severe pneumonia in children, followed by FIB, PT, D-D, and APTT. Those meant that the prolongation of PT, as an index reflecting the function of the exogenous coagulation system, is one of the most important manifestations of coagulation dysfunction, which indicates an increase in the risk of hemorrhage; APTT, as an indicator reflecting the function of endogenous coagulation system, the prolongation of APTT likewise predicts coagulation dysfunction and an increased risk of bleeding, which predicts a poor prognosis; FIB is involved in the conversion of prothrombin to thrombin, and high FIB level may lead to hypercoagulability of the blood, which is easy to form thrombus and indicates a poor prognosis; D-D, with low specificity but high sensitivity, is an important indicator for assessing activation of coagulation and fibrinolytic system, and its elevated level may manifest the presence of thrombosis or hyperfibrinolytic risk, which is of great significance in determining the prognosis of coagulation dysfunction; elevated FDP level usually reflects the activation state of fibrinolytic system in the body, which also indicates the existence of fibrinolytic activity or thrombosis in the body, which is of great value in evaluating the severity of coagulation dysfunction and its prognosis. Under normal conditions, the coagulation and fibrinolytic systems maintain a dynamic balance to maintain normal blood flow and hemostasis. However, in severe pneumonia, due to the inflammatory response and endothelial cell damage, the coagulation system is over-activated while the fibrinolytic system is relatively insufficient or inhibited, resulting in an imbalance between the coagulation and fibrinolytic systems.

This imbalance can trigger extensive microthrombosis, which further aggravates tissue and organ damage and dysfunction, and may lead to sepsis and disseminated intravascular coagulation. In summary, we also found that the three items of FIB, FDP, and APTT are independent influencing factors that affect the prognosis of children with severe pneumonia.

Therefore, detecting the levels of coagulation function indices can help clinically determine the changes in the condition of severe pneumonia and assess the prognosis, and this paper lays the foundation for studying the changes in coagulation function-related indices and their clinical significance in patients with severe pneumonia. However, due to the limitations of this study, we did not include healthy children as a normal control group for comparison, and we did not explore the diagnostic value of the combination of indicators on severe pneumonia. In addition, we did not analyze the children's body temperature, leukocytes, or biochemical indicators, which is our shortcoming, and we will carry out more in-depth studies in the future, if the conditions allow us to do so.

Conclusion

To sum up, this study unveils that the coagulation indices (D-D, FDP, FIB, APTT and PT) of children with severe pneumonia have an important early predictive value in severe pneumonia children, and by dynamically monitoring the trend of these indices and combining them with other clinical information, the severity of the disease and the prognosis of the children can be evaluated.

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Disclosure

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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