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***Case Control Study***

**Nested case-control study of the relationship between multiple serological index, Brighton pediatric early warming score and death of children with sepsis**

Xie X *et al*. Relationship between PEWS and children with sepsis

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**Abstract**

***BACKGROUND***

Currently, it is difficult to predict the complications of children at the early stage of sepsis. Brighton pediatric early warning score (PEWS) is simple and easy to operate disease risk assessment system, which has good sensitivity and specificity in children's disease recognition. Because children's detection indicators vary widely, a single indicator is difficult to assess the post-treatment status of children with sepsis.

***AIM***

To investigate the relationship between serological markers, Brighton PEWS and death in children with sepsis after treatment.

***METHODS***

A total of 205 children diagnosed with sepsis in our hospital were enrolled. The baseline data, serum scores and PEWS scores were recorded. In the nested case-control study, children who died during the study period were included in the observation group. According to the matching principle, the children who had not died in the same cohort were included in the control group. The influencing factors of death in children with sepsis after treatment and the value of each evaluation index predicting the prognosis of children were analyzed.

***RESULTS***

A total of 96 children were enrolled in the study, including 48 in the observation group and the control group. Multivariate logistic regression analysis indicated that antibacterial treatments within 1 h (*P* = 0.017), shock (*P* = 0.044), number of multiple organ dysfunction syndrome (MODS) (*P* = 0.027), serum procalcitonin (PCT) (*P* = 0.047), serum albumin (ALB) (*P* = 0.024) and PEWS (*P* = 0.012) were the independent factors for the death of children with sepsis. The area under curve of the combination of ALB, PCT, and PEWS to predict the death in children with sepsis was the highest (0.908).

***CONCLUSION***

The antibacterial treatments within 1 h, shock, MODS, PCT, ALB and PEWS are independent risk factors for the death of children with sepsis. The prediction accuracy of the combination of PCT, ALB and PEWS for the prognosis of children with sepsis is the best.

**Key words:** Serological indicators; Pediatric early warming score; Sepsis; Nested case-control study; Systemic inflammatory reaction syndrome

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**Core tip:** Currently, it is difficult to predict the complications of children at the early stage of sepsis. Brighton pediatric early warning score (PEWS) is simple and easy to operate disease risk assessment system, which has good sensitivity and specificity in children's disease recognition. In this study, the nested case-control study found that the use of antimicrobial agents within 1 h, shock, multiple organ dysfunction syndrome number, serum procalcitonin (PCT), serum albumin (ALB) and PEWS were independent risk factors for death of children with sepsis. The combination of ALB, PCT and PEWS can predict the prognosis of children with sepsis with good accuracy and can improve the sensitivity of prediction.

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**INTRODUCTION**

Sepsis is a complicated systemic inflammatory reaction syndrome. It is also the main cause of death in children's intensive care unit. Sepsis can be caused by a variety of pathogenic bacteria and can cause severe complications such as shock and multiple organ dysfunction syndrome (MODS), resulting in higher mortality in children[1-4]. Some non-specific inflammatory markers such as serum procalcitonin (PCT), C-reactive protein (CRP) and serum albumin (ALB) have certain value in the evaluation of post-treatment complications in children with sepsis, but they are inaccurate. Currently, it is difficult to make more accurate predictions of complications in children with sepsis at an early stage[5-7]. Therefore, the assessment of death in children with sepsis is still a difficult problem to be solved clinically. Brighton pediatric early warning score (Brighton PEWS) is a simple and easy-to-use disease risk assessment system based on adult early warning scores[8,9]. It has good sensitivity and specificity in children's condition recognition. Because children's detection indicators vary widely, a single indicator is difficult to assess the post-treatment status of children with sepsis. Therefore, the present study intended to assess the value of serological markers combined with Brighton PEWS in predicting the prognosis of children with sepsis utilizing nested case-control study.

**MATERIALS AND METHODS**

***Research object***

A total of 205 children with sepsis/severe sepsis were enrolled as the study subjects (sepsis: *n* = 135, severe sepsis: *n* = 70). They were all diagnosed in Gezhouba Group Central Hospital from October 2015 to December 2017. Among them, 143 were male and 62 were female. They were aged from 6 mo to 9 years and the average age was (5.5 ± 3.3) years. The diagnostic criteria of sepsis /severe sepsis in children was based on the definition of 2005 international pediatric sepsis[10]. Inclusion criteria and exclusion criteria were shown as Table 1. All patients and their families signed informed consent and the study was approved by the Ethics Committee of Gezhouba Group Central Hospital.

***Treatment***

After admission, the children began to accept broad-spectrum antibiotic treatment and retained bacterial culture. The central venous catheter was left in place and fluid was given early to prevent shock. Mechanical ventilation of endotracheal intubation was given when severe sepsis occurs. Once hypotension or lactic acidosis was detected, give fluid resuscitation. It made the central venous pressure reached 8 to 10 mmHg within 6 h before resuscitation, the mean arterial pressure > 65 mmHg, the urine volume ≥ 0.5 mL/kg per hour and the central venous mixed oxygen saturation ≥ 70%. Vasopressors or inotropes may be used when volume expansion was poorly treated, such as dopamine.

***Grouping***

This study began with patients admitted to hospital for sepsis/severe sepsis and ended with their death or discharge. The nested case-control study was used to define the child who died during the study period as the observation group. In addition, whenever a child died in the cohort, one child with similar or identical conditions such as age, sex, and infection site was enrolled as the control group by 1:1 matching in the cohort (Figure 1)[11].

***Research methods***

**Blood sample collection****:** At 8 to 12 h after admission, 3 tubes of fasting venous blood were taken from the subjects in the early morning using vacuum blood collection tube. There was 3 mL blood in each tube. One of the tubes was centrifuged (3000 r/min) for 10 min to obtain the supernatant, which was frozen in a refrigerator at -20°C.

**Indicators determination:** White blood cell (WBC), platelet (PLT) and hemoglobin (Hb) counts were measured using a XE-2100 automatic hematology analyzer. PCT was measured by a Roche E170 Electrochemiluminometer and supporting PCT kit. CRP was measured by rate scattering turbidimetric method using the IMMAGE800 Automated Immunoassay Analyzer (Beckman, USA). ALB was measured using BECK MAN LX20 automatic biochemical analyzer. The hemoglobin scavenger receptor (sCD163) was measured by enzyme-linked immunosorbent assay. The kit was supplied by THERMO of Finland and the instrument was a DENLEY DRAGON Wellscan MK3 microplate reader. The serum D-dimer (DD) used a fully automated coagulation analyzer. The kits and associated control products were manufactured by SIEMENS. The serum lactic acid value (Lac) was measured using a Hitachi 7600-120 fully automated biochemical analyzer. The reagent was provided by Beijing Lederman Biochemical Co., Ltd. Creatinine (Cr) was measured using a Bio-Rad automatic biochemical analyzer.

**Scoring criteria:** Brighton PEWS was divided by indicators as: consciousness, cardiovascular system and respiratory system. The higher the score indicated the heavier the condition, as shown in Table 2.

***Data collection***

Baseline data of the two groups were collected and the treatment status of the children was recorded, including the number of antibacterial treatments within 1 h, duration of mechanical ventilation, and duration of vasoactive drug maintenance. The patient's complications were recorded, including acute respiratory distress syndrome (ARDS), number of organs affected by dysfunction, and shock. Laboratory diagnostic indicators and PEWS scores were recorded for both groups.

***Statistical analysis***

Statistical analysis was performed using SPSS 19.0 software. The measurement data was expressed by mean ± SD, and the count data was used as a number of cases (percentage). The *t* test was used to compare the measurement data between the two groups. The comparison of the count data was performed by the χ2 test. Conditional logistic regression was used to further screen out the independent influencing factors of the death of children. A receiver operating characteristic (ROC) curve was established to analyze the ability of potential indicators to assess death in children with sepsis. The difference was considered statistically significant at *P* < 0.05.

**RESULTS**

***Patient baseline data***

According to the nested case-control study design, a total of 48 children died during the study period, with a total case fatality rate of 23.4%. They were defined as the observation group. A total of 48 children with similar conditions were recruited as the control group. Among the 96 children with sepsis, 64 were male and 32 were female, aged 9 mo to 5 years, with an average age of (2.5 ± 1.8) years. The underlying diseases in the 96 patients included: 65 cases of blood system diseases (67.7%), 19 cases of congenital heart disease (19.8%), 7 cases of nephrotic syndrome (7.3%), and 5 cases of neuromuscular diseases (5.2%). The location of the primary infection included: 54 cases of pulmonary infection (56.3%), 28 cases of digestive system infection (29.2%), and 14 cases of blood system infection (14.5%).

***Comparison between two groups of patients***

There was no significant difference between the observation group and the control group in the baseline data, primary infection site, underlying disease, duration of vasoactive drug maintenance, ARDS, WBC, Hb, CRP, and Cr (*P* > 0.05). The duration of mechanical ventilation, shock, MODS, PCT, sCD163, DD, Lac, and PEWS in the observation group was higher than those in the control group. The number of antibacterial treatments within 1 h, PLT and ALB were lower than those in the control group. The differences were statistically significant (*P* <0.05) (Table 3).

***Multivariate logistic regression analysis of death after treatment in children with sepsis***

Further multivariate logistic regression analysis showed that antibacterial treatments within 1 h (*P* = 0.017), shock (*P* = 0.044), number of MODS (*P* = 0.027), PCT (*P* = 0.047), ALB (*P* = 0.024) and PEWS (*P* = 0.012) were independent influencing factors for the death of children with sepsis (Table 4).

***Analysis of the value of PCT, ALB and PEWS in evaluating the outcome of children with sepsis***

The ROC curve was used to further analyze the predictive value of PCT, ALB and PEWS for the death of children with sepsis, as shown in Figure 2. The area under curve (AUC) of ALB was 0.761, and the best diagnostic point was 35.20 g/L. The sensitivity was 57.45%, and the specificity was 85.11%. The AUC of PCT was 0.730, and the best diagnostic point was 59.65 μg/L. The sensitivity was 53.20%, and the specificity was 85.10%. The AUC of PEWS was 0.771, and the best diagnosis point was 6.5 points. The sensitivity was 74.50%, and the specificity was 68.10%. The AUC of the combination of ALB, PCT, and PEWS predicting the death in children with sepsis was 0.908. The sensitivity was 87.23%, and the specificity was 85.11%.

**DISCUSSION**

Sepsis is an inflammatory reaction caused by infection. The infection were mainly caused by bacteria in the clinic[12]. Early detection, diagnosis and treatment have significant effects on post-treatment complications in children[13,14]. In the early stage of the disease, the clinical manifestation of the child lacks specificity. However, once the inflammatory cascade reaction is triggered, the condition of child will decrease sharply. Even if the treatment is delayed for several hours, the mortality rate of children will be significantly increased[15]. Therefore, early accurate assessment of the prognosis of children with sepsis is the most effective way to improve the complications in children with sepsis. However, there is no specific laboratory test to predict the prognosis of children with sepsis. In addition, some clinical symptoms of children with sepsis are often similar to other diseases, which increase the misdiagnosis rate of sepsis undoubtedly. Current researches show that PLT, CRP, PCT, ALB, sCD163 and PEWS can be used to assess the recovery of children with sepsis after treatment[16-18]. However, throughout the disease cycle, children's indicators vary widely by individual and environmental influences. Current assessment methods are not sufficient to accurately assess the degree of recovery after treatment in children with sepsis. In order to find a more accurate method of assessing the prognosis of children with sepsis, a nested case-control study is conducted to evaluate serologic markers in combination with PEWS in predicting death in children with sepsis.

 Epidemiological data from the United States showed that the mortality rate of children with sepsis was 10.3%. The mortality rate of children with underlying diseases increased to 12.8%. In the present study, 48 of 205 children died and the mortality rate was 23.4%, which was relatively high. The potential reason might be related to the late diagnosis. As the clinical symptoms of sepsis were mainly fever, the disease was difficult to identify early so that it was easy to misdiagnose and mistreatment. Because the clinical symptoms of sepsis are mainly caused by fever, it is difficult to pay attention to the early stage of the disease. Hence sepsis in children is easy to be misdiagnosed or mistreated.

 The sepsis in children develops rapidly after infection occurs because children have weaker immune systems. Studies have revealed that immediate antibacterial treatment within 1 hour could clear the lesion promptly, which preventing further deterioration[19]. According to the pathogenesis of sepsis, sepsis is most often associated with insufficient tissue perfusion pressure and tissue hypoxia[20]. Therefore correcting shock and appropriate ventilation should also be paid attention to in the early treatment. When the infection control of children with sepsis is not ideal or the condition deteriorates, it often appears as shock and MODS[21]. It often indicates poor prognosis of sepsis, especially when the number of MODS organs increasing. Serological indicators can objectively indicate changes in the sepsis condition and provide a direct basis for assessing the outcome of the disease after treatment. For example, CRP and PCT are clinically widely used indicators of inflammation[22,23]. They have a high specificity in the diagnosis of the degree of inflammatory[24]. In addition, blood system disease is the most common underlying disease in children with sepsis. Therefore, the degree of thrombocytopenia and changes in DD can reflect the disorders of the blood system and abnormal coagulation function, suggesting the regression of the disease[25].

Based on the analysis of existing studies on the death of children with sepsis, this study analyzed WBC, PLT, Hb, CRP, PCT, ALB, sCD163, DD, Lar, Cr and PEWS between two groups and performed a multivariate logistic regression analysis for screen the impact factors of the prognosis of sepsis. It is shown that the antibacterial treatments within 1 h, shock, MODS, PCT, ALB and PEWS were independent influencing factors of death in children. The reason why PEWS is an independent factor in the death of children may be because the scoring system is easy to operate and can monitor children's condition continuously and dynamically without using special equipment[26]. PEWS is not affected by age. It is suitable for general wards. It can identify children who need intervention in the early stage, and there is good repeatability between different operators. Studies have shown that it has a sensitivity of 70% and a specificity of 90% in critically ill children who need to be transferred to the ICU for emergency care[27].

This allows the doctor's assessment of the child's condition more objective and accurate, and avoids empirical subjective judgment. Therefore, early PEWS scores on admission to children can achieve early intervention, thereby improving the complications of death in children. PCT is a calcitonin precursor protein secreted by thyroid C cells[28]. Inflammatory mediators such as bacterial endotoxin and interleukin can stimulate the secretion of PCT by neuroendocrine cells of liver, kidney and spleen. When the level is raised, the degree of inflammatory reaction of the body can be more accurately indicated. During the process of sepsis, capillary vascular endothelial cells are destroyed due to the release of a large number of inflammatory factors in the blood, resulting in increased capillary permeability of the whole body, and hypoproteinemia caused by leakage of intravascular albumin. Hypoproteinemia can cause a decrease in plasma osmotic pressure, a reduction in effective circulating blood volume, and multiple organ dysfunction[29]. Therefore, a decrease in ALB levels can indirectly indicate the extent of inflammatory infections[30].

Because the children's detection indicators vary widely, the child compensation mechanism is more complicated than adults, which will affect the accuracy of PCT, ALB and PEWS predicting the prognosis of children[31]. Therefore, the accuracy of the single indicator predicting the death of children with sepsis is poor, and the AUC is lower. The results of this study showed that AUC was the largest when PCT and ALB were combined with PEWS, and the sensitivity was significantly higher compared to the single indicator. Therefore, the combined diagnosis of the three indicators can reduce the impact of differences in organization and body compensation and improve the accuracy.

In summary, the present study used nested case-control studies to find that the antibacterial treatments within 1 h, shock, MODS, PCT, ALB, and PEWS were independent risk factors for death in children with sepsis. The combined prediction of PCT, ALB, and PEWS in the prognosis of children with sepsis is better than the single detection indicator.

**ARTICLE HIGHLIGHTS**

***Research background***

Sepsis is an inflammatory reaction caused by infection, and the microorganisms that cause infection are mainly bacteria. In the early stage of the disease, the clinical manifestations of the child lack specificity. However, once the inflammatory reaction is stimulated, even if the treatment is delayed several hours, the mortality of the child can be significantly increased. Therefore, accurate early assessment of the prognosis of children with sepsis is the most effective way to improve the complications of children with sepsis.

***Research motivation***

There are currently no specific laboratory tests or markers that can early predict the prognosis of children with sepsis. Moreover, some clinical symptoms of children with sepsis are often similar to those of other diseases, which increase the difficulty in diagnosing sepsis. Currently, studies have shown that platelet, C-reactive protein, serum procalcitonin (PCT), serum albumin (ALB), hemoglobin scavenger receptor, pediatric early warning score (PEWS) can assess the recovery of children with sepsis after treatment, but the children's various indicators are affected by individual and environmental changes. Therefore, the clinic needs a method to make a more accurate prediction of the complications of children with sepsis at an early stage.

***Research objectives***

The present study intended to utilize nested case-control studies to assess the value of serum markers in combination with Brighton PEWS in predicting the prognosis of children with sepsis, in order to explore whether it is a more accurate means of assessing the prognosis of children with sepsis or not.

***Research methods***

A total of 205 children diagnosed with sepsis were enrolled. After admission, the patient began broad-spectrum antibiotic treatment and retained bacterial culture. The central venous catheter was indwelled and early rehydration was given to prevent shock. In the nested case-control study, patients who died during the study cohort were included in the study group, and children who had not died in the same cohort were defined as the control group. Baseline data, serological markers, and PEWS scores were recorded for the subjects. Conditional logistic regression was used to analyze the influencing factors of death in children with sepsis after treatment. Receiver operating characteristic (ROC) curve was established to evaluate the value of the indicator to predict the prognosis of the children.

***Research results***

There were 48 children in the experimental group and the control group. Multivariate logistic regression analysis indicated that antibacterial treatments within 1 h, shock, multiple organ dysfunction syndromes (MODS), PCT, ALB and PEWS were independent influencing factors of death in children. ROC curve analysis found that the area under curve of the combination of ALB, PCT, and PEWS predicting the death in children with sepsis was the highest, and the sensitivity was significantly higher than that of the three individuals. Therefore, the combined diagnosis of the three indicators can reduce the impact of differences in organizational and physical compensation on the assessment results and improve the accuracy.

***Research conclusions***

The present study found that antibacterial treatments within 1 h, shock, MODS, PCT, ALB and PEWS were independent risk factors for the death of children with sepsis. The combined prediction of PCT, ALB and PEWS for the prognosis of children with sepsis can improve the accuracy of the prediction.

***Research perspectives***

The results of the study need further evaluation because the sample size is limited. However, the results suggest that PEWS score combined with serological indicators can improve the accuracy of the prediction in the prognosis of children with sepsis, which provide useful information for the treatment of children with sepsis.

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**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 The inclusion criteria and exclusion criteria of enrolled 205 children with sepsis/severe sepsis**

|  |  |
| --- | --- |
| **Inclusion criteria** | **Exclusion criteria** |
| Data completed within 24 h after admission | Previously diagnosed with tumor disease |
| Age > 28 d | Previously diagnosed with autoimmune disease |

**Table 2 Brighton pediatric early warming score scoring criteria**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Project** | **0 Points** | **1 Points** | **2 Points** | **3 Points** |
| Consciousness | Normal | Somnolence | Irritability | Lethargy/coma |
| Reduced pain response |
| Cardiovascular System | Pink skin | Pale skin | Gray skin | Cold skin, Clammy skin |
| CRT 1-2 s | CRT 3 s | CRT 4 s | CRT ≥ 5 s |
|  |  | Heart rate increased 20 times/min | Heart rate increased 20 times/min or bradycardia than normal |
| Respiratory system | Normal | Normal respiratory frequency | Normal respiratory frequency | Normal respiratory frequency |
| Air-free depression | Increased 10 times /min, FiO2 0.3 or oxygen inhalation flow 4 L/min | Increased /min 20 times, inspiratory depression, FiO2 0.4 or oxygen inhalation flow 4 L/min | Reduced 5 times /min, with sternal inspiratory depression, moaning, FiO2 0.5 or oxygen inhalation flow 8 L/min |

CRT: Cardiac resynchronization therapy.

**Table 3 Comparison between the observation group and control group at the time of admission *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Control group (*n*= 48)** | **Observation group (*n* = 48)** | ***t/χ2*** | ***P value*** |
| Baseline data |
| Age (yr) | 2.48 ± 1.71 | 2.51 ± 1.79 | 0.084 | 0.933 |
| Gender (male/female) | 32/16 | 32/16 | 0.000 | 1.000 |
| Temperature (℃) | 37.58 ± 1.03 | 38.26 ± 1.45 | 1.597 | 0.114 |
| Weight (kg) | 15.24 ± 2.68 | 14.39±1.47 | 1.927 | 0.057 |
| Primary infection site |
| Pulmonary infection | 28 (58.3) | 31 (64.6) | 0.396 | 0.529 |
| Digestive system infections | 17 (35.4) | 16 (33.3) | 0.046 | 0.830 |
| Blood system infection | 10 (20.8) | 7 (14.6) | 0.643 | 0.423 |
| Basic disease |
| Blood system diseases | 33 (70.2) | 32 (66.7) | 0.048 | 0.827 |
| Congenital heart disease | 11 (22.9) | 8 (16.7) | 0.591 | 0.442 |
| Treatment measures |
| Antibacterial treatments within 1 h | 40 (83.3) | 33 (68.8) | 2.802 | 0.094 |
| Duration of mechanical ventilation (h) | 83.41 ± 35.17 | 144.36 ± 52.55 | 6.678 | 0.000 |
| Duration of vasoactive drug maintenance (h) | 74.02 ± 31.90 | 78.16 ± 42.56 | 0.539 | 0.591 |
| Complication |
| ARDS | 13 (27.1) | 15 (31.3) | 0.202 | 0.653 |
| Shock | 21 (43.8) | 35 (72.9) | 8.400 | 0.004 |
| Number of MODS | 1.76 ± 0.78 | 3.42 ± 1.51 | 6.767 | 0.000 |
| Laboratory examination |
| WBC (×109/L) | 13.96 ± 2.85 | 12.74 ± 3.21 | 1.969 | 0.052 |
| PLT (×109/L) | 107.38 ± 33.70 | 85.26 ± 45.35 | 2.712 | 0.008 |
| Hb (g/L) | 105.03±20.25 | 104.42 ± 22.19 | 0.141 | 0.888 |
| PCT (ng/mL) | 7.48 ± 4.51 | 19.97 ± 6.38 | 11.177 | 0.000 |
| CRP (ng/mL) | 115.67 ± 66.23 | 135.14 ± 77.62 | 1.324 | 0.189 |
| ALB (g/L) | 40.11 ± 2.57 | 33.57 ± 4.97 | 8.098 | 0.000 |
| sCD163 (mg/L) | 165.31 ± 175.26 | 253.66 ± 216.81 | 2.196 | 0.031 |
| DD (μg/L) | 802.16 ± 269.08 | 1648.93 ± 502.55 | 10.282 | 0.000 |
| Lac (mmol/L) | 3.22 ± 2.13 | 7.69 ± 5.24 | 5.475 | 0.000 |
| Cr (μmol/L) | 452.56 ± 348.72 | 336.15 ± 356.80 | 1.617 | 0.109 |
| Children's score |
| PEWS | 5.35 ± 1.89 | 7.22 ± 1.43 | 5.467 | 0.000 |

ARDS: Acute respiratory distress syndrome; MODS: Multiple organ dysfunction syndrome; WBC: White blood cell; PLT: Platelet; Hb: Hemoglobin; PCT: Serum procalcitonin; CRP: C-reactive protein; ALB: Serum albumin; DD: D-dimer; Lac: serum lactic acid value; Cr: Creatinine; PEWS: Pediatric early warning score.

**Table 4 Multivariate logistic analysis of death in children with sepsis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Assignment** | ***P*** | **OR** | **95.0% CI** |
| Antibacterial treatments within 1 h | Yes = 0, No = 1 | 0.017 | 1.654 | 1.620-1.892 |
| Duration of mechanical ventilation | - | 0.182 | 1.679 | 0.848-2.675 |
| Shock | No = 0, Yes = 1 | 0.044 | 1.574 | 1.388-3.043 |
| Number of MODS | - | 0.027 | 2.101 | 1.615-2.013 |
| PLT (109/L) | - | 0.126 | 1.086 | 0.821-1.678 |
| PCT (ng/mL) | - | 0.047 | 1.283 | 1.434-1.792 |
| ALB (g/L) | - | 0.024 | 0.842 | 0.323-2.806 |
| sCD163 (mg/L) | - | 0.563 | 1.558 | 0.466-3.850 |
| DD (μg/L) | - | 0.180 | 1.149 | 0.709-1.251 |
| Lac (mmol/L) | - | 0.115 | 1.435 | 0.562-1.785 |
| PEWS | - | 0.012 | 2.476 | 1.153-2.617 |

MODS: Multiple organ dysfunction syndrome; PLT: Platelet; PCT: Serum procalcitonin; ALB: Serum albumin; DD: D-dimer; Lac: serum lactic acid value; PEWS: Pediatric early warning score.

Matched patients in the study cohort were defined as a control group

Comparative analysis between two groups

Determine children with sepsis as a study cohort

Following up treatment

Recording data on all subjects

Patients died during treatment were defined as an observation group

**Figure 1 Schematic diagram of the design principle of a nested case-control study.**



**Figure 2 Receiver operating characteristic curve analysis of serum albumin, serum procalcitonin, pediatric early warning score and their combination to assess death in children with sepsis.** ALB: Serum albumin; PCT: Serum procalcitonin; PEWS: Pediatric early warning score.