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Value of C-reactive protein/albumin ratio, pancreatic stone protein combined with interleukin-12 on prediction of offline extubation outcomes of patients with mechanical ventilation in severe pneumonia

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Abstract: Objective To explore the predictive value of the ratio of C-reactive protein to albumin (CRP/ALB), pancreatic stone protein (PSP), and interleukin-12 (IL-12) for the outcome of offline extubation in patients with mechanical ventilation in severe pneumonia. Aiming to guide clinical decision-making and enhance weaning success rates. **Methods** Ninety patients with severe pneumonia admitted to Yuebei People's Hospital from January 2021 to December 2023 were selected as the study subjects. According to the outcome of offline extubation, they were divided into failure group and success group. The general information, serum CRP/ALB, PSP, IL-12 levels on the day of admission and before discharge were compared between the two groups. Pearson correlation coefficients were used to analyze the correlation between serum indicators and clinical pulmonary infection score (CPIS) and acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ) scores. Logistic regression equations were used to analyze the impact of serum CRP/ALB, PSP, and IL-12 on the outcome of offline extubation from mechanical ventilation in severe pneumonia. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to analyze the predictive efficacy of serum indicators. **Results** (1) Compared with the success group, the CPIS, APACHE Ⅱ score and serum CRP/ALB, PSP, IL-12 levels on the day of admission and before spontaneous breathing trial (SBT) in the failure group were higher (P<0.01)。 (2) Serum CRP/ALB, PSP, IL-12, CPIS and APACHE Ⅱ scores before SBT were selected for follow-up study according to the recency effect. In patients with severe pneumonia who failed of offline extubation from mechanical ventilation, CPIS and APACHE Ⅱ scores before SBT were positively correlated with serum CRP/ALB, PSP, and IL-12 levels, respectively (P<0.05) . (3) After adjusting, CRP/ALB, PSP, and IL-12 before SBT were still associated with failed of offline extubation from mechanical ventilation in patients with severe pneumonia (P<0.05) . (4) The predictive efficacy of CRP/ALB+ PSP+IL-12 before SBT [AUC (95%*CI*): 0.936 (0.864-0.977)] for failed of offline extubation from mechanical ventilation in patients with severe pneumonia was significantly better than that of individual predictors [0.822 (0.727-0.895) , 0.749 (0.647-0.835) , 0.827 (0.733-0.899)] . **Conclusion** Serum CRP/ALB, PSP, and IL-12 are closely related to the failure of offline extubation in patients with severe pneumonia. The combined detection of these three markers has good predictive efficacy and is helpful in guiding clinical diagnosis and treatment.

Keywords: Severe pneumonia; Mechanical ventilation; Offline extubation; Pancreatic stone protein; Interleukin-12; C-reactive protein; Albumin

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Mechanical ventilation is an effective treatment for severe pneumonia, but prolonged therapy may lead to ventilator dependence, ventilator-associated pneumonia, and an increased risk of failed extubation [1-3]. Other scholars have found that premature extubation can lead to respiratory muscle fatigue, inadequate oxygen supply, and other issues, resulting in extubation failure and prolonged hospitalization [4]. Identifying potential biomarkers can help predict the outcome of extubation in severe pneumonia at an early stage, enabling the development of individualized treatment plans and accelerating recovery. Pancreatic stone protein (PSP) can regulate the expression of pro-inflammatory/anti-inflammatory factors and is involved in the development of pulmonary inflammatory lesions [5]. Interleukin-12 (IL-12), C-reactive protein to albumin ratio (CRP/ALB) are important pro-inflammatory cytokines, and evidence has confirmed their expression in inflammatory diseases such as severe pneumonia and asthma. However, the relationship between their changes and the outcome of extubation is unknown [6-7]. Current studies often assess the predictive value of biomarkers by measuring their expression at a single time point, but dynamic observation of biomarkers in patients receiving mechanical ventilation may have a lower margin of error and could provide better stability for predicting extubation, although clinical trials are lacking for validation. This study intends to dynamically monitor the levels of serum CRP/ALB, PSP, and IL-12, analyze their combined predictive value for the extubation

outcome of severe pneumonia patients, and explore their relationships with disease-related indicators to guide clinical decision-making and improve extubation success rates.

1. Objects and Methods

1.1 Study Subjects

A total of 90 patients with severe pneumonia admitted to the Affiliated Yuebei People's Hospital of Shantou University Medical College between January 2021 and December 2023 were selected as research subjects. All patients met the diagnostic criteria of the "Chinese Expert Consensus on the Clinical Practice of Severe Pneumonia" [8], and were indicated for mechanical ventilation with endotracheal intubation. The duration of mechanical ventilation exceeded 48 hours. Family members were informed and signed the consent form. Patients with other pulmonary diseases (e.g., tuberculosis, COPD, lung tumors, pulmonary edema), history of pulmonary surgery, severe psychiatric disorders, coagulation disorders, organic lesions of vital organs, or missing clinical data were excluded.

Among the subjects, 51 were male and 39 were female. The age range was 45–75 years, with a mean age of 66.42±4.33 years. Comorbidities included 24 cases of diabetes, 19 cases of hypertension, and 19 cases of hyperlipidemia. There were 25 cases with a smoking history and 20 cases with an alcohol history. This study was approved by the Ethics Committee of Northern Guangdong People's Hospital (Approval No: KY-2021-252).

1.2 Methods

1.2.1 Grouping Criteria

The extubation criteria were based on the "Clinical Guidelines for Mechanical Ventilation (2006)" [9], with the mandatory criteria being: (1) Arterial oxygen saturation ≥ 90%; (2) Hemodynamic stability without active myocardial ischemia. Additional criteria: (1) Tidal volume >5 mL/kg of spontaneous breathing, rapid shallow breathing index <105 f/(L • min), respiratory rate ≤35 breaths/min, inspiratory pressure ≤-20 to -25 cmH2O; (2) Core body temperature ≤38-38.5 ℃; (3) Hemoglobin ≥80-100 g/L; (4) Easily awakened, alert and conscious state; (5) Serum electrolytes within normal range. Successful extubation criteria: Successful spontaneous breathing trial (SBT) and extubation, with the patient being able to breathe independently for 48 hours without requiring reintubation.

Patients were divided into the success group (n=64) and failure group (n=26) according to the extubation outcome of severe pneumonia.

1.2.2 Observation Indicators and Detection Methods

On the day of admission and before the SBT, 3 mL of fasting venous blood was collected from the elbow vein, centrifuged at 2 500 rpm for 15 minutes with a centrifuge radius of 6 cm. The upper serum layer was separated and analyzed for IL-12, PSP levels using an enzyme-linked immunosorbent assay (ELISA, Wallace Biotech Co., Beijing), for albumin (ALB) using bromocresol green method (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.), and CRP using immune turbidimetry (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.). The CRP/ALB ratio was calculated.

1.2.3 Clinical Pulmonary Infection Score (CPIS) Criteria

CPIS [10] includes seven components: temperature, chest X-ray, oxygenation index, white blood cell count, etc. Each item is scored on a scale of 0–2, with a maximum score of 12. Higher scores indicate more severe illness.

1.2.4 Acute Physiology and Chronic Health Evaluation II (APACHE II) Criteria

The APACHE II score [11] encompasses three dimensions: acute physiology, age, and chronic health status, with a theoretical maximum score of 71. Higher scores are associated with worse prognosis.

1.3 Statistical Methods

SPSS 26.0 software was used to process the data, with normality and homogeneity of variance tests performed. For normally distributed continuous variables with equal variance, data were presented as $\bar{x}\pm s$, and inter-group comparisons were made using independent samples t-test. Count data were expressed as numbers, and chi-square tests were used for comparisons. Pearson correlation analysis was performed to determine relationships between variables. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were drawn to evaluate the predictive value. A significance level of α=0.05 was used.

2. Results

2.1 Comparison of General Data Between the Two Groups

The CPIS and APACHE II scores in the failure group were significantly higher than those in the success group (P<0.01). See Table 1.

Tab.1 Comparison of general data between the two groups

Item	Failure group (n=26)	Success group (n=64)	t/χ^2 value	P value
Male/Female (case)	15/11	36/28	1.44	0.23
Age (years, $\bar{x}\pm s$)	65.52±5.11	66.78±2.84	1.203	0.232
BMI (kg/m², $\bar{x}\pm s$)	22.24±1.23	22.05±1.30	0.638	0.525
Comorbidities (case)				
Hypertension	5	14	0.078	0.78
Diabetes	8	16	0.315	0.575
Hyperlipidemia	6	13	0.085	0.771
Smoking history (case)	8	17	0.163	0.686
Alcohol drinking history	6	14	0.016	0.901
CPIS score (point, $\bar{x}\pm s$)				
At admission	6.11±1.30	5.22±1.15	3.204	<0.001
Before SBT	5.43±0.45	4.12±0.41	13.356	<0.001
APACHEII score (point, $\bar{x}\pm s$)				
At admission	18.17±2.33	16.34±1.28	4.775	<0.001
Before SBT	12.68±1.56	10.01±1.02	9.58	<0.001

2.2 Comparison of Serum CRP/ALB, PSP, and IL-12 Levels Between the Two Groups

On the day of admission and before the SBT, the serum levels of CRP/ALB, PSP, and IL-12 in the failure group were significantly higher than those in the success group (P<0.01). **See Table 2.**

2.3 Correlation of Serum Indicators with CPIS and APACHE II Scores

Based on recent effects, pre-SBT serum CRP/ALB, PSP, IL-12, CPIS, and APACHE II scores were selected for subsequent analysis. Pearson correlation analysis showed that in patients with extubation failure, the CPIS and APACHE II scores were positively correlated with serum CRP/ALB (r=0.639, 0.732), PSP (r=0.632, 0.754), and IL-12 (r=0.682, 0.727) levels (P<0.01).

2.4 Impact of Serum CRP/ALB, PSP, and IL-12 on Extubation Outcomes in Severe Pneumonia Patients

Using extubation outcomes as the dependent variable (failure=1, success=0), and pre-SBT CRP/ALB, PSP, IL-12, CPIS, and APACHE II scores as independent variables, a logistic regression model was built. Before adjustment, pre-SBT CRP/ALB, PSP, IL-12, CPIS, and APACHE II scores were associated with extubation failure (P<0.05). After adjusting for CPIS and APACHE II scores, they were still associated with extubation failure (P<0.05)**. See Table 3.**

2.5 Predictive Value of Serum CRP/ALB, PSP, and IL-12 for Extubation Outcomes in Severe Pneumonia Patients

ROC curves were plotted using the failure group as positive samples and the success group as negative samples. The results showed that pre-SBT serum CRP/ALB, PSP, and IL-12 had AUCs (95% CI) of 0.822 (0.727–0.895), 0.749 (0.647–0.835), and 0.827 (0.733–0.899), respectively. The cutoff values were 3.65, 38.53 ng/mL, and 47.13 pg/mL, with sensitivities of 84.62%, 69.23%, and 80.77%, respectively, and specificities of 70.31%, 78.12%, and 76.56%. The combined AUC for predicting extubation failure was 0.936, with a 95% CI of 0.864–0.977, sensitivity of 88.46%, and specificity of 90.62%. **See Figure 1.**

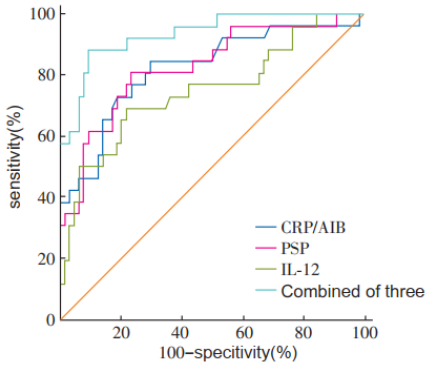

Fig.1 ROC curve for predicting extubation outcomes in severe pneumonia patients using serum CRP/ALB, PSP, and IL-12

Tab.2 Comparison of erum CRP/ALB, PSP, IL-12 levels between two groups

Group	*n*	CRP/ALB		PSP（ng/mL）		IL-12（pg/mL）	
		At admission	Before SBT	At admission	Before SBT	At admission	Before SBT
Failure group	26	4.76±1.40	3.00±0.84	45.51±13.60	34.78±8.52	60.62±18.18	51.15±13.89
Success group	64	3.31±0.95	2.13±0.58	31.88±9.51	25.99±7.12	41.56±12.55	36.68±10.44
t value		5.685	5.631	5.412	5.010	5.701	5.398
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Tab.3 Effects of serum CRP/ALB, PSP, and IL-12 on offline extubation outcomes of patients with mechanical ventilation in severe pneumonia

Independent Variable	Unadjusted					Adjusted				
	β	*S.E.*	*Wald*χ^2	*OR*（*95%CI*）	*P* value	*β*	*S.E.*	*Wald*χ^2	*OR*（*95%CI*）	*P* value
CRP/ALB	0.410	0.122	11.277	1.506（1.134-2.001）	<0.001	0.390	0.114	11.725	1.478（1.102-1.981）	<0.001
IL-12	0.597	0.146	16.746	1.818（1.345-2.456）	<0.001	0.413	0.131	9.953	9.953（1.141-2.003）	<0.001
PSP	0.471	0.128	13.546	1.602（1.200-2.138）	<0.001	0.359	0.104	11.909	11.909（1.048-1.956）	<0.001
CPIS score	0.428	0.130	10.826	1.534（1.147-2.051）	<0.001	-	-	-	-	-
APACHEIIscore	0.484	0.129	14.088	1.623（1.233-2.136）	<0.001	-	-	-	-	-
Constant	-0.200	0.056	12.702	-	<0.001	-0.117	0.026	20.126	-	<0.001

3. Discussion

Severe pneumonia is a common critical condition in clinical practice, and the primary therapeutic measure is mechanical ventilation. Once the patient's condition stabilizes, timely extubation should be performed. This approach is significant in reducing respiratory system complications, shortening hospitalization time, and lowering medical costs. Traditionally, extubation is often guided by clinical experience or SBT, but the failure rate of extubation is relatively high. Approximately 20% of patients require reintubation after extubation. The selection of highly sensitive biomarkers to predict the extubation outcomes of severe pneumonia is currently a research hotspot [12-13].

The data from this study indicated that the failure rate of extubation in severe pneumonia was 28.88%. Early identification plays a crucial role in adjusting the timing of extubation, improving extubation outcomes, and promoting prognosis. Strong evidence showed that extubation involved multiple systems and tissues, and using a single indicator to assess extubation outcomes is not sufficiently accurate [14]. Therefore, this study incorporated multiple laboratory indicators to jointly predict the extubation outcomes in severe pneumonia. Furthermore, extubation is a complex process, and measuring a single time-point change in levels is insufficient to determine the overall process. Thus, this

study selected CRP/ALB, PSP, and IL-12 levels measured on the day of admission and before SBT, and the changes in these levels before SBT were used in subsequent research based on the principle of near-cause effect. CRP is a typical pro-inflammatory factor, and its elevated levels can reflect the systemic inflammatory status and extubation outcomes in patients with severe pneumonia [15-16]. ALB is a sensitive indicator of nutritional status, and its decrease suggests malnutrition. Persistent malnutrition can impair the structure and function of respiratory muscles, reduce lung ventilation function, affect mucus clearance, and induce pneumonia. Pneumonia can release excessive inflammatory factors, increasing ALB consumption, lowering the body's defense capacity, and aggravating disease progression, which in turn affects extubation outcomes [17]. CRP/ALB can simultaneously reflect the body's inflammatory and nutritional status. Scholars such as Luo Wentao et al. [18] have clearly stated that CRP/ALB levels are higher in extubation failure patients and have predictive value for extubation outcomes, which is consistent with the findings of this study. PSP is mainly produced by the pancreas and intestines, and its levels increase in both acute and chronic pancreatitis as well as inflammatory bowel disease. Recent studies have found that PSP also increases in ventilator-associated pneumonia, and its levels are closely related to prognosis [19]. Foreign scholars have found that high PSP levels are a high-risk factor for prognosis in COVID-19 patients [20]. This study focuses on analyzing PSP expression in patients with successful and failed extubation of severe pneumonia, and the results show that PSP levels are higher in the former. It is speculated that patients with extubation failure have poor respiratory muscle endurance, cannot breathe independently for extended periods, have difficulty clearing secretions, and are prone to inflammatory changes in the lungs, which promote PSP synthesis [21]. High levels of PSP can stimulate the synthesis of chemokines and cytokines by lymphocytes and neutrophils, forming an inflammatory cascade reaction that increases the risk of extubation failure. IL-12 is primarily synthesized and secreted by B cells and monocytes and can mediate the production of pro-inflammatory cytokines by NK cells and T lymphocytes, thus participating in the body's inflammatory response [22]. Relevant studies have found that patients with pulmonary infections have higher serum IL-12 levels, which may be due to the stimulation of lymphocytes and macrophages after lung infection, leading to excessive IL-12 synthesis. High IL-12 levels can mediate lymphocyte proliferation, exacerbate the body's inflammatory response, and form a vicious cycle [23]. Based on this, the current study investigates the relationship between IL-12 and extubation outcomes in severe pneumonia. The results show that serum IL-12 levels are higher in patients with extubation failure than in those with successful extubation, with an AUC of 0.827, indicating that IL-12 has good predictive efficacy for extubation outcomes. Clinically, patients with higher IL-12 levels should be given special attention, and timely preventive and therapeutic measures should be taken to improve the extubation success rate. It should be noted that the application of IL-12 in predicting extubation outcomes is still in the preliminary stage, and the specific mechanism remains unclear and needs further research to confirm.

CPIS and APACHE II scores are key indicators for assessing the severity of severe pneumonia. The higher the values, the more severe the disease and the worse the prognosis [24-25]. The data from this study show that patients with extubation failure have higher CPIS and APACHE II scores compared to those with successful extubation, and these scores are significantly positively correlated with CRP/ALB, PSP, and IL-12. This suggests that measuring serum CRP/ALB, PSP, and IL-12 levels can help assess the condition and prognosis of severe pneumonia patients. It is noteworthy that CPIS and APACHE II scales involve many operational items, and human errors may occur during the procedure, increasing the risk of false positives or false negatives [26]. This may be one of the reasons why this study included laboratory indicators such as CRP/ALB, PSP, and IL-12. Additionally, the ROC curve analysis shows that the AUC for CRP/ALB and IL-12 prediction exceeds 0.8. When the cutoff values are 3.65 and 47.13 pg/mL, the prediction sensitivity exceeds 80%, indicating that measuring these two indicators can capture most true positive patients and reduce the risk of missed diagnosis. In clinical practice, patients exceeding the cutoff values should be considered high-risk and prioritized for intervention or close monitoring, such as upgrading antibiotic treatment or increasing immunosuppressants. The AUC for PSP alone is 0.749, and its sensitivity is only 69.23% at a cutoff value of 38.53 ng/mL, indicating that PSP alone has limited predictive value and should be used in combination with other indicators. The combined AUC for CRP/ALB, PSP, and IL-12 in predicting extubation failure in severe pneumonia patients is 0.936, with sensitivity and specificity of 88.46% and 90.62%, respectively, which are superior to single-predictor efficacy. This is likely because all three indicators participate in the body's inflammatory response and show elevated levels, which significantly improve prediction efficacy and provide scientific references for clinical decision-making.

In conclusion, serum CRP/ALB, PSP, and IL-12 levels are higher in patients with extubation failure in severe pneumonia, and they are positively correlated with CPIS and APACHE scores. The combined detection of these indicators helps improve the predictive efficacy for extubation failure and guides subsequent treatment. Due to factors such as limitations in the actual conditions of the hospital and sample size, some data may contain errors. Moreover, factors such as diaphragm and heart function, which influence extubation outcomes, were not excluded, and these could be areas for future research.

Conflict of interest None

Reference

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·论　著·

C反应蛋白/白蛋白比值、胰石蛋白联合白细胞介素-12对重症肺炎脱机拔管结局的预测价值

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摘要：目的　探讨C反应蛋白与白蛋白比值（C-reactive protein/albumin，CRP/ALB）、胰石蛋白（pancreatic stone protein，PSP）联合白细胞介素-12（interleukin-12，IL-12）预测重症肺炎患者脱机拔管结局的价值，以期指导临床决策，提高撤机成功率。**方法**　选取2021年1月至2023年12月粤北人民医院收治的90例重症肺炎患者作为研究对象，根据脱机拔管结局分为失败组（n=26）和成功组（n=64），比较两组一般资料、入院当天及自主呼吸试验（spontaneous breathing trial，SBT）前血清CRP/ALB、PSP、IL-12水平，Pearson相关系数分析血清各指标与临床肺部感染评分（clinical pulmonary infection score，CPIS）、急性生理与慢性健康状况评分系统Ⅱ（acute physiology and chronic health evaluationⅡ，APACHEⅡ）的相关性，采用logistic回归方程分析血清CRP/ALB、PSP、IL-12对重症肺炎脱机拔管结局的影响，采用受试者工作特征曲线（receiver operating characteristic，ROC）及曲线下面积（area under the curve，AUC）分析血清各指标的预测效能。**结果**　（1）与成功组比较，失败组入院当天及SBT前CPIS、APACHEⅡ评分及血清CRP/ALB、PSP、IL-12水平较高（P<0.01）。（2）根据近因效应选择SBT前血清CRP/ALB、PSP、IL-12、CPIS及APACHEⅡ评分用于后续研究。重症肺炎脱机拔管失败患者SBT前CPIS、APACHEⅡ评分分别与血清CRP/ALB、PSP、IL-12水平呈正相关（P<0.05）。（3）校正后，SBT前CRP/ALB、PSP、IL-12仍与重症肺炎患者脱机拔管失败有关（P<0.05）。（4）SBT前CRP/ALB+PSP+IL-12联合预测重症肺炎患者脱机拔管失败效能［AUC（95%*CI*）：0.936（0.864～0.977）］明显优于CRP/ALB、PSP和IL-12单一预测效能［0.822（0.727～0.895）、0.749（0.647～0.835）、0.827（0.733～0.899）］。**结论**　血清CRP/ALB、PSP、IL-12与重症肺炎患者脱机拔管失败密切相关，三者联合检测预测效能好，有助于指导临床诊治。

关键词：重症肺炎；机械通气；脱机拔管；胰石蛋白；白细胞介素-12；C反应蛋白；白蛋白
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Value of C-reactive protein/albumin ratio, pancreatic stone protein combined with interleukin-12 on prediction of offline extubation outcomes of patients with mechanical ventilation in severe pneumonia

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Abstract: Objective　To explore the predictive value of the ratio of C-reactive protein to albumin (CRP/ALB), pancreatic stone protein (PSP), and interleukin-12 (IL-12) for the outcome of offline extubation in patients with mechanical ventilation in severe pneumonia, in order to guide clinical decision-making and enhance weaning success rates. **Methods**　Ninety patients with severe pneumonia admitted to Yuebei People's Hospital from January 2021 to December 2023 were selected as the study subjects. According to the outcome of offline extubation, they were divided into failure group (n=26) and success group (n=64). The general information, serum CRP/ALB, PSP, IL-12 levels on the day of admission and before spontaneous breathing trial (SBT) were compared between the two groups. Pearson

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correlation coefficients were used to analyze the association of serum indicators with clinical pulmonary infection score (CPIS) and acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ) scores. Logistic regression equation was used to analyze the impact of serum CRP/ALB, PSP, and IL-12 on the outcome of offline extubation from mechanical ventilation in severe pneumonia. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to analyze the predictive efficacy of serum indicators. **Results** (1) Compared with the success group, the CPIS, APACHE Ⅱ score and serum CRP/ALB, PSP, IL-12 levels on the day of admission and before SBT in the failure group were higher (P<0.01). (2) Serum CRP/ALB, PSP, IL-12, CPIS and APACHE Ⅱ scores before SBT were selected for follow-up study according to the recency effect. In patients with severe pneumonia who failed of offline extubation from mechanical ventilation, CPIS and APACHE Ⅱ scores before SBT were positively correlated with serum CRP/ALB, PSP, and IL-12 levels, respectively (P<0.05). (3) After adjusting, CRP/ALB, PSP, and IL-12 before SBT were still associated with failure of offline extubation from mechanical ventilation in patients with severe pneumonia (P<0.05). (4) The predictive efficacy of CRP/ALB+ PSP+IL-12 before SBT [AUC (95%*CI*): 0.936 (0.864-0.977)] for failure of offline extubation from mechanical ventilation in patients with severe pneumonia was significantly better than that of individual predictive efficacy of CRP/ALB, PSP and IL-12 [0.822 (0.727-0.895), 0.749 (0.647-0.835), 0.827 (0.733-0.899)]. **Conclusion** Serum CRP/ALB, PSP, and IL-12 are closely related to the failure of offline extubation in patients with severe pneumonia. The combined detection of these three markers has good predictive efficacy and is helpful in guiding clinical diagnosis and treatment.

Keywords: Severe pneumonia; Mechanical ventilation; Offline extubation; Pancreatic stone protein; Interleukin-12; C-reactive protein; Albumin

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机械通气是重症肺炎的有效治疗手段，但长时间治疗可能会引起呼吸机依赖、机械通气相关肺炎，增加脱机拔管失败风险[1-3]。另有学者发现，提前撤机则会引起呼吸肌疲劳、氧供不足等，导致脱机拔管失败，延长患者住院时间[4]。明确潜在生物标志物有助于早期预测重症肺炎脱机拔管结局，制定个体化治疗方案，加快病情好转。胰石蛋白（pancreatic stone protein，PSP）可调控促炎/抗炎因子表达，参与肺部炎性病变发生发展[5]。白细胞介素-12（interleukin-12，IL-12）、C反应蛋白与白蛋白比值（C-reactive protein/albumin，CRP/ALB）是重要的促炎细胞因子，已知证据证实其在重症肺炎、哮喘等炎症性疾病中均有表达，但其变化与脱机拔管结局之间关系未知[6-7]。当前研究多通过测定某一时间点的生物标志物水平来评估其预测价值，而动态观察带机患者的生物标志物水平相对误差率偏小，可能对预测撤机具有良好的稳定性，但缺少临床试验验证。本研究拟动态监测血清CRP/ALB、PSP、IL-12水平，并分析三者联合预测重症肺炎患者脱机拔管结局的价值，及其与病情相关指标间的关系，以期指导临床决策，提高撤机成功率。

1 对象与方法

1.1 *研究对象* 选取粤北人民医院收治的重症肺炎患者90例作为研究对象（2021年1月至2023年12月），均符合《中国急诊重症肺炎临床实践专家共识》诊断标准[8]；具备机械通气指征，行气管插管；机械通气时间超过48 h；家属知晓并签署同意书；排除其他肺部病变（肺结核、慢性阻塞性肺疾病、肺良恶性肿瘤、肺水肿等）、肺部手术史、严重精神类疾病、凝血紊乱、重要脏器器质性病变、临床资料缺失者。其中男51例，女39例；年龄45～75（66.42±4.33）岁；基础疾病：24例糖尿病，19例高血压，19例高脂血症；吸烟史25例；饮酒史20例。本研究经粤北人民医院伦理委员会通过（审批号：ky-2021-252）。

1.2 *方法*

1.2.1 分组标准 撤机标准参照《机械通气临床应用指南（2006）》[9]，必要标准：（1）动脉血氧饱和度≥90%；（2）血流动力学稳定，无活动性心肌缺血。附加标准：（1）自主呼吸潮气量＞5 mL/kg，浅快呼吸指数<105 f/（L·min），呼吸频率≤35次/min，吸气负压<−25～−20 cmH_2O；（2）核心体温≤38～38.5 ℃；（3）血红蛋白≥80～100 g/L；（4）易于唤醒，意识状态清醒和警觉；（5）血清电解质正常。脱机拔管成功标准：成功通过自主呼吸试验（spontaneous breathing trial，SBT）、气管导管拔除48 h依旧能自主呼吸，无需气管插管。根据重症肺炎患者脱机拔管结局分为成功组和失败组，分别为64例、26例。

1.2.2 观察指标及检测方法 入院当天及SBT前，采集3 mL空腹肘部静脉血，离心15 min，2 500 r/min，离

心半径6 cm，分离上层血清，以酶联免疫吸附法（北京沃莱士生物技术）测定IL-12、PSP，以溴甲酚绿法（深圳迈瑞生物医疗电子）测定ALB，免疫比浊法（深圳迈瑞生物医疗电子）测定CRP，计算CRP/ALB。

1.2.3　临床肺部感染评分（clinical pulmonary infection score，CPIS）标准[10]　GPIS包含体温、X线胸片、氧合指数、白细胞计数等7个条目，各条目采用0～2级评分法，满分12分，分值越高提示病情越严重。

1.2.4　急性生理与慢性健康状况评分系统Ⅱ（acute physiology and chronic health evaluation Ⅱ，APACHE Ⅱ）标准[11]　APACHEⅡ评分涵盖急性生理、年龄、慢性健康状况3个维度，理论最高分为71分，分值越高预后越差。

1.3　统计学方法　运用SPSS 26.0软件处理数据，数据均进行正态性及方差齐性检验，计量资料符合正态分布且方差齐性采用$\bar{x}\pm s$表示，组间比较采用独立样本t检验；计数资料以例表示，采用χ^2检验；Pearson相关系数分析相关性；绘制受试者工作特征曲线（ROC）及曲线下面积（AUC）分析预测效能。检验水准α=0.05，双侧检验。

2　结　果

2.1　两组一般资料比较　失败组CPIS、APACHEⅡ评分均高于成功组（$P<0.01$）。见表1。

2.2　两组血清CRP/ALB、PSP、IL-12水平比较　失败组入院当天及SBT前血清CRP/ALB、PSP、IL-12水平均高于成功组（$P<0.01$）。见表2。

2.3　血清各指标与CPIS、APACHEⅡ评分相关性　根据近因效应选择SBT前血清CRP/ALB、PSP、IL-12、CPIS、APACHEⅡ评分用于后续研究。Pearson相关分析显示，重症肺炎脱机拔管失败患者CPIS、APACHEⅡ评分分别与血清CRP/ALB（r=0.639，0.732）、PSP（r=0.632，0.754）、IL-12（r=0.682，0.727）水平呈正相关（$P<0.01$）。

2.4　血清CRP/ALB、PSP、IL-12对重症肺炎患者脱机拔管结局的影响　以患者脱机拔管结局为因变量（失败=1，成功=0），以SBT前CRP/ALB、PSP、IL-12、CPIS及APACHEⅡ评分为自变量（原值代入）纳入logistic回归方程。校正前，SBT前CRP/ALB、PSP、IL-12、CPIS及APACHEⅡ评分与重症肺炎患者脱机拔管失败有关（$P<0.05$），校正CPIS及APACHEⅡ评分后，SBT前CRP/ALB、PSP和IL-12仍与重症肺炎患者脱机拔管失败有关（$P<0.05$）。见表3。

2.5　血清CRP/ALB、PSP、IL-12预测重症肺炎患者脱机拔管结局的价值　将失败组患者作为阳性标本，成功组患者作为阴性标本绘制ROC曲线，结果显示，SBT前血清CRP/ALB、PSP、IL-12单一预测重症肺炎患者脱机拔管失败的AUC（95%*CI*）分别为0.822（0.727~0.895）、0.749（0.647~0.835）、0.827（0.733~0.899），截断值分别为3.65、38.53 ng/mL、47.13 pg/mL，敏感度分别为84.62%、69.23%、80.77%；特异度分别为70.31%、78.12%、76.56%；三者联合预测重症肺炎患者脱机拔管失败的AUC为0.936，95%*CI*为0.864～0.977，敏感度为88.46%，特异度为90.62%。见图1。

表1　两组一般资料比较

Tab.1　Comparison of general data between the two groups

项目	失败组（n=26）	成功组（n=64）	χ^2/t值	P值
男/女（例）	15/11	36/28	1.440	0.230
年龄（岁，$\bar{x}\pm s$）	65.52±5.11	66.78±4.24	1.203	0.232
BMI（kg/m^2，$\bar{x}\pm s$）	22.24±1.23	22.05±1.30	0.638	0.525
基础疾病（例）				
高血压	5	14	0.078	0.780
糖尿病	8	16	0.315	0.575
高脂血症	6	13	0.085	0.771
吸烟史（例）	8	17	0.163	0.686
饮酒史（例）	6	14	0.016	0.901
CPIS评分（分，$\bar{x}\pm s$）				
入院当天	6.11±1.30	5.22±1.15	3.204	<0.001
SBT前	5.43±0.45	4.12±0.41	13.356	<0.001
APACHEⅡ评分（分，$\bar{x}\pm s$）				
入院当天	18.17±2.33	16.34±1.28	4.775	<0.001
SBT前	12.68±1.56	10.01±1.02	9.580	<0.001

表2　两组血清CRP/ALB、PSP、IL-12水平比较　（$\bar{x}\pm s$）

Tab.2　Comparison of serum CRP/ALB, PSP, IL-12 levels between two groups　（$\bar{x}\pm s$）

组别	例数	CRP/ALB		PSP（ng/mL）		IL-12（pg/mL）	
		入院当天	SBT前	入院当天	SBT前	入院当天	SBT前
失败组	26	4.76±1.40	3.00±0.84	45.51±13.60	34.78±8.52	60.62±18.18	51.15±13.89
成功组	64	3.31±0.95	2.13±0.58	31.88±9.51	25.99±7.12	41.56±12.55	36.68±10.44
t值		5.685	5.631	5.412	5.010	5.701	5.398
P值		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

表 3　血清 CRP/ALB、PSP、IL-12 对重症肺炎患者脱机拔管结局的影响

Tab.3　Effects of serum CRP/ALB，PSP，and IL-12 on offline extubation outcomes of patients with mechanical ventilation in severe pneumonia

自变量	校正前					校正后				
	β	*SE*	Waldχ^2	*OR*(95%*CI*)	*P* 值	*β*	*SE*	Waldχ^2	*OR*(95%*CI*)	*P* 值
CRP/ALB	0.410	0.122	11.277	1.506(1.134～2.001)	<0.001	0.390	0.114	11.725	1.478(1.102～1.981)	<0.001
IL-12	0.597	0.146	16.746	1.818(1.345～2.456)	<0.001	0.413	0.131	9.953	9.953(1.141～2.003)	<0.001
PSP	0.471	0.128	13.546	1.602(1.200～2.138)	<0.001	0.359	0.104	11.909	11.909(1.048～1.956)	<0.001
CPIS 评分	0.428	0.130	10.826	1.534(1.147～2.051)	<0.001	–	–	–	–	–
APACHE Ⅱ 评分	0.484	0.129	14.088	1.623(1.233～2.136)	<0.001	–	–	–	–	–
常量	−0.200	0.056	12.702	–	<0.001	−0.117	0.026	20.126	–	<0.001

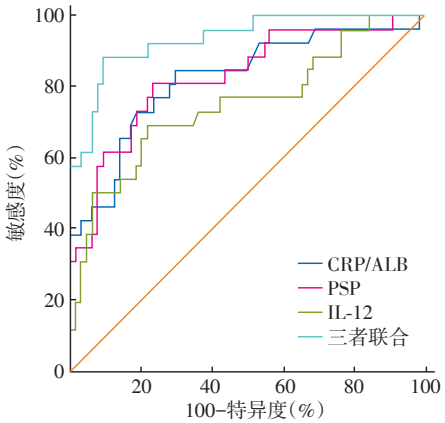

图 1　血清 CRP/ALB、PSP、IL-12 预测重症肺炎患者脱机拔管结局的 ROC 曲线

Fig.1　ROC curve of serum CRP/ALB，PSP，and IL-12 for predicting extubation outcomes in severe pneumonia patients

3　讨　论

重症肺炎属临床常见危重症，基础治疗措施为机械通气，待患者病情稳定后应及时撤机，这对减少呼吸系统并发症、缩短住院时间、降低医疗成本具有积极意义。以往临床多根据临床经验或 SBT 指导撤机，但脱机拔管失败率较高，约 20%患者撤机后需再次插管，选取敏感性高的生物标志物来预测重症肺炎脱机拔管结局是当前研究热点[12-13]。

本研究数据显示，重症肺炎脱机拔管失败率为 28.89%，早期识别对调整撤机时机，改善脱机拔管结局，促进预后改善意义重大。充足证据显示，呼吸机撤机涉及多个系统和组织，采用单个指标评估脱机拔管结局准确性欠佳[14]，故本研究纳入多个实验室指标共同预测重症肺炎脱机拔管结局。另外呼吸机的撤离属于复杂过程，检测 1 个时间点水平变化很难判定一个过程，因此本研究选择入院当天及 SBT 前 2 个时间点测定 CRP/ALB、PSP、IL-12 水平，并根据近因效应原则采用 SBT 前 CRP/ALB、PSP、IL-12 水平变化用于后续研究。CRP 是典型促炎因子，其值升高可反映重症肺炎患者全身炎症状态和脱机拔管结局[15-16]。ALB 是反映机体营养状态敏感指标，其值降低提示营养不良，持续营养不良可破坏呼吸肌结构与功能，降低肺通气功能，影响分泌物排出，诱发肺炎。肺炎可释放过量炎症因子，增加 ALB 消耗量，降低机体防御能力，加剧疾病进程，进而影响脱机拔管结局[17]。CRP/ALB 可同时反映机体炎症与营养状态，罗文滔等[18]学者明确表示，CRP/ALB 在撤机失败患者中水平较高，且对撤机结局具有预测价值，本研究观点与其有相似性。PSP 主要由胰腺和肠道产生，在急慢性胰腺炎、炎症性肠病中均呈现升高趋势，近年研究发现其在呼吸机相关肺炎中亦呈现同样趋势，且与预后密切相关[19]。国外学者发现，PSP 高水平是影响新冠肺炎患者预后的高危因素[20]。本研究重点分析 PSP 在重症肺炎撤机失败与成功患者中水平，结果发现前者 PSP 水平较高。推测原因为，撤机失败患者呼吸肌耐力差，无法长时间自主呼吸，分泌物排出困难，极易引起肺部炎症性病变，合成 PSP[21]。高 PSP 可刺激淋巴细胞、中性粒细胞合成趋化因子、细胞因子，形成炎症级联反应，增加撤机失败风险。IL-12 主要由 B 细胞、单核细胞合成分泌，可介导 NK 细胞和 T 淋巴细胞生成促炎细胞因子，参与机体炎症反应[22]。有研究发现，肺部感染患者血清 IL-12 水平较高，这可能是由于肺部感染后，可刺激淋巴细胞、巨噬细胞，合成过量 IL-12，而高 IL-12 可介导淋巴细胞增殖，加剧机体炎症反应，形成恶性循环[23]。在此基础上，本研究探究 IL-12 与重症肺炎脱机拔管结局的关系，结果发现脱机拔管失败患者血清 IL-12 水平高于脱机拔管成功患者，预测 AUC 为 0.827，提示 IL-12 对脱机拔管结局有较好的预测效能，临床应高度重视 IL-12 水平较高患者，及时采取防治措施，提高撤机成功率。需注意的是，IL-12 在脱机拔管结局预测中的应用属于初级阶段，具体机制未明，有待更深入的研究证实。

CPIS、APACHE Ⅱ 评分是评估重症肺炎病情程度的关键指标，其值越高病情越严重，预后越差[24-25]。本研究数据显示，重症肺炎脱机拔管失败患者 CPIS、

APACHEⅡ评分均高于撤机成功患者，且与CRP/ALB、PSP、IL-12呈显著正相关，可见检测血清CRP/ALB、PSP、IL-12水平有助于了解重症肺炎患者病情和预后情况。值得关注的是，CPIS、APACHEⅡ量表操作项目繁多，操作期间可能会出现人为误差，增加假阳性或假阴性风险[26]，这可能是本研究引入CRP/ALB、PSP、IL-12等实验室指标的原因之一。另绘制ROC曲线发现，CRP/ALB、IL-12预测AUC均超出0.8，当截断值分别为3.65、47.13 pg/mL时，预测敏感度超过80%，说明测定两者可捕捉到绝大多数真阳性患者，减少漏诊风险。临床实际中应将超出截断值的患者视为高风险人群，优先纳入干预或密切监测流程，比如升级抗生素治疗或是增加免疫抑制剂等。PSP单独预测AUC为0.749，截断值为38.53 ng/mL时，预测敏感度仅为69.23%，说明PSP单独预测价值有限，应与其他指标联合应用。三者联合预测重症肺炎脱机拔管失败的AUC达0.936，敏感度及特异度分别为88.46%、90.62%，均优于单一预测效能，考虑原因与三者均能参与机体炎症反应并呈现高水平有关，可显著提高预测效能，为临床学者确定正确决策提供科学参考。

综上所述，血清CRP/ALB、PSP、IL-12在重症肺炎患者机械通气脱机拔管失败患者水平较高，其与CPIS、APACHE评分分别呈正相关，三者联合检测有助于提高脱机拔管失败预测效能，指导后续治疗。受粤北人民医院实际情况等因素影响，样本数量并不充足，部分数据可能存在误差，其次是未将膈肌功能、心功能等影响脱机拔管失败的因素排除，可作为日后研究的方向之一。

利益冲突　无

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