

The Relationship Between the Expression of CRBN in Peripheral Blood and the Severity and Prognosis of Adult Sepsis

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Objective: To investigate the correlation between the expression of cereblon (CRBN) protein in peripheral blood and the severity and prognosis of sepsis.

Methods: A total of 130 patients with sepsis admitted to our hospital were selected as the observation subjects (sepsis group). The patients were divided into mild group, moderate group and severe group according to their conditions. The patients were divided into survival group and death group according to their living conditions within 28 days after admission. 130 health individuals were selected as the control group. The levels of CRBN mRNA, CRP and PCT in peripheral blood were detected.

Results: The levels of serum CRBN mRNA, CRP, and PCT in patients with sepsis were higher than those in the control group ($P<0.05$); As the condition worsens, the levels of CRBN mRNA, CRP, and PCT gradually increase, and there are statistically significant differences among patients with mild, moderate, and severe sepsis; Correlation analysis showed that the expression of CRBN mRNA in sepsis patients was positively correlated with CRP, PCT levels, APACHE II score and SOFA score ($P<0.05$); the 28-day cumulative survival rate of patients with high CRBN mRNA expression was significantly lower than that of patients with low CRBN mRNA expression ($P<0.05$); compared with the survival group, the levels of serum CRBN mRNA, CRP and PCT in the death group were significantly higher ($P<0.05$); the AUC of death in sepsis patients diagnosed by CRBN mRNA, CRP and PCT was 0.961, the combined diagnostic efficacy was higher than that of single detection ($P<0.05$).

Conclusion: The expression level of CRBN in the peripheral blood of patients with sepsis is increased, which is related to the severity and prognosis of the patients. The combination of CRP and PCT has certain diagnostic value for the death of sepsis patients.

Keywords: sepsis, cereblon protein, prognosis, severity

Sepsis is a clinically common critical disease, mainly manifested as systemic inflammation and over-immunity of the body due to infection, which easily causes organ dysfunction. The disease has a rapid progress and a high mortality rate. In recent years, sepsis or septic shock maintains high and increasing incidence, so early assessment of patients' condition, prognosis and timely treatment are particularly important.^{1,2} Cereblon (CRBN) is a binding protein that exists in the cytoplasm and nucleus, and is widely distributed in tissues such as the liver, kidney, and prostate. It can form ubiquitin ligase complexes with damaged DNA binding proteins I (DDBI) and ROC1 (Cull regulator), and exert different biological effects through different substrates. CRBN can also play a non-enzymatic role, inhibiting inflammatory reactions, protecting cells from damage, and participating in immune regulation. It is a therapeutic target for various diseases.³⁻⁵ Studies have shown that in a cecal ligation and puncture (CLP) -induced sepsis mouse model, CRBN-deficient (type KO) mice had significantly higher survival rate than wild-type mice. CRBN mediates the expression of inflammatory factors by inhibiting adenosine monophosphate activated kinase (AMPK) and heme oxygenase-1 (HO-1) activation.⁶ There are few clinical studies on CRBN in sepsis. The latest research shows that although the prognosis of sepsis is better in animals lacking CRBN, the presence of CRBN in humans does not affect its prognosis.⁷ To further investigate the

clinical value of CRBN in sepsis, this study aims to explore the correlation between the expression of CRBN protein and the condition and prognosis of sepsis patients.

Data and Methods

General Data

This study was approved by the Ethics Committee of our hospital. A total of 130 sepsis patients admitted to our hospital from September 2020 to March 2022 were retrospectively selected as the observation subjects (sepsis group), including 74 males and 56 females aged 35–75 years old, with an average age of (48.21 ± 11.85) years. Primary infection sites included 64 cases of pulmonary infection, 25 cases of abdominal infection, 20 cases of digestive system infection, 13 cases of urinary system infection, 5 cases of skin and soft tissue infection, and 3 cases of other infections.

According to the patient's condition, they were divided into a mild group of 52 cases, a moderate group of 45 cases, and a severe group of 33 cases. The mild group consisted of 30 males and 22 females, aged 34–74 years, with an average age of (47.87 ± 11.23) years; There were 25 males and 20 females in the moderate group, aged 34–76 years, with an average age of (48.04 ± 11.44) years. There were 19 males and 14 females in the severe group, aged 35–75 years, with an average age of (48.97 ± 11.75) years. The gender and age of each group were comparable ($P > 0.05$).

Inclusion criteria: (1) Meets the 2016 Sepsis-3 diagnostic criteria⁸; (2) Age greater than 18 years old; (3) Complete clinical data. Exclusion criteria: (1) Death within 24h after admission; (2) Patients complicated with malignant tumors and immunodeficiency diseases; (3) Mental anomaly; (4) Patients treated with immunosuppressive agents before admission.

A total of 130 healthy persons were selected as the control group, including 69 males and 61 females aged 35–73 years old, with an average age of (47.85 ± 12.34) years. There is comparability in gender and age between the control group and the sepsis group ($P > 0.05$). The case collection is shown in Figure 1.

Research Methods

CRBN mRNA Detection

On the day of admission and the day of physical examination of the control group, 5 mL of fasting elbow venous blood was collected. After centrifugation at 3500 r/min with a centrifugal radius of 15 cm for 15 min, the serum was separated and stored at -70°C for examination.

Real-time quantitative fluorescent PCR (qRT-PCR) was used to detect the expression of CRBN mRNA in serum. TRIzol reagent (Product Number S30876, Shanghai Yuanye Biotechnology Co., Ltd.) was used to extract total serum RNA, synthesize cDNA, and then PCR amplification was performed. Two-step SYBR Green qRT-PCR Mastermix (Product Number ALH191) was purchased from Beijing Baiao Laibo Technology Co., LTD. After the reaction, the relative expression level of CRBN mRNA was calculated by $2^{-\Delta\Delta C_t}$ method using GAPDH as internal reference. Primer sequences were purchased from Guangzhou Ribobio, Co., LTD, including CRBN upstream primer sequence (5'-3'): CTAAGGAGTCACAGGAAGACATC, downstream primer sequence (5'-3'): GTAGAATCTCTCAGACTCAAGGTTG; GAPDH upstream primer sequence (5'-3'): AACGGATTTGGTCGTATTGGG, downstream primer sequence (5'-3'): CCTGGAAGATGGTGATGGGAT.

Detection of Serum CRP and PCT Levels

Serum C-reactive protein (CRP) level was detected by immunoturbidimetric assay, with a kit (Product Number SNM261) purchased from Beijing Kemei Biotechnology Co., LTD. and serum PCT level was detected by chemiluminescence assay, with kit purchased from Wuhan Easydiagnosis Biomedicine Co., LTD.

Condition Diagnosis and Prognosis Assessment

Acute physiological function and chronic health status score system II (APACHEII) score and sequential organ failure (SOFA) score were given at admission.⁹

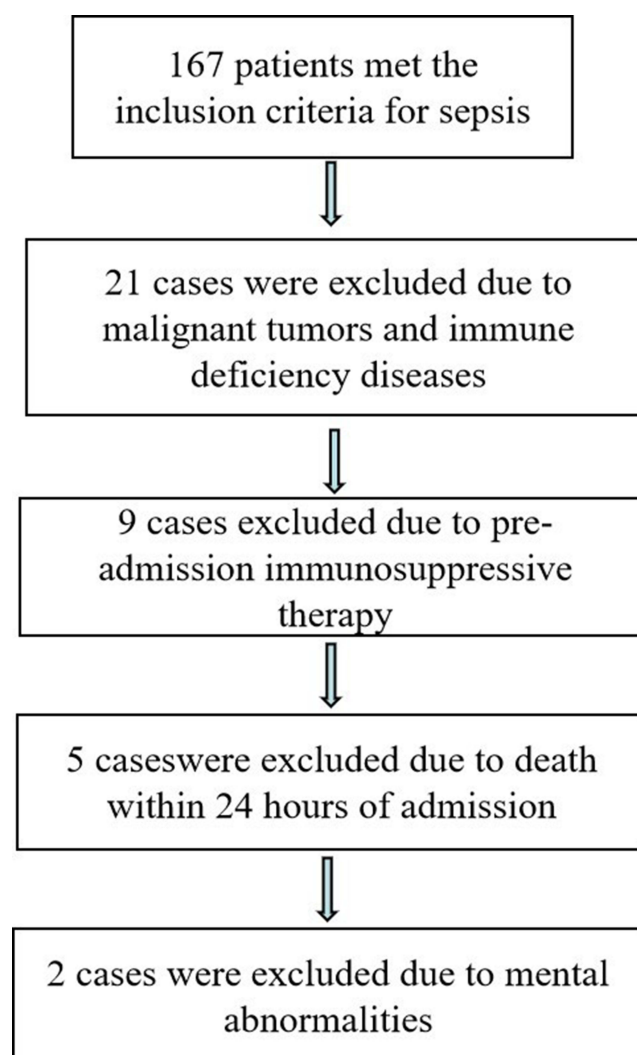


Figure 1 Flow chart of case collection.

All patients were evaluated according to their Susceptibility, Infection, Response, and Organ failure (PIRO) levels, who were divided into mild groups (symptoms such as high fever, chills, and physical fatigue after infection), moderate groups (symptoms of insufficient perfusion such as changes in consciousness, hypoxemia, oliguria, and hyperlactatemia), and severe groups (there is still hypotension or the need for vasoactive drugs after component liquid resuscitation).

The patient survival status within 28d after admission was recorded, and the patients were divided into survival group and death group.

Statistical Analysis

SPSS 23.0 was used for statistical analysis. Measurement data consistent with normal distribution were expressed as mean \pm standard deviation ($\bar{x} \pm s$). Independent sample *t*-test was used for comparison between the two groups. One-way analysis of variance was used for comparison between multiple groups, and LSD-*t* test was used for comparison between groups in pairs. Pearson method was used to analyze the correlation between CRBN mRNA and CRP, PCT, Spearman analysis was used to analyze the correlation between CRBN mRNA and APACHE II score, SOFA score. ROC curve was used to analyze the prognostic value of CRBN mRNA, CRP and PCT for sepsis patients. Kaplan-Meier survival curve was used to analyze the correlation between CRBN mRNA expression and 28-day prognosis of sepsis patients.

Results

Comparison of CRBN mRNA and Serum CRP and PCT Levels Between the Two Groups

Compared with the control group, the serum levels of CRBN mRNA, CRP and PCT were significantly increased in sepsis patients ($P < 0.05$), as shown in Table 1.

Comparison of CRBN, CRP and PCT Levels in Patients with Sepsis of Different Severity

There were statistically significant differences in CRBN mRNA, CRP and PCT levels among patients with mild, moderate and severe sepsis ($P < 0.05$). Compared with the mild group, the levels of CRBN mRNA, CRP and PCT were significantly increased in moderate and severe groups ($P < 0.05$); Compared with the moderate group, the levels of CRBN mRNA, CRP and PCT were significantly increased in the severe group ($P < 0.05$), as shown in Table 2.

Correlation Between CRBN mRNA and CRP, PCT, APACHEII Score, SOFA Score

Correlation analysis showed a significant positive correlation between CRBN mRNA expression and CRP ($r=0.498$), PCT ($r=0.563$), APACHEII score ($r=0.505$), SOFA score ($r=0.463$) in sepsis patients ($P < 0.05$), as shown in Figure 2.

Correlation Between CRBN mRNA Expression and 28-Day Prognosis of Sepsis Patients

Sepsis patients were divided into high CRBN mRNA expression group (≥ 2.36) and low CRBN mRNA expression group (< 2.36) based on the mean CRBN mRNA expression level in peripheral blood. Kaplan-Meier survival analysis showed that, patients with high CRBN mRNA expression had significantly lower 28-day cumulative survival rate than patients with low CRBN mRNA expression ($\chi^2=13.88$, $P < 0.05$), as shown in Figure 3

Table 1 Comparison of CRBN mRNA and Serum CRP and PCT Levels Between the Two Groups

Groups	Number of Cases	CRBN mRNA	CRP (mg/L)	PCT (ng/mL)
Control group	130	1.05±0.12	4.55±1.32	0.35±0.12
Sepsis group	130	2.36±0.47	56.18±10.34	11.46±3.36
<i>t</i>	–	30.792	56.473	37.676
<i>P</i>	–	<0.001*	<0.001*	<0.001*

Note: * $P < 0.05$.

Abbreviations: CRBN, cereblon protein; CRP, C-reactive protein; PCT, procalcitonin.

Table 2 Comparison of CRBN mRNA, CRP and PCT Levels in Patients with Sepsis of Different Severity

Groups	Number of Cases	CRBN mRNA	CRP (mg/L)	PCT (ng/mL)
Mild group	52	1.97±0.35	50.37±6.28	8.54±2.61
Moderate group	45	2.41±0.43 ^a	57.15±9.85 ^a	11.32±3.05 ^a
Severe group	33	2.91±0.32 ^{ab}	64.01±5.69 ^{ab}	16.25±2.67 ^{ab}
<i>F</i>	–	64.738	33.162	77.463
<i>P</i>	–	<0.001*	<0.001*	<0.001*

Notes: Compared with mild group, ^a $P < 0.05$; Compared with the moderate group, ^b $P < 0.05$; * $P < 0.05$.

Abbreviations: CRBN, cereblon protein; CRP, C-reactive protein; PCT, procalcitonin.

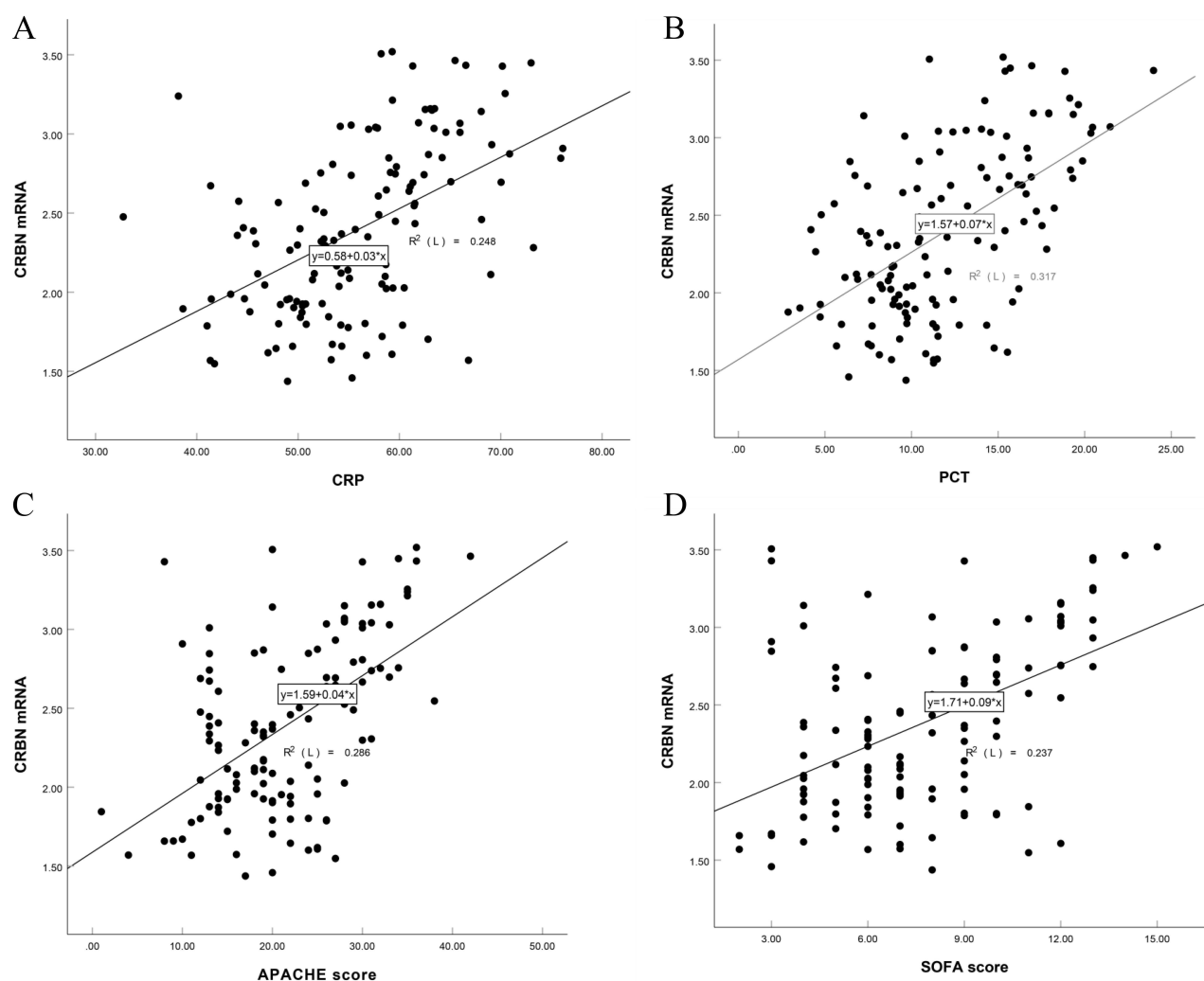


Figure 2 Correlation between CRBN mRNA and CRP, PCT, APACHE II score, SOFA score (A) Correlation analysis with CRP; (B) Correlation analysis with PCT; (C) Correlation analysis with APACHE II score; (D) Correlation analysis with SOFA score.

Abbreviations: CRBN, cereblon protein; CRP, C-reactive protein; PCT, procalcitonin; APACHE II, Acute Physiological Function and Chronic Health Status Scoring System II Score; SOFA, Sequential Organ Failure Score.

Comparison of CRBN mRNA and Serum CRP and PCT Levels Between Survival Group and Death Group

Compared with the survival group, the serum levels of CRBN mRNA, CRP and PCT were significantly increased in the death group ($P < 0.05$), as shown in Table 3.

Prognostic Value of CRBN mRNA, CRP and PCT for Sepsis Patients

Diagnosis of sepsis-induced death by CRBN mRNA had an area under ROC curve (AUC) of 0.846, an optimal cut-off value of 2.61, a sensitivity of 76.60%, and a specificity of 81.93%. Diagnosis of sepsis-induced death by CRP had an AUC of 0.822, an optimal cut-off value of 59.60 mg/L, a sensitivity of 72.34%, and a specificity of 82.34%. Diagnosis of sepsis-induced death by PCT had an AUC of 0.865, an optimal cut-off value of 12.10 ng/mL, a sensitivity of 82.98%, and a specificity of 78.31%. Combined diagnosis of sepsis-induced death by CRBN mRNA, CRP and PCT had an AUC of 0.961, a sensitivity of 95.74%, and a specificity of 86.75%. The combined diagnosis had a higher efficacy than single detection ($Z=3.003$, $P=0.002$; $Z=3.350$, $P=0.000$; $Z=2.537$, $P=0.011$), as shown in Table 4 and Figure 4.

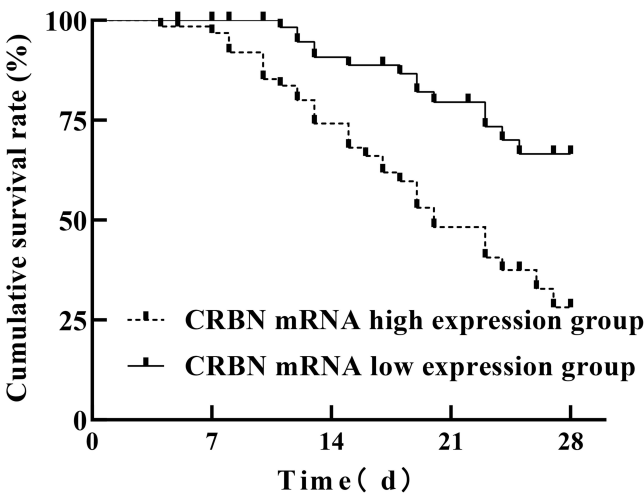


Figure 3 Correlation between CRBN mRNA expression and 28-day prognosis in sepsis patients.
Abbreviation: CRBN, cereblon protein.

Discussion

Sepsis involves a complex pathological mechanism related to the dysregulation of inflammatory response, immune dysfunction, and an abnormal circulatory system which can develop into septic shock, severe sepsis and multiple organ dysfunction. In particular, elderly patients have multiple complications, rapid disease development, and high mortality rate. Early intervention and timely effective treatment are essential to improving the prognosis. Therefore, the early assessment of patient conditions is of great significance.^{10,11}

CRBN is a substrate receptor protein of the CRL4A-E3 ubiquitin ligase complex, with its gene located at 3p26.2 of chromosome 3 and showing extensive expression in tissues such as lung, kidney, pancreas, peripheral blood leukocytes and brain cytoplasm. CRBN acts as an antagonist when activated by T cells, playing a role in the immune function of T cells by regulating the proliferation and activation of T cells and participates in the regulation of tumor drug resistance.^{12,13} Studies have shown that CRBN negatively regulates TLR4 signaling by inhibiting the ubiquitination of tumor necrosis factor receptor-associated factor (TRAF6), thereby affecting the activation of NF-κB pathway and

Table 3 Comparison of Serum CRBN mRNA, CRP and PCT Levels Between Survival Group and Death Group

Groups	Number of Cases	CRBN mRNA	CRP (mg/L)	PCT (ng/mL)
Survival group	83	2.08±0.45	53.23±8.56	9.53±3.23
Death group	47	2.85±0.36	61.39±7.63	14.87±3.76
t	—	10.046	5.991	8.529
P	—	<0.001*	<0.001*	<0.001*

Note: *P < 0.05.
Abbreviations: CRBN, cereblon protein; CRP, C-reactive protein; PCT, procalcitonin.

Table 4 Prognostic Efficacy of CRBN mRNA, CRP and PCT for Sepsis Patients

Indicators	AUC	95% CI	Cutoff value	Sensitivity	Specificity	Youden Index
CRBN mRNA	0.846	0.773~0.904	2.61	76.60%	81.93%	0.585
CRP	0.822	0.745~0.883	59.60 mg/L	72.34%	84.34%	0.567
PCT	0.865	0.794~0.919	12.10ng/mL	82.98%	78.31%	0.613
Combined diagnosis	0.961	0.911~0.987	—	95.74%	86.75%	0.825

Abbreviations: CRBN, cereblon protein; CRP, C-reactive protein; PCT, procalcitonin.

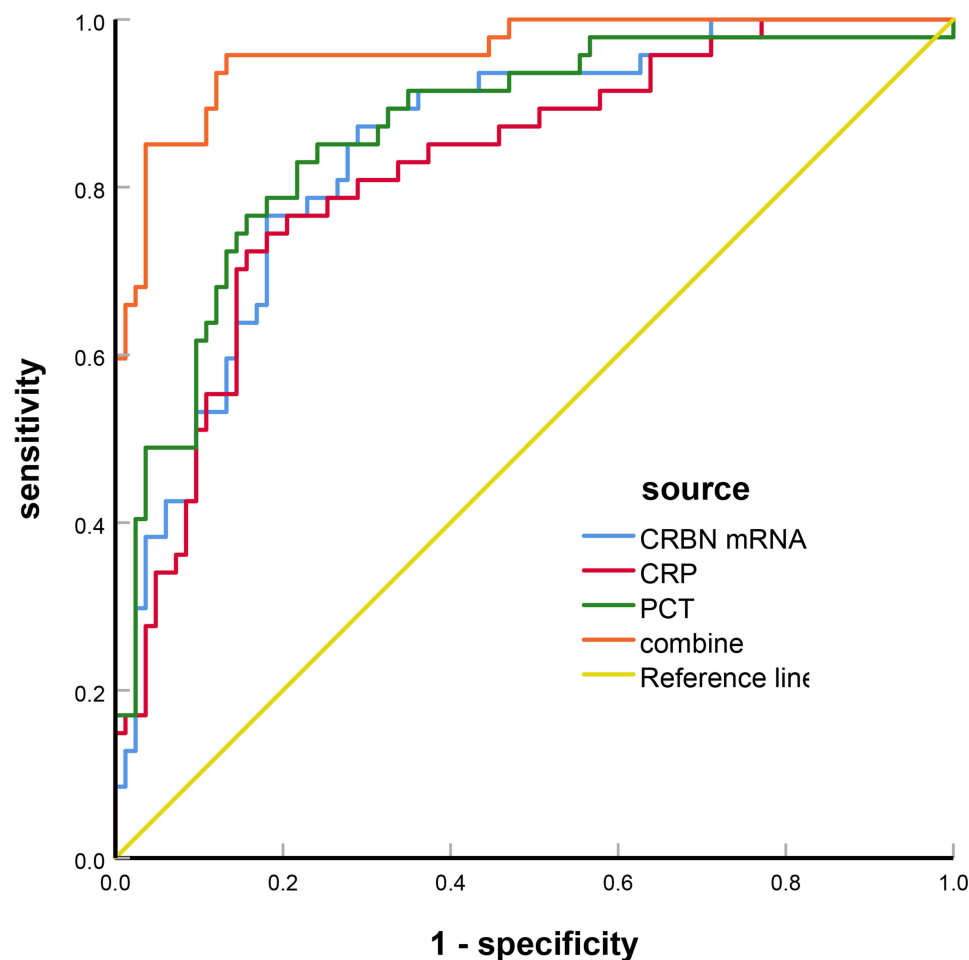


Figure 4 Prognostic value of CRBN mRNA, CRP and PCT for sepsis patients.
Abbreviations: CRBN, cereblon protein; CRP, C-reactive protein; PCT, procalcitonin.

regulating the release of inflammatory factors.¹⁴ He et al¹⁵ found that in sepsis-induced renal injury cell model established by lipopolysaccharid (LPS)-treated human renal 2 (HK2) cells, the knockout of circ_00114428 expression could regulate the CRBN expression by targeting miR-495-3p and inhibit LPS-induced apoptosis, inflammation, oxidative stress and endoplasmic reticulum stress. Other studies have shown that inhibition of CRBN expression can reduce pro-inflammatory cytokines and alleviate lipopolysaccharid-induced acute lung injury by inhibiting oxidative stress and endoplasmic reticulum stress-related NF- κ B signaling pathways.¹⁶ The results of this study show that the expression level of serum CRBN mRNA in patients with sepsis is significantly increased, indicating that abnormal expression of CRBN mRNA is related to the occurrence of sepsis. CRP is an acute inflammatory protein that significantly increases in levels during infection and is often used as a detection indicator to reflect the severity of infection in patients.¹⁷ PCT is a specific indicator of severe bacterial inflammation and fungal infection. Under normal circumstances, the body's PCT level is extremely low, and when infection occurs, serum levels increase.¹⁸ This study also shows that the expression level of serum CRBN mRNA and CRP, PCT gradually increase in patients with mild, moderate, and severe sepsis, and the expression level of CRBN mRNA is positively correlated with CRP, PCT, indicating a correlation between CRBN and the severity of sepsis and reflecting the level of inflammation in the body. This is likely because CRBN regulates the activation of NF- κ B signaling pathway through related pathways, promotes the release of inflammatory factors, aggravates tissue damage, and promotes the sepsis progression.

The APACHEII score and the SOFA score are often used to evaluate the disease severity and predict the prognosis of severe patients. A higher score indicates a more serious condition.^{19,20} In this study, CRBN mRNA expression in sepsis

patients was significantly positively correlated with APACHEII score and SOFA score, which further suggested that CRBN was related to disease severity. In addition, this study also showed that the 28d cumulative survival rate was significantly lower in patients with high CRBN mRNA expression than in patients with low CRBN mRNA expression, and the serum CRBN mRNA expression level was significantly higher in deceased patients than in surviving patients, suggesting that CRBN is associated with the prognosis of sepsis and can be used as a prognostic indicator for sepsis patients. ROC curve analysis showed that the AUC of CRBN mRNA in diagnosing death in sepsis patients was 0.846, with a sensitivity of 76.60% and a specificity of 81.93%. This suggests that CRBN mRNA has certain diagnostic value for the prognosis of sepsis patients, but its diagnostic efficacy is not high. CRP and PCT are often used to diagnose the severity and prognosis of sepsis patients.^{21,22} This study found that serum CRP and PCT levels were significantly increased in sepsis patients in a way that correlated with disease severity and patient prognosis, and CRBN mRNA expression was positively correlated with CRP and PCT levels, indicating that CRBN could reflect the condition and prognosis of sepsis patients. In addition, ROC curve analysis showed that combined diagnosis of sepsis-induced death by CRBN mRNA, CRP and PCT had an AUC of 0.961, a sensitivity of 95.74%, and a specificity of 86.75%. Combined diagnosis had higher efficacy than single detection, suggesting that serum CRBN mRNA, CRP and PCT levels had a certain guiding value in predicting the prognosis of sepsis patients, and CRBN may become a prognostic marker for clinical auxiliary diagnosis of sepsis patients.

In conclusion, the increased expression of CRBN in peripheral blood of sepsis patients is related to the disease severity and prognosis of the patients. The combination of CRP and PCT has certain diagnostic value for the death of sepsis patients. CRBN may be used as a marker for judging the condition and prognosis of sepsis patients. The limitation of this article lies in a single-center study with a small sample size and a short follow-up time for patient prognosis. Subsequent multicenter and studies with an expanded sample size will be conducted, and further in-depth research on the clinical application value of CRBN is needed.

Research Involving Human Participants and/or Animals

This retrospective study involving human participants was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Ethics Committee of Ganzhou People's Hospital (No: 202002128). Written informed consent to participate in this study was provided by the participants or participants' legal guardian (Because some patients are in a coma and unable to communicate, some patients in this study require the consent of their guardians).

Data Sharing Statement

The datasets used during the present study are available from the corresponding author upon reasonable request.

Consent for Publication

All authors have given consent for publication.

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Disclosure

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