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Diagnostic value of serum TLR9 and UCP2 for sepsis complicated with acute kidney injury

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Abstract：Objective To investigate the diagnostic value of serum Toll-like receptor 9 (TLR9) and uncoupling protein 2 (UCP2) for sepsis patients complicated with acute kidney injury（AKI），and to provide a reference for clinical diagnosis and treatment. **Methods** From October 2022 to September 2024，193 sepsis patients admitted to the Intensive Care Unit（ICU）of Sir Run Run Hospital，Nanjing Medical University，were regarded as the sepsis group，and 215 healthy volunteers who underwent physical checkups during the same period were included as the control group. According to whether the patients complicated with AKI，the sepsis patients were assigned into non-AKI group （n=125）and AKI group（n=68）. According to the severity of AKI，the AKI patients were assigned into mild group（n= 34），moderate group（n=23），and severe group（n=11）. Enzyme-linked immunosorbent assay（ELISA）was used to detect serum levels of procalcitonin（PCT），tumor necrosis factor-α（TNF-α），interleukin-1β（IL-1β），TLR9，andUCP2. Fully automated biochemical analyzer was used to detect serum levels of creatinine（Scr），blood urea nitrogen（BUN），cystatin C（CysC），C-reactive protein（CRP），and the fully automated chemiluminescence immunoassay analyzer was used to detect interleukin-6（IL-6）. The Sequential Organ Failure Assessment（SOFA）score was performed to evaluate the degree of organ dysfunction in patients，while the Acute Physiology and Chronic Health Evaluation Ⅱ（APACHE Ⅱ）score was performed to evaluate the severity of the patient's condition. Receiver operating characteristic（ROC）curve was used to analyze the diagnostic value of TLR9 and UCP2 for AKI in sepsis patients. **Results** Compared with the control group，the levels of TLR9［（1.98±0.62）pg/mL vs（1.45±0.34）pg/mL，t=10.849，P<0.05］and UCP2［（104.72±28.45）pg/mL *vs*（75.68±21.67）pg/mL，t=11.665，P<0.05］were higher in the sepsis group. The SOFA score，APACHE Ⅱ score，renal function indicators（Scr，BUN，CysC），inflammatory factors（CRP，PCT，TNF-α，IL-6，IL-β），TLR9 and UCP2 levels in the AKI group were higher than those in the non-AKI group（P< 0.05）. The levels of TLR9 and UCP2 gradually increased with the aggravation of AKI（P<0.05）. The AUC of TLR9 combined UCP2 in the diagnosis of AKI in sepsis patients was 0.917，which was superior to their individual diagnoses（0.806，0.814）（P<0.05）. **Conclusion** The levels of serum TLR9 and UCP2 are higher in sepsis patients and increase with the severity of AKI. The combined diagnosis of the two is valuable for sepsis complicated with AKI.

Keywords： Sepsis；Acute kidney injury；Toll-like receptor 9；Uncoupling protein 2；Interleukin

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, imposing heavy medical and economic burdens worldwide [1]. Acute kidney injury (AKI) is a complex syndrome with relatively high incidence and mortality rates. Meanwhile, sepsis is the main and key triggering factor for the development of AKI. Sepsis complicated with AKI not only prolongs patients' ICU stay duration and increases the risk of complications but also raises their mortality rate [2]. Therefore, diagnosing AKI in sepsis patients is crucial for improving their prognosis.

Toll-like receptor 9 (TLR9) is a pattern recognition receptor that plays a core role in the development and function of the immune system. Innate immune cells, including B cells, express various receptors that can recognize pathogen-associated molecular patterns (PAMPs) of various microorganisms and induce inflammatory immune responses [3]. Studies have found that TLR9 is involved in the pathogenesis of sepsis complicated with AKI. Inhibiting TLR9 expression can enhance autophagy, alleviate kidney injury, inhibit inflammatory responses, and thus reduce the risk of AKI in sepsis [4]. Uncoupling protein 2 (UCP2) is a homolog of uncoupling protein 1 (UCP1). Unlike UCP1, UCP2 does not perform typical H^+ leakage. Instead, it participates in oxidative stress by consuming proton motive force through the mitochondrial inner membrane [5]. Studies in animal models have shown that UCP2 participates in autophagy through adenosine monophosphate-activated protein kinase (AMPK) involved in mitochondrial membrane potential loss, thereby participating in the pathogenesis of sepsis [6]. Therefore, this study selected TLR9 and UCP2, which are related to the pathogenesis of sepsis and AKI, to explore the relationship between these two factors and AKI in sepsis patients.

1 Materials and methods

1.1 Study subjects

A total of 193 sepsis patients admitted to the

Intensive Care Unit (ICU) of Department of Emergency Medicine, Sir Run Run Hospital, Nanjing Medical University from October 2022 to September 2024 were enrolled as the sepsis group, including 98 males and 95 females with an average age of (52.34 ± 8.14) years. Another 215 healthy volunteers who received physical examinations during the same period were selected as the control group, consisting of 114 males and 101 females with an average age of (51.73 ± 7.28) years. Sepsis patients were divided into non-AKI group (*n*=125) and AKI group (*n*=68) based on whether they were complicated with Acute Kidney Injury (AKI). For the non-AKI group: infection sources included 28 cases of abdominal infection, 66 cases of pulmonary infection, and 31 cases of other infections; mechanical ventilation duration was (8.75 ± 1.83) days; ICU stay duration was (11.58 ± 3.21) days. For the AKI group: infection sources were 19 cases of abdominal infection, 36 cases of pulmonary infection, and 13 cases of other infections; mechanical ventilation duration was (9.26 ± 2.38) days; ICU stay duration was (12.43 ± 3.76) days. Patients in the AKI group were further stratified by disease severity into mild group (AKI Stage I, *n*=34), moderate group (AKI Stage II, n=23), and severe group (AKI Stage III, *n*=11).

Inclusion criteria:
(1) Sepsis patients met the diagnostic criteria for sepsis [7];
(2) AKI occurred within 48 hours after admission, with diagnosis and staging conforming to the corresponding standards [8];
(3) No mental disorders and able to cooperate with treatment;
(4) Informed consent was obtained from the subjects and their family members.

Exclusion criteria:
(1) ICU stay ≤ 48 hours;
(2) AKI induced by renal insufficiency or other non-sepsis factors;
(3) Patients with malignant tumors;
(4) Discontinuation of treatment halfway;
(5) Use of nephrotoxic drugs within 3 months prior to admission.

This study was approved by the Ethics Committee of Sir Run Run Hospital, Nanjing Medical University.

1.2 Treatment methods

1.2.1 Serum factor detection

A total of 5 mL of peripheral venous blood was collected from sepsis patients immediately after admission. The supernatant was isolated via low-temperature centrifugation. Serum levels of procalcitonin (PCT) (Elabscience, E-TSEL-H0002), tumor necrosis factor-α (TNF-α) (MLBio, ml077385), interleukin-1β (IL-1β) (Jining Biotechnology, JN19669), toll-like receptor 9 (TLR9) (Fine Biotech, EH1019), and uncoupling protein 2 (UCP2) (Keluo Bio, ELK3106) were measured using the Enzyme-Linked Immunosorbent Assay (ELISA). Serum creatinine (Scr), blood urea nitrogen (BUN), cystatin C (CysC), and C-reactive protein (CRP) were analyzed with an automatic biochemical analyzer (Shengda Yixin Medical Technology, BS-430). Interleukin-6 (IL-6) was detected via an automatic chemiluminescence immunoassay analyzer (Mindray, CL-2200i).

1.2.2 Disease severity assessment

The Sequential Organ Failure Assessment (SOFA) score was used to evaluate organ dysfunction, based on six key systems: respiratory, coagulation, liver, cardiovascular, central nervous, and renal. Scores range from 0 (normal function) to 4 (severe dysfunction), with higher scores indicating worse organ failure [9]. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score assessed overall severity via three dimensions: acute physiology, age, and chronic health status—higher scores reflect more severe illness [10].

1.3 Statistical methods

Data analysis was performed using SPSS 25.0 software. Measurement data were expressed as $\bar{x}\pm s$, independent samples t-test for two-group comparisons, and one-way analysis of variance (ANOVA) followed by Student-Newman-Keuls *q* (SNK-*q*) test for pairwise comparisons among three groups. Count data were presented as *n* (%) and compared using the chi-square test. Pearson correlation analysis was used to explore relationships between TLR9/UCP2 levels and SOFA score, APACHE II score, renal function indicators, and inflammatory factors. Receiver operating characteristic (ROC) curve analysis evaluated the diagnostic value of TLR9 and UCP2 for AKI in sepsis patients, and the *Z* test compared differences in the area under the curve (AUC). A P value < 0.05 was considered statistically significant.

2 Results

2.1 Comparison of general data and serum TLR9/UCP2 levels between sepsis group and control group

There were no statistically significant differences in general data including gender, age, body mass index (BMI) smoking status, alcohol consumption, and comorbid underlying diseases between the sepsis group and the control group (P>0.05). However, the serum levels of TLR9 and UCP2 in the sepsis group were higher than those in the control group (P<0.05). **[Table 1]**

2.2 Comparison of general data and serum TLR9/UCP2 levels between non-AKI group and AKI group

There were no statistically significant differences in general data, infection sources, or mechanical ventilation duration between the non-AKI group and the AKI group (P>0.05). The AKI group had higher SOFA scores, APACHE II scores, renal function indicators (Scr, BUN,

CysC), inflammatory factors (CRP, PCT, TNF-α, IL-6, IL-β), and serum levels of TLR9 and UCP2 compared with the non-AKI group (P<0.05). **[Table 2]**

2.3 Comparison of TLR9/UCP2 Levels in AKI patients with different severity degrees

With the increase in AKI severity, serum TLR9 and UCP2 levels gradually increased, and pairwise comparisons showed statistically significant differences (P<0.05). **[Table 3]**

2.4 Correlation Between Serum TLR9/UCP2 Levels and Clinical Indicators in AKI Patients

Pearson correlation analysis revealed that serum TLR9 and UCP2 levels in AKI patients were positively correlated with SOFA scores, APACHE II scores, renal function indicators (Scr, BUN, CysC), and inflammatory factors (CRP, PCT, TNF-α, IL-6, IL-β), respectively (P<0.05). **[Table 4]**

2.5 Diagnostic value of serum TLR9 and UCP2 for AKI occurrence in sepsis patients

The AUC values of TLR9 and UCP2 alone for diagnosing AKI in sepsis patients were 0.806 (95% *CI*: 0.743-0.860) and 0.814 (95%CI: 0.752-0.866), respectively. The AUC of their combined diagnosis was 0.917 (95% *CI*:0.869-0.952), which was superior to the AUC of each alone ($Z_{combined/TLR9}$=3.899, P<0.01; $Z_{combined/UCP2}$=3.836, P<0.01).**[Table5 & Figure1]**

Tab.1 Comparison of general data, serum TLR9 and UCP2 levels between sepsis group and control group

Item	Control group（n=215）	Sepsis group（n=193）	t/χ^2 value	P value
Gender [male, n(%)]	114（53.02）	98（50.78）	0.206	0.650
Age (years, $\bar{x}\pm s$)	51.73±7.28	52.34±8.14	0.799	0.425
BMI (kg/m², $\bar{x}\pm s$)	22.45±2.36	22.28±2.31	0.734	0.464
Smoking [n(%)]	91（42.33）	86（44.56）	0.207	0.649
Alcohol consumption [n(%)]	52（24.19）	57（29.53）	1.486	0.223
Comorbidities [n(%)]				
Hypertension	28（13.02）	22（11.40）	0.250	0.617
Diabetes mellitus	34（15.81）	25（12.95）	0.673	0.412
Coronary heart disease	21（9.77）	16（8.29）	0.269	0.604
TLR9（pg/mL,$\bar{x}\pm s$）	1.45±0.34	1.98±0.62	10.849	<0.001
UCP2（pg/mL,$\bar{x}\pm s$）	75.68±21.67	104.72±28.45	11.665	<0.001

Note: Coronary heart disease is coronary atherosclerotic cardiopathy.

Tab.2 Comparison of general data and serum TLR9, UCP2 levels between non-AKI group and AKI group

Item	Non-AKI group (n=125)	AKI group (n=68)	t/χ^2 value	P value
Male [n(%)]	61（48.80）	37（54.41）	0.555	0.456
Age (years, $\bar{x}\pm s$)	52.17±7.86	52.65±8.54	0.393	0.695
BMI (kg/m², $\bar{x}\pm s$)	22.36±2.28	22.14±2.33	0.635	0.526
Smoking [n(%)]	54（43.20）	32（47.06）	0.265	0.606
Alcohol consumption [n(%)]	36（28.80）	21（30.88）	0.092	0.762
Comorbidities [n(%)]				
Hypertension	25（20.00）	16（23.53）	0.328	0.567
Diabetes mellitus	31（24.80）	23（33.82）	1.780	0.182
Coronary heart disease	18（14.40）	12（17.65）	0.354	0.552
Infection position [n(%)]			1.179	0.555
Abdominal infection	28（22.40）	19（27.94）		
Pulmonary infection	66（52.80）	36（52.94）		
Others	31（24.80）	13（19.12）		
Mechanical ventilation duration (d,$\bar{x}\pm s$)	8.75±1.83	9.26±2.38	1.659	0.099
ICU stay duration (days,$\bar{x}\pm s$)	11.58±3.21	12.43±3.76	1.653	0.100
Total hospital stay (days, $\bar{x}\pm s$)	19.65±4.83	20.43±6.24	0.694	0.336
SOFA score (points, $\bar{x}\pm s$)	16.72±3.74	20.15±4.21	5.820	<0.001
APACHE II score (points，$\bar{x}\pm s$)	9.46±3.02	11.84±3.27	5.079	<0.001
Renal function indicators ($\bar{x}\pm s$)				
Scr (μmol/L)	47.26±13.54	72.58±21.48	10.026	<0.001
BUN (mmol/L)	6.25±1.82	8.47±2.26	7.420	<0.001
CysC (mg/L)	4.38±1.67	6.14±1.85	6.731	<0.001
Inflammatory factors ($\bar{x}\pm s$)				
CRP (mg/L)	65.47±17.36	83.51±22.49	6.198	<0.001
PCT (ng/mL)	8.52±2.68	11.64±3.17	7.236	<0.001
TNF-α (ng/L)	68.45±12.38	81.61±18.47	5.899	<0.001
IL-6 (ng/L)	114.75±28.27	136.28±38.41	4.438	<0.001
IL-β (ng/L)	32.47±7.31	38.68±8.42	5.340	<0.001
TLR9 (pg/mL)	1.85±0.38	2.21±0.62	4.997	<0.001
UCP2 (pg/mL)	95.78±23.54	121.23±36.78	5.847	<0.001

Tab.3 Comparison of TLR9 and UCP2 levels in AKI patients with different severity degrees

Group	case	TLR9（pg/mL）	UCP2（pg/mL）
Mild group	34	1.68±0.45	87.71±21.57
Moderate group	23	2.15±0.57[a]	110.38±27.46[a]
Severe group	11	2.56±0.68[ab]	145.45±41.24[ab]
***F* value**		13.076	19.136
***P* value**		<0.001	<0.001

Note: Compared with the mild hroup, [a]*P*<0.05; compared with the moderate group, [b]*P*<0.05.

Tab.4 Correlation analysis between serum TLR9, UCP2 levels and clinical indicators in AKI patients

Item	TLR9		UCP2	
	r value	*P* value	*r* value	*P* value
SOFA	0.418	<0.001	0.434	<0.001
APACHE II	0.432	<0.001	0.415	<0.001
Renal function indicators				<0.001
Scr	0.436	<0.001	0.434	<0.001
BUN	0.453	<0.001	0.426	<0.001
CysC	0.421	<0.001	0.412	<0.001
Inflammatory factors		<0.001		<0.001
CRP	0.421	<0.001	0.423	<0.001
PCT	0.458	<0.001	0.434	<0.001
TNF-α	0.426	<0.001	0.451	<0.001
IL-6	0.449	<0.001	0.439	<0.001
IL-β	0.428	<0.001	0.417	<0.001

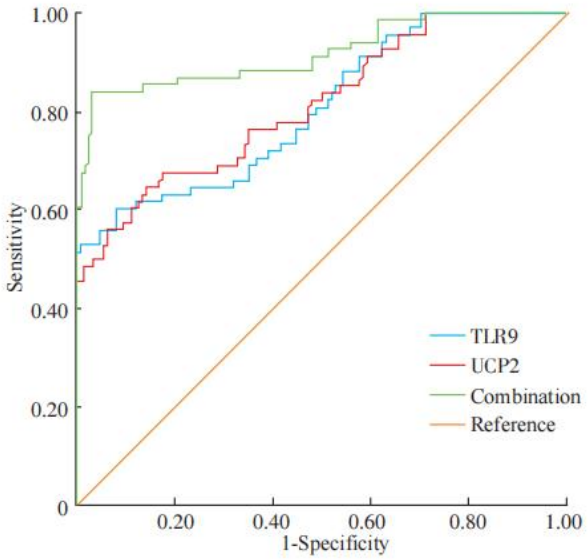

Fig.1 ROC curve of TLR9 and UCP2 for diagnosing AKI in sepsis patients

Tab.5 Diagnostic value of TLR9 and UCP2 for AKI occurrence in sepsis patients

Indicators	AUC	95%*CI*	*P* value	Cut-off value	Sensitivity（%）	Specificity（%）	Youden index
TLR9	0.806	0.743-0.860	<0.001	1.981 pg/mL	60.29	92.00	0.523
UCP2	0.814	0.752-0.866	<0.001	107.685 pg/mL	64.71	85.60	0.503
Combination	-	0.869-0.952	<0.001	-	83.82	96.80	0.806

3 Discussion

Sepsis is a life-threatening clinical syndrome characterized by organ dysfunction caused by a dysregulated host response to infection. Approximately 50% of sepsis cases originate from pulmonary infection, while infections of the digestive system, urinary system, and bloodstream can also lead to sepsis [11]. The pathogenesis of sepsis is complex, mainly due to bacterial endotoxins inducing the body's inflammatory response, causing immune dysfunction, and ultimately leading to extensive damage to various systems and organs [12]. AKI is a severe and common complication of sepsis, and also a risk factor for progression to chronic kidney disease. During sepsis, systemic inflammatory responses lead to vasodilation and increased capillary permeability. Meanwhile, inflammatory mediators can cause renal vasoconstriction, further reducing renal blood flow and glomerular filtration rate, resulting in AKI [13]. A large body of evidence shows that patients diagnosed with sepsis-related AKI have a higher risk of death than those with non-sepsis-related AKI, and usually require longer ICU and hospital stays. In addition, sepsis patients are mainly elderly; with the global aging trend, the number of patients with sepsis-related AKI may continue to increase [14]. Therefore, exploring accurate diagnostic methods is of great significance for the diagnosis and treatment of sepsis-related AKI and improving patients' quality of life.

TLR is a pattern recognition receptor that recognizes nucleic acids of bacteria and viruses, participates in the regulation of adaptive and innate immunity, and prevents microbial invasion. TLR9 recognizes endogenous mitochondrial DNA products released by damaged cells, induces gene transcription, and thus leads to inflammation and cell apoptosis. TLR9 is expressed in various immune cells, and its signaling can regulate the composition and function of the intestinal microbiota [15]. Animal experiments have shown that IL-17A levels in TLR9-knockout mice are significantly lower than those in wild-type mice. Knockout of TLR9 can alleviate AKI in mice, indicating that TLR9 in dendritic cells mediates the production of IL-17A by γδ T cells during sepsis and promotes the occurrence of sepsis-related AKI [16]. Wang *et al.* [17] found that TLR4 levels in sepsis patients were higher than those in the ICU control group and healthy control group, and positively correlated with inflammatory factors IL-6 and IL-1β; TLR4 is an independent risk factor for patient death and may be a target for regulating inflammation and treating sepsis. In this study, the TLR9 level in the sepsis group was higher and gradually increased with the severity of AKI; the SOFA score, APACHE II score, renal function indicators (Scr, BUN, CysC), inflammatory factors (CRP, PCT, TNF-α, IL-6, IL-β), and TLR9 level in the AKI group were all higher than those in the non-AKI group. This

suggests that increased TLR9 levels may activate gene transcription, leading to the release of inflammatory factors and further damage to renal function. Inflammatory factors damage the kidneys through multiple pathways: on one hand, they directly damage renal cells, leading to apoptosis and necrosis; on the other hand, they cause changes in renal hemodynamics, such as renal microvascular occlusion. Furthermore, they activate immune cells to release more inflammatory mediators, forming a cascade reaction like a waterfall, amplifying inflammation and further damaging the kidneys [18]. In this study, TLR9 levels in the AKI group were positively correlated with SOFA score, APACHE II score, renal function indicators, and inflammatory factors. This result indicates that higher TLR9 levels are associated with higher levels of systemic inflammation and more severe renal function damage, suggesting that TLR9 can be a potential indicator for predicting inflammation and renal function.

UCP2 is composed of multiple amino acids with a specific three-dimensional structure; it is a protein located in the inner mitochondrial membrane, mainly expressed in adipose tissue (participating in fat metabolism), pancreas (regulating islet cell function and insulin secretion), and also expressed in the liver (participating in gluconeogenesis and lipid metabolism) and kidneys [19]. In the kidneys, UCP2 may play a role in the function of renal tubular epithelium and renal energy metabolism. Studies have found that UCP2 expression is increased in renal tissues of mice with tubulointerstitial fibrosis; meanwhile, UCP2-knockdown mice show reduced renal fibrosis. It is speculated that UCP2 may promote renal tubular fibrosis by inducing lipid accumulation [20]. In this study, UCP2 levels in sepsis patients were higher than those in the control group, and gradually increased with the severity of AKI; UCP2 levels were also positively correlated with SOFA score, APACHE II score, renal function indicators, and inflammatory factors. This suggests that UCP2 may increase the degree of renal function damage in sepsis patients by participating in renal energy metabolism and inducing lipid accumulation; higher UCP2 levels are associated with higher inflammatory factors and lower renal function. Li *et al.* [21] found that UCP2 is a risk factor for poor prognosis in sepsis patients and can be a potential diagnostic marker for predicting the occurrence and poor prognosis of sepsis. In this study, UCP2 had high specificity for diagnosing AKI in sepsis patients. The AUC and sensitivity were significantly improved when combined with TLR9, and the combined diagnosis was superior to single diagnosis. This suggests that the combined diagnosis of TLR9 and UCP2 has more clinical significance.

In conclusion, the levels of TLR9 and UCP2 in sepsis patients are high and gradually increase with the severity of AKI. Both levels are correlated with systemic inflammation and renal function. The combined diagnosis of TLR9 and UCP2 has certain value for sepsis-related AKI and can be used for clinical personalized treatment. The limitation of this study is that it only explored the relationship between TLR9/UCP2 and the occurrence of sepsis-related AKI, while the specific mechanism of action has not been fully clarified. Future studies can further explore the signaling pathways and molecular mechanisms of the two in this disease, providing a basis for the development of new therapeutic targets.

Conflict of interest None

Reference

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·论 著·

血清TLR9和UCP2对脓毒症并发急性肾损伤的诊断价值

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摘要：目的 探讨血清Toll样受体9(TLR9)、解偶联蛋白2(UCP2)对脓毒症患者并发急性肾损伤(AKI)的诊断价值，为临床诊断和治疗提供参考。**方法** 选择2022年10月至2024年9月南京医科大学附属逸夫医院重症监护室(ICU)的193例脓毒症患者记为脓毒症组，另选同期215例体检的健康志愿者为对照组，根据脓毒症患者是否合并AKI分为非AKI组(n=125)和AKI组(n=68)，根据AKI组患者疾病严重程度分为轻度组(n=34)、中度组(n=23)和重度组(n=11)。酶联免疫吸附试验(ELISA)检测血清降钙素原(PCT)、肿瘤坏死因子-α(TNF-α)、白细胞介素-1β(IL-1β)、TLR9及UCP2水平。全自动生化分析仪检测血清肌酐(Scr)、尿素氮(BUN)、胱抑素C(CysC)及C反应蛋白(CRP)，全自动化学发光免疫分析仪检测白细胞介素-6(IL-6)水平。序贯器官衰竭评估(SOFA)评分评价患者器官功能障碍程度，急性生理与慢性健康状况(APACHE Ⅱ)评分评价患者病情严重程度。受试者工作特征(ROC)曲线分析TLR9、UCP2对脓毒症患者发生AKI的诊断价值。**结果** 与对照组相比，脓毒症组TLR9[(1.98±0.62)pg/mL *vs* (1.45±0.34)pg/mL，t=10.849，P<0.05]、UCP2[(104.72±28.45)pg/mL *vs* (75.68±21.67)pg/mL，t=11.665，P<0.05]水平较高；AKI组SOFA评分、APACHE Ⅱ评分、肾功能指标(Scr、BUN、CysC)、炎症因子(CRP、PCT、TNF-α、IL-6、IL-1β)及TLR9、UCP2水平高于非AKI组(P<0.05)；TLR9、UCP2水平随着AKI严重程度的增加逐渐升高(P<0.05)；TLR9、UCP2联合诊断脓毒症患者发生AKI的AUC为0.917，优于各自单独诊断(0.806、0.814)(P<0.05)。**结论** 脓毒症患者血清TLR9、UCP2水平较高，并随着AKI严重程度的增加而升高，两者联合诊断脓毒症并发AKI具有一定价值。

关键词： 脓毒症；急性肾损伤；Toll样受体9；解偶联蛋白2；白细胞介素
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Diagnostic value of serum TLR9 and UCP2 for sepsis complicated with acute kidney injury

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Abstract: Objective To investigate the diagnostic value of serum Toll-like receptor 9 (TLR9) and uncoupling protein 2 (UCP2) for sepsis patients complicated with acute kidney injury (AKI), and to provide a reference for clinical diagnosis and treatment. **Methods** From October 2022 to September 2024, 193 sepsis patients admitted to the Intensive Care Unit (ICU) of Sir Run Run Hospital, Nanjing Medical University, were regarded as the sepsis group, and 215 healthy volunteers who underwent physical checkups during the same period were included as the control group. According to whether the patients complicated with AKI, the sepsis patients were assigned into non-AKI group (n=125) and AKI group (n=68). According to the severity of AKI, the AKI patients were assigned into mild group (n=34), moderate group (n=23), and severe group (n=11). Enzyme-linked immunosorbent assay (ELISA) was used to detect serum levels of procalcitonin (PCT), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), TLR9, and

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UCP2. Fully automated biochemical analyzer was used to detect serum levels of creatinine (Scr), blood urea nitrogen (BUN), cystatin C (CysC), C-reactive protein (CRP), and the fully automated chemiluminescence immunoassay analyzer was used to detect interleukin-6 (IL-6). The Sequential Organ Failure Assessment (SOFA) score was performed to evaluate the degree of organ dysfunction in patients, while the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score was performed to evaluate the severity of the patient's condition. Receiver operating characteristic (ROC) curve was used to analyze the diagnostic value of TLR9 and UCP2 for AKI in sepsis patients. **Results** Compared with the control group, the levels of TLR9 [(1.98±0.62)pg/mL *vs* (1.45±0.34)pg/mL, t=10.849, P<0.05] and UCP2 [(104.72±28.45)pg/mL *vs* (75.68±21.67)pg/mL, t=11.665, P<0.05] were higher in the sepsis group. The SOFA score, APACHE Ⅱ score, renal function indicators (Scr, BUN, CysC), inflammatory factors (CRP, PCT, TNF-α, IL-6, IL-1β), TLR9 and UCP2 levels in the AKI group were higher than those in the non-AKI group (P<0.05). The levels of TLR9 and UCP2 gradually increased with the aggravation of AKI (P<0.05). The AUC of TLR9 combined UCP2 in the diagnosis of AKI in sepsis patients was 0.917, which was superior to their individual diagnoses (0.806, 0.814) (P<0.05). **Conclusion** The levels of serum TLR9 and UCP2 are higher in sepsis patients and increase with the severity of AKI. The combined diagnosis of the two is valuable for sepsis complicated with AKI.

Keywords: Sepsis; Acute kidney injury; Toll-like receptor 9; Uncoupling protein 2; Interleukin

脓毒症是一种因宿主对感染反应失调而导致的危及生命的器官功能障碍,在世界范围内造成沉重的医疗负担和经济负担[1]。急性肾损伤(acute kidney injury,AKI)是一种复杂的综合征,具有相当高的发病率和死亡率。同时,脓毒症是AKI发生的主要且关键促发因素。脓毒症合并AKI不仅延长患者在ICU治疗时间,增加并发症风险,还增加了患者的死亡率[2]。因此,诊断脓毒症患者发生AKI对改善患者预后至关重要。

Toll样受体(TLR)9是模式识别受体,在免疫系统的发育和功能中发挥核心作用,包括B细胞在内的先天免疫细胞表达各种受体,能够识别各种微生物的病原体相关分子模式,并诱导炎症免疫反应[3]。研究发现,TLR9参与脓毒症并发AKI的发病机制,抑制TLR9表达能够增强自噬,减轻肾损伤,抑制炎症反应,进而降低脓毒症发生AKI的风险[4]。解偶联蛋白2(UCP2)是解偶联蛋白1(UCP1)的同源物,与UCP1不同,UCP2不执行典型的H^+泄露,通过线粒体内膜消耗质子动力来参与氧化应激[5]。动物模型研究中发现,UCP2通过单磷酸腺苷激活蛋白激酶参与线粒体膜电位损失调控自噬,进而参与脓毒症发病机制的调控[6]。因此,本研究选择与脓毒症及AKI发病机制相关的TLR9、UCP2,探讨两者与脓毒症患者并发AKI的关系。

1 对象与方法

1.1 研究对象 选择2022年10月至2024年9月南京医科大学附属逸夫医院重症监护室(ICU)的193例脓毒症患者为研究对象(脓毒症组),其中男98例,女95例,年龄(52.34±8.14)岁。另选同期215例体检的健康志愿者为对照组,其中男114例,女101例,年龄(51.73±7.28)岁。根据患者是否合并AKI将脓毒症患者分为非AKI组(n=125)和AKI组(n=68)。非AKI组感染来源:腹腔感染28例,肺部感染66例,其他31例;机械通气时间(8.75±1.83)d,住ICU时间(11.58±3.21)d。AKI组感染来源:腹腔感染19例,肺部感染36例,其他13例;机械通气时间(9.26±2.38)d,住ICU时间(12.43±3.76)d。根据AKI组患者疾病严重程度分为轻度组(AKI Ⅰ期,n=34)、中度组(AKI Ⅱ期,n=23)和重度组(AKI Ⅲ期,n=11)。纳入标准:(1)脓毒症患者符合脓毒症诊断标准[7];(2)入院48 h内发生AKI,诊断及分期符合相应标准[8];(3)无精神疾病,且能够配合治疗;(4)受试者本人及家属知情同意。排除标准:(1)入住ICU时间≤48 h;(2)肾功能不全或其他因素诱发的AKI;(3)恶性肿瘤患者;(4)中途放弃治疗;(5)3个月内服用肾毒素性药物。本研究经南京医科大学附属逸夫医院伦理委员会批准通过。

1.2 研究方法

1.2.1 血清因子检测 取脓毒症患者入院后外周静脉血5 mL,低温离心取上清液,酶联免疫吸附试验(ELISA)检测血清降钙素原(PCT)(伊莱瑞特,E-TSEL-H0002)、肿瘤坏死因子-α(TNF-α)(酶联生物,ml077385)、白细胞介素(IL)-1β(纪宁生物,JN19669)、TLR9(菲恩生物,EH1019)、UCP2(科鹿生物,ELK3106)水平。全自动生化分析仪(晟达亿新医疗科技,BS-430)检测血清肌酐(Scr)、尿素氮(BUN)、胱抑素C(CysC)、C反应蛋白(CRP)。全自动化学发光免疫分析仪(迈瑞,CL-2200i)检测IL-6。

1.2.2 疾病严重程度评估 采用序贯器官衰竭评估

(SOFA)评分评估患者器官功能障碍程度,根据呼吸、凝血、肝脏、心血管、中枢神经和肾脏六个主要器官系统的功能状态进行评分,范围为0(功能正常)~4(严重功能障碍)分,评分越高,各器官衰竭程度也越高[9]。急性生理与慢性健康状况(APACHE Ⅱ)评分从急性生理、年龄和慢性健康三部分评估患者病情严重程度,分数越高,病情越严重[10]。

1.3 统计学方法 采用SPSS 25.0软件进行数据分析。计量资料以$\bar{x}\pm s$表示,两组比较用独立样本t检验,三组间比较用单因素方差分析及两两比较的SNK-q检验;计数资料以例(%)表示,组间用χ^2检验比较;Pearson相关用于分析TLR9、UCP2水平与SOFA评分、APACHE Ⅱ评分、肾功能指标、炎症因子的相关性;受试者工作特征(ROC)曲线分析TLR9、UCP2对脓毒症患者发生AKI的诊断价值,Z检验比较曲线下面积(AUC)的差异。P<0.05为差异有统计学意义。

2 结 果

2.1 脓毒症组和对照组一般资料及血清TLR9、UCP2水平比较 脓毒症组和对照组性别、年龄、身体质量指数(BMI)、吸烟、饮酒、合并基础疾病等一般资料比较差异无统计学意义(P>0.05),但脓毒症组TLR9、UCP2水平高于对照组(P<0.05)。见表1。

2.2 非AKI组和AKI组一般资料及血清TLR9、UCP2水平比较 非AKI组和AKI组一般资料、感染来源、机械通气时间等比较差异无统计学意义(P>0.05);AKI组SOFA评分、APACHE Ⅱ评分、肾功能指标(Scr、BUN、CysC)、炎症因子(CRP、PCT、TNF-α、IL-6、IL-1β)及TLR9、UCP2水平高于非AKI组(P<0.05)。见表2。

2.3 不同严重程度AKI患者TLR9、UCP2水平比较 随着患者AKI严重程度的增加,血清TLR9、UCP2水平逐渐升高,两两比较差异有统计学意义(P<0.05)。见表3。

2.4 AKI患者血清TLR9、UCP2水平与临床指标的相关性 Pearson相关分析显示,AKI患者血清TLR9、UCP2水平与SOFA评分、APACHE Ⅱ评分、肾功能指标(Scr、BUN、CysC)、炎症因子(CRP、PCT、TNF-α、IL-6、IL-1β)分别呈正相关(P<0.05)。见表4。

2.5 血清TLR9、UCP2对脓毒症患者发生AKI的诊断价值 TLR9、UCP2单独诊断脓毒症患者发生AKI的AUC分别为0.806(95%CI:0.743~0.860)、0.814(95%CI:0.752~0.866)。两者联合诊断的AUC为0.917(95%CI:0.869~0.952),优于各自单独诊断的AUC($Z_{\text{两者联合/TLR9}}$=3.899,P<0.01;$Z_{\text{两者联合/UCP2}}$=3.836,P<0.01)。见表5、图1。

表1 脓毒症组和对照组一般资料及血清TLR9、UCP2水平比较
Tab.1 Comparison of general data, serum TLR9 and UCP2 levels between sepsis group and control group

项目	对照组(n=215)	脓毒症组(n=193)	χ^2/t值	P值
男性[例(%)]	114(53.02)	98(50.78)	0.206	0.650
年龄(岁,$\bar{x}\pm s$)	51.73±7.28	52.34±8.14	0.799	0.425
BMI(kg/m^2,$\bar{x}\pm s$)	22.45±2.36	22.28±2.31	0.734	0.464
吸烟[例(%)]	91(42.33)	86(44.56)	0.207	0.649
饮酒[例(%)]	52(24.19)	57(29.53)	1.486	0.223
基础疾病[例(%)]				
高血压	32(14.88)	41(21.24)	2.800	0.094
糖尿病	43(20.00)	54(27.98)	3.573	0.059
冠心病	21(9.77)	30(15.54)	3.103	0.078
TLR9(pg/mL,$\bar{x}\pm s$)	1.45±0.34	1.98±0.62	10.849	<0.001
UCP2(pg/mL,$\bar{x}\pm s$)	75.68±21.67	104.72±28.45	11.665	<0.001

注:冠心病为冠状动脉粥样硬化性心脏病。

表2 非AKI组和AKI组一般资料及血清TLR9、UCP2水平比较
Tab.2 Comparison of general data, serum TLR9 and UCP2 levels between non-AKI group and AKI group

项目	非AKI组(n=125)	AKI组(n=68)	χ^2/t值	P值
男性[例(%)]	61(48.80)	37(54.41)	0.555	0.456
年龄(岁,$\bar{x}\pm s$)	52.17±7.86	52.65±8.54	0.393	0.695
BMI(kg/m^2,$\bar{x}\pm s$)	22.36±2.28	22.14±2.33	0.635	0.526
吸烟[例(%)]	54(43.20)	32(47.06)	0.265	0.606
饮酒[例(%)]	36(28.80)	21(30.88)	0.092	0.762
基础疾病[例(%)]				
高血压	25(20.00)	16(23.53)	0.328	0.567
糖尿病	31(24.80)	23(33.82)	1.780	0.182
冠心病	18(14.40)	12(17.65)	0.354	0.552
感染来源[例(%)]				
腹腔感染	28(22.40)	19(27.94)		
肺部感染	66(52.80)	36(52.94)	1.179	0.555
其他	31(24.80)	13(19.12)		
机械通气时间(d,$\bar{x}\pm s$)	8.75±1.83	9.26±2.38	1.659	0.099
住ICU时间(d,$\bar{x}\pm s$)	11.58±3.21	12.43±3.76	1.653	0.100
总住院时间(d,$\bar{x}\pm s$)	19.65±4.83	20.43±6.24	0.694	0.336
SOFA评分(分,$\bar{x}\pm s$)	16.72±3.74	20.15±4.21	5.820	<0.001
APACHE Ⅱ评分(分,$\bar{x}\pm s$)	9.46±3.02	11.84±3.27	5.079	<0.001
肾功能指标($\bar{x}\pm s$)				
Scr(μmol/L)	47.26±13.54	72.58±21.48	10.026	<0.001
BUN(mmol/L)	6.25±1.82	8.47±2.26	7.420	<0.001
CysC(mg/L)	4.38±1.67	6.14±1.85	6.731	<0.001
炎症因子($\bar{x}\pm s$)				
CRP(mg/L)	65.47±17.36	83.51±22.49	6.198	<0.001
PCT(ng/mL)	8.52±2.68	11.64±3.17	7.236	<0.001
TNF-α(ng/L)	68.45±12.38	81.61±18.47	5.899	<0.001
IL-6(ng/L)	114.75±28.27	136.28±38.41	4.438	<0.001
IL-1β(ng/L)	32.47±7.31	38.68±8.42	5.340	<0.001
TLR9(pg/mL)	1.85±0.38	2.21±0.62	4.997	<0.001
UCP2(pg/mL)	95.78±23.54	121.23±36.78	5.847	<0.001

表3　不同严重程度AKI患者TLR9、UCP2水平比较　($\bar{x}\pm s$)

Tab.3　Comparison of TLR9 and UCP2 levels in AKI patients with different severity　($\bar{x}\pm s$)

组别	例数	TLR9(pg/mL)	UCP2(pg/mL)
轻度组	34	1.68±0.45	87.71±21.57
中度组	23	2.15±0.57[a]	110.38±27.46[a]
重度组	11	2.56±0.68[ab]	145.45±41.24[ab]
*F*值		13.076	19.136
*P*值		<0.001	<0.001

注：与轻度组相比，[a]*P*<0.05；与中度组相比，[b]*P*<0.05。

表4　AKI患者血清TLR9、UCP2水平与临床指标的相关性分析

Tab.4　Associations of serum TLR9, UCP2 levels with clinical indicators in AKI patients

项目	TLR9		UCP2	
	*r*值	*P*值	*r*值	*P*值
SOFA	0.418	<0.001	0.434	<0.001
APACHE Ⅱ	0.432	<0.001	0.415	<0.001
肾功能指标				<0.001
Scr	0.436	<0.001	0.434	<0.001
BUN	0.453	<0.001	0.426	<0.001
CysC	0.421	<0.001	0.412	<0.001
炎症因子		<0.001		<0.001
CRP	0.421	<0.001	0.423	<0.001
PCT	0.458	<0.001	0.434	<0.001
TNF-α	0.426	<0.001	0.451	<0.001
IL-6	0.449	<0.001	0.439	<0.001
IL-1β	0.428	<0.001	0.417	<0.001

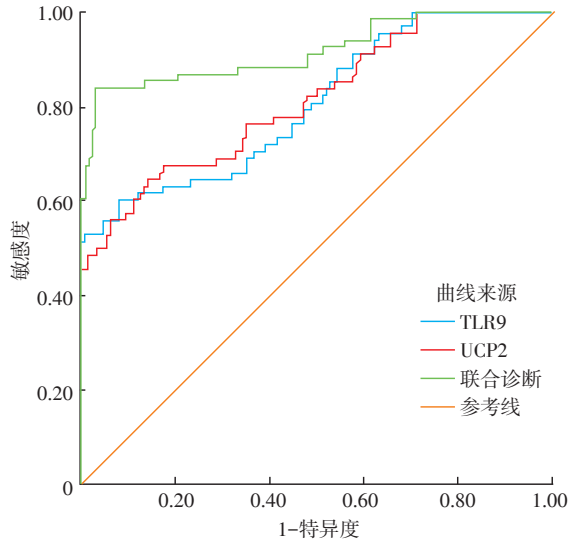

图1　TLR9、UCP2诊断脓毒症患者发生AKI的ROC曲线

Fig.1　ROC curve of TLR9 and UCP2 for diagnosing AKI in sepsis patients

表5　TLR9、UCP2对脓毒症患者发生AKI的诊断价值

Tab.5　Diagnostic value of TLR9 and UCP2 for AKI occurrence in sepsis patients

指标	AUC	95%*CI*	*P*值	截断值	敏感度(%)	特异度(%)	约登指数
TLR9	0.806	0.743~0.860	<0.001	1.981 pg/mL	60.29	92.00	0.523
UCP2	0.814	0.752~0.866	<0.001	107.685 pg/mL	64.71	85.60	0.503
联合	–	0.869~0.952	<0.001	–	83.82	96.80	0.806

3　讨　论

脓毒症是一种危及生命的临床综合征，其特征是宿主对感染的反应失调而导致的器官功能障碍，在所有脓毒症病例中，约50%病例开始于肺部感染，消化系统、泌尿系统、血液感染等也会导致脓毒症发生[11]。脓毒症发病机制复杂，主要是由于细菌内毒素诱导机体炎症反应，引起机体免疫功能紊乱，最终导致全身各系统、器官的广泛损伤[12]。AKI是脓毒症的一种严重且常见的并发症，也是进展为慢性肾脏病的危险因素。脓毒症时，全身炎症反应导致血管扩张，毛细血管通透性增加，同时，炎症介质可引起肾血管收缩，肾血流进一步减少，肾小球过滤率下降，导致AKI发生[13]。大量证据表明，被诊断为脓毒症相关AKI的患者比非脓毒症相关AKI患者具有更高的死亡风险，并且通常需要更长的ICU和住院时间。此外，脓毒症患者以老年人为主，随着全球老龄化趋势，脓毒症相关AKI患者的数量可能会继续增加[14]。因此，探索准确的诊断方法，对脓毒症相关AKI诊断和治疗、改善患者生活质量具有重要意义。

TLR是一种模式识别受体，可以识别细菌和病毒的核酸，参与适应性和先天性免疫的调节，防止微生物入侵。TLR9识别受损细胞释放的内源性线粒体DNA产物，诱导基因转录，从而导致炎症和细胞凋亡，TLR9在多种免疫细胞中表达，其信号传导可以调节肠道微生物群的组成和功能[15]。动物研究结果表明，敲除TLR9小鼠的IL-17A水平显著低于野生型小鼠，敲除TLR9可减轻小鼠的AKI，表明树突状细胞中的TLR9在脓毒症期间介导γδT细胞产生IL-17A，并促进脓毒症AKI的发生[16]。王志辉等[17]研究发现，脓毒症患者TLR4水平高于ICU对照组和健康对照组，与炎症因子IL-6、IL-1β均呈正相关，是患者死亡的独立危险因素，TLR4可能是调节炎症和脓毒症治疗的靶点。本研究中，脓毒症组TLR9水平较高，并随着AKI严重程度的增加逐渐升高，AKI组SOFA评分、APACHE Ⅱ评分、肾功能指标(Scr、BUN、CysC)、炎症因子(CRP、PCT、TNF-α、IL-6、IL-1β)及TLR9水平均高于非AKI组。提示TLR9水平增加可能激活基因转录，导致炎症因子释放，进一步损害肾功能。炎症因子通过多种途径对肾脏造成损伤，一方面，可直接损伤肾脏细胞，导致细胞凋亡和坏死；另一方面，可引起肾脏血流动力学改变，如引发肾脏微血管堵塞等；此外，还可以激活免疫细胞，释放更多的炎症介质，形成瀑布样级联反应，使炎症放大进一步损伤

肾脏[18]。本研究中，AKI组TLR9水平与SOFA评分、APACHE Ⅱ评分、肾功能指标、炎症因子均呈正相关。该结果提示，TLR9水平越高，机体炎症水平和肾功能损伤程度也越高，可作为预测炎症和肾功能的潜在指标。

UCP2由多个氨基酸组成，具有特定的三维结构，是一种存在于线粒体内膜的蛋白质，主要表达于脂肪组织（参与脂肪代谢）、胰腺（调节胰岛细胞功能和胰岛素分泌），在肝脏（参与糖异生、脂质代谢）、肾脏中也有表达[19]。在肾脏中，UCP2可能对肾小管上皮的功能和肾脏能量代谢起作用。研究发现，肾小管间质纤维化小鼠肾组织中UCP2表达增加，同时，UCP2敲低小鼠表现出肾纤维化减轻。推测，UCP2可能通过诱导脂质积累来促进肾小管纤维化[20]。本研究中，脓毒症患者UCP2水平高于对照组，并随着患者AKI严重程度增加而逐渐升高，还与SOFA评分、APACHE Ⅱ评分、肾功能指标、炎症因子呈正相关。提示，UCP2可能通过参与肾脏能量代谢诱导脂质积累来增加脓毒症患者肾功能损伤程度，其水平越高，炎症因子越高，肾功能越低。李依等[21]研究发现，UCP2是脓毒症患者预后不良的危险因素，可作为预测脓毒症发生及预后不良的潜在诊断标志物。本研究中，UCP2对诊断脓毒症患者发生AKI的特异度较高，与TLR9联合后AUC及敏感度显著提升，联合诊断优于单独诊断。提示，TLR9与UCP2联合诊断更具临床意义。

综上所述，脓毒症患者TLR9、UCP2水平较高，并随着AKI严重程度增加而逐渐升高，两者水平与机体炎症水平及肾功能具有相关性，联合诊断脓毒症相关AKI具有一定的价值，可用于临床个性化治疗。本研究不足之处在于，仅探讨了TLR9与UCP2与脓毒症相关AKI发生的关系，而对于其具体的作用机制尚未完全阐明，后续研究可深入探讨两者在该病中的信号通路及分子机制，为开发新的治疗靶点提供依据。

利益冲突 无

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