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Predictive value of serum cartilage glycoprotein-39 and mitochondrial uncoupling protein 2 for prognosis of drug-resistant *Klebsiella pneumoniae* sepsis

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Abstract：Objective To analyze the association of serum levels of cartilage glycoprotein-39（YKL-40），and mitochondrial uncoupling protein 2（UCP2）with the development and prognosis of drug-resistant *Klebsiella pneumoniae*（KP）sepsis. **Methods** A prospective study was conducted on 100 patients with drug-resistant KP sepsis admitted to Suzhou Municipal Hospital Affiliated to Anhui Medical University from January 2022 to June 2023 as the study group，and 103 healthy individuals during the same period were selected as the control group. The study group was further divided into a poor prognosis group（n=38）and a good prognosis group（n=62）based on the 28-day prognosis. Serum levels of YKL-40 and UCP2 were measured using enzyme-linked immunosorbent assay（ELISA）. Multivariate logistic regression analysis was used to identify factors influencing the prognosis of drug-resistant KP sepsis. Receiver operating characteristic（ROC）curves were used to evaluate the predictive value of serum YKL-40 and UCP2 for the prognosis of drug-resistant KP sepsis. **Results** Serum levels of YKL-40, UCP2, procalcitonin (PCT), and white blood cell count (WBC) were significantly higher in the study group compared to those in the control group（P<0.05）. The poor prognosis group had significantly higher serum levels of YKL-40 [（54.15±9.43）ng/mL vs（41.59±5.76）ng/mL，t=8.279，P<0.01] and UCP2 [（175.42 ± 26.81）ng/L *vs*（117.63 ± 17.02）ng/L，t=13.198，P<0.01] than those in the good prognosis group. Additionally，the Acute Physiology and Chronic Health Evaluation Ⅱ（APACHE Ⅱ）score，Sequential Organ Failure Assessment（SOFA）score，PCT，and WBC were significantly higher in the poor prognosis group than those in the good prognosis group（P<0.05）. Logistic regression analysis identified serum YKL - 40（OR= 1.522），UCP2（OR=1.658），APACHE Ⅱ score（OR=1.885），SOFA score（OR=1.973），and PCT（OR=2.014）as factors influencing the prognosis of drug-resistant KP sepsis（P<0.05）. ROC curve analysis showed that the area under the curve（AUC）for serum YKL-40 in predicting the prognosis of drug-resistant KP sepsis was 0.774（95%CI: 0.680-0.852）with a sensitivity of 71.05%；for serum UCP2，the AUC was 0.778（95%CI: 0.683-0.855）with a sensitivity of 68.42%. The combined prediction of serum YKL-40 and UCP2 had a sensitivity of 89.47% and an AUC of 0.899（95% CI: 0.822-0.950），which was significantly higher than the AUC for serum YKL-40 alone（Z=2.297，P=0.022）or UCP2 alone（Z=2.152，P=0.031）. **Conclusion** Serum levels of YKL-40 and UCP2 are elevated in patients with drug- resistant KP sepsis，and their combined use has a high predictive value for 28-day prognosis of drug-resistant KP sepsis.

Keywords： *Klebsiella pneumoniae*；Drug - resistant；Sepsis；Cartilage glycoprotein-39；Mitochondrial uncoupling protein 2

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Sepsis is an extremely severe organ dysfunction syndrome with a high incidence worldwide, affecting people of all ages [1]. Sepsis is mostly caused by trauma or infection; infections with pathogens such as bacteria and fungi can lead to sepsis. People with low immunity, those receiving invasive treatment, and the elderly/young children are more susceptible to the disease [2-3]. *Klebsiella pneumoniae* (KP) is one of the main bacteria causing nosocomial infections [4-5]. With the increased use of antibiotics, the number of sepsis cases caused by drug-resistant KP is also rising [6]. Serological indicators have high application value in the prognostic evaluation of sepsis. Previous studies have reported that cartilage glycoprotein-39 (YKL-40) and mitochondrial uncoupling protein 2 (UCP2) are closely related to the development and development of sepsis. Currently, there are few studies on YKL-40 in sepsis. Although some studies suggest that serum UCP2 has predictive value for sepsis prognosis, the reported predictive efficacy is inconsistent, and the predictive value of both indicators for the prognosis of drug-resistant KP sepsis remains unclear [7-8]. Therefore, this study aims to detect the

serum levels of YKL-40 and UCP2 in patients with drug-resistant KP sepsis, analyze the relationship between YKL-40/UCP2 and the development and prognosis of drug-resistant KP sepsis, and provide assistance for the clinical treatment of drug-resistant KP sepsis. The report is as follows.

1 Materials and methods

1.1 General information

A total of 100 patients with sepsis caused by drug-resistant KP admitted to Suzhou Municipal Hospital Affiliated to Anhui Medical University from January 2022 to June 2023 were prospectively selected as the study group. Inclusion criteria: (1) Age ≥ 18 years old; (2) Meeting the sepsis diagnostic criteria [9]; ,(3) Drug-resistant KP detected in blood culture; (4) Complete clinical data.Exclusion criteria: (1) Pregnant or lactating women; (2) Severe mental illness; (3) History of malignant tumors; (4) History of organ transplantation; (5) Connective tissue diseases; (6) Hematological diseases. In addition, 103 healthy volunteers during the same period were selected as the control group. Inclusion criteria: (1) Normal heart, liver and kidney functions; (2) No malignant tumors or autoimmune diseases; (3) Age ≥ 18 years old. Exclusion criteria: (1) Pregnant or lactating status; (2) History of surgery within the past six months; (3) History of infection within the past three months. This study was approved by the Medical Ethics Committee of Suzhou Municipal Hospital Affiliated to Anhui Medical University (approval number: 2115023), and all subjects participated voluntarily. There was no statistically significant difference in baseline data between the two groups ($P < 0.05$). **[Table 1]**

1.2 Methods

1.2.1 Detection of serum YKL-40 and UCP2 levels

A total of 3 mL fasting venous blood were collected from both groups in the morning (the study group's samples were obtained within 24 hours after admission). Serum was separated after centrifugation. The concentrations of serum YKL-40 (catalog number: BJ-E3161; Shanghai Bangjing Industrial Co., Ltd.) and UCP2 (catalog number: BY-P33059R; Shanghai Baiyi Biotechnology Co., Ltd.) were measured strictly following the instructions of enzyme-linked immunosorbent assay (ELISA) kits. Each sample was tested in triplicate to get the optical density (OD) value at 450 nm, and the concentrations of YKL-40 and UCP2 were calculated accordingly.

1.2.2 Detection of related scores and inflammatory indicators

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score were used to evaluate the severity of patients with drug-resistant KP sepsis. Serum procalcitonin (PCT) was detected by an electrochemiluminescence analyzer, and white blood cell count (WBC) was measured using an automatic hematology analyzer.

1.2.3 Prognosis evaluation

Based on the 28-day prognosis from admission, patients were divided into two groups: the good prognosis group (with two consecutive negative blood cultures, normalized vital signs, and recovered organ function) and the poor prognosis group (with organ failure or death).

1.3 Statistical methods

Data were processed using SPSS 25.0 software. Categorical data were expressed as *n*(%) and analyzed by chi-square test. Normally distributed continuous data were presented as $\bar{x}\pm s$, and compared using independent samples t-test. Multivariate logistic regression analysis was applied to identify the influencing factors of prognosis in drug-resistant KP sepsis patients. Receiver operating characteristic (ROC) curve was used to analyze the predictive value of serum YKL-40 and UCP2 for patient prognosis, and *Z* test was used to compare the area under the ROC curve (AUC). A *P* value < 0.05 was considered statistically significant.

2 Results

2.1 Comparison of general information and serum levels of YKL-40, UCP2 between the study group and control group

The serum levels of YKL-40, UCP2, PCT, and WBC in the study group were significantly higher than those in the control group ($P < 0.05$). **[Table 1]**

Tab.1 Comparison of general information and serum YKL-40 and UCP2 levels between study group and control group

Indicators	Study group (*n*=100)	Control group (*n*=103)	t/χ^2 value	*P* value
Age (years)[a]	65.72±8.63	64.18±8.22	1.302	0.194
Body mass index (BMI, kg/m²)[a]	23.16±2.42	23.48±2.61	0.905	0.366
YKL-40 (ng/mL)[a]	46.36±7.15	24.67±4.93	25.255	<0.001
UCP2 (ng/L)[a]	139.59±20.74	67.11±11.43	30.956	<0.001
PCT (ng/mL)[a]	5.59±0.87	0.38±0.08	60.518	<0.001
WBC (×10⁹/L)[a]	13.15±2.84	6.54±1.92	19.478	<0.001
Gender [*n* (%)]			0.139	0.710
Female	44（44.00）	55（53.40）		
Male	56（56.00）	48（46.60）		
Smoking History [*n* (%)]	38（38.00）	32（31.07）	1.079	0.299
Alcohol drinking history [*n* (%)]	42（42.00）	36（34.95）	1.065	0.302
Past medical history [*n* (%)]				
Diabetes mellitus	37（37.00）	28（27.18）	2.246	0.134
Hypertension	41（41.00）	34（33.01）	1.391	0.238
Chronic pulmonary disease	31（31.00）	27（26.21）	0.570	0.450

Note: [a] represents $\bar{x}\pm s$.

2.2 Comparison of serum YKL-40 and UCP2 levels between the good prognosis group and poor prognosis group

There were 62 patients in the good prognosis group and 38 in the poor prognosis group. The serum levels of YKL-40 and UCP2 in the poor prognosis group were higher than those in the good prognosis group ($P < 0.05$). **[Table 2]**

2.3 Comparison of clinical data between the good prognosis group and poor prognosis group

Compared with the good prognosis group, the poor prognosis group had significantly higher APACHE II scores, SOFA scores, PCT levels, and WBC counts ($P < 0.05$). **[Table 3]**

2.4 Multivariate logistic regression analysis of factors influencing the prognosis of drug-resistant KP sepsis

Taking patient prognosis (good prognosis = 0, poor prognosis = 1) as the dependent variable, and serum YKL-40, UCP2, APACHEII score, SOFA score, PCT, and WBC as independent variables (all continuous variables), logistic regression analysis was performed. The results showed that serum YKL-40 (*OR* = 1.522, 95%*CI*: 1.170–1.979), UCP2 (*OR* = 1.658, 95%*CI:* 1.253–2.194), APACHEII score (*OR* = 1.885, 95%*CI:* 1.307–2.719), SOFA score (*OR* = 1.973, 95%*CI*: 1.419–2.742), and PCT (*OR* = 2.014, 95%*CI*: 1.475–2.750) were independent influencing factors for the prognosis of drug-resistant KP sepsis ($P < 0.05$). **[Table 4]**

2.5 Predictive value of serum YKL-40 and UCP2 for the prognosis of drug-resistant KP sepsis

Taking the prognosis of drug-resistant KP sepsis as the dependent variable and serum YKL-40/UCP2 as test variables, ROC curves were plotted. The results showed that the combined prediction of serum YKL-40 and UCP2 for the prognosis of drug-resistant KP sepsis had a sensitivity of 89.47%, specificity of 82.26%, and an AUC of 0.899. This AUC was significantly higher than that of YKL-40 alone ($Z = 2.297$, $P = 0.022$) and UCP2 alone ($Z = 2.152$, $P = 0.031$). **[Figure 1 & Table 5]**

Tab.2 Comparison of serum YKL-40 and UCP2 levels between the good prognosis group and the poor prognosis group（$\bar{x} \pm s$）

Group	*n*	YKL-40（ng/mL）	UCP2（ng/L）
Good prognosis group	62	41.59±5.76	117.63±17.02
Poor prognosis group	38	54.15±9.43	175.42±26.81
***t* value**		8.279	13.198
***P* value**		＜0.001	＜0.001

Tab.3 Comparison of clinical data between good prognosis group and poor prognosis group

Indicators	Good prognosis group (n=62)	Poor prognosis group (n=38)	t/χ^2 value	*P* value
Age (years)[a]	65.48±8.45	66.11±8.93	0.354	0.724
BMI (kg/m²)[a]	23.13±2.39	23.21±2.46	0.161	0.873
Length of hospital stay (days)[a]	16.56±3.86	17.34±5.48	1.892	0.061
APACHE II score[a]	12.34±3.21	19.71±4.60	9.426	＜0.001
SOFA score[a]	4.15±0.94	8.58±2.03	14.818	＜0.001
PCT (ng/mL)[a]	3.77±0.62	8.56±1.27	25.245	＜0.001
WBC (×10⁹/L)[a]	12.45±2.76	14.28±2.98	3.122	0.002
Gender [n (%)]			0.510	0.475
Female	29（46.77）	15（39.47）		
Male	33（53.23）	23（60.53）		
Smoking history [n (%)]	25（40.32）	13（34.21）	0.374	0.541
Alcohol drinking history [n (%)]	29（46.77）	13（34.21）	1.527	0.217
Past medical history [n (%)]				
Diabetes mellitus	22（35.48）	15（39.47）	0.161	0.688
Hypertension	27（43.55）	14（36.84）	0.438	0.508
Coronary heart disease	15（24.19）	7（18.42）	0.457	0.499
Myocardial infarction	7（11.29）	5（13.16）	0.078	0.780
Heart failure	11（17.74）	6（15.79）	0.064	0.801
Chronic pulmonary disease	18（29.03）	13（34.21）	0.295	0.587

Note: [a]represents $\bar{x}\pm s$; coronary heart disease is coronary atherosclerotic cardiopathy.

Tab.4 Multivariate logistic regression analysis of prognosis in drug-resistant KP sepsis

Variables	β	*SE*	Wald $\chi 2$	*P* value	*OR* value	95% *CI*
YKL-40	0.420	0.134	9.825	0.002	1.522	1.170-1.979
UCP2	0.506	0.143	12.502	＜0.001	1.658	1.253-2.194
APACHEII score	0.634	0.187	11.482	0.001	1.885	1.307-2.719
SOFA score	0.680	0.168	16.362	＜0.001	1.973	1.419-2.742
PCT	0.700	0.159	19.389	＜0.001	2.014	1.475-2.750
WBC	0.226	0.127	3.176	0.075	1.254	0.978-1.608

Tab.5 The predictive value of serum YKL-40 and UCP2 for the prognosis of drug-resistant KP sepsis

Variable	AUC	Cut-off Value	95%CI	Sensitivity (%)	Specificity (%)	Youden Index
YKL-40	0.774	49.19 ng/mL	0.680~0.852	71.05	83.87	0.549
UCP2	0.778	160.00 ng/L	0.683~0.855	68.42	82.26	0.507
Combination	0.899		0.822~0.950	89.47	82.26	0.717

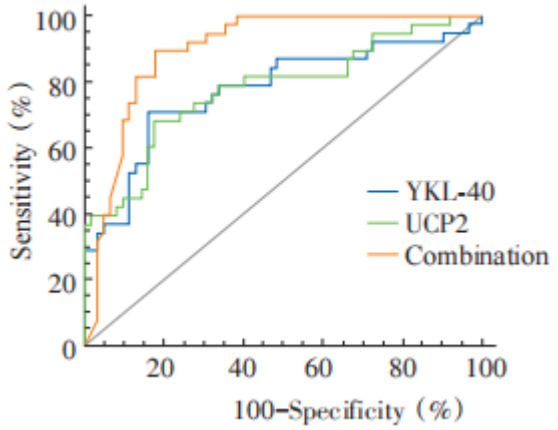

Fig.1 ROC curve of serum YKL-40 and UCP2 in predicting the prognosis of drug-resistant KP sepsis

3 Discussion

Fever/hypothermia, tachypnea, edema, and other symptoms are typical of sepsis. Sepsis caused by drug-resistant Klebsiella pneumoniae (KP) also presents with complications such as liver abscess, urinary tract infection, pneumonia, and meningitis. Moreover, sepsis induced by drug-resistant KP mostly affects inpatients and has an extremely high mortality rate [10-11]. Gram-negative bacteria are the main pathogens causing sepsis; among them, the number of sepsis cases due to drug-resistant KP is second only to Escherichia coli, and its detection rate has been rising year by year [12]. Drug-resistant KP is resistant to multiple antibiotics, possibly related to biofilm formation, inactivating enzyme production, and other factors, leading to unsatisfactory treatment outcomes for drug-resistant KP sepsis [13]. Exploring the predictive value of serum YKL-40 and UCP2 for the prognosis of drug-resistant KP sepsis has positive significance for improving its prognosis.

YKL-40 contains 383 amino acids and can be secreted by various cells such as macrophages. It is the only chitinase-like protein in the human genome, and the human YKL-40 coding gene is located on chromosome 1 [14]. YKL-40 can mediate inflammatory responses and has become a novel inflammatory marker, playing an important role in the progression of diseases like pneumonia, hepatitis B virus infection, and tumors [15]. He Wei *et al.* [16] reported that serum YKL-40 levels were elevated in patients with urinary tract infection after percutaneous nephrolithotomy, which may be associated with the inflammatory response mediated by YKL-40. In this study, serum YKL-40 in the study group was significantly higher than that in the control group, suggesting that YKL-40 levels may be linked to the occurrence of drug-resistant KP sepsis. Additionally, the results showed that serum YKL-40 levels in the poor prognosis group were higher than those in the good prognosis group, implying YKL-40 is closely related to the prognosis of drug-resistant KP sepsis. Liang Yin *et al.* [17] noted that serum YKL-40 was an independent risk factor for poor prognosis in children with viral pneumonia. Multivariate logistic regression analysis in this study also indicated that the risk of poor prognosis increases with elevated serum YKL-40 levels in patients with drug-resistant KP sepsis. The underlying reason is that higher serum YKL-40 levels indicate a more severe systemic inflammatory response and greater inflammatory damage, thus leading to poor prognosis [18]. ROC curve analysis showed that when serum YKL-40 levels at admission exceed 49.19 ng/mL in patients with drug-resistant KP sepsis, the risk of poor prognosis is higher, with a sensitivity of 71.05%, indicating serum YKL-40 is a promising marker for evaluating drug-resistant KP sepsis.

Currently, five uncoupling proteins (UCP1-UCP5) have been identified in mammals. UCP2 is a protein located on the inner mitochondrial membrane, widely distributed in organs like the heart and liver. It participates in pathophysiological processes by affecting ATP synthesis and reactive oxygen species (ROS) production, and the human UCP2 coding gene is on chromosome 11 [19]. Some studies suggest UCP2 promotes inflammasome activation by influencing macrophage lipid synthesis, thereby mediating inflammatory responses [20]. This study found that serum UCP2 levels in patients with drug-resistant KP sepsis were significantly higher than those in healthy individuals, consistent with previous research [21], indicating UCP2 is associated with the development of drug-resistant KP sepsis. Further comparison of serum UCP2 levels between patients with different prognoses revealed higher levels in the poor prognosis group than in the good prognosis group, and multivariate logistic regression analysis confirmed serum UCP2 as an influencing factor for the prognosis of drug-resistant KP sepsis. Thus, UCP2 is related to the prognosis of drug-resistant KP sepsis; it is speculated that UCP2 affects patient outcomes by mediating processes such as inflammatory responses and oxidative stress [22]. Li Yi *et al.* [23] conducted ROC curve analysis and found serum UCP2 had a sensitivity of 66.67% for predicting 28-day sepsis prognosis, with an optimal cut-off value of 137.30 pg/mL. In this study, ROC curve analysis showed serum UCP2 had an AUC of 0.778 for predicting drug-resistant KP sepsis prognosis, with high specificity—suggesting that when serum UCP2 at admission reaches 160.00 ng/L in patients with drug-resistant KP sepsis, the probability of poor prognosis increases.

Since the predictive performance of a single serum marker is inevitably limited, this study used a parallel test to

analyze the predictive value of combined serum YKL-40 and UCP2 for drug-resistant KP sepsis prognosis. The results showed the combined prediction had a higher AUC than individual markers and improved sensitivity, indicating the combination of YKL-40 and UCP2 can complement each other, compensate for the deficiencies of single-marker prediction, and provide guidance for prognostic evaluation of drug-resistant KP sepsis.

APACHE II and SOFA scores are indispensable for assessing sepsis severity. Logistic regression analysis in this study also confirmed these scores as influencing factors for drug-resistant KP sepsis prognosis. However, due to the disease's complexity, these scores still have limitations in prognostic evaluation. Cai Zhenhua *et al.* [24] reported the AUC of combined APACHE II and SOFA scores for predicting drug-resistant KP sepsis prognosis was 0.873. In this study, the AUC of combined YKL-40 and UCP2 was 0.899, comparable to the predictive efficacy of the combined score model.

In conclusion, serum YKL-40 and UCP2 levels are elevated in patients with drug-resistant KP sepsis, and their combination has high predictive value for prognosis, which helps with clinical prediction of drug-resistant KP sepsis outcomes. Due to limitations in time, personnel, and funding, the sample size of this study is small. Future research will expand the sample size to verify the predictive value of serum YKL-40 and UCP2 for drug-resistant KP prognosis.

Conflict of interest None

Reference

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·论　著·

血清软骨糖蛋白-39与线粒体解偶联蛋白2对耐药肺炎克雷伯菌脓毒症预后的预测价值

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摘要：目的　分析血清软骨糖蛋白-39（YKL-40）、线粒体解偶联蛋白（UCP）2与耐药肺炎克雷伯菌（KP）脓毒症的发生和预后的关系。**方法**　前瞻性选取安徽医科大学附属宿州医院2022年1月至2023年6月收治的100例耐药KP导致的脓毒症患者为研究组，另选取同期103例健康者为对照组。根据研究组患者28 d预后分为预后不良组（n=38）和预后良好组（n=62）。酶联免疫吸附试验（ELISA）检测血清YKL-40、UCP2水平。采用多因素logistic回归分析耐药KP脓毒症预后的影响因素；受试者工作特征（ROC）曲线分析血清YKL-40和UCP2对耐药KP脓毒症预后的预测价值。**结果**　研究组血清YKL-40、UCP2、降钙素原（PCT）水平和白细胞计数（WBC）均显著高于对照组（P<0.05）。预后不良组血清YKL-40[（54.15±9.43）ng/mL *vs*（41.59±5.76）ng/mL，t=8.279，P<0.05]、UCP2[（175.42±26.81）ng/L *vs*（117.63±17.02）ng/L，t=13.198，P<0.05]水平均较预后良好组显著增加。预后不良组急性生理与慢性健康状况Ⅱ（APACHEⅡ）评分、序贯器官衰竭评估（SOFA）评分、PCT水平和WBC显著高于预后良好组（P<0.05）。Logistic回归结果显示，血清YKL-40（OR=1.522）、UCP2（OR=1.658）、APACHEⅡ评分（OR=1.885）、SOFA评分（OR=1.973）和PCT（OR=2.014）为耐药KP脓毒症预后的影响因素（P<0.05）。ROC曲线分析显示，血清YKL-40预测耐药KP脓毒症预后的AUC为0.774（95%CI：0.680~0.852），敏感度为71.05%；血清UCP2预测的AUC为0.778（95%CI：0.683~0.855），敏感度为68.42%；血清YKL-40、UCP2联合预测的AUC为0.899（95%CI：0.822~0.950），敏感度为89.47%，联合预测的AUC显著高于血清YKL-40（Z=2.297，P=0.022）、UCP2（Z=2.152，P=0.031）单独预测的AUC。**结论**　血清YKL-40和UCP2在耐药KP脓毒症患者中水平较高，两者联合预测耐药KP脓毒症28 d预后的价值较高。

关键词：肺炎克雷伯菌；耐药；脓毒症；软骨糖蛋白-39；线粒体解偶联蛋白2
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Predictive value of serum cartilage glycoprotein-39 and mitochondrial uncoupling protein 2 for prognosis of drug-resistant *Klebsiella pneumoniae* sepsis

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Abstract: Objective　To analyze the association of serum levels of cartilage glycoprotein-39 (YKL-40), and mitochondrial uncoupling protein 2 (UCP2) with the occurrence and prognosis of drug-resistant *Klebsiella pneumoniae* (KP) sepsis. **Methods**　Prospectively, 100 patients with drug-resistant KP sepsis admitted to Suzhou Municipal Hospital Affiliated to Anhui Medical University from January 2022 to June 2023 were selected as the study group, and 103 healthy individuals during the same period were selected as the control group. The study group was further divided into a poor prognosis group (n=38) and a good prognosis group (n=62) based on the 28-day prognosis. Serum levels of YKL-40 and UCP2 were measured using enzyme-linked immunosorbent assay (ELISA). Multivariate logistic regression analysis was used to identify factors influencing the prognosis of drug-resistant KP sepsis. Receiver operating

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characteristic (ROC) curves were used to evaluate the predictive value of serum YKL-40 and UCP2 for the prognosis of drug-resistant KP sepsis. **Results** Serum levels of YKL-40, UCP2, procalcitonin (PCT), and white blood cell count (WBC) were significantly higher in the study group compared to those in the control group (P<0.05). The poor prognosis group had significantly higher serum levels of YKL-40 [(54.15±9.43) ng/mL *vs* (41.59±5.76) ng/mL, t=8.279, P<0.05] and UCP2 [(175.42±26.81) ng/L *vs* (117.63±17.02) ng/L, t=13.198, P<0.01] than those in the good prognosis group. Additionally, the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHEⅡ) score, Sequential Organ Failure Assessment (SOFA) score, PCT, and WBC were significantly higher in the poor prognosis group than those in the good prognosis group (P<0.05). Logistic regression analysis identified serum YKL-40 (OR=1.522), UCP2 (OR=1.658), APACHEⅡscore (OR=1.885), SOFA score (OR=1.973), and PCT (OR=2.014) as factors influencing the prognosis of drug-resistant KP sepsis (P<0.05). ROC curve analysis showed that the area under the curve (AUC) for serum YKL-40 in predicting the prognosis of drug-resistant KP sepsis was 0.774 (95%CI: 0.680-0.852) with a sensitivity of 71.05%; for serum UCP2, the AUC was 0.778 (95%CI: 0.683-0.855) with a sensitivity of 68.42%. The combined prediction of serum YKL-40 and UCP2 had a sensitivity of 89.47% and an AUC of 0.899 (95%CI: 0.822-0.950), which was significantly higher than the AUC for serum YKL-40 alone (Z=2.297, P=0.022) or UCP2 alone (Z=2.152, P=0.031). **Conclusion** Serum levels of YKL-40 and UCP2 are elevated in patients with drug-resistant KP sepsis, and their combined use has a high predictive value for 28-day prognosis of drug-resistant KP sepsis.

Keywords: *Klebsiella pneumoniae*; Drug-resistant; Sepsis; Cartilage glycoprotein-39; Mitochondrial uncoupling protein 2

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脓毒症是极其严重的器官功能障碍综合征,在全球具有较高的发病率,任何年龄段均会发病[1]。脓毒症多由创伤或感染引起,细菌、真菌等病原菌感染均能够导致脓毒症。免疫力低下、接受侵入性治疗、高龄/幼龄的人群更容易发病[2-3]。肺炎克雷伯菌(*Klebsiella pneumoniae*,KP)是医院感染的主要细菌之一[4-5]。随着抗生素使用的增加,耐药KP引起的脓毒症病例也越来越多[6]。血清学指标在脓毒症预后评估中具有较高应用价值,既往研究报道,软骨糖蛋白-39(cartilage glycoprotein-39,YKL-40)和线粒体解偶联蛋白(mitochondrial uncoupling protein,UCP)2与脓毒症的发生、发展紧密相关。目前,YKL-40在脓毒症中的研究较少,虽然已有研究认为血清UCP2对脓毒症预后具有预测价值,但报道的预测效能不一致,且二者对耐药KP脓毒症预后的预测价值不明确[7-8]。因此,本研究通过检测耐药KP脓毒症患者血清YKL-40和UCP2水平,分析YKL-40、UCP2与耐药KP脓毒症的发生和预后的关系,为耐药KP脓毒症临床治疗提供帮助。报道如下。

1 资料与方法

1.1 一般资料 前瞻性选取安徽医科大学附属宿州医院2022年1月至2023年6月收治的100例耐药KP导致的脓毒症患者为研究组。纳入标准:(1)年龄≥18岁;(2)符合脓毒症诊断标准[9];(3)血培养出耐药KP;(4)临床资料完整。排除标准:(1)妊娠/哺乳期妇女;(2)严重精神疾病;(3)恶性肿瘤史;(4)器官移植史;(5)结缔组织病;(6)血液系统疾病。另选取同期103例健康志愿者作为对照组。纳入标准:(1)心、肝、肾功能正常;(2)无恶性肿瘤、自身免疫系统疾病;(3)年龄≥18岁。排除标准:(1)妊娠/哺乳期;(2)近六个月内手术史;(3)近三个月感染史。本研究经安徽医科大学附属宿州医院医学伦理委员会批准(批号:2115023),所有对象自愿参与研究。两组基线资料比较差异无统计学意义(P<0.05),见表1。

1.2 方法

1.2.1 血清YKL-40、UCP2水平检测 两组对象采集晨起空腹静脉血3 mL(研究组于入院24 h内采集),离心后取血清,严格依据酶联免疫吸附法(enzyme-linked immunosorbent assay,ELISA)试剂盒说明书检测血清YKL-40(货号:BJ-E3161;上海邦景实业)、UCP2(货号:BY-P33059R;上海白益生物科技)浓度,每份样本重复检测3次,获取450 nm处光密度(optical density,OD)值,并计算样本中YKL-40、UCP2的浓度。

1.2.2 相关评分及炎症指标检测 急性生理与慢性健康状况Ⅱ(Acute Physiological and Chronic Health Conditions Ⅱ,APACHEⅡ)评分及序贯器官衰竭评估(Sequential Organ Failure Assessment,SOFA)评分用于评估耐药KP脓毒症患者严重程度。电化学发光

仪检测血清降钙素原(procalcitonin, PCT),全自动血细胞分析仪检测白细胞计数(white blood cell count, WBC)。

1.2.3　预后评估　根据患者自入院起28 d预后分为预后良好组(连续2次血培养阴性,生命体征恢复正常、器官功能恢复)和预后不良组(器官衰竭、死亡)。

1.3　统计学方法　采用SPSS 25.0软件处理数据。计数资料用例(%)表示,采用χ^2检验。正态分布的计量资料用 $\bar{x}\pm s$ 表示,采用独立样本 t 检验。采用多因素logistic回归分析耐药KP脓毒症预后的影响因素;采用受试者工作特征(receiver operating characteristic,ROC)曲线分析血清YKL-40和UCP2对患者预后的预测价值,ROC曲线下面积(area under the ROC curve, AUC)的比较采用Z检验。P<0.05为差异有统计学意义。

2　结　果

2.1　研究组与对照组一般资料及血清YKL-40、UCP2水平比较　研究组血清YKL-40、UCP2、PCT和WBC水平均显著高于对照组(P<0.05)。见表1。

2.2　预后良好组与预后不良组血清YKL-40和UCP2比较　预后良好组62例,预后不良组38例。预后不良组血清YKL-40、UCP2水平高于预后良好组(P<0.05)。见表2。

2.3　预后良好组与预后不良组临床资料比较　与预后良好组比较,预后不良组APACHEⅡ评分、SOFA评分、PCT和WBC显著较高(P<0.05)。见表3。

表1　研究组与对照组一般资料及血清YKL-40、UCP2水平比较

Tab.1　Comparison of general information, and serum YKL-40 and UCP2 levels between study group and control group

指标	研究组(n=100)	对照组(n=103)	t/χ^2值	P值
年龄(岁)[a]	65.72±8.63	64.18±8.22	1.302	0.194
身体质量指数(kg/m²)[a]	23.16±2.42	23.48±2.61	0.905	0.366
YKL-40(ng/mL)[a]	46.36±7.15	24.67±4.93	25.255	<0.001
UCP2(ng/L)[a]	139.59±20.74	67.11±11.43	30.956	<0.001
PCT(ng/mL)[a]	5.59±0.87	0.38±0.08	60.518	<0.001
WBC(×10⁹/L)[a]	13.15±2.84	6.54±1.92	19.478	<0.001
性别[例(%)]				
女性	44(44.00)	55(53.40)	0.139	0.710
男性	56(56.00)	48(46.60)		
吸烟史[例(%)]	38(38.00)	32(31.07)	1.079	0.299
饮酒史[例(%)]	42(42.00)	36(34.95)	1.065	0.302
既往疾病史[例(%)]				
糖尿病	37(37.00)	28(27.18)	2.246	0.134
高血压	41(41.00)	34(33.01)	1.391	0.238
慢性肺部疾病	31(31.00)	27(26.21)	0.570	0.450

注:[a]为以$\bar{x}\pm s$表示。

2.4　影响耐药KP脓毒症预后的多因素logistic回归分析　患者预后(预后良好=0,预后不良=1)作为因变量,将血清YKL-40、UCP2、APACHEⅡ评分、SOFA评分、PCT和WBC作为自变量(均为连续变量)行logistic回归,结果显示,血清YKL-40(OR=1.522,95%CI:1.170~1.979)、UCP2(OR=1.658,95%CI:1.253~2.194)、APACHEⅡ评分(OR=1.885,95%CI:1.307~2.719)、SOFA评分(OR=1.973,95%CI:1.419~2.742)和PCT(OR=2.014,95%CI:1.475~2.750)为耐药KP脓毒症预后的影响因素(P<0.05)。见表4。

2.5　血清YKL-40和UCP2对耐药KP脓毒症预后的预测价值　以耐药KP脓毒症预后为因变量,将血清YKL-40、UCP2作为检验变量绘制ROC曲线,结果显示,血清YKL-40、UCP2联合预测耐药KP脓毒症预后的敏感度为89.47%,特异度为82.26%,AUC(0.899)显著高于血清YKL-40(Z=2.297,P=0.022)、UCP2(Z=2.152,P=0.031)单独预测的AUC。见图1、表5。

表2　预后良好组与预后不良组血清YKL-40和UCP2比较($\bar{x}\pm s$)

Tab.2　Comparison of serum YKL-40 and UCP2 levels between good prognosis group and poor prognosis group　($\bar{x}\pm s$)

组别	例数	YKL-40(ng/mL)	UCP2(ng/L)
预后良好组	62	41.59±5.76	117.63±17.02
预后不良组	38	54.15±9.43	175.42±26.81
t值		8.279	13.198
P值		<0.001	<0.001

表3　预后良好组与预后不良组临床资料比较

Tab.3　Comparison of clinical data between good prognosis group and poor prognosis group

指标	预后良好组(n=62)	预后不良组(n=38)	t/χ^2值	P值
年龄(岁)[a]	65.48±8.45	66.11±8.93	0.354	0.724
身体质量指数(kg/m²)[a]	23.13±2.39	23.21±2.46	0.161	0.873
住院天数(d)[a]	16.56±3.86	17.34±5.48	1.892	0.061
APACHEⅡ评分[a]	12.34±3.21	19.71±4.60	9.426	<0.001
SOFA评分[a]	4.15±0.94	8.58±2.03	14.818	<0.001
PCT(ng/mL)[a]	3.77±0.62	8.56±1.27	25.245	<0.001
WBC(×10⁹/L)[a]	12.45±2.76	14.28±2.98	3.122	0.002
性别[例(%)]				
女性	29(46.77)	15(39.47)	0.510	0.475
男性	33(53.23)	23(60.53)		
吸烟史[例(%)]	25(40.32)	13(34.21)	0.374	0.541
饮酒史[例(%)]	29(46.77)	13(34.21)	1.527	0.217
既往疾病史[例(%)]				
糖尿病	22(35.48)	15(39.47)	0.161	0.688
高血压	27(43.55)	14(36.84)	0.438	0.508
冠心病	15(24.19)	7(18.42)	0.457	0.499
心肌梗死	7(11.29)	5(13.16)	0.078	0.780
心力衰竭	11(17.74)	6(15.79)	0.064	0.801
慢性肺部疾病	18(29.03)	13(34.21)	0.295	0.587

注:[a]为以$\bar{x}\pm s$表示;冠心病为冠状动脉粥样硬化性心脏病。

表 4　耐药 KP 脓毒症预后的多因素 logistic 回归分析

Tab.4　Multivariate logistic regression analysis of prognosis in drug-resistant KP sepsis

变量	β	*SE*	Wald χ^2	*P* 值	*OR* 值	95%*CI*
YKL-40	0.420	0.134	9.825	0.002	1.522	1.170~1.979
UCP2	0.506	0.143	12.502	< 0.001	1.658	1.253~2.194
APACHE Ⅱ评分	0.634	0.187	11.482	0.001	1.885	1.307~2.719
SOFA 评分	0.680	0.168	16.362	< 0.001	1.973	1.419~2.742
PCT	0.700	0.159	19.389	< 0.001	2.014	1.475~2.750
WBC	0.226	0.127	3.176	0.075	1.254	0.978~1.608

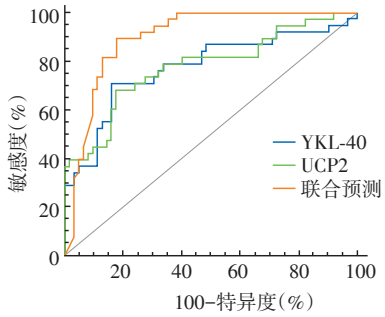

图 1　血清 YKL-40 和 UCP2 预测耐药 KP 脓毒症预后的 ROC 曲线

Fig.1　ROC curve of serum YKL-40 and UCP2 in predicting the prognosis of drug-resistant KP sepsis

表 5　血清 YKL-40 和 UCP2 对耐药 KP 脓毒症预后的预测价值

Tab.5　The predictive value of serum YKL-40 and UCP2 for the prognosis of drug-resistant KP sepsis

变量	AUC	95%*CI*	截断值	敏感度(%)	特异度(%)	约登指数
血清 YKL-40	0.774	0.680~0.852	49.19 ng/mL	71.05	83.87	0.549
血清 UCP2	0.778	0.683~0.855	160.00 ng/L	68.42	82.26	0.507
联合预测	0.899	0.822~0.950		89.47	82.26	0.717

3　讨　论

发热/低体温、气促、水肿等是脓毒症的典型症状，耐药 KP 引起的脓毒症还会表现出肝脓肿、尿路感染、肺炎、脑膜炎等并发症，且耐药 KP 引起的脓毒症多发生于住院患者，死亡率极高[10-11]。革兰阴性菌是引起脓毒症的主要病原菌，其中，耐药 KP 所致脓毒症的发病例数仅次于大肠埃希菌，且检出率逐年增高[12]。耐药 KP 对多种抗生素具有耐药性，可能与生物被膜形成、灭活酶产生等多种因素有关，导致耐药 KP 脓毒症治疗效果不理想[13]。探讨血清 YKL-40 和 UCP2 对耐药 KP 脓毒症预后的预测价值对其预后提高具有一定积极意义。

YKL-40 含 383 个氨基酸，可由巨噬细胞等多种细胞分泌，是人类基因组中唯一的壳多糖酶样蛋白，人 YKL-40 编码基因位于 1 号染色体[14]。YKL-40 能够介导炎症反应，已成为新型炎症标志物，在肺炎、乙型病毒性肝炎、肿瘤等疾病进程中扮演重要角色[15]。何伟等[16]研究报道，YKL-40 水平在经皮肾镜取石术后泌尿感染患者血清中升高，分析可能与 YKL-40 介导的炎性反应有关。本研究中，研究组血清 YKL-40 较对照组显著升高，提示 YKL-40 水平或与耐药 KP 脓毒症的发生有关。此外，本研究结果还显示，预后不良组血清 YKL-40 水平高于预后良好组，推测 YKL-40 也与耐药 KP 脓毒症预后紧密相关。梁银等[17]报道，血清 YKL-40 为病毒性肺炎患儿预后不良的独立危险因素。本研究多因素 logistic 分析也提示耐药 KP 脓毒症患者随着血清 YKL-40 水平的升高，预后不良风险也升高。究其原因，血清 YKL-40 水平越高，提示全身炎症反应程度越高，炎性损伤越重，从而造成不良预后[18]。本研究 ROC 曲线分析显示，耐药 KP 脓毒症患者入院时血清 YKL-40 水平高于 49.19 ng/mL，则预后不良风险较高，敏感度为 71.05%，表明血清 YKL-40 有望成为评估耐药 KP 脓毒症的标志物。

目前已在哺乳动物中发现 UCP1~UCP5 五种解偶联蛋白，UCP2 是位于线粒体内膜上的蛋白，在心脏、肝脏等器官中广泛分布，通过影响 ATP 合成、活性氧的产生等参与病理生理过程，人 UCP2 编码基因位于 11 号染色体[19]。有研究认为，UCP2 通过影响巨噬细胞脂质合成促进炎症小体活化，从而介导炎性反应[20]。本研究发现，相比于健康人群，耐药 KP 脓毒症患者血清中 UCP2 水平显著较高，与前人研究基本一致[21]，提示 UCP2 与耐药 KP 脓毒症发生有关。进一步比较不同预后患者血清 UCP2 水平发现，预后不良组血清 UCP2 水平较预后良好组升高，且多因素 logistic 分析也表明血清 UCP2 为耐药 KP 脓毒症预后的影响因素，可见 UCP2 与耐药 KP 脓毒症预后有一定关系，推测 UCP2 通过介导炎症反应、氧化应激等过程影响耐药 KP 脓毒症患者预后[22]。李依等[23]进行的 ROC 曲线分析显示，血清 UCP2 预测脓毒症 28 d 预后的敏感度为 66.67%，最佳截断值 137.30 pg/mL。本研究进行的 ROC 曲线分析表明，血清 UCP2 预测耐药 KP 脓毒症预后的 AUC 达 0.778，特异度较高，提示耐药 KP 脓毒症患者入院时血清 UCP2 达 160.00 ng/L

时，预后不良几率较高。由于单一血清指标的预测效能难免较低，本研究进一步采用并联法分析血清YKL-40联合UCP2对耐药KP脓毒症预后的预测效能，结果表明，二者联合预测的AUC高于单一指标，且敏感度得到提升，提示血清YKL-40和UCP2联合可互为补充，弥补单一指标预测的不足，为耐药KP脓毒症预后评估提供指导。

APACHEⅡ评分和SOFA评分在脓毒症病情评估中不可缺少，本研究进行的logistic分析也表明，APACHEⅡ评分和SOFA评分为耐药KP脓毒症预后的影响因素。但由于疾病本身的复杂性，APACHEⅡ评分和SOFA评分在预后评估上仍存在一定局限性。蔡振华等[24]研究报道，APACHEⅡ评分联合SOFA评分预测耐药KP脓毒症预后的AUC为0.873，本研究中血清YKL-40联合UCP2预测耐药KP脓毒症预后的AUC为0.899，与上述研究中APACHEⅡ评分联合SOFA评分预测效能相当。

综上所述，耐药KP脓毒症患者血清YKL-40和UCP2水平较高，且血清YKL-40联合UCP2对耐药KP脓毒症预后具有较高预测价值，有助于耐药KP脓毒症预后的临床预测。本研究因时间、人员、资金有限，收集的样本量不多，后续将继续增加样本量，验证血清YKL-40和UCP2对耐药KP预后的预测价值。

利益冲突 无

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