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Original Article

Expression of monocyte HLA-DR and blood lactic acid level in patients with sepsis and correlation with prognosis

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Abstract: Objective: To observe the expression of monocyte human leukocyte antigen-DR (HLA-DR) and the level of blood lactic acid (BLA) in patients with sepsis, and investigate the correlation with prognosis. Methods: Sixty-five patients with sepsis were selected as the sepsis group, and 50 healthy subjects were selected as the control group. In the sepsis group, patients were divided into the death group (n=25) and survival group (n=40). HLA-DR expression rates and levels of BLA of patients on the first day and third day after admission were observed, and correlations with prognosis of patients were analyzed. The value of expression rate of HLA-DR and BLA level for predicting sepsis was analyzed by ROC curve. Results: Compared with the control group, the expression rate of HLA-DR was decreased and the concentration of BLA was significantly increased in the sepsis group (t=16.77, t=79.56; P=0.001, P<0.001). Compared with the survival group, the concentration of BLA was significantly increased and the expression rate of HLA-DR was decreased in the death group (t=3.54, t=4.82; P=0.011, P<0.001). The areas under the ROC curves of the predictive values of expression rate of HLA-DR, BLA levels and the combination of two were 0.91 (95% CI: 0.82-0.99), 0.75 (95% CI: 0.63-0.90) and 0.95 (95% CI: 0.90-0.99) respectively. The expression rate of HLA-DR was negatively correlated with Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score (t=9.16, r=-0.91, P=0.032). The level of BLA was positively correlated with APACHE-II score (t=5.71, r=0.66, P=0.040). Multivariate Logistic regression analysis showed that the increased APACHE-II scale, decreased ΔHLA-DR and increased ΔBLA were independent risk factors for mortality of patients with sepsis. Conclusion: Combined detection of monocyte HLA-DR and BLA can improve the sensitivity for diagnosis of sepsis and their changes are closely related to the prognosis of sepsis, which can be used to predict poor prognosis.

Keywords: Sepsis, human leukocyte antigen-DR, blood lactic acid

Introduction

Many factors can cause sepsis, including extensive burns and scalds and serious infections of body or shocks [1]. As a common clinical complication, sepsis is featured by rapid progression and if it is not treated timely or the therapeutic effect is not ideal, high mortality rate may occur [1]. A large number of studies have shown that, application of early-stage disease assessment in the treatment of patients with sepsis and active interventions can increase the prognostic effect and dramatically reduce deaths of patients [2, 3].

Lactic acid is generated by anaerobic glycolysis of cells, which is closely associated with the state of tissue oxygenation and metabolism [4]. Studies have shown that the basal metabolism and 24 h blood lactic acid (BLA) levels of patients in the Intensive Care Unit are closely related to the prognosis [4, 5]. The expression rate of human leukocyte antigen-DR (HLA-DR) in $CD14^+$ cells, as an indicator of bacterial infection, is widely used for the judgment of sepsis [6]. The expression rate of HLA-DR at 30% or below can be used as an important indicator for judging severe sepsis. In addition, when the expression rate of HLA-DR decreases, it indicates that the patient's body is in an immunosuppressive state and the probability of infection aggravation will increase significantly [6]. Some studies showed that, when the expression rate of HLA-DR in $CD14^+$ cells decreased,

the body was in an immunosuppressive state, leading to aggravated infections [6]. At present, no studies on the diagnosis and prognosis of sepsis by using expression rate of HLA-DR combined with BLA level were reported in China, and most indicators for predicting prognosis of sepsis are single indicators.

In this study, the HLA-DR expression and BLA levels of patients with sepsis were detected and their correlation with sepsis severity and prognosis was investigated.

Materials and methods

General information

This is a retrospective study and has been approved by the Ethics Committee of The Second Affiliated Hospital of Xinjiang Medical University. A total of 65 patients with sepsis admitted to the Intensive Care Unit of The Second Affiliated Hospital of Xinjiang Medical University for treatment from January 2013 to May 2015 were included in this study. The inclusion criteria: All cases conformed to the diagnostic criteria of sepsis prepared by American College of Chest Physicians/Society of Critical Care Medicine in 2001 [7].

Exclusion criteria: Patients used immunosuppressants in the recent half a year; patients with other immune system diseases; patients with age <18 years, and patients were in pregnancy or other conditions not suitable for this study; Patients aged 23 to 66 years, with an average age of (57.20±13.20) years, including 43 males and 22 females. Among them, the numbers of patients with infections of abdominal cavity, lung and brain, skin and soft tissue, urinary system were 31, 22, 6, 3, and 3 respectively. Patients were divided into the survival group and death group according to the prognosis conditions in 30 days after admission. There were 40 cases in the survival group, aged 26 to 66 years, with an average age of (57.11±12.22) years, 26 males and 14 females; there were 25 cases in the death group, aged 23 to 66 years, with an average age of (60.43±14.21) years, 17 males and 8 females. Furthermore, 50 healthy subjects after physical examination in the hospital were selected as the control group, with an average age of (55.21±12.64) years, 35 males and 15 females.

All candidates had the right to know and signed the informed consent form.

Detection of HLA-DR and BLA

Blood (10 mL) was collected from elbow veins of patients on the first day and the third day after admission and then centrifuged at 3,000 rpm for 15 min. Later the serum was collected and stored in a refrigerator (-80°C). The BLA level of arterial blood was detected by GEMPremier 3000 Analyzer. The test kits were provided by U.S. DSL and the instructions were strictly observed during operation. In addition, 5 mL of elbow venous blood was drawn on the first day and the third day after admission respectively, and was then added to the test tubes containing mouse anti-human CD14 monoclonal antibody, mouse anti-human HLA-DR monoclonal antibody and isotype negative control rabbit anti-human IgG2a monoclonal antibody (BD Biosciences, USA). After 15 min, hemolysis (kits were purchased from BD Biosciences, USA) was performed for 10 min, centrifuged at 1,200 rpm for 5 min, and then the supernatant was removed. Then, it was washed three times with PBS, and resuspended in 300 μL of PBS and analyzed. For each test tube, 10,000 cells were collected, and the percentage of CD14/HLA-DR (ratio of double positive) was used as the expression rate of HLA-DR and recorded [6]. The percentage of CD14/HLA-DR was defined as the number of $CD14^+$ HLA-DR double positive/(the number of CD14 positive + the number of HLA-DR positive).

Observation indexes

The expression rate of HLA-DR and BLA concentrations in patients with sepsis were statistically analyzed, and Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scale of patients on the day of blood sampling were observed and recorded, and their life and death status was recorded during follow up [3]. ΔHLA-DR=(expression rate of HLA-DR on the 3rd day of admission-expression rate of HLA-DR on the 1st day of admission) [6]. ΔBLA=(BLA level on the 3rd day of admission-BLA level on the 1st day of admission). A total of 5 mL of fasting elbow venous blood was taken from the patients and was put to an anticoagulation-free blood tube, centrifuged at 4,000 rpm for 15 min, then the supernatant was collected to detect the white blood cell (WBC) and C-reaction

Table 1. Expression rates of HLA-DR and blood lactic acid levels in normal people and patients with sepsis ($\bar{x}$ ± sd)

	Expression levels of HLA-DR (%)	Blood lactic acid levels (mmol/L)
Control group	84.09±16.21	0.51±0.04
Sepsis group	40.33±10.02	4.38±0.39
t	16.77	79.56
P	0.001	<0.001

Note: HLA-DR, human leukocyte antigen-DR.

Table 2. Expression rates of HLA-DR and the blood lactic acid levels of patients in the survival group and the death group ($\bar{x}$ ± sd)

	Expression levels of HLA-DR (%)	Blood lactic acid levels (mmol/L)
Survival group	43.05±11.64	3.43±0.15
Death group	32.41±12.04	5.52±0.33
t	3.54	4.82
P	0.011	<0.001

Note: HLA-DR, human leukocyte antigen-DR.

protein (CRP) of serum on the same day using Roche test kits and Roche Automatic Immune and Biochemical Analyzer. The CRP was determined by immunodiffusion test. The CRP positive diagnostic threshold was 10 mg/L, when CRP ≥ 10 mg/L, it indicated presence of bacterial infection clinically [5].

Statistical analysis

SPSS 17.0 software was used for statistical analysis. The expression rate of HLA-DR and BLA level are expressed as mean ± sd. The expression rate of LA-DR, BLA level and APACHE-II scores were calculated in accordance with the normal distribution, and the t-test was performed on the quantitative samples between the two groups. The non-parametric statistics Mann-Whitney rank sum test was performed for the data of non-normal distribution. ROC curves were plotted to predict the deaths by the expression rate of HLA-DR and BLA level, to calculate the sensitivity and specificity, etc. [7, 8]. Correlation analysis of expression rate of HLA-DR and BLA level and APACHE-II score was performed by Pearson correlation analysis, and the analysis on prognosis-related factors of patients with sepsis was performed by Logistic regression analysis. P<0.05 was considered as a statistically significant difference.

Results

The expression rate of HLA-DR and BLA level in normal people and patients with sepsis

Compared with the healthy control group, the BLA level increased significantly and the expression rate of HLA-DR decreased markedly in the sepsis group, and difference between the two groups was statistically significant (both P<0.05). See **Table 1**.

The expression rates of HLA-DR and BLA levels in the survival group and death group

Compared with the survival group, the BLA level was higher and the expression rate of HLA-DR was lower in the death group, and the difference between the two groups was statistically significant (both P<0.05). See **Table 2**.

The AUC, sensitivity and specificity of the expression rate of HLA-DR and BLA level for predicting sepsis

The ROC curve of the expression rate of HLA-DR and BLA level for predicting sepsis was drawn; the cutoff value of the expression rate of HLA-DR was 30% and the cutoff value of the BLA level was 5 mmol/L [4]. Results showed that, the AUC of the expression rate of HLA-DR was larger than that of BLA level, with high sensitivity, and the difference between them was statistically significant (X^2=8.04, X^2=7.36; both P<0.001). The sensitivity and specificity of the combined detection of both were higher than those of detection of single index, with statistically significant difference between them (X^2=5.93, X^2=4.27, X^2=6.02, X^2=6.11; all P<0.001). See **Table 3** and **Figure 1**.

Correlation analysis of expression rates of HLA-DR, BLA levels with APACHE-II scores

The expression rate of HLA-DR was negatively correlated with APACHE-II score (t=9.16, r=-0.91, P=0.032); The BLA level was positively correlated with APACHE-II score (t=5.71, r=0.66, P=0.040). See **Figure 2**.

Factors influencing the prognosis of patients with sepsis

The age, sex, infection site, APACHE-II score, WBC, CRP, the expression rate of HLA-DR on the first day of admission, the expression rate of HLA-DR on the third day of admission, the

Table 3. Results of AUC, sensitivity and specificity of the expression rate of HLA-DR and blood lactic acid level for predicting sepsis

Index	AUC (95% CI)	Sensitivity (%)	Specificity (%)
Expression level of HLA-DR	0.91 (0.82-0.99)$^{\#,\#\#}$	83.52$^{\#,\#\#}$	82.02$^{\#,\#\#}$
Blood lactic acid level	0.75 (0.63-0.90)*	79.83*	81.65*
HLA-DR combined blood lactic acid	0.95 (0.90-0.99)	90.37	88.42
t	10.23*/1.84$^{\#}$/8.04$^{\#\#}$	5.93*/1.22$^{\#}$/4.27$^{\#\#}$	6.02*/1.27$^{\#}$/6.11$^{\#\#}$
P	<0.01*/0.24$^{\#}$/<0.01$^{\#\#}$	<0.01*/0.35$^{\#}$/<0.01$^{\#\#}$	<0.01*/0.23$^{\#}$/<0.01$^{\#\#}$

Note: Compared with HLA-DR combined blood lactic acid, *P<0.05; Compared with HLA-DR combined blood lactic acid, $^{\#\#}$P<0.05. compared with blood lactic acid, $^{\#}$P>0.05. AUC, area under the curve; HLA-DR, human leukocyte antigen-DR.

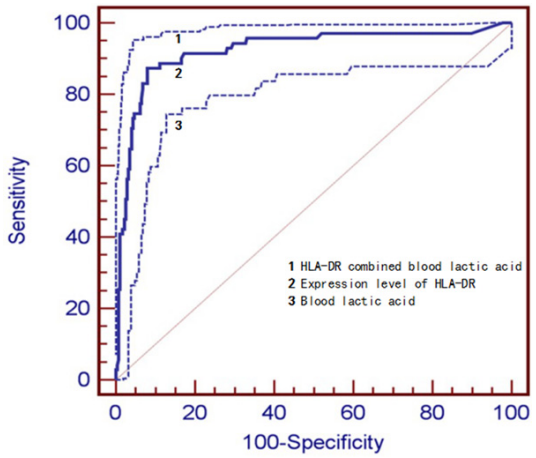

Figure 1. ROC curve of the expression rate of HLA-DR and BLA level for predicting sepsis. HLA-DR, human leukocyte antigen-DR; BLA, blood lactic acid.

dynamic change of HLA-DR (ΔHLA-DR), the BLA concentration on the first day of admission, the BLA concentration on the third day of admission, and the dynamic change of BLA (ΔBLA) were introduced into a univariate logistic regression analysis. The results showed that age, APACHE-II score, WBC, CRP, ΔHLA-DR, ΔBLA were statistically significant (all P<0.05), as shown in **Table 4**. Multivariate logistic regression model was used for stepwise screening. Multivariate logistic regression analysis of age, sex, infection site, APACHE-II score, WBC, CRP, ΔHLA-DR and ΔBLA showed that the increased APACHE-II score, decreased ΔHLA-DR and increased ΔBLA were the independent risk factors for the poor prognosis of sepsis. See **Table 5**.

Discussion

Sepsis is severe inflammatory responses caused by multiple factors such as infection or shocks, etc. If effective treatment cannot be given in time such disease can cause death [8]. Statistical data showed that the number of patients with sepsis is on the rise year by year, which arouses the attentions of clinicians [8]. For patients with sepsis, early diagnosis and early treatment is the key to improve prognosis and reduce mortality [3]. At present, many indicators, including the commonly used APACHE-II score, CPR and IL-6, are used to evaluate the disease severity and prognostic effect of patients with sepsis, but these indicators are not ideal for evaluating the prognosis of patients [2, 6]. With the progress of clinical studies, some researchers propose that HLA-DR and BLA can be used as effective indicators for diagnosis of severe infections and prediction of prognosis [9]. However, few studies on the correlations of HLA-DR and BLA level with the prognosis and survival of patients with sepsis are available. Therefore, in this study, we analyzed the values of HLA-DR and BLA levels during the evaluation of the survival of patients with sepsis [8-10].

HLA-DR is a molecule on the surface of monocyte, which is closely related to the immune process of antigen presentation to T lymphocytes. The decline of expression rate of HLA-DR indicates immunosuppression [10]. At present, studies on sepsis mainly focus on proinflammatory factors, and it is considered that the immune dysfunction is closely related to the downregulation of HLA-DR and co-stimulatory molecule CD80/86 and the decrease of antigen presentation capability [11]. Some researchers performed studies on 1,000 cases of critically ill patients and the results of these studies showed that all patients with dysfunctions of HLA-DR and inflammatory cytokine synthesis died, which suggested that the expression rate of HLA-DR in $CD14^{+}$ monocytes could be used as an important indicator for the evalu-

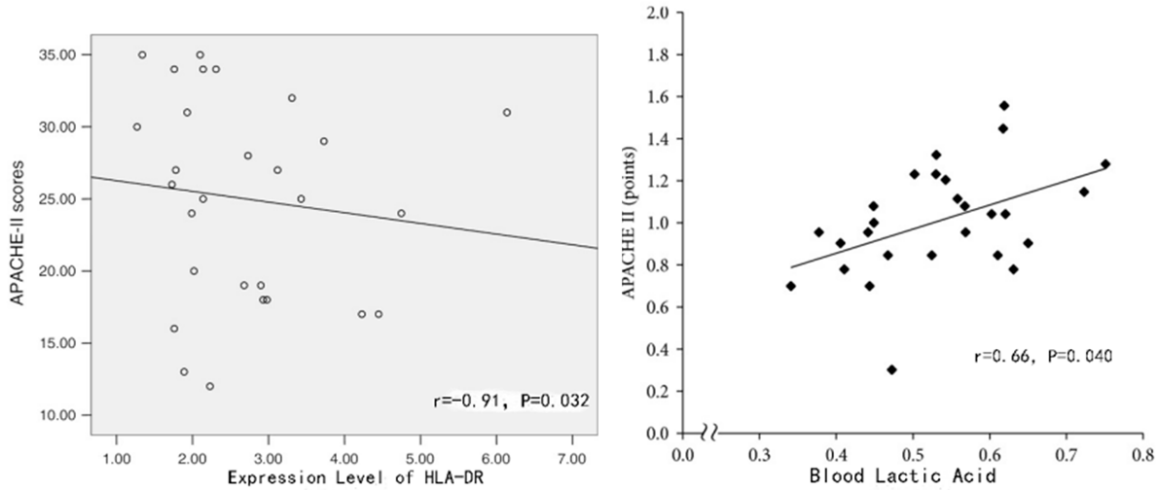

Figure 2. Correlation of expression rates of HLA-DR, BLA levels with APACHE-II scores. HLA-DR, human leukocyte antigen-DR; BLA, blood lactic acid; APACHE-II, Acute Physiology and Chronic Health Evaluation-II.

Table 4. Univariate logistic regression analysis of prognostic factors in patients with sepsis

Variable	P	OR	95% CI
Age	0.021	3.99	0.63-2.92
Gender	0.082	0.99	0.15-0.93
Infection site	0.083	1.01	0.11-1.37
APACHE-II score	<0.001	4.71	0.45-9.49
WBC	0.025	1.45	0.53-2.16
CRP	<0.001	2.28	1.39-5.26
HLA-DR of day 1	0.152	0.98	0.08-0.92
HLA-DR of day 3	0.071	1.53	1.00-1.69
ΔHLA-DR	<0.001	7.99	3.39-12.33
Blood lactic acid on day 1	0.213	0.75	1.05-3.56
Blood lactic acid on day 3	0.094	0.86	0.92-4.17
ΔBlood lactic acid	<0.001	2.76	0.85-6.73

Note: APACHE-II, Acute Physiology and Chronic Health Evaluation-II; WBC, white blood cell; CRP, C-reaction protein; HLA-DR, human leukocyte antigen-DR.

Table 5. Multivariate logistic regression analysis of prognostic factors in patients with sepsis

Variable	P	β	OR	95% CI
Age	0.084	0.04	1.04	0.62-2.91
Gender	0.092	-0.01	0.99	0.53-1.39
Infection site	0.092	-0.00	0.99	0.63-1.27
APACHE-II score	<0.001	1.04	2.82	2.13-3.56
WBC	0.444	0.33	1.39	0.93-1.78
CRP	0.266	-0.28	0.75	0.46-1.08
ΔHLA-DR	<0.001	0.79	2.20	1.79-2.80
ΔBlood lactic acid	<0.001	0.87	2.38	1.97-2.91

Note: APACHE-II, Acute Physiology and Chronic Health Evaluation-II; WBC, white blood cell; CRP, C-reaction protein; HLA-DR, human leukocyte antigen-DR.

ation of immune suppression status [12]. The expression rate of HLA-DR in healthy people or patients with mild infection is higher than 90%; and when the infections increase, the expression rate of HLA-DR will decrease, indicating that the degree of immunosuppression is exacerbated [12]. Less than 30% of expression rate of HLA-DR indicates severe sepsis with multiple organ dysfunction syndrome, or systemic inflammatory response syndrome, and in most cases, patient will have poor prognosis [11]. Results in this study showed that the level of HLA-DR in patients with sepsis was much lower than that of the normal people and the level of HLA-DR in the death group was lower than that of the survival group; the ROC curve showed that HLA-DR had higher sensitivity and specificity for the diagnosis of sepsis. These results suggest that the level of HLA-DR can be used to evaluate the severity of sepsis and the prognosis of patients with sepsis.

Lactic acid, as the product of cell metabolism in hypoxia state, mainly exists in bones and muscles, etc. It is metabolized by liver cells and excreted by the kidneys. The BLA level in human body should be less than 2 mmol/L, and if it is higher than that, it cannot be completely eliminated by the liver [4]. Studies have shown that the mortality rate increases significantly when the BLA level of patients with sepsis was higher

than 4 mmol/L [13]. Therefore, BLA levels can be considered as an important indicator of severity and prognosis of patients with sepsis [14]. For patients with septic shock, due to hypoflow perfusion and hypoxia in tissues and organs, anaerobic glycolysis accelerates its speed and produces more lactic acid; while the lactic acids cannot be completely eliminated by the liver, as a result the BLA level goes up, leading to hyperlactatemia [4]. Huang et al. have found no significant difference between the initial concentrations of BLAs of patients with severe septic shock in the survival group and those in the death group, but the 6 h BLA clearance rate in the survival group was higher than that of the death group [15]. In addition, some studies have confirmed that difference of the BLA levels in patients with septic shock between the survival group and the death group is statistically significant [16]. This study showed that, the BLA level of patients with sepsis was higher than that of the normal people, and the BLA level of patients in the death group was much higher than that of the survival group, suggesting that the BLA level can be used to assess the prognosis of patients with sepsis. This is consistent with the results of previous studies. Furthermore, some studies have shown that the BLA levels is positively correlated with the APACHE-II score, suggesting that BLA levels can reflect the severity of sepsis and is closely related with the degree of infection.

APACHE-α scores are commonly used in evaluating the severity and prognosis of clinically critical illness. APACHE-α score is closely related to the severity of the disease and with it the mortality rate of patients can be predicted accurately. It is also applicable to the evaluation of the state of critically ill patients in emergency department [17]. This study showed that the difference of APACHE-α scores between the survival group and the death group was statistically significant. Furthermore, correlation analysis showed that the expression rate of HLA-DR and the BLA level were closely related to APACHE-α scores, suggesting that HLA-DR and BLA levels could be used to evaluate the prognosis of patients with sepsis.

In recent years, combined detection of multiple biomarkers represents a new trend in clinical studies [1]. Results in this study showed that the area under the ROC curve of expression rate of HLA-DR combined with BLA level was greater than the area when the expression rate of HLA-DR or the BLA level were used as a single indicator, suggesting that the combined use of expression rate of HLA-DR ≤30% and BLA ≥ 5 mmol/L as cut-off values of sepsis have higher sensitivity and diagnostic value than a single indicator.

Chen et al. investigated the relationship between the dynamic changes of monocyte HLA-DR expression rate and the prognosis of sepsis. Results showed that patients with dynamic decline of expression rate of HLA-DR had poor prognosis [18]. Wang et al. studied the correlation between the dynamic changes of BLA levels in patients with sepsis and their prognosis. Results showed that patients with elevated arterial BLA concentration and low 6 h lactic acid clearance rate had poor prognosis [19]. Some researchers found that, early lactic acid clearance could be used as an indicator of prognosis of patients with surgical shock [20]. In this study, the multivariate Logistic regression analysis showed that the increased APACHE-II scores, decreased ΔHLA-DR and increased BLA level were independent risk factors of poor prognosis of sepsis, which are expected to be used as indicators for judging prognosis of patients.

However, due to inadequate sample number and short follow-up time, further studies should be carried out to confirm the improvement of prognosis and the exact mechanism by adding sample size, to provide references for the clinical treatment.

In summary, serum HLA-DR and BLA can be used to improve the diagnostic sensitivity of patients with sepsis and might be applicable in the evaluation of disease severity and prediction of prognosis.

Disclosure of conflict of interest

None.

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