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Original Article

Clinical significance of chemokine ligand 19 and high mobility group protein B1 levels in peripheral blood of rheumatoid arthritis patients with renal lesions

Qingyun Gao[1], Lizhong Zhang[2], Na Chai[3]

[1]Department of No. 1 Ward of Nephrology, Linyi Central Hospital, Linyi 276400, Shandong, China; [2]Department of Clinical Laboratory, Gaotang County People's Hospital, Liaocheng 252800, Shandong, China; [3]Department of Central Operating Room, Qingdao Municipal Hospital, Qingdao 266071, Shandong, China

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Abstract: Objective: To investigate the expression and clinical significance of C-C chemokine ligand 19 (CCL19) and human high mobility group protein B1 (HMGB1) in peripheral blood of rheumatoid arthritis (RA) patients with renal lesions. Method: In total, 46 RA patients with renal lesions were selected from our hospital and enrolled in the study group. Meanwhile, 46 patients with RA only, were enrolled in the control group. An automatic biochemistry analyzer was used to detect the expression level of RF. Enzyme-linked immunosorbent assay was used to test the concentrations of CCL19 and HMGB1 in serum. ROC curve was adopted to study the diagnostic value of CCL19 and HMGB1 for rheumatoid arthritis combined with renal lesions. The correlation between CCL19 and HMGB1 in rheumatoid arthritis combined with renal lesions was analyzed. Results: The serum levels of CCL19 and HMGB1 in the study group were significantly higher than those in the control group (P<0.001). ROC curve analysis results showed that the sensitivity, specificity and AUC of diagnosis with CCL19 alone were respectively 80.43%, 56.52% and 0.7108. The sensitivity, specificity and AUC of diagnosis with HMGB1 alone were respectively 82.61%, 78.26% and 0.8696. The sensitivity, specificity and AUC of diagnosis with CCL19 and HMGB1 in combination were respectively 89.13%, 76.09% and 0.8705. Both the sensitivity and AUC of the combined diagnosis were significantly higher than those of diagnosis with CCL19 alone or HMGB1 alone (P<0.05). Partial correlation analysis results showed that the expression levels of CCL19 and HMGB1 were positively correlated (r=0.784, P<0.001). Conclusions: The combined detection of CCL19 and HMGB1 can be used as an effective measure to judge the occurrence of rheumatoid arthritis combined with renal lesions.

Keywords: Rheumatoid arthritis combined with renal lesions, chemokine ligand 19, high mobility group protein B1, diagnostic performance, ROC

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory and systemic autoimmune disease. It mainly involves the surrounding symmetrical joints [1, 2]. As a systemic disease, it involves multiple systems, has high disability rate and may cause death due to serious important organs that are involved [3, 4]. Rheumatoid arthritis combined with renal lesions is one type of rheumatoid arthritis, and also a chronic, systemic and inflammatory disease [5, 6]. The pathogeny of renal lesions caused by rheumatoid arthritis is complicated. The patients often suffer from varying degrees of renal damage. Both the disease itself and drugs can cause rheumatoid arthritis combined with renal lesions [7, 8]. Among them, the pathological changes of the glomerulus and tubulointerstitium are the direct causes of renal lesions in patients with rheumatoid arthritis [9].

It has been reported that B cells play an important role in the development of rheumatoid arthritis and other such immune system deficiency diseases [10]. This chemokine is involved in the inflammatory cell infiltration in the pathogenesis of rheumatoid arthritis. It is expressed by follicular helper T (TFH) cells and regulates the generation of the B cell antibody

Table 1. General information of the two groups

Group	Observation group (n=46)	Control group (n=46)	t/X^2	*P*
Age (years)	43.01±10.63	43.18±10.66	0.077	0.939
Female (n/%)	20 (43.48)	20 (43.48)	0.000	1.000
BMI (kg/m^2)	20.98±2.64	21.12±1.57	0.309	0.758
History of diabetes (n/%)			20.850	<0.001
No	0 (0.00)	17 (36.96)		
Have	46 (100.00)	29 (63.04)		
Fasting blood glucose (mmol/L)	4.97±1.39	5.12±0.14	0.739	0.462
Blood phosphorus (mmol/L)	1.15±0.23	1.14±0.11	0.266	0.791
Renal function				
BUN (mmol/L)	11.24±5.37	5.82±1.23	6.673	<0.001
Cr (mmol/d)	14.41±3.24	6.19±1.01	16.430	<0.001

[11]. The chemokine family is composed of small molecular weight proteins and can promote the directional migration of leukocytes, endothelial cells and epithelial cells [12]. In recent years, further study has found the abnormal expression of chemokine ligand 19 (CCL19) in multiple inflammatory tissues of patients with RA [13]. The latest study of inflammatory mediators has shown that high mobility group B1 (HMGB1) plays an important role in the course of RA [14]. However, there are few studies on CCL19 and HMGB1 in RA combined with renal lesions. The relationship between CCL19, HMGB1 and the condition of RA patients with renal lesions is unknown. This study was intended to investigate the expression and clinical significance of CCL19 and HMGB1 in peripheral blood of RA patients with renal lesions.

Materials and methods

General information

In total, 46 RA patients with renal lesions were selected from our hospital and enrolled in the study group, including 26 males and 20 females. They were aged from 38 to 70 years old with average age of 43.01±10.63. During the same period, 46 patients with RA only, in our hospital were included in the control group, including 26 males and 20 males. They were aged from 41 to 69 years old with average age of 43.18±10.66. The inclusion criteria for the study group patients were as follows: The patients were diagnosed with RA combined with renal lesions by hour hospital. The clinical diagnosis met the WHO criteria for diagnosis of RA combined with renal lesions [15], including morning joint stiffness, arthritis, metacarpal, phalangeal joints, joint swelling for more than 6 or 12 weeks, symmetrical swelling, subcutaneous rheumatoid nodules, X-ray showing erosion of the face of hand and wrist joint cartilage or surrounding bone thinning changes, and positive rheumatoid factor. With four or more conditions, lasting for 6 or 12 weeks, it can be diagnosed as rheumatoid arthritis. The exclusion criteria were as follows: Patients with infectious diseases were excluded. Patients with history of hemolytic anemia, idiopathic thrombocytopenic purpura or other hematological system disorders were excluded. Patients with other primary malignant tumors were excluded. Patients with other primary malignancy diseases such as bone tumors, kidney tumors, primary liver tumors that affect CCL19 levels or HMGB1 levels were excluded. All the drugs used for the treatment brought no influences on the CCL19 level or HMGB1 level.

Prior to the study, the patients and their family members received information about the details of the study and signed an informed consent as required. The study was approved by the Ethics Committee of the hospital. The age, gender and body mass index were not significantly different between the two groups (P>0.05). They were comparable (**Table 1**).

Main reagents and test methods

Fasting venous blood was taken from patients in the morning at 9 am and tested immediately. (1) CCL19 ELISA detection kit (Shanghai Guyan Biotechnology Co., Ltd.), HMGB1 ELISA detection kit (Shanghai Guyan Biotechnology Co., Ltd.), centrifuge (Hunan Pingfan Technology Co., Ltd.), automatic washer (Nanjing Detie Laboratory Experiment Co., Ltd.), enzyme-labeled analyzer (Shanghai LNB Instrument Co., Ltd.). (2) The levels of CCL19 and HMGB1

Table 2. Expression of CCL19 and HMGB1 in peripheral blood of two groups of patients

Group	Research group	Control group	t	P
CCL19 (pg/ml)	964.11±892.23	553.67±411.31	2.878	0.005
HMGB1 (ng/ml)	17.99±2.26	15.83±0.98	4.789	<0.001
RF (U/ml)	64.75±15.89	11.14±2.21	23.732	<0.001

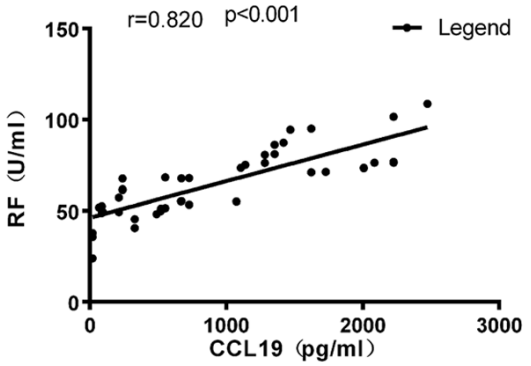

Figure 1. The partial correlation analysis results showed that the expression levels of CCL19 and RF in peripheral blood of RA patients with renal lesions were positively correlated (r=0.820, P<0.001); (legend represents the expression level of CCL19 and RF at this level point).

were detected by enzyme-linked immunosorbent assay (ELISA). The collected venous blood was put into the centrifuge. The serum was separated at 3500 r/min. The concentrations of CCL19 and HMGB1 were determined by ELISA. The test was performed in accordance with the instructions for CCL19 ELISA detection kit and human HMGB1 ELISA detection kit. Then the concentrations of CCL19 and HMGB1 were calculated. (3) The UniCel DxC 800 Synchron, an automatic biochemistry analyzer produced by Beckman Coulter Inc. was used to detect the concentrations of rheumatoid factor (RF) levels.

Outcome measures

Comparison was made not only between the study group and the control group in the serum levels of CCL19, HMGB1, and RF, but also between the combination of CCL19 and HMGB1, the single use of CCL19, and the single use of HMGB1 in the diagnostic value. In addition, the correlation between RA and CCL19, or HMGB1, or RF was separately analyzed.

Statistical method

SPSS 17.0 (Bizinsight (Beijing) Information Technology Co., Ltd.) was used for statistical analysis. The enumeration data between the two groups were analyzed with X^2 test. The measurement data were expressed with mean ± standard deviation (x ± s). The comparison of measurement data between the two groups were analyzed with independent t test. ROC curve was applied to evaluate the diagnostic value of serum CCL19 and HMGB1 for rheumatoid arthritis complicated with renal lesions. Logistic regression model was established with CCL19 and HMGB1 as independent variables, and the area under the ROC curve of joint detection was fitted by the probability value in the model. P<0.05 represented a statistically significant difference.

Results

General information

Comparing age, gender, BMI, history of diabetes, fasting blood glucose, blood phosphorus, Renal function, BUN and Cr, and BMI were not statistically different between the two groups. The two groups were comparable (**Table 1**).

Expression of CCL19 and HMGB1

The comparison results showed the expression levels of CCL19, HMGB1 and RF in the study group were significantly higher than those in the control group (P<0.05) (**Table 2**).

Correlation of CCL19 expression and HMGB1 expression in the peripheral blood of RA patients with renal lesions

(1) The partial correlation analysis results showed that the expression levels of CCL19 and RF were positively correlated (r=0.820, P<0.001) (**Figure 1**). (2) The partial correlation analysis results showed that the expression levels of HMGB1 and RF were positively correlated (r=0.815, P<0.001) (**Figure 2**). (3) The partial correlation analysis results showed that the expression levels of CCL19 and HMGB1 were positively correlated (r=0.784, P<0.001) (**Figure 3**).

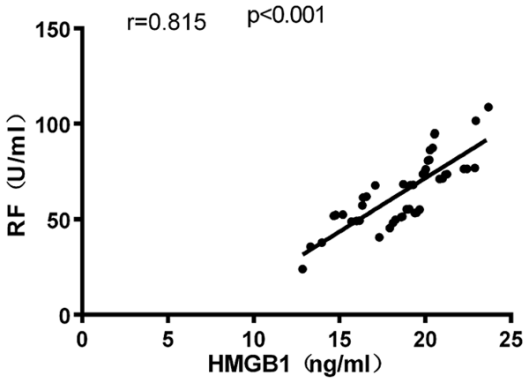

Figure 2. The partial correlation analysis results showed that the expression levels of HMGB1 and RF were positively correlated (r=0.815, P<0.001).

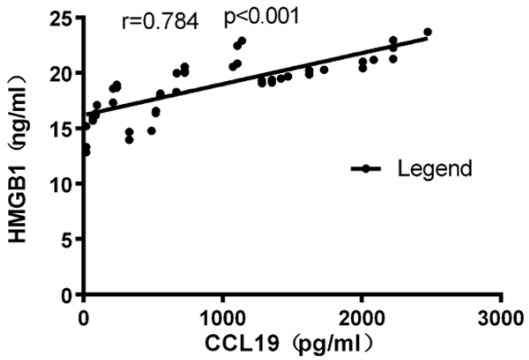

Figure 3. The partial correlation analysis results showed that the expression levels of CCL19 and HMGB1 were positively correlated (r=0.784, P<0.001).

Diagnostic value of CCL19 and HMGB1 alone and in combination in RA combined with renal lesions

In the diagnosis of RA patients with renal lesions, the sensitivity, specificity and AUC of diagnosis with CCL19 alone were respectively 80.43%, 56.52% and 0.7108. The sensitivity, specificity and AUC of diagnosis with HMGB1 alone were respectively 82.61%, 78.26% and 0.8696. Further, the logistic regression model was established with CCL19 and HMGB1 as independent variables (Logit (P combined test) = -10.182+1.420 CCL19+2.502HMGB) and the area under the ROC curve of combined test was fitted by the probability value of the mode. The sensitivity, specificity and AUC of diagnosis with CCL19 and HMGB1 in combination were respectively 89.13%, 76.09% and 0.8705. The sensitivity and AUC of combined diagnosis were significantly higher than those of single diagnosis. The specificity and AUC of CCL19 alone were significantly lower than those of HMGB1 alone and CCL19 joint HMGB1 (P<0.001, P<0.05) (**Table 3** and **Figure 4A-C**).

Discussion

In this study, the expression of RF, CCL19 and HMGB1 was detected. The biochemical results showed that the expression level of RF in peripheral blood of RA patients with renal lesions were significantly higher than that of patients with RA only. As a common detection factor to predict RA related diseases, RF is widely used in clinical detection [16]. Reports have demonstrated the overexpression of RF in serum of patients with RA related diseases [17]. After detection with enzyme-linked immunosorbent assay, we found that the expression levels of CCL19, HMGB1 and RF in the study group were significantly higher than those in the control group. In recent years, a large number of clinical studies have shown that the occurrence and development of RA is closely related to the pathogenesis of B cells. Proper clearance of B cells has a significant therapeutic effect on improvement of patients with RA [18, 19]. As the chemokine, CCL19 plays an important role in the occurrence and development of B cells [20]. Studies have demonstrated that B-cell chemokines indirectly affect RA or its lesions [21]. HMGB1 is a new-type advanced inflammatory factor and has immune stimulation and pro-inflammatory effects [22, 23]. Studies have shown that the level of HMGB1 in serum of patients with active RA were significantly higher than that of patients in remission stage and healthy subjects. An abnormal expression of HMGB1 has been confirmed in the body with acute kidney injury, chronic renal fibrosis, and renal lesions, with unusually up-regulated HMGB1 levels in renal lesions [24, 25]. This study revealed that the expression levels of CCL19 and HMGB1 were significantly different between the RA patients with renal lesions and the RA patients with no renal lesions. The CCL19 and HMGB1 were overexpressed in peripheral blood of RA patients with renal lesions.

Then, we analyzed the correlation of expression between CCL19, HMGB1 and RF in RA combined with renal lesions. The partial correlation analysis results showed that the expres-

Table 3. Diagnostic value of CCL19 and HMGB1 alone and in combination in early cervical cancer

Diagnosis method	Sensitivity	Specificity	AUC
CCL19	80.43%	56.52%*	0.7108*
HMGB1	82.61%	78.26%	0.8696
CCL19 joint HMGB1	89.13%	76.09%	0.8705
X^2	0.068	9.012	5.332
P	0.867	<0.001	0.002

*indicates that the specificity and AUC of CCL19 alone were significantly lower than those of HMGB1 alone and CCL19 joint HMGB1 (P<0.001, P<0.05).

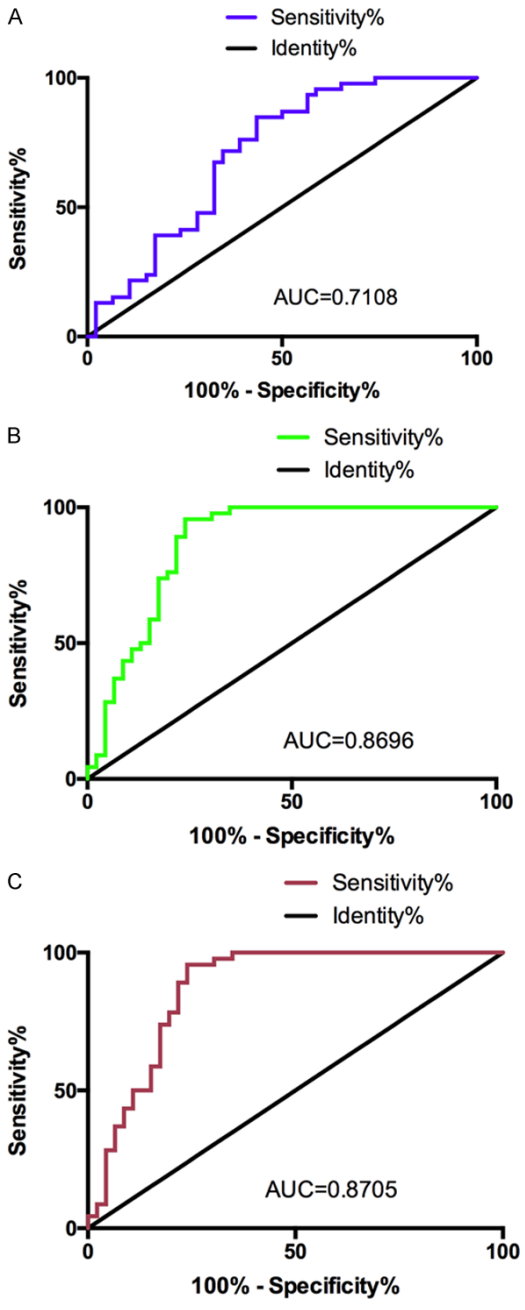

Figure 4. A-C. In the diagnosis of RA patients with renal lesions, the sensitivity, specificity and AUC of diagnosis with CCL19 alone were respectively 80.43%, 56.52% and 0.7108. The sensitivity, specificity and AUC of diagnosis with HMGB1 alone were respectively 82.61%, 78.26% and 0.8696. The sensitivity, specificity and AUC of diagnosis with CCL19 and HMGB1 in combination were respectively 89.13%, 76.09% and 0.8705. The sensitivity and AUC of combined diagnosis were significantly higher than those of single diagnosis.

sion levels of CCL19 and RF were positively correlated. The expression levels of HMGB1 and RF were positively correlated. The expression levels of CCL19 and HMGB1 were positively correlated. A large number of similar studies have also shown that the expression levels of CCL19 and HMGB1 are significantly correlated to that of RF. The above-mentioned results well support the results in this study [26, 27].

Finally, we found that both the sensitivity and AUC of diagnosis with CCL19 and HMGB1 in combination were higher than those of diagnosis with single diagnosis. Currently, there is no report on the diagnostic value of CCL19 and HMGB1 alone or in combination in RA combined with renal lesions. The scarcity of detection factors in the conventional diagnosis for RA complicated with renal lesions due to medical limitations leads to poor diagnostic specificity and blocked observation on the disease progression. After discovering the high value of the combination of CCL19 and HMGB1 for diagnosing RA patients with renal lesions, this study made a speculation that the abnormal CCL19 and GMGB1 expressions in RA patients imply a great possibility of renal injuries.

There are still some deficiencies in this study. For example, the absence of specific analysis on the relationship between renal lesions and the expression levels of CCL19 and HMGB1 in RA patients with renal lesions; the lack in the measurement of CCL19 and HMGB1 levels at different time points; and the shortage of other tests such as the urine protein detection. These limitations affect the statistics of the study. Therefore, we will refer to the latest study in real time. Meanwhile, new study protocol will be added to repair design deficiency and constantly improve this study.

In summary, the expression levels of CCL19 and HMGB1 in the peripheral blood of RA

patients with renal lesions are significantly higher than those with RA only. The expression levels of CCL19 and HMGB1 were positively correlated. Both sensitivity and AUC of diagnosis with CCL19 and HMGB1 in combination are significantly higher than those of single diagnosis.

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Disclosure of conflict of interest

None.

Address correspondence to: Na Chai, Department of Central Operating Room, Qingdao Municipal Hospital, No. 5, Donghai Middle Road, Shinan District, Qingdao 266071, Shandong, China. Tel: +86-0532-88905328; E-mail: cccnaai@163.com

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