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Original Article

High concentrations of serum CD14 and IL-1β predict severity of cerebral infarction

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Abstract: Objective: The aim of the current study was to observe serum expression levels of IL-1β and CD14 in patients with different severities of cerebral infarction, examining their predicting roles. Method: A total of 126 patients with cerebral infarction were recruited as the test group. They were divided into different degrees of cerebral infarction severity, according to NIHSS (National Institute of Health Stroke Scale) scores. In addition, 97 patients without cerebral infarction, but with similar risk factors for cerebral infarction, were recruited as the control group. All patients underwent conventional treatment for cerebral infarction. This study detected concentrations of serum CD14 and IL-1β *via* ELISA on the day of admission and days 5, 7, and 9 of standard treatment. Correlation analysis between CD14, IL-1β, and NIHSS scores, as well as infections and effective rates of treatment, was performed. Results: Concentrations of serum IL-1β and CD14 in patients with different degrees of cerebral infarction were significantly higher than those in the control group on the day of admission and days 5, 7, and 9 ($P < 0.05$). Furthermore, concentrations of serum IL-1β and CD14 in patients with cerebral infarction gradually increased with aggravation of cerebral infarction. There was a positive correlation between serum IL-1β and NIHSS scores ($r = 0.808$, $P < 0.001$). In addition, CD14 was positively correlated with NIHSS scores ($r = 0.793$ $P < 0.001$). Both serum IL-1β and CD14 were negatively correlated with effective rates of treatment and positively correlated with infection rates ($P < 0.05$). Therapeutic effects of patients with cerebral infarction gradually decreased with increased severity of cerebral infarction. The total effective treatment rate in patients with mild cerebral infarction was significantly higher than that in patients with moderate and severe cerebral infarction ($P < 0.05$). Moreover, the rate of infection in patients with mild cerebral infarction was significantly lower than that in patients with moderate and severe cerebral infarction ($P < 0.05$). The infection rate of patients with cerebral infarction gradually increased with increased severity of cerebral infarction. Conclusion: Concentrations of IL-1β and CD14, as well as rates of infection, gradually increased with severity of the disease. Serum IL-1β and CD14 may be novel indicators of the degree of inflammation and effective rates of treatment in patients with cerebral infarction.

Keywords: CD14, IL-1β, severity, cerebral infarction

Introduction

Cerebral infarction is a common cerebrovascular disease caused by a lack of blood supply to tissues, causing ischemia, hypoxia, and eventually necrosis [1]. This disease is more common in the elderly. In recent years, changes in living habits and diet have led to an increase in incidence rates of cerebral infarction [2]. Patients with early cerebral infarction have no obvious symptoms. Once they become ill, they will quickly reach the peak of disease development, seriously threatening the health of the elderly population [3]. Some studies have shown that, if the early stages of cerebral infarction can be treated, this will effectively reduce mortality and morbidity rates, improving prognosis [4].

Some studies have found that there is an inflammatory reaction involved in the ischemic injury of cerebral infarction [5]. Monocytes, the largest type of leukocytes, are an important

inflammatory cell [6]. Studies [7] have shown that they can degrade the fiber components in platelets by secreting a variety of matrix proteases, forming vulnerable plaques. This is because monocytes are both a major source of foam cells in the vulnerable segments of arteries and a major source of inflammatory factors and fibrin in platelets. CD14+ monocytes are a major subpopulation of monocytes [8]. Studies have found that CD14+ monocytes are upregulated in the blood of patients with cerebral infarction [9]. Expression of inflammatory chemokine receptors on the surface of cell membranes promote the formation of vulnerable segments. Therefore, inflammatory responses in patients with cerebral infarction may be closely related to monocytes. Interleukin-1 (IL-1), which has α and β forms, is a cytokine with multiple functions [10]. Its main form of secretion, IL-1β, has the strongest physiological function [11]. Some studies have shown that IL-1 is an important chemical medium involved in infections, ischemia, hypoxia, and stress response [12]. IL-1β can cause inflammatory reactions in brain tissues by inducing cells to produce neurotoxic factors. This, in turn, may lead to necrosis of brain tissues [13].

However, there are no relevant studies assessing expression of IL-1β and CD14 in patients with different severities of cerebral infarction. Therefore, this study investigated concentration levels of serum CD14 and IL-1β in patients with different severities of cerebral infarction. Furthermore, this study assessed changes in CD14 and IL-1β following standard treatment for cerebral infarction.

Materials and methods

General information

Prospective analysis of 126 patients with cerebral infarction was performed. The test group included 74 males and 52 females, with an average age of 70.3 ± 11.8 years. This study stratified patients according to National Institute of Health Stroke Scale (NIHSS) scores. Forty-five patients presented with mild cerebral infarction, 45 patients presented with moderate cerebral infarction, and 34 patients presented with severe cerebral infarction. In the same period, 97 patients without cerebral infarction, but with similar risk factors for cerebral infarction, were used as controls.

Inclusion criteria: Patients diagnosed with cerebral infarction according to comprehensive hospital diagnosis. Exclusion criteria: Patients with infectious diseases in the past 1-month; Serious organ diseases or tumors; Immune or blood diseases; Communication problems. Participants were also excluded if they did not consent to the study. All patients and families agreed to participate in the study and provided informed consent. This study was approved by the Ethics Committee.

Materials and reagents

Human IL-1β ELISA kits were purchased from Shenzhen Juying Biotechnology Co., Ltd. The serum CD14 ELISA kit was purchased from ADL Company, U.S. (batch number MEXN-H0032).

Experimental methods

All patients with cerebral infarction routinely received timely anti-thrombosis treatment. Patients provided fasting venous blood (3 mL) on the day of admission and days 5, 7, and 9 of treatment. Healthy controls provided 3 mL of venous blood on an empty stomach at the same time points. All venous blood was centrifuged at 3,000 r/min for 10 minutes at 4°C and the supernatant was removed. Next, IL-1β and CD14 were detected using ELISA, per manufacturer instructions. Briefly, 100 μl of sample diluent was added to a 96-well plate. This was followed by 100 ul of the serum sample. After the liquid was drained and dried, 100 μl of test solution was added to each well and incubated at 37°C for 1 hour. Next, the liquid was removed, washed 3 times with PBS, and incubated with 100 μl test solution. It was further incubated at 37°C for 1 hour, then discarded, dried, and washed 3 times with PBS. Afterward, 90 μl of substrate solution was added and the color was developed in a dark environment at 37°C. Finally, 50 μl of stop solution was added to terminate color development. Relative absorbance in each well was measured at a wavelength of 450 mm.

Outcome measures

Expression of IL-1β and CD14 on the day of admission and days 5, 7, and 9 of treatment were compared between patients and controls with different severities of cerebral infarction.

Table 1. General information of the patients

Factor	Test group n = 126	Control group n = 97	X^2	P
Sex			0.022	0.881
Male	74 (58.73)	56 (57.73)		
Female	52 (41.27)	41 (42.27)		
Age (years)			0.025	0.874
≤ 70	65 (51.59)	49 (50.52)		
> 70	61 (48.41)	48 (49.48)		
BMI (kg/m^2)			2.114	0.146
≤ 22	67 (53.17)	61 (62.89)		
< 22	59 (46.83)	36 (37.11)		
Whether or not smoking			0.059	0.808
Yes	54 (42.86)	40 (41.24)		
No	72 (57.14)	57 (58.76)		
Whether or not drinking alcohol			0.029	0.864
Yes	69 (54.76)	52 (53.61)		
No	57 (45.24)	45 (46.39)		
Classification of nerve defect				
Mild cerebral infarction	47 (37.30)	-	-	-
Moderate cerebral infarction	45 (35.71)	-	-	-
Severe cerebral infarction	34 (26.98)	-	-	-
Is there diabetes?			0.069	0.793
Yes	45 (35.71)	33 (34.02)		
No	81 (64.29)	64 (65.98)		
Atrial fibrillation	81 (64.29)	62 (63.92)	0.011	0.995
Hyperhomocysteinemia	79 (62.70)	60 (61.86)	0.008	0.996
Hypertension	97 (76.98)	73 (75.26)	0.102	0.950
High uric acid	92 (77.78)	74 (76.29)	0.321	0.852
Hyperlipidemia	93 (73.81)	71 (73.20)	0.023	0.989

Effects of treatment at 10 days between patients with different severities of cerebral infarction were scored by complete remission (NIHSS scores reduced by 91% to 100%), partial remission (NIHSS scores reduced by 18% to 90%), stable disease (NIHSS scores reduced or increased by < 18%), and progression of the disease (NIHSS score increased by > 18%). Total effective treatment rate = [(number of complete remissions + partial remissions)/ total number] 100.

Correlation analysis between concentrations of IL-1β and CD14 and NIHSS scores [14] in patients with cerebral infarction on the day of admission were performed. This study compared the success of treatment between patients with different degrees of cerebral infarction. Moreover, infections of the patients were recorded and compared, including respiratory infections, urinary tract infections, and other infections. Correlation analysis between IL-1β, CD14, effective rates of treatment, and infection rates in patients with cerebral infarction was performed.

Statistical methods

Statistical analysis was performed on experimental data using SPSS 19.0 (Bo Yi Zhixun (Beijing) Information Technology Co., Ltd.). Count data were analyzed using Chi-square tests. Measurement data are expressed using mean ± standard deviation.

Independent t-tests were used to compare between the two groups. Data at multiple time points was compared with repeated measures analysis of variance, followed by post-hoc Dunnett's tests. Comparisons among groups were analyzed by variance. Correlation coefficients of various factors were calculated with Pearson's analysis. $P < 0.05$ indicates statistical significance.

Results

Comparison of baseline data

There were no significant differences in gender, age, BMI, and risk factors between the two groups ($P > 0.05$) (**Table 1**).

Expression of IL-1β and CD14 at different time points in patients with different severities of cerebral infarction

Concentrations of serum CD14 and IL-1β in patients with different severities of cerebral infarction were significantly higher than those of the control group on the day of admission and days 5, 7, and 9 of treatment ($P < 0.05$). Furthermore, concentrations of serum IL-1β and CD14 gradually increased with the severity of cerebral infarction (**Tables 2**, **3**).

Table 2. Expression of IL-1 beta at different time points in patients with varying severities of cerebral infarction (pg/mL)

Time	Mild cerebral infarction n = 47	Moderate cerebral infarction n = 45	Severe cerebral infarction n = 34	Control group n = 97	F	P
The day of admission	21.73 ± 4.76*	23.96 ± 5.11*	25.47 ± 5.21*	8.91 ± 3.42	208.3	< 0.001
Treatment of 5 days	21.31 ± 4.22#	22.15 ± 4.98#	25.92 ± 5.03#	8.87 ± 3.35	213.3	< 0.001
Treatment of 7 days	21.01 ± 3.47&	21.76 ± 4.73&	22.22 ± 4.62&	8.92 ± 3.51	188.6	< 0.001
Treatment of 9 days	17.53 ± 3.34**	20.37 ± 4.15**	21.83 ± 4.27**	8.89 ± 3.41	166.2	< 0.001
F	9.73	5.41	7.82	0.004	-	-
P	< 0.050	< 0.050	< 0.050	0.999	-	-

Note: *, #, & and **compared with the control group, P < 0.05. *, #group compared with the **group, P < 0.05.

Table 3. Expression of CD14 at different time points in patients with varying severities of cerebral infarction (10^9/L)

Time	Mild cerebral infarction n = 47	Moderate cerebral infarction n = 45	Severe cerebral infarction n = 34	Control group n = 97	F	P
The day of admission	0.43 ± 0.15*	0.48 ± 0.19*	0.52 ± 0.24*	0.37 ± 0.13	8.740	< 0.001
Treatment of 5 days	0.42 ± 0.17#	0.46 ± 0.18#	0.51 ± 0.21#	0.36 ± 0.12	9.039	< 0.001
Treatment of 7 days	0.41 ± 0.14&	0.45 ± 0.17&	0.49 ± 0.22&	0.37 ± 0.14	5.721	< 0.001
Treatment of 9 days	0.39 ± 0.13**	0.43 ± 0.16**	0.48 ± 0.19**	0.38 ± 0.13	4.476	< 0.050

Note: *, #, &, **groups compared with the control group, P < 0.05. *, #group compared with the **group, P < 0.05.

Table 4. Comparison of effective rates of treatment in patients with varying severities of cerebral infarction [n, (%)]

	Mild cerebral infarction n = 47	Moderate cerebral infarction n = 45	Severe cerebral infarction n = 34	X^2	P
Complete remission	29 (61.70)	17 (37.78)	5 (14.71)	0.505	0.064
Partial remission	12 (25.53)	10 (22.22)	8 (23.53)	0.141	0.932
Stability of the disease	5 (10.64)	13 (28.89)	8 (23.53)	4.914	0.086
Progress of the disease	1 (2.13)	5 (11.11)	13 (38.24)	20.95	< 0.050
Total effective rate	41 (87.23)	27 (60.00)	13 (38.24)	21.19	< 0.001

Comparison of the effects of treatment between patients with different severities of cerebral infarction

The numbers of complete remissions, partial remissions, stable patients, patients in progress, and total effective treatment rates for each disease severity are shown in **Table 4.** The total effective treatment rate of patients with mild cerebral infarction was significantly higher than that in patients with moderate and severe cerebral infarction (P < 0.05). Furthermore, the total effective rate of patients with moderate cerebral infarction was significantly higher than that in patients with severe cerebral infarction (P < 0.05). Present data indicates that treatment efficiency decreased with an increase in severity of cerebral infarction.

Association between serum IL-1β, CD14, and severity of cerebral infarction

There was a positive correlation between serum IL-1β, CD14, and NIHSS scores in patients with cerebral infarction on the day of admission (IL-1β: r = 0.808, P < 0.001; CD14, r = 0.793 P < 0.001; **Figures 1**, **2**).

Rates of infection in patients with cerebral infarction

Rates of respiratory, urinary tract, and other infections relative to disease severity are shown in **Table 5.** The infection rate of patients with mild cerebral infarction was significantly lower than that in patients with moderate cere-

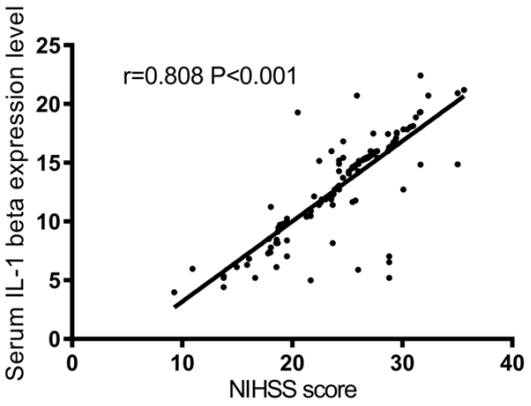

Figure 1. Correlation between serum IL-1β and NIHSS in patients with cerebral infarction on the day of admission. There was a significant positive correlation between serum IL-1β and NIHSS scores (r = 0.808 P < 0.001).

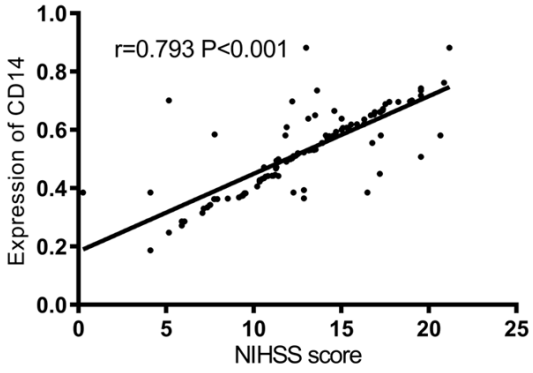

Figure 2. Correlation between serum CD14 and NIHSS in patients with cerebral infarction on the day of admission. There was a significant positive correlation between CD14 and NIHSS scores (r = 0.793 P < 0.001).

bral infarction and severe cerebral infarction (P < 0.05). Furthermore, the infection rate of patients with moderate cerebral infarction was significantly lower than that in patients with severe cerebral infarction (P < 0.05). Present data indicates that increased severity of cerebral infarction is associated with an increased risk of infection.

Correlation analysis between serum IL-1β, CD14, effective rates of treatment, and infection rates in patients with cerebral infarction

Serum IL-1β was negatively correlated with effective rates of treatment (r = -0.425 P < 0.05) and positively correlated with infection rates (r = 0.864 P < 0.05). Serum CD14 expression was negatively correlated with effective rates of treatment (r = -0.442 P < 0.05) and was positively correlated with infection rates (r = 0.795 P < 0.05) (**Figure 3A-D**).

Discussion

When blood flow to the brain is interrupted, a series of cytokines interact, forming a cascade reaction. This causes the cerebral blood vessels to narrow or even rupture, eventually leading to cerebral infarction [15]. In recent years, incidence of cerebral infarction has increased, resulting in disabilities that cause a heavy burden on families and society. Studies have found that many factors play an important role in the pathology of cerebral infarction. These factors can be measured as potential predictors of the condition, evaluating their effects [16]. CD14+ monocytes play an important role in the physiological and pathological processes of cerebral infarction. They have been considered effective therapeutic targets for cerebral infarction [17]. Some studies have shown that CD14 gene polymorphisms influence the secretion of monocytes into blood and the density of CD14, which is related to occurrence of myocardial infarction [18]. The main cause of cerebral infarction is changes in fluid dynamics, such as vascular wall lesions [19]. In addition, studies have shown that occurrence of vascular rupture and thrombosis are the causes of cerebral infarction [20]. A key factor in the formation of vulnerable plaque is the local inflammatory reaction. Immune response of plaques has a very important relationship with CD14. IL-1β is the most physiologically relevant form of IL-1. Some studies have suggested that expression levels of IL-1β are related to the severity of cerebral infarction and strokes. They may be predictive factors for outcomes of strokes [21].

The current study divided patients with cerebral infarction into different groups based on severity, measured by NIHSS scores. All patients received routine treatment for cerebral infarction. Concentrations of serum IL-1β and CD14 were measured in both groups on the day of admission and days 5, 7, and 9 of treatment. Results showed that serum IL-1β and CD14 was significantly higher in patients with cerebral infarction, compared with controls, on the day of admission and days 5, 7, and 9 of treatment (P < 0.05). Interestingly, there was a gradual increase in concentrations of serum IL-1β

Table 5. Infection in patients with varying severities of cerebral infarction [n, (%)]

	Mild cerebral infarction n = 47	Moderate cerebral infarction n = 45	Severe cerebral infarction n = 34	X^2	P
Respiratory tract infection	1 (2.13)	2 (4.44)	4 (11.76)	3.657	0.161
Urinary tract infection	0	2 (4.44)	2 (5.88)	2.588	0.274
Other infections	0	1 (2.22)	1 (2.94)	1.273	0.529
Total infection rate (%)	1 (2.13)	5 (11.11)	7 (20.59)	7.314	< 0.050

and CD14 as the severity of cerebral infarction increased. Some studies have explored the effects of cinepazide maleate on serum IL-1β, IL-6, and neurological function scores in patients with acute cerebral infarction [22]. They found that IL-1β was significantly higher in the acute phase of the disease, compared with controls. It has been reported that expression of IL-1β in the serum of patients with cerebral infarction with different degrees of neurological deficits is higher in patients with severe cerebral infarction, compared with patients with moderate or mild cerebral infarction [23]. The above two studies were consistent with present conclusions.

A previous study investigated the relationship between strokes and CD14. It found that expression of soluble CD14 in stroke patients was significantly higher than that in controls [24]. However, the relationship between CD14 and progression of the disease has not been studied. In addition, the current study found a positive correlation between serum IL-1β, CD14 levels, and NIHSS scores in patients with cerebral infarction on admission, suggesting an association of serum IL-1β and CD14 with neurological deficits in patients with cerebral infarction. The degree of neurological deficit is related to the severity of cerebral infarction. Thus, this result also reflects a positive correlation between serum IL-1β and CD14 and severity of cerebral infarction.

Previous studies have found a positive correlation between CD14 cell count and NIHSS scores in patients with cerebral infarction when assessing the relationship between different CD14 cell counts and NIHSS scores in patients with cerebral infarction [25]. These results are consistent with current conclusions.

The present study also found that serum IL-1β and CD14 are negatively correlated with the treatment efficiency of patients with cerebral infarction and positively correlated with infection rates. Several studies have found that CD14 plays a central role in the recognition and binding of a variety of mycobacterial and viral components, as well as in the amplification of subsequent host responses [26]. IL-1β has been shown to be protective in several bacterial, viral, and fungal infection models. IL-1β is one of the most powerful proinflammatory cytokines. It affects virtually every organ. Several human pathologies are primarily driven by unrestrained IL-1β production. IL-1β exerts its protective action against infections by activating several responses, including the rapid recruitment of neutrophils to inflammatory sites, activation of endothelial adhesion molecules, induction of cytokines and chemokines, induction of the febrile response, and stimulation of a specific type of adaptive immunity [27]. Both indexes indicate less infection. Thus, patients showed better effective rates. At present, few studies have measured the effects of CD14 on the treatment and prognosis of patients with cerebral infarction. Some animal experiments on CD14 [28] have suggested that CD14 monocytes can produce adverse clinical outcomes for cerebral infarction.

In summary, concentrations of serum IL-1β and CD14 in patients with cerebral infarction were significantly higher than those in healthy controls. Furthermore, this study found a positive correlation between concentrations of IL-1β, CD14, and severity of the disease. Finally, results showed that the treatment efficacy gradually decreased and infection rates increased with infarction severity. Therefore, it was hypothesized that serum IL-1β and CD14 are novel factors for prediction of the degree of inflammation and therapeutic effects in patients with cerebral infarction. However, the sample size of this experiment was small. Results lack the support of relevant studies. Therefore, future studies concerning the effects of CD14 and IL-1β are necessary.

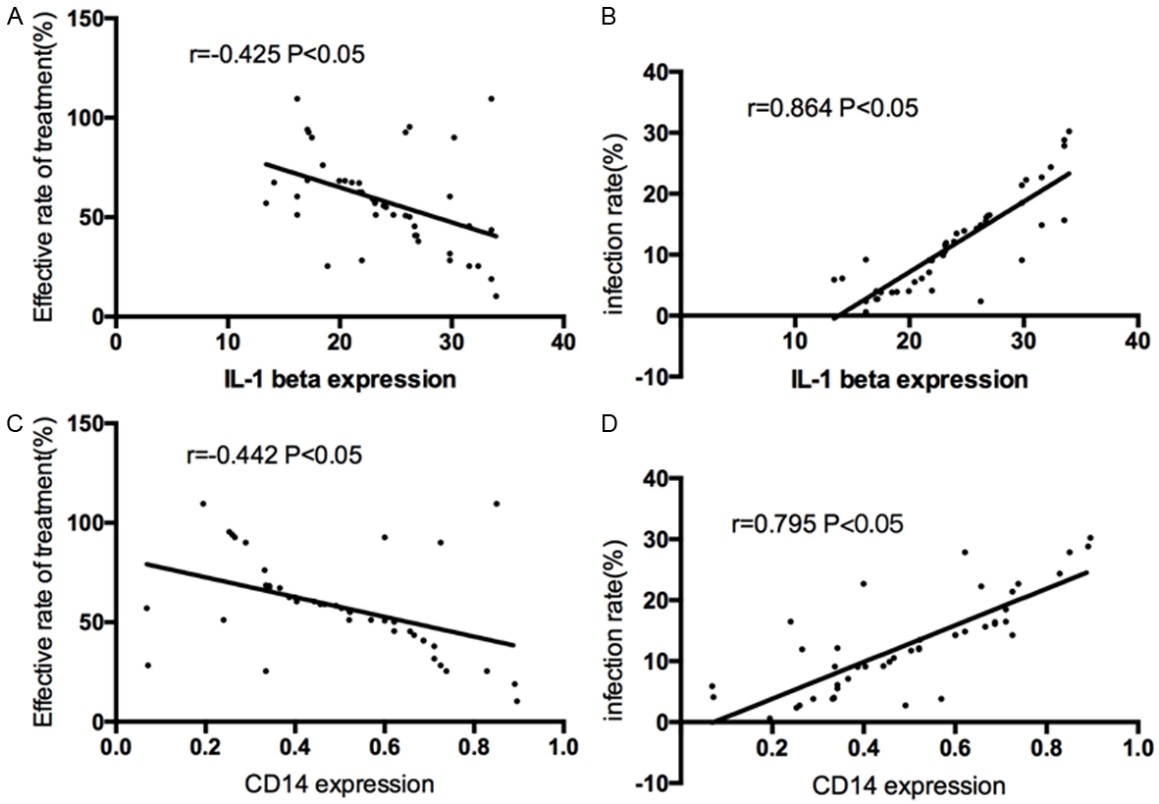

Figure 3. Correlation analysis between serum IL-1β and CD14 and effective rates of treatment and infection rates in patients with cerebral infarction. A. IL-1β was negatively correlated with effective rates of treatment ($r = -0.425$ $P < 0.05$). B. IL-1β was positively correlated with infection rates ($r = 0.864$ $P < 0.05$). C. CD14 expression was negatively correlated with effective rates of treatment ($r = -0.442$ $P < 0.05$). D. CD14 expression was positively correlated with infection rates ($r = 0.795$ $P < 0.05$).

Disclosure of conflict of interest

None.

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