Clinical efficacy of atorvastatin calcium combined with aspirin in patients with acute ischemic stroke and effect on neutrophils, lymphocytes and IL-33

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Abstract. Clinical efficacy of atorvastatin calcium combined with aspirin in patients with acute ischemic stroke (AIS) and its effect on neutrophils to lymphocytes ratio (NLR) and interleukin-33 (IL-33) were investigated. In total, 108 patients with AIS in Luoyang Central Hospital Affiliated to Zhengzhou University from April 2016 to October 2017 were selected. There were 56 cases treated with atorvastatin calcium combined with aspirin as the observation group, and 52 cases were treated with aspirin alone as the control group. The clinical effect was observed. The NLR and IL-33 levels were measured by routine blood test and enzyme linked immunosorbent assay (ELISA) before and after treatment. The scores of the National Institutes of Health Stroke scale (NIHSS) and the occurrence of complications were collected before and after treatment in the two groups. Modified Rankin Scale (MRS) was used to evaluate the curative effect. Score ≤2 points is effective in the treatment. Pearson's analysis was used to analyze the correlation between NLR, IL-33 and NIHSS score. The total hospitalization time and 1 year survival rate were compared. The total effective rate of treatment in the observation group was higher than that in the control group ($P<0.05$). There was no difference in NLR and IL-33 levels between the two groups before treatment ($P>0.05$). After treatment, the NLR in the observation group was significantly lower than that in the control group ($P<0.05$). After treatment, the NIHSS score, the total number of complications and the total hospitalization time in the observation group were significantly lower than those in the control group ($P<0.05$). Pearson's analysis showed a positive correlation between NLR and NIHSS score ($r=0.681$, $P<0.001$), and a negative correlation between IL-33 and NIHSS score ($r=-0.708$, $P<0.001$). In conclusion, atorvastatin calcium combined with aspirin has a better effective rate in the treatment of acute ischemic stroke than aspirin alone. The combination can better reduce the NLR, increase the expression level of IL-33 in serum, reduce the occurrence of complications and hospitalization time, and increase the survival rate of patients.

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Key words: atorvastatin calcium, aspirin, combined treatment, acute ischemic stroke, neutrophils to lymphocytes ratio, interleukin-33

Introduction

Cerebral apoplexy is a serious brain injury disease caused by obstruction of blood circulation in the brain, and its incidence and mortality are much higher than those of other brain injury diseases, which threatens the quality of life and health of many patients; according to statistics, the annual incidence of stroke in China is approximately 116-219 per 100,000 people (1,2). In addition, 85% of acute stroke belonged to acute ischemic stroke (AIS) (3). AIS has become the leading cause of permanent disability in adults and the second most common cause of dementia, and its mortality rate ranks third in the world (4). According to epidemiological statistics in the United States, 610,000 new cases occur every year, and the incidence is still increasing year by year. The incidence of stroke has increased by 12% in low and middle income countries over the past 30 years, and the people suffering from stroke have become younger (5-7). According to the condition of the patient, the corresponding treatment plan can be provided, but Zhong *et al* (8) reported on 2,944 patients in 22 hospitals in Suzhou and found that 3.7% of the patients died directly during in-hospital treatment. In addition, it was reported that 20% of AIS patients have cardiemphraxis and 76% of AIS patients have obvious autonomic nervous dysfunction (9,10). Zhong *et al* (11) results on 253,680 patients show that after treatment, the patients were admitted back to hospital because of infection, coronary artery disease and recurrent stroke, and the readmission rates for 30 days and 1 year were 17.4 and 42.5% respectively.

AIS causes strong inflammatory reaction, so some inflammatory indexes are closely related to AIS process (12). The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory predictor widely used in the diagnosis of cancer (13). Some

studies have also found that NLR can be used to predict the risk of cardiovascular and cerebrovascular diseases, and to predict the early clinical results of AIS (14,15). Interleukin (IL-33) is a member of the IL-1 family and binds to its receptor ST2 to prevent hypertrophy and fibrosis in the myocardium (16). The low level of serum IL-33 is associated with the large infarct volume and greater stroke severity of the AIS patient, and IL-33 can be used as a biomarker for diagnosis and for predicting the prognosis (17).

In order to prevent obstruction, patients generally need to use aspirin that can inhibit platelet aggregation (18). Atorvastatin is a drug with lipid-regulating effect, and is used for treating cardiovascular and cerebrovascular diseases such as hypercholesterolemia and coronary heart disease. Recent studies have reported that atorvastatin can also play a beneficial role in cerebral circulation and cerebral parenchyma during ischemic stroke and reperfusion, which can protect the nerves of patients with AIS. The levels of tumor necrosis factor-α, interleukin (IL)-6 and vascular cell adhesion molecule-1 in patient's plasma were significantly decreased by taking atorvastatin (19). The study of Pignatelli *et al* (20) shows that atorvastatin can rapidly reduce oxidative stress and platelet activation by directly inhibiting platelet NOx2, and finally inhibiting platelet isoprostol and thrombus A2. Aspirin has been used to treat AIS patients with anti-blocking therapy, but the specific efficacy of aspirin combined with atorvastatin and its effect on NLR and IL-33 were not clear.

Therefore, we used atorvastatin combined with aspirin in the treatment of AIS patients and observe its clinical efficacy and the effect on NLR and IL-33, so as to provide evidence and direction for clinical treatment.

Patients and methods

General patient data. This is a retrospective study. Altogether 108 patients with AIS treated in Luoyang Central Hospital Affiliated to Zhengzhou University (Luoyang, China) from April 2016 to October 2017 were selected as the subject. The patients were divided into groups according to their medical records as archived by the Luoyang Central Hospital. The 56 patients in the observation group were treated with atorvastatin combined with aspirin, and included 37 males and 19 females, with an average age of 51.63±9.41 years. Further 52 patients were treated with aspirin alone as the control group in this study, including 40 males and 12 females, with an average age of 52.46±10.54 years. This study was approved by the Medical Ethics Committee of Luoyang Central Hospital Affiliated to Zhengzhou University, and all the patients were informed and signed the informed consent form.

Inclusion and exclusion criteria. Inclusion criteria: the patient was diagnosed with AIS by imaging and pathology; the diagnostic criteria were in line with the guidelines issued by the Stroke Committee of the American Heart Association in 2013 (21); all the patients were admitted to hospital within 6 h of onset; patients with complete clinical data; patients could be followed up by telephone.

Exclusion criteria: patients with severe liver and renal insufficiency; patients with other malignant tumors; patients with serious cardiovascular and cerebrovascular diseases; patients with severe inflammation; pregnant or lactating women.

Instruments and kits. Blood analyzer (SYSMEX, XS-800i) and its matching reagent were used for detection of blood routine indexes. IL-33 enzyme-linked immunosorbent assay (ELISA) detection kit (Shanghai Enzyme-linked Biotechnology Co., Ltd., ml058087), aspirin (Shandong Xinhua Pharmaceutical Co., Ltd., SFDA approval no. H37020354), atorvastatin (Pfizer, SFDA approval no. H20051407).

Therapeutic regimen. Both groups were treated with routine treatment such as anti-infection and prevention of stress ulcer after admission. The control group was given 100 mg of oral aspirin once a day on the basis of the routine treatment. The observation group was treated with 10 mg of oral atorvastatin once a day on the basis of the treatment of the control group.

Sample collection. Aseptic venous blood (8 ml) was collected at 7:00 a.m. the next day after admission; 3 ml was added to the anticoagulant tube, and 5 ml was added to the coagulation tube. The NLR expression in venous blood of anticoagulant tube was detected by blood routine examination. The venous blood in the coagulation tube was centrifuged immediately at 3,000 x g at 4˚C for 10 min. The serum was then separated and placed in a refrigerator at -80˚C.

ELISA detection method. IL-33 was detected by ELISA. The sample was diluted with sample diluent at 1:1, and then 50 µl of the diluted sample was added to the reaction well. Then, 50 µl of diluted standard material or 50 µl of sample to be tested was added into reaction well or blank well. Immediately 50 µl of biotin labeled antibody was added. The well was covered with the membrane plate and the sample was gently shaken and mixed and incubated at 37˚C for 1 h. Then the liquid in the well was discarded and each reaction well was filled with washing fluid. Then shaken for 30 sec, discarding the washing fluid, and dried with absorbent paper. This operation was repeated 3 times. Then 80 µl of affinity enzyme-HRP was added to each well. The sample was gently shaken and mixed and incubated at 37˚C for 30 min. The liquid in the well was discarded and each reaction well was filled with washing fluid. Then shaken for 30 sec, discarding the washing fluid, and dried with absorbent paper. This stage was also repeated 3 times. Then 50 µl of substrate A and 50 µl of B were added to each well. The sample was gently shaken and mixed and incubated at 37˚C for 10 min avoid light. The enzyme standard plate was taken out and 50 µl of terminating solution was added quickly. The results were determined immediately after the termination solution was added. The optical density value (OD value) of each well was detected at the wavelength of 450 nm.

Follow-up. A total of 108 patients or family members were followed up by telephone and interview bimonthly. The follow-up time was 1 year.

Observation index. Main observation index: the NLR and IL-33 levels in observation group and control group before

Table I. Clinical data of patients [n (%), mean ± SD].

Factors	Observation group (n=56)	Control group (n=52)	t/χ^2/Z value	P-value
Sex			1.552	0.213
Male	37 (66.07)	40 (76.92)		
Female	19 (33.93)	12 (23.08)		
Age (years)	51.63±9.41	52.46±10.54	0.432	0.666
BMI (kg/m^2)	23.65±1.82	24.04±1.97	1.069	0.287
Previous medical history				
Hypertension	19 (33.93)	21 (40.38)	0.482	0.488
Diabetes	13 (23.21)	10 (19.23)	0.255	0.613
Hyperlipidemia	8 (14.29)	7 (13.46)	0.015	0.902
Smoking history			0.097	0.755
Yes	21 (37.50)	18 (34.62)		
No	35 (62.50)	34 (65.38)		
Alcohol abuse history			0.186	0.667
Yes	9 (16.07)	10 (19.23)		
No	47 (83.93)	42 (80.77)		
Residence			1.055	0.304
Urban	43 (76.79)	44 (84.62)		
Rural	13 (23.21)	8 (15.38)		
Platelet count (x10^9/l)	152.93±54.41	147.23±51.62	0.558	0.578
Blood glucose (mmol/l)	6.67±2.21	6.52±1.86	0.380	0.705
Urea nitrogen (mmol/l)	6.17±3.72	6.29±3.81	0.166	0.869
Creatine (μmol/l)	75.86±13.74	77.29±15.31	0.512	0.610
cTnT (μg/l)	5.32±2.47	5.36±2.51	0.269	0.789
cTnI (μg/l)	8.43±1.66	8.29±1.54	0.453	0.651
Total cholesterol (mmol/l)	6.58±0.87	6.54±0.83	0.244	0.808
Glycerin trilaurate (mmol/l)	3.32±0.74	3.47±0.81	1.006	0.317
Infarct location			0.537	0.999
Frontal lobe	9 (16.07)	9 (17.31)		
Temporal lobe	7 (12.50)	7 (13.46)		
Parietal lobe	6 (10.71)	5 (9.62)		
Occipital lobe	6 (10.71)	7 (13.46)		
Basal ganglion	8 (14.29)	7 (13.46)		
Thalamus	9 (16.07)	7 (13.46)		
Cerebellum	8 (14.29)	8 (15.38)		
Brainstem	3 (5.36)	2 (3.85)		
Infarct size			0.248	0.804
Lacunar infarction	32 (57.14)	28 (53.85)		
Medium infarction	16 (28.57)	17 (32.69)		
Massive infarction	8 (14.29)	7 (13.46)		

and after treatment were compared; the scores of National Institutes of Health Stroke scale (NIHSS) before and after treatment were compared; the Modified Rankin Scale (MRS) was used for evaluation of curative effect (score equal to or less than 2 points is effective in the treatment), total effective rate of treatment, and survival rate of patients 1 year after treatment.

Secondary observation index: clinical data of the two groups of patients, total length of hospitalization, the occurrence of complications.

Statistical methods. SPSS20.0 (SPSS) medical statistical analysis software was used to statistically analyze the collected data, and GraphPad Prism 7 (GraphPad) to plot figures.

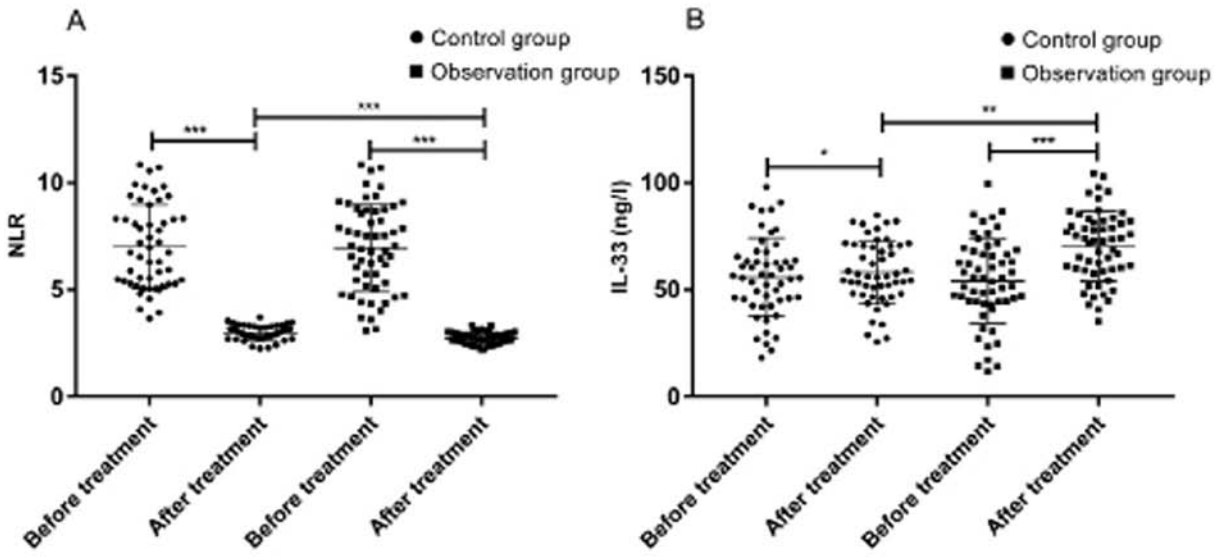

Figure 1. NLR ratio and IL-33 level before and after treatment in the two groups. (A) There was no significant difference in NLR between the two groups before treatment (t=0.192, P=0.849). After treatment, the NLR of the control group was significantly lower than that before treatment (t=14.689, P<0.001); NLR was significantly lower in the observation group than before treatment (t=15.401, P<0.001), and the NLR in the observation group was significantly lower than that in the control group (t=8.961, P<0.001). (B) There was no significant difference in IL-33 between the two groups before treatment (t=0.540, P=0.590). After treatment, IL-33 was significantly higher in the control group than before treatment (t=2.440, P=0.020); IL-33 was significantly higher than before treatment (t=4.336, P<0.001), and IL-33 was significantly higher in the observation group than in the control group (t=2.910, P=0.004). *P<0.05, **P<0.01, ***P<0.001. NLR, neutrophils to lymphocytes ratio; IL-33, interleukin-33.

Table II. NIHSS scores of patients in both groups before and after treatment (mean ± SD).

Treatment	Observation group (n=56)	Control group (n=52)	t value	P-value
Before treatment	11.36±3.74	11.41±3.78	0.234	0.816
After treatment	6.75±1.28[a]	7.86±2.34[a]	3.088	0.003
Difference	4.62±1.35	3.53±1.16	4.483	<0.001

[a]P<0.05 indicates that there is a significant difference between after treatment and before treatment. NIHSS, National Institutes of Health Stroke scale.

Enumeration data utilization rate (%) was detected by Chi-square test and represented by χ^2. Fisher's test was used when the number of samples was ≥40, and the theoretical frequency was <1. The measurement data were represented by mean ± standard deviation (mean ±SD), and all measurement data were in accordance with normal distribution. Independent sample t-test was used for comparison between the two groups. Intra-group comparison used pairing sample t-test and was represented by t. Grade data were analyzed using rank sum test, and Pearson's analysis was used to analyze the correlation between NLR, IL-33 and NIHSS score. K-M survival was used for analysis of 1 year survival of patients. The log rank test was used for analysis. P<0.05 was considered to indicate a statistically significant difference.

Results

General data of the two groups. The clinical data of the two groups were collected and compared, the results showed that there was no significant difference in sex, age, BMI, previous medical history (hypertension, diabetes, hyperlipidemia), smoking history, alcohol abuse history, residence, platelet count, blood glucose, urea nitrogen, creatine, cardiac troponin T (cTnT), cardiac troponin I (cTnI), total cholesterol, glycerin trilaurate, infarct location and infarct size between the observation group and the control group (P>0.05) (Table I).

Comparison of NLR and IL-33 level between the two groups before and after treatment. The NLR in the two groups before and after treatment was compared, but there was no difference between the observation group (6.58±2.14) and the control group (6.64±2.20) before treatment. The NLR of the observation group (2.74±0.16) and the control group (3.07±0.22) after treatment was significantly lower than that before treatment (P<0.05). The NLR of the observation group after treatment was significantly lower than that of the control group (P<0.05), and the difference was significantly higher than that of the control group (P<0.05). The level of IL-33 in the two groups before and after treatment was compared. There was no difference between

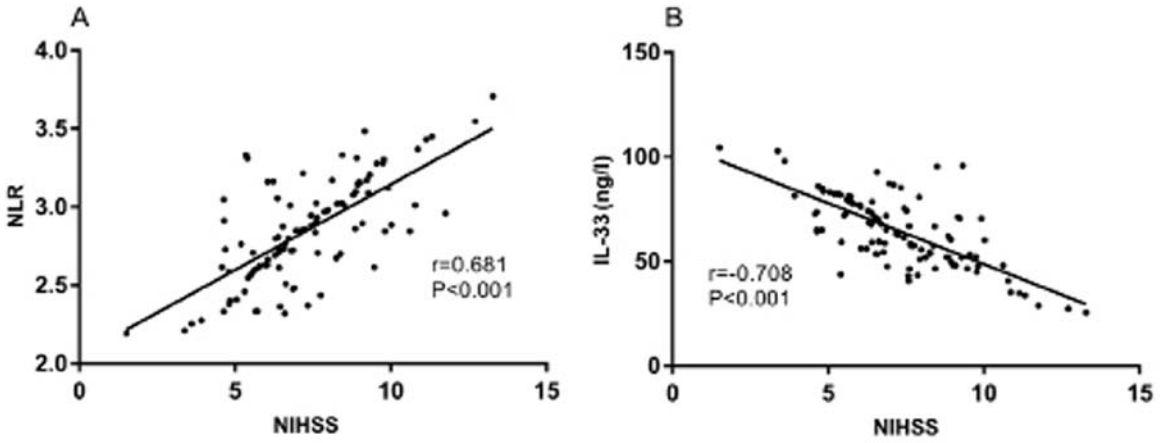

Figure 2. Correlation between NLR, IL-33 and NIHSS score. (A) NIHSS score was positively correlated with NLR expression (r=0.681, P<0.001). (B) NIHSS score was negatively correlated with IL-33 expression (r=-0.708, P<0.001). NLR, neutrophils to lymphocytes ratio; IL-33, interleukin-33; NIHSS, National Institutes of Health Stroke scale.

Table III. Complications of the two groups [n (%)].

Complication	Observation group (n=56)	Control group (n=52)	χ^2 value	P-value
Gastrointestinal bleeding	2 (3.57)	3 (5.77)	0.295	0.587
Heart rate disorder	7 (12.50)	15 (28.85)	4.441	0.035
Pulmonary infection	4 (7.14)	6 (11.54)	0.620	0.431
Epilepsia	4 (7.14)	8 (15.38)	1.854	0.173
Brain edema	6 (10.71)	13 (25.00)	3.796	0.051

the observation group (54.28±18.24 ng/l) and the control group (52.47±16.46 ng/l) before treatment. After treatment, The level of IL-33 in the two groups was significantly higher than that before treatment (P<0.05). The level of IL-33 in the observation group (68.86±15.46 ng/l) was significantly higher than that in the control group (59.27±18.74 ng/l) after treatment (P<0.05), and the difference was significantly higher than that in the control group (P<0.05) (Fig. 1).

Comparison of NIHSS score between the two groups before and after treatment. The NIHSS scores of the two groups before and after treatment were compared, and there was no difference between the two groups (P>0.05). The NIHSS scores in both groups after treatment were significantly lower than those before treatment (P<0.05). The NIHSS score in the observation group was significantly lower than that in the control group (P<0.05), and the difference was significantly higher than that in the control group (P<0.05) (Table II).

Correlation between NLR, IL-33 and NIHSS score. The relationship between NLR, IL-33 and NIHSS scores was analyzed by Pearson's correlation analysis. NLR was positively correlated with NIHSS score, and IL-33 was negatively correlated with NIHSS score (Fig. 2).

Complications in both groups. By comparing the complications between the two groups, it was found that there was no significant difference in gastrointestinal bleeding, pulmonary infection and epilepsia between the observation group and the control group (P>0.05), but the heart rate and brain edema in the observation group were significantly lower than those in the control group (P<0.05) (Table III).

Evaluation of curative effect in the two groups. By comparing the curative effect evaluation of the two groups, it was found that the total effective rate of the patients in the observation group was much higher than that in the control group (P<0.05) (Table IV).

Comparison of the total hospitalization time between the two groups. By comparing the total hospitalization time of the two groups, it was found that the total hospitalization time of the patients in the observation group (9.24±3.42 days) was significantly shorter than that in the control group (11.57±4.78 days) (P<0.05) (Fig. 3).

One year survival rate of the two groups. According to the statistics of one year survival of the two groups, 108 patients or family members were followed up; 0 patients were lost; 29 patients died; 79 survived at one year, and the survival rate was 73.15%. In the observation group, 10 cases died, 46 cases survived, the survival rate was 82.14%. In the control group, 19 cases died, 33 cases survived, the survival rate was 63.46%. By drawing the one year survival rate of the two groups, it was found that the one year survival rate of the patients in

Table IV. Evaluation of the curative effect of the two groups of patients [n (%)].

MRS	Observation group (n=56)	Control group (n=52)	χ^2 value	P-value
0 No symptoms	19 (33.93)	12 (23.08)	1.552	0.213
1 Symptomatic, no significant disability	18 (32.14)	11 (21.15)	1.658	0.198
2 Slight disability	9 (16.07)	8 (15.38)	0.010	0.922
3 Moderate disability	6 (10.71)	9 (17.31)	0.980	0.322
4 Moderately severe disability	2 (3.57)	7 (13.45)	3.453	0.063
5 Severe disability	2 (3.57)	5 (9.62)	1.625	0.202
6 Dead	0 (0.00)	0 (0.00)		>0.999
Total effective treatment	46 (82.14)	31 (59.62)	6.686	0.010

MRS, Modified Rankin Scale.

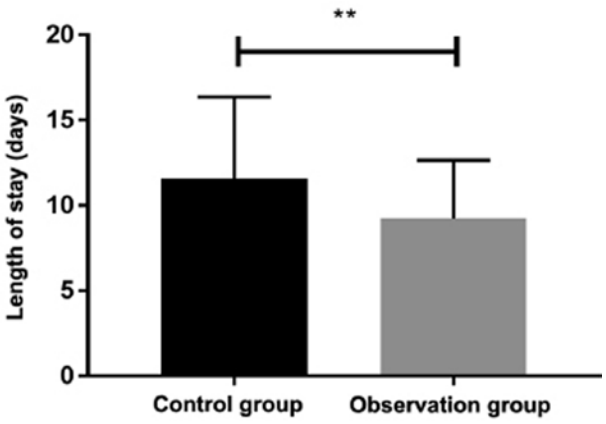

Figure 3. Comparison of total postoperative hospitalization time between the two groups. The total hospitalization time in the observation group was shorter than that in the control group, and there was a significant difference (t=2.770, P=0.004). **P<0.01.

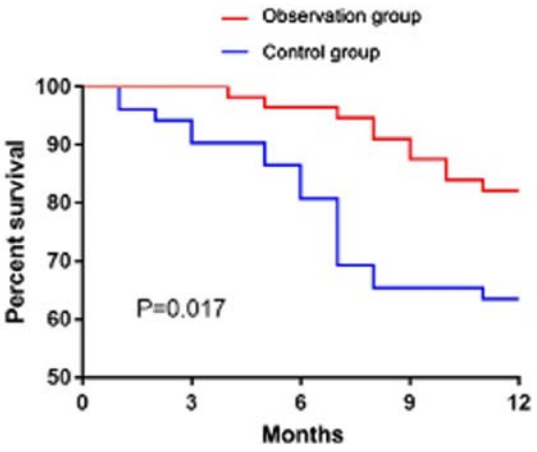

Figure 4. One year survival of patients in both groups. The one year survival rate was 82.14% in the observation group and 63.46% in the control group. The one year survival rate in the observation group was significantly better than that in the control group (P=0.017).

the observation group was much better than that in the control group (P=0.017) (Fig. 4).

Discussion

In this study, we found that the NLR of AIS patients treated with atorvastatin combined with aspirin and those treated with aspirin alone were significantly lower than those before treatment. We speculate that with the development of therapeutic efficacy, the inflammation of patients is reduced, so NLR, an inflammatory marker, also decreases. In the study of Hao *et al* (22), interventional therapy combined with routine drug therapy and single drug therapy reduced the loss of nerve function in patients with ischemic cerebrovascular disease, and NLR decreased significantly with the treatment and improvement of patients. The NLR in the observation group was significantly lower than that in the control group after treatment, which may suggest that the combination therapy is better than aspirin alone to reduce inflammation. The level of IL-33 in both groups was significantly higher than that in the control group after treatment. In the study of Yang *et al* (23), it is mentioned that the infusion of IL-33 into rats with transient middle cerebral artery occlusion can reduce the area of cerebral infarction, while IL-33 enhances the expression of IL-10, anti-inflammatory and tissue repair M2 genes in primary microglia, enhances the survival of neurons, and play a neuroprotective role. Panahi *et al* (24) also report that IL-33 converts microglia from inflammatory M1 to anti-inflammatory and tissue repair M2 phenotypes to reduce brain injury caused by ischemic stroke. Therefore, we speculate that after treatment, the level of IL-33 increases to protect and repair the nerve, and the patient's anti-inflammation and repair function are enhanced, so that the condition can be improved. After treatment, the level of IL-33 in the observation group was significantly higher than that in the control group, suggesting that the patients treated with combined medication may have more improvement and stronger ability of anti-inflammation and tissue repair than those treated with aspirin alone. This result is also similar to the results of Galun *et al* (25), finding that stroke patients with smaller cerebral infarction had higher serum IL-33, and mild stroke patients had higher serum IL-33 than severe stroke patients.

The specific pathogenesis of AIS is not clear, but inflammation and thrombosis are currently considered to be the key factors in the pathogenesis of ischemic stroke (17,26,27).

Platelet activation and coagulation thrombosis play an important role in the pathological and physiological process of recurrent ischemic vascular events in stroke patients (28). Aspirin is a conventional antiplatelet drug, but in recent years, it was reported that platelet aggregation in patients with AIS treated with statins combined with aspirin is significantly lower than that in patients without treatment, and the incidence of neurological deterioration was less than that of patients without treatment (29). Therefore, we studied the efficacy of atorvastatin combined with aspirin compared with aspirin alone.

The NIHSS scores of the two groups before and after treatment were compared. NIHSS score can be used to assess stroke severity (30). It was found that the NIHSS score of the two groups after treatment was significantly lower than that before treatment, and the score of the observation group was significantly lower than that of the control group, which indicated that the condition of the patients was improved after drug treatment, and the improvement degree of the patients in the observation group was better than that in the control group. Pearson's correlation analysis was used to detect the correlation between NLR and IL-33 and NIHSS scores. NLR was positively correlated with NIHSS score, and IL-33 was negatively correlated with NIHSS score. Then, the complications between the two groups was compared. There was no significant difference in gastrointestinal bleeding, pulmonary infection and epilepsy between the observation group and the control group. The number of heart rate disorders and brain edema and the total number of complications in the observation group were significantly lower than those in the control group. The curative effect of the two groups was evaluated by MRS score, and it was found that the total effective rate of the patients in the observation group was significantly higher than that in the control group, while the total hospitalization time in the observation group was significantly lower than that in the control group. Finally, the 1-year survival rate of all patients was studied, and it was found that the 1-year survival rate of all patients was 73.13%; that of the observation group was 82.14%, and that of the control group was 63.46%. The 1-year survival rate of the observation group was significantly higher than that of the control group. This suggests that atorvastatin combined with aspirin can improve the survival of patients.

Collectively, atorvastatin calcium combined with aspirin has a better effective rate in the treatment of acute ischemic stroke than aspirin alone. The combination can reduce the NLR, increase the expression level of IL-33 in serum, reduce the occurrence of complications and hospitalization time, and increase the survival rate of patients.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

WL and XR were responsible for ELISA. LZ analyzed and interpreted the patient data. XR helped with statistical analysis. WL wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Luoyang Central Hospital Affiliated to Zhengzhou University (Luoyang, China). Signed informed consents were obtained from the patients and/or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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