Systemic immune-inflammation index predicts a reduced risk of end-stage renal disease in Chinese patients with myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated vasculitis: A retrospective observational study

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Abstract. Chronic inflammation has been indicated to be important in the pathogenesis of anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV). The systemic immune-inflammation index (SII) is a novel marker of inflammation. The present study was thus performed to explore the association between the SII at diagnosis and inflammatory response and disease activity in Chinese patients with myeloperoxidase (MPO)-AAV. Furthermore, it was evaluated whether the SII is able to predict the progression to end-stage renal disease (ESRD) and patient survival. A total of 190 patients with MPO-AAV were included in the present study. The baseline SII was positively correlated with C-reactive protein (CRP; r=0.274, P<0.0001) and the erythrocyte sedimentation rate (ESR; r=0.481, P<0.0001). However, the SII had no obvious correlation with the Birmingham vasculitis activity score. Patients with SII≥2,136.45 exhibited better cumulative renal survival rates than those with SII<2,136.45 (P=0.001). However, no significant difference in patient survival was indicated between patients with SII≥2,136.45 and those with SII<2,136.45 at diagnosis. In conclusion, the SII was positively correlated with CRP and ESR in Chinese patients with MPO-AAV. Furthermore, the SII may be an independent factor associated with a reduced risk of ESRD.

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized as necrotizing inflammation of small-sized to medium-sized blood vessels. AAV is a common cause of chronic kidney disease in China, which is a major public health problem (1-4). ANCAs usually have specificity for either myeloperoxidase (MPO) or proteinase 3 (PR3). A total of four major phenotypes of AAV have been described: Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic GPA (EGPA) and renal-limited vasculitis. Although the pathogenesis of AAV remains elusive, accumulating evidence suggests that chronic inflammation has an essential role in AAV (5-7).

Numerous different markers of inflammation, including C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR), have been used to assess inflammatory status in AAV (6). Hu *et al* (8) developed a novel systemic immune-inflammation index (SII) based on lymphocyte, neutrophil and platelet counts and demonstrated that the SII is a useful prognostic indicator of poor outcome in patients with hepatocellular carcinoma. Since then, the SII has been reported to be a potential prognostic indicator in patients with various different types of tumor and to be associated with poor patient outcomes (9). There is currently a paucity of information regarding the clinical role of SII in patients with AAV (8). Furthermore, it has been demonstrated that there are numerous differences between patients with PR3-AAV and those with MPO-AAV and there is evidence that PR3-AAV and MPO-AAV may be two distinct diseases (10-12). The major phenotype of AAV and the major target antigen of ANCAs in Chinese patients with AAV are quite different from those in Western populations. There is a striking preponderance of MPA in Chinese patients with AAV (13). Accordingly, MPO is the major target antigen of ANCA in Chinese patients with AAV (13).

Therefore, the present study aimed to analyze the relationship between SII at diagnosis and inflammatory response and

disease activity among patients with MPO-AAV at a single center in China. Furthermore, it was evaluated whether the SII was able to predict the progression to end-stage renal disease (ESRD) and mortality in patients with MPO-AAV in this study.

Patients and methods

Patients. The present single-center, retrospective observational study included all patients with MPO-AAV who were diagnosed between January 2009 and November 2018 at the Department of Nephrology and the Department of Rheumatology and Immunology of Xiangya Hospital (Changsha, China). All patients with AAV (n=190) met the 2012 revised Chapel Hill Consensus Conference criteria for AAV and were then reclassified according to the algorithm published by the European Medicines Agency (14,15). Patients with any of the following conditions were excluded: i) EGPA or secondary vasculitis; ii) Comorbid kidney diseases, such as anti-glomerular basement membrane nephritis, IgA nephropathy, membranous nephropathy or diabetic nephropathy; and iii) Hepatitis b virus, hepatitis C virus or HIV infection. The study protocol was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Xiangya Hospital (Changsha, China).

Baseline demographic data and laboratory parameters were extracted from the electronic medical record system of the hospital. The estimated glomerular filtration rate (eGFR) was calculated as described previously (16). Vasculitis activity was assessed by determining the Birmingham vasculitis activity score (BVAS) (17). The serum ANCA level was detected by both indirect immunofluorescence assay (Euroimmun; cat. no. FA 1201-1005) and antigen-specific ELISA (Inova Diagnostics; cat. nos. 708700 and 704660) for PR3-ANCAs and MPO-ANCAs according to the manufacturer's instructions in all patients.

Renal histology. The renal biopsy specimens were evaluated using immunofluorescence, light microscopy and electron microscopy. As proposed by Berden *et al* (18), the biopsy specimens were assigned to 4 categories. All the specimens met the requirement of a minimum of 10 whole glomeruli (18). Tubulointerstitial lesions were graded semiquantitatively, as previously reported (19).

Treatment. As described previously, all patients received standard induction therapy, including oral prednisone combined with cyclophosphamide (CTX) (20). Oral prednisone was prescribed at an initial dosage of 1 mg/kg/day for 4-6 weeks, with tapering over time to 12.5-15 mg by 3 months. In general, prednisone therapy should not last longer than 24 months. CTX was prescribed intravenously at 0.5-0.75 g/m^2 once a month or a daily oral dose of 2 mg/kg/day. A 25% dose reduction of CTX was prescribed for those who were older than 65 years or those with GFR <20 ml/min/1.73 m^2, and CTX was temporarily discontinued for those who developed leukocytopenia (number of leukocytes <4x10^9/l). Certain patients with rapidly progressive glomerulonephritis or pulmonary hemorrhage received methylprednisolone pulse therapy and/or plasma exchange prior to standard induction therapy. Intravenous CTX every 3 months or daily oral azathioprine or mycophenolate mofetil was given during maintenance therapy.

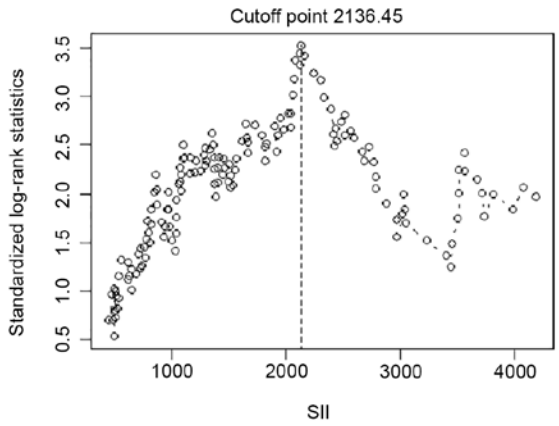

Figure 1. Selection of the cutoff point of the SII according to the maximum log-rank statistic. The maximum value of the log-rank statistic was identified as the optimal discriminator value for the SII. For every potential cutoff point, the absolute value of the standardized log-rank statistic was computed. The cutoff point that provided the best separation of the kidney survival outcome into two groups, where the standardized statistic reached its maximum, was selected as the cut-off point. SII, systemic immune-inflammation index.

Patients were evaluated at the time of diagnosis, at 1, 2 and 3 months, and then every 3 months until the end of the study. The patients were followed up until their death, progression to ESRD or the final follow-up date (May 31, 2019). ESRD was defined by dialysis dependence for >3 months or kidney transplantation. All follow-up data were collected from the hospital's electronic medical records and by contacting the individual patients directly.

Statistical analysis. The SII was calculated as follows: SII=PxN/L, where P, N and L are the absolute peripheral cell counts of platelets, neutrophils and lymphocytes, respectively. The laboratory data of absolute peripheral cell counts were collected from the most recent routine blood test prior to the commencement of immunosuppressive induction therapy, usually within 3 days before the beginning of induction therapy. The cutoff point for the SII level was selected by identifying the maximum log-rank statistic (21). Quantitative data were expressed as the mean ± standard deviation, median (interquartile range) or n (%). All analyses were performed using SPSS software (version 23.0; IBM Corp.) and R for statistical computing (version 3.5.1). The Kolmogorov-Smirnov test was used to check the normality of data distribution. Differences between the two groups were evaluated by one-way analysis of variance or the Kruskal-Wallis test for continuous variables and the χ^2 test or Fisher's test for categorical variables. To examine the correlation between two continuous variables, the Spearman correlation coefficient was calculated. Kaplan-Meier curves and log-rank tests were used to analyze patient and renal survival. P<0.05 was considered to indicate statistical significance.

Results

Patient characteristics. The cut-off point for the SII for ESRD was determined as 2,136.45 (Fig. 1). The baseline characteristics

Table I. Baseline demographic characteristics of patients with myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated vasculitis according to SII.

Variable	SII<2,136.45	SII≥2,136.45	P-value
Age (years)	57.41±15.56	61.60±11.69	0.040
Males/females	67/61	38/24	0.245
MPA/GPA/RLV	121/2/5	54/5/3	0.078
Median follow-up (months)	16.5 (7.75,29.25)	17 (6,34)	0.601
White blood cells (10^9/l)	8.23±3.31	13.60±5.26	<0.0001
Hemoglobin (g/l)	81.46±20.20	82.53±20.90	0.735
Platelet (10^9/l)	222.14±101.82	310.69±107.32	<0.0001
Neutrophil (10^9/l)	6.18±2.86	12.00±5.69	<0.0001
Lymphocyte (10^9/l)	1.50±1.07	0.93±0.47	<0.0001
Serum albumin (g/l)	36.05 (28.38,59.55)	30 (25.05,57.45)	0.049
Serum globulin (g/l)	30.1 (26.18,35.5)	28.6 (25.65,36.85)	0.323
Alanine transaminase (U/l)	11.6 (7.7,18.43)	22.8 (12.75,35.95)	<0.0001
Aspartate transaminase (U/l)	17.7 (14.03,26.2)	25.4 (17.75,35.45)	<0.0001
Total bilirubin (μmol/l)	5.65 (4.08,7.0)	6.2 (4.65,8.9)	0.007
Direct bilirubin (μmol/l)	2.5 (1.8,3.2)	2.8 (2,4.15)	0.007
Proteinuria (g/d)	1.065 (0.50,1.86)	0.99 (0.555,1.5)	0.880
Serum creatinine (μmol/l)	409.75 (195.95,642.75)	281 (103.15,484.7)	0.002
eGFR (ml/min/1.73 m^2)	12.115 (8.18,31.15)	23.09 (10.65,61.17)	0.005
ESR (mm/h)	64 (37.75,95.25)	81 (51.5,120)	0.030
CRP (mg/l)	13.5 (4.7,42.9225)	75.4 (22.05,116)	<0.0001
C3 (mg/l)	799.09±243.29	792.68±301.69	0.883
C4 (mg/l)	229.66±88.67	281.43±239.37	0.132
IgA (mg/l)	2,566.85±1,212.17	2,581.89±1,356.20	0.943
IgG (g/l)	13.95±4.58	15.03±5.11	0.171
IgM (mg/l)	1,224.26±841.65	966.80±542.51	0.043
Organ involvement			
Kidney	122 (95.31)	59 (95.16)	0.963
Pulmonary	71 (55.47)	36 (58.06)	0.735
Cardiovascular	21 (16.41)	10 (16.13)	0.961
Nervous system	30 (23.44)	19 (31.15)	0.873
BVAS	16 (11.75,20)	15 (11.5,17)	0.258
EUVAS classification			
Focal	3	1	0.801
Mixed	19	4	
Crescentic	16	4	
Sclerotic	11	1	
Tubulointerstitial injury score			
0	0	0	0.319
1	27	5	
2	15	5	
3	7	0	

Values are expressed as the mean ± standard deviation, median (interquartile range) or n (%). SII, systemic immune-inflammation index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; RLV, renal-limited vasculitis; EU/BVAS, European/Birmingham vasculitis activity score; C3, complement 3.

of patients with MPO-AAV based on a dichotomy of baseline SII are presented in Table I. A higher baseline SII was associated with older age, higher serum levels of alanine transaminase, aspartate transaminase, total bilirubin, direct bilirubin, CRP, ESR and eGFR and lower serum levels of albumin, IgM and serum creatinine.

Table II. Correlations of the systemic immune-inflammation index with laboratory findings in patients with myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated vasculitis.

Parameter	r	P-value
White blood cells	0.634	<0.0001
HB	-0.024	0.743
PLT	0.499	<0.0001
N	0.735	<0.0001
Lymphocytes	-0.414	<0.0001
ESR	0.274	<0.0001
CRP	0.481	<0.0001
C3	0.001	0.993
C4	0.006	0.936
BVAS	-0.024	0.737

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; N, neutrophils; PLT, platelets; HB, hemoglobin; BVAS, Birmingham vasculitis activity score; C3, complement 3.

Correlations of SII with clinical disease activity and clinical characteristics of patients with MPO-AAV. As presented in Table II, SII was positively correlated with CRP (r=0.274, P<0.0001) and ESR (r=0.481, P<0.0001). The SII had no significant correlation with the BVAS (r=-0.024, P=0.737).

Incidence rates of ESRD are associated with SII. It was evaluated whether the SII at diagnosis is able to predict all-cause mortality and ESRD in patients with MPO-AAV during follow-up. Kaplan-Meier analysis of cumulative renal survival and patient survival rates are provided in Fig. 2. Patients with SII≥2,136.45 exhibited better cumulative renal survival rates than those with SII<2,136.45 (P=0.001). However, no significant difference in the cumulative patient survival rates between patients with SII≥2,136.45 and those with SII<2,136.45 at diagnosis was obtained (P=0.275).

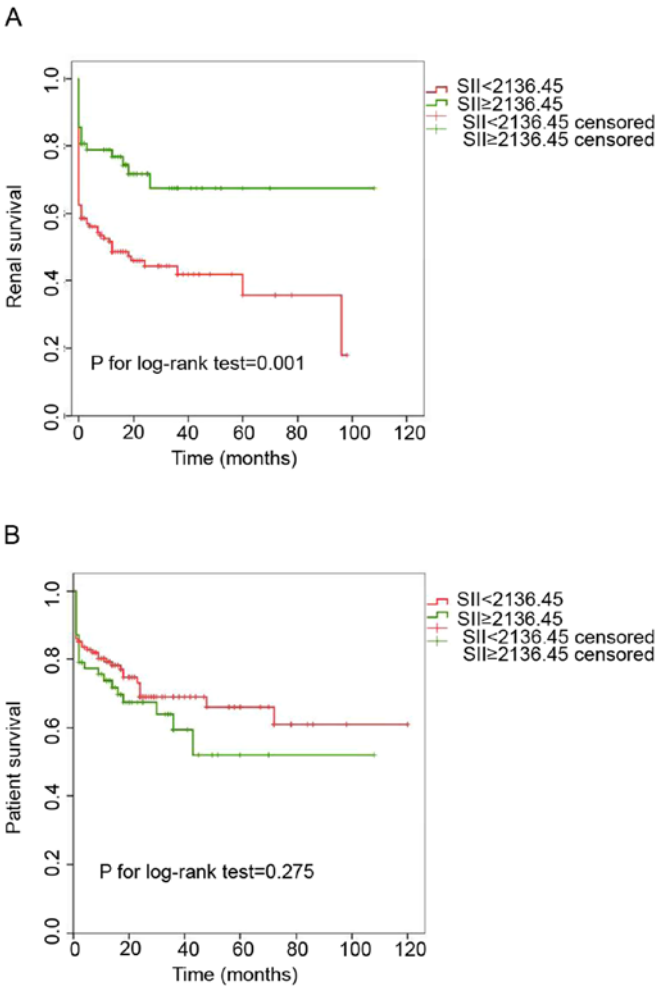

Figure 2. Kaplan-Meier analysis of (A) renal survival and (B) patient survival in association with the SII in patients with myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated vasculitis. SII, systemic immune-inflammation index.

Discussion

The key finding of the present study was that a higher SII in patients with MPO-AAV was able to predict a decreased risk of ESRD. Another important result was that the SII was positively correlated with CRP levels and the ESR in patients with MPO-AAV. These results indicated that the SII may reflect the inflammatory response and estimate prognosis during the follow-up of patients with MPO-AAV.

With accumulating evidence suggesting the detrimental role of inflammation in the pathogenesis of AAV, researchers have focused on evaluating the value of inflammatory markers in this disease. Two typical noninvasive markers of inflammation, CRP and ESR, are widely used. The SII is a relatively novel inflammatory index in routine blood tests. The calculation of SII depends on absolute cell numbers of neutrophils, lymphocytes and platelets. Neutrophils have been proven to be the key effector cells in the pathogenesis of MPO-AAV in animal models (22). *In vitro* experiments using human neutrophils and clinical evidence also suggested that neutrophils have key roles in the pathogenesis of human MPO-AAV (23). A decrease in the absolute lymphocyte number has been reported in various autoimmune diseases and an increase in the platelet count has been reported in patients with active AAV (24,25). Therefore, it may be assumed that the SII is correlated with an inflammatory response in patients with AAV. The results of the present study, which suggested that the SII was positively correlated with CRP and ESR in patients with MPO-AAV, support this hypothesis. The present results suggested that the SII may be a potential index reflecting inflammatory response in MPO-AAV. However, no significant relationship between the SII and BVAS was observed in the present study, which suggested that the value of the SII in predicting and evaluating disease activity in patients with MPO-AAV remains elusive.

The maximally selected log-rank statistical analysis rather than the receiver operating characteristic curve analysis was applied to the continuous variable in order to estimate the most appropriate cut-off values for splitting patients into groups with different renal survival probabilities (26). The decreased likelihood of ESRD in patients with a higher SII in comparison with that in patients with a lower SII is in

accordance with our clinical experience. However, this result is in contrast with data from a Korean cohort that demonstrated that patients with higher levels of SII exhibited significantly lower renal survival than those with lower levels of SII at diagnosis (27). The most plausible explanation for this difference is that a higher baseline SII was associated with lower levels of serum creatinine in the present study. The severity of renal dysfunction at presentation has been demonstrated to be a key negative prognostic factor for renal survival (28). Another explanation may be that the SII is a potential index for reflecting the inflammatory response in MPO-AAV, as mentioned above. Thus, the phenomenon resembles what is observed in malignant disease, where highly active proliferating cells are more sensitive to initial chemotherapy (29), and findings in patients with lupus nephritis, where patients having the highest activity index in kidney biopsies are most likely to enter remission (30).

The present study has several limitations. First, the duration of the follow-up was relatively short. Furthermore, with the retrospective nature of data collection, the maintenance immunosuppressive regimen was not the same in all patients. In addition, the number of patients with MPO-AAV in the present study was relatively small. Therefore, a large cohort of patients is required to validate the present results in future studies.

In conclusion, the SII was positively correlated with CRP levels and the ESR in Chinese patients with MPO-AAV. Furthermore, the SII may independently predict a reduced risk of progression to ESRD.

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Availability of data and materials

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

Authors' contributions

JBC, RT, LH, YZ, XCX, QLZ and PX designed the study, analyzed the data and wrote the manuscript. JBC, RT, YOZ, XXZ, HL, TW, YQY, TM, ZX, WL, XA, QLZ and PX contributed to patient enrollment and follow-up. JBC, RT and YZ analyzed the data. JBC and YZ checked and confirmed the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the ethics review committee of Xiangya Hospital Central South University (Changsha, China; reference. no. 20101006).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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