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ORIGINAL ARTICLE

Clinical value of systemic symptoms in IgA nephropathy with ANCA positivity

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Abstract

Our aim was to evaluate the pathogenic role of anti-neutrophil cytoplasmic antibodies (ANCAs) in patients with IgA nephropathy (IgAN). A total of 2390 patients with biopsy-confirmed IgAN were analyzed retrospectively. Thirty-five IgAN patients with ANCA and 40 IgAN patients without ANCA were enrolled. According to the Birmingham Vasculitis Activity Score (BVAS) items, the ANCA-positive patients were further divided into two subgroups which with or without systemic symptoms. The cumulative renal survival rate was calculated using Kaplan–Meier analysis. Comparisons between groups were made using the log rank test. Among the 35 ANCA-positive patients, 14 (40%) had systemic symptoms. Compared with ANCA-positive patients without systemic symptoms, ANCA-positive patients with systemic symptoms had a shorter duration of disease (1.0 [IQR, 0.3–6.8] vs. 6.0 [IQR, 2.0–21.0], $P = 0.011$); showed worse renal function with lower levels of eGFR (24.2 [IQR, 11.7–74.9] vs. 100.1 [IQR, 59.6–130.2] mL/min/1.73 m^2, $P = 0.002$), serum albumin (30.4 [IQR, 27.4–34.8] vs. 41.5 [IQR, 35.1–44.4] g/L, $P = 0.001$), and hemoglobin (96.1 ± 21.5 vs. 118.2 ± 22.4 g/L, $P = 0.006$); and presented relatively higher incidences of rapidly deteriorating kidney function (28.6 vs. 0.0%, $P = 0.039$) and moderate-to-severe tubular atrophy (78.6 vs. 23.8%, $P = 0.001$). Kaplan–Meier analysis had shown that ANCA-positive patients with systemic symptoms had lower cumulative renal survival rate compared with both ANCA-positive patients without systemic symptoms and ANCA-negative patients (log rank = 14.40, $P < 0.001$). Evaluation of systemic symptoms is a simple, readily available clinical tool to predictive the pathogenic role of ANCA in IgAN.

Keywords Anti-neutrophil cytoplasmic antibodies · Nephritis · Vasculitis

Introduction

Anti-neutrophil cytoplasmic antibodies (ANCAs) are serologic markers of ANCA-associated vasculitis (AAV) and play an important role in the pathogenesis of various autoimmune disorders [1]. Increasing evidence from animal studies and clinical observations has suggested the pathogenic role of ANCA in vasculitis [1–4]. Roth et al. suggested that the pathogenicity of ANCA might depend on epitope specificity [5]. Therefore, high sensitivity epitope excision and mass spectrometry approaches may be useful tools in the identification of pathogenic versus non-pathogenic ANCA. Nevertheless, these are time-consuming and costly diagnostic methods. In clinical practice, there is a pressing need to identify approaches that can rapidly evaluate and discern the various ANCA subsets. Such novel tools may have therapeutic implications and be of distinct prognostic value.

In the past few decades, ANCAs have been found not only in AAV but also in both pathological and normal conditions [6–12]. Recent studies have suggested the pathogenic potential of ANCA in IgA nephropathy (IgAN) [12–20]. Interestingly, studies found that most patients diagnosed with an overlap syndrome of IgAN and AAV commonly exhibited various signs and/or symptoms of vasculitis, including fever, arthralgia, keratitis, hemoptysis, and sudden visual loss. However, while these are systemic symptoms, they are mainly

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extrarenal manifestations and are not typical features of IgAN [21]. Nonetheless, ANCA seems to play a direct pathogenic role in these patients, which may be due to coexisting AAV [15]. Watts et al. [22] showed that systemic symptoms might be a poor indicator for vasculitis in ANCA-positive patients. Furthermore, the occurrence of multiple symptoms is closely related to pathogenic ANCA [23]. On this background, inclusion of systemic symptom assessment prior to therapy initiation seems reasonable.

The Birmingham Vasculitis Activity Score (BVAS) instrument is a questionnaire consisting of 56 items grouped into nine different organ systems. Each item refers to systemic symptoms frequently observed in patients with vasculitis, and these clinical symptoms are highly specific for vasculitis [24]. Therefore, we hypothesized that BVAS can serve as an aid for rapid screening of patients with pathogenic ANCA in clinical practice.

To illustrate this possibility, the current study provided the largest series of ANCA-positive IgAN patients. The selected patients were divided into two subgroups (with or without systemic symptoms) according to the BVAS items. Subsequently, a systematic analysis was performed to evaluate differences in clinicopathological features and prognosis in these patients.

Methods

Study cohort and study design

A total of 2390 patients with biopsy-confirmed IgAN were enrolled between January 2011 and June 2016 in the Department of Nephrology, Xinqiao Hospital (The Second Affiliated Hospital), Army Military Medical University (Third Military Medical University), Chongqing, China. Biopsy was based on the presence of dominant IgA in the glomerular mesangium with or without IgA deposits in peripheral glomerular capillary loops [25, 26].

The inclusion criteria for patients enrolled in this study were as follows: (1) screened for ANCAs (PR3-ANCA and MPO-ANCA) and (2) primary diagnosis without immunosuppressive therapy. The exclusion criteria were as follows: (1) history of chronic liver disease, infection, malignancies, diabetes, or other autoimmune diseases; (2) ANCAs associated with propylthiouracil or anti-tuberculosis drugs; (3) the presence of anti-GBM antibody or anti-nuclear antibody; and (4) lack of follow-up record.

Of the 2390 total patients, 35 ANCA-positive patients were selected for analysis. Another 40 patients with ANCA-negative IgAN (primary IgAN) were randomly selected as the control group.

This study was conducted according to the guidelines of the Declaration of Helsinki and was exempted from approval by the Medical Ethical Committee of Xinqiao Hospital (The Second Affiliated Hospital), Army Military Medical University (Third Military Medical University). Furthermore, the Medical Ethical Committee ruled that informed consent was not necessary given that this study involved minimal risk and no identifying information was used.

Measurements

Clinical data at renal biopsy included age, sex, time to renal biopsy, mean arterial blood pressure (MABP), serum creatinine, estimated glomerular filtration rate (eGFR), uric acid, serum albumin, erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), hemoglobin, serum IgA, serum C3, 24-h urine protein, proportion of renal insufficiency, nephrotic syndrome, rapidly deteriorating kidney function, Birmingham Vasculitis Activity Score (BVAS), and Vasculitis Damage Index (VDI). The eGFR was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) two-level race equation [27]. ANCAs were detected by indirect immunofluorescence (FA-1200-2010; Euroimmun; Lübeck, Germany) and EUROBlot kits (DL-1200-6401-3G; Euroimmun; Lübeck, Germany), according to the protocols provided by the respective manufacturers. Rapidly deteriorating kidney function was defined as "progressive renal impairment over a period of few weeks" [28]. Two investigators scored 35 ANCA-positive cases with BVAS and VDI instruments. Each investigator conducted several professional training on the VCRC website (http://www.rarediseasesnetwork.org/vcrc/investigators/outcomes).

Renal biopsy specimens from both ANCA-positive and ANCA-negative IgAN patients were analyzed and the following features based on the Oxford classification of IgAN were recorded: total glomeruli, crescent formation, fibrinoid necrosis, global glomerulosclerosis, mesangial hypercellularity rate, endocapillary hypercellularity, and tubular atrophy ([mild, T0 (0–25%); moderate, T1 (26–50%); or severe, T2 (≥ 51%)]) [25]. Additionally, the presence of IgA, IgG, IgM, C3, C4, and C1q deposits was documented (graded on a scale of 0–3 [0 for absence, + for mild, ++ for moderate, and +++ for strong]) in immunohistochemistry.

Outcomes and definition

The patients were followed up in an outpatient clinic. The regimen was adjusted according to renal function and histologic lesions. The composite endpoint of the study was defined as death or the occurrence of end-stage renal disease (ESRD). The ESRD was diagnosed in patients who had received maintenance dialysis or with eGFR < 15 mL/min/1.73 m^2 for at least 6 months. Remission was defined as patients with urinary protein < 0.3 g/day or protein-negative urine, with or without persistent

disappearance of microscopic hematuria (urinary sediment red blood cells of less than 5/HP) [29].

Statistical analysis

All statistical analyses were performed using SPSS software, version 21.0 (SPSS, Chicago, IL). The one-sample K–S test was used to determine the normality of the data distribution. Normal distribution and variance homogeneous data are presented as the average ± SD and compared with independent samples *t* test. Non-normal distribution data are presented as the median (interquartile range) and compared with the Mann–Whitney *U* test. Categorical variables compared with the chi-square test or Fisher's exact test are reported as the number and frequency. The cumulative percentage of renal function was calculated using the Kaplan–Meier method. Comparisons between groups were made using the log rank test. Spearman correlation test was applied to determine the correlations between measurements (including categorical variables and non-normal distribution data). For the predictive diagnostic value of tests, the receiver operating characteristic (ROC) curve was applied. A P value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Based on the symptoms in the BVAS score system, 35 patients with ANCA-positive were divided into two subgroups: those with systemic symptoms ($n = 14$) and patients without systemic symptoms ($n = 21$). We compared the clinical characteristics and prognosis of ANCA-positive and ANCA-negative

Table 1 Demographic and clinical characteristics of ANCA-positive IgAN patients (with and without systemic symptoms) and ANCA-negative patients (primary IgAN)

Parameter	Total	ANCA-positive		P^a	ANCA-negative
		With systemic symptoms	Without systemic symptoms		
No. of patients	35	14	21		40
Age (years)	36.9 ± 15.4	41.6 ± 17.5	33.7 ± 13.3	0.141	34.3 ± 11.5
Gender (male, %)	10 (28.6)*	3 (21.4)	7 (33.3)	0.703	21 (52.5)
Duration of disease (months)	3 (1–12)	1.0 (0.3–6.8)	6.0 (2.0–21.0)	0.011	6.0 (0.8–33)
ANCA titer	1:10 (1:10–1:32)	1:32 (1:10–1:100)	1:10 (1:8–1:10)	0.002	–
MABP (mmHg)	95.8 ± 17.5	96.1 ± 18.3	95.6 ± 17.5	0.944	95.2 ± 12.2
Serum creatinine (mg/dL)	1.0 (0.7–2.5)	2.3 (0.9–5.1)	0.9 (0.5–1.9)	0.006	1.0 (0.7–1.6)
eGFR (mL/min/1.73 m^2)	76.1 (21.5–115.6)	24.2 (11.7–74.9)	100.1 (59.6–130.2)	0.002	91.2 (42.7–115.4)
Uric acid (mg/dL)	6.2 (4.8–7.4)	6.3 (5.6–7.9)	6.2 (4.4–7.2)	0.474	6.3 (5.3–8.4)
Serum albumin (g/L)	35.7 (29.0–42.3)	30.4 (27.4–34.8)	41.5 (35.1–44.4)	0.001	39.2 (35.6–42.3)
ESR (mm/h)	31 (9–68)*	67.5 (30.8–95.0)	15.0 (7.5–34.5)	< 0.001	12 (7–17)
Hemoglobin (g/L)	109.4 ± 24.4*	96.1 ± 21.5	118.2 ± 22.4	0.006	132.6 ± 18.0#
NLR	2.6 (1.9–3.6)	3.7 (2.6–5.3)	2.1 (1.8–2.8)	0.001	2.5 (1.9–3.6)
Serum IgA (g/L)	2.3 (1.6–3.2)	2.1 (1.4–2.7)	2.7 (1.8–3.6)	0.138	2.4 (1.9–3.3)
Serum C3 (g/L)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.881	0.8 (0.8–0.9)
Urine protein (g/24 h)	1.8 (0.4–3.1)	2.2 (0.8–3.3)	0.6 (0.3–3.1)	0.298	1.2 (0.6–2.6)
BVAS	6 (0–14)	14 (10–17)	0 (0 - 0)	< 0.001	–
Nephrotic syndrome[b]	6 (18.2)	3 (23.1)	3 (15.0)	0.927	2 (5.1)
Rapidly deteriorating kidney function	4 (11.4)	4 (28.6)	0 (0.0)	0.039	0 (0.0)

Normal distribution data are presented as mean ± SD; non-normal distribution data presented as median (Q25, Q75); values for categorical variables are provided as numbers (percentages). Conversion factors for units: SCr in mg/dL to μmol/L, × 88.4; uric acid in mg/dL to μmol/L, × 59.48; MABP = [(2 × diastolic) + systolic]/3

ANCA, anti-neutrophil cytoplasmic autoantibody; *MABP*, mean arterial blood pressure; *eGFR*, estimated glomerular filtration rate calculated using epidemiology collaboration (CKD-EPI) two-level race equation; *ESR*, erythrocyte sedimentation rate; *NLR*, neutrophil-to-lymphocyte ratio

[a] Comparison between ANCA-positive IgAN patients with and without systemic symptoms

[b] Two cases without the data of 24-h urine protein

*Significant differences between ANCA-positive IgAN patients and ANCA-negative patients (primary IgAN)

[#] Significant differences between ANCA-positive IgAN patients with no systemic symptoms and ANCA-negative patients (primary IgAN)

IgAN patients and further distinguished between ANCA-positive patients with and without systemic symptoms in comparison with ANCA-negative patients. There were no significant differences in duration of disease and renal function between ANCA-positive and ANCA-negative IgAN patients ($P > 0.05$). Compared with ANCA-positive patients without systemic symptoms, ANCA-positive patients with systemic symptoms had a shorter duration of disease (1.0 [IQR, 0.3–6.8] vs. 6.0 [IQR, 2.0–21.0], $P = 0.011$); showed lower levels of eGFR (24.2 [IQR, 11.7–74.9] vs.100.1 [IQR, 59.6–130.2] mL/min/1.73 m^2, $P = 0.002$), serum albumin (30.4 [IQR, 27.4–34.8] vs. 41.5 [IQR, 35.1–44.4] g/L, $P = 0.001$), and hemoglobin (96.1 ± 21.5 vs. 118.2 ± 22.4 g/L, $P = 0.006$); and presented higher levels of serum creatinine (IQR, 2.3 [0.9–5.1] vs. 0.9 [IQR, 0.5–1.9] mg/dL, $P = 0.006$), ESR (67.5 [IQR, 30.8–95.0] vs. 15.0 [IQR, 7.5–34.5] mm/h, $P < 0.001$), NLR (IQR, 3.7 [2.6–5.3] vs. 2.1 [IQR, 1.8–2.8], $P = 0.001$), baseline BVAS score (IQR, 14 [10–17] vs. 0 [IQR, 0–0], $P < 0.001$), and ANCA titer (1:32 [IQR, 1:10–1:100] vs. 1:10 [IQR, 1:8–1:10], $P = 0.002$) (Table 1). In addition, relatively higher incidences of rapidly deteriorating kidney function was seen in ANCA-positive patients with systemic symptoms compared with ANCA-positive without systemic symptoms (28.6 vs. 0.0%, $P = 0.039$). With the exception of hemoglobin levels, no differences in clinical characteristics were observed between ANCA-positive patients without systemic symptoms and ANCA-negative patients (Table 1). In all, this data suggested that the presence of systemic symptoms in ANCA-positive was a negative factor for IgAN.

Renal histopathology

There were no significant differences in cellular/fibrous crescents, global glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy between ANCA-positive and ANCA-negative IgAN patients ($P > 0.05$). ANCA-positive patients with systemic symptoms showed significantly higher positive rate of moderate-to-severe tubular atrophy compared with ANCA-positive patients without systemic symptoms (78.6 vs. 23.8%, $P = 0.001$). No such difference was seen between ANCA-positive patients without systemic symptoms and ANCA-negative patients ($P > 0.05$), except mesangial hypercellularity rate ($P < 0.05$) (Table 2).

Table 2 Renal histologic characteristics of ANCA-positive IgAN patients (with and without systemic symptoms) and ANCA-negative patients (primary IgAN)

Parameter	Total	ANCA-positive		P^a	ANCA-negative
		With systemic symptoms	Without systemic symptoms		
No. of patients	35	14	21		40
Total glomeruli	12 (11–19)	14 (11–19)	12 (7.5–19)	0.309	13 (9–19)
Cellular crescents	4 (11.4)	3 (21.4)	1 (4.8)	0.329	4 (10.0)
Fibrous crescents	5 (14.3)	3 (21.4)	2 (9.5)	0.622	2 (5)
Global glomerulosclerosis	23 (65.7)	11 (78.6)	12 (57.1)	0.191	29 (72.5)
Global glomerulosclerosis rate (%)	10.5 (0–37.5)	19.6 (6.8–42.2)	5.3 (0–20.8)	0.164	10.0 (0–33.3
Mesangial hypercellularity rate (%)	47.8 ± 26.8*	48.8 ± 28.2	47.1 ± 26.5	0.803	60.0 ± 20.0#
Endocapillary hypercellularity	2 (5.9)	1 (7.1)	1 (4.8)	1.000	0 (0.0)
Tubular atrophy (T1 and T2)	16 (45.7)	11 (78.6)	5 (23.8)	0.001	12 (30.0)
Immune complex deposition					
IgM	3 (8.6)	0 (0.0)	3 (14.3)	0.388	3 (7.5)
IgG	15 (42.9)	8 (57.1)	7 (33.3)	0.163	23 (57.5)
Co-deposition	9 (25.7)	5 (35.7)	4 (19.0)	0.477	13 (32.5)
C3	28 (80.0)	10 (71.4)	18 (85.7)	0.546	39 (97.5)
C4	0 (0.0)	0 (0.0)	0 (0.0)	–	0 (0.0)
C1q	0 (0.0)	0 (0.0)	0 (0.0)	–	0 (0.0)

Normal distribution data are presented as mean ± SD; non-normal distribution data are presented as median (Q25, Q75); values for categorical variables are given as numbers (percentages)

IgM, IgA deposition with immune complex IgM; *IgG*, IgA deposition with immune complex IgG; *co-deposition*, IgA deposition with immune complex IgG and IgM; *C3*, immunocomplex deposition along with C3 (C3 deposition ≥ 1+); *C4*, C4 deposition ≥ 1+; *C1q*, C1q deposition ≥ 1+

[a] Comparison between ANCA-positive IgAN patients with and without systemic symptoms

*Significant differences between ANCA-positive IgAN patients and ANCA-negative patients (primary IgAN)

[#] Significant differences between ANCA-positive IgAN patients with no systemic symptoms and ANCA-negative patients (primary IgAN)

Table 3 Therapy and outcome of ANCA-positive IgAN patients (with and without systemic symptoms) and ANCA-negative patients (primary IgAN)

Parameter	Total	ANCA-positive		P^a	ANCA-negative
		With systemic symptoms	Without systemic symptoms		
No. of patients	35	14	21		40
Corticosteroid	7 (20)	2 (14.3)	5 (23.8)	0.796	14 (35.0)
Pulse methylprednisolone	4 (11.4)	3 (21.4)	1 (4.8)	0.329	2 (5.0)
Steroid and immunosuppressors	15 (42.9)	11 (78.6)	4 (19.0)	< 0.001	7 (17.5)
Hemodialysis	3 (8.6)	2 (14.3)	1 (4.8)	0.712	1 (2.5)
Remission	15 (42.9)	4 (28.6)	11 (52.4)	0.163	15 (37.5)
ESRD	6 (17.1)	5 (35.7)	1 (4.8)	0.055	2 (5.0)
Mortality	2 (5.7)	2 (14.3)	0 (0.0)	0.153	0 (0.0)

Values for categorical variables are provided as numbers (percentages)

[a] Comparison between ANCA-positive IgAN patients with and without systemic symptoms

Therapy

With the ANCA-positive group, a greater proportion of patients with systemic symptoms had been treated with steroid and immunosuppressors combination compared with patients without systemic symptoms (78.6 vs. 19.0%, $P < 0.001$). There were no significant differences in therapy and outcome between the ANCA-positive patients without systemic symptoms and patients with ANCA negativity ($P > 0.05$) (Table 3).

Survival analysis

The median follow-up time was 9 months (range 3–26) in ANCA-positive patients with systemic symptoms, 7 months (range 3–28) in ANCA-positive patients without systemic symptoms, and 25 months (range 16–31) in ANCA-negative patients, respectively. In Kaplan–Meier analysis, a significant difference in cumulative renal survival rate was seen in the ANCA-positive with systemic symptoms as compared to the other two groups (Fig. 1; log rank = 14.40, $P < 0.001$).

Correlation results

The correlation between test results was illustrated in Table 4. The BVAS scores at baseline showed significant correlations with ESRD ($r = 0.341$, $P = 0.045$), mortality ($r = 0.344$, $P = 0.043$), VDI ($r = 0.349$, $P = 0.040$), and inflammatory indicators including NLR ($r = 0.424$, $P = 0.011$) and ESR ($r = 0.502$, $P = 0.002$) in ANCA-positive IgAN patients.

Predictive diagnostic value

According to the ROC analysis, AUC of the ROC curve for BVAS showed no statistically significant to predict ESRD (AUC 0.720; $P = 0.062$) or mortality (AUC 0.833; $P = 0.059$), as shown in Fig. 2. But VDI and NLR showed

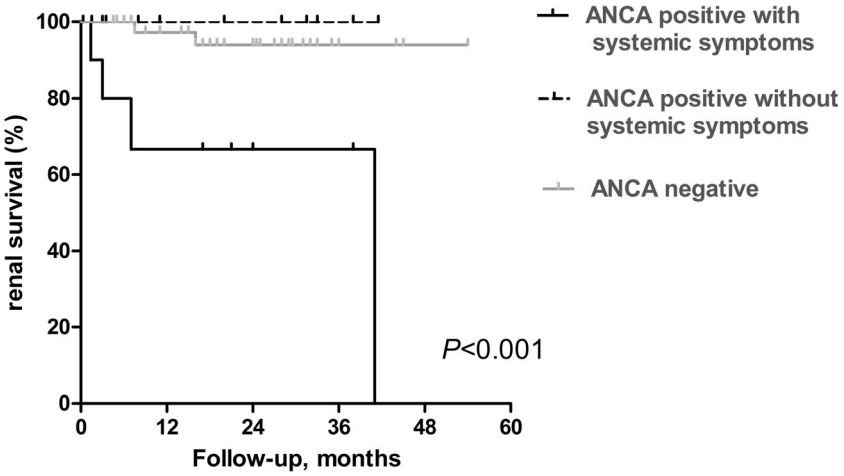

Fig. 1 Renal survival rate of ANCA-positive IgAN patients (with and without systemic symptoms) and ANCA-negative patients (primary IgAN). Kaplan–Meier analysis was used to calculate the renal survival in patient groups (log rank = 14.40, $P < 0.001$)

Table 4 Correlation results

Parameter	ESRD	Mortality	Remission	ESR (mm/h)	NLR	VDI
BVAS	$r = 0.341$	$r = 0.344$	$r = -0.323$	$r = 0.502$	$r = 0.424$	$r = 0.349$
	$P = 0.045$	$P = 0.043$	$P = 0.058$	$P = 0.002$	$P = 0.011$	$P = 0.040$
VDI	$r = 0.504$	$r = 0.323$	$r = -0.725$	$r = 0.205$	$r = 0.445$	–
	$P = 0.002$	$P = 0.059$	$P = 0.000$	$P = 0.238$	$P = 0.007$	–
NLR	$r = 0.505$	$r = 0.101$	$r = -0.318$	$r = 0.341$	–	–
	$P = 0.002$	$P = 0.563$	$P = 0.063$	$P = 0.045$	–	–
ESR (mm/h)	$r = 0.314$	$r = 0.394$	$r = -0.063$	–	–	–
	$P = 0.067$	$P = 0.019$	$P = 0.721$	–	–	–

r, correlation coefficient; *BVAS*, Birmingham Vasculitis Activity Score; *VDI*, Vasculitis Damage Index; *NLR*, neutrophil-to-lymphocyte ratio; *ESR*, erythrocyte sedimentation rate; *ESRD*, end-stage renal disease

significantly sensitivity, specificity, and accuracy to ESRD ((AUC 0.815; $P = 0.008$), (AUC 0.847; $P = 0.003$), respectively). The ESR showed the best sensitivity, specificity, and accuracy to predict mortality (AUC 0.0.906; $P = 0.022$).

Discussion

This study validated the application of BVAS items in ANCA-positive IgAN patients. We found that ANCA-positive patients with systemic symptoms typically exhibited more severe clinical features and histological lesions. Our results indicated that the identification of these symptoms included in the BVAS items might be helpful in the rapid screening of patients with pathogenic ANCA.

The BVAS is an instrument that was designed to measure disease activity [30]. The application of BVAS has been on the rise in the past decade, with its use documented in vasculitis. Further evidence has shown its utility in assessing therapeutic effect in clinical trials [31, 32]. Furthermore, a retrospective analysis by Wallace et al. [33] showed that the BVAS could effectively predict prognosis. Subsequently, Haris et al. [34] applied this clinical tool to risk stratification of patients. In that study, BVAS was used as a simple and practical screening tool in patients with suspected vasculitis. Herein, we propose that BVAS can also be applied flexibly to clinical evaluation of IgAN patients with serum ANCA positivity.

In the present study, ANCA-positive patients with systemic symptoms showed worse renal function and hypoproteinemia and manifested with obvious abnormality in inflammatory indicators. This data was consistent with previous reports for patients who had been diagnosed with IgAN and AAV [12–20]. In addition, we observed that most of the ANCA-positive patients with systemic symptoms showed moderate-to-severe tubular atrophy. Recent evidence suggests that initial eGFR, hypoproteinemia, and tubular atrophy are independent predictors of unfavorable renal outcome [35–37]. Our data showed that this sub-population had a poor prognosis, even though they received immunosuppressive treatment after renal biopsy. In a previous study, similar patients were still dialysis-dependent in spite of treatment with cyclophosphamide and corticosteroids [18]. The main reason for this dire outcome is due to the presence of severe renal damage at diagnosis without the benefit of early intervention. Furthermore, treatment toxicity caused by long-term use of immunosuppressants cannot be ruled out [38]. Therefore, there is a need for early diagnosis and more optimized treatment options. Other similar studies demonstrated that ANCA-positive IgAN patients could respond very well to immunosuppressive treatment [15, 17, 20]. However, thus far, no more than 50 cases with

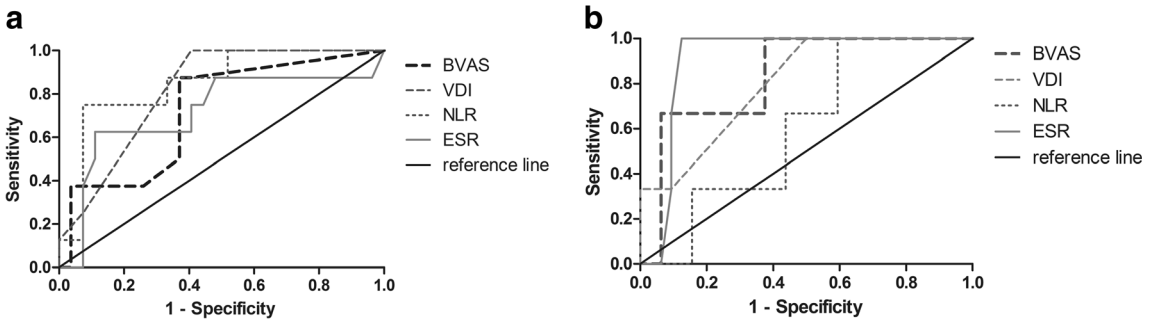

Fig. 2 Receiver operating characteristic analysis showing the predictive value of baseline BVAS, VDI, NLR, and ESR to predict **a** ESRD and **b** mortality in 35 ANCA-positive IgAN patients. *AUC*, area under the curve; *BVAS*, Birmingham Vasculitis Activity Score; *VDI*, Vasculitis Damage Index; *NLR*, neutrophil-to-lymphocyte ratio; *ESR*, erythrocyte sedimentation rate; *ESRD*, end-stage renal disease

IgAN and ANCA positivity have been reported and have mainly been case reports, three case series, and a case-control study [12, 39]. Certain specific factors could be involved in these disparities, such as demographic characteristics and patient selection criteria. In addition, previous studies have focused on the clinical manifestations and treatment response of IgAN patients with ANCA, but none has investigated the long-term prognosis using Kaplan–Meier method [12, 15, 18, 39]. In our study, ANCA-positive patients without systemic symptoms showed slow disease process similarly to primary IgAN (with ANCA-negativity). This data suggested that systemic symptoms might be an identification factor for pathogenic ANCA. Moreover, these systemic symptoms were considered only if they could not be accounted for by infectious or atherosclerotic disease, or drug toxicity [24].

In clinical practice, the BVAS is a useful checklist for clinicians to supplement their assessment of patients with suspected or diagnosed with vasculitis. Using BVAS items may facilitate rapid screening of patients with pathogenic ANCA. Previous studies have shown that this tool for measuring disease activity could be used as a prognostic tool in patients with vasculitis [24]. The damage assessment tool, Vasculitis Damage Index (VDI), is a clinical checklist for recording the accumulation of damage. Prolonged immunosuppressive treatment can be effectively avoided by using this instrument [40]. As previous studies [24, 41], we also found that the BVAS scores at baseline correlate well with renal survival, mortality, the initial VDI scores, and inflammatory indicators including NLR and ESR in ANCA-positive IgAN patients. Compared to VDI, the BVAS showed no advantage in predicting the prognosis [40]. But for the clinician, the activity assessment tool, BVAS can provide timely assessment and treatment. There may be some subjectivity based on clinical judgment. Despite this caveat, the application of BVAS is still worth considering in ANCA-positive patients. The improvement of BVAS is necessary, just like any tool without a gold standard. In our later prospective study, we will expand the sample size for further verification BVAS in ANCA-positive patients with systemic symptoms.

This study has important strengths, mainly the number of enrolled patients, diversity of the patient population, long-term follow-up, comprehensive analysis of clinical and histological specimens, and the use of standard clinical endpoints such as ESRD and death. Nonetheless, there are inherent limitations of a retrospective observational investigation, and our findings need to be validated in large cohorts and multiple centers.

In conclusion, this study validated that the presence of systemic symptoms in ANCA-positive was a negative factor for IgAN as previous report [15]. Assessment of systemic symptoms by BVAS items is a simple, readily available clinical approach to discriminate pathogenic versus non-pathogenic ANCA in IgAN with ANCA positivity. However, the application of this clinical tool for IgAN requires training and experience.

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Compliance with ethical standards This study was conducted according to the guidelines of the Declaration of Helsinki and was exempted from approval by the Medical Ethical Committee of Xinqiao Hospital (The Second Affiliated Hospital), Army Military Medical University (Third Military Medical University). Furthermore, the Medical Ethical Committee ruled that informed consent was not necessary given that this study involved minimal risk and no identifying information was used.

Disclosures None.

References

1. Falk RJ, Terrell RS, Charles LA, Jennette JC (1990) Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. Proc Natl Acad Sci U S A 87(11):4115–4119. https://doi.org/10.1073/pnas.87.11.4115
2. Xiao H, Heeringa P, Hu P, Liu Z, Zhao M, Aratani Y, Maeda N, Falk RJ, Jennette JC (2002) Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest 110(7):955–963. https://doi.org/10.1172/JCI0215918
3. Bansal PJ, Tobin MC (2004) Neonatal microscopic polyangiitis secondary to transfer of maternal myeloperoxidase-antineutrophil cytoplasmic antibody resulting in neonatal pulmonary hemorrhage and renal involvement. Ann Allergy Asthma Immunol 93(4):398–401. https://doi.org/10.1016/S1081-1206(10)61400-7
4. Jayne DRW, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, Mirapeix E, Savage COS, Sinico RA, Stegeman CA, Westman KW, van der Woude FJ, de Lind van Wijngaarden RAF, Pusey CD, on behalf of the European Vasculitis Study Group (2007) Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 18(7):2180–2188. https://doi.org/10.1681/ASN.2007010090
5. Roth AJ, Ooi JD, Hess JJ, van Timmeren MM, Berg EA, Poulton CE, McGregor JA, Burkart M, Hogan SL, Hu Y, Winnik W, Nachman PH, Stegeman CA, Niles J, Heeringa P, Kitching AR, Holdsworth S, Jennette JC, Preston GA, Falk RJ (2013) Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis. J Clin Invest 123(4):1773–1783. https://doi.org/10.1172/JCI65292
6. Radice A, Sinico RA (2005) Antineutrophil cytoplasmic antibodies (ANCA). Autoimmunity 38(1):93–103. https://doi.org/10.1080/08916930400022673
7. Anaele CU, Srisung W, Tomacruz Y, Laski M (2015) Antineutrophil cytoplasmic antibodies-negative pauci-immune crescentic glomerulonephritis associated with multiple myeloma. Case Rep Nephrol Dial 5(2):124–129. https://doi.org/10.1159/000432394

8. Tanemoto M, Miyakawa H, Hanai J, Yago M, Kitaoka M, Uchida S (1995) Myeloperoxidase-antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis complicating the course of Graves' disease: report of three adult cases. Am J Kidney Dis 26(5): 774–780. https://doi.org/10.1016/0272-6386(95)90441-7
9. Hervier B, Hamidou M, Haroche J, Durant C, Mathian A, Amoura Z (2012) Systemic lupus erythematosus associated with ANCA-associated vasculitis: an overlapping syndrome? Rheumatol Int 32(10):3285–3290. https://doi.org/10.1007/s00296-011-2055-z
10. Lindic J, Vizjak A, Ferluga D, Kovac D, Ales A, Kveder R et al (2009) Clinical outcome of patients with coexistent antineutrophil cytoplasmic antibodies and antibodies against glomerular basement membrane. Ther Apher Dial 13(4):278–281. https://doi.org/10.1111/j.1744-9987.2009.00724.x
11. Boulis E, Majithia V, McMurray R (2013) Adult-onset Henoch–Schonlein purpura with positive c-ANCA (anti-proteinase 3): case report and review of literature. Rheumatol Int 33(2):493–496. https://doi.org/10.1007/s00296-010-1608-x
12. Yang YZ, Shi SF, Chen YQ, Chen M, Yang YH, Xie XF et al (2015) Clinical features of IgA nephropathy with serum ANCA positivity: a retrospective case-control study. Clin Kidney J 8(5): 482–488. https://doi.org/10.1093/ckj/sfv078
13. Ramirez SB, Rosen S, Niles J, Somers MJ (1998) IgG antineutrophil cytoplasmic antibodies in IgA nephropathy: a clinical variant? Am J Kidney Dis 31(2):341–344. https://doi.org/10.1053/ajkd.1998.v31.pm9469508
14. Kucuk A, Solak Y, Gaipov A, Bagcaci S, Esen H, Turk S, Tunc R (2016) Co-existing proteinase 3-antineutrophil cytoplasmic antibody-associated vasculitis with immunoglobulin A nephropathy. Korean J Intern Med 31(1):194–196. https://doi.org/10.3904/kjim.2016.31.1.194
15. Bantis C, Stangou M, Schlaugat C, Alexopoulos E, Pantzaki A, Memmos D, Ivens K, Heering PJ (2010) Is presence of ANCA in crescentic IgA nephropathy a coincidence or novel clinical entity? A case series. Am J Kidney Dis 55(2):259–268. https://doi.org/10.1053/j.ajkd.2009.09.031
16. Houben E, Bax WA, van Dam B, Slieker WA, Verhave G, Frerichs FC et al (2016) Diagnosing ANCA-associated vasculitis in ANCA positive patients: a retrospective analysis on the role of clinical symptoms and the ANCA titre. Medicine 95(40):e5096. https://doi.org/10.1097/MD.0000000000005096
17. Winters MJ, Hurley RM, Lirenman DS (2002) ANCA-positive glomerulonephritis and IgA nephropathy in a patient on propylthiouracil. Pediatr Nephrol 17(4):257–260. https://doi.org/10.1007/s00467-001-0807-9
18. Haas M, Jafri J, Bartosh SM, Karp SL, Adler SG, Meehan SM (2000) ANCA-associated crescentic glomerulonephritis with mesangial IgA deposits. Am J Kidney Dis 36(4):709–718. https://doi.org/10.1053/ajkd.2000.17615
19. Ogawa N, Yano S, Yamane Y, Nishiki M, Yamaguchi T, Tsukamoto T, Muso E, Sugimoto T (2007) MPO-ANCA-positive IgA nephropathy successfully treated with tonsillectomy. Clin Exp Nephrol 11(4):326–331. https://doi.org/10.1007/s10157-007-0506-3
20. Barcelos FL, Fontes TM (2015) Case report-IgA nephropathy ANCA positive with favorable outcome. J Bras Nefrol 37:414–417, 3, DOI: https://doi.org/10.5935/0101-2800.20150063
21. Fabiano RC, Pinheiro SV, Simões E, Silva AC (2016) Immunoglobulin A nephropathy: a pathophysiology view. Inflamm Res 65(10):757–770. https://doi.org/10.1007/s00011-016-0962-x
22. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D (2007) Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 66(2):222–227. https://doi.org/10.1136/ard.2006.054593
23. Land J, Rutgers A, Kallenberg CG (2014) Anti-neutrophil cytoplasmic autoantibody pathogenicity revisited: pathogenic versus non-pathogenic anti-neutrophil cytoplasmic autoantibody. Nephrol Dial Transplant 29(4):739–745. https://doi.org/10.1093/ndt/gft416
24. Flossmann O, Bacon P, de Groot K, Jayne D, Rasmussen N, Seo P, Westman K, Luqmani R (2007) Development of comprehensive disease assessment in systemic vasculitis. Ann Rheum Dis 66(3): 283–292. https://doi.org/10.1136/ard.2005.051078
25. Roberts I, Cook T, Troyanov S, Alpers C, Amore A, Barratt J et al (2009) The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int 76(5): 546–556. https://doi.org/10.1038/ki.2009.168
26. Davin JC, Ten Berge IJ, Weening JJ (2001) What is the difference between IgA nephropathy and Henoch-Schonlein purpura nephritis? Kidney Int 59(3):823–834. https://doi.org/10.1046/j.1523-1755.2001.059003823.x
27. Kong XL, Ma YC, Chen JH, Luo Q, XQ Y, Li Y et al (2013) Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating glomerular filtration rate in the Chinese population. Nephrol Dial Transplant 28(3):641–651. https://doi.org/10.1093/ndt/gfs491
28. Bhowmik D, Sinha S, Gupt A, Tiwari SC, Agarwal SK (2011) Clinical approach to rapidly progressive renal failure. J Assoc Physicians India 59:38–41
29. Suzuki Y, Matsuzaki K, Suzuki H, Sakamoto N, Joh K, Kawamura T, Tomino Y, Matsuo S (2014) Proposal of remission criteria for IgA nephropathy. Clin Exp Nephrol 18(3):481–486. https://doi.org/10.1007/s10157-013-0849-x
30. Luqmani RA (1994) Birmingham vasculitis activity score (BVAS) in systemic necrotizing vasculitis. Q J Med 87:671–678
31. Pu L, Li GS, Zou YR, Zhang P, Wang L (2017) Clinical predictors of outcome in patients with anti-neutrophil cytoplasmic autoantibody-related renal vasculitis: experiences from a single-center. Chin Med J 130:899–905, 8, DOI: https://doi.org/10.4103/0366-6999.204099
32. YJ O, Ahn SS, Park ES, Jung SM, Song JJ, Park YB et al (2017) Birmingham vasculitis activity score at diagnosis is a significant predictor of relapse of polyarteritis nodosa. Rheumatol Int 37: 685–694
33. Wallace ZS, Miloslavsky EM, Cascino M, Unizony SH, Lu N, Hoffman GS, Kallenberg CGM, Langford CA, Merkel PA, Monach PA, Seo P, Spiera R, St.Clair EW, Specks U, Brunetta P, Choi HK, Stone JH (2017) Effect of disease activity, glucocorticoid exposure, and rituximab on body composition during induction treatment of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Care Res 69(7):1004–1010. https://doi.org/10.1002/acr.23099
34. Haris Á, Polner K, Arányi J, Braunitzer H, Kaszás I, Rosivall L, Kökény G, Mucsi I (2017) Simple, readily available clinical indices predict early and late mortality among patients with ANCA-associated vasculitis. BMC Nephrol 18:76, 1, DOI: https://doi.org/10.1186/s12882-017-0491-z
35. Le W, Liang S, Hu Y, Deng K, Bao H, Zeng C, Liu Z (2012) Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. Nephrol Dial Transplant 27(4):1479–1485. https://doi.org/10.1093/ndt/gfr527
36. Moriyama T, Tanaka K, Iwasaki C, Oshima Y, Ochi A, Kataoka H, Itabashi M, Takei T, Uchida K, Nitta K (2014) Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One 9(3):e91756. https://doi.org/10.1371/journal.pone.0091756
37. Cattran D, Coppo R, Cook T, Feehally J, Roberts I, Troyanov S et al (2009) The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int 76(5):534–545. https://doi.org/10.1038/ki.2009.243

38. Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, Savage C, Jayne D, Harper L, on behalf of the European Vasculitis Study (EUVAS) Group (2010) Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis 69:1036–1043, 6, DOI: https://doi.org/10.1136/ard.2009.109389
39. Huang X, Wang Y, Xie LJ, Zhang Y, Tang S, Yin SW et al (2015) IgA nephropathy with anti-neutrophil cytoplasmic antibody seropositivity. Clin Nephrol 84(3):156–164. https://doi.org/10.5414/CN108571
40. Bhamra K, Luqmani R (2012) Damage assessment in ANCA-associated vasculitis. Curr Rheumatol Rep 14(6):494–500. https://doi.org/10.1007/s11926-012-0291-1
41. Küçük H, Göker B, Varan Ö, Dumludag B, Haznedaroğlu Ş, Öztürk MA, Tufan A, Emiroglu T, Erten Y (2017) Predictive value of neutrophil/lymphocyte ratio in renal prognosis of patients with granulomatosis with polyangiitis. Ren Fail 39(1):273–276. https://doi.org/10.1080/0886022X.2016.1259633