The Association of Serum Anti-Lysosomal-Associated Membrane Protein-2 Antibody with Vasculitis Combined with Hypertension

1. Introduction

Hypertension is a global public health problem. It is currently the main contributor to the global burden of disease [1]. Numerous studies have confirmed that an increasing number of patients with hypertension is attributed to various diseases (e.g., kidney disease, primary aldosteronism, and vasculitis) [2–5]. Among them, the incidence of vasculitis is very insidious and harmful [6]. Because of the particularity of etiology, conventional antihypertensive therapy is not feasible. Furthermore, the target organ (renal, lung, heart, brain, etc.) damage caused by vasculitis is very similar and more serious to that caused by hypertension [7, 8]. Consequently, differential diagnosis of patients with vasculitis combined with hypertension (VAS-HTN) is extremely important in the hypertensive population.

Vasculitis is a disabling disease featuring inflammatory injury and destruction that affects all sizes of vessels in the body [9]. Recently, the incidence of vasculitis has gradually increased, which has brought a heavy economic burden to society [10, 11]. Hypertension is a common clinical feature...
of vasculitis [12, 13]. In clinical, hypertension specialists will also encounter patients with vasculitis. However, vasculitis presents with a wide range of clinical presentations and lacks specific laboratory indicators. The identification and evaluation of disease in vasculitis is a tremendous challenge. Therefore, finding novel biomarkers is very important for VAS-HTN patients to be identified from hypertensive populations and to create conditions for future treatment.

Lysoosomal-associated membrane protein-2 (LAMP-2) is a transmembrane protein that participates in molecular chaperone-mediated autophagy and the presentation of intracellular antigens [14–17]. Kain et al.’s study found that LAMP-2 was expressed on the surface of neutrophils and was considered the anti-neutrophil cytoplasmic antibody (ANCA) antigen [18]. Recent studies suggest that anti-LAMP-2 antibody has been involved in the pathogenesis of vasculitis [19–21]. Some research showed that the levels of serum anti-LAMP-2 antibody were observed to increase in small vessel vasculitis [22–24]. Nevertheless, other research demonstrated that the levels of serum anti-LAMP-2 antibody were similar in ANCA-associated vasculitis (AAV) patients compared to healthy controls (HC) [22, 23, 25]. Therefore, whether the anti-LAMP-2 antibody is associated with vasculitis remains controversial. Furthermore, serum anti-LAMP-2 antibody levels have not been evaluated in VAS-HTN, particularly in Takayasu arteritis (TA) and polyarteritis nodosa (PAN). The goal of this study was to examine whether there is a relationship between serum anti-LAMP-2 antibody levels and VAS-HTN.

2. Methods

2.1. Study Subjects. All enrolled VAS-HTN patients were seen at the People’s Hospital of Xinjiang Uygur Autonomous Region from January 2013 to December 2017, and the diagnosis was made based on clinical presentation, laboratory tests, imaging examinations, or/and pathological biopsies. Finally, 51 VAS-HTN patients (including 24 PAN, 20 AAV, and 7 TA) were included in this study. The diagnostic flow chart of VAS-HTN screening is shown in Figure 1. All vasculitis patients fulfilled the 1990 ACR and/or 2012 revised CHCC classification criteria [26–30]. The criteria for the diagnosis of vasculitis are shown in Figure 2. Also, 46 patients with age- and sex-matched essential hypertension (EH) and 46 HC subjects were include in the study.

2.2. Data Collection and Measurements. All clinical information data is derived from the electronic medical records of patients during their hospitalization. Details of the data collection and measurements can be found in previously published papers [31, 32] and online supplemental material.

2.3. Definitions of Disease Activity. Disease activity was assessed according to the third version of the Birmingham Vasculitis Activity Score (BVAS) [33]. The BVAS = 0 was considered inactive in VAS-HTN patients, and the BVAS ≥ 1 was considered active in VAS-HTN patients.

2.4. Definitions of Renal Injury. Renal injury was defined as any proteinuria and/or hematuria and/or elevated serum Scr. Proteinuria was defined as a urine routine of more than 1+ and/or urine containing more than 0.15 g of protein was collected for 24 hours. Hematuria was defined as more than 5 red blood cells per high magnification view in the urine sediment. Elevated serum Scr was defined as a female Scr > 84 μmol/L or a male Scr > 104 μmol/L [31].

2.5. Serum Sample Collection and Anti-LAMP-2 Antibody Measurement. Blood samples from all participants were drawn into procoagulation tubes, and the serum was collected after centrifugation at 3000 g at 4°C for 15 minutes as soon as possible. The serum was stored in a refrigerator at −80°C for standby. The levels of serum anti-LAMP-2 antibodies were measured using a commercial ELISA kit according to the manufacturer’s instructions (Uscn Life Sciences, Wuhan, China).

2.6. Statistical Analysis. SPSS software version 20.0 and GraphPad Prism software 5.0 were employed for statistical analysis and graphing. Mean ± standard deviation, or median and interquartile range, was used to present continuous variables, as appropriate. Categorical variables are expressed as totals and percentages. The t-test/one-way ANOVA or rank-sum test is used for comparisons across groups, as appropriate. Spearman or Pearson rank correlations were used to assess correlations. Binary logistic regression was used to determine independent factors for the diagnosis of VAS-HTN. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value for anti-LAMP-2 antibodies. P value <0.05 was regarded as significant.

![Figure 1: The screening and diagnostic flow chart for vasculitis combined with hypertension.](image-url)
3. Results

3.1. Clinical and Laboratory Features. The mean age of the patients with VAS-HTN in this study was 40.22 ± 9.62 years, and women accounted for 43.1% of all patients. Among the VAS-HTN patients, 24 were diagnosed with PAN, 20 with AAV, and 7 with TA. 16 patients were in the inactive phase and 35 patients were in the active phase according to BVAS assessment. The basic characteristics of 51 VAS-HTN patients, 46 EH patients, and 46 HC patients are presented in Tables 1 and 2.

3.2. Serum Anti-LAMP-2 Antibody Levels. The levels of anti-LAMP-2 antibody are increased in VAS-HTN patients compared with EH and HC (VAS-HTN vs. EH: (127.98 ± 54.98) vs. (53.59 ± 35.51) ng/ml, P < 0.001; VAS-HTN vs. HC: (127.98 ± 54.98) vs. (55.21 ± 25.09) ng/ml, P < 0.001) (Figure 3(a)). Also, no significant differences were found in serum anti-LAMP-2 antibody levels between EH and HC ((53.59 ± 35.51) vs. (55.21 ± 25.09) ng/ml, P = 0.850) (Figure 3(a)).

Serum anti-LAMP-2 antibody levels were remarkably higher in VAS-HTN patients with active stage and inactive stage than in HC (active vs. HC: (139.65 ± 54.02) vs. (55.21 ± 25.09) ng/ml, P < 0.001; inactive vs. HC: (102.47 ± 49.48) vs. (55.21 ± 25.09) ng/ml, P < 0.001) (Figure 3(b)). Furthermore, we found that serum anti-LAMP-2 antibody levels were remarkably increased in VAS-HTN patients with active stages compared with those in inactive stage patients ((139.65 ± 54.02) vs. (102.47 ± 49.48) ng/ml, P = 0.004) (Figure 3(b)).

Compared with HC, renal injury and non-renal injury patients had significantly increased the levels of anti-LAMP-
2 antibody (renal vs. HC (136.75±48.53) ng/ml vs. (55.21±25.09), P<0.001; non-renal vs. HC (114.39±62.56) ng/ml vs. (55.21±25.09) ng/ml, P<0.001) (Figure 3(c)). Serum anti-LAMP-2 antibody levels were slightly but not significantly higher in VAS-HTN patients with renal injury than in those with non-renal injury (136.75±48.53) ng/ml vs. (114.39±62.56) ng/ml, P=0.073) (Figure 3(c)).

Among the subsets of VAS-HTN, the levels of serum anti-LAMP-2 antibody were remarkably increased in all VAS-HTN subsets compared with HC (AAV vs. HC: (154.34±54.65) vs. (107.90±41.13) ng/ml, P<0.001; PAN vs. HC: (154.34±54.65) vs. (55.21±25.09) ng/ml, P<0.001; TA vs. HC: (94.98±54.65) vs. (55.21±25.09) ng/ml, P=0.016) (Figure 3(d)). More interestingly, serum anti-LAMP-2 antibody levels were significantly increased in PAN patients compared with AAV and TA patients (PAN vs. AAV: (154.34±54.65) vs. (107.90±41.13) ng/ml, P<0.001; PAN vs. TA: (154.34±54.65) vs. (94.98±54.65) ng/ml, P=0.001) (Figure 3(d)). There was no difference found in serum anti-LAMP-2 antibody levels between AAV and TA patients ((107.90±41.13) vs. (94.98±54.65) ng/ml, P=0.461) (Figure 3(d)).

### 3.3. Correlations between Serum Anti-LAMP-2 Antibody Levels and Clinical and Laboratory Parameters

We evaluated whether serum anti-LAMP-2 antibody levels are in correlation with clinical and laboratory parameters in VAS-HTN patients. The correlation analysis showed that there was a positive correlation between serum anti-LAMP-2

### Table 1: Demographic and laboratory features.

| Variables                  | VAS-HTN (n=51) | EH (n=46) | HC (n=46) | P value | AAV (n=20) | PAN (n=24) | TA (n=7) |
|----------------------------|----------------|-----------|-----------|---------|------------|------------|----------|
| Demographic features       |                |           |           |         |            |            |          |
| Age (years)                | 40.22±9.62     | 43.74±9.22| 42.61±15.87| 0.287   | 42.50±8.78| 38.54±9.45| 38.00±12.29|
| Females, n (%)             | 22 (43.1)      | 15 (32.6) | 26 (56.5) | 0.121   | 11 (55.0)  | 7 (29.2)   | 4 (57.1) |
| SBP (mmHg)                 | 164.65±27.33   | 142.50±17.59| 118.26±11.34| <0.001 | 161.95±29.09| 167.08±26.16| 164.00±29.54|
| DBP (mmHg)                 | 104.20±19.26   | 88.11±11.31| 73.13±8.55 | <0.001 | 99.05±24.10| 110.00±14.59| 99.00±13.40|
| BMI (kg/m²)                | 25.76±3.99     | 27.05±4.25| 23.32±3.03 | <0.001 | 25.46±3.48| 26.39±4.58 | 24.44±3.14|
| Laboratory features        |                |           |           |         |            |            |          |
| ESR (mm/h)                 | 18.43±14.21    | 10.22±7.77| 9.23±5.15  | 0.003   | 20.80±15.43| 15.25±15.95| 22.57±14.41|
| Scr (umol/L)               | 106.62±45.43   | 66.33±16.56| 72.36±12.44| <0.001 | 107.33±55.64| 108.79±38.51| 97.14±43.30|
| WBC (<10³/L)               | 7.37±2.83      | 6.22±1.43 | 6.53±1.83  | 0.026   | 6.70±2.79  | 7.33±1.80  | 9.42±4.85 |
| HB (g/L)                   | 138.59±20.95   | 145.17±11.99| 150.38±15.18| 0.015  | 134.35±25.09| 145.58±15.96| 126.71±16.31|
| PLT (<10⁹/L)               | 245.10±106.73  | 254.65±67.74| 262.50±44.85| 0.552  | 252.40±95.19| 226.63±80.71| 301.29±188.09|
| ANCA (+), n (%)            | 8 (15.7)       | 0 (0)     | 0 (0)     | <0.001 | 7 (35.0)   | 0 (0)      | 1 (14.3) |
| Hs-CRP (mg/L)              | 2.82 (0.91 to 8.35)| 1.04 (0.42 to 2.64) | 0.001 | 2.64 (0.77 to 7.22) | 2.97 (1.04 to 8.17) | 5.59 (0.72 to 26.99) |
| Proteinuria (+), n (%)     | 20 (39.2)      | 0 (0)     | 0 (0)     | <0.001 | 7 (35.0)   | 11 (45.8)  | 2 (28.6) |
| Hematuria (+), n (%)       | 7 (13.7)       | 0 (0)     | 0 (0)     | <0.001 | 3 (15.0)   | 3 (12.5)   | 1 (14.3) |
| Proteinuria (g)            | 0.20 (0.06 to 0.61)| 0.06 (0.04 to 0.09) | 0.001 | 0.12 (0.05 to 0.37) | 0.28 (0.12 to 0.71) | 0.23 (0.03 to 0.79) |
| Anti-LAMP-2 (ng/ml)        | 127.98±54.98   | 53.59±35.51| 55.21±25.09| <0.001 | 107.90±41.13| 154.34±54.65| 94.98±54.65|

Continuous variables are shown as median and interquartile range or as mean± standard deviation.

### Table 2: Clinical features of patients with vasculitis combined with hypertension.

| Clinical features          | VAS-HTN (n=51) | AAV (n=20) | PAN (n=24) | TA (n=7) |
|----------------------------|----------------|------------|------------|----------|
| Headache, n (%)            | 30 (58.8)      | 9 (45.0)   | 18 (75.0)  | 3 (42.9) |
| Constitutional symptoms, n (%) | 32 (62.7) | 13 (65.0) | 15 (62.5) | 4 (57.1) |
| Nervous systems, n (%)     | 4 (7.8)        | 2 (10.0)   | 1 (4.2)    | 1 (14.3) |
| Renal systems, n (%)       | 31 (60.8)      | 12 (60.0)  | 16 (66.7)  | 3 (42.9) |
| Cutaneous, n (%)           | 4 (7.8)        | 0 (0)      | 3 (12.5)   | 1 (14.3) |
| Arthritis/joint pain, n (%)| 2 (3.9)        | 0 (0)      | 2 (8.3)    | 0 (0)    |
| Eye, n (%)                 | 15 (29.4)      | 7 (35.0)   | 7 (29.2)   | 1 (14.3) |
| Ear nose throat, n (%)     | 0 (0)          | 0 (0)      | 0 (0)      | 0 (0)    |
| Pulmonary system, n (%)    | 9 (17.6)       | 9 (45.0)   | 0 (0)      | 0 (0)    |
| Alimentary system, n (%)  | 6 (11.8)       | 3 (15.0)   | 2 (8.3)    | 1 (14.3) |
| Cardiovascular system, n (%) | 10 (19.6) | 5 (25.0)   | 5 (20.8)   | 0 (0)    |
| Active disease, n (%)      | 35 (68.6)      | 13 (65.0)  | 19 (79.2)  | 3 (42.9) |
| BVAS                       | 11.35±8.61     | 12.35±10.82| 11.21±6.36| 9.00±9.07|

Continuous variables are shown as mean± standard deviation.
antibody levels and BVAS ($r = 0.391, P = 0.005$), Hs-CRP ($r = 0.291, P = 0.038$) (Figures 4(a) and 4(b)). However, there was no correlation between serum anti-LAMP-2 antibody levels and Scr ($r = 0.193, P = 0.176$), 24-hour proteinuria ($r = 0.276, P = 0.067$) (Figures 4(c) and 4(d)). In addition, we further analyzed the relationship between serum anti-LAMP-2 antibody levels and clinical and laboratory parameters in PAN patients. The results suggest that there was a significant positive correlation between serum anti-LAMP-2 antibody levels and BAVS, Hs-CRP (Figures 5(a) and 5(b)).

As shown in Table 3, multivariate logistic regression analysis showed that anti-LAMP-2 antibody (OR: 1.028, $P = 0.004$) and Scr (OR: 1.079, $P = 0.003$) were all independently associated with VAS-HTN.

### 3.4. ROC Curve Analysis

The diagnostic performance of serum anti-LAMP-2 antibody levels for detecting VAS-HTN patients using the ROC curves. The best cutoff values for serum anti-LAMP-2 antibody levels were determined using the highest value of the Youden index. The results showed that the best cutoff value, sensitivity, and specificity were at 76.99 ng/ml, 84.3%, and 83.7%. When assessing the active stage with serum anti-LAMP-2 antibody levels in VAS-HTN patients, a cutoff value of 117.58 ng/ml with a sensitivity of 65.7% and a specificity of 68.8% was observed according to ROC curve analysis. Further evaluation of patients with the VAS-HTN subgroup revealed that the optimal anti-LAMP-2 antibody cutoff value for identifying PAN and VAS-HTN was 132.38 ng/ml, with a sensitivity of 62.5% and specificity of 85.2%. All estimated values are shown in Table 4.

### 4. Discussion

Recently, it has been reported that anti-LAMP-2 antibody was associated with small-vessel vasculitis. Kain et al. research findings suggest that LAMP-2 autoantibodies can be detected in most AAV patients, and possibly related to the disease activity [34]. However, Roth et al. concluded that LAMP-2 antibodies may be present at very low titers in a minority of AAV patients [25]. The reason for the difference between the two results may be due to the different case selection and detection methods [35]. Therefore, the role of anti-LAMP-2 antibodies in vasculitis is still far from clear.

As far as we know, no published research has reported the relationship between serum anti-LAMP-2 antibody levels and VAS-HTN in hypertensive populations. In this study, all the selected VAS-HTN patients complained of hypertension and visited our center. Vasculitis...
included seven categories according to the 2012 CHCC classification criteria [26]. Our study has three types of vasculitis, which were included in this study. This also shows that these three types of vasculitis are more likely to lead to hypertension. This is consistent with some reports [12, 13]. We investigated further the serum anti-LAMP-2 antibody levels in VAS-HTN patients, EH, and HC based on ELISA. Our results showed that the levels of serum anti-LAMP-2 antibody were significantly higher in VAS-HTN patients compared with EH and HC. Furthermore, we found that the active stage of VAS-HTN patients was closely related to the elevated anti-LAMP-2 antibody levels. Multivariate logistic regression analysis showed that the anti-LAMP-2 antibody was an independent factor associated with VAS-HTN. On account of these results, we believe that the anti-LAMP-2 antibody could be an independent factor of VAS-HTN and might reflect the disease activity. In addition, the levels of serum anti-LAMP-2 antibody in patients with the inactive

**Figure 4:** Correlations of anti-LAMP-2 antibody levels with BVAS, Hs-CRP, Scr, and 24-hour proteinuria in patients with vasculitis combined with hypertension.

**Figure 5:** Correlations of anti-LAMP-2 antibody levels with BVAS and Hs-CRP in patients with polyarteritis nodosa.
stage still remained elevated compared with HC. These outcomes could possibly be a reflection of the persistent low-grade inflammatory activity or vascular wall lesions in spite of relatively normal clinical and laboratory parameters.

Peschel et al. discovered autoantibodies to hLAMP-2 that conjugate to natural glomeruli, suggesting an important role in the pathogenesis of ANCA-negative oligoimmune focal necrotizing glomerulonephritis [36]. Therefore, we investigated whether serum anti-LAMP-2 antibody related to renal injury in VAS-HTN. However, whether it is directly engaged in the renal damage process is unclear. As a next step, we need to expand the volume of samples to further prove this result.

In the present study, we found that all VAS-HTN subsets presented increased markedly serum anti-LAMP-2 antibody levels than in EH and HC. To our surprise, the levels of serum anti-LAMP-2 antibody were increased significantly in PAN patients compared with AAV and TA patients. Moreover, our results showed that serum anti-LAMP-2 antibody levels were significantly positively correlated with BAVS and Hs-CRP. Our results indicate that anti-LAMP-2 antibody could play a role in the pathogenesis of PAN and can reflect the disease activity. Further studies examining anti-LAMP-2 antibody levels during the course of disease in PAN are needed.

The quality of the anti-LAMP-2 antibody as a biomarker was evaluated on account of ROC analysis. For the diagnosis of VAS-HTN, the optimal cutoff values of serum anti-LAMP-2 antibody were determined to be 76.99 ng/ml. We further assess the active stage with serum anti-LAMP-2 antibody levels in VAS-HTN patients, with a cutoff value of 117.58 ng/ml with a sensitivity of 65.7% and a specificity of 68.8%. Furthermore, the analysis of patients with VAS-HTN subsets revealed that the best anti-LAMP-2 antibody cutoff value for differentiating PAN from VAS-HTN is 132.38 ng/ml with 62.5% sensitivity and 85.2% specificity. It suggests that anti-LAMP-2 antibody might serve as a potential biomarker for diagnosing VAS-HTN and to assist in the assessment of the disease activity. In addition, we believe that the detection of serum anti-LAMP-2 antibody may be a feasible method to distinguish PAN from AAV and TA.

In the present study, our data seem robust enough to conclude that the anti-LAMP-2 antibody is a suitable biomarker for the clinical diagnosis and disease assessment for VAS-HTN. It is helpful for the differential diagnosis of SV in the hypertensive population, the rational formulation of the treatment plan, the effective evaluation of treatment effect, the prediction of recurrence, and the better clinical management of VAS-HTN patients in the future. However, our study has some limitations that need to be considered. First, the present study failed to investigate the dynamics of serum anti-LAMP-2 antibody levels. Further longitudinal studies are needed to observe the dynamic changes. Second, the low number of patients requires further expanding the sample size. Finally, our study did not evaluate the comparison of diagnostic performance between anti-LAMP-2 and other vasculitis diagnosis markers, such as anti-endothelial cell

| Variable | Univariate | Multivariate |
|----------|------------|-------------|
| Age      | 0.978      | —           |
| Sex      | 1.06       | —           |
| SBP      | 1.07       | 1.046       |
| DBP      | 1.1        | 1.014       |
| BMI      | 1.035      | 0.992–1.103 |
| WBC      | 1.245      | 0.579–1.288 |
| HB       | 0.97       | 0.895–1.026 |
| PLT      | 0.998      | —           |
| Hs-CRP   | 1.22       | 0.819–1.293 |
| ESR      | 1.082      | 0.914–1.132 |
| Scr      | 1.063      | 1.026–1.135 |
| Anti-LAMP-2 | 1.044 | 1.009–1.047 |

OR: odds ratio; CI, confidence interval.

| Estimated value | VAS-HTN | Active | Subsets (PAN) |
|-----------------|---------|--------|---------------|
| Sensitivity (%) | 84.3 (71.4 to 93.0) | 65.7 (47.8 to 80.9) | 62.5 (40.6 to 81.2) |
| Specificity (%) | 83.7 (74.5 to 90.6) | 68.8 (41.3 to 89.0) | 85.2 (66.3 to 95.7) |
| PPV (%)         | 74.1 (61.0 to 84.7) | 82.1 (63.1 to 93.9) | 78.9 (54.4 to 93.9) |
| NPV (%)         | 90.6 (82.3 to 95.8) | 47.8 (26.8 to 69.4) | 71.9 (53.3 to 86.3) |
| PLR             | 5.17 (3.2 to 8.3) | 2.10 (1.0 to 4.5) | 4.22 (1.6 to 11.0) |
| NLR             | 0.19 (0.1 to 0.4) | 0.50 (0.3 to 0.9) | 0.44 (0.3 to 0.8) |
| AUC             | 0.90 (0.84 to 0.94) | 0.70 (0.55 to 0.82) | 0.77 (0.63 to 0.87) |
| YI              | 0.680 | 0.345 | 0.477 |

Values in parentheses are 95% CI.
antibody (AECA). Further studies are needed to verify the diagnostic performance of anti-LAMP-2 antibodies in the future.

5. Conclusion

The study suggests that anti-LAMP-2 antibodies were higher in patients with VAS-HTN compared to EH and HC, and might reflect the disease activity, particularly in patients with PAN. The anti-LAMP-2 antibody may be a potential biomarker for diagnosis and estimating the disease activity in VAS-HTN.

Data Availability

Data supporting the results of this research are accessible from the first author.

Disclosure

Xintian Cai and Bin Zhu are the co-first authors for this paper.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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