Positive Association Between Plasma Aldosterone Concentration and White Matter Lesions in Patients With Hypertension

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Background and Objective: White matter lesions (WMLs) are imaging changes in MRI of cerebral small vessel disease associated with vascular risk factors, increasing the risk of dementia, depression, and stroke. Aldosterone (ALD) or activation of mineralocorticoid receptor (MR) causes cerebrovascular injury in a mouse model. We aimed to analyze the relationship between ALD and WMLs in a population with hypertension.

Methods: We conducted a retrospective review of all patients screened for causes of secondary hypertension. We enrolled 547 patients with WMLs and matched these to controls without WMLs at a 1:1 ratio. White matter lesion load was assessed by using a modified Scheltens’ scale.

Results: Among the analytic sample (N = 1,094) with ages ranging from 30 to 64 years, 62.2% were male. We divided plasma ALD concentration (PAC), plasma renin activity (PRA), and ALD–renin ratio (ARR) into the third tertile (Q3), second tertile (Q2), and first tertile (Q1). We also analyzed them simultaneously as continuous variables. Multivariate logistic regression analysis showed that participants in Q3 (>17.26 ng/dl) of PAC (OR 1.59, 95% CI 1.15, 2.19), Q3 (<0.80 ng/dl) of PRA (OR 2.50, 95% CI 1.81, 3.44), and Q3 (>18.59 ng/dl per ng/ml*h) of ARR (OR 2.90, 95% CI 2.10, 4.01) had a significantly higher risk of WMLs than those in Q1 (<12.48) of PAC, Q1 (>2.19) of PRA, and Q1 (<6.96) of ARR. In linear regression analysis, we separately analyzed the correlation between the modified Scheltens’ scale score and log(PAC) (β = 2.36; 95% CI 1.30, 3.41; p < 0.001), log(PRA) (β = −1.76; 95% CI −2.09, −1.43; p < 0.001), and log(ARR) (β = 1.86; 95% CI 1.55, 2.17; p < 0.001), which were all significantly correlated with white matter lesion load, after adjusting for confounding factors. Simple mediation analyses showed that systolic blood pressure (SBP) or diastolic blood pressure (DBP) mediated −3.83% or −2.66% of
the association between PAC and white matter lesion load, respectively. In stratified analyses, there was no evidence of subgroup heterogeneity concerning the change in the risk of WMLs (p > 0.05 for interaction for all).

**Conclusion:** Higher PAC, especially in PAC >17.26 ng/dl, increased the risk of WMLs. PAC was positively associated with white matter lesion load independent of SBP or DBP.

**Keywords:** plasma aldosterone concentration (PAC), white matter lesions (WMLs), hypertension, cerebral small vessel disease, plasma renin activity (PRA)

**INTRODUCTION**

White matter lesions (WMLs), also known as white matter hyperintensities (WMHs) or leukoaraiosis refer to hyperintense lesions in the white matter visible on T2-weighted MRI (T2-MRI) and fluid-attenuated inversion recovery (FLAIR) (1, 2). WMLs are an imaging change of cerebral small vessel disease in MRI, referring to pathologies such as chronic cerebral ischemia, hypoperfusion, endothelial dysfunction, blood–brain barrier breakdown, inflammatory response, and genetic factors affecting the small cerebral arteries, arterioles, venules, and capillaries (3). These vascular pathologies eventually lead to tissue damage that can impact brain function, histologically evident as (incomplete or complete) infarcts, demyelination, loss of oligodendrocytes, and/or axonal damage (4).

WMLs increase the risks of dementia (5–7), depression (8), stroke occurrence (9), stroke recurrence (3), and even death (10). Therefore, it is of vital importance to prevent and manage these disabling chronic conditions. Many risk factors, such as age, hypertension, diabetes, hyper-homocysteinemia, anxiety, and hyperlipidemia, are associated with WMLs. Among various risk factors, hypertension is the most important leading to WMLs (11–14). Hypertension is also a higher risk factor for cognitive decline and dementia, including Alzheimer’s disease (AD) (15–18). Recent evidences suggest that inhibition of renin–angiotensin system (RAS) in this system may be beneficial in attenuating cognitive deficits observed in aging, AD, Parkinson’s disease (PD), vascular cognitive impairment, and post-stroke cognitive impairment (19–22). Renin has been identified within neurons and astrocytes (23). In the brain, renin receptor is expressed in cardiovascular regulatory nuclei and is linked to hypertension (24). Low-renin hypertension affects 30% of patients with hypertension (25, 26).

Approximately 5% to 13% of patients with hypertension have accompanying increased secretion of excessive aldosterone (ALD) and activation of the mineralocorticoid receptor (MR) (27, 28). MR mediates the cellular response to ALD. MR is, however, expressed more widely and found in many tissues and cell types, including in the cardiovascular, inflammatory, and central nervous systems (CNS), where the actions of MR extend well beyond the maintenance of sodium and potassium homeostasis (29). Several studies have found that ALD or activation of the MR causes cerebrovascular injury in mice (30–32), and these injuries are prevented by spironolactone treatment in endothelial cell MR-deficient mice (32). Verpillat et al. also found an association between ALD synthase (CYP11B2), a key enzyme gene for ALD synthesis, and WMLs seen on cerebral MRI independent of hypertension (33). The association between ALD and WMLs has been widely shown in animal models but it is still unclear in humans.

Therefore, it is necessary to analyze the association of ALD and WMLs in order to understand the damage of ALD to the cerebral small vessel. The current study investigated the relationship between ALD and WMLs and analyzed the association between plasma ALD concentration (PAC), plasma renin activity (PRA), and white matter lesion load in patients with hypertension.

**MATERIALS AND METHODS**

**Study Population**

We conducted a retrospective review of all patients screened for causes of secondary hypertension in the Hypertension Center of the People’s Hospital of Xinjiang Uygur Autonomous Region between January 1, 2011, and April 1, 2021. We employed an internal database search engine, YiDu Cloud, to identify patients of interest based on the following entry criteria: admission to Hypertension Center; age from 30 to 65 years; cerebral MRI scan results; and laboratory data on PAC and PRA both at baseline. A total of 547 patients with WMLs and 9,486 patients without WMLs were included. Among the analytic sample, patients with WMLs (n = 547) were matched with patients without WMLs (1:1 ratio) by age and sex (Figure 1). All patients were requested to discontinue angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine-calcium antagonists, and β-receptor blockers for at least 4 weeks or diuretics and mineralocorticoid antagonists for at least 6 weeks or were not taking any antihypertensive medications at least 2 weeks before the PAC and PRA measurements. Premenopausal women were not taking any oral contraceptives, and the postmenopausal women were not taking any hormone replacement therapy. When necessary, antihypertensive agents were replaced with slow-release verapamil or α1 epinephrine antagonists (doxazosin or terazosin) or a combination of the two to minimize interference with the measurement of PAC and PRA.

Thus, all included study participants received a full medical examination, consisting of complete medical record, standardized clinical examination, a cerebral MRI scan, and a blood test. The study was approved by the Ethics Committee of the People’s Hospital of Xinjiang Uygur Autonomous Region.

The inclusion criteria were as follows:
1. WML group: patients were examined by MRI, and the results showed hyperintense lesions in the white matter visible on T2-MRI and FLAIR.

2. Control group: hyperintense lesions in the visible white matter were not seen on T2-MRI or FLAIR.

The exclusion criteria were as follows:
1) Cushing's syndrome; 2) pheochromocytoma; 3) renovascular hypertension; 4) renal hypertension; 5) polycystic kidney disease; 6) hyperthyroidism; 7) hypothyroidism; 8) polycystic ovary syndrome; 9) acute stroke; 10) other causes such as immunity, infection, hypoxia, poisoning - genetics, Alzheimer, parkinson, adrenocorticotropic hormone (ACTH), cortisol, and use of statins or antiplatelet agents. All samples were collected from fasting blood. Body mass index (BMI) was computed as body weight in kilograms (kg) divided by height in square meters (m²). CAD was diagnosed by coronary CT angiography (CTA) or coronary angiography. Diabetes mellitus was defined in patients who had fasting serum glucose concentration ≥ 7.0 mmol/L, oral glucose tolerance test results (2-h serum glucose concentration ≥ 11.1 mmol/L), non-fasting serum glucose concentration ≥ 11.1 mmol/L, or use of anti-diabetic medication.

**Clinical Data Collection**

We collected all the clinical data from the medical records of study participants, including age, sex, body weight and height, smoking or alcohol consumption status, systolic blood pressure (SBP), diastolic blood pressure (DBP) on admission, duration of hypertension, medical diagnoses, history of diabetes mellitus, coronary artery disease (CAD), creatinine (Cr), hemoglobin A1c (HbA1c), fasting blood glucose (FBG), PRA, PAC, triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), serum potassium and homocysteine (Hcy), adrenocorticotropic hormone (ACTH), cortisol, and use of statins or antiplatelet agents. Blood samples were collected mid-morning after patients had been ambulant for at least 2 h and seated for 15 min. The details of the
and use of statins and antiplatelet agents). In addition to this model, we further adjusted the history of diabetes mellitus, SBP, and duration of hypertension. In linear regression analysis, PRA, PAC, and ARR were log-transformed. After adjustment for confounding factors, linear regression analysis was used to analyze the correlation between the modified Scheltens’ scale score of WMLs and log(PRA), log(PAC), and log(ARR). We used R with the “mediation” package to estimate the total, direct, and indirect effects of PAC, SBP/DBP, and white matter lesion load. The analyses were corrected for all possible confounding factors. To evaluate the potential effect modification, stratified analyses were further assessed according to age (30–50 or 51–64 years), sex, BMI (<28 or ≥28 kg/m²), estimated glomerular filtration rate (eGFR) (<90 or ≥90 ml/min/1.73 m²), and PRA (<1 or ≥1 ng/Ml/h). p-Value <0.05 was considered statistically significant.

**RESULTS**

**Baseline Characteristics of Study Subjects**

At the analysis stage, we included 1,094 participants with ages ranging from 30 to 64 years, of which 547 patients had WMLs and 547 patients had no WMLs as the control group. The baseline characteristics of the patients included in the study are shown in Table 1 according to WMLs and the control group. No significant differences were noted between the two groups, such as age, sex, BMI, smoking status, alcohol consumption, history of CAD, TG, HBAlc, FBG, ACTH, cortisol, and use of statins. However, patients with WMLs have higher prevalence of diabetes mellitus; lower levels of TC, LDL-C, and PRA; higher levels of Cr, PAC, ARR, Hcy, SBP, and DBP; longer duration of hypertension; and more use of antiplatelet agents than the control group.

**Logistic Regression Analysis**

In logistic regression analysis, we dichotomized the PAC, PRA, and ARR as to whether subjects were in the third tertile (Q3) versus second tertile (Q2) and first tertile (Q1). In a crude model, patients who were in Q3 (>17.26 ng/dl) of PAC (OR 1.54, 95% CI 1.15, 2.07), Q3 (<0.80 ng/dl) of PRA (OR 2.12, 95% CI 1.58, 2.85), and Q3 (>18.59 ng/dl per ng/ml·h) of ARR (OR 2.48, 95% CI 1.84, 3.34) had a significantly higher risk of WMLs than those in Q1 (<12.48) of PAC, Q1 (<2.19) of PRA, and Q1 (<6.96) of ARR. After adjustment for age, sex, BMI, smoking or alcohol consumption status, history of CAD or diabetes mellitus, Cr, TC, TG, LDL-C, HDL-C, HBAlc, Hcy, ACTH, cortisol, SBP, DBP, duration of hypertension, and use of statins or antiplatelet agents, patients who were in Q3 of PAC (OR 1.59, 95% CI 1.15, 2.19), Q3 of PRA (OR 2.50, 95% CI 1.81, 3.44), and Q3 of ARR (OR 2.90, 95% CI 2.10, 4.01) had a significantly higher risk of WMLs than those in Q1 of PAC, Q1 of PRA, and Q1 of ARR (Table 2).

**Linear Regression Analysis**

We analyzed PAC, PRA, and ARR continuously and evaluated the correlation between the modified Scheltens’ scale score and
the variables by using the linear regression analysis. We separately analyzed the correlation between the score and related parameters, considering their multicollinearity. In a crude model, log(PAC) ($\beta = 2.75; 95\% \text{ CI} 1.67, 3.84; p < 0.001$), log(PRA) ($\beta = -1.60; 95\% \text{ CI} -1.95, -1.25; p < 0.001$), and log(ARR) ($\beta = 1.78; 95\% \text{ CI} 1.44, 2.12; p < 0.001$) were all significantly correlated with white matter lesion load. After adjustment of all possible confounding factors, log(PAC) ($\beta = 2.36; 95\% \text{ CI} 1.30, 3.41; p < 0.001$), log(PRA) ($\beta = -1.76; 95\% \text{ CI} -2.09, -1.43; p < 0.001$), and log(ARR) ($\beta = 1.86; 95\% \text{ CI} 1.55, 2.17; p < 0.001$) were still correlated with white matter lesion load (Table 3 and Figure 3). In the multiple linear regression analysis, we also examined the topographical distribution of white matter lesion load in with PRA, PAC, and ARR after adjusting for confounders. In addition to the lack of a relationship between log(PAC) and iWMLs, log(PAC) was positively associated with pvWMLs and sWMLs. Log(ARR) was also positively associated with pvWMLs, sWMLs, bgWMLs, and iWMLs. In contrast, log(PRA) was negatively associated with pvWMLs, sWMLs, bgWMLs, and iWMLs (Table 4).

**Mediation Analysis**

Since ALD would predict the total WMLs score, simple mediation analyses were conducted to detect potential mediating effects of hypertension. We estimated that SBP or DBP mediated $-3.83\%$ or $-2.66\%$ of the association between increasing PAC and white matter lesion load, respectively (Figure 4).

**Stratified Analyses**

There was no evidence of subgroup heterogeneity regarding the change in risk of WMLs ($p > 0.05$ for interaction for all). None of the other variables, including age, sex, BMI, eGFR, and PRA, showed a significant effect modification on the PAC–WMLs association (Figure 5).
TABLE 1 | The clinical characteristic of WMLs and no-WMLs group.

| All (n=1094) | WMLs (n=547) | No-WMLs (n=547) | OR,95%CI | p. ratio | P Value |
|-------------|-------------|----------------|----------|----------|---------|
| Age 57.0 [51.0,61.0] | 57.0 [51.0,61.0] | 57.0 [51.0,61.0] | 1.00 [0.98,1.02] | 1.000 | 1.000 |
| Sex | | | | | | |
| Male (n, %) 678 (62.0%) | 339 (62.0%) | 339 (62.0%) | Ref. | Ref. | Ref. |
| Female (n, %) 416 (38.0%) | 208 (38.0%) | 208 (38.0%) | 1.00 [0.78,1.28] | 1.000 | 1.000 |
| BMI (Kg/m²) 27.0 [24.6,29.4] | 27.1 [24.6,29.3] | 26.9 [24.6,29.1] | 1.01 [0.98,1.04] | 0.496 | 0.290 |
| Smoking status (n, %) | | | | | | |
| Never 734 (67.1%) | 361 (66.0%) | 373 (68.2%) | Ref. | Ref. | Ref. |
| Current/ Former 360 (32.9%) | 186 (34.0%) | 174 (31.8%) | 1.10 [0.86,1.42] | 0.441 | |
| Alcohol consumption (n, %) | | | | | | |
| Never 778 (71.1%) | 387 (70.7%) | 391 (71.5%) | Ref. | Ref. | Ref. |
| Former/current 316 (28.9%) | 160 (29.3%) | 156 (28.5%) | 1.04 [0.80,1.35] | 0.790 | |
| Diabetes mellitus (n, %) 274 (25.0%) | 152 (27.8%) | 122 (23.3%) | 1.34 [1.02,1.77] | 0.037 | 0.043 |
| BMI (Kg/m²) 270 [12.48-17.26] | 270 [12.48-17.26] | 270 [12.48-17.26] | 1.00 [0.98,1.02] | 1.000 | 1.000 |
| Cr (umol/l) 67.8 [57.4,79.4] | 69.0 [58.8,82.7] | 65.9 [55.7,77.4] | 1.01 [1.01,1.02] | <0.001 | <0.001 |
| TG (mmol/mol) 1.6 [1.1,2.2] | 1.6 [1.1,2.2] | 1.6 [1.2,2.3] | 0.88 [0.79,0.98] | 0.016 | 0.016 |
| TC (mmol/mol) 4.5 [3.8,5.1] | 4.4 [3.7,5.0] | 4.5 [4.0,5.1] | 0.86 [0.76,0.97] | 0.016 | 0.016 |
| HDL-C (mmol/L) 1.0 [0.9,1.2] | 1.0 [0.9,1.2] | 1.0 [0.9,1.2] | 0.84 [0.73,0.97] | 0.156 | 0.108 |
| LDL-C (mmol/L) 2.7 [2.1,3.2] | 2.6 [2.1,3.2] | 2.8 [2.2,3.3] | 0.68 [0.52,0.90] | 0.168 | 0.202 |
| TC (mmol/L) 4.5 [4.0,5.1] | 4.4 [4.0,5.1] | 4.5 [4.0,5.1] | 0.86 [0.76,0.97] | 0.016 | 0.016 |
| TG (mmol/L) 1.6 [1.1,2.2] | 1.6 [1.1,2.2] | 1.6 [1.2,2.3] | 0.88 [0.79,0.98] | 0.016 | 0.016 |
| Serum potassium (mmol/l) 3.8 [3.6,4.1] | 3.7 [3.5,4.0] | 3.9 [3.7,4.1] | 0.31 [0.23,0.43] | <0.001 | <0.001 |
| hct (HbA1c (%)) 5.9 [5.6,6.3] | 5.9 [5.6,6.3] | 5.9 [5.6,6.3] | 1.73 [1.09,2.75] | 0.019 | 0.042 |
| HDL-C (mmol/L) 1.0 [0.9,1.2] | 1.0 [0.9,1.2] | 1.0 [0.9,1.2] | 1.06 [0.96,1.17] | 0.299 | 0.542 |
| LDL-C (mmol/L) 2.7 [2.1,3.2] | 2.6 [2.1,3.2] | 2.8 [2.2,3.3] | 0.84 [0.73,0.97] | 0.016 | 0.108 |
| Serum potassium (mmol/l) 3.8 [3.6,4.1] | 3.7 [3.5,4.0] | 3.9 [3.7,4.1] | 0.31 [0.23,0.43] | <0.001 | <0.001 |
| hct (HbA1c (%)) 5.9 [5.6,6.3] | 5.9 [5.6,6.3] | 5.9 [5.6,6.3] | 1.73 [1.09,2.75] | 0.019 | 0.042 |
| HDL-C (mmol/L) 1.0 [0.9,1.2] | 1.0 [0.9,1.2] | 1.0 [0.9,1.2] | 1.06 [0.96,1.17] | 0.299 | 0.542 |
| LDL-C (mmol/L) 2.7 [2.1,3.2] | 2.6 [2.1,3.2] | 2.8 [2.2,3.3] | 0.84 [0.73,0.97] | 0.016 | 0.108 |

**DISCUSSION**

In our study, the higher PAC and ARR and lower PRA increased the risk of WMLs. Furthermore, PAC and ARR were positively associated with white matter lesion load, and PRA was negatively associated with white matter lesion load. We also reached the same conclusion when we studied the topographical distribution of WMLs in relation to PRA, PAC, and ARR. These relationships between PRA, ARR, and WMLs were associated with higher PAC.

Several studies have found that higher PAC increases stroke (36), coronary artery calcium (37), heart failure (38), acute myocardial infarction (39), and renal impairment (40). Moreover, the association between ALD and atherosclerosis has been widely shown in humans, while no research has focused on the relationship between ALD and WMLs. This is the first study to focus on the association between ALD and WMLs in humans.

Dinh et al. found that ALD increases oxidative stress in the cerebral artery, and mRNA expression of the proinflammatory cytokine chemokine ligands CCL7 and CCL8 and interleukin (IL)-1β in the brain. These increases are prevented by spironolactone treatment in endothelial cell MR-deficient mice (32). CYP11B2 gene, which determines ALD synthesis, has been found in vascular endothelial cells, smooth muscle cells, cardiomyocytes, liver, kidney, brain, and other tissues. Verpillat et al. observed an association between CYP11B2 gene (especially the T allele) and WMLs (33). Similarly, MR is expressed extensively in the CNS...
TABLE 2 | The relationship of PAC, PRA, and ARR with the risk WMLs in logistic regression analysis.

| Variables | Model 1 (OR 95% CI) | p-Value | Model 2 (OR 95% CI) | p-Value | Model 3 (OR 95% CI) | p-Value |
|-----------|---------------------|---------|---------------------|---------|---------------------|---------|
| PAC (ng/dl) |                      |         |                     |         |                     |         |
| Q1 (<12.48) | Ref.                |         | Ref.                |         | Ref.                |         |
| Q2 (12.48–17.26) | 1.06 0.79, 1.42 | 0.682   | 1.19 0.87, 1.61 | 0.277   | 1.16 0.84, 1.58 | 0.368   |
| Q3 (>17.26) | 1.54 1.15, 2.07 |<0.003   | 1.69 1.24, 2.32 |<0.001   | 1.59 1.15, 2.19 |<0.005   |
| PRA (ng/ml*h) |                      |         |                     |         |                     |         |
| Q1 (>2.19) | Ref.                |         | Ref.                |         | Ref.                |         |
| Q2 (0.80–2.19) | 0.93 0.70, 1.25 | 0.647   | 1.00 0.74, 1.37 | 0.978   | 1.09 0.79, 1.50 | 0.611   |
| Q3 (<0.80) | 2.12 1.58, 2.85 |<0.001   | 2.32 1.69, 3.18 |<0.001   | 2.50 1.81, 3.44 |<0.001   |
| ARR (ng/dl per ng/ml*h) |                |         |                     |         |                     |         |
| Q1 (<5.96) | Ref.                |         | Ref.                |         | Ref.                |         |
| Q2 (6.96–18.59) | 1.12 0.83, 1.50 | 0.455   | 1.15 0.84, 1.57 | 0.390   | 1.17 0.85, 1.61 | 0.335   |
| Q3 (>18.59) | 2.48 1.84, 3.34 |<0.001   | 2.84 2.07, 3.91 |<0.001   | 2.90 2.10, 4.01 |<0.001   |

Model 1: unadjusted. Model 2: adjusted for age, sex, BMI, smoking or alcohol consumption status, history of coronary artery disease, Cr, TC, TG, LDL-C, HDL-C, HbA1c, Hcy, ACTH, cortisol, diastolic blood pressure, and use of statins and antiplatelet agents. Model 3: Model 2 + adjusted for systolic blood pressure, duration of hypertension, and history of diabetes mellitus.

PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone–renin ratio; WMLs, white matter lesions; Cr, creatinine; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; Hcy, homocysteine; ACTH, adrenocorticotrophic hormone.
The bold represents P value < 0.05.

TABLE 3 | Correlation between PAC, PRA, ARR, and score of WMLs in linear regression analyses.

| Variables | Coefficient | SE | p-Value | 95% CI | Coefficient | SE | p-Value | 95% CI | Coefficient | SE | p-Value | 95% CI |
|-----------|-------------|----|---------|--------|-------------|----|---------|--------|-------------|----|---------|--------|
| Log(PAC) ng/dl | 2.75 | 0.552 |<0.001 | 1.67, 3.84 | 2.71 | 0.543 |<0.001 | 1.64, 3.77 | 2.36 | 0.535 |<0.001 | 1.30, 3.41 |
| Log(PRA) ng/ml*h | −1.60 | 0.180 |<0.001 | −1.95, −1.25 | −1.72 | 0.173 |<0.001 | −2.06, −1.39 | −1.76 | 0.168 |<0.001 | −2.09, −1.43 |
| Log(ARR) ng/dl per ng/ml*h | 1.78 | 0.172 |<0.001 | 1.44, 2.12 | 1.86 | 0.164 |<0.001 | 1.54, 2.18 | 1.86 | 0.160 |<0.001 | 1.55, 2.17 |

Model 1: unadjusted. Model 2: adjusted for age, sex, BMI, smoking or alcohol consumption status, history of coronary artery disease, Cr, TC, TG, LDL-C, HDL-C, HbA1c, Hcy, ACTH, cortisol, diastolic blood pressure, and use of statins or antiplatelet agents. Model 3: Model 2 + adjusted for systolic blood pressure, duration of hypertension, and history of diabetes mellitus.
PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone–renin ratio; WMLs, white matter lesions; BMI, body mass index; Cr, creatinine; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; Hcy, homocysteine; ACTH, adrenocorticotrophic hormone.
The bold represents P value < 0.05.

FIGURE 3 | The scatter plot regarding univariate linear regression (WMLs score vs. log(PAC), log(PRA), and log(ARR)). WMLs, white matter lesions; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone–renin ratio.
TABLE 4 | Correlation between PAC, PRA, ARR, and score of pvWMLs, sWMLs, bgWMLs, and iWMLs in linear regression analyses.

| Variables | pvWMLs* | | | | | | sWMLs* | | | | |
|-----------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Log(PAC) ng/dl | 0.78 | 0.215 | <0.001 | 0.42, 1.14 | 1.11 | 0.236 | 0.002 | 0.65, 1.58 |
| Log(PRA) ng/ml*h | -0.60 | 0.058 | <0.001 | -0.72, -0.49 | -0.66 | 0.075 | 0.001 | -0.81, -0.51 |
| Log(ARR) ng/dl per ng/ml*h | 0.64 | 0.055 | <0.001 | 0.53, 0.74 | 0.72 | 0.072 | <0.001 | 0.58, 0.86 |

WMLs: white matter lesions; pvWMLs: periventricular WMLs; sWMLs: subcortical WMLs; bgWMLs: basal ganglia WMLs; iWMLs: infratentorial WMLs; BMI: body mass index; Cr: creatinine; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; HbA1c: hemoglobin A1c; Hcy: homocysteine; ACTH: adrenocorticotrophic hormone.

*Adjusted for age, sex, BMI, Cr, smoking or alcohol consumption status, history of coronary artery disease or diabetes mellitus, TC, TG, LDL-C, HDL-C, HbA1c, Hcy, ACTH, cortisol, diastolic blood pressure, systolic blood pressure, duration of hypertension, and use of statins or antiplatelet agents.

The bold represents P value < 0.05.

FIGURE 4 | Mediating analysis of systolic or diastolic blood pressure on PAC and white matter lesion load. (A) Systolic blood pressure mediated a -3.83% association between PAC and white matter lesion load. Adjusted for age, sex, BMI, Cr, smoking or alcohol consumption status, history of coronary artery disease or diabetes mellitus, TC, TG, LDL-C, HDL-C, HbA1c, Hcy, ACTH, cortisol, and use of statins or antiplatelet agents. IE, indirect effect; DE, direct effect; BMI, body mass index; Cr, creatinine; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; Hcy, homocysteine; ACTH, adrenocorticotrophic hormone.

FIGURE 5 | The association between PAC (Q3 compared with Q1–2) and WMLs in various subgroups. PAC, plasma aldosterone concentration; WMLs, white matter lesions; BMI, body mass index; Cr, creatinine; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; Hcy, homocysteine; ACTH, adrenocorticotrophic hormone. *Adjusted, if not stratified, for age, sex, BMI, Cr, smoking or alcohol consumption status, history of coronary artery disease or diabetes mellitus, TC, TG, LDL-C, HDL-C, HbA1c, Hcy, ACTH, cortisol, diastolic blood pressure, systolic blood pressure, duration of hypertension, and use of statins or antiplatelet agents. **Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
The function of the MR in the CNS is to mediate diverse behavioral responses, including memory and affect (43).

An animal model study confirmed that spironolactone could prevent vascular remodeling and anti-fibrosis (44). Pires et al. found that MR antagonism can reduce cerebral artery remodeling and white matter injury in those fed high fat diet without lowering blood pressure (31). Many studies have proven that hypertension is the main risk factor for WMLs (45, 46). In particular, lower DBP levels are related to lower white matter lesion load (47), but the pathological mechanism is not clear.

Our findings showed that PAC was not associated with bgWMLs or iWMLs but positively associated with pvWMLs and sWMLs. First, WMLs occur frequently in pvWMLs and sWMLs but rarely in iWMLs and bgWMLs. Second, it may be related to MR expression being low in infratentorial and basal ganglia areas and high in periventricular and subcortical areas. However, further animal models are needed to prove this result.

The mediation analysis showed that ALD contributes to white matter lesion load through SBP or DBP, but the mediation effect was low. Notably, most of the effects on WMLs could be explained independently of diastolic or SBP. Our results also highlighted the importance of considering the potential burden of elevated ALD levels on the cerebral small vessel not through hypertension.

Meanwhile, our stratified analyses showed no significant effect modification on the ALD–WML association, especially because a high level of ALD causes WMLs regardless of PRA, which could emphasize the effect of ALD and MR on WMLs. Hyperaldosteronism can occur either as primary aldosteronism (renin-independent) or secondary aldosteronism (renin-dependent). As the most common cause of secondary hypertension, primary aldosteronism is associated with increased cardiovascular risk. It is well known that ALD increases the risk of acute cardiovascular events both directly and indirectly (mostly mediated by hypertension) (43–45). Moreover, the association between ALD and atherosclerosis has also been widely shown in humans and animal models (48–50). However, no research has focused on the relationship between ALD and WMLs. We showed that ALD contributed to the white matter lesion load independent of SBP or DBP, which can help understand the effects of ALD on the nervous system, and can also increase awareness of primary aldosteronism screening in non-hypertension departments. In the future, we will evaluate whether spironolactone can decrease white matter lesion load.

There were some limitations in our study: first, the prevalence of WMLs in our hypertension center was less than that in general population because not all patients underwent cerebral MRI scans, which weakened the association of ALD and WMLs. Second, we collected the diagnosis of WMLs from our hospital’s PACS. Only images of patients diagnosed with WMLs were obtained by two radiologists, and we collected the images of patients with WMLs and were manually scored by two experienced radiologists using the modified Scheltens’ scale. However, some radiologists ignoring mild WMLs failed to indicate the diagnosis of WMLs on MRI, which would underestimate the correlation between ALD and WMLs. Third, we cannot completely rule out possible confounding factors from unmeasured factors. However, we had adjusted for potential confounders, including the most important risk factor for DBP, SBP, and duration of hypertension. In particular, our research subjects were younger than 65 years, so we can better rule out the risk factors for age.

CONCLUSION

A higher level of PAC increased the risk of WMLs. The PAC was positively associated with white matter lesion load independent of diastolic or SBP. Future studies will focus on the spatial distributions of WMLs on MRI of patients with primary aldosteronism and the effect of spironolactone on WMLs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the People’s Hospital of Xinjiang Uygur Autonomous Region.

AUTHOR CONTRIBUTIONS

YY and NL conceived and designed the present study, carried out the statistical analysis, prepared the original manuscript, and revised the submitted version. NL participated in the acquisition of fund support for the present study. YL, QZ, MH, WZ, XY, DZ, QL, MW, GC, MC, KZ, LW, JH, and NM participated in controlling the quality of the cases. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.753074/full#supplementary-material
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