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Association between Serum Immune-inflammatory Biomarkers and Target Organ Damage in Patients with Primary Aldosteronism

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ABSTRACT

This study aimed to characterize serum immune-inflammatory biomarkers in primary aldosteronism (PA) and to evaluate their correlations and independent associations with target organ damage (TOD) using a propensity score–matched cohort design.

This retrospective propensity score–matched (PSM) cohort study included 80 patients initially diagnosed with PA (PA group) and 80 matched patients with essential hypertension (EH group) between February 2021 and February 2025. Serum levels of C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and monocyte chemoattractant protein 1 (MCP-1) were measured. TOD assessment included left ventricular mass index (LVMI), carotid intima-media thickness (IMT), and renal parameters (urinary albumin to creatinine ratio [UACR] and estimated glomerular filtration rate [eGFR]). Group comparisons, correlation analyses, and multivariate logistic regression were performed.

After matching, baseline characteristics were balanced. The PA group had significantly higher levels of all four biomarkers and a higher prevalence of cardiac, vascular, and renal damage. Sensitivity analyses confirmed consistent associations across all organ systems. Elevated IL-6 and CRP strongly correlated with TOD indicators and were independently associated with composite TOD in multivariate analysis (IL-6: OR=1.86; CRP: OR=1.52).

PA is associated with a distinct immune-inflammatory phenotype. IL-6 and CRP are independently associated with multi-system TOD and may serve as practical biomarkers for early risk stratification and timely intervention.

Keywords: Biomarkers; C-reactive protein; Interleukin 6; Inflammation; Hyperaldosteronism; Target organ damage

INTRODUCTION

Primary aldosteronism (PA), traditionally classified as an endocrine disorder, is increasingly being reconceptualized as a systemic condition driven by aldosterone excess and characterized by a significant immunoinflammatory component.[1,2] Compared with essential hypertension (EH), PA carries a substantially higher risk of cardiovascular and renal target organ damage (TOD), which cannot be fully explained by blood pressure elevation alone. Aldosterone exerts direct pro-inflammatory effects primarily via mineralocorticoid

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receptor (MR) activation, driving the expression of cytokines (eg, interleukin 6 [IL-6]) and chemokines (eg, monocyte chemoattractant protein 1 [MCP-1]), which promotes macrophage infiltration and T-cell activation, thereby creating a systemic immune-inflammatory state. This state contributes directly to target organ fibrosis and dysfunction independently of blood pressure, further supporting the reconceptualization of PA as an immune-inflammatory disorder.[3,4]

The early detection and risk stratification of TOD are crucial for improving prognosis in PA. Currently, assessment relies heavily on imaging and functional tests, which often identify structural changes at later stages.[5,6] Sensitive biomarkers signaling early damage onset are lacking. Although inflammatory cytokines, such as IL-6 and C-reactive protein (CRP), are key mediators of hypertensive organ damage,[7,8] studies in PA remain limited by methodological inconsistencies and insufficient adjustment for confounders, leaving their role as independent risk factors unclear.

Therefore, this study employed a propensity score–matched (PSM) cohort design to rigorously compare PA and EH patients. We aimed to characterize serum levels of key immune-inflammatory biomarkers (CRP, IL-6, tumor necrosis factor α [TNF-α], and MCP-1); assess their correlations with multi-system TOD; and determine whether these biomarkers, particularly IL-6 and CRP, are independently associated with TOD in PA, to assess their potential for early clinical risk stratification.

MATERIALS AND METHODS

Study Design

This retrospective, PSM study enrolled consecutive patients with PA or EH between February 2021 and February 2025 into respective groups. Data were extracted from the electronic medical records, initially comprising 86 PA and 94 EH patients. Using 1:1 PSM with age, sex, body mass index (BMI), 24-hour average systolic blood pressure (SBP), and diabetes as covariates, 80 well-matched pairs (PA: n=80; EH: n=80) were generated for analysis.

Inclusion and Exclusion Criteria

PA group: Diagnosis was confirmed according to the Expert Consensus on the Diagnosis and Treatment of Primary Aldosteronism (2020), supported by a positive saline infusion test.[9]

EH group: Diagnosis was based on the Chinese Guidelines for the Prevention and Treatment of Hypertension (2023), with secondary hypertension excluded.[10]

Exclusion criteria (applied to both groups) included acute infection, autoimmune disease, malignancy, severe hepatic or renal dysfunction; use of glucocorticoids, nonsteroidal anti-inflammatory drugs, immunosuppressants, or renin-angiotensin-aldosterone system (RAAS)–affecting drugs (except conventional antihypertensives in the EH group) within the preceding month; other known causes of target organ damage; pregnancy or lactation; and incomplete clinical data.

Data Collection and Measurements

All serum samples for biomarker measurement were collected at initial diagnosis and before starting any specific antihypertensive or disease-modifying therapy. Serum CRP levels were measured by immunoturbidimetric assay; IL-6, TNF-α, and MCP-1 levels were determined using ELISA kits (R&D Systems, USA). Cardiac structure was assessed via echocardiography-derived left ventricular mass index (LVMI; hypertrophy defined as >115 g/m^2 in men or >95 g/m^2 in women).[11] Vascular evaluation included carotid intima-media thickness (IMT) by ultrasound (thickening defined as ≥1.0 mm).[12] Renal damage was defined as estimated glomerular filtration rate (eGFR) (CKD-EPI equation) <60 mL/min/1.73 m^2 or urinary albumin to creatinine ratio (UACR) ≥30 mg/g.[13,14]

Statistical Analysis

Based on prior data, a sample size of 34 per group was calculated using G*Power 3.1 (α=0.05, power=80%). Our final sample of 80 per group exceeded this requirement. Analyses were performed with SPSS 26.0. Propensity scores were estimated via logistic regression (covariates: age, sex, BMI, 24-hour SBP, and diabetes), followed by 1:1 nearest-neighbor matching without replacement (caliper width=0.2 SD). Post-matching balance was confirmed with standardized mean differences (all SMDs <0.1). Continuous and categorical data are presented as mean±SD / median (interquartile range [IQR]) and n (%), compared using *t* tests / Mann-Whitney *U* and chi-square /Fisher exact tests, respectively. Correlations were assessed with Pearson/Spearman tests. A composite TOD endpoint was defined as the presence of left ventricular hypertrophy (LVMI >115/95 g/m^2), carotid IMT ≥1.0

mm, or renal damage (eGFR <60 mL/min/1.73 m^2 or UACR≥30 mg/g), capturing the integrated burden of PA. Sensitivity analyses for each organ system were conducted. Multivariable logistic regression (forward stepwise) identified independent TOD predictors from variables with $p<0.10$ in univariate analysis or clinical relevance. Multicollinearity was assessed via variance inflation factor (VIF) (VIF < 10 acceptable). Receiver operating characteristic (ROC) curve analysis evaluated biomarker discriminative ability, with the Youden index determining optimal cut-off values. A correlation heatmap based on Spearman coefficients was generated for visualization. A 2-tailed $p<0.05$ was considered significant.

RESULTS

Comparison of Baseline Data

After PSM, the PA (n=80) and EH (n=80) groups were well-balanced for all key baseline covariates, including age, sex, BMI, blood pressure parameters, and comorbidities (all $p>0.05$, SMD < 0.1). As expected, the PA group exhibited a characteristic biochemical profile of hyperaldosteronism, with significantly higher plasma aldosterone, aldosterone-to-renin ratio (ARR), and lower serum potassium levels compared to the EH group (all $p<0.001$).

Serum Immune-Inflammatory Biomarkers

As shown in Table 1, serum levels of all four inflammatory biomarkers were significantly elevated in the PA group compared with the EH group (all $p<0.001$).

Prevalence of Target Organ Damage

The PA group had a significantly higher prevalence of target organ damage across all measured systems compared with the matched EH group: elevated LVMI (56.3% vs 35.0%; $p=0.007$), elevated UACR (47.5% vs 27.5%; $p=0.01$), and increased IMT (61.3% vs 43.8%; $p=0.027$). A reduced eGFR was more common in the EH group (31.3% vs 15.0%; $p=0.016$).

Table 1. Differences in serum immune-inflammatory biomarker profiles between the PA and EH groups.

Inflammatory biomarker	PA group (n=80)	EH group (n=80)	*p*
CRP, mg/L	2.85 (1.72, 4.30)	1.65 (0.90, 2.55)	<0.001
IL-6, pg/mL	3.45 (2.41, 4.88)	1.92 (1.30, 2.75)	<0.001
TNF-α, pg/mL	5.2 (3.7, 6.8)	4.1 (3.0, 5.5)	<0.001
MCP-1, pg/mL	355.6 (289.4, 445.1)	265.3 (215.8, 325.7)	<0.001

Data are presented as median (interquartile range [Q1, Q3]). CRP: C-reactive protein; EH: essential hypertension; IL-6: interleukin 6; MCP-1: monocyte chemoattractant protein 1; PA: primary aldosteronism; TNF-α: tumor necrosis factor α.

Correlation and Multivariate Regression Analyses

Serum levels of CRP, IL-6, TNF-α, and MCP-1 all showed significant positive correlations with LVMI, UACR, and IMT, and negative correlations with eGFR (all $p<0.05$). Among these, CRP and IL-6 demonstrated the strongest correlation coefficients (Figure 1).

ROC curve analysis revealed that the area under the curve (AUC) was 0.78 (95% CI, 0.70–0.86) for IL-6 and 0.72 (95% CI, 0.64–0.80) for CRP. The optimal cut-off value was 3.2 pg/mL for IL-6 (sensitivity 75%, specificity 72%) and 2.1 mg/L for CRP (sensitivity 70%, specificity 68%).

In the multivariate model adjusted for age, BMI, and 24-hour SBP, both IL-6 and CRP were independently associated with composite target organ damage in PA (Table 2). Sensitivity analyses for individual organ systems (cardiac, vascular, renal) confirmed that these positive associations were consistent across all endpoints.

Table 2. Independent predictors of target organ damage in PA.

Variable	Regression coefficient (β)	Standard error (SE)	OR	95% CI	*p*
IL-6 (per 1-pg/mL increase)	0.623	0.215	1.86	1.23–2.81	0.003
CRP (per 1-mg/L increase)	0.421	0.187	1.52	1.08–2.14	0.017
Age, y	0.021	0.015	1.02	0.99–1.05	0.168
BMI	0.035	0.028	1.04	0.99–1.09	0.213
24-hour SBP (per 1-mm Hg increase)	0.042	0.029	1.04	0.99–1.10	0.145

BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; IL-6: interleukin 6; OR: odds ratio; PA: primary aldosteronism; SBP: systolic blood pressure.

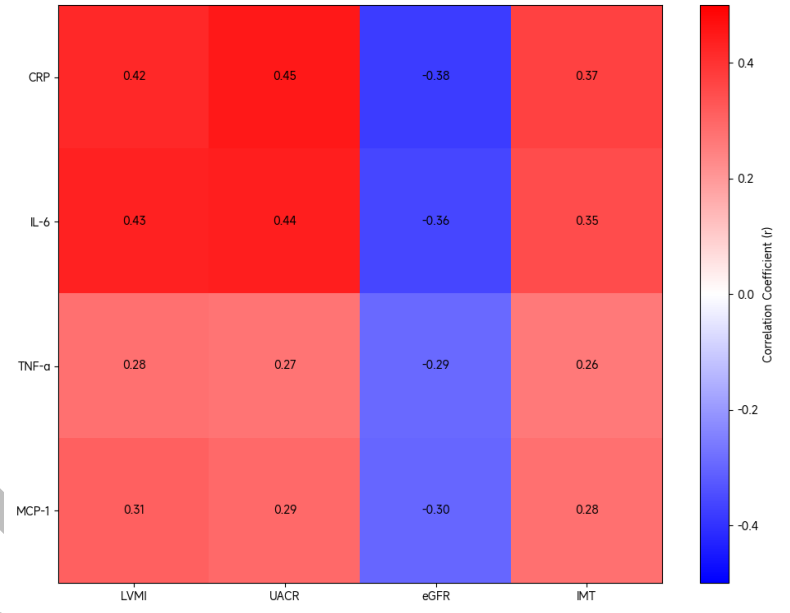

Figure 1. Correlation heatmap of serum immune-inflammatory markers and target organ damage parameters in patients with primary aldosteronism.

DISCUSSION

This PSM study provides clear evidence that PA is characterized by a state of heightened systemic inflammation, with markedly elevated levels of CRP, IL-6, TNF-α, and MCP-1 compared with matched EH controls. IL-6 and CRP were identified as independent risk factors for multi-system TOD in PA. Our findings extend beyond prior reports in general hypertensive populations by demonstrating, within a rigorously matched cohort, that the elevated inflammatory burden and its strong link to TOD are distinctive features of PA, highlighting the specific role of aldosterone excess beyond blood pressure.

The observed inflammatory phenotype aligns with the established pathophysiology of aldosterone excess. Aldosterone, via MR activation, promotes the transcription of pro-inflammatory genes, including *IL-6* and *TNF-α*, and facilitates innate immune cell infiltration.[15,16] Our findings of elevated TNF-α and MCP-1 in PA corroborate experimental models where aldosterone induces macrophage-driven tissue inflammation.[17] This chronic, low-grade inflammatory state is considered a potential key contributor to

pathological remodeling beyond the effects of hypertension itself.

Consistent with prior evidence,[18,19] PA patients in our cohort exhibited a significantly greater burden of cardiac, vascular, and renal damage. Notably, while the prevalence of albuminuria was higher in the PA group, the proportion of patients with a reduced eGFR (<60 mL/min/1.73 m^2) was lower compared to the EH group. This apparent paradox may reflect the distinct early-stage renal pathophysiology in PA, where aldosterone-driven renal hyperfiltration can transiently preserve measured eGFR, while tubular and glomerular injury manifests earlier as albuminuria—a pattern supported by previous studies.[20] This underscores the importance of using combined renal markers for a comprehensive assessment in PA. The strong correlations between inflammatory markers (particularly IL-6 and CRP) and each TOD metric mechanistically link this systemic inflammation to end-organ injury. Experimental evidence indicates that IL-6 can stimulate cardiac fibroblast proliferation and renal mesangial cell activation, while CRP is a well-established marker associated with endothelial dysfunction and atherosclerosis.[21,22]

The selection of CRP, IL-6, TNF-α, and MCP-1 was guided by their direct pathophysiological roles in aldosterone-mediated injury. IL-6 and TNF-α are key transcriptional targets of MR signaling;[23] MCP-1 drives monocyte recruitment.[24] In contrast, CRP is not a direct effector but a hepatocyte-derived acute phase reactant whose production is robustly induced by IL-6, serving as an integrated downstream marker of systemic inflammation. Its inclusion is justified by its routine clinical availability and prognostic value, complementing the more specific upstream mediators. While adaptive immune markers (eg, IL-17) are of interest, this study focused on this foundational innate immune inflammatory axis due to its direct link to aldosterone and translational feasibility for initial risk stratification.[25]

These findings highlight the potential value of incorporating inflammation-based risk stratification into PA management. Patients with elevated IL-6 or CRP could be considered a higher-risk subgroup, warranting closer follow-up. Beyond conventional therapy, our data raise the question of whether targeted immunomodulation—such as with MR antagonists or specific anti-inflammatory agents—could mitigate inflammatory burden and reduce TOD risk. Exploring such strategies in future studies may complement blood pressure control for more comprehensive organ protection.

This study has limitations. Its retrospective, single-center design may restrict generalizability. The cross-sectional nature establishes association but not causality. Although we excluded patients on major immunomodulatory drugs, residual confounding by common antihypertensive agents cannot be fully excluded. Furthermore, the lack of immune cell phenotyping limits mechanistic insight into the specific cellular drivers. Future large-scale, prospective studies are needed to validate the predictive value of these biomarkers and to assess their dynamics in response to specific PA treatments.

In summary, this study confirms a distinct immune-inflammatory phenotype in primary aldosteronism, characterized by elevated levels of key mediators such as IL-6 and CRP. Crucially, these biomarkers are independently associated with multi-system target organ damage. These findings support reconceptualizing PA as a disorder with a significant inflammatory component and highlight the potential clinical utility of IL-6 and CRP for early risk stratification and timely intervention.

STATEMENT OF ETHICS

This study was approved by The Second Hospital of Yinzhou Ethics Committee.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The data supporting the findings of this study can be obtained from the corresponding author, upon request.

AI ASSISTANCE DISCLOSURE

None declared.

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