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ORIGINAL RESEARCH

Relationship Between Plasma Aldosterone Concentrations and Non-Alcoholic Fatty Liver Disease Diagnosis in Patients with Hypertension: A Retrospective Cohort Study

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Objective: To investigate the association between plasma aldosterone concentration (PAC) and non-alcoholic fatty liver disease (NAFLD) diagnosis in Chinese hypertensive patients.

Methods: We conducted a retrospective study of all patients diagnosed with hypertension between January 1, 2010, and December 31, 2021. We included 3713 hypertensive patients based on the criteria for inclusion and exclusion. PAC measurement was performed using a radioimmunoassay. NAFLD was diagnosed using abdominal ultrasonography. Cox regression analysis was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for univariable and multivariable models. A generalized additive model was used to identify nonlinear relationships between PAC and NAFLD diagnosis.

Results: A total of 3713 participants were included in the analysis. Over a median follow-up of 30 months, 1572 hypertensive individuals developed new-onset NAFLD. When PAC was used as a continuous variable, the risk of NAFLD increased by 1.04 and 1.24-fold for each 1 ng/dL and 5 ng/dL increase in PAC, respectively. When PAC was considered a categorical variable, the HR for tertile 3 was 1.71 (95% CI, 1.47–1.98, $P < 0.001$) compared to tertile 1. Overall, there was a J-shaped relationship between PAC and new-onset NAFLD. By fitting a two-piecewise linear regression model and using a recursive algorithm, we identified a PAC inflection point at 13 ng/dL (log-likelihood ratio test, $P = 0.005$). In adjusted model 3, for PAC ≥ 13 ng/dL, a 5 ng/dL increase in PAC was associated with a 30% increase in the risk of new-onset NAFLD (95% CI, 1.25–1.35, $P < 0.001$).

Conclusion: The study revealed a non-linear relationship between elevated PAC levels and the incidence of NAFLD in hypertensive patients. Notably, the risk of new-onset NAFLD was significantly increased when PAC levels were ≥13 ng/dL. Larger, prospective studies are necessary to confirm these findings.

Keywords: plasma aldosterone concentration, non-alcoholic fatty liver disease, hypertension, cohort study

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a prevalent liver disease that affects over 25% of adults globally and is a leading cause of liver diseases.[1–3] Featuring a range of disorders from simple steatosis to the more severe non-alcoholic steatohepatitis (NASH) and fibrosis, NAFLD is a progressive disease that can result in cirrhosis and, eventually, hepatocellular carcinoma, which currently accounts for most liver transplantations.[2,4–8] Hypertension is a highly

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significant risk factor for cardiovascular disease (CVD).[9] Additionally, NAFLD can worsen the progression of atherosclerosis, boosting the development of CVD events.[10,11] Bi-directional relationships between NAFLD and hypertension have been observed, with evidence suggesting that NAFLD can both be a consequence and a cause of hypertension.[12] Moreover, the coexistence of hypertension and NAFLD is associated with considerably worse cardiovascular outcomes compared to either condition alone.[13] Thus, the identification and management of modifiable risk factors are of utmost importance in lowering the burden of NAFLD among hypertensive patients.[14]

Aldosterone, a steroid hormone, is secreted by the adrenal gland to regulate volume and electrolyte balance.[15] Elevated levels of aldosterone have been associated with moderate to severe blood pressure elevation and severe target organ damage in numerous clinical studies.[16–19] In addition, aldosterone has been linked to inflammation and organ fibrosis in both epithelial and non-epithelial tissues.[20–22] Through the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 inflammatory vesicle-associated pathways, aldosterone promotes hepatic stellate cell activation and liver fibrosis.[23] Recent observational studies have found an increased prevalence of NAFLD in patients with primary aldosteronism (PA),[24,25] and a positive association between aldosterone levels and NAFLD has been demonstrated among African American women.[26] A selective aldosterone blocker (SAB) has been shown to attenuate fibrogenesis and suppress activated hepatic stellate cells in other studies.[27] However, one study suggests that aldosterone excess may not be correlated with the development of fatty liver disease in a mouse model fed a high-fat diet.[28] Nevertheless, there is a need for further investigation into the association between high plasma aldosterone concentrations (PAC) and NAFLD in hypertensive patients, given the controversial findings.

In this study, we conducted a retrospective cohort study to investigate the associations between PAC and the risk of NAFLD in hypertensive adults and to explore their potential dose-response relationship.

Materials and Methods

Study Design and Population

From January 1, 2010 to December 31, 2021, this study investigated hypertensive patients attending the People's Hospital of Xinjiang Uygur Autonomous Region (n = 18,609). The study excluded subjects based on multiple criteria, including age <18 years (n = 3), lack of PAC data (n = 9118), pre-existing NAFLD (n = 1060), follow-up fewer than 6 months (n = 1828), inadequate abdominal ultrasound information (n = 38), history of cancer (n = 149), excessive alcohol consumption (>70 g/week for women or 140 g/week for men) or missing alcohol consumption (n = 854),[29] positive for hepatitis B or C surface antigen or missing (n = 415), use of steatogenic drugs within the past year (n = 726), and history of cirrhosis or any type of liver disease (n = 549). Ultimately, only 3713 participants were included in the analysis. Figure 1 shows the patient selection flowchart for this study. The Ethics Committee approved the ethics application (reference: KY2022080905). Also, all patients provided informed consent following the Helsinki Declaration.

Baseline Examination

Demographic characteristics, lifestyle factors, personal medical history, and medication use were extracted from medical records for all subjects. Details of specific measures, such as height, weight, smoking status, and baseline blood pressure, have been provided in the Supplementary Materials and referred to in prior publications.[30,31] Fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels were assessed through peripheral venous blood collection. Hormonal tests were conducted according to current guidelines and prior studies conducted at our center.[32,33] PAC was measured by radioimmunoassay (DSL-8600 ACTIVE Aldosterone Coated Tube Radioimmunoassay Kit; Diagnostic Systems Laboratories, Webster, TX), with participants instructed to refrain from caffeine, alcohol, smoking, and strenuous physical activity for 12 hours before blood collection. Participants sat for 30 minutes after being active for at least 2 hours before blood collection, which occurred between 8:00 and 11:00 AM.

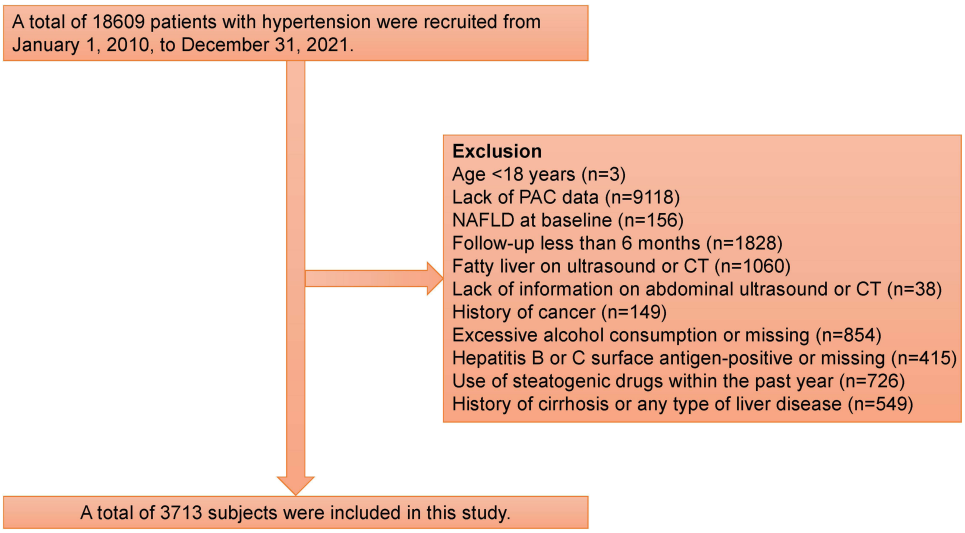

Figure 1 Flow chart of study participant selection.

Definitions

Criteria for hypertension included self-reported hypertension, current use of anti-hypertensive medication, or systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg recorded for at least three consecutive readings. T2DM was defined as fasting serum glucose ≥7.0 mmol/L, the 2-h serum glucose of the oral glucose tolerance test ≥11.1 mmol/L, or the current use of hypoglycaemic medication or insulin. A patient was diagnosed with PA as per the Endocrine Society's clinical practice guidelines, based on PAC levels ≥ 12 ng/dL, aldosterone-to-renin ratio ≥ 20, and a PAC value ≥ 10 ng/dL confirmed by saline infusion test.[32] The BMI was calculated as weight divided by height squared.

Study Outcome

The follow-up began with an initial assessment for NAFLD conducted by a clinician, followed by annual abdominal ultrasounds to assess NAFLD.[34–36] Additional information on the NAFLD assessment is available in the Supplementary Materials section.

Statistical Analysis

PAC in baseline characteristics was separated into three groups: ≤ 11.55, 11.56–16.39, and ≥ 16.40 ng/dL. Kaplan-Meier survival analysis was carried out using Log rank tests. Tests for multicollinearity were performed using the variance inflation factor test, and there was no strong correlation among any of the variables in the model (variance inflation factor < 10 for all comparisons) (Table S1). Cox regression analysis was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for univariable and multivariable models. PAC was described as a continuous variable (per 1 and 5 ng/dL increase) and a categorical variable (tertiles) and was placed into different models. A linear trend test was conducted by assigning medians to each tertile as a continuous variable in the models. We used a generalized additive model to identify the non-linear relationship. Heterogeneity across subgroups was assessed by Cox regression analysis and is presented in forest plots, and interactions between subgroups and PAC were examined by likelihood ratio testing. Lastly, to address potential unmeasured confounding, we calculated E-values.[37] Details of the statistical analysis are shown in the Supplementary Materials. All analyses were computed with R software, version 4.1.1, at a 2-sided, 5% α level of significance.

Results

Characteristics of Participants

This cohort study included 3713 participants. The average age of the participants was 52.00 ± 11.80 years, with males accounting for 61.76%. Baseline characteristics of the participants grouped by tertiles of PAC can be found in Table 1. Participants in higher tertiles of PAC had higher tendencies for current smoking, a higher BMI, elevated levels of ALT,

Table 1 Baseline Characteristics of the Study Participants According to Plasma Aldosterone Concentrations Categories

Variable	Total	PAC			P-value
		Tertile 1 ≤11.55 ng/dL	Tertile 2 11.56–16.39 ng/dL	Tertile 3 ≥16.40 ng/dL	
No. of participants	3713	1235	1235	1243	
Male, %	1922 (51.76%)	623 (50.45%)	657 (53.20%)	642 (51.65%)	0.390
Age, yr	52.00 ± 11.80	52.16 ± 11.84	51.82 ± 11.75	52.03 ± 11.82	0.764
BMI, kg/m2	24.71 ± 2.47	23.16 ± 2.52	24.91 ± 1.45	26.05 ± 2.37	<0.001
DBP, mmHg	87.96 ± 14.43	87.24 ± 14.87	88.63 ± 14.13	88.02 ± 14.25	0.058
SBP, mmHg	144.16 ± 20.71	143.70±20.81	144.62± 0.56	144.16±20.78	0.540
Current smoker, %	492 (13.25%)	113 (9.15%)	181 (14.66%)	198 (15.93%)	<0.001
Diabetes, %	912 (24.56%)	266 (22.17%)	302 (25.08%)	281 (23.36%)	0.054
PA, %	154 (4.15%)	42 (3.40%)	53 (4.29%)	59 (4.75%)	0.232
TC, mmol/L	4.50 ± 0.96	4.50 ± 0.96	4.49 ± 0.93	4.52 ± 0.97	0.750
TG, mmol/L	1.55 (1.10–2.20)	1.51 (1.09–2.20)	1.58 (1.11–2.21)	1.57 (1.12–2.20)	0.691
HDL-C, mmol/L	1.04 ± 0.25	1.05 ± 0.25	1.05 ± 0.26	1.03 ± 0.24	0.051
LDL-C, mmol/L	2.71 ± 0.82	2.69 ± 0.81	2.69 ± 0.81	2.74 ± 0.85	0.214
FBG, mmol/L	5.13 ± 1.70	5.22 ± 1.86	5.09 ± 1.77	5.07 ± 1.46	0.068
ALT, U/L	23.00 (15.00–35.05)	22.00 (14.04–33.00)	23.00 (15.00–36.12)	24.00 (16.00–36.35)	<0.001
AST, U/L	19.00 (15.00–24.79)	19.00 (15.00–24.00)	19.00 (15.63–25.00)	19.00 (15.00–25.00)	0.360
GGT, U/L	29.00 (18.00–45.38)	28.00 (18.00–43.79)	29.55 (18.00–46.39)	29.00 (18.00–46.42)	0.244
Cr, umol/L	67.31 ± 18.10	65.63 ± 16.82	66.87 ± 17.04	69.41 ± 20.08	<0.001
BUN, mmol/L	5.46 ± 2.02	5.51 ± 2.04	5.36 ± 1.95	5.51 ± 2.07	0.118
UA, umol/L	343.13 ± 96.08	332.96 ± 92.49	345.57 ± 96.28	350.82 ± 98.56	<0.001
Medications use					
Lipid-lowering drugs, %	1939 (52.22%)	628 (50.85%)	672 (54.41%)	639 (51.41%)	0.162
Antiplatelet agents, %	2273 (61.22%)	751 (60.81%)	749 (60.65%)	773 (62.19%)	0.688
Insulin, %	255 (6.87%)	107 (8.66%)	85 (6.88%)	63 (5.07%)	0.002
Oral antidiabetic agents, %	566 (15.24%)	204 (16.52%)	172 (13.93%)	190 (15.29%)	0.201
β-blockers, %	1227 (33.05%)	397 (32.15%)	417 (33.77%)	413 (33.23%)	0.684
CCB, %	2783 (74.95%)	933 (75.55%)	910 (73.68%)	940 (75.62%)	0.452
ACEI/ARB, %	2391 (64.40%)	780 (63.16%)	799 (64.70%)	812 (65.33%)	0.511
Spironolactone, %	667 (17.96%)	215 (17.41%)	256 (20.73%)	196 (15.77%)	0.005

Notes: Data are mean (standard deviation), n (%), or median (interquartile range).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; CCB, calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PAC, plasma aldosterone concentration; PA, primary aldosteronism.

Cr, and UA, and were more likely to use insulin and spironolactone when compared with those in the tertile 1 group. 1572 (42.3%) participants were diagnosed with NAFLD during the median follow-up of 30 months. The numbers of patients with incident first NAFLD and the corresponding cumulative incidence in tertiles 1 to 3 were 411 (33.28%), 393 (31.82%), and 768 (61.79%), respectively. The Kaplan-Meier curve demonstrated that participants in tertile 3 of PAC had a higher risk of developing new-onset NAFLD events than those in other groups (Log rank test, $P < 0.001$) (Figure 2).

Relationship Between PAC and NAFLD Diagnosis

Furthermore, we assessed the risk of NAFLD according to the presence of PAC (Table 2). When PAC was used as a continuous variable, it appeared that the risk of NAFLD was higher for each 1 ng/dL and 5 ng/dL increase in PAC; the HR were 1.04 (95% CI, 1.04–1.05, $P < 0.001$) and 1.24 (95% CI, 1.19–1.29, $P < 0.001$) respectively. And as a categorical variable, compared with tertile 1, the HR was 1.71 (95% CI, 1.47–1.98, $P < 0.001$) for tertile 3. Since the association between PAC and new-onset NAFLD had an E-value of 1.59, it seemed unlikely that unmeasured confounding could have caused the results (Figure S1).

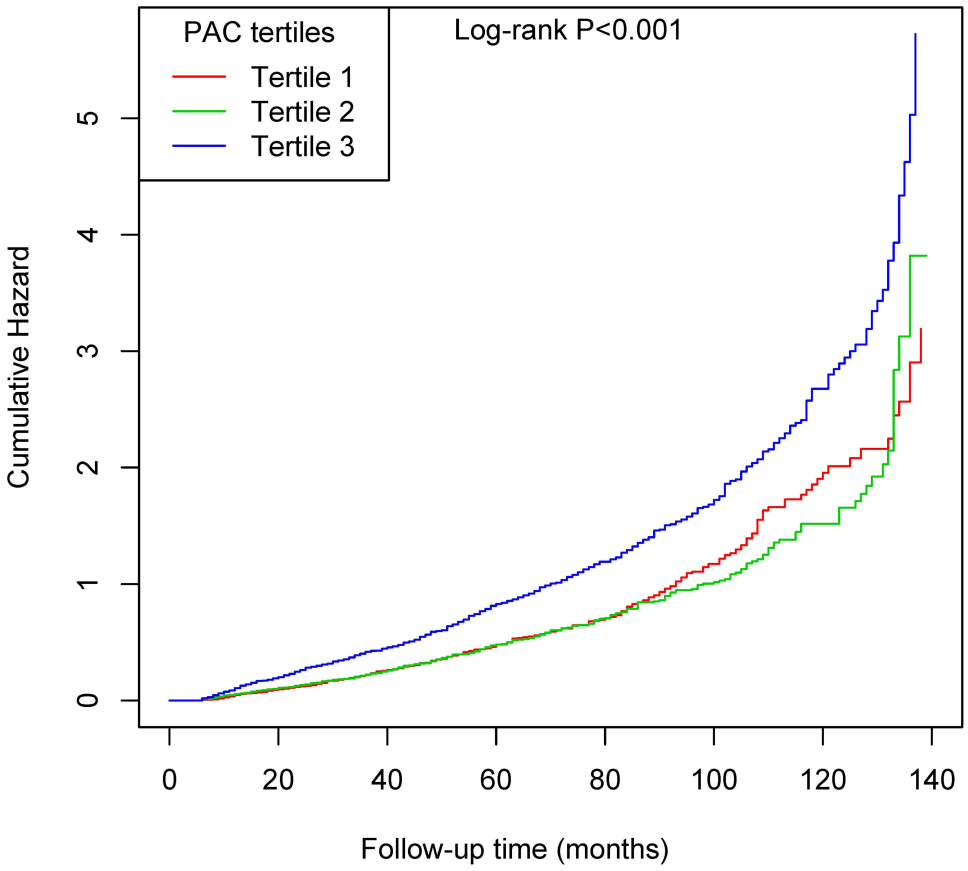

Figure 2 Cumulative hazards of the risk of new-onset NAFLD according to the tertiles of the PAC.

Nonlinearity and Threshold Effect Analysis

Both unadjusted and adjusted smoothing curves demonstrated that the relationship between PAC and new-onset NAFLD was nonlinear (Figure 3). Overall, there was a J-shaped relationship between PAC and new-onset NAFLD. We used a two-piecewise linear regression model and recursive algorithm to gain the inflection point of PAC at 13 ng/dL (log-likelihood ratio test, P = 0.005) (Table 3). In adjusted model 3, for PAC ≥ 13 ng/dL, a 5 ng/dL increase in PAC was associated with a 30% increase in the risk of NAFLD (95% CI, 1.25–1.35, P < 0.001).

Stratification Analysis and Test for Interaction

Stratified analyses were performed to assess the association of PAC (per 5 ng/dL increment) with new-onset NAFLD in various subgroups (Figure 4). We observed a significant interaction between diabetes and non-diabetes (P for interaction < 0.001), with the non-diabetes group associated with a greater increment in NAFLD (HR 1.27, 95% CI 1.22–1.32) than those with diabetes (HR 1.10, 95% CI 1.03–1.16). None of the other variables, including sex, age, duration of hypertension, PA, diabetes, current smoking, and BMI, significantly modified the association of PAC with new-onset NAFLD (all P-interactions > 0.05).

Discussion

NAFLD has emerged as the most prevalent chronic liver disease worldwide. Its incidence and prevalence are incessantly increasing, resulting in enormous clinical and economic burdens.[1–4,6] Growing evidence indicates that patients with NAFLD are at increased risk for the development of hypertension, coronary heart disease, cardiomyopathy, and cardiac arrhythmias, which clinically result in increased cardiovascular morbidity and mortality.[38–41] While lifestyle modifications remain the cornerstone of the management of NAFLD,[42] there has been a marked absence of effective

Table 2 Regression Models of Effects of PAC on New-Onset NAFLD

Exposure	Incidence Rate (Per 100 Person-Years)	Crude Model		Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Per 1 ng/dL increment		1.04 (1.03, 1.05)	< 0.001	1.05 (1.04, 1.06)	< 0.001	1.04 (1.04, 1.05)	< 0.001	1.04 (1.04, 1.05)	< 0.001
Per 5 ng/dL increment		1.21 (1.18, 1.25)	< 0.001	1.27 (1.22, 1.31)	< 0.001	1.24 (1.20, 1.29)	< 0.001	1.24 (1.19, 1.29)	< 0.001
Tertiles									
T1	10.29 (9.31, 11.33)	Reference		Reference		Reference		Reference	
T2	9.93 (8.98, 10.97)	0.97 (0.85, 1.12)	0.678	1.02 (0.88, 1.18)	0.823	1.02 (0.87, 1.20)	0.810	1.02 (0.87, 1.20)	0.765
T3	17.59 (16.72, 18.49)	1.67 (1.48, 1.88)	< 0.001	1.79 (1.56, 2.05)	< 0.001	1.72 (1.49, 1.99)	< 0.001	1.71 (1.47, 1.98)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001		< 0.001	

Notes: Crude model adjusted for none. Model 1 adjusted for age and sex. Model 2 adjusted for the variables in Model 1 plus BMI, current smoker, SBP, DBP, diabetes, PA, TG, TC, HDL-c, LDL-C, GGT, ALT, AST, BUN, Cr, UA, FPG. Model 3 adjusted for the variables in Model 2 plus lipid-lowering drugs, insulin, oral antidiabetic agents, β-blockers, CCB, antiplatelet agents, ACEI/ARB, spironolactone.

Abbreviations: CI, confidence interval; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; CCB, calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PAC, plasma aldosterone concentration; PA, primary aldosteronism.

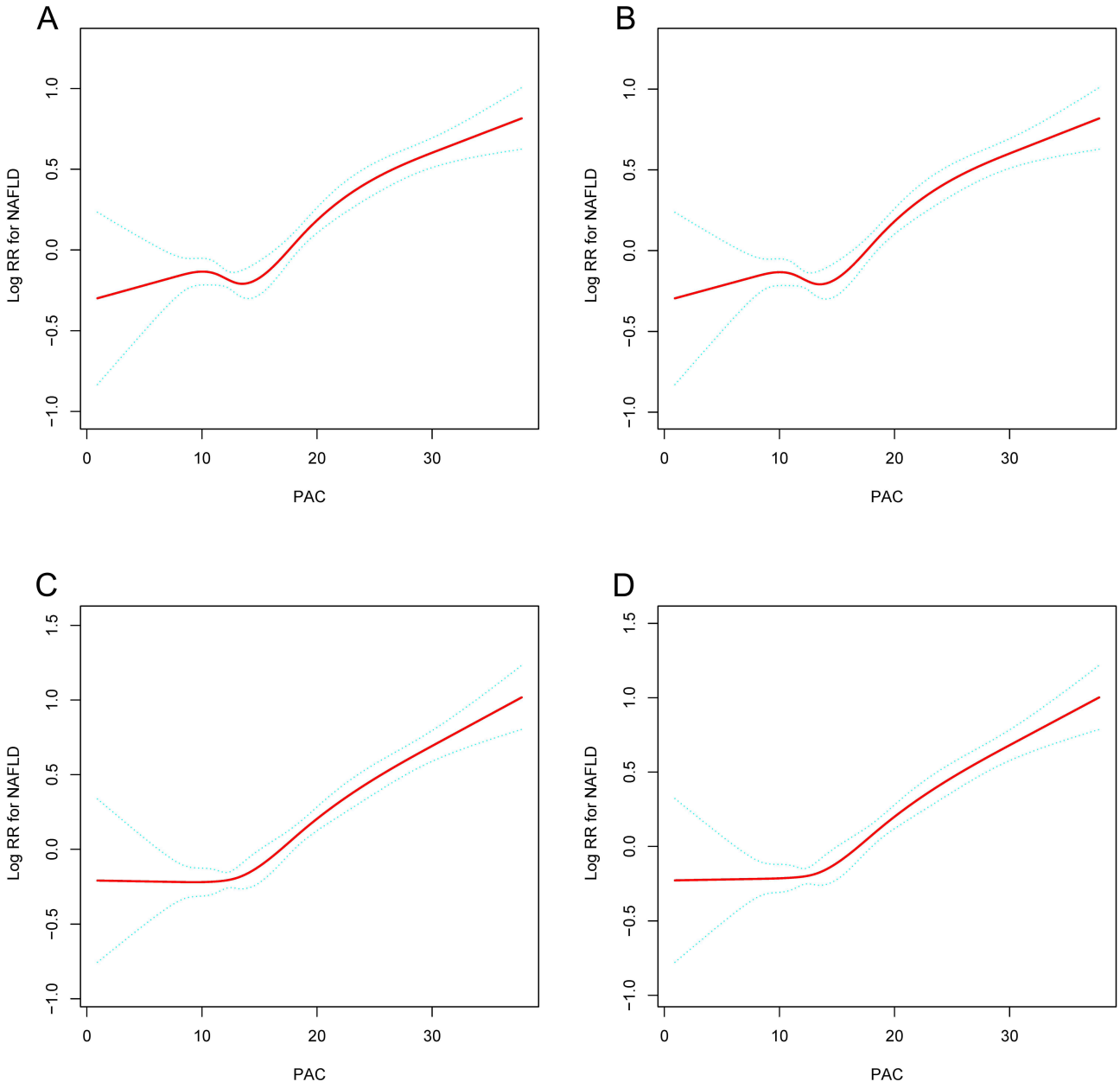

Figure 3 Dose-response relationship between PAC and the new-onset NAFLD. (**A**) crude model, (**B**) adjusted model 1, (**C**) adjusted model 2, and (**D**) adjusted model 3. Adjusted for all non-collinear variables.

pharmacological therapies approved for this condition.[43] Therefore, identifying emerging serum markers for NAFLD might help find high-risk individuals and develop auxiliary prevention or treatment strategies.

Aldosterone excess enhances oxidative stress and inflammation, induces reduction of both circulating adiponectin and adiponectin expression in visceral adipose tissue,[44,45] and directly promotes HSC activation and liver fibrosis by inducing the activation of the NLRP3 inflammasome.[23] Accumulating evidence has suggested that decreased adiponectin expression could enhance hepatic oxidative stress and play a role in the development and progression of NAFLD, from simple steatosis to NASH.[46,47] The in vivo findings revealed that adiponectin deficiency not only aggravated liver injury and steatosis but also stimulated palmitate-mediated NLRP3 inflammasome activation in hepatocytes and induced severe liver fibrosis.[48] Moreover, elevated aldosterone levels were independently associated with insulin resistance in a 10-year

Table 3 Threshold Effect Analyses of PAC (per 5 Ng/dL Increase) on the Risk of New-Onset NAFLD Using Two-Piecewise Regression Models

The Inflection Point of PAC	Crude Model		Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Model I								
Per 5 ng/dL increment	1.21 (1.18, 1.25)	< 0.001	1.27 (1.22, 1.31)	< 0.001	1.24 (1.20, 1.29)	< 0.001	1.24 (1.19, 1.29)	< 0.001
Model II								
< 13 ng/dL (per 5 ng/dL increment)	0.94 (0.80, 1.10)	0.434	1.00 (0.84, 1.19)	0.983	0.98 (0.82, 1.16)	0.804	0.98 (0.82, 1.17)	0.832
≥ 13 ng/dL (per 5 ng/dL increment)	1.26 (1.21, 1.31)	< 0.001	1.31 (1.25, 1.36)	< 0.001	1.31 (1.25, 1.36)	< 0.001	1.30 (1.25, 1.35)	< 0.001
P for log-likelihood ratio test	0.002		0.008		0.004		0.005	

Notes: Crude model adjusted for none. Model 1 adjusted for age and sex. Model 2 adjusted for the variables in Model 1 plus BMI, current smoker, SBP, DBP, diabetes, PA, TG, TC, HDL-c, LDL-C, GGT, ALT, AST, BUN, Cr, UA, FPG. Model 3 adjusted for the variables in Model 2 plus lipid-lowering drugs, insulin, oral antidiabetic agents, β-blockers, CCB, antiplatelet agents, ACEI/ARB, spironolactone. Model I, linear analysis; Model II, non-linear analysis. P for log-likelihood ratio test < 0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship.

Abbreviations: CI, confidence interval; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; CCB, calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PAC, plasma aldosterone concentration; PA, primary aldosteronism.

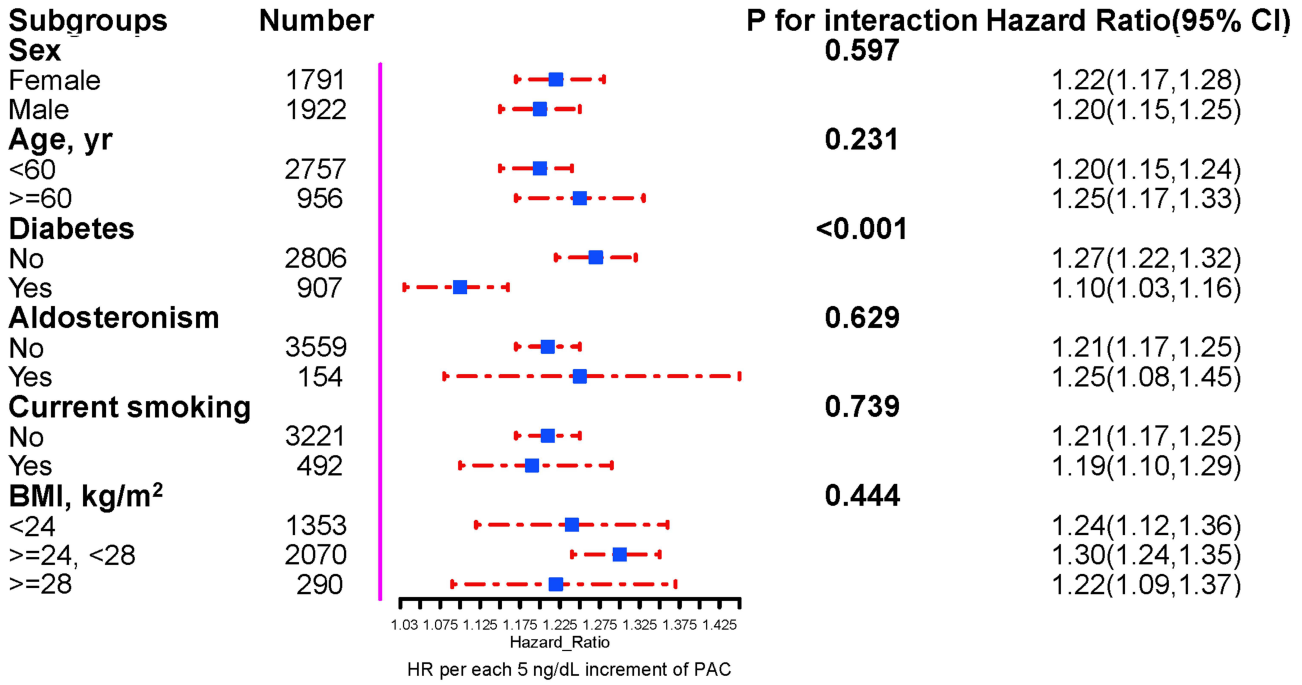

Figure 4 Association of the PAC (per 5 ng/dL increment) with new-onset NAFLD in various subgroups. Adjusted for all non-collinear variables, if not stratified.

prospective study of non-diabetic subjects from the general population.[49] However, there has been little research into the relationship between aldosterone and NAFLD in population studies.

In the present large cohort study, we found a meaningful relationship between high levels of PAC and NAFLD risk in hypertensive patients. And either as a continuous or categorical variable, elevated PAC was independently associated with new-onset NAFLD; this association was independent of other risk factors. With the PAC increasing, those in the highest tertile of the PAC had a 1.71-fold greater risk of NAFLD (T3 vs T1). This study is the first to examine the nonlinear association between PAC and the onset of NAFLD. Besides assessing the independent effects of PAC and new-onset NAFLD in hypertensive patients, we also explored the dose-response association between them. We calculated the inflection point of PAC at 13 ng/dL When PAC ≥ 13 ng/dL, PAC was significantly positively associated with the risk of NAFLD. However, when PAC < 13 ng/dL, there was no significant association between PAC and the risk of NAFLD.

Growing research has directly or indirectly found a relationship between aldosterone and NAFLD. A large retrospective cohort study demonstrated that angiotensin-converting enzyme inhibitor (ACEI) therapy was associated with a lower risk of NAFLD-related events.[50] Spironolactone is a potent mineralocorticoid receptor antagonist and may also improve glucose and lipid metabolism.[51] A small randomized controlled trial showed that the combined low-dose spironolactone and vitamin E therapeutic regimen had a favorable effect on serum insulin and HOMA-IR in NAFLD, possibly attributable to spironolactone action.[52] An in vitro study showed that SAB inhibited aldosterone-induced HSC proliferation and in vitro angiogenesis in a dose-dependent manner. Together, these treatment results indicated that aldosterone plays a pivotal role in the progression of NAFLD.[27] In subgroup analysis, our study found that the risk of NAFLD was associated with a higher PAC in hypertensive patients without diabetes than in those with diabetes. The reason underlying the association was the number of diabetes patients who accepted antidiabetic agents, including metformin, insulin, pioglitazone, glucagon-like peptide-1 agonists, sodium-glucose co-transporter-2, and dipeptidyl peptidase-4 inhibitors, which had a beneficial effect on the prevention of NAFLD.[53–56]

Our study has the strengths of a large sample size, a population-based cohort, and strict inclusion criteria. Furthermore, this research identifies the J-shaped relationship between PAC and NAFLD diagnosis in hypertensive patients for the first time. And it is important to identify and intervene with the high-risk groups for NAFLD in hypertensive patients. Despite this, study limitations require consideration. First, our study is limited by its retrospective,

observational nature. Second, although unobserved confounding is inevitable, the estimated E-values in our study indicate that confounders must have a relatively strong association with both PAC and NAFLD risk to completely clarify the observed associations. Third, abdominal ultrasonography is used to diagnose fatty liver rather than a liver biopsy. However, ultrasonography is widely used in clinical practice and epidemiological studies because of its acceptable accuracy in non-invasive fatty liver detection. Fourth, our research is restricted to Chinese hypertensive patients, and additional research is needed to validate our findings in a more extensive and diverse patient population. Fifth, this study only explored the relationship between PAC and new-onset NAFLD, without mentioning the relationship between PAC and other comorbidities associated with NAFLD. Finally, PAC obtained with a single measurement may not reflect changes over time or cumulative exposure. Future, well-designed prospective cohort studies are needed to explore whether cumulative exposure to PAC is associated with new-onset NAFLD.

Conclusion

In conclusion, this study revealed a nonlinear relationship between elevated PAC and new-onset NAFLD in patients with hypertension. Higher PAC was significantly associated with new-onset NAFLD when PAC was ≥ 13 ng/dL. Further prospective studies are needed to confirm the current findings.

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Disclosure

The authors report no conflicts of interest in this work.

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