

1 Introduction

Metabolic-dysfunction-associated fatty liver disease (MAFLD), a prevalent condition that affects approximately one-quarter of the global adult population, represents a significant health and economic burden across all societies, with a notable impact on the Asian demographic (1, 4). In 2019, a consensus was reached by an international panel of experts who proposed the term MAFLD to more accurately encapsulate the condition, regardless of alcohol consumption or the presence of other concurrent liver pathologies. This nomenclature underscores the centrality of metabolic dysfunction in the etiology, clinical presentation, progression, and outcomes of hepatic steatosis (1, 5, 7). MAFLD is recognized as the hepatic manifestation of a broader multisystem disorder, characterized by heterogeneity in its etiologies, manifestations, clinical course, and outcomes (8, 10). Epidemiological data indicate that the prevalence of MAFLD in Asian countries varies from 10% to 30% and is on an ascending trend (11, 15). Hypertension, a chronic condition with a substantial global incidence, is a well-established risk factor for cardiovascular diseases (CVD) (16, 18). Moreover, MAFLD has been shown to intensify the progression of atherosclerosis and heighten the risk of cardiovascular events (19, 20). Emerging research has delineated a bidirectional relationship between MAFLD and hypertension, with evidence implicating MAFLD as both a consequence and a precipitant of hypertensive conditions (21). The co-occurrence of hypertension and MAFLD has been associated with more adverse cardiovascular outcomes than either condition in isolation (22). Therefore, early identification, management, and intervention for the combined burden of MAFLD and hypertension are of critical importance, with far-reaching implications for public health (23).

Previous research on MAFLD has primarily focused on factors such as insulin resistance, metabolic syndrome, genetic predisposition, excessive obesity, and lifestyle influences, while notably overlooking the impact of aldosterone (1, 5, 9, 24). Aldosterone, a steroid hormone produced by the adrenal zona glomerulosa, plays a vital role in regulating sodium and water balance in the body, which significantly affects blood pressure control (25, 31). Numerous studies have identified the excessive secretion of aldosterone as a major risk factor for cardiovascular and kidney diseases, as well as metabolic disorders (26, 28, 29, 32, 33). Furthermore, recent research suggests that plasma aldosterone concentration (PAC) can influence liver metabolism (34, 35). For instance, studies have revealed a nonlinear relationship between elevated PAC levels and the incidence of non-alcoholic fatty liver disease (NAFLD) in patients with hypertension (36). Additionally, in animal models, aldosterone receptor blockers have been found to inhibit hepatic stellate cells and reduce liver fibrosis, indicating their potential effectiveness in treating fatty liver disease (37).

However, the relationship between PAC and MAFLD, a newer term for metabolic fatty liver disease, remains unexplored and unclear. This study aims to delineate the correlation between PAC and MAFLD, aspiring to provide innovative insights into the prevention and therapeutic management of metabolic fat deposition, particularly within the hypertensive patient population.

2 Material and methods

2.1 Study population

Between January 1, 2014, and December 31, 2023, a total of 41131 hospitalized patients were included in the study. Exclusion criteria were applied to participants under the age of 18 and those with incomplete data on PAC or insufficient information for the diagnosis of MAFLD. To mitigate the potential confounding effects of certain conditions and medications on study outcomes, we meticulously excluded individuals with positive serology for hepatitis B, C, or Delta viruses, autoimmune hepatitis, cirrhosis, history of liver resection, liver cancer, or gastrointestinal surgery. Furthermore, participants with a diagnosis of endocrine hypertension, severe thyroid disorders, chronic use of mineralocorticoid receptor antagonists, recent severe cardiovascular or cerebrovascular events, significant hepatic or renal impairment, or malignancies diagnosed within the preceding three months were also excluded. Individuals with a history of heavy alcohol consumption were additionally excluded to account for the impact on liver metabolism. After these exclusions, 35159 participants were included in the final analysis (Figure 1). Informed consent was obtained in writing from all patients or their legal guardians, and the study was approved by the hospital's ethics committee. Adherence to the STROBE guidelines was ensured in the reporting of this research (38).

2.2 Data collection and definitions

Data including clinical information, test findings, lifestyle variables, medical history, and medication history were obtained from the electronic medical record as baseline. Clinical data at admission included age, sex, height, weight, body mass index (BMI), systolic, diastolic, and waist circumference (WC). Smoking and alcohol drinking were classified as current or non-current. For specific measurement methods, please refer to the [Supplementary Material](#).

Peripheral venous blood was collected after an 8–10 hour fast to measure serum potassium, serum sodium, platelets (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum creatinine (Scr), uric acid (UA), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), HbA1c, high sensitivity C-reactive protein (hs-CRP), and triglyceride/glucose (TyG) index. The above blood biochemical indicators were detected by Automatic Analyzer (7600-010, Hitachi, Tokyo, Japan) according to the manufacturer's instruction. The hexokinase/glucose-6-phosphate dehydrogenase method was used to measure FBG levels, while TG levels were measured using the enzymatic colorimetric method. Before calculation, the units of TG and FBG were converted from mmol/L to mg/dL (For TG, 1 mmol/L = 88.57 mg/dL; For FBG, 1 mmol/L = 18 mg/dL), and the TyG index was then calculated as $\ln [TG (mg/dL) \times FBG (mg/dL)/2]$. Hormone measurements are based on current guidelines and our previous studies. The PAC was measured by radioimmunoassay (DSL-8600; DSL, Webster, TX).

FIGURE 1
Flowchart of the study.

(29, 36, 39). Please refer to the [Supplementary Material](#) for detailed definitions of the diseases.

2.3 Outcome

Hepatic steatosis with evidence of metabolic dysfunction defines MAFLD (11). Metabolic dysfunction was defined as satisfying one of the following three conditions: overweight or obese (BMI ≥ 23 kg/m²); type 2 diabetes mellitus (T2DM); metabolic abnormality score ≥ 2 (WC ≥ 90 cm in men and ≥ 80 cm in women; blood pressure $\geq 130/85$ mmHg or use of antihypertensives; TG ≥ 150 mg/dL or use of antidiyslipidemics; HDL-C < 40 mg/dL in men and < 50 mg/dL in women or use of antidiyslipidemics; FBG 5.6-6.9 mmol/L; hs-CRP > 2 mg/L; homeostasis model assessment of insulin resistance score [HOMA-IR] ≥ 2.5). For lack of information on HOMA-IR, we used the TyG index over the 75th percentile as an alternative to the HOMA-IR diagnostic criteria (40, 41).

2.4 Statistical analysis

Multicollinearity was assessed using the variance inflation factor test ([Supplementary Table S1](#)). The relationship between PAC levels and MAFLD was analyzed using a multivariate logistic regression model, and the odds ratio (OR) was calculated. Additionally, we used restricted cubic splines (RCS) to evaluate the dose-response relationship and conducted a two-stage comparative analysis based on the inflection points of the RCS curve. Additionally, subgroup analyses were conducted to ascertain the influence of PAC on MAFLD across a spectrum of stratifying variables. Several extra sensitivity analyses were performed to

assess the reliability of the results. [Supplementary Materials](#) provide details on the statistical analysis.

The statistical analysis was executed using R software, version 4.1.1. Significance was defined as a p-value of less than 0.05, employing a two-tailed test for statistical inference.

3 Results

3.1 Baseline characteristics

Based on the quartiles of PAC, baseline characteristics of each group are presented in [Table 1](#). A total of 35159 patients were included, among which 20078 (57.11%) were male. The high PAC group was younger, comprised more females, and had a higher BMI. In terms of test indicators, Scr, WC, and TyG indexes were significantly higher in the high PAC group compared to the low PAC group. Moreover, the high PAC group were more likely to be taking diuretics and calcium channel blockers (CCB) ([Table 1](#)). The most significant discovery was that the prevalence of MAFLD appeared to rise as PAC increased ([Figure 2](#)). Furthermore, after dichotomizing according to the presence or absence of MAFLD, there were significant differences in PAC, age, TyG index, and smoking history between the two groups ([Supplementary Table S2](#)).

3.2 Relationship between PAC and the prevalence of MAFLD

Our research has found a close association between PAC and MAFLD. In the original model, for every 5-unit increase in PAC, the risk of developing MAFLD increases by 1.57 times. This relationship remains reliable in the fully adjusted model. Compared to the Q1 group, the OR values for the Q2, Q3, and

TABLE 1 Baseline characteristics according to quartiles of PAC.

Variables	Q1	Q2	Q3	Q4	P-value
	(<11.83ng/dL)	(11.83-14.08ng/dL)	(14.08-18.65ng/dL)	(>18.65ng/dL)	
Sample size, n	8790	8790	8790	8789	
Demography					
Age, years	52.05 52.58	51.40 51.48	50.54 52.07	49.50 52.03	<0.001*
Sex, %					0.037*
Women	3705 (42.15%)	3790 (43.12%)	3714 (42.25%)	3872 (44.06%)	
Men	5085 (57.85%)	5000 (56.88%)	5076 (57.75%)	4917 (55.94%)	
BMI, kg/m ²	26.86 26.68	26.93 26.66	26.95 26.61	26.98 26.60	0.163
WC, cm	95.63 95.34	95.84 95.25	95.91 95.19	96.02 95.13	0.128
SBP, mmHg	146.13 148.39	146.07 148.20	145.70 148.24	146.17 148.34	0.31
DBP, mmHg	88.34 88.67	88.14 88.56	87.82 88.48	88.14 88.67	0.094
Current smoking, %	3115 (35.44%)	2991 (34.03%)	2959 (33.66%)	2647 (30.12%)	<0.001*
Current drinking, %	2769 (31.50%)	2762 (31.42%)	2764 (31.44%)	2553 (29.05%)	<0.001*
Biochemical indexes					
Serum potassium (mmol/L)	4.07 4.29	3.98 4.27	3.83 4.31	3.63 4.28	<0.001*
Serum sodium (mmol/L)	141.11 142.55	141.11 142.45	141.03 142.49	141.04 142.58	0.089
PLT, 10 ⁹ /L	242.29 258.68	243.15 258.15	242.90 257.83	240.01 257.66	0.001*
ALT, U/L	27.36 27.54	27.17 27.54	27.36 27.60	27.25 27.42	0.871
AST, U/L	21.10 22.24	21.00 22.16	21.08 22.17	21.05 22.31	0.877
GGT, U/L	36.25 25.77	35.53 24.80	35.86 25.17	36.09 25.30	0.261
Scr, μ mol/L	64.93 64.46	65.03 64.32	65.05 64.37	65.43 64.48	0.101
BUN, mmol/L	5.05 5.36	5.04 5.35	5.05 5.36	5.08 5.36	0.325
UA, μ mol/L	343.61 351.51	342.97 350.57	343.16 350.80	345.74 351.23	0.161
Total cholesterol, mmol/L	4.55 4.99	4.51 4.97	4.55 4.98	4.53 4.97	0.032*
Triglyceride, mmol/L	1.82 2.04	1.80 2.01	1.81 2.03	1.82 2.06	0.439
HDL-C, mmol/L	1.06 1.25	1.05 1.24	1.06 1.25	1.06 1.25	0.039*
LDL-C, mmol/L	2.73 2.83	2.74 2.82	2.78 2.82	2.77 2.82	<0.001*
FBG, mmol/L	5.05 5.07	5.03 5.04	5.00 5.02	5.03 5.05	0.032*
HbA1c, %	5.99 6.82	5.95 6.79	5.91 6.75	5.89 6.79	<0.001*
hs-CRP, mg/dL	3.40 3.01	3.58 3.12	3.50 3.03	3.54 3.13	<0.001*
TyG index	6.53 6.52	6.89 6.11	7.27 6.12	7.98 6.47	<0.001*
Previous history					
T2DM, %	1524 (17.34%)	1384 (15.75%)	1324 (15.06%)	1406 (16.00%)	<0.001*
Dyslipidemia, %	1676 (19.07%)	1682 (19.14%)	1767 (20.10%)	1540 (17.52%)	<0.001*
CAD, %	944 (10.74%)	808 (9.19%)	746 (8.49%)	745 (8.48%)	<0.001*

(Continued)

TABLE 1 Continued

Variables	Q1	Q2	Q3	Q4	P-value
	(<11.83ng/dL)	(11.83-14.08ng/dL)	(14.08-18.65ng/dL)	(>18.65ng/dL)	
Medications use					
ACEI/ARB, %	4235 (48.18%)	4016 (45.69%)	3942 (44.85%)	4034 (45.90%)	<0.001*
Diuretic, %	905 (10.30%)	893 (10.16%)	937 (10.66%)	1052 (11.97%)	<0.001*
CCB, %	2021 (22.99%)	2069 (23.54%)	2228 (25.35%)	2665 (30.32%)	<0.001*
b-blockers, %	1688 (19.20%)	1542 (17.54%)	1489 (16.94%)	1505 (17.12%)	<0.001*
Antidiabetic agents, %	758 (8.62%)	676 (7.69%)	570 (6.48%)	612 (6.96%)	<0.001*
Lipid-lowering drugs, %	1139 (12.96%)	1050 (11.95%)	980 (11.15%)	928 (10.56%)	<0.001*

Data are mean (standard deviation), n (%), or median (interquartile range). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; Scr, serumcreatinine; BUN, blood urea nitrogen; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; hs-CRP, high sensitivity C-reactive protein; TyG index, triglyceride glucose index; DM, diabetes mellitus; CAD, coronary artery disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers.
*Significant P value (P < 0.05).

Q4 groups are 1.21, 2.12, and 3.14 respectively, showing an increasing trend (Table 2). We further utilized the RCS model to identify the nonlinear dose-response relationship between PAC levels and the prevalence of MAFLD (p for nonlinear < 0.001) (Figure 3). Furthermore, we conducted a two-stage comparative analysis based on the inflection point of RCS. The results indicate that the risk of developing MAFLD for individuals with a PAC level greater than 14ng/dL is 2.32 times higher than that of individuals with a level less than 14ng/dL (Table 3).

3.3 Subgroup analysis

After stratifying the data based on basic conditions and diseases, the results remained stable across the population, with no interactions observed (Figure 4). In addition, a subgroup analysis examined the potential impact of antihypertensive drugs on outcomes, which also showed no significant changes (Supplementary Figure S1). This indicates that our findings are

not affected by these stratification factors and that PAC can predict the occurrence of MAFLD regardless of stratification. In order to eliminate any bias caused by missing data, we conducted sensitivity analyses after excluding patients with missing values and obtained essentially the same results (Supplementary Table S3). Furthermore, to mitigate the impact of alcohol abuse on the results, we excluded patients with a history of alcohol abuse and the results remained consistent (Supplementary Table S4). Additionally, to eliminate the influence of severe liver fibrosis on aldosterone inactivation, we excluded patients with severe liver fibrosis. The correlation between PAC and the prevalence of MAFLD remained largely unchanged (Supplementary Tables S5, S6). Additionally, to assess the influence of unmeasured confounders, we conducted an E-value analysis, which indicated that the impact of confounding factors was minimal and the likelihood of our results being overturned was low (Supplementary Table S7 and Supplementary Figure S2).

4 Discussion

Our study has, for the first time, uncovered the relationship between PAC levels and the prevalence of MAFLD in hypertensive patients, revealing an independent association between elevated PAC and an increased incidence of MAFLD. Our findings indicate that individuals with PAC levels exceeding 14 ng/dL exhibit a 2.32-fold heightened risk for the development of MAFLD compared to those with levels below this threshold. This suggests that maintaining PAC within a reasonable range may offer a new direction for preventing MAFLD in the future.

Aldosterone, a crucial mineralocorticoid hormone, plays an essential role in regulating the body's water and electrolyte balance (42, 45). While its excess is known to indicate hypertension and organ damage, its connection to liver steatosis remains underexplored. Fallo and colleagues highlight that patients with primary aldosteronism are more prone to insulin resistance and have a higher prevalence of NAFLD, suggesting an increased risk of metabolic and liver diseases in this subgroup (46).

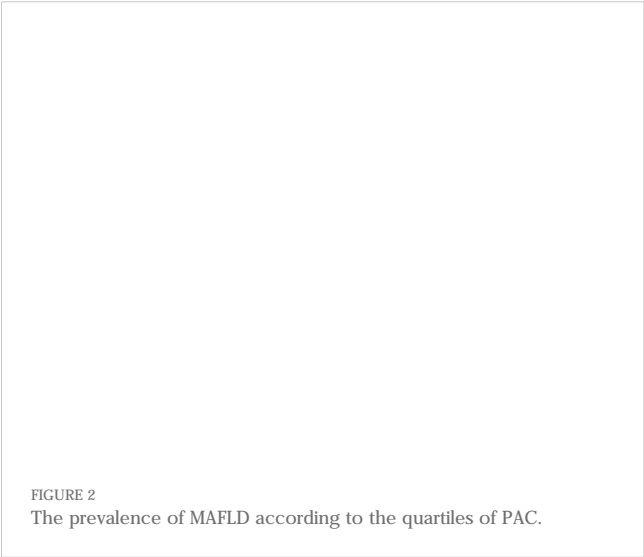


TABLE 2 The relationship between PAC and the prevalence of MAFLD in hypertensive patients.

Exposure	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
PAC (per 5 ng/dl increase)	1.57 (1.54, 1.61)	1.57 (1.54, 1.60)	1.57 (1.54, 1.60)	1.56 (1.53, 1.59)	1.56 (1.53, 1.60)
PAC quartiles					
Q1 (<11.83)	Reference	Reference	Reference	Reference	Reference
Q2 (11.83–14.08)	1.21 (1.14, 1.29)	1.21 (1.14, 1.29)	1.21 (1.14, 1.29)	1.21 (1.14, 1.28)	1.21 (1.14, 1.29)
Q3 (14.08–18.65)	2.13 (2.00, 2.26)	2.13 (2.00, 2.26)	2.13 (2.00, 2.26)	2.11 (1.99, 2.25)	2.12 (1.99, 2.25)
Q4 (>18.65)	3.20 (3.01, 3.40)	3.19 (3.00, 3.39)	3.19 (2.99, 3.39)	3.12 (2.93, 3.32)	3.14 (2.95, 3.35)
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001

Model 1: crude model.
Model 2: adjusted for age, sex, smoking status, alcohol consumption, BMI, SBP, and DBP.
Model 3: adjusted for variables in Model 2 plus DM, dyslipidemia, CAD.
Model 4: adjusted for variables in Model 3 plus Serum potassium, Serum sodium, PLT, ALT, AST, GGT, Scr, BUN, UA, Total cholesterol, Triglyceride, HDL-C, LDL-C, FBG, HbA1c, hs-CRP, TyG index.
Model 5: adjusted for variables in Model 4 plus ACEI/ARB, diuretic, CCB, b-blockers, antidiabetic agents, lipid-lowering drugs.
SD, standard deviation; OR, Odds ratio. Other abbreviations, see Table 1.

Additionally, a large cohort study observed that angiotensin-converting enzyme inhibitors are linked to a reduced risk of adverse liver events in liver steatosis patients (47). Spironolactone, an aldosterone receptor antagonist, has shown beneficial effects on serum insulin and HOMA-IR in NAFLD patients, according to animal studies (48). Further supporting this, the Jackson Heart Study, involving 2,507 participants, found a positive correlation between aldosterone levels and fatty liver in African American women (49). Research by Srinivasa et al. indicates that elevated aldosterone could be a risk factor for liver fat accumulation in HIV-infected individuals (50). A recent study shows that in hypertensive patients, the risk of developing new-onset NAFLD significantly increases when PAC levels are ≥13 ng/dL (36). This research overcomes previous studies' limitations, such as animal reliance, limited populations, small samples, and inadequate variable adjustments, providing a more comprehensive analysis.

The specific mechanisms by which PAC leads to the development of MAFLD remain unclear and may involve several

potential pathways. First, an excess of aldosterone can enhance oxidative stress and inflammation, which could potentially lead to liver damage and the progression of fatty liver disease (34, 51, 54). Second, an overabundance of aldosterone can also cause a decrease in adiponectin levels in the bloodstream, and a corresponding reduction in its expression in visceral adipose tissue. This hormone, known as adiponectin, plays a crucial regulatory role in fat storage and reducing insulin resistance (30, 55, 57). Third, aldosterone can trigger a direct sequence of events leading to the activation of hepatic stellate cells (HSC) and eventually liver fibrosis, primarily by inducing the activation of the NLRP3 inflammasome (58). Finally, more recent research has shed light on the fact that aldosterone can be locally produced during the process of liver fibrogenesis, thereby contributing to organ fibrosis (31, 35, 59). To counter these effects, the therapeutic efficacy of aldosterone antagonists has been recognized. Existing studies have reliably shown that certain aldosterone antagonists, notably spironolactone and eplerenone, can diminish the symptoms of fatty liver and liver fibrosis (33, 58, 60, 61). This significantly underlines the critical role that aldosterone plays in the pathophysiology of fatty liver disease.

Our study's strengths lie in the large sample size, strict exclusion criteria, and the first-time revelation of the relationship between PAC and MAFLD. We utilized multiple statistical methods to further validate the reliability of our research findings. These groundbreaking results may also offer new insights into the early identification and intervention of MAFLD in hypertensive patients. However, while considering these advantages, we must also acknowledge that our study may have some limitations. Firstly, our study is cross-sectional in design, which prevents us from establishing a causal relationship between PAC and MAFLD. Secondly, we did not take into account the potential influence of confounding factors such as dietary habits and level of physical activity, so we conducted an E-value analysis. The results indicate that the likelihood of our findings being overturned is very low. Thirdly, rather than using liver biopsy, abdominal ultrasound was

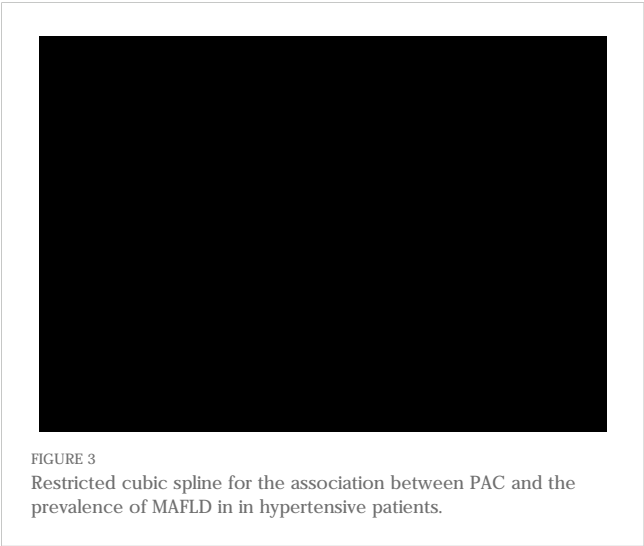


TABLE 3 Analysis of the prevalence of MAFLD Based on RCS Turning Point.

Exposure	Model 1 OR (95% CI),	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
PAC					
<14 ng/dL	Reference	Reference	Reference	Reference	Reference
14 ng/dL	2.35 (2.25, 2.45)	2.34 (2.24, 2.44)	2.34 (2.24, 2.44)	2.31 (2.22, 2.41)	2.32 (2.22, 2.42)

Model 1: crude model.
Model 2: adjusted for age, sex, smoking status, alcohol consumption, BMI, SBP, and DBP.
Model 3: adjusted for variables in Model 2 plus DM, dyslipidemia, CAD.
Model 4: adjusted for variables in Model 3 plus Serum potassium, Serum sodium, PLT, ALT, AST, GGT, Scr, BUN, UA, Total cholesterol, Triglyceride, HDL-C, LDL-C, FBG, HbA1c, hs-CRP, TyG index.
Model 5: adjusted for variables in Model 4 plus ACEI/ARB, diuretic, CCB, b-blockers, antidiabetic agents, lipid-lowering drugs.
SD, standard deviation; OR, odds ratio; CI, confidence interval. Other abbreviations, see Table 1.

used to diagnose fatty liver. Ultrasound, however, has good accuracy in non-invasive detection of fatty liver, making it widely used in clinical practice and epidemiological studies. Fourthly, our study was limited to hypertensive patients in China, and the generalizability of the conclusions may be affected, necessitating further research in a more diverse and broader patient population to validate our findings.

5 Conclusion

This study revealed a groundbreaking positive relationship between PAC and the prevalence of MAFLD, particularly with a significant increase in the risk of developing MAFLD when PAC exceeds 14ng/dL. This further suggests that maintaining PAC at a reasonable level may be beneficial in preventing the occurrence of

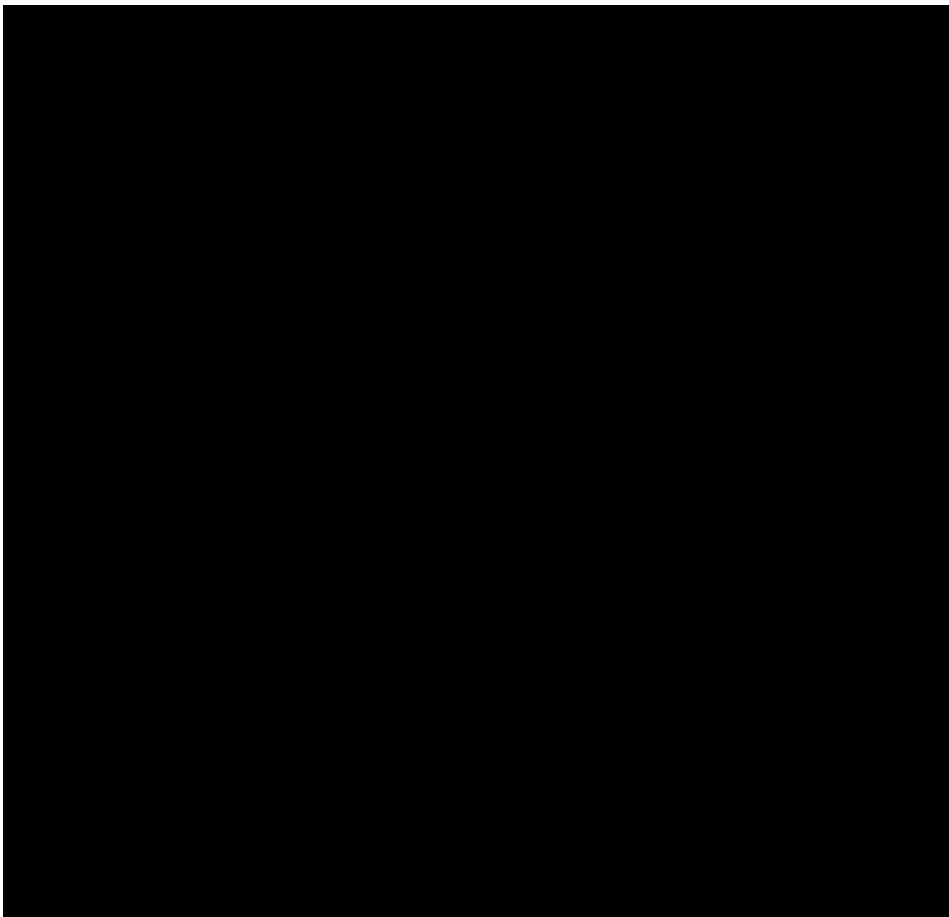


FIGURE 4
Stratified analyses of the association between PAC (per 5 ng/dL increment) and the prevalence of MAFLD in hypertensive patients.

MAFLD in hypertensive patients. However, to validate and confirm these findings, it is necessary to conduct more large-scale prospective studies in the future.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

Author contributions

DS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing $\frac{1}{2}$ original draft, Writing $\frac{1}{2}$ review & editing. XC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing $\frac{1}{2}$ original draft, Writing $\frac{1}{2}$ review & editing. JLH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Validation, Writing $\frac{1}{2}$ review & editing. SS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Writing $\frac{1}{2}$ review & editing. QZ: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Software, Validation, Writing $\frac{1}{2}$ review & editing. HM: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Validation, Writing $\frac{1}{2}$ review & editing. YZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing $\frac{1}{2}$ review & editing. RM: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing $\frac{1}{2}$ review & editing. PZ: Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing $\frac{1}{2}$ review & editing. WY: Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing $\frac{1}{2}$ review &

editing. JH: Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Writing $\frac{1}{2}$ review & editing. DZ: Conceptualization, Data curation, Investigation, Project administration, Validation, Visualization, Writing $\frac{1}{2}$ review & editing. NL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing $\frac{1}{2}$ review & editing.

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Conflict of interest

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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.2024.1451383/full#supplementary-material>

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