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ORIGINAL ARTICLE

Metabolic Dysfunction-Associated Fatty Liver Disease in Newly Diagnosed, Treatment-Naive Hypertensive Patients and Its Association with Cardiorenal Risk Markers

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Abstract

Introduction Patients with arterial hypertension frequently present with comorbidities that are associated with increased cardiorenal risk, such as metabolic dysfunction-associated fatty liver disease (MAFLD).

Aims Our study aimed to assess the prevalence and the association of MAFLD with cardiorenal risk markers in newly diagnosed, treatment-naïve hypertensive patients.

Methods We recruited 281 individuals with new-onset hypertension who were not prescribed any medication. Medical history, clinical examination findings, and laboratory test results were recorded. Liver steatosis was assessed through fatty liver index (FLI) calculation. Patients with FLI ≥ 60 together with one main metabolic abnormality (type 2 diabetes mellitus or overweight/obesity) or at least two metabolic risk abnormalities (increased waist circumference, blood pressure, plasma triglycerides, presence of prediabetes or insulin resistance, decreased plasma high-density lipoprotein) fulfilled the diagnostic criteria for MAFLD.

Results The prevalence of MAFLD in our study population was 28.7%. Individuals with MAFLD were more frequently male and had increased body mass index. Systolic, diastolic, and pulse pressure values were significantly higher in this group of patients. Moreover, lipid, renal, glucose, and inflammatory markers were considerably deranged in patients with MAFLD. After multivariate regression analysis, uric acid, ferritin, and apoE emerged as independent predictors of MAFLD. Area under receiver operating characteristics curve revealed that uric acid had the greatest diagnostic accuracy, with the ideal cutoff being ≥ 5.2 mg/dl (sensitivity: 77.6%, specificity: 76.3%).

Conclusion MAFLD represents a common comorbidity in hypertensive patients and is associated with markers of cardiorenal risk. Uric acid may be indicative of MAFLD in particular.

Keywords Metabolic dysfunction-associated fatty liver disease · Arterial hypertension · Cardiovascular risk

1 Introduction

Arterial hypertension (AH) represents a common, frequently asymptomatic, noncommunicable disease, that is characterized by worrisome epidemiological trends. Due to the increased life expectancy and the constant exposure to unhealthy lifestyles, the prevalence of AH is rising. This is especially evident in low- and middle-income countries, while the prevalence of AH in high-income countries is moderately decreasing [1]. Moreover, the new definition of hypertension (systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic BP (DBP) ≥ 80 mmHg meant that the prevalence of hypertension in the USA and China could be as high as 46% [2, 3]. Prompt diagnosis and management of AH is of great importance, since many complications arise from persistently elevated BP, such as ischemic stroke, coronary artery disease, heart failure, and chronic kidney disease (CKD), among others [1].

Patients with AH frequently present with additional comorbidities that are associated with augmented cardiovascular risk, such as metabolic dysfunction-associated fatty

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liver disease (MAFLD). This newly proposed term, which has replaced the previously used non-alcoholic fatty liver disease, provides positive criteria for hepatic insult due to metabolic derangement [4]. These include the presence of steatosis along with a main metabolic abnormality (overweight/obesity or type 2 diabetes mellitus) or at least two metabolic risk factors [4]. However, the prevalence and the association of MAFLD with cardiorenal risk markers in hypertensive patients is unclear. Therefore, this study aims to determine the prevalence and the association of MAFLD with cardiorenal risk markers in treatment-naive hypertensive patients.

2 Methods

2.1 Study Design

This was a cross-sectional study of 281 persons with new-onset hypertension who attended the Diabetes Outpatient Clinic of Ioannina University Hospital, Ioannina, Greece. Participants were not under any medical treatment. They were interviewed and clinically examined by specialized physicians. Anthropometric measurements and blood samples were collected. The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [5]. All individuals were informed about the aims of the study and provided written informed consent. The study was approved by the Ethics Committee of the Ioannina University Hospital and was carried out according to the Declaration of Helsinki (1989).

2.2 Clinical and Biochemical Assessment

Body mass index (BMI) was calculated as the weight in kilograms divided by the height squared in meters. Waist circumference was measured at the midpoint between the inferior border of the costal margin and the anterior superior iliac crest. Three blood pressure readings were obtained in the sitting position of the right arm, with a 5-min interval in rest after every measurement, in two separate visits at least 2 weeks apart. The average of the second and the third systolic and diastolic pressure readings were used. The mean of home blood pressure measurements was taken into account to confirm the diagnosis of hypertension, as well as in cases of potential masked hypertension. The methodology of home blood pressure measurements was in accordance with the latest practice guidelines of the European Society of Hypertension [6]. The diagnosis of arterial hypertension was considered in cases of office blood pressure ≥ 140/90 mmHg or home blood pressure ≥ 135/85 mmHg [7]. Pulse pressure, a marker of arterial stiffness [8], was also evaluated by subtracting DBP from SBP.

We collected the blood samples after an overnight fast. An extended lipid profile including lipoprotein (a), apolipoproteins (ApoA1, ApoB, ApoE), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) was assessed. Low-density lipoprotein cholesterol (LDL-C) concentration was calculated according to the Friedewald formula: LDL-C = TC − HDL-C + (TG/5), when triglycerides value was lower than 400 mg/dl [9]. Regarding glucose-insulin homeostasis markers, we estimated insulin resistance via calculation of the homeostasis model insulin resistance (HOMA-IR = plasma glucose (md/dl) × fasting insulin (mIU/l) ÷ 405) index [10] and the quantitative insulin sensitivity check index (QUICKI = 1/[log fasting insulin (mg/dl) + fasting glucose(μu/ml)]) after the measurement of glucose and insulin [11]. Renal function was estimated by serum urea and creatinine, with the estimation of the glomerular filtration rate (eGFR) according to the CKD-EPI formula [12]. Diagnosis of the metabolic syndrome (MtS) was based on the proposed ATP III criteria [13].

MAFLD was defined according to the recently proposed criteria. Patients should have evidence of hepatic steatosis, determined through imaging techniques, histology, or blood biomarkers/scores. We chose and calculated the fatty liver index (FLI) via the following formula: $FLI = e^y / (1 + e^y) \times 100$, where $y = 0.953 \times \ln(\text{triglycerides, mg/dl}) + 0.139 \times \text{BMI, kg/m}^2 + 0.718 \times \ln(\text{GGT, U/l}) + 0.053 \times \text{waist circumference, cm} - 15.745$. A previous study in Western population shown that at FLI cutoff of ≥ 60, the presence of hepatic steatosis is ruled in [14]. Accordingly, individuals with FLI ≥ 60 fulfilled the diagnostic criteria for MAFLD [4] if they also had at least one of the following: type 2 diabetes mellitus, overweight/obesity, or ≥ 2 metabolic risk abnormalities (increased waist circumference (≥ 102 cm in men, ≥ 88 cm in women), increased blood pressure (≥ 130/85 mmHg or specific drug treatment), increased plasma triglycerides (≥ 150 mg/dl or specific drug treatment), decreased plasma high-density lipoprotein (< 40 mg/dl in men, < 50 mg/dl in women), presence of prediabetes [fasting glucose 100–125 mg/dl or HbA1c 5.7–6.4%), insulin resistance (HOMA-IR ≥ 2.5)].

2.3 Statistical analysis

Continuous variables were tested for normality with the Kolmogorov–Smirnov test and visual inspection of P–P plots. Accordingly, they are presented as mean (standard deviation) if normally distributed, or as median (25th, 75th quartile) if not normally distributed. Categorical variables are displayed as percentages. T-tests were employed to examine the differences between 2 categories of normally distributed continuous data. Differences between categorical variables were tested by forming contingency tables

and performing χ^2-tests. Logistic regression analysis was used for the multivariate assessment of independent MAFLD predictors in our study population. We also proceeded to a receiver operating characteristics (ROC) curves' analysis by estimating the area under the ROC curve (AUROC). The ideal cutoff values were chose according to the Youden index [15], with subsequent assessment of its sensitivity and specificity. The statistical calculations were performed in SPSS software (version 25.0; SPSS Inc., Chicago, Illinois, USA). All reported p-values were based on two-sided hypotheses, with a p-value of less than 0.05 being considered statistically significant.

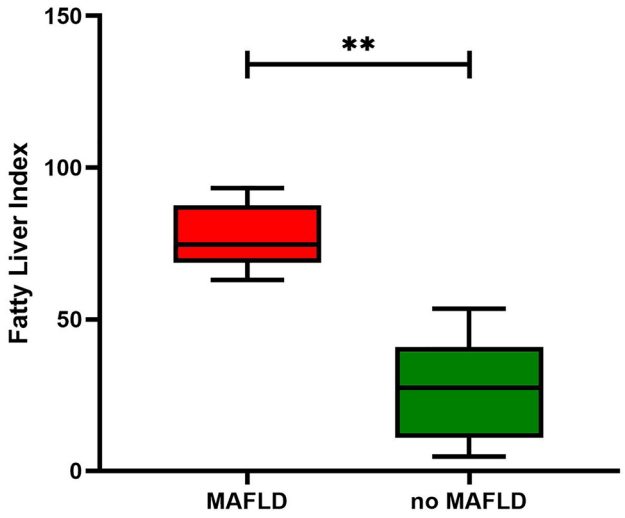

Fig. 1 Box plots demonstrating the differences in fatty liver index between individuals with and without metabolic dysfunction-associated fatty liver disease. **Statistically significant difference ($p < 0.001$)

3 Results

3.1 Anthropometric and Clinical Characteristics

In the study population of 281 individuals with treatment-naïve hypertension, 75 were found with MAFLD (prevalence 28.7%) and had significantly higher FLI compared to subjects without MAFLD (77.2 ± 11.0 vs. 27.1 ± 17.3, $p < 0.001$) (Fig. 1). The baseline characteristics of the study population are presented in Table 1. Patients with MAFLD were more frequently male (66.7% vs. 47.1%, $p = 0.004$), obese (63.0% vs. 45.3%, $p < 0.001$), and had much higher rates of metabolic syndrome (78.7% vs. 17.5%, $p < 0.001$) compared to those without MAFLD. Moreover, they presented with significantly increased office systolic BP (150 ± 23 mmHg vs. 136 ± 25 mmHg, $p < 0.001$) and diastolic BP (93 ± 12 mmHg vs. 84 ± 14 mmHg, $p < 0.001$). PP was also considerably higher in individuals with MAFLD (57 ± 18 mmHg vs. 52 ± 15 mmHg, $p = 0.01$). No differences in mean age or CKD prevalence were detected.

3.2 The Association of MAFLD with Blood Biomarkers

The association of MAFLD prevalence with markers of lipidemia, glucose and insulin homeostasis, liver function, and renal function are displayed in Table 2. Individuals with MAFLD had greater abnormalities in common and extended lipid panel parameters, such as ApoA1, ApoB, ApoE, and Lp(a). Uric acid was also significantly higher in subjects with MAFLD [6.0 (5.3, 6.8) mg/dl vs. 4.2 (3.4, 5.2) mg/dl, $p < 0.001$]. MAFLD individuals also had significantly impaired glucose levels and greater degrees of insulin resistance evidenced by HOMA-IR index and QUICKI. Moving to liver enzymes, higher levels of transaminases, alkaline phosphatase and gamma glutamyl transferase were observed in MAFLD individuals. Greater abnormalities in kidney

Table 1 Demographic and clinical characteristics of patients with and without metabolic dysfunction-associated fatty liver disease (MAFLD)

	MAFLD (N = 75)	No MAFLD (N = 206)	p
Age, years	49.9 (10.5)	49.5 (10.8)	0.81
Male sex, %	66.7	47.1	0.004
Body mass index, kg/m^2	30.3 (3.2)	25.3 (3.0)	< 0.001
Obesity, %	63.0	45.3	< 0.001
Waist circumference, cm	104.3 (7.4)	87.2 (10.2)	< 0.001
Office systolic blood pressure, mmHg	150 (23)	136 (25)	< 0.001
Office diastolic blood pressure, mmHg	93 (12)	84 (14)	< 0.001
Pulse pressure, mmHg	57 (18)	52 (15)	0.01
Metabolic syndrome, %	78.7	17.5	< 0.001
Chronic kidney disease, %	4.4	5.4	0.72

Continuous variables are presented as mean (standard deviation)

Table 2 Difference in lipid markers, glucose homeostasis, liver biochemistry, and renal function between patients with and without MAFLD

	MAFLD (N = 75)	No MAFLD (N = 206)	p
Lipid markers			
Total cholesterol, mg/dl	244 (47)	224 (39)	< 0.001
HDL-cholesterol, mg/dl	40 (34, 48)	49 (42, 58)	< 0.001
LDL-cholesterol, mg/dl	162 (143, 187)	150 (128, 180)	0.02
Triglycerides, mg/dl	170 (128, 209)	92 (74, 126)	< 0.001
ApoA1, mg/dl	138 (120, 155)	147 (132, 165)	0.004
ApoB, mg/dl	128 (30)	108 (26)	< 0.001
ApoE, mg/dl	44 (38, 53)	38 (32, 44)	<0.001
Lp(a), mg/dl	14 (7, 25)	10 (3, 22)	0.03
Uric acid, mg/dl	6.0 (5.3, 6.8)	4.2 (3.4, 5.2)	< 0.001
Glucose homeostasis markers			
Glucose, mg/dl	100 (93, 108)	93 (87, 98)	< 0.001
Insulin	12.2 (10.1, 17.0)	7.6 (5.7, 9.8)	< 0.001
HOMA-IR	3.0 (2.3, 4.5)	1.7 (1.3, 2.3)	< 0.001
QUICKI	0.33 (0.31, 0.34)	0.35 (0.33, 0.37)	< 0.001
Liver enzymes			
AST	22 (18, 26)	19 (17, 23)	< 0.001
ALT	30 (19, 38)	19 (14, 26)	< 0.001
ALP	148 (93, 186)	132 (76, 168)	0.03
γGT	36 (22, 47)	15 (11, 21)	< 0.001
Renal function			
Creatinine, mg/dl	0.99 (0.15)	0.89 (0.15)	< 0.001
eGFR, ml/min/1.73 m^2	82.8 (15.3)	88.2 (15.5)	0.01

Continuous variable are presented as either mean (standard deviation) or median (25th, 75th quartile)

MAFLD metabolic dysfunction-associated fatty liver disease, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *APO* apolipoprotein, *Lp(a)* lipoprotein (a), *HOMA* Homeostatic Model Assessment for Insulin Resistance, *QUICKI* Quantitative Insulin Sensitivity Check Index, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *γGT* gamma glutamyl transferase, *eGFR* estimated glomerular filtration rate

function markers were noted in the subgroup of individuals with MAFLD. Finally, we detected higher levels of white blood cells, ferritin, and fibrinogen in the group of MAFLD (Fig. 2).

3.3 Predictors of MAFLD in Treatment-Naïve Hypertensive Patients

We next examined the association of MAFLD with significantly different variables. Parameters included in the definition of MAFLD were excluded from this analysis. According to our findings, apoE (odds ratio 1.09, 95% confidence interval 1.02–1.17, p = 0.02), uric acid (odds ratio 2.77, 95% confidence interval 1.63–4.70, p < 0.001), and ferritin (odds ratio 1.01, 95% confidence interval 1.00–1.02, p = 0.03) emerged as independent predictors of MAFLD in our study population (Table 3).

Finally, we assessed the diagnostic performance of these parameters regarding the presence of MAFLD through ROC curve analysis (Fig. 3). Uric acid had great diagnostic accuracy (AUROC 0.829, p < 0.001), while apoE (AUROC 0.692, p < 0.001) and ferritin (AUROC 0.738, p < 0.001) had decent diagnostic accuracy. Specifically for uric acid, values above or equal 5.2 mg/dl were indicative of MAFLD with a sensitivity and specificity of 77.6% and 76.3%, respectively.

4 Discussion

In this cross-sectional study, MAFLD was detected in a significant proportion of treatment-naïve, hypertensive patients. According to our results, MAFLD was associated with several demographic and clinical characteristics, such as male sex, SBP, DBP, and pulse pressure. Concerning cardiovascular risk markers, there was a greater magnitude in lipid abnormalities, hyperuricemia, hyperglycemia, insulin resistance, disrupted liver biochemistry, and renal impairment in hypertensives with MAFLD. Moreover, increases in ferritin and fibrinogen were also noted. Finally, we found that uric acid was the most accurate predictor of MAFLD in this population, with the ideal cutoff being ≥ 5.2 mg/dl.

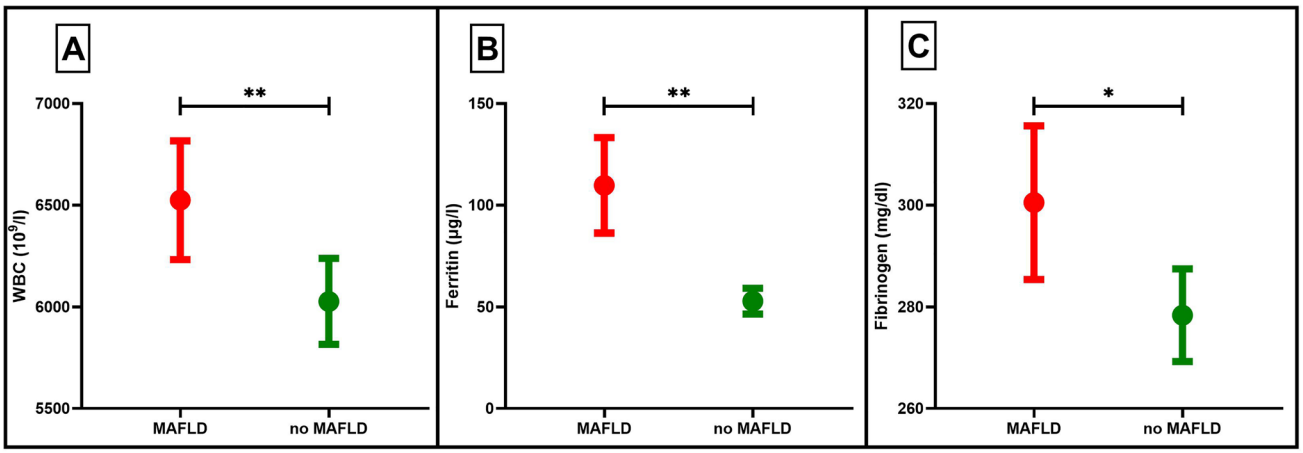

Fig. 2 Differences in **a** white blood cells (WBC), **b** ferritin, and **c** fibrinogen between hypertensive subjects with and without metabolic dysfunction-associated fatty liver disease (MAFLD). Filled circles represent the mean and error bars the 95% confidence intervals. *Statistically significant difference ($p < 0.05$). **Statistically significant difference ($p < 0.001$)

Table 3 Multivariate analysis of the variables associated with metabolic dysfunction-associated fatty liver disease

Variable	Odds ratio (95% CI)	p
Age	1.02 (0.96, 1.09)	0.49
Male sex	0.75 (0.19, 2.94)	0.68
Pulse pressure	1.00 (0.97, 1.04)	0.88
ApoA1	0.98 (0.96, 1.00)	0.98
ApoB	0.99 (0.97, 1.01)	0.44
ApoE	1.09 (1.02, 1.17)	0.02
Lp(a)	1.04 (0.99, 1.08)	0.06
AST	0.95 (0.82, 1.09)	0.42
ALT	1.06 (0.99, 1.12)	0.08
ALP	1.01 (0.99, 1.02)	0.10
Uric acid	2.77 (1.63, 4.70)	<0.001
Ferritin	1.01 (1.00, 1.02)	0.03
WBC	1.00 (0.99, 1.01)	0.99
Fibrinogen	0.99 (0.95, 1.04)	0.31
eGFR	1.00 (0.97, 1.04)	0.82

CI confidence interval, AST aspartate aminotransferase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *γGT* gamma glutamyl transferase, *WBC* white blood cells, *eGFR* estimated glomerular filtration rate

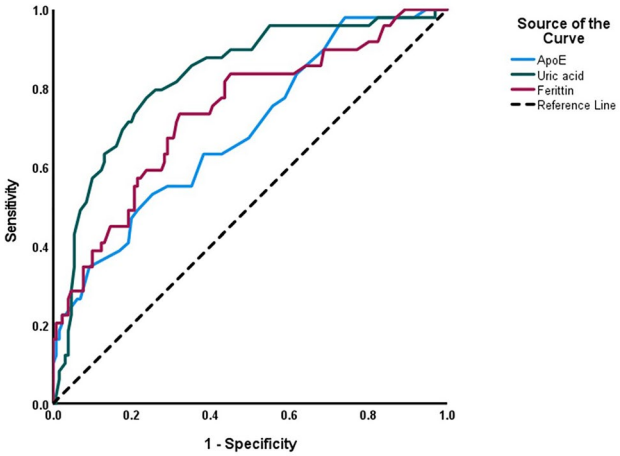

Fig. 3 Receiver operating characteristics curve analysis demonstrating the diagnostic accuracy of apoE, uric acid, and ferritin towards metabolic dysfunction-associated fatty liver disease.

MAFLD, a recently proposed term aiming to better characterize the liver pathology associated with metabolic deregulation, is being thoroughly investigated regarding its hepatic and extrahepatic complications, namely cardiovascular and kidney diseases [16, 17]. It appears that its presence may signify an augmented risk for incident cardiovascular events [18], mandating the need for prompt identification. Recent studies have shown that MAFLD may be a more appropriate prognostic indicator of incident cardiovascular and chronic kidney disease compared to non-alcoholic fatty liver disease (NAFLD) [19–21]. Moreover, medications with pleiotropic effects such as sodium-glucose cotransporter-2 inhibitors [22–24], glucagon-like peptide-1 receptor agonists [25–28], and melatonin [29–31] may even improve this poor prognosis by inducing MAFLD regression, as shown in preclinical and clinical studies.

In our population of hypertensive patients, the prevalence of MAFLD was approximately 29%, which is lower than other reports in different populations [32, 33]. To our knowledge, however, this is the first report of MAFLD prevalence and correlation with risk markers in treatment-naïve hypertensive subjects. The association between MAFLD and arterial hypertension has a strong pathophysiologic basis. Among the common pathways involved are oxidative stress, endothelial dysfunction, and gut dysbiosis

[34–39]. Moreover, the role of inflammation is central, and might be implicated in the risk of poor cardiorenal prognosis surrounding those entities. Inflammation could initiate a deleterious cascade involving promotion of endothelial dysfunction and platelet activation [38, 40, 41], ultimately leading to atherothrombotic complications [42, 43]. In our study, inflammatory markers such as ferritin and fibrinogen were significantly elevated in hypertensive patients with MAFLD compared to those without MAFLD. Ferritin has been associated with incident cardiovascular and renal disease [44–46], while the same could be argued for fibrinogen [47–51].

Significant abnormalities in the extended lipid profile of the hypertensive individuals with MAFLD were also noted, including apoA1, apoB, apoE, and Lp(a). ApoA1 has been found to be a stronger predictor of cardiovascular disease and mortality in elderly men when compared to HDL-C and LDL-C. ApoB measurement may also be superior to conventional dyslipidemia, as its lowering was associated with a greater reduction of major adverse cardiovascular event rate, even after accounting for the reductions in non-HDL-C and LDL-C [52]. Increased apoB was associated with the risk of major adverse cardiovascular events in the Swedish AMORIS cohort study [53]. Moving to Lp(a), it represents a risk factor for cardiovascular disease even at very low levels of LDL-C [54]. Those markers have been implicated also in CKD [55, 56]. On the other hand, apoE, which was found elevated in the subgroup of hypertensive patients with MAFLD, has not been associated with cardiorenal complications [57].

Uric acid appears to be crucial in metabolic dysregulation and has been recently linked with MtS incidence in the study of Cicero et al. of 923 elderly individuals in the Brisighella Heart Study [58]. In fact, serum uric acid may also be considered in the definition of MtS, as it can provide incremental and independent prognostic information [59]. Several reports have additionally highlighted uric acid's importance regarding the incidence of cardiovascular and renal complications, with the landmark URRAH project providing the evidence for lower thresholds in patient risk stratification [60–63]. Concerning MAFLD, serum uric acid has been associated with NAFLD consistently in previous reports, and this association appears to persist in MAFLD [64–67]. Xing et al. reported that uric acid normalized to renal function was an independent predictor of MAFLD in individuals with type 2 diabetes mellitus [68]. Based on the multivariate and ROC curve analysis of our study, uric acid emerged as the most potent predictor of MAFLD in hypertensive participants. Therefore, its measurement may be considered essential in newly diagnosed hypertensive patients, with values exceeding 5.2 mg/dl being indicative of MAFLD presence.

Our study has some limitations. First and foremost, the limited sample size does not allow for safe conclusions to be drawn, while the cross-sectional design is inappropriate for establishing cause-and-effect relationships. Moreover, the incidence of MAFLD in newly diagnosed hypertensive patients could not be determined through this study. Thus, our study serves the purpose of hypothesis generation, and future longitudinal studies should further assess the potential role of MAFLD in the progression of cardiovascular and renal disease. Additionally, as the participants were treatment-naïve, we were not able to evaluate any associations of modern cardiorenal pharmacotherapy with the prevalence of MAFLD. Regarding the definition of MAFLD, the presence of steatosis was defined according to a non-invasive, non-imaging risk score, the FLI, according to the latest MAFLD definition. Therefore, there is a chance for potential misclassification of the study population into the MAFLD and non-MAFLD subgroups. However, FLI is simple to obtain in every day clinical practice and can rule in the presence of ultrasonographic steatosis at a cutoff of ≥ 60 according to the study of Bedogni et al. [14]. We should also state that the FLI-derived MAFLD diagnosis has a moderate agreement with the liver elastography-derived MAFLD diagnosis, as we recently reported in an analysis of the National Health and Nutrition Examination Survey 2017–2020 [69]. As far as the studied markers are concerned, we have not examined other established, non-traditional markers of cardiovascular and renal disease prognosis in this study, such as pulse wave velocity and flow-mediated dilation. Finally, residual confounding on the multivariate associations could be present, thus the results should be interpreted with caution and further studies are required to serve as a validation.

Regarding clinical implications, since MAFLD may be present in a significant proportion of newly diagnosed hypertensive individuals, the measurement of FLI and the application of MAFLD diagnostic criteria in this group of patients could be suggested. Uric acid should be included in the initial investigations and values ≥ 5.2 mg/dl may indicate the coexistence of MAFLD. Future, adequately-sized, prospective studies should validate our results regarding the prevalence of MAFLD in hypertensive individuals and the importance of uric acid as a predictor. Moreover, the knowledge should be extended to novel agents, such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, to determine whether they are efficacious in preventing MAFLD development, halting its progression, or even induce its regression.

5 Conclusions

Metabolic dysfunction-associated fatty liver disease is a frequently encountered comorbidity in newly diagnosed, treatment-naïve hypertensive patients. It is associated with

greater abnormalities in markers of cardiorenal risk including lipid profile, glucose and insulin homeostasis, liver biochemistry, renal function, and inflammatory markers. Uric acid may be the most potent predictor of metabolic dysfunction-associated fatty liver disease in this group of patients, with a cutoff of ≥ 5.2 mg/dl. Future studies are needed to validate our findings and improve our knowledge on this deleterious association.

Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

Research involving human participants The study was approved by the Ethics Committee of the Ioannina University Hospital and was carried out according to the Declaration of Helsinki (1989).

Informed consent All individuals were informed about the aims of the study and provided written informed consent.

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Data availability statement The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions PT interpreted the results and drafted the manuscript. VT conceived and designed the study and revised the manuscript. AV interpreted the results and revised the manuscript. RGK conceived and designed the study, acquired the data, interpreted the results and drafted the manuscript.

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