Association between elevated carotid intima-media thickness and serum uric acid levels among patients with essential hypertension in primary care setting in Sungai Buloh, Malaysia

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Abstract
Aims: Our study aimed to investigate the association between elevated carotid-intima media thickness (CIMT) and serum uric acid (SUA) levels in hypertensive patients attending primary care clinics in Sungai Buloh, Malaysia.

Methods: We conducted a cross-sectional study on 140 hypertensive patients attending outpatient follow-up in two primary care clinics in Sungai Buloh, Malaysia, using a convenient sampling method. SUA levels were measured and divided into four quartiles. Two radiologist specialists performed B mode ultrasonography to assess the thickness of the right and left carotid intima media in all participants.

Results: Participants' mean SUA level was 355.75 ± 0.13. Their mean age was 53.44 (± 9.90), with a blood pressure control of 137.09 ± 13.22/81.89 ± 8.95. Elevated CIMT taken at ≥75th percentile was 0.666 for the left and 0.633 for the right common carotid arteries. By using a hierarchical method of multiple logistic regression, compared with the first quartile of the SUA level as reference group, the odd of elevated CIMT in quartile 4 in the common carotid artery was (OR = 2.00; 95% CI = 0.64-6.27, P = .576) for the right and (OR = 0.62; 95% CI = 0.20-2.00, P = .594) for the left. Waist circumference (P = .001), body mass index (P = .013), triglycerides (P < .001), and high-density lipoprotein cholesterol (P = .001) were significantly associated with the SUA quartiles.

Conclusion: Although there was an increasing trend in the odd of elevated right CIMT across the SUA quartiles, this association, however, was not significant. Preventive effort to tackle the clustering effect of metabolic markers within this study population is needed to reduce the future risk of developing cardiovascular disease.
1 | INTRODUCTION

Hypertension is a known major cause of mortality and morbidity related to cardiovascular disease (CVD). It is ranked first as a risk factor for global disease burden, as quantified by disability-adjusted life years. Malaysia observed a 36% of mortality related to CVDs.

Elevated serum uric acid (SUA) commonly co-exists within adults with hypertension, with a varying prevalence between 14.4% and 26.0%. Findings have consistently identified that elevated SUA predicts the incidence and progression of hypertension. Moreover, increasing levels of SUA have also been implicated for early atherosclerosis changes. A recent study showed an association between increased level of SUA and increased carotid intima-media thickness (CIMT) values in the hypertensive population. The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study has reported that the relationship between the SUA quartiles and CVD events among essential hypertensive participants to be J-shaped. The rate of the CVD events started to increase at a low SUA level, where the lowest distribution of the J-shaped curve was at the second quartile of the SUA level, corresponding to SUA of <4.5 mg/dL (270 µmol/L) and 3.2 mg/dL (192 µmol/L) in male and female hypertensive patients, respectively. Uric acid is an independent risk factor for CVD and modestly increases the risk of coronary heart disease events. Experimental data showed that uric acid contributes towards endothelial dysfunction by promoting proliferation, inflammation, and oxidative stress in vascular smooth muscle cells. The resultant endothelial dysfunction activates the renin-angiotensin system. These pathology processes suggested the plausible role of SUA as a surrogate marker for subclinical atherosclerosis and could compound the future risk for CVD, especially among those with hypertension.

Ultrasound of the CIMT is a reliable, non-invasive method to assess for the presence of subclinical atherosclerosis, and CIMT is now widely used as a surrogate marker for an early atherosclerotic disease. The association between early stages of atherosclerosis evidenced by subclinical atherosclerosis in the large arteries and SUA levels, however, remained controversial.

The International Society of Hypertension Global Hypertension Practice Guidelines recommend performing an additional diagnostic test using SUA in patients with hypertension. Within the resource-limited clinical practice, SUA can serve as an inexpensive test to identify hypertensive patients who are at higher risk, thereby directing them towards further evaluation. In Malaysia, hypertension is one of the top reasons for patient encounters in the public primary care clinics. With CVD disease being one of the leading causes of mortality and morbidity in Malaysia, identifying hypertensive patients with higher risk for CVD provides the best opportunity for improved management of hypertension by reducing risk and preventing the progression towards overt cardiovascular disease.

Lack of evidence limits guidance for the clinicians to decide on whether or not monitoring of SUA levels for early-stage of atherosclerosis would be a useful strategy in reducing the risks for CVD among hypertensive patients. Thus, further exploration is needed to understand the association between early atherosclerosis changes measured by elevated CIMT and the SUA levels in the hypertensive population in the primary care setting.

What’s known
- Carotid-intima-media thickness (CIMT), measured using high-resolution B-mode carotid ultrasonography, is a widely accepted and valid biomarker of subclinical atherosclerosis.
- Subclinical atherosclerosis has been identified among hypertensive patients with an elevated or normal level of serum uric acid (SUA).
- The negative effect of SUA on the vasculature in the development of atherosclerosis via increased level of endothelial damage has been investigated.
- The association between subclinical atherosclerosis in the large arteries and SUA levels on the hypertensive population has provided mixed finding, and studies conducted in outpatient hospital setting among patients with hypertension with a low prevalence of elevated SUA have not found any significant association.

What’s new
- The relative importance of SUA levels and its usefulness as a monitoring tool for detecting subclinical atherosclerosis among the hypertensive population.
- This study provides a reference for the association between elevated carotid intima-media thickness and SUA levels in patients with hypertension receiving their treatment in the primary care setting.

2 | AIM OF THE STUDY

This study aims to determine the association between elevated CIMT and SUA levels among patients with hypertension in primary care clinic settings.

3 | METHODS

3.1 | Study population

This cross-sectional study was conducted in two public primary care clinics located in Sg Buloh, Selangor, Malaysia. Between April and November 2019, researchers approached a total of 245 patients with hypertension attending outpatient hypertension follow-up appointment. The study included a total of 140 participants with essential hypertension based on their documented medical history and laboratory examinations. Inclusion criteria included age ≥30 years, having...
recent (≤3 months) investigation results that included fasting blood glucose, lipid profile, and electrocardiogram (ECG), and were able to attend an ultrasound appointment for CIMT assessment. Blood tests of no more than 3 months were taken as the maximum acceptable time to reflect on current cardio-metabolic state. Interested participants whose tests were longer than 3 months would need to have their tests repeated to be included in the study. We excluded patients on allopurinol, febuxostat, aspirin, diuretic, having gout, diabetes mellitus, cerebrovascular accident, myocardial infarction, peripheral vascular disease, heart failure, autoimmune disorders, cancer, chemotherapy, chronic kidney diseases stages III, IV, and V, glomerulonephritis, and blood pressure (BP) of >180/110 mm Hg during recruitment.

3.2 | Data collection method

The study invited all patients who fulfilled the eligibility criteria to participate in the study. Researchers gave a detailed explanation of the purpose of the study, followed by written informed consent. Following this, participants completed a self-administered questionnaire related to their sociodemographic details. Participants’ clinical data were obtained from the medical notes and transferred onto the questionnaire pro-forma by trained investigators. The pro-forma consisted of questionnaires on age, gender, ethnicity, education level, smoking, marital status, duration of hypertension, immediate family history of premature cardiovascular disease, antihypertensive medications, and cholesterol-lowering medications. Next, participants completed an ECG assessment and a research card was given for their CIMT measurement and SUA blood taking.

3.3 | Anthropometric measurement

Participants’ weight and height were measured in light clothes without shoes to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Measurement of waist circumference (WC) to the nearest 0.1 cm was performed at the umbilical level in the standing position. The BP was measured in the nondominant arm using an automated electronic sphygmomanometer (OMRON Model HEM-7130, Kyoto, Japan) twice with a 1-minute interval after at least 5 minutes of rest in the seated position.

3.4 | Biochemical measurements

Participants at the clinics routinely had their blood tests done according to predefined protocols. Overnight fasting blood samples were withdrawn from the antecubital vein the following morning between 08.00 AM and 10.00 AM. SUA levels were measured with Uricase-POD enzymatic colorimetric method using an auto-analyser (Beckman Caukter, Inc Diagnostic Division, CA, USA). Elevated level of SUA was defined as SUA levels >420 μmol/L (for male and postmenopausal woman) and >360 μmol/L (for the premenopausal woman). The fasting blood glucose levels were measured according to the hexokinase glucose-6-phosphate dehydrogenase method on an auto-analyser (Beckman Caukter, Inc Diagnostic Division, CA, USA). The fasting serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum creatinine levels were measured using oxidade-peroxidase method on the auto-analyser (Beckman Caukter, Inc Diagnostic, CA, USA). Calculation of the estimated glomerular filtration rate (eGFR) was based on the equation formula from the Chronic Kidney Disease Epidemiology Collaboration. Stage III, IV, and V chronic kidney diseases were defined as eGFR between 30 to 59, 15 to 29, and <15 mL/min per 1.73 m², respectively.

3.5 | Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) was estimated from a 12-lead ECG using the Sokolov-Lyon criteria that defined LVH as the voltage amplitude sum of S wave depth in V1 and maximum R wave in either V5 or V6 to be ≥3.5 mV.

3.6 | Carotid ultrasonography

The study used high-resolution B-mode carotid ultrasonography to assess CIMT level in all participants, using Philips IU22 Ultrasound machine (Bothell, WA, USA) with 9 to 3 MHz (L9-3) broadband linear array transducer. Two radiologist specialists (MFH and RFAK), blinded to the clinical status of the participants, conducted a detailed examination of the common carotid arteries and carotid bulbs. The far walls of the artery at 1, 2, and 3 cm from the distal CCA/bulb junction were measured. The ultrasound located the CIMT as the distance between the lumen-intima and media-adventitia interfaces. The averages of three CIMT measurements for both left and right carotid arteries were independently computed. There was good inter-observer agreement on the first 13 patients, evident by intra-class correlation between inter-observer of 0.814 (95% CI: 0.393, 0.943) for right carotid intima and 0.721 (95% CI: 0.521, 0.916) for left carotid intima.

3.7 | Elevated CIMT

In this study, we defined elevated CIMT at ≥75th percentile, as the upper limit of normal across age, gender, and race/ethnicity, indicating the presence of subclinical atherosclerosis and increased CVD risk.

3.8 | Metabolic syndrome

Presence of metabolic syndrome was based on the International Diabetes Federation (IDF) definition of metabolic syndrome.
3.9 | Sample size

Tavil et al.\textsuperscript{22} found the mean of bilateral CIMT in normouricaemic hypertensive patients to be at 0.70 ± 0.14 mm and the mean of bilateral CIMT in uricaemic hypertensive patients to be 0.57 ± 0.16 mm. By taking $\alpha = 0.05$, the estimated difference from the population mean of 0.03 and a standard deviation of 0.14, the minimum sample needed in this study was 83. The minimum sample required was 130 after adjusting for 20% attrition rate.

3.10 | Statistical analysis

Statistical analysis of the collected data was performed using Statistical Package for Social Sciences (SPSS) version 23 (SPSS, Inc, Chicago, IL, USA). A descriptive analysis on normally distributed data was presented in ± SD, and non-normally distributed data were expressed in median and interquartile range (IQR). The SUA level was ordered into quartiles in the entire study population. Frequency and percentage were used for categorical data. The $P$ values of the trends in the differences across the uric acid quartiles were analysed using analysis of variance for trends for clinical parameters with continuous variables and Chi-square linear-by-linear association for the categorical variables. Unadjusted and adjusted backward hierarchical method of multiple logistic regression was performed to ascertain the odds of having an elevated CIMT according to the SUA quartiles.

The dichotomous variables for CIMT status were defined as 0 for non-elevated CIMT and 1 for elevated CIMT. Statistical significance was accepted as $P$ value $< 0.05$.

4 | RESULTS

Out of 199 eligible participants, 140 results were analysed. The response rate was 70.3%. Participants’ sociodemographic and baseline clinical characteristics are described in Tables 1 and 2, respectively. Participants’ mean age was 53.44 ± 9.90 years with a mean BP reading of 137.09 ± 13.22/81.89 ± 8.95 mm Hg. Most participants had stage 1 hypertension status, $n = 66$ (47.1%), followed by stage 2, $n = 50$ (35.7%). Less than one third was at stage 3 hypertension $n = 24$ (17.1%). The duration of hypertension of the study participants ranges from 1 to 26 years with a mean duration of 5.54 ± 5.09 years.

The mean SUA level was 345.75 ± 85.06. Prevalence of elevated SUA was 25.7%. The mean CIMT was 0.60 ± 0.13 for the left and 0.56 ± 0.12 for the right. At ≥75th percentile of the CIMT, the cut-off definition value for elevated CIMT in this study sample was 0.633 mm for the right and 0.666 mm for the left. A total of 39 (27.8%) of participants had elevated right CIMT, while a total of 43 (31.0%) had elevated left CIMT. The majority were on at least one antihypertensive, and calcium channel blocker was the most commonly prescribed antihypertensive, $n = 106$ (75.7%). Out of the 121 participants who had ECG assessments, two participants met the LVH diagnostic criteria. More than half of our studied population, $n = 79$ (54.3%), had metabolic syndrome based on IDF criteria.\textsuperscript{21} More than half of the participants $n = 80$ (57.1%) were on simvastatin.

4.1 | Clinical characteristics of participants across the SUA quartiles

Table 3 described the clinical characteristics of the participants to the quartiles of SUA levels. The WC ($P = .001$), BMI ($P = .013$), and
| Baseline clinical characteristics | Frequency, (N = 140), n (%) | Mean ± SD/median (IQR) |
|----------------------------------|----------------------------|------------------------|
| Serum uric acid (μmol/L)         |                            | 345.75 ± 85.06         |
| Mean left CIMT (mm)              |                            | 0.60 ± 0.13            |
| Mean right CIMT (mm)             |                            | 0.56 ± 0.12            |
| Elevated CIMT (≥75th percentile) |                            |                        |
| Elevated left CIMT (≥0.666 mm)   | 43 (31.0)                  | 0.73 (IQR = 0.67-0.80) |
| Elevated right CIMT (≥0.633 mm)  | 39 (27.8)                  | 0.78 (IQR = 0.65-0.77) |
| Metabolic syndrome               | 76 (54.3)                  |                        |
| Height (cm)                      |                            | 1.61 ± 0.09            |
| Weight (kg)                      |                            | 74.45 ± 14.96          |
| Body mass index (kg/m²)          |                            | 28.93 ± 4.79           |
| Waist circumference (cm)         |                            | 93.68 ± 10.20          |
| Systolic blood pressure (mm Hg)  |                            | 137.09 ± 13.22         |
| Diastolic blood pressure (mm Hg) |                            | 81.89 ± 8.95           |
| Triglyceride (mmol/L)            |                            | 1.37 ± 0.78            |
| High-density lipoprotein (mmol/L)|                            | 1.27 ± 0.33            |
| Low-density lipoprotein (mmol/L) |                            | 3.40 ± 0.99            |
| Total cholesterol (mmol/L)       |                            | 5.14 ± 0.96            |
| Fasting blood glucose (mmol/L)   |                            | 5.21 ± 0.62            |
| Duration of hypertension         |                            | 5.54 ± 5.09            |
| Hypertensive stage               |                            |                        |
| Stage 1                          | 66 (47.1)                  |                        |
| Stage 2                          | 50 (35.7)                  |                        |
| Stage 3                          | 24 (17.1)                  |                        |
| ECG status (n = 121)             |                            |                        |
| Left ventricular hypertrophy     | 2 (1.7)                    |                        |
| No left ventricular hypertrophy  | 119 (98.3)                 |                        |
| Family history of premature cardiovascular disease |                   |                        |
| Yes                              | 30 (21.4)                  |                        |
| No                               | 110 (78.6)                 |                        |
| On calcium channel blocker       |                            |                        |
| Yes                              | 106 (75.7)                 |                        |
| No                               | 34 (24.3)                  |                        |
| On angiotensin-converting enzyme inhibitors | |                        |
| Yes                              | 43 (30.7)                  |                        |
| No                               | 97 (69.3)                  |                        |
| On angiotensin II receptor blocker |                        |                        |
| Yes                              | 13 (9.3)                   |                        |
| No                               | 127 (90.7)                 |                        |
| On beta-blocker                  |                            |                        |
| Yes                              | 11 (7.9)                   |                        |
| No                               | 129 (92.1)                 |                        |
| On cholesterol lowering medications |                        |                        |
| Simvastatin                      | 80 (57.1)                  |                        |
| Atorvastatin                     | 19 (13.6)                  |                        |
| Others                           | 1 (0.7)                    |                        |
| No medication                    | 40 (28.6)                  |                        |

Abbreviations: CIMT, carotid-intima media thickness; IQR, interquartile range.
TG ($P < .001$) showed a significant increase in linear trend across the SUA quartiles, while HDL-C ($P = .001$) showed a significant decrease in linear trend across the SUA quartiles. Figures 1 and 2 illustrate the trend of the mean CIMT across the SUA quartiles. The mean CIMT trend across the SUA quartiles was similar for both the left and the right CIMT. The mean CIMTs increased from quartile 1 to quartile 2, decreased from quartile 2 to quartile 3, and increased again from quartile 3 to quartile 4. The mean CIMT values from quartile 1 to quartile 4 were $(0.56 \pm 0.11, 0.57 \pm 0.15, 0.54 \pm 0.13, 0.60 \pm 0.11)$ mm in the right (Figure 1) and $(0.59 \pm 0.12, 0.62 \pm 0.15, 0.58 \pm 0.14$ and $0.61 \pm 0.14$) mm in the left (Figure 2).

### 4.2 | Association between elevated CIMT and SUA quartiles

Table 4 summarises the association of elevated CIMT level and SUA quartiles. All continuous independent variables were found to be linearly related to the logit of the dependent variable. There was one standardised residual with a value of $-3.068$ standard deviation, which was inspected for unusual observation and was kept in the analysis. There were no interaction and multicollinearity problem. The model reasonably fits well. Step-adjusted models were applied to evaluate the odds of having an elevated CIMT in the different uric acid quartiles, with quartile one serving as the referent group.

| TABLE 3 | Clinical characteristics of the participants by quartile of the distribution of serum uric acid quartiles |
|----------|---------------------------------------------------------------------------------------------------|
|          | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile | P value for trend |
| Number of subject (n) | 35 | 35 | 35 | 35 | |
| Uric acid level (μmol/L) | <289 | 289-342 | 343-398 | >398 | |
| Mean right CIMT (mm) | 0.56 ± 0.11 | 0.57 ± 0.15 | 0.54 ± 0.13 | 0.58 ± 0.10 | .656 |
| Mean left CIMT (mm) | 0.59 ± 0.12 | 0.62 ± 0.15 | 0.58 ± 0.14 | 0.61 ± 0.14 | .989 |
| Elevated left CIMT (≥0.666 mm) (n [%]) | 10 (28.6) | 12 (32.3) | 9 (25.7) | 12 (34.3) | .866 |
| Elevated right CIMT (≥0.633 mm) (n [%]) | 9 (25.7) | 10 (25.8) | 7 (20.0) | 13 (37.1) | .477 |
| Age (y) | 55.25 ± 8.25 | 52.24 ± 10.54 | 53.40 ± 9.89 | 52.77 ± 11.26 | .398 |
| Smoking [n (%)] | 3 (8.8) | 3 (8.8) | 5 (14.3) | 7 (20.0) | .111 |
| Duration of hypertension (y) | 5.18 ± 5.03 | 6.15 ± 5.89 | 6.09 ± 5.10 | 4.76 ± 4.33 | .742 |
| Body mass index (kg/m²) | 27.03 ± 4.14 | 29.14 ± 4.21 | 29.87 ± 5.28 | 29.73 ± 5.05 | .013 |
| Waist circumference (cm) | 89.76 ± 9.53 | 92.50 ± 9.12 | 95.40 ± 11.18 | 97.11 ± 9.64 | .001 |
| Systolic blood pressure (mm Hg) | 137.11 ± 11.21 | 136.38 ± 13.77 | 138.26 ± 16.00 | 136.57 ± 11.94 | .982 |
| Diastolic blood pressure (mm Hg) | 80.06 ± 8.34 | 82.56 ± 9.19 | 81.40 ± 9.16 | 83.60 ± 9.10 | .158 |
| Triglyceride (mmol/L) | 1.16 ± 0.61 | 1.14 ± 0.55 | 1.46 ± 0.77 | 1.73 ± 0.98 | <.001 |
| High density lipoprotein (mmol/L) | 1.40 ± 0.27 | 1.27 ± 0.41 | 1.27 ± 0.32 | 1.13 ± 0.25 | .001 |
| Low density lipoprotein (mmol/L) | 3.24 ± 0.92 | 3.34 ± 1.17 | 3.49 ± 0.91 | 3.52 ± 0.96 | .183 |
| Total cholesterol (mmol/L) | 5.11 ± 0.98 | 5.02 ± 1.12 | 5.24 ± 0.85 | 5.20 ± 0.88 | .514 |
| Fasting blood glucose (mmol/L) | 5.20 ± 0.69 | 5.19 ± 0.56 | 5.17 ± 0.59 | 5.29 ± 0.66 | .609 |
| Antihypertension medication use [n (%)] | 34 (94.4) | 33 (97.1) | 33 (94.3) | 30 (85.7) | .140 |
| Antilipidaemic medication use [n (%)] | 25 (69.4) | 25 (73.5) | 24 (68.6) | 25 (74.3) | .776 |
| Menopause [n (%)] | 14 (45.2) | 15 (62.5) | 9 (56.3) | 3 (50.0) | .539 |

Note: The data are presented as the mean standard deviation or number (percentage). The $P$ values of the trends in the differences across the uric acid quartiles were analysed using analysis of variance for trends for continuous variable and Chi-square linear-by-linear association for the categorical variables.

Abbreviation: CIMT, carotid-intima media thickness.

* $P < .05$. 

MOHD NASIR ET AL.
The logistic regression model did not observe a significant linear trend between elevated CIMT and SUA quartiles \((P = .576)\). This trend remained nonsignificant when confounding factors were grouped and controlled in hierarchical logistic models. In an unadjusted logistic regression model 1, compared with the first quartile of the SUA level, the right common carotid artery in quartile 4 showed a higher odds of an elevated CIMT \((OR = 2.00; 95\% \text{ CI } = 0.64-6.27, P = .576)\), while the left CIMT in quartile 4 showed a lower odds of having an elevated CIMT \((OR = 0.62; 95\% \text{ CI } = 0.20-2.00, P = .594)\).

The association between SUA quartiles and elevated CIMT remained nonsignificant after controlling for potential confounders in the hierarchical logistic regression models 2, 3, and 4. When adjusted for age and smoking (model 2), compared with the first quartile of the SUA level, the right CIMT in quartile 4 showed a higher odds of an elevated CIMT \((OR = 2.00; CI = 0.64-6.27, P = .576)\), while the left CIMT in quartile 4 showed a lower odds of having an elevated CIMT \((OR = 0.59; 95\% CI = 0.17-2.00, P = .501)\).

When adjusted for age, smoking, menopause, hypertension medication, and antilipidaemic medication (model 3), compared with the first quartile of the SUA level, the right CIMT in quartile 4 showed a higher odds of an elevated CIMT \((OR = 2.00; CI = 0.64-6.27, P = .576)\), while the left common carotid artery in quartile 4 showed a lower odds of having an elevated CIMT \((OR = 0.47; 95\% CI = 0.04-6.32, P = .714)\).

When adjusted for age, smoking, menopause, hypertension medication, and antilipidaemic medication, WC, SBP, DBP, HDL, LDL, TG, and FBS (model 4), compared with the first quartile of the SUA level, the right CIMT in quartile 4 showed a higher odds of an elevated CIMT \((OR = 3.01; CI = 0.22-41.84, P = .77)\), while the left CIMT in quartile 4 showed a lower odds of having an elevated CIMT \((OR = 0.15; 95\% CI = 0.01-4.64, P = .652)\).
findings showed that CIMT level was significantly associated with 8 of 11 The present study assessed whether elevated CIMT was associated with SUA levels among patients with hypertensive without known cardiovascular diseases such as stroke and myocardial infarction in primary care setting. Although this study observed an increased odds of having elevated right CIMT level in SUA quartile 4 as compared with SUA quartile 1, the study did not find it to be statistically significant.

The absence of an association between subclinical atherosclerosis as measured by elevated CIMT and SUA levels in our study sample should be addressed. Several studies had found elevated SUA to be significantly associated with subclinical atherosclerosis among the hypertensive population. Both Tavil et al and Elsayed et al found in their studies that CIMT level was statistically higher among the hypertensive population with elevated SUA when compared with a control group with normal blood pressure and normal SUA. These results were also supported by Mutluay et al whose findings showed that CIMT level was significantly associated with hyperuricemia in hypertensive subjects as compared with hypertensive subjects without elevated SUA, even after controlling for metabolic and clinical factors. Several plausible suggestions had been proposed for this association, which could be attributed by the adverse effect SUA had on the vasculature in the development of atherosclerosis via increasing endothelial dysfunction in hypertensive patients.

In contrast, other cross-sectional studies had failed to demonstrate the association between CIMT and SUA among the hypertensive population, with a low prevalence of elevated SUA. Cipolli et al conducted a study among hypertensive patients attending an outpatient clinic in a university setting in Brazil with a normal mean value for the SUA level. When they compared between the patients’ elevated and normal SUA levels, they did not find a significant association between CIMT and SUA level in either men or women’s group. Similarly, Cuspidi et al recruited never-treated grade-1 and grade-2 hypertensive patients with a low prevalence of elevated SUA (12.5% in male and 2.5% in female) in a hospital outpatient clinic observed a negligible association between CIMT and SUA after multivariate analyses.

Similar to the above studies, we did not find a significant association between subclinical atherosclerosis using CIMT and SUA levels among hypertensive patients treated in the primary care setting. The reason could be attributable to the fact that participants in this study had an average mean of SUA at 345.75 ± 85.06, reflecting a normal level of SUA. Additionally, other reasons for this could be that our study had screened out the presence of other independent cardiovascular risk factors such as myocardial infarction, stroke, type 2 diabetes mellitus, peripheral vascular disease, renal impairment, and autoimmune disease. Thus, our study population has lower compounded risks for CVD. Another plausible explanation could be attributed to blood pressure control. The mean blood pressure level among our study populations is within the high-normal

### TABLE 4 The association of elevated CIMT and serum uric acid quartiles

| Side | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile | P value for trend |
|------|-------------|-------------|-------------|-------------|-----------------|
| Right CIMT | Model 1: Unadjusted | 1 | 1.54 (0.47, 5.02) | 1.03 (0.30, 3.58) | 2.00 (0.64, 6.27) | .576 |
| | Model 2: Adjusted for age and smoking | 1 | 1.54 (0.47, 5.02) | 1.03 (0.30, 3.58) | 2.00 (0.64, 6.27) | .576 |
| | Model 3: Adjusted for menopause, hypertension medication, and antilipidaemic medication based on Model 2 | 1 | 1.54 (0.47, 5.02) | 1.03 (0.30, 3.58) | 2.00 (0.64, 6.27) | .576 |
| | Model 4: Adjusted for WC, SBP, DBP, HDL, LDL, TG, and FBS based on Model 3 | 1 | 1.68 (0.39, 7.23) | 1.01 (0.20, 5.14) | 3.01 (0.22, 41.84) | .776 |
| Left CIMT | Model 1: Unadjusted | 1 | 1.30 (0.45, 3.76) | 0.75 (0.25, 2.30) | 0.62 (0.20, 2.00) | .594 |
| | Model 2: Adjusted for age and smoking | 1 | 1.40 (0.47, 4.17) | 0.73 (0.23, 2.33) | 0.59 (0.17, 2.00) | .501 |
| | Model 3: Adjusted for menopause, hypertension medication, and antilipidaemic based on Model 2 | 1 | 1.27 (0.34, 4.71) | 0.52 (0.10, 2.52) | 0.47 (0.04, 6.32) | .714 |
| | Model 4: Adjusted for WC, SBP, DBP, HDL, LDL, TG, and FBS based on Model 3 | 1 | 0.74 (0.15, 3.74) | 0.41 (0.07, 2.45) | 0.15 (0.01, 4.64) | .652 |

Note: Model 1: Unadjusted. Model 2: Adjusted for age and smoking. Model 3: Further adjusted for menopause, hypertension medication, and antilipidaemic medication. Model 4: Further adjusted for WC, SBP, DBP, HDL, LDL, TG, and FBS. Abbreviations: CI, confidence interval; CIMT, carotid-intima media thickness; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

5 | DISCUSSION

The present study assessed whether elevated CIMT was associated with SUA levels among patients with hypertensive without known cardiovascular diseases such as stroke and myocardial infarction in primary care setting. Although this study observed an increased odds of having elevated right CIMT level in SUA quartile 4 as compared with SUA quartile 1, the study did not find it to be statistically significant.

The absence of an association between subclinical atherosclerosis as measured by elevated CIMT and SUA levels in our study sample should be addressed. Several studies had found elevated SUA to be significantly associated with subclinical atherosclerosis among the hypertensive population. Both Tavil et al and Elsayed et al found in their studies that CIMT level was statistically higher among the hypertensive population with elevated SUA when compared with a control group with normal blood pressure and normal SUA. These results were also supported by Mutluay et al whose findings showed that CIMT level was significantly associated with hyperuricemia in hypertensive subjects as compared with hypertensive subjects without elevated SUA, even after controlling for metabolic and clinical factors. Several plausible suggestions had been proposed for this association, which could be attributed by the adverse effect SUA had on the vasculature in the development of atherosclerosis via increasing endothelial dysfunction in hypertensive patients.

In contrast, other cross-sectional studies had failed to demonstrate the association between CIMT and SUA among the hypertensive population, with a low prevalence of elevated SUA. Cipolli et al conducted a study among hypertensive patients attending an outpatient clinic in a university setting in Brazil with a normal mean value for the SUA level. When they compared between the patients’ elevated and normal SUA levels, they did not find a significant association between CIMT and SUA level in either men or women’s group. Similarly, Cuspidi et al recruited never-treated grade-1 and grade-2 hypertensive patients with a low prevalence of elevated SUA (12.5% in male and 2.5% in female) in a hospital outpatient clinic observed a negligible association between CIMT and SUA after multivariate analyses.

Similar to the above studies, we did not find a significant association between subclinical atherosclerosis using CIMT and SUA levels among hypertensive patients treated in the primary care setting. The reason could be attributable to the fact that participants in this study had an average mean of SUA at 345.75 ± 85.06, reflecting a normal level of SUA. Additionally, other reasons for this could be that our study had screened out the presence of other independent cardiovascular risk factors such as myocardial infarction, stroke, type 2 diabetes mellitus, peripheral vascular disease, renal impairment, and autoimmune disease. Thus, our study population has lower compounded risks for CVD. Another plausible explanation could be attributed to blood pressure control. The mean blood pressure level among our study populations is within the high-normal
blood pressure category, suggesting a reasonable BP control. A good BP control could provide a more relevant explanation for the nonsignificant association between SUA and CIMT observed in this study, as blood pressure control is independent with a linear relationship for CVD risk.

Moreover, we also found a high prevalence of metabolic syndrome in our study population of n = 79 (54.3%). Metabolic syndrome was defined by the presence of a cluster of central obesity, raised BP, dyslipidaemia, and glucose impairment. The clustering of symptoms in metabolic syndrome puts patients at increased risk to develop cardiovascular disease and diabetes. In our study, metabolic syndrome was present in 47.4% of men and 52.6% of women. Two essential findings were drawn from the present study. Firstly, we observed that BMI, WC, and TG to steadily increased across the SUA quartiles, and secondly, we observed a significant inverse association with HDL-C. Our study findings are in line with previous studies that showed a positive association between SUA and adiposity such as overweight and obesity. Zaki et al. in a cross-sectional study among Egyptian women also reported that BMI and waist-to-hip ratio to be correlated with metabolic syndrome. Among studies conducted in Asia, BMI\(^2\rangle9\) and central obesity\(^{30}\) have been associated with SUA among adults.

With regard to lipids, similar to our study findings, some studies reported SUA levels to be positively related to TG and negatively with HDL-C.\(^{30-32}\) Several studies have found hyperuricaemia to be associated with raised TG levels. A retrospective cohort study conducted among adults attending regular health check-up in a hospital setting in China found that the incidence of hyperuricaemia is increased with higher TG levels. An increase in TG storage led to increased free fatty acid production.\(^{33}\) Increasing level of TG is associated with an increased incidence of hyperuricaemia, and the authors suggested that there could be a role in lowering TG levels to reduce the risks of hyperuricaemia.\(^{34}\) Additionally, studies have consistently found the inverse association between HDL-C and SUA.\(^{30}\) Reduction in HDL-C is multifactorial and can be contributed by changes in biochemical and metabolic in the obesity state.\(^{35}\) Low levels of HDL-C are associated with high cardiovascular risk.\(^{26}\)

## 5.1 Strength and limitations

As far as the researchers are concerned, this was the first local study conducted in a primary care setting in Malaysia, explicitly studying participants with hypertension without other known cardiovascular diseases such as stroke and myocardial infarction. It adds on to the current body of knowledge on the current controversial literature on the association between subclinical atherosclerosis measured using elevated CIMT and SUA levels in the hypertensive patients. However, this study has several limitations. The cross-sectional study design precluded analysis of cause-effect relationships. Secondly, convenient sampling may predispose this study to selection bias. However, measures were taken to reduce the sampling bias by including only hypertensive and excluding stroke and CVD participants and ensuring every hypertensive patient listed on the chronic disease clinic registry during the data collection days was approached for participation. Thirdly, the participants were mainly Malay in ethnicity. Hence, the results may not be generalisable to other ethnic groups and other populations. Therefore, the present results might not be representative of the general hypertensive population. Moreover, in this study, duration of high blood pressure was not included as a confounder. Many other cardiovascular risk factors can accumulate in patients with hypertension, and we cannot exclude the possibility of unmeasured confounding factors that might affect the association between elevated CIMT and SUA levels. Prospective population-based studies would be recommended to clarify the associations of elevated CIMT and SUA levels in hypertension patients.

### 6 Conclusion

This study did not find a significant association between elevated CIMT and SUA levels among hypertensive patients without other cardiovascular comorbidities such as stroke or myocardial infarction. These results may indicate that elevated CIMT was not associated with SUA levels among our study samples who have essential hypertension, but its association remained to be explored. The clustering effect of metabolic biomarkers among our hypertensive population placed them at a higher risk of developing CVD. In light of the importance of early detection and prevention of atherosclerosis, controlling the metabolic biomarkers is essential for avoiding future cardiovascular risks.

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### Disclosures

The authors declare that they have no competing interest.

### Author Contributions

MZMN, KAM, MRI, and MFH designed the clinical study, with the assistance of RFAK. MAMN did the data collection. MZMN, MRI, KAM, and MFH designed the statistical analysis, and all authors interpreted the data. MZMN and KAM wrote the first draft. All authors had been involved in the further drafting of the manuscript and revising it critically for valuable intellectual content, and have approved the final version to be published.

### Ethical Statement

The study received ethical approval from the Medical Research & Ethics Committee, Ministry of Health Malaysia.
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