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ORIGINAL STUDY

Blood biomarkers for new-onset hypertension in midlife women: a nested case-control study

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Abstract

Objective: Midlife in women is associated with an increase in prevalence of hypertension. Little is known on the risk factors of new-onset hypertension among middle-aged women.

Methods: In this nested case-control study, 1,430 women aged 40 to 60 years with repeated physical examinations between 2009 and 2019 were recruited. Data included age, body mass index, blood pressure (BP), and a series of blood biomarkers. Participants with hypertension were divided into two case-control samples: 388 cases with *episodic* new-onset hypertension (ie, one normal BP at the first visit and one abnormal BP during follow-up) each with two age-matched controls (n = 776) and 151 cases with *regular* new-onset hypertension (ie, normal BP at the first two visits and abnormal BP at two or more follow-up visits) each with three age-matched controls (n = 453). Multivariable-adjusted logistic regression was used to analyze the data.

Results: Our data showed very consistent results for episodic and regular new-onset hypertension, respectively, and verified known associations (odds ratio [95% confidence interval], per SD increase) with obesity (body mass index, 1.72 [1.49-1.98] and 1.81 [1.45-2.26]), inflammation (white blood cell count, 1.39 [1.23-1.58] and 1.38 [1.13-1.69]), and metabolic dysregulation (triglycerides, 1.25 [1.09-1.44] and 1.31 [1.08-1.58]; glucose, 1.46 [1.23-1.73] and 1.27 [1.05-1.54]) but, more surprisingly, also revealed positive associations with red blood cell count (1.27 [1.11-1.44] and 1.38 [1.14-1.68]), hemoglobin (1.18 [1.03-1.35] and 1.31 [1.05-1.64]), and platelet count (1.39 [1.20-1.61] and 1.33 [1.09-1.63]).

Conclusions: In addition to obesity and metabolic dysregulation, increased hemoglobin and counts of platelets, and red and white blood cells are associated with hypertension in this period. Future study may verify whether these associations are causal in nature and whether these variables are useful in risk stratification.

Key Words: Hemoglobin – New-onset hypertension – Platelet – Red blood cell – White blood cell.

Hypertension (HTN) is an important risk factor for heart disease and stroke.[1,2] Globally, 26.1% of adult women and 26.6% of adult men in the year 2000 suffered from HTN, and the prevalence of HTN among women was projected to be higher than that of men by 2025.[3]

The prevalence of HTN in women is lower than in men before the age of 60 years, but this trend changes after age 60 years during which the prevalence of HTN is higher in women than in men; thus, a relative increase in HTN in midlife women is observed.[4] Midlife in women refers to perimenopause, the time before

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Authors Contributions: ZH contributed to study design, data collection, and statistical analysis and drafted the manuscript. PY, QL, and RW organized and performed medical examination and provided research data. FZ and YW contributed to data collection and collation. C.H.L.T. contributed to statistical analysis and modified the manuscript. H.S. and Q.Z. contributed to project design, and supervised and revised the manuscript. Q.Z. provided financial support. All authors read and approved the final manuscript.

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menopause, when the endocrine, biological, and clinical characteristics of menopause commence, and the first year after the last menstrual period.[5,6] During this period, blood pressure (BP) is normal in most women, but it will increase among many of them for the first time. Indeed the increase in HTN prevalence in perimenopause is more obvious than in the periods before and after.[7] The prevalence of HTN in midlife women has been reported as high as 37.8% in a sample of US women.[8] In research based on Korean women, hypertensive prevalence was 24.4% in menopausal women (no menstruation for more than 3 mo) compared with 16.7% in nonmenopausal women.[9] Very few studies, however, did specifically investigate risk factors for HTN in this particular group of women. A series of studies set in Poland that included women aged 40 to 60 years with newly diagnosed HTN explored the role of adipocytokines,[10] and insulin-like growth factor–binding protein 2[11] in these participants. One limitation of their studies was that they could not distinguish between cases with newly diagnosed HTN and those with preexisting (previously undiagnosed) HTN, as longitudinal follow-up data were lacking. Interestingly, one retrospective study based on 1,502 women aged 42 to 53 years found that body mass index (BMI) and metabolic syndrome were risk factors of HTN during this period rather than menopause itself.[9] Nonetheless, the specific determinants of new-onset HTN in midlife women remain largely unknown.

Aim of the current study was therefore to investigate a range of potential determinants of new-onset HTN during midlife. To this end, we conducted a nested case-control study of 1,430 women, recruited from a larger cohort of women aged 40 to 60 years who had data on a wide range of clinical measures and blood biomarkers from at least two of their physical examinations as part of a regular health checkup between 2009 and 2019. Abbreviations and detailed information on blood indices are shown in Supplemental Digital Table 1, http://links.lww.com/MENO/B55.

METHODS

Study participants

The participants were female employees aged 40 to 60 years from a variety of companies and institutions in Shantou, China, who are offered free medical checkups once a year. We retrospectively collected data of this regular physical examination from Chenghai People's Hospital and the First Affiliated Hospital of Shantou University Medical College. Figure 1 shows a flowchart of inclusion criteria and design of the study. In this nested case-control study, we compared potential determinants of HTN between cases and controls using data of their first (baseline) visit before the onset of HTN: that is, on average, 3.07 years before HTN onset for episodic HTN (median follow-up time, 5 y) and 3.04 years before HTN onset (first abnormal BP) for regular HTN (median follow-up time, 6 y). This nested case-control design was possible because most women had substantial numbers of follow-up visits. For example, in both control groups, 47% of participants had at least four visits (see Supplemental Digital Table 2, http://links.lww.com/MENO/B55, which shows number of follow-up visits for regular/episodic new-onset HTN cases and controls). Women with HTN were divided into two groups: cases with episodic new-onset HTN and with regular new-onset HTN according to standard definitions from the literature.[12] The available longitudinal data allowed us to define a milder (prestage) HTN phenotype, which we called episodic new-onset HTN (ie, one normal BP [<140/90 mm Hg] at the first visit and one abnormal BP [≥140/90 mm Hg] during follow-up). Regular new-onset HTN was assigned when having normal BP (<140/90 mm Hg)

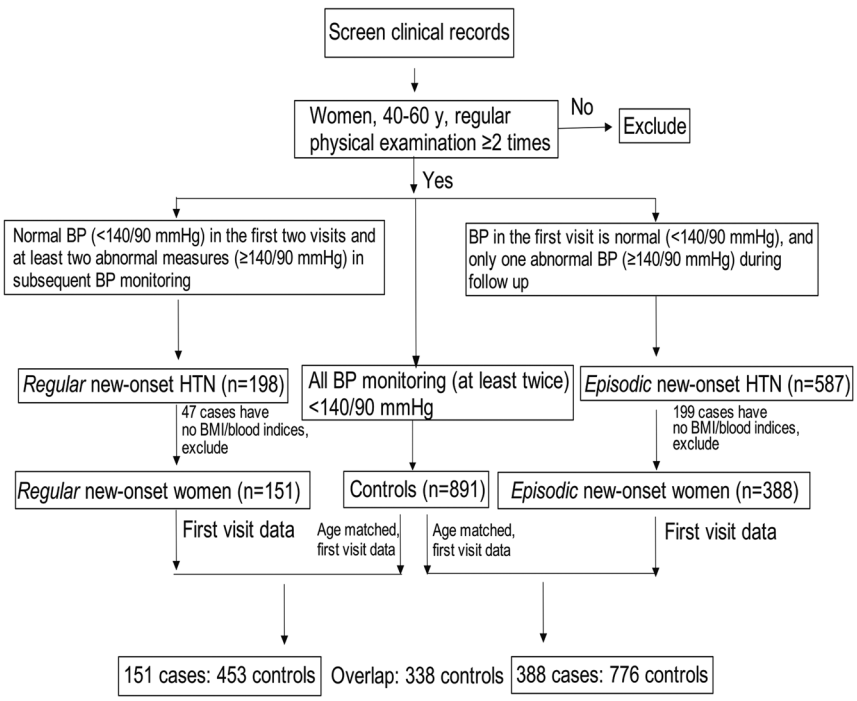

FIG. 1. Flowchart of subject selection and design of this study. BP, blood pressure; HTN, hypertension.

values in the first two visits and at least two abnormally high measurements (≥140/90 mm Hg) in the subsequent BP monitoring during follow-up. Controls were those women aged 40 to 60 years with all BP measurements (at least two) less than 140/90 mm Hg. To optimize power, we selected three age-matched controls for each regular new-onset case and two age-matched controls for each episodic new-onset case from the total pool of 891 eligible controls (Fig. 1). Rather than using survival analysis, we used this nested case-control design with age matching to analyze the data, as we did not have accurate time to event data for the onset of (episodic and regular) HTN. Thus, data from a total of 151 regular new-onset HTN and 453 age-matched controls (±2 y) and 388 episodic new-onset HTN and 776 age-matched controls (±2 y) were retrieved. The two control groups had 338 participants in common (Fig. 1). This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol of this study was approved by the Ethics Committee of Shantou University Medical College. Given the retrospective nature of the study, patient consent for inclusion was waived.

Medical records

Data from the medical records included age, sex, month and year of measurement, height, weight, BMI, BP, estimated glomerular filtration rate (eGFR), and a wide range of fasting blood indices of white and red blood cells, platelets, and metabolism (triglycerides [TGs] and fasting glucose [GLU]). Full details (including abbreviations) on measured blood biomarkers and derived variables are provided in Supplemental Digital Table 1, http://links.lww.com/MENO/B55 (which shows summary of blood biomarkers and derived measures). BP was measured twice with an automated device in the seated position after 5 minutes of rest. We calculated eGFR based on creatinine by using the modified Modification of Diet in Renal Disease equation[13] for the Chinese population:

$$\text{eGFR}\left[\text{mL}/\left(\text{min}\cdot 1.73\ \text{m}^2\right)\right] = 175 \times \text{Creatinine}^{-1.234}\ (\text{mg/dL}) \times \text{Age}^{-0.179} \times 0.79$$

Statistical analysis

Continuous data were expressed by mean ± SD or median (interquartile range [IQR]). Univariate analysis of continuous variables was conducted between episodic/regular new-onset cases and controls by using Student's *t* test, or Mann-Whitney *U* test in case of nonnormally distributed variables. Analysis of categorical data was conducted using the Fisher's exact test. First, from the wide range of blood biomarkers, we selected the most important variables representing white blood cells, red blood cells, and platelets based on physiological knowledge. Briefly, we chose the overall white blood cell count (WBC#) as representing white blood cell variables (rather than proportions of subcomponents). Furthermore, measured red blood cell count (RBC#) and hemoglobin concentration (HGB) represented red blood cell indices and measured platelet count (PLT#) represented platelet variables, rather than, for example, derived red blood cell and platelet variables (see Supplemental Digital Table 1, http://links.lww.com/MENO/B55, which shows a summary of blood biomarkers and derived measures). Then, we generated separate models, with varying degrees of covariate adjustment, for each representative variable by considering the associations of potential confounders with the biomarkers and BP on the basis of prior knowledge instead of model- or *P* value–based methods.[14] In model 1, we conducted conditional (ie, accounting for age matching of controls), unadjusted logistic regression. In model 2, we adjusted for month and year of measurement for each selected outcome variable. In model 3, we, in addition, adjusted for age. Also, for this model, we used forest plots to show standardized OR values (per unit of SD) for all independent variables to facilitate comparison of effects across these variables. In model 4, we conducted a fully adjusted logistic regression including all representative variables and covariates (ie, age, WBC#, RBC#, HGB, PLT#, TG, GLU, eGFR, BMI, and month and year of measurement). It is unlikely that all of the variables in the full model (model 4) are confounders. Once nonconfounders, such as mediators or colliders, are adjusted for, bias may be introduced. Hence, model 3 was considered as the main model because age, and month and year of measurement may influence both the biomarkers and BP, that is, potential confounders. In sensitivity analyses, we performed unconditional logistic regression models, not taking into account the age matching of controls. R (version 3.6.2) was used for analyses. $P < 0.05$ (two-tailed tests) was considered statistically significant.

RESULTS

A total of 151 regular new-onset HTN and 453 age-matched controls were included in this analysis (Table 1). Mean (SD) age of cases and controls were 47.3 (5.6) and 47.1 (5.7) years, respectively. BMI was higher in the HTN group than in the control group (median [IQR], 23.3 [3.5] vs 21.9 [3.3] kg/m^2). Sixty-nine percent of the women were recruited in summer and autumn, and the majority (>60%) enrolled in 2011 to 2014. No regular new-onset cases were recruited in 2017 to 2019 because of our definition of regular new-onset HTN, which requires cases to have completed at least four visits (ie, two normal BP values at the first two visits and at least two abnormal BP values during follow-up). BP at baseline as an outcome of this study was higher in the case group than in the control group. For the biomarkers (regular HTN group vs controls, median [IQR]), most of indicators in the white blood cell variables were nonsignificant between the two groups, with the exception of WBC# (6.50 [5.45-7.43] vs 5.94 [5.10-6.86] 10^9/L), which was positively associated with HTN. In the red blood cell variables, HTN also showed a positive association with RBC# (4.47 [4.26-4.71] vs 4.38 [4.16-4.56] 10^{12}/L), HGB (135.00 [126.00-141.00] vs 131.00 [126.00-137.00] g/L), and mean corpuscular hemoglobin concentration (344.00 [337.50-351.50] vs 341.00 [335.00-349.00] g/L). No differences were observed for mean corpuscular volume, hematocrit (HCT), or coefficient of variation of red blood cell volume distribution width. For the platelet variables, significantly higher levels of PLT (240.00 [200.50-280.50] vs 221.00 [193.00-254.00] 10^9/L) and plateletcrit (0.25% [0.21%-0.28%] vs 0.23% [0.20%-0.26%]) were found in the case group compared with the control group. Both metabolic variables TG (1.11 [0.82-1.45] vs 0.84 [0.62-1.18] mmol/L) and

TABLE 1. *General baseline characteristics and univariate analysis results of regular new-onset hypertensive women versus matched controls during midlife*

	Level	Regular HTN (n = 151)	Controls (n = 453)	*P*
General characteristics				
Age, y[a]		47.00 [43.50-51.00]	47.00 [43.00-51.00]	0.572
BMI, kg/m^{2}[a]		23.28 [21.38-24.88]	21.85 [20.31-23.60]	<0.001
Height, cm[b]		158.28 (4.77)	157.71 (4.87)	0.208
Weight, kg[a]		58.00 [53.00-63.00]	54.50 [50.50-59.50]	<0.001
Month, %	3-5	30 (19.9)	110 (24.3)	0.059
	6-8	33 (21.9)	121 (26.7)	
	9-11	80 (53.0)	183 (40.4)	
	12-2	8 (5.3)	39 (8.6)	
Year, %	2009-2010	25 (16.6)	37 (8.2)	<0.001
	2011-2012	63 (41.7)	102 (22.5)	
	2013-2014	57 (37.7)	194 (42.8)	
	2015-2016	6 (4.0)	94 (20.8)	
	2017-2019	0 (0.0)	26 (5.7)	
Blood pressure				
SBP, mm Hg[a]		126.00 [120.00-133.00]	109.00 [103.00-116.00]	<0.001
DBP, mm Hg[a]		82.00 [77.50-86.00]	68.00 [64.00-73.00]	<0.001
White blood cell variables				
WBC#[a]		6.50 [5.45-7.43]	5.94 [5.10-6.86]	0.003
LYMPH%[b]		36.41 (8.38)	36.72 (7.72)	0.672
NEUT%[b]		55.03 (8.83)	54.55 (8.17)	0.545
MONO%[a]		6.00 [5.00-6.84]	5.94 [5.04-7.00]	0.669
EO%[a]		1.70 [1.10-2.65]	2.00 [1.30-2.90]	0.275
BASO%[a]		0.30 [0.20-0.50]	0.30 [0.20-0.50]	0.644
Red blood cell variables				
RBC#[a]		4.47 [4.26-4.71]	4.38 [4.16-4.56]	0.002
MCH[a]		30.10 [29.00-31.30]	30.30 [29.20-31.10]	0.392
HGB[a]		135.00 [126.00-141.00]	131.00 [126.00-137.00]	0.003
HCT[a]		0.39 [0.37-0.41]	0.38 [0.37-0.40]	0.051
MCV[a]		87.30 [83.50-89.90]	88.10 [85.00-90.90]	0.026
MCHC[a]		344.00 [337.50-351.50]	341.00 [335.00-349.00]	0.013
RDW-CV[a]		13.00 [12.40-13.55]	12.90 [12.50-13.40]	0.577
Platelet variables				
PLT#[a]		240.00 [200.50-280.50]	221.00 [193.00-254.00]	<0.001
PCT[a]		0.25 [0.21-0.28]	0.23 [0.20-0.26]	<0.001
MPV[b]		10.14 (0.99)	10.23 (0.91)	0.307
Metabolic variables				
TG[a]		1.11 [0.82-1.45]	0.84 [0.62-1.18]	<0.001
GLU[a]		5.30 [4.98-5.69]	5.13 [4.86-5.50]	0.009
Kidney function				
eGFR[a]		101.26 [92.23-115.07]	99.25 [87.23-114.52]	0.150

BASO%, basophil percentage of white cells; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EO%, eosinophil percentage of white cells; GLU, fasting glucose; HCT, hematocrit; HGB, hemoglobin concentration; HTN, hypertension; LYMPH%, lymphocyte percentage of white cells; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MONO%, monocyte percentage of white cells; MPV, mean platelet volume; NEUT%, neutrophil percentage of white cells; PCT, plateletcrit; PLT#, platelet count; RBC#, red blood cell count; RDW-CV, coefficient of variation of red blood cell volume distribution width; SBP, systolic blood pressure; TG, triglycerides; WBC#, white blood cell count.
[a]Median [interquartile range].
[b]Mean (SD).

GLU (5.30 [4.98-5.69] vs 5.13 [4.86-5.50] mmol/L) were higher in the case group than in the control group.

As shown in Table 2, 388 episodic HTN and 776 age-matched controls were included in this analysis, and comparison of the indices between cases and their controls was listed. Mean (SD) age of cases and controls were 47.3 (6.1) and 46.8 (6.2) years, respectively. We found that general characteristics (BMI, weight), outcomes (systolic BP [SBP], diastolic BP [DBP]), white blood cell variables (WBC#), red blood cell variables (RBC#, HGB, hematocrit), platelet variables (PLT#, plateletcrit), and metabolic variables (TG, GLU) were higher in the case group than in the control group (all $P \leq 0.05$). Taken together, these results for episodic HTN were consistent with those for regular new-onset HTN in Table 1, with the exception of mean corpuscular hemoglobin concentration, and month and year of measurement.

To further explore risk factors of regular new-onset HTN in this period, we evaluated the effects of the most important variables representing white blood cells (WBC#), red blood cells (RBC#, HGB), and platelets (PLT#) as well as those for metabolic variables (TG, GLU), kidney function (eGFR), and BMI. With the exception of eGFR, all selected variables were positively associated with HTN (all $P < 0.05$), in the case of crude and multivariate analyses adjusted for age, and month and year of measurement (Table 3). Very similar results were found for episodic new-onset HTN for crude and multivariate analyses adjusted for age, and month and year of measurement. The only difference was that the crude OR of GLU was significant in this instance (Table 3). Figure 2 shows OR values of the model adjusted for age, and month and year of measurement per unit of SD (OR [95% CI]) for all variables confirming the significance

TABLE 2. *General baseline characteristics and univariate analysis results of episodic new-onset hypertensive women versus matched controls during midlife*

	Level	Episodic HTN (n = 388)	Controls (n = 776)	*P*
General characteristics				
Age, y[a]		48.00 [42.75-52.00]	47.00 [42.00-51.00]	0.217
BMI, kg/m^2[a]		23.34 [21.36-25.24]	21.70 [20.14-23.61]	<0.001
Height, cm[b]		158.07 (5.04)	157.84 (4.67)	0.430
Weight, kg[a]		58.50 [53.50-63.50]	54.00 [50.00-59.00]	<0.001
Month, %	3-5	85 (21.9)	220 (28.4)	0.024
	6-8	116 (29.9)	176 (22.7)	
	9-11	146 (37.6)	296 (38.1)	
	12-2	41 (10.6)	84 (10.8)	
Year, %	2009-2010	38 (9.8)	75 (9.7)	0.647
	2011-2012	89 (22.9)	193 (24.9)	
	2013-2014	174 (44.8)	314 (40.5)	
	2015-2016	71 (18.3)	153 (19.7)	
	2017-2019	16 (4.1)	41 (5.3)	
Blood pressure				
SBP, mm Hg[a]		125.00 [119.00-132.00]	110.00 [104.00-116.00]	<0.001
DBP, mm Hg[a]		80.00 [75.00-85.00]	69.00 [65.00-74.00]	<0.001
White blood cell variables				
WBC#[a]		6.37 [5.48-7.55]	5.87 [5.08-6.87]	<0.001
LYMPH%[b]		35.86 (7.68)	36.23 (7.88)	0.457
NEUT%[b]		55.44 (8.15)	55.07 (8.34)	0.480
MONO%[a]		5.90 [5.00-6.80]	5.94 [5.00-7.00]	0.374
EO%[a]		1.90 [1.20-2.70]	1.80 [1.10-2.75]	0.249
BASO%[a]		0.40 [0.20-0.60]	0.30 [0.20-0.50]	0.342
Red blood cell variables				
RBC#[a]		4.44 [4.26-4.65]	4.36 [4.16-4.56]	<0.001
MCH[a]		30.20 [28.80-31.00]	30.30 [29.20-31.13]	0.087
HGB[a]		133.00 [127.00-139.00]	131.00 [125.00-137.00]	<0.001
HCT[a]		0.39 [0.37-0.40]	0.38 [0.37-0.40]	<0.001
MCV[a]		87.95 [83.60-90.43]	88.20 [84.97-90.90]	0.038
MCHC[a]		342.00 [336.00-349.00]	341.00 [334.75-349.00]	0.446
RDW-CV[a]		13.00 [12.60-13.50]	12.90 [12.50-13.50]	0.124
Platelet variables				
PLT#[a]		236.00 [206.00-274.25]	223.00 [191.00-260.00]	<0.001
PCT[a]		0.24 [0.21-0.27]	0.23 [0.20-0.26]	<0.001
MPV[a]		10.10 [9.50-10.80]	10.20 [9.70-10.80]	0.149
Metabolic variables				
TG[a]		1.04 [0.72-1.44]	0.84 [0.63-1.16]	<0.001
GLU[a]		5.40 [5.00-5.74]	5.15 [4.85-5.49]	<0.001
Kidney function				
eGFR[a]		100.19 [86.90-113.65]	100.56 [88.71-115.25]	0.461

BASO%, basophil percentage of white cells; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EO%, eosinophil percentage of white cells; GLU, fasting glucose; HCT, hematocrit; HGB, hemoglobin concentration; HTN, hypertension; LYMPH%, lymphocyte percentage of white cells; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; MONO%, monocyte percentage of white cells; NEUT%, neutrophil percentage of white cells; PCT, plateletcrit; PLT#, platelet count; RBC#, red blood cell count; RDW-CV, coefficient of variation of red blood cell volume distribution width; SBP, systolic blood pressure; TG, triglycerides; WBC#, white blood cell count.
[a]Median [interquartile range].
[b]Mean (SD).

of effects of most variables and similarity of effect sizes between episodic and regular new-onset HTN groups, with BMI being the strongest risk factor for HTN in both (BMI: 1.72 [1.49-1.98] and 1.81 [1.45-2.26] kg/m^2; WBC#, 1.39 [1.23-1.58] and 1.38 [1.13-1.69]; TG, 1.25 [1.09-1.44] and 1.31 [1.08-1.58]; GLU, 1.46 [1.23-1.73] and 1.27 [1.05-1.54]; RBC#, 1.27 [1.11-1.44] and 1.38 [1.14-1.68]; HGB, 1.18 [1.03-1.35] and 1.31 [1.05-1.64]; and PLT#, 1.39 [1.20-1.61] and 1.33 [1.09-1.63]). In the full models, PLT# and BMI remained significant, but WBC# and TG became nonsignificant, in both groups. Furthermore, GLU was positively associated with HTN only in episodic but not regular HTN women, and HGB and RBC# were only significant in regular HTN (Table 3). In addition, multicollinearity in the full models was tested, but this yielded no significant results in any of the full models.

Sensitivity analyses, using unconditional logistic regression, yielded results that were highly consistent with those derived from conditional logistic regression (see Supplemental Digital Table 3 and Figure, http://links.lww.com/MENO/B55, which show unstandardized and standardized estimated odds ratios from multivariate unconditional logistic regression for regular/episodic new-onset HTN vs controls respectively).

DISCUSSION

In the present nested case-control study, we aimed to explore risk factors of HTN in midlife women. We found that higher WBC#, RBC#, HGB, and PLT# were associated with a higher risk of both regular and episodic new-onset HTN in this population, in addition to obesity (BMI) and metabolic dysregulation (TG and GLU). The association between eGFR and HTN was

TABLE 3. *Estimated odds ratios from multivariate conditional logistic regression for regular/episodic new-onset HTN versus controls*

	Regular new-onset HTN (n = 151) vs controls (n = 453)		Episodic new-onset HTN (n = 388) vs controls (n = 776)	
Adjustments	OR (95% CI)	*P*	OR (95% CI)	*P*
WBC#				
Crude	1.215 (1.078-1.369)	0.001	1.239 (1.144-1.342)	1.6×10^{-7}
Month + year	1.228 (1.078-1.399)	0.002	1.239 (1.143-1.342)	1.7×10^{-7}
Month + year + age	1.233 (1.081-1.406)	0.002	1.242 (1.144-1.347)	2.1×10^{-7}
Full model[a]	1.074 (0.920-1.254)	0.364	1.090 (0.993-1.195)	0.069
RBC#				
Crude	1.781 (1.098-2.891)	0.019	1.895 (1.370-2.622)	1.2×10^{-4}
Month + year	2.435 (1.426-4.159)	0.001	1.945 (1.397-2.709)	8.3×10^{-5}
Month + year + age	2.422 (1.420-4.130)	0.001	1.847 (1.315-2.596)	4.1×10^{-4}
Full model[b]	2.116 (1.152-3.890)	0.016	1.404 (0.970-2.031)	0.072
HGB				
Crude	1.018 (1.001-1.036)	0.035	1.014 (1.003-1.025)	0.013
Month + year	1.022 (1.004-1.041)	0.019	1.014 (1.003-1.025)	0.013
Month + year + age	1.022 (1.004-1.041)	0.019	1.014 (1.003-1.025)	0.016
Full model[a]	1.026 (1.006-1.047)	0.012	1.010 (0.998-1.022)	0.105
PLT#				
Crude	1.006 (1.003-1.010)	4.2×10^{-4}	1.005 (1.003-1.007)	1.2×10^{-5}
Month + year	1.005 (1.001-1.009)	0.006	1.005 (1.003-1.007)	1.2×10^{-5}
Month + year + age	1.005 (1.002-1.009)	0.005	1.005 (1.003-1.007)	1.5×10^{-5}
Full model[a]	1.005 (1.001-1.010)	0.016	1.003 (1.001-1.006)	0.009
TG				
Crude	1.500 (1.168-1.926)	0.001	1.341 (1.120-1.605)	0.001
Month + year	1.449 (1.122-1.872)	0.005	1.344 (1.122-1.609)	0.001
Month + year + age	1.430 (1.110-1.841)	0.006	1.340 (1.117-1.609)	0.002
Full model[a]	1.214 (0.919-1.602)	0.172	1.109 (0.913-1.347)	0.297
GLU				
Crude	1.154 (0.945-1.410)	0.159	1.544 (1.288-1.850)	2.7×10^{-6}
Month + year	1.294 (1.039-1.612)	0.022	1.550 (1.291-1.862)	2.8×10^{-6}
Month + year + age	1.319 (1.056-1.647)	0.015	1.494 (1.245-1.792)	1.6×10^{-5}
Full model[a]	1.196 (0.945-1.514)	0.136	1.313 (1.093-1.577)	0.004
eGFR				
Crude	1.008 (0.999-1.017)	0.072	0.999 (0.993-1.004)	0.666
Month + year	1.006 (0.996-1.015)	0.232	0.999 (0.993-1.004)	0.629
Month + year + age	1.006 (0.997-1.016)	0.185	0.995 (0.994-1.006)	0.995
Full model[a]	1.007 (0.997-1.017)	0.163	0.999 (0.992-1.005)	0.716
BMI				
Crude	1.220 (1.131-1.316)	2.5×10^{-7}	1.223 (1.162-1.286)	6.9×10^{-15}
Month + year	1.243 (1.145-1.349)	2.0×10^{-7}	1.222 (1.162-1.286)	7.2×10^{-15}
Month + year + age	1.247 (1.148-1.355)	1.9×10^{-7}	1.218 (1.157-1.282)	4.4×10^{-14}
Full model[a]	1.202 (1.099-1.314)	6.0×10^{-5}	1.171 (1.110-1.236)	6.7×10^{-9}

Logistic regression estimates are for each unit increase of the risk factors.
BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; GLU, fasting glucose; HGB, hemoglobin; HTN, hypertension; OR, odds ratio; PLT#, platelet count; RBC#, red blood cell count; TG, triglycerides; WBC#, white blood cell count.
[a]Variables in the full model included age, WBC#, HGB, PLT#, TG, GLU, eGFR, BMI, and month and year of measurement.
[b]Variables in the full model included age, WBC#, RBC, PLT#, TG, GLU, eGFR, BMI, and month and year of measurement.

not significant. The results were robust to adjustment for potential confounders.

As a biomarker representing inflammation, data on association between WBC# and HTN are scarce, but findings of most studies were in line with our results. In a community-based cross-sectional survey on the association of WBC# and HTN involving 33,021 Chinese participants, WBC# was positively associated with risk of HTN independent of potential confounders.[15] Moreover, Siedlinski et al[16] conducted a Mendelian randomization study among ~750,000 UK Biobank and International Consortium of Blood Pressure Genome-Wide Association Studies participants and found that there was a positive causal relationship of lymphocyte count with SBP and DBP. Our results are consistent with those aforementioned studies and further add that a positive association between WBC, and HTN exists in women aged 40 to 60 years.

There are limited data available on the associations of RBC# and HGB with HTN, but most previous studies with large sample sizes support our results.[17–21] In a longitudinal cohort study encompassing 6,453 Chinese participants with routine health checkups, RBC# was associated with the risk of HTN (risk ratio, 2.0; 95% CI, 1.6-2.6).[17] In the present study, in middle-aged women, the association of HGB and RBC with HTN was consistent in the two case-control samples and robust to adjustment for potential confounders. Similarly, based on data analyses of more than 100,000 Dutch voluntary blood donors, Atsma et al[19] found that SBP increased by 1.8 (95% CI, 1.6-2.0) and 1.3 (95% CI, 1.1-1.4) mm Hg for each micromoles per liter in HGB for women and men, respectively, and similar patterns for DBP were observed. In summary, most of the studies mentioned previously, including our results, suggested that RBC# and HGB might play a role in the development of HTN.

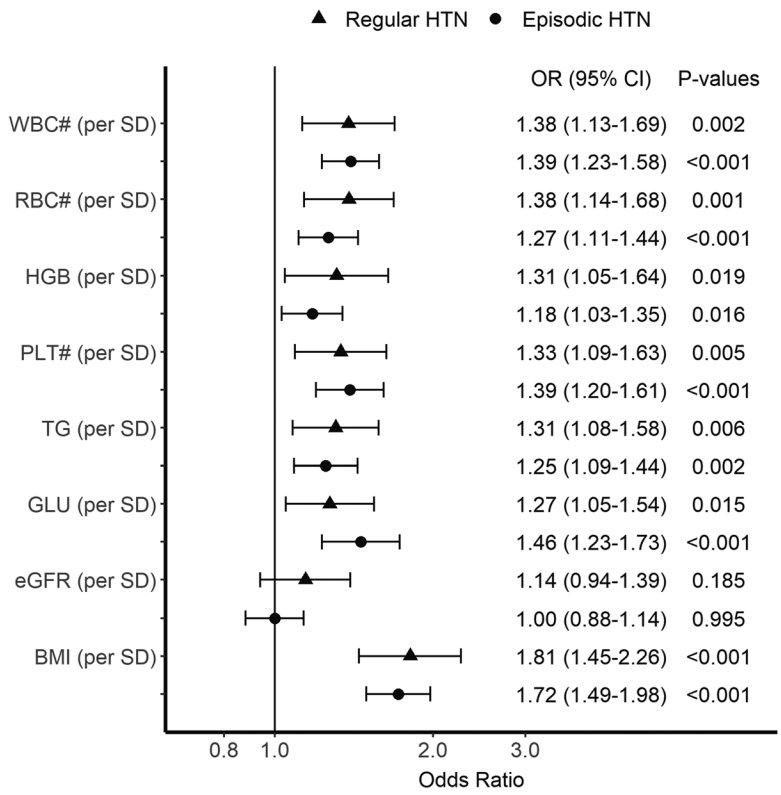

FIG. 2. Estimated odds ratios (per unit of SD) from multivariate conditional logistic regression for regular/episodic new-onset HTN versus controls (adjusted for month, year, and age). Error bars indicate 95% CI. CI, confidence interval; eGFR, estimated glomerular filtration rate; GLU, fasting glucose; HGB, hemoglobin; HTN, hypertension; OR, odds ratio; PLT#, platelet count; RBC#, red blood cell count; TG, triglycerides; WBC#, white blood cell count.

Nevertheless, none of the above studies have focused on middle-aged women.

There have been very few studies investigating the association between PLT# and HTN, and the relationship between PLT# and cardiovascular disease is controversial.[22–24] In a longitudinal study involving physical examination data of 6,515 Chinese participants with 6-year follow-up, PLT# was shown to associate with DBP with a 0.42 (95% CI, 0.02-0.82) and 0.52 (95% CI, 0.04-1.00) increase in the highest quartile of PLT# compared with the lowest quartile of PLT# in men and women, respectively, but no significant association between PLT# and SBP was found.[25] Our results agree with the aforementioned study with a 30% increase in the OR of regular new-onset HTN per SD of PLT#, suggesting that PLT# might be involved in HTN during midlife.

The mechanisms underlying the positive associations of WBC#, RBC#, HGB, and PLT# with HTN are complicated and not entirely known. Activated platelets might increase the concentration of intracellular calcium ions for vascular smooth muscle cells through a number of mediators including 5-hydroxytryptamine and lysophosphatidic acid, which promotes vasoconstriction and catecholamine response,[26] and further increase BP. Activated platelets may also lead to an increase of reactive oxygen species (ROS).[26,27] The production of these ROS might inhibit the bioactivity of nitric oxide (NO),[28] a substance predominantly generated by endothelial cells with a hypotensive effect through vasodilatation of vascular smooth muscle cells caused by interaction between NO and guanylyl cyclase.[29] The effect of red blood cells and platelets on HTN might depend on the same signaling pathways in part. Microparticles released by breakdown of red blood cells could reduce NO bioavailability.[30] Moreover, free HGB, even at low levels, released after disruption of red blood cells could not only exhibit significant NO scavenging activity via dioxygenation reactions but also result in inflammation, vasoconstriction, and oxidative stress, a state with more than a normal physiological amount of ROS.[30–32] In our study, we observed that white blood cells count, a biomarker representing inflammation, was higher in HTN than in control groups. Guzik and Touyz[33] summarized that oxidative stress and inflammation, as essential components affecting microvascular and macrovascular function, led to a vicious cycle between elevated BP, vascular remodeling, stiffness, persistent HTN, and its atherosclerotic complications.

As expected, higher levels of BMI, TG, and GLU were associated with a higher risk of HTN in this population, and these associations have been well established.[34–39] As such, our study demonstrated similar results with consistent effect directions of the association.

In our study, we used a matched case-control design. Although we matched for age between the cases and the controls, we still adjusted for the matching factor. In fact, matching on age may introduce bias because it makes the controls more comparable with the cases not only for age but potentially also for the exposures of interest.[40] Therefore, we also used unconditional logistic regression in the sensitivity analysis (Supplemental Digital Table 3,

http://links.lww.com/MENO/B55). Important to note is that both conditional and unconditional logistic regressions yielded highly consistent results. In our study, some well-known risk factors were no longer significant in the fully adjusted model 4, such as TG for episodic and regular new-onset HTN and GLU for regular new-onset HTN only (Table 3). This is most likely due to adjustment for BMI in model 4, which is known to be strongly associated with indicators of metabolic dysregulation such as TG and GLU. Part of BMI's effect on HTN may be mediated by TG and GLU. Because inclusion of such mediators (and/or colliders) in model 4 may have introduced bias of effect sizes, we used model 3 as the main model, which only included age, and month and year of measurement as covariates.

This study had several limitations. First, detailed information on history of disease and medication use, waist circumference, and demographic and lifestyle factors, such as education, occupation, physical exercise, and smoking of these participants, was not collected during the medical checkups. Furthermore, information on total cholesterol, high-density lipoprotein, and low-density lipoprotein was unfortunately not collected in the majority of the women. Thus, we could not account for potential confounding effects of these variables. Based on the available data on BMI and blood biomarkers, we concluded, however, that our sample of female employees was relatively healthy. That is, occurrence of different diseases based on clinical cutoff values in our sample was lower than in comparable samples of women in this age group: 0.5% for chronic kidney disease [eGFR < 60 mL/(min · 1.73 m^2)],[41] 2.6% for type 2 diabetes (GLU ≥7 mmol/L),[42] 14.3% for anemia (HGB <120 g/L),[43] 1.6% for infections based on WBC# (WBC# >10 × 10^9/L),[44] and 6.1% for of hypertriglyceridemia (TG ≥2.26 mmol/L).[45] Furthermore, we already adjusted for the continuous traits underlying these comorbidities in the full model (Table 3), and we found that estimates for the observed associations of RBC#, HGB, and PLT# remained consistent in the fully adjusted model. Second, we used middle age as a proxy for perimenopause, but data on menstrual history were not available. This is a limitation in that we could not ascertain the influence of timing or severity of menopause on HTN, nor could we exclude late postmenopausal women. A representative cross-sectional study, however, revealed that average age at natural menopause was 48.9 years for women (n = 9,939) in Guangdong Province, south of China,[46] whereas the mean age of women in the current study was 47.3 years, indicating that a large proportion of postmenopausal women in our samples seem unlikely. Furthermore, age matching (±2 years) between cases and controls will have limited any impact of overrepresentation or underrepresentation of late postmenopausal women on our study. Third, the nested case-control design of the study may have lower power than a cohort study. Furthermore, this was a retrospective study that involved women from the years 2009 to 2019. During this period, variation in staff and measurement materials may have induced measurement error. Although we adjusted for year and month of measurement, we cannot completely rule out bias due to such measurement error. In addition, multiple testing may explain some of the associations. After applying a Bonferroni *P* value correction for multiple testing (α = 0.00625 [0.05/8]), the associations of HGB and GLU with regular HTN and HGB with episodic HTN were no longer statistically significant. Associations of the remaining biomarkers, however, retained their significance. Furthermore, the clinical implications may be limited given that observed differences in biomarkers levels are within the normal range for both the case and control groups. This study, however, mainly focused on investigating these biomarkers as potential etiological factors. Although the levels are within normal range, they still shed some light on possible causal mechanisms. Finally, the observational nature of this study precludes strong causal conclusions.

Unfortunately, information on medication use (eg, antihypertensive medication) was not collected during the free medical checkups, and the retrospective nature of this study precludes the obtainment of these data. This may partly have led to misclassification in the control group. Such bias would be in the direction of the null hypothesis, so we may have underestimated the true effect size of the blood biomarkers.

Our study also has a number of strengths. For example, we investigated both regular and episodic new-onset HTN with three and two age-matched (±2 y) controls for each case, respectively. Also, we conducted sensitivity analyses using unconditional logistic regression, which yielded very consistent results. Our matched nested case-control study is an efficient design, which will not only have reduced the likelihood of selection and information bias but also have saved human and financial resources. In addition, the cases and controls are from the same cohort with good comparability, which is a main strength of the study.

During midlife in women, which is referred to as perimenopause, prevalence of HTN in women increases.[4] This period therefore offers a unique window of opportunity for screening and preventative measures, to improve control of cardiovascular disease risk. In this context, the higher levels of blood indices of white and red blood cells and platelets we observed before the onset of HTN may prove useful in early screening and prevention efforts of HTN in midlife women. Future study may investigate whether these risk factors are indeed causally related to HTN and whether the risk factors improve risk prediction of HTN in midlife women.

CONCLUSIONS

In addition to obesity and metabolic dysregulation, the findings of our study indicate that higher WBC#, RBC#, HGB, and PLT# are associated with a higher risk of HTN in midlife women. Knowledge on the effects of these variables on HTN will contribute to defining more specific strategies for prevention and treatment of HTN in this population.

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