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Katarzyna Dziedzic-Jankowska[1], Adam Bujanowicz[2], Michał Szyszka[2], Anna Stelmaszczyk-Emmel[3], Piotr Skrzypczyk[1]

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Subclinical inflammation in paediatric patients with primary hypertension and white coat hypertension

Subkliniczny stan zapalny u pacjentów pediatrycznych z nadciśnieniem tętniczym pierwotnym i nadciśnieniem białego fartucha

[1] Department of Paediatrics and Nephrology, Medical University of Warsaw, Warsaw, Poland
[2] Department of Paediatrics and Nephrology, Doctoral School, Medical University of Warsaw, Warsaw, Poland
[3] Department of Laboratory Diagnostics and Clinical Immunology of Developmental Age, Medical University of Warsaw, Warsaw, Poland
Correspondence: Piotr Skrzypczyk, Chair and Clinic of Paediatrics and Nephrology, Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland, e-mail: piotr.skrzypczyk@wum.edu.pl

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ORCID iDs
1. Adam Bujanowicz https://orcid.org/0009-0007-1369-8304
2. Michał Szyszka https://orcid.org/0000-0002-7336-7327
3. Anna Stelmaszczyk-Emmel https://orcid.org/0000-0003-3667-1220
4. Piotr Skrzypczyk https://orcid.org/0000-0002-1959-8255

Abstract

Introduction and objective: Evaluation of subclinical inflammation in patients with primary hypertension (PH) and white coat hypertension (WCH). **Materials and methods:** In 56 untreated paediatric patients with PH, 40 with WCH, and 30 healthy individuals (control group, CG), we evaluated high sensitivity C-reactive protein (hsCRP), interleukin 18 (IL-18) levels, complete blood count-derived markers of inflammation, office and ambulatory blood pressure, and selected clinical and biochemical parameters. **Results:** hsCRP was significantly higher in PH patients compared to CG, and neutrophil and monocyte counts were significantly higher in PH and WCH patients compared to CG. Receiver operating characteristic analysis revealed good prognostic profiles for hsCRP, neutrophil, lymphocyte, monocyte, and platelet counts, as well as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-neutrophil ratio, and platelet-to-mean platelet volume ratio as predictors of the presence of PH. In multivariate analysis, monocyte-to-lymphocyte ratio (MLR) and platelet count ($\beta = 0.217$, $\beta = 0.191$) were significant predictors of office diastolic blood pressure Z-score, while neutrophil count predicted 24 h systolic blood pressure Z-score ($\beta = 0.365$), MLR, lymphocyte count, IL-18, and NLR predicted 24 h diastolic blood pressure Z-score ($\beta = 0.305$, $\beta = 0.253$, $\beta = -0.197$, $\beta = -0.189$), and neutrophil count together with IL-18 predicted 24 h mean arterial pressure Z-score ($\beta = 0.210$, $\beta = -0.209$). **Conclusions:** 1. Patients with PH and WCH are characterised by similar levels of subclinical inflammation, which are significantly higher compared to healthy peers. 2. Complete blood count-derived indices, especially neutrophil count and MLR, can serve as important adjuncts to the clinical evaluation of paediatric patients with PH.

Keywords: children, inflammation, primary hypertension, white coat hypertension

Streszczenie

Wprowadzenie i cel: Ocena subklinicznego stanu zapalnego u pacjentów z nadciśnieniem tętniczym pierwotnym (NTP) i nadciśnieniem białego fartucha (BF). **Materiał i metoda:** U 56 nieleczonych pacjentów pediatrycznych z NTP, 40 z BF i 30 zdrowych dzieci (grupa kontrolna, GK) oceniono stężenie wysoko czułego białka C-reaktywnego (*high sensitivity C-reactive protein*, hsCRP) i interleukiny 18 (IL-18), markery stanu zapalnego na podstawie morfologii krwi, ciśnienie tętnicze gabinetowe i w pomiarze całodobowym oraz wybrane parametry kliniczne i biochemiczne. **Wyniki:** Stężenie hsCRP było istotnie wyższe u pacjentów z NTP w porównaniu z GK, liczba neutrofilów i monocytów była istotnie wyższa u pacjentów z NTP i BF w porównaniu z GK. Analiza krzywej ROC (*receiver operating characteristic*) wykazała dobry profil prognostyczny dla hsCRP, liczby neutrofilów, limfocytów, monocytów i płytek krwi, a także wskaźnika neutrofilowo-limfocytarnego (*neutrophil-to-lymphocyte ratio*, NLR), wskaźnika monocytowo-neutrofilowego oraz wskaźnika płytki krwi – średnia objętość płytki jako predyktorów NTP. W analizie wieloczynnikowej wskaźnik monocytowo-limfocytarny (*monocyte-to-lymphocyte ratio*, MLR) i liczba płytek krwi ($\beta = 0{,}217$, $\beta = 0{,}191$) były istotnymi predyktorami rozkurczowego ciśnienia gabinetowego, liczba neutrofili była predyktorem dla 24-godzinnego ciśnienia skurczowego ($\beta = 0{,}365$), MLR, liczba limfocytów, IL-18

i NLR – dla 24-godzinnego ciśnienia rozkurczowego (β = 0,305, β = 0,253, β = −0,197, β = −0,189), a liczba neutrofilów i IL-18 – dla 24-godzinnego ciśnienia średniego (β = 0,210, β = −0,209). **Wnioski:** 1. Pacjenci z NTP i BF charakteryzują się podobnym poziomem subklinicznego stanu zapalnego, istotnie wyższym w porównaniu ze zdrowymi rówieśnikami. 2. Wskaźniki pochodne morfologii krwi, zwłaszcza liczba neutrofilów i wskaźnik MLR, mogą być istotnym uzupełnieniem oceny stanu klinicznego pacjentów pediatrycznych z NTP.

Słowa kluczowe: dzieci, zapalenie, nadciśnienie tętnicze pierwotne, nadciśnienie białego fartucha

INTRODUCTION

The prevalence of arterial hypertension is estimated to be 4.0% among paediatric patients[1]. Although the definition of arterial hypertension is based on office blood pressure measurements, both home blood pressure measurements (HBPM) and ambulatory blood pressure measurements (ABPM) have been found to correlate more strongly with hypertension-mediated organ damage (HMOD) in children and hard end-points in adults[2]. ABPM enables the evaluation of blood pressure across different periods, providing data that can be used to calculate nighttime blood pressure dipping, morning blood pressure surge, indirect markers of arterial stiffness, and finally, various indices of blood pressure variability[3]. HBPM and ABPM are especially useful in differentiating patients with sustained hypertension from those with intermediate conditions like white coat hypertension (WCH) and masked hypertension (MH). Interestingly, children and adolescents with WCH and MH were found to be commonly affected by HMOD (e.g. left ventricular hypertrophy)[4].

Recent data suggest that essential primary hypertension (PH) accounts for approximately half of hypertensive cases during the developmental period. Primary hypertension (PH) is a complex disease emerging from numerous causative factors[5]. Studies over the last few years have highlighted the significant role of subclinical, low-grade inflammation in the pathogenesis of PH and HMOD in adults and children[6,7]. Experimental and clinical data suggest that even a slight rise in blood pressure leads to endothelial damage and the release of neoantigens, triggering immune system activation. An interplay between the immune system, renin–angiotensin–aldosterone system (RAAS), sympathetic system, vitamin D, and salt sensitivity has been revealed in both experimental and clinical studies[8].

Subclinical inflammation can be evaluated through the concentration of inflammatory mediators (e.g. interleukins) or precise inflammatory indicators (e.g. high-sensitivity C-reactive protein – hsCRP). Numerous studies have suggested that neutrophil count, neutrophil-to-lymphocyte ratio (NLR), platelet count, platelet-to-lymphocyte ratio (PLR), as well as mean platelet volume (MPV), are associated with cardiovascular diseases such as acute coronary syndromes, heart failure, and hypertension[9]. Conversely, hsCRP elevation has been observed in adult hypertensive patients and was found to be an independent predictor of cardiovascular sequelae[10]. Recent data suggest that interleukin 18 (IL-18) can be involved in the pathogenesis of primary hypertension, non-dipping pattern of hypertension, and HMOD like common carotid artery intima–media thickness[11,12].

The world literature lacks comparisons of the severity of subclinical inflammation in paediatric patients with PH and WCH. Additionally, there are no data assessing the detailed relationship between inflammation and ABPM recordings. Therefore, our goals were:

1. To assess subclinical inflammation in paediatric patients with PH and WCH compared to healthy peers.
2. To evaluate the usefulness of determining subclinical inflammation in children with PH and WCH for clinical practice.

MATERIALS AND METHODS

We retrospectively analysed all patients hospitalised in one tertiary centre of paediatric nephrology due to suspicion of arterial hypertension in 2017–2021. The inclusion criterion for the PH group was arterial hypertension diagnosed according to the European Society of Hypertension (ESH) guidelines[2] and confirmed by ABPM. The inclusion criteria for the WCH group were clinical suspicion of arterial hypertension based on elevated office measurements and exclusion of arterial hypertension by ABPM[2]. The control group (CG) comprised a total of 30 age- and sex-matched healthy children. The exclusion criteria for all participants were lack of consent to participate in the study, acute and chronic inflammatory conditions, known allergic diseases, chronic kidney disease, congenital or acquired heart defects or heart failure, and – for the PH group – secondary forms of hypertension and pharmacological antihypertensive treatment. In all study participants, potential sources of inflammation that could have influenced the results were analysed on the basis of medical records (physical examination and history). Such patients were excluded from the analysis. The flowchart of patients is presented in Fig. 1.

The researchers obtained approval from the local bioethics committee to conduct the study (approval No. KB/58/2016, 15 March 2016, amendment No. KB/53/A2023, 12 June 2023). All procedures involving human participants were carried out in accordance with the highest ethical standards of the institutional research committee and complied with the Declaration of Helsinki on the treatment of human subjects and its later amendments. All participants and their legal representatives signed informed consent before entering the study.

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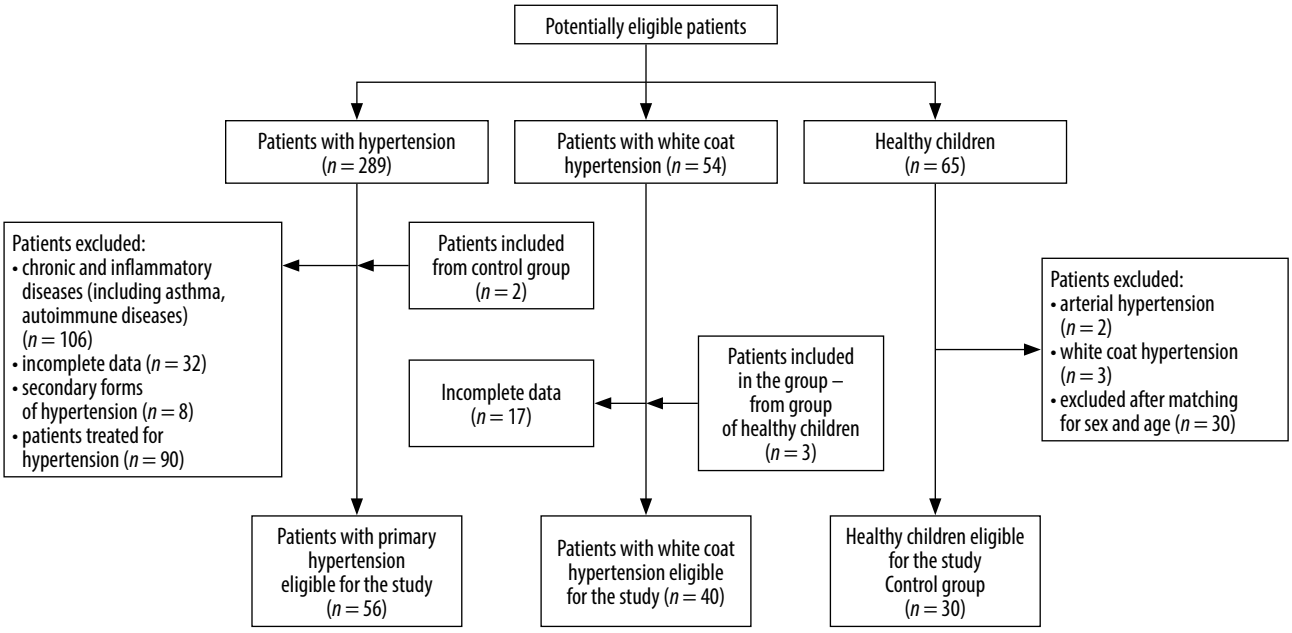

Fig. 1. Flowchart of patients included in the study

All examinations were performed upon admission based on the same protocol. The following clinical parameters were assessed: age, sex (male/female), duration of arterial hypertension, duration of pregnancy, and birth weight. Basic anthropometric parameters, such as height, weight, and body mass index (BMI) were analysed and expressed as Z-scores[13]. Overweight and obesity were classified according to World Health Organization definitions: BMI in the ≥85th and <95th percentiles for overweight, and BMI ≥95th percentile for obesity.

Peripheral office systolic and diastolic blood pressure (SBP, DBP) was measured oscillometrically using Welch Allyn VSM Patient Monitor 300 (Welch Allyn Inc., Skaneateles Falls, NY, USA) [mm Hg] according to the ESH 2016 guidelines[2] and expressed as [mm Hg] and as Z-scores[14]. Also, office pulse pressure (PP) was calculated for all patients using the formula: PP = SBP – DBP [mm Hg]. Suntech Oscar 2 oscillometric device (SunTech Medical, Inc., Morrisville, NC, USA) was used to evaluate 24-hour blood pressure parameters. The following parameters of ambulatory blood pressure recordings were analysed[15]: systolic, diastolic, and mean blood pressure during 24 hours (SBP, DBP, mean arterial pressure – MAP, 24 h) expressed as [mm Hg] and Z-scores[15], SBP and DBP loads (SBPL, DBPL) during 24 hours expressed as [%], pulse pressure (PP) defined as the difference between SBP and DBP during 24 hours, SBP and DBP dipping (SBP DIP, DBP DIP) defined as the difference between mean daytime blood pressure and mean nighttime blood pressure expressed as a percentage of the daytime value, ambulatory arterial stiffness index (AASI) defined as 1 minus the regression slope of diastolic over SBP values as recorded by the ABPM[16], and morning blood pressure surge defined as morning blood pressure (mean blood pressure during the first 2 hours after wake-up) minus pre-waking blood pressure (2 hours average blood pressure before wake-up).

The level of subclinical inflammation was evaluated using serum inflammatory indices and blood complete-blood count mediators. Blood samples were collected after two hours in an upright position in the morning (between 7 am and 10 am) after a 12-hour fasting period in a euvolemic state according to our local protocol. All patients were advised to follow a normal sodium diet at least seven days before admission. Complete blood count (CBC) was performed using Coulter LH 780 haematologic analyser (Sysmex XN-1000, Sysmex Corporation, Kobe, Japan), and the following CBC-derived inflammatory indicators were evaluated: neutrophil count (NEU; 1000/μL), lymphocyte count (LYM; 1000/μL), platelet count (PLT; 1000/μL), mean platelet volume (MPV; fL), and neutrophil-to-lymphocyte, platelet-to-lymphocyte, monocyte-to-lymphocyte and platelet-to-mean platelet volume ratios (NLR, PLR, MLR, and platelet-to-MPV ratio – PMPVR). Blood for hsCRP and IL-18 evaluation was allowed to clot, then promptly centrifuged under controlled conditions and frozen at –80°C. The levels of hsCRP [mg/L] and IL-18 [pg/mL] were determined by the enzyme-linked immunosorbent assay method (DRG® CRP, HS C-Reactive Protein Catalog Number EIA-3954, DRG International Inc., Springfield, NJ, USA and Human IL-18 ELISA Kit, Catalogue Number BMS267-2, ThermoFisher Scientific, Austria, Vienna) using Biochrom Asys UVM 340 Scanning Microplate Reader (Biochrom Ltd., Cambridge, UK).

Other parameters evaluated from peripheral blood included those assessed by standard local laboratory methods [dry chemistry (VITROS 5600, Ortho Clinical Diagnostics, USA)]: serum creatinine [mg/dL], urea [mg/dL], uric acid [mg/dL], lipid profile: total, high-density lipoprotein

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Parameter	Primary hypertension	White coat hypertension	Control group	*p*
Number of patients [*n*]	56	40	30	–
Age [years]	15.3 (13.9–16.8)	15.9 (12.3–17.3)	14.5 (13.8–15.9)	0.411
Sex [M/F]	40/16	25/15	19/11	0.596
Height [cm]	171.8 ± 12.4	166.4 ± 14.7	168.1 ± 7.3	0.092
Height Z-score	0.76 ± 0.99	0.54 ± 1.07	0.38 ± 0.80	0.209
Weight [kg]	78.7 ± 19.5	67.1 ± 21.2	57.3 ± 7.8	<0.001[1,2,3]
Weight Z-score	1.61 ± 0.92	1.01 ± 1.19	0.30 ± 0.72	<0.001[1,2,3]
BMI [kg/m^2]	26.4 ± 4.9	23.8 ± 4.8	20.2 ± 2.2	<0.001[1,2,3]
BMI Z-score	1.47 ± 0.86	0.98 ± 1.26	0.13 ± 0.72	<0.001[1,2,3]
Birth weight [g]	3201.1 ± 634.9	3427.7 ± 429.2	3435.4 ± 416.2	*p* = 0.180
Weeks of gestation [week]	40 (40–40)	40 (39–40)	40 (40–40)	0.830
Creatinine [mg/dL]	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.1	0.364
Urea [mg/dL]	26.4 ± 5.7	27.1 ± 5.9	25.1 ± 5.5	0.369
GFRS [mL/min/1.73 m^2]	93.3 (84.9–113.8)	95.5 (87.9–106.7)	100.9 (88.8–112.9)	0.834
Uric acid [mg/dL]	6.1 ± 1.5	5.7 ± 1.5	5.1 ± 1.1	0.008[2]
Total cholesterol [mg/dL]	157.5 (145.5–179)	160.0 (137–185)	152.0 (133–182)	0.568
LDL cholesterol [mg/dL]	86.7 (69.5–105.7)	86.9 (69.2–111)	79.4 (64.6–109)	0.527
HDL cholesterol [mg/dL]	50.7 ± 12.9	49.7 ± 11.9	57.8 ± 11.1	0.014[2,3]
Triglyceride [mg/dL]	101.5 (65.5–144)	90.0 (63.5–139)	56.0 (50–78)	<0.001[2,3]
ACR [mg/g]	7.7 (5–11.4)	5.6 (3.3–12.6)	7.3 (4–11.8)	0.388

M – male; **F** – female; **BMI** – body mass index; **GFRS** – glomerular filtration rate according to Schwartz formula; **LDL** – low-density lipoprotein; **HDL** – high-density lipoprotein; **ACR** – albumin-to-creatinine ratio.
[1] Primary hypertension vs. white-coat hypertension.
[2] Primary hypertension vs. control group.
[3] White coat hypertension vs. control group.

Tab. 1. Clinical and biochemical parameters in the study group

Inflammatory indicator	Primary hypertension	White coat hypertension	Control group	*p*
hsCRP [mg/L]	2.9 (1.5–7.3)	1.4 (0.6–6.0)	0.9 (0.5–1.9)	0.002[1]
IL-18 [pg/mL]	74.7 (21.6–130.4)	70.2 (19.7–115.9)	91.3 (43.7–117.5)	0.514
Neutrophils [×10^3/μL]	3.89 ± 1.44	3.40 ± 1.75	2.63 ± 0.96	0.001[1,2]
Monocytes [×10^3/μL]	0.53 (0.45–0.65)	0.50 (0.40–0.63)	0.44 (0.34–0.53)	0.026[1,2]
Lymphocytes [×10^3/μL]	2.31 (1.90–2.71)	2.03 (1.59–2.46)	2.05 (1.70–2.38)	0.087
Platelets [×10^3/μL]	254.0 (227.0–297.0)	247.0 (203.5–278.5)	234.0 (215–258)	0.215
Mean platelet volume (MPV) [fL]	10.44 ± 1.34	10.52 ± 1.59	10.92 ± 0.73	0.253
Neutrophil-to-lymphocyte ratio (NLR)	1.52 (1.22–2.0)	1.30 (1.07–1.88)	1.29 (0.92–1.55)	0.055
Platelet-to-lymphocyte ratio (PLR)	117.15 ± 34.25	129.09 ± 55.91	118.59 ± 32.35	0.362
Monocyte-to-lymphocyte ratio (MLR)	0.25 ± 0.08	0.27 ± 0.13	0.22 ± 0.06	0.146
Monocyte-to-neutrophil ratio (MNR)	0.15 (0.11–0.19)	0.17 (0.13–0.20)	0.18 (0.14–0.22)	0.149
Platelet-to-MPV ratio (PMPVR) [10^{12}]	24.92 (20.85–30.09)	23.19 (18.03–28.86)	21.50 (19.8–23.45)	0.088

hsCRP – high sensitivity C-reactive protein; **IL-18** – interleukin 18.
[1] Primary hypertension vs. control group.
[2] White-coat hypertension vs. control group.

Tab. 2. Inflammatory markers in the study group

(HDL), and low-density lipoprotein (LDL) cholesterol [mg/dL], triglycerides [mg/dL], morning urinary albumin [mg/L], and creatinine [mg/dL] with calculation of the albumin-creatinine ratio [mg/g]. In all participants, the estimated glomerular filtration rate (GFR_S) was calculated according to the 2009 abbreviated Schwartz formula: GFR_S = 0.413 × height [cm] / serum creatinine [mg/dL] [mL/min/1.73 m^2][17]. Albumin-creatinine ratios ≥30 mg/g were considered abnormal[2], and uric acid >5.5 mg/dL was considered elevated, according to Feig et al.[18]. Due to the retrospective nature of the study, three sets of data were incomplete: urinary albumin excretion (*n* = 120), duration of pregnancy (*n* = 100), and birth weight (*n* = 74).

Statistical data were analysed using Dell Statistica 13.0 PL software (TIBCO Software Inc., Palo Alto, CA, USA). The normality of data distribution was analysed with the Shapiro–Wilk test. Data were reported as absolute numbers, mean ± standard deviation (*SD*) (for normally distributed

Blood pressure	Primary hypertension	White coat hypertension	Control group	*p*
Office SBP [mm Hg]	141.7 ± 10.2	131.1 ± 11.2	113.5 ± 7.6	<0.001[1,2,3]
Office SBP Z-score	2.26 ± 0.90	1.56 ± 1.06	−0.15 ± 0.81	<0.001[1,2,3]
Office DBP [mm Hg]	83.1 ± 10.2	80.0 ± 9.1	65.1 ± 5.8	<0.001[2,3]
Office DBP Z-score	2.39 ± 1.39	2.03 ± 1.28	−0.01 ± 0.81	<0.001[2,3]
Office pulse pressure [mm Hg]	58.6 ± 9.8	51.1 ± 9.1	48.3 ± 6.1	<0.001[1,2]
24 h ABPM SBP [mm Hg]	134.6 ± 5.3	119.5 ± 6.3	113.4 ± 5.9	<0.001[1,2,3]
24 h ABPM SBP Z-score	2.34 ± 0.86	0.53 ± 0.73	−0.31 ± 0.68	<0.001[1,2,3]
24 h ABPM DBP [mm Hg]	72.2 ± 7.1	67.6 ± 4.0	62.7 ± 3.8	<0.001[1,2,3]
24 h ABPM DBP Z-score	0.77 ± 1.27	0.00 ± 0.78	−0.91 ± 0.74	<0.001[1,2,3]
24 h ABPM MAP [mm Hg]	92.2 ± 6.3	84.1 ± 4.2	75.9 ± 4.7	<0.001[1,2,3]
24 h ABPM MAP Z-score	1.52 ± 1.26	0.23 ± 0.68	−1.05 ± 0.68	<0.001[1,2,3]
PP 24 h [mm Hg]	62.4 ± 7.2	52.0 ± 5.8	50.9 ± 5.4	<0.001[1,2]
HR [bpm]	80.6 ± 12.8	81.9 ± 12.1	77.4 ± 9.5	0.365
24 h HR Z-score	−0.22 ± 1.39	−0.21 ± 1.24	−0.66 ± 1.35	0.287
SBPL/24 h [%]	57.8 ± 19.4	16.9 ± 10.6	7.8 ± 6.2	<0.001[1,2,3]
DBPL/24 h [%]	20.5 (12.5–36.5)	10.0 (5.5–16)	3.0 (1–6)	<0.001[1,2,3]
SBP DIP [%]	11.8 ± 5.5	11.6 ± 4.9	12.9 ± 4.3	0.509
DBP DIP [%]	16.4 ± 8.6	17.6 ± 7.5	19.6 ± 7.0	0.203
Morning BP surge [mm Hg]	10.9 ± 12.0	13.4 ± 8.1	15.2 ± 8.1	0.141
AASI	0.4 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.141

SBP – systolic blood pressure; **DBP** – diastolic blood pressure; **ABPM** – ambulatory blood pressure monitoring; **MAP** – mean arterial pressure; **PP** – pulse pressure; **HR** – heart rate; **bpm** – beats per minute; **SBPL** – systolic blood pressure level; **DBPL** – diastolic blood pressure level; **DIP** – dipping; **BP** – blood pressure; **AASI** – ambulatory arterial stiffness index.
[1] Primary hypertension vs. white-coat hypertension.
[2] Primary hypertension vs. control group.
[3] White-coat hypertension vs. control group.

Tab. 3. Office and ambulatory blood pressure in the study group

data), or median value and interquartile range (IQR) (for data with non-normal distribution). The sample size estimated based on the available literature with a statistical power of 0.8, $p = 0.05$, and an effect size of 0.50 had to be at least 30. The following tests were used (depending on the distribution of variables): Student's *t*-test, *U* Mann–Whitney test, Kruskal–Wallis test, ANOVA test [with post-hoc analysis using least significant difference (LSD) Fisher test], Pearson's linear correlation, Spearman rank correlation, chi-square test, Fisher's exact test, and receiver operating characteristic (ROC) analysis. Multivariate analysis was performed using a general multivariate regression model (GLM). Parameters that correlated blood pressure in univariate analysis with *p* below 0.10 were included in the model. A *p*-value below 0.05 was considered statistically significant.

RESULTS

The basic clinical parameters and results of key laboratory tests for the examined groups are presented in Tab. 1. There was no significant difference between children with PH, WCH, and CG regarding age and sex. Body weight, body weight Z-score, BMI, and BMI Z-score were significantly higher in children with PH compared to those with WCH and CG. All four of these anthropometric variables were higher in WCH patients compared to those with CG. There were 19 (33.9%) overweight and 17 (30.4%) obese children in the PH group and 16 (40.0%) and 8 (20.0%) in the WCH group, respectively. In the hypertensive group, the median duration of arterial hypertension was 7 (IQR: 2.5–17.0) months. The groups did not differ in kidney function, and all children had normal GFR. Uric acid levels were significantly higher in patients with PH compared to healthy children. Thirty-four (50.6%) patients with PH and 21 (52.5%) patients with WCH had elevated serum uric acid. There was no difference between the groups in total cholesterol and LDL cholesterol levels. HDL cholesterol levels were significantly lower, and triglyceride levels were significantly higher in patients with PH and WCH compared to healthy children.

The inflammatory markers are shown in Tab. 2. The concentration of hsCRP was significantly higher in children with PH compared to the control group. Neutrophil and monocyte counts were significantly higher in the groups with PH and WCH compared to the control group. The groups did not exhibit significant differences in concentrations

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Parameter	SBP Z-score	DBP Z-score	ABPM SBP 24 h Z-score	ABPM DBP 24 h Z-score	ABPM MAP 24 h Z-score
Age [years]	***R* = −0.183** ***p* = 0.040**	*R* = −0.002 *p* = 0.985	*R* = −0.081 *p* = 0.366	*R* = −0.006 *p* = 0.994	*R* = −0.077 *p* = 0.932
BMI Z-score	***R* = 0.316** ***p* < 0.001**	***R* = 0.234** ***p* = 0.008**	***R* = 0.347** ***p* < 0.001**	***R* = 0.191** ***p* < 0.032**	***R* = 0.265** ***p* < 0.003**
Weeks of gestation [weeks]	*R* = 0.140 *p* = 0.164	*R* = −0.011 *p* = 0.916	*R* = −0.104 *p* = 0.305	*R* = −0.037 *p* = 0.715	*R* = −0.012 *p* = 0.904
Birth weight [g]	*R* = −0.152 *p* = 0.196	*R* = −0.027 *p* = 0.819	*R* = −0.203 *p* = 0.083	*R* = −0.068 *p* = 0.565	*R* = −0.082 *p* = 0.486
Duration of hypertension [months]	***R* = 0.295** ***p* = 0.001**	*R* = 0.147 *p* = 0.100	*R* = 0.173 *p* = 0.053	*R* = 0.050 *p* = 0.576	*R* = 0.173 *p* = 0.052
hsCRP [mg/L]	*R* = 0.147 *p* = 0.100	*R* = 0.097 *p* = 0.282	*R* = 0.173 *p* = 0.053	*R* = 0.086 *p* = 0.338	*R* = 0.150 *p* = 0.093
IL-18 [pg/mL]	*R* = 0.027 *p* = 0.764	*R* = −0.050 *p* = 0.579	*R* = −0.965 *p* = 0.283	***R* = −0.206** ***p* = 0.020**	***R* = −0.194** ***p* = 0.030**
Neutrophils [×10³/μL]	*R* = 0.172 *p* = 0.239	***R* = 0.239** ***p* = 0.007**	***R* = 0.290** ***p* = 0.001**	***R* = 0.342** ***p* < 0.001**	***R* = 0.330** ***p* < 0.001**
Monocytes [×10³/μL]	*R* = 0.153 *p* = 0.087	***R* = 0.235** ***p* = 0.008**	***R* = 0.225** ***p* = 0.012**	***R* = 0.258** ***p* = 0.004**	***R* = 0.222** ***p* = 0.012**
Lymphocytes [×10³/μL]	*R* = 0.099 *p* = 0.268	*R* = 0.022 *p* = 0.805	***R* = 0.215** ***p* = 0.016**	***R* = 0.178** ***p* = 0.046**	***R* = 0.186** ***p* = 0.037**
Platelets [×10³/μL]	*R* = 0.151 *p* = 0.091	***R* = 0.188** ***p* = 0.035**	***R* = 0.192** ***p* = 0.031**	***R* = 0.261** ***p* = 0.003**	***R* = 0.256** ***p* = 0.004**
MPV [fL]	*R* = −0.110 *p* = 0.219	*R* = −0.135 *p* = 0.131	*R* = −0.105 *p* = 0.243	*R* = −0.082 *p* = 0.361	*R* = −0.152 *p* = 0.089
NLR	*R* = 0.095 *p* = 0.288	***R* = 0.209** ***p* = 0.019**	*R* = 0.085 *p* = 0.343	***R* = 0.200** ***p* = 0.027**	***R* = 0.179** ***p* = 0.045**
PLR	*R* = 0.500 *p* = 0.579	*R* = 0.155 *p* = 0.083	*R* = −0.046 *p* = 0.609	*R* = 0.069 *p* = 0.445	*R* = 0.054 *p* = 0.552
MLR	*R* = 0.093 *p* = 0.301	***R* = 0.234** ***p* = 0.008**	*R* = 0.017 *p* = 0.853	*R* = 0.140 *p* = 0.118	*R* = 0.103 *p* = 0.252
MNR	*R* = −0.074 *p* = 0.409	*R* = −0.124 *p* = 0.168	***R* = −0.182** ***p* = 0.041**	***R* = −0.192** ***p* = 0.031**	***R* = −0.197** ***p* = 0.027**
PMPVR [10¹²]	***R* = 0.182** ***p* = 0.041**	***R* = 0.222** ***p* = 0.012**	***R* = 0.198** ***p* = 0.026**	***R* = 0.241** ***p* = 0.007**	***R* = 0.272** ***p* = 0.002**
Uric acid [mg/dL]	*R* = 0.095 *p* = 0.291	***R* = 0.184** ***p* = 0.039**	*R* = 0.135 *p* = 0.131	***R* = 0.234** ***p* = 0.009**	***R* = 0.186** ***p* = 0.037**
Total cholesterol [mg/dL]	*R* = 0.074 *p* = 0.411	***R* = 0.176** ***p* = 0.048**	*R* = 0.031 *p* = 0.734	*R* = 0.145 *p* = 0.106	*R* = 0.058 *p* = 0.518
LDL cholesterol [mg/dL]	*R* = 0.018 *p* = 0.845	*R* = 0.128 *p* = 0.154	*R* = −0.003 *p* = 0.978.	*R* = 0.093 *p* = 0.300	*R* = 0.011 *p* = 0.905
HDL cholesterol [mg/dL]	*R* = −0.049 *p* = 0.584	*R* = −0.049 *p* = 0.583	*R* = 0.583 *p* = −0.080	*R* = −0.075 *p* = 0.405	*R* = −0.081 *p* = 0.370
Triglycerides [mg/dL]	***R* = 0.226** ***p* = 0.011**	***R* = 0.234** ***p* = 0.008**	***R* = 0.187** ***p* = 0.036**	***R* = 0.261** ***p* = 0.003**	***R* = 0.233** ***p* = 0.009**
ACR [mg/g]	*R* = −0.019 *p* = 0.835	*R* = −0.043 *p* = 0.644	*R* = −0.008 *p* = 0.932	*R* = −0.036 *p* = 0.694	*R* = 0.004 *p* = 0.963

SBP – systolic blood pressure; **DBP** – diastolic blood pressure; **ABPM** – ambulatory blood pressure monitoring; **MAP** – mean arterial pressure; **BMI** – body mass index; **hsCRP** – high sensitivity C-reactive protein; **IL-18** – interleukin 18; **MPV** – mean platelet volume; **NLR** – neutrophil-to-lymphocyte ratio; **PLR** – platelet-to-lymphocyte ratio; **MLR** – monocyte-to-lymphocyte ratio; **MNR** – monocyte-to-neutrophil ratio; **PMPVR** – platelet-to-MPV ratio; **LDL** – low-density lipoprotein; **HDL** – high-density lipoprotein; **ACR** – albumin-to-creatinine ratio.

Tab. 4. Correlation coefficients of blood pressure in the studied children

of the remaining inflammatory markers, including IL-18. We combined children with PH and WCH and divided them into subgroups of lean patients (n = 36, 26 males, 10 females) and overweight/obese patients (n = 60, 39 males, 21 females). Lean patients were significantly older (median value – 16.2, IQR: 14.5–17.4 vs. median value – 14.8, IQR: 12.5–16.6 [years], p = 0.013) and had significantly lower lymphocyte counts (median value – 2.00, IQR: 1.70–2.38 vs. median value – 2.31, IQR: 1.93–2.77 [×10³/μL], p = 0.011) compared to overweight/obese patients. There were no other significant differences in markers of inflammation between the subgroups.

Office and ambulatory blood pressure in the studied children is presented in Tab. 3. All blood pressure indices,

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Parameter	AUC (95 CI)	*p*	Inflammatory marker cut-off value	Sensitivity	Specificity	ACC
hsCRP [mg/L]	**0.668**	**0.0005**	**1.50**	**0.750**	**0.600**	**0.667**
IL-18 [pg/mL]	0.526	0.6210	14.82	0.857	0.250	0.587
MPV [fL]	0.548	0.3519	10.00	0.786	0.339	0.587
Neutrophils [$\times 10^3$/µL]	**0.691**	**0.0001**	**3.48**	**0.589**	**0.757**	**0.683**
Monocytes [$\times 10^3$/µL]	**0.622**	**0.0148**	**0.49**	**0.696**	**0.586**	**0.635**
Lymphocytes [$\times 10^3$/µL]	**0.615**	**0.0230**	**2.26**	**0.536**	**0.671**	**0.611**
Platelets [$\times 10^3$/µL]	**0.606**	**0.0364**	**274.00**	**0.446**	**0.771**	**0.627**
Neutrophil-to-lymphocyte ratio (NLR)	**0.619**	**0.0181**	**1.34**	**0.679**	**0.543**	**0.603**
Platelet-to-lymphocyte ratio (PLR)	0.511	0.8303	89.36	0.843	0.268	0.587
Monocyte-to-lymphocyte ratio (MLR)	0.529	0.5841	0.23	0.589	0.557	0.571
Monocyte-to-neutrophil ratio (MNR)	**0.617**	**0.0204**	**0.17**	**0.571**	**0.625**	**0.595**
Platelet-to-MPV ratio (PMPVR) [10^{12}]	**0.606**	**0.0370**	**22.68**	**0.643**	**0.586**	**0.611**

AUC – area under curve; **CI** – confidence interval; **ACC** – accuracy; **hsCRP** – high sensitivity C-reactive protein; **IL-18** – interleukin 18; **MPV** – mean platelet volume.

Tab. 5. Diagnostic accuracy of inflammatory markers in predicting primary hypertension

Blood pressure (dependent variable)	R^2	Independent variable	Standardised beta	*p*
Office SBP Z-score	10.27%	BMI Z-score	0.294	<0.001
		PMPVR [10^{12}]	0.133	0.124
Office DBP Z-score	11.44%	MLR	0.217	0.011
		Platelets [$\times 10^3$/µL]	0.191	0.027
		BMI Z-score	0.182	0.036
ABPM 24 h SBP Z-score	17.60%	Neutrophils [$\times 10^3$/µL]	0.365	0.005
		BMI Z-score	0.258	0.004
		NLR	–0.222	0.071
ABPM 24 h DBP Z-score	16.93%	MLR	0.305	0.002
		Lymphocytes [$\times 10^3$/µL]	0.253	0.010
		IL-18 [pg/mL]	–0.197	0.019
		MNR	–0.189	0.029
		PMPVR [10^{12}]	0.158	0.073
ABPM 24 h MAP Z-score	17.26%	Neutrophils [$\times 10^3$/µL]	0.210	0.027
		IL-18 [pg/mL]	–0.209	0.012
		PMPVR [10^{12}]	0.172	0.057
		BMI Z-score	0.161	0.066

SBP – systolic blood pressure; **DBP** – diastolic blood pressure; **ABPM** – ambulatory blood pressure monitoring; **MAP** – mean arterial pressure; **BMI** – body mass index; **PMPVR** – platelet-to-MPV ratio; **MLR** – monocyte-to-lymphocyte ratio; **NLR** – neutrophil-to-lymphocyte ratio; **MNR** – monocyte-to-neutrophil ratio; **IL-18** – interleukin 18.

Tab. 6. Predictors of blood pressure in the studied children (multivariate regression)

as well as blood pressure loads, were significantly higher in children with PH compared to those with WCH and healthy children. Additionally, children with WCH exhibited significantly higher values for the mentioned variables compared to healthy children. There were no differences between the groups regarding heart rate, SBP DIP, DBP DIP, morning blood pressure surge, and AASI.

Determinants of blood pressure in the entire group of 126 patients are presented in Tab. 4. In the studied children, blood pressure correlated positively with neutrophil, lymphocyte, and platelet counts, NLR, MLR, and PMPVR. Conversely, blood pressure correlated negatively with IL-18 levels and MNR. In addition, blood pressure also correlated positively with BMI Z-score and levels of uric acid, total cholesterol, and triglycerides.

In the group of 126 patients, the following significant correlations of indices of subclinical inflammation were also identified: lymphocyte and platelet counts, and PMPVR correlated negatively with age ($R = -0.238$, $p = 0.007$, $R = -0.346$, $p < 0.001$, $R = -0.296$, $p < 0.001$). Neutrophil, monocyte, and lymphocyte counts correlated positively with BMI Z-scores ($R = 0.341$, $p < 0.001$, $R = 0.314$, $p < 0.001$,

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$R = 0.239$, $p < 0.007$); IL-18 correlated negatively with birth weight ($R = -0.337$, $p = 0.003$) and the duration of gestation ($R = -0.228$, $p = 0.023$); hsCRP and IL-18 correlated positively with the duration of hypertension ($R = 0.281$, $p = 0.036$, $R = 0.210$, $p = 0.018$). MNR correlated positively and platelet count, PLR, and PMPVR correlated negatively with AASI ($R = 0.189$, $p = 0.034$, $R = -0.248$, $p = 0.005$, $R = -0.247$, $p = 0.005$, $R = -0.234$, $p = 0.008$), MPV correlated positively and PMPVR correlated negatively with morning blood pressure surge ($R = 0.200$, $p = 0.025$, $R = -0.180$, $p = 0.044$). Regarding biochemical parameters, uric acid correlated positively with hsCRP concentration, and neutrophil and monocyte counts ($R = 0.248$, $p = 0.005$, $R = 0.179$, $p = 0.045$, $R = 0.227$, $p = 0.011$); HDL cholesterol correlated negatively with hsCRP, and neutrophil, monocyte, and lymphocyte counts ($R = -0.270$, $p = 0.002$, $R = -0.268$, $p = 0.002$, $R = -0.295$, $p = 0.001$, $R = -0.228$, $p = 0.010$). In contrast, triglycerides correlated positively with neutrophil and lymphocyte counts and negatively with MNR ($R = 0.215$, $p = 0.016$, $R = 0.217$, $p = 0.015$, $R = -0.178$, $p = 0.046$).

The results of ROC analysis are presented in Tab. 5. ROC analysis demonstrated good diagnostic profiles (area under the curve, sensitivity, and specificity) for hsCRP, neutrophil, lymphocyte, monocyte, and platelet counts, as well as for NLR, MNR, and PMPVR as predictors of primary hypertension. Among the significant predictors, the highest sensitivity was found for hsCRP, specificity, and AUC for neutrophils.

The results of multivariate analysis of predictors of blood pressure are shown in Tab. 6. BMI Z-score was the only significant predictor of office SBP Z-score, while MLR, platelet count, and BMI Z-score were significant predictors of office DBP Z-score. For ambulatory blood pressure, neutrophil count and BMI Z-score predicted 24 h SBP Z-score; MLR, IL-18, lymphocyte count, and NLR predicted 24 h DBP Z-score; and neutrophil count along with IL-18 predicted 24 h MAP Z-score.

DISCUSSION

In our single-centre cross-sectional study, we found that children with primary hypertension exhibited higher levels of inflammatory markers compared to healthy peers but similar to children with white coat hypertension. hsCRP might be a promising marker of subclinical inflammation in PH. ROC analysis revealed that hsCRP and neutrophil count showed the best accuracy in predicting hypertension in adolescents. In addition, there were numerous positive correlations between markers of inflammation and blood pressure indices. Multivariate analysis revealed that complete blood count-derived inflammatory markers, particularly neutrophil count and monocyte–lymphocyte ratio, were significant predictors for blood pressure values in the analysed cohort.

In the last two decades, experimental studies have unveiled pathophysiological pathways linking immune system activation, blood pressure rise, and HMOD. According to current hypotheses, prohypertensive factors, such as sodium chloride and shear stress, promote the polarisation of naive T cells towards a proinflammatory Th17 phenotype, stimulate the production of cytokines, weaken anti-inflammatory actions, and impair the immunosuppressive function of regulatory T lymphocytes (Tregs)[19,20]. Activated immune cells produce reactive oxygen species (ROS) and proinflammatory cytokines, such as interleukin 17. Without the inhibitory influence of Tregs, these factors exacerbate sodium retention, constriction of vascular smooth muscle cells, and further blood pressure elevation[21].

C-reactive protein (CRP) is a significant cardiovascular risk factor and correlates with atherosclerosis burden and cardiovascular events in adults[10]. Elevated CRP has also been reported in children with cardiovascular risk factors such as dyslipidaemia or arterial hypertension. Notably, paediatric studies by Trojanek, Wasilewska, and Hou et al. showed that serum hsCRP levels were significantly higher in hypertensive patients than healthy peers[22–24]. In our study, the hsCRP level was significantly higher in children with PH than in the control group. ROC analysis demonstrated good diagnostic profiles for hsCRP as a predictor of arterial hypertension and revealed the highest sensitivity for hsCRP among all analysed indices.

IL-18 and its receptor are expressed on endothelial cells, vascular smooth muscle cells, and macrophages[25], suggesting a potential role in vascular disease. Yamagami et al. showed that levels of IL-18 were higher in men than in women, and in patients with hypertension, compared to those without[12]. In his literature review, Rabkin analysed five studies comparing serum IL-18 concentration in patients with and without hypertension. In four out of five studies, individuals with hypertension had significantly higher levels of IL-18[11]. In our study, the groups did not differ significantly in IL-18 levels, but IL-18 was a significant predictor of ambulatory blood pressure in multivariate analysis.

Interestingly, IL-18 also correlated positively with the duration of hypertension and negatively with birth weight and the duration of pregnancy. The possible mechanism underlying this association remains unclear. Serum IL-18 levels were elevated in children with intrauterine growth retardation compared to control infants, which may point to elevated subclinical inflammation in children with low birth weight[26].

White blood cells (WBCs) and their subtypes, along with platelets, are the essential players in the inflammatory cascade. Therefore, blood cell parameters and indices like NLR, LMR, and PLR have garnered increasing attention in chronic inflammation diseases. They are related to cardiovascular diseases in adults, including atherosclerosis, heart failure, acute coronary syndromes, and arterial hypertension[9]. Hou showed that the WBC count, neutrophil count, and NLR were significantly higher in hypertensive children compared to the control group[24]. Similarly, Musiał et al. found higher NLR and PLR but lower LMR in paediatric patients with PH compared to their healthy peers[27]. In our study, basic inflammatory markers (neutrophil and monocyte counts) were significantly higher in the groups with

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primary hypertension and white coat hypertension than in the control group. Moreover, ROC analysis showed that neutrophil, monocyte, lymphocyte counts, and NLR, MNR, and PMPVR values might predict the presence of primary hypertension. Also, in the overall group of 126 patients, NLR, MLR, and PMPVR correlated positively with office diastolic blood pressure Z-scores, while all white blood cell populations, platelets, and PMPVR correlated positively with 24-hour blood pressure indices. Multivariate analysis revealed the strongest association between MLR, neutrophil count, and blood pressure. Notably, it is currently difficult to unequivocally assess the practical significance of our results, since the associations observed, although statistically significant, were not very strong.

Of note, in our study, patients with PH and WCH were characterised by similar levels of inflammatory markers, significantly higher than those of healthy peers. WCH has long been considered as an intermediate condition between normotension and sustained hypertension. Also, paediatric data indicate that patients with WCH may already have HMOD comparable to that of PH patients[4]. Our results reveal that subclinical inflammation is present in paediatric patients with WCH. Thus, this group of individuals should be closely monitored, and non-pharmacological measures should be implemented to reduce inflammation and prevent progression to sustained hypertension. It should be noted that patients with PH and WCH also exhibited similar metabolic disorders (comparable prevalence rates of obesity and overweight as well as similar uric acid levels and lipid parameters), which could have influenced their inflammatory parameters. Indeed, we showed that inflammatory parameters correlated with BMI Z-scores, uric acid levels, HDL cholesterol, and triglyceride concentrations.

Obesity in children and adolescents is a global health issue, often persisting into adulthood, and is associated with cardiometabolic and psychosocial comorbidities as well as premature mortality[28]. Inflammation, obesity, and insulin resistance frequently coexist and contribute to the development of cardiovascular diseases. In their systematic review, Silva et al. showed that obese patients had higher CRP concentrations than non-obese individuals[29]. In our study, more than 60% of PH and more than 50% of WCH patients were overweight or obese. We found a positive correlation between BMI Z-score and neutrophil, monocyte, and lymphocyte counts. In multivariate analysis, BMI Z-score was found to be an independent predictor of systolic blood pressure. Importantly, the inclusion of BMI in multivariate analysis did not eliminate inflammatory markers as predictors of blood pressure value.

The strengths of our study include the analysis of multiple inflammatory markers, detailed blood pressure analysis, and the inclusion of white-coat hypertension patients. However, limitations include relatively small study groups, no evaluation of hypertension-mediated organ damage (except for albumin-to-creatinine ratio), and the cross-sectional nature of the study preventing final conclusions on the causal relationship between a rise in blood pressure and the inflammatory process. Although we recommended no salt restriction in patients' diets one week before the study, we did not assess sodium intake (systematic dietary analysis or assessment of urinary sodium excretion), which may have affected the results. In addition, despite collecting a detailed medical history and performing a thorough physical examination, we did not, for example, conduct a systematised dental consultation, while Polish authors have suggested that oral health might be an important factor in the development of PH in children[7].

CONCLUSIONS

1. Patients with primary hypertension and white coat hypertension are characterised by similar levels of subclinical inflammation, which are significantly higher compared to healthy peers.
2. Complete blood count-derived indices, especially neutrophil count and MLR, can serve an important adjuncts to the clinical evaluation of paediatric patients with primary hypertension.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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Author contribution

Original concept of study: KDJ, PK. Collection, recording and/or compilation of data: KDJ, AB, MS, ASE. Analysis and interpretation of data: KDJ, AB, MS, ASE, PS. Writing of manuscript: KDJ, AB, MS, ASE, PS. Critical review of manuscript: PS. Final approval of manuscript: PS.

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