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Health measurement profile of older adults in Sleman District, Yogyakarta: its correlation with low-grade chronic inflammation in hypertension

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ABSTRACT

The older adult often experiences a low-grade chronic inflammation that commonly manifests in various conditions without infection, including hypertension. The serum neutrophil-to-lymphocyte ratio (NLR) and hyperuricemia are important markers for various diseases including hypertension. Older adult accounts for 17.33% of the total population of Yogyakarta Special Province, which is the highest compared to other provinces. The study aimed to evaluate the relationship between NLR and hyperuricemia with hypertension among adult patients in Sleman District, Yogyakarta, Indonesia. It was a community-based cross-sectional nested study involving 90 older adults aged ≥74 y.o. living around of the Sleman Health and Demographic Surveillance System (HDSS). Data of demographic and health characteristics of the subjects were collected. Independent t test, and Mann Whitney test were used to analyze mean differences between normotensive and hypertensive groups. Multivariate analysis with logistic regression was used to analyze correlation between all variables. The results showed 59 respondents (65%) suffered from hypertension and 31 (35%) respondents had normal and pre-hypertension. No significantly different in almost of the subject characteristics between the normotensive and the hypertensive groups was observed (p>0.05). However, significantly different between the normotensive group and the hypertensive group was observed in the history of hypertension, blood pressure/BP, mean arterial pressure/MAP, abdominal circumstance/AC, fasting blood glucose/FBG, triglyceride, and hemoglobin (p<0.05). No significantly different in the NLR and HsCRP levels of the normotensive group compared to the hypertensive groups were observed (p>0.05). However, the uric acid level of the hypertensive group [5.6 (2.9-9.4 mg/dL)] was significantly higher than that the normotensive group [4.7 (2.9-8.0 mg/dL)] (p=0.042), although it was no significantly relationship with hypertension (p>0.05). In conclusion, there is no relationship between NLR, HsCRP and uric acid with hypertension among middle old and oldest old in Sleman District.

Keywords:
low grade inflammation;
hyperuricemia;
hypertension;
neutrophil lymphocyte ratio;
older adult provinsi

ABSTRAK

Lansia seringkali mengalami peradangan kronis tingkat rendah yang umumnya bermanifestasi dalam berbagai kondisi tanpa infeksi, termasuk hipertensi. Rasio serum neutrofil-limfosit (*neutrophil-to-lymphocyte ratio*/NLR) dan hiperurisemia merupakan penanda penting untuk berbagai penyakit termasuk hipertensi. Lansia menyumbang 17,33% dari total penduduk Provinsi Daerah Istimewa Yogyakarta, tertinggi dibandingkan

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provinsi lain. Penelitian ini bertujuan untuk mengevaluasi hubungan NLR dan hiperurisemia dengan hipertensi pada pasien dewasa di Kabupaten Sleman, Yogyakarta, Indonesia. Ini adalah penelitian potong lintang bersarang berbasis komunitas yang melibatkan 90 orang lansia berusia ≥74 tahun yang tinggal di sekitar Sleman Health and Demographic Surveillance System (*Health and Demographic Surveillance System*/HDSS). Data karakteristik demografi dan kesehatan subjek dikumpulkan. Uji t independen dan uji Mann Whitney digunakan untuk menganalisis perbedaan rata-rata antara kelompok normotensi dan hipertensi. Analisis multivariat dengan regresi logistik digunakan untuk menganalisis korelasi seluruh variabel. Hasil penelitian menunjukkan 59 responden (65%) menderita hipertensi dan 31 (35%) responden normal dan pra hipertensi. Tidak ada perbedaan yang signifikan pada hampir semua karakteristik subjek antara kelompok normotensif dan hipertensi yang diamati (p>0,05). Namun terdapat perbedaan bermakna antara kelompok normotensi dan kelompok hipertensi pada riwayat hipertensi, tekanan darah/TD, tekanan arteri rata-rata/MAP, keadaan abdominal/AC, glukosa darah puasa/FBG, trigliserida, dan hemoglobin (p<0,05). Tidak ada perbedaan signifikan antara kadar NLR dan HsCRP kelompok normotensi dibandingkan dengan kelompok hipertensi (p>0,05). Namun, kadar asam urat kelompok hipertensi [5,6 (2,9-9,4 mg/dL)] secara signifikan lebih tinggi dibandingkan kelompok normotensi [4,7 (2,9-8,0 mg/dL)] (p=0,042), meskipun tidak terdapat hubungan bermakna dengan hipertensi (p>0,05). Kesimpulannya, tidak ada hubungan NLR, HsCRP dan asam urat dengan kejadian hipertensi pada lansia paruh baya dan lanjut usia di Kabupaten Sleman.

INTRODUCTION

In 2017, the Ministry of Health of Republic of Indonesia reported that the world's population is currently in the era of population over 60 years, exceeding 7% of the total population. The Central Statistics Agency of Republic of Indonesia reported that the number of older adults who are > 65 y.o. in 2020 was 10.7% of the total population and it is estimated to reach 19.9% in 2045. In Yogyakarta in 2020, the older adult population was 379,214 people (9.76% of the total population) with a life expectancy of 74 yr for men and 76 yr for women.[1-3]

The Framingham study reported that 90% of patients > 65 y.o. who initially have normal blood pressure will develop hypertension several years later. The rate of diagnosis of hypertension increases dramatically over the age of 75 y.o. reaching 85.6% of women and 80% of men. Older adults are a vulnerable population due to often experience the chronic inflammatory process. This low-grade chronic inflammation occurs in the absence of infection and represents a significant risk factor for morbidity such as diabetes, cardiovascular disease, stroke, atherosclerosis, cancer, and hypertension even mortality.[4,5] The chronic low-grade inflammation plays a role in the pathophysiology of hypertension. Several studies reported a positive relationship between hypertension and an increase in the number of leukocytes, C reactive protein (CRP), and interleukin-6 (IL-6).[4,6,7]

Uric acid was also considered an independent risk factor for hypertension. It is an independent determinant of the possibility of an increase in systolic blood pressure in later life.[8] An increase of uric acid is associated with hypertension through increased juxtaglomerular renin, decreased nitric oxide, increased vascular smooth muscle cell proliferation, increased atherosclerosis, and induce sodium sensitivity.[4,6,7] Uric acid may induce oxidative stress, endothelial dysfunction and stimulate vascular inflammation and fibrosis. Hyperuricemia stimulates nicotinamide adenine dinucleotide phosphate oxidase activity and oxygen

species synthesis, decreases nitric oxide production, activates the renin-angiotensin system that may contribute to arterial stiffness and increase vascular tone. Oxidative stress may mediate angiotensin 2 activation and stimulate vascular fibrosis and lead to hypertension. Hyperuricemia also induces the production of endothelin 1 which will increase arterial stiffness and induce high blood pressure.[9]

Neutrophil secretes elastase, myeloperoxidase, oxygen free radicals and various hydrolytic enzymes that are related to tissue damage and plaque disruption, and lead to hypertension. In vascular, reactive oxygen species (ROS) induce vasoconstriction and cause retention of water and sodium in the kidney that will lead to hypertension[7] Serum neutrophil-lymphocyte ratio (NLR) is a reliable biomarker for hypertension. Measurements are easy to perform only from the calculation of the differential leukocyte count, inexpensive and very widely available compared to other chronic inflammatory biomarkers.[7,10-13] The NLR shows a relationship between innate and adaptive cellular immune responses during various conditions. The normal value of NLR is between 1-2. If the value is > 3.0 or < 0.7 in adults, it is indicating pathological conditions. Serum NLR between 2.3-3 may serve as a warning condition such as cancer, atherosclerosis, infection, inflammation, psychiatric disorders, and stress. Serum NLR is a good predictor to differentiate severe disease and mild disease. It is cheap, simple, and easily available for inflammation marker with high sensitivity and low specificity.[14]

The Special Region of Yogyakarta (DIY) is a province with the largest portion of the population aged over 60 y.o. nationally. Based on data from the Directorate General of Population and Civil Registration (DUKCAPIL), the number of elderly residents in DIY will reach 637,353 in December 2021.[15] That number accounts for 17.33% of the total population of DIY, which is 3.68 million people. This portion is the largest compared to other provinces and exceeds the national average of only 11.01%.[15] The DIY is a province that has the highest life expectancy among the provinces in Indonesia, which is 74 y.o. for men and 76 y.o. for women.[3] Studies examining NLR with hypertension in the older adult population who achieve middle-old (75-84 y.o.) and oldest-old (≥85 y.o.) have never been conducted before in the Sleman Distict. This study was conducted to investigate whether this inflammatory process is also a characteristic of hypertensive patients who reach the age of older adults in the Sleman District, DIY, Indonesia.

MATERIAL AND METHODS

Design, time, and location of study

This a community-based cross-sectional analytic study was conducted in the Melati and Depok Subdsitrict, the Sleman District, DIY, Yogyakarta through the Health and Demographic Surveillance System (HDSS) nested research from September-November 2021. Sleman District, a semi-urban city, consists of 17 sub-districts and 86 villages and is 574.82 km^2 wide, with a population of 1.136.474 in 2021, and 3.14 % are >74 y.o. The Sleman HDSS is a longitudinal household-based survey, and the survey has been conducted annually since 2015.[15]

Subjects of study

The population study were all hypertensive and non-hypertensive patients aged ≥74 y.o. who met the inclusion and exclusion criteria. The inclusion criteria were older adults ≥74 y.o. for men and ≥76 y.o. for women, who were engaging in normal daily life activities and were willing to take part in the study. The exclusion criteria were having an active infection, being

hospitalized, chronic obstructive pulmonary disease (COPD), cancer, congestive heart failure (CHF) with New York Heart Association (NYHA) functional classification of class III and class IV, acute coronary heart disease, acute stroke, liver cirrhosis, undergoing chemotherapy or immunosuppressant treatment, disturbances in daily activities or paralysis or blindness, undergoing hemodialysis, taking immunosuppressants or steroids or having bone marrow disorders.

A cluster sampling approach was used to collect samples from older adults. Older adults aged ≥74 y.o. with a frailty index <2 were selected from data extraction of HDSS cycles 2-6. The village cadres were involved to assist in the recruitment of the elderly who met the inclusion and exclusion criteria during pandemic COVID-19. Subjects were taken until a total of 90 patients were obtained. The subjects were categorized into old age (74 y.o.), middle old (75-84 y.o.) and oldest-old (≥85 y.o.).[16]

Sample size estimation

A previous study evaluating NLR in newly diagnosed non-diabetic hypertensive patients with ascending aortic dilatation had a result of r = 0.524.[17] It has an estimated sample size total of 90 samples combined with estimation using WHO sample size determinator in health study for single population mean (people ≥74 y.o.). Based on previous study by Avşar *et al.*,[18] the standard deviation of the study was 0.27. The clinical significance difference was obtained from the average neutrophil lymphocyte ratio value of 2.67 for the white coat hypertension group compared to 2.46 in the normal group. The sample size of the calculation results added with an anticipated loss of 10%, namely 2, so the total sample is 16. The biggest estimated sample size total of 90 people was then taken.

Procedure of study

The detailed explanation concerning this study was provided and an informed consent forms were obtained from all subjects. Medical history such as hypertension, diabetes, cardiovascular disease, stroke, and lifestyle habits (smoking, and alcohol consumption) was collected by questionnaire. Smoking was defined as the current state of tobacco consumption. Cadres calculate geriatrics (≥74 y.o.) based on the geriatric frailty index (5 validated questions) then for subjects' eligibility it is carried out by a research team. Alcohol consumption was categorized as non-drinkers (< 1 drink per wk) or drinkers (≥ 1 drink per wk). All subjects were measured for weight and height with clothes without shoes, upper arm circumference (UAC), and abdominal circumference (AC). Subjects were also assessed for independence with the Barthel index to ensure that the inclusion criteria were older adults who could carry out normal daily activities. Subjects' blood pressure was measured after 5 min of rest with a calibrated digital sphygmomanometer in a sitting position and 2 measurements were made 5 min apart and then averaged.[9] This measurement was to exclude mask hypertension in meeting time restrictions during the COVID-19 pandemic. For routine blood examination we used Sysmex KX 21 with the reagent, which is a closed system from the tool in the Laboratory of Clinical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada. Creatinine was measured by the Jaffe method and uric acid was measured by Photometer Mikrolab 300 with reagent Dyasis. The diagnosis of hypertension followed the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII (JNC VII) when the subject was on hypertension therapy, or the systolic blood pressure was 140 mmHg or diastolic 90 mmHg (TABLE 1).[19]

TABLE 1. Diagnosis of hypertension based on JNC VII

Blood pressure	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Prehypertension	120-139	80-89
Hypertension (HT) stage I	140-159	90-99
Hypertension stage (HT) 2	≥160	≥100

Hyperuricemia was defined when uric acid levels were 7 mg/dL in men and 6 mg/dL in women, or if the patient was taking uric acid-lowering drugs. Body mass index (BMI) was calculated by dividing weight in kg by height in $m.^2$ The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Protocol of the study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia with number of KE/FK/0495/EC/2021.

Statistical analysis

Subjects were divided into two groups i.e. normotensive (blood pressure <140/90 mmHg) and hypertensive group (≥140/90 mmHg) according to JNC VII. Continuous variables were expressed in terms of mean ± standard deviation (SD) for a normal distribution and median (interquartile range) for an abnormal distribution. The normality test used Kolmogorov-Smirnov tests and examination of the normal distribution graph. The categorical variables are presented in percentages. The independent t test, Mann Whitney test and Anova test were used to analyze mean differences between hypertensive and non-hypertensive groups. Multivariate analysis with logistic regression was used to analyze correlation between all variables. All statistical analyses were performed with SPSS 23 (IBM Corp., Armonk, NY) and two-tailed results with p-value < 0.05 were considered statistically significant.

RESULTS

In this study, 59 respondents (65%) suffered from hypertension stage 1 and 2 and 31 (35%) respondents had normal and pre-hypertension. The characteristics of subject are presented in TABLE 2. No significantly different in almost of the subject characteristics between the normotensive group and the hypertensive group was observed (p>0.05). However, significantly different between the normotensive group and the hypertensive group was observed in the history of hypertension (14 subjects or 45.2% vs. 56 subjects or 94.9%; p=0.000), blood pressure/BP [129 (100-135 mmHg) vs. 150 (120-189 mmHg); p<0.001 in systolic; 74 (50-80 mmHg vs. 90 (70-103 mmHg); p<0.001 in diastolic], mean arterial pressure/MAP [90 (73.3-106.7 mmHg) vs. 106.7 (93.3-131.7 mmHg); p<0.001], abdominal circumstance/AC (84.84 ± 13.5cm vs. 91.15 ± 11.22cm; p=0.020), fasting blood glucose/FBG [93 (79-150 mg/dL) vs. 99 (56-269 mg/dL); p=0.037], triglyceride [94 (64-259 mg/dL) vs. 119 (68-312 mg/dL); p=0.007], and hemoglobin (12.73 ±1.58 ng/dL vs. 13.55 ± 1.45 ng/dL; p=0.016) (TABLE 2). Although the mean of the triglyceride and hemoglobin levels of the hypertension group were statistically significant higher than those the normotensive group, these both parameters were within normal value and did not have clinically significant effects.

TABLE 2. Characteristics of the patients

Characteristics	Normal-pre HT (n=31)	HT stage 1-2 (n=59)	p
Age			
• Total [median (min-max) y.o.]	79 (74-91)	80 (74-98)	0.264
• Old [n (%)]	4 (12.9)	3 (5.1)	
• Middle old [n (%)]	21 (67.7)	44 (74.6)	0.419
• Oldest old [n (%)]	6 (19.4)	12 (20.3)	
Gender [n (%)]			
• Male	16 (51.6)	31 (52.5)	0.933
• Female	15 (48.4)	28 (47.5)	
Smoker [n (%)]			
• Non-smoker	19 (61.3)	39 (66.1)	
• Smoker	4 (12.9)	10 (16.9)	0.582
• Ex-smoker	8 (25.8)	10 (16.9)	
History of hypertension [n (%)]			
• Yes	14 (45.2)	56 (94.9)	0.000*
• No	17 (54.8)	3 (5.1)	
Hypertension medication [n (%)]			
• Yes	13 (41.9)	27 (45.8)	0.728
• No	18 (58.1)	32 (54.2)	
Pain medication [n (%)]			
• Yes	4 (12.9)	6 (10.2)	0.732
• No	27 (87.1)	53 (89.8)	
Uric acid medication [n (%)]			
• Yes	2 (6.5)	2 (3.4)	0.606
• No	29 (93.5)	57 (96.6)	
BMI [median (min-max) kg/m^2	22.6 (14.3-33.6)	22.6 (16.1-35)	0.696
Nutritional status [n (%)]			
• Underweight (<18.5 kg/m^2)	7 (22.6)	7 (11.9)	
• Normal (18.50-22.9 kg/m^2)	10 (32.3)	28 (47.5)	0.963
• Overweight (23-24.9 kg/m^2)	4 (12.9)	8 (13.6)	
• Obese (≥25 kg/m^2)	10 (32.3)	16 (27.1)	
BP [median (min-max) mmHg]			
• Systolic	129 (100-135)	150 (120-189)	<0.001*
• Diastolic	74 (50-80)	90 (70-103)	<0.001*
MAP [median (min-max) mmHg]	90 (73.3-106.7)	106.7 (93.3-131.7)	<0.001*
HR (mean ± SD times/min)	82.29 ± 11.47	79.97 ± 13.26	0.411
RR [median (min-max) times/min]	20 (16-24)	20 (16-84)	0.385
Temperature [median (min-max) ^{o}C]	36.6 (36.2-37)	36.6 (36-37.1)	0.332
Weight (mean ±SD kg)	53.62 ± 14.5	54 (39.9-89.7)	0.314
AC (mean ± SD cm)	84.84 ± 13.5	91.15 ± 11.22	0.020*

TABLE 2. Cont.

Variable	Normal-pre HT (n=31)	HT stage 1-2 (n=59)	p
Central obesity [n (%)]			
• Male (> 90 cm)	16 (51.6)	42 (71.2)	0.065
• Female (> 80 cm)	15 (48.4)	17 (28.8)	
UC [n (%) cm]	25 (18-36)	26 (21-39)	0.197
Barthel index [n (%)]	20 (17-20)	20 (14-20)	0.414
Geriatric depression scale [n (%)]	2 (0-6)	1 (0-11)	0.326
FBG [n (%) mg/dL]	93 (78-150)	99 (56-269)	0.037*
Urea (mean ± SD mg/dL)	30.71 ± 6.63	30.34 ± 6.32	0.795
Creatinine [n (%) mg/dL]	1.03 (0.61-1.67)	0.98 (0.50-1.73)	0.102
EGFR [n (%) mL/min/1.73 m^2]	66.8 (29.7-96.3)	69.3 (37.7-168.8)	0.346
Hyperuricemia [n (%)]			
• Yes	6 (19.4)	12 (20.3)	0.912
• No	25 (80.6)	47 (79.7)	
Total cholesterol (mean ± SD mg/dL)	187.26 ± 35.16	193.49 ± 40.92	0.474
HDL [median (min-max) mg/dL]	51 (31-61)	47 (17-63)	0.848
LDL (mean ± SD mg/dL)	118.37 ± 32.80	119.28 ± 27.41	0.909
Triglyceride [median (min-max) mg/dL]	94 (64-259)	119 (68-312)	0.007*
Leucocyte (mean ± SD $10^3/mm^3$)	6.95 ± 1.8	7.32 ± 1.94	0.381
Hemoglobin (mean ± SD ng/dL)	12.73 ± 1.58	13.55 ± 1.45	0.016*
Hematocrit (mean ± SD %)	37.91 ± 4.62	39.67 ± 4.34	0.076
Thrombocyte [median (min-max) $10^3/\mu L$]	252 (159-473)	253 (132-495)	0.779
Neutrophil (mean ± SD %)	60.75 ± 10.30	58.95 ± 10.29	0.431
Lymphocyte (mean ±SD %)	29.04 ± 8.79	30.85 ± 9.64	0.387
Monocyte [median (min-max) #]	10.5 (3.8-16.3)	9.3 (1.1-19.7)	0.352
Neutrophil [median (min-max) #]	4.4 (1.6-6.5)	4.2 (2.1-10.7)	0.696
Lymphocyte [median (min-max) #]	1.9 (0.6-4.5)	2.1 (0.7-8.3)	0.229
Monocyte [median (min-max) #]	0.7 (0.2-1.2)	0.7 (0.1-1.3)	0.857

Note: *significant ($p<0.005$); SD=standard deviation; HT=hypertension; BMI= body mass index; BP= blood pressure; MAP=means arterial pressure. HR= heart rate; RR=respiratory rate; AC=abdominal circumference; UC= upper arm circumference; FBG= fasting blood glucose; EFGR=estimated glomerular filtration rate; HDL=high density lipoprotein; LDL=low density lipoprotein; NLR=neutrophil-lymphocyte ratio.

TABLE 3. Uric acid level of patients with hypertension based on JNC 7 (n=86 excluding patients with allopurinol).

Type of hypertension	Uric acid (mg/dL)	p
Normal	5.94 ± 2.33	0.082
Prehypertension	4.75 ± 1.25	
HT stage 1	5.42 ± 1.59	
HT stage 2	5.95 ± 1.57	

No significantly different in the NLR and HsCRP levels of the normotensive group compared to the hypertensive groups were observed (p>0.05). However, the uric acid level of the hypertensive group [5.6 (2.9-9.4 mg/dL)] was significantly higher than that the normotensive group [4.7 (2.9-8.0 mg/dL)] (p=0.042) (TABLE 4), although it did not have clinically significant effects. Further analysis to compare the NLR level between controlled hypertension and uncontrolled hypertension was conducted (TABLE 5). The results showed, no significantly.

In this study, an achievement of normal blood pressure of some subjects was observed during in hypertensive treatment. Therefore, the NLR value between controlled and uncontrolled hypertension groups were compared (TABLE 5). However, no significantly different between the both groups were observed (p=0.836).

For some variables showing significantly different between normal-prehypertension and hypertension stage 1-2 (TABLE 2), multivariate analysis using logistic regression was conducted (TABLE 6). No significantly relationship between the variables with hypertension was observed (p>0.05).

TABLE 4. Inflammation markers levels (NLR, AU, HsCRP) of patients with hypertension

Inflammation marker	Normotension [median (min-max)]	Hypertension [median (min-max)]	p
NLR	2.22 (0.95-9.50)	2.00 (0.50-8.23)	0.410
Uric acid (mg/dL)	4.7 (2.9-8)	5.6 (2.9-9.4)	0.042*
HsCRP (mg/L)	1.7 (0.3-17.1)	1.2 (0.2-8.2)	0.524

HsCRP: high-sensitivity C-reactive protein; *significant (p<0.05)

TABLE 5. NLR level of patients with controlled and uncontrolled hypertension (n = 69)

Hypertension status	NLR (mean±SD)	p
Controlled (<140/90 mmHg; n=15)	2.19 ± 0.89	0.836
Uncontrolled (≥140/90 mmHg; n=54)	2.13 ±1.03	

TABLE 6. Multivariate analysis with hypertension group

Parameter	OR	95%CI	p
AC	1.019	0.977-1.064	0.377
FBG	1.012	0.989-1.035	0.321
Hemoglobin	1.367	0.964-1.940	0.080
Triglyceride	1.010	0.997-1.023	0.132
NLR	0.775	0.536-1.120	0.175
Uric acid	1.273	0.897-1.807	0.176

Note: AC=abdominal circumference; FBG=fasting blood glucose; NLR= neutrophil-lymphocyte ratio.

DISCUSSION

Hypertension in the elderly can be caused by physical changes such as decreased elasticity of the arteries. Decreased arterial elasticity occurs due to fracture of the aortic elastic lamella and thickening due to hyperplasia of the arterial intima. Increasing age reduces aldosterone production, increases net basal sympathetic nervous system, and norepinephrine, decreases β-adrenergic responsiveness, and baroreceptor sensitivity.[20] Aging can increase local secretion of angiotensin II resulting in vasoconstriction, increased renin, and aldosterone which results in increased sodium reabsorption, potassium secretion, and vascular tone that may lead to hypertension.[20] Aging, even in normotensive individuals, is characterized by an increase in pulse pressure.[22,23] This study found that even in the normotensive group the MAP was 90 (73.3-106.7 mmHg). Generally, the plasma renin activity at the age of 60 y.o. is 40-60% of the level in young individuals. One of the important pathophysiology considerations that plays a role in hypertension is chronic low-grade inflammation. Several studies have shown a positive relationship between hypertension and an increase in leukocyte count, CRP, and IL-6.[4,6,7]

Currently, chronic inflammation is thought to be a risk factor for various age-related diseases such as hypertension, diabetes, cardiovascular disease, stroke, atherosclerosis, and cancer. Several factors may initiate and cause this inflammatory response such as aging, an unbalanced diet, low sex hormones, and smoking. Compared with young people, older adult people always show a consistent increase in levels of inflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor-α (TNF-α). Reactive oxygen species also increases with aging and will disrupt mitochondria and cause dysfunction of cell aerobic metabolism.[4,5,21] Cell senescence leading to activation of the p53 tumor suppressor and/or cyclin-dependent kinase inhibitor p16. These aging cells secrete various inflammatory cytokines and cause low-grade inflammation. Immunosenescence, which is an age-related dysregulation of the innate immune system, is also characterized by a persistent immune response and can lead to increased susceptibility to cancer, autoimmune disease, infection, decreased immunization response, and delayed wound healing. Increased inflammation through the protease-activated receptor (PAR) will increase the activity of coagulation and fibrinolysis and the risk of atherosclerosis.[4,5] Increased proinflammatory cytokines, T lymphocyte infiltration-stimulating chemokines, and macrophages result in injury to blood vessels. In addition, there is an increase in TNF-α, matrix chemoattractant protein 1 (MCP-1), and Il-6 which cause endothelial dysfunction through upregulation of matrix metalloproteinase (MMP) so that increased collagen deposition, decreased elastin and increased vascular calcification which ends in arterial stiffness and leads to hypertension.[22]

Neutrophils have an important role in an individual's initial immune response against invading pathogens through several mechanisms such as phagocytosis, chemotaxis, ROS, granular proteins, and the production and release of cytokines. Neutrophils regulate the innate immune response which plays a role in recruiting, activating, programming other immune cells, secreting various pro-inflammatory and immunomodulatory cytokines and chemokines which can increase the recruitment and effector function of other immune cells such as dendritic cells, B cells, NK (natural killer) cells, CD4, CD8, and others. Neutrophils also play a role in adaptive immunity as key effectors during the systemic inflammatory

response (SIRS). Increasing the number of neutrophils influences increasing NLR.[24]

Neutrophil-leucocyte ratio is a reliable biomarker to show systemic inflammatory status that is easy to measure by calculating the differential leukocyte count. The measurement is cheap, and very widely available compared to other chronic inflammatory biomarkers. Although cheaper, the NLR has the same confidence value as the assessment of other inflammatory cytokines such as CRP, TNF-α, and IL-6. Thus, in population screening, NLR is easier to perform, and it is superior to total leukocytes in predicting and diagnosing inflammation.[7,10-13]

Several cross-sectional studies abroad have shown the possibility of NLR being positively associated with hypertension. The NLR has a positive correlation with vascular calcification and TNF-α levels. Generally, the higher the NLR, the higher the overall mortality. A 40 years of study involving 9,383 patients concluded that leukocyte counts, especially neutrophil counts, are important risk factors for hypertension[7,10-13,25] In contrast this study showed no significance relationship between the leucocyte, neutrophil, lymphocyte, NLR and HsCRP with hypertension in older adult (TABLE 6).

Hypertension is a chronic disease that can last the entire life and is one of the factors for metabolic syndrome (diabetes mellitus, hypertension, dyslipidemia, and central obesity). The mechanisms of increasing blood pressure which is one of the risk factors for cardiovascular disease in older adults include increased arterial stiffness, high sodium intake, increased obesity, lack of physical activity, alcohol consumption, increased cholesterol, and smoking. Several studies have demonstrated unique aging changes in the nitric oxide and angiotensin II pathways. This effect will increase matrix metalloproteinase type II (MMP2), calpain-1, ROS, and transforming growth factor (TGF)-β1 which causes structural and molecular changes in arteries.[4,6,7,23] Visceral fat tissue in obese individuals will also produce Il-6 and TNF-α. Smoking will also cause an increase in inflammation including ROS, and pro-inflammatory cytokines such as IL-6, TNF-α, and interleukin-1β (IL-1β).[4,5,20] This study found that subjects in the hypertension group (91.15 ± 11.22 cm) had a bigger AC compared to the normotensive group (84.84 ± 13.5 cm; p=0.020). The FBG in the hypertension group [99 (56-269 mg/dL)] in this study was higher compared to the normotensive group [93 (78-150 mg/dL); p=0.037]. The triglyceride level in the hypertension group [119 (68-312 mmHg)] was higher compared to the normotensive group [94 (64-259 mmHg); p=0.007]. Nowadays, evidence shows that hypertriglyceridemia is associated with increasing risk of atherosclerotic cardiovascular disease which lead to increase mortality.[26]

Uric acid increases the renin-angiotensin-aldosterone system, causes vascular rigidity of the cytoskeleton in endothelial cells and extracellular matrix fibrosis. Uric acid will stimulate the production of endothelin 1, which is a potent vasoconstrictor. A study demonstrated the role of uric acid in increasing oxidative stress and reducing nitric oxide bioavailability, changing non-cross-linked soluble elastin which will reduce arterial wall distensibility.[9] Experimental studies showed that hyperuricemia causes an increase in blood pressure through an increase in juxtaglomerular renin and a decrease in nitric oxide synthase expression in the macula dense. These changes cause arteriolar vasoconstriction in afferent and efferent, which will activate the renin-angiotensin system and increase blood pressure. Uric acid will also increase the proliferation of vascular smooth muscle cells through the activation

of specific mitogen-activated protein kinase (Erk1/2 and p38) and nuclear transcription factors (NF-kB and AP1). In addition, based on previous studies, uric acid can induce sodium sensitivity through activation of MAP kinase, PDGF and COX_2. Hyperuricemia can also cause hypertension through mechanisms of insulin resistance and pro-inflammatory conditions.[27-29] Experimental and clinical studies also showed a positive association with increased uric acid levels in patients with hypertension and obesity. A cohort study also confirmed that hyperuricemia can also cause hypertension through insulin resistance.[27,29]

Uric acid is associated with various inflammatory markers such as white blood cells, CRP, IL1, IL-6, IL-10, and IL-18 which has led to the theory that hyperuricemia is a pro-inflammatory condition.[27] This low-grade inflammatory condition is thought to have a role in the pathophysiology of hypertension. Two studies have shown that hyperuricemia is associated with leukocyte counts.[30,31] In Contrast, the previous studies done by Sevencan and Ozcan in 2019, show that no statistically significant differences were detected between the NLR and uric acid.[8] In this study, the results showed a no significantly correlation between uric acid and hypertension (TABLE 6).

One limitation of this study is that the subject was small that can not generalizable to other settings. Other inflammation markers were also not examined such as interleukin as a comparison among current biomarkers. The advantage of this study is that the population of subjects included the older adults who reach middle-old and oldest-old. Further research should be conducted in cohort and using ambulatory monitoring blood pressure to record blood pressure over 24 h.

CONCLUSION

In conclusion, there is no relationship between NLR, HsCRP and uric acid with hypertension among middle old and oldest old in Sleman District, Yogyakarta Special Region. Although previous studies showed that chronic inflammation has a role in the pathogenesis of hypertension and aging, in this study the relationship is not demonstrated. Another pathogenesis other than chronic inflammation might be involved in hypertensive older adults.

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