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Relation of neutrophil/lymphocyte ratio to resistant hypertension

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ABSTRACT

Objectives. Resistant hypertension has unfavourable effects on cardiovascular and other systems. The aim of this study was to investigate the association of neutrophil/lymphocyte (N/L) ratio and resistant hypertension. ***Methods.*** A total of 140 patients were included in the study. Ambulatory 24-hour blood pressure monitoring, transthoracic echocardiography and blood sample analyzing were performed in all patients. There were 60 patients with resistant hypertension group (mean age=55.1±9.7 years) and 80 patients with non-resistant hypertension group (mean age=56.8±14.1 years). ***Results.*** Mean neutrophil levels were significantly higher in resistant hypertension group (71.7±6.1% vs. 65.9±5.4%, $p<0.001$), while lymphocyte levels were significantly higher in non-resistant hypertension group (22±4.7% vs. 17.5±4.1%, $p<0.001$). N/L ratio was significantly higher in resistant hypertension group (4.3±1.2 vs. 3.1±0.9, $p<0.001$). In multivariate analysis, diabetes mellitus (odds ratio [OR]=2.857; 95% confidence interval [CI], 1.349-6.053; $p=0.006$), N/L ratio (OR=2.699; 95% CI, 1.821-4.002; $p<0.001$) and obesity (OR=3.429; 95% CI, 1.675-7.019; $p=0.001$) were independent predictors of resistant hypertension. ***Conclusion.*** The N/L ratio, which is cheaply and easily measurable laboratory data, is independently associated with resistant hypertension.

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Keywords: Resistant hypertension; ambulatory blood pressure monitoring, neutrophil/lymphocyte ratio

Introduction

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not treated appropriately [1]. Resistant hypertension has more unfavorable effects on cardiovascular and other systems when compared with non-resistant hypertension. Several risk factors including obesity, excessive alcohol consumption, high sodium intake,

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obstructive sleep apnea and undetected secondary forms of hypertension have been demonstrated for resistant hypertension [2].

Resistant hypertension is defined as persistent elevation of blood pressure above goal despite concurrent use of three antihypertensive drugs, each of unique class with a diuretic included among the treatment regimen, and with all drugs at target dose [2]. The main pathophysiological mechanisms of resistant hypertension have not been clearly understood. For many years, researchers have focused to determine the underlying pathophysiological mechanisms for better understanding the resistant hypertension and to produce new therapeutic targets to reduce the mortality and morbidity from cardiovascular disorders.

Cardiovascular disorders are the most important reason for death around the world [3, 4]. Recent years, with the growing understanding of the role of inflammation in cardiovascular disorders, studies have focused on to investigate the relation of inflammatory markers and cardiovascular outcomes.

Neutrophil/lymphocyte (N/L) ratio is the sign of balance between neutrophil and lymphocyte levels in the body and an indicator of systemic inflammation [3, 4]. The N/L ratio has been associated with poor outcomes in cardiovascular disorders [5-8]. Little is known, however, regarding the association of N/L ratio levels with resistant hypertension. The goal of this study was to evaluate the association of the N/L ratio with resistant hypertension.

Methods

Patients

This is a multicenter, cross-sectional study from four different outpatient clinics. We use official and ambulatuar blood pressure monitoring to diagnose resistant hypertension. Five hundred and eighty-two patients with hypertension for this study were screened between January and December 2015. The study population included 60 patients with resistant hypertension (21 female; mean age=55.1±9.7 years) and 80 patients with non-resistant hypertension as control group (26 female; mean age=56.8±14.1 years). Patients included in the study were older than 18 years and had both non-resistant hypertension and resistant hypertension. Age, gender, body mass index, risk factors, current therapy and biochemical measurements, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels were recorded.

The exclusion criteria were cardiovascular disease including coronary artery disease, congestive heart failure, congenital heart disease, moderate and severe valvular heart disease, peripheral vascular disease, established chronic renal failure or serum creatinine levels >1.5 mg/dl (132 μmol/l), chronic obstructive pulmonary disease, thyroid dysfunction, known malignancy, known inflammatory disease, hematological disease, autoimmune disease, acute infection, pregnancy, anticoagulant agent use, white blood cell count >12 000 cells per μL or <4000 cells per μL, and high body temperature >37.3 ^{0}C, anemia, other medication that would affect blood pressure such as nasal decongestants. Fifty-eight patients including 22 patients with coronary artery disease, 13 patients with congestive heart failure, 2 patients with chronic renal failure and 21 patients refused to participate were excluded from the study.

The class of antihypertensive drugs were thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARB), beta blockers and alfa adrenergic receptor antagonists. There were hundred and ninety-eight patients taking one or more drugs including diuretics.

A 12-lead electrocardiography and transthoracic echocardiography (TTE) were performed for each patient. This study complied with the Declaration of Helsinki, informed consent was obtained from all patients and the protocol was approved by our local ethics committee.

Echocardiographic study

TTE was performed by two independent echocardiographers with a 2.5-MHz transducer and harmonic imaging in the cardiology department according to the recommendations of the American Society of Echocardiography. Left ventricular systolic and diastolic diameters were measured by M-mode echocardiography. The left ventricular ejection fraction (LVEF) was assessed using with Teichholz method [9]. Additionally, diameter of the left atrium, abnormal blood flows due to valve insufficiency, and if present, the degree of valvular stenosis were evaluated with 2D, M-mode, Doppler, and tissue Doppler studies. Systolic pulmonary artery pressure was calculated by adding the estimated right atrial pressure to the right ventricle systolic pressure obtained from the tricuspid insufficiency peak velocity.

Blood Pressure Monitoring

Clinical blood pressure was measured 3 times in the seated position by a cardiologist using a mercury sphygmomanometer after 10 minutes resting. The average of the 3 measurements was used for the representative examination value. Proper cuff size was determined based on arm circumference. The measurement was performed under controlled condition in a quiet room.

Twenty-four hours ambulatory blood pressure monitoring was performed for all subjects with Space-Labs 90207 (Redmond, WA USA). The cuff was mounted on the non-dominant arm between 8 and 9 AM and removed 24 h later. Cuff size was chosen according to arm circumference. Device was programmed to register blood pressure at 30-min intervals in day-time and one hour intervals in night-time for the 24-h period. The majority of records were performed on working days. Subjects were instructed to maintain their usual activities and keep their arm immobile at the time of each cuff inflation. Valid records had to fulfill a series of pre-established criteria, including at least 80% of systolic blood pressure and diastolic blood pressure successful recordings during the day-time and night-time periods, 24-h duration, and at least one blood pressure measurement per hour. Evaluation was performed taking the mean values of day and night blood pressures into account. Subjects were classified as hypertensive if the day-time value of systolic blood pressure >135 mmHg or diastolic blood pressure >85 mmHg, or night-time value of systolic blood pressure >120 mmHg or diastolic BP>70 mmHg on ambulatory blood pressure monitoring according to recommendations for the management of hypertension in the European guidelines [10]. Resistant hypertension is defined as resistance to treatment when a therapeutic strategy that includes lifestyle modification plus a diuretic and two different classes of antihypertensive drugs at adequate doses fails to control systolic and diastolic blood pressure (10). Each reading was edited by the computer and manually, and outliers (systolic blood pressure <80 mm Hg or >260 mm Hg; or diastolic blood pressure <40 mmHg or >150 mmHg; and heart rate <40 or >150 beats/min) were deleted.

Blood Samples

In all patients, antecubital venous blood samples for the laboratory analysis were drawn on admission in the hospital. The blood samples were drawn in the morning. Common blood counting parameters were stored in citrate-based anticoagulated tubes and measured by Sysmex K-1000 auto analyzer within 5 minutes of sampling. Hematology tests are essential for determining the number of blood cells that are responsible for oxygen transport or hemostasis. Reference counts were obtained by a standardized Sysmex K-1000 auto analyzer (Sysmex Corporation, Kobe, Japan). Comparisons between HemoCue white blood cell and the reference analyser were assessed in several groups, namely white blood cell below normal, within normal range, above normal range, and at borderline between normal and abnormal. Glucose, creatinine, blood urea nitrogen, lipid profile (total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, triglyceride were determined by standard methods.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using Student t-test or Mann-Whitney U test between groups. Categorical variables were summarized as percentages and compared with the Chi-square test. The effects of different variables on resistant hypertension were calculated in univariate analysis for each. The variables for which the unadjusted p value was <0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination multivariate logistic regression analyses and we eliminated potential risk markers by using likelihood ratio tests. A two tailed p value <0.05 was considered significant and confidence interval was 95%. All statistical analyses were performed with the SPSS version 21 (SPSS Inc., Chicago, Illinois).

Results

The baseline demographic, biochemical characteristics, history of medicine use of patients in both groups are shown in Table 1. Age, gender, biochemical parameters, smoking, hypercholesterolemia were similar between groups. With respect to baseline laboratory status, fasting glucose, cholesterol parameters, blood urea nitrogen levels were not significantly different between groups (Table 1). The presence of diabetes mellitus, obesity and creatinine levels were significantly higher in the

Table 1. Baseline characteristics of patients in groups

Variable	*Non-resistant Hypertension (n=80)*	*Resistant Hypertension (n=60)*	*p*
Age, years	56.8±14.1	55.1±9.7	0.41
Gender, female/male	26/54	21/39	0.75
Body mass index, kg/m^2	25.2±4.1	27.9±4.1	<0.001
Obesity, n (%)	20 (25)	32 (53.3)	0.001
Smoking, n (%)	21 (26.3)	20 (33.3)	0.36
Hypercholesterolemia, n (%)	28 (35)	27 (45)	0.23
Diabetes mellitus, n (%)	16 (20)	25 (41.7)	0.005
Mean Official Blood Pressure			
Systolic (mmHg)	119.4±10.5	161.6±14.5	<0.001
Diastolic (mmHg)	70.7±7.8	108.9±11.8	<0.001
Heart rate, beats/min	74.3±9.3	75.3±9.8	0.54
Biochemical parameters			
Total cholesterol, mg/dl	184±39.7	173.5±38.5	0.11
High density lypoprotein, mg/dl	36.2±6.3	35.8±6.2	0.72
Low density lypoprotein, mg/dl	128.3±28.5	122.3±29.3	0.23
Plasma triglycerides, mg/dl	120.1±40	123.5±49.4	0.66
Fasting glucose, mg/dL	111.3±46.5	128.4±44.8	0.03
Blood urea nitrogen, mg/dL	23.4±7.5	23.8±7.3	0.93
Creatinine, mg/dL	1.15±0.26	1.35±0.35	<0.001
hs-CRP (mg/L)	3.9±2.2	7.5±4.2	<0.001
Current therapy			
Treated with 3 drugs, n (%)	19 (23.8)	47 (78.3)	<0.001
Treated with 4 drugs, n (%)	0	9 (15)	<0.001
Treated with 5 drugs, n (%)	0	4 (2.9)	0.02

Data are expressed as mean ± standart deviation. hs-CRP=high-sensitivity C-reactive protein

resistant hypertension group when compared to the other group (p=0.005, p=0.001, p<0.001, respectively). The mean systolic and diastolic blood pressures were significantly higher in resistant hypertension group (161.6±14.5 vs. 119.4±10.5, p<0.001; 108.9±11.8 vs. 70.7±7.8, p<0.001, respectively) (Table 1). High-sensitivity C-reactive protein (hs-CRP) levels were significantly higher in resistant hypertension group than in non-resistant hypertension group (7.5±4.2 vs. 3.9±2.2, p<0.001).

The ambulatory blood pressure monitoring and echocardiographic parameters for each group are shown in Table 2. Patients with resistant hypertension had significantly higher 24-h, day-time and night-time mean blood pressure levels. The mean LVEF was similar between groups (55.6±6.7 vs. 54.2±5.0, p=0.16).

Hemoglobin, white blood cell, platelet count and mean platelet volume were similar between groups. With respect to white blood cell distribution, mean neutrophil levels were significantly higher in resistant hypertension group (71.7±6.1% vs. 65.9±5.4%, p<0.001), while lymphocyte levels were significantly higher in non-resistant hypertension group (22±4.7% vs. 17.5±4.1%, p<0.001). N/L ratio was also significantly higher in resistant hypertension group (4.3±1.2 vs. 3.1±0.9, p<0.001) (Table 3). There were positive correlations between the N/L ratio and day-time systolic ambulatory blood pressure (r : 0.328, p<0.001) and night-time systolic ambulatory blood pressure (r : 0.427, p<0.001).

In the groups, some of variables that can be effective on resistant hypertension were significantly different between groups. Thus, the effects of multiple variables on the resistant hypertension analyzed with univariate and multivariate logistic regression analyses. The variables for which the unadjusted p value was <0.10 in univariate analysis were identified as potential risk markers for resistant hypertension and included in the full model. In multivariate logistic

Table 2. Comparison of ambulatory blood pressure monitoring and echocardiographic parameters of patients in groups

Variable	Non-resistant Hypertension (n=80)	Resistant Hypertension (n=60)	*p*
Mean 24-hour systolic ABP (mmHg)	118.2±10.9	146.5±14.9	<0.001
Mean 24-hour diastolic ABP (mmHg)	73.8±8.4	82±12.9	<0.001
Mean 24-hour heart rate	76±9.8	78.±9.7	0.24
Mean day-time systolic ABP (mmHg)	118.4±10.4	148.1±13.8	<0.001
Mean day-time diastolic ABP (mmHg)	71.9±7.2	83.7±14.9	<0.001
Mean night-time systolic ABP (mmHg)	107.6±11.3	140.6±11.2	<0.001
Mean night-time diastolic ABP (mmHg)	65.2±8.9	81.9±11.9	<0.001
Mean night/day systolic BP	0.91±0.09	0.95±0.11	0.001
Mean night/day diastolic BP	0.88±0.14	0.81±0.09	<0.001
Conventional echocardiography			
LVEDD, mm	50.5 ± 4.5	49.2 ± 4.5	0.09
LVESD, mm	32.5 ± 3.8	30.9 ± 4.5	0.02
IVS thickness, mm	12 ± 1.6	12.6 ± 1.5	0.04
PW thickness, mm	11.9 ± 1.4	12.2 ± 1.4	0.20
LVEF, %	55.6 ± 6.7	54.2 ± 5.0	0.16

Data are expressed as mean ± standard deviation. ABP=ambulatory blood pressure, BP=blood pressure, IVS=interventricular septum, LVEDD=left ventricular end-diastolic diameter, LVEF=left ventricular ejection fraction, LVESD=left ventricular end-systolic diameter, PW=posterior wall

regression analysis, diabetes mellitus (odds ratio [OR]=2.857; 95% confidence interval [CI], 1.349-6.053; *p*=0.006), N/L ratio (OR=2.699; 95% CI, 1.821-4.002; *p*<0.001) and obesity (OR=3.429; 95% CI, 1.675-7.019; *p*=0.001) were independent predictors of resistant hypertension (Table 4).

Discussion

In the present study, we hypothesized that N/L ratio as a marker of inflammatory status in the body could be associated with resistant hypertension and a widely available predictor for resistant hypertension in hypertensive patients. We found that N/L ratio was significantly higher in resistant hypertensive patients than in non-resistant hypertensive patients. Additionally, N/L ratio is independent predictor of resistant hypertension.

Hypertension is the most common condition seen

Table 3. Common blood counting parameters of patients

Variable	*Non-resistant Hypertension (n=80)*	*Resistant Hypertension (n=60)*	*p*
Hemoglobin, g/dL	12.4±1.6	12.5±1.5	0.57
White blood cell count, x 10^9/L	6.9±2.3	7.3±2.0	0.27
Platelet count, x 10^9/L	270±70	286.5±79.3	0.20
Red blood cell count, x 10^6/mL	4.7±0.8	4.8±0.9	0.98
Mean corpuscular volume, fl	84±5.4	85.3±5.7	0.20
Mean platelet volume, fl	8.8±0.8	8.9±0.9	0.64
White cell distribution			
Neutrophil, %	65.9±5.4	71.7±6.1	<0.001
Lymphocyte, %	22±4.7	17.5±4.1	<0.001
Eosinophils, %	2.2±0.5	2.1±0.7	0.47
Monocytes, %	6.8±1.4	6.4±1.4	0.11
Neutrophil/lymphocyte ratio	3.1±0.9	4.3±1.2	<0.001

Data are expressed as mean ± standard deviation

Table 4. Effects of various variables on resistant hypertension in logistic regression analyses

Variables	Univariate			Multivariate		
	Unadjusted OR	95% CI	*p*	Adjusted OR*	95% CI	*p*
Age	0.994	0.958 - 1.030	0.729			
Gender	1.337	0.522 – 3.424	0.545			
Diabetes mellitus	2.798	1.141 – 6.864	0.025	2.857	1.349 – 6.053	0.006
Smoking	1.737	0.690 – 4.376	0.241			
Hypercholesterolemia	1.637	0.690 – 3.887	0.264			
Obesity	3.934	1.643 – 9.419	0.002	3.429	1.675 – 7.019	0.001
Hemoglobin	1.075	0.836 – 1.383	0.571			
Neutrophil/lymphocyte ratio	2.878	1.872 – 4.426	0.046	2.699	1.821 – 4.002	<0.001

*Adjusted for, age, gender, diabetes mellitus, smoking, hypercholesterolemia, hemoglobin and neutrophil/lymphocyte.
OR= odds ratio, CI= confidence interval

in primary care and leads to myocardial infarction, stroke, renal failure, and death if not treated appropriately [1]. During last 20 years clinical investigations have demonstrated an important correlation between ambulatory blood pressure monitoring readings and prevalence and extent of cardiovascular events [11].

Resistant hypertension is defined as resistance to treatment when a therapeutic strategy that includes lifestyle modification plus a diuretic and two different classes of antihypertensive drugs at adequate doses fails to lower systolic value to 140 mmHg and diastolic blood pressure value to 90 mmHg [10]. Resistant hypertension has more unfavorable effects on cardiovascular and other systems when compared with non-resistant hypertension. Several risk factors have been demonstrated for resistant hypertension. Obesity, excessive alcohol consumption, high sodium intake, obstructive sleep apnea and undetected secondary forms of hypertension have been well established causes of resistant hypertension [2]. According to current literature, association between inflammatory status and hypertension has been demonstrated. Previous studies have suggested that there is a relation between hypertension and systemic inflammation [12]. The relationship between circulating subtype of white blood cell and hypertension has also been well documented [13, 14]. In a large cohort with a long follow-up period, Tatsukawa *et al.* [13] aimed to investigate the relationship between white blood cell count, including differential white blood cell count, and the incidence of hypertension over a 40-year period in 9,383 subjects who did not have hypertension at baseline. They concluded that the neutrophil and total white blood cell counts are significantly associated with the incidence of hypertension. Tian *et al.* [14] showed in their study that increased neutrophils and decreased lymphocytes are significantly correlated with the regulation of blood pressure and the development of hypertension. However, inflammatory status and resistant hypertension has not been fully elucidated. The purpose of the present study is to examine this relation. According to this study, inflammation has also been implicated in the development and the progression of resistant hypertension.

The effects of neutrophils on the development of hypertension may follow from their role in inflammation. Recent evidences suggest that the pro-inflammatory cytokines, especially IL-6 and IL-8, are associated with obesity [15, 16], diabetes mellitus [17], and cardiovascular disease [18]. IL-8 is also the main cytokine that responsible for neutrophil recruitment and activation [19]. Activated neutrophils adhere to vascular endothelium with higher affinity, which may result in capillary increased vascular resistance [20]. Activated neutrophils also release reactive oxygen specifies which contribute to oxidative stress [21, 22], and impair the endothelium-dependent vasorelaxation [23].

In respect to role of lymphocytes in hypertension, there is controversial data in the literature. Low grade activated immune system with lymphocyte subtypes cause the renal damage with tubulointerstitial area via maintaining the autoimmune reactivity [24]. After the oxidative stress-induced renal vasoconstriction, modified oxidative proteins can serve as autoantigens that aggravate auto-inflammatory response [25] and result with tubulointerstitial infiltration of lymphocytes and macrophages [26]. However, the association of lymphocytes infiltration and circulating lymphocytes has not been explained. In a previous

study, Guzik *et al.* [27] showed that in genetically altered mice lacking B and T cells do not develop hypertension or vascular damage. When they transferred T cells, then hypertension was occurred. This evidence supports that lymphocytes have a pivotal role and a positive association in the pathogenesis of hypertension. In another aspect, normally functional T-lymphocytes are required for the genesis of hypertension. However, in the pathological process with activated autoimmune system, auto-antibodies attacked to lypmphocytes [28]. Lymphocyte destruction may release ROS with the activation of NADPH oxidase activity and Ang II via the AT1 receptors [27]. With the inflammatory process, more chemotactic cytokines and intracellular adhesion molecules were produced which could attract more lymphocytes into tissue including the kidneys. Consequently, circulating lymphocytes decrease with the destruction and infiltration to tubulointerstitiel area [26]. In the present study, neutrophil count was significantly higher while lymphocyte count was significantly lower in resistant hypertensive patients suggest that more inflammation cause more uncontrolled hypertension.

Obesity is a very common feature of patients with resistant hypertension. The mechanisms by which obesity contributes to blood pressure elevation and interferes with blood pressure control are complex. Insulin resistance and hyperinsulinemia, impaired sodium excretion, increased sympathetic nervous system activity, increases in aldosterone sensitivity related to visceral adiposity, and obstructive sleep apnea have all been implicated as potential reasons [29]. The patients with resistant hypertension had higher albuminuria, lower eGFR and higher prevalence of any chronic kidney disease and advanced diabetic retinopathy than non-resistant hypertension patients. Also, these variables were independently associated with resistant hypertension versus non-resistant hypertension, and resistant hypertension was twice more prevalent in patients with than in those without chronic kidney disease. This is the first evidence on an association between diabetic retinopathy and resistant hypertension, though it is in keeping with the high frequency of retinal lesions in nondiabetic patients with resistant hypertension [30].

The Limitations of the Study

The major limitations of the present study may be represented by the small number of patients. The hematological parameters may vary depending on body mass index, hs-CRP levels, presence of diabetes mellitus, and the medication history affecting white blood cell count such as steroid, or other medical history of physical or emotional stress status. However, our population contain homogeneous unselected patients with resistant hypertension, therefore mirroring the real world scenario. Finally, these conclusions may not extend to the general population; therefore, the results of this study need confirmation in larger studies.

Conclusions

In the light of these evidences, in the present study we aimed to investigate the role of inflammation in resistant hypertension. We used an index that N/L ratio to reflect the inflammatory status of the body. We showed that N/L ratio is significantly higher in resistant hypertensive patients and a significant predictor of resistant hypertension even after multivariate model. We suggest that in addition to previously described factors inflammatory status should be considered in the underlying mechanisms of resistant hypertension. Therefore, for treatment of resistant hypertension, it might be more accurate to target of inflammation.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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