

# Neutrophil to Lymphocyte Ratio is Increased and Associated with Left Ventricular Diastolic Function in Newly Diagnosed Essential Hypertension Children.

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## Research article

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# Abstract

**Aim** Hypertension is associated with cardiac structural and functional changes, including left ventricular hypertrophy (LVH), LV systolic dysfunction, and diastolic dysfunction. Neutrophil to lymphocyte ratio (NLR) is a novel inflammatory biomarker associated with cardiovascular diseases. The current study aimed to evaluate NLR in children with newly diagnosed essential hypertension and its relationship between blood pressure and cardiac changes.

**Methods and subjects** 44 children with newly diagnosed essential hypertension and 43 healthy children were included. Clinical characteristics, blood cell counts and biochemical parameters were collected. LVH was assessed by calculation of LV mass index (LVMI), and LV systolic function was evaluated by measuring LV ejection fraction and fractional shortening. LV diastolic function was primarily assessed with E/E' ratio by doppler and echocardiography.

**Results** The hypertension children had significantly higher LVMI and E/E' ratio compared to the controls, whereas there was no difference in LV systolic function between two groups. The NLR was significantly higher in the hypertension group than the control group. Moreover, NLR and it was positively correlated with SBP and DBP levels in the hypertension group. Additionally, a significantly positive correlation between NLR and E/E' ratio was found in the hypertension group. However, NLR was not related to LVH and LV systolic function indicators in hypertension children.

**Conclusion** The higher NLR may be a potential indicator of increased risk for the development of hypertension in children. Moreover, NLR may help to assess the presence of LV diastolic dysfunction in hypertension children.

## Background

Hypertension is the leading risk factor for cardiovascular disease and mortality in adults, with a prevalence of 31.1% worldwide [1]. Moreover, over the last few decades, in parallel with the growing prevalence of childhood obesity, it is becoming an increasing problem among children. According to American Heart Association, the prevalence of high blood pressure is 14.2% for US children [2], and the incidence of high blood pressure is 14.13%-17.00% for children aged 7–17 years in China [3]. A recent longitudinal study has demonstrated that blood pressure in childhood is the strongest independent predictor of future blood pressure in adulthood [4], which emphasizes the importance of blood pressure management in childhood.

Growing evidence shows that hypertension results in target organ damage, even in pre-hypertension children [5]. The increases left ventricular mass (LVM) and abnormalities in cardiac function are the early change of target organ damage [6]. Therefore, screening for rapid and straightforward indicators to reflect the target organ damage has become a useful strategy in the management of childhood hypertension.

Over the last years, ample data have demonstrated the pivotal role of low-grade inflammation in the pathogenesis of essential hypertension and target organ damage in both adults [7] and children [8]. As known, the white blood cells (WBCs) and their subtypes with platelets are the essential cells of inflammation. Therefore, blood cell parameters have attracted increasing attention in chronic inflammation disease. The neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocytes (LMR) and platelet-to-lymphocyte ratio (PLR) were proposed as the inexpensive, easily accessible and widely available inflammatory markers. They have been shown to be related to cardiovascular diseases in adults, including atherosclerosis[9], heart failure[10], acute coronary syndromes[11], and hypertension[12]. Moreover, Skrzypczyk and colleagues reported NLR correlated with 24-hour ambulatory mean arterial pressure levels in adolescent [13], which suggest that blood cell parameter may also be useful in pediatrics population. To date, no studies have investigated the possible link between NLR and target organ damage in hypertension children. Therefore, our study aimed to evaluate blood cell derived inflammatory markers in children with newly diagnosed essential hypertension, and to explore the possible link between NLR and cardiac structural and functional changes.

## Methods

### Ethics Committee Approval

The local Ethics Committee of Children's Hospital of Soochow University approved the research project. All procedures performed involving human participants were following the Declaration of Helsinki, and the informed consent was obtained from all participants and their parents included in the study.

### Study Group

In the current study, we retrospectively studied 44 children (32 boys, 12 girls) with newly diagnosed essential hypertension hospitalized in the cardiology department in the Children's Hospital of Soochow University from January 2016 to December 2019, and 43 age and sex match healthy children were enrolled as the control group.

Clinical parameters, including age, gender, and body mass index (BMI; kg/m<sup>2</sup>) were obtained in all analyzed children. Hypertension was defined as systolic and/or diastolic pressure  $\geq$  95th percentile for sex, age, and height according to the reference value of the Chinese Child Blood Pressure References Collaborative Group [14]. Office Blood pressure was measured by an automated oscillometric device (Datascope Accutor Plus) with the appropriate size cuff that had been validated for use in children [15]. The appropriate cuff size (with bladder width of about 40 - 50% of the arm circumference and the bladder length of at least 80% of the arm circumference) was determined by measuring the mid-upper arm circumference. Blood pressure was measured in the non-dominant arm in triplicate at 3 min intervals after a 15 min rest in the sitting position with the arm and back supported, after excluding the first reading, the average of two subsequent readings was calculated for analysis.

To exclude secondary hypertension, a thorough medical history, physical examination, and auxiliary examination was carried out following the guideline of the American Academy of Pediatrics [16]. In addition, based on medical history, physical examination, and determined the high-sensitivity C-reactive protein (hsCRP) levels, children with active inflammation were excluded in the current study.

## Laboratory assessment.

Blood was obtained from an antecubital venous catheter after 10–12 h of night fasting. All specimens were EDTA-K2 anticoagulated and tested within 30 minutes of collection. The hematological parameters, including white blood cell (WBC), differential WBC counts (neutrophils, lymphocytes and monocytes), platelet count (Plt) were measured by an automated hematology analyzer. The neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) were calculated.

Moreover, plasma glucose, triglycerides, total cholesterol, LDL-C, HDL-C, hsCRP, alanine aminotransferase (ALT) and Creatinine were determined at the Department of Clinical Laboratory of the Children's Hospital of Soochow University.

## Echocardiographic assessment.

All echocardiographic parameters were performed using commercially available ultrasound equipment iE33 (Phillips Healthcare, North Andover, Massachusetts, USA)

## Left ventricular geometry

The M-mode tracing was used to measure the end-diastolic interventricular septal wall thickness (IVSd), left ventricular end-diastolic diameter (LVIDd), left ventricular end-systolic diameter (LVIDs), and end-diastolic posterior wall thickness (PWTd). The left ventricular mass (LVM) was then calculated using the following formula:  $LVM = 0.8 \times 1.04 \times [(IVSd + LVIDd + PWTd)^3 - LVIDd^3] + 0.6$ , LVM index (LVMI) =  $LVM / \text{height}^{2.7}$ , relative wall thickness (RWT) =  $(IVSd + PWTd) / LVIDd$ . LV hypertrophy (LVH) in children and adolescents is defined as the LVMI  $\geq$  95th percentile on sex-specific normative LVMI data published by Khoury et al. [17].

## Left ventricular systolic function

LV systolic function was assessed by the LV ejection fraction (EF) and Fractional Shortening (FS) [18].

## Left ventricular diastolic function

**Pulsed Doppler assessment.** Mitral inflow velocities were acquired with pulsed wave Doppler. The velocities during the early transmitral flow (E) and inflow with atrial contraction (A) were measured, and E/A ratio was calculated.

**Tissue Doppler imaging.** Myocardial flow velocities were obtained in the apical four-chamber view. The peak early E' and late A' velocities were recorded, then E'/A' ratio and E/E' ratio were calculated [19], and the left ventricular diastolic dysfunction was defined as E/E' ratio >14, according to the recommendations of the American Society of Echocardiography [20].

## Statistics

Statistical analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL). Values were expressed as mean and SD. The Shapiro–Wilk test was used to determine the normality of data. Means were compared using an independent t-test between hypertension and control groups. Qualitative variables were compared using the chi-square test. Correlations between variables were evaluated using Pearson's tests. A *P* value <0 .05 was considered significant.

## Results

### 1. Clinical characterizes and biochemical parameter in hypertension and control group

The Clinical characterizes and biochemical parameters in this study were shown in Table 1. There were no difference in terms of age and sex between two groups. SBP, DBP, pulse pressue and BMI was significantly higher in hypertension group than control groups. Also, the serum uric acid, ALT and hsCRP levels in children with hypertension were significantly higher than the control group, respectively. However, there were no differences in lipids and glucose levels between two groups (Table 1).

Table 1  
Clinical characterizes and biochemical parameter in hypertension group and control group

	Control group	Hypertension group	P value
<b>Clinical characteristics</b>			
Gender(M/F)	34/9	32/12	0.48
Age, years	12.27 ± 2.42	12.47 ± 2.11	0.69
BMI(kg/m <sup>2</sup> )	18.83 ± 2.02	26.88 ± 17.60	< 0.01
SBP(mmHg)	108.49 ± 8.468	140.3 ± 12.98	< 0.01
DBP(mmHg)	67.59 ± 7.67	84.20 ± 13.39	< 0.01
PP(mmHg)	40.77 ± 8.67	56.11 ± 14.10	< 0.01
<b>Biochemical variables</b>			
Uric acid, μmol/L	337.82 ± 93.35	398.54 ± 116.80	0.02
ALT, μmol/L	15.48 ± 8.29	30.64 ± 11.55	0.02
Creatinine, μmol/L	65.32 ± 13.21	70.86 ± 19.45	0.13
TG, mmol/L	1.12 ± 0.33	1.08 ± 0.47	0.65
TC, mmol/L	3.43 ± 1.13	3.73 ± 1.01	0.18
HDL-c, mmol/L	1.21 ± 0.45	1.19 ± 0.33	0.81
LDL-c, mmol/L	2.21 ± 1.34	2.14 ± 1.02	0.78
Glucose, mmol/L	4.18 ± 1.04	4.23 ± 1.27	0.84
hsCRP, mg/dl	0.27 ± 0.43	1.75 ± 3.21	< 0.01
SBP, systolic blood pressure; DBP, Diastolic blood pressure, PP, pulse pressue; TG, triglyceride; TC, Total cholesterol, HDL-c, High density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol.			

## 2. Echocardiography Parameters In Hypertension And Control Group

The LVM, RWT and LVMI were higher in the hypertension group compared with the control group, and 5 of 44 children in the hypertension group had LVH (11.36%). Besides, E/E' ratio was higher in the hypertension group in comparison with the control group, LV diastolic dysfunction was found in 1 of 44 hypertensive subjects (2.27%) (Table 2). However, there was no difference in LV ejection fraction and FS between the two groups.

Table 2  
Echocardiography parameters in the hypertension group and control group

	Control group	Hypertension group	P value
LVM, g	112.34 ± 41.86	144.56 ± 69.22	< 0.01
LVMI, g/m <sup>2.7</sup>	32.26 ± 8.77	39.98 ± 13.82	< 0.01
RWT(%)	30.75 ± 4.57	34.29 ± 6.58	< 0.01
LV hypertrophy, n (%)	/	5(11.36%)	/
E', cm/sec	12.87 ± 1.84	12.79 ± 1.79	0.80
E'/A' ratio	2.17 ± 0.57	1.93 ± 0.66	0.10
E/A ratio	2.02 ± 0.58	2.04 ± 0.75	0.87
E/E' ratio	7.01 ± 3.41	8.99 ± 1.87	< 0.01
Diastolic dysfunction, n (%)	/	1(2.27%)	/
LVEF (%)	73.34 ± 3.45	72.07 ± 6.52	0.81
FS(%)	42.32 ± 4.97	42.71 ± 6.67	0.76
LVM, left ventricular mass; LVMI, left ventricular mass index; RWT, Relative wall thickness; LVEF, left ventricular ejection fraction; FS, Fractional Shortening.			

### 3. Blood Cell Counts In Hypertension And Control Group

The WBC count and neutrophil counts were significantly higher in hypertension children than that in the control group, whereas lymphocyte, monocytes and platelet counts were similar between the two groups (Table 3). Moreover, NLR is higher in the hypertension group than the control group. However, there was no difference in PLR and LMR between the hypertension group and the control group (Table 3).

Table 3  
Blood cell counts in hypertension and control group

	Control group	Hypertension group	<i>P</i> value
WBC( $10^9/L$ )	6.66 ± 1.74	7.81 ± 2.36	0.01
N ( $10^9/L$ )	3.72 ± 1.30	4.72 ± 1.79	0.01
L ( $10^9/L$ )	2.41 ± 0.79	2.49 ± 0.96	0.68
M ( $10^9/L$ )	0.41 ± 0.12	0.45 ± 0.15	0.20
Plt ( $10^9/L$ )	269.18 ± 71.17	295.77 ± 82.73	0.12
NLR	1.68 ± 0.80	2.22 ± 1.23	0.02
PLR	119.51 ± 38.61	133.11 ± 58.22	0.12
LMR	6.14 ± 1.82	6.91 ± 8.45	0.58
WBC, white blood cell count; N, neutrophils count; L, lymphocytes count; M, monocytes count; Plt, platelet count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyt-to- monocyte ratio;			

4.

#### Correlation between Blood cell counts and office blood pressure in hypertension children

In the hypertension group, univariate correlation analysis was determined a significant positive correlation between NLR with office SBP ( $r = 0.38$ ,  $P < 0.01$ ) and DBP ( $r = 0.38$ ,  $P < 0.01$ ) levels (Fig. 1). However, WBC counts, neutrophil counts, lymphocyte counts, monocytes counts, platelet counts, PLR, and LMR were not correlated with office blood pressure levels (supplemental Table 1).

5.

#### Correlation between Blood cell counts and left ventricular hypertrophy with diastolic function in hypertension children

NLR was negatively correlated with  $E'$  ( $r = -0.37$ ,  $P = 0.01$ ) and  $E'/A'$  ratio ( $r = -0.48$ ,  $P < 0.01$ ), and positively correlated with  $E/E'$  ratio ( $r = 0.33$ ,  $P = 0.04$ ) in the hypertension group (Fig. 2). Neutrophil counts were also found to correlate negatively with  $E'$  ( $r = -0.38$ ,  $P = 0.01$ ) and  $E'/A'$  ratio ( $r = -0.38$ ,  $P < 0.01$ ) in the hypertension group. However, there was no correlation between WBC, lymphocyte, monocytes, platelet counts with left ventricular hypertrophy (Supplemental Table 2) and diastolic function parameters (Supplemental Table 3).

## Discussion

The incidence of hypertension among children is overgrowing in recently years, and high blood pressure can induce cardiac structural and functional target organ damage [21]. Our study demonstrated the elevation of LVMI and the reduction of diastolic function in newly diagnosed essential hypertension children. Moreover, we found elevated NLR in the hypertension group, and it is positively correlated with office blood pressure levels, which might imply that the possible link between the inflammation and elevation of blood pressure in the hypertension children. Interestingly, NLR was positively correlated with left ventricular diastolic parameter E/E' ratio in hypertension children, which suggests NLR may serve as a useful indicator to reflect diastolic dysfunction in hypertension children. To our knowledge, this is the first study that analyzes the change of NLR and its relationship between LV diastolic function in newly diagnosed essential hypertension children.

It is well established that LVH is an independent risk factor for cardiovascular morbidity and mortality in adulthood [22, 23]. Previously studies have proved LVH was common in hypertensive children [24]. However, there is limited data available in Chinese pediatric population. In this study, we found LVM and LVMI were both higher in hypertension children, and among 44 hypertension adolescents, 11.36% (5/44) of them had LVH. Similar, Litwin et al. demonstrated 10.3% of 44 hypertension children had some form of LV hypertrophy in the USA population [25], and Falkner reported among 35 African-American adolescents, 19% of them had LV hypertrophy [26]. Also, a cross-sectional study of 101 primary hypertension children reported that 34% of them had LV hypertrophy [27]. All these studies demonstrated that LVH was common in hypertensive children. However, the prevalence of LVH varies among these studies, which may be explained by the differences in ethnic and hypertension grades of these participants.

Several studies have shown that NLR is elevated and related to poor clinical outcomes of cardiovascular disease in adults, including acute coronary syndrome, atherosclerosis, and heart failure [28–30]. However, few studies have looked at NLR levels in children with newly diagnosed hypertension [13, 31]. In the current study, we found the neutrophil counts and NLR were significantly higher in hypertension children than healthy children, and the elevated NLR may reflect the upregulation of overall inflammatory and stress status in these children. Likewise, Derya et al. found that NLR is increased in newly diagnosed hypertension adults and associated positively with low-grade inflammation indicator C-reactive protein levels [32], which is consistent with our findings.

Further, we demonstrated that NLR positively correlated with both office SBP and DBP levels in hypertension children. Similarly, Cimen and colleagues reported NLR correlated with blood pressure levels in adults [33]. The increase of NLR may reflect the activity of two different immune pathways in the process of blood pressure regulation. On the one hand, neutrophils secrete many cytokines that trigger and amplify inflammatory reactions [34], and activated neutrophils release a variety of proteolytic enzymes that promote endothelial damage and tissue destruction [35, 36]. Also, neutrophils can lead to the release of reactive oxygen species [37], and ROS induced oxidative stress has been shown to cause vasoconstriction [38] with sodium and water retention in the kidney [39]. On the other hand, lymphocytes are the primary cells in the regulatory pathway of the immune system, and T lymphocytes cells have been shown to play a crucial role in the BP elevation caused by angiotensin II response to sodium and volume

challenges [40]. Therefore, NLR gives more information than either of the above parameters in hypertension, which indicates that inflammation may play an essential role in the development of hypertension.

We also try to explore the potential correlation between NLR and target organ damage of heart in these hypertension children. As known, LVH and LV diastolic dysfunction are both the early complication of hypertension [41], and there were 5 children had LVH and 1 children had diastolic dysfunction in the hypertension group. Interestingly, we found NLR positively correlated with E/E' ratio among hypertension children. In general, E/E' ratio seems to be the most reliable parameter to evaluated LV diastolic function in patients with heart disease, and the increasing of E/E' ratio reflects LV diastolic dysfunction [42]. To our best knowledge, this is the first study to report the correlation between NLR and diastolic function in hypertension children. However, there was no correlation between LVH parameters and blood cell parameters, suggest the LV diastolic dysfunction in these hypertensive children is due to systematic inflammation [43] rather than left ventricular hypertrophy. These results indicate that NLR may serve as a useful marker to evaluate the LV diastolic function in hypertension children.

There are several limitations to this study. Firstly, this is a single-center retrospective study, and the sample size is relatively small. Secondly, since this is an observational study, we cannot make any causal inferences. Thirdly, due to the physiological characterizes in the blood cell counts of children under 5 years of age [44], the results cannot be extrapolated to this population.

In conclusion, we demonstrated that NLR is elevated in hypertension children, and it is associated positively with office blood pressure levels and LV diastolic dysfunction parameters. Our results indicate that inflammation may play a crucial role in the development of hypertension, and the higher NLR may indicate the increased risk for the development of hypertension in children. Moreover, NLR can serve as a useful marker to reflect left ventricular diastolic dysfunction in pediatric patients with primary hypertension.

## **Declarations**

### **Ethics approval and consent to participate**

The local Ethics Committee of Children's Hospital of Soochow University approved this research project. Written informed consent was obtained from all participants and their parents included in the study.

### **Consent for publication**

Written informed consent for publication was obtained from all participants.

### **Availability of data and materials**

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no conflict of interest

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## Authors' contributions

Miao Hou, Lei Cao, Yueyue Ding and Ling Sun conceived and designed the study, Miao Hou, Lei Cao, Yueyue Ding, Ye Chen, Bo Wang, Jie Shen, Wanping Zhou, Jie Huang, Qiuqin Xu, Haitao Lv and Ling Sun performed this study. Miao Hou, Lei Cao, Yueyue Ding and Ling Sun wrote the paper. Ye Chen, Bo Wang, Jie Shen, Wanping Zhou, Jie Huang, Qiuqin Xu, Haitao Lv reviewed and edited the manuscript.

All authors read and approved the manuscript.

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Not applicable

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## Figures

Figure 1

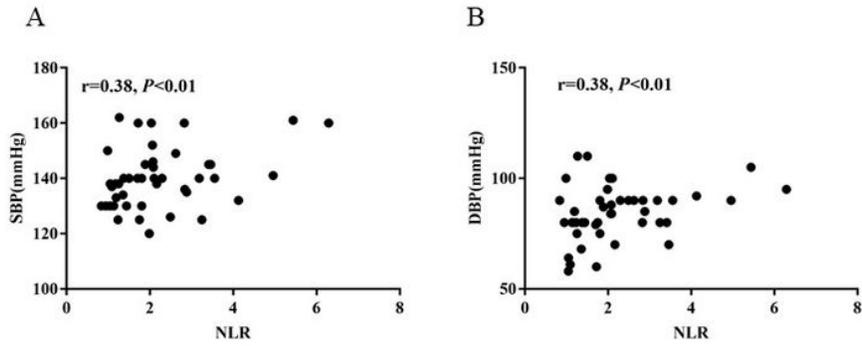
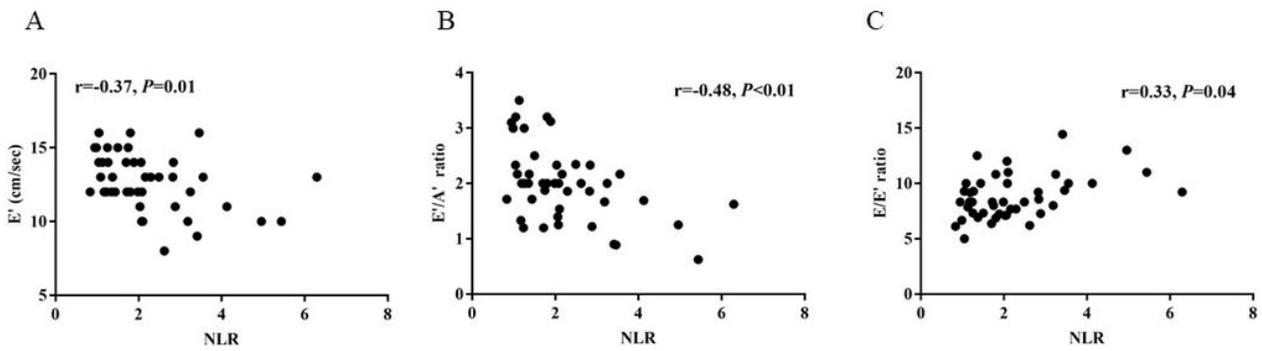


Figure 1

Correlations between NLR and systolic blood pressure (A) and diastolic blood pressure (B) levels in hypertension children

Figure 2



## Figure 2

Correlations between NLR and left ventricular diastolic function parameters E' (A), E'/A' ratio (B) and E/E' ratio (C) in hypertension children