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Red cell distribution width and related indices in relation to target-organ damage in children with hypertension

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Abstract

Background The purpose of this paper is to examine the relationship between target organ damage in children with primary hypertension and red cell distribution width (RDW) and related indices to elucidate their potential clinical implications.

Method A cross-sectional retrospective study was conducted on data collected from patients with primary hypertension. Demographic variables, body mass index (BMI), hemoglobin, RDW, leukocyte count, platelet count and albumin results were recorded. RPR was defined as the ratio of RDW to platelet count and RAR was defined as the ratio of RDW to albumin. A comprehensive evaluation was conducted on all patients to ascertain the presence of target organ damage. This evaluation included echocardiography, retinal examination, and urine analysis.

Results The study included 219 hypertensive children and 57 healthy controls. The majority of patients were male (61.6%) and had elevated BMI (69.4%). Overall, 45.7% had left ventricular hypertrophy (LVH), 5.5% had hypertensive retinopathy and 4.5% had proteinuria. The mean RDW level in patient group was higher than that of controls ($13.1 \pm 0.9\%$ and $12.8 \pm 0.7\%$, $p < 0.05$). The mean RDW level and RPR in children with LVH were higher than that of children without LVH (respectively, $13.3 \pm 1\%$ and 13 ± 0.7, $p < 0.05$ and 0.048 ± 0.012 and 0.044 ± 0.010, $p < 0.01$). An elevated white blood cell count was observed in children with a high BMI. However, the mean RDW and RAR values remained comparable. The RPR value was found to be higher in the patients with normal BMI. The male gender was identified as a significant risk factor for LVH.

Conclusion Elevated RDW and RPR levels were associated with LVH in hypertensive children, suggesting their potential role as markers of target organ damage, whereas RAR showed limited utility. Male gender emerged as an independent risk factor for LVH. Obese children demonstrated higher leukocyte counts, indicating a link between obesity and systemic inflammation. However, RDW and RAR did not vary with BMI, and unexpectedly, RPR was higher in children with normal BMI. These findings suggest that hematological parameters may provide insights into both cardiovascular risk and obesity-related changes in pediatric populations.

Keywords Hypertension, Children, Left ventricular hypertrophy, Hypertensive retinopathy, Target organ damage

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Introduction

It is estimated that approximately 5% of children have hypertension [1]. Hypertensive children exhibit evidence of target-organ damage, including altered retinal vasculature, left ventricular hypertrophy(LVH) and renal damage, in comparison to normotensive childrens [2, 3].

Red cell distribution width (RDW) is a routine analysis in complete blood count tests and specifically measures the variation in size of peripheral red blood cells (RBCs). The greater the disparity in RBC sizes within the bloodstream, the higher the RDW value. RDW is also used to diagnosis anemia, based on its role of reflecting the degree of anisocytosis. The increased RDW levels are attributable to numerous biological processes, including, but not limited to, anaemia, abnormal haematopoiesis, inflammation, oxidative stress, chronic disease, nutritional deficiency and ageing [4]. RDW is a biomarker indicative of red blood cell dysfunction, with elevated levels indicating systemic inflammation, hypoxemia and/or iron deficiency. Iron deficiency can be categorised as either absolute or functional. The latter is characterised by impaired iron mobilisation from stores, which is driven by inflammatory factors such as IL-6, hepcidin and macrophage iron retention [5].

Recent studies have indicated a potential correlation between hypertension and RDW. The routine blood cell count (RDW) has been utilised as a diagnostic tool for various forms of anaemia, in addition to its prognostic value in predicting morbidity and mortality, particularly in the context of cardiovascular diseases. A number of studies have indicated a positive correlation between elevated RDW and the risk of developing a range of diseases. Observations have indicated that an elevated RDW level functions as an independent predictor of coronary heart disease risk within the general population [6]. The association of RDW with hypertension involves RAAS(Renin-Angiotensin-Aldosterone System) activation and inflammation. RAAS is key to neurohumoral function and hypertension, with angiotensin II a main player [7]. Increases in angiotensin II promote erythropoietin (EPO) secretion and enhance erythropoiesis. This results in the expansion of RDW [8, 9].

As indicated by the findings of recent studies, the ratio of RDW to platelets (RPR) and the ratio of RDW to albumin concentration (RAR) have been identified as novel inflammatory parameters. These parameters have consequently been investigated for their association with various pathological conditions. RPR has been proposed as a novel laboratory index to predict mortality in various diseases, including acute pancreatitis and chronic hepatitis B [10–12]. RAR was initially utilized to evaluate the outcomes in patients with solid stroke and acute respiratory distress syndrome (ARDS), and it is postulated to accurately reflect the extent of inflammation [13, 14]. A survey of the literature reveals a paucity of information concerning RDW among inflammatory markers in paediatric cases of primary hypertension. However, RDW-related indices, including RPR and RAR levels, were not evaluated in children with primary hypertension.

A deeper understanding of the relationship between target organ damage in children with hypertension and red blood cell indices, such as RDW, red blood cell count (RBC), RAR and RPR could provide valuable insights into the pathophysiology of target organ damage in hypertension and offer novel avenues for its management and treatment. The objective of the present study was to evaluate RDW, RPR and RAR levels according to a healthy control group, and to determine the presence or absence of target organ damage in primary hypertensive children. The study was undertaken to elucidate their potential clinical implications and therapeutic significance.

Materials and methods

Study population

A cross-sectional retrospective study was conducted on data collected from patients who had been evaluated for hypertension using ambulatory blood pressure monitoring (ABPM) at the Paediatric Nephrology outpatient clinic. Hypertension was defined with 24 h ABPM (Spacelab On Track). The protocol stipulated that blood pressure be measured and recorded at 30-minute intervals. The children were instructed to remain motionless and sedentary while the device was inflated. In order to ascertain the overnight hours, sleep and wake times for each child were meticulously recorded and subsequently adjusted. The measurement result was deemed to be reliable if the measurement time exceeded 23 h and the result exceeded 85%. Hypertension was defined according to the 2014 American Heart Association guidelines as an ABPM reading exceeding the 95th percentile for blood pressure, with BP load—calculated as the proportion of readings above the pediatric 95th percentile—considered abnormal when greater than 25%. At least 1–2 valid reading per hour, including during sleep, is recommended to consider an ABPM study to be adequate [15].

All patients were subjected to a comprehensive examination to identify any secondary causes of hypertension with detailed history, clinical examination and blood parameters before treatment. Children with secondary hypertension were excluded from analysis. Hemoglobin, RDW, leukocyte count, platelet count and albumin results were recorded for analysis. RPR was calculated as the ratio of RDW to platelet count (RDW/platelet count (10^3/mm^3)) and RAR was calculated as the ratio of RDW to albumin (RDW/albumin).

All patients underwent examination for target organ damage with echocardiogram by a pediatric cardiologist, retinal examination by an ophtalmologist and urine

analysis for proteinuria. Children with left ventricular hypertrophy, hypertensive retinopathy and proteinuria were recorded. The demographic characteristics of the patients were derived from the patients' files. The patient's body mass index (BMI) was calculated by dividing their weight by the square of their height. The children were categorised as either having a normal BMI or an elevated BMI. The BMI of children was evaluated using age- and sex-specific percentiles. Categorisation of BMI values was as follows: values above the 95th percentile were classified as obese, values between the 85th and 95th percentiles were classified as overweight, and values below the 85th percentile were classified as normal [16]. The rate of overweight and obese children were recorded as elevated BMI.

The study included a healthy control group of children who were similar to the patient group in terms of age and gender, and who did not have iron deficiency anaemia, infection or chronic diseases.

The Ankara Education and Research Hospital Institutional Review Board granted approval for this study protocol (The number of ethical approval: 449/2020).

Statistical analysis

Analysis of results were done by SPSS 22. Categorical variables were expressed in number and percentage, countable variables were expressed as mean and standart deviation, minimum and maximum levels. Normality of data was assessed using the Shapiro–Wilk test. The primary dependent variable was the presence of target organ damage (categorical, yes/no). Independent variables included age, BMI, hemoglobin, RDW, RPR, RAR, platelet, and leukocyte counts (all continuous), as well as sex (categorical). Group comparisons were performed using the Student's *t*-test or Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Independent predictors of target organ damage were evaluated by binary logistic regression, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs).In all statistical the significance level was set at $p < 0.05$ for the analyses. The evaluation of relationships was conducted with a 95% confidence interval.

Table 1 Comparison of variables in patients and control group

Variables	Patient group $n=219$	Control group $n=57$	*p*
Age (year)	14 ± 3	13 ± 3	0.068
Sex (Female/Male)	84/135	24/33	0.607
Hemoglobin (mean ± SD, g/DL	14.3 ± 1.8	13.7 ± 1.5	0.051
RDW (mean ± SD, %)	13.1 ± 0.9	12.8 ± 0.7	0.028*
Leukocyte count (mean, 10^3/mm^3)	7.8 ± 2.2	7.6 ± 2.0	0.528
Platelet count (mean ± SD, 10^3/mm^3)	299 ± 69	311 ± 66	0.243
RPR (mean ± SD)	0.046 ± 0.011	0.043 ± 0.011	0.131

*$p < 0.05$

Results

A total of 516 children were evaluated and 290 of them were diagnosed with hypertension based on the results of ABPM. Children with secondary hypertension and insufficient information were excluded from the study. Children with primary hypertension were included in the study ($n = 219$). The mean age of the patient group was 14 ± 3 years (5–18 years) and the majority of patients were male ($n = 135$, 61.6%). Most of the patients had elevated BMI (21%, $n = 46$ were overweight, 48.4%, $n = 106$ were obese) and 30.6% ($n = 67$) had normal BMI. Overall, 45.7% ($n = 100$) had LVH and 5.5% ($n = 12$) had hypertensive retinopathy. Most of the children ($n = 209$, 95%) did not have proteinuria while 10 children (4.5%) had proteinuria. Fifty-seven healthy children were included in the study. The comparison of the mean values of the healthy control group and the patient group is presented in Table 1. The mean hemoglobin level of patient group was 14.3 ± 1.8 g/dl, the mean leukocyte count(10^3/mm^3) was 7.8 ± 2.2, the mean platelet count(10^3/mm^3) was 299 ± 69, the mean RDW level (%) was 13.1 ± 0.9, the mean albumin level (g/L) was 4.6 ± 0.5,the mean RPR level was 0.046 ± 0.011, the mean RAR level was 2.91 ± 0.51 (Table 1). As demonstrated in Table 1, the mean RDW level was significantly higher in the patient group (13.1 ± 0.9%) compared to the healthy control group (12.8 ± 0.7%), with a statistically significant difference ($p < 0.05$). The remaining parameters demonstrated no significant disparities between the two groups. The serum albumin level was not studied in the healthy control group. Consequently, a comparison of the results of albumin-related indices was not possible.

The presence of LVH was detected in 54% of males and 32% of females ($p < 0.01$). Both the mean RDW and RPR levels were significantly higher in children with LVH compared to those without LVH (RDW: 13.3 ± 1% vs. 13 ± 0.7%, $p < 0.05$; RPR: 0.048 ± 0.012 vs. 0.044 ± 0.010, $p < 0.01$). The mean age, hemoglobin, leukocyte count, platelet count, RAR level, albumin and rate of elevated BMI were similar between children with LVH and without LVH (Table 2).

As illustrated in Table 3, the mean haemoglobin, RDW, platelet count, leukocyte count, albumin, RPR and RAR levels were compared in patients with a normal BMI and those with an elevated BMI. The mean leukocyte level was found to be elevated in children with elevated BMI in comparison to children with normal BMI. The mean RPR level was found to be higher in children with a normal BMI compared to those with an elevated BMI.

In binary logistic regression analysis, left ventricular hypertrophy was designated as the dependent variable, while male gender, RDW, hemoglobine, leukocyte count,

Table 2 Comparison of variables in patients with target organ damage and no-target organ damage

Variables	LVH (+) *n* = 100	LVH (-) *n* = 119	*p*	Retinopathy (+) *n* = 12	Retinopathy (-) *n* = 207	*p*	Proteinuria (+) *n* = 10	Proteinuria (-) *n* = 209	*p*
Age (year)	14 ± 3	14 ± 3	0.382	14.4 ± 2.4	14.1 ± 3.0	0.786	13.5 ± 3.7	14.2 ± 3.0	0.471
Sex (Female/Male)	27/73	57/62	0.001**	7/5	77/130	0.145	3/7	81/128	0.580
Height (cm)	165 ± 16	161 ± 15	0.069	165 ± 11	163 ± 16	0.663	157 ± 20	163 ± 15	0.220
Body weight (kg)	75 ± 24	71 ± 22	0.16	79 ± 21	72 ± 23	0.293	57 ± 22	73 ± 23	0.056
Rate of elevated BMI (%)	69%	69.7%	0.905	75%	69%	0.667	70%	71%	0.051
Hemoglobin (mean ± SD, g/DL	14.5 ± 2	14.1 ± 1.6	0.157	13.7 ± 2.1	14.3 ± 1.8	0.230	14.6 ± 1.5	14.3 ± 1.8	0.605
RDW (mean ± SD, %)	13.3 ± 1	13 ± 0.7	0.035*	13.2 ± 1.1	13.1 ± 0.9	0.859	13.1 ± 1.2	13.1 ± 0.9	0.864
Leukocyte count (mean, $10^3/mm^3$)	7.7 ± 2.4	8.0 ± 2.0	0.362	9.2 ± 3.4	7.7 ± 2.1	0.051	7.3 ± 1.6	7.9 ± 2.1	0.459
Platelet count (mean ± SD, $10^3/mm^3$)	289 ± 73	307 ± 64	0.057	282 ± 72	299 ± 69	0.408	280 ± 65	299 ± 69	0.395
RPR (mean ± SD)	0.048 ± 0.012	0.044 ± 0.010	0.008**	0.049 ± 0.013	0.046 ± 0.011	0.346	0.049 ± 0.012	0.046 ± 0.011	0.492
RAR (mean ± SD)	2.88 ± 0.40	2.93 ± 0.59	0.507	2.83 ± 0.47	2.91 ± 0.51	0.588	2.84 ± 0.27	2.91 ± 0.52	0.678
Albumin (mean ± SD, g/dl)	4.6 ± 0.5	4.5 ± 0.6	0.171	4.7 ± 0.4	4.6 ± 0.5	0.471	4.6 ± 0.3	4.6 ± 0.5	0.933

*$p < 0.05$, **$p < 0.01$

Table 3 The comparison of variables in children with normal BMI and high BMI

Variables	Normal BMI *N* = 67	High BMI *N* = 152	*P*
Hemoglobin(mean ± SD, g/dl)	14.4 ± 1,9	14.2 ± 1.7	0.508
RDW ((mean ± SD, %)	13.1 ± 0.9	13.1 ± 0.9	0.938
Platelet ((mean ± SD, $10^3/mm^3$)	286 ± 71	304 ± 67	0.085
RPR (mean ± SD)	0.049 ± 0.013	0.045 ± 0.010	0.041*
Albumin((mean ± SD, g/dl)	4.5 ± 0.5	4.6 ± 0,5	0.511
RAR (mean ± SD)	2.9 ± 0.5	2.9 ± 0,4	0.585
Leukocyte count (mean, $10^3/mm^3$)	7.2 ± 1.6	8.1 ± 2.4	0.003**

*$p < 0.05$,**$p < 0.01$

Table 4 Binary logistic regression analysis for risk factors for left ventricular hypertrophy

Variables	OR	95%CI	*p*
Male sex	2.296	1.193–4.421	0.013*
RDW	1.808	0.796–4104	0.157
Hemoglobin	1.030	0.855–1.110	0.752
Leukocyte count	0.974	0.855–1.110	0.693
RAR	0.213	0.007–6.088	0.366
BMI	1.075	0.575–2.011	0.821

*$p < 0.05$

RAR, BMI were designated as independent variables. The findings of the study demonstrated that the presence of the male gender was identified as a significant risk factor for LVH (Table 4).

Discussion

This study presents, for the first time, the results of RDW, RPR and RAR levels in children with primary hypertension. The hypertensive children exhibited higher RDW levels in comparison to the healthy children. The hypertensive children with LVH demonstrated higher RDW and RPR levels in comparison to those without LVH. The mean RAR levels were found to be similar in both groups. A comparison of the characteristics of children with and without LVH revealed a higher prevalence of males in the LVH group. There were no significant differences in the variables between patients with and without hypertensive retinopathy, nor between those with and without renal damage. The male gender was identified as a significant risk factor for LVH.

Recent studies have indicated that inflammation plays a role not only in the pathogenesis of hypertension but also in the development of target organ damage. A substantial body of experimental research has demonstrated that modifying inflammation, whether through the inactivation of specific genes or the pharmacological reduction of inflammatory mediators, results in a significant reduction in renal and vascular damage, or the attenuation of the effects of hypertension on the central nervous system. These modifications occur with minimal impact on blood pressure. The results of this study indicate that the target organ damage observed in hypertension is a consequence of local inflammation and is not contingent on blood pressure levels [17]. Given the pivotal role of inflammation in the pathogenesis of HT and related target organ damage, numerous inflammatory biomarkers have been proposed as potential predictors of HT and related target organ damage. A number of novel haematological parameters have been identified that are capable of reflecting the inflammatory response and platelet activation [18, 19]. The increase in RDW in inflammation can be explained by angiotensin II which has been demonstrated to have a physiological role in erythropoiesis. Angiotensin II has been shown to increase erythropoietin secretion and act as a growth factor for erythroid precursors [20].

A review of the literature on adult studies has revealed an association between elevated RDW and hypertension.

A study observed a higher RDW level in hypertensive adults with LVH than in the non-LVH group. The findings of this study indicated that RDW may be a valuable tool for predicting LVH in hypertensive patients without treatment. A cut-off value of 12.9 was identified, with RDW demonstrating a sensitivity of 72.4% and a specificity of 60.3% in predicting LVH status among hypertensive patients [21]. In a study conducted by Seo et al. [22], it was demonstrated that the prevalence of hypertension was markedly elevated in adults with elevated RDW levels in comparison to those with lower RDW levels. This finding was obtained from an 11-year longitudinal study, in which it was determined that hypertension demonstrated a substantial, independent correlation with RDW levels. It is evident that the mean RDW levels in our study were found to be elevated comparing with the results of adult studies.The observed discrepancy may be attributed to the fact that our study population comprised children, and RDW levels were found to be elevated during this developmental stage.

Nevertheless, research examining the correlation between RDW and hypertension in paediatric populations remains scarce. A study was conducted in China by Hu et al. [23] in which 80 children diagnosed with orthostatic hypertension and 51 healthy children of a similar age and sex were examined. The findings of the study demonstrated that RDW levels exhibited a marked increase in paediatric subjects diagnosed with orthostatic hypertension in contrast to those observed in the healthy children. And also, the researchers ascertained that an elevation in RDW is a risk factor for orthostatic hypertension in children, subsequent to the control of other potential confounding variables. A recently published paper has examined the relationship between RDW and hypertension in paediatric patients. The study recruited 429 children and adolescents with essential hypertension who had not yet received any treatment. The participants were categorised into LVH group (n = 114) and non-LVH group (n = 315). The children diagnosed with hypertension and categorised within the LVH group had higher RDW levels than that of in those categorised as non-LVH (13.0 [12.0, 13.0] vs. 12.4 [12.0, 13.0] %, p = 0.001). Following the adjustment of potential confounding factors, RDW was identified as an independent risk factor for LVH (odds ratio [OR] = 1.946, 95% confidence interval [CI]: 1.324–2.861, P = 0.001). Furthermore, RDW has been identified as a potential predictor of LVH in untreated paediatric essential hypertension [24]. Our study revealed also children diagnosed with hypertension had higher RDW than healthy children and hypertensive children with LVH had higher RDW levels than non-LVH group. However, no significant differences were observed between patients with hypertensive retinopathy and those without hypertensive retinopathy, as well as between patients with renal damage and those without renal damage. It was postulated that elevated RDW levels in children with hypertension and left ventricular hypertrophy might be attributable to chronic inflammation. This may subsequently result in an elevated risk of cardiovascular disease [18].

In recent studies, RPR and RAR have been identified as novel inflammatory parameters that have been examined in the context of a range of pathological conditions. RPR levels have been observed in the context of inflammatory and infectious conditions, with elevated RPR levels correlating with adverse outcomes [25, 26]. In the present study, hypertensive children had similar RPR levels with healthy children. The hypertensive children with LVH had higher RPR levels than without LVH suggesting that these hematological parameters may serve as potential markers for predicting target-organ damage.

The RAR has been identified as a valuable prognostic marker in a range of clinical conditions. Recent studies have demonstrated the efficacy of this marker in predicting outcomes in critically ill patients, particularly those with conditions such as diabetic retinopathy, sepsis, pneumonia, and acute myocardial infarction [27–30]. A review of the literature revealed no studies investigating the potential association between RAR and essential hypertension. Although RAR is an inflammatory parameter, no significant differences in RAR levels were observed between hypertensive children with and without target organ damage.

It has been demonstrated that systemic inflammation also occurs due to the release of inflammatory markers from adipose tissue in obesity, and that these inflammatory markers are elevated as a result. Leukocytosis and thrombocytosis have been reported, particularly in obese children [31]. In our study, RDW and RAR values, which were evaluated as inflammatory markers, were found to be similar in children with high BMI and those with normal BMI. However, the RPR value was found to be higher in the group with normal BMI. Although not statistically significant, the mean platelet count was higher in children with high BMI, and RDW values were similar. Therefore, a difference in the RPR ratio was considered. The higher leukocyte count in children with high BMI compared to the group with normal BMI suggested obesity-related inflammation.

The present study was subject to certain limitations, namely the smaller number of children with hypertensive retinopathy and renal damage. The absence of longitudinal data of patients precluded the reporting of alterations in follow-up of patients.

As a conclusion, our study demonstrated that elevated RDW and RPR levels were found to be associated with LVH in hypertensive children, suggesting that these hematological parameters may serve as potential markers

for predicting target organ damage. In contrast, RAR levels did not differ significantly, indicating a limited clinical utility of this parameter in the assessment of target organ damage. Furthermore, the identification of male gender as an independent risk factor for LVH highlights the importance of considering sex-related differences in the cardiovascular impact of pediatric hypertension. Children with elevated BMI demonstrated higher white blood cell counts, indicating a possible link between obesity and systemic inflammation. RDW and RAR values did not differ significantly across BMI groups, while unexpectedly, RPR values were higher in children with normal BMI. These findings suggest that while certain hematological parameters reflect obesity-related changes, others may not directly correlate with body weight status in pediatric populations.

Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
BMI	Body mass ındex
EPO	Erythropoietin
LVH	Left ventricular hypertrophy
RAAS	Renin-Angiotensin-Aldosterone System
RAR	Ratio of red blood cell distribution width to albumin
RDW	Red blood cell distribution width
RPR	Ratio of red blood cell distribution width to albumin
RBC	Red blood cell

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

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ankara Training and Research Hospital (Date: 11/05/2020/No:449/2020). Informed consent was waived at each site due to the use of de-identified patient data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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