Association between red blood cell distribution width and Henoch–Schonlein purpura nephritis

Hui Xu, BSa, Wei Li, MSc, Jian-hua Mao, MD, PhDb, Yan-xiang Pan, MSac, ∗

Abstract
To investigate whether red blood cell distribution width (RDW) is a marker of the risk of Henoch–Schonlein purpura (HSP) nephritis (HSPN), a total of 669 HSP patients and 168 healthy controls were included in this retrospective study. Two hundred fifty-six (38.3%) of the patients had kidney involvement. Compared with the HSP group, RDW was significantly higher in the HSPN group (P < .001). Binary logistic regression identified that HSPN was independently associated with age, RDW, platelet, and total cholesterol (odds ratio = 1.409, 1.353, 0.996, and 2.019, respectively). In addition, RDW values of HSPN patients with crescents on histopathology (classes III, IV, and V) were higher compared with those of HSPN without crescents (classes I and II) (P = .019). The receiver–operating characteristic curve analysis showed that the RDW at a cut-off point of 13.25 has 61% sensitivity and 79% specificity in predicting the presence of crescents on histopathology. It was first shown that RDW levels in HSPN are significantly higher than those in HSP without nephritis and healthy controls. RDW can be an independent predictor of HSPN and its levels greater than 13.25 were useful in the predicting the presence of crescents on histopathology.

Abbreviations: CBC = complete blood count, ESR = erythrocyte sedimentation rate, GFR = glomerular filtration rate, HGB = hemoglobin, HSP = Henoch–Schonlein purpura, HSPN = Henoch–Schonlein purpura nephritis, MCV = mean cell volume, MPV = mean platelet volume, RDW = red blood cell distribution width, WBC = white blood cell.

Keywords: Henoch–Schonlein purpura, nephritis, proteinuria, red blood cell distribution width

1. Introduction
Henoch–Schonlein purpura (HSP) is the most frequent vasculitides in children. In general, HSP is acute and self-limited. However, HSP nephritis (HSPN) is potentially the most severe complication, and the prognosis largely depends on the severity of nephritis.[1,2] It was reported that 20% to 55% of children with HSP develop nephritis and 12.8% of HSPN patients have an unfavorable outcome.[3–5] Now, HSPN is the most common secondary glomerular disease in children,[6] and has become more of a concern to pediatricians. Red blood cell distribution width (RDW), routinely reported as a parameter of standard automated complete blood count (CBC), reflects the variability in size of the erythrocytes in the circulation. RDW is traditionally used to differentiate the types of anemia. In recent years, several studies demonstrated that RDW is associated with cardiovascular, liver, and renal diseases.[7–9] Additionally, RDW has also been known as a novel inflammatory marker in various forms of inflammatory diseases including septic shock, inflammatory bowel disease, and acute appendicitis.[10–12] More recently, Xu et al.[13] showed that higher RDW is associated with coronary artery lesions in patients with Kawasaki disease, which was also known as one of the most common forms of vasculitides. However, the study of evaluating RDW in HSP and its complication, HSPN, has never been reported before. Therefore, the purpose of this study was to investigate whether RDW is increased in HSPN patients, whether RDW is a marker of the risk of HSPN, and to evaluate its possible association with disease severity.

2. Patients and methods
We reviewed the medical records of patients who hospitalized for HSP in the Zhejiang University of Children’s Hospital between June 2012 and May 2015. Patients who had been diagnosed with HSP according to the European League Against Rheumatism criteria,[14] Nephritis was defined as the presence of any hematuria and/or proteinuria. Hematuria was defined as more than 5 red blood cells per high-power field in urine sediment. Proteinuria was defined as a 24-hour urine collection containing more than 150 mg of proteins and was considered nephrotic when ≥50 mg/kg/day. The patients were excluded if they were with other systemic vasculitis, thrombocytopenic purpura, systemic lupus erythematosus, juvenile dermatomyositis, diabetes, and skin, or kidney biopsy findings not compatible with HSP. This study was approved by the medical ethics committee of the Children’s Hospital of Zhejiang University School of Medicine, and informed consent was obtained from parents. Demographic data, renal biopsy findings, signs and symptoms of disease, and following laboratory data at the time of diagnosis were recorded from the computerized hospital database: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (HGB), mean cell volume (MCV), RDW, white blood cell (WBC).
multiplying the result by 100. CBC testing were measured (SD) of erythrocyte volume by the mean MCV and then by the automated analyzer by dividing the standard deviation.

RDN are included in routine CBC testing, which is calculated by the automated analyzer by dividing the standard deviation (SD) of erythrocyte volume by the mean MCV and then multiplying the result by 100.17 CBC testing were measured using the Minding BC-5380 automated hematology analyzer (Shenzhen Minding Bio-Medical Electronics Co., Ltd, Shenzhen, China), which was subject to daily quality control. The normal range for RDW in our laboratory is 11.5% to 14.5%.

2.1. Statistical analysis

All analyses were performed with the statistical software SPSS version17.0 (SPSS Inc., Chicago, IL). Normality of continuous data was determined by the Kolmogorov-Smirnov normality test. Continuous variables are presented as mean ± SD or median (interquartile range) and categorical variables as numbers (percentage). The significance of the mean differences between groups was assessed by independent sample t test. The Mann-Whitney U test was used to test abnormally distributed variables. Categorical variables were evaluated using the χ² test. Binary logistic regression was used to identify independent predictors of the presence of HSPN. Relationships between variables were tested using Pearson’s correlation analysis. A receiver-operating characteristic (ROC) curve was used to determine a cut-off value with the highest sensibility and specificity for predicting HSPN. All P values given were 2-sided and a P value <.05 was regarded as significant.

3. Results

A total of 669 patients with HSP and 168 healthy controls were included in this retrospective study. Demographic and clinical characteristics of patients and controls are presented in Table 1. No age and sex difference were observed between HSP patients and control group (P >.05, for all). Compared with healthy controls, a significant decrease in HGB (P <.001) and increase in WBC counts, neutrophil counts, platelet counts, and RDW (P <.001, for all) was found in children with HSP.

Demographic and clinical variables between patients with and without nephritis are shown in Table 2. All HSP patients demonstrated skin lesions. Among 669 patients with HSP, 256 had nephritis (38.3%). The mean onset age of the HSPN group was 8.9 ± 2.7 years and 6.8 ± 2.6 years for patients without nephritis. The mean onset age of HSPN patients was significantly higher than that of patients without nephritis (P <.001). There was no difference in frequency of arthritis or gastrointestinal complication between patients with and without nephritis (P >.05, for all). In addition, no significant differences between 2 groups in sex, WBC counts, neutrophil counts, ESR, and eGFR were found. Whereas, children with HSPN had significantly higher HGB, MCV, MPV, RDW, serum creatinine, and total cholesterol levels and lower platelet counts and CRP compared with patients without nephritis.

Multivariate logistic regression analysis showed that age (OR: 1.409, P <.001), RDW (OR: 1.353, P =.005), total cholesterol (OR: 2.019, P <.001), and platelet count (OR: 0.996, P =.001) were all independently associated with HSPN (Table 3).

Although RDW was higher in patients with nephrotic range proteinuria (>50 mg/kg/day) than in HSPN with non-nephrotic proteinuria (<50 mg/kg/day) (13.6 ± 1.17 and 13.38 ± 1.07, respectively), no statistically significant difference in RDW between the subgroups was observed according to the severity of proteinuria (P =.109) (Fig. 1B). Whereas, we divided patients

### Table 1

| Demographic and clinical characteristics in patients and controls. | Controls (n = 166) | HSP (n = 669) | P value |
|---|---|---|---|
| Age, years | 7.7 ± 1.6 | 7.6 ± 2.8 | .444 |
| Gender (male/female) | 95/71 | 364/299 | .606 |
| WBC, ×10^9/L | 7.1 ± 1.3 | 9.9 ± 4.2 | <.001 |
| Neutrophil, ×10^9/L | 3.7 ± 1.1 | 6.6 ± 4.0 | <.001 |
| HGB, g/L | 130 ± 8 | 127 ± 12 | <.001 |
| MCV, fL | 87.1 ± 3.8 | 87.8 ± 5.2 | .054 |
| PLT, ×10^9/L | 289 ± 54 | 338 ± 102 | <.001 |
| MPV, fL | 9.0 ± 1.0 | 8.9 ± 1.2 | .357 |
| RDW, % | 12.83 ± 0.72 | 13.21 ± 1.02 | <.001 |

Data were presented as mean±SD. HGB = hemoglobin, HSP = Henoch-Schönlein purpura, MCV = mean cell volume, MPV = mean platelet volume, PLT = platelet, RDW = red blood cell distribution width, SD = standard deviation, WBC = white blood cell.

### Table 2

| Clinical characteristics in patients with and without nephritis. | HSP with nephritis | No (n = 413) | Yes (n = 256) | P value |
|---|---|---|---|---|
| Age at disease onset, years | 6.8 ± 2.6 | 8.0 ± 2.7 | <.001 |
| Gender (male/female) | 238/175 | 130/126 | .084 |
| Purpuric rash | 413 (100%) | 256 (100%) |
| Arthralgias and/or arthritis | 243 (59%) | 140 (55%) | .292 |
| Gastrointestinal manifestations | 293 (71%) | 189 (74%) | .419 |
| WBC, ×10^9/L | 10.1 ± 4.0 | 9.6 ± 4.5 | .104 |
| Neutrophil, ×10^9/L | 6.7 ± 4.0 | 6.5 ± 3.9 | .481 |
| HGB, g/L | 125 ± 11 | 129 ± 13 | <.001 |
| MCV, fL | 87.4 ± 5.2 | 88.5 ± 5.0 | .007 |
| PLT, ×10^9/L | 395 ± 108 | 312 ± 86 | <.001 |
| MPV, fL | 8.8 ± 1.1 | 9.1 ± 1.3 | <.001 |
| RDW, % | 13.10 ± 6.91 | 13.52 ± 1.10 | <.001 |
| CRP, mg/L | 4 (1–8) | 2 (1–5) | <.001 |
| ESR, mm/h | 11 (7–18) | 10 (6–18) | .267 |
| Total cholesterol, mmol/L | 3.91 ± 0.80 | 4.66 ± 1.60 | <.001 |
| Serum creatinine, mg/dL | 0.49 ± 0.10 | 0.52 ± 0.17 | .010 |
| Proteinuria, mg/kg/day | 1.3 (0.7–2.1) | 3.06 (13.9–80.3) | <.001 |
| eGFR, ml/min/1.73 m² | 138 ± 23 | 135 ± 30 | .140 |

Data were presented as numbers (percentage), mean±SD or median (interquartile range). CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, ESR = erythrocyte sedimentation rate, HGB = hemoglobin, HSP = Henoch-Schönlein purpura, MCV = mean cell volume, MPV = mean platelet volume, PLT = platelet, RDW = red blood cell distribution width, SD = standard deviation, WBC = white blood cell.
who had underwent renal needle biopsies (n = 140) into 2 groups according to the presence of crescents, a significant difference in terms of RDW between those without crescents (classes I and II) and those with crescents on histopathology (classes III to V) was found (P < .019) (Fig. 1A).

When assessing the presence of crescents on histopathology with RDW in the patients, a cut-off value of 13.25 with a sensitivity 61% and a specificity 79% was observed according to ROC curve analysis (Fig. 2). The area under the curve was 0.749 (95% confidence intervals 0.684 to 0.814, P < .001).

There were inverse correlations between RDW and HGB, MCV, and ESR (P < .001, for all), whereas positive correlations between RDW and WBC, neutrophil, total cholesterol, and proteinuria (P < .001, for all) were observed (Table 4).

4. Discussion

To our knowledge, this retrospective study is the first to analyze RDW in HSP patients. We found that RDW values were increased significantly in patients with HSP compared to healthy controls. RDW values, meanwhile, were higher in patients with nephritis than in those without nephritis, and RDW value was independently associated with the presence of nephritis in HSP patients. The ROC curve indicated that the cut-off value of 13.25 of RDW can be valuable for predicting the presence of crescents on histopathology. In addition, in line with the previous study,[18] our study also demonstrated that older age at onset was one of the significant risk factors of renal involvement of HSP.

RDW reflects the heterogeneity in circulating erythrocytes size. The higher RDW values indicate greater variability and show that there is the presence of increased red cell destruction or ineffective red cell production. Recently, increased RDW has been recognized as an important unfavorable prognostic determinant in sepsis or septic shock, stroke, and heart failure.[10,19,20] Factors that alter the erythrocyte homeostasis such as systemic inflammation, malnutrition, and impaired renal function might play a significant role in the underlying pathological processes.[20]

Inflammation state and oxidative stress have been regarded as the important determinants of RDW.[21] Several studies have been published regarding the relationship between RDW and inflammatory disease. RDW can be used as a novel potential parameter to evaluate disease activity in inflammatory bowel disease, Behçet disease, and systemic lupus erythematosus.[11,22,23] and RDW was correlated with inflammatory parameters such as CRP, ESR, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6).[23,24] Oxidative stress, which might be effective in damaging erythrocyte membrane, perturbing normal energy metabolism in erythrocytes, and reducing erythrocyte life span,[24] was also reported to be associated with RDW.[21,24] Increased oxidative stress may also play important roles in the pathogenesis of HSP vasculitis.[27,28] In the present

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**Table 3**

| Patients with nephritis logistic regression analysis. |
|-----------------------------------------------------|
| **Univariate analysis** | **Multivariate analysis** |
| **OR** | **95% CI** | **P value** | **OR** | **95% CI** | **P value** |
| Age, years | 1.337 | 1.253–1.427 | <.001 | 1.409 | 1.298–1.529 | <.001 |
| Gender | 1.338 | 0.976–1.855 | .070 | 1.389 | 0.943–2.047 | .096 |
| HGB | 1.028 | 1.014–1.042 | <.001 | 0.999 | 0.982–1.017 | .929 |
| MCV | 1.046 | 1.012–1.081 | .007 | 0.997 | 0.957–1.038 | .875 |
| PLT | 0.996 | 0.994–0.997 | <.001 | 0.996 | 0.994–0.998 | .001 |
| MPV | 1.284 | 1.122–1.471 | <.001 | 0.974 | 0.850–1.178 | .784 |
| RDW | 1.434 | 1.217–1.690 | <.001 | 1.353 | 1.095–1.673 | .005 |
| CRP | 0.976 | 0.959–0.994 | .009 | 0.985 | 0.965–1.004 | .123 |
| CREA | 1.021 | 1.005–1.037 | .010 | 0.996 | 0.979–1.012 | .588 |
| CHOL | 1.890 | 1.589–2.248 | <.001 | 2.019 | 1.631–2.409 | <.001 |

CHOL = cholesterol, CI = confidence interval, CREA = creatinine, CRP = C-reactive protein, HGB = hemoglobin, MCV = mean cell volume, MPV = mean platelet volume, OR = odds ratio, PLT = platelet, RDW = red blood cell distribution width.
study, RDW values were increased significantly in patients with HSP compared to healthy controls. In addition, RDW was significantly positively correlated with WBC and neutrophil which indicates the influence of inflammation on variability of erythrocyte size.

Recently, several studies assessed renal functions or renal damages with RDW in various diseases. Li et al. reported that there is a positive correlation between RDW and albumin-to-creatinine ratio in hypertensive patients. Zhang et al. reported that there is a positive correlation between RDW and albumin-to-total cholesterol ratio. Ujszaszi et al. indicated that RDW was an independent risk factor of microalbuminuria in patients with newly diagnosed type 2 diabetes mellitus. gå had indicated that lower eGFR is significantly associated with higher RDW in kidney transplant recipients. However, there is no study related to renal involvement in HSP patients with RDW. The results of the present study indicate that RDW is higher in patients with nephritis than in those without. Multivariate logistic regression analysis showed that increased RDW was independently associated with HSPN. Higher total cholesterol, older age at onset, and lower platelet count were other independent predictors of HSPN. In addition, RDW was significantly positively correlated with total cholesterol and proteinuria. Similarly, a study on heart failure found that there is a strong relationship of RDW with total cholesterol.

However, as compared to our results, Solak et al did not observe any association between RDW and total cholesterol in patients with chronic kidney disease.

Furthermore, although mean RDW levels were not different between the groups according to the severity of proteinuria, it is clear that higher RDW values may be a useful index in the assessment of patients with the presence of crescents on histopathology.

This study has some limitations that need to be considered. First, it is a retrospective cross-sectional study and we did not observe the dynamic changes of the RDW level. Second, the relation between the RDW levels and the prognosis of HSPN was not assessed. Third, the relationships between RDW and oxidative stress and other more sensitive inflammatory markers such as IL-6 and TNF-α were not evaluated.

In conclusion, we have demonstrated that RDW levels in HSPN are significantly higher than those in HSP without nephritis and healthy controls. Additionally, our study confirms that RDW can be an independent predictor of HSPN and levels greater than 13.25 were useful in prediction of the presence of crescents on histopathology. However, further studies are needed to explore the exact role of RDW in this association.

References

[1] Saulsbury FT. Henoch-Schönlein purpura. Curr Opin Rheumatol 2001;13:35–40.
[2] Davin JC, Coppo R. Henoch-Schönlein purpura nephritis in children. Nat Rev Nephrol 2014;10:563–73.
[3] Narchi H. Risk of long term renal impairment and duration of follow up recommended for Henoch-Schönlein purpura with normal or minimal urinary findings: a systematic review. Arch Dis Child 2003;90:916–20.
[4] Jauhola O, Konkainen J, Koskimies O, et al. Renal manifestations of Henoch-Schönlein purpura in a 6-month prospective study of 223 children. Arch Dis Child 2010;95:877–82.
[5] Soyleresoglu O, Ozkaya O, Ozen S, et al. Henoch–Schönlein nephritis: a nationwide study. Nephron Clin Pract 2009;112:159–204.
[6] Yin XL, Zou MX, Zhang Y, et al. Twenty-three-year review of disease patterns from renal biopsies: an experience from a pediatric renal center. J Nephrol 2013;26:699–707.
[7] Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular disease. J Thorac Dis 2015;7:E402–11.
[8] Xu WS, Qiu XM, Ou QS, et al. Red blood cell distribution width levels correlated with liver fibrosis and inflammation: a noninvasive serum marker panel to predict the severity of fibrosis and inflammation in patients with hepatitis B. Medicine (Baltimore) 2015;94:e612.
[9] Oh HJ, Park JT, Kim JK, et al. Red blood cell distribution width is an independent predictor of mortality in acute kidney injury patients treated with continuous renal replacement therapy. Nephrol Dial Transplant 2012;27:389–94.
[10] Kj, Kim CH, Park JT, Kim EJ, et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. Crit Care 2013;17:R282.
[11] Song CS, Park DJ, Yoon MY, et al. Association between red cell distribution width and disease activity in patients with inflammation bowel disease. Dig Dis Sci 2012;57:1033–8.
[12] Bozlu G, Taskinlar H, Unal S, et al. Diagnostic value of red blood cell distribution width in pediatric acute appendicitis. Pediatr Int 2016;58:202–5.
[13] Xu H, Fu S, Wang W, et al. Predictive value of red blood cell distribution width for coronary artery lesions in patients with Kawasaki disease. Cardiol Young 2015;5:1–7.
Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis 2006;65:936–41.

Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629–37.

Counahan RWM, White RH, Heaton JM, et al. Prognosis of Henoch–Schönlein nephritis in children. Br Med J 1977;2:11–4.

Evans TC, Jehle D. The red blood cell distribution width. J Emerg Med 1991;9(Suppl 1):71–4.

Elnas AT, Tabel Y. Platelet counts in children with Henoch–Schönlein purpura—relationship to renal involvement. J Clin Lab Anal 2016;30:71–4.

Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. J Neurol Sci 2009;277:103–8.

Forhecz Z, Gombox T, Borgulya G, et al. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009;158:659–66.

Semba RD, Patel KV, Ferrucci L, et al. Serum antioxidants and inflammation predict red cell distribution width in older women: The Women’s Health and Aging Study I. Clin Nutr 2010;29:600–4.

Aksoy ŞN, Savas E, Sucu M, et al. Association between red blood cell distribution width and disease activity in patients with Behçet’s disease. J Int Med Res 2015;43:765–73.

Hu ZD, Chen Y, Zhang L, et al. Red blood cell distribution width is a potential index to assess the disease activity of systemic lupus erythematosus. Clin Chim Acta 2013;425:202–5.

Lorente I, Martín MM, Abreu-González P, et al. Red blood cell distribution width during the first week is associated with severity and mortality in septic patients. PLoS One 2014;9:e105436.

Miyamoto K, Inai K, Takeuchi D, et al. Relationships among red cell distribution width, anemia, and interleukin-6 in adult congenital heart disease. Circ J 2015;79:1100–6.

Ansari FA, Ali SN, Mahmood R. Sodium nitrite-induced oxidative stress causes membrane damage, protein oxidation, lipid peroxidation and alters major metabolic pathways in human erythrocytes. Toxicol In Vitro 2015;29:1878–86.

Ece A, Kelekçi S, Kocamaz H, et al. Antioxidant enzyme activities, lipid peroxidation, and total antioxidant status in children with Henoch–Schönlein purpura. Clin Rheumatol 2008;27:163–9.

Keskin N, Civrilbal M, Elevlü M, et al. Elevated plasma advanced oxidation protein products in children with Henoch–Schönlein purpura. Pediatr Nephrol 2011;26:1989–93.

Li ZZ, Chen L, Yuan H, et al. Relationship between red blood cell distribution width and early-stage renal function damage in patients with essential hypertension. J Hypertens 2014;32:2450–5.

Zhang M, Zhang Y, Li C, et al. Association between red blood cell distribution and renal function in patients with untreated type 2 diabetes mellitus. Ren Fail 2015;37:659–63.

Ujszaszi A, Molnár MZ, Czira ME, et al. Renal function is independently associated with red cell distribution width in kidney transplant recipients: a potential new auxiliary parameter for the clinical evaluation of patients with chronic kidney disease. Br J Haematol 2013;161:715–25.

Solak Y, Yılmaz ML, Sağlam M, et al. Red cell distribution width is independently related to endothelial dysfunction in patients with chronic kidney disease. Am J Med Sci 2014;347:118–24.