Research Article

Platelet count as Predictive Factor of Renal Involvement in Pediatric Henoch-Schonlein Purpura

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ABSTRACT

BACKGROUND: Platelets are involved in inflammatory processes associated with disease pathology. Henoch-Schönlein Purpura (HSP) is the most common systemic vasculitis in children. Renal involvement is the most common complication of HSP.

AIM: The aim of this study is to analyze the usefulness of increasing platelet count as a predictive factor of renal involvement in pediatric Henoch-Schönlein Purpura.

METHODS: Cross sectional study was conducted in Department of Child Health, Hasan Sadikin hospital using medical records of children with newly diagnosed Henoch-Schönlein Purpura from 2017–2019. Chi-square, t-test, and Mann-Whitney U test were used to analyse the data. (P <0.05 is considered significant).

RESULTS: There were 52 patients with mean age of 9.12 ± 3.306. Renal involvement was present in 24 patients (46.2%). Eight patients (33.3%) had mild renal involvement and the other 16 (66.7%) had severe renal involvement. Patients with renal involvement had significantly higher platelet counts than those without renal involvement (564630 ± 174894 vs 405890 ± 124058, P=0.000). Increasing platelet count (>450000/μL) was predictive of renal involvement with odds ratio of 5.400 (95% CI 1.169-18.012). ROC analysis showed that platelet count had area under the curve of 0.757 (95% CI 0.624-0.889, P=0.002) for predicting renal involvement in pediatric Henoch-Schönlein Purpura patients.

LIMITATIONS: The limitation of this study are its retrospective data collection method, its small sample size, and that all of the data were collected from one center.

CONCLUSION: Increased platelet count was associated with renal involvement in pediatric Henoch-Schönlein Purpura.

KEYWORDS: Henoch-Schönlein Purpura, Platelet Count, Renal Involvement.

INTRODUCTION

Henoch-Schönlein Purpura (HSP) is the most common vasculitis in children caused by immunoglobulin-A (IgA) deposition in vascular wall that causes symptoms involving various organs such as the skin, joints, gastrointestinal system, and the kidneys.[1,2] Henoch-Schönlein Purpura is primarily manifested as nonthrombocytopenic purpura, abdominal pain, arthritis, and nephritis.[3,4] The annual incidence of HSP varied between 6-24/100000 children <17 years of age.[2]

Renal involvement in HSP, which is also known as Henoch-Shonlein Nephritis (HSN), is the most common and severe complication of HSP.[5] It is also known to be the primary cause of morbidity in HSP.[2] Long-term prognosis of HSP depends mainly on the severity of the renal involvement.[3] Therefore, an early and precise diagnosis of renal involvement is crucial in determining the prognosis of HSP.[5] The main methods used for detecting the presence of renal involvement in HSP is renal biopsy and urinalysis. However, both methods have their own shortfall in clinical practices. Renal biopsy is an invasive method, therefore carry many complications and is rarely done in pediatric patients.[5] Urinalysis has rather low sensitivity and previous studies had found HSP

patients that presented with normal urinalysis but exhibited renal lesion in biopsy.[5,6] Therefore, the presence of a marker that can predict renal involvement is very useful in achieving early and accurate detection of renal involvement in HSP patients.

Platelet count is considered as one of the most accessible and important inflammatory marker to showcase the severity of a disease.[7,8] Platelets are anucleate cell fragments that were traditionally considered purely function to regulate hemostasis. Nowadays, platelets are also thought to be involved in inflammatory processes associated with disease pathology.[7,9] Platelets are the first effectors that respond during vascular injury and endothelial damage, therefore platelet count may be regarded as a marker that can resemble the immunological activity of vasculitis, such as HSP. When stimulated, platelet releases its granules into the extracellular environment via exocytosis or expresses the inner granule to its surface. These actions will cause the release of granule-derived mediators that contribute to inflammation.[9,10] Furthermore, pro-inflammatory cytokines can in turn increase platelet production.[11] Consequently, patients with higher platelet count may have more extensive inflammation.[12] Inflammation is a major indicator of severity of various autoimmune diseases, including Henoch-Schönlein Purpura.[8]

Henoch-Schönlein Purpura patients usually present with normal or high platelet count.[13,14] In previous studies, thrombocytosis was found in about 41-58% of HSP patients.[15–17]. Thrombocytosis in HSP patients might be correlated to severity of this disease.[14,18] Thrombocytosis can be divided into two different forms based on its origin. Primary (clonal) thrombocytosis, which is associated with myeloproliferative disorder and secondary (reactive) thrombocytosis, which can be caused by various underlying conditions such as infection, inflammation, tissue damage, hemolysis, and other causes of acute phase responses.[19] Thrombocytosis in Henoch-Schönlein Purpura is known to be a reactive type of thrombocytosis.[18] Many studies have suggested that thrombocytosis is associated with more severe form of HSP, those with more extensive inflammatory processes, particularly HSP with renal involvement.[3,8,12,16,20] The aim of this study is to analyze the usefulness of increasing platelet count as a predictive factor of the renal involvement in pediatric Henoch-Schönlein Purpura.

METHODS

A cross sectional study was conducted in Department of Child Health Faculty of Medicine Universitas Padjadjaran – Dr. Hasan Sadikin General Hospital using medical records of children diagnosed with Henoch-Schönlein Purpura from January 1, 2017 – June 30, 2019. The criterias of inclusion were age ≤18 years and a diagnosis of HSP according to *EULAR/PRINTO/PRES 2008* diagnostic criteria. Children who were diagnosed with sepsis, active tuberculosis, systemic infection, or those who had received oral steroid before the blood count analysis, were excluded from this study.

Data was taken after obtaining Ethical Clearance issued by Research Ethics Committee of Universitas Padjadjaran Bandung No. 673/UN6.KEP/EC/2019 and Research Licensing Letter issued by Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung No. LB.02.01/X.2.2.1/10037/2019. Data including sex, age at diagnosis, and initial symptoms were collected. The clinical manifestations and incidence of each manifestation were also reviewed. Renal involvement was defined as the presence of proteinuria or hematuria or red blood cell casts.[6] Severity of renal involvement was graded as follows: mild renal involvement (hematuria and/or proteinuria (<1 g/day or <40 mg/m^2/hour)) and severe renal involvement (acute nephritic syndrome and/or nephrotic syndrome, proteinuria (>1 g/day or >40 mg/m^2/hour), and classification of ISKDC of >grade IIIa). Acute nephritic syndrome was defined as hematuria and minimal one of the following: increasing serum creatinine, hypertension, or oliguria. Nephrotic syndrome was defined as massive proteinuria (>40 mg/m^2/hour or urine protein/creatinine ratio >2 or urine dipstick ≥2+), serum albumin ≤2,5g/dL, with edema.[21,22]

Hematological tests (carried out using 3 mL peripheral venous blood samples and measured using SYSMEX-XN©) and urinalysis were conducted routinely on patient's admission. Laboratory data and urine analyses results were also evaluated. Data analysis was carried out using the SPSS software for mac (version 21.0; SPSS, Inc., Chicago, IL). Chi-square, t-test, and Mann-Whitney U test were performed ($P < 0.05$ is considered significant). The receiver operating characteristics (ROC) curve was constructed to assess the diagnostic value of platelet count for predicting renal involvement in pediatric HSP patients.

RESULTS

There were 52 patients, consisting of more male patients (59.6%) than female, with the ratio of 1.48:1. The mean age during diagnosis was 9.12 ± 3.306. Most patients (78.8%) had purpura as their initial symptom. All patients (100%) complained of purpura. Joint problems were present in 25 patients (48.1%), gastrointestinal problems in 39 patients (75%), and renal involvement in 25 patients (43.9%) (Table 1).

Table 1. Characteristic of HSP patients

Characteristic	Subject (n=52)
Age (years)	
Mean ± SD	9.12 ± 3.306
Gender, n(%)	
Male	31 (59.6%)
Female	21 (40.4%)
Initial symptom, n(%)	
Purpura	41 (78.8%)
Gastrointestinal problems	7 (13.5%)
Joint problems	4 (7.7%)
Clinical manifestations, n(%)	
Purpura	57 (100%)
Gastrointestinal problems	39 (75%)
Joint problems	25 (48.1%)
Renal involvement	24 (46.2%)

In the group of patients with renal involvement, there were 13 males and 11 females with the ratio of 1.18:1. There were no significant differences of sex between the group with renal involvement and the group without. Mean age of patients with renal involvement was 8.21 ± 2.797. Renal manifestations varied from proteinuria, hematuria, and the combination of both. Thirteen patients (54.2%) develop both proteinuria and hematuria, six patients (25%) develop only hematuria, and the other five patients (20.8%) had only proteinuria. Patients with renal involvement were classified into two groups based on the severity of the renal involvement. Eight out of those 25 patients (33.3%) had mild renal involvement and the other 16 (66.7%) had severe renal involvement.
Mean platelet count in patients with mild renal involvement and severe renal involvement were compared. Although not significant, mean platelet count was higher in patients with severe renal involvement (593760 ± 177937), as opposed to those with mild renal involvement (489750 ± 145598) (P=0.164).

We also compared various laboratory parameters between patients with and without renal involvement. Patients with renal involvement had significantly higher platelet counts compared to those without renal involvement (564630 ± 174894 vs 405890 ± 124058, P=0.000). There were no significant difference of WBC count, haemoglobin, and haematocrit between those with and without renal involvement (Table 3).

Table 3. Comparison of various laboratory parameters of patients with and without renal involvement

Laboratory parameters	Renal involvement (-)	Renal involvement (+)	P
WBC count	14184.29 ± 6950.53	13749.17 ± 5213.67	0.802a
Haemoglobin	12.60 (11.65–13.40)	12.90 (10.37–15.15)	0.804b
Haematocrit	37.80 (34.82–40.42)	37.70 (33.70–43.85)	0.720b
Platelet count	405890 ± 124058	564630 ± 174894	0.000a

[a]Unpaired t-test
[b]Mann-Whitney test

Thrombocytosis (platelet count >450000/μL) was found in 75% with renal involvement. Thrombocytosis was predictive of renal involvement (P = 0.011 and odds ratio = 5.400) (Table 4).

Table 4. Relationship between thrombocytosis and renal involvement

		Renal involvement		P*	OR (95% CI)
		(-)	(+)		
Thrombocytosis	(-)	18/28 (64.3%)	6/24 (25%)	0.011	5.400 (1.169-18.012)
	(+)	10/28 (35.7%)	18/24 (75%)		

**Chi square test*, p<0.05 is significant

To evaluate the potential diagnostic value of platelet count as prediction tool of renal involvement in HSP patients, we performed ROC curve analysis. The area under the curve was 0.757 (95% CI 0.624-0.889, P=0.002) (Figure 1). The cut-off value of platelet count with optimal sensitivity and specificity was 457500 (sensitivity 75.0%, specificity 64.3%). When the cut-off value of platelet count was changed to 485500, the sensitivity and specificity became 66.7% and 71.4% respectively (Table 5).

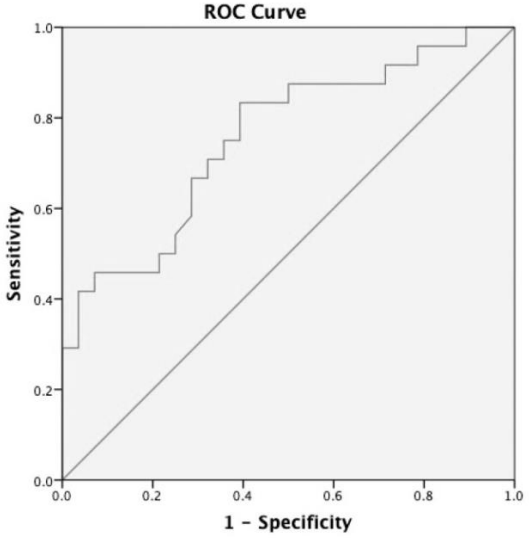

Figure 1. ROC curve of platelet count for prediction of renal involvement in HSP patients

Table 5. Platelet count cut-off value of renal involvement prediction in HSP patients

Platelet count cut-off value	Sensitivity (100%)	Specificity (100%)
411500	83.3	60.7
457500	75.0	64.3
485500	66.7	71.4

DISCUSSION

In this study, there were 52 patients diagnosed with Henoch-Schönlein Purpura. The mean age during diagnosis was 9.12 ± 3.306, which is higher than in other studies[23,24]. This needs to be evaluated further to determine whether HSP is indeed diagnosed at 9 years old or this is due to a late diagnosis or referral of HSP. There were more male patients compared to female patients, which is in accordance with the study by Setiabudiawan, et.al.[25] Purpura, which is the main diagnostic criteria, was present in all patients. Gastrointestinal manifestations were present in 75% of patients, which is slightly higher than in the study conducted by Nickavar, et.al (73.23%) but lower than in the study by Sugianti, et.al (79%).[24,26] Joint manifestations were found in 48.1% of patients which is lower than in the study conducted by Chen, et.al (65.8%) and Ghrahani, et.al (55.5%).[15,23]

Renal involvement is one of the most severe manifestation of HSP.[5] It is also a major determinant of long term prognosis in HSP patients.[3] Previous studies had found that renal involvement in HSP patients varied between 20-50%[15,27]. Our study showed that renal involvement occurred in 24 out of 52 patients (46.2%) which is consistent with those literatures. In the group of patients with renal involvement, there was a male preponderance (male:female ratio of 1.18:1) with mean age of 8.21 ± 2.797 which is similar with the study by Elmas, et.al (8.7 ± 4.1).[16]

Platelets are considered to be involved in inflammatory processes associated with disease pathology.[7,9] Thrombocytosis is frequently observed in HSP patients during an acute attack and might be related to the

degree of inflammation and severity of the disease.[12] In this study, platelet count was found to be significantly higher in patients with renal involvement compared to those without renal involvement (564630 ± 174894 vs 405890 ± 124058, P=0.000), which is consistent with other literatures that showed similar result.[16,28] This finding might occur due to inflammatory cytokines that stimulate platelet production and therefore increases platelet count.[11,18] The study by Balta, et.al stated that patients with more extensive inflammation may have higher platelet count, which might explain why in this study, patients with renal involvement had higher platelet count compared to those without renal involvement.[12]

Previous studies had suggested that older age of onset, male gender, gastrointestinal bleeding, thrombocytosis, and leukocytosis were associated with renal involvement in HSP.[15,16,28] However, in this study, thrombocytosis was the sole factor associated with renal involvement. We found that patients with thrombocytosis were 5.278 times more likely of having renal involvement compared to those without thrombocytosis. In our study, the optimal platelet count cut-off value for predicting renal involvement in HSP patients was 457500 with sensitivity of 75% and specificity of 64.3%. We suggest that this platelet count cut-off value might be used in HSP patients to consider the possibility of having renal involvement.

The limitation of this study are its retrospective data collection method, its small sample size, and that all of the data were collected from one center. Therefore, prospective multicenter studies with larger sample size are needed to generalize and confirm our result.

We concluded that increased platelet count was associated with renal involvement in HSP. Platelet count is an important and easily accessible inflammatory marker that does not required specialized equipment. We proposed that platelet count may be regarded as a useful predictive marker of renal involvement in Henoch-Schönlein Purpura.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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REFERENCES

1. Fu H, Mao J, Xu Y, Gu W, Zhu X, Liu A, et al. Clinical features and outcomes of diffuse endocapillary proliferation Henoch-Schönlein purpura nephritis in children. Clinics. 2016;71(9):550–4.
2. Chen JY, Mao JH. Henoch-Schönlein purpura nephritis in children: incidence, pathogenesis and management. Vol. 11, World Journal of Pediatrics. 2014. p. 29–34.
3. Chan H, Tang Y-L, Lv X-H, Zhang G-F, Wang M, Yang H-P, et al. Risk Factors Associated with Renal Involvement in Childhood Henoch-Schönlein Purpura: A Meta-Analysis. Reboldi G, editor. PLoS One. 2016;11(11):e0167346.
4. Heineke MH, Ballering A V., Jamin A, Ben Mkaddem S, Monteiro RC, Van Egmond M. New insights in the pathogenesis of immunoglobulin A vasculitis (Henoch-Schönlein purpura). Autoimmun Rev. 2017;16(12):1246–53.
5. Sun L, Xie B, Zhang Q, Wang Y, Wang X, Gao B, et al. Biomarkers identification by a combined clinical and metabonomics analysis in Henoch-Schonlein purpura nephritis children. Oncotarget. 2017 Dec 26;8(69):114239–50
6. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010 May 1;69(5):798–806.
7. Ghoshal K, Bhattacharyya M. Overview of platelet physiology: its hemostatic and nonhemostatic role in disease pathogenesis. ScientificWorldJournal. 2014;2014:781857.
8. Bostan Gayret O, Erol M, Tekin Nacaroglu H, Training B, Hospital R. The Relationship of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio with Gastrointestinal Bleeding in Henoch-Schonlein Purpura. 2016;26(5):8191.
9. Thomas MR, Storey RF. The role of platelets in inflammation. Thromb Haemost. 2015;114(9):449–58.
10. Morrell CN, Aggrey AA, Chapman LM, Modjeski KL. Emerging roles for platelets as immune and inflammatory cells. Blood. 2014 May 1;123(18):2759–67.
11. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. Mediators Inflamm. 2019 Apr 17;2019:1–14.
12. Balta S, Demirkol S, Kucuk U. The platelet lymphocyte ratio may be useful inflammatory indicator in clinical practice. Hemodial Int. 2013;17(4):668–9.
13. Kliegman RM, Stanton BMD, Geme JS, Schor NF. Nelson Textbook of Pediatrics E-Book: 2-Volume Set. Elsevier Health

Sciences; 2015.
14. Gonzales-Gay MA, Blanco R, Pina T. IgA Vasculitis (Henoch-Schonlein Purpura). In: Gene, V.Ball; Barri, J. Fessler; Jr. SLB, editor. Oxford Textbook of Vasculitis. 3rd ed. 2014. p. 527.
15. Ghrahani R, Ledika MA, Sapartini G, Setiabudiawan B. Age of onset as a risk factor of renal involvement in Henoch-Schönlein purpura. Asia Pac Allergy. 2014;4(1):42–7.
16. Elmas AT, Tabel Y. Platelet Counts in Children With Henoch – Schonlein Purpura — Relationship to Renal Involvement. 2016;74:71–4.
17. Hung SP, Yang YH, Lin YT, Wang LC, Lee JH, Chiang BL. Clinical Manifestations and Outcomes of Henoch-Schönlein Purpura: Comparison between Adults and Children. Pediatr Neonatol. 2009;
18. Lin C-Y, Yang Y-H, Lee C-C, Huang C-L, Wang L-C, Chiang B-L. Thrombopoietin and interleukin-6 levels in Henoch-Schönlein purpura. Vol. 39, J Microbiol Immunol Infect. 2006.
19. Subramaniam N, Mundkur S, Kini P, Bhaskaranand N, Aroor S. Clinicohematological Study of Thrombocytosis in Children. ISRN Hematol. 2014;2014:1–4.
20. Makay B, Gücenmez ÖA, Duman M, Ünsal E. The relationship of neutrophil-to-lymphocyte ratio with gastrointestinal bleeding in Henoch-Schonlein purpura. Rheumatol Int. 2014;34(9):1323–7.
21. Shin J Il, Lee JS. Treatment of Severe Henoch-Schoenlein Purpura Nephritis in Children. 2010;14(1):10–21.
22. Loricera J, Martín L, Alvarez L, Mata C, Gortázar P, Arias M, et al. Henoch-Schönlein purpura nephritis and IgA nephropathy: a comparative clinical study. 2013;1:24–6.
23. Chen O, Zhu XB, Ren P, Wang YB, Sun R, Wei DE. Henoch Schonlein Purpura in children: Clinical analysis of 120 cases. Afr Health Sci. 2013;13(1):94–9.
24. Nickavar A, Mehrazma M, Lahouti A. Clinicopathologic correlations in Henoch-Schonlein nephritis. Iran J Kidney Dis. 2012;6(6):437–40.
25. Setiabudiawan B, Ghrahani R, Sapartini G, Kadir MR. Infeksi Gigi sebagai Faktor Pencetus Terbanyak Henoch-Schonlein Purpura dengan Keterlibatan Ginjal. 2013;14(6):369–73.
26. Sugianti I, Akib AA, Soedjatmiko S. Karakteristik Purpura Henoch-Schönlein pada Anak di Rumah Sakit Cipto Mangunkusumo. Sari Pediatr. 2016;16(2):128.
27. Pohl M. Henoch–Schönlein purpura nephritis. Pediatr Nephrol. 2015 Feb 15;30(2):245–52.
28. Chan H, Tang Y-L, Lv X-H, Zhang G-F, Wang M, Yang H-P, et al. Risk Factors Associated with Renal Involvement in Childhood Henoch-Schönlein Purpura: A Meta-Analysis. PLoS One. 2016;11(11):e0167346.