



Predictive value of platelet indices in children with idiopathic nephrotic syndrome

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Abstract

Introduction: Different biomarkers have been investigated for prognosis of patients with nephrotic syndrome. Qualitative and quantitative changes have been reported in platelets in these patients.

Objectives: The aim of this study was to identify platelet abnormalities and their prognostic value of steroid response in children with idiopathic nephrotic syndrome.

Patients and Methods: Platelet counts and indices (mean platelet volume [MPV], platelet distribution width [PDW] and platelet larger cell ratio [PLCR]) were evaluated and compared in 122 children with active nephrotic syndrome (64%; steroid resistant and 36%; steroid sensitive).

Results: Mean age at diagnosis was 55 months (6 to 169 months), and males outnumbered females (1.7/1). Steroid resistant patients had significantly higher platelet counts and lower PLCR, compared to steroid sensitive group. Regarding area under the ROC curve, low MPV, high PDW and low PLCR showed relatively acceptable correlation with steroid resistance.

Conclusion: Increased platelet counts in addition to low PLCR are the suggestive indicators of steroid resistance in children with idiopathic nephrotic syndrome.

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Introduction

Platelets play an essential role in primary hemostasis. They are important mediators of immunomodulation and inflammatory reactions by releasing different cytokines and growth factors (1,2).

Quantitative and qualitative changes in platelet characteristics such as mean platelet volume (MPV) and platelet counts, in addition to platelet activation and increased surface expression of activation-dependent platelet markers, have been suggested as potential predictive markers of different inflammatory disorders, including nephrotic syndrome. In addition, activation and release of inflammatory mediators, with increased coagulability and thrombus formation might influence the process of nephrotic syndrome (2-4).

Objectives

There is little experience about the clinical utility of platelet testing in nephrotic syndrome. This study was conducted to identify alterations of platelet indices and their predictive value of steroid response in children with idiopathic nephrotic syndrome.

Key point

In a study on 122 children with active nephrotic syndrome (64%; steroid resistant and 36%; steroid sensitive), we found that steroid resistant patients had significantly higher platelet counts and lower platelet larger cell ratio compared to steroid sensitive group. Regarding area under the ROC curve, low mean platelet volume, high platelet distribution width and low platelet larger cell ratio showed relatively acceptable correlation with steroid resistance.

Patients and Methods

This study was performed in 122 children with idiopathic nephrotic syndrome (64%; steroid resistant and 36%; steroid sensitive) admitted in two children's hospitals (2015-2018). Patients with persistent hypertension, history of thrombotic and bleeding disorders, systemic disease, bone marrow insufficiency, infectious and inflammatory disorders were excluded from the study. Patients who fulfilled the diagnostic criteria of active nephrotic syndrome including generalized edema, massive proteinuria (more than 40 mg/kg/d or urine protein/Cr >2.0 mg/mg), hypoalbuminemia (serum albumin <2.5 g/dL) and hyperlipidemia were included in



the study. Patients were divided in two groups 1) steroid resistant (SR); persistent 2+ or more proteinuria after 6-8 weeks of steroid treatment and 2) steroid sensitive (SS); 0-trace urine protein in 3 consecutive days, post-steroid treatment.

About 2 cc of citrated blood was analyzed by Sysmex coulter KX-21N and Sysmac 300-XP machine with the same direct impedance method. Platelet histogram was derived from measurement of high angle light scatter. Platelet characteristics including platelet counts, MPV, platelet distribution width (PDW; variation of platelet size) and platelet large cell ratio (PLCR) were measured. Biochemical parameters were measured with spectrophotometric methods on Abbott Architect C-8000 device (Abbott Diagnostics, Santa Clara, CA).

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Babol University of Medical Sciences approved this study (ethical code; IR. MUBABOL.HRI.REC.1397.302). This study was extracted from M.D, the thesis of Ehsan Abiry at this University (Thesis #5688). Written informed consent was taken from all legal guardians, before any intervention.

Statistical analysis

Analyses of data were performed by SPSS version 23. Student *t* test and Mann-Whitney U test were used to compare means between the two groups. For categorical demographics, Fisher's exact and chi-square test were used where appropriate. A receiver operating characteristic (ROC) curve was used to identify specificity and sensitivity of platelet indices for predicting steroid response. Correlations were determined by Spearman's rank test. *P* value <0.05 was considered significant.

Results

Mean age at diagnosis was 55 months (6-169) and males outnumbered females (1.7/1). Demographic and laboratory characteristics of patients are shown in Table 1. SR children had significantly higher platelet counts,

lower PLCR and higher triglyceride level compared to the SS group. SR patients had lower MPV with higher PDW without any significance level. Regarding area under the ROC curve, MPV, PDW and PLCR showed relatively acceptable correlation with steroid resistance in nephrotic syndrome (Table 2 and Figure 1).

Discussion

An inverse correlation exists between MPV and platelet counts in healthy individuals. Recent studies showed higher platelet counts and lower MPV in the active phase of inflammatory disorders such as inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis and ankylosing spondylitis in accordance with disease activity (4).

This study was conducted to identify alteration of platelet characteristics and their prognostic value in children with nephrotic syndrome. We found significantly increased platelet counts with lower PLCR in children with SRNS. In addition, lower MPV and higher PDW had a positive acceptable correlation with steroid resistance.

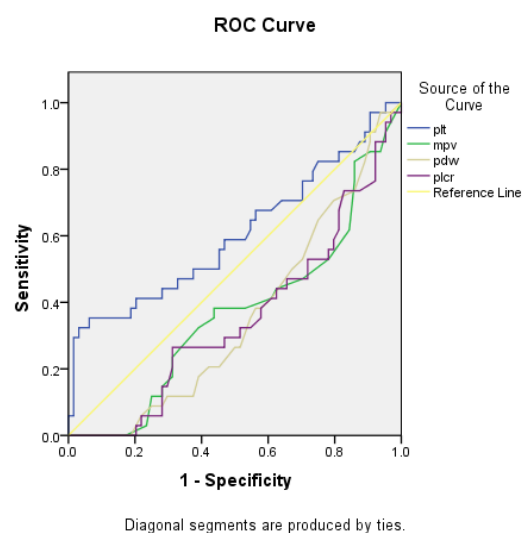


Figure 1. Sensitivity and specificity of platelet indices in relation to steroid resistance in nephrotic syndrome.

Table 1. Demographic characteristics of both groups of patients

Variables	SSNS=78 (64%)	SRNS=44 (36%)	<i>P</i> value
Mean age (y)	4.5 ± 3.3 (0.5-13)	4.8 ± 3.5 (1-13)	0.793
Platelet counts (μL) (150-400×10 ³)	402 ± 127×10 ³ (110-918×10 ³)	463 ± 197×10 ³ (113-939×10 ³)	0.043
MPV (fL) (8.9-11.8)	8.4 ± 1 (6.8-12.5)	8.1 ± 0.9 (6.8-11.8)	0.23
PDW (9.6-15.3)	9.9 ± 1.5 (7.7-14.5)	9.5 ± 1.6 (7.7-17.3)	0.287
PLCR (15.6-39.5)	14.8 ± 5.9 (5.6-33.9)	11.8 ± 3.9 (9.4-19.7)	0.004
Urine protein (mg/24 h)	3085 ± 2991 (462-11025)	3316 ± 1985 (364-6670)	0.778
Albumin (g/dL)	2.2 ± 0.4 (1.5-3.5)	2.4 ± 0.6 (2.4-4.2)	0.066
Cholesterol (mg/dL)	431 ± 159 (7-947)	431 ± 141 (140-800)	0.990
Triglycerides (mg/dL)	350 ± 217 (122-1400)	467 ± 285 (109-1454)	0.028

Abbreviations: MPV, mean platelet volume; PDW, platelet distribution width; PLCR, platelet larger cell ratio.

Table 2. Area under the ROC curve for platelet indices

Variables	AUC	SE	95% CI	P value
Platelet counts	0.604	0.064	0.478-0.730	0.091
MPV	0.632	0.059	0.517-0.747	0.032
PDW	0.643	0.056	0.534-0.752	0.020
PLCR	0.648	0.057	0.536-0.761	0.016

AUC: area under the curve, SE: standard error, CI: confidence interval

Previously, Bang et al showed a pathogenic role between urinary protein excretion with enhanced platelet function. Proteinuria was found to be correlated with the severity of spontaneous platelet aggregation and platelet adhesion.

In 1981, Walter et al reported increased platelet counts and spontaneous aggregation in children with nephrotic syndrome, which normalized after long-term remission (2). The exact mechanism of increased platelet counts has not been completely understood in nephrotic syndrome. However, a correlation has been reported between hypoalbuminemia and hypercholesterolemia with platelet hyper-aggregation and elevated platelet counts (2-4).

Decreased MPV and platelet mode, in addition to increased spontaneous aggregation and sensitivity to aggregating agents were reported in patients with idiopathic nephrotic syndrome by Zdrojewski et al (1).

MPV, proteinuria, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, total protein, albumin, and C-reactive protein levels significantly decreased after 12 months in partial and complete remission in the study by Kocyigit et al. They showed an important association of MPV with proteinuria, and MPV was considered a prognostic factor of steroid response in primary nephrotic syndrome (5).

Accordingly, Wasilewska et al reported higher platelet counts, with greater size diversity (PDW) and lower MPV in the active phase of nephrotic syndrome, which improved after two weeks of steroid treatment, with earlier normalization of serum albumin compared to platelet and MPV values. However, improvement of platelet indices occurred after six weeks of steroid treatment in other reports. They reported a negative linear correlation between platelet counts with MPV and serum albumin, with no correlation between platelet and cholesterol level, and positive relation of MPV and serum albumin during relapse of nephrotic syndrome (3).

Similar to our results, higher platelet counts with lower MPV was found in patients with active nephrotic syndrome by Gulleroglu et al, which was in accordance with disease activity and mean serum lipid level. Those with higher serum triglyceride had higher platelet counts with lower MPV. The highest platelet counts and lowest MPV were detected in patients with focal segmental

glomerular sclerosis, and MPV was considered as a prognostic factor of steroid resistance. Besides, platelet hyperactivity was correlated with complicated renal failure in long-term follow up. They recommended careful follow-up of nephrotic syndrome in patients with low MPV accompanied by increased platelet counts (4).

Conclusion

To conclude, increased platelet counts, low MPV and PLCR, with high PDW were relatively good indices for prediction of steroid resistance in nephrotic syndrome. Multi-centric studies with higher number of patients are recommended for identification of the accurate prognostic value of platelet indices in children with idiopathic nephrotic syndrome and prevention of further thrombotic complications.

Limitations of the study

A multi-centric study with a larger number of patients is recommended in future studies. In addition, identification of platelet indices is suggested for prediction of different pathologic variants of idiopathic nephrotic syndrome.

Authors' contribution

SSM collected the data and conducted the study. AN collected the data and managed the project. EA performed the study. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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