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Research Article

Evaluation of Immature Platelet Parameters as Novel Biomarkers in Psoriasis: Association with Platelet Activation

Liu R[1], Shen L[2], Jiang H[2], Wang Z[3], Li D[3], Yan K[4] and Fan Z[5#]*

[1]Department of General Education, Anhui Institute of Information Technology, China

[2]Department of Laboratory Medicine, Huashan Hospital, Fudan University, China

[3]Department of Transfusion Medicine, Huashan Hospital, Fudan University, China

[4]Department of Dermatology, Huashan Hospital, Fudan University, China

[5]Department of Laboratory Medicine, Beijing Chaoyang Hospital, Beijing Center for Clinical Laboratories, The Third Clinical Medical College of Capital Medical University, China

Abstract

Introduction: Platelet activation may be involved in the pathophysiology of psoriasis contributing to increased cardiovascular risks. The study aimed to evaluate the association between platelet activation and psoriasis severity by investigating the values of novel activation markers.

Materials and methods: The levels of Immature Platelet Fraction (IPF), Immature Platelet Count (IPC), Mean Platelet Volume (MPV), and Platelet Distribution Width (PDW) were estimated in all study populations. The relationships between these platelet indexes and disease severity measured by the Psoriasis Area and Severity Index (PASI) were assessed.

Results: The expression levels of IPF, IPC, MPV, and PDW in patients were higher than those in healthy controls. IPF (OR=1.292, 95% CI=1.023-1.633, p=0.032) and IPC (OR=1.124, 95% CI=1.003-1.260, p=0.044) were significantly associated with the severity of psoriasis after adjusting for potential confounding factors. Besides, the increased levels of IPF and IPC dramatically reduced after effective treatment (p=0.002 and p=0.0003, respectively).

Conclusion: Our study showed increased platelet activation in psoriatic patients, especially those with severe cases. IPF and IPC, associated with the severity of psoriasis, could be utilized as sensitive markers of platelet activation in the management of psoriasis in further studies.

Keywords: Psoriasis; Platelets; Immature platelet fraction; Immature platelet count; Mean platelet volume

Introduction

Psoriasis is an immune-mediated inflammatory skin disease characterized by hyperproliferation of keratinocytes. The prevalence has been gradually increasing over recent years. It is well established that psoriasis is associated with an increased risk of cardiovascular comorbidities and venous thromboembolism [1,2]. Furthermore, patients suffering from severe conditions are more inclined to increase vascular morbidity and mortality which may be the worst one of all adverse comorbid diseases [3,4]. Accumulating evidence supported that platelet activation could link persistent inflammation and the formation of thrombus resulting in the presence of cardiovascular complications in psoriasis [5].

Previous studies have shown the increased levels of platelet activation in patients with psoriasis. On activation, platelets could generate microparticles from the budding of surface membrane and release soluble p-selectin into plasma. The levels of platelet-derived microparticles and soluble p-selectin were higher in psoriasis and were correlated with the psoriasis severity [6-8]. Besides, patients were also found to have other significantly increased platelet indexes such as Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) that were approved as platelet activation markers [9,10]. Platelet activation markers could be capable to identify patients at a higher risk of vascular complications, or prone to form thrombosis in psoriasis.

Although some platelet activation markers have been discussed in psoriasis, research results were still contradictory. For instance, several studies about MPV showed no significant differences when compared with healthy individuals [11], even negative correlations with disease severity [12,13]. Despite evidence of increased platelet activation markers in patients with psoriasis, there is a paucity of data examining which markers are appropriate and accurate to identify patients who are at risk of aggravating the severity of the disease.

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***Corresponding author:** Kexiang Yan, Department of Dermatology, Huashan Hospital, Fudan University, 12 Wulumuqi Middle Road, Shanghai, 200040, China

Zhijia Fan, Department of Laboratory Medicine, Beijing Chaoyang Hospital, Beijing Center for Clinical Laboratories, The Third Clinical Medical College of Capital Medical University, Beijing, 100020, China

Currently, immature platelet parameters including Immature Platelet Fraction (IPF) and Immature Platelet Count (IPC) have been of particular interest [14]. And these parameters reflect the amount of younger and larger circulating platelets which still have cytoplasmatic content of RNA distinguished from mature platelets [15]. They have also been demonstrated to be associated with more active and aggressive platelets which are potential indicators of platelet activation [16,17]. However, IPF and IPC have not previously been investigated in psoriatic patients and little is known about the relationship between disease severity and them.

In this study, to validate IPF and IPC as potential biomarkers of platelet activation in psoriasis, we prospectively investigated these parameters and simultaneously assessed the degree of platelet activation based on MPV and PDW values in psoriatic patients and healthy controls, and evaluated the correlation between these parameters and disease severity.

Materials and Methods

Study population

A total of 120 patients with psoriasis and 120 sex-matched healthy controls from Huashan Hospital were enrolled in the study. Patients were recruited from the dermatology clinics while healthy individuals were selected from the center of Health Examination.

The Medical Ethics Committee of our institute approved the protocol following the Declaration of Helsinki principles, and informed consent was obtained from all involved participants prior to participation in this study.

Study design

Patients who were diagnosed with psoriasis were recruited in our study whether they had psoriatic arthritis or not. Patients were excluded if they received ultraviolet radiation therapy, methotrexate, or other systemic treatments for psoriasis or arthropathy within 1 month of study initiation. None of the patients or control subjects had received topical medications that impair platelet function during the 2 weeks before the study. The contraindications and restrictions on the use of methotrexate were recommended by European guidelines [18]. All enrolled patients were treated by the MTX. The initial MTX dosage was 7.5 mg-10 mg orally once weekly, which was increased by 2.5 mg every 2 to 4 weeks to a maximum of 15 mg weekly depending on clinical response and side-effects. Two dermatologists evaluated the severity and extent of disease independently using the Psoriasis Area and Severity Index (PASI) score and assessed the psoriatic arthritis using the Classification Criteria for the Study of Psoriatic Arthritis (CASPAR) [19].

Sample collection and biomarkers measurement

The complete blood count including White Blood Cell (WBC), Red Blood Cell (RBC), Platelet Count (PLT), Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW), and new reticulocyte parameters including Immature Platelet Count (IPC), Immature Platelet Fraction (IPF) were all performed on a Sysmex XN 9000 hematology analyzer (Sysmex Corporation, Kobe, Japan).

Statistical analysis

Analysis of results was done using the Statistical Program for Social Science version 22 (IBM SPSS, Inc).Continuous data were presented as mean and Standard Deviation (SD) or median and interquartile range (IQR: 25^{th}-75^{th} percentiles), and the student's t-test and Mann-Whitney U test were used as appropriate. To compare changes of variables at the baseline and 4 weeks after the treatment, a paired t-test (parametric test) or a two-tailed Wilcoxon rank test (nonparametric test) was used. Univariate and multivariate logistic regression analyses, with adjustment for potential confounding factors such as age, sex, age at onset, and concomitant diseases (i.e. hypertension, diabetes, and arthritis), were performed to evaluate whether platelet parameters could be associated with the psoriasis severity. Odds Ratios (ORs) with 95% Confidence Intervals (CI) were calculated for the estimated association. A p-value <0.05 was considered statistically significant in all analyses.

Results

A total of 120 patients with a diagnosis of psoriasis including 80 males and 40 females (ages, 42.74 ± 15.4 years) were enrolled in this study. Laboratory analysis data were presented in Table 1. A marked increase in White Blood Cell (WBC) count suggested the inflammatory response of patients (6.61 ± 1.68 *vs.* 6.13 ± 1.28, p=0.015). And we observed significant platelet activation in psoriasis, as demonstrated by the elevation in these platelet parameters, the psoriasis group showed higher values of IPF (P=0.042), IPC (P=0.011), PDW (P=0.029), and MPV (P=0.047) with statistical significance when compared with those in the control group. There were no statistically significant differences for these platelet parameters in patients with and without high cardiovascular risks, as well as in patients with and without arthritis (Table 2).

As shown in Table 3, and as calculated by the Spearman correlation coefficient, we analyzed the correlation of IPF and IPC with other platelet biomarkers in the study cohort. A significantly negative correlation was observed between platelet count with IPF (r=-0.433, P<0.0001). Furthermore, IPF had strong positive correlation with IPC (r=0.910, p<0.0001), PDW (r=0.840, p<0.0001) and MPV (r=0.895, p<0.0001). IPC was also found to be significantly associated with PDW(r=0.733, p<0.0001) and MPV (r=0.781, p<0.0001), except for no correlation between IPC and platelet count.

Table 1: Summary of clinical characteristics and laboratory data in study and control groups.

Variables	psoriasis	control	P value
Ages (years), mean ± SD	42.7 ± 15.4	42.2 ± 12.8	0.782
Sex, n (%)			
Male	80 (66.7%)	80 (66.7%)	1
Female	40 (33.3%)	40 (33.3%)	1
WBC count (10^9/L), mean ± SD	6.61 ± 1.68	6.13 ± 1.28	0.015*
PLT count (10^9/L), mean ± SD	244.8 ± 60.7	259.2 ± 56.2	0.058
PDW (fL), mean ± SD	13.17 ± 2.13	12.64 ± 1.57	0.029*
MPV (fL), mean ± SD	10.93 ± 0.92	10.72 ± 0.70	0.047*
P-LCR (%), median (range)	31.35 (26.90, 36.88)	30.60 (26.08, 34.35)	0.124
IPF (%), median (range)	2.70 (1.70, 3.90)	2.40 (1.70, 3.20)	0.042*
IPC (10^9/L), mean ± SD	7.58 ± 4.33	6.40 ± 2.56	0.011*
Psoriasis characteristics			
Age at disease onset (years), median (range)	27 (20, 37)		
Disease duration (years), median (range)	12 (5, 21)		
Arthritis, n (%)	44 (36.7%)		
Hypertension, n (%)	26 (21.7%)		
Diabetes, n (%)	11 (9.2%)		

SD: Standard Deviation; WBC: White Blood Cell; PLT: Platelet; PDW: Platelet Distribution Width; MPV: Mean Platelet Volume; P-LCR: Platelet-Large Cell Rate; IPF: Immature Platelet Fraction; IPC: Immature Platelet Count; *P<0.05.

Table 2: Comparison of laboratory data in psoriatic patients with different subgroups.

Variables	patients with high cardiovascular risk[a]			patients with arthritis		
	Yes	No	p value	Yes	No	p value
PLT count (10^9/L), mean ± SD	237 ± 61.6	250 ± 61.7	0.351	254 ± 64.3	239 ± 59.1	0.229
PDW (fL), mean ± SD	12.63 ± 1.39	13.19 ± 2.15	0.189	12.91 ± 2.09	13.11 ± 1.87	0.628
MPV (fL), mean ± SD	10.71 ± 0.65	10.93 ± 0.94	0.232	10.84 ± 0.92	10.89 ± 0.83	0.784
P-LCR (%), median(range)	30.80 (25.35, 34.40)	31.20 (27.20, 38.00)	0.293	30.60 (25.43,35.90)	31.20 (27.60,36.50)	0.59
IPF (%), median (range)	2.80 (1.85, 3.38)	2.60 (1.65,4.50)	0.466	2.55 (1.60,3.83)	2.90 (1.70,4.10)	0.372
IPC (10^9/L), mean ± SD	6.43 ± 2.95	7.87 ± 4.28	0.179	7.40 ± 4.19	7.45 ± 3.81	0.946

[a]High cardiovascular risk: psoriatic patients with hypertension or diabetes.

SD: Standard Deviation; PLT: Platelet; PDW: Platelet Distribution Width; MPV: Mean Platelet Volume; P-LCR: Platelet-Large Cell Rate; IPF: Immature Platelet Fraction; IPC: Immature Platelet Count.

Table 3: Association analysis of IPF and IPC with platelet activation markers.

Parameters	IPF		IPC	
	r value	P value	r value	P value
IPC (10^9/L)	0.91	<0.0001*	-	-
PLT count (10^9/L)	-0.433	<0.0001*	-0.068	0.461
PDW (fL)	0.84	<0.0001*	0.733	<0.0001*
MPV (fL)	0.895	<0.0001*	0.781	<0.0001*

PDW: Platelet Distribution Width; MPV: Mean Platelet Volume; IPF: Immature Platelet Fraction; IPC: Immature Platelet Count. *P<0.05.

Table 4: Univariate and multivariate logistic regression analyses for the association with psoriasis severity.

Predictors	Univariate analysis		multivariate analysis[a]	
	OR (95%CI)	P value	OR (95%CI)	P value
IPF (%)	1.287 (1.069,1.548)	0.008*	1.292 (1.023,1.633)	0.032*
IPC (10^9/L)	1.139 (1.033,1.255)	0.009*	1.124 (1.003,1.260)	0.044*
MPV (fL)	1.626 (1.008,2.624)	0.046*	1.727 (0.990,3.014)	0.054
PDW (fL)	1.222 (1.002,1.489)	0.047*	1.288 (0.967,1.715)	0.083

[a]Adjusted for age, gender, age at disease onset, hypertension, diabetes, and arthritis.

IPF: Immature Platelet Fraction; IPC: Immature Platelet Count; MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; OR: Odds Ratio; CI: Confidence Interval. *P<0.05.

To investigate the association of these platelet parameters with the disease severity, we performed the logistic regression analyses (Table 4). In the univariate logistic regression analysis, all the parameters including IPF, IPC, MPV, and PDW in patients were significantly correlated with the severity of psoriasis (p=0.008, p=0.009, p=0.046, and p=0.047, respectively). And in the multivariate analysis, following adjustment for potential confounding factors (i.e. age, sex, age at onset, hypertension, diabetes, and arthritis), only IPF (OR=1.292, 95% CI=1.023-1.633, p=0.032) and IPC (OR=1.124, 95% CI=1.003-1.260, p=0.044) could emerge as available markers to evaluate the severity of psoriasis, whereas MPV and PDW were no longer significantly associated with psoriasis severity.

We also compared the levels of these biomarkers before and after successful treatment in 16 patients with psoriasis who were treated with methotrexate. And after treatment, the PASI score markedly decreased accompanied by the significant reduction of IPF and IPC, and other markers had no significant difference around treatment (Figure 1).

Discussion

In this study, we evaluated the association of platelet activation with psoriasis. We found that the levels of IPF, IPC, MPV, and PDW were higher in patients than in healthy controls. The platelet biomarkers above associated significantly with each other. Simultaneously, they were positively correlated with the disease severity. After adjusting for confounding factors, only IPF and IPC could be more sensitive markers of platelet activation for assessing disease severity.

MPV has been analyzed in psoriasis as an approved marker for platelet activation. We showed a significantly increased value of MPV in accordance with the majority of studies [9,10]. However, there are still some conflicting results in the published literature concerning the disease severity and the MPV level. Some studies have reported a positive correlation between MPV and PASI [20]. In contrast, data from Unal [12] and Capo [13] suggested that MPV was negatively correlated with PASI, while there was no correlation of MPV with disease severity found in our study. Thus, MPV could not be a reliable marker of determining disease severity in psoriasis. There have also been a few reports on PDW in psoriatic patients, advocating the evaluation of PDW as a marker of platelet activation and our result was also in line with these studies [21]. Higher PDW reveals increased heterogeneity of platelet volume that platelets with different sizes were in circulation.

Although MPV and PDW have been investigated extensively, their capability of predicting the disease severity is moderate. An alternative to platelet size measurement is the analysis of immature platelet parameters (IPF and IPC), also known as reticulated platelets which seem to be a hot topic at the present. IPF and IPC could be reliable markers of thrombocytopenic etiology to differentiate patients with immune thrombocytopenia and predict future bleeding risk [22,23]. Besides, they have also been increasingly ascertained as platelet activation markers in other clinical conditions, such as acute coronary syndrome [24], diabetes mellitus [25], and sepsis [26].

Our findings showed that both IPF and IPC levels significantly increased in psoriasis and they were positively associated with disease severity. Besides, we found that patients with high cardiovascular risks or arthritis showed no significant differences in these platelet markers. This indicated that psoriasis per se, not the cardiovascular state or arthritis, might be associated with platelet activation and lead to an elevated IPF and IPC. Of note, a significant reduction in IPF and IPC levels was observed after effective treatment. These findings suggested that IPF and IPC may be used to evaluate the disease severity and assess the benefit of disease therapy as auxiliary markers.

Platelets play an important role in the pathogenesis of psoriatic inflammation, in addition to their main role in promoting the formation of thrombosis. Increased activated platelets could release pro-inflammatory cytokines, mediate the extravasation of leukocytes to the cutaneous inflamed sites, and aggravate the inflammatory response through platelet-leucocyte aggregates [27]. As regarding the vital function of platelets, detection of platelet activation precisely would be helpful to the prediction of disease severity. Besides, the method applied for obtaining the data of platelet indexes is simple, accessible with operability, and the blood collection requirement has already been a standard operating procedure among all

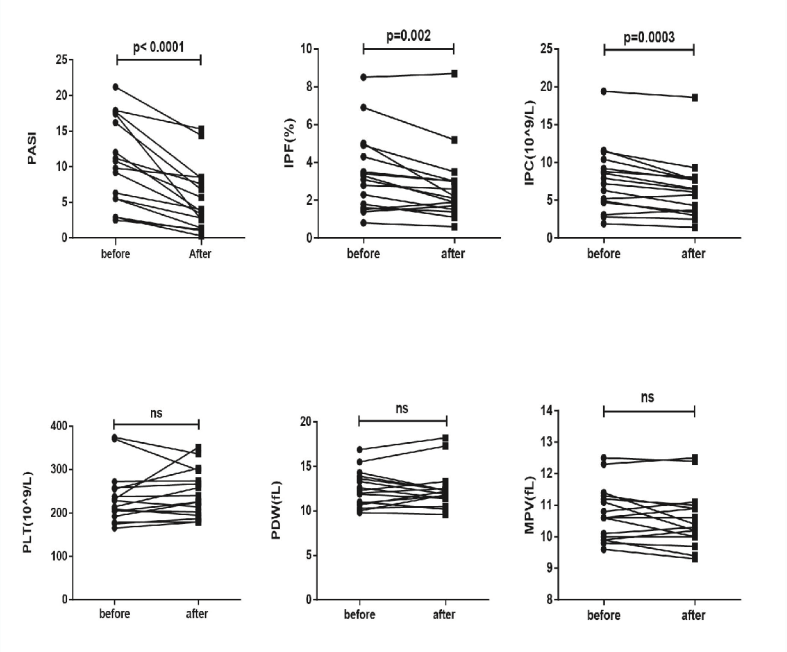

Figure 1: Comparison of activation markers levels in patients between before and after the treatment with methotrexate. ns: no significance

hospitals. Therefore, further studies are required to focus the current applicability of IPF and IPC as relatively stable markers for platelet activation in psoriasis in the routine clinical practice.

There were several limitations to this study. The study was conducted for a short period and the number of patients in the follow-up was relatively small. Large-scale and multi-center studies with a large sample size would clarify the relationship between platelet activation and psoriasis. The potential mechanisms of platelet activation in psoriasis management needed to be further explored.

Conclusion

In summary, our results indicated that there was significant platelet activation in psoriasis measured by specific platelet indexes. Increasing levels of platelet markers are found in psoriasis with an increase in IPF and IPC, which could contribute to increased risks of disease severity. IPF and IPC may be more sensitive biomarkers of all studied platelet parameters. Given the simple convenience of these parameters for routine clinical laboratories, considerably more work will be needed to confirm the value of IPF and IPC in the management of psoriasis.

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