

## Relationship between platelet morphology indices and uremic pruritus in maintenance hemodialysis patients

Zhen Ai<sup>1,2</sup>, Qixia Lei<sup>1</sup>, Naya Huang<sup>1,2</sup>, Xiaoqing Ye<sup>1</sup>, Raoping Wang<sup>1</sup>, Yuanwen Xu<sup>1</sup>, Wei Chen<sup>1,2</sup>

<sup>1</sup>Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510080, China;

<sup>2</sup>Key Laboratory of Nephrology, National Health Commission and Guangdong Province, Guangzhou, Guangdong 510080, China.

*To the Editor:* Uremic pruritus is a common and distressing complication that affects >65% of patients undergoing maintenance hemodialysis (MHD). The intensity of uremic pruritus is associated with depression, impaired sleep, reduced quality of life, and increased mortality in MHD patients; however, the pathogenesis of uremic pruritus is poorly understood and no effective treatments currently exist.<sup>[1]</sup> In cutaneous inflammatory diseases such as atopic dermatitis and psoriasis, platelets are involved in the immune responses in the skin and interact with leukocytes and endothelium to regulate inflammation, promote allergic sensitization, and provoke pruritus.<sup>[2]</sup> Currently, the role of platelets in the pathogenesis of pruritic skin disease is unclear. Therefore, this study aimed to explore the relationships between the severity of uremic pruritus and platelet parameters, including platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR), and plateletcrit (PCT).

We conducted a single-center, cross-sectional study under the approval of the Human Ethics Committees of the First Affiliated Hospital of Sun Yat-Sen University (No. 2016-215). Patients diagnosed with end-stage renal disease (ESRD) receiving regular MHD for >3 months were enrolled. Patients <18 years old, with cholestatic liver disease or acute hepatitis, active infection, active malignancy, primary skin disorder, or communication difficulties were excluded from this study. Written informed consent was obtained from all participants.

In this study, patients received only topical moisture agents for pruritus, except one patient who received oral antihistamine and three patients who received topical corticosteroid. We used a 10-point visual analogue scale (VAS) to evaluate the severity of pruritus: <4 points was considered to suggest no or mild pruritus and >4 points

indicated moderate-to-severe pruritus. The patients answered the VAS questionnaire based on their experiences during the previous month.

All blood samples were collected immediately before patients' mid-week hemodialysis (HD) treatment and all laboratory tests were performed in the central laboratory of our hospital. Demographic data included age, sex, duration of HD, and comorbidities. Laboratory data included high-sensitivity C-reactive protein (hs-CRP), white blood cell (WBC) count, hemoglobin, platelet indices (including PC, MPV, PDW, P-LCR, and PCT), and levels of serum calcium, serum phosphorus, intact parathyroid hormone (iPTH), blood urea nitrogen, serum creatinine, serum albumin, total cholesterol, triglyceride, serum ferritin, and  $\beta$ 2-microglobulin. Dialysis adequacy was expressed as Kt/V values.

Data were expressed as mean  $\pm$  standard deviation or median with interquartile range for continuous variables and percentages (%) for categorical data. Mann-Whitney U-test was used to compare continuous variables between groups and the Chi-squared test was applied to compare categorical variables. Spearman's rank correlation analysis was used to assess the correlations between two variables. Unadjusted and adjusted logistic regression models were constructed to evaluate the associations between platelet indices and the severity of uremic pruritus, expressed using odds ratios (ORs) and 95% confidence intervals (CIs). In adjusted models, age, sex, hepatitis C infection, WBC, hs-CRP, serum phosphorus, iPTH, and serum ferritin were included together with platelet indices. Data analysis was performed using SPSS 16.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Overall, 195 eligible MHD patients were enrolled in this study (mean age: 55.0  $\pm$  14.2 years, 57.95% male), with a

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**Correspondence to:** Prof. Wei Chen, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, 58th Zhongshan Road II, Guangzhou, Guangdong 510080, China  
E-Mail: chenwei99@mail.sysu.edu.cn

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median HD duration of 57.97 months (interquartile range: 17.90–132.30 months). The median PC, MPV, PDW, P-LCR, and PCT levels for all patients were  $191 \times 10^9/L$  (range:  $46\text{--}379 \times 10^9/L$ ), 10.10 fL (range: 6.60–13.00 fL), 11.30 fL (range: 7.70–21.00 fL), 25.15% (range: 2.70%–48.20%), and 0.19% (range: 0.05%–0.45%). Of these patients, 64.10% had no or mild pruritus and 35.90% had moderate-to-severe pruritus. Patients who complained of moderate-to-severe pruritus had significantly higher rates of hepatitis C infection and higher levels of serum phosphorus ( $P < 0.05$ ), as well as significantly lower levels of PC ( $P < 0.01$ ) and PCT ( $P = 0.01$ ) compared with those with no or mild pruritus [Supplementary Table 1, <http://links.lww.com/CM9/B11>, Supplementary Figure 1, <http://links.lww.com/CM9/B11>]. Patients in the lowest tertile of PC (PC tertile 1,  $PC \leq 165.00 \times 10^9/L$ ) and PCT (PCT tertile 1,  $PCT \leq 0.16\%$ ) had significantly higher rates of moderate-to-severe pruritus and lower levels of WBC and hs-CRP [Supplementary Tables 2, <http://links.lww.com/CM9/B11> and 3, <http://links.lww.com/CM9/B11>].

Spearman’s rank correlation analyses indicated that PC was positively correlated with PCT, diabetes, WBC, hs-CRP, and total cholesterol, and was negatively correlated with MPV, PDW, P-LCR, BUN, hepatitis C infection, and VAS score. PCT had a similar correlation to that of PC [Supplementary Table 4, <http://links.lww.com/CM9/B11>].

In an unadjusted logistic regression model, PC tertile 1 (OR = 2.67, 95% CI 1.29–5.54,  $P < 0.01$ ) and PCT tertile 1 (OR = 2.49, 95% CI 1.23–5.05,  $P = 0.01$ ) were significantly associated with increased risks of moderate-to-severe pruritus.

Logistic regression models of platelet (PLT) indices were further adjusted for age, sex, and the reported risk factors of uremic pruritus (including hepatitis C infection, WBC, hs-CRP, serum phosphorus, iPTH, and serum ferritin).<sup>[1,3]</sup> In adjusted logistic regression models, the lowest PC tertile and the lowest PCT tertile remained strongly associated with increased risks for moderate-to-severe pruritus (OR = 3.06, 95% CI 1.26–7.44,  $P = 0.01$  and OR = 3.29, 95% CI 1.33–8.14,  $P = 0.01$ , respectively). The risk of developing moderate-to-severe pruritus in the middle tertile of PC and PCT did not significantly differ from the highest tertile. None of the associations in the MPV, PDW, and P-LCR analyses reached statistical significance [Table 1].

In this study, we thoroughly explored the relationship between platelet indices and uremic pruritus in Chinese ESRD patients undergoing HD. The present study demonstrated that low PC and PCT were independently associated with increased risk of moderate-to-severe uremic pruritus in HD. The mechanisms of uremic pruritus are complex; primary hypotheses include metabolic disturbances, inflammation, immune dysregulation,

**Table 1: Adjusted ORs of moderate-to-severe pruritus by groups of platelet indices (Logistic regression analysis).**

Model	PC tertile 1		PC tertile 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Unadjusted	2.67 (1.29, 5.54)*	<0.01	1.19 (0.56, 2.52)	0.66
Adjusted†	3.06 (1.26, 7.44)*	0.01	1.46 (0.63, 3.38)	0.37
Model	PCT tertile 1		PCT tertile 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Unadjusted	2.49 (1.23, 5.05)*	0.01	1.02 (0.46, 2.22)	0.97
Adjusted†	3.29 (1.33, 8.14)*	0.01	1.25 (0.53, 2.98)	0.61
Model	MPV tertile 1		MPV tertile 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Unadjusted	0.77 (0.37, 1.58)	0.47	1.06 (0.52, 2.17)	0.88
Adjusted†	0.82 (0.38, 1.79)	0.62	0.97 (0.44, 2.13)	0.94
Model	PDW tertile 1		PDW tertile 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Unadjusted	0.63 (0.30, 1.34)	0.23	0.91 (0.45, 1.83)	0.91
Adjusted†	0.73 (0.32, 1.66)	0.45	1.09 (0.50, 2.37)	0.82
Model	P-LCR tertile 1		P-LCR tertile 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Unadjusted	0.61 (0.29, 1.31)	0.20	1.03 (0.50, 2.12)	0.94
Adjusted†	0.72 (0.32, 1.62)	0.42	1.08 (0.48, 2.40)	0.85

Reference group is tertile 3 of PC, PCT, MPV, PDW, and P-LCR, respectively. \*  $P < 0.05$ . † Adjusted: Models were further adjusted for age, sex, hepatitis C infection, WBC, hs-CRP, serum phosphorus, iPTH, and serum ferritin. CI: Confidence interval; hs-CRP: High-sensitivity C-reactive protein; iPTH: Intact parathyroid hormone; MPV: Mean platelet volume; OR: Odds ratio; PC: Platelet count; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet-large cell ratio; WBC: White blood cell.

imbalances in the endogenous opioidergic system, and neural systemic dysfunction.

Platelets are cellular mediators of thrombosis, and there is growing evidence for their important immune and inflammatory roles in health and disease. Platelets are involved in the pathogenesis of inflammatory skin disease and may contribute to the development of uremic pruritus by secreting numerous itch-related mediators including histamine and platelet-activating factor (PAF).<sup>[2]</sup> Platelet indices are markers of platelet activation. The association of PLT indices and pruritus was reported in chronic liver disease populations. Akuta *et al*<sup>[4]</sup> assessed the predictors of pruritus in 673 Japanese patients with chronic liver disease and reported that a low PC of  $<10.00 \times 10^4/\text{mm}^3$  (OR = 2.39;  $P=0.02$ ) was a significant determinant of severe pruritus. Decreased PC and PCT in MHD patients with moderate-to-severe pruritus was observed in this study, suggesting an underlying activation of platelets in uremic pruritus. PCT is a measure of total platelet mass, which is determined by the combination of PC and MPV, thus providing more accurate information than PC or MPV alone.<sup>[5]</sup> PC was strongly positively correlated with PCT and negatively correlated with MPV, PDW, and P-LCR, consistent with observations in a previous study.<sup>[5]</sup> Regarding reduced platelet production, newly synthesized platelets have a large volume and are highly active, as a result of compensation. Large platelets that are metabolically and enzymatically more active than small platelets contain more  $\alpha$ -granules, which release various potential pruritogens, including histamine, serotonin, PAF, and prostaglandin E2 microparticles. Thus, additional studies are needed to investigate the pathogenic role of platelets in uremic pruritus.

This is a rare study to investigate the relationships between platelet morphology indices and uremic pruritus. We found that lower PC or lower PCT were strongly associated with a greater risk of developing moderate-to-severe pruritus in MHD patients. PC and PCT may be useful parameters to identify patients at risk of uremic pruritus.

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### Conflicts of interest

None.

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