

Correlation between Platelet-to-Albumin Ratio and Clinical and Pathological Features in IgA Nephropathy: Postprint

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Abstract

Background IgA nephropathy (IgAN) is a chronic inflammatory disease involving multiple factors and genes. The platelet/albumin ratio (PAR) is considered a novel inflammatory marker, but the relationship between PAR and IgAN remains unclear. Objective To investigate the correlation between PAR and clinical and pathological indicators of IgAN, and to evaluate the clinical significance of PAR in IgAN. Methods A total of 210 IgAN patients diagnosed by renal biopsy in the Department of Nephrology, First Affiliated Hospital of Kunming Medical University from October 2019 to August 2020 were selected as study subjects. Baseline data including general parameters [gender, age, systolic blood pressure, diastolic blood pressure, and disease duration] and laboratory indicators [white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), platelet count (PLT), serum albumin (ALB), serum uric acid (SUA), blood urea nitrogen (BUN), serum creatinine (Scr), immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), serum complement C3, serum complement C4, urinary red blood cell count (URBC), 24-hour total urinary protein (24 h-MTP), 24-hour total microalbumin (24 h-mALB)] were collected retrospectively. Renal biopsy pathological results were obtained. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), PAR, immunoglobulin A/complement C3 ratio (IgA/C3), immunoglobulin G/complement C3 ratio (IgG/C3), complement C3/complement C4 ratio (C3/C4), and estimated glomerular filtration rate (eGFR) were calculated. Based on PAR percentiles, subjects were divided into three groups: Q1 group (PAR \leq 5.626 5), Q2 group (5.626 56.984 3). Differences in baseline data among the three groups were compared. Spearman rank correlation analysis and multivariate Logistic regression analysis were used to explore the relationship between

PAR and clinical and pathological indicators of IgAN. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of PAR for pathological indicators. Results There were statistically significant differences among the three groups in gender, WBC, ANC, PLT, PLR, PAR, URBC, ALB, IgG/C3, 24 h-mALB, 24 h-MTP, M lesions, and Lee' s classification ($P<0.05$). Correlation analysis showed that PAR was positively correlated with PLT, WBC, ANC, PLR, URBC, 24 h-mALB, 24 h-MTP, M lesions, E lesions, and Lee' s classification ($P<0.05$), and negatively correlated with ALB and IgG/C3 ($P<0.05$). Multivariate Logistic regression analysis revealed that PAR [OR=2.688, 95%CI (1.178, 6.135)] and ALB [OR=0.736, 95%CI (0.587, 0.923)] were independent influencing factors for M1 lesions in IgAN patients ($P<0.05$), and ALB [OR=0.896, 95%CI (0.824, 0.973)] was an independent influencing factor for E1 lesions ($P<0.05$). ROC curves showed that the area under the curve for PAR predicting M1 and E1 lesions in IgAN patients was 0.727 and 0.599, respectively. Conclusion PAR is significantly correlated with clinical manifestations and M and E lesion severity in IgAN, and has certain clinical value in evaluating IgAN activity. More aggressive treatment protocols may be considered for IgAN patients with high PAR values to suppress active lesions and improve renal outcomes.

Full Text

Abstract

Background: IgA nephropathy (IgAN) is a chronic inflammatory disease involving multiple factors and genes. The platelet-albumin ratio (PAR) is considered a novel inflammatory marker, but its relationship with IgAN remains unclear. **Objective:** To investigate the correlation between PAR and clinicopathological indicators of IgAN and evaluate the clinical significance of PAR in IgAN. **Methods:** We retrospectively enrolled 210 patients with biopsy-proven IgAN from the Department of Nephrology, First Affiliated Hospital of Kunming Medical University, between October 2019 and August 2020. General information (gender, age, systolic blood pressure, diastolic blood pressure, and disease duration) and laboratory parameters were collected, including white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), platelet count (PLT), serum albumin (ALB), serum uric acid (SUA), blood urea nitrogen (BUN), serum creatinine (Scr), immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), serum complement C3, serum complement C4, urinary red blood cell count (URBC), 24-hour total urinary protein (24 h-MTP), and 24-hour urinary microalbumin (24 h-mALB). Renal biopsy pathology results were obtained, and the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), PAR, IgA-to-complement C3 ratio (IgA/C3), IgG-to-complement C3 ratio (IgG/C3), complement C3-to-C4 ratio (C3/C4), and estimated glomerular filtration rate (eGFR) were calculated. Patients were divided into three groups based on PAR percentiles: Q1 ($PAR \leq 5.6265$), Q2 ($5.6265 < PAR \leq$

6.9843), and Q3 (PAR > 6.9843). Baseline characteristics were compared across groups. Spearman rank correlation and multivariate logistic regression analyses were used to explore the relationship between PAR and clinicopathological indicators. Receiver operating characteristic (ROC) curves were constructed to assess the predictive value of PAR for pathological lesions. **Results:** Significant differences were observed among the three groups in gender, WBC, ANC, PLT, PLR, PAR, URBC, ALB, IgG/C3, 24 h-mALB, 24 h-MTP, M lesions, and Lee classification ($P < 0.05$). Spearman correlation analysis revealed that PAR was positively correlated with PLT, WBC, ANC, PLR, URBC, 24 h-mALB, 24 h-MTP, M lesions, E lesions, and Lee classification ($P < 0.05$), and negatively correlated with ALB and IgG/C3 ($P < 0.05$). Multivariate logistic regression showed that PAR [OR = 2.688, 95% CI (1.178, 6.135)] and ALB [OR = 0.736, 95% CI (0.587, 0.923)] were independent influencing factors for M1 lesions ($P < 0.05$), while ALB [OR = 0.896, 95% CI (0.824, 0.973)] was an independent influencing factor for E1 lesions ($P < 0.05$). ROC curve analysis demonstrated that the area under the curve (AUC) for PAR in predicting M1 and E1 lesions was 0.727 and 0.599, respectively. **Conclusion:** PAR is significantly correlated with clinical manifestations and the severity of M and E lesions in IgAN, demonstrating clinical value in assessing IgAN activity. Patients with high PAR values may benefit from more aggressive treatment to suppress active lesions and improve renal outcomes.

Keywords: Glomerulonephritis, IgA; Oxford classification of IgA nephropathy; Platelet-albumin ratio; Clinicopathological features

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and a leading cause of end-stage renal disease (ESRD), with 10–60% of patients progressing to ESRD within 10 years [1]. The pathogenesis of IgAN involves multiple factors that remain incompletely understood, but inflammation and immune responses are critical in its development and progression [2]. Platelets play multifaceted roles beyond hemostasis and thrombosis, releasing numerous pro-inflammatory mediators and recruiting leukocytes to inflammatory sites, thereby contributing to inflammation initiation and persistence [3]. Recently, platelet-related parameters such as the platelet-albumin ratio (PAR) and platelet-to-lymphocyte ratio (PLR) have emerged as novel inflammatory markers and prognostic biomarkers in various malignancies, including cholangiocarcinoma and non-small cell lung cancer [4,5]. One study demonstrated that PAR is an independent risk factor for ESRD in IgAN patients [HR = 3.35, 95% CI (1.38, 8.14), $P = 0.008$] and exhibits good predictive value for ESRD development [6]. However, research on the correlation between PAR and IgAN pathological indicators remains limited.

1. Materials and Methods

1.1 Study Population

We retrospectively enrolled 210 patients with biopsy-proven IgAN from the Department of Nephrology, First Affiliated Hospital of Kunming Medical University, between October 2019 and August 2020, including 91 males and 119 females. Inclusion criteria were: (1) diagnosis of IgAN confirmed by renal biopsy showing diffuse, globular or granular IgA-dominant deposits in the mesangial region; (2) first renal biopsy; and (3) complete clinical and pathological data. Exclusion criteria included: (1) secondary IgAN due to systemic lupus erythematosus, Henoch-Schönlein purpura, etc.; (2) prior glucocorticoid and/or immunosuppressant use for >3 months; (3) coexisting pathological changes such as membranous nephropathy or acute tubular necrosis; (4) malignancy or severe cardiovascular disease; (5) <5 glomeruli in biopsy specimens; and (6) transplant kidney biopsy. This study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University (Approval No.: 2022-050), and all patients or their families provided informed consent.

1.2 Research Methods

1.2.1 Clinical and Laboratory Data Collection We collected general information including gender, age, systolic blood pressure, diastolic blood pressure, and disease duration. Fasting venous blood samples (>12 hours) were obtained on the morning after admission. WBC, ANC, ALC, AMC, and PLT were measured using a Sysmex hematology analyzer. Serum was separated by centrifugation (3,000 r/min for 10 minutes) and analyzed for ALB, SUA, BUN, and Scr using a Roche automatic biochemical analyzer (Beckman Coulter, USA). IgA, IgM, IgG, serum complement C3, and C4 were measured using an automatic immunoassay analyzer. Clean-catch midstream morning urine samples (20 ml) were collected for measurement of URBC, 24 h-MTP, and 24 h-mALB using an ACR fully quantitative urine analyzer. NLR, PLR, PAR, IgA/C3, IgG/C3, C3/C4, and eGFR (calculated using the CKD-EPI formula [7]) were computed.

1.2.2 Renal Biopsy Pathology Renal tissue specimens were paraffin-embedded, and sections were stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), periodic acid-silver methenamine (PASM), and Masson trichrome. Immunofluorescence was performed to detect IgA, IgM, and complement C3 deposition intensity and location. Pathological features were evaluated according to Lee's classification [8] and the Oxford classification [9], which includes: (1) mesangial hypercellularity (M): M score ≤ 0.5 (M0) or >0.5 (M1); (2) endocapillary hypercellularity (E): absent (E0) or present (E1); (3) segmental glomerulosclerosis (S): absent (S0) or present (S1); (4) tubular atrophy/interstitial fibrosis (T): $\leq 25\%$ (T0), 26–50% (T1), or >50% (T2); and (5) cellular/fibrous crescents (C): absent (C0), $\leq 25\%$ (C1), or >25% (C2). All pathological assessments were reviewed by two specialized pathologists.

1.2.3 Grouping Method Patients were stratified into three groups based on PAR percentiles: Q1 ($PAR \leq 5.6265$), Q2 ($5.6265 < PAR \leq 6.9843$), and Q3 ($PAR > 6.9843$), with 70 patients in each group.

1.3 Statistical Analysis

Statistical analysis was performed using SPSS 27.0. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data were expressed as mean \pm standard deviation and compared among groups using ANOVA with LSD-t test for post-hoc pairwise comparisons. Non-normally distributed data were presented as median (P25, P75) and analyzed using the Kruskal-Wallis test with post-hoc pairwise comparisons. Categorical variables were expressed as frequencies and compared using the χ^2 test. Correlations between variables were assessed using Spearman rank correlation analysis. Multivariate logistic regression was used to identify influencing factors for M1 and E1 lesions. ROC curves were constructed to evaluate the predictive performance of PAR for M1 and E1 lesions. Statistical significance was defined as $P < 0.05$.

2. Results

2.1 Comparison of General Characteristics

No significant differences were observed among the three groups in age, systolic blood pressure, diastolic blood pressure, or disease duration ($P > 0.05$). However, gender distribution differed significantly ($P < 0.05$).

2.2 Comparison of Clinical Indicators

Significant differences were found among the three groups in WBC, ANC, PLT, PLR, PAR, URBC, ALB, IgG/C3, 24 h-mALB, and 24 h-MTP ($P < 0.05$). Specifically, the Q3 group showed higher WBC, ANC, PLT, PLR, PAR, URBC, IgG/C3, 24 h-mALB, and 24 h-MTP, and lower ALB compared with the Q1 group ($P < 0.05$). The Q3 group also had higher PLT, PAR, and URBC, and lower ALB compared with the Q2 group ($P < 0.05$). The Q2 group exhibited higher PLT, PLR, PAR, and IgG/C3 than the Q1 group ($P < 0.05$). No significant differences were observed in ALC, AMC, NLR, BUN, Scr, eGFR, SUA, serum IgM, IgG, IgA, C3, C4, IgA/C3, or C3/C4 ($P > 0.05$).

2.3 Comparison of Pathological Indicators

Significant differences were observed among the three groups in M lesions and Lee classification ($P < 0.05$). The Q3 group had a higher proportion of M1 lesions and Lee grades III-V compared with the Q1 group ($P < 0.05$). No significant differences were found in E, S, T, C lesions or IgA, IgM, C3 deposition ($P > 0.05$).

Spearman correlation analysis revealed that PAR was positively correlated with PLT, WBC, ANC, PLR, URBC, 24 h-mALB, 24 h-MTP, M lesions, E lesions,

and Lee classification ($P < 0.05$), and negatively correlated with ALB and IgG/C3 ($P < 0.05$). PAR showed no correlation with S, T, or C lesions ($P > 0.05$).

2.5 Correlation Analysis of M Lesions

Spearman correlation analysis demonstrated that M lesion severity in IgAN was positively correlated with AMC, PAR, URBC, BUN, serum IgA, IgA/C3, 24 h-mALB, and 24 h-MTP ($P < 0.05$), and negatively correlated with ALB and serum IgM ($P < 0.05$). No correlations were found with WBC, ANC, ALC, PLT, NLR, PLR, Scr, eGFR, SUA, serum IgG, C3, C4, IgG/C3, or C3/C4 ($P > 0.05$).

2.6 Logistic Regression Analysis of M1 Lesions

Using the presence of M lesions as the dependent variable ($M0 = 0$, $M1 = 1$) and statistically significant indicators from correlation analysis as independent variables, univariate logistic regression identified PAR and ALB as influencing factors ($P < 0.05$). After adjustment, multivariate logistic regression confirmed that PAR [OR = 2.688, 95% CI (1.178, 6.135)] and ALB [OR = 0.736, 95% CI (0.587, 0.923)] were independent influencing factors for M1 lesions ($P < 0.05$).

2.7 Correlation Analysis of E Lesions

Spearman correlation analysis showed that E lesion severity was positively correlated with PAR, URBC, 24 h-mALB, and 24 h-MTP ($P < 0.05$), and negatively correlated with ALB, serum IgG, and IgG/C3 ($P < 0.05$). No correlations were observed with WBC, ANC, ALC, AMC, PLT, NLR, PLR, BUN, Scr, eGFR, SUA, serum IgM, serum IgA, C3, C4, IgA/C3, or C3/C4 ($P > 0.05$).

2.8 Logistic Regression Analysis of E1 Lesions

Using the presence of E lesions as the dependent variable ($E0 = 0$, $E1 = 1$) and statistically significant indicators as independent variables, univariate logistic regression identified PAR, ALB, serum IgG, IgG/C3, 24 h-mALB, and 24 h-MTP as influencing factors ($P < 0.05$). However, multivariate logistic regression revealed that only ALB was an independent risk factor for E1 lesions ($P < 0.05$).

2.9 ROC Curve Analysis for M1 Lesions

ROC curve analysis showed that the AUC of PAR for predicting M1 lesions was 0.727 [95% CI (0.604, 0.851), $P = 0.011$], with an optimal cutoff value of 5.6605, sensitivity of 67.3%, and specificity of 81.8% [Figure 1: see original paper].

2.10 ROC Curve Analysis for E1 Lesions

ROC curve analysis demonstrated that the AUC of PAR for predicting E1 lesions was 0.599 [95% CI (0.514, 0.683), $P = 0.023$], with an optimal cutoff value of 5.992, sensitivity of 70.3%, and specificity of 49.3% [Figure 2: see original paper].

Discussion

IgAN is a chronic inflammatory disease characterized by aberrant production of galactose-deficient IgA1 (Gd-IgA1), which forms immune complexes with IgG or IgA in circulation and deposits in glomeruli, triggering inflammatory cascades that ultimately lead to renal function decline [2]. Platelets play crucial roles in inflammation, releasing pro- and anti-inflammatory factors during activation and aggregation to recruit and activate other immune cells, thereby modulating immune and inflammatory responses [10]. Platelet-related parameters such as PAR have been shown to reflect disease activity and chronic inflammatory status [11,12]. Our results demonstrate that the high PAR group had more severe clinical manifestations and pathological grades, with PAR positively correlated with M and E lesion severity. Multivariate logistic regression identified PAR as an independent influencing factor for M1 lesions, while ALB was independently associated with both M1 and E1 lesions. PAR exhibited predictive value for these active lesions.

Our study revealed significant differences among groups in URBC, ALB, IgG/C3, 24 h-mALB, and 24 h-MTP, indicating that higher PAR values correlate with more severe clinical presentations, including heavy proteinuria, hematuria, and hypoalbuminemia. These findings align with previous research showing that, aside from hypoalbuminemia and thrombocytosis, high PAR is associated with more severe proteinuria and greater likelihood of immunosuppressive therapy [6]. Pathologically, significant differences in M1 lesion proportion and Lee classification were observed across groups, with increasing PAR values associated with higher M1 percentages and Lee grades, suggesting a relationship between PAR and renal pathological injury. Spearman correlation analysis confirmed positive correlations between PAR and M/E lesion severity. Multivariate logistic regression identified PAR as an independent risk factor for M1 lesions but not for E1 lesions, contrasting with previous reports showing differences in E and C lesions between high and low PAR groups [6]. This discrepancy likely stems from our smaller sample size and different grouping criteria, necessitating multicenter, large-scale studies for validation.

IgAN is a slowly progressive disease with various active and chronic histological lesions, where active lesions include M, E, and C lesions [13]. Our findings suggest that PAR has predictive value for M1 lesions [AUC = 0.727, 95% CI (0.604, 0.851)] and E1 lesions [AUC = 0.599, 95% CI (0.514, 0.683)], indicating that elevated PAR should raise suspicion for active lesions and prompt consideration of more aggressive treatment. A 35-year follow-up of the VALIGA cohort

demonstrated that M1 lesions independently correlate with >50% eGFR decline or kidney failure, particularly in patients not receiving immunosuppression [14]. Furthermore, M1 lesions are associated with unresponsiveness to ACEI/ARB therapy [13], while E1 lesions are more likely to receive immunosuppressive treatment that can partially reverse E1 lesions and slow renal function loss [15]. Therefore, early identification and suppression of active lesions before progression to interstitial fibrosis is crucial. Although renal biopsy is often limited by its invasive nature, PAR can assist in predicting active pathological changes in IgAN. PAR offers advantages of being inexpensive, easy to calculate, stable, and comprehensive in reflecting inflammatory-nutritional status. Clinicians should monitor PAR values and consider more aggressive treatment for patients with high PAR to improve renal outcomes.

Albumin, the most abundant plasma protein, possesses anti-inflammatory, antioxidant, and anti-platelet aggregation properties [16]. Strong evidence indicates that hypoalbuminemia is a powerful prognostic marker in cardiovascular diseases, reflecting the severity of malnutrition-inflammation syndrome [17]. In renal disease, low serum albumin is an independent risk factor for ESRD in IgAN, with each 1 g/dl decrease increasing ESRD risk by 1.89-fold. Experimental studies using hydrogen peroxide-induced oxidative stress models in mouse mesangial and human renal cells demonstrated that albumin dose-dependently inhibits intracellular reactive oxygen species and mitochondrial damage [18]. Additionally, hypoalbuminemia in hemodialysis patients is associated with higher rates of peripheral arterial occlusive disease, hospitalization, and mortality [19], suggesting that albumin exerts renoprotective effects and may serve as a potentially reversible marker of systemic nutritional-inflammatory status. Our study identified serum albumin as an independent risk factor for both M1 and E1 lesions, possibly because massive urinary albumin loss diminishes its antioxidant and anti-inflammatory effects, exacerbating active renal lesions and creating a vicious cycle.

This study has several limitations: (1) as a single-center retrospective study, it cannot establish causality between PAR and IgAN active lesions, requiring large-scale prospective cohort studies; (2) the relatively small sample size may introduce bias; and (3) not all potentially relevant clinical variables were included, which might omit important clinical information.

In conclusion, PAR is significantly correlated with clinical and pathological indicators in IgAN and holds important clinical value in assessing IgAN activity, potentially aiding in early diagnosis, risk stratification, treatment selection, and response prediction.

Author Contributions

Zhou Wenjing: study design, conceptualization, and drafting of the initial manuscript; Shang Shili: data collection; Yang Qian: data organization; Zhou Wenjing and Feng Yuerong: statistical analysis and interpretation of results; Li

Jun: manuscript revision, quality control, and overall supervision.

Conflict of Interest

The authors declare no conflict of interest.

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