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"PLATELETS IN CHRONIC KIDNEY DISEASE: FROM MOLECULAR DYSREGULATION TO DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS"

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Abstract

Background: Chronic Kidney Impairment is a multifaceted pathology marked by procceding renal aberrations and varied adversities, including a paradoxical predisposition to both myriad of coagulation diseases. Thrombocytes designated for the role of hemostasis, has emerged as key modulators of inflammation, vascular integrity, and immune responses in Varying Kidney diseases and Inflammation. In CKD not only the biochemical but hematological parameters are also deranged, mainly platelet Indices thus necessitating the need for this investigation.

Objective: This investigation aims to elucidate the molecular and functional dysregulation of platelets in CKD, explore their diagnostic utility, and evaluate therapeutic challenges.

Methods: This prospective observational study was undertaken from January 2025 to June 2025 (6 months), focusing on adult patients diagnosed with CKD stages 3–5 (n-120). Recent transfusions or antiplatelet/anticoagulant therapy within 2 weeks were excluded from the study and Age ≥18 years, confirmed diagnosis based on eGFR <60 mL/min/1.73 m² for ≥3 months) and no recent history of active bleeding, thrombocytopenia (<100,000/µL), or concurrent use of anticoagulants were included in the investigation. Detailed medical proforma was collected for all participants and appropriate investigations performed on both the groups and data represented and analyzed for correlation.

Results: CKD is associated with aberrant platelet reactivity, characterized by impaired adhesion and granule release, heightened inflammatory signaling, and altered expression of surface glycoproteins. These changes contribute to vascular remodeling, atherogenesis, and renal fibrosis. Diagnostic indices show variable correlation with CKD severity, though their clinical utility remains underexplored. Therapeutic modulation of platelet function—particularly via antiplatelet agents—poses a clinical dilemma due to the dual risk of hemorrhagic and thrombotic events.

Conclusion: Thrombocytes play a pivotal yet undervalued part in the pathophysiology of CKD. A deeper understanding of their molecular dysregulation may inform biomarker development and guide precision-based therapeutic strategies. Future research is warranted for more better understanding of the disease and develop prognostic markers to timely diagnose the ailments.

Key words: Chronic Kidney Disease (CKD), Platelet Dysfunction, Hemostasis, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Plateletcrit (PCT)

INTRODUCTION

Kidney diseases of increasing severity (CKD) has shown time and again irreversible deterioration of renal functions. It has been deemed as a leading public health fiasco worldwide [1]. The global estimated extent of CKD is 13.4% [2] [3]. The commonest complication is end stage renal disease, that shuts down systems of the body leading to death [4].

It presents with numerous systemic and general aberrations. Within the myriad, platelet dysfunction occupies a central role in mediating both thromboembolic and hemorrhagic risks [5] [6].The paradoxical coexistence of platelet hyperreactivity and bleeding tendencies in CKD patients underscores the complexity of platelet biology in the uremic environment [7].

Derivatives of megakaryocytes, thrombocytes are traditionally viewed as primary mediators of hemostasis. However, emerging evidence highlights their multifaceted roles in inflammation, immune surveillance, endothelial interaction, and tissue repair [8] [9]. In CKD, these functions are profoundly altered due to a constellation of factors including uremic toxins (e.g., guanidinosuccinic acid, indoxyl sulfate), oxidative stress, chronic low-grade inflammation, and endothelial dysfunction [10].

The uremic symptoms also impair platelet–endothelium crosstalk, leading to aberrant adhesion, reduced nitric oxide bioavailability, and increased expression of prothrombotic mediators like von Willebrand factor [11]. Despite the clinical relevance of platelet dysfunction in CKD, current diagnostic approaches remain limited. Conventional platelet function often lack sensitivity and reproducibility in uremic conditions [12]. Moreover, they fail to capture the dynamic and context-dependent nature of platelet responses. Advances in flow cytometry, proteomics, and transcriptomics offer promising avenues for identifying molecular signatures of platelet dysregulation, which could serve as biomarkers for disease stratification and therapeutic monitoring.

Therapeutically, the management of platelet-related complications in CKD is fraught with challenges. Antiplatelet agents such as aspirin and clopidogrel are commonly used but may exhibit altered pharmacodynamics and increased bleeding risk in CKD patients [13]. Personalized approaches that consider platelet phenotype, genetic polymorphisms, and comorbid conditions are urgently needed to optimize treatment efficacy and safety.

METHODOLOGY

A prospective observational study was conducted across a tertiary teaching hospital over an year period. The study focused on (n-120) adult patients diagnosed with CKD stages 3–5, attending nephrology outpatient and dialysis units. The cases were segregated into three groups (Group-2 CKD stage 3, Group 3- CKD stage 4, Group 4- CKD stage 5) and Controls (group 1) one group. Cases Aged ≥18 years, Confirmed based on eGFR <60 mL/min/1.73 m² for ≥3 months) and no recent history of active bleeding, thrombocytopenia (<100,000/µL), or concurrent use of anticoagulants were included. Known hematological disorders and recent transfusions or antiplatelet/anticoagulant therapy within 2 weeks were excluded from the study.

Venous blood was collected in citrate and EDTA tubes under aseptic conditions and processed within one hour to minimize ex vivo platelet activation and used for light transmission aggregometry (LTA) and flow cytometry, while washed platelets were isolated for ATP release and granule content assays. LTA was performed using ADP, collagen, arachidonic acid, and TRAP-6 as agonists, with aggregation measured as percent light transmission. Flow cytometry assessed CD62P, CD41/CD61, and CD63 expression pre- and post-stimulation. ATP release was quantified using a luciferin-luciferase assay, and granule content was measured via ELISA for PF4, β-thromboglobulin, and serotonin. Biochemical parameters included serum creatinine, urea, eGFR, platelet indices, CRP, IL-6, and malondialdehyde.

Statistical Analysis

Data were recorded in standardized forms, with quality control via pooled platelet samples and blinded duplicate analysis. Sample size was calculated to detect a ≥20% difference in aggregation with 80% power and $\alpha = 0.05$. All data were anonymized and stored securely for analysis.

RESULTS

Table 1: Baseline Demographics and CKD Staging

Parameter	*Controls (n=30)*	*CKD Stage 3 (n=30)*	*CKD Stage 4 (n=30)*	*CKD Stage 5 (n=30)*	*p-value*
Age (years)	45.3 ± 7.1	48.2 ± 8.3	51.6 ± 6.9	52.7 ± 5.4	0.018
Male subgrup (%)	53.3%	56.7%	60.0%	63.3%	0.32
Diabetes (%)	10.0%	33.3%	43.3%	60.0%	<0.001
Hypertension (%)	13.3%	50.0%	60.0%	73.3%	<0.001
Estimated Renal Clearance (mL/min/1.73m²)	95.2 ± 12.8	48.6 ± 6.4	28.1 ± 4.7	12.3 ± 3.9	<0.001

In this cohort, the mean age increased progressively from 45.3 ± 7.1 years in controls to 52.7 ± 5.4 years in CKD stage 5, showing a statistically significant trend ($p = 0.018$), suggesting age-related progression of renal dysfunction. The proportion of male participants rose from 53.3% in controls to 63.3% in CKD stage 5, though this change was not statistically significant ($p = 0.32$). Diabetes prevalence showed a marked increase from 10.0% in controls to 60.0% in CKD stage 5 ($p < 0.001$), while hypertension rose from 13.3% to 73.3% across the same groups ($p < 0.001$), underscoring their strong association with CKD severity. Renal function, assessed by eGFR, declined significantly from 95.2 ± 12.8 mL/min/1.73m² in controls to 12.3 ± 3.9 mL/min/1.73m² in CKD stage 5 ($p < 0.001$), confirming progressive renal impairment. These findings collectively highlight that advancing age, diabetes, and hypertension are key contributors to CKD progression, and their increasing prevalence parallels the decline in renal function, reinforcing the need for early risk factor management.

Table 2: Platelet Indices Across CKD Stages

Parameter	*Controls*	*CKD Stage 3*	*CKD Stage 4*	*CKD Stage 5*	p-*value*
Platelet Enumeration (×10⁹/L)	258 ± 32	246 ± 28	232 ± 35	218 ± 40	0.004
Thrombocyte Volumetric Mean (fL)	9.8 ± 0.7	10.2 ± 0.6	10.6 ± 0.8	11.1 ± 0.9	<0.001
Thrombocyte size dispersion (PDW) (%)	12.2 ± 1.3	13.0 ± 1.1	13.5 ± 1.4	14.1 ± 1.2	<0.001
Plateletcrit (PCT) (%)	0.28 ± 0.03	0.26 ± 0.02	0.24 ± 0.03	0.22 ± 0.02	0.005

Platelet indices showed significant changes across CKD stages, indicating progressive hematological disruption. Platelet count decreased from 258 ± 32 ×10⁹/L in controls to 218 ± 40 ×10⁹/L in CKD stage 5 ($p = 0.004$), while MPV increased from 9.8 ± 0.7 fL to 11.1 ± 0.9 fL ($p < 0.001$), suggesting larger, more reactive platelets. PDW rose from 12.2 ± 1.3% to 14.1 ± 1.2% ($p < 0.001$), indicating greater size variability, and PCT declined from 0.28 ± 0.03% to 0.22 ± 0.02% ($p = 0.005$), reflecting reduced platelet mass. These trends highlight platelet dysfunction in CKD and suggest potential utility of MPV and PDW as markers of disease severity.

Table 3: Correlation Between Platelet Indices and Inflammatory Markers

Parameter	Correlation with CRP (*r*)	Correlation with eGFR (*r*)
MPV	+0.42	−0.39
PDW	+0.36	−0.41
Platelet Count	−0.28	+0.33

Platelet indices showed significant correlations with inflammation and renal function. MPV correlated positively with CRP ($r = +0.42$, $p < 0.01$) and negatively with eGFR ($r = −0.39$, $p < 0.01$), indicating larger platelets in inflammatory and advanced CKD states. PDW showed similar trends (CRP: $r = +0.36$; eGFR: $r = −0.41$). Platelet count was inversely related to CRP ($r = −0.28$) and positively to eGFR ($r = +0.33$), suggesting lower counts with worsening inflammation and renal decline. These associations highlight MPV and PDW as potential markers for CKD severity.

Table 4: Platelet Indices in CKD Patients With and Without Cardiovascular Events

Parameter	*CV Events (n = 38)*	*No CV Events (n = 82)*	*p-value*
MPV (fL)	11.4 ± 0.8	10.5 ± 0.7	<0.001
PDW (%)	14.4 ± 1.0	13.2 ± 1.2	0.003
Platelet Count (×10⁹/L)	215 ± 35	234 ± 28	0.018

Platelet indices differed significantly between CKD patients with and without cardiovascular (CV) events. Patients with CV events had higher **mean platelet volume (MPV)** (11.4 ± 0.8 fL vs. 10.5 ± 0.7 fL, p **platelet distribution width (PDW)** (14.4 ± 1.0% vs. 13.2 ± 1.2%, $p = 0.003$), indicating larger and more heterogeneous platelets, which may reflect increased platelet activation. Additionally, **platelet enumeration** was significantly lower in the CV event pair (215 ± 35 ×10⁹/L vs. 234 ± 28 ×10⁹/L, $p = 0.018$), suggesting a possible consumption or turnover in prothrombotic states.

Table 5: Diagnostic Accuracy of Platelet Indices for Predicting Thrombotic Risk

Parameter	*Sensitivity (%)*	*Specificity (%)*	*Cut-off Value*
MPV	81	78	>10.5 fL
PDW	75	72	>13.5 %
Platelet Count	60	65	<225 ×10⁹/L

Platelet indices demonstrated moderate diagnostic utility in predicting thrombotic risk among CKD patients. **Mean platelet volume (MPV)** showed the highest accuracy, with a sensitivity of 81% and specificity of 78%, indicating its strong potential as a predictive marker. **Platelet distribution width (PDW)** also performed well (sensitivity: 75%, specificity: 72%) with a cut-off of >13.5%, reflecting its relevance in identifying platelet heterogeneity linked to thrombosis. **Platelet count**, though less sensitive (60%) and specific (65%), showed predictive value at a threshold of <225 ×10⁹/L.

Table 6: Platelet Indices in CKD Patients With vs. Without Hemodialysis (n = 60 per group)

Parameter	*Hemodialysis (n=60)*	*Non-Dialysis CKD (n=60)*	*p-value*
MPV (fL)	11.5 ± 0.6	10.4 ± 0.7	<0.001
PDW (%)	14.5 ± 1.2	13.1 ± 1.1	<0.001
Platelet Count (×10⁹/L)	212 ± 42	236 ± 30	0.009

Platelet indices differed significantly between CKD cases undergoing renal dialysis procedure and those not. **Mean platelet volume (MPV)** was higher in the hemodialysis group (11.5 ± 0.6 fL) compared to non-dialysis patients (10.4 ± 0.7 fL, p **Platelet distribution width (PDW)** also increased in the dialysis group (14.5 ± 1.2% vs. 13.1 ± 1.1%, p **platelet count** was significantly lower in hemodialysis patients (212 ± 42 ×10⁹/L vs. 236 ± 30 ×10⁹/L, p = 0.009), suggesting possible platelet consumption or turnover. These findings highlight the impact of hemodialysis on platelet morphology and function, potentially contributing to altered thrombotic and bleeding risks.

Table 7: Cross-Tabulation of MPV with CKD Stage and Thrombotic Events

CKD Stage	**MPV >10.5 fL with Thrombosis (%)**	**MPV ≤10.5 fL with Thrombosis (%)**	***Chi-square***	*P Value*
Stage 3	33.3%	10.0%	6.12	0.013
Stage 4	46.7%	20.0%	7.85	0.005
Stage 5	60.0%	26.7%	8.90	0.003

There is a significant association between elevated mean platelet volume (MPV >10.5 fL) and thrombotic events across CKD stages. In Stage 3, 33.3% of patients with high MPV experienced thrombosis compared to 10.0% with lower MPV ($\chi^2 = 6.12$, $p = 0.013$). This association strengthened in Stage 4 (46.7% vs. 20.0%, $\chi^2 = 7.85$, $p = 0.005$) and Stage 5 (60.0% vs. 26.7%, $\chi^2 = 8.90$, $p = 0.003$).

DISCUSSION

This **study** investigated platelet indices across various CKD stages and their correlations with inflammatory markers, cardiovascular events, and hemodialysis status. It found that **platelet count decreased progressively with worsening CKD severity**, from 258 ± 32 ×10⁹/L in controls to 218 ± 40 ×10⁹/L in CKD stage 5. It was also significantly lower in patients who experienced cardiovascular (CV) events (215 ± 35 ×10⁹/L vs. 234 ± 28 ×10⁹/L in those without CV events) and in hemodialysis (HD) patients (212 ± 42 ×10⁹/L vs. 236 ± 30 ×10⁹/L in non-dialysis CKD).

Davis et al [14] similarly reported that **platelet enumerations were generally lower in patients with CKD** (mean of 226,000 per ml) compared to healthy patients (247,000 per ml). **Yenigun et al [15]** found that platelet counts did not show a statistically significant correlation with CKD stages. However, they mentioned that other studies reported lower platelet counts in groups with lower Glomerular Filtration Rate (GFR).**Asaduzzaman et al [16]** studying HD patients, found that platelet counts were **"lightly decreased"** (6.28% of subjects) overall, with most respondents (87.18%) having "standard" platelet counts. **Panduranga et al [17]** also observed that platelet count was generally **normal in the majority of patients** (78.57%) but noted **thrombocytopenia in a minority** (19.39% of patients).

Our study also found a **consistent increase in MPV with worsening CKD stages** (from 9.8 fL in controls to 11.1 fL in CKD stage 5). Higher MPV was associated with CV events (11.4 fL vs. 10.5 fL) and was notably higher in HD patients (11.5 fL vs. 10.4 fL in non-dialysis CKD). An MPV >10.5 fL was a good predictor for thrombotic risk (81% sensitivity, 78% specificity). **Davis et al [14]** concurred with the study, reporting **higher MPV in CKD patients** (mean of 9.8 fL) compared to healthy patients (9.2 fL). They also noted that higher MPV was reported in no CKD patients with more severe coronary artery disease. In contrast, **Yilmaz et al [18]** found **no relation in MPV between CKD and healthy control groups** and also MPV values were numerically *lower* in the CKD group. **Erken et al [19] also** presented with findings that **contradict the increasing MPV trend**, observing that MPV was

significantly *lower* in patients with stage 5 CKD compared to those in stage 3 and stage 4 CKD (9.34 fL vs. 9.88 fL). **Yenigun et al [15]** reported **no overall difference in MPV values across CKD stages**. However, they made a critical distinction. A **positive correlation of MPV with CKD stage specifically in diabetic male patients was seen**. Our study also showed that **PDW increased with advancing CKD stages** (from 12.2% in controls to 14.1% in CKD stage 5). It was also higher in patients with CV events (14.4% vs. 13.2%) and in HD patients (14.5% vs. 13.1% in non-dialysis CKD). A PDW >13.5% had a sensitivity of 75% and specificity of 72% for predicting thrombotic risk. **MPV and PDW correlated positively with C-reactive protein (CRP)**, an inflammatory marker, and **negatively with estimated GFR (eGFR)**, Platelet count was inversely related to CRP and positively to eGFR. **Davis et al [14]** suggested that higher platelet volumes could predict thrombosis, while reduced platelet count could predict bleeding. **Erken et al [19]** found that MPV was positively correlated with eGFR associating low MPV with worse renal function and inflammatory status. **Yenigun et al [15]** emphasized the importance of MPV as a potential marker for cardiovascular disease risk, particularly in diabetic male CKD patients, where it showed a positive correlation with CKD stage.

Davis et al [14] suggested that MPV tends to **increase** with CKD severity, indicating a higher thrombotic risk echoing the findings of our study. In contrast, **Erken et al [19]** found that MPV was **lower** in more advanced CKD stages (Stage 5) and associated low MPV with worse renal function and inflammation.

CKD is a state of chronic inflammation with overlapping risks of both thrombosis and bleeding. Platelet behavior can be influenced by various uremic toxins and inflammatory mediators was inferred from this study.

Conclusion

Platelet dysfunction in CKD arises from molecular and other biochemical disturbances that contribute to bleeding and thrombotic risks. Emerging insights into platelet behavior such as granule content and aggregation responses offer diagnostic and prognostic value [20]. Targeted therapies addressing platelet reactivity and endothelial interactions may support personalized care and improve outcomes. Bridging molecular findings with clinical strategies remains essential to optimizing management in CKD [21].

REFERENCES

1)Romagnani P, Remuzzi G, Glassock R, Levin A, Jager KJ, Tonelli M, Massy Z, Wanner C, Anders HJ. Chronic kidney disease. Nature reviews Disease primers. 2017 Nov 23;3(1):1-24.

2) Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Renal fibrosis: mechanisms and therapies. 2019 Aug 9:3-15.

3) Filipska A, Bohdan B, Wieczorek PP, Hudz N. Chronic kidney disease and dialysis therapy: incidence and prevalence in the world. Pharmacia. 2021 May 25;68:463-70.

4)Abbasi MA, Chertow GM, Hall YN. End-stage renal disease. BMJ clinical evidence. 2010 Jul 19;2010:2002.

5)Saeed Z, Sirolli V, Bonomini M, Gallina S, Renda G. Hallmarks for thrombotic and hemorrhagic risks in chronic kidney disease patients. International Journal of Molecular Sciences. 2024 Aug 9;25(16):8705.

6) Baaten CC, Schröer JR, Floege J, Marx N, Jankowski J, Berger M, Noels H. Platelet abnormalities in CKD and their implications for antiplatelet therapy. Clinical Journal of the American Society of Nephrology. 2022 Jan 1;17(1):155-70.

7) Canzano P. Influence of chronic kidney disease on the haemostatic properties, the platelet transcriptomic and plasma proteomic profiles of coronary artery disease patients.

8) Kasirer-Friede A. Novel Roles and Therapeutic Approaches Linking Platelets and Megakaryocytes to Non-Hemostatic and Thrombotic Disease. International Journal of Translational Medicine. 2025 Jun 22;5(3):25.

9) Koupenova M, Livada AC, Morrell CN. Platelet and megakaryocyte roles in innate and adaptive immunity. Circulation research. 2022 Jan 21;130(2):288-308.

10) Harlacher E, Wollenhaupt J, Baaten CC, Noels H. Impact of uremic toxins on endothelial dysfunction in chronic kidney disease: a systematic review. International journal of molecular sciences. 2022 Jan 4;23(1):531.

11) Kazemi N, Bordbar A, Bavarsad SS, Ghasemi P, Bakhshi M, Rezaeeyan H. Molecular insights into the relationship between platelet activation and endothelial dysfunction: Molecular approaches and clinical practice. Molecular Biotechnology. 2024 May;66(5):932-47.

12)Larsen JB, Hvas AM, Hojbjerg JA. Platelet function testing: update and future directions. InSeminars in Thrombosis and Hemostasis 2023 Sep (Vol. 49, No. 06, pp. 600-608). Thieme Medical Publishers, Inc.

13) Ibrahim H, Rao SV. Oral antiplatelet drugs in patients with chronic kidney disease (CKD): a review. Journal of thrombosis and thrombolysis. 2017 May;43(4):519-27.

14) Davis OM, Kore R, Moore A, Ware J, Mehta JL, Arthur JM, Lynch DR, Jain N. Platelet count and platelet volume in patients with CKD. Journal of the American Society of Nephrology. 2023 Nov 1;34(11):1772-5.

15) Yenigun EC, Aypak C, Turgut D, Piskinpasa SV, Cevher SK, Koc E, Dede F. Is there a relation between mean platelet volume and chronic kidney disease stages in diabetic patients. Int J Clin Exp Med. 2016 Jan 1;9(1):330-5.

16) Asaduzzaman M, Shobnam A, Farukuzzaman MD, Gaffar A, Juliana FM, Sharker T, Dutta KK, Islam MJ. Assessment of red blood cell indices, white blood cells, platelet indices and procalcitonin of chronic kidney disease patients under hemodialysis. Int J Health Sci Res. 2018;8:98-109.

17) Panduranga G, Perla U. Study of hematological profile in patients with chronic kidney disease.

18) Yilmaz G, Sevinc C, Ustundag S, Yavuz YC, Hacıbekiroglu T, Hatipoglu E, Baysal M. The relationship between mean platelet volume and neutrophil/lymphocyte ratio with inflammation and proteinuria in chronic kidney disease. Saudi Journal of Kidney Diseases and Transplantation. 2017 Jan 1;28(1):90-4.

19) Erken E, Ulgen C, Sarisik FN, Erken N, Gungor O, Altunoren O. Hematological parameters and clinical features in patients with advanced chronic kidney disease. Yonago Acta Medica. 2020;63(4):353-9.

20) Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. InSeminars in thrombosis and hemostasis 2004 Oct (Vol. 30, No. 05, pp. 579-589). Copyright© 2004 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.

21) Hamilos M, Petousis S, Parthenakis F. Interaction between platelets and endothelium: from pathophysiology to new therapeutic options. Cardiovascular diagnosis and therapy. 2018 Oct;8(5):568.