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Platelet Count and Platelet Volume in Patients with Chronic Kidney Disease

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Thrombotic cardiovascular disease, including heart attack and stroke, is one of the leading causes of death in patients with chronic kidney disease (CKD).[1] Compared to patients who do not have CKD, patients with worsening severity of CKD have a 2- to 4-fold increase in risk of thrombotic cardiovascular disease. This heightened risk occurs despite guideline-based treatments. CKD is also associated with bleeding risks that are approximately 10-fold higher than those of the general population.[1] This is exacerbated by antiplatelet therapies, which are commonly given for thrombotic complications. Not surprisingly, antiplatelet therapy is one of the top 4 reasons for emergency hospitalizations for patients 65 years or older,[1] and this CKD subgroup is at a disproportionately higher risk of bleeding from such therapy.[2] Thus, determining which CKD patient is prone to thrombosis, and which CKD patient is prone to bleeding on antiplatelet treatment remain elusive. There are several overlapping patient characteristics (e.g., age and kidney function) that are associated with both thrombosis and bleeding,[3] and this makes it difficult to identify CKD patients at risk for these complications. Clinicians are faced with the dilemma of which risk is greater for a given patient. In CKD state, there are several potential drivers of thrombosis including platelet activation, heightened inflammation, uremic toxins and accelerated atherosclerosis; and, of bleeding including platelet dysfunction, reduced platelet adherence to vessel wall, and uremic toxins. Thus, simple and innovative strategies are needed to improve risk prediction models for these complications in patients with CKD. In this perspective, we argue that subtle changes in platelet count and platelet volume in patients with CKD may indicate an increased risk of bleeding, and thrombosis. Thus, complete blood count may be a useful metric to predict risk of thrombosis and bleeding in patients with CKD in order to optimize use of antiplatelet drugs in this patient population.

Platelet Count and Platelet Volume in CKD

A literature review of studies evaluating platelet count and platelet volume in CKD is summarized in **Table 1**.[4-7] In most studies, platelet counts were lower in patients with CKD than in healthy patients: 226,000 per µL in patients with CKD versus 247,000 per µL in healthy patients (we report the calculated mean of the means from the studies shown in **Table 1**). On the other hand, platelet volumes were higher in patients with CKD than in healthy patients: 9.8 fL in patients with CKD versus 9.2 fL in healthy patients (mean of the means shown in **Table 1**). Only 2 of the studies shown in Table 1 reported significant clinical relationships with platelet indices— one study reported reduced platelet count correlated with worse bleeding time in CKD patients on chronic hemodialysis ($p<0.05$) and the other study reported higher platelet volume in patients with non-dialysis CKD who had more severe coronary artery disease detected on coronary angiogram (no *p*-value reported). Notably, the decrease in platelet count and the increase in platelet volume in CKD patients fall within normal laboratory ranges.[8] Even so, these subtle changes in platelet count and volume may indicate increased risk for bleeding and thrombosis and should not be ignored.

Platelet Volume and Risk of Thrombosis in CKD

A relatively higher platelet volume in CKD patients than in healthy patients could mean higher thrombotic risk. In patients with coronary artery disease, higher levels of pro-inflammatory molecules such as C - reactive protein and interleukin 6 in the blood activates platelet production in the bone marrow and produce large-volume, young platelets.[9] Young platelets display higher thrombotic ability because of a higher number of dense granules, higher activity of mitochondria, and increased expression of cell adhesion molecules on their surfaces.[9] These cellular changes in large-volume, young platelets also correlate with increased platelet aggregation and enhanced synthesis and release of platelet microparticles, thromboxane A2

and β-thromboglobulin;[9] as a result, higher platelet volume is associated with higher thrombotic risk in the cardiovascular literature.[10] Similar to coronary artery disease, CKD is a pro-inflammatory state with heightened blood levels of pro-inflammatory molecules which can activate large-volume, young platelets in the circulation. Previous studies reported heightened release of platelet microparticles in CKD patients that are assumed to be released from large-volume, young platelets; however, did not report platelet volume.[11] A recent review summarized the role of uremic toxins (e.g., indoxyl sulfate) in increasing platelet aggregation and release of platelet microparticles that led to thrombotic phenotype in mice; however platelet volumes were not reported.[1] Given this information, changes to platelet volume of CKD patients might predict underlying thrombotic risk.

Platelet Count and Risk of Bleeding in CKD

A platelet count below 100,000 per µL is considered a bleeding risk in the cardiovascular literature.[3] Reduced platelet count leads to defective adhesion of platelets to vessel walls and renders primary hemostasis abnormal; as a result, reduced platelet adhesion increases bleeding risk. A slight reduction in platelet count of CKD patients might also suggest underlying risk of bleeding. In health, platelet count is maintained by megakaryocytes in the bone marrow, and regulated by a glycoprotein hormone thrombopoietin.[9] As platelet counts drop, more thrombopoietin is available to support megakaryocytes in platelet production. In CKD patients, increased platelet apoptosis results in their shorter life-span.[12] As a result, reduced platelet count occurs in CKD patients which, in turn, increases blood TPO levels. A slightly reduced platelet count (229,000 per µL in CKD vs 262,000 per µL in controls) was shown to correlate with increased bleeding time in CKD patients receiving hemodialysis[4] and in those not on dialysis.[1] A recent review summarized the role of uremic toxins (e.g., urea and guanidinosuccinic acid) in inhibiting platelet aggregation, and of impaired platelet adhesion to

vessel wall that was seen in CKD patients with bleeding complications; however, platelet counts were not reported in these studies.[1,8] Given this information, a slightly reduced platelet count of CKD patients might predict underlying bleeding risk.

Clinical Relevance

In contemporary clinical practice, the role of platelets in thromboses and bleeding complications of CKD remains poorly defined and is a research area that greatly needs to be expanded. In the last five decades, studies that reported platelet phenotype in CKD state were based on platelet function assays that used human samples, which resulted in some studies reporting pro-thrombotic phenotype and others pro-bleeding phenotype.[1,8] Numerous assays are available for functional assessment of platelets, each with its strengths and limitations.[1,8] Current clinical practice guidelines do not recommend testing platelet function in patients with CKD because optimizing antiplatelet therapy based on routine platelet function testing does not reduce adverse outcomes in the cardiovascular literature.[13] Simple and readily available strategies are needed to improve risk prediction models for thrombosis and bleeding in patients with CKD. Due to lack of understanding mechanisms related to the CKD complications, optimal antiplatelet therapy remains a clinical dilemma, as it requires a balance between efforts to reduce risks for thrombosis while minimizing bleeding complications in this patient population.

The two seemingly different pathophysiological complications of thrombosis and bleeding likely fit with the platelet paradigm of a temporal sequence of events in the hemostatic cascade that involves adhesion followed by aggregation. If platelet adhesion is abnormal, then bleeding is likely; if platelet aggregation is abnormal, then thrombosis likely. On one hand, platelet volume may be a predictor of thrombosis as large-volume, young platelets are more likely to aggregate. On the other hand, reduced platelet count may be a predictor of bleeding in CKD patients due to reduced platelet adhesion. If so, information from complete blood counts could

be used in models to predict risk of thrombosis and bleeding in CKD patients. For example, CKD patients with higher platelet volumes might be treated with more potent antiplatelet drugs when clinically indicated to reduce the underlying risk of thrombosis. Alternatively, CKD patients with reduced platelet count might be treated with antiplatelet drugs cautiously to minimize the underlying risk of bleeding. As a result, this information could be used to optimize the use of antiplatelet therapies in CKD patients.

Knowledge Gaps and Future Directions

We must overcome several challenges before complete blood count can be used to predict thrombosis and bleeding risk in CKD patients. Cut-offs for platelet count and platelet volume need to be defined that are associated with bleeding and thrombosis in CKD patients. Studies must also confirm underlying mechanisms related to these CKD complications, e.g., whether higher platelet volumes of CKD patients confer thrombotic risk and whether reduced platelet count from altered apoptosis of CKD platelets is sufficient to confer bleeding risk. Finally, preclinical studies are needed to determine when and how platelet indices change as CKD progresses. Answering these questions could fill knowledge gaps in our understanding of CKD pathophysiology; subsequently, this would promote the use of platelet count and platelet volume in predictive models of risk for thrombosis and bleeding in CKD patients. The goal would be to optimize use of antiplatelet therapies in this patient population so that optimal therapy can be implemented with fewer thrombotic and bleeding complications of CKD state.

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Table 1. Literature reporting platelet count and volume in chronic kidney disease

Study	Study Population	n	Platelet Count (SD), (X1000/μL)	Mean Platelet Volume (SD), fL	Findings
Michalak 1991 PMID: 2024233	CKD receiving HD	CKD: 66 HC: 32	CKD: 229 (15) HC: 262 (12)	CKD: 8.1 (0.2) HC: 9.3 (0.3)	Reduced PC may contribute to the uremic bleeding diathesis in CKD as noted by inverse correlation between platelet count and bleeding time (correlation coefficient = -0.51, p<0.05).
Corken 2022 PMID: 36591354	Stage 4 or 5 CKD	CKD: 48 HC: 25	CKD: 236 (61) HC: 266 (58)	CKD: 11 HC: 9	CKD patients (vs HC) have reduced PC and elevated MPV, both p<0.05.
Zhu 2018 PMID: 29701174	PD	338	201 (48)	9.3 (1.4)	There was no significant association of either MPV or PC with death. However, for each 0.01 unit increase in the ratio of MPV to PC, there was reduced risk of death, hazard ratio 0.67 (95% CI: 0.51, 0.89).
Ucar 2013 PMID: 23772896	CAD	471	GFR < 60: 225 (34) GFR > 60: 243 (55)	GFR < 60: 10.7 (1.6) GFR > 60: 8.6 (1.7)	MPV negatively correlates with GFR (β = -0.55) and PC (β = -0.12), both *p*<0.05.
Verdoia 2016 PMID: 27039166	CAD	GFR < 60: 1,044	216 (74)	10.9 (1.0)	CKD is associated with a significant odds of higher MPV, odds ratio 1.56 (95% CI: 1.23, 1.99).
Yenigun 2016 PMID*	Stage 1 to 5 CKD	812	Not available	Not available	Higher MPV (β = 0.22, *p*<0.05) and lower PC (β = 0.02, *p*>0.05) are associated with worsening CKD severity.
Bilen 2014 PMID: 24028675	Stage 3 or 4 CKD, HD, PD and RT	200	CKD: 243 (82) HD: 220 (88) PD: 260 (79) RT: 244 (59)	CKD: 8.0 (1.1) HD: 7.9 (1.2) PD: 7.8 (1.2) RT: 8.0 (0.9)	No differences in MPV and PC between CKD, HD, PD and RT groups (*p*>0.05).
Kemec 2020 PMID: 32579406	Non-diabetic, non-hypertensive CKD with	CKD: 41 HC: 57	CKD: 306 (95) HC: 288 (84)	CKD: 8.3 (0.7) HC: 8.4 (0.9)	Proteinuria is not associated with platelet indices (*p*>0.05).

	nephrotic range proteinuria and HC				
Erken 2020 PMID: 33253334	CKD Stage 3 to 5 including HD	627	238 (79)	9.7 (1.6)	PC (correlation coefficient = -0.13, p<0.05) and serum creatinine concentration (correlation coefficient = -0.14, p<0.05) correlated inversely with MPV values.
Larsen 2014 PMID: 24465602	CAD	581	GFR < 60: 236 GFR > 60: 221	GFR < 60: 10.7 GFR > 60: 10.8	Patients with a GFR < 60 had significantly higher PCs than patients with a GFR > 60.
Hancer 2020 PMID**	CAD	121	Stage 3: 241 (73) Stage 4: 233 (68) Stage 5: 197 (54)	Stage 3: 8.5 (1.6) Stage 4: 8.4 (1.7) Stage 5: 8.0 (1.3)	More severe CAD noted with a higher MPV value and larger MPV to PC ratio (no p-value reported).

*Yenigun EC et al. Int J Clin Exp Med 2016;9(1):330-335 and **Hancer H, Kayabasi H. Acta Medica Mediterranea, 2020, 36: 2027; not in PMID.
Abbreviations: β, standardized regression coefficient; CAD, coronary artery disease; CKD, chronic kidney disease; CI, confidence interval; GFR, estimated glomerular filtration rate; HC, healthy control; HD, hemodialysis; PC, platelet count; PD, peritoneal dialysis; RT, renal transplant; Stage 3 defined as GFR 30-60 ml/min/1.73m^2; stage 4 defined as GFR 15-30 ml/min/1.73m^2; stage 5 CKD defined as non-dialysis CKD with GFR <15 ml/min/1.73m^2.